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CLIA #: 14D0917593 CAP #: 18827-49

SLC9A6 sequencing for X-linked Angelman-like syndrome

Clinical Features:

Features of patients with *SLC9A6* mutations include mental retardation, microcephaly, truncal ataxia, grand mal epilepsy and lack of speech (1) [OMIM #300243]. The clinical features of these patients suggest a similarity to Angelman syndrome, with developmental delay, ataxia, flexed arms, excessive drooling, happy demeanor with spontaneous smiling and laughter, as well as progressive microcephaly by two years of age (2). Patients have minimal to absent language skills despite normal hearing. Seizures typically occur before two years of age. Characteristic physical features can include a long face with pointed jaw, opthalmoplegia, swallowing difficulties, kyphoscoliosis and poor growth (1, 2). Most patients are found to have a slender body habitus, which differs from Angelman syndrome, where patients tend to become obese with age (2). Heterozygous females can show variability in phenotype, with a range from normal to mild cognitive handicaps (1, 2).

Male patients exhibiting an Angelman-like syndrome phenotype who are negative for relevant genetic testing (normal methylation of the 15q11-q13 region as well as normal *UBE3A* sequencing), as well as *MECP2* negative patients, may be considered for mutations in the *SLC9A6* gene.

Molecular and Biochemical Genetics:

Mutations of the *SLC9A6* [OMIM #300231] gene have been identified in patients with X-linked mental retardation with features similar to Angelman syndrome (2). *SLC9A6* has 16 coding exons and is ubiquitously expressed, with the highest expression in mitochondrion-rich tissues such as brain and skeletal muscle (3). It is thought that the *SLC9A6* protein product, the Na+/H+ exchanger protein NHE6, is important for sodium/hydrogen exchange as well as normal mitochondrial function (3).

Inheritance:

Mutations in *SLC9A6* are inherited in an X-linked pattern and result in clinical features in affected males and occasionally some mild features in carrier females. Multiple families have been identified with *SLC9A6* mutations, including several families with multiple affected boys over several generations (1, 2). A woman who has more than one affected son is an obligate carrier. Recurrence risk for carrier mothers is 50%.

Additional Resources:

Angelman Syndrome Foundation
4255 Westbrook Drive, Ste. 216, Aurora, IL 60504
Phone: 630-978-4245; 800-432-6435
Email: info@angelman.org
www.angelman.org

Testing Methods:

We offer mutation analysis of all 16 coding exons and intron/exon boundaries of *SLC9A6* by direct sequencing of amplification products in both the forward and reverse directions. We also offer deletion/duplication analysis of the *SLC9A6* gene by oligonucleotide array-CGH to identify copy number changes involving one or more exons. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Array-CGH will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

SLC9A6 sequencing analysis

Sample specifications:	3 to 10cc of blood in a purple top (EDTA) tube
Cost:	$1500
CPT codes:	81406
Turn-around time:	4 weeks

SLC9A6 deletion/duplication analysis

Sample specifications:	3 to 10cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81405
Turn-around time:	4 weeks

Testing for a known mutation in additional family members by sequence analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$390
CPT codes:	81403
Turn-around time:	3 weeks

Prenatal testing for a known mutation by sequence analysis

Sample specifications:	2 T25 flasks of cultured cells from amniocentesis or CVS or 10 mL of amniotic fluid
Cost:	$540
CPT codes:	81403
Turn-around time:	1 week

Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

References:

1. Christianson AL, Stevenson RE, van der Meyden CH et al. X linked severe mental retardation, craniofacial dysmorphology, epilepsy, ophthalmoplegia, and cerebellar atrophy in a large South African kindred is localised to Xq24-q27. J Med Genet 1999: 36: 759-766.
2. Gilfillan GD, Selmer KK, Roxrud I et al. SLC9A6 mutations cause X-linked mental retardation, microcephaly, epilepsy, and ataxia, a phenotype mimicking Angelman syndrome. Am J Hum Genet 2008: 82: 1003-1010.
3. Numata M, Petrecca K, Lake N et al. Identification of a mitochondrial Na+/H+ exchanger. J Biol Chem 1998: 273: 6951-6959.

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