### Condition Description

Mutations in the ACSL4, also known as FACL4, gene (Xq22.3) have been associated with severe non-syndromic X-linked intellectual disability. Affected males show nonspecific, nonprogressive intellectual disability, ranging from severe to moderate without seizures, whereas carrier females showed highly variable cognitive capacities, ranging from moderate intellectual disability to normal intelligence. ACSL4 deletions have also been found in patients with Alport syndrome, elliptocytosis, and intellectual disability.

Long chain acyl-CoA synthetase (LACS) or long chain fatty acid-CoA ligase (FACL) converts free long chain fatty acids into fatty acyl-CoA esters, which are key intermediates in the synthesis of complex lipids. The ACSL4/FACL4 gene encodes a form of LACS and is expressed in several tissues, including the brain. Both point mutations and deletions have been reported in the gene. Reduction of FACL activity may lead to deranged fatty acid metabolism in neurons, causing defects of neuron outgrowth, synaptogenesis, and other developmental functions important for normal brain development.

For patients with a suspected ACSL4-related disorder, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

### Genes

- **ACSL4**, FACL4

### Indications

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of an ACSL4/FACL4-related disorder.
- Carrier testing in adult females with a family history of an ACSL4/FACL4-related disorder.

### Methodology

PCR amplification of 14 exons contained in the ACSL4/FACL4 gene is performed on the patient's genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions using automated fluorescence dideoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions or other regulatory elements, and does not detect large deletions.

### Detection

Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns, other regulatory element mutations, and large deletions will not be detected by this analysis.

Analytical Sensitivity: ~99%.

Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

### Specimen Requirements

**Submit only 1 of the following specimen types**

#### Type: Saliva

**Specimen Requirements:**

Oragene™ Saliva Collection Kit

Oragene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

**Specimen Collection and Shipping:**

Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

#### Type: DNA, Isolated

**Specimen Requirements:**

Microtainer

8µg

Isolation using the Perkin Elmer™Chemagen™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.
Specimen Collection and Shipping:
Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

**Type: Whole Blood (EDTA)**

**Specimen Requirements:**
EDTA (Purple Top)
Infants and Young Children (2 years of age to 10 years old): 3-5 ml
Older Children & Adults: 5-10 ml
Autopsy: 2-3 ml unclotted cord or cardiac blood

**Specimen Collection and Shipping:**
Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

**Special Instructions**
Please submit copies of diagnostic biochemical test results along with the sample, if appropriate. Contact the laboratory if further information is needed. Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition.

**Related Tests**
- **ACSL4** deletion/duplication analysis (RY) is available for those individuals in whom sequence analysis is negative.
- An X-Linked Intellectual Disability panel with sequencing and deletion/duplication analysis of 110 genes is available.
- **Known Mutation Analysis (KM)** is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- **Prenatal Custom Diagnostics** is available to adult females who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.