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)
  - Progressive muscle weakness
  - Atrophy/muscle wasting
  - Fasciculation
- Upper motor neuron (UMN) degeneration in one or more of four regions (bulbar, cervical, thoracic, or lumbosacral)
  - Spasticity
  - Abnormal reflexes
  - Extensor plantar response
  - Bulbar findings (dysarthria, dysphagia)
- Cognitive decline in some, but not all cases
  - Frontotemporal dementia (FTD)
  - Executive function impairment

Diagnosis

- Affected individuals with at least one other affected relative are considered to have familial ALS (FALS)
  - 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
  - Clinical features
  - Electromyogram (EMG)
  - Pathology on autopsy
  - Histology of muscle biopsy
  - Exclusion of other disorders
  - Molecular genetic testing to determine subtype

Consensus/diagnostic criteria

According to the revised El Escorial World Federation of Neurology criteria

- Diagnosis of ALS requires
  - Signs of LMN degeneration by clinical, electrophysiological, or neuropathologic exam, **and**
  - Signs of UMN degeneration by clinical exam, **and**
  - Progression of signs within a region or spread to other regions, **and**
  - 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
  - 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
  - Clinically probable ALS
    - UMN and LMN signs in at least two regions with some UMN signs rostral to LMN signs
  - 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

- Clinically 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

Inconclusive

- Mutations detected
  - Whether they are pathogenic or benign is unknown
  - Whether they support diagnosis of ALS or increase the risk for ALS is unknown

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

- Agosta F, Al-Chalabi A, et al. The El Escorial criteria: strengths and weaknesses. Amyotroph Lat Scler and Frontotemp Degen. 2015;16(1-2):1-7
- Brooks BR. El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. Subcommittee on Motor Neuron Diseases/Amyotrophic Lateral Sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases and the El Escorial "Clinical limits of amyotrophic lateral sclerosis" workshop contributors. J Neurol. Sci. 1994;124:Suppl:96-107
- Ludolph A, Drory V, et al. A revision of the El Escorial criteria. Amyotroph Lat Scler and Frontotemp Degen. 2015;16(5-6): 291-292

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

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