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CHD4 Neurodevelopmental Disorder

Synonyms: Sifrim-Hitz-Weiss Syndrome, SIHIWES

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Summary

Clinical characteristics

CHD4 neurodevelopmental disorder (*CHD4*-NDD) is associated with developmental delay, speech delay, and usually mild-to-moderate intellectual disability. Variability between individuals with *CHD4*-NDD is significant, and a few have normal intelligence. Other manifestations can include brain anomalies, heart defects, and skeletal abnormalities; less common features are hypogonadism in males, hearing impairment, and ophthalmic abnormalities. Most affected individuals have mild nonspecific dysmorphic facial features with or without macrocephaly.

Diagnosis/testing

The diagnosis of *CHD4*-NDD is established in a proband with suggestive findings and a heterozygous pathogenic variant in *CHD4* identified by molecular genetic testing.

Management

Treatment of manifestations: Developmental delay / intellectual disability, cervical spine instability and risk of spinal cord compression, refractive errors and strabismus, hearing impairment, congenital heart defects, behavioral issues, growth delay, hypogonadism in males, and renal anomalies are managed per standard care.

Surveillance: Follow up of the common manifestations at each clinic visit.

Agents/circumstances to avoid: Activities that involve rapid neck motion and/or possible trauma to the head and neck region (e.g., contact sports or thrill rides at amusement parks) because of the possible increased risk for cervical spine instability and spinal cord compression.

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Genetic counseling

CHD4-NDD is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant. If the *CHD4* pathogenic variant identified in the proband is not identified in either parent, the risk to sibs is low (~1%) but greater than that of the general population because of the possibility of parental germline mosaicism. Once the *CHD4* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

Formal diagnostic criteria for *CHD4* neurodevelopmental disorder (*CHD4*-NDD) have not been established.

Suggestive Findings

CHD4-NDD **should be considered** in individuals with the following clinical and brain MRI findings.

Clinical findings. Developmental delay or mild-to-moderate intellectual disability AND any of the following features presenting in infancy or childhood:

- Generalized hypotonia of infancy
- Macrocephaly or relative macrocephaly
- Congenital heart defects (septal defects, conotruncal anomalies, and valvular abnormalities)
- Skeletal and limb anomalies (vertebral fusion, carpal/tarsal coalition, syndactyly, polydactyly)
- Hypogonadism in males (cryptorchidism and/or microphallus)
- Ophthalmologic abnormalities (strabismus, hypermetropia, astigmatism)
- Hearing impairment (conductive and/or sensorineural)
- Moyamoya disease with congenital or infantile stroke

Brain MRI findings. Brain anomalies including the following (detected in 92% [22/24] of affected individuals):

- Mild-to-moderate ventriculomegaly (in 41%)
- Chiari 1 malformation (29%)
- Hydrocephalus requiring shunting (18%)
- Other. Thin corpus callosum and syringomyelia

Establishing the Diagnosis

The diagnosis of *CHD4*-NDD **is established** in a proband with suggestive findings and a heterozygous pathogenic variant in *CHD4* identified by molecular genetic testing (see Table 1).

Note: Identification of a heterozygous *CHD4* variant of uncertain significance does not establish or rule out the diagnosis of this disorder.

Molecular genetic testing in any child with developmental delay or an older individual with intellectual disability typically begins with **chromosomal microarray analysis** (CMA), which uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications that cannot be detected by sequence analysis.

If CMA is not diagnostic, the next step is typically either a multigene panel or exome sequencing. Note: Single-gene testing (sequence analysis of *CHD4*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **An intellectual disability (ID) multigene panel** that includes *CHD4* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition in a person with a

nondiagnostic CMA 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*. Of note, given the rarity of *CHD4*-NDD, some panels for intellectual disability may not include this gene. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

- **Comprehensive genomic testing** does not require the clinician to determine which gene is 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 ID, whereas some multigene panels may not. If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by exome sequencing. Note: To date such variants have not been identified as a cause of CHD4-NDD.

  Genome sequencing is also possible.

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

Table 1. Molecular Genetic Testing Used in *CHD4* Neurodevelopmental Disorder

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method [3]
CHD4	Sequence analysis [4]	100%
	Gene-targeted deletion/duplication analysis [5]	None

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. Sifrim et al [2016], Weiss et al [2016], Weiss et al [2020], and unpublished data
4. 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.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

CHD4 neurodevelopmental disorder (*CHD4*-NDD) is associated with developmental delay, speech delay, and usually mild-to-moderate intellectual disability. Variability among individuals with *CHD4*-NDD is significant, and some have normal intelligence. Other manifestations can include brain anomalies, heart defects, and skeletal abnormalities; less common features are hypogonadism in males, hearing impairment, and ophthalmic abnormalities. Most affected individuals have mild nonspecific dysmorphic facial features with or without macrocephaly.

To date, 33 individuals have been identified with a heterozygous *CHD4* pathogenic missense variant or in-frame insertion/deletion [Sifrim et al 2016, Weiss et al 2016, Weiss et al 2020, and unpublished data]. The following description of *CHD4*-NDD phenotypic features is based on these reports.

Table 2. Select Features of *CHD4* Neurodevelopmental Disorder

Feature	% of Persons with Feature	Comment
Speech delay	94% (29/31)	
Motor delay	91% (29/32)	
Intellectual disability	83% (19/23)	Mostly mild-to-moderate ID
Ophthalmologic abnormalities	74% (14/19)	
Congenital heart defect	72% (21/29)	
Hypotonia	71% (17/24)	
Hearing impairment	58% (11/19)	
Cryptorchidism	52% (11/21)	
Macrocephaly	46% (13/28)	>90th %ile
Skeletal/limb anomalies	42% (14/33)	
Hypogonadotropic hypogonadism	38% (8/21)	Reported in males only
Short stature	31% (9/29)	Some w/growth hormone deficiency
Hydrocephalus requiring shunting	18% (6/33)	

Developmental delay (DD) and intellectual disability (ID). The majority of individuals have developmental delay. Speech delay is common, but the majority communicate verbally using short sentences; absence of speech has not been reported. A cognitive assessment identified intellectual disability in the mild-to-moderate range in 82%; in four individuals IQ score was in the low normal or borderline range.

The average age of independent ambulation is 30 months. Three children achieved independent ambulation after age five years.

Other neurodevelopmental features include hypotonia during infancy and early childhood. While some infants have feeding difficulties, few require nasogastric tube feeding or gastrostomy.

Hydrocephalus requiring shunting has been associated with intellectual disability ranging from mild to moderate.

Behavioral or psychiatric problems are not a frequent finding. Autism spectrum disorder was reported in three individuals and attention-deficit disorder, impulsivity, and anxiety were reported in three.

Growth. The majority are born after an uneventful pregnancy with an average birth weight and head circumference. Some individuals develop macrocephaly; a few have microcephaly. Short stature is seen in 30%. Seven of 30 individuals had obesity at late childhood or adulthood. Growth hormone deficiency was reported in four individuals, all of whom were treated with growth hormone with an overall good response.

Congenital heart defects include septal defects, conotruncal anomalies, and valve anomalies. To date the following malformations (by frequency) have been reported: atrial septal defect, ventricular septal defect, pulmonary stenosis, patent ductus arteriosus, tetralogy of Fallot, mitral valve anomalies, Ebstein anomaly, and truncus arteriosus.

Skeletal and limb anomalies. The most common are hand or foot syndactyly, polydactyly, scoliosis (acquired), vertebral anomalies (mainly cervical fusions), and tarsal or carpal coalition. In those with cervical vertebral anomalies, the risk for cervical instability is increased.

Because some individuals with *CHD4*-NDD did not have a skeletal survey, the true frequency of bone fusions and other skeletal anomalies could be higher.

Hypogonadism is common in males. When performed, the hormonal profile was consistent with hypogonadotropic hypogonadism.

To date, there are no reports of hypogonadism or infertility in females; however, the majority of individuals reported to date are children.

Sensory impairment. Of those with hearing impairment, the majority of affected individuals have sensorineural hearing loss; a few have conductive or mixed hearing impairment. Recurrent otitis media is not common.

Significant vision impairment has not been reported, but ophthalmic anomalies (by frequency) include: strabismus, astigmatism, hypermetropia, glaucoma, small optic nerves, iris coloboma, and myopia.

Moyamoya disease. Of the three children who had a stroke after birth or during infancy, two were diagnosed with moyamoya disease. A link between *CHD4* variants and moyamoya disease has also been described by Pinard et al [2020].

Facial features. Mild nonspecific dysmorphic features observed in some individuals include widely spaced eyes, periorbital fullness, a short nose, and a square face.

Cancer risk. Cancer has not been reported in individuals with *CHD4*-NDD.

Prognosis. It is unknown whether life span in *CHD4*-NDD is abnormal. One individual is alive at age 30 years [Weiss et al 2020], demonstrating that survival into adulthood is possible. However, severe congenital abnormalities may shorten the life span. Since many adults with disabilities have not undergone advanced genetic testing, it is likely that adults with *CHD4*-NDD are underrecognized and underreported.

Genotype-Phenotype Correlations

The majority of *CHD4* variants are missense substitutions that fall in the ATPase / C terminal helicase domain (amino acids 724-1281). Data to date are insufficient to support genotype-phenotype correlations.

Penetrance

Because the vast majority of individuals with *CHD4*-NDD reported to date have *de novo* variants, it is currently thought the penetrance is close to 100%.

Prevalence

CHD4-NDD is rare. The authors are aware of approximately 50 affected individuals worldwide.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *CHD4*.

Differential Diagnosis

Because the phenotypic features associated with *CHD4* neurodevelopmental disorder are not sufficient to diagnose this condition, all disorders with intellectual disability without other distinctive findings should be considered in the differential diagnosis. See OMIM Autosomal Dominant, Autosomal Recessive, Nonsyndromic X-Linked, and Syndromic X-Linked Intellectual Developmental Disorder Phenotypic Series.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *CHD4* neurodevelopmental disorder (*CHD4*-NDD), 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 *CHD4* Neurodevelopmental Disorder

System/Concern	Evaluation	Comment
Constitutional	Measurement of weight, height, head circumference	Baseline assessment, given ↑ risk for hydrocephalus that may require shunting
Neurologic	Neurologic eval	Assess for: • Evidence of congenital or infantile stroke; • Signs of ↑ intracranial pressure / herniation / cord compression. Consider: • Brain & cervical spine MRI for detection of hydrocephalus / Chiari 1/ syringomyelia; • MRA for persons w/suspected stroke or infants undergoing brain imaging.
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric eval	Persons age >12 mos: if suspected, screen for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD
Musculoskeletal	Orthopedics / physical medicine & rehab / PT/OT eval	Assess: • For skeletal & limb anomalies; • Gross motor & fine motor skills; • Mobility, ADLs, & need for adaptive devices; • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills).
Spine	• Flexion-extension radiographs of lateral cervical spine • Flexion-extension MRI if instability & compression seen on radiographs or interpretation is limited (e.g., in young persons w/delayed ossification of cervical vertebral bodies)	Evaluate for cervical instability & risk of spinal cord compression.
Eyes	Ophthalmologic eval	To assess for refractive error, strabismus, glaucoma, & coloboma

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Hearing	Audiologic eval	To assess for conductive &/or sensorineural hearing loss
Cardiovascular	For congenital heart defects	Echocardiogram for detection of conotruncal & valve anomalies
Endocrine	Hypogonadism	Males: • Assess for cryptorchidism & microphallus. • Refer to endocrinologist & obtain FSH/LH & testosterone levels in 1st yr of life & in puberty. Females: consider endocrinology assessment during or after puberty.
	Growth hormone deficiency	All persons w/short stature: consider growth hormone testing.
Renal	Renal US exam	Assess for vesicoureteral reflux.
Genetic counseling	By genetics professionals [1]	To inform affected persons & families re nature, MOI, & implications of *CHD4*-NDD 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.	

ADHD = attention-deficit/hyperactivity disorder; ADL = activity of daily living; ASD = autism spectrum disorder; FSH = follicle-stimulating hormone; LH = luteinizing hormone; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; US = ultrasound

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

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with *CHD4* Neurodevelopmental Disorder

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Hydrocephalus / Chiari 1 malformation / Syringomyelia	Standard treatment(s) per neurosurgeon	
Cervical spine instability	Surgical management (C1-C2 fixation or other)	
Skeletal & limb anomalies	Orthopedics / physical medicine & rehab / PT/OT	
Refractive error &/or strabismus	Standard treatment(s) per ophthalmologist	
Hearing	Hearing aids may be helpful; per otolaryngologist.	Community hearing services through early intervention or school district if hearing loss warrants
Cardiac anomalies	Standard treatment per cardiologist/cardiac surgeon	
Endocrine	For cryptorchidism/microphallus: standard treatment per endocrinologist	
	For growth hormone deficiency: standard treatment per endocrinologist	No data exists re safety of growth hormone treatment in *CHD4*-NDD.

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	Consider involvement in adaptive sports or Special Olympics.

OT = occupational therapy; PT = physical therapy

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

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, antiparkinsonian medications, or orthopedic procedures.

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 *CHD4* Neurodevelopmental Disorder

System/Concern	Evaluation	Frequency
Neurologic	For infants & young children: monitor head circumference because of ↑ risk of hydrocephalus.	At each visit
	Consider brain MRI/MRA.	If new neurologic manifestations such as seizures & stroke
	Assess for new manifestations (e.g., changes in muscle tone, hemiparesis, pyramidal signs, seizures).	At each visit
Spine	Flexion-extension radiograph; flexion-extension MRI if instability & compression on radiographs or limited interpretation on radiographs	Per orthopedist based on clinical findings or planned surgery
Development	Monitor developmental progress & educational needs.	At each visit
Psychiatric/ Behavioral	Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior	Every 1-3 yrs
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	At each visit
	Orthopedist	As needed
Eyes	Ophthalmologic assessment	Every 1-3 yrs
Cardiovascular	Echocardiogram	Follow up as needed
Endocrine	Assessment for hypogonadism when indicated (See Table 4.)	At time puberty is expected
	Assessment for growth hormone deficiency when indicated (See Table 4.)	When indicated
Hearing	Hearing test	Every 1-3 yrs
Miscellaneous/ Other	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	At each visit

OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

Avoid activities that involve rapid neck motion and/or possible trauma to the head and neck region (e.g., contact sports or thrill rides at amusement parks) because of the possible increased risk for cervical spine instability.

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

CHD4 neurodevelopmental disorder (*CHD4*-NDD) is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- Almost all probands reported to date with *CHD4*-NDD have the disorder as a result of a *de novo CHD4* pathogenic variant.
- Presumed parent-to-child transmission was reported in one family in which the parent had features of *CHD4*-NDD; however, the presumed transmitting parent was not available for molecular genetic testing [Weiss et al 2020].
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the *CHD4* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the pathogenic variant most likely occurred *de novo* in the proband. Another possible explanation is that the proband inherited a pathogenic variant from a parent with germline mosaicism. Although theoretically possible, no instances of germline mosaicism have been reported to date.
- Theoretically, if the parent is the individual in whom the *CHD4* pathogenic variant first occurred, the parent may have somatic mosaicism for the variant and may be mildly/minimally affected.

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 has the *CHD4* pathogenic variant, the risk to the sibs of inheriting the variant is 50%.
- If the *CHD4* pathogenic variant found in the proband 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].

Offspring of a proband. Each child of an individual with *CHD4*-NDD has a 50% chance of inheriting the *CHD4* pathogenic variant.

Other family members. Given that almost all probands with *CHD4*-NDD reported to date have the disorder as a result of a *de novo CHD4* pathogenic variant, the risk to other family members is presumed to be low.

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 parents of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Risk to future pregnancies is presumed to be low as the proband most likely has a *de novo CHD4* pathogenic variant. There is, however, a recurrence risk (~1%) to sibs based on the theoretic possibility of parental germline mosaicism [Rahbari et al 2016]. Given this risk, prenatal and preimplantation genetic testing may be considered.

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.

- **American Association on Intellectual and Developmental Disabilities (AAIDD)**

  Phone: 202-387-1968

  Fax: 202-387-2193

  www.aaidd.org

- **CDC - Developmental Disabilities**

  Phone: 800-CDC-INFO

  Email: cdcinfo@cdc.gov

  Intellectual Disability

- **MedlinePlus**

  Intellectual Disability

- **Human Disease Genes Website Series - Registry**

  This website was created to share and collect information about the clinical features, management and research projects to gather more knowledge and provide better treatment of patients with mutations in the CHD4 gene.

  CHD4

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. CHD4 Neurodevelopmental Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
CHD4	12p13.31	Chromodomain-helicase-DNA-binding protein 4	CHD4	CHD4

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 CHD4 Neurodevelopmental Disorder (View All in OMIM)

603277	CHROMODOMAIN HELICASE DNA-BINDING PROTEIN 4; CHD4
617159	SIFRIM-HITZ-WEISS SYNDROME; SIHIWES

Molecular Pathogenesis

CHD4 encodes an ATP-dependent chromatin remodeler, a core component of the *nu*cleosome *r*emodeling and histone *d*eacetylation (NuRD) complex that is widely expressed and acts mainly, but not exclusively, as a

transcriptional repressor. It contains a histone deacetylase (HDAC1/2) and methyl-CpG binding domain protein (MBD2) which bind histone H3 and methylated DNA, respectively. The NuRD complex is involved in multiple processes including stem cell differentiation, embryonic development, cell cycle progression, and DNA damage repair.

Mechanism of disease causation. A dominant-negative mechanism is suspected but not proven. Most reported *CHD4* variants are missense variants or in-frame insertions/deletions. In addition, a few individuals with *de novo* loss-of-function *CHD4* variants have been reported; however, the clinical significance of these variants is unclear due to lack of functional studies or a strong phenotypic similarity.

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Chapter Notes

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- 3 September 2020 (bp) Review posted live
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