PIAS1^{S510G} is a protective genetic modifier of Huntington's disease

A new study from Academia Sinica revealed a protective variant (PIAS1^{S510G}) modifying the age-at-onset of polyglutamine diseases by lowering the SUMO-modification of mutant huntingtin protein, which leads to lower accumulation of mutant huntingtin protein in the brain. This study was published in "Movement Disorders" in December, 2021.

Polyglutamine (polyQ) diseases are neurodegenerative disorders caused by polyQ-encoding CAG trinucleotide repeats expansion in the disease-causing gene. Among the polyQ diseases, Huntington's disease (HD) is caused by the expanded CAG repeat in exon 1 of the *HTT* gene and has the highest prevalence worldwide. Meanwhile, spinocerebellar ataxia type 3 (SCA3), which is caused by the CAG repeat expansion in the *ATXN3* gene, has the highest prevalence in Taiwan. The major symptom of both polyQ diseases (i.e., HD and SCA3) is motor dysfunction. The age-at-onset is determined mainly by the length of the CAG repeats. The longer the CAG repeats, the faster the accumulation of the mutant protein, and hence the earlier onset of the disease. Interestingly, expression of genetic modifier(s) may accelerate or delay the disease onset of polyQ diseases by altering the pathogenesis. To identify novel genetic modifiers, we enrolled 337 patients with HD or SCA3 and sequenced 583 genes implicated in proteinopathies. Bioinformatic analyses revealed 16 genes that contain variants associating with late-onset polyQ diseases. Among them, a genetic variant of *PIAS1* (A445T, Ser510Gly) is associated with the delayed onset. PIAS1 is an E3 SUMO ligase involved in SUMO-modification of huntingtin (HTT) protein, which can modulate the stability and accumulation of mutant HTT protein. When compared with the normal PIAS1, PIAS1^{S510G} interacts with mutant HTT poorly and thus leads to less SUMO-modification and more accumulation of mutant HTT. We next created a HD mouse model that had its normal PIAS1 replaced with Pias1^{S510G}. Similar to patients expressing PIAS1^{S510G}, HD mice harboring Pias1^{S510G} have milder HD-like deficits and lower mutant HTT accumulation in the brain. Our study suggests that PIAS1 is a genetic modifier of polyQ diseases. The naturally occurring variant, PIAS1^{S510G}, is associated with late-onset HD and milder disease severity. Our study highlights the possibility of targeting PIAS1 or pathways governing protein homeostasis as a disease-modifying approach for treating patients with HD.

The study was accomplished by teams led by Dr. Yijuang Chern (Academia Sinica), Dr. Bing-Wen Soong (Shuang-Ho Hospital), Dr. Tzu-Hao Cheng and Dr. Ueng-Cheng Yang (National Yang Ming Chiao Tung University) and funded by the Academia Sinica and Ministry of Science and Technology, Taiwan. The first author (Ms. Yan-Hua Lee) is a Ph. D. student of Taiwan International Graduate Program in Molecular Medicine, National Yang Ming Chiao Tung University and Academia Sinica, Taiwan.

The article entitled "A PIAS1 Protective Variant S510G Delays polyQ Disease Onset by Modifying Protein Homeostasis", can be read online at:

https://movementdisorders.onlinelibrary.wiley.com/doi/10.1002/mds.28896