Intellectual Disability, \textit{DLG3}-related: \textit{DLG3} Gene Sequencing

\textbf{Test Code: SY}
\textbf{Turnaround time: 4 weeks}
\textbf{CPT Codes: 81479 x1}

\textbf{Condition Description}

Mutations in the \textit{DLG3} gene have been shown to cause non-syndromic intellectual disability. Non-syndromic intellectual disability patients do not manifest other clinical signs.

\textit{DLG3} encodes synapse-associated protein 102 (SAP102), a member of the membrane-associated guanylate kinase protein family. Neuronal SAP102 is expressed during early brain development and is localized to the postsynaptic density of excitatory synapses. It is composed of three amino-terminal PDZ domains, an src homology domain, and a carboxyl-terminal guanylate kinase domain. The PDZ domains interact directly with the NR2 subunits of the NMDA glutamate receptor and with other proteins responsible for NMDA receptor localization, immobilization, and signaling. NMDA receptors have been implicated in the induction of certain forms of synaptic plasticity, such as long-term potentiation and long-term depression, and these changes in synaptic efficacy have been proposed as neural mechanisms underlying memory and learning. The disruption of NMDA receptor targeting or signaling, as a result of the loss of SAP102, may lead to altered synaptic plasticity and may explain the intellectual impairment observed in individuals with \textit{DLG3} mutations.

For patients with suspected \textit{DLG3}-related intellectual disability, 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.

\textbf{Genes}

\textit{DLG3}

\textbf{Indications}

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of \textit{DLG3}-related intellectual disability.
- Carrier testing in adult females with a family history of \textit{DLG3}-related intellectual disability.

\textbf{Methodology}

\textbf{Next Generation Sequencing:} In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

\textbf{Detection}

Clinical sensitivity is unknown. Mutations in the promoter region, some mutations in the introns or other regulatory element mutations, and large deletions cannot be detected by this analysis.

Analytical Sensitivity: ~99%.

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

\textbf{Specimen Requirements}

\textit{Submit only 1 of the following specimen types}

\textbf{Type: Whole Blood (EDTA)}

\textbf{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

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

\textbf{Type: Saliva}

\textbf{Specimen Requirements:}
Oragene™ Saliva Collection Kit
Orangene™ 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™ 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.

**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 form.

**Related Tests**

- DLG3-Related Intellectual Disability: DLG3 Gene Deletion/Duplication (SZ) is available for those individuals in whom sequence analysis is negative.
- Known Mutation Analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available to couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.