THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

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:

Comprehensive sequence coverage of the coding regions and splice junctions of the *SLC9A6* gene is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. The constructed genomic DNA library is sequenced using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20bp.

Deletion/duplication analysis is performed by oligonucleotide array-CGH. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. 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:	$1000
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

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.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

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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