

Huntington Disease

Clinical Description: Huntington Disease (HD) features progressive motor, cognitive and psychiatric disturbances. Patients may experience clumsiness, balance and gait disturbances as well as other issues with both voluntary and involuntary movement, dysarthria, oculomotor disturbances, weakness, weight loss, personality changes, and depression. Age of onset is usually in the 4th decade. Patients with Juvenile HD have a similar set of symptoms but experience a more rapid decline. Motor and cerebellar symptoms are prominent. Onset is usually before age 20. Seizures occur in cases with onset before age 10.

Inheritance Pattern: Autosomal Dominant

Genotype-Phenotype Correlation: Repeat length is associated with age at symptom onset (Juvenile HD versus classic HD), faster progression of disease, and decreased variability in age at symptom onset. Reduced penetrance alleles are described.

Test Method: DNA extraction (if applicable); PCR and capillary electrophoresis of sample; analysis and review by multiple staff members.

Clinical Utility: Identification of causative variants in known or highly suspicious cases of a Huntington Disease; Rule-out HD in the presence of equivocal clinical presentation; Predictive testing in relatives of a proband with an HTT variant.

Clinical Sensitivity: Of patients meeting clinical diagnostic criteria for Huntington Disease, 98-99% (Andrew et al. (1994) Am J Hum Genet 54:852-863; Rosenblatt et al. (1998) Neurol 51: 215-220) will have an expanded CAG repeat in exon 1 of the HTT gene. Reduced penetrance (60% by age 65 and 70% by age 75) has been identified in individuals with expansions from 36 to 39 CAG repeats [Quarrell et al. (2007) J Med Genet. 44 e68 (<https://jmedgenet.com/cgi/content/full/44/3/e68>)

Analytical Sensitivity: The repeat size provided is +/- 1 CAG repeat up to 40; +/- 2 CAG repeats 41-60; and, +/- 3 CAG repeats when >60 repeats. This assay may not detect expansions larger than 101 repeats. Our analysis parameters are not designed to detect mosaicism.

Huntington Disease-Like 2

Clinical Description: Huntington Disease-like 2 (HDL2) is clinically similar to Juvenile onset Huntington Disease. Patients experience adult onset (usually by the 4th decade) of symptoms that include progressive movement disorder (parkinsonism, chorea), cognitive and emotional decline (dementia, psychiatric disturbances). Unlike Juvenile onset HD, seizures and eye movement abnormalities are usually not described. Some cases may follow a pattern of symptom onset more like classic Huntington Disease.

Inheritance Pattern: Autosomal Dominant

Genotype-Phenotype Correlation: None; known intra- and inter-familial variability; Reduced penetrance expansion alleles have been described.

Test Method: DNA extraction (if applicable); PCR and capillary electrophoresis of sample; analysis and review by multiple staff members.

Clinical Utility: Identification of causative variants in known or highly suspicious cases of a Huntington Disease-like phenotype, especially when HD testing is negative; Rule-out HDL2 in the presence of equivocal clinical presentation; Predictive testing in relatives of a proband with a JPH3 variant.



Huntington Disease-Like 2 (continued)

Clinical Sensitivity: HDL2 is a rare disorder and the clinical significance of some repeat lengths is still being characterized. Of patients of African ancestry with symptoms of Huntington disease who tested negative for HTT expansions, 7 of 20 (35%) had expansions of the JPH3 gene consistent with HDL2 [Krause et al. (2002). *Am J Hum Genet*. Abstract 2098; Margolis et al. (2003). *Clin Neurosci Res* 3:187-196.]. In North Americans, 3/374 patient (<1%) with symptoms of Huntington disease had JPH3 expansions [Margolis et al. (2004). *Ann Neurol*. 56: 670–4; Rosenblatt et al. (1998). *Neurology* 51: 215–20; Stevanin et al. (2003). *Brain* 126: 1599–603.]. Penetrance is not known. This test is only validated for inherited gene alterations associated with the phenotype(s) specified above.

Analytical Sensitivity: The repeat size provided is +/- 1 CTG repeat up to 40; +/- 2 CTG repeats 41-60; and, +/- 3 CTG repeats when >60 repeats. This assay may not detect expansions larger than 60 repeats. Our analysis parameters are not designed to detect mosaicism.