Dentatorubral-Pallidoluysian Atrophy Repeat Analysis

DISORDER ALSO KNOWN AS
DRPLA, Haw River syndrome, Naito-Oyanagi disease, NOD

CLINICAL FEATURES
DRPLA is a neurodegenerative disorder characterized by ataxia, choreoathetosis, epilepsy, and dementia.[1]The age of onset ranges from 1-72 years of age; with the mean age of onset being 31.5 years.[2] The clinical presentation varies depending on the age of onset. Juvenile onset disease presents with ataxia, myoclonus, seizures, and intellectual deterioration, whereas adult onset disease presents with ataxia, choreoathetosis, dementia, and psychiatric issues.[2,3] Seizures are less likely to be a feature of disease as age of onset increases, and are rarely observed in individuals with onset after 40 years of age.[2,3] Cerebellum and brain stem atrophy are typical findings on brain MRI.[4] Intranuclear inclusions can be observed on histological evaluation.[5] The prevalence of DRPLA in the Japanese population is estimated at 0.48 in 100,000 and is observed less frequently in other ethnic groups.[6]

INHERITANCE PATTERN/GENETICS
DRPLA is an autosomal dominant disorder caused by the expansion of a CAG trinucleotide repeat in exon 5 of the *ATN1* gene.[1,3] Normal alleles have 20 or fewer repeats, premutation alleles (mutable normal) have 21-35 repeats, incompletely penetrant alleles have 36-47 repeats, and pathogenic alleles have 48 or greater repeats.[1,7] To date, no allelels with greater than 150 repeats have been reported in the *ATN1* gene. The clinical subtypes associated with disease alleles fall along a spectrum that is loosely based on CAG repeat numbers; where the mildest, latest onset forms are associated with the smallest number of repeats and the more severe, earlier-onset form is associated with the greatest number of repeats.[1,8] The CAG repeat is meiotically unstable, which can result in expansion of the repeat during transmission from parent to offspring. Therefore, incompletely penetrant (mutable normal) alleles are not associated with disease, but the offspring of individuals with these alleles have an increased risk for inheriting pathogenic alleles. Furthermore, individuals may inherit pathogenic alleles that are longer than the parental allele, resulting in 'anticipation' or the occurrence of increasing severity and decreasing age of onset in subsequent generations, especially when inherited from a father.[3,9] The clinical significance of these alleles should be interpreted within the context of clinical presentation and family history.

TEST METHODS
Using genomic DNA from the submitted specimen, standard PCR fragment analysis is performed to identify alleles with 100 or fewer repeats and repeat primed PCR is used to identify alleles with >100 repeats, as well as determine the number of repeats in alleles with 100 or fewer repeats. Nucleotide repeat numbers of 50 or fewer are reported with an accuracy of +/- 2 repeats and repeat numbers from 51-100 are reported with an accuracy of +/- 5 repeats. Internal standards are analyzed along with clinical samples to evaluate assay performance. The exact number of repeats cannot be determined for alleles with greater than 100 repeats. Southern blot analysis is required to determine the number of repeats in alleles larger than this and is not completed as part of this test.

CLINICAL SENSITIVITY
The clinical sensitivity for analysis of the CAG repeat in *ATN1* depends on the clinical phenotype of the patient. All individuals with DRPLA have an expansion of the CAG repeat in exon 5 of the *ATN1* gene, which is detectable by this targeted analysis. The technical sensitivity of fragment analysis is estimated to be greater than 95%.

REFERENCES:
1.Veneziano L. DRPLA. 1999 Aug 6 [Updated 2016 Jun 9]. In: Pagon RA, Adam MP, Bird TD, et al., editors. GeneReviews™[Internet]. Seattle (WA): University of Washington, Seattle; 1993-2013. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1491/#drpla.REF.hasegawa.2010.1694
2.Hasegawa A et al. Long-term disability and prognosis in de ntatorubral-pallidoluysian atrophy: a correlation with CAG repeat length. Movement Disorders: Official Journal Of The Movement Disorder Society. 2010 Aug 15 25(11):1694-700.20589872 (PMID: 20589872)

3.Yamada M. Dentatorubral- pallidoluysian atrophy (DRPLA): The 50th Anniversary of Japanese Society of Neuropathology. Neuropathology : Official Journal Of The Japanese Society Of Neuropathology. 2010 Oct 30(5):453-7.20500452 (PMID: 20500452)
4.Suna mi Y et al. Radiolo gic and neuropatho logic findings in patients in a family with dentatorubra l-pallidoluysian atrophy. Ajnr. American Journal Of Neuroradiology. 2011 Jan 32(1):109-14.20966051 (PMID: 20966051)
5.Mori F et al. Autophagy-related proteins (p62, NBR1 and LC3) in intranuclear inc lusions in neurodege nerative diseases. Neuroscience Letters. 2012 Aug 01 522(2):134-8.22728060 (PMID: 22728060)
6.Tsuji S et al. Sporadic ataxias in Japan--a population-based epidemiological study. Cerebellum (London, England). 2008 7(2):189-97.18418674 (PMID: 18418674)
7.Carroll LS et al. Dentatorubral-pallidoluysian Atrophy: An Update. Tremor And Other Hyperkinetic Movements (New York, N.Y.). 2018 8:577 (PMID: 30410817)
8.Shimojo Y et al. Severe infantile dentatorubral pallidoluysian atrophy with extreme expansion of CAG repeats. Neurology. 2001 Jan 23 56(2):277-8.11160976 (PMID: 11160976)
9.Vinton A et al. Dentatorubral-pallidoluysian atrophy in three generations, with clinical courses from nearly asymptomatic elderly tosevere juvenile, in an Australian family of Macedonian descent. American Journal Of Medical Genetics. Part A. 2005 Jul 15136(2):201-4.15948186 (PMID: 15948186)