Unbiased Computational Estimation of Huntington's Disease Mutation Frequency and Repeat Instability

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Huntington's disease (HD) is a fatal genetic neurogenerative disorder caused by expansion of CAG trinucleotide repeats in the huntingtin (HTT) gene greater than 35 repeats. The expanded CAG repeats exhibit repeat instability, and further expand in germ cells and brain, contributing to genetic anticipation and accelerated pathogenesis. Prevalence of HD based on diagnosed patients is 1 in 10,000 people, but frequency of HD mutation may be higher due to reduced penetrance. Unbiased estimation of mutation frequency in normal population and identification of factors responsible for repeat instability are critical to improve diagnosis and develop disease- modifying interventions. Here, objective computational approaches were used to investigate mutation frequency and repeat instability of HD. Log-linear models revealed 1) mutation frequency of 1 mutant chromosome in 700 chromosomes and 2) strong influence from reduced penetrance. In addition, mutant CAG repeats showed similar lengths across HTT haplotypes, arguing against HTT haplotype-influenced repeat instability. This proposition was further supported by observations in HD families, indicating that neither change in CAG repeat length nor variance in CAG repeat length within families were associated with haplotype. However, gender and CAG repeat length of transmitting parents were associated with repeat length changes in offspring. Taken together, these findings support that 1) mutation frequency is significantly higher than expected and 2) repeat instability depends on certain genetic factors. These data provide novel insights into HD mutation frequency and frameworks to investigate factors that drive non-pathogenic polymorphism into disease-causing mutation, significantly contributing to development of therapeutic strategies for HD and other repeat disorders.