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Hypomyelination and Congenital Cataract

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Summary

Clinical characteristics

Hypomyelination and congenital cataract (HCC) is usually characterized by bilateral congenital cataracts and normal psychomotor or only mildly delayed development in the first year of life, followed by slowly progressive neurologic impairment manifest as ataxia, spasticity (brisk tendon reflexes and bilateral extensor plantar responses), and mild-to-moderate cognitive impairment. Dysarthria and truncal hypotonia are observed. Cerebellar signs (truncal titubation and intention tremor) and peripheral neuropathy (muscle weakness and wasting of the legs) are present in the majority of affected individuals. Seizures can occur. Cataracts may be absent in some individuals.

Diagnosis/testing

The diagnosis of HCC can be established in individuals with typical clinical findings, characteristic abnormalities on brain MRI, and biallelic pathogenic variants in *HYCC1* (formerly *FAM126A*) identified by molecular genetic testing.

Management

Treatment of manifestations: Cataract extraction usually in the first months of life. Therapy support for developmental delays; special education; physical medicine and rehabilitation for spasticity and ataxia. Consider pharmacologic agents for spasticity; anti-seizure medication as needed. Treatment for scoliosis and contractures per orthopedist; feeding therapy and or gastrostomy tube as needed.

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Surveillance: Eye examinations if cataracts were not identified in neonatal period. Developmental, neurologic, and musculoskeletal assessments at each visit. Growth measurement, nutrition assessment, and assessment of family need for social work support and care coordination at each visit.

Genetic counseling

HCC is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *HYCC1* 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. Once the *HYCC1* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Hypomyelination and congenital cataract (HCC) **should be suspected** in individuals with the following clinical findings [Biancheri et al 2007] and characteristic abnormalities on brain MRI [Rossi et al 2008].

Clinical findings

- Bilateral congenital cataracts. One individual had juvenile cataract [Ugur & Tolun 2008]; one individual had only a mild lens opacity, noted at age three years [Biancheri et al 2011].
- Nystagmus present from the first few weeks of life
- Classic presentation shows normal or mildly delayed psychomotor development in the first year of life, followed by slowly progressive neurologic impairment manifest as:
  - Ataxia
  - Spasticity
  - Loss of the ability to walk
  - Mild-to-moderate cognitive impairment
- Uncommon presentations [Biancheri et al 2011]
  - Early-onset severe variant. Hypotonia and feeding difficulties in the neonatal period, developmental delay in the first months of life, and wheelchair dependency in early childhood
  - Late-onset mild variant. Normal development in the first two years of life with subsequent sudden motor regression

MRI findings

- Diffusely abnormal supratentorial white matter in all individuals
- Abnormal white matter signal behavior consistent with hypomyelination:
  - Hyperintense on T_2-weighted images (intermediate hyperintensity between that of myelinated white matter and CSF) (Figure 1)
  - Isointense to slightly hypointense on T_1-weighted images (Figure 2)
- Areas of higher T_2-weighted signal intensity with corresponding low-signal intensity on T_1-weighted images consistent with areas of increased white matter water content of variable extension in some individuals (Figure 3)
- White matter bulk loss in older individuals (Figure 4)
- Medullary centers of the cerebellar hemispheres showing mildly increased T_2-weighted signal intensity, paralleling that of the adjacent cortical gray matter and resulting in a "blurred" gray-white matter interface in some individuals (Figure 5)
- Sparing of the cortical and deep gray matter structures

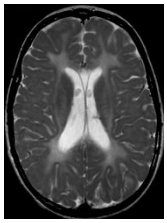

Figure 1. Axial T_2-weighted image shows diffuse hyperintensity of supratentorial white matter consistent with hypomyelination.

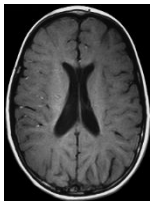

Figure 2. Axial T_1-weighted image shows diffusely isointense white matter with poor demarcation from adjacent gray matter, consistent with hypomyelination.

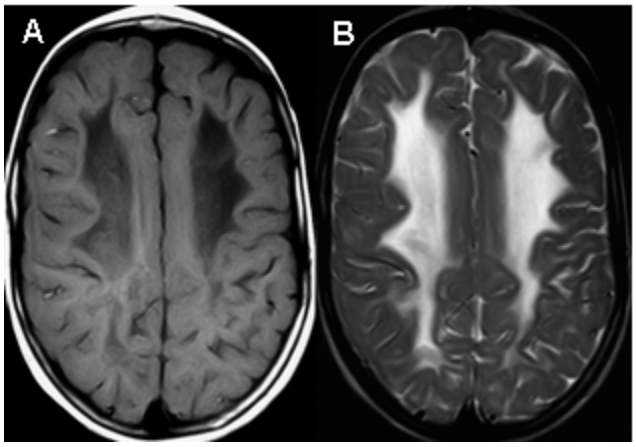

Figure 3. Axial T_1-weighted image (panel A) and axial T_2-weighted image (panel B) show areas of increased water content involving the deep frontal white matter.

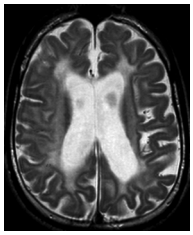

Figure 4. Axial T_2-weighted image in a 15-year-old shows enlargement of ventricles and subarachnoid spaces consistent with cerebral atrophy. The periventricular white matter is more hyperintense than the subcortical white matter, suggesting superimposed gliosis.

Establishing the Diagnosis

The diagnosis of HCC **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *HYCC1* (formerly *FAM126A*) identified by molecular genetic testing (see Table 1).

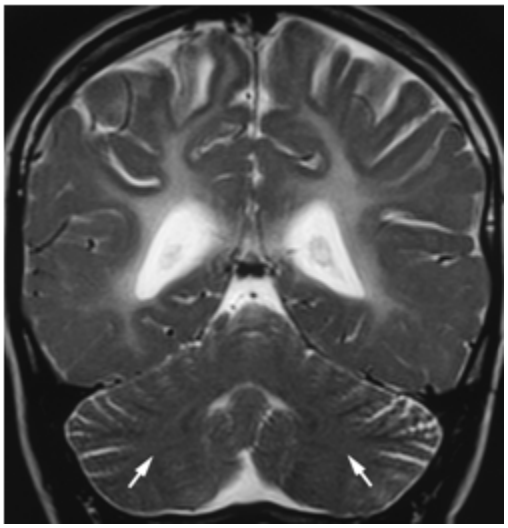

Figure 5. Coronal T_2-weighted image shows poor gray-white matter demarcation at the level of the medullary centers of the cerebellum, suggesting abnormal myelination of the cerebellar white matter.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include any likely pathogenic variants. (2) Identification of biallelic *HYCC1* variants of uncertain significance (or of one known *HYCC1* pathogenic variant and one *HYCC1* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, 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 with a phenotype indistinguishable from many other inherited disorders with cataracts and/or leukodystrophy are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *HYCC1* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. 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.

A multigene panel that includes *HYCC1* and other genes of interest (see Differential Diagnosis) may also be considered. 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*; thus, clinicians need to determine which multigene panel 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. (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

When the phenotype is indistinguishable from many other inherited disorders characterized by cataracts and/or leukodystrophy, **comprehensive genomic testing** (which does not require the clinician to determine which gene is likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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 Hypomyelination and Congenital Cataract

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
HYCC1 (*FAM126A*)	Sequence analysis [3]	16/17 [4]
	Gene-targeted deletion/duplication analysis [5]	One family [6]

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 missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Missense and splice-site variants in all probands were identified by sequence analysis of the entire coding region and the exon-intron boundaries of *HYCC1* [Zara et al 2006, Biancheri et al 2011, Traverso et al 2013a, Traverso et al 2013b].
5. 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.
6. One such analysis involving *HYCC1* identified a homozygous deletion in a proband from a large consanguineous Turkish family [Ugur & Tolun 2008].

Clinical Characteristics

Clinical Description

Hypomyelination and congenital cataract (HCC) phenotype is quite consistent in the affected individuals described to date.

Table 2. Hypomyelination and Congenital Cataract: Frequency of Select Features

Feature	Proportion of Persons w/Feature	Comment
Bilateral congenital cataracts	26/30	
Developmental delay	30/30	
Intellectual disability	30/30	
Dysarthria	26/26	
Truncal hypotonia	26/26	

Table 2. continued from previous page.

Feature	Proportion of Persons w/Feature	Comment
Brisk tendon reflexes & bilateral extensor plantar responses	30/30	
Cerebellar signs	11/25	Truncal titubation, intention tremor
Peripheral neuropathy	22/24	Muscle weakness, muscle wasting of the legs
Seizures	4/28	Seizures may be prolonged & w/fever.

Prenatal/perinatal. All affected individuals have normal prenatal and perinatal histories.

Ophthalmologic. Bilateral congenital cataracts identified at birth or within the first month of life are the first clinical sign. All children underwent ocular surgery in the first months of life with the exception of the one child who had adolescent-onset cataracts [Ugur & Tolun 2008].

Psychomotor development is normal up until the end of the first year of life, when developmental delays appear [Biancheri et al 2007]. The ability to walk with support is achieved between ages 12 and 24 months. Independent walking is not achieved in all individuals. Slowly progressive neurologic impairment then becomes apparent with gradual loss of the ability to walk. Most individuals become wheelchair bound between ages eight and nine years [Biancheri et al 2007].

Feeding issues occur as a result of neurologic impairment. Swallowing may become difficult, and growth may be affected by suboptimal intake.

Cognitive skills. All individuals have mild-to-moderate intellectual disability without deterioration in cognitive ability over time.

Neurologic findings. Clinical examination reveals the following from the onset of the disease course:

- Dysarthria
- Truncal hypotonia
- Pyramidal signs and spasticity. Tendon reflexes may be decreased or lost as a result of peripheral neuropathy.
- Cerebellar signs/ataxia (including truncal titubation and intention tremor)
- Peripheral neuropathy, present in most individuals, manifest as muscle weakness, wasting of the legs and ataxia. Peripheral neuropathy is absent in individuals with a milder form of the disorder (see Genotype-Phenotype Correlations).

Seizures including those triggered by fever may occur, but are not a predominant clinical feature.

Neurophysiologic investigations show the following from the onset of the disease course:

- **Motor nerve conduction velocity.** Slightly to markedly slowed in most individuals, with lower values in older persons
- **Compound muscle action potentials.** Reduced amplitude
- **Electromyography.** Signs of denervation in the absence of spontaneous activity
- **Waking EEG.** Irregular background activity; multifocal epileptiform discharges may be recorded.
- **Brain stem auditory evoked potentials.** Increased I-V interpeak conduction time in individuals older than age two years
- **Electroretinogram.** Normal

Neuropathologic findings

- Sural nerve biopsy of individuals with peripheral neuropathy shows a slight-to-severe reduction in density of myelinated fibers, with several axons surrounded by a thin myelin sheath or devoid of myelin.
- Uncompaction of the myelin sheath, which in some fibers appears redundant and irregularly folded, is occasionally seen.
- Electron microscopy confirms the presence of axons devoid of myelin, together with thinly myelinated fibers, sometimes surrounded by few Schwann cells processes, forming small onion bulbs.

Orthopedic issues. A slowly progressive scoliosis appears concurrently with the loss of the ability to walk [Biancheri et al 2007].

Life expectancy is unknown; the oldest living affected individual is age 34 years.

Genotype-Phenotype Correlations

Pathogenic variants leading to the complete absence of *HYCC1* (formerly *FAM126A*) protein expression are associated with the full phenotype of bilateral cataract, central nervous system hypomyelination, and peripheral nerve hypomyelination.

Pathogenic variants leading to a partial protein deficiency are associated with the milder form without peripheral nervous system involvement.

An individual with deletion of exons 8 and 9 did not have congenital cataracts; cataracts developed at age nine years. A second individual had congenital unilateral cataract. However, of the four children in this family who survived beyond age two years, none was able to walk even with support after age six years [Ugur & Tolun 2008].

Because of the limited number of individuals with HCC described so far, these correlations should be further confirmed.

Penetrance

Penetrance is complete.

Prevalence

HCC is likely a rare disorder. No epidemiologic studies are available.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *HYCC1* (formerly *FAM126A*).

Differential Diagnosis

The association of congenital cataract and CNS hypomyelination is typical of hypomyelination and congenital cataract (HCC). However, the differential diagnosis with other hypomyelinating disorders should include the disorders summarized in Table 3. MRI usually shows areas with an even higher T_2-weighted signal in HCC, whereas the white matter signal is homogeneously hyperintense in other hypomyelinating disorders.

Table 3. Hypomyelinating Disorders of Interest in the Differential Diagnosis of Hypomyelination and Congenital Cataract

Gene(s)	DiffDx Disorder	MOI	Features of DiffDx Disorder	
			Overlapping w/HCC	Distinguishing from HCC
PLP1	Pelizaeus-Merzbacher disease (See *PLP1* Disorders.)	XL	Spasticity/ataxia; nystagmus; hypomyelination	No congenital cataracts; pure hypomyelination on MRI; peripheral neuropathy rare; X-linked inheritance
GJC2	Hypomyelinating leukodystrophy 2 (OMIM 608804)	AR	Spasticity/ataxia; nystagmus; hypomyelination, peripheral neuropathy, epilepsy	No congenital cataracts; hypomyelinating MRI pattern different
TUBB4A	*TUBB4A*-related leukodystrophy	AD	Spasticity/ataxia; nystagmus; hypomyelination	Hypomyelination, cerebellar atrophy, & (in most cases) atrophy of the basal ganglia on MRI
POLR1C *POLR3A* *POLR3B* *POLR3K*	POLR3-related leukodystrophy	AR	Ataxia, hypodontia, hypogonadotropic hypogonadism, high myopia	Specific pattern of hypomyelination & cerebellar atrophy on MRI

AD = autosomal dominant; AR = autosomal recessive; DiffDx = differential diagnosis; HCC = hypomyelination and congenital cataract; MOI = mode of inheritance; XL = X-linked

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with hypomyelination and congenital cataract (HCC), 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 Hypomyelination and Congenital Cataract

System/Concern	Evaluation	Comment
Cataracts	Ophthalmologic exam	
Developmental delay	Developmental assessment	• Incl motor, adaptive, cognitive, & speech-language eval for dysarthria • Eval for early intervention / special education
Neurologic	Neurologic eval for evidence of spasticity, ataxia, seizures	Consider EEG if seizures are a concern.
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Contractures, clubfoot, & kyphoscoliosis • Mobility, activities of daily living, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider eval for gastrostomy tube placement in those w/dysphagia &/or aspiration risk.
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of HCC to facilitate medical & personal decision making

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with Hypomyelination and Congenital Cataract

Manifestation/ Concern	Treatment	Considerations/Other
Cataract	Cataract extraction	Usually in the first months of life
DD/ID	• Adjuvant therapies incl PT, OT, & speech therapy for persons w/identified DDs • Individualized education plans for learning disorders & school performance issues	
Spasticity	• Pharmacologic agents (e.g., baclofen, incl intrathecal baclofen) • Orthopedics / physical medicine & rehab / PT/OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard.
Ataxia	Physical medicine & rehab	
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for HCC. • Education of parents/caregivers [1]
Scoliosis & contractures	Prevention/treatment per orthopedist	
Feeding	Feeding therapy; gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia

ASM = anti-seizure medication; DD = developmental delay; HCC = hypomyelination and congenital cataract; ID = intellectual disability; OT = occupational therapy; PT = physical therapy
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Surveillance

Table 6. Recommended Surveillance for Individuals with Hypomyelination and Congenital Cataract

System/Concern	Evaluation	Frequency
Cataracts	Eye exam if cataracts were not identified in the neonatal period	

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Development	Monitor developmental progress & educational needs.	At each visit
Neurologic	Monitor those w/seizures as clinically indicated.	
	Assess for new manifestations incl seizures, changes in tone, movement disorders.	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	
Family/ Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	

OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

None are known. Some individuals are prone to febrile seizures.

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 in the US and EU Clinical Trials Register in Europe for access to 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

Hypomyelination and congenital cataract (HCC) 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 *HYCC1* [formerly *FAM126A*] 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 a *HYCC1* 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 a *HYCC1* 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. Unless an affected individual's reproductive partner also has HCC or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *HYCC1*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *HYCC1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *HYCC1* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk 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.

Prenatal Testing and Preimplantation Genetic Testing

Once the *HYCC1* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk 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 Library of Medicine Genetics Home Reference**
  Hypomyelination and congenital cataract
- **European Leukodystrophy Association (ELA)**
  Phone: 03 83 30 93 34
  www.ela-asso.com
- **National Eye Institute**
  31 Center Drive
  MSC 2510
  Bethesda MD 20892-2510
  Cataracts
- **Prevent Blindness America**
  211 West Wacker Drive

Suite 1700
Chicago IL 60606
Phone: 800-331-2020 (toll-free)
Email: info@preventblindness.org
Cataract

- **Myelin Disorders Bioregistry Project**
  Phone: 215-590-1719
  Email: sherbinio@chop.edu
  Myelin Disorders Bioregistry Project

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. Hypomyelination and Congenital Cataract: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
HYCC1	7p15.3	Hyccin	FAM126A database	HYCC1	HYCC1

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 Hypomyelination and Congenital Cataract (View All in OMIM)

610531	HYCCIN, PI4KA LIPID KINASE COMPLEX, SUBUNIT 1; HYCC1
610532	LEUKODYSTROPHY, HYPOMYELINATING, 5; HLD5

Molecular Pathogenesis

HYCC1 (formerly *FAM126A*) encodes the membrane protein hyccin [Zara et al 2006]. This protein belongs to a complex needed for the synthesis of phosphatidylinositol 4-phosphate, essential for the growth of the myelin sheaths [Baskin et al 2016].

Splicing variants (c.414+1G>T and c.51+1G>A) lead to the premature truncation of protein. Missense variant c.158T>C does not alter mRNA expression but leads to severe protein deficit through unknown cellular pathways. The genomic deletion 531-439_743+348del is expected to result in a 308-amino acid deletion. The effect of the latter variant was not investigated by immunoblot analysis.

Mechanism of disease causation. Loss of function

Table 7. Notable *HYCC1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1])	Reference
NM_032581.3	c.51+1G>A (IVS2+1G>A)	--	Zara et al [2006]
	c.414+1G>T (IVS5+1G>T)	--	
NM_032581.3 NP_115970.2	c.158T>C	p.Leu53Pro	
	(531-439_743+348del)	(Arg209fsTer213)	Ugur & Tolun [2008]

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). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

Chapter Notes

Acknowledgments

We thank the *Cell Line and DNA Bank from Patients Affected by Genetic Diseases* collection, supported by the Italian Telethon, for allowing us to obtain samples.

Revision History

- 14 January 2021 (sw) Comprehensive update posted live
- 4 June 2015 (me) Comprehensive update posted live
- 27 October 2011 (cd) Revision: mutation scanning and deletion/duplication analysis no longer available clinically; sequence analysis now available clinically
- 27 January 2011 (cd) Revision: prenatal testing available clinically
- 16 November 2010 (me) Comprehensive update posted live
- 14 October 2008 (me) Review posted live
- 14 May 2008 (rb) Original submission

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