# Juvenile Amyotropic Lateral Sclerosis (Juvenile ALS) Panel

## Sequence Analysis and Exon-Level Deletion/Duplication Testing of 16 Genes

**Disorder also known as**: Juvenile Lou Gehrig's disease, pediatric motor neuron disease, JALS

**Panel Gene List: ALDH18A1, ALS2, BICD2, BSCL2, C19orf12, FUS, HEXA, SETX, SIGMAR1, SLC52A2, SLC52A3, SOD1, SPAST, SPG11, UBQLN2, ZFYVE26**

**Clinical Features:**
Juvenile amyotrophic lateral sclerosis (JALS) is a pediatric motor neuron diseases that is characterized by progressive upper (UMN) and lower (LMN) motor neuron degeneration with onset before age 25.[1] UMN signs in juvenile ALS include spasticity, hyperreflexia, extensor plantar response, and uncontrolled laughter and weeping (pseudobulbar syndrome).[1] LMN signs include weakness, muscle wasting (atrophy), hyporeflexia, and muscle cramps.[2] Juvenile ALS is a clinically and genetically heterozgenous disorder, with clinical, pathological and genetic overlap with other neurological conditions.[3] The clinical presentation and age of onset varies widely between and within families.[1,3] This panel includes genes that share clinical overlap with JALS and are associated with hereditary spastic paraplegias and spinal muscular atrophy.

**Inheritance Pattern/Genetics:**
The Juvenile ALS Panel at GeneDx includes sequencing and deletion/duplication analysis of 16 genes associated with juvenile onset ALS. The complete list of genes and associated disorders is included in the table below. Some of the genes associated with juvenile ALS can also cause adult onset forms of the disorder. JALS is most often inherited in an autosomal recessive pattern, however autosomal dominant and X-linked inheritance also occurs. JALS displays genetic and phenotypic heterogeneity, making diagnosis based on clinical examination or histological appearances alone difficult.[1] The Juvenile ALS gene panel at GeneDx can assist in confirming a clinical diagnosis, defining the sub-type of JALS, or guiding the development of a comprehensive medical plan. A molecular confirmation of a diagnosis can allow for more accurate recurrence risk assessment for the family and facilitate access to specific therapies and clinical trials.

**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 were simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads were assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data were analyzed to identify sequence variants and most deletions and duplications involving coding exons. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. 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 HEXA gene, sequencing but not deletion/duplication analysis, is performed. Testing for the hexanucleotide repeat expansion in the *C9orf72* gene is not recommended for minors and is not performed as part of the Juvenile Amyotrophic Lateral Sclerosis Pane .[4,5,6]

**References:**

1. Teoh et al. (2017) Neural Plast. 2017 :6509493 (PMID: 28634552)
2. Harms et al. (2013) Neurol Clin 31 (4):929-50 (PMID: 24176417)
3. Orlacchio et al. (2010) Brain : A Journal Of Neurology 133 (Pt 2):591-8 (PMID: 20110243)
4. Ross LF, Saal HM, David KL, Anderson RR; American Academy of Pediatrics; American College of Medical Genetics and Genomics. Technical report: Ethical and policy issues in genetic testing and screening of children. Genet Med. 2013 Mar;15(3):234-45.
5. COMMITTEE ON BIOETHICS, COMMITTEE ON GENETICS, AND THE AMERICAN COLLEGE OF MEDICAL GENETICS AND GENOMICS SOCIAL, ETHICAL, AND LEGAL ISSUES COMMITTEE. POLICY STATEMENT. Ethical and Policy Issues in Genetic Testing and Screening of Children. Pediatrics. 2013;131:620–622.
6. NSGC Executive Office. Genetic Testing of Minors for Adult-Onset Conditions Position Statement (Adopted 2012).

# Juvenile Amyotrophic Lateral Sclerosis (JALS) Panel: Sequence and Exon-Level Deletion/Duplication Analysis of 16 Genes

| Gene | Disease Name | Inheritance | Disease Associations |
|---|---|---|---|
| ALDH18A1 | Cutis laxa and hereditary spastic paraplegia (HSP); SPG9A; SPG9B | AD, AR | Rare[1]; differential diagnosis of juvenile ALS |
| ALS2 | Juvenile ALS 2 / Juvenile primary lateral sclerosis | AR | Rare[2,3]; known to be associated with JALS |
| BICD2 | Lower-Extremity Predominant Spinal Muscular Atrophy 2 | AD | Rare[4]; differential diagnosis of juvenile ALS |
| BSCL2 | Spastic paraplegia 17/Silver syndrome/ Distal hereditary motor neuropathy, type V, (dHMNV)/ Congenital generalized lipodystrophy, type 2 | AD | Rare[1,4]; differential diagnosis of juvenile ALS |
| C19orf12 | Spastic paraplegia 43 (SPG43); Neurodegeneration with brain iron accumulation 4 | AR | Rare[4]; differential diagnosis of juvenile ALS |
| FUS | ALS 6 | AD/AR | 1-5% of all ALS, known to be associated with JALS [3] |
| HEXA | Tay Sachs disease; GM2-gangliosidosis | AR | Rare[2]; differential diagnosis of juvenile ALS |
| SETX | Juvenile ALS 4; Ataxia with oculomotor apraxia type 2 (AOA2) | AD | Rare[3,4] |
| SIGMAR1 | Juvenile ALS 16; Distal Spinal Muscular Atrophy 2 | AR | Rare[4] |
| SLC52A2 | Riboflavin transporter deficiency - Brown-Vialetto-Van-Laere syndrome (BVVL) syndrome type 2 | AR | Rare[4]; differential diagnosis of juvenile ALS |
| SLC52A3 | Riboflavin transporter deficiency - BVVL syndrome type 1 | AR | Rare[4]; differential diagnosis of juvenile ALS |
| SOD1 | ALS 1 | AD, AR | 20% of FALS and 3% of sporadic ALS; known to be associated with JALS[3] |
| SPAST | Spastic paraplegia 4 (SPG4) | AD | Rare[4]; differential diagnosis of JALS |
| SPG11 | Juvenile amyotrophic lateral sclerosis type 5 (ALS5); Spastic paraplegia 11 (SPG11); Charcot-Marie-Tooth 2X | AR | 40% of autosomal recessive juvenile ALS5 in one study[5] |
| UBQLN2 | ALS 15 | XLD | Rare[6] |
| ZFYVE26 | Spastic paraplegia 15 (SPG15) | AR | Rare[1]; differential diagnosis of juvenile ALS |

References: 1. De Souza et al. (2017) Cerebellum 16 (2):525-551 (PMID: 27271711); 2. Kinsley L, Siddique T. Amyotrophic Lateral Sclerosis Overview. 2001 Mar 23 [Updated 2015 Feb 12]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1450/; 3. Zou et al. (2015) Ann Transl Med 3 (15):221 (PMID: 26488017); 4. Teoh et al. (2017) Neural Plast. 2017 :6509493 (PMID: 28634552); 5. Orlacchio et al. (2010) Brain: A Journal Of Neurology 133 (Pt 2):591-8 (PMID: 20110243); 6. Deng et al. (2011) Nature 477 (7363):211-5 (PMID: 21857683)