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STIP1 Homology And U-Box Containing Protein 1 (STUB1/CHIP) mutants as a key factor on TATA-box binding protein (TBP) behaviour in digenic spinocerebellar ataxia type 17 (SCA17-DI)

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Spinocerebellar ataxias (SCAs) are hereditary, progressive and fatal, very heterogenous neurodegenerative diseases (NDs). SCA type 17 (SCA17) is characterized by the presence of expanded CAG nucleotide repeats of the TATA-box binding (TBP) gene that codes for an abnormally long polyglutamine (polyQ) tract in the N-terminal of the protein. This leads to reduced solubility and accumulation of mutated TBP in neurons. Strikingly, TBP forms containing an intermediate polyQ tract (41-47 Qs) show incomplete penetrance (SCA17-DI), which seems to be correlated to the presence of mutations in STIP1 Homology And U-Box Containing Protein 1 (STUB1/CHIP). STUB1 is an E3 ubiquitin-ligase which has a key role in the protein quality control (PQC) system. Given the hypothesis that both TBP and STUB1 may be involved in SCA17-DI, we investigated their behaviour and interplay for a deeper understanding of the underlying molecular mechanisms in the disease.

Our data show a punctate distribution and insoluble protein accumulation of overexpressed elongated polyQ TBP (TBP-Q54) that it is not present in the wild type (TBP-WT) or intermediate polyQ TBP (TBP-Q43) expressing neurons. Interestingly, TBP accumulation is reverted by STUB1 over-expression suggesting that TBP degradation is mediated by STUB1. Since STUB1 plays a role in both ubiquitin proteasome system (UPS) and autophagy, we alternatively inhibited these pathways to study TBP behaviour. Our preliminary findings suggest that different pathways are responsible for STUB1-mediated TBP-Qs removal based on the different sizes of the polyQ tract. Moreover, other analyses show that STUB1 SCA17-DI-linked mutations are characterized by a reduced activity on TBP clearance.

Collectively, our data demonstrate that STUB1 mutations affect TBP biochemical behaviour in SCA17-DI. Therefore, our goal is to further investigate TBP and STUB1 interplay in order to better understand their pathological role in this form of ataxia, leading to a deeper knowledge of the disease.

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