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DCX-Related Disorders

Goekhan Uyanik, MD
Department of Neurology
University of Regensburg
Regensburg, Germany
goekhan.uyanik@klinik.uni-regensburg.de

Ludwig Aigner, PhD
Department of Neurology
University of Regensburg
Regensburg, Germany
ludwig.aigner@klinik.uni-regensburg.de

Sebastien Couillard-Despres, PhD
Department of Neurology
University of Regensburg
Regensburg, Germany
sebastien.couillard-despres@klinik.uni-regensburg.de

Ute Hehr, MD
Center for Human Genetics and Department of Human Genetics
University of Regensburg
Regensburg, Germany
ute.hehr@humangenetik-regensburg.de

Juergen Winkler, MD
Department of Neurology
University of Regensburg
Regensburg, Germany
juergen.winkler@klinik.uni-regensburg.de

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Summary

Disease characteristics. *DCX*-related disorders include the neuronal migration disorders classic lissencephaly (also known as lissencephaly type 1) in males and subcortical band heterotopia (SBH)/double cortex syndrome primarily in females. Males with classic lissencephaly typically have global developmental delay, infantile-onset seizures (infantile spasms, West syndrome, focal and generalized seizures), and severe mental retardation. In individuals with SBH/double cortex syndrome cognitive abilities range from normal to learning disabilities and/or severe mental retardation; focal seizures are seen in about 50% and generalized seizures in about 50%. In about 65% the epilepsy is refractory to antiepileptic therapy. Behavior problems may be observed. In SBH/double cortex syndrome the severity of symptoms correlates with the degree of the underlying brain malformation.

Diagnosis/testing. The diagnosis of *DCX*-related disorders is suspected on MRI findings and confirmed by molecular genetic testing. The lissencephaly observed in *DCX*-related disorders is termed classic lissencephaly as it is characterized by absent gyria (agyria) or reduced gyration (pachygyria) with thickened cortex. *DCX*-associated SBH/double cortex syndrome occurs predominantly in the frontal-parietal lobes. *DCX* is the only gene known to be associated with *DCX*-related disorders. Sequence analysis including all coding exons and exon-intron

boundaries in hemizygous males from families with lissencephaly in at least one male and SBH in at least one female detects most *DCX* mutations reported to date. In heterozygous females, deletion analysis is used to detect deletions of a single exon or several exons.

Management. *Treatment of manifestations:* antiepileptic drugs (AEDs) for epileptic seizures; special feeding strategies in newborns with poor suck; physical therapy to promote mobility and prevent contractures; special adaptive chairs or positioners as needed; occupational therapy to improve fine motor skills and oral-motor control; participation in educational training and enrichment programs. *Surveillance:* regular neurologic examination and EEG to monitor seizures; measurement of height, weight, and head circumference during routine health maintenance examinations; monitoring for orthopedic complications such as foot deformity or scoliosis.

Genetic counseling. *DCX*-related disorders are inherited in an X-linked manner. Individuals with *DCX*-related classic lissencephaly may either have inherited the *DCX* mutation from their mother or may have the disorder as the result of a new gene mutation; the proportion of cases caused by *de novo* mutations is unknown. Approximately 10% of unaffected mothers of children with a *DCX* mutation may have somatic mosaicism or germline mosaicism. If a woman has a *DCX* mutation, the chance of transmitting the *DCX* mutation in each pregnancy is 50%. Males who inherit the mutation will be affected with *DCX*-related lissencephaly; females who inherit the mutation will be carriers and will be at risk of developing the variable phenotype associated with SBH. Carrier testing for at-risk family members and prenatal testing for pregnancies at increased risk is possible if the disease-causing mutation has been identified in the family.

Diagnosis

Clinical Diagnosis

DCX-related conditions include the neuronal migration disorders:

- Classic lissencephaly (also known as lissencephaly type 1), in males only
- Subcortical band heterotopia (SBH)/double cortex syndrome, primarily in females

The diagnosis of *DCX*-related disorders relies on the combination of clinical features, MRI, and family history consistent with X-linked inheritance.

Males with classic lissencephaly

Clinical examination. Typically seen in males with classic lissencephaly:

- Global developmental delay
- Infantile-onset seizures (infantile spasms, West syndrome, focal and generalized seizures)
- Severe mental retardation

No distinctive clinical findings are observed aside from manifestations of the brain malformations.

Brain imaging. Ultrasound examination of the head or CT scan can help establish the diagnosis of classic lissencephaly in small children, but cranial MRI is necessary to visualize minimal or subtle pathologic changes. If necessary, imaging should be performed under anesthesia.

The lissencephaly observed in *DCX*-related disorders is termed classic lissencephaly as it is characterized by absent gyria (agyria) or reduced gyration (pachygyria) with thickened cortex that can be classified further according to the following six-grade system for classic lissencephaly, which evaluates both severity and anterior-posterior gradient [Dobyns & Truwit 1995, Dobyns et al 1999]:

1. Complete agyria
2. Diffuse agyria with a few undulations at the occipital poles
3. Mixed agyria and pachygyria
4. Diffuse pachygyria, or mixed pachygyria and normal or simplified gyri
5. Diffuse pachygyria or simplified gyri at the frontal regions with subcortical band heterotopia in the occipital poles
6. Subcortical band heterotopia only

Usually grades 2-4 (which are part of the classic lissencephaly spectrum) and grade 5 (overlap between classic lissencephaly and band heterotopia) are seen in *DCX*-related lissencephaly.

In *DCX*-related disorders the lissencephaly or SBH/double cortex syndrome is more severe anteriorly, referred to as an anterior to posterior (A>P) gradient [Pilz et al 1998, Dobyns et al 1999].

Individuals with SBH/double cortex syndrome

Clinical examination. Wide phenotypic variability is observed even among affected members of the same family [Aigner et al 2003, Martin et al 2004].

- Approximately 50% of affected females have focal seizures and 50% have generalized seizures. The epilepsy is refractory to antiepileptic therapy in about 65% of affected individuals [Guerrini & Carrozzo 2001].
- Cognitive performance ranges from normal to learning disabilities and/or severe mental retardation.
- Behavioral problems may be observed.

Brain imaging. Cranial MRI is the most reliable method of visualizing SBH/double cortex syndrome. If necessary, imaging should be performed under anesthesia.

DCX-associated SBH/double cortex syndrome is predominantly located in the frontoparietal lobe and is grade 6 (complete band heterotopia). Grade 5, a more severe malformation that overlaps with classic lissencephaly and band heterotopia, is characterized by SBH in the occipital regions and pachygyria in the frontal regions [Dobyns et al 1999]. In some individuals with a *DCX* mutation, only focal SBH in the frontal lobes has been described.

Family history. A detailed family history should be obtained. Special attention should be paid to epilepsy, miscarriages, stillbirths, children who died at a young age without obvious birth defects, and mental retardation, especially in females.

Testing

Chromosome analysis. An X:autosome translocation affecting the *DCX* locus has been associated with X-linked lissencephaly [Dobyns et al 1992, Gleeson et al 1998].

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *DCX* is the only gene currently known to be associated with *"DCX*-related" disorders (classic lissencephaly in males; SBH/double cortex syndrome, primarily in females).

Clinical testing

- **Sequence analysis.** *DCX* mutations can be identified in all multiplex families with SBH/double cortex syndrome and families with SBH/double cortex syndrome in females and lissencephaly in males [des Portes et al 1998, Gleeson et al 1998, Gleeson et al 1999, Matsumoto et al 2001]. Direct sequencing of the *DCX* gene including all coding exons and exon-intron boundaries in hemizygous males should detect most *DCX* mutations reported to date, including frameshifts, exonic and whole-gene deletions, and missense, nonsense, and splice-site mutations.

  Note: (1) In males without a detectable *DCX* mutation, the non-coding first three exons should also be analyzed. (2) In heterozygous females deletion analysis is necessary to detect deletions of a single exon or several exons because these cannot be detected by sequence analysis. (See also Table 1, Footnotes 5-6.)

- **Deletion analysis for females.** In female probands with SBH/double cortex syndrome without a detectable *DCX* mutation, additional strategies to detect small exonic deletions or insertions have to be employed, such as multiplex ligation dependent probe amplification (MLPA), real-time PCR, or Southern hybridization [Mei et al 2007].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in *DCX*-Related Disorders

Test Method	Mutations Detected	Mutation Detection Frequency [1]		Test Availability
		Familial [2]	Simplex [3]	
Sequence analysis	*DCX* sequence variants (in males and females); *DCX* intragenic and gene deletions (males only)	100% [4]	Males [5] Females [6]	Clinical Testing
Deletion testing [7]	*DCX* intragenic and full gene deletions (females); Mosaic intragenic and gene deletions (males)	~10% in females [8]		

1. Proportion of affected individuals with a mutation(s) as classified by test method and number of occurrences in a family
2. Familial: families with the combined occurrence of lissencephaly in males and SBH in females
3. Simplex: a single occurrence in a family
4. Gleeson et al 1999, Matsumoto et al 2001
5. Mutation detection frequency in male simplex cases of SBH/double cortex syndrome is 29% [D'Agostino et al 2002] and in simplex cases of lissencephaly is approximately 12% [Pilz et al 1998] because the presentation of *DCX*-related lissencephaly and other lissencephalies can be similar.
6. Mutation detection frequency in female simplex cases is approximately 80% and can range from 38% to 90% [des Portes et al 1998, Gleeson et al 1998, Gleeson et al 1999, Matsumoto et al 2001] presumably because of inclusion of females with SBH/double cortex syndrome resulting from mosaic *DCX* mutations present only in neural tissue, inclusion of females with SBH/double cortex syndrome from other genetic causes, and lack of deletion testing.
7. May include MLPA assay, Southern hybridization, real-time PCR
8. Mei et al 2007

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

When no *DCX* mutation is found in a proband of either sex, somatic mosaicism, a common finding in *DCX*-related conditions, needs to be considered [Demelas et al 2001, D'Agostino et al 2002, Poolos et al 2002, Aigner et al 2003]. Somatic mosaicism for *DCX* mutations is the presence of a *DCX* mutation in some, but not all, cells of an individual.

Findings on sequence analysis suggestive of somatic mosaicism include the following:

- Heterozygosity for wild type and mutant *DCX* sequences in males with SBH/double cortex syndrome. In these males other causes of heterozygosity, such as a 47,XXY karyotype, should be sought.
- Marked unequal peak height of wild type and mutant *DCX* sequences in females with mild clinical features (i.e., partial SBH/focal SBH)

Somatic mosaicism should be confirmed by analysis of DNA from different tissues (e.g., hair roots, buccal swabs).

Testing Strategy

To establish the diagnosis of a *DCX*-related disorder in a proband

- The diagnosis of classic lissencephaly or SBH/double cortex syndrome is established by cranial MRI.
- Chromosome analysis should be performed prior to molecular genetic testing in individuals with classic lissencephaly or SBH/double cortex syndrome associated with additional dysmorphic and/or extracerebral features.
- Sequence analysis of the *DCX* gene should be considered for any individual with frontally pronounced classic lissencephaly or SBH/double cortex syndrome.
- If sequence analysis in a female with SBH/double cortex syndrome does not reveal a mutation, deletion testing to detect a *DCX* intragenic or gene deletion should be performed.
- In rare males with SBH/double cortex syndrome, somatic mosaicism should be considered (see Interpretation of test results in section on Testing).
- If no *DCX* mutation is identified after completion of the above tests, further testing depending upon MRI findings could include sequence analysis and deletion testing for mutations in *LIS1*. (See Differential Diagnosis.)

Carrier testing for at-risk relatives requires prior identification of the disease-causing *DCX* mutation in the family.

Note: Carriers are heterozygotes for this X-linked disorder and may or may not have clinical findings of *DCX*-related conditions.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutation in the family.

Genetically Related (Allelic) Disorders

DCX germline mutations have not been associated with any other phenotypes.

Clinical Description

Natural History

Males. Males with *DCX*-related lissencephaly have severe mental retardation, cerebral palsy and epileptic seizures. Severity of symptoms usually (not always) correlates with the degree of the underlying brain malformation.

The rare male with subcortical band heterotopia (SBH)/double cortex syndrome has findings similar to those of females with SBH/double cortex syndrome [D'Agostino et al 2002, Poolos et al 2002, Aigner et al 2003].

Females. The SBH/double cortex syndrome phenotype in heterozygous females is less pronounced than the classic lissencephaly phenotype in males [des Portes et al 1998, Gleeson et al 1998]. The phenotype of SBH/double cortex syndrome varies from complete absence of symptoms to severe mental retardation and epileptic seizures [Barkovich et al 1994, Matsumoto et al 2001, Guerrini & Filippi 2005, Mei et al 2007]. Age at onset of epilepsy varies. Seizures are usually focal.

The severity of epilepsy and mental retardation in SBH/double cortex syndrome correlates with the extent and thickness of the subcortical band. In cases with focal SBH the phenotype can be nearly normal without mental retardation and epilepsy [Pilz et al 1999].

Learning disabilities and/or behavioral problems may be observed.

Somatic mosaicism. Somatic mosaicism for *DCX* mutations has been reported in several females and in males with milder disease (e.g., SBH/double cortex syndrome) [Demelas et al 2001, D'Agostino et al 2002, Poolos et al 2002, Aigner et al 2003].

Pathophysiology. In hemizygous males all neurons express the mutated allele and are disturbed in their migratory properties leading to smoothened and disorganized cortex resulting in classic lissencephaly.

In females heterozygous for a *DCX* mutation inactivation of one of the two X-chromosomes in neural/somatic cells is thought to result in two neuronal populations: (1) cells expressing the wild type allele that form the normal cortex; (2) cells expressing the mutant allele that accumulate in the white matter between the cortex and lateral ventricles as a heterotopic band of neurons.

Genotype-Phenotype Correlations

In a study of 39 unrelated individuals/families with SBH/double cortex syndrome and *DCX* mutations, Matsumoto et al (2001) reported a weak association between type and location of *DCX* mutation and phenotype. In this report, nonsense/truncating mutations were exclusively observed in simplex cases (i.e., a single occurrence in a family). Furthermore, nonsense/truncating mutations were more frequently associated with generalized subcortical bands than missense mutations, which were more common in individuals with SBH/double cortex syndrome with frontal band heterotopia only [Matsumoto et al 2001, Leventer 2005]. This finding is supported by Gleeson et al (1999), who reported only missense mutations in familial cases. In contrast, Aigner et al (2003) reported the presence of nonsense mutations in familial cases; however, somatic mosaicism was present in some of the families studied.

As in all X-linked disorders, X-chromosome inactivation makes phenotype-genotype correlations in females difficult.

Penetrance

Penetrance is greater than 90%; however, heterozygous females with missense and nonsense mutations may have no obvious brain malformation or seizures [Aigner et al 2003, Guerrini et al 2003].

Nomenclature

Lissencephaly type 1 is also called classic lissencephaly. Lissencephaly type 2 is also called cobblestone lissencephaly.

To emphasize its X-linked inheritance, *DCX*-related lissencephaly and SBH/double cortex syndrome have variably been termed and abbreviated:

- X-linked lissencephaly (XLIS)
- Lissencephaly, X-linked (LISX)
- Isolated lissencephaly, X-linked (ILSX)
- Subcortical laminar heterotopia, X-linked (SCLH)
- Subcortical band heterotopia, X-linked (SBHX)

Prevalence

A Dutch study reported a prevalence of 1:85,000 for lissencephaly type 1 [de Rijk-van Andel et al 1991]. However, the study presumably included individuals with non-*DCX*-related lissencephaly.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

***LIS1*-associated disorders.** Mutations in *DCX* together with mutations in the *LIS1* gene are the major genetic cause of nonsyndromic classic lissencephaly in males and of SBH/double cortex syndrome in females [Kato & Dobyns 2003]. *LIS1*-associated lissencephaly is more prominent in the posterior regions of the brain, showing a posterior to anterior (P>A) gradient. In contrast, *DCX*-associated lissencephaly presents with an A>P gradient. The following are *LIS1*-associated disorders:

- **Miller-Dieker syndrome** (MDS), the syndrome most frequently associated with classic lissencephaly, is caused by a microdeletion of chromosome region 17p13.3 that includes the *LIS1* gene, the modifying gene 14-3-3-ε, and additional genes [Cardoso et al 2003]. The diagnosis is established by FISH analysis using a *LIS1*-specific probe (PAC95H6), or more recently by MLPA.

  Miller-Dieker syndrome is characterized by distinctive facial features (i.e., prominent forehead, bitemporal hollowing, short nose with upturned tip and anteverted nostrils, protuberant upper lip with thin vermillion border) and severe lissencephaly type 1, which is classified as grade 1-2 according to the classic lissencephaly classification scheme of Dobyns et al (1999). Cardiac malformations and omphalocele can also be seen.

- ***LIS1*-associated isolated lissencephaly sequence (ILS),** in which classic lissencephaly (lissencephaly type 1) is associated with microdeletions of the entire *LIS1* gene, microdeletions within the gene, or intragenic mutations, is the most frequently observed form of isolated lissencephaly and is usually grade 2-4.

- ***LIS1*-associated subcortical band heterotopia (SBH)/double cortex syndrome** can result from germline or somatic intragenic *LIS1* mutations [Lo Nigro et al 1997, Pilz et al 1999, Sicca et al 2003, Uyanik et al 2007].

X-linked lissencephaly with ambiguous genitalia (XLAG). X-linked lissencephaly can also result from loss-of-function mutations in the *ARX* gene associated with XLAG [Kitamura et al 2002], the most severe end of the spectrum of *ARX*-related disorders [Uyanik et al 2003, Kato et al 2004]. Hemizygous males have agenesis of the corpus callosum and a specific form of lissencephaly with an intermediate thickening of the cortex, showing more pachygyria than agyria (lissencephaly grade 3-4) with a P>A gradient rather than A>P, as seen in *DCX*-related lissencephaly [Kato et al 2004]. The genital abnormalities in individuals with a 46,XY karyotype range from micropenis and cryptorchidism to ambiguous to nearly normal female external genitalia. Other findings of XLAG include refractory seizures usually beginning within hours after birth, abnormal body temperature regulation with a tendency for hypothermia, and diarrhea.

***RELN*-associated lissencephaly.** Hong et al (2000) reported mutations of the *RELN* gene, encoding reelin, in two consanguineous families with autosomal recessive lissencephaly with cerebellar hypoplasia. Affected individuals had pronounced frontal pachygyria, marked brain stem and cerebellar hypoplasia, and lymphedema of the hands.

Lissencephaly type 2 (cobblestone lissencephaly) comprises a group of autosomal recessive syndromic disorders associated with congenital muscular dystrophy and eye malformations (anterior chamber malformation, cataract, coloboma, retinal detachment, persistent hyperplastic primary vitreous). Walker-Warburg syndrome (WWS), muscle-eye-brain (MEB) disease, and Fukuyama congenital muscular dystrophy (FCMD) are the most common forms. (See Congenital Muscular Dystrophy Overview.) The lissencephalic cortex has areas with pachygyria and areas with polymicrogyria, giving a cobblestone-like appearance that led to the name "cobblestone lissencephaly."

The shared underlying molecular defect in the lissencephaly type 2 disorders is disturbed O-gylcosylation (O-mannosylation) leading to hypogylcosylatedα-dystroglycan, which can be diagnosed by α-dystroglycan staining of a skeletal muscle biopsy [van Reeuwijk et al 2005]. The genes associated with these disorders:

- *POMT1*, encoding protein O-mannosyltransferase 1
- *POMT2*, encoding protein O-mannosyl-transferase 2
- *POMGNT1*, encoding protein O-linked-mannose beta-1,2-N-acetylglucosaminyltransferase 1
- *FCMD*, encoding fukutin
- *FKRP*, encoding fukutin-related protein
- *LARGE*, encoding glycosyltransferase-like protein LARGE1

Microlissencephaly is characterized by extreme microcephaly at birth with thickened cortex and broadened gyration, whereas (extreme) microcephaly at birth is not observed in *DCX*-related disorders. It should be differentiated from microcephalies with simplified gyration (MSG) [Dobyns & Barkovich 1999].

Polymicrogyria (PMG) is characterized by a small and increased number of gyri of the cortex. (See Polymicrogyria Overview.) MRI is required to establish the diagnosis because ultrasound examination and CT scan are often unable to distinguish polymicrogyria from pachygyria. Different forms, distinguished by cortical pattern, include perisylvian PMG, bilateral frontal

PMG, bilateral frontoparietal PMG, bilateral posterior PMG, parasagittal parietooccipital PMG, and bilateral generalized PMG [Chang et al 2004]. Non-genetic factors leading to PMG such as intrauterine infections (e.g., cytomegalovirus) have been postulated. Familial occurrence supports the notion that genetic factors may cause PMG. Up to now three different loci are associated with different forms of PMG. For instance, in individuals with bilateral frontoparietal polymicrogyria (BFFP) mutations in the *GPR56* gene have been identified [Piao et al 2004].

Periventricular nodular heterotopia (PVNH). Although the MRI findings are quite distinct, SBH/double cortex syndrome is sometimes confused with periventricular nodular heterotopia, the accumulation of nodules of grey matter along the walls of both lateral ventricles. See X-Linked Periventricular Heterotopia.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with a *DCX*-related disorder, the following evaluations are recommended:

- Neurologic evaluation, including EEG and brain MRI
- Developmental assessment including assessment of motor skills, cognition, and speech
- Ophthalmologic evaluation
- Feeding and swallowing assessment in individuals lacking head control or the ability to sit without support

Treatment of Manifestations

Epileptic seizures require antiepileptic drugs (AEDs). Individual treatment strategies should be developed depending upon the type and frequency of seizures, EEG results, and responsiveness.

In addition, appropriate management can prolong survival and improve quality of life for individuals with lissencephaly type 1.

- Feeding problems in newborns may require special strategies to deal with weak or uncoordinated sucking.
- Physical therapy helps promote mobility and prevent contractures. Special adaptive chairs or positioners may be required.
- Occupational therapy may help improve fine motor skills and oral motor control.
- A full range of educational training and enrichment programs should be available.

Surveillance

The following are appropriate:

- Monitoring of seizure activity by regular neurologic examination and EEG
- In the event of new neurologic findings or neurologic deterioration, evaluation for seizures
- Measurement of height, weight, and head circumference as a part of health maintenance evaluations

- Monitoring of orthopedic complications including foot deformity and scoliosis

Testing 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 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.

Other

Callosotomy (surgical disconnection of the cerebral hemispheres by cutting through the corpus callosum) has improved drop attacks in a few patients.

Surgery for focal seizures yields poor results [Guerrini & Filippi 2005].

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

DCX-related disorders are inherited in an X-linked manner.

Risk to Family Members — Male Proband with Lissencephaly

Parents of a proband

- The father of an affected male will not have the disease.
- In a family with more than one affected individual, the mother of an affected male is an obligate carrier of the mutation.
- Individuals diagnosed with *DCX*-related lissencephaly may either have inherited the *DCX* mutation from their mother or have the disorder as the result of a new gene mutation. Currently the number of evaluated proband/parent pairs is too small to give a valid estimation of the proportion of cases caused by *de novo* mutations.
- Preliminary data suggest that as many as 15% of unaffected mothers of children with a *DCX* mutation may have somatic mosaicism or germline mosaicism [Gleeson et al 2000].

- Recommendations for evaluation of the mother of a proband with an apparent *de novo* mutation include the following:
  - Neurologic/clinical examination
  - Molecular genetic testing if the *DCX* mutation has been identified in the male proband
- If molecular genetic testing is not informative or if such testing is not possible (e.g., DNA from the proband is not available), cranial MRI of the mother can be helpful because some carrier females with subcortical band heterotopia (SBH)/double cortex syndrome can be asymptomatic. However, it is important to note that asymptomatic carrier females without obvious structural changes of the brain have been reported [Demelas et al 2001, Aigner et al 2003].

Sibs of a proband

- The risk to sibs depends upon the genetic status of the mother.
- If the proband's mother has a *DCX* mutation, the chance of transmitting the *DCX* mutation in each pregnancy is 50%.
  - Male sibs who inherit the mutation will be affected with *DCX*-related lissencephaly.
  - Female sibs who inherit the mutation will be carriers and will be at risk of developing the variable phenotype associated with SBH.
- If the *DCX* mutation identified in the proband cannot be detected in the DNA extracted from the mother's leukocytes, the risk to sibs of the proband is about 5% because of the possibility of germline mosaicism in the mother [Gleeson et al 2000, Guerrini & Filippi 2005].

Offspring of a proband. Affected males are usually severely affected and do not reproduce; to date, no instances of offspring have been reported.

Risk to Family Members — Female Proband with SBH/Double Cortex Syndrome

Parents of a proband

- Individuals diagnosed with *DCX*-related SBH/double cortex syndrome may either have inherited the *DCX* mutation from their mother or have the disorder as the result of a new gene mutation. Currently the number of evaluated proband/parent pairs is too small to give a valid estimation of the proportion of cases caused by *de novo* mutations.
- Furthermore, preliminary data suggest that about 15% of unaffected mothers of children with *DCX* mutation may have somatic mosaicism or germline mosaicism [Gleeson et al 2000].
- Recommendations for the evaluation of mother of a proband with an apparent *de novo* mutation include the following:
  - Neurologic/clinical examination
  - Molecular genetic testing if the *DCX* mutation has been identified in the proband
- If molecular genetic testing is not informative or if such testing is not possible (e.g., DNA from the proband is not available), cranial MRI of the mother can be helpful because some carrier females with SBH/double cortex syndrome can be

asymptomatic. However, it is important to note that asymptomatic carrier females without obvious structural changes of the brain have been reported [Demelas et al 2001, Aigner et al 2003].

Sibs of a proband

- The risk to sibs depends upon the genetic status of the mother.
- If the proband's mother has a *DCX* mutation, the chance of transmitting the *DCX* mutation in each pregnancy is 50%.
  - Male sibs who inherit the mutation will be affected with *DCX*-related lissencephaly.
  - Female sibs who inherit the mutation will be carriers and at risk of developing the variable phenotype associated with SBH/double cortex syndrome.
- If the *DCX* mutation identified in the proband cannot be detected in the DNA extracted from the mother's leukocytes, the risk to sibs of the proband is about 5% because of the possibility of germline mosaicism in one of the parents [Gleeson et al 2000, Guerrini & Filippi 2005].

Offspring of a proband. Each offspring of a female with a *DCX* mutation has a 50% risk of inheriting the mutation. Males who inherit the mutation will be affected with *DCX*-related lissencephaly; females who inherit the mutation will be carriers and at risk of developing the variable phenotype associated with SBH/double cortex syndrome.

Carrier Detection

Carrier testing for at-risk family members is available on a clinical basis once the mutations have been identified in the family.

Related Genetic Counseling Issues

Risks to family members of individuals with mild disease forms

- *DCX* germline mutations have been described in individuals with less severe forms of the disease, e.g., SBH in males and focal SBH in females [Pilz et al 1999].
  - Recurrence risks to sibs and offspring of the proband are similar to those for the severe disease forms.
  - Although the disease course of affected sibs and offspring would also be expected to be less severe, the current experience is too limited to allow a certain prediction.
- Several females and males with less severe forms of the disease resulting from somatic mosaicism for *DCX* mutations, e.g., SBH/double cortex syndrome in males, have been reported [Demelas et al 2001, D'Agostino et al 2002, Poolos et al 2002, Aigner et al 2003].
  - The recurrence risk for sibs of these probands is negligible.
  - The risk to the offspring of these probands depends on the level of mosaicism in the germ cells.

X-chromosome inactivation. As in all X-linked disorders, X-chromosome inactivation makes phenotype-genotype correlations in females difficult.

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal 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 affected or at risk.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Molecular genetic testing. Prenatal testing for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. Some families may decide to undergo prenatal testing for male fetuses only; in these individuals chromosome analysis of fetal cells should be offered prior to molecular testing. The disease-causing allele in the family member must be identified before prenatal testing can be performed. Accurate prediction of the expected phenotype in a female diagnosed prenatally to have a *DCX* mutation is not possible.

Fetal ultrasonography/MRI. During fetal development, first gyri appear around the 20th week of gestation and a reduced gyration pattern when compared to postnatal images remains physiologic until late gestation. Therefore, lissencephaly cannot be detected by level II ultrasound examination. In addition, SBH is not detectable. Some instances of MRI/ultrasound examination detecting SBH or X-linked lissencephaly at later stages of gestation have been reported [Ghai et al 2006].

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of DCX-Related Disorders

Gene Symbol	Chromosomal Locus	Protein Name
DCX	Xq22.3-q23	Neuronal migration protein doublecortin

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for DCX-Related Disorders

300067	LISSENCEPHALY, X-LINKED
300121	DOUBLECORTIN; DCX

Table C. Genomic Databases for DCX-Related Disorders

Gene Symbol	Entrez Gene	HGMD
DCX	1641 (MIM No. 300121)	DCX

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

The *DCX* gene shares homology with a group of genes that have a conserved doublecortin (DC) domain comprising two tandemly repeated 80-amino acid regions (pep1 and pep2) [Sapir et al 2000, Taylor et al 2000]. This gene family is composed of eleven paralogs in human and in mouse and includes genes like *RP1* (OMIM 603937), associated with a form of retinitis pigmentosa, and *DCDC2* (OMIM 605755), associated with dyslexia [Reiner et al 2006].

Normal allelic variants: The *DCX* gene spans 118 kb of genomic DNA and comprises nine exons; exons 1-3 are untranslated.

Pathologic allelic variants: Disease-causing alleles include missense and nonsense mutations, frameshifts, intragenic and gene deletions, small deletions, insertions, or single-base changes. A majority of missense mutations occur in the conserved tandem repeat region in the DC domain [Gleeson et al 1999, Sapir et al 2000].

Normal gene product: Neuronal migration protein doublecortin (DCX) is a microtubule-binding protein containing two in-tandem-organized microtubule-binding domains, in the so-called DCX domain, not previously described in other microtubule-associated proteins (MAPs). Microtubules constitute a central element of the cytoskeleton and as such play a crucial role in many cellular processes such as cell division, cell migration, and maintenance of cellular morphology. In vitro, DCX can promote microtubule polymerization and stabilization of the microtubules. Therefore, DCX is thought to promote elongation and stabilization of the microtubule network within the leading process of migrating neuroblasts. DCX could also be involved in the somal translocation occurring during neuroblast migration and influence as well the course of neuroblast proliferation.

DCX is a phosphoprotein that can be a substrate for several protein kinases, such as JNK, PKA, MARK, and Cdk5. Phosphorylation of DCX alters its interaction with microtubules and thereby possibly its function. The impact of DCX phosphorylation on its reported interaction with other proteins, such as LIS1, neurabin II, or clathrin-associated protein µ1A, remains to be investigated.

Abnormal gene product: Abnormal DCX products may affect proper microtubule formation and perturb the mitotic machinery, although not all abnormal products appear to do so to the same extent [Sapir et al 2000, Couillard-Despres et al 2004]. The effect of *DCX* mutations on protein function is therefore not yet fully understood.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

The Lissencephaly Network, Inc (Canada)
1549 Regent Street
Regina S4N 1S1
Canada
Phone: 306-569-0146
Fax: 306-522-1153
Email: dbloor@cableregina.com
www.lissencephaly.org

The Lissencephaly Network, Inc (USA)
10408 Bitterroot Court
Fort Wayne IN 46804
Phone: 260-432-4310
Fax: 260-432-4310
Email: lissnet@lissencephaly.org
www.lissencephaly.org

American Epilepsy Society
342 North Main Street
West Hartford CT 06117-2507
Phone: 860-586-7505
Fax: 860-586-7550
Email: info@aesnet.org
www.aesnet.org

Epilepsy Foundation
8301 Professional Place
East Landover, MD 20785-2238
Phone: 800-EFA-1000 (800-332-1000); 301-459-3700
Fax: 301-577-4941
Email: webmaster@efa.org
www.efa.org

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Suggested Readings

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Chapter Notes

Author Notes

www.humangenetik-regensburg.de

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