Amyotrophic Lateral Sclerosis / Frontotemporal Lobar Degeneration (ALS / FTLD) Panel

Sequence Analysis and Exon-Level Deletion/Duplication Testing of 24 Genes

DISORDER ALSO KNOWN AS: Lou Gehrig's disease, Frontotemporal dementia (FTD)

PANEL GENE LIST:
ANG, ALS2, CHCHD10, CHMP2B, FUS, GRN, HNRNPA2B1, MAPT, MATR3, OPTN, PFN1, PRPH, SETX, SLC52A3, SOD1, SPG11, SQSTM1, TAF15, TARDBP, TBK1,TUBA4A, UBQLN2, VAPB, VCP

CLINICAL FEATURES:
Amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD) are clinically related syndromes with overlapping molecular pathogenesis.[1] Amylotrophic lateral sclerosis (ALS) is the most common motor neuron disease in 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] Although ALS and FTLD have traditionally been considered two different disorders, it is now well established that they represent a continuum from pure motor neuron involvement to pure FTD, with many cases a mixture of both entities (ALS-FTLD).[3,4] The finding that up to 50% of all patients present with some degree of both ALS and FTD, supports this ALS/FTD continuum.[5] ALS and FTLD can be observed in the same individual or family and can be caused by the same genes.[4]

ALS is a progressive neurodegenerative disease that results from the death of lateral neurons in the cerebral cortex and spinal cord that control voluntary muscles.[6] ALS affects both the upper motor neurons (UMN), located in the brain and spinal cord, and the lower motor neurons (LMN), which control muscle activity.[7] UMN signs in ALS include spasticity, hyperreflexia, extensor plantar response, and pseudobulbar palsy. LMN signs include weakness, muscle wasting (atrophy), hyporeflexia, muscle cramps, and fasciculations. A diagnosis of ALS is made when there is evidence of LMN degeneration by clinical, electrophysiologic, or neuropathologic examination, and evidence of UMN degeneration by clinical examination.[7]
Although the majority of individuals with ALS have adult onset disease, rare forms of juvenile ALS have been documented.[7,8]

FTLD is a syndrome of progressive behavioral and language changes, although not memory dysfunction, that results from the loss of neurons in the frontal and temporal lobes.[4,9,10] Common features include inappropriate actions (loss of initiative and insight, social disinhibition), loss of empathy, apathy, distractibility, repetitive compulsive behavior, and a decline in personal hygiene. Speech and language difficulty, as well as movement disorders may also be present in some individuals. Generalized atrophy of the frontal and temporal lobes of the brain — the areas generally associated with personality, behavior, and language – can be seen on MRI.[10] Subtypes of FTLD can be distinguished according to the symptoms that appear first and most predominantly.

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Usually, FTLD has relatively little effect on the parts of the nervous system that control movement, and so many FTLD patients remain physically strong and relatively agile until late in the illness.[4] However, 10-15% of patients experience motor neuron involvement.[4]

INHERITANCE PATTERN/GENETICS:

ALS and FTLD are part of a clinical, pathological and genetic continuum, and result from pathogenic variants in genes involved in the development or maintenance of corticospinal tract neurons.[11] The ALS/FTLD Panel at GeneDx includes sequencing and deletion/duplication analysis of 24 genes associated with ALS and/or FTLD. The complete list of genes and associated disorders is included in the table below. ALS/FTLD can be inherited in an autosomal dominant, autosomal recessive, or X-linked manner. A genetic diagnosis is identified in approximately 18-21% of individuals with ALS, 15-40% of individuals with FTLD, and 20% of individuals with ALS and FTLD, who tested negative for the *C9ORF72* repeat expansion.[11,12,13] Wide clinical variability occurs between and within families.[4] A clinical diagnosis of ALS and/or FTLD is based on medical and family history, neurological and neuropsychological evaluations, neuropathological studies, other ancillary testing, and exclusion of other disorders with similar clinical presentations.[3,4] However, clinical evaluation alone may not be sufficient to distinguish the various genetic causes of ALS/FTLD given their phenotypic and genetic heterogeneity. The ALS/FTLD gene panel at GeneDx can assist in confirming a clinical diagnosis, defining the sub-type of ALS/FTLD, or aiding in the development of a comprehensive medical plan including symptom management and recurrence risk assessment. ALS and FTLD are adult onset disorders for which there is currently no specific medical intervention that, if initiated in childhood, would alter the clinical course. Therefore, in accordance with policy and position statements from the American College of Medical Genetics (ACMG)[14,15], American Society of Human Genetics (ASHG)[16], and the American Academy of Pediatrics[15], samples from individuals younger than 18 years of age will not be accepted for this testing. The Juvenile ALS Panel or other neurogenetic testing could be considered for symptomatic minors.

TEST METHODS:

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. 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.

TEST SENSITIVITY:

The technical sensitivity of sequencing is estimated to be > 99% at detecting single nucleotide events. It will not reliably detect 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 cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size. For the *GRN* gene, sequencing but not deletion/duplication

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analysis, is performed. The hexanucleotide repeat expansion in the *C9orf72* gene is not performed as part of the Amyotrophic Lateral Sclerosis / Frontotemoporal Lobar Degeneration Panel.

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AMYOTROPHIC LATERAL SCLEROSIS / FRONTOTEMPORAL LOBAR DEGENERATION (ALS / FTLD) PANEL

SEQUENCE AND EXON-LEVEL DELETION/DUPLICATION ANALYSIS OF 24 GENES

Gene	Disease Name	Inheritance	Disease Associations
ALS2	Juvenile ALS 2 / Juvenile primary lateral sclerosis	AR	Rare[1] cause of ALS
ANG	ALS 9	AD	Rare[2] cause of ALS
CHCHD10	FTLD/ALS 2	AD	1.4%-3.5% of individuals of European ancestry with ALS or ALS/FTLD[3]
CHMP2B	ALS 17 / FTLD	AD	1% of ALS and FTLD[4]
FUS	ALS 6 with or without FTLD	AD	1-5% of ALS with or without FTLD[5]
GRN	FTLD with ubiquitin-positive inclusions	AD, AR	5% of all FTLD; 20% of familial FTLD[6] ; Rare cause of AR adult-onset NCL[24]
HNRNPA2B1	Inclusion body myopathy earlyonset with Paget disease with or without frontotemporal dementia	AD	Rare[7] cause of FTLD
MAPT	MAPT-related FTLD	AD	13-30% of familial FTLD; 1-4% of sporadic FTLD[8]
MATR3	ALS 21	AD	Rare[9] cause of ALS

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OPTN	ALS 12	AD, AR	Rare[10] cause of ALS
PFN1	ALS 18	AD	Rare[11] cause of ALS
PRPH	ALS	AD, AR	Rare[12] cause of ALS
SETX	Juvenile ALS 4	AD	Rare[13] cause of ALS
SLC52A3	Riboflavin transporter deficiency - BVVL syndrome	AR	Rare[14] overall, differential diagnosis of juvenile ALS
SOD1	ALS 1	AD, AR	20% of FALS and 3% of sporadic ALS[15]
SPG11	Juvenile ALS 5	AR	40% of autosomal recessive juvenile ALS[16]
SQSTM1	FTLD/ALS 3	AD	2-3% of FTLD/ALS some with Paget disease of bone[17]
TAF15	ALS	AD	Rare[18] cause of ALS
TARDBP	ALS 10 / TARDBP-related FTLD	AD	1.5-3% of ALS with or without FTLD[5]
TBK1	FTLD/ALS 4	AD	1.7% -4.5% of ALS/FTLD[19]
TUBA4A	ALS 22 with or without FTLD	AD	Rare[20] cause of ALS with or without FTLD
UBQLN2	ALS 15 with or without FTLD	XL	Rare[21] cause of ALS with or without FTLD
VAPB	ALS 8	AD	Rare[22] cause of ALS
VCP	ALS 14 with or without FTLD	AD	Rare[23] cause of ALS with or without FTLD

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