Does *trans* size matter in Huntington disease?

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Huntington disease (HD) is a progressive neurodegenerative disorder resulting in involuntary movements with psychiatric and cognitive dysfunction. HD is caused by a polyglutamine repeat within the HTT protein and is inherited in an autosomal dominant pattern.[1,2] Although generally considered an archetypal monogenic disorder, there remains a high degree of phenotypic heterogeneity among patients with HD, particularly with respect to age at onset of motor manifestations. The length of the expanded repeat allele affects presentation and correlates with age at onset of motor manifestations, although this alone does not explain the variance that is observed.[3,4] Therefore studies are ongoing to identify other genetic disease modifiers that may provide alternative therapeutic targets.

In this issue of *Neurology*®, the study of Lee et al.[5] attempts to address the question of whether the size of the *HTT* repeat on the *trans* allele affects the age at onset of motor symptoms. This study represents a response to the study by Aziz et al.,[6] published in the October 20, 2009, issue of *Neurology*, which suggested that the mutant and normal alleles interact with both repeat lengths determining age at onset and therefore apparent penetrance. The earlier study examined age at onset in 921 patients with HD, demonstrating a significant effect on age at onset, with longer normal repeat alleles appearing to lower age at onset in patients with a smaller range mutant repeat allele (36–40 repeats). In contrast, in patients with a longer mutant allele (60–64), the longer normal allele was associated with a later age at onset. Notably, the investigators in Aziz et al. did not report a significant effect of the normal allele in isolation (table e-1 in their article); rather, they reported only a significant interactive effect when the normal and mutant alleles are both taken into account. The authors postulated the observed effect may be due to a direct interaction between the polyglutamine tracts of the mutant and normal HTT protein.

Initially, the study of Lee et al., examining 4,068 patients with HD, appeared to support the findings of Aziz et al., with the length of the normal allele showing an interaction with the mutant allele on age at onset of motor symptoms. However, if this association reflected a true functional effect it would likely be observed consistently across the series. As the authors plotted the expanded allele data against age at onset they noticed a single outlier was driving the association and they removed this subject from the analysis.

Lee et al. then employed a series of alternate analytical approaches including removal of patients carrying rare alleles and refocusing the analysis on the bulk of individuals who fall under the center of the bell curve of a "normal distribution." No interaction between the mutant and normal allele lengths was observed with respect to age at onset. Subsequent studies on outliers and comparison of the two extremes, short and long normal repeat lengths, also did not show any significant interaction. Additional support for a purely dominant effect for HD symptomatic presentation is garnered from a small series of patients (n = 10) who are homozygous for mutant alleles. These patients present with age at onset that would be predicted based on the longer of the mutant alleles suggesting that disease penetrance is driven by the longest allele and not affected by the *trans* allele, expanded or not.

Lack of replication is a phenomenon that has plagued the field of clinical genetics and has been a major obstacle in the identification of disease-related genes and the subsequent development of therapeutics. When considering known gene disorders with heterogeneous presentation it is likely there will be multiple modifiers acting in unison which will add to the complexity of the analysis. It is remarkable that in

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the study of Lee et al. a single outlier data point could have such a dramatic influence over the outcome and raises concerns for future genetic modifier studies in expanded repeat disorders. Alternate analytical approaches will be needed to assess the influence of genetic modifiers on disease presentation. To identify true modifiers, sample sizes will likely need to be larger than has been necessary for gene identification. Daunting hurdles need to be overcome regarding age at onset analysis, due in part to the fact that the vast majority of patients will fall into a small window of variation flanking the mean. Confounding factors including other genetic and environmental determinants will only add to this analytical burden. In the case of expanded repeat disorders, particularly if the length of the mutated allele is modifying symptomatic presentation such as in HD, there is a need to optimize the study design. As proposed by Lee et al., removing notable outliers and rarer alleles may help, keeping in mind the caveat that allelic extremes may in fact act as rare phenotypic modifiers.

It has been over 25 years since the CAG repeat in the *HTT* gene was found to be the underlying genetic cause of HD and as yet no therapy is forthcoming.[1,7] Given the phenotypic heterogeneity, targeting disease modifiers is an attractive alternative approach to developing HTT-related drugs. However, the two studies highlighted here show the inherent challenges in identifying genetic modifiers of disease even under the ideal conditions of a true "monogenic " disorder. Optimizing analytical methodologies within this context will be crucial before they are applied to more heterogenous polygenic neurodegenerative disorders like multiple sclerosis, Alzheimer disease, and Parkinson disease.

AUTHOR CONTRIBUTIONS

Dr. Ross drafted the manuscript, analyzed and acquired data, and obtained funding. Dr. Singleton drafted the manuscript and reviewed the literature.

DISCLOSURE

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