# Expanding the genetics of huntingtonism

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The lines defining many clinical syndromes have become blurred. A patient presenting with what appears to be Parkinson disease may in fact have one of several genetic mutations (e.g., *LRRK2*, *parkin*), an atypical parkinsonian syndrome (e.g., multisystem atrophy, progressive supranuclear palsy), sporadic idiopathic Parkinson disease, or a number of other conditions. Conversely, known genetic mutations may have classical presentations, but they may also present with widely varying signs and symptoms.

Huntington disease (HD) provides an example of both of these phenomena. HD remains a clinical diagnosis based on the presence of the classical triad of a movement disorder (most often involving chorea), psychiatric changes, and cognitive impairment, in the setting of a known family history.[1] The clinical presentation, however, can be mimicked by many other conditions, including paraneoplastic syndromes, infectious/inflammatory diseases, metabolic disorders, and other genetic neurodegenerative disorders (e.g., HDL1, HDL2, spinocerebellar ataxias, neuroacanthocytosis[2]). From the genetic perspective, the CAG trinucleotide expansion that causes HD can produce widely varying clinical presentations ranging from the classical triad to isolated signs (especially in early HD) of dementia, psychiatric changes, or a movement disorder, as well as parkinsonism and seizures (in juvenile-onset HD) and varying degrees of eye movement disorders, gait and balance problems, hyperreflexia, and weight loss. Though genetic testing for HD is not needed for patients with classical signs and symptoms and a known family history, genetic testing is more commonly performed in patients without a family history or for those with an unusual or atypical presentation in an effort to confirm or exclude the diagnosis of HD.

In this issue of *Neurology*®, Hensman Moss et al.[3] describe a study in which 514 symptomatic patients who had tested negative for the HD gene mutation were tested for the *C9orf72* gene hexanucleotide expansion, a known cause of frontotemporal lobar degeneration and amyotrophic lateral sclerosis.[4] They found that 10 of these patients carried the *C9orf72* mutation, making it the "commonest identified genetic cause of HD phenocopy presentations," accounting for almost 2% of the cohort. In addition to expanding the known causes of HD-like clinical presentations, the study also "extends the known phenotype of the *C9orf72* expansion."

This study has several strengths. It utilized a large cohort of patients referred to a tertiary referral center for genetic testing, but it is likely that this population is representative of the broader clinical population in which genetic testing for HD is usually performed. Interestingly, the authors note that at their center 63.5% of individuals with clinical manifestations of HD ("symptomatic") who undergo genetic testing for HD test negative; this somewhat surprising result likely occurs because typical HD presentations do not require genetic testing, while those undergoing testing either lack a known family history or have atypical clinical features. Another strength of the study is that it was hypothesis-driven and was not a brute force search for multiple genetic abnormalities in this population. The article also presents a very helpful algorithm for genetic testing in patients who test negative for HD (figure 2). One minor weakness relates to the use of the term "HD phenocopy," a term that implies a very close clinical resemblance to HD. The authors define this term as any individual that is suspected of having HD who tests negative for the HD gene mutation. But levels of suspicion for HD can vary considerably, and some patients with atypical presentations may undergo genetic testing even when clinical suspicion of HD is relatively low and the clinician may fully expect the test to be negative. Based on information in table 2, subjects 2, 3, and 6 in the present study do not appear to have typical HD clinical presentations, and it seems inappropriate to refer to such patients as HD "phenocopies"; perhaps the other term the authors (and others) use, "HD-like," would be better. Alternatively, the term huntingtonism offers an appealing parallel to the prototypical hypokinetic movement disorder of parkinsonism.

The clinical implications of the current findings relate mostly to diagnosis and genetic counseling. Being able to provide a firm genetic diagnosis for

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some patients would likely curtail further testing, though this particular test and the other known genetic causes of HD-like presentations in total account for a relatively small percentage of these patients. With regard to genetic counseling, having the *C9orf72* genetic mutation appears to have different consequences for at-risk individuals than the HD gene mutation or the other genetic causes for HD-like presentations, particularly given the highly variable penetrance associated with this mutation. These findings do not currently have implications for disease management, as treatments for these conditions remain symptomatic, directed at depression, chorea, or other symptoms regardless of genetic etiology. Perhaps disease-specific therapies will be developed in the future; if so, testing for *C9orf72* expansions and other genetic causes of HD-like presentations may become more critical. Finally, although none of the subjects in this study was reported as having been studied at autopsy, neuropathologic examination of *C9orf72*-positive cases with HD-like clinical syndromes will also contribute to our understanding of regional susceptibility to neurodegeneration.


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## DISCLOSURE

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