Amyotrophic Lateral Sclerosis

Indications for Ordering

Confirm clinical diagnosis of amyotrophic lateral sclerosis (ALS)

Test Description

Massively parallel sequencing/exonic oligonucleotide-based comparative genomic hybridization microarray

Tests to Consider

Typical testing strategy

• Diagnosis of ALS is based on clinical and laboratory findings
• Molecular genetic testing is used to support diagnosis, determine subtype, and assess risk for family members

Primary test

Amyotrophic Lateral Sclerosis (ALS) Panel, Sequencing and Deletion/Duplication, 11 Genes 2011152

• Most comprehensive genetic testing for ALS
• Not recommended for asymptomatic individuals
• ALS consent form is required

Related test

Familial Mutation, Targeted Sequencing 2001961

• Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Prevalence – 4-8/100,000 for all types of ALS
• 10% of cases are familial

Average age of onset – 40s for familial ALS; 50s for sporadic ALS

Symptoms

• Progressive, fatal neurodegenerative disease
• Lower motor neuron (LMN) degeneration in one or more of four regions (bulbar, cervical, thoracic, or lumbosacral)
  o Progressive muscle weakness
  o Atrophy/muscle wasting
  o Fasciculation
• Upper motor neuron (UMN) degeneration in one or more of four regions (bulbar, cervical, thoracic, or lumbosacral)
  o Spasticity
  o Abnormal reflexes
  o Extensor plantar response
  o Bulbar findings (dysarthria, dysphagia)

• Cognitive decline in some, but not all cases
  o Frontotemporal dementia (FTD)
  o Executive function impairment

Diagnosis

• Affected individuals with at least one other affected relative are considered to have familial ALS (FALS)
  o Most likely to have a genetic etiology
• Affected individuals with no family history of ALS are considered to have sporadic ALS (SALS)
• Diagnosis is based on combination of
  o Clinical features
  o Electromyogram (EMG)
  o Pathology on autopsy
  o Histology of muscle biopsy
  o Exclusion of other disorders
  o Molecular genetic testing to determine subtype

Consensus/diagnostic criteria

According to the revised El Escorial World Federation of Neurology criteria

• Diagnosis of ALS requires
  o Signs of LMN degeneration by clinical, electrophysiological, or neuropathologic exam, and
  o Signs of UMN degeneration by clinical exam, and
  o Progression of signs within a region or spread to other regions, and
  o Absence of electrophysiological, pathologic, or neuroimaging evidence of other disease processes that would explain the clinical findings

• Certainty of diagnosis determined by affected regions and progression
  o Clinically definite ALS
    ▪ UMN and LMN signs in bulbar region and at least two spinal regions, or
    ▪ UMN and LMN signs in at least three regions
  o Clinically probable ALS
    ▪ UMN and LMN signs in at least two regions with some UMN signs rostral to LMN signs
  o Clinically probable – laboratory-supported ALS
    ▪ UMN and LMN signs in only one region, or
    ▪ UMN signs in one region and LMN signs by EMG in two regions with exclusion of other causes, or
    ▪ UMN and LMN signs in at least one region with a family history of an identified ALS-causing gene mutation, and other causes excluded
Clinical possible ALS
- UMN and LMN signs together in only one region, or
- UMN signs alone in two or more regions, or
- LMN signs found rostral to UMN signs and diagnosis of clinically probable – laboratory-supported cannot be made

Prognosis
- Average length of survival after diagnosis – 3 years
- Progressive loss of respiratory muscle function is usually the cause of death

Genetics
See table

Test Interpretation

Clinical sensitivity – 30-40% for FALS (see table below for details)

Results
- Positive
  - Pathogenic mutation(s) detected
    - Supports a diagnosis of ALS
  - Negative
    - No mutations detected
    - Genetic cause of ALS not identified
    - Reduces, but does not exclude, the likelihood of FALS

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Gene Name</th>
<th>NM #</th>
<th>OMIM #</th>
<th>Associated Disorder*</th>
<th>Inheritance**</th>
<th>Clinical Sensitivity for ALS</th>
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</thead>
<tbody>
<tr>
<td>ALS2</td>
<td>Amyotrophic lateral sclerosis 2 (juvenile)</td>
<td>NM_020919</td>
<td>606352</td>
<td>Juvenile ALS; primary lateral sclerosis</td>
<td>AR</td>
<td>Rare</td>
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<tr>
<td>ANG</td>
<td>Angiogenin, ribonuclease, RNase A family, 5</td>
<td>NM_001145</td>
<td>105850</td>
<td>FALS and SALS</td>
<td>AD</td>
<td>Rare</td>
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<tr>
<td>FIG4</td>
<td>FIG4 homolog (S. cerevisiae)</td>
<td>NM_014845</td>
<td>609390</td>
<td>FALS and SALS; Charcot-Marie-Tooth type 4J (CMT4J)</td>
<td>AD for ALS; AR for CMT4J</td>
<td>2%</td>
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<tr>
<td>FUS</td>
<td>Fusion (involved in t(12;16) in malignant liposarcoma)</td>
<td>NM_004960</td>
<td>137070</td>
<td>FALS and SALS; juvenile ALS; FTD</td>
<td>AD and AR; possible reduced penetrance</td>
<td>~5% for FALS</td>
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<tr>
<td>OPTN</td>
<td>Optineurin</td>
<td>NM_021980</td>
<td>602432</td>
<td>FALS and SALS; glaucoma</td>
<td>AD and AR</td>
<td>1% for FALS</td>
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<tr>
<td>SETX</td>
<td>Senataxin</td>
<td>NM_015046</td>
<td>608465</td>
<td>Juvenile ALS; motor neuronopathy; Spinocerebellar ataxia (SCAR1)</td>
<td>AD for ALS; AR for SCAR1</td>
<td>Rare</td>
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<tr>
<td>SOD1</td>
<td>Superoxide dismutase 1 (soluble)</td>
<td>NM_000454</td>
<td>147450</td>
<td>FALS and SALS</td>
<td>AD with reduced penetrance; rarely AR</td>
<td>&gt;20% for FALS; 1-3% for SALS</td>
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<tr>
<td>TARDBP</td>
<td>TAR DNA binding protein</td>
<td>NM_007375</td>
<td>605078</td>
<td>FALS and SALS; FTD</td>
<td>AD</td>
<td>3-5% for FALS; &lt;4% for SALS</td>
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<tr>
<td>UBQLN2</td>
<td>Ubiquilin 2</td>
<td>NM_013444</td>
<td>300264</td>
<td>FALS and SALS; FTD</td>
<td>XL</td>
<td>Rare</td>
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<tr>
<td>VAPB</td>
<td>VAMP (vesicle-associated membrane protein)-associated protein B and C</td>
<td>NM_004738</td>
<td>605704</td>
<td>FALS; Finkel type (late onset) spinal muscular atrophy (SMA)</td>
<td>AD</td>
<td>Rare</td>
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<td>VCP</td>
<td>Valosin-containing protein</td>
<td>NM_007126</td>
<td>601023</td>
<td>FALS; inclusion body myopathy with Paget disease of the bone and FTD</td>
<td>AD</td>
<td>1-2% for FALS</td>
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</tbody>
</table>

*FALS = familial amyotrophic lateral sclerosis; SALS = sporadic amyotrophic lateral sclerosis; FTD = frontotemporal dementia
**AD = autosomal dominant; AR = autosomal recessive; XL = X-linked dominant

Limitations
- Does not detect C9orf72 hexanucleotide repeats, which are the most common cause of FALS, SALS, and familial FTD
- Diagnostic errors can occur due to rare sequence variations
- Regulatory region mutations, deep intronic mutations, and mutations in genes other than those tested will not be detected

References