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## Hereditary Motor and Sensory Neuropathy with Agenesis of the Corpus Callosum

Synonyms: Agenesis of Corpus Callosum with Peripheral Neuropathy (ACCPN), Andermann Syndrome

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### Summary

#### Clinical characteristics

Hereditary motor and sensory neuropathy with agenesis of the corpus callosum (HMSN/ACC), a neurodevelopmental and neurodegenerative disorder, is characterized by severe progressive sensorimotor neuropathy with resulting hypotonia, areflexia, and amyotrophy, and by variable degrees of dysgenesis of the corpus callosum. Mild-to-severe intellectual disability and "psychotic episodes" during adolescence are observed. Sensory modalities are moderately to severely affected beginning in infancy. The average age of onset of walking is 3.8 years; the average age of loss of walking is 13.8 years; the average age of death is 33 years.

#### Diagnosis/testing

The diagnosis of HMSN/ACC is established in a proband with suggestive findings and biallelic pathogenic variants in *SLC12A6* identified by molecular genetic testing.

#### Management

*Treatment of manifestations:* Walking aids such as canes or walkers are required. As the disease progresses, orthoses for upper and lower limbs and physiotherapy are needed to prevent contractures. Early developmental/educational intervention addresses cognitive delays. Depending on severity, individuals with HMSN/ACC usually require corrective surgery for scoliosis. Neuroleptics may be used to treat psychiatric manifestations, usually during adolescence.

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*Surveillance:* Monitor in the early teens for scoliosis and in the late teens for psychiatric manifestations.

## Genetic counseling

HMSN/ACC is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Heterozygotes (carriers) are asymptomatic. Once the *SLC12A6* pathogenic variants have been identified in an affected family member, carrier testing for at-risk family members and prenatal and preimplantation genetic testing are possible.

## Diagnosis

Consensus diagnostic criteria for hereditary motor and sensory neuropathy with agenesis of the corpus callosum (HMSN/ACC) have not been established.

## Suggestive Findings

Hereditary motor and sensory neuropathy with agenesis of the corpus callosum (HMSN/ACC) **should be suspected** in individuals with the following clinical, electrophysiologic, and neuroimaging findings, and family history [Dupré et al 2003].

### Clinical findings

- Severe progressive sensorimotor neuropathy with areflexia
- Developmental delay / intellectual disability ranging from mild to severe

### Electrophysiology

- Sensory nerve action potentials cannot be recorded at the median, ulnar, or sural nerves even in children in their first year of life.
- Compound motor action potentials usually show diminished amplitudes.
- Nerve conduction velocities for the median, ulnar, and tibial nerves are variable.
- Needle electromyography may show mild signs of active denervation (e.g., fibrillation potentials).

### Neuroimaging

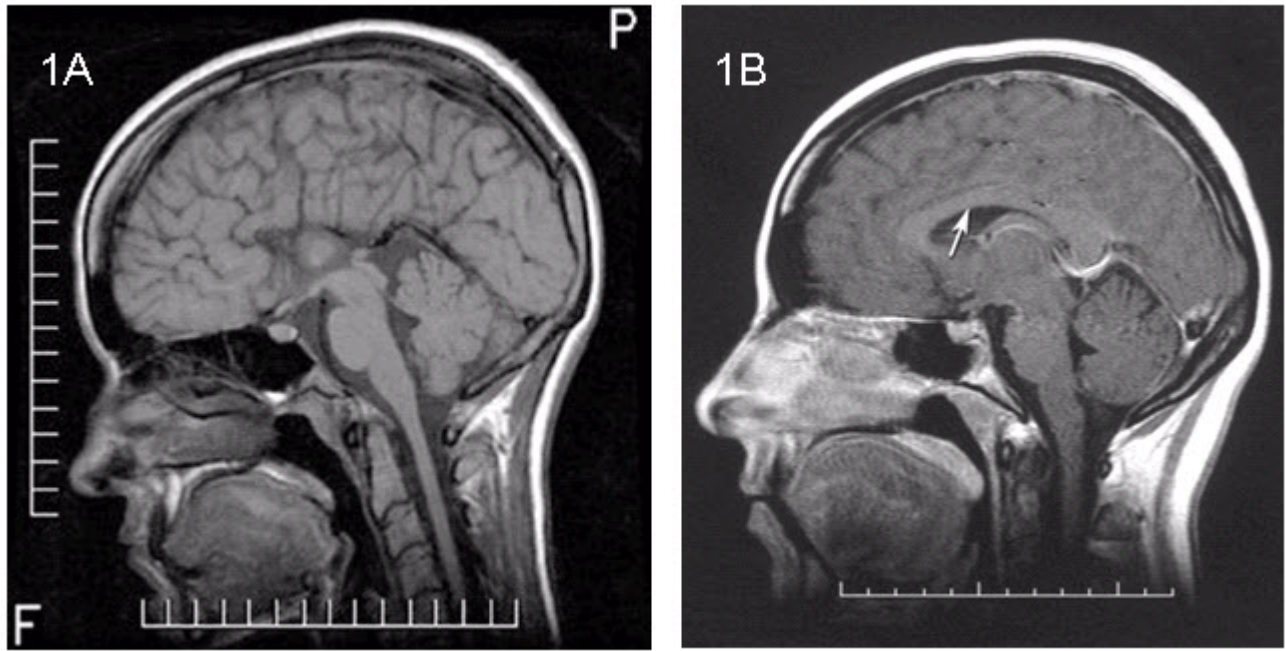
- Brain MRI showing complete agenesis of the corpus callosum in 60% of individuals (Figure 1A, 2A), partial agenesis in 10%, and normal corpus callosum in 30% (Figure 1B, 2B)
- Mild cortical or cerebellar atrophy at a later age

**Family history** is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

## Establishing the Diagnosis

The diagnosis of hereditary motor and sensory neuropathy with agenesis of the corpus callosum (HMSN/ACC) **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *SLC12A6* identified by molecular genetic testing (see Table 1).

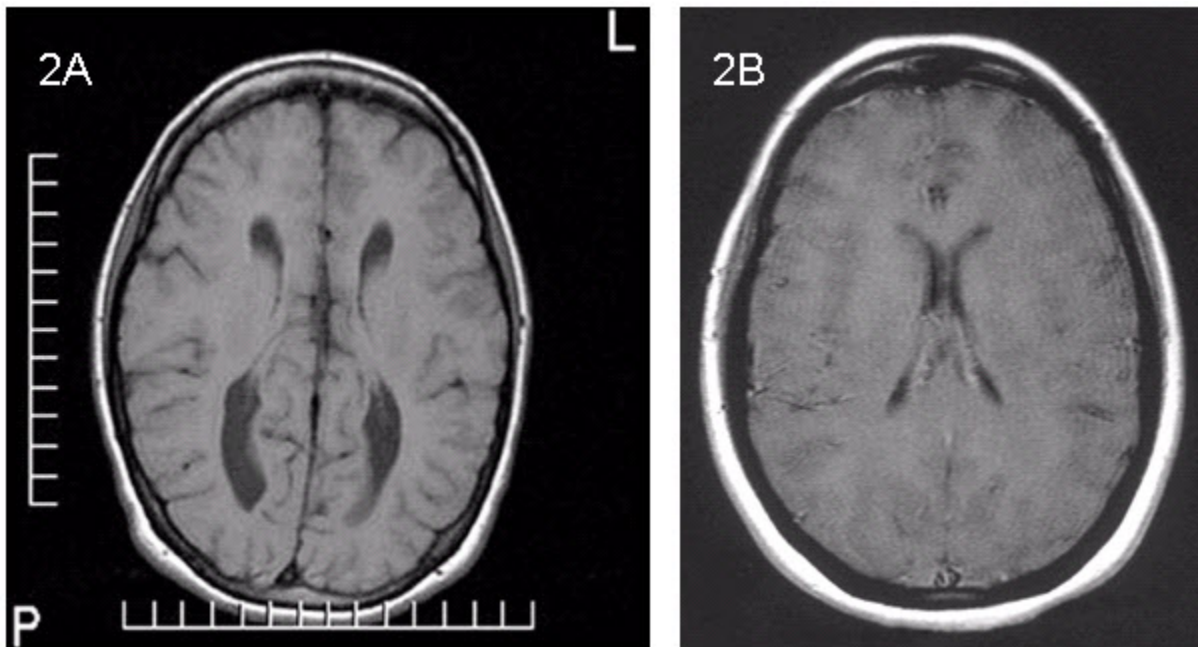
Note: (1) Per ACMG variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *SLC12A6* variants of uncertain significance (or identification of



**Figure 1.** Sagittal T<sub>1</sub>-weighted MRI

A. Complete agenesis of the corpus callosum

B. Normal corpus callosum (arrow)



**Figure 2.** Axial T<sub>1</sub>-weighted MRI

A. Agenesis of the corpus callosum with parallelism of the ventricles

B. Normal ventricles

one known *SLC12A6* pathogenic variant and one *SLC12A6* variant of uncertain significance) does not establish or rule out a diagnosis of this disorder.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing or multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of HMSN/ACC has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

## Option 1

**Single-gene testing.** Sequence analysis of *SLC12A6* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

Note: In individuals of French Canadian origin who have the typical phenotype, targeted analysis for the c.2436+1delG pathogenic variant can be performed first, followed by sequence analysis if only one or no variant is identified.

**An agenesis of the corpus callosum panel, an intellectual disability panel, or a comprehensive neuropathy panel** (multigene panels that include *SLC12A6* and other genes of interest; see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

## Option 2

**Comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

**Table 1.** Molecular Genetic Testing Used in Hereditary Motor and Sensory Neuropathy with Agenesis of the Corpus Callosum

Gene <sup>1</sup>	Method	Proportion of Pathogenic Variants <sup>2</sup> Detectable by Method
SLC12A6	Sequence analysis <sup>3</sup>	>90% <sup>4, 5</sup>
	Gene-targeted deletion/duplication analysis <sup>6</sup>	1 reported <sup>7</sup>

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

4. Howard et al [2002], Uyanik et al [2006], and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

5. Nearly all (>99%) individuals of French Canadian descent, who make up most of the affected population, have the c.2436+1delG variant, which is detectable by sequence analysis.

6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

7. Antoniadi et al [2015]

## Clinical Characteristics

### Clinical Description

Hereditary motor and sensory neuropathy with agenesis of the corpus callosum (HMSN/ACC) is both a neurodevelopmental disorder (with variable degrees of dysgenesis of the corpus callosum and mild-to-severe intellectual disability) and a neurodegenerative disorder (severe progressive sensorimotor neuropathy).

The neurologic findings of HMSN/ACC in 64 individuals (ages 2 to 34 years) in the French Canadian population reported by Mathieu et al [1990] are summarized in Table 2, with additional information from Larbrisseau et al [1984], Salin-Cantegrel et al [2007], and Auer et al [2016].

**Table 2.** Hereditary Motor and Sensory Neuropathy with Agenesis of the Corpus Callosum: Select Features

Feature	% of Persons w/Feature	Comment	
<b>Motor &amp; sensory neuropathy</b>	100%		
<b>Cranial nerve involvement</b>	<b>Ptosis</b>	33%-59%	Symmetric or asymmetric
	<b>Gaze palsy</b>	13%-30%	
	<b>Horizontal nystagmus</b>	20%	
	<b>Facial weakness</b>	34%-100%	Symmetric or asymmetric; may be assoc w/hemifacial atrophy
<b>Cognitive function</b>	<b>Normal</b>	8%	Based on Taft clinical classification to stratify cognitive function in 53 persons <sup>1</sup>
	<b>Mild ID</b>	49%	
	<b>Moderate ID</b>	40%	
	<b>Severe ID</b>	4%	
<b>Psychotic episodes</b>	39% (25/64)	After age 15 yrs <sup>1</sup>	
<b>Scoliosis</b>	86%	Average onset age 10.4 yrs	

Table 2. continued from previous page.

Feature	% of Persons w/Feature	Comment
<b>Pulmonary restrictive syndrome</b>	Unknown	Related to scoliosis & axonal loss affecting respiratory muscles <sup>2</sup>
<b>Contractures</b>	59%	MCP joint (flexion) contracture
	50%	Valgus foot deviation
	47%	Early Achilles tendon retraction
	31%	Varus foot deviation
<b>Seizures</b>	17%	Generalized, absence, or focal seizures <sup>3</sup>
<b>Tremor</b>	25%	

ID = intellectual disability; MCP = metacarpophalangeal  
Based on Larbrisseau et al [1984] and Mathieu et al [1990]

1. Mathieu et al [1990]

2. Auer et al [2016]

3. Salin-Cantegrel et al [2007]

### Progressive motor and sensory neuropathy

- Reflexes invariably absent from infancy
- Hypotonia invariably present in the first year of life
- Progressive distal and proximal symmetric limb weakness
- Muscle atrophy
- Diffuse limb tremor (probably secondary to polyneuropathy)
- Contractures
- Loss of sensation to touch and pinprick in a glove and stocking distribution; easier to evaluate in older children

The average age of onset for sitting alone is 2.1 years, for standing is more than two years, for walking is 3.8 years, and average age of loss of ability to walk is 13.8 years.

**Cognitive function.** The Taft clinical classification uses an IQ test to rank individuals in four categories: normal intelligence (IQ >75), mild intellectual disability (IQ = 50-75), moderate intellectual disability (IQ = 25-50), and severe intellectual disability (IQ <25). Individuals with mild intellectual disability can achieve five to six years of elementary school and live independently. Individuals with moderate intellectual disability can help with activities of daily living but require supervision on a daily basis. Individuals with severe intellectual disability require assistance for daily living and supervision but may be able to take care of some routine daily needs. The range of intelligence of individuals with HSMN/ACC is normal IQ to severe intellectual disability.

**Psychotic episodes.** Mathieu et al [1990] reported that after age 15 years, 39% (25/64) developed "psychotic episodes" characterized by paranoid delusions, depressive states, visual hallucinations, auditory hallucinations, or "autistic-like" features.

**Life expectancy.** Average age of death is 33 years and is usually related to respiratory insufficiency [Larbrisseau & Sarnat 2017].

### Other

- **Lumbar puncture** usually reveals mild elevation of CSF proteins [Dupré et al 2003].

- **Sural nerve biopsy** shows an almost total lack of large myelinated fibers, signs of axonal loss (ovoids of Wallerian degeneration), and some enlarged axons that on electron microscopy show decreased density of neurofilaments. Isolated fibers may have disproportionately thin myelin sheaths, suggesting that the axoplasm is swollen. Electron microscopy may show decreased packing density of neurofilaments, without signs of their degradation [Dupré et al 2003, Auer et al 2016].

Note: Sural nerve biopsy is unnecessary to confirm the diagnosis, now that molecular genetic testing is possible.

- **EEG** may be normal or with epileptiform abnormalities [Dupré et al 2003, Salin-Cantegrel et al 2007].
- **Muscle biopsy** shows nonspecific signs of chronic denervation atrophy [Dupré et al 2003, Auer et al 2016].

**Autopsy examination.** The hallmark is swollen axons in cranial nerve samples (especially cranial nerves 3 and 7), as well as in the dorsal and ventral nerve roots. Swollen axons can also be scattered in the white matter. The brain shows either no agenesis of the corpus callosum (ACC), partial ACC, or complete ACC with preservation of Probst bundle [Dupré et al 2003, Auer et al 2016].

## Genotype-Phenotype Correlations

The data from affected individuals are insufficient to establish genotype-phenotype correlations.

## Nomenclature

HMSN/ACC may also be referred to as Charlevoix disease.

## Prevalence

In the French Canadian population of the Saguenay and Lac-St-Jean regions of Quebec, Canada, the overall incidence of HMSN/ACC is 1:2,117 live births; the carrier rate is 1:23 inhabitants due to the c.2436+1delG (also known as c.2436delG) founder variant. Otherwise, HMSN/ACC is extremely rare worldwide. Three pairs of sibs (of Italian, Mexican, and Turkish origin) have been reported to have molecularly confirmed HMSN/ACC.

## Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with mutation of *SLC12A6*.

## Differential Diagnosis

**Table 3.** Autosomal Recessive Neurodegenerative Disorders in the Differential Diagnosis of Hereditary Motor and Sensory Neuropathy with Agenesis of the Corpus Callosum

Gene(s)	DiffDx Disorder	Clinical Characteristics	Features of DiffDx Disorder Distinguishing It from HMSN/ACC
<i>EGR2</i> <i>FGD4</i> <i>FIG4</i> <i>GDAP1</i> <i>MTMR2</i> <i>NDRG1</i> <i>PRX</i> <i>SBF1</i> <i>SBF2</i> <i>SH3TC2</i>	Autosomal recessive HMSN (Previously CMT4; see <a href="#">CMT Overview</a> .)	Severe early-onset neuropathy	Absence of ID & dysgenesis of CC
<i>PLA2G6</i>	Classic infantile neuroaxonal dystrophy (INAD) (See <a href="#">PLA2G6 Neurodegeneration</a> .)	<ul style="list-style-type: none"> <li>• Classic INAD: typical onset age 6 mos to 3 yrs w/developmental regression, hypotonia, progressive psychomotor delay, &amp; progressive spastic tetraparesis; strabismus, nystagmus, &amp; optic atrophy common; ± partial ACC</li> <li>• Rapid disease progression: many affected children never learn to walk or lose this ability shortly after attaining it; severe spasticity, progressive cognitive decline, &amp; visual impairment typically → death in 1st decade.</li> <li>• Atypical NAD: see footnote 1.</li> </ul>	<ul style="list-style-type: none"> <li>• Faster &amp; more severe regression of motor skills</li> <li>• Spasticity</li> </ul>
<i>ARSA</i>	<a href="#">Arylsulfatase A deficiency</a> (metachromatic leukodystrophy [MLD])	<ul style="list-style-type: none"> <li>• Infantile- &amp; early-juvenile-onset MLD present w/CNS &amp;/or peripheral nervous system manifestations; affected persons eventually lose motor &amp; intellectual functions.</li> <li>• Disease course is ~3-10 yrs in late-infantile-onset MLD &amp; ~20 yrs in juvenile-onset MLD; death is most commonly from pneumonia or other infection.</li> </ul>	<ul style="list-style-type: none"> <li>• Absence (typically) of ACC</li> <li>• Leukodystrophy</li> </ul>
<i>GAN</i>	<a href="#">Giant axonal neuropathy</a>	<ul style="list-style-type: none"> <li>• Presents w/severe peripheral motor &amp; sensory neuropathy in infancy; evolves into CNS impairment (ID, seizures, cerebellar signs, &amp; pyramidal tract signs); pathologic hallmark is "giant axons" assoc w/massive disorganization &amp; aggregation of neurofilaments.</li> <li>• Most persons become wheelchair dependent in 2nd decade of life &amp; eventually bedridden w/severe polyneuropathy, ataxia, &amp; dementia; death usually occurs in 3rd decade.</li> </ul>	<ul style="list-style-type: none"> <li>• Absence (typically) of ACC</li> <li>• Atrophy of CC in some affected persons</li> </ul>



Table 3. continued from previous page.

Gene(s)	DiffDx Disorder	Clinical Characteristics	Features of DiffDx Disorder Distinguishing It from HMSN/ACC
SPG11	Spastic paraplegia 11	<ul style="list-style-type: none"> <li>Progressive spasticity &amp; weakness of lower limbs frequently assoc w/mild ID w/learning difficulties in childhood &amp;/or progressive cognitive decline, peripheral neuropathy, pseudobulbar involvement, &amp; ↑ reflexes in upper limbs.</li> <li>Less frequent findings: cerebellar signs (ataxia, nystagmus, saccadic pursuit), retinal degeneration, pes cavus, scoliosis, parkinsonism</li> <li>Onset occurs mainly in infancy or adolescence; most affected persons become wheelchair bound 1-2 decades after disease onset.</li> </ul>	<ul style="list-style-type: none"> <li>Hyperreflexia of upper limbs &amp; spasticity</li> <li>Thin CC in some affected persons</li> </ul>
GALC	Krabbe disease (GALC deficiency, globoid cell leukodystrophy)	<ul style="list-style-type: none"> <li>Infantile form presents before age 12 mos w/extreme irritability, axial hypotonia, spasticity, loss of acquired milestones, &amp; peripheral neuropathy; average age at death is 24 mos.</li> <li>Late-onset form presents after age 12 mos (childhood-7th decade) &amp; may present as DD or regression; disease course is variable &amp; may be assoc w/ spastic paraparesis, peripheral neuropathy, seizures, &amp; vision loss.</li> </ul>	<ul style="list-style-type: none"> <li>Spastic paraparesis (in late onset form)</li> <li>Thin CC in some affected persons</li> </ul>

ACC = agenesis of corpus callosum; CC = corpus callosum; CNS = central nervous system; DD = developmental delay; DiffDx = differential diagnosis; HMSN = hereditary motor and sensory neuropathy; ID = intellectual disability

1. Atypical neuroaxonal dystrophy is more varied than the classic form. In general, onset is in early childhood, but can be as late as the late teens. The presenting signs may be similar to the classic form with gait instability or ataxia, but may be speech delay and autistic features, which may remain as the only evidence of disease for a year or more. The course is fairly stable during early childhood and resembles static encephalopathy, but is followed by neurologic deterioration between ages seven and 12 years.

## Management

Consensus clinical management recommendations for hereditary motor and sensory neuropathy with agenesis of the corpus callosum (HMSN/ACC) have not been published.

## Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with hereditary motor and sensory neuropathy with agenesis of the corpus callosum (HMSN/ACC), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

**Table 4.** Recommended Evaluations Following Initial Diagnosis in Individuals with Hereditary Motor and Sensory Neuropathy with Agenesis of the Corpus Callosum

System/Concern	Evaluation	Comment
<b>Motor &amp; sensory neuropathy</b>	Neurologic exam	<ul style="list-style-type: none"> <li>Obtain EEG.</li> <li>Consider MRI if not previously performed.</li> </ul>
<b>Seizures</b>		
<b>Musculoskeletal</b>	Orthopedics / physical medicine & rehab / PT & OT eval	<p>To incl assessment of:</p> <ul style="list-style-type: none"> <li>Gross motor &amp; fine motor skills</li> <li>Possible contractures (esp Achilles tendon)</li> <li>Need for PT (to improve gross motor skills) &amp;/or OT (to improve fine motor skills)</li> <li>Mobility, self-help skills, ADL, &amp; need for adaptive devices</li> </ul>
<b>Scoliosis</b>	Orthopedics & pulmonary medicine	<ul style="list-style-type: none"> <li>Baseline eval for scoliosis</li> <li>Baseline pulmonary function assessment given ↑ risk for restrictive lung disease</li> </ul>
<b>Extraocular muscle involvement</b>	Ophthalmologic exam	Assess for ptosis, esotropia or exotropia, gaze palsy, & nystagmus.
<b>Developmental delay / Intellectual disability</b>	Developmental assessment	<ul style="list-style-type: none"> <li>To incl motor, adaptive, cognitive, &amp; speech/language eval</li> <li>Eval for early intervention / special education / community &amp; social activities</li> </ul>
<b>Psychotic episodes</b>	Obtain history of possible events.	When concerns, refer for psychiatric eval.
<b>Genetic counseling</b>	By genetics professionals <sup>1</sup>	To inform affected persons & their families re nature, MOI, & implications of HMSN/ACC to facilitate medical & personal decision making
<b>Family support &amp; resources</b>	<p>Assess need for:</p> <ul style="list-style-type: none"> <li>Community or online resources such as <a href="#">Parent to Parent</a>;</li> <li>Social work involvement for parental support;</li> <li>Home nursing referral.</li> </ul>	

ADL = activities of daily living; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy

1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

## Treatment of Manifestations

Care is best provided by a multidisciplinary team that comprises a pediatrician or pediatric neurologist, developmental pediatrician, psychiatrist, orthopedist, physiotherapist, and occupational therapist.

**Table 5.** Treatment of Manifestations in Individuals with Hereditary Motor and Sensory Neuropathy with Agenesis of the Corpus Callosum

Manifestation/Concern	Treatment	Considerations/Other
<b>Seizures</b>	Standardized treatment w/ASM by experienced neurologist	<ul style="list-style-type: none"> <li>• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder.</li> <li>• Valproate may also be beneficial for behavioral problems.</li> <li>• Education of parents/caregivers <sup>1</sup></li> </ul>
<b>Extraocular muscle involvement</b>	Standard treatment(s) per ophthalmologist	
<b>Musculoskeletal</b>	Orthopedics / physical medicine & rehab / PT & OT	<ul style="list-style-type: none"> <li>• Regular physiotherapy to maximize mobility &amp; ↓ risk for later orthopedic complications (e.g., hand &amp; foot contractures, scoliosis)</li> <li>• Walking aids incl canes or walkers when appropriate</li> <li>• Use of orthoses for upper &amp; lower limbs as needed</li> <li>• Durable medical equipment &amp; positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers)</li> <li>• Disability parking placard for caregivers</li> </ul>
<b>Scoliosis</b>	Orthopedics	Depending on degree of severity, scoliosis usually requires surgical correction.
	Pulmonary medicine	Intervention per standard care
<b>Developmental delay / Intellectual disability</b>	See Developmental Delay / Intellectual Disability Management Issues.	
<b>Psychotic episodes</b>	Psychiatric eval	Low-dose neuroleptics may be useful.
<b>Family support/ resources</b>	<ul style="list-style-type: none"> <li>• Ensure appropriate social work involvement to connect families w/local resources, respite, &amp; support.</li> <li>• Coordinate care to manage multiple subspecialty appointments, equipment, medications, &amp; supplies.</li> </ul>	

ASM = anti-seizure medication; OT = occupational therapy; PT = physical therapy

1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on nonmedical interventions and coping strategies for children diagnosed with epilepsy, see [Epilepsy Foundation Toolbox](#).

## Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

**Ages 0-3 years.** Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

**Ages 3-5 years.** In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

**All ages.** Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

## Surveillance

**Table 6.** Recommended Surveillance for Individuals with Hereditary Motor and Sensory Neuropathy with Agenesis of the Corpus Callosum

System/Concern	Evaluation	Frequency
<b>Motor &amp; sensory neuropathy</b>	Neurologic exam	Annual
<b>Seizures</b>	Evaluate response to current treatment.	Per treating neurologist
	Assess for new-onset seizures	At each visit
<b>Musculoskeletal</b>	Per treating PT/OT	Annual or biannual
<b>Scoliosis</b>	Per treating orthopedist	<ul style="list-style-type: none"> <li>• Esp in early teen yrs when significant scoliosis is likely to appear</li> <li>• Annual or biannual</li> </ul>
<b>Restrictive lung disease</b>	Monitor for evidence of respiratory insufficiency.	As needed if symptoms are present
<b>Extraocular muscle involvement</b>	Ophthalmologic exam	Per treating ophthalmologist
<b>Developmental delay / Intellectual disability</b>	Monitor developmental progress & educational needs.	At each visit

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Psychotic episodes	Evaluate response to current treatment.	<ul style="list-style-type: none"> <li>As needed</li> <li>Refer to psychiatrist.</li> </ul>
	Evaluate for new-onset psychosis & paranoid delusions.	At each visit, esp in late teens when onset is typical

OT = occupational therapist; PT = physical therapist

## Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

## Therapies Under Investigation

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

## Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.*

## Mode of Inheritance

Hereditary motor and sensory neuropathy with agenesis of the corpus callosum (HMSN/ACC) is inherited in an autosomal recessive manner.

## Risk to Family Members

### Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one *SLC12A6* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *SLC12A6* pathogenic variant and to allow reliable recurrence risk assessment. (*De novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

### Sibs of a proband

- If both parents are known to be heterozygous for an *SLC12A6* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

**Offspring of a proband.** Due to the severity of the disorder, individuals with HMSN/ACC do not reproduce.

**Other family members.** Each sib of the proband's parents is at a 50% risk of being a carrier of an *SLC12A6* pathogenic variant.

## Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *SLC12A6* pathogenic variants in the family.

See Related Genetic Counseling Issues, **Population screening** for information about carrier testing in individuals who do not have a family history of HMSN/ACC.

## Related Genetic Counseling Issues

### Family planning

- The optimal time for determination of genetic risk, clarification of genetic status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are carriers or are at risk of being carriers.

**Population screening.** Individuals with a genealogic link to regions with high HMSN/ACC carrier rates may choose to have carrier testing for the c.2436+1delG French Canadian HMSN/ACC founder variant (see Prevalence and Table 7).

## Prenatal Testing and Preimplantation Genetic Testing

Once the *SLC12A6* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

## Resources

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).*

- **National Organization for Disorders of the Corpus Callosum**  
**Email:** [info@nodcc.org](mailto:info@nodcc.org)  
[www.nodcc.org](http://www.nodcc.org)
- **Hereditary Neuropathy Foundation**  
**Phone:** 855-435-7268 (toll-free); 212-722-8396  
**Fax:** 917-591-2758  
**Email:** [info@hnf-cure.org](mailto:info@hnf-cure.org)  
[www.hnf-cure.org](http://www.hnf-cure.org)
- **Muscular Dystrophy Canada**  
Canada  
**Phone:** 800-567-2873  
**Email:** [info@muscle.ca](mailto:info@muscle.ca)  
[www.muscle.ca](http://www.muscle.ca)
- **National Institute of Neurological Disorders and Stroke (NINDS)**  
PO Box 5801

Bethesda MD 20824

**Phone:** 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)

[Agenesis of the Corpus Callosum Information Page](#)

## Molecular Genetics

*Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information.* —ED.

**Table A.** Hereditary Motor and Sensory Neuropathy with Agenesis of the Corpus Callosum: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
<i>SLC12A6</i>	15q14	Solute carrier family 12 member 6	<a href="#">SLC12A6 homepage - Leiden Muscular Dystrophy pages</a>	<a href="#">SLC12A6</a>	<a href="#">SLC12A6</a>

Data are compiled from the following standard references: gene from [HGNC](#); chromosome locus from [OMIM](#); protein from [UniProt](#). For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click [here](#).

**Table B.** OMIM Entries for Hereditary Motor and Sensory Neuropathy with Agenesis of the Corpus Callosum ([View All in OMIM](#))

<a href="#">218000</a>	AGENESIS OF THE CORPUS CALLOSUM WITH PERIPHERAL NEUROPATHY; ACCPN
<a href="#">604878</a>	SOLUTE CARRIER FAMILY 12 (POTASSIUM/CHLORIDE TRANSPORTER), MEMBER 6; SLC12A6

## Molecular Pathogenesis

*SLC12A6* encodes solute carrier family 12 member 6 (KCC3) whose protein structure includes:

- 12 putative membrane-spanning helices with large NH2 and COOH termini;
- A large extracellular loop between transmembrane domains 7 and 8 with five potential sites for N-linked glycosylation;
- Two consensus cAMP-dependant protein kinase phosphorylation sites;
- Four consensus protein kinase C phosphorylation sites in the COOH terminus.

KCC3, a cell cotransporter of the peripheral and central nervous system throughout neurologic development and adulthood, is necessary for the transport of chloride and potassium for the regulation of axonal cell volume [Delpire & Kahle 2017, Flores et al 2019]. Absence of KCC3 alters maintenance of homeostasis of the membrane threshold, leading to neuronal degeneration [Flores et al 2019].

KCC3 is also involved in the precise propagation of the paranodal action potential [Sun et al 2016]. This is consistent with brain autopsies of individuals with HMSN/ACC in whom regenerative clusters in the peripheral nervous system indicate ongoing degeneration [Auer et al 2016].

Although both loss of function and gain of function of KCC3 can cause peripheral neuropathy, gain of KCC3 function causes peripheral neuropathy without abnormalities of the corpus callosum or cognitive abilities [Flores et al 2019].

Studies on mice lacking *Kcc3* have demonstrated a normal-appearing corpus callosum, suggesting that *Kcc3* may not play a role in either embryonic or postnatal formation of the corpus callosum in mice [Shekarabi et al 2012].

**Mechanism of disease causation.** Loss of function

**Table 7.** Notable *SLC12A6* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_133647.1 NP_598408.1	c.2436+1delG (c.2436delG <sup>1</sup> )	--	Founder variant in French Canadian population [Howard et al 2002]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

*GeneReviews* follows the standard naming conventions of the Human Genome Variation Society ([varnomen.hgvs.org](http://varnomen.hgvs.org)). See [Quick Reference](#) for an explanation of nomenclature.

1. Alternate designation

## Chapter Notes

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