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CHD2-Related Neurodevelopmental Disorders

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Summary

Clinical characteristics

CHD2-related neurodevelopmental disorders are characterized by early-onset epileptic encephalopathy (i.e., refractory seizures and cognitive slowing or regression associated with frequent ongoing epileptiform activity). Seizure onset is typically between ages six months and four years. Seizure types typically include drop attacks, myoclonus, and rapid onset of multiple seizure types associated with generalized spike-wave on EEG, atonic-myoclonic-absence seizures, and clinical photosensitivity. Intellectual disability and/or autism spectrum disorders are common.

Diagnosis/testing

The diagnosis of a *CHD2*-related neurodevelopmental disorder is established in a proband with suggestive findings and a heterozygous pathogenic variant in *CHD2* identified by molecular genetic testing.

Management

Treatment of manifestations: Seizures should be managed by an experienced pediatric neurologist. At this time, no specific guidelines regarding choice of specific anti-seizure medications exist, as the best regimen for *CHD2*-related neurodevelopmental disorders is not yet established. Most Individuals remain refractory to treatment and require multiple anti-seizure medications. Support services for those with developmental delay, intellectual disability, and/or associated psychiatric/behavioral disorders.

Surveillance: At each visit assess for new seizures or change in seizures; evaluate developmental progress and educational needs; behavioral assessment for anxiety, attention, and aggressive or self-injurious behavior; assess family need for social work support and care coordination.

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Agents/circumstances to avoid: Because clinical photosensitivity may result in injuries due to the consequences of induced seizures, it is recommended that stimuli that may provoke seizures (e.g., intensely flickering lights) be avoided.

Genetic counseling

CHD2-related neurodevelopmental disorders are autosomal dominant disorders typically caused by a *de novo* pathogenic variant. If the *CHD2* pathogenic variant identified in the proband is not identified in either parent, the risk to sibs is low but greater than that of the general population because of the possibility of parental germline mosaicism. Once the *CHD2* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

CHD2-related neurodevelopmental disorders **should be suspected** in individuals with the following:

- Early-onset developmental and epileptic encephalopathy (i.e., refractory seizures and cognitive slowing or regression associated with frequent ongoing epileptiform activity [Scheffer et al 2017]), particularly those with:
  - Seizure onset between ages six months and four years
  - Drop attacks and rapid onset of multiple seizure types associated with generalized spike-wave on EEG
  - Atonic-myoclonic-absence seizures (See Clinical Description.)
  - Clinical photosensitivity

  Note: Photic stimulation during an EEG may be a helpful diagnostic modality (even though not all individuals with a *CHD2*-related neurodevelopmental disorder and clinical photosensitivity show an EEG response to photic stimulation). However, the possible increased risk for photic-induced seizures in individuals with this disorder should be taken into account when obtaining an EEG with photic stimulation.
- Intellectual disability and/or autism spectrum disorders, particularly when epilepsy is also present

Establishing the Diagnosis

The diagnosis of a ***CHD2*-related neurodevelopmental disorder is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *CHD2* identified by molecular genetic testing (see Table 1).

Note: Per ACMG variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) or **genomic testing** (chromosomal microarray analysis [CMA] or comprehensive genomic sequencing).

Gene-targeted testing requires the clinician to determine which gene(s) are likely involved, whereas genomic testing may not. Because the phenotypes of many genetic epileptic encephalopathies overlap, most children with *CHD2*-related neurodevelopmental disorder with epilepsy are diagnosed by the following recommended testing (a multigene panel or CMA) or testing to be considered (comprehensive genomic sequencing).

Recommended Testing

An epilepsy or intellectual disability multigene panel that includes *CHD2* 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.

Chromosome microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *CHD2*) that cannot be detected by sequence analysis.

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

Testing to Consider

Comprehensive genomic testing does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used and yields results similar to an intellectual disability multigene panel with the additional advantage that exome sequencing includes genes recently identified as causing intellectual disability whereas some multigene panels may not.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Resolution of variants of uncertain significance (VUS). Many disorders that perturb regulators of epigenetic processes result in a very specific DNA methylation pattern that is common to all affected individuals with pathogenic variants in that gene [Aref-Eshghi et al 2020]. Identification of an "episignature" characteristic of *CHD2*-related neurodevelopmental disorders can be used to resolve VUS in *CHD2*.

Table 1. Molecular Genetic Testing Used in *CHD2*-Related Neurodevelopmental Disorders

Gene [1]	Method	Proportion of Probands with a *CHD2* Pathogenic Variant [2] Detectable by Method
CHD2	Sequence analysis [3]	129/139 (93%) [4]
	CMA [5]	10/139 (7%) [6]
	Gene-targeted deletion/duplication analysis [7]	Unknown [8]

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. Data derived from author review of variants reported in the literature, large-scale cohort exome studies, and data from genetic testing companies [Author, personal communication]
5. Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *CHD2*) that cannot be detected by sequence analysis. The ability to determine the size of the deletion/duplication depends on the type of microarray used and the density of probes in the 15q26 region. CMA designs in current clinical use target the 15q26 region.
6. Individuals with features of *CHD2*-related disorders who have deletions encompassing *CHD2* (with or without deletion of *RGMA)* have been reported [Dhamija et al 2011, Capelli et al 2012, Chénier et al 2014, Courage et al 2014, Pinto et al 2014].
7. 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.
8. No intragenic *CHD2* multiexon deletions or duplications have been reported.

Clinical Characteristics

Clinical Description

To date 139 individuals with a *CHD2*-related neurodevelopmental disorder have been reported [Carvill et al 2013, Suls et al 2013, O'Roak et al 2014, Deciphering Developmental Disorders Study Group 2015, Thomas et al 2015, Heyne et al 2018, Ko et al 2018, Truty et al 2019, Chen et al 2020].

A systematic single study of individuals with *CHD2*-related neurodevelopmental disorders has not yet been published. To date, epilepsy is a consistent feature across the phenotypic spectrum of *CHD2*-related neurodevelopmental disorders and most individuals reported have presented with developmental and epileptic encephalopathy. However, as genetic testing becomes more widely available and less targeted (i.e., more genes are included in multigene panels) the phenotypic spectrum is evolving.

The most common clinical features of these individuals are described below.

Table 2. Select Features of *CHD2*-Related Neurodevelopmental Disorders

Feature	% of Persons w/Feature
Seizures	96% (108/113)
Developmental delay / Intellectual disability	95% (81/85)
Autism spectrum disorder	56% (39/70)

Seizures. The age of onset ranges from six months to 12 years; median seizure onset is 30 months (2.5 years).

Seizure onset, which is explosive in many children, is characterized by multiple daily myoclonic and absence seizures.

Although *CHD2*-related epilepsy has been compared to Dravet syndrome in at least one study, febrile seizures, which are characteristic of Dravet syndrome, have only been reported in 11 individuals with *CHD2* variants [Carvill et al 2013, Suls et al 2013, Thomas et al 2015, Petersen et al 2018, Chen et al 2020].

A classic seizure type termed "atonic-myoclonic-absence seizure," a progressive seizure pattern comprising an abrupt head nod and atonia followed by a myoclonic absence phase and progression to a "ratchet-like" tonic abduction of the upper limbs, was observed in video footage of three children aged two to seven years. Seizures were brief (2-8 seconds) and awareness rapidly returned [Thomas et al 2015]. Many of the components of this seizure pattern have been described in other affected individuals; thus, future video monitoring and video EEG monitoring will be important in determining if this seizure pattern is a hallmark of *CHD2*-related neurodevelopmental disorders.

Clinical photosensitivity (i.e., seizures triggered by photic stimulation) is a distinguishing feature reported in a total of 80% (20/25) of individuals where it was specifically queried. A small number of individuals could self-induce seizures, suggesting an unusually strong degree of photosensitivity. In contrast, a photoparoxysmal response (an epileptiform EEG response to intermittent photic stimulation) has only been recorded in two affected individuals [Lund et al 2014, Thomas et al 2015, Trivisano et al 2015]. Of note, some individuals with a *CHD2* pathogenic variant have a diagnosis of eyelid myoclonia with absences, a particularly photosensitive epilepsy syndrome [Galizia et al 2015].

Seizures are often refractory to currently available anti-seizure medications (ASMs). Only 13 of 33 affected individuals have been reported to be seizure free on ASM treatment for two to five years (see Management) [Thomas et al 2015, Chen et al 2020].

Psychomotor development prior to seizures can be delayed (n=20) but is often not reported and this feature requires further evaluation. When specifically reported in the literature, intellectual disability ranges from mild (in 7/15 individuals) to severe (8/15 individuals).

Behavior and neuropsychiatric phenotypes. Autism spectrum disorder or autistic features have been reported in 56% (39/70) of individuals. Challenging behaviors, most often aggression, have been described, with three requiring medical treatment with risperidone [Thomas et al 2015]. Attention-deficit/hyperactivity disorder and psychosis have also been reported in a small number of individuals. There is also a single individual diagnosed with schizophrenia [Poisson et al 2020]. It is currently unclear to what extent a specific behavior phenotype is part of the phenotypic spectrum and this requires further investigation for management.

Neuroimaging. In some affected individuals MRI has shown atrophy that tends to be more posterior and can be progressive. In those with ataxia, cerebellar atrophy was more pronounced [Suls et al 2013, Thomas et al 2015].

Genotype-Phenotype Correlations

No genotype-phenotype correlation has been observed between the location/nature of the pathogenic variant and clinical outcome.

Penetrance

Penetrance for *CHD2*-related neurodevelopmental disorders is unknown but assumed to be complete. There are a small number of instances where the *CHD2* variant is inherited from a presumably unaffected parent or a parent with a milder phenotype [Petersen et al 2018, Chen et al 2020]. In such instances it is important to evaluate the parent for somatic mosaicism.

Prevalence

The prevalence of *CHD2*-related neurodevelopmental disorders is not known.

A *de novo CHD2* pathogenic variant was present in an estimated 1% of individuals included in cohorts with various developmental and epileptic encephalopathies [Allen et al 2013, Carvill et al 2013]. In another report of nearly 10,000 individuals referred for genetic testing using a comprehensive epilepsy panel, 0.25% of individuals has a *CHD2* pathogenic variant identified [Truty et al 2019]. In individuals with a neurodevelopmental disorder that included epilepsy, *CHD2* was the fourth most highly implicated gene [Heyne et al 2018].

In each of four studies of exome-based sequencing of hundreds to thousands of individuals with neurodevelopmental disorders including intellectual disability and autism spectrum disorders, one to three individuals with a *de novo CHD2* pathogenic variant were identified [Neale et al 2012, Rauch et al 2012, O'Roak et al 2014, Deciphering Developmental Disorders Study Group 2015].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *CHD2*.

Differential Diagnosis

Phenotypic features associated with *CHD2* pathogenic variants are not sufficient to diagnose *CHD2*-related neurodevelopmental disorders.

For children with a phenotype consistent with early-onset epileptic encephalopathy, all genes known to be associated with epileptic encephalopathy (~90 have been identified; see OMIM Phenotypic Series) should be included in the differential diagnosis.

For children with intellectual disability and epilepsy, all genes associated with juvenile myoclonic epilepsy (see OMIM Phenotypic Series), idiopathic generalized epilepsy (see OMIM Phenotypic Series), and generalized epilepsy with febrile seizures plus (see OMIM Phenotypic Series) should be included in the differential diagnosis.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with a *CHD2*-related neurodevelopmental disorder, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *CHD2*-Related Neurodevelopmental Disorders

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval	
	EEG	• To assess degree of epileptic encephalopathy • May lead to more focused use of ASMs
	MRI	• To differentiate genetic epilepsy from lesional epilepsy • May lead to intensified conservative treatment rather than presurgical work up
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric eval	For persons age >12 mos: screening for behavior concerns incl sleep disturbances, ADHD, anxiety, aggression, &/or traits suggestive of ASD

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *CHD2*-related neurodevelopmental disorders to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; ASMs = anti-seizure medications; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with *CHD2*-Related Neurodevelopmental Disorders

Manifestation/Concern	Treatment	Considerations/Other
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none have been demonstrated effective specifically for this disorder. [1, 2] • Education of parents/caregivers [3]
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	

ASMs = anti-seizure medications
1. Most individuals remain refractory to treatment and require multiple ASMs.
2. Although a ketogenic diet may be a treatment option, it was not effective in three affected individuals [Thomas et al 2015].
3. 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.

Developmental Delay / Intellectual Disability Management Issues

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

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

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

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

- IEP services:

- An IEP provides specially designed instruction and related services to children who qualify.
- IEP services will be reviewed annually to determine whether any changes are needed.
- Special education law requires that children participating in an IPE be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
- PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
- As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.

- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction. Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications. Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

Table 5. Recommended Surveillance for Individuals with *CHD2*-Related Neurodevelopmental Disorders

System/Concern	Evaluation	Frequency
Neurologic	Monitor those w/seizures as clinically indicated & assess for new-onset seizures.	At each visit
Development	Monitor developmental progress & educational needs.	
Psychiatric/ Behavioral	Assess behavior for anxiety, attention, & aggressive or self-injurious behavior.	
Family/ Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	

Agents/Circumstances to Avoid

Because clinical photosensitivity may result in injuries due to the consequences of induced seizures, the following are recommended:

- Avoid flickering lights that may provoke seizures.
- Advise affected individuals and families that exposure to intensely flickering lights may provoke seizures including eyelid myoclonias, absence seizures, and generalized tonic-clonic seizures. Of note, most televisions do not transmit in the frequency range that is particularly provocative.

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

CHD2-related neurodevelopmental disorders are autosomal dominant disorders typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- Almost all individuals diagnosed with a *CHD2*-related neurodevelopmental disorder have the disorder as the result of a *de novo* pathogenic variant.
- In rare families, individuals diagnosed with a *CHD2*-related neurodevelopmental disorder have the disorder as the result of a *CHD2* pathogenic variant inherited from a parent. For example:
  - A child with a severe presentation of *CHD2*-related neurodevelopmental disorder inherited a *CHD2* pathogenic variant from her heterozygous, less severely affected mother [Petersen et al 2018]. Her mother had seizures as a child (well controlled with anti-seizure medications) and neuropsychiatric features (including bipolar disorder, ADHD, language delays, and dyslexia) but no learning difficulties throughout childhood [Petersen et al 2018].
  - A child with epilepsy and myoclonic seizures inherited a splice variant from his apparently unaffected heterozygous father [Chen et al 2020].
- Molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent, the following 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 (or somatic and germline) mosaicism. Presumed parental germline mosaicism was reported in a family with unaffected parents and sib recurrence [Lebrun et al 2017]. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism.
- The family history of an individual diagnosed with a *CHD2*-related neurodevelopmental disorder may appear to be negative because of failure to recognize the disorder in family members. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

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 is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- If the proband has a known *CHD2* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism [Lebrun et al 2017].
- If the parents have not been tested for the *CHD2* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for a *CHD2*-related neurodevelopmental disorder because of the possibility of parental germline mosaicism [Lebrun et al 2017, Myers et al 2018].

Offspring of a proband. Each child of an individual with a *CHD2*-related neurodevelopmental disorder has a 50% chance of inheriting the *CHD2* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *CHD2* 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 and reproductive options) to young adults who are affected or at risk of having a child with a *CHD2*-related neurodevelopmental disorder.

Prenatal Testing and Preimplantation Genetic Testing

Once the *CHD2* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for a *CHD2*-related neurodevelopmental disorder 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.

- **Coalition to Cure CHD2**
  www.curechd2.org
- **American Epilepsy Society**
  www.aesnet.org
- **Autism Society**
  Phone: 800-328-8476
  Email: info@autism-society.org
  www.autismsociety.org
- **Canadian Epilepsy Alliance**
  Canada
  Phone: 1-866-EPILEPSY (1-866-374-5377)
  www.canadianepilepsyalliance.org
- **Citizens United for Research in Epilepsy (CURE)**
  www.cureepilepsy.org
- **Epilepsy Foundation**
  Phone: 301-459-3700
  Fax: 301-577-2684
  www.epilepsy.com
- **Simons Searchlight Registry**

Simons Searchlight aims to further the understanding of rare genetic neurodevelopmental disorders.

Phone: 855-329-5638

Fax: 570-214-7327

Email: coordinator@simonssearchlight.org

www.simonssearchlight.org

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. CHD2-Related Neurodevelopmental Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
CHD2	15q26.1	Chromodomain-helicase-DNA-binding protein 2	CHD2	CHD2

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 CHD2-Related Neurodevelopmental Disorders (View All in OMIM)

602119	CHROMODOMAIN HELICASE DNA-BINDING PROTEIN 2; CHD2
615369	DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY 94; DEE94

Molecular Pathogenesis

CHD2 encodes the chromodomain DNA helicase binding protein 2. CHD2 and additional members of this family of proteins are responsible for remodeling chromatin, which controls the three-dimensional architecture of the genome and gene expression. The protein consists of two chromodomains and a putative DNA binding domain; these domains are known or hypothesized to bind DNA [Marfella & Imbalzano 2007, Liu et al 2015]. The ATP-helicase and DEDX-helicase domain are known in other family members to remodel chromatin using the energy of ATP hydrolysis [Marfella & Imbalzano 2007, Bouazoune & Kingston 2012].

The overwhelming majority of *CHD2* pathogenic variants lead to either truncation of the protein or loss of gene expression by whole-gene deletion. The pathogenic missense variants cluster in the functional domains and likely impair the ability of CHD2 to either bind to DNA targets and/or remodel chromatin. Collectively this suggests that *CHD2*-related neurodevelopmental disorders result from haploinsufficiency of CHD2.

To date the majority of individuals with a *CHD2* pathogenic variant have a brain-restricted phenotype, suggesting a unique role for CHD2 in the human brain. The function of CHD2 in the human brain is not known. Complete CHD2 loss in a human stem cell model resulted in defects in the development of inhibitory interneurons and altered expression of genes important in neurotransmission [Meganathan et al 2017]. A heterozygous Chd2 loss mouse showed deficits in neuronal development including reduced number of both excitatory and inhibitory neurons and severe impairments in long-term memory. These animals did not exhibit seizures [Kim et al 2018].

Mechanism of disease causation. The majority of pathogenic variants lead to truncation of *CHD2*. The few reported *de novo* missense pathogenic variants occur in the highly conserved DNA-binding or helicase domains and likely hinder the ability of CHD2 to remodel chromatin. *CHD2* pathogenic variants are likely all loss of function, resulting in *CHD2*-related neurodevelopmental disorders due to haploinsufficiency of CHD2.

Chapter Notes

Author Notes

The Epilepsiome: A knowledge base for genes related to human epilepsies:
CHD2 – this is what you need to know in 2015

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