



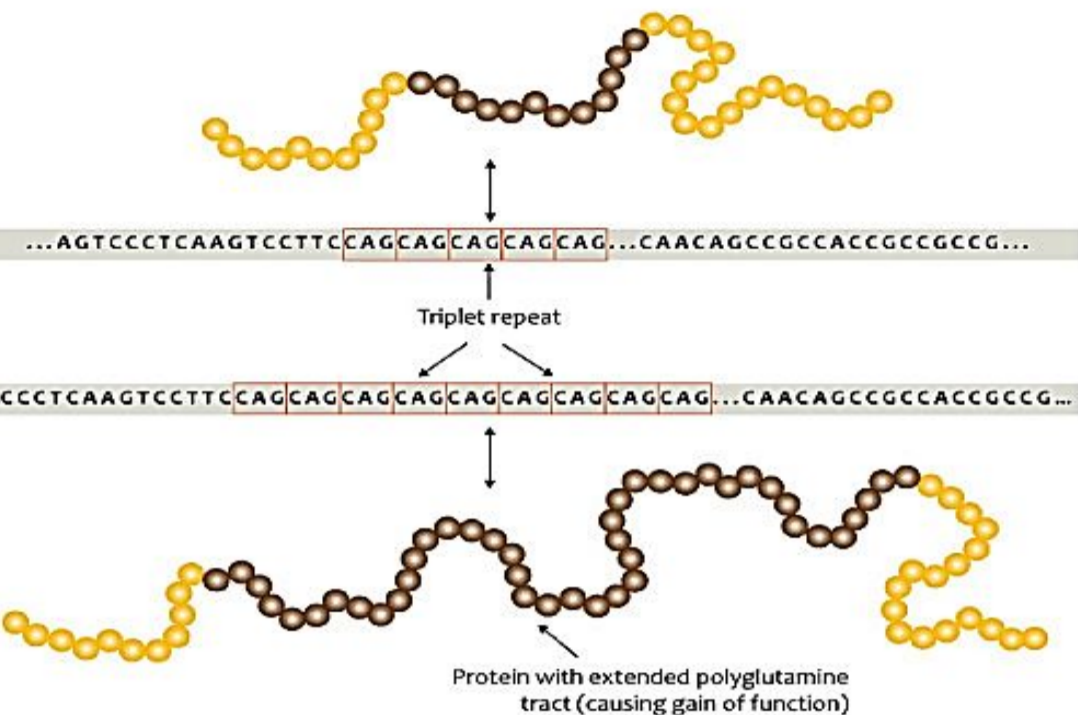
Clinical scales and eye movements show changes in time since preclinical stages in Machado-Joseph Disease/Spinocerebellar Ataxia Type 3 (BIGPRO study)

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Background

- Spinocerebellar Ataxia Type 3/Machado-Joseph Disease (SCA3/MJD) is an autosomal dominant disorder caused by a CAG repeat expansion (CAGexp) at the ATXN3.



- Causal treatment is not available yet. Considering that a therapy will probably be more efficient if started early in life, reliable biomarkers for pre-clinical stages are needed.

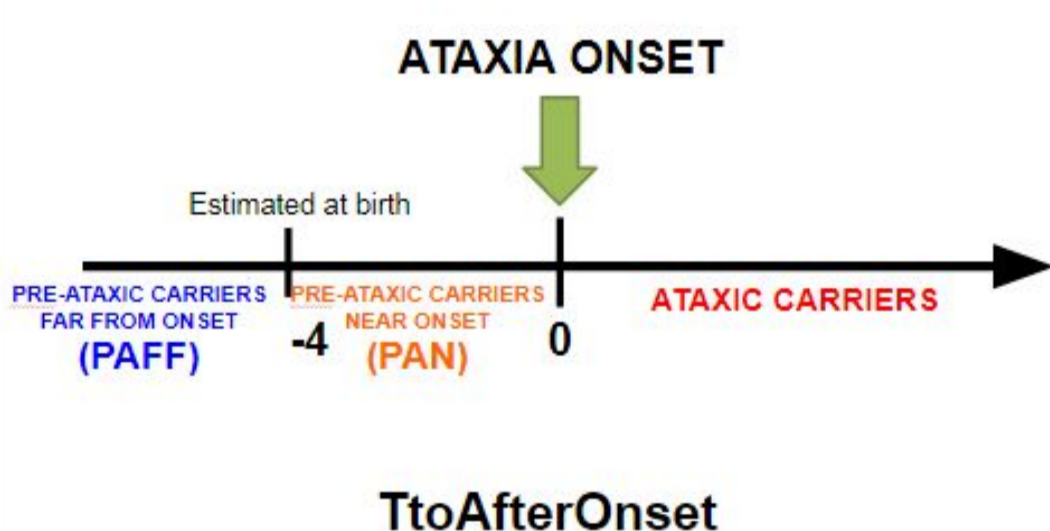
- BIGPRO (Biomarkers and genetic modifiers in a study of presymptomatic and symptomatic SCA3/MJD carriers) is a longitudinal study aiming to validate biomarkers for disease progression in SCA3/MJD since pre-clinical periods.

Aims

To report baseline findings obtained from clinical scales and eye movement recordings with video-oculography, including saccades, pursuit, gaze-evoked nystagmus and central nystagmus

Methods

- Baseline data on clinical scales and oculomotor neurophysiology were collected from 95 subjects – 36 symptomatic and 59 at 50% risk for SCA3/MJD.
- Age at onset (AO) was considered the age at which the subject and her/his relatives first noticed gait ataxia. Time after onset was considered the time elapsed since the AO for each symptomatic subject.
- Genetic tests performed in at risk subjects were double-blind.
- For pre-ataxic carriers (SARA<3), the average time left until the onset of gait ataxia was called “time to onset”.
- The CAGexp was used to estimate time to onset both at birth and corrected by age.



- For pre-ataxic carriers, time left until the onset of gait ataxia was estimated by their CAGexp and was called “time to onset”; they were classified as far from (AFF) or near (AN) (4 years or less) the predicted age at onset (AO).
- Time to/time after onset (TtoAfterOnset) was a unique dimension of time versus start of gait ataxia, estimated to all SCA3/MJD carriers.

- Clinical outcome assessments of interest for this report were parameters of three different domains of eye movements: saccades, pursuit and fixation, measured by video- oculography.
- The parameters chosen for comparisons were average reflex vertical saccade velocity (RVS), horizontal and vertical pursuit gains, slow-phase velocity of central (SPV-C) and gaze-evoked nystagmus (SPV-GE).

Results

- Overall characteristics of the 95 subjects, classified in four groups are shown in **Table 1**.

Table 1 – Overall characteristics of BIGPRO cohort

	Symptomatic carriers	AN	AFF	Related controls	p
Males/total (%)	19/36 (52.8%)	6/13 (46.2%)	10/24 (41.7%)	8/22 (36.4%)	0.647*
Age at evaluation (years)	41.08 (9.71)*	33.31 (9.25)*	27.17 (5.54)*	31.32 (9.44)*	<0.001**
CAG repeat larger allele	75.22 (3.00)*	77.00 (3.19)*	74.21 (2.38)*		0.021**
CAG repeat larger allele	75.22 (3.00)	75.19 (2.97)			0.962***
TtoAfterOnset (Time versus start of gait ataxia, in years)	5.69 (4.15)*	-4.85 (0.80)*	-14.46 (6.63)*		<0.001**

*Chi-square test; ** Anova; ***t test. Tukey tests: different letters mean significant differences.

- All parameters under study – RVS, horizontal and vertical pursuit, SPV-C and SPV-GE – showed statistically significant differences when the four groups were studied.(**Table 2**).

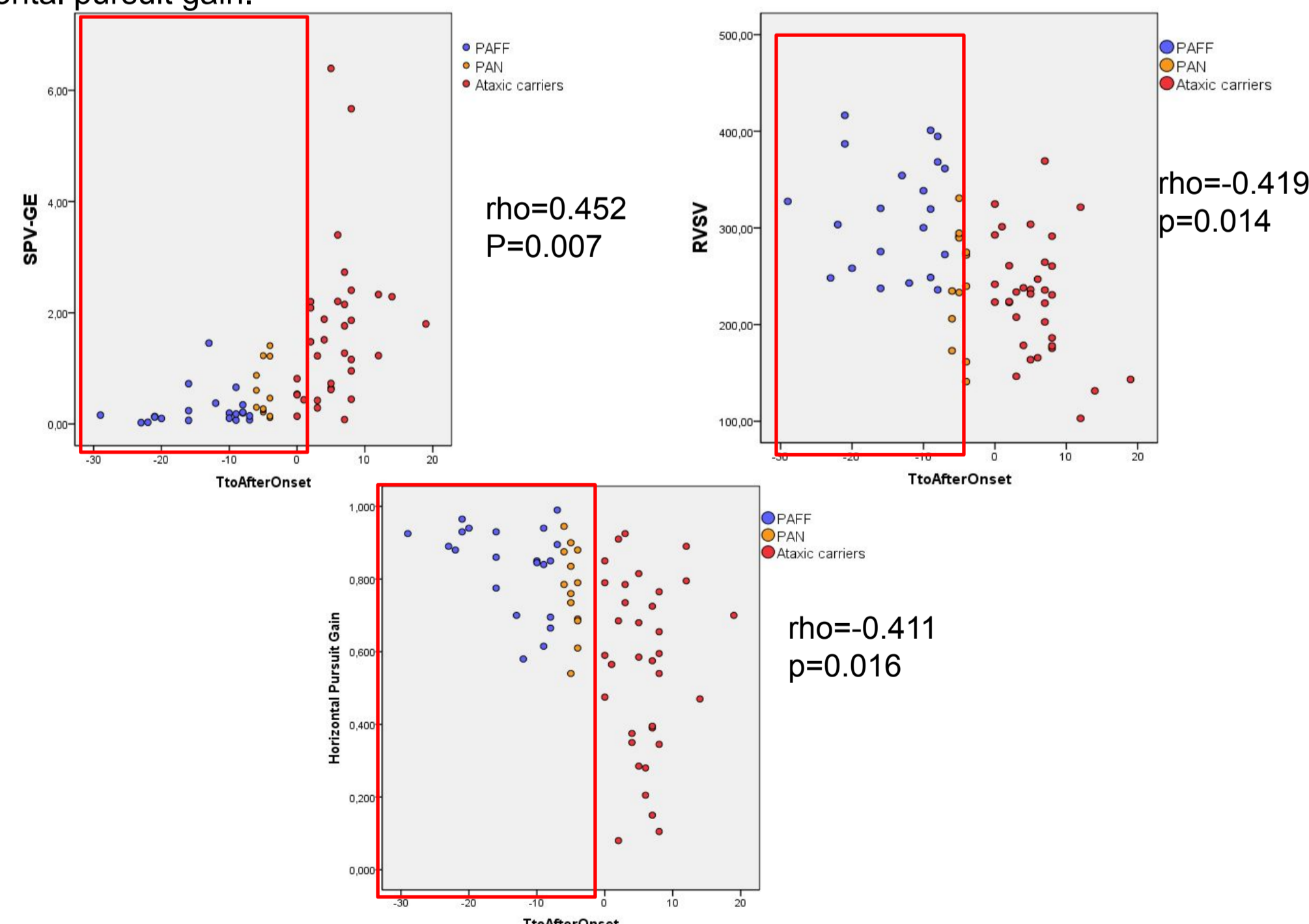
Table 2 – Results

	Symptomatic carriers	AN	AFF	Related controls	p
RVS	228.25 (60.06)*	241.71 (57.87)*	314.88 (59.05)*	366.35 (52.67)*	<0.001
Vertical pursuit gain	0.56 (0.24)*	0.77 (0.12)*	0.84 (0.12)*	0.80 (0.13)*	<0.001
Horizontal pursuit gain	0.49 (0.21)*	0.65 (0.20)*	0.64 (0.14)*	0.60 (0.14)*	0.007
SPV-GE	1.38 (0.60-2.20)*	0.30 (0.23-1.05)*	0.16 (0.09-0.29)*	0.10 (0.06-0.17)*	<0.001
SPV-C	0.23 (0.09-0.56)*	0.20 (0.07-0.50)*	0.08 (0.05-0.14)*	0.08 (0.02-0.15)*	0.001

Tukey tests: different letters mean significant differences.

- However, only RVS and SPV-GE results showed significant differences between controls and AN.

- TtoAfterOnset obtained from all 73 carriers of CAGexp correlated strongly with SPV-GE and moderately with RVS and horizontal pursuit.
- When considering only pre-ataxic carriers, time to onset correlated with SPV-GE, RVS and horizontal pursuit gain.



Conclusions

- These results suggest that reflex vertical saccade velocity is the best candidate as biomarker among eye movement parameters for the pre-ataxic period in SCA3/MJD.
- Longitudinal observations will deepen these observations and perhaps confirm these findings.