

C9orf72 Gene Analysis for Amyotrophic Lateral Sclerosis and Frontotemporal Lobar Degeneration

Disorder also known as: c9FTD/ALS, *C9orf72* – Related ALS/FTD

Clinical Features: Amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD) are clinically related syndromes with overlapping molecular pathogenesis.¹ Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease of adults.² Frontotemporal lobar degeneration (FTLD), which results in the symptoms of frontotemporal dementia, is the second most common cause of dementia in the presenile age group (<65 years) and accounts for 5–15% of all dementias.¹ *C9orf72*-related ALS and FTLD is characterized by upper and/or lower motor neuron dysfunction, frontotemporal lobar degeneration resulting in progressive changes in behavior, executive dysfunction, language impairment, and some degree of Parkinsonism.³ Disease manifestations may initially include only ALS or FTLD and additional features may or may not appear as part of disease progression. The age of onset ranges from 30-70 years of age, with the average age of onset in the late 50's.⁴

Inheritance Pattern/Genetics: *C9orf72*-related ALS/FTLD is an autosomal dominant disorder caused by the expansion a GGGGCC (G₄C₂) hexanucleotide repeat in the 5' UTR of the chromosome 9 open reading frame 72 gene (*C9orf72*). The *C9orf72* repeat expansion is the most common genetic cause of ALS and FTLD and accounts for up to 50% of ALS, 29% of FTLD and 88% of patients with features of both ALS and FTLD in the Northern European population.⁴ Conversely, *C9orf72* repeat expansions account for notably fewer cases of ALS/FTLD in other populations.⁴ Normal alleles have 24 or fewer G₄C₂ repeats, while disease alleles have 60 or greater repeats; disease alleles can have up to 2,000 repeats.^{4,5} Repeat expansions between 25-59 repeats are of uncertain clinical significance, as they have been identified in the general population, as well as in individuals with FTLD or ALS.⁶ Clinical significance of these alleles should be interpreted within the context of clinical presentation and family history.³

The *C9orf72* repeat expansion is associated with an age dependent cumulative penetrance, with almost 100% penetrance by age 80. However, reduced penetrance has been described in some families and repeat size does not necessarily correlate with age of onset or clinical course.⁴ Targeted testing of at-risk adult relatives is available if molecular genetic testing has identified a hexanucleotide repeat expansion in the family. *C9orf72*-related ALS/FTLD is an adult onset disorder for which there is no specific treatment in childhood or change in medical management. Therefore, in accordance with policy and position statements from American College of Medical Genetics (ACMG)^{8,9}, National Society of Genetic Counselors (NSGC)¹¹, American Society of Human Genetics (ASHG)^{10,13}, and the American Medical Association (AMA)¹², samples from individuals younger than 18 years of age will not be accepted.

Test Methods:

Using genomic DNA obtained from blood (2-5 mL in EDTA), repeat analysis is performed via the Asuragen AmplideX PCR/CE *C9orf72* kit. The sample is evaluated by repeat-primed PCR to identify expanded alleles, as well as determine the number of repeats in alleles with fewer than 145 repeats. Southern blot analysis is required to determine the number of repeats in alleles larger than 145 repeats, but is **not completed as part of this test**.

Test Sensitivity:

The clinical sensitivity for analysis of the repeat region in *C9orf72* depends on the clinical phenotype of the patient. Up to 50% of ALS, 29% of FTLD and 88% of patients with features of both ALS and FTLD have a repeat expansion in the *C9orf72* gene.⁴ The technical sensitivity of repeat primed PCR is estimated to be 95%, with 98% specificity.⁷

References:

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