Friedreich Ataxia Repeat Analysis(*FXN* repeat analysis)

DISORDER ALSO KNOWN AS
FA, FRDA, Friedreich spinocerebellar ataxia, Friedreich's ataxia

CLINICAL FEATURES
Friedreich ataxia (FRDA) is one of the most common forms of hereditary ataxia, with a prevalence of 1 in 30-50,000 individuals of Caucasian descent and a carrier frequency of 1 in 85-100 individuals.[1,2] Approximately 75% of affected individuals present prior to 25 years of age with progressive ataxia, muscle weakness and wasting, dysarthria, dysphagia, lower limb spasticity, and impaired vibration sense. Cardiomyopathy, ophthalmic abnormalities, scoliosis, and diabetes mellitus are less commonly associated findings.[1,3] The remaining individuals with FRDA have atypical forms including very early onset FRDA, late onset FRDA (LOFA), very late onset FRDA (VLOFA) or FRDA with retained reflexes. Individuals with very early onset FRDA typically present prior to 5 years of age with more severe clinical features and rapid deterioration, whereas those with late or very late onset present after 25 and 40 years of age, respectively.[3,4] Clinical features tend to be milder and have a slower progression in those with LOFA and VLOFA.[3,5] Although most individuals with typical FRDA are are flexic, reflexes are maintained in individuals with FRDA with retained reflexes.[3,5] While cognition is not typically impaired, specific deficits have been reported, particularly in those with early onset disease.3.5 Neuroimaging is often normal in the early stages of FRDA; however, atrophy of the cervical spinal cord and cerebellum has been reported.[1,5,6]

INHERITANCE PATTERN/GENETICS
FRDA is an autosomal recessive disorder caused by bi-allelic pathogenic variants in the *FXN* gene. FRDA is most commonly due to bi-allelic inheritance of a GAA repeat expansion in intron 1, but the remaining 4% of affected individuals have one allele with an expanded GAA repeat and a single nucleotide or intragenic copy-number variant on the other allele.[1,5] Normal alleles have 33 or fewer repeats, premutation alleles (mutable normal) have 34-43 repeats, incomplete penetrance alleles have 44-65 repeats, and fully penetrant pathogenic alleles have 66 or greater repeats.[5] Alleles in the incomplete penetrance range have been identified in individuals with LOFA and VLOFA, as well as unaffected individuals, indicating that disease association relies, in part, on the length of the second allele, but is poorly understood at this time. [5] The clinical subtypes associated with pathogenic alleles fall along a spectrum that is loosely based on GAA 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.[1,5] Rarely, interuptions of the GAA repeat with other nucleotides have been observed and it is unknown if interuptions modulate the phenotype of full lengthexpansions.[5] The exact demarcation between repeat ranges and age of onset is poorly defined. 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 repeat s, as w ell as determine the number of repeats in alleles with 100 or fewer repeat s. 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 repeat s in alleles larger than this and is not completed as part of this test.

CLINICAL SENSITIVITY

The clinical sensitivity of FXN testing by GAA repeat analysis depends on the clinical phenotype of the patient. Approximately 96% of individuals with FRDA have an expansion of the GAA repeat in intron 1 of the FXN gene, which is detectable by this analysis. The remaining 4% of affected individuals have an allele with an expanded GAA repeat and a single nucleotide variant on the other allele.[1,5] Together the technical sensitivity of fragment analysis and sequencing is estimated to be greater than 95%.

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