

The University of Chicago Genetic Services Laboratories



5841 S. Maryland Ave., Rm. G701, MC 0077, Chicago, Illinois 60637
Toll Free: (888) UC GENES ☐ (888) 824 3637
Local: (773) 834 0555 ☐ FAX: (773) 702 9130
ucgslabs@genetics.uchicago.edu ☐ dnatesting.uchicago.edu
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SLC12A6 Analysis for Hereditary Motor and Sensory Neuropathy with Agenesis of the Corpus Callosum

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:

The University of Chicago Laboratory offers mutation analysis of all coding exons and intron/exon boundaries of *SLC12A6* by direct sequencing of amplification products in both the forward and reverse directions. Deletion/duplication analysis of the *SLC12A6* gene 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.

SLC12A6 sequencing analysis

Sample specifications:	3 to 10cc of blood in a purple top (EDTA) tube
Cost:	\$2200
CPT codes:	81406
Turn-around time:	4 - 6 weeks

SLC12A6 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

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$390
CPT codes:	81403
Turn-around time:	3 – 4 weeks

Prenatal testing for a known mutation

Sample specifications:	2 T25 flasks of cultured cells from amnio or CVS or 10ml of amniotic fluid
Cost:	\$540
CPT codes:	81403
Turn-around time:	1-2 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.

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-CI 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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