

Friedreich Ataxia Sequencing and Del/Dup (*FXN* sequence and deletion/duplication 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} Deletions or duplications of the *FXN* gene are expected to be rare.⁵

TEST METHODS

Using genomic DNA from the submitted specimen, the coding regions and splice junctions of the requested gene are PCR amplified and capillary sequencing is performed. Bi-directional sequence is assembled, aligned to reference gene sequences based on NCBI RefSeq transcript and human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Concurrent deletion/duplication testing is performed for most, if not all, of the coding exons using exon-level oligo array CGH (ExonArrayDx), and data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. Reported clinically significant variants are confirmed by an appropriate method. Sequence and copy number variants are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events, but less for deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test identify most deletions and duplications involving coding exons but are less reliable for detecting copy number variants of less than 500 base pairs. Assessment of copy number events also depends on the inherent sequence properties of the targeted regions, including shared homology and exon size. Mosaicism detection is limited and balanced chromosome aberrations cannot be identified.

CLINICAL SENSITIVITY

The clinical sensitivity of *FXN* testing by sequencing and exon array depends on the clinical phenotype of the patient. Approximately 4% of individuals with FRDA have an allele with an expanded GAA repeat and a single nucleotide variant on the other allele.^{1,5} The proportion of individuals with a deletion or duplication of *FXN* is expected to be rare.⁵ Together the technical sensitivity of fragment analysis and sequencing is estimated to be greater than 95%.

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