### Condition Description

Mutations in the gene SLC9A6 (Xq26.3) lead to an X-linked mental retardation syndrome associated with microcephaly, seizures, ataxia, and absent speech. Many identified patients also display a happy demeanor with frequent smiling and spontaneous laughter reminiscent of Angelman syndrome. Affected individuals appear normal at birth, then display deceleration of head growth in the first year of life and a thin body habitus. Seizures typically begin to occur around 1-2 years of age. Many individuals have a happy demeanor with frequent smiling and episodes of unprovoked laughter. There is an absence of expressive language and profound mental retardation, along with ataxia and eye squint. Other possible features include an open mouth with profuse drooling, swallowing difficulties, hyperkinetic movements, and facial features such as a long, narrow face and pointed jaw. The clinical spectrum of features seems to resemble Angelman syndrome in younger patients and Christianson syndrome in older patients. There appears to be a range of carrier phenotypes in carrier females, from mental retardation to absence of symptoms.

The SLC9A6 gene encodes the Na+/H+ exchanger protein NHE6. NHE6 is a membrane protein found in early recycling endosomal membranes and transiently associates with the plasma membrane. It is believed to have a role in regulating the lumen pH, and a consequence of NHE6 inactivity could be lowered endosomal pH and decreased monovalent ion content, both of which might affect protein folding and trafficking. The disruption in recycling endosome trafficking is likely to disturb the growth of dendritic spines during long-term potentiation, which is the process involved in memory and learning. Abnormalities in synaptic development and plasticity have also been shown to be involved in the pathogenesis of Angelman syndrome; UB3A is involved in the intracellular protein-processing apparatus at the level of protein ubiquination.


For patients with mutations not identified by full gene sequencing, a separate deletion/duplication assay is available using a targeted CGH array (PN).

### Genes

SLC9A6

### Indications

This test is indicated for male individuals with an Angelman-like phenotype who have tested negative for 15q11-13 findings and for MECP2 mutations.

### Methodology

**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.

### Specimen Requirements

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragenetm Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.
Special Instructions

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. Please submit copies of previous test results (i.e. Angelman testing, Rett testing)

Related Tests

- *SLC9A6* Gene Deletion/Duplication (PN) is available for those individuals in whom sequence analysis is negative.
- X-Linked Intellectual Disability panels are available for 30, 60, and 90+ genes.
- Prader-Willi/Angelman Methylation Studies (PW).
- Rett Syndrome Sequencing of Methyl CpG-Binding Protein (*MECP2*) Gene (SR).
- X-Linked Mental Retardation Deletion/Duplication Array CGH (OL)