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Beyond the CAG triplet number: exploring potential predictors of delayed age of onset in Huntington's disease

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Objective: Huntington's disease (HD) is a genetic neurodegenerative disease characterized by cognitive, motor and psychiatric dysfunction. It is caused by an expansion of the trinucleotide repeat sequence cytosine-adenine-guanine (CAG) in the Huntington gene on chromosome 4. Onset typically occurs in the fourth or fifth decade, ranging from childhood to late adulthood. The CAG triplet number is generally inversely proportional to the age of onset, but the repeat number only accounts for ~70% of the variability in age of onsetSeveral studies demonstrated the impact of genetic modifiers on the age of disease onset [1,2]. In addition to genetics, we also explored the demographic, anamnestic and socio-environmental factors that can affect the age of onset, to help us understand the non-genetic variability of the age of onset in HD.

Methods: We analyzed the retrospective data of the ENROLL-HD global registry study [3], particularly focusing on the continuum of ages, to include sociodemographic, genetic and anamnestic psychobehavioral variables in a multivariate regression model aimed at identifying the potential predictors of age of motor onset (n=5053). We ran the same regression model in the sample of subjects with the same number of triplets (41 CAG, n=593) and in the sample whose family history was absent/unknown (n=630).

Results: Patients with delayed onset more frequently have unknown/missing family history, are married or widowed, live in larger urbanized contexts and have a lower educational level. Individuals with earlier onset more frequently develop psychobehavioral symptoms.

Conclusions: The HD gene was considered the epitome of genetic determinism in the past. Our results are consistent with recent evidence that other factors might modulate its impact. These findings allow characterizing the determinants of the age of onset beyond the CAG expansions and provide valuable information for stratifying patients' for future clinical trial designs.

References:

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