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CHD7 Disorder

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Summary

Clinical characteristics

CHD7 disorder encompasses the entire phenotypic spectrum of heterozygous *CHD7* pathogenic variants that includes CHARGE syndrome as well as subsets of features that comprise the CHARGE syndrome phenotype. The mnemonic CHARGE syndrome, introduced in the premolecular era, stands for *c*oloboma, *h*eart defect, choanal *a*tresia, *r*etarded growth and development, *g*enital hypoplasia, *e*ar anomalies (including deafness). Following the identification of the genetic cause of *CHD7* disorder, the phenotypic spectrum expanded to include cranial nerve anomalies, vestibular defects, cleft lip and/or palate, hypothyroidism, tracheoesophageal anomalies, brain anomalies, seizures, and renal anomalies. Life expectancy highly depends on the severity of manifestations; mortality can be high in the first few years when severe birth defects (particularly complex heart defects) are present and often complicated by airway and feeding issues. In childhood, adolescence, and adulthood, decreased life expectancy is likely related to a combination of residual heart defects, infections, aspiration or choking, respiratory issues including obstructive and central apnea, and possibly seizures. Despite these complications, the life expectancy for many individuals can be normal.

Diagnosis/testing

The diagnosis of *CHD7* disorder is established in a proband with suggestive clinical and imaging findings and a heterozygous pathogenic variant in or deletion of *CHD7* identified by molecular genetic testing.

Management

Treatment of manifestations: Management of the manifestations of *CHD7* disorder can be complex and require a multidisciplinary approach involving clinicians, therapists, and educators.

Surveillance: Requires routine follow up of manifestations identified in infancy/childhood, as well as ongoing monitoring of growth, development, educational progress, behavior, and possible endocrine issues.

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Agents/circumstances to avoid: Because of the increased risk of post-anesthesia airway complications, procedures requiring anesthesia should be minimized and combined whenever possible.

Genetic counseling

CHD7 disorder is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant. In rare instances, an individual with *CHD7* disorder inherits a pathogenic variant from a heterozygous parent. The risk to the sibs of the proband depends on the genetic status of the proband's parents: (1) If a parent of the proband has a *CHD7* pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%; (2) If the *CHD7* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the empiric recurrence risk to sibs of a proband is approximately 1%-2% because of the possibility of parental germline mosaicism. Although many individuals with *CHD7* disorder are not able to reproduce, each child of an individual with *CHD7* disorder has a 50% chance of inheriting the pathogenic variant. Once the *CHD7* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

GeneReview Scope

With the current widespread use of multigene panels and comprehensive genomic testing, it has become apparent that the phenotypic spectrum of heterozygous *CHD7* pathogenic variants has broadened to encompass CHARGE syndrome as well as subsets of features that comprise the CHARGE syndrome phenotype. The title of this chapter, *CHD7* disorder, refers to the entire phenotypic spectrum that can be associated with heterozygous *CHD7* pathogenic variants and emphasizes both the need to evaluate an individual found to have a *CHD7* pathogenic variant for medically actionable manifestations in the entire phenotypic spectrum (regardless of clinical findings that prompted molecular genetic testing) and the importance of counseling families that the finding of a *CHD7* pathogenic variant is not equivalent to a diagnosis of CHARGE syndrome.

Diagnosis

Suggestive Findings

CHD7 disorder should be suspected in individuals with combinations of the following findings and family history.

Clinical and imaging findings

- Coloboma of the iris, retina, choroid, and/or disc, and/or anophthalmos or microphthalmos
- Choanal atresia or stenosis: unilateral or bilateral, bony or membranous, confirmed by axial sections of non-enhanced axial CT scan
- Cleft palate with or without cleft lip (Note: Choanal atresia is rare in the presence of a cleft palate.)
- Cranial nerve dysfunction or anomaly
  - Cranial nerve I. Hyposmia or anosmia
  - Cranial nerve VII. Facial palsy (unilateral or bilateral)
  - Cranial nerve VIII. Sensorineural hearing loss and/or balance problems, hypoplasia or aplasia on imaging
  - Cranial nerve IX/X. Difficulty with sucking/swallowing and aspiration, gut motility problems
- Ear malformations (most characteristic of *CHD7* disorder)
  - Auricle. Short, wide ear with little or no lobe, "snipped-off" helix, prominent antihelix that is often discontinuous with tragus, triangular concha, decreased cartilage; often protruding and usually asymmetric (See Figure 1.)

    - Middle ear. Ossicular malformations (resulting in a typical wedge-shaped audiogram due to mixed sensorineural and conductive hearing loss)
    - Temporal bone abnormalities (most commonly determined by temporal bone CT scan). Mondini defect of the cochlea (cochlear hypoplasia), absent or hypoplastic semicircular canals
- Tracheoesophageal fistula or esophageal atresia
- Cardiovascular malformation, including conotruncal defects (e.g., tetralogy of Fallot), AV canal defects, and aortic arch anomalies [Corsten-Janssen & Scambler 2017]
- Hypogonadotropic hypogonadism
    - Males at birth. Micropenis and cryptorchidism
    - Females at birth. Hypoplastic labia, abnormal or (rarely) absent uterus
    - Males and females. Delayed or absent puberty, often in combination with anosmia [Bergman et al 2011a]
- Developmental delay / intellectual disability, delayed motor milestones, often secondary to sensory and balance deficits
- Growth deficiency. Short stature, usually postnatal with or without growth hormone deficiency
- Other clinical features
    - Face. Square-shaped with broad forehead, broad nasal bridge, prominent nasal columella, flattened malar area, facial palsy or other asymmetry, cleft lip, and small chin (gets larger and broader with age) (See Figure 2.)
    - Neck. Short and wide with sloping shoulders [O'Grady et al 2016] (See Figure 2.)
    - Hands. Typically, short, wide palm with hockey-stick crease, short fingers, and finger-like thumb (see Figure 3); polydactyly and reduction defects in a small percentage [Van de Laar et al 2007]
- Brain MRI. Clivus hypoplasia [de Geus et al 2018], hypoplasia of cerebellar vermis [Donovan et al 2017]

Family history is consistent with autosomal dominant inheritance. While the majority of individuals with *CHD7* disorder are simplex cases (i.e., a single occurrence in a family resulting from a *de novo CHD7* pathogenic variant), familial occurrences consistent with autosomal dominant inheritance and germline mosaicism have been reported [Bergman et al 2011b, Legendre et al 2017]. Note: Absence of a family history of features consistent with *CHD7* disorder does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *CHD7* disorder **is established** in a proband with suggestive clinical and imaging findings and a heterozygous pathogenic (or likely pathogenic) variant in *CHD7* identified 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 can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a heterozygous *CHD7* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (*CHD7* single-gene testing, multigene panel) and **comprehensive genomic testing** (chromosomal microarray, exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determines which gene(s) are likely involved, whereas genomic testing does not. Individuals with suggestive findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with atypical findings are more likely to be diagnosed using genomic testing (see Option 2).

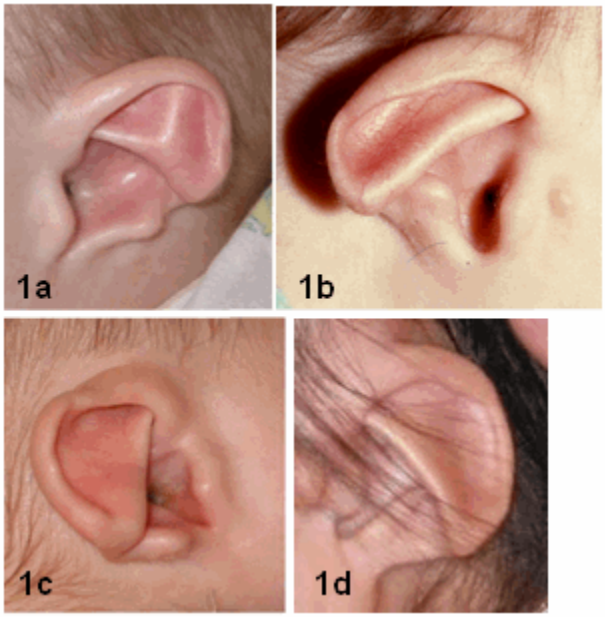

Figure 1. Ears

1a. Clipped-off helix, prominent antihelix that extends to the outer helical rim, antihelix discontinuous with the antitragus; absent lobe

1b. Antihelix discontinuous with the antitragus; very small lobe. Preauricular tag occurs occasionally.

1c. Clipped-off helix, prominent antihelix that extends to helical margin and does not connect with antitragus, triangular concha, and absent lobe

1d. Thin, unfolded helix, prominent inferior antihelix with notch between it and antitragus, rudimentary lobe

Option 1

Single-gene testing. Sequence analysis of *CHD7* is performed to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications and/or chromosomal microarray (CMA) to detect whole-gene deletions.

A multigene panel (e.g., for developmental delay, coloboma, deafness, heart defects, Kallmann syndrome, normosmic hypogonadotropic hypogonadism) that includes *CHD7* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Figure 2. Face

2a. Female age 2.5 years; square face, round eye, straight nose with broad nasal root, unilateral facial palsy

2b. Female age five years; mild expression of CHARGE facies; relatively square face, prominent columella of the nose. Note sloping shoulders.

2c. Male age seven years; square face, somewhat broad nasal root. Note prominent ear with unfolded helix and wide neck.

2d. Female age nine years; square face, round eyes, wide neck, sloping shoulders. Note lack of facial expression as a result of bilateral facial palsy.

2e. Male age 15 years. Note longer but still somewhat square face, wide neck with sloping shoulders.

2f. Female age 18 years; square, asymmetric face, prominent ears, head tilted back, wide neck, and sloping shoulders

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

Because *CHD7* disorder typically includes multiple congenital anomalies, it is also reasonable to pursue **chromosomal microarray** testing first, unless classic features of *CHD7* disorder (e.g., the CHARGE syndrome phenotype) are apparent.

Alternatively, 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 sequence analysis.

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

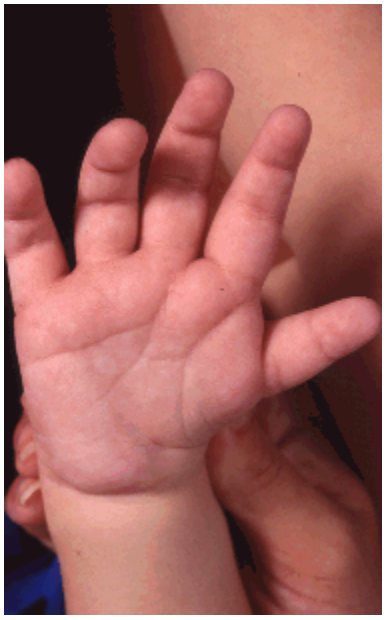

Figure 3. Hand

Typical CHARGE hand: square hand, short fingers, finger-like thumb, hockey-stick palmar crease

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 *CHD7* disorder [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 *CHD7* disorder but in whom no pathogenic variant in *CHD7* has been identified via sequence analysis or genomic testing; or (2) suggestive findings of *CHD7* disorder and a 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 *CHD7* Disorder

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method [3]
CHD7	Sequence analysis [4]	98%
	Gene-targeted deletion/duplication analysis [5, 6]	2%

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. Percentages based on information from the locus-specific database CHD7.org [Janssen et al 2012]
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; 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.
6. Most deletions detected to date are whole-gene deletions that can be detected with gene-targeted deletion/duplication analysis; however, this method will not provide the size of a larger deletion that may include *CHD7* and contiguous genes. Such deletions may also be identifiable by chromosomal microarray analysis [Vuorela et al 2007, Bergman et al 2008, Janssen et al 2012].

Clinical Characteristics

Clinical Description

In the premolecular era, the acronym CHARGE was proposed for the combination of the clinical features *c*oloboma, *h*eart defect, choanal *a*tresia, *r*etarded growth and development, *g*enital hypoplasia, *e*ar anomalies (including deafness) of unknown cause [Pagon et al 1981]. Clinical diagnostic criteria were refined for what became called CHARGE association [Blake et al 1998, Verloes 2005]. Following the discovery that heterozygous *CHD7* variants and deletions cause CHARGE syndrome [Vissers et al 2004], molecular genetic testing of family members of probands with CHARGE syndrome expanded the phenotypic spectrum to include phenotypes that do not fulfill the previously proposed CHARGE syndrome clinical diagnostic criteria [Lalani et al 2006, Delahaye et al 2007, Jongmans et al 2009, Bergman et al 2011b, Hale et al 2016]. Thus, *CHD7* disorder exhibits a high degree of clinical variability even among individuals in the same family and among individuals from different families with the same pathogenic variant [Jongmans et al 2008].

This section discusses only those reports in which a *CHD7* pathogenic variant has been confirmed in affected individuals. To date reports of isolated manifestations of *CHD7* disorder have been rare – many of which did not document a clinical workup sufficient to identify other features in the *CHD7* disorder phenotypic spectrum. Thus, the percentages in Table 2 (based on persons with molecularly confirmed CHARGE syndrome [van Ravenswaaij-Arts & Martin 2017]) are likely to change over time as individuals with a *CHD7* pathogenic variant ascertained through use of a multigene panel or genomic testing undergo a complete clinical evaluation (see Table 5).

Table 2. Features of *CHD7* Disorder in Individuals Ascertained for CHARGE Syndrome

Feature		% of Persons w/ Feature	Comment
Ocular coloboma (ranging from small retinal coloboma to anophthalmia)		80%	Light sensitivity, refractive error, loss of upper visual field/central visual field, blindness, ↑ risk of retinal detachment
Choanal atresia/stenosis		45%	• Interferes w/breathing & feeding • May require several surgeries to remain patent • Unilateral stenosis may be easily missed.
Cranial nerve dysfunction/ anomaly	I: hyposmia or anosmia	90%	↓ or absent sense of smell predicts hypogonadotropic hypogonadism.
	VII: facial palsy	40%	• Asymmetric face or lack of facial expression • Facial nerve often has an aberrant course, which correlates w/SNHL & can be damaged during cochlear implant surgery.
	VIII: SNHL &/or vestibular dysfunction	>95%	• Hearing loss • Cochlear implant may not be successful.
	IX/X: suck & swallow, abnormal GI motility	60%-80%	• Lack of coordination of suck & swallow, aspiration, &/or gastroesophageal reflux • Oral defensiveness • Digestive & constipation issues

Table 2. continued from previous page.

Feature		% of Persons w/ Feature	Comment
Ear malformations	Abnormal auricle	90%	• See description in Suggestive Findings, Characteristic ear malformations. • SNHL, esp high frequency
	Ossicular malformations	80%	• Conductive hearing loss, which may fluctuate w/middle ear disease • Complex mixed hearing loss may present as a wedge-shaped audiogram.
	Mondini defect	90%	SNHL, esp high frequency
	Semicircular canal defect	94%	Affects balance & visual processing, → delayed motor development
Cleft lip and/or palate		25%-50%	
Endocrine [1]	Hypogonadotropic hypogonadism	50%-70%	• Micropenis, cryptorchidism • Small labia, uterine abnormality • Delayed or absent puberty & infertility • Often in combination w/anosmia
	Growth deficiency	70%	May be due to growth hormone deficiency (in ~10%)
	Hypothyroidism	15%-20%	
Developmental delay / Intellectual disability		>90% / 60%	DD due to sensory deficits (hearing, vision, balance), illness, & hospitalizations
Cardiovascular malformation		74%	• Conotruncal/outflow defects are particularly common; isolated ASD, VSD, PDA, PFO also occur. • Vascular sling/aberrant aortic artery may result in choking.
Tracheoesophageal anomalies		20%	Esophageal atresia w/or w/o fistula, laryngotracheomalacia, & gastroesophageal reflux, → feeding & breathing difficulties, aspiration (pneumonia), & sinusitis
Brain	Clivus hypoplasia Hypoplasia/J-shaped sella	95%	
	Other	50%	Microcephaly, ventriculomegaly, Dandy-Walker malformation, hypoplastic corpus callosum (30%), hypoplasia of cerebellar vermis (50%), brain stem, &/or frontal lobe
Seizures		30%	Onset at any age, mostly general tonic-clonic convulsions as well as absence epilepsy
Renal anomalies		30%	• Missing, hypoplastic, horseshoe, ectopic, or cystic kidney • Vesicoureteral reflux & hydronephrosis

ASD = atrial septal defect; DD = developmental delay; PDA = patent ductus arteriosus; PFO = patent foramen ovale; SNHL = sensorineural hearing loss; VSD = ventricular septal defect

Based on individuals with molecularly confirmed typical or partial CHARGE syndrome [van Ravenswaaij-Arts & Martin 2017]. Note: percentages in this table are highly ascertainment dependent (i.e., the reason for molecular genetic testing). With the increasing use of multigene panels and genomic testing, it is likely that more individuals with presentations atypical for classic CHARGE syndrome will be diagnosed with *CHD7* disorder.

1. Balasubramanian & Crowley [2017], Xu et al [2018]

Because the majority of individuals with a pathogenic *CHD7* variant have a typical CHARGE syndrome or CHARGE syndrome-like phenotype, the clinical features described below are relevant for most individuals with *CHD7* disorder. In contrast, isolated hypogonadotropic hypogonadism with or without anosmia due to a pathogenic *CHD7* missense variant appears to be rare [Xu et al 2018].

Development

Motor delay is invariably present due to vestibular anomalies and presents as poor head control, five-point crawl, delayed motor milestones, and reduced fine motor skills.

Language delay is caused by hearing loss, vision loss, vestibular anomalies, hospitalizations and illness, and/or cognitive impairment.

Assessment of cognitive abilities is difficult because of the multiple sensory deficits (vision, hearing, balance, smell), and much of the delay observed in motor and speech/language abilities is secondary to these deficits. Nonetheless, intellectual outcome is within the normal range in 50% of the individuals with clinical features consistent with CHARGE syndrome [Vesseur et al 2016b].

Children with better walking skills and fewer medical problems exhibit better adaptive behavior than children with less mobility and more medical problems [Salem-Hartshorne & Jacob 2005].

Behavioral features often reported are attention-deficit/hyperactivity disorder, repetitive behavior, and obsessive-compulsive behaviors. Self-abuse is occasionally seen. An increased pain threshold may predispose children to behaviors that are incorrectly interpreted by others as aggressive [Hartshorne et al 2005].

Many adults with clinical features consistent with CHARGE syndrome live independently, including many who have college or even advanced degrees. However, the level of independence comprises a broad spectrum [Blake et al 2005, Hartshorne et al 2016], depending, for each individual, on the combination of clinical features, educational program designed to address specific needs, and resources available.

Other Features

Gastrointestinal problems are frequently seen, mainly GI-related motility issues such as gastroesophageal reflux disease, constipation, and abdominal pain. Feeding challenges often result in tube feeding and problems with aspiration.

Late-onset issues can include malrotation of intestines, intussusception, and choking due to mouth overstuffing [Hudson et al 2015, Blake & Hudson 2017].

Immunodeficiency due to absent thymus (rarely) or decreased number or function of T-cells may occur [Wong et al 2015b]. Recurrent upper airway infections are common.

Skeletal involvement can include craniosynostosis, vertebral anomalies, scoliosis (in the majority of affected individuals) [Doyle & Blake 2005], extra or missing ribs, absent long bones (rare), ectrodactyly, polydactyly, finger-like thumb, and (more commonly) brachydactyly [Van de Laar et al 2007].

Hypermobility and contractures can be part of the syndrome.

Neuromuscular problems are common in CHARGE syndrome, mostly hypotonia (often resulting in scoliosis) and abnormal shoulder girdle muscles [O'Grady et al 2016]. Proprioception is diminished and, when in combination with balance problems, often results in a preference for pressure-building postures (upside-down position, legs twisted around one another) [Brown 2005].

Dental problems may include overbite, hypodontia, and poor mineralization of teeth [Chetty et al 2020].

Life expectancy highly depends on the severity of manifestations, since the phenotypic spectrum of *CHD7* disorder is substantial. Mortality can be high in the first few years, when severe birth defects (particularly complex heart defects) are present, and are often complicated by airway and feeding issues. Feeding difficulties are usually due to cranial nerve abnormalities and improve gradually.

Multiple complex surgeries, along with the breathing problems or difficulty with anesthesia reported in CHARGE syndrome [Blake et al 2009], increase the risks associated with procedures.

After the first two or three years, mortality (and certainly morbidity and medical fragility) remains increased, with parents reporting frequent illnesses, infections, and hospitalizations [Bergman et al 2010].

In childhood, adolescence, and adulthood, increased mortality is likely related to a combination of residual heart defects, infections, aspiration or choking [Corsten-Janssen et al 2016], respiratory issues including obstructive and central apnea, and possibly seizures.

A number of families have reported serious (and in some instances lethal) intestinal issues such as volvulus [Lai & Feng 2006] and intussusception.

Despite these complications, the life span for many individuals can be normal. Individuals with clinical features consistent with CHARGE syndrome in their 60s who are in good health have been observed.

Genotype-Phenotype Correlations

While no clear genotype-phenotype correlations exist for *CHD7*-related CHARGE syndrome [Legendre et al 2017], in general, but not as a rule, missense variants are associated with a less severe phenotype [Bergman et al 2012].

CHD7-related hypogonadotropic hypogonadism with or without anosmia is more likely to be due to missense variants than nonsense variants.

Prevalence

Because of the more widespread use of genomic testing, it is currently difficult to assess the prevalence of *CHD7* disorder.

In the past, when the diagnosis of CHARGE syndrome was based on clinical features or gene-specific molecular testing, its estimated prevalence ranged from one in 15,000 newborns in the Netherlands [Janssen et al 2012] to one in 8,500 in Canada [Issekutz et al 2005].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *CHD7*.

Differential Diagnosis

Genetic disorders with multiple features overlapping those associated with *CHD7* disorder are summarized in Table 3 and Table 4.

Table 3. Genes to Consider in the Differential Diagnosis of *CHD7* Disorder

Gene	Disorder	MOI	Clinical Features of the Differential Disorder	
			Overlapping w/*CHD7* Disorder	Distinguishing from *CHD7* Disorder
≥34 genes	Joubert syndrome	AR XL Digenic	Bilateral chorioretinal coloboma, interstitial fibrosis of kidney → renal insufficiency, hepatic fibrosis, neonatal tachypnea, cerebellar vermis aplasia/hypoplasia, polydactyly	"Molar tooth" sign on neuroimaging, characteristic radiologic features, absence of dysmorphic features of *CHD7* disorder
EYA1 *SIX1* *SIX5*	Branchiootorenal spectrum disorder	AD	Deafness, external ear deformity, lateral semicircular canal hypoplasia, renal malformation	Branchial fistulae & cysts, absence of dysmorphic features of *CHD7* disorder
KDM6A *KMT2D*	Kabuki syndrome	AD XL	Cleft palate, heart defects, occasional coloboma, hearing loss, growth restriction	Typical facial features: long palpebral fissures w/eversion of lateral 3rd of lower eyelids, sparse eyebrows, large prominent ears (all more prominent w/age), prominent fingertip pads
PAX2	*PAX2* disorder (renal coloboma syndrome)	AD	Retinal/optic nerve colobomas; kidney abnormalities; occasional hearing loss	Absence of multiple congenital anomalies
BMP4	Syndromic microphthalmia 6 (OMIM 607932)	AD	Colobomas, external ear anomalies, hearing loss, congenital heart defect, genital hypoplasia, cleft lip/palate, pituitary problems, renal anomalies	Anophthalmia is more common than in *CHD7* disorder.
EFTUD2	Mandibulofacial dysostosis w/microcephaly	AD	Choanal atresia, external ear anomalies, hearing loss, congenital heart defect, growth deficiency, cleft lip/palate, esophageal atresia	Typical craniofacial features due to malar hypoplasia
FGFR1	*FGFR1* Kallmann syndrome [1] (OMIM 147950)	AD	Colobomas, hearing loss, genital hypoplasia, ↓ or absent sense of smell, cleft lip/palate [1]	
GLI2	Culler-Jones syndrome (OMIM 615849)	AD	External ear anomalies, hearing loss, cleft lip/palate, growth deficiency, pituitary problems, renal anomalies	Midface hypoplasia & postaxial polydactyly
GLI3	Pallister-Hall syndrome	AD	Colobomas, external ear anomalies, congenital heart defect, growth deficiency, genital hypoplasia, cleft lip/palate, pituitary problems, renal anomalies	Hypothalamic hamartomas, central polydactyly
JAG1 *NOTCH2*	Alagille syndrome	AD	Congenital heart defect, renal anomalies	Cholestasis, butterfly vertebrae, posterior embryotoxon, triangular-shaped face
MYCN	Feingold syndrome 1	AD	Hearing loss, heart defect, esophageal atresia, renal anomalies	Brachymesophalangy
OTX2	Syndromic microphthalmia 5 (OMIM 610125)	AD	Colobomas, growth deficiency, genital hypoplasia, cleft palate, pituitary problems	Anophthalmia more common than in *CHD7* disorder; corpus callosum agenesis; may appear as otocephaly-dysgnathia complex
POLR1C *POLR1D* *TCOF1*	Treacher Collins syndrome	AD AR	Choanal atresia, external ear anomalies, hearing loss, cleft palate	Typical craniofacial features due to malar hypoplasia; normal intellect

Table 3. continued from previous page.

Gene	Disorder	MOI	Clinical Features of the Differential Disorder	
			Overlapping w/*CHD7* Disorder	Distinguishing from *CHD7* Disorder
SOX2	*SOX2* disorder	AD	Colobomas, hearing loss, congenital heart defect, growth deficiency, genital hypoplasia, esophageal atresia, pituitary problems	Anophthalmia is more common than in *CHD7* disorder.
TBX22	Abruzzo-Erickson syndrome (OMIM 302905)	XL	Colobomas, hearing loss, growth deficiency, cleft palate	Radioulnar synostosis, large & protruding ears
ZEB2	Mowat-Wilson syndrome	AD	External ear anomalies, congenital heart defect, growth deficiency, genital hypoplasia, cleft palate, renal anomalies	Distinctive facial features (incl uplifted ear lobes), Hirschsprung disease, hypospadias in males

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; XL = X-linked
1. If hyposmia or anosmia is the presenting feature, Kallmann syndrome must be considered, especially Kallmann syndrome caused by pathogenic variants in *FGFR1* (pathogenic variants in 16 genes, including *CHD7*, are known to be associated with Kallmann syndrome).

Table 4 lists the chromosomal syndromes that overlap significantly with *CHD7* disorder. Many other chromosome deletions have at least a few features that overlap with *CHD7* disorder.

Table 4. Chromosomal Syndromes that Significantly Overlap with *CHD7* Disorder

Genetic Mechanism	Disorder	Clinical Features of Differential Disorder	
		Overlapping w/*CHD7* Disorder	Distinguishing from *CHD7* Disorder
Deletion 22q11.2	22q11.2 deletion syndrome	Congenital heart disease, palatal abnormalities, [1] learning difficulties, immune deficiency, significant feeding problems, renal anomalies, hearing loss, laryngotracheoesophageal anomalies, growth hormone deficiency, skeletal abnormalities	Abnormalities of semicircular canals rarely seen; ocular colobomas rare; feeding difficulties typically end sooner than in children w/*CHD7* disorder; dysmorphic features (face, ears, hands) are different
Inv dup 22q11	Cat-eye syndrome (OMIM 115470)	Coloboma of iris, anal atresia w/fistula, preauricular tags &/or pits, frequent occurrence of heart & renal malformations	Absence of dysmorphic & otologic features of *CHD7* disorder

VACTERL association (OMIM 192350). *CHD7* disorder and VACTERL association can both include vertebral anomalies, cardiac anomalies, tracheoesophageal fistula (or esophageal atresia), renal anomalies, and limb anomalies. Anal atresia, common in VACTERL, is rare in *CHD7* disorder. Typical *CHD7* disorder findings of temporal bone anomaly, choanal atresia, characteristic ear findings (outer and inner), and cranial nerve anomalies are rarely reported in VACTERL. The genetic basis of VACTERL association is unknown.

CHARGE syndrome-like features secondary to prenatal teratogen exposure. Exposure to Accutane™ at any time during the first trimester may result in malformations associated with abnormal migration of neural crest cells. These may include microtia/anotia, micrognathia, cleft palate, conotruncal heart defects, and aortic-arch abnormalities, thymic defects, retinal or optic nerve abnormalities, and central nervous system malformations [Lammer et al 1985].

Exposure to antithyroid agents, especially methimazole, has been reported to result in a variety of congenital anomalies including choanal and esophageal atresia, iris and retinal coloboma, hearing loss, and delayed

neurodevelopment. The risk of birth defects in fetuses exposed during the first trimester of pregnancy has been estimated at 2%-3% [Andersen et al 2013, Komoike et al 2013, Andersen et al 2017].

Management

The management of the manifestations of *CHD7* disorder can be complex and require a multidisciplinary approach involving clinicians, therapists, and educators. Published CHARGE syndrome guidelines (including one-page summaries) for clinical management [Trider et al 2017] (see Figure 4) and cranial imaging guidelines [de Geus et al 2017] (full text) are available.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with *CHD7* disorder, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

CHARGE Syndrome Checklist: Health Supervision Across The Life Span (From Head To Toe)

*Shaded boxes indicate key assessment points

		INFANCY (0-2 years)	CHILDHOOD (3-11 years)	ADOLESCENCE (12-17 years)	ADULTHOOD (18+ years)
Genetics	Clinical diagnosis (Blake et al. or Verloes or Hale et al. criteria)				
	Genetic testing – Genetics consult (CHD7 analysis, array CGH)				
	Genetic counselling				
Neurology	CNS malformations/hypoplasia olfactory bulb/temporal bone (semi-circular canal) malformations – requires MRI/CT				
	Seizures – more common at older ages – consider EEG				
	Cranial nerve problems – monitor for absent sense of smell, facial nerve palsy, sensorineural hearing loss, vertigo, swallowing problems				
Eyes, Ears, Nose and Throat	Coloboma, risk of retinal detachment - Ophthalmology consult (dilated eye exam in infancy, vision assessments)				
	Corneal exposure – lubricating eye drops				
	Photophobia – tinted glasses, sunhat				
	Choanal atresia/cleft palate/tracheoesophageal fistula - ENT/Plastics consult				
	Audiometry and tympanometry, monitor for recurrent ear infections				
	Adaptive services for individuals with deafness/blindness				
	Cochlear implant assessment if applicable				
	Obstructive sleep apnea – monitor for tonsil/adenoid hypertrophy				
	Excessive secretions – consider Botox, medication				
	Dental issues – consider cleaning under anaesthetic				
Cardiology Respirology	Cardiac malformations common – major/minor defects, vascular ring or arrhythmias possible (echocardiogram, chest x-ray, ECG) - Cardiology consult				
	Sinusitis, pneumonia, asthma - monitor				
	Anesthesia risk (difficult intubations/post-op airway obstruction/aspiration) – extensive pre-operative assessment, combine surgical procedures				
Gastroenterology Genitourinary	Gastroesophageal reflux – Gastroenterology consult – consider motility agents with proton pump inhibitor				
	Poor suck/chew/swallow - feeding team assessment/intervention				
	Aspiration risk, tracheoesophageal fistula – swallowing studies				
	May need supplemental feeds – frequently requires gastrostomy tube or gastrojejunostomy tube				
	Constipation – consider Senna glycoside with polyethylene glycol				
	Renal anomalies – abdominal u/s +/- VCUG, blood pressure monitoring				
Endocrinology	Hypogonadotropic hypogonadism – LH, FSH by 3 months				
	Genital hypoplasia (if undescended testes - consider orchidoplexy)				
	Delayed puberty – Endocrinology consult - gonadotropin levels, HRT				
	Osteoporosis – DEXA scan				
	Poor growth – Endocrinology consult – GH stimulation test, GH therapy				
	Obesity - monitor				
	Fertility and contraception - discuss				
Immune System	Note presence of thymus at open heart surgery				
	Routine immunizations/antibody titres to immunizations in adolescence				
	Recurrent infections – Immunology consult				
MSK	Scoliosis/kyphosis- monitor				
	Mobility (affected by ataxia, hypotonia) - evaluate				
Psychology Developmental	Assess gross and fine motor skills – Occupational Therapy, Physiotherapy				
	Communication, language, writing abilities – Speech Language Therapy				
	Consider deaf-blind consultant				
	Prepare for transitions to school, situations, places, systems				
	Psychoeducational assessment, Individualized Education Plan				
	Sleep disturbances – consider melatonin				
	Behavior management – self-regulation, impulse control, anxiety, obsessions, compulsions, anger				
	Toileting skills - support				
	Life skills/adaptive behaviour/social skills/social play				
	Address sexuality				
	Family stress – offer supports and resources				
	Medical self-management – work on managing medications, understanding conditions, seeing healthcare provider independently				

Figure 4. CHARGE syndrome checklist

Reproduced from Trider et al [2017]

Table 5. Recommended Evaluations Following Initial Diagnosis in an Individual with a *CHD7* Disorder

System/Concern	Evaluation	Comment
Constitutional	Measurement of weight, length/height, & head circumference	To assess for growth failure &/or obesity
Eyes	Ophthalmology eval	• Best corrected visual acuity; assess for refractive error, possible amblyopia • Assess for iris coloboma, photophobia, & possible corneal exposure due to VIIth nerve palsy. • Dilated fundus exam for chorioretinal coloboma, optic nerve coloboma, retinal detachment • Functional visual assessment incl visual fields in older individuals
Hearing / Vestibular involvement	Audiology eval [1]	Assess for conductive & sensorineural hearing impairment.
	Clinical assessment for balance issues	
	MRI/CT temporal bone	Evaluate semicircular canals, cochlea, & cranial nerves (see Figure 5 for details).
Nose/Throat	Clinical eval for choanal atresia/stenosis	• Suggestive findings in neonates & infants incl apnea & unilateral nasal discharge • Referral to otolaryngologist
	Assessment for tracheoesophageal fistula	If: • Aspiration pneumonia • Coughing or choking w/feeding • Infant has a full, round abdomen
	Tonsils & adenoids	If evidence of obstructive apnea
Mouth	Clinical eval for cleft palate, submucous cleft palate, & velopharyngeal insufficiency	Consider referral to craniofacial team.
	Baseline eval by dentist, typically from age ~3 yrs (or earlier in those w/cleft palate)	• Abnormal shape & # of teeth [2] • Complications due to craniofacial abnormalities &/or bruxism
Cardiovascular	EKG & echocardiogram [3]	Referral to cardiologist as indicated
Respiratory	Consider polysomnogram.	To assess for sleep apnea
	Consider pulmonary function tests.	In older individuals w/severe scoliosis who may have restrictive lung disease
Gastrointestinal/ Feeding	Assess for signs & symptoms of dysphagia & aspiration.	Consider VFSS & nutrition/feeding team eval for those w/ suggestive features or aspiration & pneumonia.
	Assess for history of GERD & GI motility issues. [4]	Referral to GI specialist as indicated
Genitourinary	Males: assess for micropenis &/or cryptorchidism.	• Cryptorchidism: referral to urologist • Micropenis: see **Endocrine** in this table
	Females: consider pelvic ultrasound examination.	• To assess for uterine & ovarian anomalies • Note that ability of US exam &/or MRI to detect uterine anomalies in prepubertal girls is limited.
Musculoskeletal	Clinical assessment for scoliosis	• Consider spine radiographs as a baseline. • Consider referral to orthopedist.

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Neurologic	Clinical assessment for cranial nerve abnormalities	• To incl assessment for swallowing dysfunction (See **Gastrointestinal/Feeding** in this table.) • If present, consider CT &/or MRI imaging [5]
	Cranial MRI & EEG if seizures are suspected	Consider referral to neurologist.
Development	Developmental assessment	• A team approach is necessary. • Incl motor, speech/language eval, general cognitive abilities, educational needs, &/or vocational opportunities. • Incl appropriate testing to assess cognitive function in those w/sensory deficits. • Abilities may be underestimated, especially in early yrs. • Evaluate for early intervention/special education, referral to deaf-blind programs when appropriate.
Psychiatric/ Behavioral	Consider neuropsychiatric eval.	• Adapt testing environment as needed to ↑ patient comfort. • Screen for ADHD, anxiety, obsessive-compulsive symptomatology.
Endocrine	• Males w/micropenis: consider HCG stimulation test, ideally before age 6 mos. • Males & females w/delayed or absent puberty: eval for hypogonadotropic hypogonadism [6]	Anosmia may be indicative for GnRH dysfunction.
	• Measure calcium & vitamin D levels. [7] • Thyroid function tests • Consider referral to endocrinologist.	
Renal	Renal US exam	To assess for renal anomalies, hydronephrosis, & calcifications
	Blood pressure measurement	To assess for hypertension
Immune	Consider immunologic eval [8] & referral to immunologist.	For those w/recurrent or unexplained infection
Genetic counseling	By genetics professionals [9]	To inform affected persons & their families re nature, MOI, & implications of *CHD7* disorder to facilitate medical & personal decision making

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
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; GERD = gastroesophageal reflux disease; GnRH = gonadotropin-releasing hormone; HCG = human chorionic gonadotropin; MOI = mode of inheritance; US = ultrasound; VFSS = video fluoroscopic swallow study
1. See Hereditary Hearing Loss and Deafness Overview for details about audiologic evaluations. Also perform audiology evaluation when there was a normal newborn hearing screen.
2. Chetty et al [2020]
3. To assess for arrhythmias and structural heart defects including vascular anomalies [Corsten-Janssen et al 2013]
4. Other issues may include malrotation, constipation, chronic abdominal pain, bloating, and late dumping syndrome [Morgan et al 2017].
5. de Geus et al [2017]
6. May include measurement of serum concentration of luteinizing hormone, follicle-stimulating hormone, and sex hormones (total testosterone in males, estrogen in females). See also Isolated Gonadotropin-Releasing Hormone (GnRH) Deficiency.
7. In adolescents and adults
8. May include immunoglobulin levels (IgG, IgM, IgA) and T and B cell subsets in case of a history of recurrent infections [Wong et al 2015a]
9. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Management of children with a *CHD7* disorder requires coordinated multidisciplinary care (Table 6).

Table 6. Treatment of Manifestations in Individuals with a *CHD7* Disorder

Manifestation/Concern	Treatment	Considerations/Other
Growth failure	See **Dysphagia / Inadequate nutrition** n this table.	• Nutrition optimization (team approach) • If poor linear growth remains, consider growth hormone stimulation test &/or growth hormone therapy.
Obesity	Weight-bearing exercises & dietary intervention	Adaptations in school physical education, which may also address sensory needs
Poor visual acuity / Blindness	Corrective lenses / standard treatment	Community vision services through early intervention or school district; deaf-blind services where available
Corneal exposure	Lubricating eye drops	
Photophobia	Tinted glasses or sun hat	
Hearing impairment / Deafness	Treatment of SNHL & conductive hearing loss depend on degree of hearing impairment. [1]	• Start hearing habilitation (auditory & speech training, sign language) as soon as possible. • Community hearing services through early intervention or school district
	Cochlear implant	CT of bony landmarks & MRI of vestibular & facial nerves as part of pre-cochlear implant assessment [2, 3]
	BAHA	If middle ear is disrupted due to abnormalities of middle ear bones but cochlear nerve is intact
	FM system	For those who are school age

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Chronic otitis media	PET placement	May need to be replaced multiple times until teenage yrs.
Poor balance	Adjustments to classroom or therapy setting (incl supine position) to allow for better truncal support	Frequent rest periods may be needed; consult w/OT, PT, & orientation & mobility services as needed
	Karate & other programs that promote good balance	
	Consideration of myofascial release	May improve posture & flexibility
Communication	Depends on degree of hearing & vision loss	Refer to community deaf-blind services & state deaf-blind projects as soon as possible after birth.
Choanal atresia/ stenosis	Infants: airway bypass by tracheotomy or endotracheal intubation	Multiple surgeries/dilatations are often required to maintain patency of nasal airway.
	Surgical correction	
Esophageal atresia / TEF	Standard surgical repair	
Cleft palate	Surgical correction	Ideally by craniofacial team
Dental decay / Hypodontia	May require sedated dental rehab	See Agents/Circumstances to Avoid.
Excessive secretions	Standard medication, incl glycopyrrolate or Botox®	
Congenital heart defect / Arrhythmia / POTS	Treatment per cardiologist	
Obstructive sleep apnea	Consider tonsillectomy & adenoidectomy.	CPAP is sometimes helpful.
Sleep disturbance	Sleep hygiene; consider trial of melatonin.	Consider referral to sleep disorder specialist.
Dysphagia / Inadequate nutrition	Nasogastric or gastrostomy tube may be required.	Low threshold for clinical feeding eval &/or radiographic swallowing study when clinical signs or symptoms of dysphagia are present
	GERD: standard treatment	
Constipation	Medication treatment, incl stimulant & osmotic laxatives	• Simple measures (e.g., ↑ fluid uptake) are often unsuccessful. • Referral to gastroenterologist as needed
Cryptorchidism	Standard treatment per urologist	
Severe scoliosis	Standard treatment per orthopedist	May have skeletal &/or neuromuscular causes
Seizure disorder	Standard treatment per neurologist	Standard ASMs are usually effective.
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	Utilize deafblind services where available.
Behavioral issues	For OCD, PDD: mindfulness treatment (psychologist & deafblind specialist), then consider medications	• Behavior therapy combined w/stress reduction may be helpful. • Behavior issues may be exacerbated by sensory processing issues.
	For ADHD: establish appropriate method of communication & provide adequate stimulation for exploration in safe environment.	This may be more helpful than medication.

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Hypogonadotropic hypogonadism	Standard treatment per endocrinologist	Typically, HRT to induce puberty & for general health reasons incl prevention of osteoporosis; see Isolated Gonadotropin-Releasing Hormone (GnRH) Deficiency.
Hypothyroidism	Standard treatment per endocrinologist	
Renal malformation	Standard therapy per urologist	
Hypertension	Standard therapy	
Recurrent infections	Standard therapy per immunologist	Revaccination may be required.
Family needs	Ensure appropriate social work involvement to connect families w/ local resources, respite, & support.	Ongoing assessment of need for home nursing
	Care coordination to manage multiple subspecialty appointments, equipment, medications, & supplies	Consider involvement in adaptive sports or Special Olympics.

ADHD = attention-deficit/hyperactivity disorder; ASM = anti-seizure medication; BAHA = bone-anchored hearing aid; CPAP = continuous positive airway pressure; DD = developmental delay; HRT = hormone replacement treatment; ID = intellectual disability; OCD = obsessive-compulsive disorder; OT = occupational therapist; PDD = pervasive developmental disorders; PET = pressure-equalizing tube; POTS = postural orthostatic tachycardia; PT = physical therapist; SNHL = sensorineural hearing loss; TEF = tracheoesophageal fistula

1. See Hereditary Hearing Loss and Deafness Overview for details about treatment options.

2. Evaluation of bony landmarks and the structure and pathways of the vestibular and facial nerves (which can be abnormal) is important in surgical planning [Vesseur et al 2016c]. See also Figure 5.

3. In some individuals, an aberrant course of the facial nerve may be a contraindication for cochlear implant [Vesseur et al 2016a, Vesseur et al 2016c].

CT AND MR SCANNING IN CHARGE SYNDROME

Objective	Uniformity in MRI and CT scanning in CHARGE syndrome Awareness of difficult airway in patients with CHARGE syndrome

Background

CHARGE syndrome is a rare congenital anomaly syndrome with a highly variable clinical spectrum. Common symptoms are coloboma of the eye (C), congenital heart defects (H), choanal atresia (A), retardation of growth or development (R), genital hypoplasia (G) and ear abnormalities (E). Additionally, cleft lip/palate, cranial nerve hypo- or aplasia and vestibular dysplasia are common. Individuals with CHARGE syndrome have a significantly increased risk of post-anesthesia airway complications due to a combination of factors, such as cranial nerve dysfunction and abnormal anatomy of the upper airways. The wide spectrum of symptoms in CHARGE syndrome requires imaging for several different indications. For many children, CT and MR imaging will have to be performed under anesthesia. To reduce the risk of anesthesia and minimize exposure to radiation, we recommend:

- performing comprehensive CT and MRI scanning in one session
- comprehensive pre-anesthesia screening, including cardiac screening, by a pediatric anesthesiologist

Scans to be performed

Indicated in all CHARGE patients:

- CT temporal bone/mastoid
- MRI brain

On indication: CT thorax (larynx, trachea, bronchial tree), cervical MRI, preoperative navigational CT of choanae

Typical abnormalities in cranial imaging in CHARGE syndrome

- Cranial nerves: hypoplasia or aplasia of cranial nerves, aberrant course of the facial nerve, colobomata
- Cochlea: various types of malformations
- Middle ear: dysplasia of the stapes/incus, absent or stenotic oval and round windows, persistent petrosquamous sinus, aberrant emissary vein, underpneumatization of the mastoid
- Semicircular canals and utriculus/vestibulum: aplasia or dysplasia
- Brain: cerebellar vermis hypoplasia, ventriculomegaly, frontal lobe hypoplasia, ectopic posterior pituitary, anterior pituitary hypoplasia, hypo- or aplasia of the olfactory nerve/bulb and effacement of olfactory groove
- Skull base: basioccipital hypoplasia, clivus hypoplasia, hypoplasia/J-shaped sella

Advised scanning techniques and sequences

CT temporal bone

Patient in supine position; minimize radiation dose to the lens (e.g. scan parallel to the inferior orbitomeatal line)

Scan range should include tegmen tympani up to the mastoid tip

Axial acquired volume of the temporal bone. Perform volume scan acquisition if the target can be covered in one single rotation. Otherwise, perform a helical acquisition in 4-slice mode with 0.5-0.625 mm as slice thickness (i.e. 4x0.5 mm or 4x0.625 mm collimation)

Zoomed in reconstructions (field of view=90mm, slice thickness 0.5-0.625mm and same or halved image spacing) of each ear magnified separately, selecting an ultrahigh resolution reconstruction algorithm specific for bone:

- axial plane: parallel to horizontal semicircular canal
- coronal plane: perpendicular to axial MPR

MRI brain

The MR imaging should ideally be performed on a 1.5 or 3 Tesla MRI

- Brain, including cerebellum: axial T_2-TSE, 2D or 3D FLAIR, IR, SWI, DWI, and a sagittal MPRAGE through the entire brain and skull base. Sagittal T_2 for additional imaging of cerebellar and clival pathology
- Orbits and choanal area: axial T_2 images and coronal STIR and T_1
- Clivus: sagittal T_1. In neonates, with less contrast between marrow and bone, T_2 may be useful
- Olfactory nerves: coronal T_2-FSE from the frontal basis to the brain stem, to include the olfactory nerves and sulci. MPRAGE/3D T_1/SPACE from the frontal basis, to the brain stem through to the level of the hypoglossal nerve, to include the olfactory nerves
- Other cranial nerves and labyrinth: T_2 CISS 3D from the level of the olfactory nerves through to the foramen magnum with sagittal and coronal reconstructed slices
- Pituitary gland: small field of view sagittal and coronal T_1 and T_2

If the child is restless acquisitions with radial k-space filling (e.g. BLADE, PROPELLOR, MultiVane) may be used in order to minimize artifacts, while retaining the contrast and spatial resolution

Acronyms and synonyms: CISS - Constructive Interference in the Steady State. Synonym: FIESTA-C; DWI - diffusion weighted images; FLAIR - fluid-attenuated Inversion recovery; IR - Inversion recovery; MPRAGE - Magnetization Prepared Rapid Gradient Echo. Synonyms: 3D T_1-TFE; 3D BRAVO; PROPELLOR - Periodically Rotated Overlapping Parallel Lines with Enhanced Reconstruction. Synonym: MultiVane; STIR - short T_1 inversion recovery; SWI - susceptibility weighted images; TSE - turbo spin echo. Synonym: FSE

Centre of Expertise for CHARGE syndrome, University Medical Center Groningen, the Netherlands

Figure 5. CT and MR Scanning in CHARGE Syndrome

Reproduced from de Geus et al [2017]

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 and 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 may be provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies 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.
  - 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.
- State deaf-blind services:
  - In addition to the educational services in the US discussed above, state-level federally funded programs are mandated to provide services for individuals from birth to age 21 years with combined hearing and vision issues (nationaldb.org/). Of note, the designation "deaf-blind," used to qualify

individuals with combined vision and hearing loss for these services, does not imply total hearing loss or total vision loss.
- State deaf-blind services typically provide information and training to families, technical assistance to schools and early intervention programs, and assistance with IEPs and transitions.

Communication

A growing body of evidence indicates that normal language development can occur if hearing habilitation is started prior to age six months for hearing-impaired children, whether or not they are visually impaired. (See Hereditary Hearing Loss and Deafness Overview, which provides details about management.)

Depending on the degrees of hearing and vision loss, communication may start with touch cues, followed by object cues and proceeding to auditory/oral and/or sign language. Communication training initiated by age three years is critical to the eventual development of symbolic communication [Thelin & Fussner 2005]. Use of all available means of communication (visual, oral, touch, and incorporating gestures, sign and oral languages) is advisable early on. Most affected children are able to migrate to oral communication as they get older, even if they start with sign and/or total communication.

Surveillance

Table 7. Recommended Surveillance for Individuals with *CHD7* Disorder

System/Concern	Evaluation	Frequency
Constitutional	Measurement of length/height & weight for evidence of linear growth failure or obesity	At each visit
Eyes	Ophthalmologic exam for changes in best corrected visual acuity, cataract, &/or retinal detachment (in those w/chorioretinal coloboma)	Every 6 mos or as clinically indicated
	Eval by deaf-blind specialist to assess functional vision	As clinically indicated
Ears/Nose/ Throat	Audiologic eval to determine type & extent of hearing loss & success w/hearing habilitation	Annually or as clinically indicated
	Assessment for chronic ear infections &/or effusions	At each visit through puberty
Mouth	Dental eval	At least every 6 mos after age 3 yrs
Cardiovascular	EKG & Holter monitor if suspicion of arrhythmia (esp in those w/ complex cardiac anomaly)	Starting in late childhood/early adolescence, as clinically indicated
	Blood pressure	At each visit
	Clinical assessment for signs & symptoms of POTS	At each visit in adolescents & adults
Respiratory	Clinical assessment for sleep disturbance &/or obstructive sleep apnea [1]	At each visit
Gastrointestinal/ Feeding	Assess for signs & symptoms of feeding anomalies incl dysphagia [2], reflux, constipation, & abdominal pain / abdominal migraine.	At each visit; note that new feeding issues can arise in adolescents & adults.
Musculoskeletal	Clinical &/or radiographic eval for scoliosis	At each visit until growth is complete (can be into early 20s)
Neurologic	Assessment for symptoms of seizures	At each visit
Development	Assessment of gross motor skills, fine motor skills, & communication abilities; school assessment for learning challenges	

Table 7. continued from previous page.

System/Concern	Evaluation	Frequency
Endocrine	Assessment of secondary sexual characteristics for evidence of delayed puberty or pubertal arrest due to hypogonadotropic hypogonadism	Between ages ~7 & 17 yrs
	For evidence of hypothyroidism	Based on symptoms
	DXA scan for bone mineral density	Periodically starting in adolescence [3]
Psychiatric/ Behavioral	Assessment of overall behavior, incl self-regulation, impulse control, anxiety, obsessions, compulsion, & anger	At each visit after infancy

DXA = dual-energy x-ray absorptiometry; EKG = electrocardiogram; POTS = postural orthostatic tachycardia
1. Including clinical evaluation of tonsil hypertrophy in those with retained tonsils
2. With low threshold to perform swallowing study, even in adolescents and adults
3. Particularly those with hypogonadotropic hypogonadism or those undergoing routine hormone replacement therapy

Agents/Circumstances to Avoid

Anesthesia. Airway problems associated with anesthesia are common in individuals with CHARGE syndrome. They may be attributed to choanal atresia, cleft lip and palate, and other upper-airway structural anomalies and associated cranial nerve abnormalities. Soft cartilage and resultant floppy trachea add to potential anesthesia risk. Neurogenic incoordination of swallow and closure of the epiglottis may complicate the postoperative course, especially with repeated general anesthetics [Blake et al 2009]. Because of the increased risk of post-anesthesia airway complications, procedures requiring anesthesia should be minimized and combined whenever possible [de Geus et al 2017].

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

CHD7 disorder is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with a *CHD7* disorder have the disorder as the result of a *de novo* pathogenic variant [Janssen et al 2012].

- In rare instances, an individual with *CHD7* disorder has the disorder as the result of a pathogenic variant inherited from a heterozygous parent. A parent who is heterozygous for a *CHD7* pathogenic variant may have one or more features associated with *CHD7* disorder [Mitchell et al 1985, Lalani et al 2006, Delahaye et al 2007, Bergman et al 2011b].
- Molecular genetic testing is recommended for the parents of a proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the *CHD7* pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a parent with somatic/germline mosaicism. Somatic mosaicism for a *CHD7* pathogenic variant has been documented [Jongmans et al 2008]. (Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism.)

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 a *CHD7* pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%.
- If the *CHD7* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the empiric recurrence risk to sibs of a proband is approximately 1%-2% because of the possibility of parental germline mosaicism [Jongmans et al 2008, Pauli et al 2009].
- The severity of *CHD7* disorder in a proband does not predict the severity of the disorder in sibs who inherit a pathogenic variant. (A high degree of clinical variability is observed *CHD7* disorder; see Clinical Characteristics.)

Offspring of a proband

- Many individuals with *CHD7* disorder are not able to reproduce.
- Each child of an individual with *CHD7* disorder has a 50% chance of inheriting the pathogenic variant.
- The severity of *CHD7* disorder in the proband does not predict the severity of the disorder in heterozygous offspring (a high degree of clinical variability is observed in *CHD7* disorder; see Clinical Characteristics).

Other family members. The risk to other family members depends on the genetic status of the proband's parents; if a parent has the *CHD7* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

For a review of genetic counseling issues in families in which a child has been diagnosed with CHARGE syndrome, see Hefner & Fassi [2017].

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 the parents of affected children and to young adults who are mildly affected.

Prenatal Testing and Preimplantation Genetic Testing

Once the *CHD7* 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.

- **Association CHARGE Enfant Soleil**
  France
  www.associationcharge.fr
- **CHARGE Family Support Group**
  London
  United Kingdom
  Phone: 020 8265 3604
  Email: si_howard@hotmail.com
  www.chargesyndrome.org.uk
- **CHARGE Information Pack**
  Sense
  CHARGE syndrome
- **CHARGE Syndrome Association of Australasia**
  Australia
  Phone: 61 480 121 345
  Email: admin@chargesyndrome.org.au
  www.chargesyndrome.org.au
- **CHARGE Syndrome e.V.**
  Germany
  Phone: 0049 – (0)9104 – 826 345
  Email: info@charge-syndrom.de
  www.charge-syndrom.de
- **CHARGE Syndrome Foundation**
  18 Half Day Road #305
  Buffalo Grove IL 60089
  Phone: 800-442-7604 (toll-free); 516-684-4720
  Fax: 516-883-9060
  Email: info@chargesyndrome.org
  www.chargesyndrome.org

- **Perkins School for the Blind**
  e-learning videos on CHARGE syndrome
- **Face Equality International**
  United Kingdom
  faceequalityinternational.org
- **National Consortium on Deaf-Blindness (NCDB)**
  Bibliography and links to state deafblind project resources
  345 North Monmouth Avenue
  Monmouth OR 97361
  Phone: 800-438-9376 (toll-free); 800-854-7013 (TTY)
  Fax: 503-838-8150
  Email: info@nationaldb.org
  www.nationaldb.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. CHD7 Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CHD7	8q12.2	Chromodomain-helicase-DNA-binding protein 7	CHD7 database	CHD7	CHD7

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 CHD7 Disorder (View All in OMIM)

214800	CHARGE SYNDROME
608892	CHROMODOMAIN HELICASE DNA-BINDING PROTEIN 7; CHD7
612370	HYPOGONADOTROPIC HYPOGONADISM 5 WITH OR WITHOUT ANOSMIA; HH5

Molecular Pathogenesis

CHD7 encodes a chromodomain protein that is involved in the ATP-dependent remodeling of chromatin. *CHD7* binds to more than 10,000 sites in the mammalian genome and interacts with dozens of other genes. Features of *CHD7*-related disorders may be due to loss of ribosomal biogenesis or other mechanisms.

CHD7 functions in a multiprotein complex and uses the energy of ATP to remodel nucleosomes. CHD7 is considered an epigenetic regulator because it modifies the degree to which chromatin is "open" or "closed," making it more or less accessible, respectively, to other proteins that activate or repress gene expression. The broad variability in phenotypes observed in individuals with *CHD7* disorder is not fully understood, but is likely related to its unique roles in specific cells and tissues at various times during development.

Mechanism of disease causation. Decreased function or loss of function of CHD7 leads to the clinical manifestations of *CHD7* disorder.

Chapter Notes

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Revision History

- 29 September 2022 (sw) Revision: epigenetic signature analysis (Establishing the Diagnosis, Option 2)
- 17 September 2020 (bp) Comprehensive update posted live
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- 14 April 2005 (jwb) Original submission

References

Literature Cited

Andersen SL, Lönn S, Vestergaard P, Törring O. Birth defects after use of antithyroid drugs in early pregnancy: a Swedish nationwide study. Eur J Endocrinol 2017;177:369-78. PubMed PMID: 28780518.

Andersen SL, Olsen J, Wu CS, Laurberg P. Birth defects after early pregnancy use of antithyroid drugs: a Danish nationwide study. J Clin Endocrinol Metab. 2013;98:4373-81. PubMed PMID: 24151287.

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.

Balasubramanian R, Crowley WF Jr. Reproductive endocrine phenotypes relating to CHD7 mutations in humans. Am J Med Genet Part C Semin Med Genet. 2017;175:507-15. PubMed PMID: 29152903.

Bergman JE, Blake KD, Bakker MK, du Marchie Sarvaas GJ, Free RH, van Ravenswaaij-Arts CM. Death in CHARGE syndrome after the neonatal period. Clin Genet. 2010;77:232-40. PubMed PMID: 20447140.

Bergman JE, Bocca G, Hoefsloot LH, Meiners LC, van Ravenswaaij-Arts CM. Anosmia predicts hypogonadotropichypogonadism in CHARGE syndrome. J Pediatr. 2011a:158:474-9. PubMed PMID: 20884005.

Bergman JE, de Wijs I, Jongmans MC, Admiraal RJ, Hoefsloot LH, van Ravenswaaij-Arts CM. Exon copy number alterations of the CHD7 gene are not a major cause of CHARGE and CHARGE-like syndrome. Eur J Med Genet. 2008;51:417-25. PubMed PMID: 18472328.

Bergman JE, Janssen N, Hoefsloot LH, Jongmans MC, Hofstra RM, van Ravenswaaij-Arts CM. CHD7 mutations and CHARGE syndrome: the clinical implications of an expanding phenotype. J Med Genet. 2011b;48:334-42. PubMed PMID: 21378379.

Bergman JE, Janssen N, van der Sloot AM, de Walle HEK, Schoots J, Rendtorff ND, Tranebjaerg L, Hoefsloot LH,van Ravenswaaij-Arts CM, Hofstra RM. A novel classification system to predict the pathogenic effects of CHD7 missense variants in CHARGE syndrome. Hum Mutat. 2012;33:1251-60. PubMed PMID: 22539353.

Blake K, MacCuspie J, Hartshorne TS, Roy M, Davenport SL, Corsten G. Postoperative airway events of individuals with CHARGE syndrome. Int J Pediatr Otorhinolaryngol. 2009;73:219-26. PubMed PMID: 19058860.

Blake KD, Davenport SL, Hall BD, Hefner MA, Pagon RA, Williams MS, Lin AE, Graham JM Jr. CHARGE association: an update and review for the primary pediatrician. Clin Pediatr (Phila). 1998;37:159-73. PubMed PMID: 9545604.

Blake KD, Hudson AS. Gastrointestinal and feeding difficulties in CHARGE syndrome: a review from head to toe. Am J Med Genet C Semin Med Genet. 2017;175:496-506. PubMed PMID: 29082627.

Blake KD, Salem-Hartshorne N, Abi Daoud M, Gradstein J. Adolescent and adult issues in CHARGE syndrome. Clin Pediatr (Phila) 2005;44:151-9. PubMed PMID: 15735833.

Brown D. CHARGE syndrome "behaviors": challenges or adaptations. Am J Med Genet A. 2005;133A:268-72. PubMed PMID: 15666302.

Chetty M, Roberts TS, Elmubarak M, Bezuidenhout H, Smit L, Urban M. CHARGE syndrome: genetic aspects and dental challenges, a review and case presentation. Head Face Med. 2020;16:10. PubMed PMID: 32384900.

Corsten-Janssen N, Kerstjens-Frederikse WS, du Marchie Sarvaas GJ, Baardman ME, Bakker MK, Bergman JE, Hove HD, Heimdal KR, Rustad CF, Hennekam RC, Hofstra RM, Hoefsloot LH, van Ravenswaaij-Arts CM. The cardiac phenotype in patients with a CHD7 mutation. Circ Cardiovasc Genet. 2013;6:248-54. PubMed PMID: 23677905.

Corsten-Janssen N, Scambler PJ. Clinical and molecular effects of CHD7 in the heart. Am J Med Genet C Semin Med Genet. 2017;175:487-95. PubMed PMID: 29088513.

Corsten-Janssen N, van Ravenswaaij-Arts CM, Kaputsa L. Congenital arch vessel anomalies in CHARGE syndrome: a frequent feature with risk for co-morbidity. Int J Cardiol Heart Vasc. 2016;12:21-5. PubMed PMID: 28616537.

de Geus CM, Bergman JE, van Ravenswaaij-Arts CM, Meiners LC. Imaging of clival hypoplasia in CHARGE syndrome and hypothesis for development: a case-control study. AJNR Am J Neuroradiol. 2018;39:1938-42. PubMed PMID: 30237300.

de Geus CM, Free RH, Verbist BM, Sival DA, Blake KD, Meiners LC, van Ravenswaaij-Arts CM. Guidelines in CHARGE syndrome and the missing link: cranial imaging. Am J Med Genet Part C Semin Med Genet. 2017;175:450-64. PubMed PMID: 29168326.

Delahaye A, Sznajer Y, Lyonnet S, Elmaleh-Berges M, Delpierre I, Audollent S, Wiener-Vacher S, Mansbach A-L, Amiel J, Baumann C, Bremond-Cignac D, Attié-Bitach T, Verloes A, Sanlaville D. Familial CHARGE syndrome because of CHD7 mutation: clinical intra- and interfamilial variability. Clin Genet. 2007;72:112-21. PubMed PMID: 17661815.

Donovan AP, Yu T, Ellegood J, Riegman KL, de Geus C, van Ravenswaaij-Arts C, Fernandes C, Lerch JP, Basson MA. Cerebellar vermis and midbrain hypoplasia upon conditional deletion of Chd7 from the embryonic mid-hindbrain region. Front Neuroanat. 2017;11:86. PubMed PMID: 29046629.

Doyle C, Blake KD. Scoliosis in CHARGE: a prospective survey and two case reports. Am J Med Genet A. 2005;133A:340-3. PubMed PMID: 15688383.

Hale CL, Niederriter AN, Green GE, Martin DM. Atypical phenotypes associated with pathogenic CHD7 variants and a proposal for broadening CHARGE syndrome clinical diagnostic criteria. Am J Med Genet A. 2016;170A:344-54. PubMed PMID: 26590800.

Hartshorne N, Hudson A, MacCuspie J, Kennert B, NacaratoT, Hartshorne T, Blake K. Quality of life in adolescents and adults with CHARGE syndrome. Am J Med Genet Part A. 2016;170:2012-21. PubMed PMID: 27273681.

Hartshorne TS, Hefner MA, Davenport SL. Behavior in CHARGE syndrome: introduction to the special topic. Am J Med Genet A. 2005;133A:228-31. PubMed PMID: 15637707.

Hefner MA, Fassi E. Genetic counseling in CHARGE syndrome: diagnostic evaluation through follow up. Am J Med Genet C Semin Med Genet. 2017;175:407-16. PubMed PMID: 29088501.

Hudson A, Colp M, Blake K. Pocketing of food in cheeks during eating in an adolescent with CHARGE syndrome. J Paediatr Child Health. 2015;51:1143-4. PubMed PMID: 26541624.

Issekutz KA, Graham JM, Prasad C, Smith IM, Blake KD. An epidemiological analysis of CHARGE syndrome: preliminary results from a Canadian study. Am J Med Genet A. 2005;133A:309-17. PubMed PMID: 15637722.

Janssen N, Bergman JE, Swertz MA, Tranebjaerg L, Lodahl M, Schoots J, Hofstra RM, van Ravenswaaij-Arts CM, Hoefsloot LH. Mutation update on the CHD7 gene involved in CHARGE syndrome. Hum Mutat. 2012;33:1149-60. PubMed PMID: 22461308.

Jongmans MC, Hoefsloot LH, van der Donk KP, Admiraal RJ, Magee A, van de Laar I, Hendriks Y, Verheij JB, Walpole I, Brunner HG, van Ravenswaaij CM. Familial CHARGE syndrome and the CHD7 gene: a recurrent missense mutation, intrafamilial recurrence and variability. Am J Med Genet. 2008;146A:43-50. PubMed PMID: 18074359.

Jongmans MC, van Ravenswaaij-Arts CM, Pitteloud N, Ogata T, Sato N, Claahsen-van der Grinten HL, van der Donk K, Seminara S, Bergman JE, Brunner HG, Crowley WF Jr, Hoefsloot LH. CHD7 mutations in patients initially diagnosed with Kallmann syndrome--the clinical overlap with CHARGE syndrome. Clin Genet. 2009;75:65-71. PubMed PMID: 19021638.

Komoike Y, Matsuoka M, Kosaki K. Potential teratogenicity of methimazole: exposure of zebrafish embryos to methimazole causes similar developmental anomalies to human methimazole embryopathy. Birth Defects Res B Dev Reprod Toxicol. 2013;98:222-9. PubMed PMID: 23630110.

Lai H-S, Feng C-Y. Cecal volvulus in a child with CHARGE syndrome. Am Surg. 2006;72:356-8. PubMed PMID: 16676864.

Lalani SR, Safiullah AM, Fernbach SD, Harutyunyan KG, Thaller C, Peterson LE, McPherson JD, Gibbs RA, White LD, Hefner M, Davenport SL, Graham JM, Bacino CA, Glass NL, Towbin JA, Craigen WJ, Neish SR, Lin AE, Belmont JW. Spectrum of CHD7 mutations in 110 individuals with CHARGE syndrome and genotype-phenotype correlation. Am J Hum Genet. 2006;78:303-14. PubMed PMID: 16400610.

Lammer EJ, Chen DT, Hoar RM, Agnish ND, Benke PJ, Braun JT, Curry CJ, Fernhoff PM, Grix Jr AW, Lott IT. Retionic acid embryopathy. N Engl J Med. 1985;313:837-41. PubMed PMID: 3162101.

Legendre M, Abadie V, Attié-Bitach T, Philip N, Busa T, Bonneau D, Colin E, Dollfus H, Lacombe D, Toutain A, Blesson S, Julia S, Martin-Coignard D, Geneviève D, Leheup B, Odent S, Jouk PS, Mercier S, Faivre L, Vincent-Delorme C, Francannet C, Naudion S, Mathieu-Dramard M, Delrue MA, Goldenberg A, Héron D,

Parent P, Touraine R, Layet V, Sanlaville D, Quélin C, Moutton S, Fradin M, Jacquette A, Sigaudy S, Pinson L, Sarda P, Guerrot AM, Rossi M, Masurel-Paulet A, El Chehadeh S, Piguel X, Rodriguez-Ballesteros M, Ragot S, Lyonnet S, Bilan F, Gilbert-Dussardier B. Phenotype and genotype analysis of a French cohort of 119 patients with CHARGE syndrome. Am J Med Genet C Semin Med Genet. 2017;175:417-30. PubMed PMID: 29178447.

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.

Mitchell JA, Giangiacomo J, Hefner MA, Thelin JW, Pickens JM. Dominant CHARGE association. Ophthalmic Paediatr Genet. 1985;6:271-6. PubMed PMID: 3934623.

Morgan A, Hudson A, Arra-Robar A, Blake K. Late dumping syndrome in a 17-year-old female with Charge syndrome. J Paediatr Child Health. 2017;53:1244-5. PubMed PMID: 29205658.

O'Grady GL, Ma A, Sival D, Wong MT, Peduto T, Menezes MP, Young H, Waddell L, Ghaoui R, Needham M, Lek M, North KN, MacArthur DG, van Ravenswaaij-Arts CM, Clarke NF. Prominent scapulae mimicking an inherited myopathy expands the phenotype of CHD7-related disease. Eur J Hum Genet. 2016;24:1216-9. PubMed PMID: 26813943.

Pagon RA, Graham JM Jr, Zonana J, Yong SL. Coloboma, congenital heart disease, and choanal atresia with multiple anomalies: CHARGE association. J Pediatr. 1981;99:223-7. PubMed PMID: 6166737.

Pauli S, Pieper L, Häberle J, Grzmil P, Burfeind P, Steckel M, Lenz U, Michelmann HW. Proven germline mosaicism in a father of two children with CHARGE syndrome. Clin Genet. 2009;75:473-9. PubMed PMID: 19475719.

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.

Salem-Hartshorne N, Jacob S. Adaptive behavior in children with CHARGE syndrome. Am J Med Genet A. 2005;133A:262-7. PubMed PMID: 15641025.

Thelin JW, Fussner JC. Factors related to the development of communication in CHARGE syndrome. Am J Med Genet A. 2005;133A:282-90. PubMed PMID: 15669098.

Trider C-L, Arra-Robar A, van Ravenswaaij-Arts C, Blake K. Developing a CHARGE syndrome checklist: health supervision across the lifespan (from head to toe). Am J Med Genet A. 2017;173:684-91. PubMed PMID: 28160409.

Van de Laar I, Dooijes D, Hoefsloot L, Simon M, Hoogeboom J, Devriendt K. Limb anomalies in patients with CHARGE syndrome: an expansion of the phenotype. Am J Med Genet A. 2007;143A:2712-5. PubMed PMID: 17937444.

van Ravenswaaij-Arts C, Martin DM. New insights and advances in CHARGE syndrome: diagnosis, etiologies, treatments, and research discoveries. Am J Med Genet Part C Semin Med Genet. 2017;175:397-406. PubMed PMID: 29171162.

Verloes A. Updated diagnostic criteria for CHARGE syndrome: a proposal. Am J Med Genet A. 2005;133A:306-8. PubMed PMID: 15666308.

Vesseur A, Free R, Langereis M, Snels C, Snik A, van Ravenswaaij-Arts C, Mylanus E. Suggestions for a guideline for cochlear implantation in CHARGE syndrome. Otol Neurotol. 2016a;37:1275-83. PubMed PMID: 27636388.

Vesseur A, Langereis M, Free R, Snik A, van Ravenswaaij-Arts C, Mylanus E. Influence of hearing loss and cognitive abilities on language development in CHARGE syndrome. Am J Med Genet A. 2016b;170:2022-30. PubMed PMID: 27145116.

Vesseur AC, Verbist BM, Westerlaan HE, Kloostra FJ, Admiraal RJ, van Ravenswaaij-Arts CM, Free RH, Mylanus EA. CT findings of the temporal bone in CHARGE syndrome: aspects of importance in cochlear implant surgery. Eur Arch Otorhinolaryngol. 2016c;273:4225-40. PubMed PMID: 27324890.

Vissers LE, van Ravenswaaij CM, Admiraal R, Hurst JA, de Vries BB, Janssen IM, van der Vliet WA, Huys EH, de Jong PJ, Hamel BC, Schoenmakers EF, Brunner HG, Veltman JA, Geurts van Kessel A. Mutations in a new member of the chromodomain gene family cause CHARGE syndrome. Nat Genet. 2004;36:955-7. PubMed PMID: 15300250.

Vuorela P, Ala-Mello S, Saloranta C, Penttinen M, Pöyhönen M, Huoponen K, Borozdin W, Bausch B, Botzenhart EM, Wilhelm C. Kääriäinen H, Kohlhase J. Molecular analysis of the CHD7 gene in CHARGE syndrome: identification of 22 novel mutations and evidence for a low contribution of large CHD7 deletions. Genet Med. 2007;9:690-4. PubMed PMID: 18073582.

Wong MT, Lambeck AJ, van der Burg M, la Bastide-van Gemert S, Hogendorf LA, van Ravenswaaij-Arts CM, Scholvinck EH. Immune dysfunction in children with CHARGE syndrome: a cross-sectional study. PLoS One. 2015a;10:e0142350. PubMed PMID: 26544072.

Wong MT, Schölvinck EH, Lambeck AJ, van Ravenswaaij-Arts CM. CHARGE syndrome: a review of the immunological phenotype. Eur J Hum Genet. 2015b;23:1451-9. PubMed PMID: 25689927.

Xu C, Cassatella D, van der Sloot AM, Quinton R, Hauschild M, de Geyter C, Flück C, Feller K, Bartholdi D, Nemeth A, Halperin I, Djurdjevic SP, Maeder P, Papadakis G, Dwyer AA, Marino L, Favre L, Pignatelli D, Niederländer NJ, Acierno J, Pitteloud N. Evaluating CHARGE syndrome in congenital hypogonadotropic hypogonadism patients harboring CHD7 variants. Genet Med. 2018;20:872-81. PubMed PMID: 29144511.

Suggested Reading

Hartshorne T, Hefner M, Davenport SLH, Thelin J. CHARGE Syndrome, 1 ed. Plural Publishing. 2011.

Issue devoted entirely to CHARGE syndrome. Am J Med Genet C Semin Med Genet 2017;175(4).

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