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Congenital Mirror Movements

Synonym: Congenital Mirror Movement Disorder

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Summary

Clinical characteristics

The disorder of congenital mirror movements (CMM) is characterized by early-onset, obvious mirror movements (involuntary movements of one side of the body that mirror intentional movements on the opposite side) in individuals who typically have no other clinical signs or symptoms. Although mirror movements vary in severity, most affected individuals have strong and sustained mirror movements of a lesser amplitude than the corresponding voluntary movements. Mirror movements usually persist throughout life, without deterioration or improvement, and are not usually associated with subsequent onset of additional neurologic manifestations. However, a subset of affected individuals with a heterozygous pathogenic variant in *DCC* may have CMM with abnormalities of the corpus callosum and concomitant cognitive and/or neuropsychiatric issues.

Diagnosis/testing

The diagnosis of CMM is established in a proband with suggestive clinical findings and occasionally by identification of a heterozygous pathogenic variant in *DCC*, *NTN1*, or *RAD51*.

Management

Treatment of manifestations: Adaptation of the school environment (e.g., allocation of extra time during examinations and limitation of the amount of handwriting) is recommended. Stigmatizing children and adolescents should be avoided to assure that educational opportunities are not lost as a result of mirror movements. Adolescents and young adults should be encouraged to consider a profession that does not require

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complex bimanual movements, repetitive or sustained hand movements, or extensive handwriting. Standard therapy for any neurocognitive issues is recommended.

Agents/circumstances to avoid: Complex bimanual movements or sustained/repetitive hand activity in order to reduce pain or discomfort in the upper limbs.

Genetic counseling

CMM is generally inherited in an autosomal dominant (AD) manner. (Autosomal recessive inheritance has been suggested in one family.) For AD inheritance: most individuals with CMM resulting from a pathogenic variant in *DCC*, *NTN1*, or *RAD51* inherited the pathogenic variant from a parent who may be symptomatic or asymptomatic. If a parent of the proband is affected and/or has a *DCC*, *NTN1*, or *RAD51* pathogenic variant, the risk to the sibs of inheriting the variant is 50%. Of note, the sibs of a proband who has clinically unaffected parents are still at increased risk for CMM because of the significant possibility of reduced penetrance in a heterozygous parent. Each child of an individual with AD CMM has a 50% chance of inheriting the causative variant; however, because of reduced penetrance, offspring who inherit the pathogenic variant may not manifest CMM. Once the CMM-causing pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

The diagnosis of the disorder of congenital mirror movements (CMM) is established by clinical findings and, in some instances, molecular genetic testing.

Suggestive Findings

CMM **should be suspected** in individuals with the following clinical features, imaging findings, and family history.

Clinical features

- Onset of mirror movements (defined as involuntary movements of one side of the body that mirror intentional movements on the opposite side) in infancy or early childhood
- Predominant involvement of the upper limbs, with more severe distal involvement, especially in the muscles controlling the fingers and hands, which are always involved
- Persistence of mirror movements throughout adulthood and **absence** of the following:
  - Evidence of other clinical findings that would suggest an underlying syndrome [Bonnet et al 2010] (See Differential Diagnosis.)
  - Subsequent development of additional neurologic findings

Imaging findings include normal brain MRI or partial or complete agenesis of the corpus callosum.

Family history is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of CMM **is established** in a proband with suggestive clinical findings and occasionally by identification of a heterozygous pathogenic (or likely pathogenic) variant in *DCC*, *NTN1*, or *RAD51* by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP 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 [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *DCC*, *NTN1*, or *RAD51* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (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 CMM has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic findings suggest the diagnosis of CMM, molecular genetic testing approaches include use of a **multigene panel**.

A multigene panel that includes *DCC*, *NTN1*, and *RAD51* 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 panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of CMM has not been considered because an individual has atypical phenotypic features, comprehensive genomic testing may be pursued.

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 – and particularly when evidence supports autosomal dominant inheritance – **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 Congenital Mirror Movements

Gene [1]	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method	
	Sequence analysis [3]	Gene-targeted deletion/duplication analysis [4]
DCC	24/25 [5]	1/25 [6]
NTN1	3/3 [7]	None reported [7]
RAD51	7/7 [8]	None reported [8]

Table 1. continued from previous page.

Gene [1]	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method	
	Sequence analysis [3]	Gene-targeted deletion/duplication analysis [4]
Unknown [9]	NA	

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. 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.
5. Srour et al [2010], Depienne et al [2011], Djarmati-Westenberger et al [2011], Depienne et al [2012], Ahmed et al [2014], Méneret et al [2014a], Méneret et al [2014b], Franz et al [2015], Marsh et al [2017], Bierhals et al [2018], Sagi-Dain et al [2020]
6. Méneret et al [2014a]
7. Méneret et al [2017]
8. Srour et al [2010], Depienne et al [2011], Djarmati-Westenberger et al [2011], Depienne et al [2012], Ahmed et al [2014], Méneret et al [2014a], Méneret et al [2014b], Franz et al [2015], Trouillard et al [2016], Demirayak et al [2018]
9. Significant locus heterogeneity is hypothesized. Pathogenic variants in *DNAL4* have been suggested, but not confirmed, as a cause of CMM [Ahmed et al 2014, Méneret et al 2014b].

Clinical Characteristics

Clinical Description

Physiologic mild mirror movements may be seen in young children, but their persistence after age seven years is pathologic [Galléa et al 2011]. The disorder of congenital mirror movements (CMM) is characterized by early-onset obvious mirror movements that persist throughout adulthood in individuals who typically have no other clinical disorders. In particular, the mirror movements are not usually associated with subsequent onset of additional neurologic manifestations. However, a subset of individuals with a heterozygous *DCC* pathogenic variant may have concomitant cognitive and/or neuropsychiatric issues, particularly if abnormalities of the corpus callosum are present (see Phenotype Correlations by Gene and Genetically Related Disorders). Mirror movements usually persist throughout life, without deterioration or improvement.

Mirror movements (MM) predominantly involve the upper limbs, with more severe distal involvement. The muscles that control the fingers and hands are always involved. Muscles involving the toes may be slightly involved, without interfering with ambulation.

Although mirror movements vary in severity, most affected individuals have strong and sustained mirror movements of a lesser amplitude than the corresponding voluntary movements.

The severity of the mirror movements is defined according to the Woods and Teuber scale [Woods & Teuber 1978] as follows:

1. No MM
2. Barely discernible but repetitive MM
3. Slight but sustained MM or stronger but briefer MM
4. Strong and sustained repetitive MM
5. MM equal to that observed in the intended hand

Affected individuals have moderate difficulties with activities of daily living, including inability to perform pure unimanual movements, difficulty with tasks requiring skilled bimanual coordination, and occasional pain in the upper limbs during sustained manual activities [Galléa et al 2011, Méneret et al 2015].

Sensory issues. There are no sensory issues in CMM, but clinical examination in rare affected individuals may show sensory coupling, which is the perception of a sensation in the limb contralateral to the one being stimulated [Spencer-Smith et al 2020].

Neuroimaging. Brain MRI is normal in most cases but may show partial or complete agenesis of the corpus callosum (ACC) in some individuals with a heterozygous pathogenic *DCC* variant (see Phenotype-Correlations by Gene).

Phenotype Correlations by Gene

DCC. Individuals with a heterozygous *DCC* pathogenic variant may have CMM with or without partial or complete agenesis of the corpus callosum. These individuals may also have specific neuropsychological deficits associated with variable cognitive outcomes [Marsh et al 2017, Brown & Paul 2019, Spencer-Smith et al 2020]. The possible occurrence of slight neuropsychological deficits has also been suggested in individuals with a heterozygous *DCC* pathogenic variant without ACC [Spencer-Smith et al 2020].

***NTN1* and *RAD51*.** So far, there have been no reports of individuals with a heterozygous pathogenic variant in *NTN1* or *RAD51* who have corpus callosum abnormalities.

Genotype-Phenotype Correlations

There are no clear and validated genotype-phenotype correlations for *NTN1* or *RAD51*.

DCC

- Pathogenic variants in the NTN1 binding interface may predispose to abnormalities in the development of the corpus callosum with or without CMM [Spencer-Smith et al 2020] (see Genetically Related Disorders).
- Males with truncating *DCC* pathogenic variants are more likely to present with CMM, while females with truncating *DCC* pathogenic variants are more likely to present with isolated ACC (see Genetically Related Disorders) [Marsh et al 2017].

Penetrance

Penetrance is incomplete regardless of whether the causative pathogenic variant is in *DCC*, *NTN1*, or *RAD51*. Penetrance for the CMM phenotype was estimated to be 42% in those with a heterozygous pathogenic *DCC* variant – the most frequent cause of CMM [Marsh et al 2017].

Nomenclature

The term "synkinesis" may be appropriate, although it is more often used to describe mirror movements acquired later in life, as a result of either neurodegenerative diseases or acute brain lesions [Cox et al 2012].

The term "bimanual synergia" is mentioned in OMIM as having been used by William Bateson (1861-1926) in a family with CMM of apparent autosomal dominant inheritance and incomplete penetrance (OMIM 157600).

Prevalence

Congenital mirror movements is a very rare disorder, with an estimated prevalence of <1:1,000,000 (Orphanet 238722; accessed 9-21-20), although the actual prevalence could be significantly higher due to underdiagnosis, especially in individuals with milder manifestations.

Genetically Related (Allelic) Disorders

DCC

- **Isolated ACC.** Heterozygous pathogenic variants in *DCC* can result in isolated ACC without congenital mirror movements (CMM) [Marsh et al 2017].
- **Familial horizontal gaze palsy with progressive scoliosis with impaired intellectual development** (OMIM 617542), also known as split-brain syndrome, is a recessive disorder caused by biallelic loss-of-function variants in *DCC.* Affected individuals have no commissure between the right and left brain hemispheres, and they exhibit intellectual disability, horizontal gaze palsy, and scoliosis [Jamuar et al 2017].
- **Sporadic tumors** (including colorectal and esophageal cancer) occurring as single tumors in the absence of any other findings of CMM frequently harbor somatic variants in *DCC* that are **not** present in the germline. In these circumstances predisposition to these tumors is not heritable. For more information, see Cancer and Benign Tumors.

NTN1. No phenotypes other than the one discussed in this *GeneReview* are proven to be associated with pathogenic variants in *NTN1*.

RAD51

- **Fanconi anemia,** complementation group R (OMIM 617244), is characterized by physical abnormalities such as short stature and microcephaly, bone marrow failure, and predisposition to cancer. It is inherited in an autosomal dominant manner due to dominant-negative *RAD51* variants.
- **Sporadic tumors** (including breast cancer) occurring as single tumors in the absence of any other findings of CMM may harbor somatic variants in *RAD51* that are **not** present in the germline. In these circumstances predisposition to these tumors is not heritable. For more information, see Cancer and Benign Tumors.

Differential Diagnosis

The differential diagnosis of congenital mirror movements (CMM) from mirror movements of other causes is mainly theoretic, as the findings in CMM are distinctive, isolated, and easily recognized.

Physiologic mirror movements. The intensity of the mirror movements and their persistence after age seven years clearly differentiate pathologic from physiologic mirror movements. Mild physiologic mirror movements are frequent in normally developing young children. They usually disappear completely before age seven years and tend to recur gradually in old age [Bonnet et al 2010, Koerte et al 2010].

Syndromes with early-onset (congenital) mirror movements. Early-onset mirror movements are not always isolated; they may be a component of complex syndromes (see Table 2) and congenital hemiplegia (the most common form of cerebral palsy) [Norton et al 2008]. Although the clinical characteristics of mirror movements have been less comprehensively investigated in these conditions, they resemble those of CMM. In practice, differential diagnosis of CMM is rarely an issue, as the associated findings are generally more significant. When the diagnosis is in doubt, brain and cervical MRI may be considered in children or adolescents with mirror movements.

Table 2. Syndromes with Early-Onset Mirror Movements

Disorder	Gene(s)	MOI	Mirror Movements	Other Features
ANOS1 Kallmann syndrome (KS) (See Isolated GnRH Deficiency.)	*ANOS1* (*KAL1*)	XL	• MM in persons w/KS is almost always linked to *ANOS1* [1] (*ANOS1*-KS accounts for ~5%-10% of isolated GnRH deficiency). • Prevalence of MM in *KAL1*-KS is 75%. [1]	Hyposmia & hypogonadotropic hypogonadism
Joubert syndrome	≥34 genes	AR XL [2]	CMM is observed in some affected persons. [3]	Hypoplasia of cerebellar vermis w/ characteristic neuroradiologic molar tooth sign & variable accompanying neurologic symptoms
Klippel-Feil syndrome (KFS) (OMIM PS118100) [4]	*GDF3* *GDF6* *MEOX1* *MYO18B*	AD AR	MM is present in minority of persons w/KFS (MM is likely linked to cervicomedullary neuroschisis).	• Congenital fusion of cervical vertebrae • Typical phenotype incl low posterior hairline, short neck, & ↓ amplitude of neck movements
Moebius syndrome (OMIM 157900)	Unknown	AD	MM is only occasionally reported. [5]	Minimum criteria are congenital, non-progressive facial weakness in assoc w/ limited abduction of 1 or both eyes.
Nevoid basal cell carcinoma syndrome (Gorlin syndrome)	PTCH1 (PTCH2) [6] SUFU	AD	MM reported in 1 person [7]	Multiple basal cell carcinomas, jaw keratocysts, & skeletal malformations
Seckel syndrome (OMIM PS210600)	*ATR* *CENPJ* *CEP152* *CEP63* *DNA2* *NIN* *NSMCE2* *RBBP8* *TRAIP*	AR	1 reported person w/MM [8]	Primary microcephaly, intellectual disability, & often prenatal-onset growth restriction
Wildervanck syndrome (OMIM 314600)	Unknown	XL?	1 reported person w/MM [9]	• Klippel-Feil syndrome w/ congenital perceptive deafness & Duane syndrome [10] • Affected persons are almost exclusively female.

AD = autosomal dominant; AR = autosomal recessive; CMM = congenital mirror movements; GnRH = gonadotropin-releasing hormone; MM = mirror movements; MOI = mode of inheritance; XL = X-linked

1. Dodé & Hardelin [2010], Manara et al [2015]

2. Digenic inheritance has been reported.

3. Ferland et al [2004]

4. Tassabehji et al [2008], Mohamed et al [2013]

5. Webb et al [2014]

6. Occasional variants in *PTCH2* have been found in individuals with NBCCS but these may not be conclusive (see Nevoid Basal Cell Carcinoma Syndrome).

7. Sag et al [2016]

8. Thapa & Mukherjee [2010]

9. Högen et al [2012]

10. Duane syndrome = abducens palsy with narrowing of the palpebral fissure

Acquired mirror movements. Age of onset differentiates acquired mirror movements (usually associated with neurodegenerative disorders in adults) from congenital mirror movements.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with congenital mirror movements (CMM), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Congenital Mirror Movements

System/Concern	Evaluation	Comment
Neurologic	Evals to document difficulties w/ADL	Consider referral to rehab specialist.
	Consider head MRI imaging.	To assess for abnormalities of CC, esp in those w/ pathogenic *DCC* variant
	Consider neuropsychological eval. [1]	In those w/abnormalities of CC
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of CMM to facilitate medical & personal decision making
Family support & resources	Assess: • Use of community or online resources such as Parent to Parent; • Need for social work involvement for parental support.	

ADL = activities of daily living; CC = corpus callosum; CMM = congenital mirror movements; MOI = mode of inheritance
1. Spencer-Smith et al [2020]
2. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with Congenital Mirror Movements

Manifestation/Concern	Treatment/Counseling	Considerations/Other
Mirror movements	Adaptation of school environment	Incl allocation of extra time during exams & limitation of amount of handwriting
	Avoid stigmatizing children & adolescents.	To assure that educational opportunities incl university are not lost as result of mirror movements
	Education of parents & teachers	Reassurance that intellectual disability is not typically associated
	Education of affected persons	Encourage a profession that does not require complex bimanual movements, repetitive or sustained hand movements, or extensive handwriting.
Developmental delay / Neurocognitive deficits	Standard treatment	Consider referral to neurodevelopmental specialist.

Agents/Circumstances to Avoid

Complex bimanual movements or sustained/repetitive hand activity should be limited in order to reduce the occurrence of pain or discomfort in the upper limbs.

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Botulinum toxin injections have been successfully tried in one affected individual [Allegra et al 2017] but are not usually proposed, as the risk of inducing a motor deficit generally exceeds the possible benefit.

Noninvasive modulation of brain interhemispheric communication may be a possibility in the future [Galléa et al 2014].

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.

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

The disorder of congenital mirror movements (CMM) is generally inherited in an autosomal dominant manner.

Possible autosomal recessive inheritance of CMM was reported in one family [Ahmed et al 2014]; further studies are needed to confirm this finding.

Risk to Family Members (Autosomal Dominant Inheritance)

Parents of a proband

- Most individuals with CMM resulting from a pathogenic variant in *DCC*, *NTN1*, or *RAD51* inherited this variant from a parent, who may be symptomatic or asymptomatic [Méneret et al 2014a, Méneret et al 2017].
- A proband with CMM may have the disorder as the result of a *de novo* pathogenic variant [Méneret et al 2014a]. The proportion of CMM caused by a *de novo* pathogenic variant is unknown.
- If the causative pathogenic variant has been identified in the proband, molecular genetic testing is recommended for the parents of the proband. If the pathogenic variant identified in the proband is not identified in either parent, several possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a parent with germline mosaicism. Although no instances of germline mosaicism have been reported, it remains a possibility.
- The family history of some individuals diagnosed with CMM may appear to be negative because of reduced penetrance or failure to recognize the disorder in family members. Therefore, when the molecular basis of CMM is known, molecular genetic testing is the most accurate means of determining the genetic status of at-risk individuals.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected and/or has a *DCC*, *NTN1*, or *RAD51* pathogenic variant, the risk to the sibs of inheriting the variant is 50%. Sibs who inherit a pathogenic variant may or may not manifest CMM (see Penetrance).
- If the proband has a known *DCC*, *NTN1*, or *RAD51* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents of the proband are clinically unaffected but their genetic status is unknown, sibs are still at increased risk for CMM because of the significant possibility of reduced penetrance in a parent and the theoretic possibility of parental germline mosaicism.

Offspring of a proband

- Each child of an individual with CMM caused by a pathogenic variant in *DCC*, *NTN1*, or *RAD51* has a 50% chance of inheriting the variant.
- Because of reduced penetrance in CMM, offspring who inherit a *DCC*, *NTN1*, or *RAD51* pathogenic variant may or may not manifest CMM.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected and/or has the *DCC*, *NTN1*, or *RAD51* pathogenic variant, the parent's family members may be at risk.

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) to young adults who are affected or at risk of having the *DCC*, *NTN1*, or *RAD51* pathogenic variant.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the CMM-causing pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for CMM 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**
  Congenital mirror movement disorder

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. Congenital Mirror Movements: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
DCC	18q21.2	Netrin receptor DCC		DCC	DCC
NTN1	17p13.1	Netrin-1		NTN1	NTN1
RAD51	15q15.1	DNA repair protein RAD51 homolog 1	RAD51 database	RAD51	RAD51

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 Congenital Mirror Movements (View All in OMIM)

120470	DCC NETRIN 1 RECEPTOR; DCC
157600	MIRROR MOVEMENTS 1; MRMV1
179617	RAD51 RECOMBINASE; RAD51
601614	NETRIN 1; NTN1
614508	MIRROR MOVEMENTS 2; MRMV2
618264	MIRROR MOVEMENTS 4; MRMV4

Molecular Pathogenesis

Two of the genes (*DCC* and *NTN1*) associated with CMM encode proteins that have a role in axonal guidance, whereas the role of *RAD51* remains unclear.

DCC encodes DCC, a transmembrane receptor for netrin-1, a protein that helps guide axons of the developing nervous system across the midline of the body [Tcherkezian et al 2010]. Loss of DCC may lead to disruption of axonal guidance with abnormal decussation of the corticospinal tracts and persistence of an abnormal ipsilateral corticospinal tract [Srour et al 2010, Depienne et al 2011].

NTN1 encodes the DCC ligand, netrin-1. Netrins play a role in neuronal guidance.

RAD51 encodes RAD51, a protein with an established role in DNA repair. RAD51 contains a helix-hairpin-helix domain and an ATPase domain [Park et al 2008]. Association with CMM has revealed an unsuspected role of RAD51 in central nervous system development [Galléa et al 2013]. The precise mechanisms linking RAD51 deficiency to mirror movements remain unclear. Regulation of netrin-1 signaling by RAD51 has been hypothesized [Glendining et al 2017].

Mechanism of disease causation. Loss of function is hypothesized to be the main mechanism for all three known genes, although the impact of missense variants remains to be studied.

Cancer and Benign Tumors

Genes associated with CMM have also been associated with tumors or genomic integrity in individuals who do not have CMM.

- ***DCC.*** Sporadic tumors (including colorectal and esophageal cancers) frequently harbor somatic variants in *DCC* that are not present in the germline [Rasool et al 2014].
- ***NTN1.*** Sporadic tumors may harbor variants in *NTN1* that are not present in the germline [Hao et al 2020].
- ***RAD51.*** RAD51 is essential for maintaining genomic integrity through its role in homologous recombination; therefore, variants in *RAD51* have long been predicted to increase the risk of developing cancers [Klein 2008]. However, a single germline missense variant of doubtful pathogenicity was reported in only two individuals with breast cancer, suggesting that *RAD51* is not a major cancer predisposition gene in this tissue [Kato et al 2000]. In addition, sporadic tumors may harbor rare variants in *RAD51* that are not present in the germline [Marshall et al 2019].

Chapter Notes

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References

Literature Cited

Ahmed I, Mittal K, Sheikh TI, Vasli N, Rafiq MA, Mikhailov A, Ohadi M, Mahmood H, Rouleau GA, Bhatti A, Ayub M, Srour M, John P, Vincent JB. Identification of a homozygous splice site mutation in the dynein axonemal light chain 4 gene on 22q13.1 in a large consanguineous family from Pakistan with congenital mirror movement disorder. Hum Genet. 2014;133:1419–29. PubMed PMID: 25098561.

Allegra C, Girlanda P, Morgante F. Treating congenital mirror movements with botulinum toxin. Mov Disord Clin Pract. 2017;4:895–7. PubMed PMID: 30713984.

Bierhals T, Korenke GC, Baethmann M, Marín LL, Staudt M, Kutsche K. Novel DCC variants in congenital mirror movements and evaluation of disease-associated missense variants. Eur J Med Genet. 2018;61:329–34. PubMed PMID: 29366874.

Bonnet C, Roubertie A, Doummar D, Bahi-Buisson N, Cochen de Cock V, Roze E. Developmental and benign movement disorders in childhood. Mov Disord. 2010;25:1317–34. PubMed PMID: 20564735.

Brown WS, Paul LK. The neuropsychological syndrome of agenesis of the corpus callosum. J Int Neuropsychol Soc. 2019;25:324–30. PubMed PMID: 30691545.

Cox BC, Cincotta M, Espay AJ. Mirror movements in movement disorders: a review. Tremor Other Hyperkinet Mov (N Y). 2012;2:tre-02-59-398-1.

Demirayak P, Onat OE, Gevrekci AÖ, Gülsüner S, Uysal H, Bilgen RS, Doerschner K, Özçelik TS, Boyacı H. Abnormal subcortical activity in congenital mirror movement disorder with RAD51 mutation. Diagn Interv Radiol. 2018;24:392–401. PubMed PMID: 30406765.

Depienne C, Bouteiller D, Méneret A, Billot S, Groppa S, Klebe S, Charbonnier-Beaupel F, Corvol JC, Saraiva JP, Brueggemann N, Bhatia K, Cincotta M, Brochard V, Flamand-Roze C, Carpentier W, Meunier S, Marie Y, Gaussen M, Stevanin G, Wehrle R, Vidailhet M, Klein C, Dusart I, Brice A, Roze E. RAD51 haploinsufficiency causes congenital mirror movements in humans. Am J Hum Genet. 2012;90:301–7. PubMed PMID: 22305526.

Depienne C, Cincotta M, Billot S, Bouteiller D, Groppa S, Brochard V, Flamand C, Hubsch C, Meunier S, Giovannelli F, Klebe S, Corvol JC, Vidailhet M, Brice A, Roze E. A novel DCC mutation and genetic heterogeneity in congenital mirror movements. Neurology. 2011;76:260–4. PubMed PMID: 21242494.

Djarmati-Westenberger A, Brüggemann N, Espay AJ, Bhatia KP, Klein C. A novel DCC mutation and genetic heterogeneity in congenital mirror movements. Neurology. 2011;77:1580. PubMed PMID: 22006891.

Dodé C, Hardelin JP. Clinical genetics of Kallmann syndrome. Ann Endocrinol (Paris). 2010;71:149–57. PubMed PMID: 20362962.

Ferland RJ, Eyaid W, Collura RV, Tully LD, Hill RS, Al-Nouri D, Al-Rumayyan A, Topcu M, Gascon G, Bodell A, Shugart YY, Ruvolo M, Walsh CA. Abnormal cerebellar development and axonal decussation due to mutations in AHI1 in Joubert syndrome. Nat Genet. 2004;36:1008–13. PubMed PMID: 15322546.

Franz EA, Chiaroni-Clarke R, Woodrow S, Glendining KA, Jasoni CL, Robertson SP, Gardner RJM, Markie D. Congenital mirror movements: phenotypes associated with DCC and RAD51 mutations. J Neurol Sci. 2015;351:140–5. PubMed PMID: 25813273.

Galléa C, Popa T, Billot S, Méneret A, Depienne C, Roze E. Congenital mirror movements: a clue to understanding bimanual motor control. J Neurol. 2011;258:1911–9. PubMed PMID: 21633904.

Galléa C, Popa T, Hubsch C, Valabregue R, Brochard V, Kundu P, Schmitt B, Bardinet E, Bertasi E, Flamand-Roze C, Alexandre N, Delmaire C, Méneret A, Depienne C, Poupon C, Hertz-Pannier L, Cincotta M, Vidailhet M, Lehericy S, Meunier S, Roze E. RAD51 deficiency disrupts the corticospinal lateralization of motor control. Brain. 2013;136:3333–46. PubMed PMID: 24056534.

Galléa C, Popa T, Meunier S, Roze E. Reply: Congenital mirror movements: lack of decussation of pyramids Mirror movement: from physiopathology to treatment perspectives. Brain. 2014;137:e293. PubMed PMID: 24727566.

Glendining KA, Markie D, Gardner RJ, Franz EA, Robertson SP, Jasoni CL. A novel role for the DNA repair gene Rad51 in Netrin-1 signalling. Sci Rep. 2017;7:39823. PubMed PMID: 28057929.

Hao W, Yu M, Lin J, Liu B, Xing H, Yang J, Sun D, Chen F, Jiang M, Tang C, Zhang X, Zhao Y, Zhu Y. The pan-cancer landscape of netrin family reveals potential oncogenic biomarkers. Sci Rep. 2020;10:5224. PubMed PMID: 32251318.

Högen T, Chan WM, Riedel E, Brüning R, Chang HH, Engle EC, Danek A. Wildervanck's syndrome and mirror movements: a congenital disorder of axon migration? J Neurol. 2012;259:761–3. PubMed PMID: 21947222.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389–97. PubMed PMID: 35834113.

Jamuar SS, Schmitz-Abe K, D'Gama AM, Drottar M, Chan WM, Peeva M, Servattalab S, Lam AN, Delgado MR, Clegg NJ, Zayed ZA, Dogar MA, Alorainy IA, Jamea AA, Abu-Amero K, Griebel M, Ward W, Lein ES, Markianos K, Barkovich AJ, Robson CD, Grant PE, Bosley TM, Engle EC, Walsh CA, Yu TW. Biallelic mutations in human DCC cause developmental split-brain syndrome. Nat Genet. 2017;49:606–12. PubMed PMID: 28250456.

Kato M, Yano K, Matsuo F, Saito H, Katagiri T, Kurumizaka H, Yoshimoto M, Kasumi F, Akiyama F, Sakamoto G, Nagawa H, Nakamura Y, Miki Y. Identification of Rad51 alteration in patients with bilateral breast cancer. J Hum Genet. 2000;45:133–7. PubMed PMID: 10807537.

Klein HL. The consequences of Rad51 overexpression for normal and tumor cells. DNA Repair (Amst). 2008;7:686–93. PubMed PMID: 18243065.

Koerte I, Eftimov L, Laubender RP, Esslinger O, Schroeder AS, Ertl-Wagner B, Wahllaender-Danek U, Heinen F, Danek A. Mirror movements in healthy humans across the lifespan: effects of development and ageing. Dev Med Child Neurol. 2010;52:1106–12. PubMed PMID: 21039436.

Manara R, Salvalaggio A, Citton V, Palumbo V, D'Errico A, Elefante A, Briani C, Cantone E, Ottaviano G, Pellecchia MT, Greggio NA, Weis L, D'Agosto G, Rossato M, De Carlo E, Napoli E, Coppola G, Di Salle F, Brunetti A, Bonanni G, Sinisi AA, Favaro A. Brain anatomical substrates of mirror movements in Kallmann syndrome. Neuroimage. 2015;104:52–8. PubMed PMID: 25300200.

Marsh AP, Heron D, Edwards TJ, Quartier A, Galea C, Nava C, Rastetter A, Moutard ML, Anderson V, Bitoun P, Bunt J, Faudet A, Garel C, Gillies G, Gobius I, Guegan J, Heide S, Keren B, Lesne F, Lukic V, Mandelstam SA, McGillivray G, McIlroy A, Méneret A, Mignot C, Morcom LR, Odent S, Paolino A, Pope K, Riant F, Robinson GA, Spencer-Smith M, Srour M, Stephenson SE, Tankard R, Trouillard O, Welniarz Q, Wood A, Brice A, Rouleau G, Attié-Bitach T, Delatycki MB, Mandel JL, Amor DJ, Roze E, Piton A, Bahlo M, Billette de Villemeur T, Sherr EH, Leventer RJ, Richards LJ, Lockhart PJ, Depienne C. Mutations in DCC cause isolated agenesis of the corpus callosum with incomplete penetrance. Nat Genet. 2017;49:511–4. PubMed PMID: 28250454.

Marshall CH, Fu W, Wang H, Baras AS, Lotan TL, Antonarakis ES. Prevalence of DNA repair gene mutations in localized prostate cancer according to clinical and pathologic features: association of Gleason score and tumor stage. Prostate Cancer Prostatic Dis. 2019;22:59–65. PubMed PMID: 30171229.

Méneret A, Depienne C, Riant F, Trouillard O, Bouteiller D, Cincotta M, Bitoun P, Wickert J, Lagroua I, Westenberger A, Borgheresi A, Doummar D, Romano M, Rossi S, Defebvre L, De Meirleir L, Espay AJ, Fiori S, Klebe S, Quélin C, Rudnik-Schöneborn S, Plessis G, Dale RC, Sklower Brooks S, Dziezyc K, Pollak P, Golmard JL, Vidailhet M, Brice A, Roze E. Congenital mirror movements: mutational analysis of RAD51 and DCC in 26 cases. Neurology. 2014a;82:1999–2002. PubMed PMID: 24808016.

Méneret A, Franz EA, Trouillard O, Oliver TC, Zagar Y, Robertson SP, Welniarz Q, Gardner RJM, Gallea C, Srour M, Depienne C, Jasoni CL, Dubacq C, Riant F, Lamy JC, Morel MP, Guérois R, Andreani J, Fouquet C, Doulazmi M, Vidailhet M, Rouleau GA, Brice A, Chédotal A, Dusart I, Roze E, Markie D. Mutations in the netrin-1 gene cause congenital mirror movements. J Clin Invest. 2017;127:3923–36. PubMed PMID: 28945198.

Méneret A, Trouillard O, Vidailhet M, Depienne C, Roze E. Congenital mirror movements: no mutation in DNAL4 in 17 index cases. J Neurol. 2014b;261:2030–1. PubMed PMID: 25236653.

Méneret A, Welniarz Q, Trouillard O, Roze E. Congenital mirror movements: From piano player to opera singer. Neurology. 2015;84:860. PubMed PMID: 25713113.

Mohamed JY, Faqeih E, Alsiddiky A, Alshammari MJ, Ibrahim NA, Alkuraya FS. Mutations in MEOX1, encoding mesenchyme homeobox 1, cause Klippel-Feil anomaly. Am J Hum Genet. 2013;92:157–61. PubMed PMID: 23290072.

Norton JA, Thompson AK, Chan KM, Wilman A, Stein RB. Persistent mirror movements for over sixty years: the underlying mechanisms in a cerebral palsy patient. Clin Neurophysiol. 2008;119:80–7. PubMed PMID: 18042427.

Park JY, Yoo HW, Kim BR, Park R, Choi SY, Kim Y. Identification of a novel human Rad51 variant that promotes DNA strand exchange. Nucleic Acids Res. 2008;36:3226–34. PubMed PMID: 18417535.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126–33. PubMed PMID: 26656846.

Rasool S, Rasool V, Naqvi T, Ganai BA, Shah BA. Genetic unraveling of colorectal cancer. Tumour Biol. 2014;35:5067–82. PubMed PMID: 24573608.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of

Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Sag E, Gocmen R, Yildiz FG, Ozturk Z, Temucin C, Teksam O, Utine E. Congenital mirror movements in Gorlin syndrome: a case report with DTI and functional MRI features. Pediatrics. 2016;137:e20151771. PubMed PMID: 26917672.

Sagi-Dain L, Kurolap A, Ilivitzki A, Mory A, Paperna T. Regeneron Genetics Center, Kedar R, Gonzaga-Jauregui C, Peleg A, Baris Feldman H. A novel heterozygous loss-of-function DCC Netrin 1 receptor variant in prenatal agenesis of corpus callosum and review of the literature. Am J Med Genet A. 2020;182:205–12. PubMed PMID: 31697046.

Spencer-Smith M, Knight JL, Lacaze E. Irc5 Consortium, Depienne C, Lockhart PJ, Richards LJ, Heron D, Leventer RJ, Robinson GA. Callosal agenesis and congenital mirror movements: outcomes associated with DCC mutations. Dev Med Child Neurol. 2020;62:758–62. PubMed PMID: 32060908.

Srour M, Rivière JB, Pham JM, Dubé MP, Girard S, Morin S, Dion PA, Asselin G, Rochefort D, Hince P, Diab S, Sharafaddinzadeh N, Chouinard S, Théoret H, Charron F, Rouleau GA. Mutations in DCC cause congenital mirror movements. Science. 2010;328:592. PubMed PMID: 20431009.

Tassabehji M, Fang ZM, Hilton EN, McGaughran J, Zhao Z, de Bock CE, Howard E, Malass M, Donnai D, Diwan A, Manson FD, Murrell D, Clarke RA. Mutations in GDF6 are associated with vertebral segmentation defects in Klippel-Feil syndrome. Hum Mutat. 2008;29:1017–27. PubMed PMID: 18425797.

Tcherkezian J, Brittis PA, Thomas F, Roux PP, Flanagan JG. Transmembrane receptor DCC associates with protein synthesis machinery and regulates translation. Cell. 2010;141:632–44. PubMed PMID: 20434207.

Thapa R, Mukherjee K. Seckel syndrome with asymptomatic tonsillar herniation and congenital mirror movements. J Child Neurol. 2010;25:231–3. PubMed PMID: 19372093.

Trouillard O, Koht J, Gerstner T, Moland S, Depienne C, Dusart I, Méneret A, Ruiz M, Dubacq C, Roze E. Congenital mirror movements due to RAD51: cosegregation with a nonsense mutation in a Norwegian pedigree and review of the literature. Tremor Other Hyperkinet Mov (N Y). 2016;6:424. PubMed PMID: 27830107.

Webb BD, Frempong T, Naidich TP, Gaspar H, Jabs EW, Rucker JC. Mirror movements identified in patients with moebius syndrome. Tremor Other Hyperkinet Mov (N Y). 2014;4:256. PubMed PMID: 25120946.

Woods BT, Teuber HL. Mirror movements after childhood hemiparesis. Neurology. 1978;28:1152–7. PubMed PMID: 568735.

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