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# CHARGE Syndrome

[*CHARGE Association, Hall-Hittner Syndrome*]

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## Summary

**Disease characteristics.** CHARGE is a mnemonic that stands for **c**oloboma, **h**eart defects, choanal **a**tresia, **r**etarded growth and development, **g**enital abnormalities, and **e**ar anomalies. CHARGE syndrome is characterized by unilateral or bilateral coloboma of the iris, retina-choroid, and/or disc with or without microphthalmos (80%-90% of individuals); unilateral or bilateral choanal atresia or stenosis (50%-60%); cranial nerve dysfunction resulting in hyposomia or anosmia, unilateral or bilateral facial palsy (40%), impaired hearing, and/or swallowing problems (70%-90%); abnormal outer ears, ossicular malformations, Mondini defect of the cochlea, and absent or hypoplastic semicircular canals; cryptorchidism in males and hypogonadotrophic hypogonadism in both males and females; developmental delay; cardiovascular malformations (75%-85%); growth deficiency (70%-80%); orofacial clefts (15%-20%); and tracheoesophageal fistula (15%-20%). Neonates with CHARGE syndrome often have multiple life-threatening medical conditions. Feeding difficulties are a major cause of morbidity in all age groups.

**Diagnosis/testing.** The diagnosis of CHARGE syndrome is based on clinical findings and temporal bone imaging. *CHD7*, encoding the chromodomain helicase DNA binding protein, is the only gene currently known to be associated with CHARGE syndrome. Sequence analysis/mutation scanning of the *CHD7* coding region detects mutations in approximately 60%-65% of individuals with CHARGE syndrome.

**Management.** Neonates require immediate evaluation of their airway, feeding, heart, and hearing. Management involves: tracheostomy and surgical correction of choanal atresia as needed; a multidisciplinary approach to feeding therapy including specialists in speech-language pathology, occupational therapy, and nutrition and gastrostomy as needed; routine care for heart defects; and hearing aids and hearing habilitation as soon as hearing loss is documented. Psychological/school evaluations should be performed by a team that includes specialists in Deafblindness when dual sensory loss is present. Special attention is required for potential airway problems associated with anesthesia. Surveillance includes: regular ophthalmologic evaluations, frequent audiologic evaluations, and testing for hypogonadotropic hypogonadism by age 13-14 years if puberty has not occurred.

**Genetic counseling.** CHARGE syndrome caused by mutation of *CHD7* is inherited in an autosomal dominant manner. Most individuals diagnosed with CHARGE syndrome represent simplex cases (i.e., a single occurrence in a family). If a parent of the proband has CHARGE syndrome or has a *CHD7* mutation, the risk to the sibs of inheriting the mutation is 50%. If neither parent is affected, the empiric risk to sibs of a proband is about 1%-2%, most likely attributable to germline mosaicism. Prenatal diagnosis for pregnancies at increased risk is possible if the disease-causing *CHD7* mutation has been identified in an affected family member.

## Diagnosis

### Clinical Diagnosis

Diagnostic criteria for CHARGE syndrome, a multiple malformation syndrome, are based on a combination of major and minor diagnostic characteristics. (CHARGE is a mnemonic that stands for **c**oloboma, **h**eart defects, choanal **a**tresia, **r**etarded growth and development, **g**enital abnormalities, and **e**ar anomalies.)

As described by Blake et al (1998), and modified by Amiel et al (2001) and Verloes (2005), the major diagnostic characteristics of CHARGE syndrome are the following:

- **Definite CHARGE syndrome.** Individuals with all four major characteristics (Table 1) or three major and three minor characteristics (Table 2)
- **Probable/possible CHARGE syndrome.** Individuals with one or two major characteristics and several minor characteristics

**Major characteristics** are those that are common in CHARGE syndrome and relatively uncommon in other syndromes:

Table 1. Major Diagnostic Characteristics of CHARGE Syndrome

| Characteristics | Manifestations | Frequency |
|---|---|---|
| Ocular coloboma | Coloboma of the iris, retina, choroid, disc; microphthalmos | 80%-90% |
| Choanal atresia or stenosis [1, 2] | Unilateral/bilateral: bony/membranous, atresia/stenosis | 50%-60% |
| Cranial nerve dysfunction or anomaly | I: hyposmia or anosmia | Frequent |
| | VII: facial palsy (unilateral or bilateral) | 40% |
| | VIII: hypoplasia of auditory nerve | Frequent |
| | IX/X: swallowing problems with aspiration | 70%-90% |
| Characteristic CHARGE syndrome ear | Outer ear: 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) [3] | 90%-100% |
| | Middle ear: ossicular malformations [4] | |
| | Mondini defect of the cochlea [5] | |
| | Temporal bone abnormalities; absent or hypoplastic semicircular canals [5] | |

1. Cleft palate may substitute for this characteristic in some individuals.
2. The diagnosis is confirmed by non-enhanced CT scan in axial sections.
3. Davenport, Hefner, Thelin et al (1986)
4. The combination of ossicular malformations and inner defects can result in a mixed (conductive and sensorineural) hearing loss with a wedge-shaped audiogram.
5. Most commonly determined by CT of the temporal bones

**Minor characteristics** are common in CHARGE syndrome but are either less specific to CHARGE syndrome (e.g., heart defects), more difficult to evaluate consistently (e.g., characteristic CHARGE syndrome face), or not readily apparent in infancy:

Table 2. Minor Diagnostic Characteristics of CHARGE Syndrome

| Characteristics | Manifestations | Frequency |
|---|---|---|
| Genital hypoplasia | Males: micropenis, cryptorchidism; females: hypoplastic labia | 50%-60% |
| | Males and females: delayed puberty secondary to hypogonadotropic hypogonadism | Frequent |
| Developmental delay [1] | Delayed milestones, hypotonia | ≤100% |
| Cardiovascular malformation | Including conotruncal defects (e.g., tetralogy of Fallot), AV canal defects, and aortic arch anomalies | 75%-85% |
| Growth deficiency | Short stature, usually postnatal with or without growth hormone deficiency | 70%-80% |
| Orofacial cleft | Cleft lip and/or palate | 15%-20% |
| Tracheoesophageal (TE) fistula | TE defects of all types | 15%-20% |
| Distinctive facial features | Square face with broad prominent forehead, prominent nasal bridge and columella, flat midface (see Figure2) [2] | 70%-80% |

1. May be primarily the result of illness, dual sensory impairment, and vestibular dysfunction
2. Davenport, Hefner, Mitchell et al (1986)

Occasional findings include the following:

- DiGeorge sequence
- Omphalocele or umbilical hernia
- Bony scoliosis or hemivertebrae
- Renal anomalies, such as dysgenesis, horseshoe/ectopic kidney

- Hand anomalies, such as polydactyly, altered palmar flexion creases (see Figure 3), atypical split hand/split foot deformity
- Additional features, such as short webbed neck, sloping shoulders, and nipple anomalies

## Testing

**Cytogenetic analysis.** The majority of individuals with CHARGE syndrome have a normal karyotype; on rare occasions, variable chromosomal abnormalities are seen.

The following chromosome abnormalities that disrupt the *CHD7* gene (locus 8q12) have been reported:

- Balanced chromosomal translocation, t(6;8)(6p8p;6q8q) [Hurst et al 1991]
- *De novo* balanced chromosomal rearrangement t(8;13)(q11.2;q22) [Johnson et al 2005]
- Interstitial deletion of 8q11.2-q13 [Arrington et al 2005]

The following chromosome abnormalities that possibly indicate locus heterogeneity have been reported:

- Partial trisomy 19q and partial monosomy 21q [De Krijger et al 1999]
- Inverted duplication (14)(q22-->q24.3) [North et al 1995]
- Balanced translocation t(2;7)(p14;q21.11) [Martin et al 2001]
- Trisomy for 2q33->qter [Lev et al 2000].
- der(9)t(9;13) from a paternal translocation [Sanlaville et al 2002]
- der(6)t(4;6) of unknown origin [Sanlaville et al 2002]

### Molecular Genetic Testing

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

**Molecular Genetic Testing—Gene.** *CHD7*, encoding the chromodomain helicase DNA binding protein, is the gene currently known to be associated with CHARGE syndrome [Vissers et al 2004].

**Clinical uses**

- Confirmatory diagnostic testing
- Prenatal diagnosis

**Clinical testing**

- **Sequence analysis/mutation scanning** of the *CHD7* coding region detects mutations in approximately 60%-65% of individuals diagnosed with CHARGE syndrome on the basis of clinical features [Vissers et al 2004, Jongmans et al 2006, Lalani et al 2006].

Table 3 summarizes molecular genetic testing for this disorder.

Table 3. Molecular Genetic Testing Used in CHARGE Syndrome

| Test Method | Mutations Detected | Mutation Detection Frequency [1] | Test Availability |
|---|---|---|---|
| Sequence analysis/mutation scanning | *CHD7* coding region mutations | 60%-65% | Clinical Testing |
| Chromosomal microarray analysis/ duplication deletion testing | Large *CHD7* gene deletions | Rare | |

1. Proportion of affected individuals with a mutation(s) as classified by gene/locus, phenotype, population group, genetic mechanism, and/or test method

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

### Testing Strategy

The diagnosis of CHARGE syndrome is primarily established by clinical findings.

When the diagnosis of CHARGE syndrome is suspected, it is recommended that routine cytogenetic analysis be performed, as various cytogenetic aberrations involving the *CHD7* locus on chromosome 8 have been described.

Molecular testing for *CHD7* may be useful to confirm the diagnosis or to provide information for genetic counseling regarding recurrence risk and prenatal diagnosis.

### Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutations in the *CHD7* gene.

## Clinical Description

### Natural History

**Morbidity and mortality.** Neonates with CHARGE syndrome often have multiple life-threatening medical conditions. Blake et al (1990) reported poor survival if one or more of the following were present: cyanotic cardiac lesions, bilateral posterior choanal atresia, and tracheoesophageal fistula. In another study, poor life expectancy correlated with male gender, central nervous system (CNS) malformation, bilateral choanal atresia, and tracheoesophageal fistula [Tellier et al 1998]. Issekutz et al (2005) reported high mortality in infants with atrioventricular septal defects and in infants with a combination of ventriculomegaly and brainstem/cerebellar anomalies (13%). They also showed that feeding difficulties were a major cause of morbidity at all ages.

**Choanal atresia.** At birth, bilateral choanal atresia causes respiratory distress requiring immediate resuscitation. Unilateral choanal atresia may go undiagnosed until the child presents with persistent unilateral rhinorrhea.

**Heart defects** are present in 75%-85% of individuals with CHARGE syndrome and are often complex. Although many types of heart defects occur, conotruncal anomalies (tetralogy of Fallot, interrupted aortic arch, perimembranous ventricular septal defect, double outlet right ventricle, and truncus arteriosus), AV canal defects, and aortic arch anomalies (vascular ring, and aberrant subclavian artery), are described frequently. Other common structural defects include ASD, VSD, and PDA.

**Esophageal atresia or tracheoesophageal fistula** occurs in about 15%-20% of infants with CHARGE syndrome and can further exacerbate feeding difficulties and respiratory distress in the first few days of life. Preoperatively, the greatest risk to the infant is aspiration. Early

diagnosis with appropriate clinical management greatly improves survival [Engum et al 1995].

**Swallowing problems.** Feeding can be associated with coughing, choking, nasal regurgitation, aspiration, and/or gastroesophageal reflux [Dobbelsteyn et al 2005]. Aspiration and swallowing dysfunction are common in children with CHARGE syndrome and are primarily the result of cranial nerve IX/X abnormalities often complicated by choanal atresia or cleft palate.

Flexible endoscopic evaluation of swallowing (FEES) and/or video swallow study (VSS) often show pooling, premature spillage, poor hypopharyngeal motility, or laryngeal penetration [White et al 2005]. A large number of children require nasogastric or gastric (G-tube) feeding, often for several years. The swallowing may eventually improve spontaneously; however, some adults continue to avoid certain foods that are difficult to swallow.

Gastroesophageal reflux is common.

**Airway** problems are primarily the result of a structural defect such as choanal atresia but can also be secondary to aspiration of gastric contents caused by swallowing incoordination and gastroesophageal reflux [Sporik et al 1997]. Without interventions such as Nissen fundoplication and gastrostomy and tracheostomy, recurrent pneumonia and long-term lung damage can result.

**Facial palsy.** Unilateral or bilateral facial palsy is present in almost 50% of individuals with CHARGE syndrome. Bilateral facial palsy results in lack of facial expression, which may hinder interpersonal communication.

**Colobomata** are found in one or both eyes of 80%-90% of individuals with CHARGE syndrome. Asymmetry in the size and extent of involvement of the eyes is frequent. Iris colobomas do not interfere with vision but may predispose to light sensitivity. A uveo-retinal coloboma commonly extends posteriorly to the optic nerve, which may be severely dysplastic and reduce vision. The macula may be involved, most commonly in moderately to severely microphthalmic eyes, further compromising vision. Any uveo-retinal coloboma increases the risk of retinal detachment because of the thin marginal adhesion to the edge of the retinal pigment epithelium.

**Hearing loss** is one of the most common features of CHARGE syndrome. Hearing loss can vary from mild to profound (see Hereditary Hearing Loss and Deafness Overview). The hearing loss can be difficult to quantify, requiring multiple brainstem audio evoked response (BAER) tests over several months. Thelin et al (1986) reported a characteristic wedge-shaped audiometric pattern of mixed hearing loss and verified that hearing loss is progressive in some individuals [Thelin & Fussner 2005]. The presence of facial paralysis was found to predict reliably the presence of sensorineural hearing loss [Edwards et al 1995, Edwards et al 2002].

The **sensorineural** component of the hearing loss is often associated with a Mondini malformation of the cochlea. Hypoplasia of the auditory nerve has also been described.

The **conductive** component of the hearing loss may result from malformed or absent ossicles, fixation of the ossicular chain to the wall of the tympanic cavity, absence of the stapedius muscle, absence of the oval window, and obliteration of the round window [Dhooge et al 1998]. The conductive component may fluctuate with middle ear disease.

Chronic recurrent otitis media is common.

**Vestibular abnormalities.** With appropriate imaging, abnormalities of the semicircular canals are found in as many as 95% of affected individuals [Admiraal & Huygen 1997, Murofushi et al 1997, Lemmerling et al 1998, Tellier et al 1998, Wiener-Vacher et al 1999, Abadie et al 2000, Bauer et al 2002].

Absence or hypoplasia of the semicircular canals impairs balance, especially when combined with visual loss. The resulting poor balance contributes to delays in motor development.

**Genitourinary abnormalities.** About 50%-60% of males have genital hypoplasia manifesting as micropenis and cryptorchidism. Wheeler et al (2000) suggested that central hypogonadism is responsible not only for the genital hypoplasia in males, but also for the lack of secondary sexual development in both males and females. Hypogonadotropic hypogonadism, evidenced by lack of pubertal development and/or abnormally low serum concentrations of LH and FSH, was reported in all nine individuals in this study.

Renal anomalies, including solitary kidney, hydronephrosis, and renal hypoplasia, occur in about 25%-40% of children with CHARGE syndrome [Blake et al 1998, Ragan et al 1999].

**Growth retardation.** Children with CHARGE syndrome usually have normal birth weight and birth length. By late infancy, linear growth usually declines from the normal curve [Blake et al 1993].

In a study of 25 children with normal nutritional status age five years and older, Pinto et al (2005) reported normal growth hormone (GH) secretion in 22 and GH deficiency in three. The three with GH deficiency had height more than 3 SD below the mean, growth rate less than 4 cm/yr, insufficient response to two GH stimulation tests, and IGF-I levels greater than 2 SD below the mean for age and pubertal stage.

**Developmental delay.** Children with CHARGE syndrome usually show marked delays in motor development. Prolonged hospitalization, truncal hypotonia with ligamentous laxity, decreased visual acuity, hearing impairment and vestibular disturbance all contribute to this delay. Many infants show poor head control and often move using a combat crawl, pushing with their feet in the supine position or by using a five-point crawl (using the head for additional support). When walking is initiated, the gait is often unsteady.

In one report, mean age for head holding was five months, sitting independently 14.8 months, and walking unaided 33 months [Tellier et al 1998].

**Speech/language delay.** Language development is often delayed because of hearing loss and further exacerbated by reduced vision that impairs lip reading and perception of body language cues.

**Brain abnormalities.** Reported central nervous system anomalies include arrhinencephaly, holoprosencephaly, hypoplasia of the cerebellum, inferior cerebellar vermis, and brainstem, cerebellar heterotopias, and absence of the septum pellucidum [Lin et al 1990, Tellier et al 1998].

Chalouhi et al (2005) reported anomalies of the olfactory tracts and bulbs varying from moderate hypoplasia to complete aplasia causing olfactory deficiency in all individuals studied.

The course of the facial nerve can be anomalous.

**Cognitive development and psychological assessment.** Delayed motor and/or language development cannot be used to predict cognitive potential of these individuals [Raqbi et al 2003; Brown 2005; Hartshorne, Hefner et al 2005].

Assessment of cognitive abilities is difficult because of lack of standardized tools to evaluate individuals with both visual and hearing impairment. Raqbi et al (2003) showed that the intellectual performance of individuals with CHARGE syndrome ranged from major learning disability with no speech and poor communication to almost normal. They demonstrated that despite marked delay in motor milestones in children between birth and three years, intellectual outcome in 50% was satisfactory. Only 25% of the studied group had a poor intellectual outcome. Raqbi et al (2003) also showed that microcephaly, brain malformation, and extensive bilateral coloboma resulting in low vision were the only findings predictive of poor intellectual outcome. The results suggest that for about half of children with CHARGE syndrome, motor and speech/language delay is mainly secondary to multiple sensory deficits and not to CNS dysfunction.

Salem-Hartshorne & Jacob (2005) showed that adaptive behavior scores (ABES) in individuals with CHARGE syndrome have a broader and higher range than previously reported. Those children with better walking skills and fewer medical problems scored higher on this scale than children with poorer walking skills and more medical problems. In this study, one-half of the individuals obtained a standard score higher than 70 on the ABES at follow-up. Thirteen percent scored above a standard score of 90.

Many adults with CHARGE syndrome are known to live independently and several are college graduates with advanced degrees [Hartshorne, Hefner et al 2005; personal communication].

**Limb/bone abnormalities.** Limb abnormalities are observed in over one-third of individuals with CHARGE syndrome [Brock et al 2003]. Although no consistent pattern is observed, the more commonly reported anomalies include hypoplastic nails, clinodactyly (fifth finger, second toe), polydactyly, contractures, brachydactyly, missing digits, club foot, tibial anomalies, and joint hyperflexibility. Hip dislocation, missing ribs, and abnormal vertebrae have also been described [Prasad et al 1997].

**Scoliosis** is common [Doyle & Blake 2005].

**Dental** anomalies include protruding jaw, overbite, hypodontia of permanent dentition, and poor mineralization of the enamel [Stromland et al 2005].

**Sinusitis** may be a major problem in childhood often caused by "silent" gastroesophageal reflux in older children. Sinusitis is a frequent cause of severe pain, often manifested by sudden changes in behavior, including apparently aggressive behaviors.

**Behavioral profile** includes autistic-like, repetitive, obsessive-compulsive, aggressive, and self-abusive behaviors [Bernstein & Denno 2005; Hartshorne, Grialou et al 2005; Hartshorne, Hefner et al 2005; Smith et al 2005]. Attention-deficit hyperactivity disorder (ADHD) is also seen in many individuals with CHARGE syndrome [Hartshorne & Cypher 2004].

Many behaviors regarded as aberrant or disruptive are attempts at communication about pain, unease, or frustration [Brown 2005, Salem-Hartshorne & Jacob 2005].

## Genotype-Phenotype Correlations

No clear genotype-phenotype correlations exist [Jongmans et al 2006, Sanlaville et al 2006, Lalani et al 2006].

Lalani et al (2006) determined that all individuals with combination of coloboma, choanal atresia, and hypoplastic semicircular canals had mutations in *CHD7*.

### Penetrance

To date, penetrance in those with *CHD7* mutations is 100%; i.e., all individuals who are heterozygous for a *CHD7* mutation have some features of CHARGE syndrome.

### Prevalence

CHARGE syndrome occurs in at least one in 10,000 births. Issekutz et al (2005) suggest occurrence in one in 8,500 births.

No teratogen or exposure is known to increase the risk of CHARGE syndrome.

## Differential Diagnosis

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

**22q11.2 deletion**. The 22q11.2 deletion syndrome (del 22q11.2) is characterized by congenital heart disease, particularly conotruncal malformations (tetralogy of Fallot, interrupted aortic arch type IB, perimembranous ventricular septal defect, double outlet right ventricle, and truncus arteriosus); palatal abnormalities, particularly velopharyngeal incompetence (VPI), submucosal cleft palate, and cleft palate; characteristic facial features; and learning difficulties. Additional findings include: immune deficiency, hypocalcemia, significant feeding problems, renal anomalies, hearing loss (both conductive and sensorineural), laryngotracheoesophageal anomalies, growth hormone deficiency, autoimmune disorders, seizures (without hypocalcemia), and skeletal abnormalities. The 22q11.2 deletion syndrome is diagnosed in individuals with a submicroscopic deletion of chromosome 22 detected by fluorescence in situ hybridization (FISH) using DNA probes from the DiGeorge chromosomal region (DGCR).

The features of del 22q11.2 syndrome and CHARGE syndrome differ significantly. Feeding difficulties typically last longer in children with CHARGE syndrome; the abnormalities of the semicircular canals that are common in CHARGE syndrome are rarely seen in 22q11.2 deletion syndrome.

**VACTERL association.** VACTERL association is a combination of **v**ertebral anomalies, **a**nal atresia, **c**ardiac anomalies, **t**racheo**e**sophageal fistula or esophageal atresia, and **r**enal and **l**imb anomalies. VACTERL association generally differs from CHARGE syndrome by the absence of colobomas, choanal atresia, characteristic ear deformity, and cranial nerve anomalies. The temporal bone anomaly frequently seen in CHARGE syndrome is rarely reported in VACTERL. VACTERL usually occurs sporadically. The cause is unknown.

**Kabuki syndrome.** Ming et al (2003) reported that phenotypic overlap between CHARGE syndrome and Kabuki syndrome (cleft palate, heart defects, occasional coloboma, growth retardation) can sometimes lead to the consideration of CHARGE syndrome in individuals with Kabuki syndrome. However, the typical features in Kabuki syndrome (long palpebral fissures with eversion of lateral third of lower eyelids, sparse eyebrows, and large prominent ears) are distinct from those in CHARGE syndrome. Kabuki syndrome usually occurs sporadically. The cause is unknown.

***PAX2* mutation (coloboma, kidney abnormalities, and occasional hearing loss).** Papillorenal syndrome, caused by mutations in *PAX2* gene, is characterized by retinal/optic nerve colobomas and renal hypoplasia. Some individuals have vesicoureteral reflux, high-frequency hearing loss, central nervous system anomalies, and/or genital anomalies. Individuals with a *PAX2* mutation do not have the multiple congenital anomalies seen in

CHARGE syndrome. No individual with a clinical diagnosis of CHARGE syndrome has been found to have a mutation in *PAX2* [Tellier et al 2000].

**Cat-eye syndrome.** Cat-eye syndrome, characterized by the combination of coloboma of the iris and anal atresia with fistula, preauricular tags and/or pits, and frequent occurrence of heart and renal malformations, is caused by inv dup(22)(q11) (presence of a supernumerary bisatellited chromosome 22 that often has two centromeres). Individuals with cat-eye syndrome do not fulfill the clinical diagnostic criteria for CHARGE syndrome.

**Joubert syndrome** with bilateral chorioretinal coloboma is characterized by interstitial fibrosis leading to renal insufficiency, hepatic fibrosis, neonatal tachypnea, cerebellar vermis aplasia/ hypoplasia, and polydactyly. 'Molar tooth' sign on neuroimaging is diagnostic of Joubert syndrome. The characteristic radiologic features and the absence of other major diagnostic characteristics of CHARGE syndrome distinguish this condition from CHARGE syndrome. Mutations in at least three genes are known to cause Joubert syndrome; inheritance is autosomal recessive.

**Choanal atresia** can be an isolated birth defect or occur as part of a syndrome. Other conditions in which choanal atresia occurs:

- Chromosome abnormalities
- Craniosynostosis syndromes (see *FGFR*-related craniosynostosis)
- Treacher Collins syndrome
- Prenatal exposure to methimazole [Greenberg 1987]

**Retinoic embryopathy secondary to prenatal Accutane™ exposure.** Exposure to Accutane™ during any time within the first trimester produces malformations associated with abnormal migration of neural crest cells. Malformations 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]. Although some overlap, especially the conotruncal cardiac malformations, is seen with CHARGE syndrome, infants with retinoic embryopathy do not meet diagnostic criteria for the syndrome.

## Management

### Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with CHARGE syndrome:

- Dilated ophthalmologic examination by pediatric ophthalmologist to determine the type and extent of the coloboma and associated findings such as strabismus, refractive error, or central vision impairment (CVI); when possible, clinical testing of visual fields
- Cardiac evaluation for cardiovascular anomalies
- Assessment for unilateral or bilateral choanal atresia and/or stenosis by nasal endoscopy or CT scan
- ENT and audiologic evaluation
  - In infants, brainstem auditory evoked response (BAER) to evaluate hearing as soon as the baby is medically stable

- In older children and adults, hearing evaluation as appropriate for age and developmental status

  See Hereditary Hearing Loss and Deafness Overview for discussion of types of audiologic evaluation.

- CT scan of the temporal bones to evaluate for middle ear and inner ear defects
- Evaluation for cleft palate, including submucous cleft palate
- Assessment of cranial nerve function by physical examination for evidence of facial palsy and by swallowing studies
- Evaluation for esophageal atresia or tracheoesophageal (TE) fistula with posteroanterior and lateral plain chest radiographs and radiographic visualization of a rigid nasogastric tube that fails to pass from the mouth to the stomach (Contrast-enhanced studies are rarely indicated because of the risk of aspiration but may be necessary to identify or locate a fistula.)
- Renal ultrasound examination

## Treatment of Manifestations

Management of children with CHARGE syndrome requires coordinated multidisciplinary care:

- **Airway** can be compromised from choanal atresia, TE fistula, aspiration pneumonias, tracheomalacia, or an aberrant subclavian vessel impinging on the trachea. Studies have shown that 15%-60% of individuals with CHARGE syndrome require tracheostomy [Asher et al 1990, Morgan et al 1993, Roger et al 1999, White et al 2005].
- **Heart defects** are managed as in any individual with a congenital heart defect.
- **Choanal atresia.** Surgical correction by means of transnasal, transpalatal, or sublabial routes or airway bypass by tracheotomy or endotracheal intubation is usually necessary early in life.
- **Feeding/swallowing dysfunction.** In infancy, feeding can be compromised by oral-motor and/or sensory deficits. A multidisciplinary approach to therapy with specialists in speech-language pathology, occupational therapy, and nutrition can help promote early oral exploration and prevent or minimize oral defensiveness. For children with a G-tube, oral stimulation needs to be maintained to reduce future oral sensitivity/aversion.
- **Gastroesophageal reflux** can be significant enough to cause aspiration, often requiring Nissen fundoplication and G-tube insertion. Silent reflux should be considered in the evaluation of recurrent sinusitis.
- **Renal evaluation.** Renal ultrasound examination and voiding cystourethrogram are recommended in all children. Evaluation for urinary tract infection is recommended in cases of unexplained fever or irritability in children unable to communicate.
- **Endocrine evaluation.** Individuals with hypogonadotropic hypogonadism may be considered for hormone replacement therapy for induction of puberty and for general health reasons, such as prevention of osteoporosis.

  Early referral for endocrinology consultation is appropriate, especially if linear growth is falling from the normal curve in spite of adequate nutrition and normalized

cardiac status. Some of these children may have growth hormone deficiency, which requires growth hormone replacement therapy.

- **Coloboma.** Tinted glasses or a dark visor can be helpful for the photophobia that often accompanies iris colobomas.

  Parents, therapists, and teachers need to take into account visual field defects resulting from retinal coloboma and central visual defects resulting from optic nerve involvement and macular coloboma. For example, visual stimuli and sign language may need to be presented in child's lower visual field.

  For eyes with visual potential, cycloplegic refraction and spectacle correction may be necessary, since substantive refractive errors of mildly or even moderately micro-ophthalmic eyes have been observed.

  Retinal detachment, a potential complication of retinal coloboma, can result in total blindness; therefore, any change in vision status should be treated as a medical emergency.

- **Hearing loss.** Hearing aids and hearing habilitation (which may include sign language in addition to the auditory and speech training) should be started as soon as hearing loss is documented. Many children benefit from bone conduction aids or (especially at school) an FM system. Head bands can be used to help keep the hearing aids in place if the ear cartilage is floppy or if the tape that secures the aid to the scalp is ineffective.

  PE tube placement for chronic serous otitis is common and often needs to continue until adolescence.

  Cochlear implants have been successful in providing sound awareness and even speech recognition in the presence of cochlear abnormalities. Bauer et al (2002) reported successful completion of cochlear implantation and measurable benefit in five individuals with CHARGE syndrome. Of note, variations in the temporal bone anatomy can lead to technical challenges and risk to the facial nerve during implantation. In some individuals, an aberrant course of the facial nerve may be a contraindication for cochlear implant [Bauer et al 2002].

- **Communication.** Establishing an appropriate system of communication is more difficult in the presence of both hearing loss and vision loss than in the presence of hearing loss alone. 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].

- **Deaf-blind service referral.** Children with CHARGE syndrome who have combined vision and hearing loss can be considered "deafblind," an important designation used for qualifying for educational resources in many states. Of note, "deafblind" does not mean total hearing loss or total vision loss; most children with CHARGE syndrome have some residual vision and/or hearing but are still classified as "deafblind."

  Referral to deafblind education services (e.g., the Deafblind Project within the state of residence) should be made as early as possible after birth so that the parents and project personnel can begin to plan together. 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. Assistance of the Deafblind team to provide consultation to the early

childhood education team is highly recommended since most educators and speech therapists have little or no experience with dual sensory loss.

- **Psychological/school evaluations** should be performed by a team that includes specialists in Deafblindness when dual sensory loss is present. If a deafblind specialist is not available when a psychologist does an evaluation, a vision educator can show the tester where to place materials and whether the lighting and contrast of the printed materials is adequate. A hearing educator can help place the child for optimal hearing and/or do sign language interpretation.
- **Dental** procedures, when necessary, may be performed under general anesthesia.
- **Low muscle tone and poor balance** predispose children to rapid exhaustion. Many children need adjustments to the classroom or therapy setting to allow for better truncal support. Frequent rest breaks may be needed. Many children can work for longer periods if allowed to do so in a supine position [Williams & Hartshorne 2005].

  Unpublished data suggest that hippotherapy (horseback riding) can be a helpful adjunct to physical therapy to prevent scoliosis as it requires frequent shifts in truncal muscular control — as do karate and other programs that promote good balance. Myofacial release by a trained therapist can improve posture and flexibility.
- **Sleep cycles** are frequently disturbed even in those without significant visual impairments. Occasionally, sleep studies show obstructive apnea. If the cause is unknown, melatonin has been helpful for some children while others with severe visual impairment may need other medications to regulate sleep.
- **Chronic constipation** usually does not respond to simple measures such as increased fluid intake. GI consultation is often indicated.
- **Obsessive-compulsive disorder.** Behavioral therapy combined with stress reduction is sometimes helpful alone, but treatment with medications can be a useful adjunct.
- **Autistic-like behaviors.** While the behaviors may mimic autism, there are differences [Hartshorne, Grialou et al 2005]. Sensory processing issues are likely implicated. Management by behavior therapy, stress reduction, and sometimes medication is indicated.
- **Attention-deficit hyperactivity disorder.** In many instances, establishing an appropriate method of communication and providing adequate stimulation for exploration in a safe environment are more helpful than medication.
- **Increased pain threshold** may predispose children to behaviors that are incorrectly interpreted by others as aggressive. Understanding this is critical to devising appropriate interventional strategies.

## Prevention of Secondary Complications

**Facial palsy.** Because the facial nerves are often ectopic, an MRI to determine the location of the facial nerves is appropriate before craniofacial surgery or cochlear implantation is considered.

**Anesthesia.** The airway problems associated with anesthesia in individuals with CHARGE syndrome can be attributed to choanal atresia, cleft lip and palate, and other upper-airway problems observed in about half of individuals with CHARGE syndrome [Stack & Wyse 1991]. The 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. If possible, procedures should be combined to reduce the number of anesthesias.

### Surveillance

Regular ophthalmologic evaluations are appropriate to follow changes in acuity and risks for retinal detachment and/or cataract. Monitoring nonverbal infants and children who are unable to report subjective loss of vision can permit timely detection of retinal detachment and appropriate surgical repair where necessary.

Frequent retesting of hearing by a pediatric audiologist may be necessary to determine the exact type and extent of hearing loss and to assess the success of hearing habilitation.

Frequent clinical and radiologic dental evaluations should be performed.

Wheeler et al (2000) recommended that LH and FSH be obtained between age two and three months, or by age 13-14 years if puberty has not occurred. If there is reason to suspect hypogonadotropic hypogonadism, a gonadotropin-releasing hormone (GnRH) stimulation test may be helpful.

### Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

### Other

Prophylaxis for retinal detachment is not appropriate.

**Genetics clinics**, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

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

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## Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the* GeneTests Clinic Directory.

## Mode of Inheritance

CHARGE syndrome is typically a sporadic disorder, although rare familial cases inherited in an autosomal dominant manner have been described [Mitchell et al 1985, Lalani et al 2006].

## Risk to Family Members

### Parents of a proband

- Most individuals diagnosed with CHARGE syndrome do not have an affected parent, although the mild end of the spectrum is not yet known.
- A proband with CHARGE syndrome usually has the disorder as the result of a new gene mutation. About 60%-65% of the affected individuals have a detectable mutation in the *CHD7* gene.
- If a parent has any features of CHARGE syndrome, molecular genetic testing is appropriate if a *CHD7* mutation has been identified in the proband.

Note: Although almost all individuals diagnosed with CHARGE syndrome are the only affected individuals in the family, the family history may appear to be negative because of failure to recognize the disorder in family members.

### Sibs of a proband

- The risk to the sibs of the proband depends upon the genetic status of the proband's parents.
- If a parent of the proband is affected or has a *CHD7* mutation, the risk to the sibs of inheriting the mutation is 50%.
- If neither parent is affected, the empiric risk to sibs of a proband is about 1%-2%, most likely attributable to germline mosaicism.
- Because CHARGE syndrome caused by a *CHD7* mutation typically occurs as the result of a *de novo* mutation, the risk to the sibs of a proband is small. However, several sib pairs born to unaffected parents have been reported [Pagon et al 1981, Jongmans et al 2006, Lalani et al 2006], suggesting the possibility of germline mosaicism in a parent.
- The presence of one or two major characteristics along with multiple congenital anomalies in a sib of a proband should prompt complete evaluation for CHARGE syndrome. Molecular genetic testing of the sib is appropriate if a *CHD7* mutation has been identified in the proband.

### Offspring of a proband

- Severely affected individuals with CHARGE syndrome do not reproduce.
- Each child of a mildly affected individual with CHARGE syndrome has a 50% chance of inheriting the mutation.
- The severity of CHARGE syndrome in a parent does not predict the severity of CHARGE syndrome in the offspring. Variable expression has been observed in the familial cases.

**Other family members of a proband.** The risk to other family members depends upon the genetic status of the proband's parents. If a parent has the disease causing mutation in *CHD7* gene, his or her 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 testing is before pregnancy.

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

### Prenatal Testing

**Molecular genetic testing.** Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal molecular testing can be performed.

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

**Ultrasound examination.** Some of the clinical findings in CHARGE syndrome, including polyhydramnios, heart defects, cleft lip/palate, CNS anomalies, and kidney and gastrointestinal anomalies, may be apparent on targeted level II ultrasound examination in the second trimester. Sanlaville et al (2006) proposed performing focused fetal ultrasound and/or brain MRI for detection of external ear anomalies, choanal atresia, semicircular canal agenesis, and arrhinencephaly for a higher prenatal detection rate of CHARGE syndrome. 4D ultrasound of the ears may be helpful if CHARGE syndrome is suspected.

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

## Molecular Genetics

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

Table A. Molecular Genetics of CHARGE Syndrome

| Gene Symbol | Chromosomal Locus | Protein Name |
|---|---|---|
| *CHD7* | 8q12.1 | Chromodomain-helicase-DNA-binding protein 7 |

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

Table B. OMIM Entries for CHARGE Syndrome

| | |
|---|---|
| 214800 | CHARGE SYNDROME |
| 608892 | CHROMODOMAIN HELICASE DNA-BINDING PROTEIN 7; CHD7 |

Table C. Genomic Databases for CHARGE Syndrome

| Gene Symbol | Entrez Gene | HGMD |
|---|---|---|
| *CHD7* | 55636 (MIM No. 608892) | CHD7 |

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

**Normal allelic variants:** *CHD7* consists of 38 exons and has a genomic size of 188 kb. The 8.9-kb cDNA encodes a 2997-residue protein.

**Pathologic allelic variants:** Ten heterozygous *CHD7* mutations were described by Vissers et al (2004), with seven stop-codon mutations, two missense mutations, and one mutation at an intron-exon boundary. Additionally, two single-copy 8q12 deletions of *CHD7* were reported, indicating haploinsufficiency of the gene accounting for most cases of CHARGE syndrome. Subsequently, in two larger studies, 69/107 individuals [Jongmans et al 2006] and 64/110 individuals [Lalani et al 2006] were reported to have *CHD7* mutations. These mutations are distributed throughout the gene.

**Normal gene product:** CHD proteins belong to a superfamily of proteins called chromodomain helicase DNA binding protein, with two N-terminal chromodomains, a SNF2-like ATPase/helicase domain and a DNA-binding domain. Chromatin remodeling is one of the mechanisms by which gene expression is regulated developmentally. CHD genes likely play an important role in regulating early embryonic development and cell cycle control by affecting chromatin structure and gene expression. Swi/Snf proteins can cause ATP-dependent disruption of nucleosome structure at a promoter and enhance the binding of transcription factors to their binding sites. The action of these proteins can lead to changes in chromatin conformation, resulting in profound transcriptional activation or repression of a gene or region.

**Abnormal gene product:** In the majority of affected individuals, haploinsufficiency of the *CHD7* gene is likely the underlying basis of CHARGE syndrome, based on the rare microdeletion cases involving the *CHD7* gene as well as the stop mutations resulting in premature truncation of the protein.

## Resources

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

**CHARGE Syndrome Foundation, Inc**
**Phone:** 800-442-7604; 573-499-4694
**Email:** info@chargesyndrome.org
www.chargesyndrome.org

**AboutFace International**
123 Edward Street Suite 1003
Toronto M5G 1E2
Canada
**Phone:** 800-665-FACE (800-665-3223)
**Fax:** 416-597-8494
**Email:** info@aboutfaceinternational.org
www.aboutfaceinternational.org

**Children's Craniofacial Association**
13140 Coit Road Suite 517
Dallas TX 75240
**Phone:** 800-535-3643; 214-570-9099
**Fax:** 214-570-8811
**Email:** contactCCA@ccakids.com
www.ccakids.com

**DB-LINK: The National Information Clearinghouse on Children Who Are Deaf-Blind**
*Bibliography and links to state deafblind project resources.*
345 N Monmouth Ave
Monmouth OR 97361
**Phone:** 800-438-9376; 800-854-7013 (TTY)
**Fax:** 503-838-8150
**Email:** dblink@tr.wou.edu
www.tr.wou.edu/dblink

**National Eye Institute**
Low Vision

**SeeHear Newsletter**
*A Quarterly Newsletter For Families And Professionals On Visual Impairments And Deafblindness.*
SeeHear newsletter

## References

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

### Published Statements and Policies Regarding Genetic Testing

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

### Literature Cited

Abadie V, Wiener-Vacher S, Morisseau-Durand MP, Poree C, Amiel J, Amanou L, Peigne C, Lyonnet S, Manac'h Y. Vestibular anomalies in CHARGE syndrome: investigations on and consequences for postural development. Eur J Pediatr. 2000;159:569–74. [PubMed: 10968232]

Admiraal RJ, Huygen PL. Vestibular areflexia as a cause of delayed motor skill development in children with the CHARGE association. Int J Pediatr Otorhinolaryngol. 1997;39:205–22. [PubMed: 9152748]

Amiel J, Attiee-Bitach T, Marianowski R, Cormier-Daire V, Abadie V, Bonnet D, Gonzales M, Chemouny S, Brunelle F, Munnich A, Manach Y, Lyonnet S. Temporal bone anomaly proposed as a major criteria for diagnosis of CHARGE syndrome. Am J Med Genet. 2001;99:124–7. [PubMed: 11241470]

Arrington CB, Cowley BC, Nightingale DR, Zhou H, Brothman AR, Viskochil DH. Interstitial deletion 8q11.2-q13 with congenital anomalies of CHARGE association. Am J Med Genet A. 2005;133:326–30. [PubMed: 15672384]

Asher BF, McGill TJ, Kaplan L, Friedman EM, Healy GB. Airway complications in CHARGE association. Arch Otolaryngol Head Neck Surg. 1990;116:594–5. [PubMed: 1691649]

Bauer PW, Wippold FJ II, Goldin J, Lusk RP. Cochlear implantation in children with CHARGE association. Arch Otolaryngol Head Neck Surg. 2002;128:1013–7. [PubMed: 12220204]

Bernstein V, Denno LS. Repetitive behaviors in CHARGE syndrome: differential diagnosis and treatment options. Am J Med Genet A. 2005;133:232–9. [PubMed: 15688425]

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: 9545604]

Blake K, Kirk JM, Ur E. Growth in CHARGE association. Arch Dis Child. 1993;68:508–9. [PubMed: 8503679]

Blake KD, Russell-Eggitt IM, Morgan DW, Ratcliffe JM, Wyse RK. Who's in CHARGE? Multidisciplinary management of patients with CHARGE association. Arch Dis Child. 1990;65:217–23. [PubMed: 2317068]

Brock KE, Mathiason MA, Rooney BL, Williams MS. Quantitative analysis of limb anomalies in CHARGE syndrome: correlation with diagnosis and characteristic CHARGE anomalies. Am J Med Genet A. 2003;123:111–21. [PubMed: 14626219]

Brown D. CHARGE syndrome "behaviors": challenges or adaptations? Am J Med Genet A. 2005;133:268–72. [PubMed: 15666302]

Chalouhi C, Faulcon P, Bihan CL, Hertz-Pannier L, Bonfils P, Abadie V. Olfactory evaluation in children: application to the CHARGE syndrome. Pediatrics. 2005;116:81–88. [PubMed: 15958661]

Davenport SL, Hefner MA, Mitchell JA. The spectrum of clinical features in CHARGE syndrome. Clin Genet. 1986;29:298–310. [PubMed: 2424647]

Davenport SL, Hefner MA, Thelin JW. CHARGE syndrome. Part I. External ear anomalies. Int J Pediatr Otorhinolaryngol. 1986;12:137–43. [PubMed: 3570680]

De Krijger RR, Mooy CM, Van Hemel JO, Sulkers EJ, Kros JM, Bartelings MM, Govaerts LC. CHARGE association-related ocular pathology in a newborn with partial trisomy 19q and partial monosomy 21q, from a maternal translocation (19;21) (q13.1;q22.3). Pediatr Dev Pathol. 1999;2:577–81. [PubMed: 10508883]

Dhooge I, Lemmerling M, Lagache M, Standaert L, Govaert P, Mortier G. Otological manifestations of CHARGE association. Ann Otol Rhinol Laryngol. 1998;107:935–41. [PubMed: 9823842]

Dobbelsteyn C, Marche DM, Blake K, Rashid M. Early oral sensory experiences and feeding development in children with CHARGE syndrome: a report of five cases. Dysphagia. 2005;20:89–100. [PubMed: 16172816]

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

Edwards BM, Kileny PR, Van Riper LA. CHARGE syndrome: a window of opportunity for audiologic intervention. Pediatrics. 2002;110:119–26. [PubMed: 12093956]

Edwards BM, Van Riper LA, Kileny PR. Clinical manifestations of CHARGE Association. Int J Pediatr Otorhinolaryngol. 1995;33:23–42. [PubMed: 7558639]

Engum SA, Grosfeld JL, West KW, Rescorla FJ, Scherer LR III. Analysis of morbidity and mortality in 227 cases of esophageal atresia and/or tracheoesophageal fistula over two decades. Arch Surg. 1995;130:502–8. [PubMed: 7748088]

Greenberg F. Choanal atresia and athelia: methimazole teratogenicity or a new syndrome? Am J Med Genet. 1987;28:931–4. [PubMed: 3688031]

Hartshorne TS, Cypher AD. Challenging behavior in CHARGE syndrome. Mental Health Aspects Dev Dis. 2004;7:41–52.

Hartshorne TS, Grialou TL, Parker KR. Autistic-like behavior in CHARGE syndrome. Am J Med Genet A. 2005;133:257–61. [PubMed: 15637726]

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

Hurst JA, Meinecke P, Baraitser M. Balanced t(6;8)(6p8p;6q8q) and the CHARGE association. J Med Genet. 1991;28:54–5. [PubMed: 1999835]

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

Johnson D, Morrison N, Grant L, Turner T, Fantes J, Connor JM, Murday V. Confirmation of CHD7 as a cause of CHARGE association identified by mapping a balanced chromosome translocation in affected monozygotic twins. J Med Genet. 2006;43:280–4. [PubMed: 16118347]

Jongmans MC, Admiraal RJ, van der Donk KP, Vissers LE, Baas AF, Kapusta L, van Hagen JM, Donnai D, de Ravel TJ, Veltman JA, Geurts van Kessel A, De Vries BB, Brunner HG, Hoefsloot LH, van Ravenswaaij CM. CHARGE syndrome: the phenotypic spectrum of mutations in the CHD7 gene. J Med Genet. 2006;43:306–14. [PubMed: 16155193]

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: 16400610]

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

Lemmerling M, Dhooge I, Mollet P, Mortier G, Van Cauwenberge P, Kunnen M. CT of the temporal bone in the CHARGE association. Neuroradiology. 1998;40:462–5. [PubMed: 9730349]

Lev D, Nakar O, Bar-Am I, Zudik A, Watemberg N, Finkelstien S, Katzin N, Lerman-Sagie T. CHARGE association in a child with de Novo chromosomal aberration 46, X,der(X)t(X;2)(p22.1;q33) detected by spectral karyotyping. J Med Genet. 2000;37:E47. [PubMed: 11106365]

Lin AE, Siebert JR, Graham JM Jr. Central nervous system malformations in the CHARGE association. Am J Med Genet. 1990;37:304–10. [PubMed: 2260555]

Martin DM, Sheldon S, Gorski JL. CHARGE association with choanal atresia and inner ear hypoplasia in a child with a de novo chromosome translocation t(2;7)(p14;q21.11). Am J Med Genet. 2001;99:115–9. [PubMed: 11241468]

Ming JE, Russell KL, Bason L, McDonald-McGinn DM, Zackai EH. Coloboma and other ophthalmologic anomalies in Kabuki syndrome: distinction from charge association. Am J Med Genet A. 2003;123:249–52. [PubMed: 14608645]

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

Morgan D, Bailey M, Phelps P, Bellman s, Grace A, Wyse R. Ear-nose-throat abnormalites in the CHARGE association. Arch Otolayngol head Neck Surg. 1993;119:49–54.

Murofushi T, Ouvrier RA, Parker GD, Graham RI, da Silva M, Halmagyi GM. Vestibular abnormalities in charge association. Ann Otol Rhinol Laryngol. 1997;106:129–34. [PubMed: 9041817]

North KN, Wu BL, Cao BN, Whiteman DA, Korf BR. CHARGE association in a child with de novo inverted duplication (14)(q22-->q24.3). Am J Med Genet. 1995;57:610–4. [PubMed: 7573139]

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: 6166737]

Pinto G, Abadie V, Mesnage R, Blustajn J, Cabrol S, Amiel J, Hertz-Pannier L, Bertrand AM, Lyonnet S, Rappaport R, Netchine I. CHARGE syndrome includes hypogonadotropic hypogonadism and abnormal olfactory bulb development. J Clin Endocrinol Metab. 2005;90:5621–6. [PubMed: 16030162]

Prasad C, Quackenbush EJ, Whiteman D, Korf B. Limb anomalies in DiGeorge and CHARGE syndromes. Am J Med Genet. 1997;68:179–81. [PubMed: 9028454]

Ragan DC, Casale AJ, Rink RC, Cain MP, Weaver DD. Genitourinary anomalies in the CHARGE association. J Urol. 1999;161:622–5. [PubMed: 9915472]

Raqbi F, Le Bihan C, Morisseau-Durand MP, Dureau P, Lyonnet S, Abadie V. Early prognostic factors for intellectual outcome in CHARGE syndrome. Dev Med Child Neurol. 2003;45:483–8. [PubMed: 12828403]

Roger G, Morisseau-Durand MP, Van Den Abbeele T, Nicollas R, Triglia JM, Narcy P, Abadie V, Manac'h Y, Garabedian EN. The CHARGE association: the role of tracheotomy. Arch Otolaryngol Head Neck Surg. 1999;125:33–8. [PubMed: 9932584]

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

Sanlaville D, Etchevers HC, Gonzales M, Martinovic J, Clement-Ziza M, Delezoide AL, Aubry MC, Pelet A, Chemouny S, Cruaud C, Audollent S, Esculpavit C, Goudefroye G, Ozilou C, Fredouille C, Joye N, Morichon-Delvallez N, Dumez Y, Weissenbach J, Munnich A, Amiel J, Encha-Razavi F, Lyonnet S, Vekemans M, Attie-Bitach T. Phenotypic spectrum of CHARGE syndrome in fetuses

with CHD7 truncating mutations correlates with expression during human development. J Med Genet. 2006;43:211–217. [PubMed: 16169932]

Sanlaville D, Romana SP, Lapierre JM, Amiel J, Genevieve D, Ozilou C, Le Lorch M, Brisset S, Gosset P, Baumann C, Turleau C, Lyonnet S, Vekemans M. A CGH study of 27 patients with CHARGE association. Clin Genet. 2002;61:135–8. [PubMed: 11940088]

Smith IM, Nichols SL, Issekutz K, Blake K. Behavioral profiles and symptoms of autism in CHARGE syndrome: preliminary Canadian epidemiological data. Am J Med Genet A. 2005;133:248–56. [PubMed: 15688419]

Sporik R, Dinwiddie R, Wallis C. Lung involvement in the multisystem syndrome CHARGE association. Eur Respir J. 1997;10:1354–5. [PubMed: 9192943]

Stack CG, Wyse RK. Incidence and management of airway problems in the CHARGE Association. Anaesthesia. 1991;46:582–5. [PubMed: 1862904]

Stromland K, Sjogreen L, Johansson M, Ekman Joelsson BM, Miller M, Danielsson S, Billstedt E, Gillberg C, Jacobsson C, Norinder JA, Granstrom G. CHARGE association in Sweden: malformations and functional deficits. Am J Med Genet A. 2005;133:331–9. [PubMed: 15633180]

Tellier AL, Amiel J, Delezoide AL, Audollent S, Auge J, Esnault D, Encha-Razavi F, Munnich A, Lyonnet S, Vekemans M, Attie-Bitach T. Expression of the PAX2 gene in human embryos and exclusion in the CHARGE syndrome. Am J Med Genet. 2000;93:85–8. [PubMed: 10869107]

Tellier AL, Cormier-Daire V, Abadie V, Amiel J, Sigaudy S, Bonnet D, de Lonlay-Debeney P, Morrisseau-Durand MP, Hubert P, Michel JL, Jan D, Dollfus H, Baumann C, Labrune P, Lacombe D, Philip N, LeMerrer M, Briard ML, Munnich A, Lyonnet S. CHARGE syndrome: report of 47 cases and review. Am J Med Genet. 1998;76:402–9. [PubMed: 9556299]

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

Thelin JW, Mitchell JA, Hefner MA, Davenport SL. CHARGE syndrome. Part II. Hearing loss. Int J Pediatr Otorhinolaryngol. 1986;12:145–63. [PubMed: 3570681]

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

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, van Kessel AG. Mutations in a new member of the chromodomain gene family cause CHARGE syndrome. Nat Genet. 2004;36:955–7. [PubMed: 15300250]

Wheeler PG, Quigley CA, Sadeghi-Nejad A, Weaver DD. Hypogonadism and CHARGE association. Am J Med Genet. 2000;94:228–31. [PubMed: 10995509]

White DR, Giambra BK, Hopkin RJ, Daines CL, Rutter MJ. Aspiration in children with CHARGE syndrome. Int J Pediatr Otorhinolaryngol. 2005;69:1205–9. [PubMed: 15890414]

Wiener-Vacher SR, Amanou L, Denise P, Narcy P, Manach Y. Vestibular function in children with the CHARGE association. Arch Otolaryngol Head Neck Surg. 1999;125:342–7. [PubMed: 10190809]

Williams GL, Hartshorne TS. Understanding balance problems in children with CHARGE syndrome. Deaf-Blind Perspectives. 2005;12:5–7.

## Suggested Readings

American Journal of Medical Genetics. Articles on CHARGE syndrome from the 6th International Charge Conference. Available at www.chargesyndrome.org/resources-articles.asp . 2005

Hefner M, Davenport SLH. CHARGE syndrome: a management manual for parents, version 2.1. CHARGE Syndrome Foundation, Inc, Columbia, MO. Available at www.chargesyndrome.org . 1999, 2001

Moss K. Looking at Self-Stimulation in the Pursuit of Leisure or I'm Okay, You Have a Mannerism. SeeHear Vol 5, no. 3 TSBVI Deafblind Outreach www.tsbvi.edu/Outreach/seehear/archive/mannerism.html . Spring 1993

## Chapter Notes

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### Revision History

- 6 June 2007 (cd) Revision: mutation scanning added
- 2 October 2006 (me) Review posted to live Web site
- 14 April 2005 (jwb) Original submission

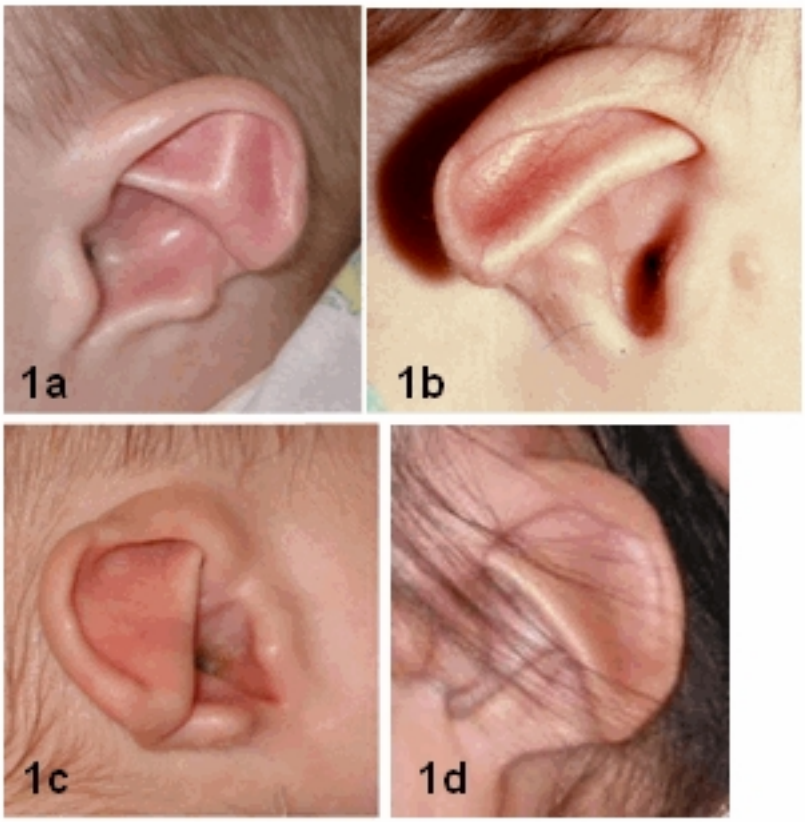


**Figure 1. Ears**
1a. Clipped off helix, prominent antihelix that extends to the outer helical rim, antihelix discontinuous with the antitragus; absent lobe.
1b. Antihelix discontinuous with the antitragus; very small lobe. Preauricular tag occurs occasionally.
1c. Clipped off helix, prominent antihelix 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


**Figure 2. Face**

2a. 2 1/2-year-old female; square face, round eye, straight nose with broad nasal root, unilateral facial palsy

2b. Five-year-old female; mild expression of CHARGE facies; relatively square face, prominent columella of the nose. Note sloping shoulders.

2c. Seven-year-old male; square face, somewhat broad nasal root. Note prominent ear with unfolded helix and wide neck.

2d. Nine-year-old female; square face, round eyes, wide neck, sloping shoulders. Note lack of facial expression as a result of bilateral facial palsy.

2e. Fifteen-year-old male. Note longer but still somewhat square face, wide neck with sloping shoulders.

2f. Eighteen-year-old female; square, asymmetric face, prominent ears, head tilted back, wide neck and sloping shoulders

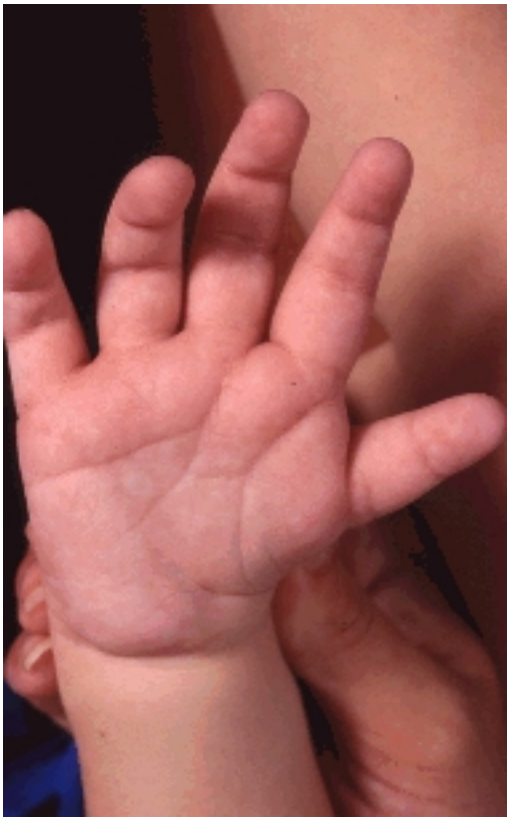

**Figure 3.** Typical CHARGE hand: square hand, short fingers, finger-like thumb, hockey-stick palmar crease