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CHD8-Related Neurodevelopmental Disorder with Overgrowth

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Summary

Clinical characteristics

CHD8-related neurodevelopmental disorder with overgrowth (*CHD8*-NDD) is characterized by generalized overgrowth, developmental delay / intellectual disability (DD/ID), autism spectrum disorder (ASD), neuropsychiatric issues, neurologic problems, sleep disturbance, and gastrointestinal issues The most common findings are the development of macrocephaly (most often during infancy) and tall stature (most typically during puberty), which is often accompanied by ASD and/or DD/ID. Most, if not all, affected individuals have some degree of DD, most commonly speech and motor delays. When present, ID is most often in the mild-to-moderate range. Sleep disturbance is characterized by difficulty with both initiation (delayed sleep onset) and maintenance (frequent night awakenings) of sleep. The most common gastrointestinal issue is constipation with or without periods of diarrhea. Less common features are hypotonia (about 30% of affected individuals), seizures (10%-15%), dystonia (rare), and Chiari I malformation (rare).

Diagnosis/testing

The diagnosis of *CHD8*-NDD is established in a proband by identification of a heterozygous pathogenic (or likely pathogenic) variant in *CHD8* by molecular genetic testing.

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Management

Treatment of manifestations: Sleep disturbance may be addressed through behavioral interventions and/or pharmacologic treatment; if Chiari I malformation is present, surgical treatment may be required; standard treatment for DD/ID, seizures, and bowel dysfunction.

Surveillance: At each visit: measurement of growth parameters (including head circumference); assessment of developmental progress and educational needs; monitor for signs and symptoms of anxiety, attention-deficit/hyperactivity disorder, and aggressive or self-injurious behavior; assess for new manifestations, such as seizures, changes in tone, and signs/symptoms of cerebrospinal fluid obstruction and/or spinal cord dysfunction; screen for signs/symptoms of sleep disturbance; monitor for constipation. Consider serial imaging for asymptomatic or minimally symptomatic Chiari I malformation as clinically indicated.

Genetic counseling

CHD8-NDD is inherited in an autosomal dominant fashion. However, most probands reported to date whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo CHD8* pathogenic variant. Each child of an individual with *CHD8*-NDD has a 50% chance of inheriting the *CHD8* pathogenic variant. Once the *CHD8* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for *CHD8*-related neurodevelopmental disorder with overgrowth (*CHD8*-NDD) have been published.

Suggestive Findings

CHD8-NDD **should be considered** in individuals with the following clinical and family history findings.

Clinical findings

- Developmental delay (DD) and/or intellectual disability (ID) (typically in the mild-to-moderate range)
- Neuropsychiatric disorders, including autism spectrum disorder (ASD)
- Generalized overgrowth, including tall stature and macrocephaly
- Sleep disturbance
- Gastrointestinal problems, especially constipation

Family history. The majority of cases of *CHD8*-NDD are due to a *de novo* pathogenic variant, and most probands represent a simplex case (i.e., a single occurrence in a family). A minority of cases of *CHD8*-NDD are inherited in an autosomal dominant manner (e.g., affected males and females in multiple generations).

Establishing the Diagnosis

The diagnosis of *CHD8*-NDD **is established** in a proband by identification of a heterozygous pathogenic (or likely pathogenic) variant in *CHD8* by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variant" in this *GeneReview* is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *CHD8* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing in a child with DD/ID and/or ASD with macrocephaly may include *FMR1* analysis (molecular genetic testing for fragile X syndrome), chromosomal microarray analysis (CMA), multigene panels, and exome/genome sequencing. Note: Single-gene testing (sequence analysis of *CHD8*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **Chromosomal microarray analysis (CMA)** uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *CHD8*) that may not be detected by sequencing.
- **An ID, ASD, and/or overgrowth multigene panel** that includes *CHD8* 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.* (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.
- **Further comprehensive genomic testing** does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used. **Genome sequencing** may also be performed and yields results similar to an ID multigene panel with the additional advantage that exome sequencing includes genes recently identified as causing ID, ASD, and/or overgrowth, 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.
- **Epigenetic signature analysis / methylation array.** A distinctive epigenetic signature (disorder-specific genome-wide changes in DNA methylation profiles) in peripheral blood leukocytes has been identified in individuals with *CHD8*-NDD [Aref-Eshghi et al 2020, Levy et al 2021]. Epigenetic signature analysis of a peripheral blood sample or DNA banked from a blood sample can therefore be considered to clarify the diagnosis in individuals with: (1) suggestive findings of *CHD8*-NDD but in whom no pathogenic variant in *CHD8* has been identified via sequence analysis or genomic testing; or (2) suggestive findings of *CHD8*-NDD and a *CHD8* variant of uncertain clinical significance identified by molecular genetic testing. For an introduction to epigenetic signature analysis click here.

Table 1. Molecular Genetic Testing Used in *CHD8*-Related Neurodevelopmental Disorder with Overgrowth

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
CHD8	Sequence analysis [3]	~45%-50% [4]
	Gene-targeted deletion/duplication analysis [5]	~50%-55% [4]
	Chromosomal microarray [6]	See footnote 7.

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic 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 the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
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. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (e.g., those described by Prontera et al [2014], Terrone et al [2014], and Yasin et al [2019]) may not be detected by these methods.
6. Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *CHD8*) 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 14q11.2 region. CMA designs in current clinical use target the 14q11.2 region.
7. The vast majority of exon-level deletions/duplications in *CHD8* can be detected by BOTH CMA and gene-targeted deletion/duplication analysis.

Clinical Characteristics

Clinical Description

To date, 115 individuals have been identified with a pathogenic heterozygous sequence variant in *CHD8* for whom some phenotypic information is reported [Neale et al 2012, O'Roak et al 2012, Talkowski et al 2012, Bernier et al 2014, McCarthy et al 2014, Kimura et al 2016, Merner et al 2016, Stolerman et al 2016, Tatton-Brown et al 2017, Du et al 2018, Guo et al 2018, Wang et al 2018, Douzgou et al 2019, Ostrowski et al 2019, Alotaibi & Ramzan 2020, An et al 2020, Beighley et al 2020, Husson et al 2020, Tran et al 2020, Wu et al 2020, Coll-Tané et al 2021, Doummar et al 2021, Sadler et al 2021, Yamada et al 2021].

Of the 103 individuals for whom sex is known, 69 (67%) are male. This suggests a 2:1 male-to-female ratio, which is lower than the sex disparity previously reported [Douzgou et al 2019]. The reason for this sex difference is unknown, but it mirrors that of other neurodevelopmental disorders, indicating a possible ascertainment bias in who is referred for genetic testing.

The following description of the phenotypic features associated with *CHD8*-related neurodevelopmental disorder with overgrowth (*CHD8*-NDD) is based on these reports.

Table 2. Select Features of *CHD8*-Related Neurodevelopmental Disorder with Overgrowth

Feature	% of Persons w/Feature	Comment
Macrocephaly	80%	
Tall stature	80%	
ASD	75%-80%	

Table 2. continued from previous page.

Feature	% of Persons w/Feature	Comment
DD/ID	75%-80%	• Most, if not all, affected persons have some degree of DD. • Speech & motor delays are common. • ID is usually mild to moderate. • Possible developmental regression is observed in up to half of affected persons.
Sleep disturbances	67%	
Gastrointestinal problems	63%	Most frequently constipation
ADHD	50%	
Anxiety	29%	
Hypotonia	27%	
Seizures	12%	

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; DD = developmental delay; ID = intellectual disorder

Neurodevelopmental/neuropsychiatric issues

- **Developmental delay (DD)** in early childhood is common in individuals with *CHD8*-NDD. The majority are reported to have some degree of speech and/or motor delay, although the severity varies greatly. Developmental regression of social, speech, and/or motor skills in infancy and early childhood is reported in up to half of affected individuals [Bernier et al 2014, Merner et al 2016, Stolerman et al 2016, Wang et al 2018, An et al 2020, Wu et al 2020, Doummar et al 2021].
- **Speech/language delays.** While most individuals gain verbal speech, there are several case reports of individuals who are nonverbal in later childhood [Douzgou et al 2019, An et al 2020].
- **Motor delays**
  - When reported, delayed early motor milestones are present in 90% of affected individuals.
  - For those with delays, independent walking is usually achieved by age two years, although there is significant variability; one affected child was not yet walking at age nine years [Douzgou et al 2019].
  - Some affected individuals experience ongoing motor coordination difficulties, including poor fine motor skills [Stolerman et al 2016, Wang et al 2018, Douzgou et al 2019, Doummar et al 2021].
- **Intellectual disability (ID)** is present in a majority of individuals with *CHD8*-NDD.
  - The severity ranges from mild to severe, although most individuals show cognitive impairment in the mild-to-moderate range.
  - Some individuals do not have ID but may have borderline intellectual functioning or learning disabilities [Bernier et al 2014].
- **Autism spectrum disorder (ASD)** is diagnosed in most individuals with *CHD8*-NDD.
  - The average severity of autism symptoms is within the moderate range as measured by the Autism Diagnostic Observation Schedule (ADOS-2) [Bernier et al 2014].
  - A majority of affected individuals (approximately 80%) with *CHD8*-NDD who have ASD also have ID, ranging in severity from mild-to-severe cognitive impairment.
- **Other psychiatric conditions.** Approximately 30% of individuals with *CHD8*-NDD have a psychiatric or behavioral diagnosis, with attention-deficit/hyperactivity disorder and anxiety disorders being the most commonly reported conditions.
  - However, the majority of reports in the current literature describe children and may underrepresent the prevalence of adult-onset psychiatric conditions.

- There are several case reports of more severe adult-onset psychiatric manifestations, including psychosis, schizophrenia, and catatonia [McCarthy et al 2014, Kimura et al 2016, Ostrowski et al 2019].
- Aggression and self-injury have also been noted in several individuals with *CHD8*-NDD [Stolerman et al 2016, Douzgou et al 2019, Alotaibi & Ramzan 2020, An et al 2020, Wu et al 2020, Kurtz-Nelson et al 2021].

Neurologic features

- **Hypotonia.** About 30% of affected individuals present with hypotonia [Bernier et al 2014, Merner et al 2016, Guo et al 2018, Douzgou et al 2019, Ostrowski et al 2019, Wu et al 2020, Doummar et al 2021].
- **Seizures** are reported in 10%-15% of published affected individuals. Typically, seizures are reported as brief or isolated events. Some individuals have abnormal EEG activity, such as nonspecific background slowing or subclinical seizure activity, without overt seizures observed [Bernier et al 2014, Wang et al 2018]. Types of seizures reported include febrile, absence, and tonic-clonic [Bernier et al 2014, Douzgou et al 2019, An et al 2020, Beighley et al 2020].
- **Dystonia.** Two individuals with *CHD8*-NDD and childhood-onset, generalized dystonia were reported by Zech et al [2020]. Another case series described two additional unrelated affected individuals with childhood-onset progressive dystonia [Doummar et al 2021]. In this study, neither individual's dystonia responded to pharmacologic therapy, but improvement was achieved with deep brain stimulation in both (see Management).
- **Other neurologic features.** Four individuals with *CHD8*-NDD were reported to have "cerebral palsy," although details about the phenotype, such as physiologic and topographic classification, were not provided [Bernier et al 2014, Moreno-De-Luca et al 2021].
- **Neuroimaging.** Results of brain imaging have been published for a small minority of affected individuals, and within this group about half had abnormal findings (12/22) [Wang et al 2018, Douzgou et al 2019, An et al 2020, Doummar et al 2021, Sadler et al 2021]. Published MRI findings, when details are available, include:
  - Ventriculomegaly (3 affected individuals)
  - Increased signal of periventricular white matter (2 affected individuals)
  - Cerebellar vermis atrophy (2 affected individuals)
  - Lack of white matter bulk (1 affected individual)
  - Chiari I malformation (3 affected individuals who all also had macrocephaly)

Macrocephaly and tall stature (typically defined as head circumference and height, respectively, that are more than 2 standard deviations above the mean for age and sex) are the most common findings among individuals with *CHD8*-NDD.

- Macrocephaly is sometimes apparent at birth but often develops or is accentuated in infancy [Wang et al 2018].
- Tall stature often becomes apparent in puberty [An et al 2020].
- While some individuals are also reported to be overweight [Douzgou et al 2019], more often they present with a slender habitus [Bernier et al 2014], possibly because of impaired adipogenesis [Kita et al 2018]. One case study described an individual with features reminiscent of Marfan syndrome [Yamada et al 2021].

Sleep disturbance. About 70% of individuals with *CHD8*-NDD have disrupted sleep, including difficulty with both initiation (delayed sleep onset) and maintenance (frequent night awakenings) of sleep. While sleep problems are common among many children with neurodevelopmental disorders, there is evidence that those with *CHD8*-NDD experience greater difficulty falling asleep [Earl et al 2021] and higher rates of frequent or prolonged awakenings at night, possibly as a result of developmental hyperserotonemia [Coll-Tané et al 2021].

Gastrointestinal issues. Various gastrointestinal problems are common in *CHD8*-NDD, with the most prevalent being recurrent constipation with or without periods of diarrhea [Bernier et al 2014, Wang et al 2018, An et al 2020]. Other gastrointestinal problems in isolated case reports include the following [Kimura et al 2016, Stolerman et al 2016, Douzgou et al 2019]:

- Inflammatory bowel disease
- Gastropathy (without further definition of the specific issues in this particular affected individual [Bernier et al 2014])
- Cyclical vomiting
- Gastroesophageal reflux
- Eosinophilic esophagitis

Facial features. Many individuals with *CHD8*-NDD share similar facial features, including a prominent supraorbital ridge, broad forehead with increased occipitofrontal circumference, widely spaced eyes, downslanted palpebral fissures, pointed chin, and large and/or posteriorly rotated ears [Talkowski et al 2012, Bernier et al 2014, Merner et al 2016, Alotaibi & Ramzan 2020, An et al 2020, Doummar et al 2021].

Other features reported (each in 1-2 affected individuals)

- **Respiratory abnormalities.** "Respiratory problems" were reported in two affected individuals, but no details were given [Bernier et al 2014].
- **Feeding issues.** Unspecified feeding problems were reported in two affected children [Guo et al 2018, Wu et al 2020].
- **Endocrine**
  - Autoimmune diabetes mellitus was reported in one individual with progressive dystonia [Doummar et al 2021].
  - Precocious puberty was diagnosed in two girls [Talkowski et al 2012, Bernier et al 2014].
- **Malignancy.** There have been two people older than age 40 years who developed tumors [Bernier et al 2014]. However, there is no evidence that individuals with *CHD8*-NDD have an increased risk over the general populuation risk of developing a malignancy, and no tumor surveillance guidelines for this condition have been published.

Prognosis. There is no evidence that life span in individuals with *CHD8*-NDD is shortened, although limited information is available on affected adults. One reported individual is alive at age 53 years [Doummar et al 2021], demonstrating that survival into adulthood is possible. Since many adults with disabilities have not undergone advanced genetic testing, it is likely that adults with this condition are underrecognized and underreported.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Prevalence

Large population-based studies are lacking, making prevalence estimates difficult to calculate for the general population.

In one study, nine in 2,446 individuals with autism spectrum disorder and eight in 3,730 individuals with a variety of neurodevelopmental disorders were found to have a *de novo* loss-of-function pathogenic *CHD8* variant [Bernier et al 2014]. Another study estimated the prevalence of *de novo CHD8* pathogenic variants to be as high as one in 500 in a population of individuals with autism spectrum disorder [Wilkinson et al 2015]. Pathogenic *CHD8* variants are particularly prevalent (12 in 710, 1.7%) among individuals with both overgrowth and intellectual disability [Tatton-Brown et al 2017].

Genetically Related (Allelic) Disorders

Chromosome 14q11.2 deletion syndrome / Zahir-Friedman syndrome (ZFS) (OMIM 613457). Heterozygous deletions of various sizes for which the critical region includes both *CHD8* and *SUPT16H* have been reported to cause ZFS [Prontera et al 2014, Terrone et al 2014, Yasin et al 2019]. Clinical features of these affected individuals include developmental delay, intellectual disability, autism spectrum disorder, and dysmorphic features. Because additional genes are deleted in these individuals, it is not possible to rule out their added contribution to the phenotype. Isolated *de novo* pathogenic variants in *SUPT16H* have been reported to cause corpus callosum anomalies and neurodevelopmental disorders [Bina et al 2020], so it is likely that loss of this gene, in addition to *CHD8*, contributes to the developmental features of ZFS.

Congenital myasthenic syndrome. Lee et al [2020] reported monozyotic twins with features of congenital myasthenic syndrome who each had a heterozygous missense variant in *CHD8* that affected the 110-kilodalton isoform of the CHD-8 protein. They hypothesized that this missense variant was associated with the myasthenic phenotype in the twins.

Differential Diagnosis

Overgrowth conditions of interest in the differential diagnosis of *CHD8*-related neurodevelopmental disorder with overgrowth (*CHD8*-NDD) are summarized in Table 3.

Table 3. Overgrowth Conditions to Consider in the Differential Diagnosis of *CHD8*-Related Neurodevelopmental Disorder with Overgrowth

Gene(s)/Genetic Mechanism	Differential Disorder	MOI	Clinical Features of Differential Disorder	
			Overlapping w/*CHD8*-NDD	Distinguishing from *CHD8*-NDD
CDKN1C / 11p15 epigenetic & genomic alterations [1]	Beckwith-Wiedemann syndrome	Varies by genetic mechanism	Macrosomia	Neonatal hypoglycemia, macroglossia, hemihyperplasia, omphalocele, embryonal tumors, visceromegaly, adrenocortical cytomegaly, renal abnormalities, ear creases/pits
DNMT3A	Tatton-Brown-Rahman syndrome	AD	Overgrowth, DD/ID, ASD, behavior problems, hypotonia	Kyphoscoliosis, cryptorchidism, hematologic malignancies, obesity
EED	*EED*-related overgrowth (Cohen-Gibson syndrome)	AD	Overgrowth (tall stature, macrocephaly), mild-to-severe ID	Characteristic craniofacial features, facial hypotonia
EZH2	*EZH2*-related Weaver syndrome (See *EZH2*-Related Overgrowth.)	AD	Tall stature, normal intellect to severe ID	Characteristic facial appearance, advanced bone age, poor coordination, soft doughy skin, camptodactyly of fingers/toes, umbilical hernia, abnormal tone, hoarse low cry in infancy
FMR1	Fragile X syndrome (See *FMR1* Disorders.)	XL	DD/ID, ASD, anxiety & behavior problems, hypotonia, seizures, GI problems, sleep disorders	Characteristic craniofacial features, strabismus, joint laxity, flat feet, scoliosis, recurrent otitis media; adults may have mitral valve prolapse or aortic root dilatation.

Table 3. continued from previous page.

Gene(s)/Genetic Mechanism	Differential Disorder	MOI	Clinical Features of Differential Disorder	
			Overlapping w/*CHD8*-NDD	Distinguishing from *CHD8*-NDD
GPC3 *GPC4*	Simpson-Golabi-Behmel syndrome type 1	XL	Pre- & postnatal macrosomia, mild-to-severe ID	Distinctive craniofacial features, congenital anomalies, skeletal problems
NFIX	Malan syndrome (OMIM 614753)	AD	Overgrowth, macrocephaly, DD, learning disability, ASD, hypotonia	Distinctive facial appearance, pectus excavatum, coxa valga, livedo reticularis, abnormalities on brain MRI
NSD1	Sotos syndrome	AD	Learning disability, mild-to-severe ID, ASD, overgrowth, seizures	Distinctive facial appearance, advanced bone age, cardiac anomalies, joint hyperlaxity, renal anomalies, scoliosis
PTCH1 *SUFU*	Nevoid basal cell carcinoma syndrome	AD	Macrocephaly, gross motor delays	Jaw keratocytes, basal cell carcinomas, frontal bossing, coarse facial features, facial milia, skeletal anomalies, ectopic calcification of falx, cardiac & ovarian fibromas
PTEN	*PTEN* hamartoma tumor syndrome	AD	Macrocephaly, DD, ASD	Benign & malignant tumors of thyroid, breast, kidney, & endometrium, trichilemmomas, papillomatous papules
SUZ12	Imagawa-Matsumoto syndrome (OMIM 618786)	AD	Overgrowth, macrocephaly, hypotonia, DD, mild-to-severe ID	Characteristic facial features, advanced bone age, umbilical hernia, cryptorchidism

AD = autosomal dominant; ASD = autism spectrum disorder; *CHD8*-NDD = *CHD8*-related neurodevelopmental disorder with overgrowth; DD = developmental delay; ID = intellectual disability; GI = gastrointestinal; MOI = mode of inheritance; XL = X-linked
1. Beckwith-Wiedemann syndrome is associated with abnormal regulation of gene transcription in two imprinted domains on chromosome 11p15.5 (also known as the BWS critical region). Regulation may be disrupted by any one of numerous mechanisms (see Beckwith-Wiedemann Syndrome).

Developmental delay / intellectual disability. Because the clinical presentation of *CHD8*-NDD typically includes nonspecific developmental delays, all disorders associated with intellectual disability and/or developmental delay, with or without overgrowth, 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

No clinical practice guidelines for *CHD8*-related neurodevelopmental disorder with overgrowth (*CHD8*-NDD) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *CHD8*-NDD, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *CHD8*-Related Neurodevelopmental Disorder with Overgrowth

System/Concern	Evaluation	Comment
Constitutional	Measurement of all growth parameters incl head circumference	To assess for signs of macrocephaly & generalized overgrowth
Development	Developmental assessment	• To incl eval of cognitive, speech/language, adaptive, social/emotional, & motor skills • Eval for early intervention / special education • Consider referral to developmental pediatrician, psychologist, &/or speech-language pathologist as warranted.
Psychiatric/ Behavioral	Behavioral history & exam	• Incl screening for behavior concerns such as sleep disturbances, ADHD, anxiety, & traits suggestive of ASD • Consider referral to psychologist &/or psychiatrist as warranted.
Neurologic	Neurologic history & exam [1]	• To incl brain MRI if HC ≥3 SDs above mean, person has rapidly ↑ HC, or signs/symptoms of CSF obstruction [2] or compression of brain stem, cerebellum, or cranial nerves. [3] Consider brain MRI if HC >2 SDs above mean, in absence of other symptoms. • To incl spinal cord MRI if signs/symptoms of spinal cord dysfunction [1] • To incl EEG if history of signs/symptoms suggestive of seizures • Consider neurology consultation as clinically indicated.
Sleep	• Assessment for signs/symptoms of sleep problems • Consider polysomnogram.	• To incl assessment for difficulty falling asleep & frequent or prolonged awakenings at night • Consider referral to sleep medicine &/or psychologist, as warranted.
Gastrointestinal/ Feeding	GI- & feeding-directed history & exam	• To incl eval for constipation & other GI problems • Consider referral to gastroenterologist, as warranted.
Genetic counseling	By genetics professionals [4]	To inform affected persons & their families re nature, MOI, & implications of *CHD8*-NDD to facilitate medical & personal decision making
Family support & resources		Assess need for: • Community & online resources such as Parent to Parent; • Social work involvement for parental support; • Other services such as home nursing.

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; CSF = cerebrospinal fluid; EEG = electroencephalography; GI = gastrointestinal; HC = head circumference; MOI = mode of inheritance; MRI = magnetic resonance imaging; SD = standard deviation

1. For example, for weakness, abnormal tone, abnormal deep tendon reflexes, loss of pain and temperature sensation, numbness/tingling of hands or feet

2. For example, valsalva-induced occipital headache or cervical pain

3. For example, dysphagia, central sleep apnea, hoarseness or dysarthria, dizziness, tinnitus, ataxia

4. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for *CHD8*-NDD.

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 5).

Table 5. Treatment of Manifestations in Individuals with *CHD8*-Related Neurodevelopmental Disorder with Overgrowth

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability / Behavioral issues	See Developmental Delay / Intellectual Disability Management Issues.	
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for *CHD8*-NDD. • Education of parents/caregivers [1]
Dystonia	Standard treatment per neurologist	2 affected persons w/childhood-onset progressive dystonia that was unresponsive to pharmacologic therapy experienced improvement w/deep brain stimulation. [2]
Chiari I malformation	Surgical treatment may incl bony decompression of foramen magnum & dorsal arch of C1.	
Sleep disturbance	• Behavioral interventions [3] • Pharmacologic interventions may also be considered.	
Bowel dysfunction	Standard treatment of constipation & other GI problems	Fluids, dietary fiber, bulk laxatives, osmotic agents, stimulant laxatives, or emollients as needed
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.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; C1 = first cervical vertebra; GI = gastrointestinal
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.
2. Doummar et al [2021]
3. For example, cognitive behavioral therapy, including sleep restriction 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.
- Special education law requires that children participating in an IEP 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.
- 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.

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-based interventions, including naturalistic developmental behavioral interventions (NDBI), are targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed or supervised by 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, or other psychiatric or behavioral symptoms when necessary.

Concerns about aggressive or self-injurious behavior can be addressed by a pediatric psychiatrist or board-certified behavior analyst.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the following evaluations are recommended.

Table 6. Recommended Surveillance for Individuals with *CHD8*-Related Neurodevelopmental Disorder with Overgrowth

System/Concern	Evaluation	Frequency
Constitutional	Measurement of growth parameters incl head circumference	At each visit [1]
Development	Monitor developmental progress & educational needs.	
Psychiatric/ Behavioral	Monitor for signs/symptoms of anxiety, psychosis, ASD, ADHD, & aggressive or self-injurious behavior.	
Neurologic	Monitor those w/seizures as clinically indicated.	
	Assess for new manifestations such as seizures; changes in tone/movement disorders; & signs/symptoms of CSF obstruction, [2] compression of brain stem, cerebellum, or cranial nerves, [3] or spinal cord dysfunction. [4]	
	Consider serial imaging for asymptomatic or minimally symptomatic Chiari I malformation detected previously. [5]	As clinically indicated
Sleep	Screening for signs/symptoms of sleep disturbance	At each visit
Gastrointestinal	Monitor for signs/symptoms of constipation & feeding issues.	
Family/ Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder
1. Head circumference should be measured until adulthood.
2. For example, valsalva-induced occipital headache or cervical pain
3. For example, dysphagia, central sleep apnea, hoarseness or dysarthria, dizziness, tinnitus, ataxia
4. For example, weakness, abnormal tone, abnormal deep tendon reflexes, loss of pain and temperature sensation, numbness/tingling of hands or feet
5. In some situations, an asymptomatic or minimally symptomatic Chiari I malformation that does not require immediate surgical intervention may be detected and may require clinical and MRI monitoring.

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

CHD8-related neurodevelopmental disorder with overgrowth (*CHD8-NDD*) is an autosomal dominant disorder; the majority of affected individuals have a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- Most probands (85%-90%) reported to date with *CHD8*-NDD whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo CHD8* pathogenic variant.
- An individual diagnosed with *CHD8*-NDD may have inherited a *CHD8* pathogenic variant from a heterozygous parent. Details about heterozygous parents are scarce; one study reported three such parents with autistic features and nonverbal IQ scores in the borderline range [Guo et al 2018]. Another study described two parents who transmitted pathogenic *CHD8* variants to their children, one from a father with autistic features, large head circumference, and recurrent sleep and gastrointestinal difficulties, and the other from a mother with mild autistic features, large head circumference, learning difficulties, and a history of childhood sleep problems [Bernier et al 2014]. There have been no published cases of parents who have the same pathogenic variant as their affected child but have no clinical features of the condition.
- 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 and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

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 known to have the *CHD8* pathogenic variant identified in the proband, the sibs have a 50% chance of inheriting the variant.
- If the *CHD8* 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 *CHD8*-NDD has a 50% chance of inheriting the *CHD8* 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 *CHD8* 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 parents of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *CHD8* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Unique: Understanding Rare Chromosome and Gene Disorders**
  United Kingdom
  Phone: +44 (0) 1883 723356
  Email: info@rarechromo.org
  www.rarechromo.org
- **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. CHD8-Related Neurodevelopmental Disorder with Overgrowth: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
CHD8	14q11.2	Chromodomain-helicase-DNA-binding protein 8	CHD8	CHD8

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 CHD8-Related Neurodevelopmental Disorder with Overgrowth (View All in OMIM)

610528	CHROMODOMAIN HELICASE DNA-BINDING PROTEIN 8; CHD8
615032	INTELLECTUAL DEVELOPMENTAL DISORDER WITH AUTISM AND MACROCEPHALY; IDDAM

Molecular Pathogenesis

CHD8 encodes chromodomain-helicase-DNA-binding protein 8 (CHD-8), a DNA helicase involved in several processes including transcriptional regulation, epigenetic remodeling, promotion of cell proliferation, and regulation of RNA synthesis. CHD-8 acts as a repressor by remodeling chromatin structure and recruiting

histone H1 to target genes, an example being suppressing p53/TP53-mediated apoptosis. CHD-8 acts as a negative regulator of Wnt signaling by regulating beta-catenin (*CTNNB1*) activity. CHD-8 also acts as a transcription activator by participating in U6 RNA polymerase III transcription through interactions with zinc finger protein 143.

CHD8 is primarily expressed in both the adult and fetal brain [Weissberg & Elliott 2021]. Interestingly, increased head circumference is the most replicated finding across both human and animal studies of *CHD8*-related neurodevelopmental disorder with overgrowth (*CHD8*-NDD), with mouse and zebra fish models demonstrating an increase in brain volume that is the result of overproliferation of progenitor cells in the frontal cortex during development [Sugathan et al 2014, Durak et al 2016, Katayama et al 2016, Suetterlin et al 2018].

Preliminary research in a zebra fish model suggests that gastrointestinal problems associated with *CHD8* pathogenic variants may be caused by a reduced number of vagal neural crest cells, decreased intestinal mobility, and increased inflammation (see bioRxiv).

Somatic *CHD8* variants may play a role in the cell cycle of gastric/colorectal cancers [Kim et al 2011]; however, there is no current evidence that individuals with *CHD8*-NDD are at increased risk for developing cancer. Additional research, including longitudinal studies, is needed to determine whether individuals with germline *CHD8* pathogenic variants are at increased risk for specific cancer types.

Heterozygous pathogenic loss-of-function variants cause *CHD8*-NDD. The majority of pathogenic variants reported in association with *CHD8*-NDD have been deletions and truncating and splicing variants. The gene is highly intolerant to loss-of-function variants in the general population [Karczewski et al 2020]. Some *de novo* missense variants that potentially disrupt function have been identified [O'Roak et al 2012, Bernier et al 2014, McCarthy et al 2014, Wang et al 2018].

Mechanism of disease causation. Heterozygous loss of function

Chapter Notes

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References

Literature Cited

Alotaibi M, Ramzan K. A de novo variant of CHD8 in a patient with autism spectrum disorder. Discoveries (Craiova). 2020;8:e107. PubMed PMID: 32309624.

An Y, Zhang L, Liu W, Jiang Y, Chen X, Lan X, Li G, Hang Q, Wang J, Gusella JF, Du Y, Shen Y. De novo variants in the Helicase-C domain of CHD8 are associated with severe phenotypes including autism, language disability and overgrowth. Hum Genet. 2020;139:499–512. PubMed PMID: 31980904.

Aref-Eshghi E, Kerkhof J, Pedro VP, Groupe DI. France, Barat-Houari M, Ruiz-Pallares N, Andrau JC, Lacombe D, Van-Gils J, Fergelot P, Dubourg C, Cormier-Daire V, Rondeau S, Lecoquierre F, Saugier-Veber P, Nicolas G, Lesca G, Chatron N, Sanlaville D, Vitobello A, Faivre L, Thauvin-Robinet C, Laumonnier F, Raynaud M, Alders M, Mannens M, Henneman P, Hennekam RC, Velasco G, Francastel C, Ulveling D, Ciolfi A, Pizzi S, Tartaglia M, Heide S, Héron D, Mignot C, Keren B, Whalen S, Afenjar A, Bienvenu T, Campeau PM, Rousseau J, Levy MA, Brick L, Kozenko M, Balci TB, Siu VM, Stuart A, Kadour M, Masters J, Takano K, Kleefstra T, de Leeuw N, Field M, Shaw M, Gecz J, Ainsworth PJ, Lin H, Rodenhiser DI, Friez MJ, Tedder M, Lee JA, DuPont BR, Stevenson RE, Skinner SA, Schwartz CE, Genevieve D, Sadikovic B. Evaluation of DNA methylation episignatures for diagnosis and phenotype correlations in 42 mendelian neurodevelopmental disorders. Am J Hum Genet. 2020;106:356–70. PubMed PMID: 32109418.

Beighley JS, Hudac CM, Arnett AB, Peterson JL, Gerdts J, Wallace AS, Mefford HC, Hoekzema K, Turner TN, O'Roak BJ, Eichler EE, Bernier RA. Clinical phenotypes of carriers of mutations in CHD8 or its conserved target genes. Biol Psychiatry. 2020;87:123–31. PubMed PMID: 31526516.

Bernier R, Golzio C, Xiong B, Stessman HA, Coe BP, Penn O, Witherspoon K, Gerdts J, Baker C, Vulto-van Silfhout AT, Schuurs-Hoeijmakers JH, Fichera M, Bosco P, Buono S, Alberti A, Failla P, Peeters H, Steyaert J, Vissers LELM, Francescatto L, Mefford HC, Rosenfeld JA, Bakken T, O'Roak BJ, Pawlus M, Moon R, Shendure J, Amaral DG, Lein E, Rankin J, Romano C, de Vries BBA, Katsanis N, Eichler EE. Disruptive CHD8 mutations define a subtype of autism early in development. Cell. 2014;158:263–76. PubMed PMID: 24998929.

Bina R, Matalon D, Fregeau B, Tarsitano JJ, Aukrust I, Houge G, Bend R, Warren H, Stevenson RE, Stuurman KE, Barkovich AJ, Sherr EH. De novo variants in SUPT16H cause neurodevelopmental disorders associated with corpus callosum abnormalities. J Med Genet. 2020;57:461–5. PubMed PMID: 31924697.

Coll-Tané M, Gong NN, Belfer SJ, van Renssen LV, Kurtz-Nelson EC, Szuperak M, Eidhof I, van Reijmersdal B, Terwindt I, Durkin J, Verheij MMM, Kim CN, Hudac CM, Nowakowski TJ, Bernier RA, Pillen S, Earl RK, Eichler EE, Kleefstra T, Kayser MS, Schenck A. The CHD8/CHD7/Kismet family links blood-brain barrier glia and serotonin to ASD-associated sleep defects. Sci Adv. 2021;7:eabe2626. PubMed PMID: 34088660.

Doummar D, Treven M, Qebibo L, Devos D, Ghoumid J, Ravelli C, Kranz G, Drenn M, Demailly D, Cif L, Davion JB, Zimprich F, Burglen L, Zech M. Childhood-onset progressive dystonia associated with pathogenic truncating variants in CHD8. Ann Clin Transl Neurol. 2021;8:1986–90. PubMed PMID: 34415117.

Douzgou S, Liang HW, Metcalfe K, Somarathi S, Tischkowitz M, Mohamed W, Kini U, McKee S, Yates L, Bertoli M, Lynch SA, Holder S, Banka S, et al. The clinical presentation caused by truncating CHD8 variants. Clin Genet. 2019;96:72–84. PubMed PMID: 31001818.

Du X, Gao X, Liu X, Shen L, Wang K, Fan Y, Sun Y, Luo X, Liu H, Wang L, Wang Y, Gong Z, Wang J, Yu Y, Li F. Genetic diagnostic evaluation of trio-based whole exome sequencing among children with diagnosed or suspected autism spectrum disorder. Front Genet. 2018;9:594. PubMed PMID: 30555518.

Durak O, Gao F, Kaeser-Woo YJ, Rueda R, Martorell AJ, Nott A, Liu CY, Watson LA, Tsai LH. Chd8 mediates cortical neurogenesis via transcriptional regulation of cell cycle and Wnt signaling. Nature Neurosci. 2016;19:1477–88. PubMed PMID: 27694995.

Earl RK, Ward T, Gerdts J, Eichler EE, Bernier RA, Hudac CM. Sleep problems in children with ASD and gene disrupting mutations. J Genet Psychol. 2021;182:317–34. PubMed PMID: 33998396.

Guo H, Wang T, Wu H, Long M, Coe BP, Li H, Xun G, Ou J, Chen B, Duan G, Bai T, Zhao N, Shen Y, Li Y, Wang Y, Zhang Y, Baker C, Liu Y, Pang N, Huang L, Han L, Jia X, Liu C, Ni H, Yang X, Xia L, Chen J, Shen L, Li Y, Zhao R, Zhao W, Peng J, Pan Q, Long Z, Su W, Tan J, Du X, Ke X, Yao M, Hu Z, Zou X, Zhao J, Bernier RA, Eichler EE, Xia K. Inherited and multiple de novo mutations in autism/developmental delay risk genes suggest a multifactorial model. Mol Autism. 2018;9:64. PubMed PMID: 30564305.

Husson T, Lecoquierre F, Cassinari K, Charbonnier C, Quenez O, Goldenberg A, Guerrot AM, Richard AC, Drouin-Garraud V, Brehin AC, Soleimani M, Taton R, Rotharmel M, Rosier A, Chambon P, Le Meur N, Joly-Helas G, Saugier-Veber P, Boland A, Deleuze JF, Olaso R, Frebourg T, Nicolas G, Guillin O, Campion D. Rare genetic susceptibility variants assessment in autism spectrum disorder: detection rate and practical use. Transl Psychiatry. 2020;10:77. PubMed PMID: 32094338.

Karczewski KJ, Francioli LC, Tiao G, Cummings BB, Alföldi J, Wang Q, Collins RL, Laricchia KM, Ganna A, Birnbaum DP, Gauthier LD, Brand H, Solomonson M, Watts NA, Rhodes D, Singer-Berk M, England EM, Seaby EG, Kosmicki JA, Walters RK, Tashman K, Farjoun Y, Banks E, Poterba T, Wang A, Seed C, Whiffin N, Chong JX, Samocha KE, Pierce-Hoffman E, Zappala Z, O'Donnell-Luria AH, Minikel EV, Weisburd B, Lek M, Ware JS, Vittal C, Armean IM, Bergelson L, Cibulskis K, Connolly KM, Covarrubias M, Donnelly S, Ferriera S, Gabriel S, Gentry J, Gupta N, Jeandet T, Kaplan D, Llanwarne C, Munshi R, Novod S, Petrillo N, Roazen D, Ruano-Rubio V, Saltzman A, Schleicher M, Soto J, Tibbetts K, Tolonen C, Wade G, Talkowski ME, Neale BM, Daly MJ, MacArthur DG, et al. The mutational constraint spectrum quantified from variation in 141,456 humans. Nature. 2020;581:434–43. PubMed PMID: 32461654.

Katayama Y, Nishiyama M, Shoji H, Ohkawa Y, Kawamura A, Sato T, Suyama M, Takumi T, Miyakawa T, Nakayama KI. CHD8 haploinsufficiency results in autistic-like phenotypes in mice. Nature. 2016;537:675–9. PubMed PMID: 27602517.

Kim MS, Chung NG, Kang MR, Yoo NJ, Lee SH. Genetic and expressional alterations of CHD genes in gastric and colorectal cancers. Histopathology. 2011;58:660–8. PubMed PMID: 21447119.

Kimura H, Wang C, Ishizuka K, Xing J, Takasaki Y, Kushima I, Aleksic B, Uno Y, Okada T, Ikeda M, Mori D, Inada T, Iwata N, Ozaki N. Identification of a rare variant in CHD8 that contributes to schizophrenia and autism spectrum disorder susceptibility. Schizophr Res. 2016;178:104–6. PubMed PMID: 27595554.

Kita Y, Katayama Y, Shiraishi T, Oka T, Sato T, Suyama M, Ohkawa Y, Miyata K, Oike Y, Shirane M, Nishiyama M, Nakayama KI. The autism-related protein CHD8 cooperates with C/EBPβ to regulate adipogenesis. Cell Rep. 2018;23:1988–2000. PubMed PMID: 29768199.

Kurtz-Nelson EC, Tham SW, Ahlers K, Cho D, Wallace AS, Eichler EE, Bernier RA, Earl RK. Brief report: associations between self-injurious behaviors and abdominal pain among individuals with ASD-associated disruptive mutations. J Autism Dev Disord. 2021;51:3365–73. PubMed PMID: 33175317.

Lee CY, Petkova M, Morales-Gonzalez S, Gimber N, Schmoranzer J, Meisel A, Böhmerle W, Stenzel W, Schuelke M, Schwarz JM. A spontaneous missense mutation in the chromodomain helicase DNA-binding protein 8 (CHD8) gene: a novel association with congenital myasthenic syndrome. Neuropathol Appl Neurobiol. 2020;46:588–601. PubMed PMID: 32267004.

Levy MA, McConkey H, Kerkhof J, Barat-Houari M, Bargiacchi S, Biamino E, Bralo MP, Cappuccio G, Ciolfi A, Clarke A, DuPont BR, Elting MW, Faivre L, Fee T, Fletcher RS, Cherik F, Foroutan A, Friez MJ, Gervasini C, Haghshenas S, Hilton BA, Jenkins Z, Kaur S, Lewis S, Louie RJ, Maitz S, Milani D, Morgan AT, Oegema R, Østergaard E, Pallares NR, Piccione M, Pizzi S, Plomp AS, Poulton C, Reilly J, Relator R, Rius R, Robertson S, Rooney K, Rousseau J, Santen GWE, Santos-Simarro F, Schijns J, Squeo GM, St John M, Thauvin-Robinet C, Traficante G, van der Sluijs PJ, Vergano SA, Vos N, Walden KK, Azmanov D, Balci T, Banka S, Gecz J, Henneman P, Lee JA, Mannens MMAM, Roscioli T, Siu V, Amor DJ, Baynam G, Bend EG, Boycott K, Brunetti-Pierri N, Campeau PM, Christodoulou J, Dyment D, Esber N, Fahrner JA, Fleming MD, Genevieve D, Kerrnohan KD, McNeill A, Menke LA, Merla G, Prontera P, Rockman-Greenberg C, Schwartz C, Skinner SA, Stevenson RE, Vitobello A, Tartaglia M, Alders M, Tedder ML, Sadikovic B. Novel diagnostic DNA methylation episignatures expand and refine the epigenetic landscapes of Mendelian disorders. HGG Adv. 2021;3:100075. PubMed PMID: 35047860.

McCarthy SE, Gillis J, Kramer M, Lihm J, Yoon S, Berstein Y, Mistry M, Pavlidis P, Solomon R, Ghiban E, Antoniou E, Kelleher E, O'Brien C, Donohoe G, Gill M, Morris DW, McCombie WR, Corvin A. De novo

mutations in schizophrenia implicate chromatin remodeling and support a genetic overlap with autism and intellectual disability. Mol Psychiatry. 2014;19:652–8. PubMed PMID: 24776741.

Merner N, Forgeot d'Arc B, Bell SC, Maussion G, Peng H, Gauthier J, Crapper L, Hamdan FF, Michaud JL, Mottron L, Rouleau GA, Ernst C. A de novo frameshift mutation in chromodomain helicase DNA-binding domain 8 (CHD8): a case report and literature review. Am J Med Genet A. 2016;170A:1225–35. PubMed PMID: 26789910.

Moreno-De-Luca A, Millan F, Pesacreta DR, Elloumi HZ, Oetjens MT, Teigen C, Wain KE, Scuffins J, Myers SM, Torene RI, Gainullin VG, Arvai K, Kirchner HL, Ledbetter DH, Retterer K, Martin CL. Molecular diagnostic yield of exome sequencing in patients with cerebral palsy. JAMA. 2021;325:467–75. PubMed PMID: 33528536.

Neale BM, Kou Y, Liu L, Ma'ayan A, Samocha KE, Sabo A, Lin CF, Stevens C, Wang LS, Makarov V, Polak P, Yoon S, Maguire J, Crawford EL, Campbell NG, Geller ET, Valladares O, Schafer C, Liu H, Zhao T, Cai G, Lihm J, Dannenfelser R, Jabado O, Peralta Z, Nagaswamy U, Muzny D, Reid JG, Newsham I, Wu Y, Lewis L, Han Y, Voight BF, Lim E, Rossin E, Kirby A, Flannick J, Fromer M, Shakir K, Fennell T, Garimella K, Banks E, Poplin R, Gabriel S, DePristo M, Wimbish JR, Boone BE, Levy SE, Betancur C, Sunyaev S, Boerwinkle E, Buxbaum JD, Cook EH Jr, Devlin B, Gibbs RA, Roeder K, Schellenberg GD, Sutcliffe JS, Daly MJ. Patterns and rates of exonic de novo mutations in autism spectrum disorders. Nature. 2012;485:242–5. PubMed PMID: 22495311.

O'Roak BJ, Vives L, Fu W, Egertson JD, Stanaway IB, Phelps IG, Carvill G, Kumar A, Lee C, Ankenman K, Munson J, Hiatt JB, Turner EH, Levy R, O'Day DR, Krumm N, Coe BP, Martin BK, Borenstein E, Nickerson DA, Mefford HC, Doherty D, Akey JM, Bernier R, Eichler EE, Shendure J. Multiplex targeted sequencing identifies recurrently mutated genes in autism spectrum disorders. Science. 2012;338:1619–22. PubMed PMID: 23160955.

Ostrowski PJ, Zachariou A, Loveday C, Beleza-Meireles A, Bertoli M, Dean J, Douglas AGL, Ellis I, Foster A, Graham JM, Hague J, Hilhorst-Hofstee Y, Hoffer M, Johnson D, Josifova D, Kant SG, Kini U, Lachlan K, Lam W, Lees M, Lynch S, Maitz S, McKee S, Metcalfe K, Nathanson K, Ockeloen CW, Parker MJ, Pierson TM, Rahikkala E, Sanchez-Lara PA, Spano A, Van Maldergem L, Cole T, Douzgou S, Tatton-Brown K. The CHD8 overgrowth syndrome: A detailed evaluation of an emerging overgrowth phenotype in 27 patients. Am J Med Genet C Semin Med Genet. 2019;181:557–64. PubMed PMID: 31721432.

Prontera P, Ottaviani V, Toccaceli D, Rogaia D, Ardisia C, Romani R, Stangoni G, Pierini A, Donti E. Recurrent ~100 Kb microdeletion in the chromosomal region 14q112, involving CHD8 gene is associated with autism and macrocephaly. Am J Med Genet A. 2014;164A:3137–41. PubMed PMID: 25257502.

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

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Sadler B, Wilborn J, Antunes L, Kuensting T, Hale AT, Gannon SR, McCall K, Cruchaga C, Harms M, Voisin N, Reymond A, Cappuccio G, Brunetti-Pierri N, Tartaglia M, Niceta M, Leoni C, Zampino G, Ashley-Koch A, Urbizu A, Garrett ME, Soldano K, Macaya A, Conrad D, Strahle J, Dobbs MB, Turner TN, Shannon CN, Brockmeyer D, Limbrick DD, Gurnett CA, Haller G. Rare and de novo coding variants in chromodomain genes in Chiari I malformation. Am J Hum Genet. 2021;108:100–14. PubMed PMID: 33352116.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197–207. PubMed PMID: 32596782.

Stolerman ES, Smith B, Chaubey A, Jones JR. CHD8 intragenic deletion associated with autism spectrum disorder. Eur J Med Genet. 2016;59:189–94. PubMed PMID: 26921529.

Suetterlin P, Hurley S, Mohan C, Riegman KL, Pagani M, Caruso A, Ellegood J, Galbusera A, Crespo-Enriquez I, Michetti C, Yee Y, Ellingford R, Brock O, Delogu A, Francis-West P, Lerch JP, Scattoni ML, Gozzi A, Fernandes C, Basson MA. Altered neocortical gene expression, brain overgrowth and functional over-connectivity in Chd8 haploinsufficient mice. Cereb Cortex. 2018;28:2192–206. PubMed PMID: 29668850.

Sugathan A, Biagioli M, Golzio C, Erdin S, Blumenthal I, Manavalan P, Ragavendran A, Brand H, Lucente D, Miles J, Sheridan SD, Stortchevoi A, Kellis M, Haggarty SJ, Katsanis N, Gusella JF, Talkowski ME. CHD8 regulates neurodevelopmental pathways associated with autism spectrum disorder in neural progenitors. Proc Nat Acad Sci. 2014;111:E4468–E4477. PubMed PMID: 25294932.

Talkowski ME, Rosenfeld JA, Blumenthal I, Pillalamarri V, Chiang C, Heilbut A, Ernst C, Hanscom C, Rossin E, Lindgren AM, Pereira S, Ruderfer D, Kirby A, Ripke S, Harris DJ, Lee JH, Ha K, Kim HG, Solomon BD, Gropman AL, Lucente D, Sims K, Ohsumi TK, Borowsky ML, Loranger S, Quade B, Lage K, Miles J, Wu BL, Shen Y, Neale B, Shaffer LG, Daly MJ, Morton CC, Gusella JF. Sequencing chromosomal abnormalities reveals neurodevelopmental loci that confer risk across diagnostic boundaries. Cell. 2012;149:525–37. PubMed PMID: 22521361.

Tatton-Brown K, Loveday C, Yost S, Clarke M, Ramsay E, Zachariou A, Elliott A, Wylie H, Ardissone A, Rittinger O, Stewart F, Temple IK, Cole T, Mahamdallie S, Seal S, Ruark E, Rahman N, et al. Mutations in epigenetic regulation genes are a major cause of overgrowth with intellectual disability. Am J Hum Genet. 2017;100:725–36. PubMed PMID: 28475857.

Terrone G, Cappuccio G, Genesio R, Esposito A, Fiorentino V, Riccitelli M, Nitsch L, Brunetti-Pierri N, Del Giudice E. A case of 14q112 microdeletion with autistic features, severe obesity and facial dysmorphisms suggestive of Wolf-Hirschhorn syndrome. Am J Med Genet A. 2014;164A:190–3. PubMed PMID: 24243641.

Tran KT, Le VS, Bui HTP, Do DH, Ly HTT, Nguyen HT, Dao LTM, Nguyen TH, Vu DM, Ha LT, Le HTT, Mukhopadhyay A, Nguyen LT. Genetic landscape of autism spectrum disorder in Vietnamese children. Sci Rep. 2020;10:5034. PubMed PMID: 32193494.

Wang J, Liu J, Gao Y, Wang K, Jiang K. Autism spectrum disorder early in development associated with CHD8 mutations among two Chinese children. BMC Pediatr. 2018;18:338. PubMed PMID: 30376831.

Weissberg O, Elliott E. The mechanisms of CHD8 in neurodevelopment and autism spectrum disorders. Genes. 2021;12:1133. PubMed PMID: 34440307.

Wilkinson B, Grepo N, Thompson BL, Kim J, Wang K, Evgrafov OV, Lu W, Knowles JA, Campbell DB. The autism-associated gene chromodomain helicase DNA-binding protein 8 (CHD8) regulates noncoding RNAs and autism-related genes. Transl Psychiatry. 2015;5:e568. PubMed PMID: 25989142.

Wu H, Li H, Bai T, Han L, Ou J, Xun G, Zhang Y, Wang Y, Duan G, Zhao N, Chen B, Du X, Yao M, Zou X, Zhao J, Hu Z, Eichler EE, Guo H, Xia K. Phenotype-to-genotype approach reveals head-circumference-associated genes in an autism spectrum disorder cohort. Clin Genet. 2020;97:338–46. PubMed PMID: 31674007.

Yamada M, Yamaguchi Y, Uehara T, Yagihashi T, Kosaki K. Heterozygous nonsense variant of CHD8 in a patient with forme-fruste Marfan syndrome and intellectual disability. Congenital Anomalies. 2021;61:30–2. PubMed PMID: 32951261.

Yasin H, Gibson WT, Langlois S, Stowe RM, Tsang ES, Lee L, Poon J, Tran G, Tyson C, Wong CK, Marra MA, Friedman JM, Zahir FR. A distinct neurodevelopmental syndrome with intellectual disability, autism spectrum disorder, characteristic facies, and macrocephaly is caused by defects in CHD8. J Hum Genet. 2019;64:271–80. PubMed PMID: 30670789.

Zech M, Jech R, Boesch S, Škorvánek M, Weber S, Wagner M, Zhao C, Jochim A, Necpál J, Dincer Y, Vill K, Distelmaier F, Stoklosa M, Krenn M, Grunwald S, Bock-Bierbaum T, Fečíková A, Havránková P, Roth J, Příhodová I, Adamovičová M, Ulmanová O, Bechyně K, Danhofer P, Veselý B, Haň V, Pavelekova P, Gdovinová Z, Mantel T, Meindl T, Sitzberger A, Schröder S, Blaschek A, Roser T, Bonfert MV, Haberlandt E, Plecko B, Leineweber B, Berweck S, Herberhold T, Langguth B, Švantnerová J, Minár M, Ramos-Rivera GA, Wojcik MH, Pajusalu S, Õunap K, Schatz UA, Pölsler L, Milenkovic I, Laccone F, Pilshofer V, Colombo R, Patzer S, Iuso A, Vera J, Troncoso M, Fang F, Prokisch H, Wilbert F, Eckenweiler M, Graf E, Westphal DS, Riedhammer KM, Brunet T, Alhaddad B, Berutti R, Strom TM, Hecht M, Baumann M, Wolf M, Telegrafi A, Person RE, Zamora FM, Henderson LB, Weise D, Musacchio T, Volkmann J, Szuto A, Becker J, Cremer K, Sycha T, Zimprich F, Kraus V, Makowski C, Gonzalez-Alegre P, Bardakjian TM, Ozelius LJ, Vetro A, Guerrini R, Maier E, Borggraefe I, Kuster A, Wortmann SB, Hackenberg A, Steinfeld R, Assmann B, Staufner C, Opladen T, Růžička E, Cohn RD, Dyment D, Chung WK, Engels H, Ceballos-Baumann A, Ploski R, Daumke O, Haslinger B, Mall V, Oexle K, Winkelmann J. Monogenic variants in dystonia: an exome-wide sequencing study. Lancet Neurol. 2020; 2020;19:908–18. PubMed PMID: 33098801.

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