



Hereditary Motor and Sensory Neuropathy with Agenesis of the Corpus Callosum: Mutation Analysis of *SLC12A6*

Clinical Features:

Hereditary Motor and Sensory Neuropathy with Agenesis of the Corpus Callosum (HMSN/ACC) [OMIM #218000] is an autosomal recessive condition characterized by severe progressive sensorimotor neuropathy resulting in hypotonia, areflexia and amyotrophy, variable degrees of dysgenesis of the corpus callosum and dysmorphic features (1). MRI shows complete callosal agenesis in 60% of individuals, partial callosal agenesis in 10%, and normal corpus callosum in 30% (2). Dysmorphic features can include hypertelorism, syndactyly and high-arched palates. Individuals are able to stand or walk with support at 4 – 6 years. Physical and intellectual ability deteriorate over time and most affected individuals are severely impaired by adolescence (2).

Molecular Genetics:

Mutations of the *SLC12A6* [OMIM #604878] gene have been identified in patients with HMSN/ACC (3). *SLC12A6* has 25 coding exons and is located at 15q14. *SLC12A6* encodes the potassium-chloride cotransporter KCC3 and is highly expressed in the brain. A founder mutation (c.2436delG) in exon 18 is identified in almost all patients of French-Canadian descent. Sequencing of all exons has an estimated detection rate of over 90% (1). To date truncating (frameshift and nonsense) and missense mutations have been identified in the *SLC12A6* gene.

Inheritance and Epidemiology:

SLC12A6 mutations are inherited in an autosomal recessive pattern. Parents of an affected child are likely carriers. Recurrence risk for carrier parents is 25%. HMSN/ACC has a high prevalence in the French Canadian population of the Saguenay-Lac-St-Jean region and Charlevoix County of northeastern Quebec. The overall incidence at birth is approximately 1 in 2000 live births and the carrier rate is approximately 1 in 23 in this specific population (1).

Test Methods:

Comprehensive sequence coverage of the coding regions and splice junctions of the *SLC12A6* gene is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed 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 20 bp. Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

SLC12A6 sequencing and deletion/duplication analysis

Sample specifications:	3 to 10cc of blood in a purple top (EDTA) tube
Cost:	\$1000
CPT codes:	81405, 81406
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 or email.

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

References:

1. Dupre N, Howard H, Rouleau G. Hereditary Motor and Sensory Neuropathy with Agenesis of the Corpus Callosum. In: Pagon R, Bird T, Dolan C, eds. GeneReviews [Internet]. Seattle: University of Washington, 2006.
2. Dupré N, Howard HC, Mathieu J et al. Hereditary motor and sensory neuropathy with agenesis of the corpus callosum. *Ann Neurol* 2003; 54: 9-18.
3. Howard HC, Mount DB, Rochefort D et al. The K-Cl cotransporter KCC3 is mutant in a severe peripheral neuropathy associated with agenesis of the corpus callosum. *Nat Genet* 2002; 32: 384-392.

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