

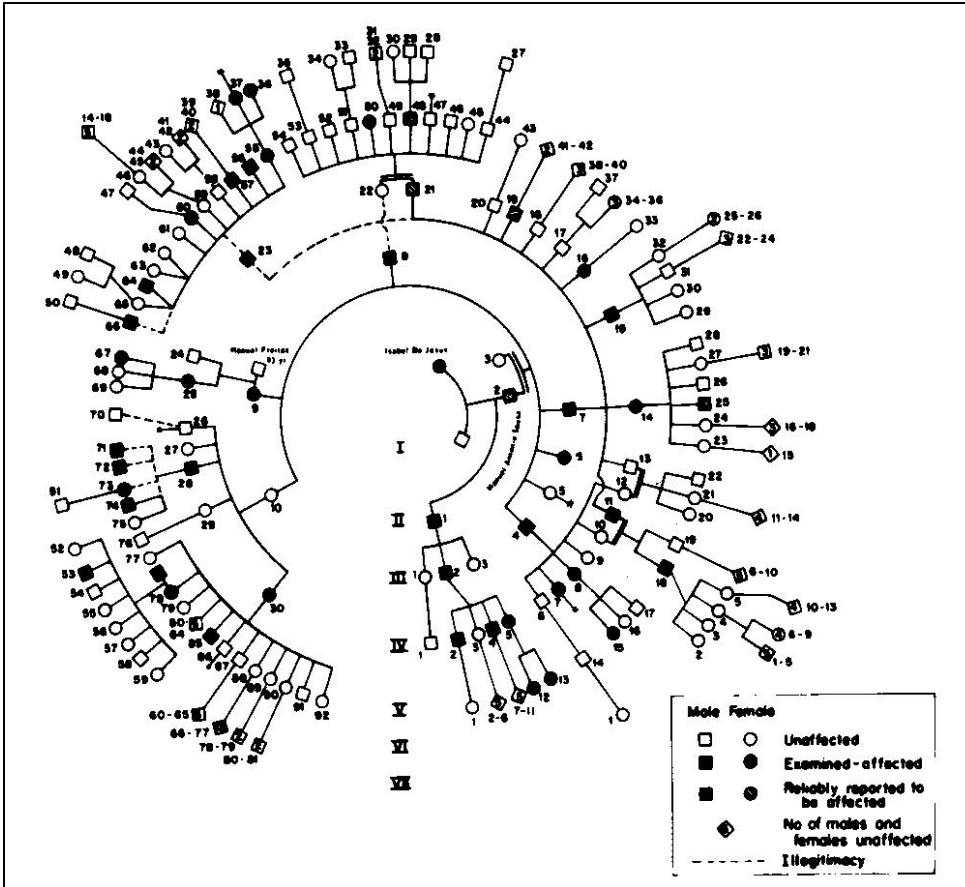
# Results from European spinocerebellar ataxia type 3/MJD Initiative (ESMI) and outlook on trials

Thomas Klockgether

EURO ATAXIA Conference  
18 June 2021



# Spinocerebellar ataxia type 3 (SCA3)/Machado-Joseph disease (MJD)



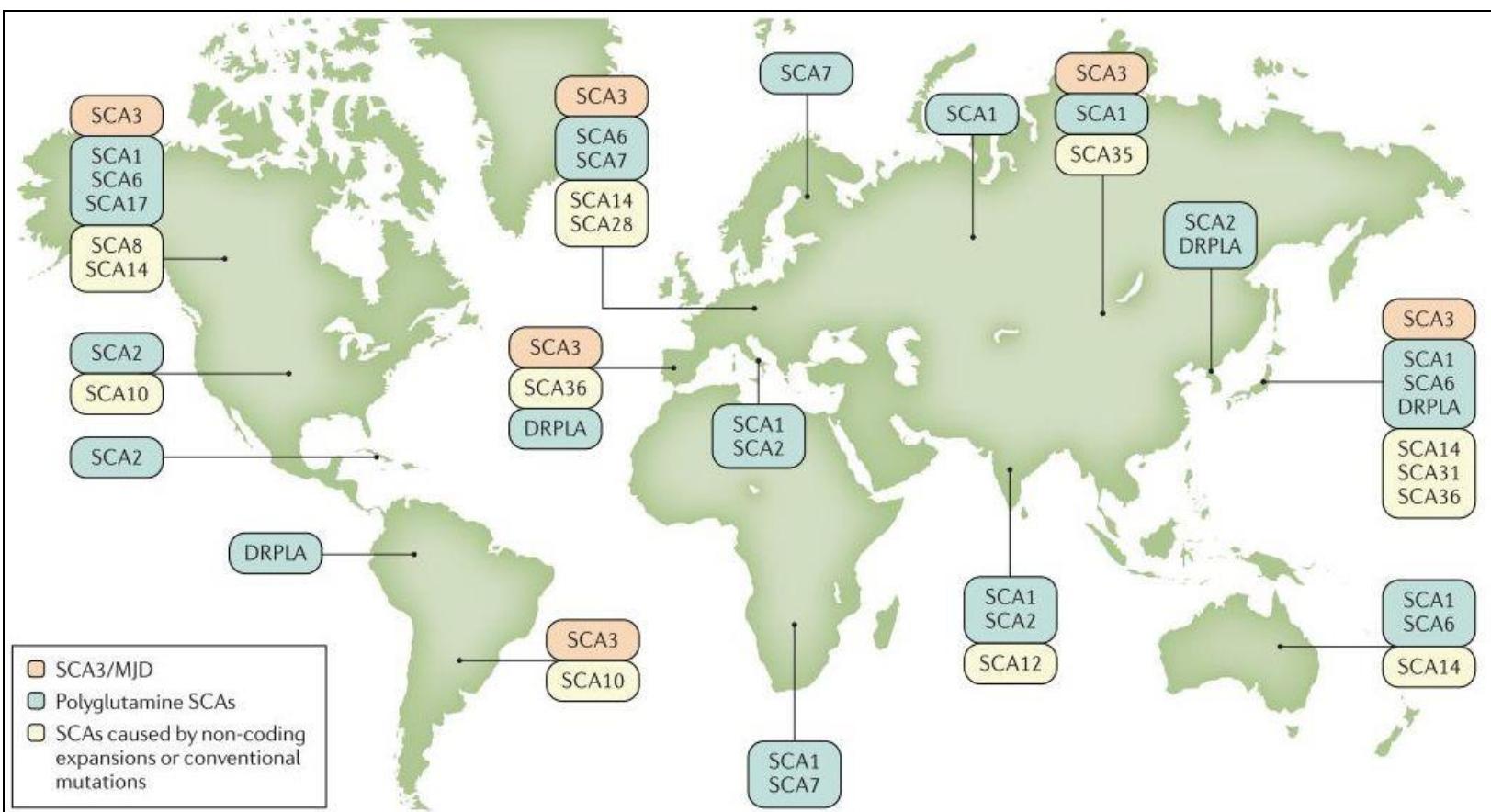
CAG repeat

normal: 12 – 40

expanded: 51 - 86

Coutinho & Andrade. Neurology 1978;28:703-9

# Regional distribution



Genotype	Prevalence (%)
SCA3	20 - 50
SCA2	13 - 18
SCA6	13 - 15
SCA1	3 - 16
Other SCAs	< 5

# European SCA3/MJD initiative (ESMI)

- Prospective, observational (trial ready) cohort study of SCA3 mutation carriers
- Start of recruitment 2017
- Baseline visit followed by annual visits
- Focus on imaging and fluid biomarkers



	Total	Healthy controls	SCA3 pre-ataxic	SCA3 ataxic
Baseline	414	118	65	231
1 year FU	294	57	42	195
2 year FU	139	13	21	105

ESMI

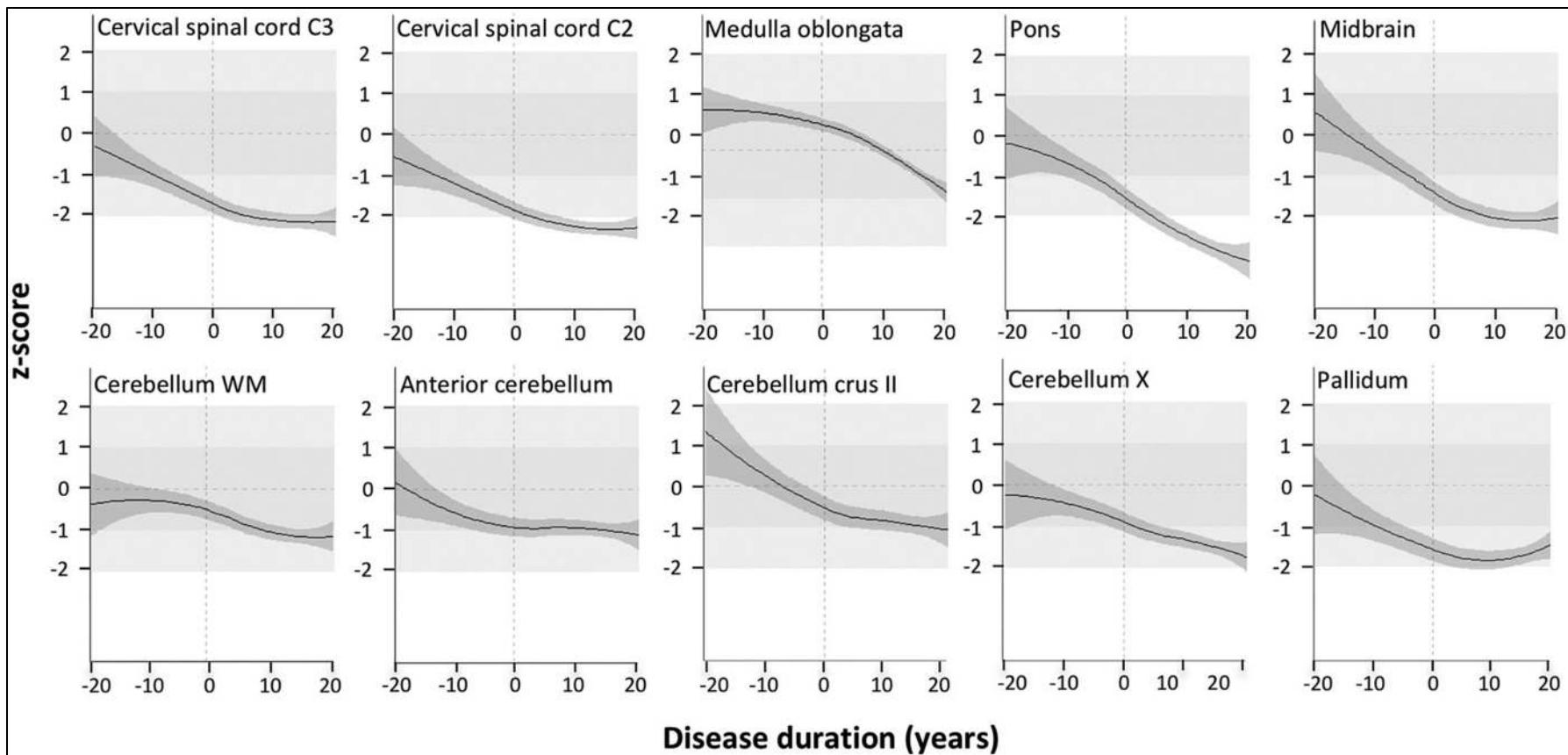
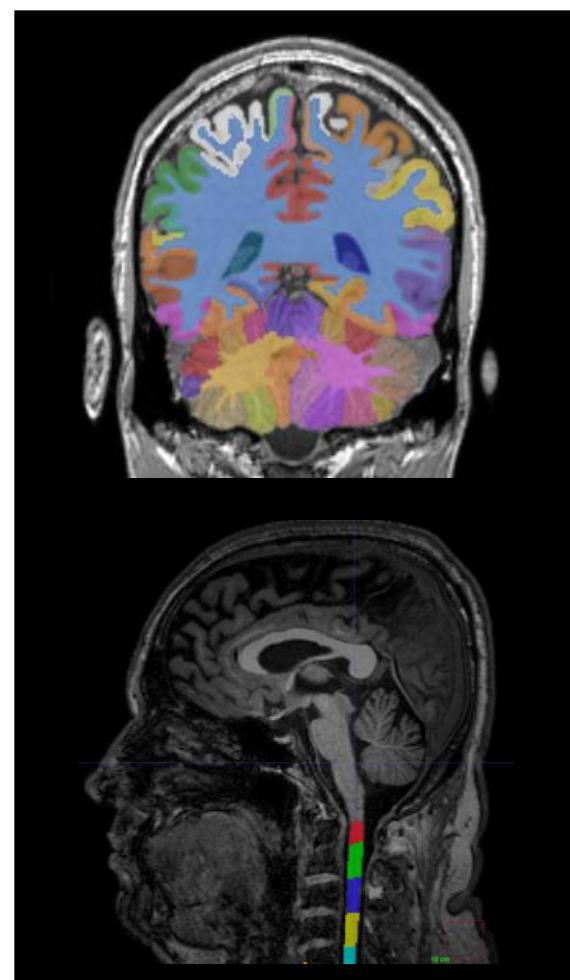
# Biomarker

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A biomarker is an objective and measurable feature that provides information on a biological process.

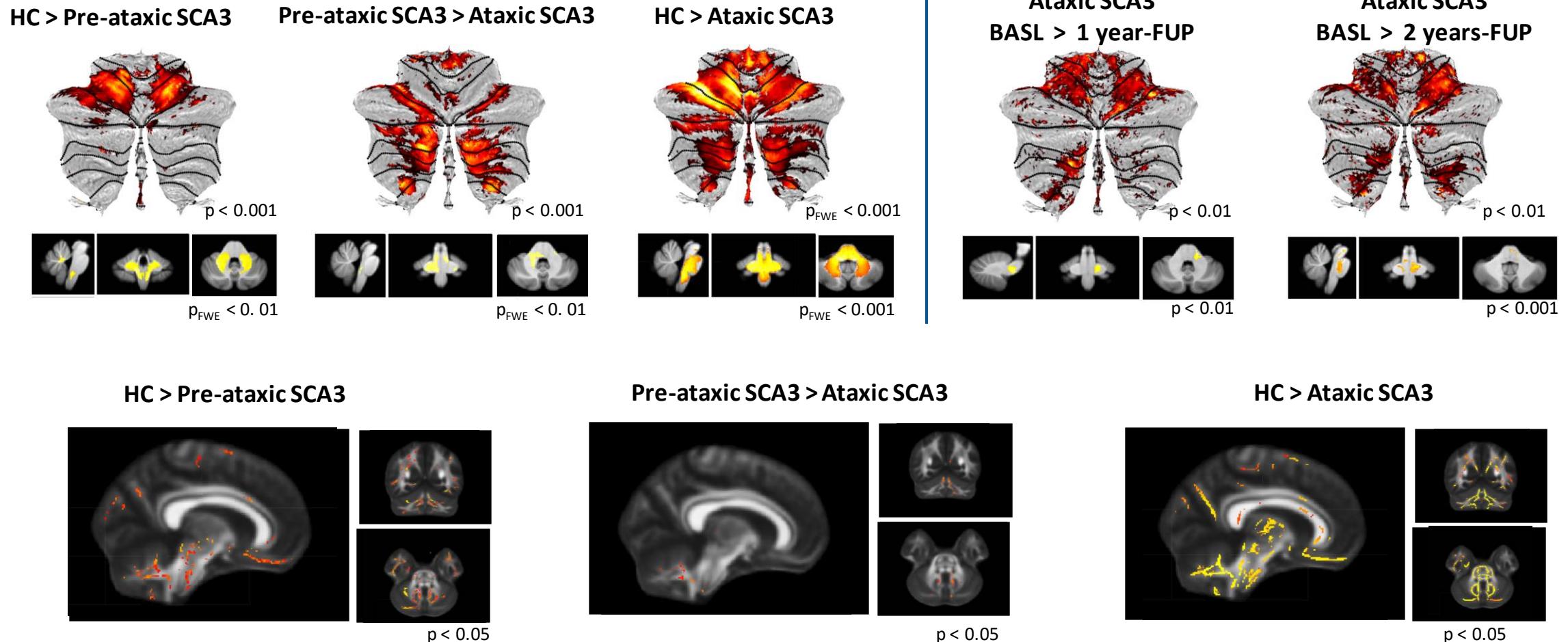
- Diagnostic biomarker (molecular genetic test)
- Progression/pharmacodynamics biomarker (indicating the severity of the disease/efficacy of drugs)
- Target engagement marker (indicating interaction of test compound with target biomolecules)

# MRI volumetry

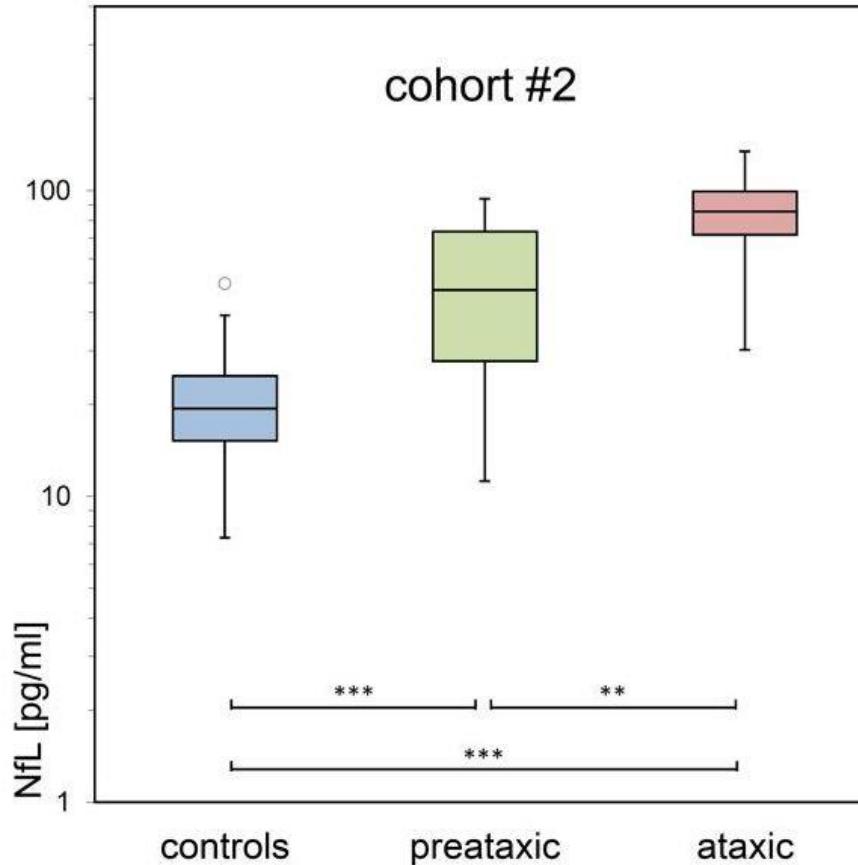
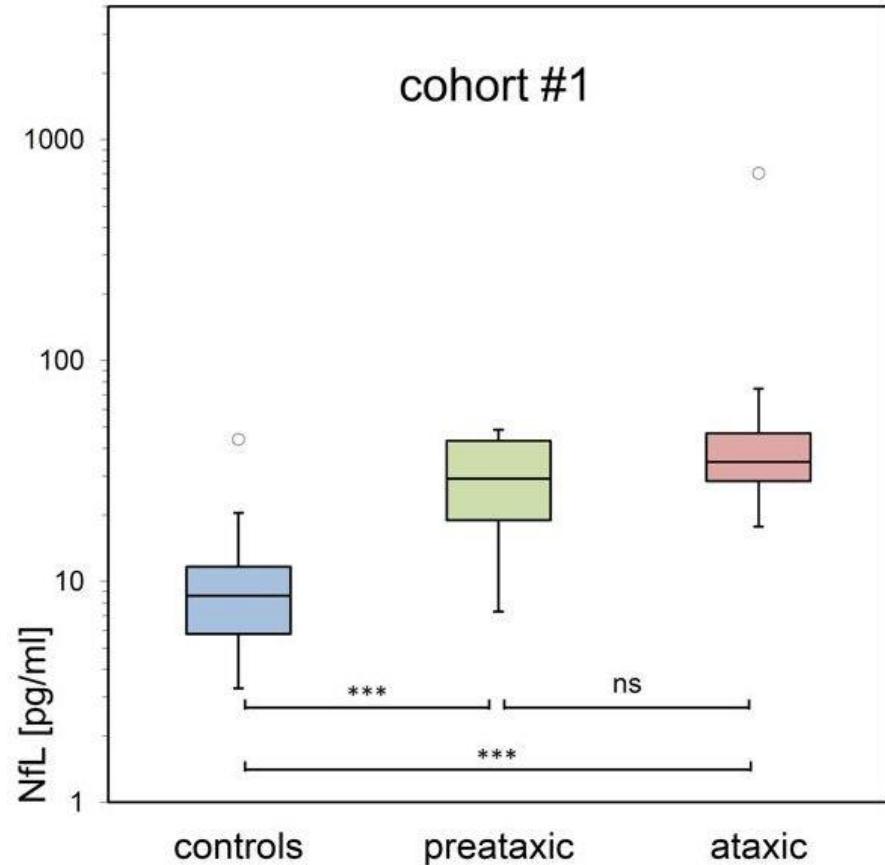


	Total	Healthy controls	SCA3 pre-ataxic	SCA3 ataxic
Baseline	341	63	68	210

# Voxel-based morphometry and DTI in SCA3

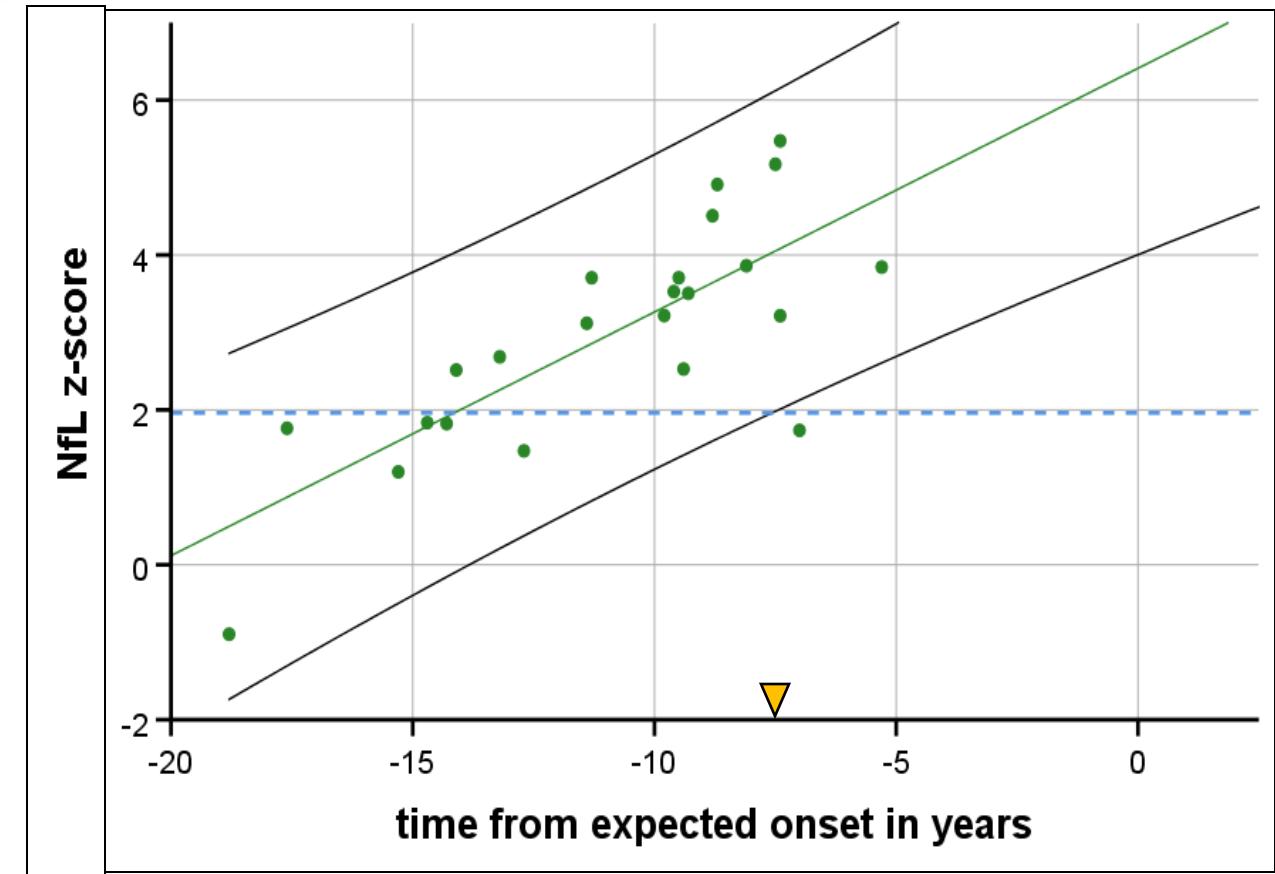
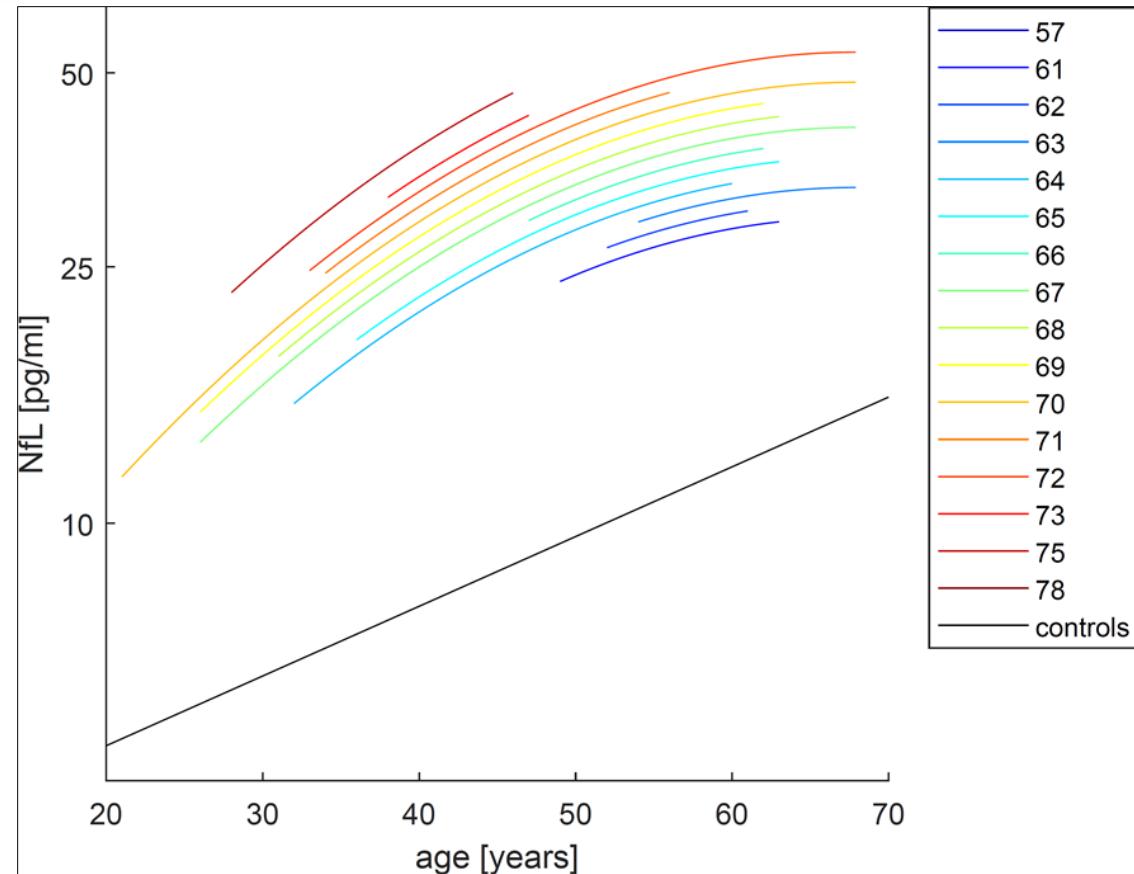


# Blood neurofilament light chain (NfL)

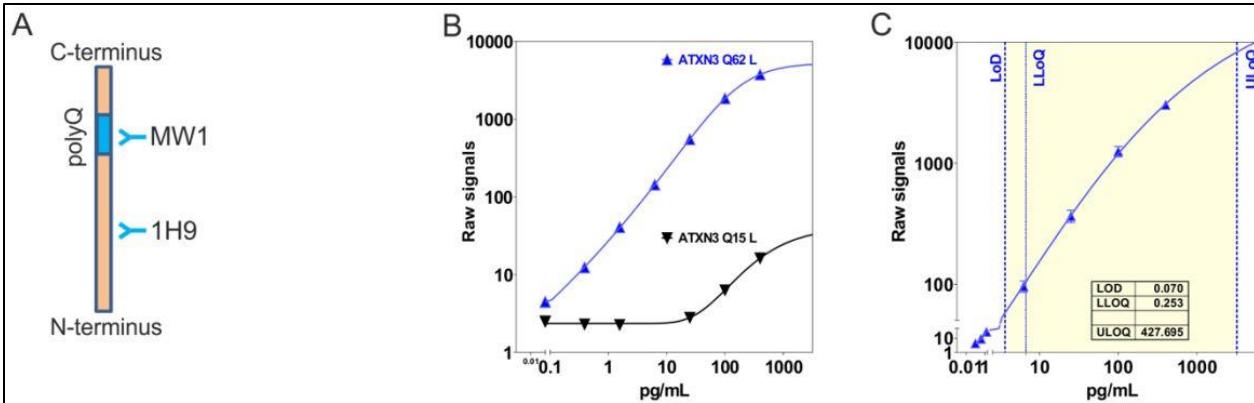


# Blood neurofilament light chain (NfL)

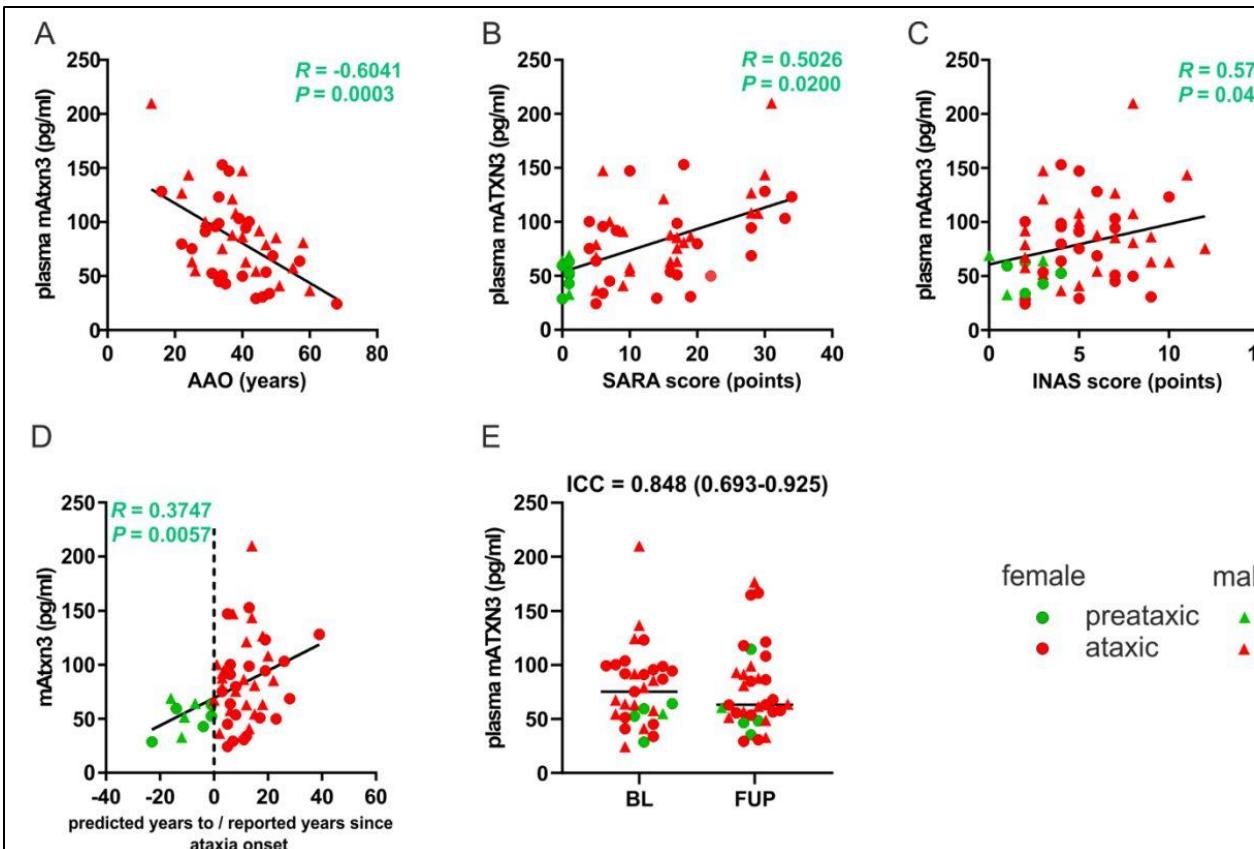
## Validation of NfL as a progression marker



# Expanded ataxin-3

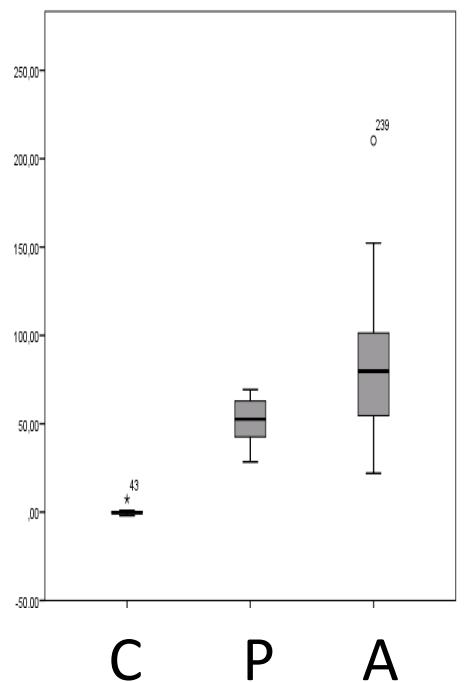


Ultrasensitive immunoassay for expanded ataxin-3 using SMC™ technology (Single Molecule Counting technology, Singulex)

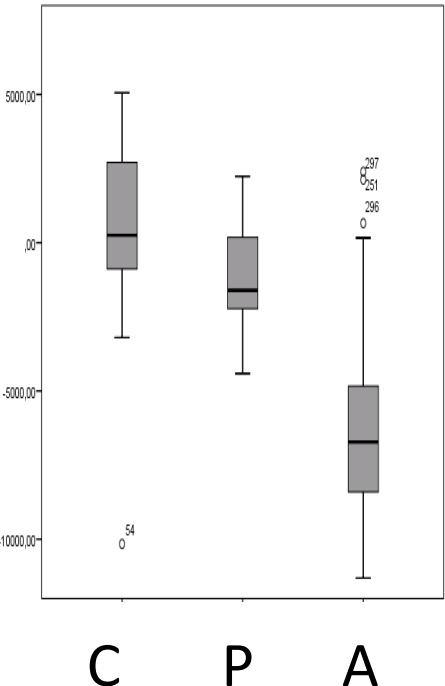


# Biomarkers

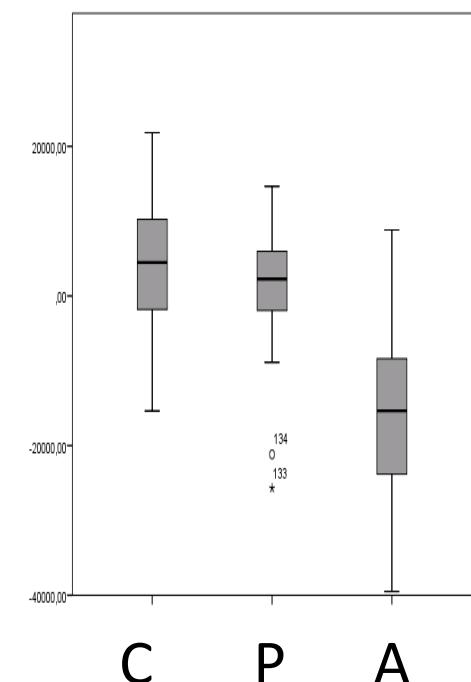
Ataxin-3



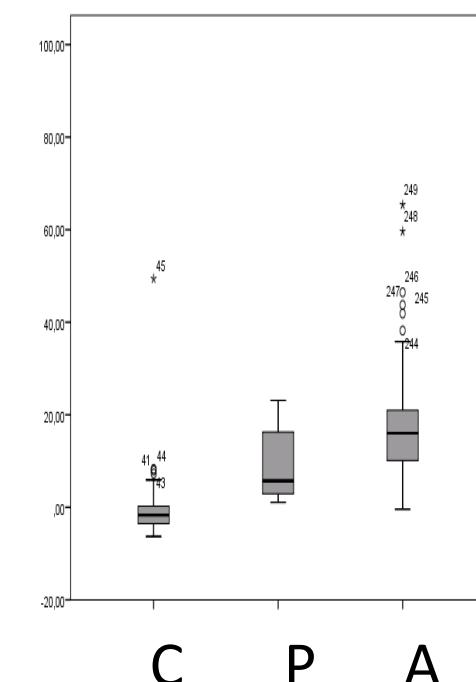
Pontine volume



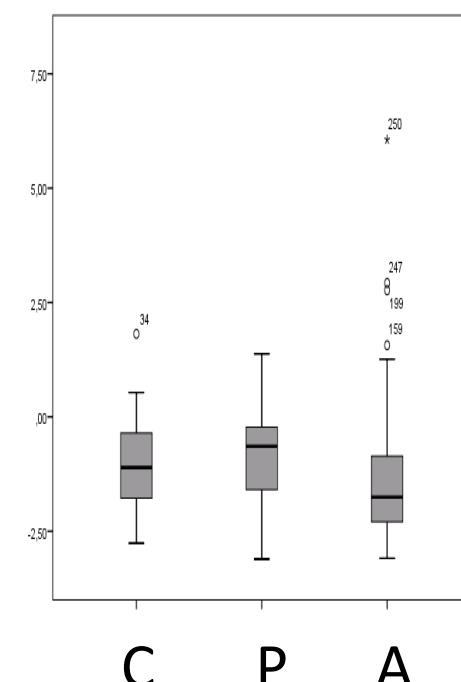
Cerebellar volume



NfL



Tau

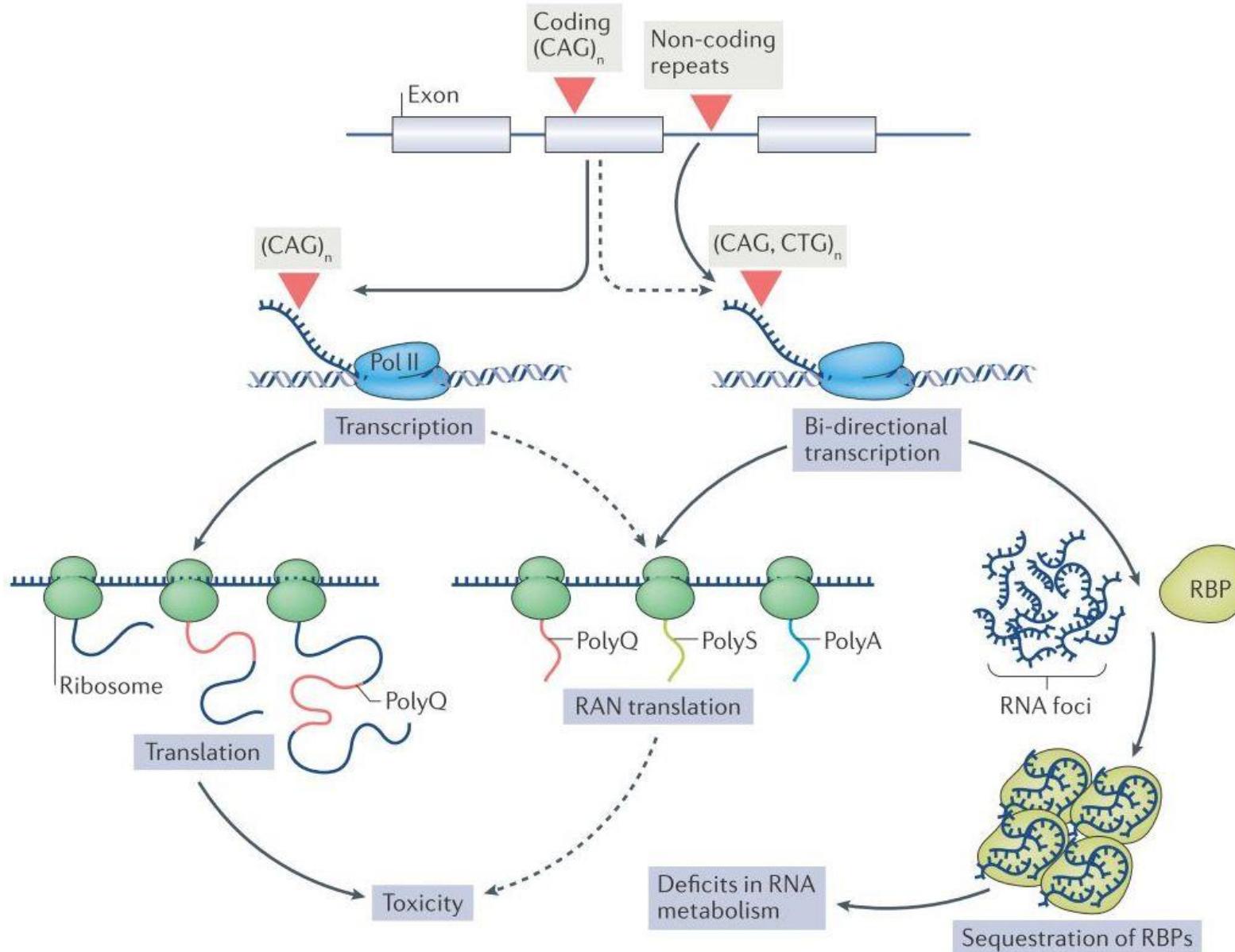


## ESMI continuation

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- JPND funding of ESMI has ended
- A number of pharmaceutical companies are interested to fund the continuation of ESMI and use the results for preparation of future interventional trials
- Negotiations with one company are far advanced

# Pathophysiology of polyglutamine diseases



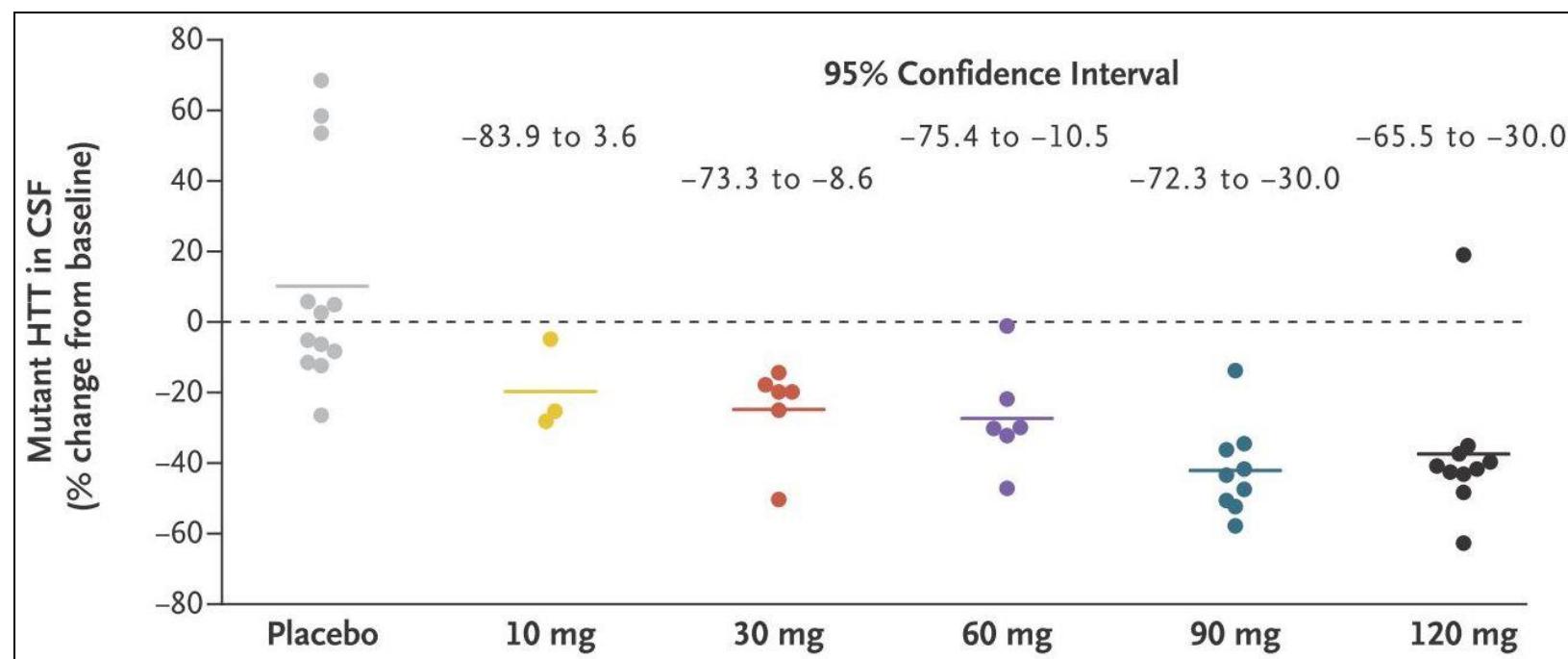
# Antisense oligonucleotide treatment in HD

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Targeting Huntingtin Expression in Patients with Huntington's Disease

Sarah J. Tabrizi, M.B., Ch.B., Ph.D., Blair R. Leavitt, M.D., C.M.,  
G. Bernhard Landwehrmeyer, M.D., Edward J. Wild, M.B., B.Chir., Ph.D.,  
Carsten Saft, M.D., Roger A. Barker, M.R.C.P., Ph.D., Nick F. Blair, M.B., B.S.,\*  
David Craufurd, M.B., B.S., Josef Priller, M.D., Hugh Rickards, M.D.,  
Anne Rosser, M.B., B.Chir., Ph.D., Holly B. Kordasiewicz, Ph.D.,  
Christian Czech, Ph.D., Eric E. Swayze, Ph.D., Daniel A. Norris, Ph.D.,  
Tiffany Baumann, B.S., Irene Gerlach, Ph.D., Scott A. Schobel, M.D.,  
Erika Paz, B.S., Anne V. Smith, Ph.D., C. Frank Bennett, Ph.D.,  
and Roger M. Lane, M.D.



# Generation HD trial

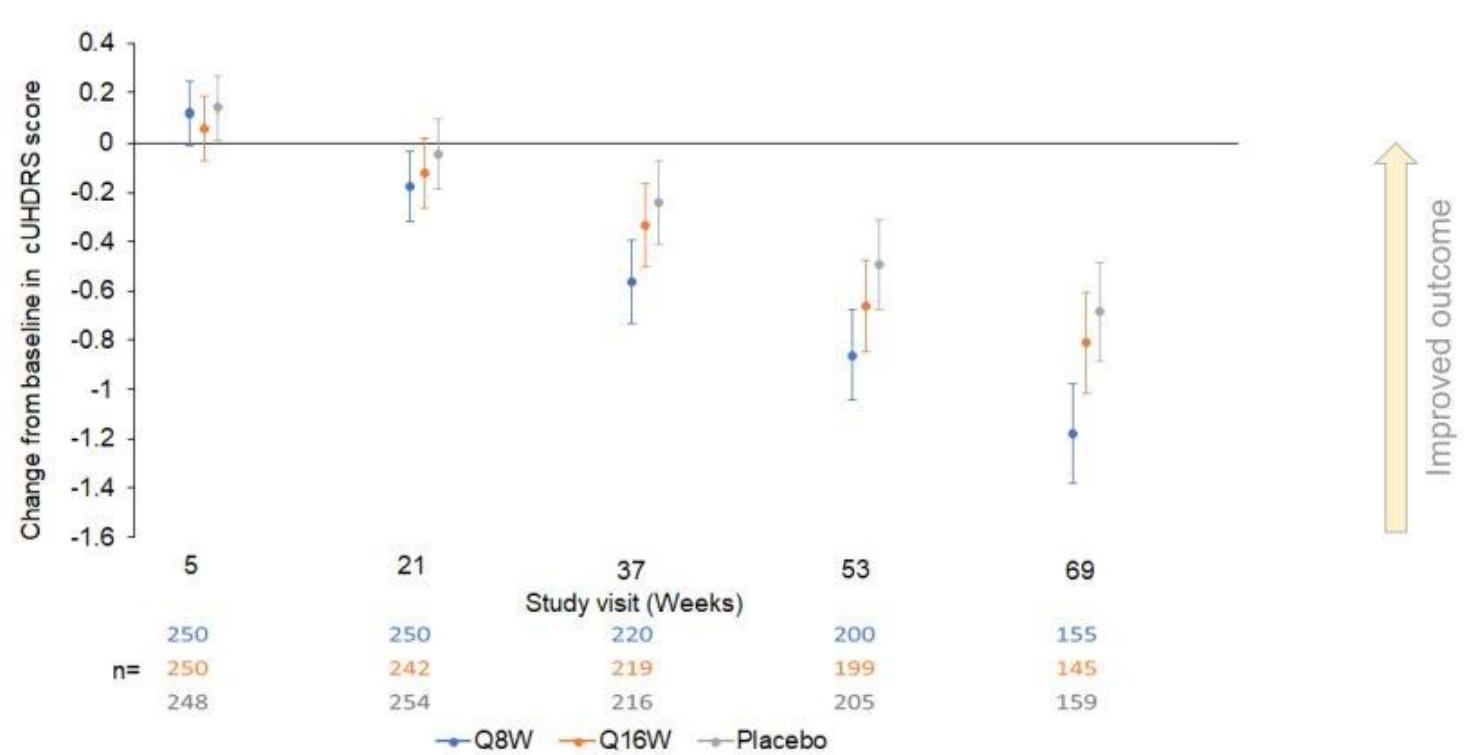
## Media & Investor Release



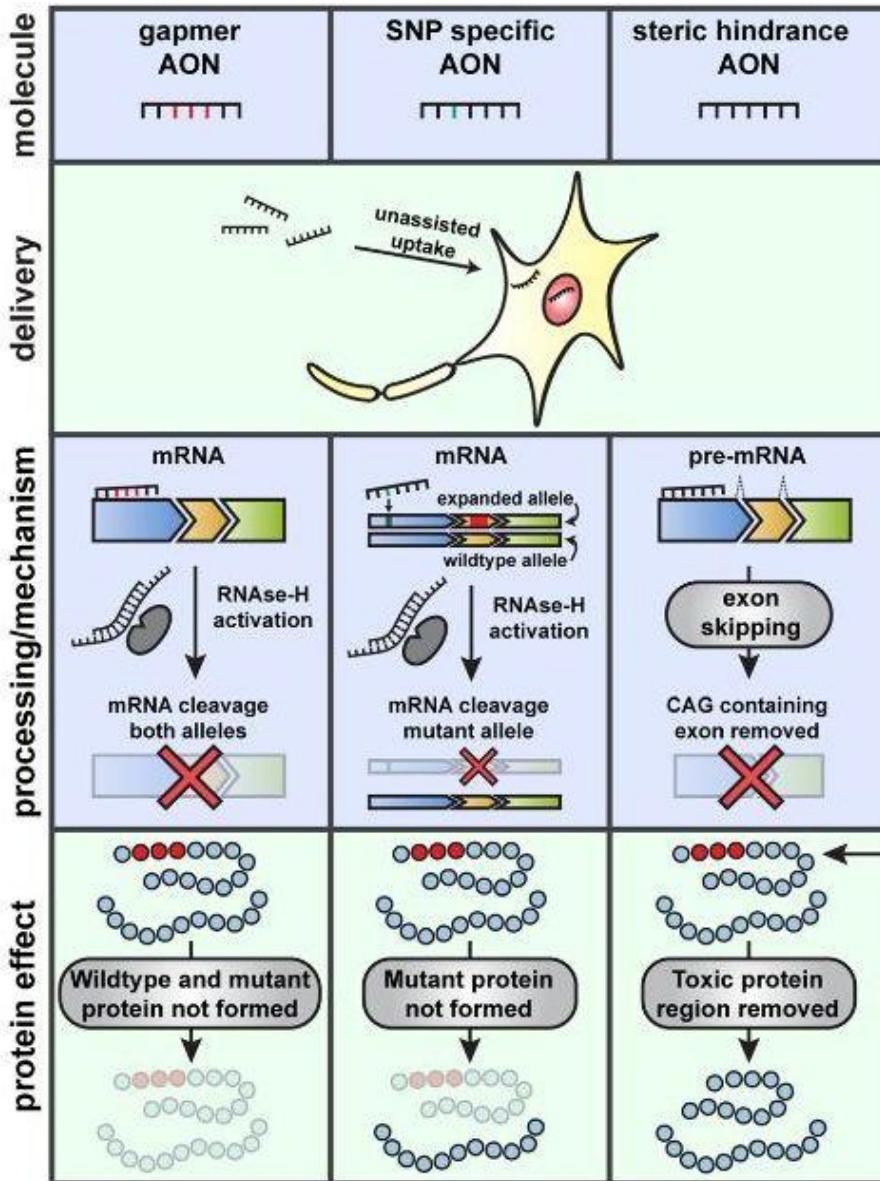
### Roche provides update on tominersen programme in manifest Huntington's disease

- Dosing to stop in Phase III clinical study of tominersen following recommendation from an Independent Data Monitoring Committee (IDMC)
- No new safety signals were identified for tominersen in the IDMC's review

Basel, 22 March 2021 - Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced the decision to discontinue dosing in the Phase III GENERATION HD1 study of tominersen in manifest Huntington's disease (HD). The decision was based on the results of a pre-planned review of the data from the Phase III study conducted by an unblinded Independent Data Monitoring Committee (IDMC). The IDMC made its recommendation based on the investigational therapy's potential benefit/risk profile for study participants. No new or emerging safety signals were identified for tominersen in the review of the data from this study. Roche intends to continue following participants for safety and clinical outcomes, without the dosing of the investigational medicine or placebo. Once full data from the Phase III study are available and analysed, Roche will share learnings and future plans with the HD community.



# Antisense oligonucleotide-based therapy



- ASOs reversibly knockdown specific genes
- All ASO treatment require repeated intrathecal injections (lumbar puncture)

## Approaches

Unspecific *ATXN3* knockdown

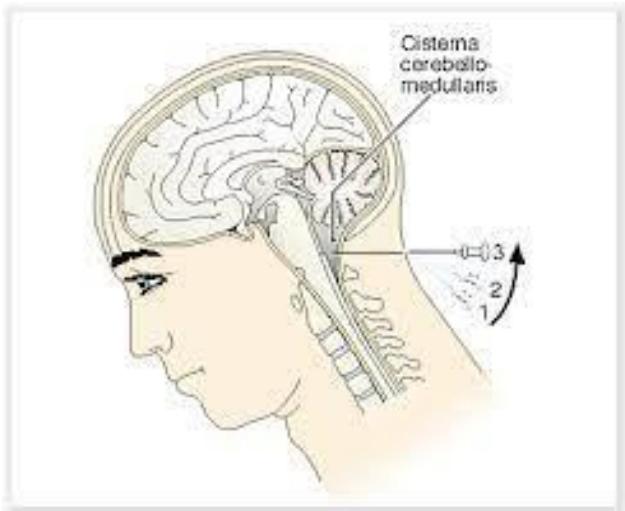
Allele-specific *ATXN3* knockdown

Knockdown of genes containing expanded CAG tracts

Knockdown of genes involved in somatic expansion

# Gene therapy

- Irreversible knockdown of *ATXN3* gene by a specific miRNA using viral gene transfer (AAV)
- Single CT-guided injection into cisterna cerebellomedullaris



[www.gesundheit.de/lexika/medizin-lexikon/subokzipitalpunktion](http://www.gesundheit.de/lexika/medizin-lexikon/subokzipitalpunktion)