30 PolyQ-expanded ataxin-3: a potential target engagement marker for SCA3 in peripheral blood

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In view of upcoming clinical trials, quantitative molecular markers accessible in peripheral blood are of critical importance as pharmacodynamic markers in genetic neurodegenerative diseases, such as Spinocerebellar Ataxia Type 3 (SCA3), in particular for signalling target engagement. As multiple targeted disease-protein lowering therapies in polyQ disease such as SCA3 are currently being developed, there is a pressing need for sensitive (molecular) biomarkers for target engagement. Using SCA3 mouse models, it was previously shown that targeting the ataxin-3 protein by specific micro RNAs or antisense oligonucleotides in SCA3 mouse models results in lowers polyQ-expanded ataxin-3 levels and reduces aggregation. To get prepared for ataxin-3 lowering therapies in upcoming clinical trials, our study aimed to establish sensitive methods to measure polyQ-expanded ataxin-3 protein in peripheral blood.

We established two different sensitive techniques:(I) a TR-FRET-based immunoassay to measure polyQ-expanded ataxin-3 specifically in mononuclear cells and (II) a more sensitive Singulex-based assay to also detect very low amounts of polyQ-expanded ataxin-3, such as those expected to be present in plasma and cerebrospinal fluids of SCA3 subjects. Both assays revealed significantly higher levels of polyQ-expanded ataxin-3 protein in SCA3 mutation carriers compared to healthy controls. The Singulex-based immunoassay also allowed to discriminate between pre-ataxic and ataxic mutation carriers. Additionally, polyQ-expanded ataxin-3 protein levels in both mononuclear cells and plasma correlate with disease progression and clinical severity as assessed by the Scale for the Assessment and Rating of Ataxia (SARA), possibly suggesting its use not only as a target engagement biomarker, but also as a disease progression and disease severity biomarker

In conclusion, polyQ-expanded ataxin-3 protein seems to be a promising candidate as a molecular target engagement marker in SCA3 in future clinical trials, determinable even in - easily accessible - peripheral blood biomaterials.