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Investigação da atuação de mecanismos genéticos, epigenéticos e ambientais no desenvolvimento da obesidade

Porto Alegre

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Esta Tese de Doutorado segue o formato proposto pelo Programa de Pós-Graduação em Ciências Médicas: Endocrinologia, Metabolismo e Nutrição da Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, sendo apresentada em forma de uma breve introdução sobre o assunto, seguida dos manuscritos originais sobre o tema da Tese.

Artigo 1: "Systems biology approach identifies key genes and related pathways in childhood obesity"

Artigo 2: "Network Insights into Childhood Obesity: Unveiling Methylated-Differentially Expressed Genes and Pathways through Integrative Bioinformatics Analysis"

Artigo 3: "Western style-based cafeteria diet induces alterations in weight, metabolic profile, and expression of a set of metabolic and inflammatory genes in C57BL/6 mice"

Artigo 4: "Dietary blueberry supplementation attenuates the effects of a cafeteria diet on weight gain and metabolic parameters, enhancing nutrigenomic profiles in C57BL/6 mice"

"*I had my ups and downs, but I always find the inner strength to pull myself up. I was served lemons, but I made lemonade*."

Hattie White, on *Freedom* by Beyoncé

RESUMO

A obesidade é uma doença crônica caraterizada pelo acúmulo de gordura no tecido adiposo, sendo decorrente do desequilíbrio entre a ingesta e o gasto calórico. Devido ao aumento exponencial da prevalência da obesidade no mundo, esta doença tem sido considerada como a epidemia do século 21. Além de ser frequente em indivíduos adultos, a frequência em crianças também tem crescido mundialmente e estudos mostram que a doença tende a permanecer na vida adulta. A obesidade é uma doença complexa e multifatorial visto que sua fisiopatologia envolve a interação entre fatores genéticos, epigenéticos e ambientais.

Diversos fatores genéticos influenciam a suscetibilidade à obesidade, explicando cerca de 65% da variabilidade da doença. A análise integrativa de dados genéticos de diferentes populações, através de biologia de sistemas, pode contribuir para um melhor entendimento da fisiopatologia da obesidade infantil. Dessa forma, no primeiro artigo, realizamos uma busca sistemática de genes candidatos relacionados à obesidade infantil utilizando o banco de dados público DisGeNET. Foram identificados 191 genes associados com a doença, sendo que 12 destes genes foram considerados como *hub-bottleneck* (*INS*, *LEP*, *STAT3*, *POMC*, *ALB*, *TNF*, *BDNF*, *CAT*, *GCG*, *PPARG*, *VEGFA* e *ADIPOQ*) após análises de rede de interação proteína-proteína. As análises de enriquecimento funcional indicam que estes genes estão envolvidos em vias relacionadas à inflamação, termogênese, metabolismo de glicose e lipídeos e sinalização de citocinas. Além disso, foram identificados 4 módulos funcionais para este grupo de 191 genes. De um modo geral, este estudo foi capaz de identificar um grupo de genes altamente interconectados associado com a obesidade infantil.

Os fatores genéticos não conseguem explicar isoladamente a variabilidade e o aumento da prevalência de obesidade. Neste contexto, mudanças em mecanismos epigenéticos foram observadas em adultos e crianças com obesidade. A metilação, um dos principais mecanismos epigenéticos, regula negativamente a expressão gênica em resposta a fatores ambientais. Apesar de alguns estudos sugerirem que genes diferencialmente metilados (DMGs) estão associados com a obesidade infantil, os resultados ainda são inconclusivos. Além disso, padrões de metilação tendem a ser persistentes ao longo da vida. Dessa forma, a identificação de genes diferencialmente expressos (DEGs) regulados por metilação (MeDEGs) pode contribuir para o entendimento dos eventos moleculares complexos envolvidos na obesidade infantil.

Neste contexto, no segundo artigo da tese, investigamos MeDEGs associados com a obesidade infantil através de uma análise integrativa *in silico*. Para isto, 4 *datasets* contendo dados globais de expressão (um de expressão gênica e 3 de metilação) foram obtidos no banco de dados público *Gene Expression Omnibus*. Após a sobreposição das listas dos 859 DEGs e 3,455 DMGs, foram identificados 70 MeDEGs. Entre eles, 25 genes apresentaram padrão hipermetilado-expressão reduzida e 45 apresentaram padrão hipometilado-expressão aumentada no tecido adiposo visceral (TAV) de crianças com obesidade comparado a crianças sem obesidade. A rede de interação proteína-proteína desses MeDEGs apresentou 3 genes *hub-bottleneck* (*CCL5*, *STAT1* e *GATA3*) e dois módulos funcionais. Análises de enriquecimento funcional demonstram que estes MeDEGs estão envolvidos em processos de diferenciação celular, inflamação, sinalização de citocinas, metabolismo de glicose e lipídeos, resistência à insulina (RI) e apoptose. Os resultados deste estudo indicam uma lista de MeDEGs envolvidos na obesidade infantil, bem como identifica vias metabólicas em que eles

atuam, fornecendo uma compreensão mais profunda dos mecanismos reguladores da obesidade infantil mediados por metilação de DNA.

Embora a suscetibilidade genética e os mecanismos epigenéticos apresentem papel importante no desenvolvimento da obesidade, fatores ambientais, como sedentarismo e padrões de dieta, são considerados fatores-chave por trás do aumento exponencial de doenças metabólicas relacionadas à obesidade. A dieta de cafeteria (DCAF) ou dieta ocidental é hipercalórica e rica em alimentos ultraprocessados e de baixa densidade nutricional, possuindo potencial inflamatório e oxidativo. A exposição de camundongos à DCAF mimetiza os padrões de consumo alimentar humano e serve como modelo de estudo da obesidade; entretanto, as alterações metabólicas e nutrigenômicas nesse modelo são pouco conhecidas.

Sendo assim, no 3° artigo da tese, implementamos um modelo de obesidade induzida por DCAF em camundongos para investigar as alterações metabólicas associadas, bem como a expressão de diversos genes relacionados a rotas das adipocitocinas, inflamação, apoptose e metabolismo da glicose no TAV, tecido adiposo subcutâneo (TAS), fígado e músculo. Para isto, foram incluídos 40 camundongos C57BL/6 machos, sendo 20 que receberam dieta padrão (DP) e 20, DCAF (CAF). Após 16 semanas de seguimento, o grupo CAF ganhou mais peso e apresentou uma glicemia média maior comparado aos controles. Ainda, o escore de esteatose hepática, índice de RI e níveis de adiponectina e leptina foram maiores no grupo CAF. Com relação às análises de expressão gênica, observou-se 19 genes desregulados no TAV, 6 genes no TAS, 11 genes no fígado e 4 genes no músculo esquelético destes animais comparados ao grupo DP. Além disso, a relação *Itgax/Llgl1* foi aumentada no TAV dos camundongos expostos à DCAF, indicando uma mudança no fenótipo dos macrófagos de M2 para M1, que é o inflamatório. Com isso, foi possível padronizar um modelo de DCAF em

camundongos C57BL/6 e descrever as alterações metabólicas e moleculares associadas a este modelo.

Alguns estudos têm demonstrado que o mirtilo apresenta ação benéfica na obesidade, reduzindo a inflamação e o estresse oxidativo, bem como atenuando o ganho de peso em humanos e em modelos animais. Entretanto, nenhum estudo testou a eficácia da adição do mirtilo a uma dieta como a DCAF. Dessa forma, no nosso 4° artigo, avaliamos o efeito do consumo de mirtilo sobre parâmetros biométricos, metabólicos e nutrigenômicos em camundongos expostos à DCAF. Foram incluídos 32 camundongos C57BL/6 machos distribuídos em 3 grupos experimentais: controle (n= 10; DP), DCAF (n= 12, CAF) e mirtilo + DCAF (n= 10, BB). O consumo de mirtilo preveniu o ganho de peso induzido pela DCAF visto que após 16 semanas de seguimento, os animais apresentaram peso similar aos animais do grupo DP. O índice de Lee (equivalente ao índice de massa corporal) e o delta-peso (peso final - peso inicial) também foram maiores no grupo CAF comparado aos grupos DP e BB. Além disso, o mirtilo foi capaz de prevenir parcialmente o aumento da glicemia de jejum, RI e protegeu contra a esteatose hepática e estresse oxidativo no fígado e hipotálamo. As análises de expressão gênica demonstraram que o mirtilo foi capaz de modular 16 genes no TAV, 10 genes no TAS, 4 no tecido adiposo marrom, 12 genes no fígado, 5 no músculo esquelético e 4 no hipotálamo dos animais do grupo BB. Ainda, a relação *Itgax/Llgl1* também foi aumentada no TAV dos camundongos DCAF comparado aos grupos BB e DP.

Em conclusão, os estudos incluídos nesta tese evidenciaram o papel de fatores genéticos, epigenéticos e ambientais no desenvolvimento da obesidade. Em especial, foram identificados genes candidatos e MeDEGs envolvidos na patogênese da obesidade infantil, bem como as vias e processos biológicos nas quais estes genes estão

envolvidos. Ainda, foi possível implementar um modelo de DCAF para a indução de obesidade em camundongos C57BL/6, bem como avaliar as alterações biométricas, metabólicas e nutrigenômicas envolvidas neste modelo. Por fim, foi possível investigar o importante efeito do consumo de mirtilos para tratamento da obesidade, o qual melhorou desfechos biométricos, glicêmicos, metabólicos, de estresse oxidativo e nutrigenômicos. Assim, podemos considerar o consumo de mirtilo como uma estratégia dietética promissora para prevenir disfunções metabólicas associadas à obesidade.

Palavras-chave: Obesidade. Obesidade infantil. Metilação de DNA. Dieta de cafeteria. Mirtilo. Nutrigenômica.

ABSTRACT

Obesity is a chronic disease characterized by the accumulation of fat in adipose tissue, resulting from an imbalance between calorie intake and expenditure. Due to the exponential increase in the prevalence of obesity worldwide, this disease has been considered the epidemic of the 21st century. In addition to being prevalent in adults, its prevalence in children has also grown worldwide, and studies have shown that the disease tends to persist into adulthood. Obesity is a complex and multifactorial disease as its pathophysiology involves the interaction between genetic, epigenetic, and environmental factors.

Several genetic factors influence the susceptibility to obesity, explaining approximately 65% of the disease variability. The integrative analysis of genetic data from different populations through systems biology approach can contribute to a better understanding of the pathophysiology of childhood obesity. Thus, in the first article, we conducted a systematic search for candidate genes related to childhood obesity using the public database DisGeNET. We identified 191 genes associated with the disease, of which 12 were considered hub-bottleneck genes (*INS*, *LEP*, *STAT3*, *POMC*, *ALB*, *TNF*, *BDNF*, *CAT*, *GCG*, *PPARG*, *VEGFA*, and *ADIPOQ*) after protein-protein interaction network analyses. Functional enrichment analyses indicate that these genes are involved in pathways related to inflammation, thermogenesis, glucose and lipid metabolism, and cytokine signaling. Additionally, four functional modules were identified for this group of 191 genes. Overall, this study was able to identify a group of highly interconnected genes associated with childhood obesity.

Genetic factors alone cannot fully explain the variability and increasing prevalence of obesity. In this context, changes in epigenetic mechanisms have been

observed in both adults and children with obesity. Methylation, one of the main epigenetic mechanisms, negatively regulates gene expression in response to environmental factors. Although some studies have suggested that differentially methylated genes (DMGs) are associated with childhood obesity, the results remain inconclusive. Additionally, methylation patterns tend to persist throughout life. Therefore, the identification of differentially expressed genes (DEGs) regulated by methylation (MeDEGs) can contribute to the understanding of the complex molecular events involved in childhood obesity.

In this context, in the second article of this thesis, we investigated MeDEGs associated with childhood obesity through an integrative *in silico* analysis. For this, four datasets containing global expression data (one for gene expression and three for methylation) were obtained from the public database Gene Expression Omnibus. After overlapping the lists of 859 DEGs and 3,455 DMGs, 70 MeDEGs were identified. Among them, 25 genes showed a hypermethylated-low expression pattern, and 45 showed a hypomethylated-high expression pattern in visceral adipose tissue (VAT) of children with obesity compared to children without obesity. The protein-protein interaction network of these MeDEGs presented 3 hub-bottleneck genes (*CCL5*, *STAT1*, and *GATA3*) and two functional modules. Functional enrichment analyses demonstrate that these MeDEGs are involved in processes of cell differentiation, inflammation, cytokine signaling, glucose and lipid metabolism, insulin resistance (IR), and apoptosis. The results of this study indicate a list of MeDEGs involved in childhood obesity, and identifies metabolic pathways in which they act, providing a deeper understanding of the regulatory mechanisms of childhood obesity mediated by DNA methylation.

Although genetic susceptibility and epigenetic mechanisms play an important role in the development of obesity, environmental factors, such as sedentary lifestyle

and dietary patterns, are considered key factors behind the exponential increase in obesity-related metabolic diseases. The cafeteria diet (CAFD) or Western diet is hypercaloric and rich in ultra-processed foods with low nutritional density, having inflammatory and oxidative potential. Exposure of mice to CAFD mimics human dietary consumption patterns and serves as a model for studying obesity; however, the metabolic and nutrigenomic alterations in this model are poorly understood.

Thus, in the third article of the thesis, we implemented a model of obesity induced by CAFD in mice to investigate the associated metabolic changes, as well as the expression of various genes related to adipocytokine, inflammation, apoptosis, and glucose metabolism pathways in VAT, subcutaneous adipose tissue (SAT), liver, and muscle. For this, 40 male C57BL/6 mice were included, with 20 receiving a standard diet (SD) and 20 receiving CAFD (CAF). After 16 weeks of follow-up, the CAF group gained more weight and had higher mean blood glucose compared to controls. Furthermore, hepatic steatosis score, IR index, and adiponectin and leptin levels were higher in the CAF group. Regarding gene expression analyses, 19 genes were dysregulated in VAT, 6 in SAT, 11 in the liver, and 4 in skeletal muscle of these animals compared to the SD group. Additionally, the *Itgax/Llgl1* ratio was increased in the VAT of mice exposed to CAFD, indicating a shift in macrophage phenotype from M2 to M1, which is inflammatory. Therefore, we standardized a CAFD model in C57BL/6 mice and described the metabolic and molecular alterations associated with this model.

Some studies have shown that blueberries (BB) have beneficial effects on obesity, reducing inflammation and oxidative stress, as well as attenuating weight gain in humans and animal models. However, no study has tested the effectiveness of adding BB to a diet like CAFD. Therefore, in our fourth article, we evaluated the effect of BB consumption on biometric, metabolic, and nutrigenomic parameters in mice exposed to

CAFD. Thirty-two male C57BL/6 mice were included and categorized into 3 experimental groups: control (n=10; SD), CAFD (n=12, CAF), and BB + CAFD (n=10, BB). BB consumption prevented the weight gain induced by CAFD as after 16 weeks of follow-up the animals had a similar weight to those in the SD group. The Lee index (equivalent to body mass index) and delta-weight (final weight - initial weight) were also higher in the CAF group compared to the SD and BB groups. Additionally, BB partially prevented the increase in fasting blood glucose, IR, and protected against hepatic steatosis and oxidative stress in the liver and hypothalamus of the BB group. Gene expression analyses showed that BB was able to modulate 16 genes in VAT, 10 in SAT, 4 in brown adipose tissue, 12 in the liver, 5 in skeletal muscle, and 4 in the hypothalamus of these animals. Furthermore, the *Itgax/Llgl1* ratio was also increased in the VAT of CAF mice compared to the BB and SD groups.

In conclusion, the studies included in this thesis have highlighted the role of genetic, epigenetic, and environmental factors in the development of obesity. Specifically, candidate genes and MeDEGs involved in the pathogenesis of childhood obesity were identified, along with the biological pathways and processes in which these genes are involved. Furthermore, a CAFD model was successfully implemented for inducing obesity in C57BL/6 mice, allowing for the description of the biometric, metabolic, and nutrigenomic alterations involved in this model. Finally, the significant effect of BB consumption in the treatment of obesity was investigated, improving biometric, glycemic, metabolic, oxidative stress, and nutrigenomic outcomes. Thus, BB consumption can be considered a promising dietary strategy for preventing metabolic dysfunctions associated with obesity.

Keywords: Obesity. Childhood obesity. DNA methylation. Cafeteria diet. Blueberry. Nutrigenomics.

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LISTA DE ABREVIATURAS E SIGLAS

INTRODUÇÃO

ALT	Alanina aminotransferase
AST	Aspartato aminotransferase
AUC	Área sob a curva
BB	*Blueberry* (mirtilo)
CC	Circunferência da cintura
DCAF	Dieta de cafeteria
DEGs	*Differentially expressed genes*
DM2	Diabetes mellitus tipo 2
DMGs	*Differentially methylated genes*
DNMTs	DNA metiltransferases
EROs	Espécies reativas de oxigênio
GEO	*Gene Expression Omnibus*
GMCSF	Fator estimulador de colônia de macrófagos granulócitos
GWAS	*Genome Wide Association Studies*
HbA1c	Hemoglobina glicada
HFD	*High-fat diet*
HFHS	*High-fat, high-sucrose diet*
HNE	Hidroxinonenal
HOMA-IR	Modelo de avaliação da homeostase da resistência à insulina
HSD	*High-sugar diet*
IL6	Interleucina 6
IMC	Índice de massa corporal

MCP-1	Proteína de quimiotaxia de macrófagos
MDA	Malondialdeído
MetS	Síndrome metabólica
PBMCs	*Peripheral blood mononuclear cells*
RI	Resistência à insulina
TA	Tecido adiposo
TAB	Tecido adiposo branco
TAM	Tecido adiposo marrom
TAS	Tecido adiposo subcutâneo
TAV	Tecido adiposo visceral
TBARS	Substâncias reativas ao ácido tiobarbitúrico
TLR4	Receptor tipo Toll 4
TNF	Fator de necrose tumoral
TOTG	Teste oral de tolerância à glicose

ARTIGOS

Adipoq	Adiponectin
ARRIVE	Animal Research: Reporting of In Vivo Experiments
AT	Adipose tissue
BAT	Brown adipose tissue
BB	Blueberry
BMI	Body mass index
BP	Biological process
CAFD	Cafeteria diet

CC	Cell components
DEGs	Differentially expressed genes
DIO	Diet-induced obesity
DMGs	Differentially methylated genes
EWAS	Epigenome-Wide Association Study
FDR	False Discovery Rate
GEO	Gene Expression Omnibus
GO	Gene Ontology
GSH	Glutathione
GST	Glutathione-S-transferase
GWAS	Genome Wide Association Studies
HF	High fat
HFD	High-fat diet
HGNC	HUGO Gene Nomenclature Committee
HOMA-IR	Homeostasis model assessment of insulin resistance
HS	High sugar
IR	Insulin resistance
KEGG	Kyoto Encyclopedia of Genes and Genomes
Lep	Leptin
MCODE	Molecular Complex Detection
MeDEGs	Methylated-differentially expressed genes
MetS	Metabolic Syndrome
MF	Molecular functions
NAFLD	Non-alcoholic fatty liver disease
OGTT	Oral glucose tolerance test

PBMCs	Peripheral blood mononuclear cells
PPI	Protein-protein interaction
ROS	Reactive oxygen species
SAT	Subcutaneous adipose tissue
SD	Standard diet
SD	Standard diet
SOD	Superoxide dismutase
STRING	Search Tool for the Retrieval of Interacting Genes
T2DM	Type 2 diabetes mellitus
TBARS	Thiobarbituric acid reactive species
UPF	Ultra-processed food
VAT	Visceral adipose tissue
WAT	White adipose tissue

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1 INTRODUÇÃO

1.1 Obesidade

A obesidade é uma doença crônica multifatorial caracterizada por um acúmulo de gordura excessivo no tecido adiposo (TA) que pode prejudicar a saúde (1). Decorrente de um desequilíbrio entre a ingesta e o gasto calórico, a obesidade pode levar a uma redução da qualidade e expectativa de vida (1, 2). O índice de massa corporal [IMC; peso (kg) / altura m²)] é o parâmetro mais utilizado para avaliar o grau de sobrepeso ou obesidade dos indivíduos em ambos os sexos (1). A classificação pelo IMC ocorre seguindo os critérios estabelecidos pela Organização Mundial da Saúde, conforme descrito na **Tabela 1**.

Tabela 1. Critérios da Organização Mundial da Saúde para classificação do grau de sobrepeso e obesidade utilizando o índice de massa corporal.

Índice de massa corporal (kg/m²)	Classificação	Grau de obesidade
<18,5	Baixo peso	0
≥18,5 até 24,9	Normal ou eutrófico	0
≥25,0 até 29,9	Sobrepeso	0
≥30,0 até 34,9	Obesidade	I
≥35,0 até 39,9	Obesidade	II
≥40,0	Obesidade grave	III

Fonte: Organização Mundial da Saúde (1).

A prevalência da obesidade tem aumentado progressivamente em indivíduos de todas as idades e grupos étnicos, tornando-se cada vez mais um grave problema de saúde pública mundial (1, 3). Nas últimas três décadas, a prevalência da obesidade

triplicou na população, fato que está associado à urbanização, estilo de vida sedentário e aumento do consumo de alimentos ultraprocessados (4). Segundo a Federação Mundial de Obesidade, em 2020, 2,6 bilhões de indivíduos adultos apresentavam algum grau de sobrepeso, sendo que destes, 988 milhões possuíam obesidade (5). No contexto da obesidade infantil, esse quadro também é grave: 175 milhões de crianças e adolescentes com idades entre 5-19 anos foram reportados com obesidade até 2020 (5). Além disso, 38 milhões de indivíduos com idade igual ou inferior a 5 anos foram diagnosticados com sobrepeso (5).

Segundo dados do Ministério da Saúde (6), em 2023, a frequência de excesso de peso [IMC: ≥25 kg/m² e ≤29,9 kg/m²] foi de 61,4% na população brasileira com ≥18 anos, sendo maior entre homens (63,4%) do que entre mulheres (59,6%). Porto Alegre foi a capital brasileira com maior percentual de homens adultos (69%) com sobrepeso (6). Entre as mulheres adultas, 57% da população de Porto Alegre apresentou sobrepeso (6). Com relação aos indivíduos diagnosticados com obesidade (IMC ≥30 kg/m²), 24,3% da população apresentou a doença, sendo a frequência semelhante entre homens (23,8) e mulheres (24,8%) (6). Ainda, Porto Alegre foi a terceira capital brasileira com maior percentual tanto de homens (27%), quanto de mulheres (30%) com obesidade, ambos acima da média nacional (6).

Estimativas da Federação Mundial de Obesidade indicam que até o ano de 2035, caso não sejam tomadas medidas para modificar a trajetória da epidemia de obesidade, mais de 4 bilhões de pessoas com ≥5 anos poderão apresentar algum grau de sobrepeso na população mundial, afetando cerca de 51% dos indivíduos (5). Além disso, as estimativas apontam que cerca de 3% do produto interno bruto mundial deverá ser investido em custos no tratamento de indivíduos com sobrepeso e obesidade, totalizando cerca de 4 trilhões de dólares (5). Considerando o Brasil, conforme ilustrado

na **Figura 1**, até 2035 é esperado que 41% da população com ≥18 anos e 28% de indivíduos entre 5-18 anos apresentem obesidade (5).

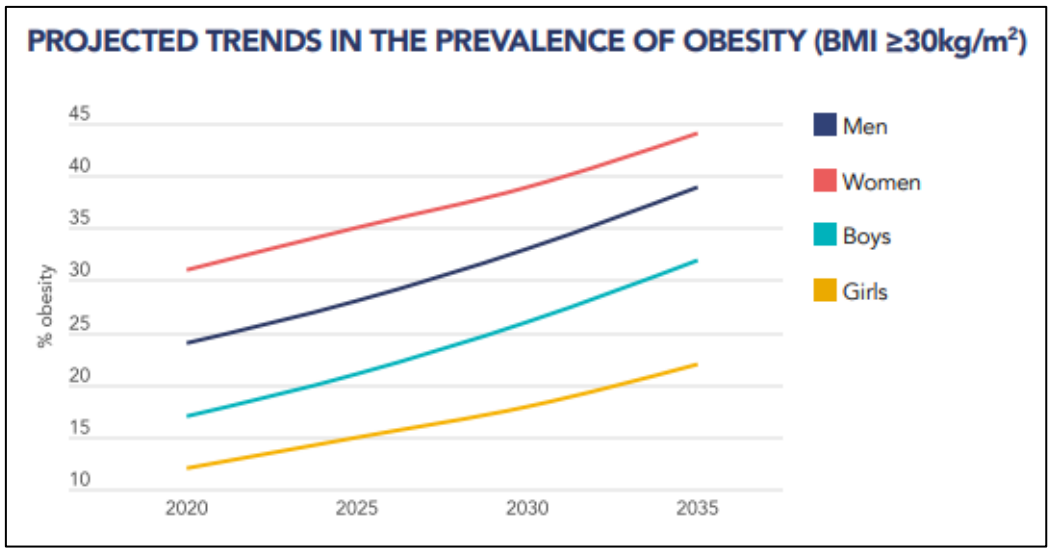

Figura 1. Estimativas do percentual de indivíduos com ≥5 anos de idade com obesidade na população do Brasil entre os anos de 2020 e 2035.
Fonte: Atlas de 2023 da Federação Mundial de Obesidade (5).

O aumento de casos de obesidade está associado ao aumento de morbidade e mortalidade, bem como ao desenvolvimento de comorbidades, que podem incluir: distúrbios do sono, dificuldades respiratórias, problemas nas articulações e nos ossos, diabetes mellitus tipo 2 (DM2), hipertensão, resistência à insulina (RI), dislipidemia, problemas cardiovasculares e alguns tipos de câncer (7, 8).

A obesidade é caracterizada pelo aumento do TA, que é um órgão endócrino responsável pelo armazenamento de energia através da síntese de triglicerídeos e que é capaz de responder rapidamente a estímulos ambientais através de hipertrofia e hiperplasia de adipócitos, influenciando na homeostase do organismo (9, 10). A habilidade do TA em responder às variações de fornecimento de energia depende da interação de suas funções e respostas endócrinas e metabólicas, além de mudanças dinâmicas em sua composição celular (9, 10). O TA é comumente dividido em dois

grupos: TA branco (TAB) e TA marrom (TAM), sendo o TAB o principal órgão de armazenamento de energia em forma de triglicerídeos dentro dos adipócitos. O TAB pode sofrer um aumento no número de adipócitos e composição de triglicerídeos devido ao desequilíbrio entre a ingesta e o gasto calórico, podendo levar à obesidade (10, 11). O TAM, por sua vez, é especializado na queima de lipídeos para transformar energia em calor, processo conhecido como termogênese, e que é fundamental para a homeostase da temperatura corporal (12).

O TAB está presente em diferentes regiões no organismo humano, determinando variações funcionais importantes, especialmente em termos de secreção de hormônios e adipocinas (9). Existem dois tipos principais de TAB: o TAB subcutâneo (TAS) e o TAB visceral (TAV) (9). O TAS é encontrado abaixo da pele e nas regiões abdominal e glúteo-femoral, associado a um perfil metabólico mais favorável (9, 11). O TAV, por sua vez, é localizado na cavidade abdominal, revestindo os principais órgãos metabólicos, e seu acúmulo excessivo é associado com complicações metabólicas como RI e DM2, dislipidemia e doença cardiovascular (9, 11).

O remodelamento do TA está patologicamente alternado no contexto da obesidade, o que em geral pode envolver diminuição no remodelamento da angiogênese que é a resposta da produção de vasos sanguíneos devido ao aumento do TA, superprodução de elementos da matriz extracelular, além do infiltrado de células do sistema imune que levam a respostas pró-inflamatórias (11, 13, 14). Neste sentido, a obesidade é acompanhada por inflamação crônica de baixo grau, a qual está associada ao desenvolvimento das comorbidades decorrentes dessa doença, incluindo a RI e o DM2 (13, 14).

A obesidade é uma doença complexa e multifacetada decorrente de diversos fatores de risco, incluindo fatores genéticos, epigenéticos, ambientais,

sociodemográficos, neuroendócrinos, entéricos, psicológicos e comportamentais (2, 15, 16). Com relação aos fatores de risco ambientais, os principais são: maus hábitos alimentares, que incluem o alto consumo de alimentos ultraprocessados contendo altos teores de carboidratos de composição simples e ácidos graxos saturados, consumo de *fast food* e redução da atividade física e sedentarismo (2, 16). Os fatores genéticos podem aumentar o ganho de peso devido à sua interação com fatores ambientais, visto que estudos em gêmeos monozigóticos demonstraram que 50-70% dos valores de IMC podem ser explicados por fatores genéticos (17).

1.2 Obesidade infantil

De acordo com a Organização Mundial da Saúde, o IMC pode ser usado como critério de diagnóstico para a obesidade tanto em indivíduos adultos, quanto em crianças (1). Os padrões normais de IMC de uma criança variam de acordo com seu sexo e idade (1). O diagnóstico de magreza, sobrepeso ou obesidade na infância e adolescência é feito de acordo com curvas predefinidas, seguindo percentis (para crianças menores de 5 anos) ou o escore z (para crianças e adolescentes entre 5-19 anos) (1), conforme descrito na **Tabela 2**.

Crianças em grupos étnicos socialmente minoritários, bem como crianças que vivem abaixo da linha da pobreza estão em grupo de risco mais elevado para desenvolver obesidade (5, 18). A obesidade e suas comorbidades afetam uma grande parte da população infantil mundial e estão associadas com a diminuição da contribuição destes indivíduos com a sociedade (18, 19). As comorbidades relacionadas ao sobrepeso e obesidade infantil estão associadas com os sistemas cardiovascular, endócrino, ortopédico, gastrintestinal, neurológico, pulmonar e psicossocial (18, 19). A

adiposidade e acúmulo de gordura durante a adolescência estão positivamente associadas com aterosclerose na vida adulta (20).

Tabela 2. Valores de referência para diagnóstico de obesidade infantil utilizando curvas de IMC corrigidas para sexo e idade.

Diagnóstico de indivíduos com ≤5 anos	**Diagnóstico de indivíduos com 5 a 19 anos**	**Classificação**
< Percentil 0,1	< Escore z -3	Magreza acentuada
≥ Percentil 0,1 e < Percentil 3	≥ Escore z -3 e < Escore -2	Magreza
≥ Percentil 3 e < Percentil 85	≥ Escore z -2 e < Escore +1	Eutrofia
≥ Percentil 85 e < Percentil 97	≥ Escore z -1 e < Escore +2	Sobrepeso
≥ Percentil 97 e ≤ Percentil 99,9	≥ Escore z +2 e < Escore +3	Obesidade
> Percentil 99,9	> Escore z +3	Obesidade grave

Fonte: Organização Mundial da Saúde (1).

Uma grande porcentagem de crianças com obesidade permanece nessa condição em sua vida adulta (5). As condições que podem contribuir para isso incluem a idade em que a criança começa a desenvolver a doença, a severidade da condição e o histórico familiar de obesidade (4, 5).

Em crianças e adolescentes, o estado de sobrepeso geralmente é causado por baixa frequência de atividade física e padrões de alimentação não-saudáveis que resultam em excesso de ingestão de calorias com consequente baixo gasto calórico (18, 21). Sabe-se que uma alimentação rica em gorduras e carboidratos simples e sedentarismo estão altamente associados com risco para obesidade (18, 21). Em crianças, a relação entre calorias absorvidas e gastas é crítica para o seu desenvolvimento (18, 21). Hábitos alimentares estabelecidos desde o início da vida têm

impacto significante na qualidade da dieta, crescimento e risco para sobrepeso e obesidade, e interferem diretamente com fatores genético e epigenéticos, os quais podem acentuar a gravidade da doença (18, 21).

1.3 Fatores genéticos e obesidade

Fatores genéticos são importantes na patogênese da obesidade visto que a probabilidade de uma criança que tem pais com obesidade desenvolver a doença é 3 vezes mais alta quando comparado a crianças que não têm pais com obesidade (22). Além disso, se sabe que mais de 1.100 diferentes *loci* estão associados com a patogênese da obesidade (23).

O TA, conforme anteriormente descrito, é um dos tecidos mais importantes para o estudo da obesidade (13). A descoberta mais importante sobre o TA no contexto da obesidade, é que este tecido aumenta a secreção do hormônio tecido-específico leptina que é responsável por sinalizar a saciedade pós-prandial, caracterizando uma resistência à leptina nestes indivíduos (24). Além disso, a produção elevada da citocina fator de necrose tumoral (TNF) por esse tecido diminui a sensibilidade à insulina (24). Estudos de expressão gênica em larga escala promovem descobertas relacionadas aos eventos moleculares desencadeados nas mais diversas doenças humanas e o TA tem sido bastante avaliado nestes estudos com o objetivo de identificar mudanças de expressão gênica na obesidade (24). A identificação das diferenças no padrão de expressão de genes candidatos para a obesidade em diferentes tecidos é de grande importância para uma melhor compressão da patogenia da doença a nível tecidual (24).

Utilizando a plataforma *Illumina HiSeq* 4000, Zhou et al. (25) analisaram o transcriptoma do TAV em 11 indivíduos eutróficos e 48 pacientes com obesidade. Como principais achados, os autores relatam que os pacientes com obesidade apresentavam

um perfil de expressão de genes inflamatórios mais acentuado comparado aos controles, sendo 12 dos 34 genes diferencialmente expressos entre os dois grupos associados com vias de inflamação (25). Além disso, os autores sugeriram que tanto o IMC quanto fatores relacionados a uma dieta saudável podem modular o perfil de expressão gênica no TAV (25). O estudo de Ronquillo et al. (26) teve como objetivo identificar genes diferencialmente expressos (*differentially expressed genes*, DEGs) no TAV e TAS de 8 indivíduos eutróficos e 8 indivíduos com obesidade utilizando ensaios de *microarray*. No TAS, um total de 327 DEGs foram associados com a obesidade, enquanto no TAV, 488 DEGs foram encontrados em indivíduos com obesidade, incluindo genes superexpressos como *PPAP2C*, *CYP4A11* e *CYP17A1* (26).

Utilizando a plataforma *Affymetrix U133 Plus* 2.0, Muniandy et al. (27) realizaram a identificação de um perfil de expressão gênica alterado no TAS de 26 pares de gêmeos monozigóticos discordantes para obesidade, com idades entre 23 e 36 anos, através de análise de transcriptômica. Foram identificados 2108 DEGs nos indivíduos com obesidade, sendo estes genes relacionados a rotas de estresse mitocondrial e inflamação (27). Além disso, os autores demonstraram que aqueles irmãos com obesidade apresentavam um nível de glicemia em jejum aumentado comparado aos irmãos sem obesidade e que estes níveis se correlacionavam com a expressão de alguns DEGs identificados no estudo (27).

Ainda neste contexto, um estudo avaliou a expressão de 19 genes candidatos para a obesidade em células mononucleares de 30 pacientes com obesidade e 20 indivíduos eutróficos (28). Foi verificado que a expressão dos genes *TFEC* e *CCL2* foi negativamente correlacionada com o IMC, composição de gordura total, percentual de gordura, relação cintura/quadril e concentrações plasmáticas de leptina (28). Ainda, as expressões de *TNFAIP2*, *VCAN*, *ASSI*, *IRF1* e *HK3* foram negativamente

correlacionadas com o IMC e a composição corporal (28). Em contraste, as expressões de *TNF* e *LPL* foram positivamente correlacionados com a relação cintura/quadril (28).

Apesar da influência comprovada de fatores genéticos na patogenia da obesidade, isoladamente, estes não consegue explicar o aumento da prevalência dessa doença (29). Nesse contexto, a interação entre fatores genéticos e ambientais tem sido estudada para explicar melhor o desenvolvimento da doença (29). Os fatores epigenéticos podem estar envolvidos na patogênese da obesidade, uma vez que eles possuem papel fundamental no controle da expressão gênica e são ativados por fatores ambientais diversos (29).

1.4 Mecanismos epigenéticos

Fatores epigenéticos regulam o diálogo entre fatores genéticos e ambientais sem alterar a sequência do DNA e incluem metilação de DNA, modificação de histonas e RNAs não-codificantes (30). As modificações epigenéticas são capazes de controlar a forma na qual um gene é transcrito ou expresso através da regulação da acessibilidade da maquinaria de transcrição em um determinado gene, fazendo com que este gene seja ativo ou não em um dado período da vida (31). Além disso, podem bloquear ou diminuir a expressão de um gene através de ligação ao seu mRNA alvo no citoplasma. Os mecanismos epigenéticos podem ser modulados de acordo com o ambiente no qual o indivíduo está inserido, principalmente referente às questões nutricionais e de atividade física (15). Assim, os mecanismos epigenéticos são importantes para a manutenção da vida, sendo descritos também como potenciais biomarcadores e alvos terapêuticos para algumas doenças, incluindo a obesidade (31, 32).

1.4.1 Metilação de DNA e obesidade infantil

A metilação de DNA é a adição de grupos metil no carbono 5' de uma citosina que é seguido de uma guanina (ilhas CpG) (29, 32). A distribuição e o padrão das ilhas CpG não é uniforme ao longo do genoma e estima-se que 70% das regiões promotoras de genes contêm ilhas CpG (33). Ilhas CpG não-metiladas correspondem a regiões onde há transcrição gênica ativa, enquanto ilhas metiladas apresentam regiões onde há a repressão da expressão gênica (33). A metilação do DNA pode atuar através da interferência na ligação de fatores de transcrição na região de transcrição (33).

Em mamíferos, três enzimas DNA metiltransferases (DNMTs) estão envolvidas na metilação do DNA: DNMT1, DNMT3A e DNMT3B (34). Estas enzimas são responsáveis pela transferência do grupo metil de uma molécula de S-adenosil-L-metionina para o carbono 5' de uma citosina (34). DNMT3A e DNMT3B adicionam grupos metil em regiões não-modificadas do DNA e estão ativas principalmente na vida intrauterina (34). Já a enzima DNMT1 é responsável por manter a metilação (34).

A relação entre mecanismos de metilação de DNA e a obesidade tem sido apontada como um campo de estudo promissor com potencial clínico (29, 35). O perfil de metilação na região promotora de alguns genes associados à obesidade foi demonstrado como alterado em crianças com essa doença quando comparado com crianças sem obesidade (36). Estudos que avaliem a metilação de DNA em crianças com obesidade são especialmente importantes, visto que evidências mostram que padrões de metilação estabelecidos no início da vida podem ser persistentes (29, 35). A **Tabela 3** descreve os principais estudos que identificaram genes diferencialmente metilados na obesidade infantil, bem como o número amostral utilizado, tipo de amostra e técnica usada em cada estudo.

Com o rápido desenvolvimento de tecnologias de sequenciamento de alto rendimento foi necessário criar bancos de dados nos quais pesquisadores pudessem depositar os seus achados (37). O *Gene Expression Omnibus* (GEO) é um banco de dados internacional e público capaz de arquivar e distribuir gratuitamente conjuntos de dados (*datasets*) de expressão gênica e de padrões de metilação de alto rendimento e outras análises funcionais (37). Nos últimos anos, a comunidade científica tem utilizado dados disponíveis no GEO a fim de realizar novos estudos, combinando dados de diversos *datasets* com o objetivo de aumentar o poder estatístico destas análises (38-41). Além disso, abordagens utilizando análises de bioinformática e algoritmos de biologia de sistemas têm surgido como uma estratégia promissora para identificar e categorizar DEGs e genes diferencialmente metilados (*differentially methylated genes*, DMGs) (39, 41, 42). Assim, análises integrativas utilizando *datasets* de expressão gênica e metilação de DNA de pacientes com obesidade, previamente documentados em estudos depositados no GEO, pode facilitar a descoberta de novas e potenciais vias moleculares e genes candidatos para a obesidade (39, 42).

Tabela 3. Metilação de DNA em genes previamente estudados na obesidade infantil e seus principais achados.

Gene	Tecido analisado	Amostra	Metodologia	Principais achados	Ref.
LEP e *LEPR*	Sangue total	120 crianças com média de idade de 17 meses	*MassArray EpiTyper*	Correlação inversa entre a % de metilação no *LEP* e duração da amamentação e peso no nascimento.	(43)
	Sangue total	106 crianças e adolescentes (10-16 anos)	MSP	% de metilação na região promotora do *LEP* foi negativamente associado com IMC, RI e níveis de TG, colesterol e insulina.	(44)
	Sangue de cordão umbilical	182 recém-nascidos	*Illumina Infinium HumanMethylation 450k Bead-Chip*	% de metilação de 4 ilhas CpG no *LEP* demonstrou correlação inversa com níveis de leptina	(45)
	Sangue de cordão umbilical	114 recém-nascidos	*Illumina Infinium HumanMethylation 450k Bead-Chip*	% de metilação de 5 ilhas CpG na região promotora de *LEP* foi negativamente com IMC materno antes da gravidez.	(46)
	Saliva	431 crianças e adolescentes (10-15 anos)	*PyroMark CpG Assays (Qiagen)*	% de metilação no *LEP* foi inversamente correlacionado com IMC, circunferência da cabeça e % de gordura corporal em meninos.	(47)
	Saliva	64 crianças (5-6 anos)	*Methylation-sensitive restriction enzyme digestion e RT-qPCR*	Não foram encontradas correlações significativas.	(48)
ADIPOQ e ADIPOR	Sangue total	106 crianças e adolescentes (10-16 anos)	MSP	% de metilação da ilha CpG na posição -74 da região promotora do *ADIPOQ* foi negativamente correlacionada com IMC, RI, TG, colesterol, glicose e insulina. % de metilação na região -238 foi menor em indivíduos com RI.	(44)

	Sangue total	69 crianças (9 anos)	*Illumina Infinium HumanMethylation 450k Bead-Chip*	Sem relação entre metilação de *ADIPOR* e medidas antropométricas.	(49)
PPARG	Sangue total	69 crianças (9 anos)	*Illumina Infinium HumanMethylation 450k Bead-Chip*	Sem relação entre metilação de *PPARG* e medidas antropométricas.	(49)
	Sangue total e de cordão umbilical	373 recém-nascidos e 245 crianças (9 anos)	*Illumina Infinium HumanMethylation 450k Bead-Chip*	% de metilação das ilhas CpG 1 e 20 no *PPARG*: associação inversa com peso ao nascimento e IMC z-score aos 9 anos.	(50)
HIF3A	Sangue total	692 crianças e adolescentes (12-15 anos)	Tratamento com bissulfito + pirosequenciamento	↑ % de metilação em ilhas CpG do *HIF3A* em indivíduos com obesidade e correlação positiva com IMC, circunferência de quadril e glicose em jejum.	(51)
	Tecido de cordão	991 recém-nascidos	*Illumina Infinium HumanMethylation 450k Bead-Chip*	Peso ao nascimento e IMC positivamente correlacionados com % de metilação no *HIF3A*.	(52)
	Sangue total e sangue de cordão umbilical	914 recém-nascidos, 973 crianças (idade média de 7,5 anos) e 974 adolescentes (idade média de 17,1 anos)	*Illumina Infinium HumanMethylation 450k Bead-Chip*	A % de metilação no *HIF3A* em crianças foi positivamente correlacionada com peso ao nascimento.	(53)
	PBMCs	212 crianças e adolescentes (7-17 anos)	*MassArray EpiTyper*	Crianças com obesidade apresentaram ↑ % de metilação de 2 ilhas CpG neste gene, sendo uma delas positivamente correlacionada com níveis de ALT.	(54)
IGF2	Sangue total	82 crianças e	Tratamento com bissulfito	Correlação negativa entre ↑ IMC e ↓ % de metilação	(55)

		adolescentes (3-18 anos)	+ sequenciamento	do *IGF2*.	
	Sangue do cordão umbilical	204 recém-nascidos com 1 ano de *follow-up*	Tratamento com bissulfito + pirosequenciamento	3 ilhas CpG foram associadas com sobrepeso ou obesidade em crianças com 1 ano. Crianças com obesidade que não foram amamentadas no 1° ano de vida apresentaram maior % de metilação comparado a crianças eutróficas que não foram amamentadas.	(56)
	Sangue total	315 adolescentes (17 anos)	*MassArray EpiTyper*	% de metilação foi positivamente correlacionada com níveis de adiposidade. A % de metilação de 2 ilhas CpG foi negativamente correlacionada com circunferência da cabeça.	(57)
	Linfócitos	79 crianças (média de idade de 11,6 anos)	*Methyl-Profiler DNA Methylation qPCR Assay* (*SA Biosciences*)	Crianças com nível intermediário de metilação (entre 10%-60% do total de metilação) na região promotora do *IGF2* apresentaram níveis maiores de TG, proteína C reativa e razão TG/HDL.	(58)
	Placenta	50 amostras	Tratamento com bissulfito + pirosequenciamento	Circunferência do tórax e peso ao nascimento foram correlacionados com a % de metilação.	(59)
	Sangue de cordão umbilical	576 crianças (1-3 anos)	Tratamento com bissulfito + pirosequenciamento	↓ % metilação de *IGF2* foi positivamente correlacionada com peso em meninos.	(60)
LINE-1	PBMCs	553 crianças (5-12)	Tratamento com bissulfito + pirosequenciamento	Correlação inversa entre % metilação no *LINE-1*, IMC z-score e circunferência da cintura em meninos.	(61)
	Sangue de cordão umbilical e placenta	319 recém-nascidos	Tratamento com bissulfito + pirosequenciamento	Crianças prematuras ou com baixo (<2500g) ou alto (4000g) peso ao nascer tiveram ↓ % metilação no *LINE-1* no sangue de cordão. Na placenta, apenas crianças com baixo peso ao nascer tiveram menor %	(62)

			metilação de *LINE-1*.	
Saliva	431 crianças e adolescentes (10-15 anos)	*Pyro-Mark CpG Assays* (Qiagen)	Não foi encontrada nenhuma associação entre metilação de *LINE-1* e obesidade.	(47)

Legenda: IMC: índice de massa corporal; RI: resistência à insulina; TG: triglicerídeos; ALT: alanina aminotransferase; PBMCs: *periferal blood mononuclear cells*; MSP: *methylation-specific PCR*. Tabela retirada e adaptada de Lima et al (29).

1.5 A dieta de cafeteria (DCAF) como modelo de indução de obesidade em animais

Dentre os fatores ambientais obesogênicos, o principal fator impulsionador para ganho de peso é a dieta (63). A qualidade da dieta pode exercer efeito sobre o balanço energético através de vias hormonais e neurológicas que influenciam a saciedade e outros mecanismos (63). Além disso, o ambiente alimentar, a comercialização de alimentos pouco saudáveis, comportamentos sedentários e redução de atividade física também possuem papel determinante na patogênese da obesidade (63, 64). Ainda, o rápido crescimento econômico e a urbanização de países em desenvolvimento resultaram na mudança de padrões alimentares tradicionais devido ao aumento do consumo de alimentos ultraprocessados e de baixa densidade nutricional (63, 64).

A dieta de cafeteria (DCAF), descrita pela primeira vez por Sclafani e Springer em 1976 (65), é a intervenção dietética que mais se assemelha a dieta ocidental humana, sendo um modelo de obesidade exógena, no qual é oferecido ao animal um maior aporte calórico através de uma sobrecarga de carboidratos e gordura (65, 66). É considerada como uma dieta de alta palatabilidade, que faz com que os animais substituam a dieta padrão pela DCAF (66). Em modelos experimentais atuais, além da ração padrão, são oferecidos aos animais alimentos altamente calóricos que variam de acordo com os diferentes países, como *bacon* ou banha, castanhas, leite condensado, refrigerantes, chocolate, amendoim, guloseimas, etc. (64, 66). Essa dieta produz um incremento de peso corporal total de aproximadamente 30-40% ao final de 12 semanas de estudo, além de produzir aumento significativo na quantidade de gordura visceral e estar associada à RI, hiperleptinemia e elevação da pressão arterial (67).

Além disso, o livre acesso aos alimentos altamente palatáveis pode levar a alterações cerebrais no sistema de recompensa, levando ao vício e consequente hiperfagia, contribuindo para o desenvolvimento de obesidade (66). Isso ocorre, pois

esse tipo de dieta ativa o comportamento hedônico, estimulado por sinais sensoriais como cheiro e sabor, que promovem alto consumo em roedores (66). Neste sentido, em comparação com a dieta *high fat*, a DCAF é mais eficiente em induzir RI, intolerância à glicose e inflamação (66, 67). Os alimentos que compõe a DCAF são encontrados com facilidade em supermercados, por isso são chamados de "*junk foods*", "*supermarket diet*" e, por se aproximarem mais de uma dieta de consumo ocidental, são chamadas também de "*western diet*" (66, 68).

A popularidade da DCAF como modelo de indução de obesidade alcançou aproximadamente 60% dos estudos em animais conduzidos na espécie *Mus musculus* (camundongos), considerando que a fisiologia destes roedores é mais próxima da dos humanos quando comparado a não mamíferos (68, 69). Seu pequeno tamanho, alta fecundidade e ciclo de vida curto explicam sua popularidade, especialmente comparado ao uso de animais de grande porte (67). Assim, modelos animais que utilizam a DCAF são considerados bons modelos obesogênicos e podem também ser usados para buscar o entendimento de adaptações moleculares, identificando genes que são sensíveis a desregulação por esse tipo de dieta (67, 70).

1.6 O mirtilo como auxiliar na redução do ganho de peso e na melhora de parâmetros associados à obesidade

O mirtilo, também conhecido como *blueberry* (BB) em inglês, é uma fruta da família das *Ericaceae*, gênero *Vaccinium*, que pertence ao grupo de pequenas frutas, como amoras, morangos e framboesas (71). O BB é originário de algumas regiões da Europa e América do Norte, sendo apreciado pelo seu sabor exótico, valor econômico e por seu potencial medicinal, que se devem principalmente ao alto conteúdo de antocianinas (pigmentos de cor azul-púrpura), tanto na casca quanto na polpa (72). As

antocianinas fazem parte de um amplo grupo de polifenóis conhecidos como flavonoides, os quais apresentam potencial antioxidante e anti-inflamatório (72). Neste contexto, o BB é uma das frutas frescas mais ricas em antioxidantes (73).

O BB contém baixas concentrações de lipídeos e altas concentrações de fibras fermentáveis (71). Interessantemente, altas concentrações de antocianinas foram encontradas no intestino, interagindo diretamente com a microbiota intestinal, caracterizando o BB como alimento prebiótico (74). Conforme mencionado, a obesidade é acompanhada por inflamação crônica de baixo grau, a qual é associada com infiltração de monócitos e outras células do sistema imune no TA, levando a disfunções metabólicas (14). Neste contexto, uma revisão de literatura conduzida recentemente pelo nosso grupo de pesquisa (75), mostrou que o consumo de BB é capaz de reduzir a atividade de NF-kB (**Figura 2**), o qual é um fator de transcrição que regula respostas imunológicas e de estresse oxidativo (75). Assim, com a atenuação de vias inflamatórias e oxidativas, o consumo de polifenóis e antocianinas presentes no BB pode diminuir o recrutamento de macrófagos tipo M1 para o TA, melhorar a composição da microbiota e diminuir os níveis glicêmicos, além de proteger contra esteatose hepática e disfunção endotelial (**Figura 2**) (75).

Interessantemente, alguns estudos sugeriram que polifenóis e antocianinas protegem as células do estresse oxidativo, reduzindo o risco para obesidade, síndrome metabólica (MetS), RI e DM2 (76-78). Estudos em humanos demonstraram que o consumo de BB melhorou a pressão sanguínea, sensibilidade à insulina, metabolismo lipídico, bem como parâmetros inflamatórios e de estresse oxidativo (79-82). Ainda, estudos em animais demonstraram que o consumo de BB melhorou o metabolismo de glicose e de lipídeos e diminuiu o estresse oxidativo e a inflamação nestes animais (83-

86). O consumo de BB também está associado com perda de peso e melhora no perfil de adipocinas, como leptina e resistina em camundongos (87).

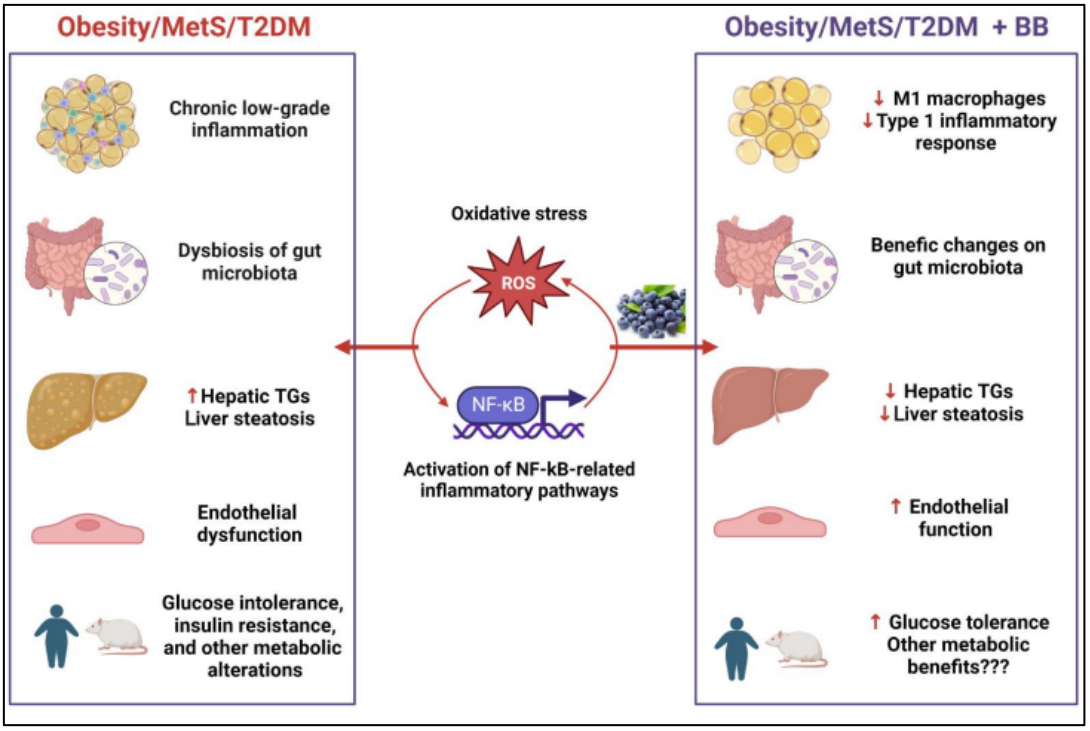

Figura 2. Efeitos do consumo de BB em desfechos relacionados com a obesidade, MetS e DM2. BB: *blueberry*/mirtilo; MetS: síndrome metabólica; T2DM: diabetes mellitus tipo 2; TGs: triglicerídeos; ROS: espécies reativas de oxigênio (EROs).
Fonte: Retirado de Oliveira et al. (75).

Entretanto, ao analisarmos os estudos descritos nas Tabelas 4 e 5, podemos verificar que os resultados dos estudos com intervenção dietética contendo BB são bastante heterogêneos, tanto em humanos (**Tabela 4**), quanto em camundongos (**Tabela 5**). Os parâmetros avaliados nos estudos, em geral, incluem medidas biométricas, bioquímicas e de marcadores inflamatórios. Além disso, até o presente momento, nenhum estudo investigou se a adição de BB à DCAF influencia os parâmetros biométricos e inflamatórios em camundongos C57BL/6.

Tabela 4. Estudos clínicos que avaliaram o efeito do consumo do BB na obesidade e seus parâmetros metabólicos relacionados.

Ref.	Amostra	Tratamento	Tempo de seguimento	Principais achados (BB vs. placebo/controle)
(79)	48 pacientes com MetS: BB (n= 25) e controles (n= 23).	50g de BB liofilizado em uma bebida, diariamente	8 semanas	Sem diferenças: peso, CC, HbA1c, HOMA-IR, GJ, perfil lipídico, IL6, adiponectina e PCR. ↓ PA, LDL e peroxidação lipídica (MDA e HNE).
(88)	115 pacientes com MetS: 150g BB (n= 37), 75g BB (n= 39) e controles (n= 39)	75g ou 150g de BB fresco	6 meses	Sem diferenças: PA, colesterol total, LDL, GJ, HbA1c, insulina e RI. ↑ HDL (150g) e TG (75g) e melhora da função endotelial (150g).
(89)	45 pacientes com MetS: BB (n= 23) e controles (n= 22)	26g de BB liofilizado (= 150g de BB fresco)	24 horas	Sem diferenças: TG, LDL, PA. ↓ glicose pós-prandial (0-24h), insulina e colesterol total. ↑ HDL e melhora da função endotelial.
(82)	27 pacientes com MetS: BB (n= 15) e controles (n= 26)	22,5g de BB liofilizado, 2x dia	6 semanas	↓ Superóxido e EROs total, expressões de *TNF*, *IL6* e *TLR4* (em monócitos) e de GMCSF (marcador inflamatório sérico).
(90)	52 homens com DM2: BB (n= 26) e placebo (n= 26)	22g de BB liofilizado, 2x dia		Sem diferenças: GJ, insulina, colesterol total, LDL, HDL, PCR, PA e peso. ↓ HbA1c, frutosamina, TG, AST e ALT.
(80)	32 pacientes com obesidade e RI:	22,5g de BB liofilizado em uma bebida, 2x dia (45g/dia)	6 semanas	Sem diferenças: peso, IMC, marcadores inflamatórios (PCR, TNF e MCP-1), perfil lipídico, insulina e PA. ↑

	BB (n= 15) e controles (n= 17)			sensibilidade à insulina.
(91)	44 pacientes com MetS: BB (n= 23) e controles (n= 21)	22,5g de BB liofilizado em uma bebida, 2x dia (45g/dia)	6 semanas	Sem diferenças: peso, IMC, PA, GJ, insulina e perfil lipídico. ↑ função endotelial.

Legenda: MetS: síndrome metabólica; BB = mirtilo; CC: circunferência da cintura; HbA1c: hemoglobina glicada; HOMA-IR: modelo de avaliação da homeostase da resistência à insulina; GJ: glicemia em jejum; IL6: interleucina 6; PCR: proteína C reativa; PA: pressão arterial; MDA: malondialdeído (marcador de peroxidação lipídica); HNE: hidroxinonenal (marcador de peroxidação lipídica); RI: resistência à insulina; TG: triglicerídeos; EROs: espécies reativas de oxigênio; TNF: fator de necrose tumoral; TLR4: receptor tipo Toll 4; AST: aspartato aminotransferase; ALT: alanina aminotransferase; MCP-1: proteína de quimiotaxia de macrófagos; GMCSF: fator estimulador de colônia de macrófagos granulócitos; ↑: valores aumentados; ↓: valores diminuídos. Fonte: Retirado e adaptado de Oliveira et al. (75).

Tabela 5. Estudos em camundongos que avaliaram o efeito do consumo de BB na obesidade e seus parâmetros metabólicos relacionados.

Ref.	Amostra	Tratamento	Tempo de seguimento	Principais achados (BB vs. placebo/controle)
(92)	Camundongos *wild type*: HSD (n= 8) e HSD + BB (n= 8)	4% (*wt:wt*) de BB liofilizado	3 meses	↑ tolerância à glicose. ↓ peso e expressão de *Lep* no TA.
(93)	Camundongos C57BL/6 machos: HFD (n= 8) e HFD + BB (n= 8)	4% (*wt:wt*) de BB liofilizado	8 semanas	Sem diferenças: peso, insulina e expressão de *AdipoQ*, *Lep*, *Ccl2* (Mcp-1), *Il6* e *iNos* no TA. ↓ glicose sérica, AUC da glicose após TOTG, recrutamento de macrófagos M1 (*Cd11c+/Mgl1-*) para o TA, expressão de *Tnf* e *Il10* no TA, morte de adipócitos e RI. ↑ da expressão de *Gsh-Px* no TA.
(83)	Camundongos C57BL/6 machos: HFD (n= 5) e HFD + BB (n= 5)	4% (*wt:wt*) de BB liofilizado	14 semanas	Sem diferenças: peso e GJ. ↓ AUC da glicose após TOTG, insulina e RI.
(74)	Camundongos C57BL/6 machos: Dieta HFHS (n= 13) e HFHS + BB (n= 14)	4% (*wt:wt*) de BB liofilizado	12 semanas	Sem diferenças: peso, GJ, AUC da glicose após TOTG, insulina, RI, TG hepático, colesterol total, AST e ALT, TBARS e expressão de *Il2*, *Il6*, *Ifng*, *Tnf*, *Ccl2* e *Ccl5* no TA.
(94)	Camundongos C56BL/6 machos: HFD (n= 6) e HFD + BB (n= 6)	5% (*wt:wt*) de BB liofilizado	12 semanas	Sem diferenças: peso, ganho de peso, GJ, ácidos graxos livres e pressão sistólica.

(95)	Camundongos C57BL/6 machos: HFD (n= 12) e HFD + BB (n= 12)	10% (*wt:wt*) de BB liofilizado	92 dias	Sem diferenças: GJ e AUC da glicose após TOTG. ↑ peso.
(87)	Camundongos C57BL/6 machos: HFD e HFD + BB	10% (*wt:wt*) de suco de BB	72 dias	Sem diferenças: peso, ganho de peso, colesterol total, TGs, GJ, insulina e RI.↓ dos níveis séricos de leptina.
(96)	Camundongos C57BL/6 machos: HFD (n= 12) e HFD + BB (n= 8)	BB liofilizado (normalizado para 400µg/g de antocianinas)	12 semanas	Sem diferenças: peso, expressões de *AdipoQ*, *Fasn*, *Cpt1a*, *Pparg* e *Ppargc1a* no TA. ↓ expressão de *Lep* no TA. ↑ gasto energético.

Legenda: BB: mirtilo; HSD: *high-sugar diet*; HFD: *high-fat diet*; HFHS: *high-fat, high-sucrose diet*; TA: tecido adiposo; AUC: área sob a curva; TOTG: teste oral de tolerância à glicose; MCP-1: proteína de quimiotaxia de macrófagos; RI: resistência à insulina; GJ: glicemia em jejum; AST: aspartato aminotransferase; ALT: alanina aminotransferase; TG: triglicerídeos; TBARS: substâncias reativas ao ácido tiobarbitúrico; *wt:wt*: composição da dieta. Fonte: Retirado e adaptado de Oliveira et al. (75).

2 JUSTIFICATIVA

A prevalência da obesidade tem aumentado exponencialmente nas últimas décadas, tornando-a uma epidemia. A obesidade infantil é de especial interesse, pois esta condição pode persistir por toda a vida do indivíduo, podendo acarretar uma menor contribuição destes com a sociedade devido a diversas comorbidades associadas. Por ser uma doença complexa e multifatorial, a obesidade é decorrente da complexa interação entre fatores genéticos, epigenéticos e ambientais.

Diversos fatores genéticos que influenciam a suscetibilidade à obesidade já foram identificados, explicando 65% da variabilidade desta doença. Recentemente, alterações induzidas pela epigenética na expressão gênica surgiram como uma forma alternativa na qual os fatores ambientais podem influenciar a obesidade. A metilação de DNA é uma das principais alterações epigenéticas, regulando negativamente a expressão gênica em resposta a fatores ambientais/nutricionais, influenciando então o ganho de peso e susceptibilidade à obesidade. Estudos que avaliem a metilação de DNA em crianças com obesidade são especialmente importantes, visto que padrões de metilação estabelecidos no início da vida podem ser persistentes. Entretanto, os estudos encontrados na literatura são inconclusivos, sendo que poucos realizam análises mais aprofundadas das rotas nas quais os genes regulados por metilação estão envolvidos. A análises de metadados de metilação disponíveis no banco de dados GEO pode ter um impacto importante no estudo da patogênese da obesidade infantil, dado o aumento do poder estatístico para detectar potenciais ilhas CpG diferencialmente metiladas e, consequentemente, genes regulados por metilação envolvidos nessa doença. Além disso, estudos que envolvam análises integrativas através da bioinformática têm sido apontados como ferramentas de ponta para o estudo dos mecanismos moleculares envolvidos em diversas doenças.

Os fatores ambientais envolvidos na obesidade incluem sedentarismo e uma dieta pobre em nutrientes, mas rica em gorduras e carboidratos simples. Esta dieta obesogênica inclui alimentos ultraprocessados que apresentam alta palatabilidade, sendo também conhecidos como "*junk foods*", os quais apresentam consumo amplo e difundido em países ocidentais. Estudos mostram que a DCAF mimetiza os padrões de consumo moderno de alimentação e é conhecida por induzir obesidade, inflamação, MetS e DM2 em modelos animais. Ainda, a DCAF é considerada um modelo robusto para estudo de obesidade em modelos animais quando comparado a outros modelos de dieta obesogênica. No entanto, o consumo de diferentes alimentos nos mais diversos países faz com que seja necessária a adaptação e padronização deste modelo para a população de interesse. Com isso, se faz necessária a investigação de mecanismos moleculares envolvidos na nutrigenômica após a exposição à DCAF.

Devido às mudanças no estilo de vida e na dieta ocidental nas últimas décadas, são necessárias novas abordagens a fim de evitar o aumento da epidemia de obesidade, bem como de suas comorbidades, como o DM2 e danos cardiovasculares, que comprometem a qualidade de vida e produtividade dos indivíduos, gerando grandes custos ao sistema de saúde. Neste contexto, evidências sugerem que o BB adicionado à dieta possui propriedades que podem contribuir para a redução do ganho de peso e atenuar disfunções inflamatórias, no TA, fígado, músculo, hipotálamo e outros órgãos associados à obesidade, melhorando parâmetros associados à doença, como a RI. Entretanto, os estudos que obtiveram estas evidências utilizaram um modelo de dieta que pouco se compara a dieta humana ou estudaram grupos muito específicos. Até o momento, nenhum estudo avaliou o efeito benéfico do BB nos parâmetros biométricos e inflamatórios utilizando o modelo animal de obesidade e RI baseado na DCAF, que é a dieta mais próxima da dieta humana ocidental e altamente densa em energia. Logo,

estudos são necessários para avaliar se o potencial benéfico das propriedades do BB em tecidos afetados pela obesidade se mantém utilizando a DCAF.

3 OBJETIVOS

3.1 Objetivos gerais

- Identificar, através de uma abordagem de biologia de sistemas, genes candidatos relacionados com a obesidade infantil e as vias metabólicas nas quais estes genes estão envolvidos, utilizando dados de bancos públicos.

- Identificar perfis globais alterados de metilação de DNA e expressão gênica associados com a obesidade infantil através de uma abordagem de bioinformática integrativa de dados públicos de pacientes pediátricos com e sem obesidade.

- Avaliar o efeito da exposição à DCAF em parâmetros biométricos, glicêmicos, de RI e de esteatose hepática em camundongos C57BL/6, bem como o efeito desta dieta na expressão de genes envolvidos nas vias de sinalização das adipocitocinas, de estresse oxidativo, pró-inflamatórias, apoptóticas e do metabolismo de lipídeos e da glicose no TAV, TAS, músculo esquelético e fígado destes animais.

- Avaliar o efeito do consumo de BB em parâmetros biométricos, glicêmicos, de RI e de esteatose hepática em camundongos C57BL/6 alimentados com a DCAF, bem como o efeito do consumo de BB na expressão de genes envolvidos nas vias de sinalização das adipocitocinas, de estresse oxidativo, pró-inflamatórias, apoptóticas e do metabolismo de lipídeos e da glicose no TAV, TAS, TAB, músculo esquelético, hipotálamo e fígado destes animais.

3.2 Objetivos específicos

3.2.1 Objetivos específicos do Artigo 1

- Identificar genes candidatos para a obesidade infantil através de uma busca sistemática utilizando o banco de dados público DisGeNET.

- Construir uma rede de interação proteína-proteína, identificar os genes *hub-bottleneck* e realizar análises de enriquecimento funcional com base nos termos de *Gene Ontology* e *KEGG Pathways* para os genes candidatos para a obesidade infantil.

3.2.2 Objetivos específicos do Artigo 2

- Identificar genes diferencialmente expressos (DEGs) e diferencialmente metilados (DMGs) em indivíduos com e sem obesidade infantil a partir de análise de bioinformática de dados obtidos no banco de dados públicos GEO.

- Selecionar os genes presentes em ambos os conjuntos (DEGs e DMGs) para identificar aqueles DEGs regulados por metilação (MeDEGs).

- Construir uma rede de interação proteína-proteína, identificar os genes *hub-bottleneck* e realizar análises de enriquecimento funcional com base nos termos de *Gene Ontology* e *KEGG Pathways*.

3.2.3 Objetivos específicos do Artigo 3

- Investigar o efeito da exposição de camundongos C57BL/6 à DCAF sobre parâmetros biométricos, glicêmicos, RI e esteatose hepática.

- Avaliar o efeito da exposição de camundongos C57BL/6 à DCAF sobre a expressão de genes relacionados à via de sinalização de adipocinas, estresse oxidativo, pró-inflamatórias, apoptose e de metabolismo da glicose e de lipídeos no fígado, TAS, TAV e músculo esquelético destes animais.

- Avaliar a correlação entre o perfil de expressão gênica de genes diferencialmente expressos no TAV com características clínicas relacionadas à obesidade nestes animais.

3.2.4 Objetivos específicos do Artigo 4

- Investigar o efeito do consumo de BB em camundongos C57BL/6 expostos à DCAF sobre parâmetros biométricos, glicêmicos, RI e esteatose hepática.

- Investigar o efeito do consumo de BB em camundongos C57BL/6 expostos à DCAF sobre parâmetros inflamatórios e de estresse oxidativo no cérebro e fígado.

- Avaliar o efeito do consumo de BB em camundongos C57BL/6 expostos à DCAF sobre a expressão de genes relacionados à via de sinalização de adipocinas, estresse oxidativo, pró-inflamatórias, apoptose e de metabolismo da glicose e de lipídeos no fígado, TAS, TAV, TAM, músculo esquelético e hipotálamo destes animais.

- Avaliar a correlação entre o perfil de expressão gênica de genes diferencialmente expressos no TAV com características clínicas relacionadas à obesidade nestes animais.

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CAPÍTULO 2

Fatores genéticos e obesidade infantil

ARTIGO 1

“Systems biology approach identifies key genes and related pathways in childhood obesity”

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Systems biology approach identifies key genes and related pathways in childhood obesity

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Abstract

Background: Childhood obesity is triggered by a complex interplay of environmental, genetic, and epigenetic factors; however, the molecular mechanisms behind this disease are not completely elucidated. Thus, the aim of this study was to investigate molecular mechanisms involved in childhood obesity by implementing a systems biology approach.

Methods: Experimentally validated and computationally predicted genes related to childhood obesity were downloaded from DisGeNET database. A protein-protein interaction (PPI) network was constructed using the STRING database and analyzed at Cytoscape web-tool. Hub-bottleneck genes and functional clusters were identified through CytoHubba and MCODE plugins, respectively. Functional enrichment analyses were performed based on Gene Ontology terms and KEGG Pathways.

Results: The DisGeNET search retrieved 191 childhood obesity-related genes. The resulting PPI network contained 12 hub-bottleneck genes (*INS*, *LEP*, *STAT3*, *POMC*, *ALB*, *TNF*, *BDNF*, *CAT*, *GCG*, *PPARG*, *VEGFA*, and *ADIPOQ*) and 4 functional clusters, with cluster 1 showing the highest interaction score. Genes at this cluster were enriched at inflammation, carbohydrate, and lipid metabolism pathways. With exception of *POMC*, all hub-bottleneck genes were found in cluster 1, which contains highly connected genes that possibly play key roles in obesity-related pathways.

Conclusions: Our systems biology approach revealed a set of highly interconnected genes associated with childhood obesity, providing comprehensive information regarding genetic and molecular factors involved in the pathogenesis of this disease.

Keywords: Childhood obesity, systems biology methodology, target genes.

1. Introduction

Childhood obesity is a metabolic disorder characterized by excessive body weight in relation to height, which can be attributed to a long-term imbalance between caloric intake and expenditure [1, 2]. The prevalence of obesity in children aged 2 to 18 years is continuously increasing [1, 3]; thus, strategies aimed at decreasing weight are of special interest because children with obesity tend to maintain excess weight in adulthood [1, 4]. A meta-analysis including 23 studies showed that children with high body mass index (BMI) are 5 times more likely to have obesity in adulthood compared to normal weight children [4]. Furthermore, these children also present increased risk of developing comorbidities, such as cardiovascular and pulmonary diseases, type 2 diabetes, and cancer [5, 6], increasing adulthood mortality and risk of premature death [7].

Childhood obesity is triggered by a complex interplay between environmental and genetic factors [2, 7]. The probability of a child with one parent with obesity to have obesity in adulthood is three times higher than those with normal weighted parents, supporting the involvement of both genetic and environmental factors, such as dietary patterns and physical inactivity, in this disease [8].

Some studies have demonstrated that approximately 65% of the variance associated with obesity is due to genetic factors [2, 9, 10]. Inherited susceptibility to obesity can be attributed to the cumulative effect of several polymorphisms with individually modest effects on energy homeostasis, leading to excessive fat deposition [11]. To date, a number of genes are known to play a key role in obesity development, including genes related to energy intake regulation (e.g., *MC4R*, *POMC*, *LEP*, *LEPR*, and *FTO*), lipid metabolism and adipogenesis (e.g., *PLIN1*, *APOA5*, and *FABP2*),

thermogenesis (e.g., *ADBRs* and *UCP*s), adipocytokine synthesis (e.g., *ADIPOQ*), and transcription factors (e.g. *PPARG* and *TCF7L2*) [2, 12, 13].

Considering that childhood obesity is a complex disease, integrative analyses of multiple data, including genes previously associated with childhood obesity and metabolic pathways, might contribute to a better understanding of the pathophysiology of this disease. In this context, a systems biology approach allows us to elucidate candidate genes, proteins, and their interconnections within cells, tissues, organs, and organismal phenotypes and diseases [14]. Thus, through a systems biology approach, we aimed to identify childhood obesity-related genes and the biological pathways in which they are involved, using publicly available databases.

2. Methods

2.1. Search for childhood obesity-related genes

Childhood obesity-related genes were obtained through a systematic search at DisGeNET v.7.0 database [15] using "pediatric obesity" (C2362324) as a query term. The search was completed in July 2021, and the downloaded data refer to the most updated version of the platform at the time of preparation of this manuscript. The DisGeNET database is a comprehensive discovery platform that contains one of the largest available collections of genes and variants associated with human diseases. It includes data from expert curated repositories, text mining data extracted from literature, experimentally validated data, and referred data [15]. Importantly, all retrieved genes from the DisGeNET database were used in the following analyses. Genes identifiers were mapped to HUGO Gene Nomenclature Committee (HGNC) [16].

Moreover, aiming to identify genes exclusively associated with pediatric obesity, we also searched on DisGeNET for genes associated with overall obesity, using "obesity" (C0028754) as research term.

2.2. Protein-protein interaction network construction

The entire list of pediatric obesity-related genes obtained from DisGeNET was submitted to Search Tool for the Retrieval of Interacting Genes (STRING, v.11.0, http://string-db.org/ [17]) database to construct the protein-protein interaction (PPI) network. An interaction score > 0.4 and $P < 0.05$ were considered as statistically significant. The data obtained from this analysis was imported into Cytoscape 3.8.2 [18] for the network analysis and visualization.

2.3. Systems biology approach to analyze the PPI network based on childhood obesity-related genes

Complex system-level network of molecular interactions may be represented and analyzed as computable networks. Nodes and edges are the basic components of a network. Nodes are connected by edges (also called links or lines). Edges describe relationships between the nodes [19]. In our study, the nodes are genes, and the edges are the link between them, thus forming a PPI network. Understanding how these molecular interactions work give rise to emergent biological processes. Moreover, the identification of important nodes and other topological features in the network, which are key to controlling them, are crucial to understanding complex phenotypes in health and disease [20].

The relevance of each node (gene) for the network structure and functionality was assessed using two centrality measurements: degree and betweenness. The degree

quantifies the number of edges from a given node and those nodes highly connected are called hubs and tend to be important points of control in the network [21]. The betweenness corresponds to the number of minimum non-redundant paths between two nodes that pass-through a given node. Nodes with high betweenness are called bottlenecks and play key roles in mediating communication within a network because they facilitate information flow between clusters [22, 23]. Here, we defined as hubs and bottlenecks the nodes in the top 10% of the degree and betweenness distributions [24], respectively. Hubs and bottlenecks genes were identified using the plugin CytoHubba v.0.1 [25] for Cytoscape.

Genes or proteins that occur clusters tend to be enriched for common biological functions [20]. Thus, identifying clusters in networks allows the detection of coordinated biological functions or processes that are not well captured in established canonical pathway annotations [26]. In our study, clustering analysis to identify the clusters within the PPI network was performed using the Molecular Complex Detection (MCODE) v.2.0.0 plugin [27], on Cytoscape environment [18], applying number of nodes > 4.0 as a cut-off. This algorithm identifies densely connected regions in the network that are candidates for representing functional interaction complexes [27].

2.4. Functional enrichment analysis

Functional enrichment analysis was performed to assess Gene Ontology (GO) terms and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways. GO analysis is extensively used to identify the characteristic biological attributes of genes, gene products, and sequences, including biological process (BP), cell components (CC), and molecular functions (MF) [28]. KEGG is a collection of databases dealing with genomes, biological pathways, diseases, and chemical substances [29]. Here, GO term analyses

were performed using ClueGO/Cluepedia v2.5.7 [30] on Cytoscape environment [18], while KEGG pathways annotations were obtained using the pathDIP v4.0.21.3 database [31]. Of note, the functional enrichment analysis was performed to investigate the role of hub-bottleneck genes. In the same way, this analysis was also done to verify the pathways in which the genes in each cluster participate.

2.5 Microarray data and data processing

After performing the previous described analyses, we assessed the Gene Expression Omnibus (GEO, https://www.ncbi.nlm.nih.gov/geo) repository, which is a database containing public data of microarrays, next-generation sequencing, and several forms of high-throughput functional genomics, aiming to identify the gene expression pattern of the hub-bottleneck genes. The following search strategy in GEO was used: "childhood obesity" [MeSH terms] AND "gene expression" [Filter] AND "*Homo sapiens*" [Organism]. In this context, one dataset was retrieved from the GEO search and was included in our study. The GSE9624 dataset (GPL570; Affymetrix Human Genome U133 Plus 2.0 Array) included analysis of omental adipose tissue from 5 pediatric patients with obesity and 6 normal weight children [32].

GEO2R (http://www.ncbi.nlm.nih. gov/geo/geo2r/) is a web tool that allows the comparison of two or more groups of samples in a GEO dataset. This tool was used to analyze the included dataset and identify differentially expressed genes (DEGs) in omental adipose tissue of cases with childhood obesity compared to normal weight children. DEGs were defined based on absolute log2-Fold Change (logFC) > 1.0 and $P < 0.05$.

2.6. Statistical analyses and data visualization

Cytoscape v3.8.1 software [18] was used to analyze and visualize the PPI network formed by childhood obesity-related genes. The statistical tests used for the enrichment analyses were based on the hypergeometric test, and P-*values* were corrected for multiple tests using the Benjamini-Hochberg procedure, which provides a False Discovery Rate (FDR) adjusted-P *value* (q-*value*). GO terms and KEGG pathways associated with a q-*value* < 0.05 were considered significantly enriched. Graphics were constructed using Ploty chart studio (https://chart-studio.plotly.com).

3. Results

3.1. Protein-protein interaction network

A total of 191 genes were identified as being associated with childhood obesity in our systematic search on the DisGeNET database (**Table S1**). Nodes represent the proteins encoded by each of the genes and the edges represent protein-protein associations. Those nodes that did not present interconnections within the network were excluded. Thus, the PPI network generated in the STRING database included 179 nodes (genes) and 1,503 edges (linking lines), with a PPI enrichment P-*value* of 1.0^{-16}.

3.2. Identification of hub-bottleneck genes and functional enrichment analysis

The PPI network topography was analyzed using the Cytoscape software in order to identify the hub-bottleneck genes, as described in the Methods section. A total of 17 genes with the highest degree score were classified as hub genes, while the 17 genes with highest betweenness were classified as bottleneck genes (**Figure 1** and **Table S2**). Superimposing the lists of hubs and bottlenecks, 12 genes (*INS*, *LEP*, *STAT3*, *POMC*, *ALB*, *TNF*, *BDNF*, *CAT*, *GCG*, *PPARG*, *VEGFA*, and *ADIPOQ*) were found as hub-

bottlenecks (**Figure 1**). Hub-bottleneck genes are key elements in the functional analysis of a network because they tend to be functionally important proteins [33]. The topological analysis of the 12 hub-bottleneck genes is described in **Table 1**. In addition, the gene expression patterns of these hub-bottleneck genes were assessed by analyzing the GSE9624 dataset, and the results are described in **Table 1** and **Figure S1**.

Using the 12 reported hub-bottleneck genes, we performed functional enrichment analyses to better describe the roles of this subset of genes. As result of our functional enrichment analysis, a total of 38 KEGG pathways were enriched by at least two genes out of the 12 hub-bottleneck genes (**Table S3**). Of note, many of these pathways are well established to be involved with childhood obesity, including pathways involved in glucose and lipid metabolism, thermogenesis, and inflammation, such as Jak-STAT signaling pathway and cytokine-cytokine receptor interaction, as demonstrated in **Figure 2A**. GO term analyses showed the 12 hub-bottleneck genes participate in 420 BP, 22 MF, and 13 CC (**Table S3**). Regarding the most enriched BP, these 12 genes participate in the glucose and carbohydrate homeostasis, kidney epithelium development, regulation of peptidyl-serine phosphorylation, and in the positive regulation of DNA-binding factor activity, as shown in **Figure 2B**.

3.3. Clustering and functional enrichment analyses

Clustering is also known as modularity, and algorithms that perform this type of analysis are capable of demonstrating groups of functionally linked molecules that work together [34]. In the PPI network, we identified four significant functional clusters. The highest score cluster was cluster 1 (24.7), which included 32 out of 179 genes. Cluster 2 (8.9), cluster 3 (5.6), and cluster 4 (4.2) comprised 27, 6, and 11 genes, respectively (**Figure 3**).

Of note, all hub-bottleneck genes are present in cluster 1, except for the *POMC* gene, which is in cluster 4.

Following the clustering analysis, we carried out functional enrichment analyses for the genes in each of the 4 clusters aiming to identify the KEGG pathways and GO terms in which these genes are involved. The most significant enriched pathways of each cluster are shown in **Figure 4**. Clusters 1, 2, 3, and 4 were enriched in 71, 23, 3, and one pathway, respectively (**Table S4**). Briefly, genes present in cluster 1 are enriched in pathways related to inflammation (e.g., TNF and JAK-STAT signaling pathways, cytokine-cytokine receptor interaction, and adipocytokine signaling), regulation of glucose and lipid metabolisms (e.g., insulin secretion, insulin resistance, regulation of lipolysis, and glucagon signaling), longevity regulation, and hypoxia (HIF-1 signaling), among others. Genes from clusters 2, 3, and 4 are enriched in the neuroactive ligand-receptor interaction pathway. In addition, clusters 1 and 2 share some pathways, such as thermogenesis, regulation of lipolysis in adipocytes, PI3K-Akt, MAPK, and insulin resistance. Interestingly, enriched pathways showed little overlap among clusters, indicating that they are functionally distinct (**Figure 4**).

Regarding the GO analyses, clusters 1, 2, 3, and 4 were enriched in 903, 307, 3, and 50 BP, respectively (**Table S5**). In the context of MF, we identified 40, 16, 3, and 8 enriched processes for cluster 1, 2, 3, and 4, respectively. In addition, 17, 8, and 5 enriched CC processes were detected for cluster 1, 2, and 4, respectively. We did not find any statistically significant CC for cluster 3. Interestingly, the 4 clusters did not share any BP or MF, but the genes in cluster 1, 2, and 4 are present in the extracellular space (CC component). These results may suggest that the clusters play distinct and delimited functions.

3.4. Identification of childhood obesity-related genes compared to overall obesity

In an exploratory analysis, we superimposed the lists of genes retrieved for childhood obesity and for overall obesity. Interestingly, 2,821 genes were associated with overall obesity, and as already mentioned, a total of 191 genes were associated with childhood obesity (**Table S6**). Of these, 160 genes were associated both with childhood obesity and overall obesity, while 31 genes were exclusively related to childhood obesity (**Table S6**).

4. Discussion

Pediatric patients represent an important and valuable population to study the series of events associated with obesity pathogenesis as these patients usually maintain their adiposity throughout adulthood [2, 8]. The increasing prevalence of childhood obesity is associated with the emergence of comorbidities (e.g., type 2 diabetes and hypertension), hence impacting the healthcare costs [1]. Childhood obesity is a complex disease that involves genetic and epigenetic factors; however, the complexity of its molecular mechanisms is not completely elucidated [35]. In this context, the increasing availability of genetic and epigenetic data regarding childhood obesity represent opportunities to investigate the molecular basis of this disease. PPI network analysis play an important role in predicting the functionality of interacting genes and sheds light into cellular and molecular behavior and functions [36, 37].

In the present study, 12 hub-bottleneck genes (*INS*, *LEP*, *STAT3*, *POMC*, *ALB*, *TNF*, *BDNF*, *CAT*, *GCG*, *PPARG*, *VEGFA*, and *ADIPOQ*) involved in childhood obesity were identified by applying systems biology approaches. These genes were highly interconnected and participate in well-known obesity-related pathways, including inflammation and glucose and lipid metabolism pathways. It is noteworthy that hub-

bottleneck genes are central points in controlling the communication among other genes in the network [24].

Regarding inflammation-related pathways, the adipocytokine signaling was identified as the most enriched KEGG pathway since 5 hub-bottleneck genes were annotated for this pathway: *ADIPOQ*, *LEP*, *POMC*, *STAT3*, and *TNF*. Chronic low-grade inflammation is a well know factor involved in obesity [38], and children with obesity have higher levels of TNF and leptin compared to lean controls [39].

Leptin, codified by the *LEP* gene, is an adipokine involved in the regulation of energy balance and its signaling occurs through induction of the mitogen-activated protein kinases (MAPKs) and signal transducer activator of transcription 3 (STAT3) [40]. In our analysis, *LEP* was found as enriching some KEGG pathways, such as adipocytokine, AMP-activated protein kinase (AMPK), and Jak-STAT signaling, as well as in the non-alcoholic fatty liver disease (NAFLD). Taking this information into account, the overactivation of such pathways could result in increased production of pro-inflammatory cytokines, including TNF, which is considered as a regulator of fat storage through leptin [38]. Additionally, *LEP* and *ALB* genes were found upregulated in omental adipose tissue samples of children with obesity compared to controls [40], and the expression of *LEP* and *TNF* in the adipose tissue and their respective serum concentration levels were positively correlated [38]. Consistently, one study also reported that the *LEP* gene was upregulated in subcutaneous adipose tissue of patients with childhood obesity [41], while the *TNF* gene was upregulated both in peripheral blood cells [42] and subcutaneous adipose tissue [43].

Our pathways analysis also demonstrated an involvement of 8 hub-bottleneck genes in glucose and lipid metabolism as well as cell proliferation and differentiation: *INS*, *CGC*, *LEP*, *POMC*, *VEGFA*, *STAT3*, *TNF*, and *BDNF*. The brain-derived

neurotrophic factor (*BDNF*) gene has a key role in neuronal growth and energy homeostasis. BDNF controls the appetite through a combination of central and peripheral pathways, and it is widely expressed in the fed state but suppressed after food deprivation [44]. Mechanistically, this protein seems to function as a downstream regulator of the leptin-proopiomelanocortin (POMC) pathway. Leptin and insulin act within the hypothalamic arcuate nucleus, suppressing orexigenic signaling and promoting anorexigenic signaling from neurons that express *POMC* [44]. Interestingly, our analyses revealed that the *POMC* gene was upregulated in omental adipose tissue of children with obesity (GSE9624) [32]; in contrast, a study [45] demonstrated that the *POMC* gene was downregulated in peripheral blood cells of patients with childhood obesity, suggesting that the expression of POMC gene is tissue-specific.

In contrast, glucagon (*GCG* gene) is secreted in response to several metabolic signals, such as decreased blood glucose concentrations and stress [46]. Our results demonstrated that the *GCG* gene enriched KEGG pathways such as insulin secretion. In this context, glucagon acts as a counter-regulatory hormone, suppressing the secretion of leptin and insulin, hence reactivating the orexigenic signaling [44]. Consistently, a study demonstrated that children with obesity showed an increased concentration of fasting glucagon compared to lean patients [47].

Besides that, pathways related to metabolic stress response were also associated with the hub-bottleneck genes found in our analyses. Obesity is associated with oxidative stress, and the catalase (CAT) antioxidant enzyme plays a crucial role in oxidative stress regulation by degrading superoxide radical residues [48]. Our results showed the *CAT* gene enriches KEGG pathways such as the forkhead box O (FoxO). Interestingly, *CAT* expression was significantly lower in children with obesity compared to lean controls [48]. Moreover, a positive correlation was observed between *CAT* expression and BMI,

fasting glucose levels, insulin resistance, and lipid profile [48]. The adiponectin gene (*ADIPOQ*) is an adipokine that has important anti-inflammatory, insulin-sensitizing and anti-atherogenic properties, and its levels are decreased in obesity [39, 49], suggesting a crosstalk between adiposity, immune cell dysregulation, and inflammation pathways with fatty acid metabolism and insulin signaling [39]. Interestingly, the *ADIPOQ* gene was downregulated in omental adipose tissue in our analyses of the GSE9624 dataset [32].

In addition, pathways related to gene transcription regulation and protein synthesis also seem to play an important role in childhood obesity according to our data. The peroxisome proliferator-activated receptor γ (*PPARG*) gene is highly expressed in adipose tissue and acts as an important transcriptional regulator of metabolism and adipocyte differentiation, thus being involved in adipogenesis and insulin sensitivity [50]. Furthermore, PPARG is a receptor that plays a key role in nutrient sensing and regulation of carbohydrate and lipid metabolism, being involved in anabolic and anti-inflammatory pathways [51]. Our analyses of the GSE9624 [32] dataset demonstrated that the *PPARG* gene was downregulated in omental adipose tissue of children with obesity. Interestingly, a study showed that the *PPARG* expression was lower in peripheral blood mononuclear cells (PBMCs) of children with obesity compared to controls, suggesting an alteration of biochemical homeostasis [50].

Obesity-related disorders are associated with vascular dysfunction and consequent adipose tissue hypoxia [52]. Considering this, our results demonstrated the involvement of childhood obesity with pathways related to adaptive hypoxia responses. The vascular endothelial growth factor A (*VEGFA*) gene is essential for the formation of new blood vessels [52]. Of note, the enhancement of angiogenesis in the adipose tissue prevented mice to develop obesity and metabolic disorders [53]. Nevertheless, the *VEGFA* gene was

identified as being downregulated in patients with childhood obesity [54], and our results demonstrate that the *VEGFA* gene enriches KEGG pathways such as MAPK and PI3K.

Cellular functions are likely to be carried out in a highly modular manner. In general, modularity refers to a group of physically or functionally linked molecules that work together aiming to achieve a distinct function [34]. Therefore, using a network with large number of interconnections, cluster identification algorithms provide a smaller number of genes that are interconnected and likely have a common biological role [37]. Consistent with this information, our approach demonstrated the analyzed network shows 4 functional clusters. The functional enrichment analysis showed these clusters may overlap for given pathways, but the genes seem to present different functions regarding each cluster, suggesting these molecules share common pathways related to childhood obesity.

Even considering all the efforts and the strength of the applied algorithms and methods, a few limitations should be considered in interpreting our results. First, our results are based on the available literature at the time of preparation of this manuscript. Second, we cannot exclude the possibility that other genes could be key factors for the pathophysiology of childhood obesity. Third, there was only one gene expression dataset available in the literature, which investigated the expression of a myriad of genes in omental adipose tissue of children with obesity compared to controls; of note, the gene expression evaluation in multiple tissues would help to improve even more the knowledge regarding the genetic basis of childhood obesity. Fourth, considering that childhood obesity is a complex disease, our results may not be used uniformly for all children across the globe, since there is an important interaction of genetic factors with epigenetic and environmental factors that could lead to different phenotypic traits of childhood obesity,

especially considering the diversity of regional eating habits and physical activity that could trigger several obesogenic mechanisms within the cells.

5. Conclusion

In conclusion, we identified 12 hub-bottleneck genes that are highly interconnected and may play a key role in childhood obesity pathogenesis. Moreover, functional enrichment analyses demonstrated these genes are involved in several biological processes and pathways related to obesity pathogenesis. Our approach also detected 4 main functional clusters of gene interaction. These clusters present specific enriched pathways, showing the functional differences among the clusters. Of note, overlapped pathways may suggest the interconnection among clusters. Further experimental analyses should be carried out in order to understand the crosstalk between childhood obesity and genetic factors.

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Conflict of interest

The authors declare that they have no conflict of interest.

Author's contributions

FMP: Conceptualization, Methodology, Formal analysis, Investigation, Writing – Original Draft, Writing – Review & Editing, Visualization. **DC:** Conceptualization, Methodology, Formal analysis, Resources, Writing – Review & Editing, Supervision, Funding acquisition. **TSA:** Conceptualization, Methodology, Formal analysis, Writing – Review & Editing, Supervision. This manuscript has been read and approved by all authors and all authors believe that this study represents honest work.

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Figure Legends

Figure 1. Protein-protein interaction (PPI) network topography's analysis demonstrating the hub-bottleneck, hub, and bottleneck genes. The green diamonds represent the 12 hub-bottleneck genes. The hub genes are shown in blue, while the bottleneck genes are shown in pink.

Figure 2. Functional enrichment analyses for the 12 hub-bottleneck genes: **A)** Main KEGG pathways associated with childhood obesity. **B)** GO analysis demonstrating the main biological processes (BP) involved with these genes.

Figure 3. Clustering analysis depicting the genes present in each functional cluster: **A)** Cluster 1, **B)** Cluster 2, **C)** Cluster 3, and **D)** Cluster 4. Diamond nodes indicate the hub-bottleneck genes identified in the PPI network analysis.

Figure 4. Functional enrichment analysis demonstrating the enriched KEGG pathways of each functional cluster.

Supplementary Material

Figure S1. Protein-protein interaction (PPI) network showing the interconnections among the 12 hub-bottleneck genes and the gene expression patterns in omental adipose tissue of children with obesity. The green ellipses indicate the down-regulated genes, while the red ellipses depict the up-regulated genes. Genes that were not analyzed by the **GSE9624** dataset are represented by white ellipses.

Table S1. All 191 genes recovered from the DisGeNET database and previously associated with Pediatric Obesity.

Table S2. Topological analysis results (degree and betweenness) for the entire network.

Table S3. Results of the functional enrichment analyses for the 12 hub-bottleneck genes.

Table S4. KEGG pathways associated with the 4 functional clusters.

Table S5. GO processes associated with the 4 functional clusters.

Table S6. Genes associated with pediatric obesity and obesity in adulthood and genes associated exclusively with pediatric obesity.

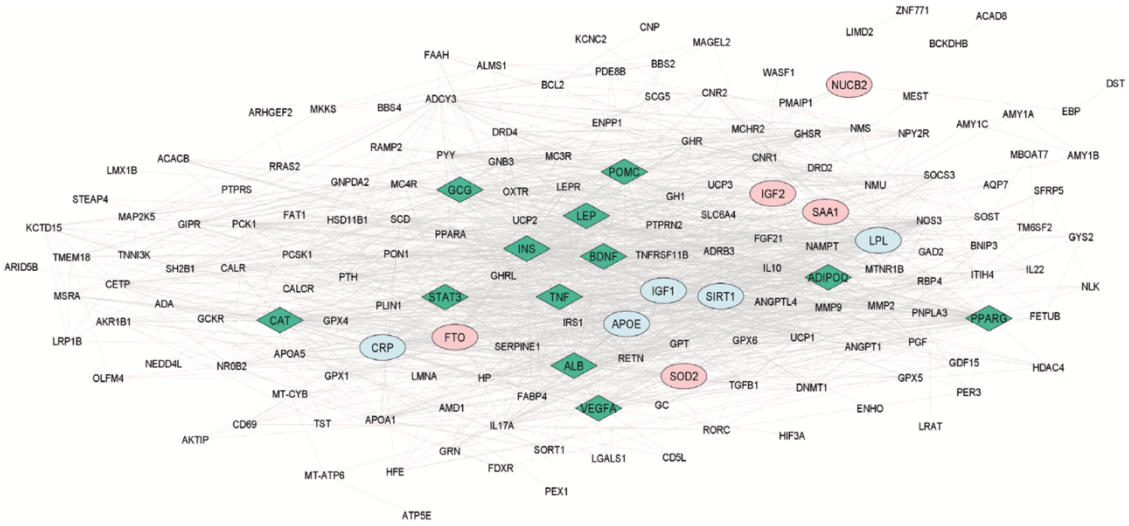
Table 1. The 12 hub-bottleneck genes identified in the main protein-protein interaction network and their gene expression pattern in omental adipose tissue.

				GSE9624 [32]	
Gene symbol	**Gene Name**	**Degree**	**Betweenness**	**Expression pattern**	**logFC**
INS	*Insulin*	99	0.17657276347126075	ND	NA
LEP	*Leptin*	71	0.06592203730364159	ND	-0.57145
STAT3	*Signal transducer and activator of transcription 3*	53	0.06540267500913678	ND	0.86165
POMC	*Proopiomelanocortin*	56	0.0620898764259297	↑	14.336
ALB	*Albumin*	71	0.05653250741865474	ND	-0.39182
TNF	*Tumor necrosis factor*	66	0.04786056217507144	↓	-41.224
BDNF	*Brain derived neurotrophic factor*	44	0.03712316221499156	ND	-0.5938
CAT	*Catalase*	45	0.03422945172156209	ND	-0.4354
GCG	*Glucagon*	52	0.029243365438519367	ND	NA

PPARG	*Peroxisome proliferator activated receptor gamma*	58	0.028288264153597666	↓	-15.435
VEGFA	*Vascular endothelial growth factor A*	42	0.02553720222461292	ND	-0.8076
ADIPOQ	*Adiponectin, C1Q and collagen domain containing*	57	0.02515775391146283	↓	-16.265

NA: not available. ND: not different. ↓: down-regulated in cases compared to controls. ↑: up-regulated in cases compared to controls.

Figure 1. Protein-protein interaction (PPI) network topography's analysis demonstrating the hub-bottleneck, hub, and bottleneck genes. The green diamonds represent the 12 hub-bottleneck genes. The hub genes are shown in blue, while the bottleneck genes are shown in pink.



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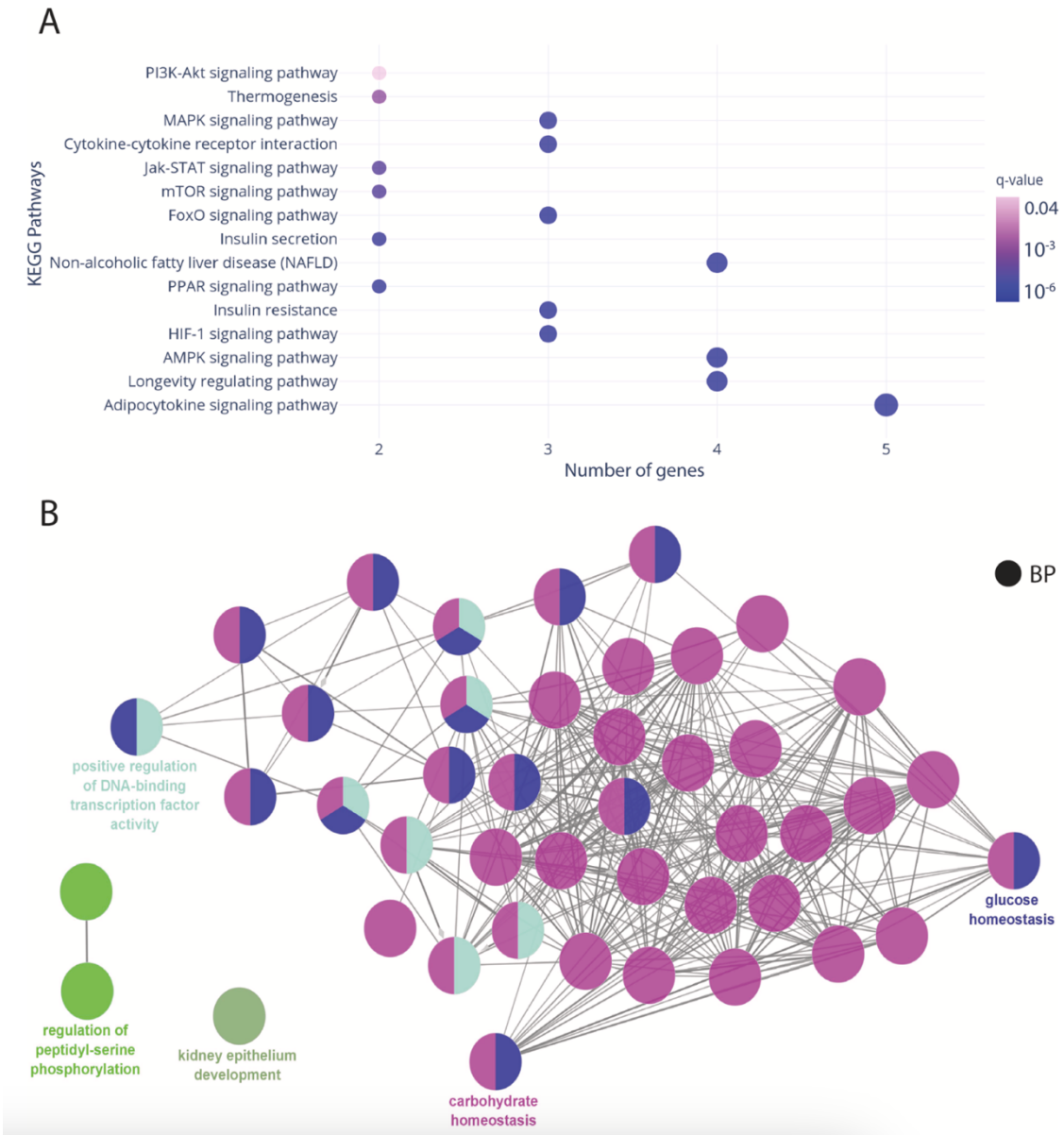

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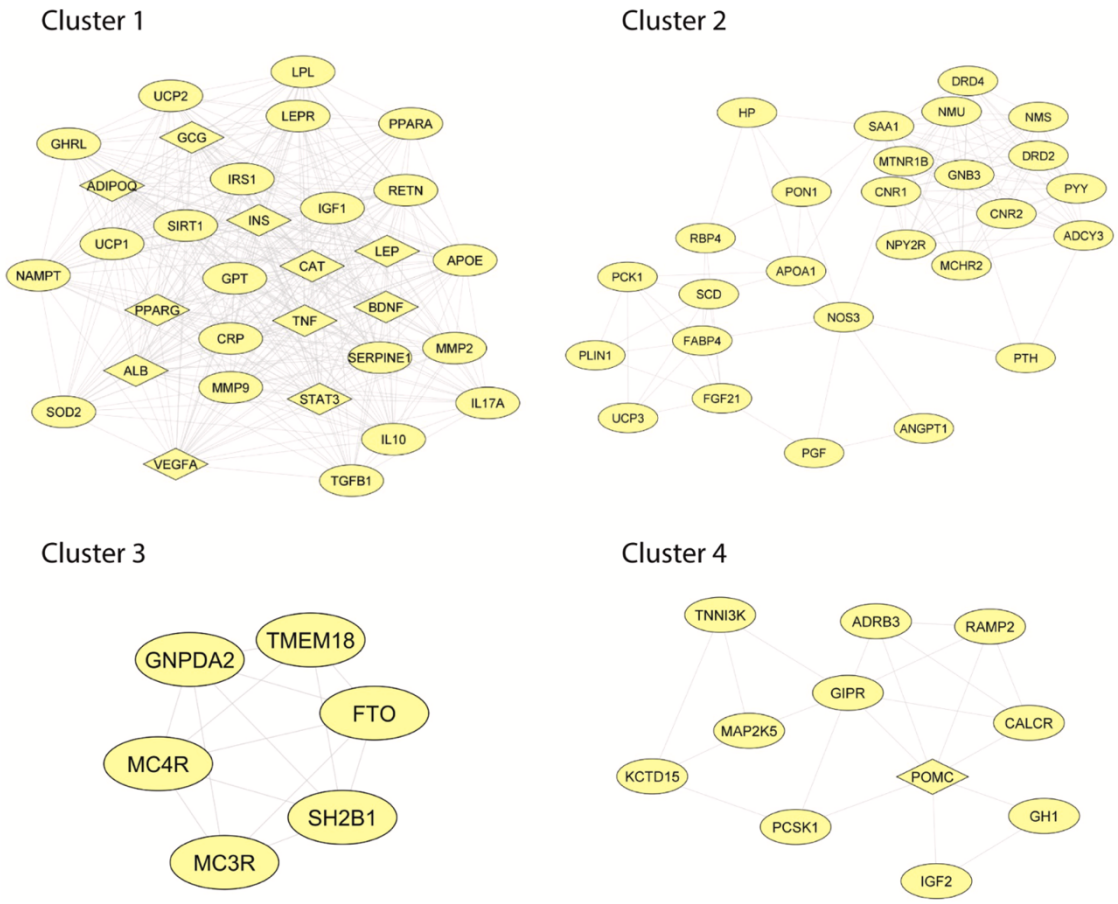


Figure 4. Functional enrichment analysis demonstrating the enriched KEGG pathways of each functional cluster.

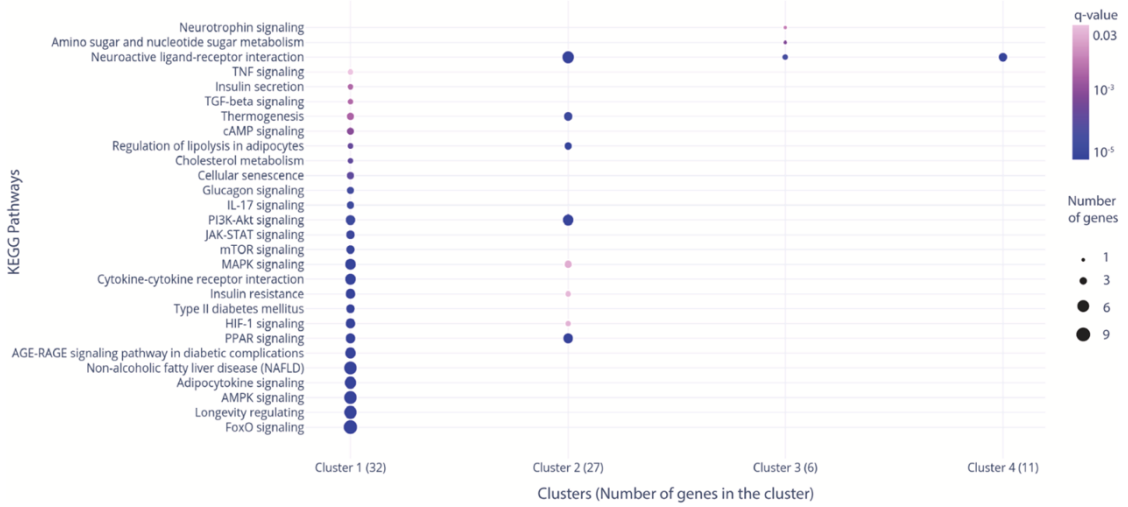


Table S1. All 191 genes recovered from the DisGeNET database and previously associated with Pediatric Obesity.

Gene	Gene_Full_Name
FTO	FTO alpha-ketoglutarate dependent dioxygenase
CETP	cholesteryl ester transfer protein
APOA5	apolipoprotein A5
APOA1	apolipoprotein A1
MC3R	melanocortin 3 receptor
MC4R	melanocortin 4 receptor
ADIPOQ	adiponectin, C1Q and collagen domain containing
LEP	leptin
PPARG	peroxisome proliferator activated receptor gamma
POMC	proopiomelanocortin
INS	insulin
LEPR	leptin receptor
DRD2	dopamine receptor D2
PPARA	peroxisome proliferator activated receptor alpha
FABP4	fatty acid binding protein 4
APOE	apolipoprotein E
ALMS1	ALMS1 centrosome and basal body associated protein
GCG	glucagon
ANGPTL4	angiopoietin like 4
GPT	glutamic--pyruvic transaminase
BDNF	brain derived neurotrophic factor
ADRB3	adrenoceptor beta 3
ENPP1	ectonucleotide pyrophosphatase/phosphodiesterase 1
NMU	neuromedin U
IL10	interleukin 10
UCP3	uncoupling protein 3
AMD1	adenosylmethionine decarboxylase 1
UCP2	uncoupling protein 2
IGF1	insulin like growth factor 1
TST	thiosulfate sulfurtransferase
OLFM4	olfactomedin 4
GRN	granulin precursor
RBP4	retinol binding protein 4
PNPLA3	patatin like phospholipase domain containing 3
BCL2	BCL2 apoptosis regulator
HP	haptoglobin
VEGFA	vascular endothelial growth factor A
TMEM18	transmembrane protein 18
MMP9	matrix metallopeptidase 9
IL17A	interleukin 17A
CAT	catalase
PON1	paraoxonase 1
FAAH	fatty acid amide hydrolase
CNR2	cannabinoid receptor 2
SIRT1	sirtuin 1
GNB3	G protein subunit beta 3

BCKDHB	branched chain keto acid dehydrogenase E1 subunit beta
ZNF771	zinc finger protein 771
TM6SF2	transmembrane 6 superfamily member 2
LRP1B	LDL receptor related protein 1B
PLIN1	perilipin 1
PCSK1	proprotein convertase subtilisin/kexin type 1
SNORA73A	small nucleolar RNA, H/ACA box 73A
PMAIP1	phorbol-12-myristate-13-acetate-induced protein 1
MIR412	microRNA 412
GHRL	ghrelin and obestatin prepropeptide
BBS4	Bardet-Biedl syndrome 4
BBS2	Bardet-Biedl syndrome 2
PEX1	peroxisomal biogenesis factor 1
PGF	placental growth factor
MAGEL2	MAGE family member L2
NLK	nemo like kinase
RETN	resistin
PYY	peptide YY
PTH	parathyroid hormone
PTPRN2	protein tyrosine phosphatase receptor type N2
MAP2K5	mitogen-activated protein kinase kinase 5
KLF13	Kruppel like factor 13
PTPRS	protein tyrosine phosphatase receptor type S
ATP5F1E	ATP synthase F1 subunit epsilon
UCP1	uncoupling protein 1
NR0B2	nuclear receptor subfamily 0 group B member 2
ARID5B	AT-rich interaction domain 5B
MKKS	McKusick-Kaufman syndrome
CALR	calreticulin
LIMD2	LIM domain containing 2
TMEM134	transmembrane protein 134
CALCR	calcitonin receptor
STEAP4	STEAP4 metalloreductase
MCHR2	melanin concentrating hormone receptor 2
LINC00839	long intergenic non-protein coding RNA 839
GDF15	growth differentiation factor 15
LRAT	lecithin retinol acyltransferase
CD5L	CD5 molecule like
ARHGEF2	Rho/Rac guanine nucleotide exchange factor 2
SOCS3	suppressor of cytokine signaling 3
WASF1	WASP family member 1
PER3	period circadian regulator 3
PDE8B	phosphodiesterase 8B
MBOAT7	membrane bound O-acyltransferase domain containing 7
KCTD15	potassium channel tetramerization domain containing 15
HDAC4	histone deacetylase 4
HIF3A	hypoxia inducible factor 3 subunit alpha
SFRP5	secreted frizzled related protein 5
TNMD	tenomodulin
SCD	stearoyl-CoA desaturase

SAA1	serum amyloid A1
SORT1	sortilin 1
RORC	RAR related orphan receptor C
AKTIP	AKT interacting protein
SCG5	secretogranin V
TNF	tumor necrosis factor
TGFB1	transforming growth factor beta 1
STAT3	signal transducer and activator of transcription 3
DST	dystonin
SOD2	superoxide dismutase 2
BNIP3	BCL2 interacting protein 3
SLC6A8	solute carrier family 6 member 8
SLC6A4	solute carrier family 6 member 4
CD69	CD69 molecule
ADA	adenosine deaminase
SH2B1	SH2B adaptor protein 1
GPX6	glutathione peroxidase 6
GAD2	glutamate decarboxylase 2
NEDD4L	NEDD4 like E3 ubiquitin protein ligase
AKR1B1	aldo-keto reductase family 1 member B
RRAS2	RAS related 2
FDXR	ferredoxin reductase
SKA1	spindle and kinetochore associated complex subunit 1
FGF21	fibroblast growth factor 21
MYCBP	MYC binding protein
ACAD8	acyl-CoA dehydrogenase family member 8
FETUB	fetuin B
GIPR	gastric inhibitory polypeptide receptor
GHSR	growth hormone secretagogue receptor
GHR	growth hormone receptor
GH1	growth hormone 1
GCKR	glucokinase regulator
GC	GC vitamin D binding protein
FAT1	FAT atypical cadherin 1
ALB	albumin
HCP5	HLA complex P5
EBP	EBP cholestenol delta-isomerase
CTPP	Cataract, posterior polar
RAMP2	receptor activity modifying protein 2
NAMPT	nicotinamide phosphoribosyltransferase
MIR642B	microRNA 642b
MIR1203	microRNA 1203
RAMP2-AS1	RAMP2 antisense RNA 1
ADCY3	adenylate cyclase 3
CNP	2',3'-cyclic nucleotide 3' phosphodiesterase
ELAVL2	ELAV like RNA binding protein 2
DRD4	dopamine receptor D4
DNMT1	DNA methyltransferase 1
CRP	C-reactive protein
GNPDA2	glucosamine-6-phosphate deaminase 2

CORD1	cone rod dystrophy 1 (autosomal dominant)
NMS	neuromedin S
CNR1	cannabinoid receptor 1
AMY1A	amylase alpha 1A
AMY1B	amylase alpha 1B
AMY1C	amylase alpha 1C
CYTB	cytochrome b
ATP6	ATP synthase F0 subunit 6
MSRA	methionine sulfoxide reductase A
MMP2	matrix metallopeptidase 2
MEST	mesoderm specific transcript
ARSD	arylsulfatase D
MIR27A	microRNA 27a
MIR216A	microRNA 216a
MTNR1B	melatonin receptor 1B
NOS3	nitric oxide synthase 3
PCK1	phosphoenolpyruvate carboxykinase 1
SOST	sclerostin
IL22	interleukin 22
SERPINE1	serpin family E member 1
OXTR	oxytocin receptor
TNFRSF11B	TNF receptor superfamily member 11b
NUCB2	nucleobindin 2
NPY2R	neuropeptide Y receptor Y2
MIR17	microRNA 17
LPL	lipoprotein lipase
HSD11B1	hydroxysteroid 11-beta dehydrogenase 1
ACACB	acetyl-CoA carboxylase beta
HFE	homeostatic iron regulator
GYS2	glycogen synthase 2
GPX5	glutathione peroxidase 5
GPX4	glutathione peroxidase 4
GPX1	glutathione peroxidase 1
ANGPT1	angiopoietin 1
IGF2	insulin like growth factor 2
IMPDH2	inosine monophosphate dehydrogenase 2
LMX1B	LIM homeobox transcription factor 1 beta
LMNA	lamin A/C
LGALS1	galectin 1
ENHO	energy homeostasis associated
KCNC2	potassium voltage-gated channel subfamily C member 2
ITIH4	inter-alpha-trypsin inhibitor heavy chain 4
IRS1	insulin receptor substrate 1
AQP7	aquaporin 7
TNNI3K	TNNI3 interacting kinase

Table S2. Topological analysis results (degree and betweenness) for the entire PPI network.

Node_name	Degree	Betweenness Centrality
INS	99.0	0.17657276347126075
LEP	71.0	0.06592203730364159
STAT3	53.0	0.06540267500913678
POMC	56.0	0.0620898764259297
ALB	71.0	0.05653250741865474
TNF	66.0	0.04786056217507144
SAA1	34.0	0.04661227648150417
BDNF	44.0	0.03712316221499156
CAT	45.0	0.03422945172156209
FTO	33.0	0.029248898050653036
GCG	52.0	0.029243365438519367
PPARG	58.0	0.028288264153597666
SOD2	32.0	0.02775125835915001
VEGFA	42.0	0.02553720222461292
ADIPOQ	57.0	0.02515775391146283
NUCB2	5.0	0.02409460458240946
IGF2	24.0	0.02279957221775803
GNB3	28.0	0.022746240070189296
APOE	48.0	0.02248400177111057
CNR1	30.0	0.019199549448034665
IGF1	54.0	0.017594385091370898
DNMT1	17.0	0.015852156208785065
MAP2K5	14.0	0.014363011916680733
SIRT1	43.0	0.01370623501883351
MC4R	33.0	0.013402801940576026
GHRL	38.0	0.013013252078652114
SLC6A4	13.0	0.012904688742893399
GAD2	10.0	0.012756240486786821
IL10	41.0	0.01252581235383816
RBP4	20.0	0.01249266392028568
RRAS2	3.0	0.01216331066178627
BCL2	4.0	0.012156380615360656
EBP	2.0	0.012121212121212121
MT-ATP6	3.0	0.012121212121212121
LEPR	38.0	0.011875110045991765
SERPINE1	37.0	0.011380184616903396
HP	27.0	0.011092975346166418
ADCY3	28.0	0.010964848028879294
GPT	35.0	0.01071898422360407
CRP	46.0	0.009670678194551812
PNPLA3	11.0	0.009379913283048283

LPL	43.0	0.008542702386279428
MTNR1B	22.0	0.007909142601707348
RETN	40.0	0.007869939267940307
APOA1	28.0	0.007305317927940126
NOS3	42.0	0.00715372068214605
MMP9	32.0	0.006748559063921476
PTH	26.0	0.006564450527375702
PYY	29.0	0.00618953351791967
SH2B1	20.0	0.006105567555742599
MT-CYB	6.0	0.006077841082204604
DRD2	24.0	0.005778290368807188
SOCS3	23.0	0.00575081342295269
IRS1	38.0	0.005402807147627513
UCP2	36.0	0.00501855381899261
PPARA	33.0	0.004929861132614247
TGFB1	22.0	0.004749873802232693
NR0B2	16.0	0.004682782878849713
BBS2	7.0	0.004080196995928582
PCSK1	19.0	0.004067650409772017
GHSR	21.0	0.003883594264292105
IL17A	24.0	0.003845147942807929
NAMPT	26.0	0.0034671036368127345
ADRB3	21.0	0.0034452337788960213
TMEM18	15.0	0.0033918827229134927
GIPR	21.0	0.0033760620261793104
MSRA	11.0	0.0033382221160678503
BBS4	6.0	0.0032804496540692766
TM6SF2	5.0	0.0032723399240650905
ALMS1	4.0	0.0031941027887050825
ENPP1	10.0	0.0030428203853602558
APOA5	19.0	0.0030092565284654837
GNPDA2	17.0	0.002964405548657188
PCK1	25.0	0.0026924170758608344
FGF21	32.0	0.002683126296238377
MMP2	27.0	0.002665418904979787
CALR	12.0	0.0025699338005496604
ITIH4	11.0	0.0024229147358523946
FABP4	29.0	0.002331481837826863
GHR	13.0	0.002323421198825162
SCD	24.0	0.0022910698354931835
UCP1	30.0	0.001967712998115287
MC3R	22.0	0.001919759920868057
GDF15	8.0	0.001730260535525295
GC	12.0	0.001690654307640811
GPX1	14.0	0.0016074440702793678
DRD4	18.0	0.0014605275123139132

LMNA	9.0	0.001443121983890744
BNIP3	7.0	0.0013888439871448598
PMAIP1	6.0	0.0013760904786076047
OXTR	15.0	0.0013273075203874963
AKR1B1	9.0	0.0013239853092353784
CNR2	16.0	0.0012988416847382475
CALCR	14.0	0.0012238183759433066
PON1	20.0	0.0011407392219078098
SOST	7.0	0.001061981944716686
KCTD15	12.0	0.0010489037356041385
ACAD8	1.0	0.0
ADA	7.0	0.0
AMD1	1.0	0.0
AMY1A	3.0	0.0
AMY1B	3.0	0.0
AMY1C	3.0	0.0
AQP7	4.0	0.0
ARHGEF2	1.0	0.0
ARID5B	1.0	0.0
ATP5E	1.0	0.0
BCKDHB	1.0	0.0
CNP	1.0	0.0
DST	1.0	0.0
ENHO	1.0	0.0
GPX5	5.0	0.0
HIF3A	1.0	0.0
KCNC2	1.0	0.0
LGALS1	4.0	0.0
LIMD2	1.0	0.0
LMX1B	1.0	0.0
LRAT	1.0	0.0
MBOAT7	2.0	0.0
MEST	1.0	0.0
PEX1	1.0	0.0
PTPRS	3.0	0.0
RAMP2	10.0	0.0
STEAP4	2.0	0.0
WASF1	1.0	0.0
ZNF771	1.0	0.0
RORC	7.0	4,27E+12
ANGPTL4	14.0	4,09E+12
GPX6	5.0	4,04E+12
NLK	4.0	2,89E+12
PER3	5.0	2,76E+12
LRP1B	5.0	2,72E+12
IL22	9.0	2,48E+12

OLFM4	4.0	2,41E+12
NPY2R	15.0	2,40E+12
NMU	17.0	2,38E+12
FETUB	6.0	2,19E+12
HFE	7.0	2,06E+12
PDE8B	4.0	2,03E+12
NEDD4L	3.0	1,98E+12
SORT1	8.0	1,69E+12
MCHR2	16.0	1,63E+12
NMS	16.0	1,63E+12
CD69	7.0	1,53E+12
MAGEL2	3.0	1,39E+12
AKTIP	3.0	1,23E+12
FAT1	5.0	1,16E+12
UCP3	22.0	9,24E+11
PGF	16.0	8,09E+11
GCKR	7.0	8,00E+11
PLIN1	18.0	7,71E+11
TNNI3K	11.0	7,48E+11
TNFRSF11B	17.0	7,11E+11
MKKS	4.0	7,07E+11
TST	5.0	5,73E+11
CETP	14.0	5,24E+11
GPX4	9.0	4,63E+11
PTPRN2	5.0	4,35E+11
GH1	16.0	3,37E+11
FAAH	6.0	3,08E+11
SFRP5	4.0	2,39E+11
GRN	9.0	2,17E+11
FDXR	4.0	1,77E+11
GYS2	5.0	7,48E+10
ACACB	9.0	7,40E+10
SCG5	5.0	3,24E+10
CD5L	3.0	2,64E+10
HDAC4	6.0	2,44E+10
ANGPT1	12.0	8,36E+09
HSD11B1	9.0	7,26E+09

Table S3. Results of the functional enrichment analyses for the 12 hub-bottleneck genes.
KEGG Pathways

#Term ID	Term description	Gene count	Strength	FDR	Matching proteins in the network (labels)
hsa04920	Adipocytokine signaling pathway	5	2.11	3.36e-08	STAT3, LEP, POMC, ADIPOQ, TNF
hsa04211	Longevity regulating pathway	4	1.91	8.08e-06	CAT, PPARG, INS, ADIPOQ
hsa04152	AMPK signaling pathway	4	1.77	1.79e-05	PPARG, LEP, INS, ADIPOQ
hsa04932	Non-alcoholic fatty liver disease (NAFLD)	4	1.68	3.12e-05	LEP, INS, ADIPOQ, TNF
hsa04930	Type II diabetes mellitus	3	2.06	5.27e-05	INS, ADIPOQ, TNF
hsa04066	HIF-1 signaling pathway	3	1.74	0.00039	STAT3, INS, VEGFA
hsa04931	Insulin resistance	3	1.7	0.00039	STAT3, INS, TNF
hsa04933	AGE-RAGE signaling pathway in diabetic complications	3	1.74	0.00039	STAT3, TNF, VEGFA
hsa04068	FoxO signaling pathway	3	1.61	0.00059	CAT, STAT3, INS
hsa05205	Proteoglycans in cancer	3	1.44	0.0017	STAT3, TNF, VEGFA
hsa04940	Type I diabetes mellitus	2	1.95	0.0024	INS, TNF
hsa04060	Cytokine-cytokine receptor interaction	3	1.31	0.0034	LEP, TNF, VEGFA
hsa05014	Amyotrophic lateral sclerosis (ALS)	2	1.85	0.0034	CAT, TNF
hsa04010	MAPK signaling pathway	3	1.26	0.0041	INS, TNF, VEGFA
hsa04213	Longevity regulating pathway - multiple species	2	1.77	0.0041	CAT, INS
hsa05321	Inflammatory bowel disease (IBD)	2	1.76	0.0041	STAT3, TNF
hsa04917	Prolactin signaling pathway	2	1.71	0.0045	STAT3, INS
hsa03320	PPAR signaling pathway	2	1.69	0.0046	PPARG, ADIPOQ
hsa05212	Pancreatic cancer	2	1.68	0.0046	STAT3, VEGFA
hsa01521	EGFR tyrosine kinase inhibitor resistance	2	1.66	0.0049	STAT3, VEGFA
hsa04911	Insulin secretion	2	1.63	0.0054	INS, GCG
hsa05323	Rheumatoid arthritis	2	1.63	0.0054	TNF, VEGFA
hsa05145	Toxoplasmosis	2	1.51	0.0081	STAT3, TNF
hsa04380	Osteoclast differentiation	2	1.46	0.0100	PPARG, TNF
hsa05160	Hepatitis C	2	1.43	0.0106	STAT3, TNF
hsa05200	Pathways in cancer	3	1.02	0.0106	STAT3, PPARG, VEGFA
hsa05418	Fluid shear stress and atherosclerosis	2	1.43	0.0106	TNF, VEGFA
hsa05161	Hepatitis B	2	1.4	0.0111	STAT3, TNF
hsa04150	mTOR signaling pathway	2	1.38	0.0116	INS, TNF
hsa05206	MicroRNAs in cancer	2	1.38	0.0116	STAT3, VEGFA
hsa04217	Necroptosis	2	1.36	0.0119	STAT3, TNF
hsa04630	Jak-STAT signaling pathway	2	1.35	0.0123	STAT3, LEP
hsa05167	Kaposi's sarcoma-associated herpesvirus infection	2	1.29	0.0154	STAT3, VEGFA
hsa04015	Rap1 signaling pathway	2	1.24	0.0182	INS, VEGFA
hsa04014	Ras signaling pathway	2	1.19	0.0222	INS, VEGFA
hsa04714	Thermogenesis	2	1.19	0.0222	PPARG, GCG
hsa05165	Human papillomavirus infection	2	1.05	0.0393	TNF, VEGFA
hsa04151	PI3K-Akt signaling pathway	2	1.01	0.0456	INS, VEGFA

Table S3. Functional enrichment analyses results for the 12 hub-bottleneck genes.
GO Terms: Biological Processess

#term ID	term description	Gene count	strength	FDR	matching proteins in your network (labels)
GO:0062012	regulation of small molecule metabolic process	8	1.63	2.38e-09	STAT3,PPARG,LEP,INS,POMC,GCG,ADIPOQ,TNF
GO:0010675	regulation of cellular carbohydrate metabolic process	6	1.9	4.28e-08	STAT3,LEP,INS,POMC,GCG,ADIPOQ
GO:0042981	regulation of apoptotic process	10	1.07	4.28e-08	CAT,STAT3,PPARG,ALB,LEP,INS,GCG,ADIPOQ,TNF,VEGFA
GO:0062013	positive regulation of small molecule metabolic process	6	1.92	4.28e-08	STAT3,PPARG,INS,GCG,ADIPOQ,TNF
GO:0042593	glucose homeostasis	6	1.8	5.16e-08	STAT3,PPARG,LEP,INS,POMC,ADIPOQ
GO:0043434	response to peptide hormone	7	1.54	5.16e-08	CAT,STAT3,PPARG,LEP,INS,GCG,ADIPOQ
GO:0070887	cellular response to chemical stimulus	11	0.86	5.67e-08	CAT,STAT3,PPARG,ALB,LEP,INS,POMC,GCG,ADIPOQ,TNF,VEGFA
GO:0031667	response to nutrient levels	7	1.44	1.81e-07	CAT,PPARG,ALB,LEP,POMC,GCG,ADIPOQ
GO:0009725	response to hormone	8	1.22	2.57e-07	CAT,STAT3,PPARG,LEP,INS,GCG,ADIPOQ,TNF
GO:0010906	regulation of glucose metabolic process	5	1.95	2.57e-07	LEP,INS,POMC,GCG,ADIPOQ
GO:0043066	negative regulation of apoptotic process	8	1.22	2.57e-07	CAT,STAT3,ALB,LEP,INS,GCG,TNF,VEGFA
GO:0010243	response to organonitrogen compound	8	1.21	2.63e-07	CAT,STAT3,PPARG,LEP,INS,GCG,ADIPOQ,TNF
GO:0046883	regulation of hormone secretion	6	1.61	2.63e-07	LEP,INS,POMC,GCG,ADIPOQ,TNF
GO:0071310	cellular response to organic substance	10	0.9	3.35e-07	CAT,STAT3,PPARG,LEP,INS,POMC,GCG,ADIPOQ,TNF,VEGFA
GO:0045598	regulation of fat cell differentiation	5	1.87	3.95e-07	PPARG,LEP,INS,ADIPOQ,TNF
GO:0001936	regulation of endothelial cell proliferation	5	1.86	4.08e-07	STAT3,PPARG,LEP,TNF,VEGFA
GO:0006111	regulation of gluconeogenesis	4	2.3	4.08e-07	LEP,INS,GCG,ADIPOQ
GO:1902533	positive regulation of intracellular signal transduction	8	1.17	4.08e-07	CAT,STAT3,LEP,INS,GCG,ADIPOQ,TNF,VEGFA
GO:0010469	regulation of signaling receptor activity	7	1.33	4.43e-07	LEP,INS,POMC,GCG,ADIPOQ,TNF,VEGFA
GO:1905952	regulation of lipid localization	5	1.84	4.43e-07	PPARG,LEP,POMC,ADIPOQ,TNF
GO:0001101	response to acid chemical	6	1.52	6.12e-07	CAT,PPARG,LEP,ADIPOQ,TNF,VEGFA
GO:0044093	positive regulation of molecular function	9	0.97	9.23e-07	CAT,STAT3,PPARG,LEP,INS,GCG,ADIPOQ,TNF,VEGFA
GO:0008015	blood circulation	6	1.46	1.33e-06	PPARG,LEP,INS,POMC,ADIPOQ,VEGFA
GO:0050731	positive regulation of peptidyl-tyrosine phosphorylation	5	1.69	1.84e-06	STAT3,LEP,INS,ADIPOQ,VEGFA
GO:0046324	regulation of glucose import	4	2.03	2.60e-06	LEP,INS,ADIPOQ,TNF
GO:0033197	response to vitamin E	3	2.65	3.12e-06	CAT,PPARG,LEP
GO:0032868	response to insulin	5	1.62	3.62e-06	CAT,PPARG,LEP,INS,ADIPOQ
GO:0048584	positive regulation of response to stimulus	9	0.89	3.62e-06	CAT,STAT3,LEP,INS,POMC,GCG,ADIPOQ,TNF,VEGFA
GO:0009966	regulation of signal transduction	10	0.77	3.63e-06	CAT,STAT3,PPARG,LEP,INS,POMC,GCG,ADIPOQ,TNF,VEGFA
GO:0009636	response to toxic substance	6	1.36	3.75e-06	CAT,STAT3,ALB,LEP,ADIPOQ,TNF
GO:0043085	positive regulation of catalytic activity	8	1.01	3.86e-06	STAT3,PPARG,LEP,INS,GCG,ADIPOQ,TNF,VEGFA
GO:0002682	regulation of immune system process	8	1.01	3.99e-06	STAT3,PPARG,LEP,INS,POMC,ADIPOQ,TNF,VEGFA
GO:0071417	cellular response to organonitrogen compound	6	1.34	4.32e-06	STAT3,PPARG,INS,GCG,ADIPOQ,TNF
GO:0009605	response to external stimulus	9	0.87	4.51e-06	CAT,PPARG,ALB,LEP,POMC,GCG,ADIPOQ,TNF,VEGFA
GO:0097305	response to alcohol	5	1.58	4.56e-06	CAT,STAT3,PPARG,LEP,ADIPOQ
GO:1901700	response to oxygen-containing compound	8	1.0	4.56e-06	CAT,STAT3,PPARG,LEP,INS,GCG,ADIPOQ,TNF
GO:0051050	positive regulation of transport	7	1.14	4.65e-06	PPARG,LEP,INS,GCG,ADIPOQ,TNF,VEGFA

GO:1901701	cellular response to oxygen-containing compound	7	1.14	4.65e-06	STAT3,PPARG,LEP,INS,GCG,ADIPOQ,TNF
GO:0071375	cellular response to peptide hormone stimulus	5	1.56	5.01e-06	STAT3,PPARG,INS,GCG,ADIPOQ
GO:0045860	positive regulation of protein kinase activity	6	1.31	5.06e-06	LEP,INS,GCG,ADIPOQ,TNF,VEGFA
GO:0010888	negative regulation of lipid storage	3	2.5	5.11e-06	PPARG,LEP,TNF
GO:0006950	response to stress	10	0.74	5.25e-06	CAT,STAT3,PPARG,ALB,LEP,INS,GCG,ADIPOQ,TNF,VEGFA
GO:0032270	positive regulation of cellular protein metabolic process	8	0.98	5.25e-06	STAT3,PPARG,LEP,INS,GCG,ADIPOQ,TNF,VEGFA
GO:0051091	positive regulation of DNA-binding transcription factor activity	5	1.55	5.25e-06	CAT,PPARG,INS,TNF,VEGFA
GO:0001934	positive regulation of protein phosphorylation	7	1.12	5.34e-06	STAT3,LEP,INS,GCG,ADIPOQ,TNF,VEGFA
GO:0032101	regulation of response to external stimulus	7	1.12	5.81e-06	PPARG,LEP,INS,POMC,ADIPOQ,TNF,VEGFA
GO:0065009	regulation of molecular function	10	0.73	5.81e-06	CAT,STAT3,PPARG,LEP,INS,POMC,GCG,ADIPOQ,TNF,VEGFA
GO:0051338	regulation of transferase activity	7	1.11	5.92e-06	PPARG,LEP,INS,GCG,ADIPOQ,TNF,VEGFA
GO:0032368	regulation of lipid transport	4	1.85	6.93e-06	PPARG,LEP,POMC,ADIPOQ
GO:0048878	chemical homeostasis	7	1.1	6.93e-06	STAT3,PPARG,LEP,INS,POMC,ADIPOQ,VEGFA
GO:0048519	negative regulation of biological process	11	0.6	7.30e-06	CAT,STAT3,PPARG,ALB,LEP,INS,POMC,GCG,ADIPOQ,TNF,VEGFA
GO:0032870	cellular response to hormone stimulus	6	1.26	7.82e-06	STAT3,PPARG,LEP,INS,GCG,ADIPOQ
GO:0065008	regulation of biological quality	10	0.7	8.97e-06	STAT3,PPARG,ALB,LEP,INS,POMC,GCG,ADIPOQ,TNF,VEGFA
GO:0006006	glucose metabolic process	4	1.8	9.24e-06	LEP,INS,ADIPOQ,TNF
GO:0032879	regulation of localization	9	0.8	1.02e-05	STAT3,PPARG,LEP,INS,POMC,GCG,ADIPOQ,TNF,VEGFA
GO:0002521	leukocyte differentiation	5	1.45	1.06e-05	STAT3,PPARG,LEP,TNF,VEGFA
GO:0006355	regulation of transcription, DNA-templated	10	0.69	1.09e-05	CAT,STAT3,PPARG,LEP,INS,POMC,GCG,ADIPOQ,TNF,VEGFA
GO:0051049	regulation of transport	8	0.91	1.09e-05	PPARG,LEP,INS,POMC,GCG,ADIPOQ,TNF,VEGFA
GO:0051241	negative regulation of multicellular organismal process	7	1.05	1.09e-05	STAT3,PPARG,LEP,INS,POMC,ADIPOQ,TNF
GO:0071495	cellular response to endogenous stimulus	7	1.05	1.11e-05	STAT3,PPARG,LEP,INS,GCG,ADIPOQ,TNF
GO:0070482	response to oxygen levels	5	1.44	1.12e-05	CAT,PPARG,LEP,ADIPOQ,VEGFA
GO:0040008	regulation of growth	6	1.21	1.28e-05	STAT3,PPARG,LEP,INS,TNF,VEGFA
GO:0050727	regulation of inflammatory response	5	1.42	1.36e-05	PPARG,LEP,INS,ADIPOQ,TNF
GO:0031347	regulation of defense response	6	1.2	1.38e-05	PPARG,LEP,INS,POMC,ADIPOQ,TNF
GO:0045471	response to ethanol	4	1.73	1.47e-05	CAT,STAT3,LEP,ADIPOQ
GO:0045834	positive regulation of lipid metabolic process	4	1.72	1.50e-05	PPARG,INS,ADIPOQ,TNF
GO:0043408	regulation of MAPK cascade	6	1.18	1.78e-05	LEP,INS,GCG,ADIPOQ,TNF,VEGFA
GO:0019216	regulation of lipid metabolic process	5	1.38	2.03e-05	PPARG,LEP,INS,ADIPOQ,TNF
GO:0030334	regulation of cell migration	6	1.15	2.37e-05	STAT3,PPARG,INS,ADIPOQ,TNF,VEGFA
GO:0051094	positive regulation of developmental process	7	0.99	2.51e-05	STAT3,PPARG,LEP,INS,ADIPOQ,TNF,VEGFA
GO:0060341	regulation of cellular localization	6	1.14	2.54e-05	LEP,INS,GCG,ADIPOQ,TNF,VEGFA
GO:0080134	regulation of response to stress	7	0.98	2.64e-05	PPARG,LEP,INS,POMC,ADIPOQ,TNF,VEGFA
GO:0051173	positive regulation of nitrogen compound metabolic process	9	0.74	2.78e-05	STAT3,PPARG,LEP,INS,POMC,GCG,ADIPOQ,TNF,VEGFA
GO:2000377	regulation of reactive oxygen species metabolic process	4	1.62	3.05e-05	STAT3,LEP,INS,TNF
GO:0031952	regulation of protein autophosphorylation	3	2.09	3.19e-05	INS,ADIPOQ,VEGFA
GO:0032374	regulation of cholesterol transport	3	2.09	3.19e-05	PPARG,LEP,ADIPOQ
GO:0046890	regulation of lipid biosynthetic process	4	1.61	3.26e-05	LEP,INS,ADIPOQ,TNF
GO:0008217	regulation of blood pressure	4	1.6	3.40e-05	PPARG,LEP,POMC,ADIPOQ

GO:0033993	response to lipid	6	1.11	3.40e-05	CAT,STAT3,PPARG,LEP,ADIPOQ,TNF
GO:1903531	negative regulation of secretion by cell	4	1.6	3.43e-05	LEP,INS,ADIPOQ,TNF
GO:0031325	positive regulation of cellular metabolic process	9	0.72	3.45e-05	STAT3,PPARG,LEP,INS,POMC,GCG,ADIPOQ,TNF,VEGFA
GO:0010677	negative regulation of cellular carbohydrate metabolic process	3	2.06	3.57e-05	STAT3,INS,ADIPOQ
GO:0010604	positive regulation of macromolecule metabolic process	9	0.72	3.61e-05	STAT3,PPARG,LEP,INS,POMC,GCG,ADIPOQ,TNF,VEGFA
GO:0060284	regulation of cell development	6	1.1	3.73e-05	STAT3,PPARG,INS,ADIPOQ,TNF,VEGFA
GO:1904705	regulation of vascular smooth muscle cell proliferation	3	2.04	4.13e-05	PPARG,ADIPOQ,TNF
GO:0014070	response to organic cyclic compound	6	1.09	4.34e-05	CAT,STAT3,PPARG,LEP,ADIPOQ,TNF
GO:1903827	regulation of cellular protein localization	5	1.28	4.50e-05	LEP,INS,ADIPOQ,TNF,VEGFA
GO:0048523	negative regulation of cellular process	10	0.6	4.56e-05	CAT,STAT3,PPARG,ALB,LEP,INS,GCG,ADIPOQ,TNF,VEGFA
GO:0071229	cellular response to acid chemical	4	1.56	4.56e-05	PPARG,LEP,TNF,VEGFA
GO:0031327	negative regulation of cellular biosynthetic process	7	0.93	4.79e-05	STAT3,PPARG,LEP,INS,ADIPOQ,TNF,VEGFA
GO:0032880	regulation of protein localization	6	1.07	4.83e-05	LEP,INS,GCG,ADIPOQ,TNF,VEGFA
GO:0042493	response to drug	6	1.07	4.83e-05	CAT,STAT3,PPARG,LEP,ADIPOQ,TNF
GO:0045597	positive regulation of cell differentiation	6	1.07	4.92e-05	STAT3,PPARG,INS,ADIPOQ,TNF,VEGFA
GO:0090276	regulation of peptide hormone secretion	4	1.54	4.92e-05	LEP,INS,GCG,TNF
GO:0007584	response to nutrient	4	1.53	5.18e-05	CAT,PPARG,LEP,ADIPOQ
GO:0032768	regulation of monooxygenase activity	3	1.98	5.19e-05	LEP,INS,TNF
GO:0051240	positive regulation of multicellular organismal process	7	0.9	6.05e-05	STAT3,PPARG,LEP,INS,ADIPOQ,TNF,VEGFA
GO:0043410	positive regulation of MAPK cascade	5	1.24	6.20e-05	LEP,INS,GCG,TNF,VEGFA
GO:0022603	regulation of anatomical structure morphogenesis	6	1.05	6.45e-05	STAT3,PPARG,LEP,ADIPOQ,TNF,VEGFA
GO:0002376	immune system process	8	0.78	6.61e-05	CAT,STAT3,PPARG,LEP,INS,POMC,TNF,VEGFA
GO:0014823	response to activity	3	1.93	7.03e-05	CAT,LEP,ADIPOQ
GO:0042127	regulation of cell population proliferation	7	0.89	7.03e-05	STAT3,PPARG,LEP,INS,ADIPOQ,TNF,VEGFA
GO:0030100	regulation of endocytosis	4	1.49	7.06e-05	PPARG,ADIPOQ,TNF,VEGFA
GO:0032800	receptor biosynthetic process	2	2.85	7.06e-05	PPARG,TNF
GO:0033591	response to L-ascorbic acid	2	2.85	7.06e-05	CAT,LEP
GO:0014068	positive regulation of phosphatidylinositol 3-kinase signaling	3	1.91	7.47e-05	CAT,LEP,INS
GO:0050764	regulation of phagocytosis	3	1.89	8.81e-05	PPARG,ADIPOQ,TNF
GO:0010871	negative regulation of receptor biosynthetic process	2	2.77	8.98e-05	PPARG,ADIPOQ
GO:0034097	response to cytokine	6	1.01	9.10e-05	STAT3,LEP,POMC,ADIPOQ,TNF,VEGFA
GO:0048522	positive regulation of cellular process	10	0.56	9.16e-05	CAT,STAT3,PPARG,LEP,INS,POMC,GCG,ADIPOQ,TNF,VEGFA
GO:0009628	response to abiotic stimulus	6	1.01	9.79e-05	CAT,PPARG,LEP,ADIPOQ,TNF,VEGFA
GO:0045595	regulation of cell differentiation	7	0.87	9.79e-05	STAT3,PPARG,LEP,INS,ADIPOQ,TNF,VEGFA
GO:0019395	fatty acid oxidation	3	1.85	0.00011	PPARG,LEP,ADIPOQ
GO:1903426	regulation of reactive oxygen species biosynthetic process	3	1.84	0.00011	STAT3,INS,TNF
GO:0010557	positive regulation of macromolecule biosynthetic process	7	0.85	0.00012	STAT3,PPARG,INS,POMC,GCG,TNF,VEGFA
GO:0045935	positive regulation of nucleobase-containing compound metabolic process	7	0.85	0.00012	STAT3,PPARG,INS,POMC,GCG,TNF,VEGFA
GO:0045944	positive regulation of transcription by RNA polymerase II	6	0.99	0.00012	STAT3,PPARG,POMC,GCG,TNF,VEGFA
GO:0001817	regulation of cytokine production	5	1.16	0.00013	LEP,INS,POMC,ADIPOQ,TNF
GO:0009895	negative regulation of catabolic process	4	1.41	0.00013	STAT3,LEP,INS,TNF

GO:0044092	negative regulation of molecular function	6	0.98	0.00013	CAT,PPARG,INS,ADIPOQ,TNF,VEGFA
GO:0045765	regulation of angiogenesis	4	1.41	0.00013	STAT3,PPARG,LEP,VEGFA
GO:0051223	regulation of protein transport	5	1.16	0.00013	LEP,INS,GCG,ADIPOQ,TNF
GO:0070372	regulation of ERK1 and ERK2 cascade	4	1.41	0.00013	GCG,ADIPOQ,TNF,VEGFA
GO:0070542	response to fatty acid	3	1.81	0.00013	CAT,PPARG,ADIPOQ
GO:0001666	response to hypoxia	4	1.39	0.00014	CAT,LEP,ADIPOQ,VEGFA
GO:0010628	positive regulation of gene expression	7	0.83	0.00014	STAT3,PPARG,INS,POMC,GCG,TNF,VEGFA
GO:0019217	regulation of fatty acid metabolic process	3	1.79	0.00014	PPARG,INS,ADIPOQ
GO:1903829	positive regulation of cellular protein localization	4	1.39	0.00014	LEP,INS,TNF,VEGFA
GO:0031328	positive regulation of cellular biosynthetic process	7	0.83	0.00015	STAT3,PPARG,INS,POMC,GCG,TNF,VEGFA
GO:0033210	leptin-mediated signaling pathway	2	2.6	0.00015	STAT3,LEP
GO:0019221	cytokine-mediated signaling pathway	5	1.13	0.00016	STAT3,LEP,POMC,TNF,VEGFA
GO:0043900	regulation of multi-organism process	5	1.13	0.00016	PPARG,LEP,INS,POMC,TNF
GO:0045892	negative regulation of transcription, DNA-templated	6	0.96	0.00016	STAT3,PPARG,LEP,ADIPOQ,TNF,VEGFA
GO:0002673	regulation of acute inflammatory response	3	1.76	0.00017	PPARG,INS,TNF
GO:0007631	feeding behavior	3	1.75	0.00017	STAT3,LEP,GCG
GO:0046677	response to antibiotic	4	1.37	0.00017	CAT,STAT3,LEP,ADIPOQ
GO:0051239	regulation of multicellular organismal process	8	0.71	0.00017	STAT3,PPARG,LEP,INS,POMC,ADIPOQ,TNF,VEGFA
GO:0062014	negative regulation of small molecule metabolic process	3	1.76	0.00017	STAT3,INS,ADIPOQ
GO:0032102	negative regulation of response to external stimulus	4	1.36	0.00018	PPARG,LEP,INS,ADIPOQ
GO:0043467	regulation of generation of precursor metabolites and energy	3	1.73	0.00019	STAT3,INS,POMC
GO:0002573	myeloid leukocyte differentiation	3	1.72	0.00021	PPARG,TNF,VEGFA
GO:0002674	negative regulation of acute inflammatory response	2	2.47	0.00023	PPARG,INS
GO:0033138	positive regulation of peptidyl-serine phosphorylation	3	1.71	0.00023	GCG,TNF,VEGFA
GO:0051781	positive regulation of cell division	3	1.7	0.00024	CAT,INS,VEGFA
GO:2000278	regulation of DNA biosynthetic process	3	1.69	0.00024	PPARG,ADIPOQ,VEGFA
GO:0010745	negative regulation of macrophage derived foam cell differentiation	2	2.44	0.00026	PPARG,ADIPOQ
GO:0030162	regulation of proteolysis	5	1.08	0.00026	STAT3,PPARG,INS,TNF,VEGFA
GO:0032147	activation of protein kinase activity	4	1.31	0.00026	LEP,INS,TNF,VEGFA
GO:0045721	negative regulation of gluconeogenesis	2	2.44	0.00026	INS,ADIPOQ
GO:0032680	regulation of tumor necrosis factor production	3	1.67	0.00029	LEP,POMC,ADIPOQ
GO:0046325	negative regulation of glucose import	2	2.41	0.00029	LEP,TNF
GO:0002697	regulation of immune effector process	4	1.29	0.00030	LEP,INS,POMC,TNF
GO:0002792	negative regulation of peptide secretion	3	1.66	0.00030	LEP,INS,TNF
GO:0050728	negative regulation of inflammatory response	3	1.66	0.00030	PPARG,INS,ADIPOQ
GO:0051222	positive regulation of protein transport	4	1.29	0.00030	LEP,INS,GCG,TNF
GO:1903532	positive regulation of secretion by cell	4	1.29	0.00030	LEP,INS,GCG,TNF
GO:0046628	positive regulation of insulin receptor signaling pathway	2	2.38	0.00031	LEP,INS
GO:0032355	response to estradiol	3	1.63	0.00035	CAT,STAT3,LEP
GO:0090335	regulation of brown fat cell differentiation	2	2.35	0.00035	LEP,INS
GO:0000122	negative regulation of transcription by RNA polymerase II	5	1.04	0.00036	STAT3,PPARG,LEP,TNF,VEGFA

GO:0043086	negative regulation of catalytic activity	5	1.04	0.00036	PPARG,INS,ADIPOQ,TNF,VEGFA
GO:0001819	positive regulation of cytokine production	4	1.26	0.00037	LEP,INS,ADIPOQ,TNF
GO:0045807	positive regulation of endocytosis	3	1.62	0.00037	PPARG,TNF,VEGFA
GO:0046887	positive regulation of hormone secretion	3	1.61	0.00038	LEP,INS,GCG
GO:0050901	leukocyte tethering or rolling	2	2.32	0.00038	LEP,TNF
GO:0052548	regulation of endopeptidase activity	4	1.26	0.00038	STAT3,PPARG,TNF,VEGFA
GO:0006091	generation of precursor metabolites and energy	4	1.25	0.00039	CAT,LEP,POMC,ADIPOQ
GO:0030224	monocyte differentiation	2	2.3	0.00040	PPARG,VEGFA
GO:1904706	negative regulation of vascular smooth muscle cell proliferation	2	2.3	0.00040	PPARG,ADIPOQ
GO:1905562	regulation of vascular endothelial cell proliferation	2	2.3	0.00040	STAT3,PPARG
GO:0050777	negative regulation of immune response	3	1.59	0.00041	PPARG,INS,TNF
GO:0033189	response to vitamin A	2	2.27	0.00043	CAT,PPARG
GO:0051092	positive regulation of NF-kappaB transcription factor activity	3	1.57	0.00045	CAT,INS,TNF
GO:0034284	response to monosaccharide	3	1.57	0.00046	CAT,LEP,ADIPOQ
GO:0050708	regulation of protein secretion	4	1.23	0.00046	LEP,INS,GCG,TNF
GO:0002683	negative regulation of immune system process	4	1.22	0.00047	PPARG,INS,ADIPOQ,TNF
GO:0002831	regulation of response to biotic stimulus	4	1.22	0.00047	PPARG,LEP,INS,POMC
GO:0008284	positive regulation of cell population proliferation	5	1.01	0.00047	STAT3,LEP,INS,TNF,VEGFA
GO:0051172	negative regulation of nitrogen compound metabolic process	7	0.73	0.00047	STAT3,PPARG,LEP,INS,ADIPOQ,TNF,VEGFA
GO:0002684	positive regulation of immune system process	5	1.0	0.00048	STAT3,LEP,POMC,TNF,VEGFA
GO:0032874	positive regulation of stress-activated MAPK cascade	3	1.56	0.00049	LEP,TNF,VEGFA
GO:0034114	regulation of heterotypic cell-cell adhesion	2	2.23	0.00049	ADIPOQ,TNF
GO:0055093	response to hyperoxia	2	2.23	0.00049	CAT,PPARG
GO:0001959	regulation of cytokine-mediated signaling pathway	3	1.55	0.00051	PPARG,ADIPOQ,TNF
GO:0032869	cellular response to insulin stimulus	3	1.54	0.00052	PPARG,INS,ADIPOQ
GO:0032098	regulation of appetite	2	2.21	0.00053	LEP,POMC
GO:0050995	negative regulation of lipid catabolic process	2	2.21	0.00053	INS,TNF
GO:0051093	negative regulation of developmental process	5	0.99	0.00053	STAT3,PPARG,LEP,ADIPOQ,TNF
GO:0051897	positive regulation of protein kinase B signaling	3	1.53	0.00055	LEP,INS,TNF
GO:0071295	cellular response to vitamin	2	2.19	0.00056	PPARG,LEP
GO:1900745	positive regulation of p38MAPK cascade	2	2.19	0.00056	LEP,VEGFA
GO:0010950	positive regulation of endopeptidase activity	3	1.53	0.00057	STAT3,PPARG,TNF
GO:0003018	vascular process in circulatory system	3	1.52	0.00059	LEP,INS,VEGFA
GO:0051224	negative regulation of protein transport	3	1.52	0.00059	INS,ADIPOQ,TNF
GO:1903427	negative regulation of reactive oxygen species biosynthetic process	2	2.17	0.00059	STAT3,INS
GO:0060259	regulation of feeding behavior	2	2.15	0.00063	STAT3,INS
GO:0050796	regulation of insulin secretion	3	1.49	0.00068	LEP,GCG,TNF
GO:0002703	regulation of leukocyte mediated immunity	3	1.48	0.00072	LEP,POMC,TNF
GO:0032770	positive regulation of monooxygenase activity	2	2.12	0.00072	INS,TNF
GO:0042594	response to starvation	3	1.48	0.00072	PPARG,ALB,GCG
GO:2001171	positive regulation of ATP biosynthetic process	2	2.12	0.00072	STAT3,INS

GO:0051704	multi-organism process	7	0.69	0.00073	STAT3,PPARG,ALB,LEP,POMC,ADIPOQ,TNF
GO:0031954	positive regulation of protein autophosphorylation	2	2.1	0.00075	INS,VEGFA
GO:0032501	multicellular organismal process	10	0.44	0.00076	CAT,STAT3,PPARG,ALB,LEP,INS,POMC,ADIPOQ,TNF,VEGFA
GO:0071407	cellular response to organic cyclic compound	4	1.15	0.00077	STAT3,PPARG,ADIPOQ,TNF
GO:0010605	negative regulation of macromolecule metabolic process	7	0.69	0.00079	STAT3,PPARG,LEP,INS,ADIPOQ,TNF,VEGFA
GO:0032269	negative regulation of cellular protein metabolic process	5	0.94	0.00079	STAT3,INS,ADIPOQ,TNF,VEGFA
GO:0097237	cellular response to toxic substance	3	1.44	0.00092	CAT,ALB,TNF
GO:0006357	regulation of transcription by RNA polymerase II	7	0.67	0.00093	STAT3,PPARG,LEP,POMC,GCG,TNF,VEGFA
GO:0042755	eating behavior	2	2.05	0.00093	STAT3,LEP
GO:0045923	positive regulation of fatty acid metabolic process	2	2.05	0.00093	PPARG,ADIPOQ
GO:0070374	positive regulation of ERK1 and ERK2 cascade	3	1.43	0.00093	GCG,TNF,VEGFA
GO:0010638	positive regulation of organelle organization	4	1.11	0.0010	INS,GCG,TNF,VEGFA
GO:0031669	cellular response to nutrient levels	3	1.41	0.0010	PPARG,ALB,LEP
GO:0044281	small molecule metabolic process	6	0.78	0.0010	CAT,PPARG,LEP,INS,ADIPOQ,TNF
GO:0070873	regulation of glycogen metabolic process	2	2.02	0.0010	INS,POMC
GO:0010907	positive regulation of glucose metabolic process	2	1.99	0.0011	INS,GCG
GO:0043281	regulation of cysteine-type endopeptidase activity involved in apoptotic process	3	1.41	0.0011	PPARG,TNF,VEGFA
GO:0043901	negative regulation of multi-organism process	3	1.4	0.0011	PPARG,INS,TNF
GO:0001937	negative regulation of endothelial cell proliferation	2	1.97	0.0012	PPARG,TNF
GO:0006110	regulation of glycolytic process	2	1.97	0.0012	STAT3,INS
GO:0007154	cell communication	9	0.49	0.0012	STAT3,PPARG,ALB,LEP,INS,POMC,GCG,TNF,VEGFA
GO:0021700	developmental maturation	3	1.39	0.0012	PPARG,LEP,VEGFA
GO:0030811	regulation of nucleotide catabolic process	2	1.97	0.0012	STAT3,INS
GO:0051130	positive regulation of cellular component organization	5	0.9	0.0012	PPARG,INS,GCG,TNF,VEGFA
GO:0051179	localization	9	0.49	0.0012	CAT,STAT3,PPARG,ALB,LEP,INS,ADIPOQ,TNF,VEGFA
GO:2000279	negative regulation of DNA biosynthetic process	2	1.96	0.0012	PPARG,ADIPOQ
GO:0042110	T cell activation	3	1.38	0.0013	STAT3,LEP,INS
GO:0090184	positive regulation of kidney development	2	1.95	0.0013	ADIPOQ,VEGFA
GO:2000026	regulation of multicellular organismal development	6	0.76	0.0013	STAT3,PPARG,LEP,ADIPOQ,TNF,VEGFA
GO:0007259	receptor signaling pathway via JAK-STAT	2	1.94	0.0014	STAT3,LEP
GO:0030336	negative regulation of cell migration	3	1.35	0.0014	STAT3,PPARG,ADIPOQ
GO:0031330	negative regulation of cellular catabolic process	3	1.36	0.0014	STAT3,LEP,INS
GO:0043065	positive regulation of apoptotic process	4	1.07	0.0014	PPARG,LEP,ADIPOQ,TNF
GO:0080135	regulation of cellular response to stress	4	1.06	0.0014	LEP,INS,TNF,VEGFA
GO:0030155	regulation of cell adhesion	4	1.06	0.0015	LEP,ADIPOQ,TNF,VEGFA
GO:0046326	positive regulation of glucose import	2	1.92	0.0015	INS,ADIPOQ
GO:0050714	positive regulation of protein secretion	3	1.35	0.0015	INS,GCG,TNF
GO:0001754	eye photoreceptor cell differentiation	2	1.89	0.0016	STAT3,VEGFA
GO:0001818	negative regulation of cytokine production	3	1.34	0.0016	POMC,ADIPOQ,TNF
GO:0001822	kidney development	3	1.33	0.0016	CAT,ADIPOQ,VEGFA
GO:0006953	acute-phase response	2	1.9	0.0016	STAT3,INS

GO:0008104	protein localization	6	0.73	0.0016	CAT,STAT3,PPARG,LEP,ADIPOQ,TNF
GO:0044060	regulation of endocrine process	2	1.9	0.0016	LEP,POMC
GO:0045599	negative regulation of fat cell differentiation	2	1.89	0.0016	ADIPOQ,TNF
GO:0045637	regulation of myeloid cell differentiation	3	1.33	0.0016	STAT3,ADIPOQ,TNF
GO:0045927	positive regulation of growth	3	1.33	0.0016	LEP,INS,VEGFA
GO:0048511	rhythmic process	3	1.33	0.0016	PPARG,LEP,ADIPOQ
GO:0048513	animal organ development	7	0.63	0.0016	CAT,STAT3,PPARG,LEP,ADIPOQ,TNF,VEGFA
GO:0050766	positive regulation of phagocytosis	2	1.88	0.0016	PPARG,TNF
GO:0050999	regulation of nitric-oxide synthase activity	2	1.9	0.0016	LEP,INS
GO:0006810	transport	8	0.54	0.0017	CAT,STAT3,PPARG,ALB,LEP,INS,TNF,VEGFA
GO:0010648	negative regulation of cell communication	5	0.85	0.0017	PPARG,LEP,INS,ADIPOQ,TNF
GO:0032720	negative regulation of tumor necrosis factor production	2	1.87	0.0017	POMC,ADIPOQ
GO:0032757	positive regulation of interleukin-8 production	2	1.87	0.0017	ADIPOQ,TNF
GO:0045824	negative regulation of innate immune response	2	1.86	0.0017	PPARG,INS
GO:0008285	negative regulation of cell population proliferation	4	1.03	0.0018	STAT3,PPARG,ADIPOQ,TNF
GO:0023057	negative regulation of signaling	5	0.85	0.0018	PPARG,LEP,INS,ADIPOQ,TNF
GO:0045596	negative regulation of cell differentiation	4	1.02	0.0019	STAT3,PPARG,ADIPOQ,TNF
GO:0001960	negative regulation of cytokine-mediated signaling pathway	2	1.82	0.0020	PPARG,ADIPOQ
GO:0051196	regulation of coenzyme metabolic process	2	1.82	0.0020	STAT3,INS
GO:0060688	regulation of morphogenesis of a branching structure	2	1.83	0.0020	TNF,VEGFA
GO:0006635	fatty acid beta-oxidation	2	1.8	0.0021	LEP,ADIPOQ
GO:0010803	regulation of tumor necrosis factor-mediated signaling pathway	2	1.8	0.0021	ADIPOQ,TNF
GO:0032722	positive regulation of chemokine production	2	1.8	0.0021	ADIPOQ,TNF
GO:0097755	positive regulation of blood vessel diameter	2	1.8	0.0022	LEP,INS
GO:0010876	lipid localization	3	1.26	0.0023	PPARG,LEP,TNF
GO:0045600	positive regulation of fat cell differentiation	2	1.78	0.0023	PPARG,INS
GO:0001910	regulation of leukocyte mediated cytotoxicity	2	1.77	0.0024	LEP,POMC
GO:0042531	positive regulation of tyrosine phosphorylation of STAT protein	2	1.77	0.0024	STAT3,LEP
GO:0046631	alpha-beta T cell activation	2	1.77	0.0024	STAT3,INS
GO:0046888	negative regulation of hormone secretion	2	1.77	0.0024	LEP,ADIPOQ
GO:0050900	leukocyte migration	3	1.26	0.0024	LEP,TNF,VEGFA
GO:0051641	cellular localization	6	0.69	0.0024	CAT,STAT3,ALB,INS,ADIPOQ,TNF
GO:0007166	cell surface receptor signaling pathway	6	0.69	0.0025	STAT3,LEP,INS,POMC,TNF,VEGFA
GO:0031329	regulation of cellular catabolic process	4	0.98	0.0025	STAT3,LEP,INS,TNF
GO:0048638	regulation of developmental growth	3	1.25	0.0025	STAT3,LEP,VEGFA
GO:0051345	positive regulation of hydrolase activity	4	0.98	0.0025	STAT3,PPARG,TNF,VEGFA
GO:0015031	protein transport	5	0.81	0.0026	CAT,STAT3,PPARG,LEP,TNF
GO:0071300	cellular response to retinoic acid	2	1.72	0.0029	PPARG,LEP
GO:0015908	fatty acid transport	2	1.71	0.0030	PPARG,LEP
GO:0035295	tube development	4	0.95	0.0030	CAT,LEP,TNF,VEGFA
GO:0048545	response to steroid hormone	3	1.22	0.0030	PPARG,ADIPOQ,TNF

GO:0097006	regulation of plasma lipoprotein particle levels	2	1.71	0.0030	ALB,ADIPOQ
GO:1900182	positive regulation of protein localization to nucleus	2	1.71	0.0030	LEP,INS
GO:0051128	regulation of cellular component organization	6	0.67	0.0031	PPARG,INS,GCG,ADIPOQ,TNF,VEGFA
GO:0051193	regulation of cofactor metabolic process	2	1.7	0.0031	STAT3,INS
GO:0043405	regulation of MAP kinase activity	3	1.2	0.0032	ADIPOQ,TNF,VEGFA
GO:0046889	positive regulation of lipid biosynthetic process	2	1.69	0.0032	INS,TNF
GO:0048585	negative regulation of response to stimulus	5	0.78	0.0033	PPARG,LEP,INS,ADIPOQ,TNF
GO:0071902	positive regulation of protein serine/threonine kinase activity	3	1.2	0.0033	ADIPOQ,TNF,VEGFA
GO:1900407	regulation of cellular response to oxidative stress	2	1.68	0.0033	INS,TNF
GO:0060964	regulation of gene silencing by miRNA	2	1.66	0.0036	STAT3,PPARG
GO:0035556	intracellular signal transduction	5	0.76	0.0037	STAT3,LEP,INS,GCG,TNF
GO:0051098	regulation of binding	3	1.18	0.0037	PPARG,GCG,ADIPOQ
GO:0007165	signal transduction	8	0.48	0.0038	STAT3,PPARG,LEP,INS,POMC,GCG,TNF,VEGFA
GO:0045088	regulation of innate immune response	3	1.17	0.0038	PPARG,LEP,INS
GO:0022407	regulation of cell-cell adhesion	3	1.16	0.0039	LEP,ADIPOQ,TNF
GO:0033554	cellular response to stress	5	0.76	0.0039	CAT,PPARG,ALB,TNF,VEGFA
GO:0006955	immune response	5	0.76	0.0040	CAT,STAT3,PPARG,POMC,TNF
GO:0008585	female gonad development	2	1.63	0.0040	LEP,VEGFA
GO:0050776	regulation of immune response	4	0.91	0.0040	PPARG,LEP,INS,TNF
GO:0050810	regulation of steroid biosynthetic process	2	1.63	0.0040	LEP,TNF
GO:1901888	regulation of cell junction assembly	2	1.63	0.0040	TNF,VEGFA
GO:0006919	activation of cysteine-type endopeptidase activity involved in apoptotic process	2	1.62	0.0041	PPARG,TNF
GO:0045785	positive regulation of cell adhesion	3	1.15	0.0041	LEP,TNF,VEGFA
GO:0050794	regulation of cellular process	11	0.27	0.0041	CAT,STAT3,PPARG,ALB,LEP,INS,POMC,GCG,ADIPOQ,TNF,VEGFA
GO:0031058	positive regulation of histone modification	2	1.62	0.0042	GCG,VEGFA
GO:0098869	cellular oxidant detoxification	2	1.62	0.0042	CAT,ALB
GO:0043535	regulation of blood vessel endothelial cell migration	2	1.61	0.0043	PPARG,VEGFA
GO:0045321	leukocyte activation	4	0.9	0.0043	CAT,STAT3,LEP,INS
GO:0001938	positive regulation of endothelial cell proliferation	2	1.6	0.0044	STAT3,VEGFA
GO:0031640	killing of cells of other organism	2	1.6	0.0044	ALB,POMC
GO:0044364	disruption of cells of other organism	2	1.6	0.0044	ALB,POMC
GO:0045639	positive regulation of myeloid cell differentiation	2	1.6	0.0044	STAT3,TNF
GO:0072594	establishment of protein localization to organelle	3	1.13	0.0047	CAT,STAT3,TNF
GO:0001558	regulation of cell growth	3	1.12	0.0048	PPARG,INS,VEGFA
GO:2000379	positive regulation of reactive oxygen species metabolic process	2	1.58	0.0048	LEP,TNF
GO:0048608	reproductive structure development	3	1.12	0.0049	PPARG,LEP,VEGFA
GO:0055114	oxidation-reduction process	4	0.88	0.0049	CAT,PPARG,LEP,ADIPOQ
GO:0090277	positive regulation of peptide hormone secretion	2	1.57	0.0049	INS,GCG
GO:0044255	cellular lipid metabolic process	4	0.88	0.0051	CAT,PPARG,LEP,ADIPOQ
GO:0045444	fat cell differentiation	2	1.55	0.0053	PPARG,ADIPOQ
GO:0006606	protein import into nucleus	2	1.55	0.0054	STAT3,TNF

GO:0016192	vesicle-mediated transport	5	0.72	0.0054	CAT,ALB,LEP,INS,VEGFA
GO:0032940	secretion by cell	4	0.87	0.0054	CAT,ALB,LEP,VEGFA
GO:0043254	regulation of protein complex assembly	3	1.1	0.0055	INS,TNF,VEGFA
GO:0002705	positive regulation of leukocyte mediated immunity	2	1.51	0.0062	POMC,TNF
GO:0008203	cholesterol metabolic process	2	1.51	0.0062	CAT,LEP
GO:0055088	lipid homeostasis	2	1.51	0.0063	PPARG,INS
GO:0030335	positive regulation of cell migration	3	1.07	0.0064	INS,TNF,VEGFA
GO:0050709	negative regulation of protein secretion	2	1.5	0.0064	INS,TNF
GO:0002698	negative regulation of immune effector process	2	1.5	0.0065	INS,TNF
GO:0002761	regulation of myeloid leukocyte differentiation	2	1.49	0.0068	ADIPOQ,TNF
GO:0050715	positive regulation of cytokine secretion	2	1.48	0.0069	INS,TNF
GO:0090066	regulation of anatomical structure size	3	1.06	0.0069	LEP,INS,VEGFA
GO:0043123	positive regulation of I-kappaB kinase/NF-kappaB signaling	2	1.46	0.0074	ADIPOQ,TNF
GO:0006954	inflammatory response	3	1.04	0.0075	STAT3,INS,TNF
GO:0071396	cellular response to lipid	3	1.04	0.0076	PPARG,LEP,TNF
GO:0010720	positive regulation of cell development	3	1.04	0.0078	PPARG,ADIPOQ,VEGFA
GO:0002687	positive regulation of leukocyte migration	2	1.45	0.0079	TNF,VEGFA
GO:0002576	platelet degranulation	2	1.44	0.0081	ALB,VEGFA
GO:0007169	transmembrane receptor protein tyrosine kinase signaling pathway	3	1.03	0.0081	STAT3,INS,VEGFA
GO:0032103	positive regulation of response to external stimulus	3	1.03	0.0081	POMC,TNF,VEGFA
GO:1905330	regulation of morphogenesis of an epithelium	2	1.44	0.0081	TNF,VEGFA
GO:0030217	T cell differentiation	2	1.43	0.0083	STAT3,LEP
GO:0002706	regulation of lymphocyte mediated immunity	2	1.43	0.0085	LEP,TNF
GO:0044057	regulation of system process	3	1.01	0.0088	LEP,POMC,ADIPOQ
GO:0007623	circadian rhythm	2	1.41	0.0089	LEP,ADIPOQ
GO:0030856	regulation of epithelial cell differentiation	2	1.41	0.0089	ADIPOQ,TNF
GO:0051726	regulation of cell cycle	4	0.8	0.0089	STAT3,LEP,INS,TNF
GO:0051384	response to glucocorticoid	2	1.41	0.0090	ADIPOQ,TNF
GO:0009968	negative regulation of signal transduction	4	0.79	0.0097	PPARG,INS,ADIPOQ,TNF
GO:0001890	placenta development	2	1.39	0.0098	PPARG,LEP
GO:0048469	cell maturation	2	1.39	0.0098	PPARG,VEGFA
GO:0051707	response to other organism	4	0.78	0.0100	PPARG,POMC,ADIPOQ,TNF
GO:0051235	maintenance of location	2	1.38	0.0103	ALB,TNF
GO:0014074	response to purine-containing compound	2	1.37	0.0104	PPARG,ADIPOQ
GO:0045936	negative regulation of phosphate metabolic process	3	0.98	0.0107	STAT3,ADIPOQ,TNF
GO:0072659	protein localization to plasma membrane	2	1.36	0.0109	ADIPOQ,TNF
GO:0030307	positive regulation of cell growth	2	1.35	0.0113	INS,VEGFA
GO:0006952	defense response	4	0.76	0.0117	STAT3,PPARG,INS,TNF
GO:0016310	phosphorylation	4	0.76	0.0117	STAT3,LEP,INS,TNF
GO:0045766	positive regulation of angiogenesis	2	1.34	0.0117	STAT3,VEGFA
GO:0071453	cellular response to oxygen levels	2	1.34	0.0119	PPARG,VEGFA

GO:0007186	G protein-coupled receptor signaling pathway	4	0.76	0.0120	PPARG,INS,POMC,GCG
GO:0048639	positive regulation of developmental growth	2	1.33	0.0120	LEP,VEGFA
GO:0051099	positive regulation of binding	2	1.32	0.0129	PPARG,GCG
GO:0030522	intracellular receptor signaling pathway	2	1.31	0.0130	STAT3,PPARG
GO:0051129	negative regulation of cellular component organization	3	0.93	0.0143	INS,ADIPOQ,TNF
GO:0022414	reproductive process	4	0.72	0.0156	STAT3,PPARG,LEP,VEGFA
GO:0034613	cellular protein localization	4	0.72	0.0162	CAT,STAT3,ADIPOQ,TNF
GO:0008283	cell population proliferation	3	0.9	0.0169	STAT3,GCG,TNF
GO:0033157	regulation of intracellular protein transport	2	1.25	0.0169	LEP,ADIPOQ
GO:1903039	positive regulation of leukocyte cell-cell adhesion	2	1.25	0.0170	LEP,TNF
GO:0043903	regulation of symbiosis, encompassing mutualism through parasitism	2	1.24	0.0171	POMC,TNF
GO:0046907	intracellular transport	4	0.71	0.0171	CAT,STAT3,INS,TNF
GO:2000027	regulation of animal organ morphogenesis	2	1.24	0.0177	TNF,VEGFA
GO:0045055	regulated exocytosis	3	0.89	0.0178	CAT,ALB,VEGFA
GO:0048699	generation of neurons	4	0.7	0.0183	STAT3,PPARG,LEP,VEGFA
GO:0043393	regulation of protein binding	2	1.22	0.0185	GCG,ADIPOQ
GO:0030154	cell differentiation	6	0.49	0.0187	STAT3,PPARG,LEP,ADIPOQ,TNF,VEGFA
GO:0015980	energy derivation by oxidation of organic compounds	2	1.21	0.0191	CAT,LEP
GO:0034612	response to tumor necrosis factor	2	1.21	0.0191	ADIPOQ,TNF
GO:2001234	negative regulation of apoptotic signaling pathway	2	1.21	0.0192	INS,TNF
GO:0044419	interspecies interaction between organisms	3	0.87	0.0200	STAT3,ALB,POMC
GO:0050767	regulation of neurogenesis	3	0.86	0.0204	STAT3,PPARG,VEGFA
GO:0045165	cell fate commitment	2	1.19	0.0212	STAT3,PPARG
GO:0045926	negative regulation of growth	2	1.18	0.0220	PPARG,TNF
GO:0031334	positive regulation of protein complex assembly	2	1.17	0.0229	TNF,VEGFA
GO:0032409	regulation of transporter activity	2	1.16	0.0238	PPARG,INS
GO:0006959	humoral immune response	2	1.15	0.0248	POMC,TNF
GO:0043270	positive regulation of ion transport	2	1.15	0.0248	LEP,GCG
GO:0007568	aging	2	1.14	0.0252	CAT,STAT3
GO:0072359	circulatory system development	3	0.82	0.0261	PPARG,LEP,VEGFA
GO:0043406	positive regulation of MAP kinase activity	2	1.13	0.0267	TNF,VEGFA
GO:0009888	tissue development	4	0.64	0.0279	CAT,PPARG,LEP,VEGFA
GO:0006886	intracellular protein transport	3	0.81	0.0283	CAT,STAT3,TNF
GO:0016043	cellular component organization	7	0.38	0.0294	CAT,STAT3,ALB,INS,ADIPOQ,TNF,VEGFA
GO:0048871	multicellular organismal homeostasis	2	1.1	0.0300	STAT3,VEGFA
GO:0009887	animal organ morphogenesis	3	0.79	0.0308	STAT3,TNF,VEGFA
GO:0001525	angiogenesis	2	1.08	0.0327	LEP,VEGFA
GO:0035690	cellular response to drug	2	1.06	0.0354	ADIPOQ,TNF
GO:0051348	negative regulation of transferase activity	2	1.06	0.0354	PPARG,ADIPOQ
GO:0051260	protein homooligomerization	2	1.06	0.0356	CAT,ADIPOQ
GO:0006468	protein phosphorylation	3	0.76	0.0362	LEP,INS,TNF

GO:0050804	modulation of chemical synaptic transmission	2	1.05	0.0363	INS,ADIPOQ
GO:0043933	protein-containing complex subunit organization	4	0.6	0.0364	CAT,ALB,ADIPOQ,TNF
GO:0000165	MAPK cascade	2	1.04	0.0376	INS,TNF
GO:0030182	neuron differentiation	3	0.75	0.0377	STAT3,LEP,VEGFA
GO:0006417	regulation of translation	2	1.04	0.0384	STAT3,TNF
GO:0044237	cellular metabolic process	9	0.26	0.0402	CAT,STAT3,PPARG,ALB,LEP,INS,POMC,ADIPOQ,TNF
GO:0043062	extracellular structure organization	2	1.02	0.0408	ALB,TNF
GO:0031331	positive regulation of cellular catabolic process	2	1.02	0.0416	INS,TNF
GO:0031346	positive regulation of cell projection organization	2	1.02	0.0416	INS,VEGFA
GO:0045861	negative regulation of proteolysis	2	1.01	0.0428	INS,VEGFA
GO:0019538	protein metabolic process	6	0.41	0.0443	CAT,PPARG,ALB,LEP,INS,TNF
GO:0031349	positive regulation of defense response	2	0.99	0.0464	POMC,TNF
GO:0042176	regulation of protein catabolic process	2	0.99	0.0470	INS,TNF
GO:0006979	response to oxidative stress	2	0.98	0.0482	CAT,ADIPOQ

Table S3. Functional enrichment analyses results for the 12 hub-bottleneck genes.
GO Terms: Molecular Function

#term ID	term description	gene count	strength	FDR	matching proteins in your network (labels)
GO:0005102	signaling receptor binding	10	1.07	1.20e-08	CAT,STAT3,PPARG,LEP,INS,POMC,GCG,ADIPOQ,TNF,VEGFA
GO:0048018	receptor ligand activity	7	1.43	9.24e-08	LEP,INS,POMC,GCG,ADIPOQ,TNF,VEGFA
GO:0005179	hormone activity	5	1.86	1.84e-07	LEP,INS,POMC,GCG,ADIPOQ
GO:0042802	identical protein binding	9	0.96	5.30e-07	CAT,STAT3,PPARG,ALB,INS,GCG,ADIPOQ,TNF,VEGFA
GO:0005515	protein binding	11	0.47	0.00016	CAT,STAT3,PPARG,ALB,LEP,INS,POMC,GCG,ADIPOQ,TNF,VEGFA
GO:0005504	fatty acid binding	2	2.12	0.0021	PPARG,ALB
GO:0031406	carboxylic acid binding	3	1.46	0.0021	PPARG,ALB,ADIPOQ
GO:0051427	hormone receptor binding	3	1.49	0.0021	STAT3,PPARG,LEP
GO:0005125	cytokine activity	3	1.39	0.0026	ADIPOQ,TNF,VEGFA
GO:0001664	G protein-coupled receptor binding	3	1.29	0.0043	STAT3,POMC,GCG
GO:0004879	nuclear receptor activity	2	1.85	0.0043	STAT3,PPARG
GO:0005126	cytokine receptor binding	3	1.29	0.0043	STAT3,TNF,VEGFA
GO:0046983	protein dimerization activity	5	0.83	0.0043	CAT,STAT3,PPARG,ADIPOQ,VEGFA
GO:0042803	protein homodimerization activity	4	0.93	0.0067	CAT,STAT3,ADIPOQ,VEGFA
GO:0016209	antioxidant activity	2	1.65	0.0068	CAT,ALB
GO:0035258	steroid hormone receptor binding	2	1.6	0.0083	STAT3,PPARG
GO:0016922	nuclear receptor binding	2	1.51	0.0119	STAT3,PPARG
GO:0019903	protein phosphatase binding	2	1.46	0.0139	STAT3,PPARG
GO:0002020	protease binding	2	1.42	0.0159	INS,TNF
GO:0019899	enzyme binding	5	0.61	0.0246	CAT,STAT3,PPARG,INS,TNF
GO:0000976	transcription regulatory region sequence-specific DNA binding	3	0.81	0.0485	STAT3,PPARG,TNF
GO:0050662	coenzyme binding	2	1.11	0.0485	CAT,ALB

Table S3. Functional enrichment analyses results for the 12 hub-bottleneck genes.
GO Terms: Celular Component

#term ID	term description	gene count	strength	FDR	matching proteins in your network (labels)
GO:0005615	extracellular space	8	1.1	8.62e-07	ALB,LEP,INS,POMC,GCG,ADIPOQ,TNF,VEGFA
GO:0034774	secretory granule lumen	6	1.52	8.62e-07	CAT,ALB,INS,POMC,GCG,VEGFA
GO:0005576	extracellular region	9	0.81	7.51e-06	CAT,ALB,LEP,INS,POMC,GCG,ADIPOQ,TNF,VEGFA
GO:0031410	cytoplasmic vesicle	7	0.75	0.00063	CAT,ALB,INS,POMC,GCG,TNF,VEGFA
GO:0005782	peroxisomal matrix	2	1.83	0.0035	CAT,POMC
GO:0005788	endoplasmic reticulum lumen	3	1.25	0.0036	ALB,INS,GCG
GO:0012505	endomembrane system	8	0.52	0.0036	CAT,ALB,INS,POMC,GCG,ADIPOQ,TNF,VEGFA
GO:0031093	platelet alpha granule lumen	2	1.72	0.0042	ALB,VEGFA
GO:0005783	endoplasmic reticulum	5	0.69	0.0096	CAT,ALB,INS,GCG,ADIPOQ
GO:0070013	intracellular organelle lumen	8	0.44	0.0096	CAT,STAT3,PPARG,ALB,INS,POMC,GCG,VEGFA
GO:0005737	cytoplasm	11	0.24	0.0100	CAT,STAT3,PPARG,ALB,LEP,INS,POMC,GCG,ADIPOQ,TNF,VEGFA
GO:0090575	RNA polymerase II transcription factor complex	2	1.41	0.0105	STAT3,PPARG
GO:0009986	cell surface	3	0.89	0.0219	ADIPOQ,TNF,VEGFA

Table S4. KEGG pathways associated with the 4 functional clusters.
Cluster 1

#term ID	term description	gene count	strength	FDR	matching proteins in your network (labels)
hsa04068	FoxO signaling pathway	9	1.63	1.20e-10	SIRT1,TGFB1,CAT,STAT3,IGF1,IRS1,INS,IL10,SOD2
hsa04211	Longevity regulating pathway	8	1.74	1.66e-10	SIRT1,CAT,PPARG,IGF1,IRS1,INS,ADIPOQ,SOD2
hsa04152	AMPK signaling pathway	8	1.61	1.15e-09	SIRT1,PPARG,IGF1,IRS1,LEP,LEPR,INS,ADIPOQ
hsa04920	Adipocytokine signaling pathway	7	1.79	1.15e-09	STAT3,IRS1,LEP,LEPR,PPARA,ADIPOQ,TNF
hsa04932	Non-alcoholic fatty liver disease (NAFLD)	8	1.52	3.57e-09	TGFB1,IRS1,LEP,LEPR,INS,PPARA,ADIPOQ,TNF
hsa04213	Longevity regulating pathway - multiple species	6	1.78	2.52e-08	SIRT1,CAT,IGF1,IRS1,INS,SOD2
hsa04933	AGE-RAGE signaling pathway in diabetic complicati	6	1.57	3.15e-07	MMP2,TGFB1,SERPINE1,STAT3,TNF,VEGFA
hsa05205	Proteoglycans in cancer	7	1.34	5.31e-07	MMP2,TGFB1,STAT3,IGF1,MMP9,TNF,VEGFA
hsa05321	Inflammatory bowel disease (IBD)	5	1.69	1.18e-06	TGFB1,STAT3,IL17A,TNF,IL10
hsa03320	PPAR signaling pathway	5	1.63	2.14e-06	UCP1,PPARG,LPL,PPARA,ADIPOQ
hsa04060	Cytokine-cytokine receptor interaction	7	1.21	2.80e-06	TGFB1,LEP,LEPR,IL17A,TNF,IL10,VEGFA
hsa04066	HIF-1 signaling pathway	5	1.49	7.69e-06	SERPINE1,STAT3,IGF1,INS,VEGFA
hsa04931	Insulin resistance	5	1.46	1.08e-05	STAT3,IRS1,INS,PPARA,TNF
hsa04930	Type II diabetes mellitus	4	1.73	1.29e-05	IRS1,INS,ADIPOQ,TNF
hsa05206	MicroRNAs in cancer	5	1.31	4.48e-05	SIRT1,STAT3,IRS1,MMP9,VEGFA
hsa04010	MAPK signaling pathway	6	1.1	6.86e-05	TGFB1,IGF1,INS,TNF,BDNF,VEGFA
hsa05323	Rheumatoid arthritis	4	1.46	0.00010	TGFB1,IL17A,TNF,VEGFA
hsa05200	Pathways in cancer	7	0.92	0.00014	MMP2,TGFB1,STAT3,PPARG,IGF1,MMP9,VEGFA
hsa05142	Chagas disease (American trypanosomiasis)	4	1.38	0.00018	TGFB1,SERPINE1,TNF,IL10
hsa05145	Toxoplasmosis	4	1.35	0.00023	TGFB1,STAT3,TNF,IL10
hsa04960	Aldosterone-regulated sodium reabsorption	3	1.7	0.00025	IGF1,IRS1,INS
hsa05219	Bladder cancer	3	1.65	0.00032	MMP2,MMP9,VEGFA
hsa04926	Relaxin signaling pathway	4	1.27	0.00040	MMP2,TGFB1,MMP9,VEGFA
hsa05144	Malaria	3	1.59	0.00041	TGFB1,TNF,IL10
hsa05418	Fluid shear stress and atherosclerosis	4	1.26	0.00041	MMP2,MMP9,TNF,VEGFA
hsa05161	Hepatitis B	4	1.24	0.00049	TGFB1,STAT3,MMP9,TNF
hsa04150	mTOR signaling pathway	4	1.22	0.00055	IGF1,IRS1,INS,TNF
hsa04630	Jak-STAT signaling pathway	4	1.18	0.00071	STAT3,LEP,LEPR,IL10
hsa05140	Leishmaniasis	3	1.42	0.0011	TGFB1,TNF,IL10
hsa04151	PI3K-Akt signaling pathway	5	0.94	0.0012	IGF1,IRS1,INS,BDNF,VEGFA
hsa05212	Pancreatic cancer	3	1.39	0.0012	TGFB1,STAT3,VEGFA

hsa01521	EGFR tyrosine kinase inhibitor resistance	3	1.37	0.0013	STAT3,IGF1,VEGFA
hsa05016	Huntington's disease	4	1.1	0.0013	UCP1,PPARG,BDNF,SOD2
hsa05410	Hypertrophic cardiomyopathy (HCM)	3	1.35	0.0014	TGFB1,IGF1,TNF
hsa05414	Dilated cardiomyopathy (DCM)	3	1.32	0.0018	TGFB1,IGF1,TNF
hsa04657	IL-17 signaling pathway	3	1.3	0.0019	IL17A,MMP9,TNF
hsa01522	Endocrine resistance	3	1.29	0.0020	MMP2,IGF1,MMP9
hsa04014	Ras signaling pathway	4	1.03	0.0020	IGF1,INS,BDNF,VEGFA
hsa05146	Amoebiasis	3	1.29	0.0020	TGFB1,TNF,IL10
hsa05215	Prostate cancer	3	1.28	0.0020	IGF1,MMP9,INS
hsa04659	Th17 cell differentiation	3	1.25	0.0022	TGFB1,STAT3,IL17A
hsa04922	Glucagon signaling pathway	3	1.26	0.0022	SIRT1,PPARA,GCG
hsa05310	Asthma	2	1.64	0.0036	TNF,IL10
hsa04380	Osteoclast differentiation	3	1.17	0.0037	TGFB1,PPARG,TNF
hsa05160	Hepatitis C	3	1.15	0.0042	STAT3,PPARA,TNF
hsa05143	African trypanosomiasis	2	1.56	0.0048	TNF,IL10
hsa05330	Allograft rejection	2	1.54	0.0050	TNF,IL10
hsa04218	Cellular senescence	3	1.07	0.0063	SIRT1,TGFB1,SERPINE1
hsa04940	Type I diabetes mellitus	2	1.49	0.0063	INS,TNF
hsa04672	Intestinal immune network for IgA production	2	1.44	0.0072	TGFB1,IL10
hsa05010	Alzheimer's disease	3	1.04	0.0074	APOE,LPL,TNF
hsa05202	Transcriptional misregulation in cancer	3	1.04	0.0074	PPARG,IGF1,MMP9
hsa05152	Tuberculosis	3	1.03	0.0076	TGFB1,TNF,IL10
hsa04979	Cholesterol metabolism	2	1.41	0.0079	APOE,LPL
hsa04913	Ovarian steroidogenesis	2	1.4	0.0080	IGF1,INS
hsa05014	Amyotrophic lateral sclerosis (ALS)	2	1.39	0.0082	CAT,TNF
hsa04923	Regulation of lipolysis in adipocytes	2	1.36	0.0090	IRS1,INS
hsa04024	cAMP signaling pathway	3	0.97	0.0099	GHRL,PPARA,BDNF
hsa04015	Rap1 signaling pathway	3	0.96	0.0108	IGF1,INS,VEGFA
hsa04115	p53 signaling pathway	2	1.25	0.0137	SERPINE1,IGF1
hsa04917	Prolactin signaling pathway	2	1.25	0.0137	STAT3,INS
hsa05211	Renal cell carcinoma	2	1.25	0.0137	TGFB1,VEGFA
hsa04714	Thermogenesis	3	0.91	0.0139	UCP1,PPARG,GCG
hsa05133	Pertussis	2	1.22	0.0150	TNF,IL10
hsa04146	Peroxisome	2	1.18	0.0176	CAT,SOD2
hsa04350	TGF-beta signaling pathway	2	1.17	0.0181	TGFB1,TNF

hsa04911	Insulin secretion	2	1.16	0.0182	INS,GCG
hsa04914	Progesterone-mediated oocyte maturation	2	1.11	0.0222	IGF1,INS
hsa05322	Systemic lupus erythematosus	2	1.11	0.0222	TNF,IL10
hsa04660	T cell receptor signaling pathway	2	1.09	0.0238	TNF,IL10
hsa04668	TNF signaling pathway	2	1.05	0.0276	MMP9,TNF
hsa04670	Leukocyte transendothelial migration	2	1.04	0.0291	MMP2,MMP9
hsa01200	Carbon metabolism	2	1.02	0.0306	CAT,GPT
hsa04114	Oocyte meiosis	2	1.02	0.0306	IGF1,INS
hsa04722	Neurotrophin signaling pathway	2	1.02	0.0306	IRS1,BDNF
hsa04140	Autophagy - animal	2	0.99	0.0338	IRS1,INS
hsa04371	Apelin signaling pathway	2	0.96	0.0374	SERPINE1,UCP1
hsa04910	Insulin signaling pathway	2	0.96	0.0374	IRS1,INS
hsa04915	Estrogen signaling pathway	2	0.96	0.0374	MMP2,MMP9
hsa04550	Signaling pathways regulating pluripotency of stem c	2	0.95	0.0385	STAT3,IGF1
hsa04390	Hippo signaling pathway	2	0.91	0.0454	TGFB1,SERPINE1
hsa04217	Necroptosis	2	0.9	0.0465	STAT3,TNF
hsa04022	cGMP-PKG signaling pathway	2	0.88	0.0487	IRS1,INS

Table S4. KEGG pathways associated with the 4 functional clusters.
Cluster 2

#term ID	term description	gene count	strength	FDR	matching proteins in your network (labels)
hsa03320	PPAR signaling pathway	5	1.7	5.52e-06	APOA1,FABP4,PLIN1,PCK1,SCD
hsa04080	Neuroactive ligand-receptor interaction	7	1.27	5.52e-06	DRD4,MTNR1B,MCHR2,NPY2R,DRD2,CNR1,CNR2
hsa04015	Rap1 signaling pathway	6	1.33	9.99e-06	ADCY3,DRD2,CNR1,ANGPT1,PGF,FGF21
hsa04151	PI3K-Akt signaling pathway	6	1.1	0.00016	GNB3,NOS3,PCK1,ANGPT1,PGF,FGF21
hsa04371	Apelin signaling pathway	4	1.34	0.00063	GNB3,ADCY3,NOS3,PLIN1
hsa04923	Regulation of lipolysis in adipocytes	3	1.61	0.00091	FABP4,ADCY3,PLIN1
hsa04014	Ras signaling pathway	4	1.1	0.0035	GNB3,ANGPT1,PGF,FGF21
hsa04713	Circadian entrainment	3	1.37	0.0035	GNB3,MTNR1B,ADCY3
hsa04714	Thermogenesis	4	1.1	0.0035	ADCY3,PLIN1,CNR1,FGF21
hsa04728	Dopaminergic synapse	3	1.23	0.0068	DRD4,GNB3,DRD2
hsa04926	Relaxin signaling pathway	3	1.22	0.0068	GNB3,ADCY3,NOS3
hsa04723	Retrograde endocannabinoid signaling	3	1.17	0.0085	GNB3,ADCY3,CNR1
hsa05200	Pathways in cancer	4	0.75	0.0360	GNB3,ADCY3,PGF,FGF21
hsa04010	MAPK signaling pathway	3	0.87	0.0423	ANGPT1,PGF,FGF21
hsa04066	HIF-1 signaling pathway	2	1.17	0.0423	NOS3,ANGPT1
hsa04540	Gap junction	2	1.22	0.0423	ADCY3,DRD2
hsa04727	GABAergic synapse	2	1.22	0.0423	GNB3,ADCY3
hsa05032	Morphine addiction	2	1.2	0.0423	GNB3,ADCY3
hsa04931	Insulin resistance	2	1.13	0.0460	NOS3,PCK1
hsa04724	Glutamatergic synapse	2	1.11	0.0469	GNB3,ADCY3
hsa04725	Cholinergic synapse	2	1.12	0.0469	GNB3,ADCY3
hsa04152	AMPK signaling pathway	2	1.08	0.0493	PCK1,SCD
hsa04611	Platelet activation	2	1.07	0.0494	ADCY3,NOS3

Table S4. KEGG pathways associated with the 4 functional clusters.
Cluster 3

#term ID	term description	gene count	strength	FDR	matching proteins in your network (labels)
hsa04080	Neuroactive ligand-receptor interaction	2	1.38	0.0113	MC3R,MC4R

Table S4. KEGG pathways associated with the 4 functional clusters.
Cluster 4

#term ID	term description	gene count	strength	FDR	matching proteins in your network (labels)
hsa04080	Neuroactive ligand-receptor interaction	4	1.42	0.00032	GH1,ADRB3,CALCR,GIPR

Table S5. GO processes associated with the 4 functional clusters.

BP - Cluster 1				
#Term ID	**term description**	**gene count**	**Strength**	**FDR**
GO:0010033	response to organic substance	28	0.78	1.82e-16
GO:1901700	response to oxygen-containing compound	23	0.99	1.88e-16
GO:0070887	cellular response to chemical stimulus	27	0.79	5.18e-16
GO:0042221	response to chemical	30	0.65	1.68e-15
GO:0071310	cellular response to organic substance	25	0.84	2.43e-15
GO:0009719	response to endogenous stimulus	21	0.98	1.34e-14
GO:0060548	negative regulation of cell death	19	1.09	1.34e-14
GO:0010941	regulation of cell death	22	0.91	2.47e-14
GO:0032879	regulation of localization	25	0.78	2.47e-14
GO:0062012	regulation of small molecule metabolic process	14	1.41	2.47e-14
GO:1901652	response to peptide	15	1.33	2.47e-14
GO:0009725	response to hormone	18	1.11	2.65e-14
GO:0043066	negative regulation of apoptotic process	18	1.11	2.71e-14
GO:0010243	response to organonitrogen compound	18	1.1	3.32e-14
GO:1905952	regulation of lipid localization	11	1.72	3.63e-14
GO:0051049	regulation of transport	22	0.89	3.74e-14
GO:0051050	positive regulation of transport	18	1.09	3.74e-14
GO:0042981	regulation of apoptotic process	21	0.93	3.82e-14
GO:0043434	response to peptide hormone	14	1.37	3.82e-14
GO:1901701	cellular response to oxygen-containing compound	18	1.09	3.82e-14
GO:0006109	regulation of carbohydrate metabolic process	11	1.63	2.00e-13
GO:0010469	regulation of signaling receptor activity	15	1.2	5.81e-13
GO:0032870	cellular response to hormone stimulus	15	1.2	6.80e-13
GO:0051094	positive regulation of developmental process	19	0.96	6.80e-13
GO:0032880	regulation of protein localization	17	1.06	7.00e-13
GO:0048583	regulation of response to stimulus	27	0.63	8.62e-13
GO:0071495	cellular response to endogenous stimulus	18	1.0	8.91e-13
GO:0051240	positive regulation of multicellular organismal process	20	0.9	9.43e-13

GO:0051223	regulation of protein transport	15	1.17	1.33e-12
GO:0010675	regulation of cellular carbohydrate metabolic process	10	1.66	1.64e-12
GO:0043255	regulation of carbohydrate biosynthetic process	9	1.82	1.73e-12
GO:1904705	regulation of vascular smooth muscle cell proliferation	8	2.0	2.62e-12
GO:0032868	response to insulin	11	1.5	2.89e-12
GO:0006950	response to stress	25	0.67	3.11e-12
GO:1903530	regulation of secretion by cell	15	1.14	3.20e-12
GO:0065009	regulation of molecular function	25	0.66	4.38e-12
GO:0050708	regulation of protein secretion	13	1.27	4.63e-12
GO:0010906	regulation of glucose metabolic process	9	1.74	6.58e-12
GO:0050727	regulation of inflammatory response	12	1.34	9.81e-12
GO:0031667	response to nutrient levels	13	1.24	1.05e-11
GO:0048522	positive regulation of cellular process	28	0.54	1.17e-11
GO:0065008	regulation of biological quality	25	0.63	1.85e-11
GO:0009605	response to external stimulus	21	0.78	1.89e-11
GO:0001936	regulation of endothelial cell proliferation	9	1.65	2.95e-11
GO:0048660	regulation of smooth muscle cell proliferation	9	1.64	3.81e-11
GO:0062013	positive regulation of small molecule metabolic process	9	1.63	4.57e-11
GO:0010646	regulation of cell communication	24	0.64	5.18e-11
GO:0023051	regulation of signaling	24	0.64	6.34e-11
GO:0010883	regulation of lipid storage	7	2.01	6.79e-11
GO:0009628	response to abiotic stimulus	16	0.97	7.59e-11
GO:0009966	regulation of signal transduction	23	0.67	8.84e-11
GO:0048584	positive regulation of response to stimulus	20	0.77	9.41e-11
GO:0050678	regulation of epithelial cell proliferation	11	1.33	9.54e-11
GO:0045597	positive regulation of cell differentiation	15	1.0	1.46e-10
GO:0050793	regulation of developmental process	21	0.73	1.46e-10
GO:0062014	negative regulation of small molecule metabolic process	8	1.72	1.69e-10
GO:0051239	regulation of multicellular organismal process	22	0.68	1.81e-10
GO:0042127	regulation of cell population proliferation	18	0.84	1.93e-10
GO:0032101	regulation of response to external stimulus	15	0.98	2.74e-10

GO:0051716	cellular response to stimulus	29	0.46	2.74e-10
GO:0032368	regulation of lipid transport	8	1.69	2.93e-10
GO:0042593	glucose homeostasis	9	1.51	3.50e-10
GO:0050896	response to stimulus	31	0.38	3.93e-10
GO:1903532	positive regulation of secretion by cell	11	1.27	4.09e-10
GO:0048878	chemical homeostasis	15	0.96	4.43e-10
GO:0045595	regulation of cell differentiation	18	0.81	4.73e-10
GO:0044093	positive regulation of molecular function	18	0.81	5.54e-10
GO:0050731	positive regulation of peptidyl-tyrosine phosphorylation	9	1.49	5.54e-10
GO:0019221	cytokine-mediated signaling pathway	13	1.08	5.58e-10
GO:0040008	regulation of growth	13	1.08	6.40e-10
GO:0048585	negative regulation of response to stimulus	17	0.85	6.93e-10
GO:0031347	regulation of defense response	13	1.07	7.92e-10
GO:0031325	positive regulation of cellular metabolic process	22	0.64	9.35e-10
GO:0010604	positive regulation of macromolecule metabolic process	22	0.64	1.06e-09
GO:0008284	positive regulation of cell population proliferation	14	0.99	1.17e-09
GO:0080134	regulation of response to stress	16	0.88	1.18e-09
GO:0040012	regulation of locomotion	14	0.99	1.19e-09
GO:0033674	positive regulation of kinase activity	12	1.12	1.36e-09
GO:0051093	negative regulation of developmental process	14	0.97	1.78e-09
GO:0048523	negative regulation of cellular process	25	0.54	1.82e-09
GO:0048519	negative regulation of biological process	26	0.51	1.83e-09
GO:0006111	regulation of gluconeogenesis	6	2.01	1.93e-09
GO:0002521	leukocyte differentiation	10	1.29	1.97e-09
GO:0045834	positive regulation of lipid metabolic process	8	1.56	1.97e-09
GO:0070482	response to oxygen levels	10	1.28	2.46e-09
GO:0030334	regulation of cell migration	13	1.02	2.50e-09
GO:0051051	negative regulation of transport	11	1.17	2.82e-09
GO:1905953	negative regulation of lipid localization	6	1.96	3.20e-09
GO:0051338	regulation of transferase activity	14	0.95	3.36e-09
GO:0050790	regulation of catalytic activity	19	0.71	3.52e-09

GO:0009636	response to toxic substance	11	1.16	4.04e-09
GO:0042327	positive regulation of phosphorylation	14	0.94	4.27e-09
GO:0050714	positive regulation of protein secretion	9	1.36	4.73e-09
GO:0042325	regulation of phosphorylation	16	0.82	5.53e-09
GO:0071417	cellular response to organonitrogen compound	11	1.14	5.53e-09
GO:0051098	regulation of binding	10	1.23	5.69e-09
GO:0010888	negative regulation of lipid storage	5	2.25	5.95e-09
GO:0051222	positive regulation of protein transport	10	1.22	7.08e-09
GO:0007568	aging	9	1.33	7.39e-09
GO:0010648	negative regulation of cell communication	15	0.86	7.39e-09
GO:0034097	response to cytokine	14	0.92	7.39e-09
GO:0023057	negative regulation of signaling	15	0.86	7.45e-09
GO:0008015	blood circulation	10	1.21	8.27e-09
GO:0019216	regulation of lipid metabolic process	10	1.21	8.27e-09
GO:0045912	negative regulation of carbohydrate metabolic process	6	1.87	8.27e-09
GO:0046883	regulation of hormone secretion	9	1.32	8.43e-09
GO:2000377	regulation of reactive oxygen species metabolic process	8	1.46	8.43e-09
GO:0043549	regulation of kinase activity	13	0.97	8.46e-09
GO:0045860	positive regulation of protein kinase activity	11	1.11	9.20e-09
GO:1903531	negative regulation of secretion by cell	8	1.44	1.17e-08
GO:2000026	regulation of multicellular organismal development	17	0.74	1.66e-08
GO:0001666	response to hypoxia	9	1.28	1.79e-08
GO:0051704	multi-organism process	19	0.66	1.83e-08
GO:1901653	cellular response to peptide	9	1.28	1.83e-08
GO:0010647	positive regulation of cell communication	16	0.78	2.15e-08
GO:0023056	positive regulation of signaling	16	0.78	2.25e-08
GO:0043085	positive regulation of catalytic activity	15	0.82	2.25e-08
GO:0050728	negative regulation of inflammatory response	7	1.56	2.25e-08
GO:0002792	negative regulation of peptide secretion	7	1.56	2.32e-08
GO:0001934	positive regulation of protein phosphorylation	13	0.93	2.50e-08
GO:0060259	regulation of feeding behavior	5	2.09	2.50e-08

GO:0045598	regulation of fat cell differentiation	7	1.55	2.53e-08
GO:1901342	regulation of vasculature development	9	1.26	2.63e-08
GO:0051173	positive regulation of nitrogen compound metabolic process	20	0.62	2.76e-08
GO:0032102	negative regulation of response to external stimulus	9	1.25	2.94e-08
GO:1902533	positive regulation of intracellular signal transduction	13	0.92	2.95e-08
GO:0022603	regulation of anatomical structure morphogenesis	13	0.92	3.01e-08
GO:0060341	regulation of cellular localization	12	0.98	3.05e-08
GO:0046324	regulation of glucose import	6	1.74	3.31e-08
GO:0007154	cell communication	25	0.47	3.89e-08
GO:0050795	regulation of behavior	6	1.73	3.89e-08
GO:0001101	response to acid chemical	9	1.23	3.99e-08
GO:0045859	regulation of protein kinase activity	12	0.97	4.05e-08
GO:0031326	regulation of cellular biosynthetic process	23	0.52	4.17e-08
GO:0010743	regulation of macrophage derived foam cell differentiation	5	2.02	4.29e-08
GO:0001817	regulation of cytokine production	11	1.04	4.30e-08
GO:0009967	positive regulation of signal transduction	15	0.79	5.51e-08
GO:1902531	regulation of intracellular signal transduction	16	0.74	5.51e-08
GO:0032270	positive regulation of cellular protein metabolic process	15	0.79	5.62e-08
GO:0033993	response to lipid	12	0.95	6.38e-08
GO:1904707	positive regulation of vascular smooth muscle cell proliferation	5	1.98	6.38e-08
GO:0032501	multicellular organismal process	27	0.4	6.68e-08
GO:1905954	positive regulation of lipid localization	6	1.68	6.68e-08
GO:0033210	leptin-mediated signaling pathway	4	2.43	7.39e-08
GO:0010942	positive regulation of cell death	11	1.01	8.70e-08
GO:0048661	positive regulation of smooth muscle cell proliferation	6	1.66	8.73e-08
GO:0071375	cellular response to peptide hormone stimulus	8	1.3	9.75e-08
GO:0010907	positive regulation of glucose metabolic process	5	1.93	1.05e-07
GO:0045596	negative regulation of cell differentiation	11	0.99	1.15e-07
GO:0009891	positive regulation of biosynthetic process	16	0.72	1.21e-07
GO:0031323	regulation of cellular metabolic process	26	0.42	1.21e-07
GO:0019217	regulation of fatty acid metabolic process	6	1.63	1.26e-07

GO:0045944	positive regulation of transcription by RNA polymerase II	13	0.86	1.32e-07
GO:0007166	cell surface receptor signaling pathway	17	0.67	1.34e-07
GO:0051224	negative regulation of protein transport	7	1.42	1.39e-07
GO:0003018	vascular process in circulatory system	7	1.42	1.44e-07
GO:0042493	response to drug	12	0.91	1.49e-07
GO:0044092	negative regulation of molecular function	13	0.85	1.50e-07
GO:0001819	positive regulation of cytokine production	9	1.15	1.63e-07
GO:0001932	regulation of protein phosphorylation	14	0.8	1.63e-07
GO:0010556	regulation of macromolecule biosynthetic process	22	0.51	1.63e-07
GO:0051130	positive regulation of cellular component organization	13	0.85	1.63e-07
GO:0002682	regulation of immune system process	14	0.79	1.93e-07
GO:0051099	positive regulation of binding	7	1.4	2.04e-07
GO:0010745	negative regulation of macrophage derived foam cell differentiation	4	2.27	2.11e-07
GO:0032374	regulation of cholesterol transport	5	1.85	2.11e-07
GO:0045765	regulation of angiogenesis	8	1.25	2.15e-07
GO:0050707	regulation of cytokine secretion	7	1.39	2.15e-07
GO:0031329	regulation of cellular catabolic process	11	0.96	2.37e-07
GO:0050679	positive regulation of epithelial cell proliferation	7	1.38	2.48e-07
GO:1904018	positive regulation of vasculature development	7	1.38	2.56e-07
GO:0007565	female pregnancy	7	1.38	2.64e-07
GO:0007165	signal transduction	23	0.47	2.72e-07
GO:0010677	negative regulation of cellular carbohydrate metabolic process	5	1.82	2.73e-07
GO:0002573	myeloid leukocyte differentiation	6	1.56	2.86e-07
GO:0046628	positive regulation of insulin receptor signaling pathway	4	2.21	3.23e-07
GO:0000302	response to reactive oxygen species	7	1.35	3.53e-07
GO:1901215	negative regulation of neuron death	7	1.35	3.77e-07
GO:0010557	positive regulation of macromolecule biosynthetic process	15	0.72	3.84e-07
GO:0044281	small molecule metabolic process	15	0.71	4.46e-07
GO:0009890	negative regulation of biosynthetic process	14	0.76	4.52e-07
GO:0050709	negative regulation of protein secretion	6	1.52	4.69e-07
GO:0030335	positive regulation of cell migration	9	1.09	4.92e-07

GO:0090276	regulation of peptide hormone secretion	7	1.32	5.58e-07
GO:0080090	regulation of primary metabolic process	25	0.41	5.67e-07
GO:1904706	negative regulation of vascular smooth muscle cell proliferation	4	2.13	5.70e-07
GO:0010628	positive regulation of gene expression	15	0.7	6.04e-07
GO:1903827	regulation of cellular protein localization	9	1.07	6.06e-07
GO:0032370	positive regulation of lipid transport	5	1.74	6.26e-07
GO:0032268	regulation of cellular protein metabolic process	17	0.62	6.78e-07
GO:0031328	positive regulation of cellular biosynthetic process	15	0.7	6.80e-07
GO:2000112	regulation of cellular macromolecule biosynthetic process	21	0.5	6.80e-07
GO:0043393	regulation of protein binding	7	1.3	7.08e-07
GO:0060255	regulation of macromolecule metabolic process	25	0.4	7.44e-07
GO:0006355	regulation of transcription, DNA-templated	20	0.52	7.93e-07
GO:0050794	regulation of cellular process	31	0.26	7.97e-07
GO:2001234	negative regulation of apoptotic signaling pathway	7	1.29	8.02e-07
GO:0051248	negative regulation of protein metabolic process	12	0.83	8.11e-07
GO:0043062	extracellular structure organization	8	1.16	8.13e-07
GO:0046888	negative regulation of hormone secretion	5	1.71	8.13e-07
GO:0051241	negative regulation of multicellular organismal process	12	0.82	9.96e-07
GO:0007169	transmembrane receptor protein tyrosine kinase signaling pathway	9	1.04	9.99e-07
GO:0048513	animal organ development	18	0.58	9.99e-07
GO:0022414	reproductive process	13	0.77	1.02e-06
GO:0034391	regulation of smooth muscle cell apoptotic process	4	2.05	1.03e-06
GO:0002684	positive regulation of immune system process	11	0.88	1.05e-06
GO:0030100	regulation of endocytosis	7	1.27	1.05e-06
GO:0014068	positive regulation of phosphatidylinositol 3-kinase signaling	5	1.67	1.12e-06
GO:1900120	regulation of receptor binding	4	2.03	1.18e-06
GO:0007623	circadian rhythm	6	1.43	1.24e-06
GO:0032677	regulation of interleukin-8 production	5	1.66	1.27e-06
GO:0007167	enzyme linked receptor protein signaling pathway	10	0.94	1.30e-06
GO:0006357	regulation of transcription by RNA polymerase II	17	0.6	1.39e-06
GO:0006979	response to oxidative stress	8	1.12	1.53e-06

GO:0034284	response to monosaccharide	6	1.41	1.54e-06
GO:0043408	regulation of MAPK cascade	10	0.93	1.54e-06
GO:0009968	negative regulation of signal transduction	12	0.8	1.66e-06
GO:0048511	rhythmic process	7	1.23	1.76e-06
GO:0048514	blood vessel morphogenesis	8	1.11	1.76e-06
GO:0051091	positive regulation of DNA-binding transcription factor activity	7	1.23	1.76e-06
GO:1900407	regulation of cellular response to oxidative stress	5	1.62	1.93e-06
GO:0031099	regeneration	6	1.39	2.03e-06
GO:0030162	regulation of proteolysis	10	0.92	2.15e-06
GO:1903426	regulation of reactive oxygen species biosynthetic process	5	1.6	2.30e-06
GO:0032800	receptor biosynthetic process	3	2.56	2.40e-06
GO:0001558	regulation of cell growth	8	1.09	2.52e-06
GO:0048869	cellular developmental process	19	0.52	2.55e-06
GO:0051090	regulation of DNA-binding transcription factor activity	8	1.08	2.55e-06
GO:0031327	negative regulation of cellular biosynthetic process	13	0.73	2.59e-06
GO:0009892	negative regulation of metabolic process	17	0.58	2.60e-06
GO:0045935	positive regulation of nucleobase-containing compound metabolic process	14	0.68	2.65e-06
GO:0032502	developmental process	23	0.42	2.70e-06
GO:0045766	positive regulation of angiogenesis	6	1.35	2.90e-06
GO:0070542	response to fatty acid	5	1.57	2.97e-06
GO:0009895	negative regulation of catabolic process	7	1.19	3.02e-06
GO:0010871	negative regulation of receptor biosynthetic process	3	2.49	3.43e-06
GO:0031324	negative regulation of cellular metabolic process	16	0.6	3.43e-06
GO:0045923	positive regulation of fatty acid metabolic process	4	1.88	3.43e-06
GO:0032269	negative regulation of cellular protein metabolic process	11	0.82	3.63e-06
GO:0035295	tube development	10	0.89	3.65e-06
GO:0040013	negative regulation of locomotion	7	1.18	3.84e-06
GO:0050796	regulation of insulin secretion	6	1.33	3.88e-06
GO:0001775	cell activation	11	0.82	3.93e-06
GO:0010468	regulation of gene expression	21	0.45	3.94e-06
GO:0043535	regulation of blood vessel endothelial cell migration	5	1.54	3.94e-06

GO:0043065	positive regulation of apoptotic process	9	0.96	3.96e-06
GO:0046890	regulation of lipid biosynthetic process	6	1.32	4.06e-06
GO:0001938	positive regulation of endothelial cell proliferation	5	1.54	4.09e-06
GO:0072359	circulatory system development	10	0.88	4.13e-06
GO:0043086	negative regulation of catalytic activity	10	0.88	4.21e-06
GO:0006810	transport	20	0.47	4.77e-06
GO:0030155	regulation of cell adhesion	9	0.95	4.97e-06
GO:0032885	regulation of polysaccharide biosynthetic process	4	1.83	4.97e-06
GO:0048731	system development	20	0.47	4.99e-06
GO:0048638	regulation of developmental growth	7	1.15	5.21e-06
GO:0010605	negative regulation of macromolecule metabolic process	16	0.58	5.35e-06
GO:0001937	negative regulation of endothelial cell proliferation	4	1.81	5.94e-06
GO:0006110	regulation of glycolytic process	4	1.81	5.94e-06
GO:0030811	regulation of nucleotide catabolic process	4	1.81	5.94e-06
GO:0060284	regulation of cell development	10	0.86	6.04e-06
GO:0043467	regulation of generation of precursor metabolites and energy	5	1.49	6.40e-06
GO:0045444	fat cell differentiation	5	1.49	6.70e-06
GO:0090278	negative regulation of peptide hormone secretion	4	1.79	7.04e-06
GO:0097237	cellular response to toxic substance	6	1.27	7.25e-06
GO:0071229	cellular response to acid chemical	6	1.27	7.41e-06
GO:0014070	response to organic cyclic compound	10	0.85	7.81e-06
GO:1905459	regulation of vascular associated smooth muscle cell apoptotic process	3	2.31	7.85e-06
GO:0051179	localization	22	0.41	7.94e-06
GO:0008285	negative regulation of cell population proliferation	9	0.92	8.37e-06
GO:0051128	regulation of cellular component organization	15	0.6	8.56e-06
GO:0051172	negative regulation of nitrogen compound metabolic process	15	0.6	8.56e-06
GO:0071396	cellular response to lipid	8	1.0	8.56e-06
GO:0071900	regulation of protein serine/threonine kinase activity	8	1.0	8.75e-06
GO:0051896	regulation of protein kinase B signaling	6	1.26	8.76e-06
GO:0046326	positive regulation of glucose import	4	1.75	8.78e-06
GO:0051781	positive regulation of cell division	5	1.46	8.78e-06

GO:0009653	anatomical structure morphogenesis	14	0.63	9.23e-06
GO:0030154	cell differentiation	18	0.5	9.33e-06
GO:1903202	negative regulation of oxidative stress-induced cell death	4	1.74	9.47e-06
GO:0043405	regulation of MAP kinase activity	7	1.1	9.64e-06
GO:0051171	regulation of nitrogen compound metabolic process	23	0.38	9.68e-06
GO:0032103	positive regulation of response to external stimulus	8	0.99	9.94e-06
GO:0010632	regulation of epithelial cell migration	6	1.24	9.96e-06
GO:0016192	vesicle-mediated transport	13	0.67	1.00e-05
GO:0055088	lipid homeostasis	5	1.44	1.01e-05
GO:0071902	positive regulation of protein serine/threonine kinase activity	7	1.1	1.01e-05
GO:1900180	regulation of protein localization to nucleus	5	1.44	1.05e-05
GO:0031331	positive regulation of cellular catabolic process	7	1.1	1.06e-05
GO:0006006	glucose metabolic process	5	1.43	1.08e-05
GO:0045599	negative regulation of fat cell differentiation	4	1.73	1.08e-05
GO:0002376	immune system process	15	0.59	1.13e-05
GO:0032147	activation of protein kinase activity	7	1.09	1.13e-05
GO:0043410	positive regulation of MAPK cascade	8	0.98	1.16e-05
GO:2001169	regulation of ATP biosynthetic process	4	1.72	1.16e-05
GO:0044703	multi-organism reproductive process	10	0.82	1.17e-05
GO:0051101	regulation of DNA binding	5	1.42	1.20e-05
GO:0009409	response to cold	4	1.71	1.23e-05
GO:0050715	positive regulation of cytokine secretion	5	1.42	1.24e-05
GO:0034762	regulation of transmembrane transport	8	0.97	1.35e-05
GO:0010889	regulation of sequestering of triglyceride	3	2.18	1.44e-05
GO:0033197	response to vitamin E	3	2.18	1.44e-05
GO:0051152	positive regulation of smooth muscle cell differentiation	3	2.18	1.44e-05
GO:0050680	negative regulation of epithelial cell proliferation	5	1.4	1.49e-05
GO:0050994	regulation of lipid catabolic process	4	1.68	1.51e-05
GO:0022407	regulation of cell-cell adhesion	7	1.07	1.53e-05
GO:0032940	secretion by cell	10	0.8	1.59e-05
GO:0032355	response to estradiol	5	1.38	1.70e-05

GO:0097305	response to alcohol	6	1.2	1.70e-05
GO:0010885	regulation of cholesterol storage	3	2.15	1.72e-05
GO:0031330	negative regulation of cellular catabolic process	6	1.2	1.72e-05
GO:0043388	positive regulation of DNA binding	4	1.66	1.72e-05
GO:0045721	negative regulation of gluconeogenesis	3	2.15	1.72e-05
GO:0051196	regulation of coenzyme metabolic process	4	1.66	1.82e-05
GO:0030336	negative regulation of cell migration	6	1.19	1.84e-05
GO:0002576	platelet degranulation	5	1.37	1.87e-05
GO:0010638	positive regulation of organelle organization	8	0.95	1.87e-05
GO:0035296	regulation of tube diameter	5	1.37	1.87e-05
GO:0045807	positive regulation of endocytosis	5	1.37	1.87e-05
GO:0046887	positive regulation of hormone secretion	5	1.37	1.92e-05
GO:0046321	positive regulation of fatty acid oxidation	3	2.12	2.03e-05
GO:0055089	fatty acid homeostasis	3	2.12	2.03e-05
GO:0032768	regulation of monooxygenase activity	4	1.64	2.05e-05
GO:0097755	positive regulation of blood vessel diameter	4	1.63	2.18e-05
GO:0052548	regulation of endopeptidase activity	7	1.04	2.30e-05
GO:0050777	negative regulation of immune response	5	1.35	2.34e-05
GO:0010875	positive regulation of cholesterol efflux	3	2.09	2.40e-05
GO:0048521	negative regulation of behavior	3	2.09	2.40e-05
GO:0097746	regulation of blood vessel diameter	5	1.35	2.41e-05
GO:0045927	positive regulation of growth	6	1.16	2.50e-05
GO:0090335	regulation of brown fat cell differentiation	3	2.06	2.79e-05
GO:0014823	response to activity	4	1.59	3.08e-05
GO:0045725	positive regulation of glycogen biosynthetic process	3	2.03	3.25e-05
GO:0051147	regulation of muscle cell differentiation	5	1.32	3.38e-05
GO:0042306	regulation of protein import into nucleus	4	1.58	3.42e-05
GO:0032095	regulation of response to food	3	2.01	3.72e-05
GO:1905562	regulation of vascular endothelial cell proliferation	3	2.01	3.72e-05
GO:0032869	cellular response to insulin stimulus	5	1.3	3.85e-05
GO:0048646	anatomical structure formation involved in morphogenesis	9	0.82	3.85e-05

GO:0009266	response to temperature stimulus	5	1.29	4.08e-05
GO:1903037	regulation of leukocyte cell-cell adhesion	6	1.12	4.11e-05
GO:0006641	triglyceride metabolic process	4	1.55	4.16e-05
GO:0015908	fatty acid transport	4	1.55	4.16e-05
GO:0050764	regulation of phagocytosis	4	1.55	4.16e-05
GO:1900182	positive regulation of protein localization to nucleus	4	1.55	4.16e-05
GO:0051897	positive regulation of protein kinase B signaling	5	1.29	4.24e-05
GO:0097006	regulation of plasma lipoprotein particle levels	4	1.54	4.31e-05
GO:0051193	regulation of cofactor metabolic process	4	1.54	4.53e-05
GO:0010629	negative regulation of gene expression	12	0.64	4.69e-05
GO:0050807	regulation of synapse organization	5	1.28	4.71e-05
GO:1902176	negative regulation of oxidative stress-induced intrinsic apoptotic signaling pathway	3	1.96	4.71e-05
GO:1903829	positive regulation of cellular protein localization	6	1.11	4.71e-05
GO:0032642	regulation of chemokine production	4	1.52	5.19e-05
GO:0048639	positive regulation of developmental growth	5	1.27	5.21e-05
GO:0010876	lipid localization	6	1.1	5.24e-05
GO:0030225	macrophage differentiation	3	1.94	5.25e-05
GO:0034114	regulation of heterotypic cell-cell adhesion	3	1.94	5.25e-05
GO:0043900	regulation of multi-organism process	8	0.87	5.49e-05
GO:0050900	leukocyte migration	6	1.09	5.49e-05
GO:0001525	angiogenesis	6	1.09	5.58e-05
GO:0032098	regulation of appetite	3	1.92	5.87e-05
GO:0090066	regulation of anatomical structure size	7	0.96	5.87e-05
GO:0010558	negative regulation of macromolecule biosynthetic process	11	0.67	6.35e-05
GO:0045321	leukocyte activation	9	0.79	6.37e-05
GO:0071496	cellular response to external stimulus	6	1.08	6.40e-05
GO:0031100	animal organ regeneration	4	1.49	6.44e-05
GO:0042594	response to starvation	5	1.24	6.66e-05
GO:0008217	regulation of blood pressure	5	1.24	7.01e-05
GO:0002719	negative regulation of cytokine production involved in immune response	3	1.88	7.32e-05
GO:0006954	inflammatory response	7	0.95	7.32e-05

GO:0051043	regulation of membrane protein ectodomain proteolysis	3	1.88	7.32e-05
GO:1903427	negative regulation of reactive oxygen species biosynthetic process	3	1.88	7.32e-05
GO:0045055	regulated exocytosis	8	0.85	7.91e-05
GO:0045833	negative regulation of lipid metabolic process	4	1.46	7.91e-05
GO:0050810	regulation of steroid biosynthetic process	4	1.46	7.91e-05
GO:0002021	response to dietary excess	3	1.87	8.01e-05
GO:0071677	positive regulation of mononuclear cell migration	3	1.87	8.01e-05
GO:0051149	positive regulation of muscle cell differentiation	4	1.46	8.20e-05
GO:0006629	lipid metabolic process	10	0.71	8.51e-05
GO:0031058	positive regulation of histone modification	4	1.45	8.52e-05
GO:0098869	cellular oxidant detoxification	4	1.45	8.52e-05
GO:0048545	response to steroid hormone	6	1.05	8.53e-05
GO:0033273	response to vitamin	4	1.45	8.83e-05
GO:0044255	cellular lipid metabolic process	9	0.76	9.44e-05
GO:0071407	cellular response to organic cyclic compound	7	0.93	9.46e-05
GO:0032770	positive regulation of monooxygenase activity	3	1.83	9.64e-05
GO:0034369	plasma lipoprotein particle remodeling	3	1.83	9.64e-05
GO:2001171	positive regulation of ATP biosynthetic process	3	1.83	9.64e-05
GO:0032092	positive regulation of protein binding	4	1.43	9.86e-05
GO:0003008	system process	12	0.6	0.00010
GO:0007631	feeding behavior	4	1.42	0.00011
GO:0051336	regulation of hydrolase activity	10	0.69	0.00011
GO:2000379	positive regulation of reactive oxygen species metabolic process	4	1.42	0.00011
GO:0033157	regulation of intracellular protein transport	5	1.18	0.00012
GO:0043112	receptor metabolic process	4	1.41	0.00012
GO:2001243	negative regulation of intrinsic apoptotic signaling pathway	4	1.41	0.00012
GO:0031669	cellular response to nutrient levels	5	1.17	0.00013
GO:0033554	cellular response to stress	11	0.64	0.00013
GO:0007584	response to nutrient	5	1.17	0.00014
GO:0043281	regulation of cysteine-type endopeptidase activity involved in apoptotic process	5	1.17	0.00014
GO:0046649	lymphocyte activation	6	1.01	0.00014

GO:0002874	regulation of chronic inflammatory response to antigenic stimulus	2	2.61	0.00015
GO:0043537	negative regulation of blood vessel endothelial cell migration	3	1.76	0.00015
GO:0043901	negative regulation of multi-organism process	5	1.16	0.00015
GO:0001503	ossification	5	1.15	0.00016
GO:0021700	developmental maturation	5	1.15	0.00016
GO:0033138	positive regulation of peptidyl-serine phosphorylation	4	1.37	0.00016
GO:0060968	regulation of gene silencing	4	1.38	0.00016
GO:0070328	triglyceride homeostasis	3	1.74	0.00016
GO:0090322	regulation of superoxide metabolic process	3	1.74	0.00016
GO:0097009	energy homeostasis	3	1.74	0.00016
GO:0045785	positive regulation of cell adhesion	6	0.99	0.00017
GO:0045936	negative regulation of phosphate metabolic process	7	0.88	0.00017
GO:0097421	liver regeneration	3	1.73	0.00017
GO:0034599	cellular response to oxidative stress	5	1.14	0.00018
GO:0043491	protein kinase B signaling	3	1.72	0.00018
GO:0046676	negative regulation of insulin secretion	3	1.72	0.00018
GO:1902893	regulation of pri-miRNA transcription by RNA polymerase II	3	1.72	0.00018
GO:0008203	cholesterol metabolic process	4	1.35	0.00019
GO:0009888	tissue development	11	0.62	0.00019
GO:0030098	lymphocyte differentiation	5	1.13	0.00019
GO:0042110	T cell activation	5	1.13	0.00019
GO:0051052	regulation of DNA metabolic process	6	0.98	0.00019
GO:0032675	regulation of interleukin-6 production	4	1.34	0.00020
GO:0000122	negative regulation of transcription by RNA polymerase II	8	0.78	0.00021
GO:0002698	negative regulation of immune effector process	4	1.34	0.00021
GO:1902952	positive regulation of dendritic spine maintenance	2	2.49	0.00021
GO:0032680	regulation of tumor necrosis factor production	4	1.33	0.00022
GO:0032715	negative regulation of interleukin-6 production	3	1.68	0.00022
GO:0045926	negative regulation of growth	5	1.11	0.00022
GO:1903672	positive regulation of sprouting angiogenesis	3	1.68	0.00022
GO:0022409	positive regulation of cell-cell adhesion	5	1.11	0.00023

GO:0034763	negative regulation of transmembrane transport	4	1.32	0.00023
GO:0048608	reproductive structure development	6	0.96	0.00025
GO:0090184	positive regulation of kidney development	3	1.66	0.00025
GO:0001818	negative regulation of cytokine production	5	1.1	0.00026
GO:0007162	negative regulation of cell adhesion	5	1.1	0.00026
GO:0050729	positive regulation of inflammatory response	4	1.31	0.00026
GO:0010891	negative regulation of sequestering of triglyceride	2	2.39	0.00029
GO:0019752	carboxylic acid metabolic process	8	0.76	0.00029
GO:0033591	response to L-ascorbic acid	2	2.39	0.00029
GO:0034614	cellular response to reactive oxygen species	4	1.29	0.00029
GO:0035630	bone mineralization involved in bone maturation	2	2.39	0.00029
GO:0042307	positive regulation of protein import into nucleus	3	1.64	0.00029
GO:0080135	regulation of cellular response to stress	7	0.84	0.00029
GO:1904179	positive regulation of adipose tissue development	2	2.39	0.00029
GO:2000481	positive regulation of cAMP-dependent protein kinase activity	2	2.39	0.00029
GO:0003006	developmental process involved in reproduction	7	0.84	0.00030
GO:0031952	regulation of protein autophosphorylation	3	1.63	0.00030
GO:0002687	positive regulation of leukocyte migration	4	1.28	0.00031
GO:0002683	negative regulation of immune system process	6	0.94	0.00032
GO:0051129	negative regulation of cellular component organization	7	0.83	0.00032
GO:0006953	acute-phase response	3	1.61	0.00033
GO:0044060	regulation of endocrine process	3	1.61	0.00033
GO:0050776	regulation of immune response	8	0.75	0.00033
GO:0050999	regulation of nitric-oxide synthase activity	3	1.61	0.00033
GO:0030217	T cell differentiation	4	1.27	0.00034
GO:0043406	positive regulation of MAP kinase activity	5	1.06	0.00035
GO:0045776	negative regulation of blood pressure	3	1.6	0.00035
GO:0002706	regulation of lymphocyte mediated immunity	4	1.26	0.00036
GO:0009749	response to glucose	4	1.26	0.00036
GO:0010887	negative regulation of cholesterol storage	2	2.31	0.00036
GO:0042536	negative regulation of tumor necrosis factor biosynthetic process	2	2.31	0.00036

GO:0045348	positive regulation of MHC class II biosynthetic process	2	2.31	0.00036
GO:0045471	response to ethanol	4	1.26	0.00036
GO:0051346	negative regulation of hydrolase activity	6	0.92	0.00036
GO:0010634	positive regulation of epithelial cell migration	4	1.25	0.00038
GO:0032720	negative regulation of tumor necrosis factor production	3	1.58	0.00039
GO:0032757	positive regulation of interleukin-8 production	3	1.58	0.00039
GO:0045892	negative regulation of transcription, DNA-templated	9	0.67	0.00039
GO:0006869	lipid transport	5	1.05	0.00040
GO:0051384	response to glucocorticoid	4	1.25	0.00040
GO:0070372	regulation of ERK1 and ERK2 cascade	5	1.05	0.00041
GO:2000677	regulation of transcription regulatory region DNA binding	3	1.57	0.00041
GO:0001501	skeletal system development	6	0.9	0.00044
GO:0051092	positive regulation of NF-kappaB transcription factor activity	4	1.24	0.00044
GO:0010742	macrophage derived foam cell differentiation	2	2.24	0.00045
GO:0034372	very-low-density lipoprotein particle remodeling	2	2.24	0.00045
GO:0042326	negative regulation of phosphorylation	6	0.9	0.00045
GO:0043271	negative regulation of ion transport	4	1.23	0.00045
GO:1905461	positive regulation of vascular associated smooth muscle cell apoptotic process	2	2.24	0.00045
GO:0001890	placenta development	4	1.23	0.00047
GO:0002889	regulation of immunoglobulin mediated immune response	3	1.55	0.00047
GO:0071222	cellular response to lipopolysaccharide	4	1.22	0.00048
GO:0002819	regulation of adaptive immune response	4	1.22	0.00049
GO:0060688	regulation of morphogenesis of a branching structure	3	1.54	0.00049
GO:0006066	alcohol metabolic process	5	1.02	0.00051
GO:0045840	positive regulation of mitotic nuclear division	3	1.53	0.00052
GO:0017038	protein import	4	1.21	0.00053
GO:0035556	intracellular signal transduction	10	0.6	0.00053
GO:0051235	maintenance of location	4	1.21	0.00053
GO:0006631	fatty acid metabolic process	5	1.02	0.00054
GO:0032667	regulation of interleukin-23 production	2	2.18	0.00054
GO:0032787	monocarboxylic acid metabolic process	6	0.89	0.00054

GO:0032922	circadian regulation of gene expression	3	1.52	0.00054
GO:0034371	chylomicron remodeling	2	2.18	0.00054
GO:0042129	regulation of T cell proliferation	4	1.21	0.00054
GO:0043536	positive regulation of blood vessel endothelial cell migration	3	1.52	0.00054
GO:0061178	regulation of insulin secretion involved in cellular response to glucose stimulus	3	1.52	0.00054
GO:0071363	cellular response to growth factor stimulus	6	0.89	0.00054
GO:0072577	endothelial cell apoptotic process	2	2.18	0.00054
GO:2000252	negative regulation of feeding behavior	2	2.18	0.00054
GO:0006952	defense response	9	0.65	0.00055
GO:0030198	extracellular matrix organization	5	1.01	0.00055
GO:0032722	positive regulation of chemokine production	3	1.52	0.00056
GO:0006955	immune response	10	0.59	0.00061
GO:0010720	positive regulation of cell development	6	0.87	0.00061
GO:0050710	negative regulation of cytokine secretion	3	1.5	0.00061
GO:0046677	response to antibiotic	5	1.0	0.00062
GO:0010950	positive regulation of endopeptidase activity	4	1.19	0.00063
GO:0022408	negative regulation of cell-cell adhesion	4	1.19	0.00063
GO:0030307	positive regulation of cell growth	4	1.19	0.00063
GO:0001542	ovulation from ovarian follicle	2	2.13	0.00064
GO:0032000	positive regulation of fatty acid beta-oxidation	2	2.13	0.00064
GO:0033034	positive regulation of myeloid cell apoptotic process	2	2.13	0.00064
GO:0034115	negative regulation of heterotypic cell-cell adhesion	2	2.13	0.00064
GO:1900402	regulation of carbohydrate metabolic process by regulation of transcription from RNA polymerase II pr	2	2.13	0.00064
GO:0044089	positive regulation of cellular component biogenesis	6	0.87	0.00065
GO:0042531	positive regulation of tyrosine phosphorylation of STAT protein	3	1.49	0.00066
GO:0014910	regulation of smooth muscle cell migration	3	1.48	0.00069
GO:0002637	regulation of immunoglobulin production	3	1.47	0.00072
GO:0044242	cellular lipid catabolic process	4	1.17	0.00074
GO:0008343	adult feeding behavior	2	2.09	0.00075
GO:1900122	positive regulation of receptor binding	2	2.09	0.00075
GO:1902532	negative regulation of intracellular signal transduction	6	0.85	0.00075

GO:2000833	positive regulation of steroid hormone secretion	2	2.09	0.00075
GO:0044057	regulation of system process	6	0.85	0.00077
GO:0000165	MAPK cascade	5	0.98	0.00078
GO:0043117	positive regulation of vascular permeability	2	2.05	0.00087
GO:0045722	positive regulation of gluconeogenesis	2	2.05	0.00087
GO:1903708	positive regulation of hemopoiesis	4	1.14	0.00090
GO:0040014	regulation of multicellular organism growth	3	1.42	0.00094
GO:0007610	behavior	6	0.83	0.00096
GO:0048589	developmental growth	5	0.95	0.00096
GO:0002674	negative regulation of acute inflammatory response	2	2.01	0.00099
GO:0030812	negative regulation of nucleotide catabolic process	2	2.01	0.00099
GO:0032099	negative regulation of appetite	2	2.01	0.00099
GO:0045820	negative regulation of glycolytic process	2	2.01	0.00099
GO:0050872	white fat cell differentiation	2	2.01	0.00099
GO:0051198	negative regulation of coenzyme metabolic process	2	2.01	0.00099
GO:0060965	negative regulation of gene silencing by miRNA	2	2.01	0.00099
GO:1900121	negative regulation of receptor binding	2	2.01	0.00099
GO:0042632	cholesterol homeostasis	3	1.41	0.00100
GO:0045862	positive regulation of proteolysis	5	0.94	0.0010
GO:0009617	response to bacterium	6	0.82	0.0011
GO:0019395	fatty acid oxidation	3	1.39	0.0011
GO:0034103	regulation of tissue remodeling	3	1.4	0.0011
GO:0034116	positive regulation of heterotypic cell-cell adhesion	2	1.97	0.0011
GO:0044130	negative regulation of growth of symbiont in host	2	1.97	0.0011
GO:0045861	negative regulation of proteolysis	5	0.94	0.0011
GO:0046889	positive regulation of lipid biosynthetic process	3	1.4	0.0011
GO:0002697	regulation of immune effector process	5	0.93	0.0012
GO:0007492	endoderm development	3	1.38	0.0012
GO:0014854	response to inactivity	2	1.94	0.0012
GO:0031349	positive regulation of defense response	5	0.92	0.0012
GO:0035358	regulation of peroxisome proliferator activated receptor signaling pathway	2	1.94	0.0012

GO:0044126	regulation of growth of symbiont in host	2	1.94	0.0012
GO:0046325	negative regulation of glucose import	2	1.94	0.0012
GO:0048009	insulin-like growth factor receptor signaling pathway	2	1.94	0.0012
GO:0051960	regulation of nervous system development	7	0.72	0.0012
GO:0060964	regulation of gene silencing by miRNA	3	1.37	0.0012
GO:0070374	positive regulation of ERK1 and ERK2 cascade	4	1.1	0.0012
GO:1905564	positive regulation of vascular endothelial cell proliferation	2	1.94	0.0012
GO:0031214	biomineral tissue development	3	1.36	0.0013
GO:0032088	negative regulation of NF-kappaB transcription factor activity	3	1.36	0.0013
GO:0044146	negative regulation of growth of symbiont involved in interaction with host	2	1.91	0.0014
GO:0050765	negative regulation of phagocytosis	2	1.91	0.0014
GO:1903039	positive regulation of leukocyte cell-cell adhesion	4	1.08	0.0014
GO:2001170	negative regulation of ATP biosynthetic process	2	1.91	0.0014
GO:0008585	female gonad development	3	1.34	0.0015
GO:0044144	modulation of growth of symbiont involved in interaction with host	2	1.88	0.0015
GO:0048145	regulation of fibroblast proliferation	3	1.34	0.0015
GO:0051044	positive regulation of membrane protein ectodomain proteolysis	2	1.88	0.0015
GO:0051726	regulation of cell cycle	8	0.64	0.0015
GO:2001023	regulation of response to drug	3	1.34	0.0015
GO:0007346	regulation of mitotic cell cycle	6	0.78	0.0016
GO:0044282	small molecule catabolic process	5	0.9	0.0016
GO:0098542	defense response to other organism	7	0.7	0.0016
GO:0009887	animal organ morphogenesis	7	0.69	0.0017
GO:0032930	positive regulation of superoxide anion generation	2	1.86	0.0017
GO:0034375	high-density lipoprotein particle remodeling	2	1.86	0.0017
GO:0044087	regulation of cellular component biogenesis	7	0.69	0.0017
GO:0045639	positive regulation of myeloid cell differentiation	3	1.31	0.0017
GO:0048732	gland development	5	0.89	0.0017
GO:0050901	leukocyte tethering or rolling	2	1.86	0.0017
GO:1990845	adaptive thermogenesis	2	1.86	0.0017
GO:0030224	monocyte differentiation	2	1.83	0.0018

GO:0045821	positive regulation of glycolytic process	2	1.83	0.0018
GO:0046486	glycerolipid metabolic process	5	0.88	0.0018
GO:0051707	response to other organism	8	0.62	0.0018
GO:0070886	positive regulation of calcineurin-NFAT signaling cascade	2	1.83	0.0018
GO:0071404	cellular response to low-density lipoprotein particle stimulus	2	1.83	0.0018
GO:2000727	positive regulation of cardiac muscle cell differentiation	2	1.83	0.0018
GO:0002673	regulation of acute inflammatory response	3	1.3	0.0019
GO:0002821	positive regulation of adaptive immune response	3	1.29	0.0019
GO:0000303	response to superoxide	2	1.81	0.0020
GO:0009056	catabolic process	10	0.52	0.0020
GO:0030813	positive regulation of nucleotide catabolic process	2	1.81	0.0020
GO:0031065	positive regulation of histone deacetylation	2	1.81	0.0020
GO:0033189	response to vitamin A	2	1.81	0.0020
GO:0051195	negative regulation of cofactor metabolic process	2	1.81	0.0020
GO:0051197	positive regulation of coenzyme metabolic process	2	1.81	0.0020
GO:0090190	positive regulation of branching involved in ureteric bud morphogenesis	2	1.81	0.0020
GO:0090277	positive regulation of peptide hormone secretion	3	1.29	0.0020
GO:1903706	regulation of hemopoiesis	5	0.87	0.0020
GO:0042035	regulation of cytokine biosynthetic process	3	1.28	0.0021
GO:0051153	regulation of striated muscle cell differentiation	3	1.28	0.0021
GO:0061387	regulation of extent of cell growth	3	1.28	0.0021
GO:0016525	negative regulation of angiogenesis	3	1.27	0.0022
GO:0042752	regulation of circadian rhythm	3	1.27	0.0022
GO:0051000	positive regulation of nitric-oxide synthase activity	2	1.79	0.0022
GO:0006606	protein import into nucleus	3	1.26	0.0023
GO:0033036	macromolecule localization	11	0.47	0.0023
GO:0043254	regulation of protein complex assembly	5	0.86	0.0023
GO:0046395	carboxylic acid catabolic process	4	1.01	0.0023
GO:0055093	response to hyperoxia	2	1.77	0.0023
GO:2000637	positive regulation of gene silencing by miRNA	2	1.77	0.0023
GO:0032091	negative regulation of protein binding	3	1.25	0.0024

GO:0008152	metabolic process	25	0.2	0.0025
GO:0014912	negative regulation of smooth muscle cell migration	2	1.74	0.0025
GO:0030258	lipid modification	4	1.0	0.0025
GO:0050995	negative regulation of lipid catabolic process	2	1.74	0.0025
GO:0098868	bone growth	2	1.74	0.0025
GO:2001237	negative regulation of extrinsic apoptotic signaling pathway	3	1.25	0.0025
GO:0008283	cell population proliferation	6	0.73	0.0026
GO:0045637	regulation of myeloid cell differentiation	4	0.99	0.0026
GO:0001822	kidney development	4	0.99	0.0027
GO:0042742	defense response to bacterium	4	0.99	0.0027
GO:0051817	modification of morphology or physiology of other organism involved in symbiotic interaction	3	1.23	0.0027
GO:0071295	cellular response to vitamin	2	1.73	0.0027
GO:1900745	positive regulation of p38MAPK cascade	2	1.73	0.0027
GO:2000278	regulation of DNA biosynthetic process	3	1.23	0.0027
GO:0035902	response to immobilization stress	2	1.71	0.0029
GO:0045672	positive regulation of osteoclast differentiation	2	1.71	0.0029
GO:0051194	positive regulation of cofactor metabolic process	2	1.71	0.0029
GO:1903038	negative regulation of leukocyte cell-cell adhesion	3	1.22	0.0029
GO:2000679	positive regulation of transcription regulatory region DNA binding	2	1.71	0.0029
GO:1902105	regulation of leukocyte differentiation	4	0.97	0.0030
GO:0019433	triglyceride catabolic process	2	1.69	0.0031
GO:1902895	positive regulation of pri-miRNA transcription by RNA polymerase II	2	1.69	0.0031
GO:0002761	regulation of myeloid leukocyte differentiation	3	1.2	0.0033
GO:0032692	negative regulation of interleukin-1 production	2	1.67	0.0033
GO:0045940	positive regulation of steroid metabolic process	2	1.67	0.0033
GO:2001025	positive regulation of response to drug	2	1.67	0.0033
GO:0045662	negative regulation of myoblast differentiation	2	1.66	0.0035
GO:1902692	regulation of neuroblast proliferation	2	1.66	0.0035
GO:0007435	salivary gland morphogenesis	2	1.64	0.0037
GO:0019915	lipid storage	2	1.64	0.0037
GO:0031954	positive regulation of protein autophosphorylation	2	1.64	0.0037

GO:0050767	regulation of neurogenesis	6	0.7	0.0037
GO:0050873	brown fat cell differentiation	2	1.64	0.0037
GO:0071695	anatomical structure maturation	3	1.18	0.0037
GO:1903792	negative regulation of anion transport	2	1.64	0.0037
GO:0009987	cellular process	31	0.11	0.0038
GO:0043280	positive regulation of cysteine-type endopeptidase activity involved in apoptotic process	3	1.17	0.0038
GO:0051962	positive regulation of nervous system development	5	0.8	0.0038
GO:0010035	response to inorganic substance	5	0.79	0.0039
GO:0016043	cellular component organization	17	0.3	0.0039
GO:0045995	regulation of embryonic development	3	1.17	0.0039
GO:0048871	multicellular organismal homeostasis	4	0.94	0.0039
GO:0051345	positive regulation of hydrolase activity	6	0.69	0.0039
GO:0010800	positive regulation of peptidyl-threonine phosphorylation	2	1.61	0.0041
GO:0038111	interleukin-7-mediated signaling pathway	2	1.61	0.0041
GO:0045922	negative regulation of fatty acid metabolic process	2	1.61	0.0041
GO:2000108	positive regulation of leukocyte apoptotic process	2	1.61	0.0041
GO:0071901	negative regulation of protein serine/threonine kinase activity	3	1.15	0.0043
GO:1905330	regulation of morphogenesis of an epithelium	3	1.15	0.0043
GO:0014896	muscle hypertrophy	2	1.6	0.0044
GO:0031663	lipopolysaccharide-mediated signaling pathway	2	1.6	0.0044
GO:0035774	positive regulation of insulin secretion involved in cellular response to glucose stimulus	2	1.6	0.0044
GO:0042311	vasodilation	2	1.6	0.0044
GO:0050865	regulation of cell activation	5	0.78	0.0044
GO:0060325	face morphogenesis	2	1.6	0.0044
GO:0006897	endocytosis	5	0.78	0.0045
GO:0097190	apoptotic signaling pathway	4	0.92	0.0045
GO:0002696	positive regulation of leukocyte activation	4	0.91	0.0046
GO:0010721	negative regulation of cell development	4	0.91	0.0046
GO:0032148	activation of protein kinase B activity	2	1.58	0.0046
GO:0042755	eating behavior	2	1.58	0.0046
GO:1900015	regulation of cytokine production involved in inflammatory response	2	1.58	0.0046

GO:0014065	phosphatidylinositol 3-kinase signaling	2	1.57	0.0048
GO:0043552	positive regulation of phosphatidylinositol 3-kinase activity	2	1.57	0.0048
GO:0007267	cell-cell signaling	7	0.6	0.0049
GO:0009267	cellular response to starvation	3	1.13	0.0049
GO:0030534	adult behavior	3	1.13	0.0049
GO:0030856	regulation of epithelial cell differentiation	3	1.13	0.0049
GO:0043524	negative regulation of neuron apoptotic process	3	1.12	0.0050
GO:0045191	regulation of isotype switching	2	1.56	0.0050
GO:0050921	positive regulation of chemotaxis	3	1.12	0.0050
GO:1900271	regulation of long-term synaptic potentiation	2	1.56	0.0050
GO:1902107	positive regulation of leukocyte differentiation	3	1.12	0.0050
GO:0015833	peptide transport	8	0.54	0.0052
GO:0032965	regulation of collagen biosynthetic process	2	1.54	0.0052
GO:0035690	cellular response to drug	4	0.9	0.0052
GO:0051348	negative regulation of transferase activity	4	0.9	0.0052
GO:0048699	generation of neurons	8	0.54	0.0054
GO:0031062	positive regulation of histone methylation	2	1.53	0.0055
GO:0050804	modulation of chemical synaptic transmission	4	0.89	0.0055
GO:1901031	regulation of response to reactive oxygen species	2	1.53	0.0055
GO:0002891	positive regulation of immunoglobulin mediated immune response	2	1.52	0.0057
GO:0030574	collagen catabolic process	2	1.52	0.0057
GO:2000008	regulation of protein localization to cell surface	2	1.52	0.0057
GO:0032874	positive regulation of stress-activated MAPK cascade	3	1.09	0.0058
GO:1903034	regulation of response to wounding	3	1.09	0.0058
GO:0000187	activation of MAPK activity	3	1.09	0.0059
GO:0030316	osteoclast differentiation	2	1.51	0.0060
GO:0001959	regulation of cytokine-mediated signaling pathway	3	1.08	0.0061
GO:0007566	embryo implantation	2	1.5	0.0063
GO:0097756	negative regulation of blood vessel diameter	2	1.5	0.0063
GO:2000279	negative regulation of DNA biosynthetic process	2	1.5	0.0063
GO:0034381	plasma lipoprotein particle clearance	2	1.49	0.0065

GO:0042304	regulation of fatty acid biosynthetic process	2	1.49	0.0065
GO:0044058	regulation of digestive system process	2	1.49	0.0065
GO:0040011	locomotion	7	0.57	0.0066
GO:0007259	receptor signaling pathway via JAK-STAT	2	1.47	0.0068
GO:0035987	endodermal cell differentiation	2	1.47	0.0068
GO:0048468	cell development	8	0.52	0.0070
GO:0031346	positive regulation of cell projection organization	4	0.85	0.0071
GO:0043124	negative regulation of I-kappaB kinase/NF-kappaB signaling	2	1.46	0.0071
GO:0061138	morphogenesis of a branching epithelium	3	1.06	0.0071
GO:0050770	regulation of axonogenesis	3	1.05	0.0073
GO:0030308	negative regulation of cell growth	3	1.05	0.0075
GO:0071453	cellular response to oxygen levels	3	1.05	0.0075
GO:0044003	modulation by symbiont of host process	2	1.44	0.0076
GO:0060348	bone development	3	1.04	0.0077
GO:0031400	negative regulation of protein modification process	5	0.71	0.0078
GO:0043122	regulation of I-kappaB kinase/NF-kappaB signaling	3	1.04	0.0078
GO:0032459	regulation of protein oligomerization	2	1.43	0.0079
GO:0090199	regulation of release of cytochrome c from mitochondria	2	1.43	0.0079
GO:0001754	eye photoreceptor cell differentiation	2	1.42	0.0082
GO:0046850	regulation of bone remodeling	2	1.42	0.0082
GO:0009755	hormone-mediated signaling pathway	3	1.03	0.0083
GO:0045088	regulation of innate immune response	4	0.83	0.0083
GO:0030522	intracellular receptor signaling pathway	3	1.03	0.0085
GO:0035722	interleukin-12-mediated signaling pathway	2	1.42	0.0085
GO:0050766	positive regulation of phagocytosis	2	1.42	0.0085
GO:0051055	negative regulation of lipid biosynthetic process	2	1.42	0.0085
GO:0009790	embryo development	6	0.62	0.0086
GO:0098657	import into cell	5	0.7	0.0086
GO:0030195	negative regulation of blood coagulation	2	1.41	0.0088
GO:0042176	regulation of protein catabolic process	4	0.82	0.0088
GO:0050866	negative regulation of cell activation	3	1.02	0.0090

GO:0035094	response to nicotine	2	1.4	0.0091
GO:0043269	regulation of ion transport	5	0.69	0.0091
GO:0045824	negative regulation of innate immune response	2	1.4	0.0091
GO:0050832	defense response to fungus	2	1.4	0.0091
GO:0045787	positive regulation of cell cycle	4	0.81	0.0094
GO:0045806	negative regulation of endocytosis	2	1.39	0.0094
GO:0048260	positive regulation of receptor-mediated endocytosis	2	1.39	0.0094
GO:0030278	regulation of ossification	3	1.01	0.0095
GO:0006915	apoptotic process	6	0.6	0.0096
GO:0016310	phosphorylation	7	0.54	0.0096
GO:0035065	regulation of histone acetylation	2	1.38	0.0096
GO:0008104	protein localization	9	0.45	0.0098
GO:0006468	protein phosphorylation	6	0.6	0.0100
GO:0006909	phagocytosis	3	1.0	0.0100
GO:0055114	oxidation-reduction process	6	0.6	0.0104
GO:0001960	negative regulation of cytokine-mediated signaling pathway	2	1.35	0.0106
GO:0015909	long-chain fatty acid transport	2	1.35	0.0106
GO:0045428	regulation of nitric oxide biosynthetic process	2	1.35	0.0106
GO:0048146	positive regulation of fibroblast proliferation	2	1.35	0.0106
GO:0071398	cellular response to fatty acid	2	1.35	0.0106
GO:0030182	neuron differentiation	6	0.59	0.0108
GO:0019538	protein metabolic process	14	0.31	0.0109
GO:0044403	symbiont process	5	0.67	0.0110
GO:0050870	positive regulation of T cell activation	3	0.98	0.0110
GO:0072594	establishment of protein localization to organelle	4	0.79	0.0110
GO:0006635	fatty acid beta-oxidation	2	1.34	0.0112
GO:0010803	regulation of tumor necrosis factor-mediated signaling pathway	2	1.34	0.0112
GO:0046686	response to cadmium ion	2	1.34	0.0112
GO:0061448	connective tissue development	3	0.98	0.0112
GO:0006091	generation of precursor metabolites and energy	4	0.79	0.0113
GO:0042130	negative regulation of T cell proliferation	2	1.33	0.0116

GO:0071383	cellular response to steroid hormone stimulus	3	0.97	0.0116
GO:0044248	cellular catabolic process	8	0.47	0.0117
GO:0022617	extracellular matrix disassembly	2	1.32	0.0119
GO:0055082	cellular chemical homeostasis	5	0.66	0.0119
GO:0071702	organic substance transport	9	0.43	0.0121
GO:0030858	positive regulation of epithelial cell differentiation	2	1.32	0.0122
GO:0045600	positive regulation of fat cell differentiation	2	1.32	0.0122
GO:0048844	artery morphogenesis	2	1.32	0.0122
GO:0043903	regulation of symbiosis, encompassing mutualism through parasitism	3	0.96	0.0124
GO:0030072	peptide hormone secretion	2	1.31	0.0125
GO:0046631	alpha-beta T cell activation	2	1.31	0.0125
GO:0061098	positive regulation of protein tyrosine kinase activity	2	1.31	0.0125
GO:0071230	cellular response to amino acid stimulus	2	1.31	0.0125
GO:0048568	embryonic organ development	4	0.77	0.0127
GO:1901564	organonitrogen compound metabolic process	16	0.27	0.0127
GO:0006796	phosphate-containing compound metabolic process	9	0.43	0.0129
GO:2000027	regulation of animal organ morphogenesis	3	0.95	0.0129
GO:0001933	negative regulation of protein phosphorylation	4	0.76	0.0132
GO:0006112	energy reserve metabolic process	2	1.29	0.0132
GO:0051054	positive regulation of DNA metabolic process	3	0.94	0.0132
GO:0009612	response to mechanical stimulus	3	0.94	0.0134
GO:0050769	positive regulation of neurogenesis	4	0.76	0.0134
GO:0061035	regulation of cartilage development	2	1.29	0.0135
GO:0071479	cellular response to ionizing radiation	2	1.28	0.0139
GO:0001570	vasculogenesis	2	1.27	0.0143
GO:0051965	positive regulation of synapse assembly	2	1.27	0.0143
GO:0015980	energy derivation by oxidation of organic compounds	3	0.93	0.0145
GO:0034612	response to tumor necrosis factor	3	0.93	0.0145
GO:0007569	cell aging	2	1.27	0.0146
GO:0006928	movement of cell or subcellular component	7	0.5	0.0148
GO:0050801	ion homeostasis	5	0.64	0.0148

GO:0022600	digestive system process	2	1.25	0.0154
GO:0071300	cellular response to retinoic acid	2	1.25	0.0154
GO:0006839	mitochondrial transport	3	0.92	0.0155
GO:0046717	acid secretion	2	1.25	0.0158
GO:0071326	cellular response to monosaccharide stimulus	2	1.25	0.0158
GO:0030512	negative regulation of transforming growth factor beta receptor signaling pathway	2	1.24	0.0161
GO:0008630	intrinsic apoptotic signaling pathway in response to DNA damage	2	1.24	0.0165
GO:0030279	negative regulation of ossification	2	1.24	0.0165
GO:1902930	regulation of alcohol biosynthetic process	2	1.24	0.0165
GO:0015031	protein transport	7	0.49	0.0167
GO:0043407	negative regulation of MAP kinase activity	2	1.23	0.0168
GO:0061061	muscle structure development	4	0.73	0.0168
GO:0043933	protein-containing complex subunit organization	8	0.44	0.0170
GO:0010507	negative regulation of autophagy	2	1.22	0.0172
GO:0042060	wound healing	4	0.72	0.0172
GO:0032755	positive regulation of interleukin-6 production	2	1.22	0.0176
GO:0043627	response to estrogen	2	1.22	0.0176
GO:0032943	mononuclear cell proliferation	2	1.21	0.0185
GO:0050772	positive regulation of axonogenesis	2	1.21	0.0185
GO:0031334	positive regulation of protein complex assembly	3	0.88	0.0186
GO:0001678	cellular glucose homeostasis	2	1.2	0.0188
GO:0010951	negative regulation of endopeptidase activity	3	0.88	0.0188
GO:0045930	negative regulation of mitotic cell cycle	3	0.88	0.0189
GO:0048666	neuron development	5	0.61	0.0189
GO:0042475	odontogenesis of dentin-containing tooth	2	1.2	0.0192
GO:0051289	protein homotetramerization	2	1.2	0.0192
GO:0019953	sexual reproduction	5	0.6	0.0195
GO:0032409	regulation of transporter activity	3	0.87	0.0195
GO:0048013	ephrin receptor signaling pathway	2	1.19	0.0196
GO:0007507	heart development	4	0.7	0.0200
GO:0010976	positive regulation of neuron projection development	3	0.86	0.0205

GO:0043270	positive regulation of ion transport	3	0.86	0.0206
GO:0008286	insulin receptor signaling pathway	2	1.17	0.0208
GO:0030516	regulation of axon extension	2	1.17	0.0208
GO:1904063	negative regulation of cation transmembrane transport	2	1.17	0.0208
GO:0090287	regulation of cellular response to growth factor stimulus	3	0.86	0.0209
GO:0045778	positive regulation of ossification	2	1.17	0.0212
GO:0051651	maintenance of location in cell	2	1.17	0.0212
GO:1901888	regulation of cell junction assembly	2	1.17	0.0212
GO:1990542	mitochondrial transmembrane transport	2	1.17	0.0212
GO:0006919	activation of cysteine-type endopeptidase activity involved in apoptotic process	2	1.16	0.0221
GO:0050768	negative regulation of neurogenesis	3	0.85	0.0221
GO:0001657	ureteric bud development	2	1.15	0.0225
GO:1903076	regulation of protein localization to plasma membrane	2	1.15	0.0229
GO:0007179	transforming growth factor beta receptor signaling pathway	2	1.14	0.0233
GO:0032006	regulation of TOR signaling	2	1.14	0.0237
GO:0071704	organic substance metabolic process	22	0.17	0.0241
GO:0060191	regulation of lipase activity	2	1.13	0.0242
GO:1901655	cellular response to ketone	2	1.13	0.0242
GO:0002690	positive regulation of leukocyte chemotaxis	2	1.13	0.0246
GO:0043154	negative regulation of cysteine-type endopeptidase activity involved in apoptotic process	2	1.13	0.0246
GO:0042102	positive regulation of T cell proliferation	2	1.12	0.0250
GO:1901576	organic substance biosynthetic process	14	0.26	0.0250
GO:0097191	extrinsic apoptotic signaling pathway	2	1.12	0.0255
GO:0032649	regulation of interferon-gamma production	2	1.1	0.0274
GO:0010506	regulation of autophagy	3	0.81	0.0277
GO:0007517	muscle organ development	3	0.81	0.0279
GO:0048598	embryonic morphogenesis	4	0.65	0.0283
GO:0072593	reactive oxygen species metabolic process	2	1.07	0.0305
GO:0001952	regulation of cell-matrix adhesion	2	1.07	0.0315
GO:0016032	viral process	4	0.63	0.0328
GO:1901575	organic substance catabolic process	7	0.42	0.0328

GO:0002274	myeloid leukocyte activation	4	0.63	0.0333
GO:0051260	protein homooligomerization	3	0.77	0.0344
GO:0050830	defense response to Gram-positive bacterium	2	1.04	0.0347
GO:0031644	regulation of neurological system process	2	1.04	0.0352
GO:0042542	response to hydrogen peroxide	2	1.04	0.0352
GO:0045667	regulation of osteoblast differentiation	2	1.04	0.0352
GO:0060560	developmental growth involved in morphogenesis	2	1.04	0.0352
GO:1903828	negative regulation of cellular protein localization	2	1.04	0.0352
GO:0044237	cellular metabolic process	21	0.16	0.0355
GO:0050778	positive regulation of immune response	4	0.62	0.0359
GO:0044238	primary metabolic process	21	0.16	0.0360
GO:0042157	lipoprotein metabolic process	2	1.03	0.0361
GO:0019935	cyclic-nucleotide-mediated signaling	2	1.03	0.0367
GO:0120035	regulation of plasma membrane bounded cell projection organization	4	0.61	0.0381
GO:0002252	immune effector process	5	0.52	0.0390
GO:0098727	maintenance of cell number	2	1.01	0.0395
GO:0006811	ion transport	6	0.45	0.0400
GO:0042177	negative regulation of protein catabolic process	2	1.0	0.0401
GO:0055002	striated muscle cell development	2	1.0	0.0401
GO:0043123	positive regulation of I-kappaB kinase/NF-kappaB signaling	2	1.0	0.0406
GO:0002366	leukocyte activation involved in immune response	4	0.6	0.0412
GO:0030879	mammary gland development	2	1.0	0.0412
GO:0031175	neuron projection development	4	0.6	0.0412
GO:0001654	eye development	3	0.73	0.0417
GO:0048565	digestive tract development	2	0.99	0.0428
GO:0050806	positive regulation of synaptic transmission	2	0.99	0.0428
GO:0030595	leukocyte chemotaxis	2	0.97	0.0451
GO:0035304	regulation of protein dephosphorylation	2	0.97	0.0451
GO:0034250	positive regulation of cellular amide metabolic process	2	0.97	0.0456
GO:0043401	steroid hormone mediated signaling pathway	2	0.97	0.0456
GO:0002460	adaptive immune response based on somatic recombination of immune receptors built from immunoglo	2	0.97	0.0461

GO:0034249	negative regulation of cellular amide metabolic process	2	0.96	0.0468
GO:0015850	organic hydroxy compound transport	2	0.96	0.0474
GO:0048754	branching morphogenesis of an epithelial tube	2	0.96	0.0474
GO:0001816	cytokine production	2	0.95	0.0491
GO:0051641	cellular localization	8	0.35	0.0491
GO:1902600	proton transmembrane transport	2	0.95	0.0491
GO:0034613	cellular protein localization	6	0.43	0.0499

BP - Cluster 2

#term ID	term description	gene count	strength	FDR
GO:0007186	G protein-coupled receptor signaling pathway	15	0.94	1.40e-08
GO:0042592	homeostatic process	16	0.89	1.40e-08
GO:0048878	chemical homeostasis	14	1.01	1.40e-08
GO:0002791	regulation of peptide secretion	10	1.2	1.24e-07
GO:0007187	G protein-coupled receptor signaling pathway, coupled to cyclic nucleotide second messenger	8	1.45	1.24e-07
GO:0050708	regulation of protein secretion	9	1.19	1.06e-06
GO:0065008	regulation of biological quality	19	0.59	1.09e-06
GO:0009636	response to toxic substance	9	1.14	1.93e-06
GO:0042493	response to drug	11	0.95	1.93e-06
GO:0050896	response to stimulus	25	0.36	1.93e-06
GO:0051048	negative regulation of secretion	7	1.4	1.93e-06
GO:0051049	regulation of transport	14	0.77	1.93e-06
GO:0051716	cellular response to stimulus	23	0.43	1.93e-06
GO:1901700	response to oxygen-containing compound	13	0.82	1.93e-06
GO:1903530	regulation of secretion by cell	10	1.03	1.93e-06
GO:0051051	negative regulation of transport	8	1.11	1.15e-05
GO:0031667	response to nutrient levels	8	1.11	1.19e-05
GO:0007188	adenylate cyclase-modulating G protein-coupled receptor signaling pathway	6	1.38	1.36e-05
GO:0009605	response to external stimulus	14	0.67	1.36e-05
GO:0032879	regulation of localization	15	0.63	1.36e-05

GO:0046677	response to antibiotic	7	1.22	1.36e-05
GO:0051050	positive regulation of transport	10	0.91	1.36e-05
GO:0007154	cell communication	20	0.44	2.43e-05
GO:0007218	neuropeptide signaling pathway	5	1.52	2.79e-05
GO:0007610	behavior	8	1.03	2.85e-05
GO:0042221	response to chemical	18	0.5	2.85e-05
GO:0007165	signal transduction	19	0.46	3.05e-05
GO:0010033	response to organic substance	15	0.59	3.90e-05
GO:0097305	response to alcohol	6	1.27	3.90e-05
GO:0019725	cellular homeostasis	9	0.91	4.23e-05
GO:0010646	regulation of cell communication	16	0.54	4.58e-05
GO:0065009	regulation of molecular function	16	0.54	4.58e-05
GO:0033993	response to lipid	9	0.9	4.72e-05
GO:0023051	regulation of signaling	16	0.54	4.95e-05
GO:0045471	response to ethanol	5	1.43	5.18e-05
GO:0048521	negative regulation of behavior	3	2.16	7.98e-05
GO:0048871	multicellular organismal homeostasis	6	1.19	8.82e-05
GO:0050795	regulation of behavior	4	1.63	0.00011
GO:0010035	response to inorganic substance	7	1.01	0.00014
GO:0042593	glucose homeostasis	5	1.33	0.00014
GO:0008217	regulation of blood pressure	5	1.31	0.00015
GO:0045187	regulation of circadian sleep/wake cycle, sleep	3	2.02	0.00015
GO:0050804	modulation of chemical synaptic transmission	6	1.14	0.00015
GO:1903531	negative regulation of secretion by cell	5	1.31	0.00015
GO:0010817	regulation of hormone levels	7	1.0	0.00016
GO:0051952	regulation of amine transport	4	1.55	0.00017
GO:0062012	regulation of small molecule metabolic process	6	1.12	0.00017
GO:2001023	regulation of response to drug	4	1.54	0.00018
GO:0007193	adenylate cyclase-inhibiting G protein-coupled receptor signaling pathway	4	1.53	0.00019
GO:0060259	regulation of feeding behavior	3	1.94	0.00022
GO:0071377	cellular response to glucagon stimulus	3	1.92	0.00024

GO:0090276	regulation of peptide hormone secretion	5	1.25	0.00024
GO:2001025	positive regulation of response to drug	3	1.92	0.00024
GO:0007631	feeding behavior	4	1.49	0.00025
GO:0051341	regulation of oxidoreductase activity	4	1.49	0.00025
GO:0051354	negative regulation of oxidoreductase activity	3	1.91	0.00025
GO:0008015	blood circulation	6	1.07	0.00027
GO:0014059	regulation of dopamine secretion	3	1.89	0.00027
GO:0042752	regulation of circadian rhythm	4	1.47	0.00028
GO:0006874	cellular calcium ion homeostasis	6	1.05	0.00032
GO:0001975	response to amphetamine	3	1.85	0.00033
GO:0032228	regulation of synaptic transmission, GABAergic	3	1.82	0.00038
GO:0010243	response to organonitrogen compound	8	0.82	0.00040
GO:0090207	regulation of triglyceride metabolic process	3	1.81	0.00040
GO:0033602	negative regulation of dopamine secretion	2	2.68	0.00041
GO:0050709	negative regulation of protein secretion	4	1.41	0.00041
GO:0051586	positive regulation of dopamine uptake involved in synaptic transmission	2	2.68	0.00041
GO:0051954	positive regulation of amine transport	3	1.79	0.00041
GO:1904640	response to methionine	2	2.68	0.00041
GO:1901615	organic hydroxy compound metabolic process	6	1.01	0.00045
GO:0048511	rhythmic process	5	1.16	0.00046
GO:0055082	cellular chemical homeostasis	7	0.88	0.00052
GO:0038171	cannabinoid signaling pathway	2	2.56	0.00053
GO:0002793	positive regulation of peptide secretion	5	1.14	0.00054
GO:0032101	regulation of response to external stimulus	8	0.78	0.00060
GO:0006869	lipid transport	5	1.12	0.00063
GO:0050801	ion homeostasis	7	0.86	0.00070
GO:0050999	regulation of nitric-oxide synthase activity	3	1.68	0.00070
GO:0045776	negative regulation of blood pressure	3	1.67	0.00072
GO:0019220	regulation of phosphate metabolic process	10	0.64	0.00074
GO:0048584	positive regulation of response to stimulus	11	0.59	0.00078
GO:0043271	negative regulation of ion transport	4	1.31	0.00079

GO:0097366	response to bronchodilator	3	1.64	0.00085
GO:0050789	regulation of biological process	25	0.21	0.00086
GO:0042220	response to cocaine	3	1.63	0.00087
GO:0050994	regulation of lipid catabolic process	3	1.63	0.00087
GO:0032102	negative regulation of response to external stimulus	5	1.07	0.00098
GO:0015909	long-chain fatty acid transport	3	1.6	0.0010
GO:0007267	cell-cell signaling	8	0.73	0.0011
GO:0044281	small molecule metabolic process	10	0.61	0.0011
GO:0010898	positive regulation of triglyceride catabolic process	2	2.26	0.0012
GO:0043086	negative regulation of catalytic activity	7	0.8	0.0012
GO:0045759	negative regulation of action potential	2	2.26	0.0012
GO:0051001	negative regulation of nitric-oxide synthase activity	2	2.26	0.0012
GO:0051241	negative regulation of multicellular organismal process	8	0.72	0.0012
GO:2000252	negative regulation of feeding behavior	2	2.26	0.0012
GO:0003008	system process	10	0.6	0.0013
GO:0014823	response to activity	3	1.54	0.0013
GO:0044092	negative regulation of molecular function	8	0.71	0.0013
GO:0050707	regulation of cytokine secretion	4	1.22	0.0013
GO:0050727	regulation of inflammatory response	5	1.03	0.0013
GO:0050790	regulation of catalytic activity	11	0.55	0.0013
GO:0050796	regulation of insulin secretion	4	1.23	0.0013
GO:0050805	negative regulation of synaptic transmission	3	1.54	0.0013
GO:0051966	regulation of synaptic transmission, glutamatergic	3	1.55	0.0013
GO:0010469	regulation of signaling receptor activity	6	0.88	0.0014
GO:0031348	negative regulation of defense response	4	1.21	0.0014
GO:0051926	negative regulation of calcium ion transport	3	1.52	0.0014
GO:0097164	ammonium ion metabolic process	4	1.21	0.0014
GO:0006641	triglyceride metabolic process	3	1.5	0.0015
GO:0007195	adenylate cyclase-inhibiting dopamine receptor signaling pathway	2	2.16	0.0015
GO:0007626	locomotory behavior	4	1.2	0.0015
GO:0032870	cellular response to hormone stimulus	6	0.87	0.0015

GO:0046717	acid secretion	3	1.5	0.0015
GO:1903532	positive regulation of secretion by cell	5	1.0	0.0015
GO:0031652	positive regulation of heat generation	2	2.12	0.0016
GO:0034776	response to histamine	2	2.12	0.0016
GO:0006629	lipid metabolic process	8	0.69	0.0017
GO:0014070	response to organic cyclic compound	7	0.76	0.0017
GO:0019216	regulation of lipid metabolic process	5	0.99	0.0017
GO:0048518	positive regulation of biological process	17	0.35	0.0017
GO:0051239	regulation of multicellular organismal process	12	0.49	0.0017
GO:0051240	positive regulation of multicellular organismal process	9	0.62	0.0017
GO:0072347	response to anesthetic	3	1.47	0.0017
GO:0019233	sensory perception of pain	3	1.46	0.0018
GO:0033004	negative regulation of mast cell activation	2	2.08	0.0018
GO:0006898	receptor-mediated endocytosis	4	1.14	0.0020
GO:0007584	response to nutrient	4	1.14	0.0020
GO:0048870	cell motility	7	0.74	0.0020
GO:0002028	regulation of sodium ion transport	3	1.42	0.0021
GO:0048149	behavioral response to ethanol	2	2.02	0.0021
GO:0048583	regulation of response to stimulus	14	0.42	0.0021
GO:0051967	negative regulation of synaptic transmission, glutamatergic	2	2.02	0.0021
GO:0010647	positive regulation of cell communication	9	0.6	0.0022
GO:0042391	regulation of membrane potential	5	0.95	0.0022
GO:0099537	trans-synaptic signaling	5	0.95	0.0022
GO:0023056	positive regulation of signaling	9	0.6	0.0023
GO:0044255	cellular lipid metabolic process	7	0.73	0.0023
GO:0002683	negative regulation of immune system process	5	0.93	0.0025
GO:0031347	regulation of defense response	6	0.81	0.0026
GO:0050714	positive regulation of protein secretion	4	1.08	0.0030
GO:0090277	positive regulation of peptide hormone secretion	3	1.36	0.0030
GO:0000303	response to superoxide	2	1.88	0.0034
GO:0007263	nitric oxide mediated signal transduction	2	1.88	0.0034

GO:1901386	negative regulation of voltage-gated calcium channel activity	2	1.88	0.0034
GO:0007204	positive regulation of cytosolic calcium ion concentration	4	1.06	0.0035
GO:0007568	aging	4	1.06	0.0037
GO:0048148	behavioral response to cocaine	2	1.86	0.0037
GO:0009410	response to xenobiotic stimulus	4	1.04	0.0039
GO:0045937	positive regulation of phosphate metabolic process	7	0.68	0.0039
GO:0019932	second-messenger-mediated signaling	4	1.04	0.0041
GO:0070887	cellular response to chemical stimulus	11	0.47	0.0042
GO:0019218	regulation of steroid metabolic process	3	1.29	0.0044
GO:0070168	negative regulation of biomineral tissue development	2	1.8	0.0045
GO:0002719	negative regulation of cytokine production involved in immune response	2	1.78	0.0049
GO:0050482	arachidonic acid secretion	2	1.78	0.0049
GO:0050728	negative regulation of inflammatory response	3	1.27	0.0049
GO:0050794	regulation of cellular process	23	0.2	0.0049
GO:0019433	triglyceride catabolic process	2	1.76	0.0051
GO:0043410	positive regulation of MAPK cascade	5	0.85	0.0051
GO:0001666	response to hypoxia	4	1.0	0.0052
GO:0006066	alcohol metabolic process	4	1.0	0.0052
GO:0044057	regulation of system process	5	0.85	0.0052
GO:0048585	negative regulation of response to stimulus	8	0.59	0.0052
GO:0060359	response to ammonium ion	3	1.25	0.0052
GO:0002092	positive regulation of receptor internalization	2	1.75	0.0053
GO:0006950	response to stress	12	0.43	0.0053
GO:0002700	regulation of production of molecular mediator of immune response	3	1.24	0.0054
GO:0048522	positive regulation of cellular process	15	0.35	0.0054
GO:0016477	cell migration	6	0.73	0.0056
GO:0032496	response to lipopolysaccharide	4	0.99	0.0056
GO:0042417	dopamine metabolic process	2	1.73	0.0056
GO:0050806	positive regulation of synaptic transmission	3	1.24	0.0056
GO:0003206	cardiac chamber morphogenesis	3	1.23	0.0057
GO:0046058	cAMP metabolic process	2	1.71	0.0058

GO:0048519	negative regulation of biological process	15	0.34	0.0058
GO:0062013	positive regulation of small molecule metabolic process	3	1.23	0.0058
GO:2000352	negative regulation of endothelial cell apoptotic process	2	1.71	0.0058
GO:2001024	negative regulation of response to drug	2	1.7	0.0060
GO:0001662	behavioral fear response	2	1.68	0.0064
GO:0009617	response to bacterium	5	0.81	0.0064
GO:0050777	negative regulation of immune response	3	1.2	0.0064
GO:0007623	circadian rhythm	3	1.2	0.0065
GO:0001101	response to acid chemical	4	0.95	0.0068
GO:0043278	response to morphine	2	1.66	0.0068
GO:0001659	temperature homeostasis	2	1.64	0.0071
GO:0045987	positive regulation of smooth muscle contraction	2	1.64	0.0071
GO:0048873	homeostasis of number of cells within a tissue	2	1.64	0.0071
GO:0007600	sensory perception	6	0.68	0.0082
GO:0032147	activation of protein kinase activity	4	0.92	0.0085
GO:0001894	tissue homeostasis	3	1.15	0.0086
GO:0045777	positive regulation of blood pressure	2	1.59	0.0086
GO:0050877	nervous system process	7	0.6	0.0090
GO:0051180	vitamin transport	2	1.58	0.0090
GO:0051930	regulation of sensory perception of pain	2	1.58	0.0090
GO:0009966	regulation of signal transduction	11	0.42	0.0092
GO:0043269	regulation of ion transport	5	0.77	0.0092
GO:0051179	localization	15	0.32	0.0092
GO:0032501	multicellular organismal process	17	0.28	0.0094
GO:0043434	response to peptide hormone	4	0.9	0.0094
GO:0044058	regulation of digestive system process	2	1.56	0.0095
GO:0043436	oxoacid metabolic process	6	0.66	0.0096
GO:0080134	regulation of response to stress	7	0.59	0.0096
GO:0050704	regulation of interleukin-1 secretion	2	1.55	0.0097
GO:0044093	positive regulation of molecular function	8	0.53	0.0102
GO:0045785	positive regulation of cell adhesion	4	0.89	0.0102

GO:1902533	positive regulation of intracellular signal transduction	6	0.66	0.0102
GO:0032374	regulation of cholesterol transport	2	1.53	0.0104
GO:0046326	positive regulation of glucose import	2	1.53	0.0104
GO:0048678	response to axon injury	2	1.53	0.0104
GO:0050918	positive chemotaxis	2	1.53	0.0104
GO:0006953	acute-phase response	2	1.51	0.0110
GO:0050866	negative regulation of cell activation	3	1.09	0.0110
GO:0055081	anion homeostasis	2	1.51	0.0110
GO:0002040	sprouting angiogenesis	2	1.5	0.0113
GO:0006094	gluconeogenesis	2	1.5	0.0113
GO:0001932	regulation of protein phosphorylation	7	0.57	0.0119
GO:0046486	glycerolipid metabolic process	4	0.86	0.0120
GO:0071310	cellular response to organic substance	9	0.47	0.0120
GO:0007268	chemical synaptic transmission	4	0.86	0.0121
GO:0035094	response to nicotine	2	1.47	0.0122
GO:0043085	positive regulation of catalytic activity	7	0.57	0.0122
GO:0000302	response to reactive oxygen species	3	1.06	0.0123
GO:0002682	regulation of immune system process	7	0.56	0.0125
GO:0015711	organic anion transport	4	0.85	0.0130
GO:0034764	positive regulation of transmembrane transport	3	1.05	0.0131
GO:0031279	regulation of cyclase activity	2	1.45	0.0133
GO:0070374	positive regulation of ERK1 and ERK2 cascade	3	1.05	0.0134
GO:0051339	regulation of lyase activity	2	1.44	0.0137
GO:0090181	regulation of cholesterol metabolic process	2	1.43	0.0141
GO:0008016	regulation of heart contraction	3	1.03	0.0142
GO:0009628	response to abiotic stimulus	6	0.62	0.0142
GO:0043536	positive regulation of blood vessel endothelial cell migration	2	1.42	0.0145
GO:0046903	secretion	6	0.61	0.0153
GO:0050710	negative regulation of cytokine secretion	2	1.4	0.0159
GO:0048523	negative regulation of cellular process	13	0.33	0.0170
GO:0043542	endothelial cell migration	2	1.38	0.0173

GO:0009967	positive regulation of signal transduction	7	0.53	0.0175
GO:0090257	regulation of muscle system process	3	0.99	0.0184
GO:0032787	monocarboxylic acid metabolic process	4	0.78	0.0202
GO:0009987	cellular process	26	0.11	0.0205
GO:0045859	regulation of protein kinase activity	5	0.66	0.0205
GO:0022600	digestive system process	2	1.33	0.0207
GO:0050878	regulation of body fluid levels	4	0.78	0.0207
GO:0060193	positive regulation of lipase activity	2	1.33	0.0207
GO:0071331	cellular response to hexose stimulus	2	1.33	0.0207
GO:0007611	learning or memory	3	0.96	0.0208
GO:0006935	chemotaxis	4	0.77	0.0215
GO:0042632	cholesterol homeostasis	2	1.31	0.0217
GO:0072359	circulatory system development	5	0.65	0.0217
GO:1902930	regulation of alcohol biosynthetic process	2	1.31	0.0217
GO:0046470	phosphatidylcholine metabolic process	2	1.3	0.0220
GO:0051707	response to other organism	6	0.57	0.0220
GO:0032409	regulation of transporter activity	3	0.95	0.0222
GO:0042127	regulation of cell population proliferation	7	0.5	0.0230
GO:0008306	associative learning	2	1.29	0.0232
GO:0008344	adult locomotory behavior	2	1.29	0.0232
GO:0043270	positive regulation of ion transport	3	0.94	0.0233
GO:0051704	multi-organism process	9	0.41	0.0233
GO:0031100	animal organ regeneration	2	1.26	0.0249
GO:0034762	regulation of transmembrane transport	4	0.74	0.0250
GO:0010941	regulation of cell death	7	0.49	0.0254
GO:0016042	lipid catabolic process	3	0.91	0.0255
GO:0019752	carboxylic acid metabolic process	5	0.63	0.0255
GO:0099565	chemical synaptic transmission, postsynaptic	2	1.25	0.0255
GO:0072001	renal system development	3	0.91	0.0258
GO:0060078	regulation of postsynaptic membrane potential	2	1.24	0.0269
GO:0019217	regulation of fatty acid metabolic process	2	1.23	0.0278

GO:0098869	cellular oxidant detoxification	2	1.23	0.0278
GO:0001523	retinoid metabolic process	2	1.22	0.0283
GO:0007189	adenylate cyclase-activating G protein-coupled receptor signaling pathway	2	1.22	0.0288
GO:0046165	alcohol biosynthetic process	2	1.2	0.0302
GO:0051094	positive regulation of developmental process	6	0.53	0.0302
GO:0003073	regulation of systemic arterial blood pressure	2	1.2	0.0306
GO:0006811	ion transport	6	0.53	0.0306
GO:0043266	regulation of potassium ion transport	2	1.2	0.0306
GO:0044283	small molecule biosynthetic process	4	0.71	0.0306
GO:0006631	fatty acid metabolic process	3	0.87	0.0313
GO:0048771	tissue remodeling	2	1.19	0.0313
GO:0001505	regulation of neurotransmitter levels	3	0.87	0.0315
GO:0002027	regulation of heart rate	2	1.18	0.0317
GO:0050900	leukocyte migration	3	0.87	0.0317
GO:0001525	angiogenesis	3	0.86	0.0318
GO:0007166	cell surface receptor signaling pathway	8	0.42	0.0318
GO:1902531	regulation of intracellular signal transduction	7	0.46	0.0340
GO:0010906	regulation of glucose metabolic process	2	1.16	0.0342
GO:0032411	positive regulation of transporter activity	2	1.16	0.0347
GO:0060548	negative regulation of cell death	5	0.58	0.0357
GO:0032526	response to retinoic acid	2	1.14	0.0362
GO:0046660	female sex differentiation	2	1.14	0.0362
GO:0098657	import into cell	4	0.68	0.0363
GO:0003014	renal system process	2	1.13	0.0377
GO:0051781	positive regulation of cell division	2	1.13	0.0377
GO:0007200	phospholipase C-activating G protein-coupled receptor signaling pathway	2	1.12	0.0387
GO:0007613	memory	2	1.12	0.0387
GO:0008203	cholesterol metabolic process	2	1.12	0.0387
GO:0010811	positive regulation of cell-substrate adhesion	2	1.12	0.0387
GO:0010038	response to metal ion	3	0.81	0.0419
GO:0071774	response to fibroblast growth factor	2	1.1	0.0419

GO:0019637	organophosphate metabolic process	5	0.55	0.0426
GO:0050715	positive regulation of cytokine secretion	2	1.09	0.0428
GO:2000026	regulation of multicellular organismal development	7	0.43	0.0436
GO:0035270	endocrine system development	2	1.08	0.0446
GO:0050729	positive regulation of inflammatory response	2	1.08	0.0446
GO:0072006	nephron development	2	1.08	0.0450
GO:0003231	cardiac ventricle development	2	1.06	0.0475
GO:0050793	regulation of developmental process	8	0.38	0.0493

BP - Cluster 3

#term ID	term description	gene count	strength	FDR
GO:0001659	temperature homeostasis	2	2.3	0.0067
GO:0060259	regulation of feeding behavior	2	2.42	0.0067
GO:0007189	adenylate cyclase-activating G protein-coupled receptor signaling pathway	2	1.87	0.0191

BP - Cluster 4

#term ID	term description	gene count	strength	FDR
GO:0007154	cell communication	10	0.53	0.0039
GO:0007165	signal transduction	9	0.53	0.0039
GO:0007189	adenylate cyclase-activating G protein-coupled receptor signaling pathway	3	1.78	0.0039
GO:0007190	activation of adenylate cyclase activity	2	2.15	0.0039
GO:0008217	regulation of blood pressure	3	1.48	0.0039
GO:0008277	regulation of G protein-coupled receptor signaling pathway	3	1.57	0.0039
GO:0009966	regulation of signal transduction	8	0.67	0.0039
GO:0023051	regulation of signaling	9	0.68	0.0039
GO:0023052	signaling	10	0.54	0.0039
GO:0035556	intracellular signal transduction	6	0.84	0.0039
GO:0040014	regulation of multicellular organism growth	3	1.89	0.0039
GO:0043410	positive regulation of MAPK cascade	5	1.24	0.0039

GO:0048584	positive regulation of response to stimulus	7	0.78	0.0039
GO:0097647	amylin receptor signaling pathway	2	2.71	0.0039
GO:1902533	positive regulation of intracellular signal transduction	6	1.05	0.0039
GO:0040018	positive regulation of multicellular organism growth	2	2.03	0.0045
GO:0070873	regulation of glycogen metabolic process	2	2.02	0.0045
GO:0010469	regulation of signaling receptor activity	4	1.09	0.0049
GO:0051239	regulation of multicellular organismal process	7	0.65	0.0050
GO:0010033	response to organic substance	7	0.65	0.0051
GO:0045927	positive regulation of growth	3	1.33	0.0065
GO:0007186	G protein-coupled receptor signaling pathway	5	0.85	0.0067
GO:0040008	regulation of growth	4	1.03	0.0067
GO:0042221	response to chemical	8	0.53	0.0067
GO:0010604	positive regulation of macromolecule metabolic process	7	0.61	0.0076
GO:0050790	regulation of catalytic activity	6	0.68	0.0103
GO:0065009	regulation of molecular function	7	0.57	0.0110
GO:0031016	pancreas development	2	1.69	0.0113
GO:0071902	positive regulation of protein serine/threonine kinase activity	3	1.2	0.0115
GO:0033993	response to lipid	4	0.94	0.0117
GO:0009725	response to hormone	4	0.92	0.0127
GO:0065008	regulation of biological quality	7	0.54	0.0140
GO:0048522	positive regulation of cellular process	8	0.46	0.0149
GO:0006091	generation of precursor metabolites and energy	3	1.13	0.0154
GO:0032501	multicellular organismal process	9	0.39	0.0157
GO:0031667	response to nutrient levels	3	1.07	0.0200
GO:0010628	positive regulation of gene expression	5	0.69	0.0219
GO:0032355	response to estradiol	2	1.45	0.0234
GO:0010817	regulation of hormone levels	3	1.02	0.0255
GO:0051173	positive regulation of nitrogen compound metabolic process	6	0.56	0.0264
GO:0031325	positive regulation of cellular metabolic process	6	0.54	0.0314
GO:0051897	positive regulation of protein kinase B signaling	2	1.36	0.0320
GO:0003018	vascular process in circulatory system	2	1.34	0.0332

GO:0032870	cellular response to hormone stimulus	3	0.96	0.0334
GO:0050731	positive regulation of peptidyl-tyrosine phosphorylation	2	1.3	0.0393
GO:0007166	cell surface receptor signaling pathway	5	0.61	0.0397
GO:0071310	cellular response to organic substance	5	0.6	0.0409
GO:0034764	positive regulation of transmembrane transport	2	1.26	0.0429
GO:0043085	positive regulation of catalytic activity	4	0.71	0.0451
GO:1901700	response to oxygen-containing compound	4	0.7	0.0491

Table S5. GO processes associated with the 4 functional clusters.

MF - Cluster 1				
#term ID	**term description**	**gene count**	**strength**	**FDR**
GO:0005102	signaling receptor binding	23	0.97	1.25e-16
GO:0048018	receptor ligand activity	14	1.27	8.16e-13
GO:0042802	identical protein binding	17	0.77	1.77e-08
GO:0098772	molecular function regulator	17	0.76	1.99e-08
GO:0005515	protein binding	28	0.41	2.27e-08
GO:0005179	hormone activity	7	1.54	5.67e-08
GO:0005125	cytokine activity	7	1.3	2.09e-06
GO:0005488	binding	31	0.2	8.00e-05
GO:0005159	insulin-like growth factor receptor binding	3	2.06	0.00011
GO:0005126	cytokine receptor binding	6	1.13	0.00013
GO:0008083	growth factor activity	5	1.28	0.00016
GO:0005158	insulin receptor binding	3	1.9	0.00021
GO:0016209	antioxidant activity	4	1.49	0.00021
GO:0005504	fatty acid binding	3	1.83	0.00029
GO:0017077	oxidative phosphorylation uncoupler activity	2	2.61	0.00045
GO:0004879	nuclear receptor activity	3	1.56	0.0015
GO:0044877	protein-containing complex binding	8	0.7	0.0019
GO:0051427	hormone receptor binding	4	1.15	0.0026
GO:0031406	carboxylic acid binding	4	1.12	0.0033
GO:0036041	long-chain fatty acid binding	2	1.97	0.0033
GO:0042803	protein homodimerization activity	7	0.71	0.0038
GO:0008289	lipid binding	6	0.74	0.0076
GO:0050750	low-density lipoprotein particle receptor binding	2	1.74	0.0076
GO:0061629	RNA polymerase II-specific DNA-binding transcription factor binding	4	0.98	0.0083
GO:0071813	lipoprotein particle binding	2	1.69	0.0086
GO:0046983	protein dimerization activity	8	0.58	0.0087
GO:0050662	coenzyme binding	4	0.95	0.0090
GO:0001103	RNA polymerase II repressing transcription factor binding	2	1.62	0.0097

GO:0002020	protease binding	3	1.13	0.0118
GO:0019899	enzyme binding	10	0.44	0.0151
GO:0035257	nuclear hormone receptor binding	3	1.09	0.0151
GO:0008201	heparin binding	3	1.06	0.0173
GO:0019902	phosphatase binding	3	1.04	0.0190
GO:0030170	pyridoxal phosphate binding	2	1.36	0.0250
GO:0003707	steroid hormone receptor activity	2	1.32	0.0292
GO:0046914	transition metal ion binding	6	0.54	0.0403
GO:0030295	protein kinase activator activity	2	1.2	0.0432
GO:0048037	cofactor binding	4	0.71	0.0443
GO:0000978	RNA polymerase II proximal promoter sequence-specific DNA binding	4	0.7	0.0467
GO:0016811	hydrolase activity, acting on carbon-nitrogen (but not peptide) bonds, in linear amid	2	1.17	0.0467

MF - Cluster 2

#term ID	term description	gene count	strength	FDR
GO:0005102	signaling receptor binding	11	0.72	0.00049
GO:0004949	cannabinoid receptor activity	2	2.68	0.0018
GO:0001664	G protein-coupled receptor binding	5	1.12	0.0022
GO:0048018	receptor ligand activity	6	0.98	0.0022
GO:0001591	dopamine neurotransmitter receptor activity, coupled via Gi/Go	2	2.26	0.0027
GO:0004930	G protein-coupled receptor activity	7	0.79	0.0027
GO:0070405	ammonium ion binding	3	1.52	0.0027
GO:0098772	molecular function regulator	10	0.61	0.0027
GO:0035240	dopamine binding	2	2.05	0.0035
GO:0099106	ion channel regulator activity	3	1.34	0.0063
GO:0005515	protein binding	18	0.3	0.0070
GO:0005319	lipid transporter activity	3	1.21	0.0115
GO:0008289	lipid binding	5	0.73	0.0233
GO:0015459	potassium channel regulator activity	2	1.45	0.0233
GO:0031406	carboxylic acid binding	3	1.07	0.0233

GO:0043178	alcohol binding	2	1.26	0.0473

MF - Cluster 3

#term ID	term description	gene count	strength	FDR
GO:0004980	melanocyte-stimulating hormone receptor activity	2	3.34	3.76e-05
GO:0042923	neuropeptide binding	2	2.45	0.00037
GO:0017046	peptide hormone binding	2	2.18	0.00093

MF - Cluster 4

#term ID	term description	gene count	strength	FDR
GO:0017046	peptide hormone binding	3	2.09	0.00020
GO:0097642	calcitonin family receptor activity	2	2.77	0.00030
GO:0097644	calcitonin family binding	2	2.85	0.00030
GO:0005179	hormone activity	3	1.64	0.00082
GO:0004930	G protein-coupled receptor activity	4	0.94	0.0102
GO:0008083	growth factor activity	2	1.35	0.0271
GO:0005488	binding	11	0.22	0.0273
GO:0005102	signaling receptor binding	4	0.67	0.0419

Table S5. GO processes associated with the 4 functional clusters.

CC - Cluster 1				
#term ID	**term description**	**gene count**	**strength**	**FDR**
GO:0005615	extracellular space	19	1.01	1.07e-13
GO:0005576	extracellular region	22	0.73	3.82e-11
GO:0060205	cytoplasmic vesicle lumen	11	1.3	2.81e-10
GO:0034774	secretory granule lumen	10	1.28	2.86e-09
GO:0030141	secretory granule	11	0.91	1.37e-06
GO:0031093	platelet alpha granule lumen	5	1.65	2.92e-06
GO:0031410	cytoplasmic vesicle	14	0.58	6.97e-05
GO:0031012	extracellular matrix	5	1.03	0.0012
GO:0070013	intracellular organelle lumen	19	0.35	0.0012
GO:0005788	endoplasmic reticulum lumen	5	1.01	0.0013
GO:0042627	chylomicron	2	1.97	0.0026
GO:0034361	very-low-density lipoprotein particle	2	1.79	0.0054
GO:0009986	cell surface	6	0.73	0.0068
GO:0012505	endomembrane system	15	0.32	0.0143
GO:0005739	mitochondrion	8	0.5	0.0184
GO:0005737	cytoplasm	26	0.15	0.0269
GO:0070062	extracellular exosome	2	1.18	0.0497

CC - Cluster 2				
#term ID	**term description**	**gene count**	**strength**	**FDR**
GO:0034364	high-density lipoprotein particle	4	2.02	1.47e-05
GO:0034366	spherical high-density lipoprotein particle	3	2.38	2.75e-05
GO:0005615	extracellular space	10	0.81	3.67e-05
GO:0071682	endocytic vesicle lumen	3	2.06	7.42e-05
GO:0030139	endocytic vesicle	5	1.12	0.00066
GO:0005576	extracellular region	12	0.54	0.00086
GO:0005887	integral component of plasma membrane	8	0.57	0.0138

GO:0120025	plasma membrane bounded cell projection	8	0.48	0.0399

CC - Cluster 3

No significant CC were identified for this cluster.

CC - Cluster 4

#term ID	term description	gene count	strength	FDR
GO:0038037	G protein-coupled receptor dimeric complex	2	2.65	0.00026
GO:0043235	receptor complex	4	1.37	0.00026
GO:1903440	amylin receptor complex	2	2.95	0.00026
GO:0034774	secretory granule lumen	3	1.22	0.0068
GO:0005615	extracellular space	4	0.8	0.0180

Table S6. Genes associated with pediatric obesity and obesity in adulthood and genes associated exclusively with pediatric obesity.

C2362324 (PO):	C2362324 (PO) AND C0028754 (Ob):			
CNR2	FTO	CAT	SORT1	ATP6
BCKDHB	CETP	PON1	RORC	MSRA
ZNF771	APOA5	FAAH	SCG5	MMP2
SNORA73A	APOA1	SIRT1	TNF	MEST
MIR412	MC3R	GNB3	TGFB1	ARSD
NLK	MC4R	TM6SF2	STAT3	MIR27A
PTPRN2	ADIPOQ	LRP1B	DST	MIR216A
ARID5B	LEP	PLIN1	SOD2	MTNR1B
LIMD2	PPARG	PCSK1	BNIP3	NOS3
TMEM134	POMC	PMAIP1	SLC6A8	PCK1
LINC00839	INS	GHRL	SLC6A4	SOST
ARHGEF2	LEPR	BBS4	CD69	IL22
PDE8B	DRD2	BBS2	ADA	SERPINE1
AKTIP	PPARA	PEX1	SH2B1	OXTR
GPX6	FABP4	PGF	GAD2	TNFRSF11B
RRAS2	APOE	MAGEL2	NEDD4L	NUCB2
SKA1	ALMS1	RETN	AKR1B1	NPY2R
HCP5	GCG	PYY	FDXR	MIR17
CTPP	ANGPTL4	PTH	FGF21	LPL
MIR642B	GPT	MAP2K5	MYCBP	HSD11B1
MIR1203	BDNF	KLF13	ACAD8	ACACB
RAMP2-AS1	ADRB3	PTPRS	FETUB	HFE
CNP	ENPP1	ATP5F1E	GIPR	GPX4
CORD1	NMU	UCP1	GHSR	GPX1
NMS	IL10	NR0B2	GHR	ANGPT1
GYS2	UCP3	MKKS	GH1	IGF2
GPX5	AMD1	CALR	GCKR	LMNA
IMPDH2	UCP2	CALCR	GC	LGALS1
LMX1B	IGF1	STEAP4	FAT1	
KCNC2	TST	MCHR2	ALB	
ITIH4	OLFM4	GDF15	EBP	
	GRN	LRAT	RAMP2	
	RBP4	CD5L	NAMPT	
	PNPLA3	SOCS3	ADCY3	
	BCL2	WASF1	ELAVL2	
	HP	PER3	DRD4	
	VEGFA	MBOAT7	DNMT1	
	TMEM18	KCTD15	CRP	
	MMP9	HDAC4	GNPDA2	
	IL17A	HIF3A	CNR1	
	ENHO	SFRP5	AMY1A	
	IRS1	TNMD	AMY1B	
	AQP7	SCD	AMY1C	
	TNNI3K	SAA1	CYTB	

Figure S1. Protein-protein interaction (PPI) network showing the interconnections among the 12 hub-bottleneck genes and the gene expression patterns in omental adipose tissue of children with obesity. The green ellipses indicate the down-regulated genes, while the red ellipses depict the up-regulated genes. The light green ellipses represent genes that demonstrated a logFC between 1- and 0, while the beige ellipse indicates the gene with a logFC between 0 and 1. Genes that were not analyzed by the GSE9624 dataset are represented by white ellipses.

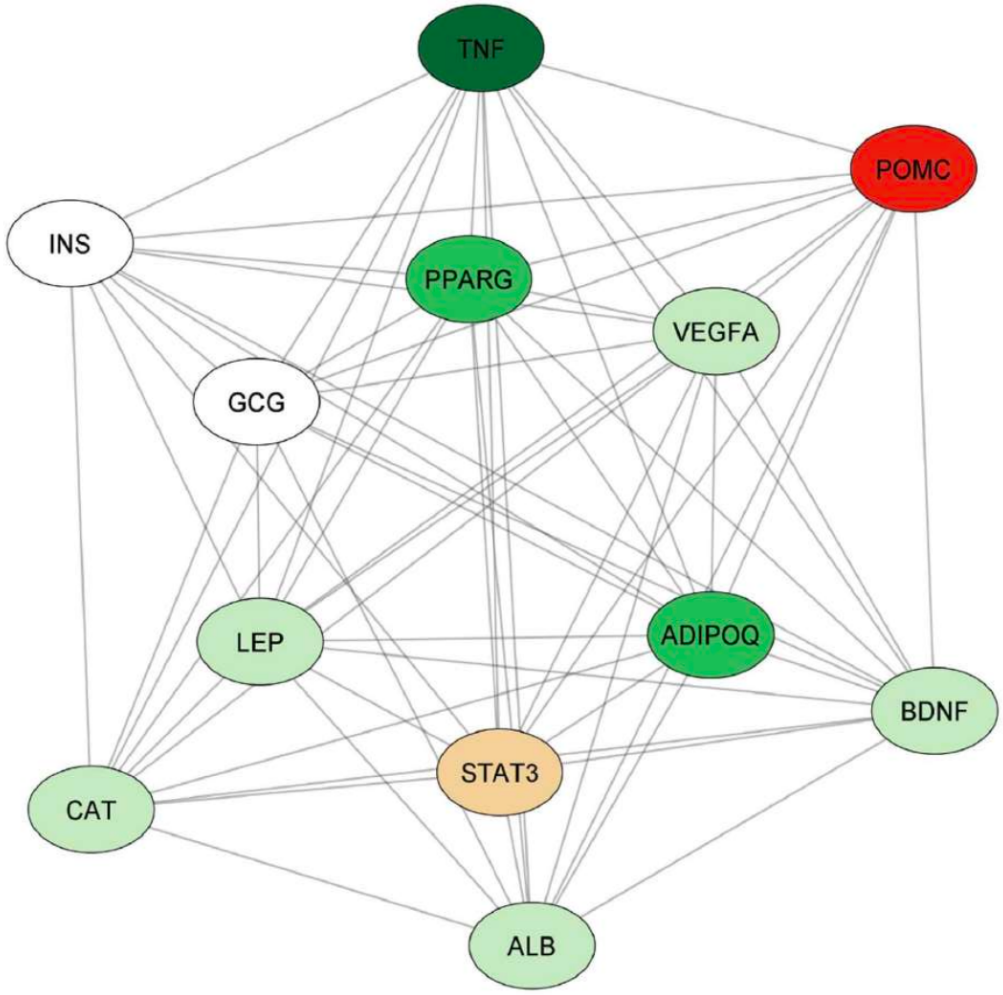
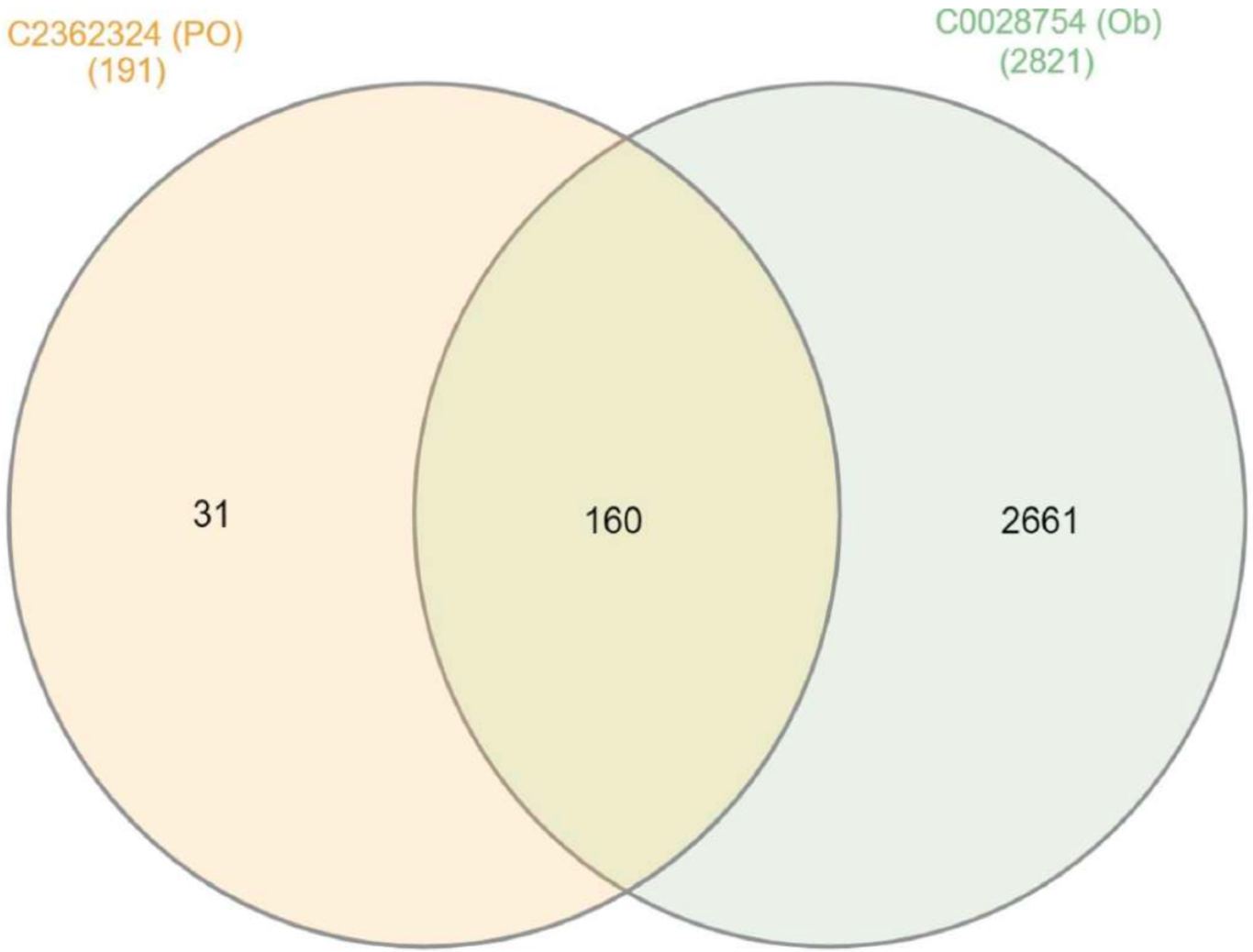


Figure S2. Venn diagram demonstrating the superimposition of the lists of genes associated with childhood obesity and overall obesity retrieved from the DisGeNET database. PO: pediatric obesity; Ob: obesity.



CAPÍTULO 3

Fatores epigenéticos e obesidade infantil

ARTIGO 2

“Network Insights into Childhood Obesity: Unveiling Methylated-Differentially Expressed Genes and Pathways through Integrative Bioinformatics Analysis”

Artigo submetido na revista European Journal of Human Genetics

Fator de Impacto: 3,7

CAPÍTULO 4

Fatores ambientais e obesidade

ARTIGO 3

“Western style-based cafeteria diet induces alterations in weight, metabolic profile, and expression of a set of metabolic and inflammatory genes in C57BL/6 mice”

Artigo submetido na revista Endocrine Connections

Fator de Impacto: 2,6

CAPÍTULO 5

O consumo do mirtilo e a obesidade

ARTIGO 4

“Dietary blueberry supplementation attenuates the effects of a cafeteria diet on weight gain and metabolic parameters, enhancing nutrigenomic profiles in C57BL/6 mice”

CONSIDERAÇÕES FINAIS

A obesidade apresenta etiologia complexa e multifatorial, sendo que fatores genéticos, epigenéticos e ambientais (como alimentação e sedentarismo) influenciam diretamente em sua patogênese. No entanto, devido à sua complexidade, os mecanismos moleculares e bioquímicos envolvidos no desenvolvimento da obesidade ainda não são completamente elucidados. Apesar disso, estudos vêm demonstrando que padrões alterados de expressão gênica e de metilação de DNA podem afetar indivíduos desde a infância, sendo que estes padrões podem persistir na vida adulta, especialmente quando estes indivíduos estão cronicamente expostos a ambientes considerados obesogênicos. Neste sentido, esta tese é composta de quatro estudos que avaliaram fatores genéticos, epigenéticos e ambientais envolvidos na obesidade.

No primeiro estudo, identificamos 191 genes previamente associados com a obesidade infantil através de uma busca sistemática no banco de dados DisGeNET. As análises de topografia de rede demonstraram 12 genes altamente interconectados, os quais foram considerados como genes *hub-bottleneck* (*INS*, *LEP*, *STAT3*, *POMC*, *ALB*, *TNF*, *BDNF*, *CAT*, *GCG*, *PPARG*, *VEGFA* e *ADIPOQ*). Análises de enriquecimento funcional demonstraram que estes 12 genes estão envolvidos em 38 vias KEGG, incluindo vias relacionadas ao metabolismo da glicose e de lipídeos, termogênese e inflamação. Ainda, foram destacados quatro módulos funcionais na rede de interação, os quais contém genes envolvidos no metabolismo de carboidratos e de lipídeos, inflamação, hipóxia, resistência à insulina e regulação de adipocitocinas.

No segundo estudo desta tese, realizamos a identificação de MeDEGs envolvidos na obesidade infantil utilizando bancos de dados públicos de expressão gênica e de metilação de DNA depositados no banco GEO. A partir da sobreposição de

DEGs e DMGs, foi possível identificar 70 MeDEGs, sendo que 25 genes apresentaram padrão hipermetilado-expressão reduzida e 45 apresentaram padrão hipometilado-expressão aumentada em pacientes com obesidade infantil comparado a controles eutróficos. As análises de topografia de rede de interação demonstraram que os genes *STAT1*, *CCL5* e *GATA3* apresentaram maior interconexão, sendo, portanto, considerados como genes *hub-bottleneck*. As análises de enriquecimento funcional demonstraram que estes três genes estão envolvidos em vias de senescência celular, apoptose, PI3K-Akt, além de vias relacionadas a inflamação. Em resumo, nossos resultados sugerem que novos MeDEGs podem ter um papel importante na obesidade infantil.

No terceiro estudo, realizamos a padronização e oferta da DCAF a camundongos C57BL/6. Nossos dados demonstraram que a exposição à DCAF levou os animais a desenvolverem obesidade, visto que após 16 semanas de acompanhamento, os camundongos do grupo DCAF ganharam mais peso comparado aos animais do grupo controle. Além disso, os animais do grupo DCAF desenvolveram desordens metabólicas associadas à obesidade, como hiperglicemia, hiperinsulinemia, RI, hiperleptinemia, hiperadiponectinemia e esteatose hepática. Também demonstramos que a exposição à DCAF induziu a desregulação de alguns genes relacionados à via das adipocitocinas, de inflamação, de apoptose e do metabolismo da glicose e de lipídeos no TAV, TAS, fígado e músculo destes animais. Interessantemente, a relação *Itgax/Llgl1* estava aumentada no TAV dos camundongos expostos à DCAF, o que indica uma mudança no fenótipo dos macrófagos de M2 para M1. É importante ressaltar que o fenótipo M1 de macrófagos é considerado pró-inflamatório, o que pode contribuir para a inflamação crônica de baixo grau observada em indivíduos com obesidade.

No nosso quarto estudo, avaliamos o efeito do consumo de mirtilo sobre parâmetros biométricos, metabólicos e nutrigenômicos em camundongos C57BL/6

expostos à DCAF. Este trabalho evidenciou que o consumo de mirtilo preveniu o ganho de peso induzido pela DCAF, sendo que após 16 semanas de seguimento, os animais do grupo BB demonstraram peso similar aos animais do grupo controle. Além disso, o consumo de mirtilo foi capaz de prevenir parcialmente o aumento da glicemia de jejum e os níveis circulantes de adiponectina. Ainda, o escore de esteatose hepática e os níveis séricos de leptina e de irisina também foram semelhantes entre os grupos controle e BB, e aumentados no grupo DCAF. O consumo de mirtilo também foi capaz de regular a capacidade antioxidante do cérebro e do fígado nestes animais. Por fim, verificamos que a exposição ao mirtilo favoreceu a modulação de uma miríade de genes envolvidos em rotas de apoptose, metabolismo de glicose e lipídeos, estresse oxidativo, inflamação e de adipocitocinas no TAV, TAS, TAM, músculo, fígado e hipotálamo destes animais. Considerando estes achados, o consumo de mirtilos poderia contribuir no tratamento da obesidade e de seus desfechos associados.

Como perspectivas futuras, pretendemos realizar análises moleculares em outros órgãos obtidos dos camundongos oriundos do quarto estudo, tais como: coração, rins, pâncreas, tecido adiposo epididimal e fezes (análises da composição da microbiota). Nestas futuras análises, pretendemos identificar um perfil modificado de expressão gênica nestes órgãos, bem como caracterizar a composição da microbiota destes animais submetidos à DCAF e ao consumo do mirtilo.

OUTRAS PRODUÇÕES NO PERÍODO DO DOUTORADO

Artigos produzidos durante o período do doutorado como primeiro autor.

1. **The rs2304256 Polymorphism in TYK2 Gene Is Associated with Protection for Type 1 Diabetes Mellitus**

   Autores: **Felipe Mateus Pellenz**, Cristine Dieter, Guilherme Coutinho Kullmann Duarte, Luís Henrique Canani, Bianca Marmontel de Souza, Daisy Crispim.

   Diabetes & Metabolism Journal, 2021;45(6):899-908.

2. **Association of TYK2 polymorphisms with autoimmune diseases: A comprehensive and updated systematic review with meta-analysis**

   Autores: **Felipe Mateus Pellenz**, Cristine Dieter, Natália Emerim Lemos, Andrea Carla Bauer, Bianca Marmontel de Souza, Daisy Crispim.

   Genetics and Molecular Biology, 2021;44(2):e20200425.

Demais produções no período do Doutorado.

1. **Involvement of miR-126 rs4636297 and miR-146a rs2910164 polymorphisms in the susceptibility for diabetic retinopathy: a case-control study in a type 1 diabetes population**

   Autores: Eloísa Toscan Massignam, Cristine Dieter, **Felipe Mateus Pellenz**, Taís Silveira Assmann, Daisy Crispim.

   Acta Ophthalmologica, 2021;99(4):e461-e469.

2. **The A allele of the rs759853 single nucleotide polymorphism in the *AKR1B1* gene confers risk for diabetic kidney disease in patients with type 2 diabetes from a Brazilian population**

   Autores: Cristine Dieter, Natália Emerim Lemos, Nathalia Rodrigues de Faria Corrêa, **Felipe Mateus Pellenz**, Luís Henrique Canani, Daisy Crispim, Andrea Carla Bauer.

   Archives of Endocrinology and Metabolism, 2022; 66(1):12-18.

3. **Polymorphisms in *ACE1*, *TMPRSS2*, *IFIH1*, *IFNAR2*, and *TYK2* Genes Are Associated with Worse Clinical Outcomes in COVID-19**

   Autores: Cristine Dieter, Letícia de Almeida Brondani, Natália Emerim Lemos, Ariell Freires Schaeffer, Caroline Zanotto, Denise Taurino Ramos, Eliandra Girardi, **Felipe Mateus Pellenz**, Joíza Lins Camargo, Karla Suzana Moresco, Lucas Lima da Silva, Mariana Rauback Aubin, Mayara Souza de Oliveira, Tatiana Helena Rech, Luís Henrique Canani, Fernando Gerchman, Cristiane Bauermann Leitão, Daisy Crispim.

   Genes, 2022; 14(1):29.

4. **Blueberry Consumption and Changes in Obesity and Diabetes Mellitus Outcomes: A Systematic Review**

   Autores: Mayara Souza de Oliveira, **Felipe Mateus Pellenz**, Bianca Marmontel de Souza, Daisy Crispim.

   Metabolites, 2022; 13(1):19.

5. **The rs3931283/*PVT1* and rs7158663/*MEG3* polymorphisms are associated with diabetic kidney disease and markers of renal function in patients with type 2 diabetes mellitus**

   Autores: Cristine Dieter, Natália Emerim Lemos, Eliandra Girardi, Denise Taurino Ramos, **Felipe Mateus Pellenz**, Luís Henrique Canani, Taís Silveira Assmann, Daisy Crispim.

   Molecular Biology Reports, 2023; 50(3):2159-2169.

6. **Polymorphisms in *TIE2* and *ANGPT-1* genes are associated with protection against diabetic retinopathy in a Brazilian population**

   Autores: Cristine Dieter, Natália Emerim Lemos, Nathalia Rodrigues de Faria Corrêa, Taís Silveira Assmann, **Felipe Mateus Pellenz**, Luís Henrique Canani, Letícia de Almeida Brondani, Andrea Carla Bauer, Daisy Crispim.

   Archives of Endocrinology and Metabolism, 2023; 67(5):e000624.

7. **Integrated bioinformatics approach reveals methylation-regulated differentially expressed genes in obesity**

   Autores: Guilherme Coutinho Kullmann Duarte, **Felipe Mateus Pellenz**, Daisy Crispim, Taís Silveira Assmann.

Archives of Endocrinology and Metabolism, 2023; 67(4):e000604.

8. **Identification of metabolic pathways and key genes associated with atypical parkinsonism using a systems biology approach**

   Autores: Amanda Pasqualotto, Vinícus da Silva, **Felipe Mateus Pellenz**, Artur Francisco Schumacher Schuh, Ida Vanessa Doederlein Schwartz, Marina Siebert.

   Metabolic Brain Disease, 2024; doi: 10.1007/s11011-024-01342-7. Online ahead of print.

Artigos em fase de finalização/submissão.

1. **Identifying genetically predisposed type 1 diabetes mellitus individuals in a Southern Brazilian population: the construction of a genetic risk score**

   Autores: **Felipe Mateus Pellenz**, Mayara Souza de Oliveira, Guilherme Coutinho Kullmann Duarte, Cristine Dieter, Luís Henrique Canani, Taís Silveira Assmann, Daisy Crispim.

   Artigo submetido na Genetics and Molecular Biology.

2. **In silico prediction: systems biology applied to the analysis of genes and metabolic pathways linked to Crohn's Disease and Ulcerative Colitis**

   Autores: Vinícius da Silva, **Felipe Mateus Pellenz**, Amanda Pasqualotto, Marina Siebert.

   Artigo submetido na Bulletin of the National Research Centre.

3. **Association of polymorphisms in SLC30A8 gene with risk for type 1 diabetes mellitus and decreased serum triglyceride levels.**

   Autores: Raif Gregorio Nasre Nasser, Cristine Dieter, **Felipe Mateus Pellenz**, Anna Carolina Meirelles, Luciane Moretto, Guilherme Coutinho Kullmann Duarte, Taís Silveira Assmann, Luís Henrique Canani, Daisy Crispim.

4. **Relationship between zinc and the proteasome in type 1 diabetes patients: evaluation of polymorphisms in proteasome subunit genes with zinc binding sites.**

   Autores: Raif Gregorio Nasre Nasser, Cristine Dieter, **Felipe Mateus Pellenz**, Anna Carolina Meirelles, Luciane Moretto, Guilherme Coutinho Kullmann Duarte, Taís Silveira Assmann, Luís Henrique Canani, Daisy Crispim.

PREMIAÇÕES E MENÇÕES HONROSAS RECEBIDAS DURANTE O DOUTORADO

1. 2022 - **Prêmio Newton Freire-Maia - Genética Humana, Médica e Farmacogenética**, Sociedade Brasileira de Genética. Trabalho "*Genetic risk score predicts type 1 diabetes mellitus susceptibility in a Southern Brazilian population*"

2. 2022 - **Menção Honrosa** – Trabalho "*Inflammasome related genes are dysregulated in visceral and subcutaneous adipose tissue of C57BL/6 mice fed with cafeteria diet*", Sociedade Brasileira de Genética.

3. 2022 - **Melhor trabalho da 42ª Semana Científica HCPA**, com o trabalho "*The rs1799752/ACE1, rs12329760/TMPRSS2 and rs1990760/IFIH1 polymorphisms are associated with risk to COVID-19 in women*, Hospital de Clínicas de Porto Alegre.

4. 2024 – **Prêmio da Sociedade Brasileira de Patologia: Categoria Melhor Pôster, 6º Lugar**, com o trabalho "*A influência do consumo de mirtilos na melhora da esteatose hepática, parâmetros biométricos e metabólicos em camundongos com obesidade induzida por dieta de cafeteria*", Sociedade Brasileira de Patologia.