Huntington disease

More common than you think?

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Recent advances in molecular genetics have enabled a fundamentally new approach in establishing the prevalence of neurogenetic disorders. Rather than relying on traditional epidemiologic approaches, increasingly available and rapid genetic testing methods can now determine the genetic prevalence of a particular disorder in large cohorts with great accuracy. Some studies at least suggest that the genetic prevalence of neurogenetic disorders traditionally considered as comparatively rare may be considerably more common than previously thought.[1,2]

The prevalence and penetrance of Huntington disease (HD) was previously derived largely from studies of individuals with symptomatic disease and their family members.[3] In this issue of *Neurology*®, Kay et al.[4] present data on the frequency of *HTT* alleles with an exon 1 CAG repeat of ≥36 CAG repeats in cohorts of individuals recruited from the general population.

HD is due to a heterozygous expansion of a CAG trinucleotide repeat in exon 1 of *HTT*. Normally, individuals have <27 CAG repeats on both alleles. Those with ≥40 repeats (fully penetrant alleles) will develop symptoms of HD if they live to old age. Those with intermediate alleles (27–35 CAG repeats) do not develop HD but there is a risk of expansion to an allele of ≥36 repeats in offspring, particularly if the allele is passed from the father. Finally, those with 36–39 CAG repeats (reduced penetrance alleles [RPA]) may or may not develop symptomatic HD.

Kay et al. tested the *HTT* CAG repeat size in 7,315 individuals from 3 separate cohorts. The relatively large number of individuals included from 3 geographically distinct cohorts is a particular strength of the study. Around 1 in 400 individuals had an allele with ≥36 CAG repeats. The different cohorts from Canada, the United States, and Scotland all had a similar frequency of alleles with ≥36 CAG repeats. The authors estimated disease penetrance in individuals with alleles between 36 and 38 repeats and concluded that penetrance is far lower than previous studies have suggested. For individuals ≥65 years of age, they estimate a minimum penetrance of 0.2% for those with 37 repeats and 2% for those with 38 repeats. The explanation for the findings of a higher incidence of alleles ≥36 CAG repeats and lower penetrance of RPA compared to previous studies is that those studies are based on individuals ascertained through families with at least one individual with symptomatic HD,[5] whereas this cohort is essentially unbiased and drawn from the population at large.

The data are important for a number of reasons. First, the data showed that considerably more individuals have mutations that could lead to symptomatic HD than was previously suspected. The authors hypothesize that there are a number of elderly individuals with relatively mild symptomatic disease due to RPA that are undiagnosed as a result of their age, lack of family history, and subtlety of symptoms. The author's advice that there should be a low threshold for *HTT* genetic testing in elderly individuals with subtle symptoms is well made. Second, as the authors point out, it is likely that next-generation sequencing technology will soon be able to identify expanded repeats such as the *HTT* CAG repeat, and therefore around 1 in 400 individuals who have whole exome or whole genome sequencing could be identified as being at risk of developing symptomatic HD. This article provides important data to enable counseling of such individuals about their risk of developing symptomatic disease.

There are a number of questions that the study does not answer due to the nature of its design. The DNA samples were all anonymized. This means that the 18 individuals who had ≥36 CAG repeats could not be examined nor could their family history be ascertained. Were this possible, it would have provided interesting information; for example, the disease penetrance would be higher than estimated by the authors if some of the individuals had subtle early manifestations of HD. In addition, the age of the individuals whose DNA is included in the study is not reported, and if the cohort is young, it would require a longer period of follow-up to answer questions of penetrance.

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Clinicians who identify individuals with RPA in families with manifest HD should not use the low penetrance figures identified in this study, but rather should use penetrance figures identified from studies of families where there is clinical HD present.[6]

A somewhat surprising finding from the study was the identification of 3 individuals with fully penetrant alleles. Two individuals had 42 CAG repeats and 1 had 44 CAG repeats. This finding equates to an incidence of a fully penetrant *HTT* CAG repeat of 41/100,000. If these results were to hold up in larger studies, then one would need to assume that the prevalence of HD may be an order of magnitude greater than the reported prevalence of between 2.17 and 7.33 per 100,000 in largely Caucasian populations.[3] A further, purely speculative explanation for the discrepancy between the epidemiologic data from previous clinical studies[3] and the comparatively high genetic prevalence in the study by Kay et al.[4] is the possibility of nonpenetrance in some individuals who carry ≥40 CAG repeats. However, the absolute number of individuals identified with ≥40 repeats is clearly too small to draw any firm conclusions.

While the study by Kay et al. is impressive in its scale and intriguing in its results, it is likely to be superseded by efforts to sequence the entire genome in considerably larger cohorts such as the 100,000 Genomes Project currently being carried out in the United Kingdom (www.genomicsengland.co.uk).

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REFERENCES

1. Chinnery PF, Elliott HR, Hudson G, Samuels DC, Relton CL. Epigenetics, epidemiology and mitochondrial DNA diseases. Int J Epidemiol 2012;41:177–187.
2. Coffey AJ, Durkie M, Hague S, et al. A genetic study of Wilson's disease in the United Kingdom. Brain 2013;136:1476–1487.
3. Rawlins MD, Wexler NS, Wexler AR, et al. The prevalence of Huntington's disease. Neuroepidemiology 2016;46:144–153.
4. Kay C, Collins JA, Miedzybrodzka Z, et al. Huntington disease reduced penetrance alleles occur at high frequency in the general population. Neurology 2016;87:282–288.
5. Semaka A, Hayden MR. Evidence-based genetic counselling implications for Huntington disease intermediate allele predictive test results. Clin Genet 2014;85:303–311.
6. Langbehn DR, Brinkman RR, Falush D, Paulsen JS, Hayden MR; International Huntington's Disease Collaborative Group. A new model for prediction of the age of onset and penetrance for Huntington's disease based on CAG length. Clin Genet 2004;65:267–277.