Congenital Central Hypoventilation Syndrome

Includes: Haddad Syndrome

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Summary

Disease characteristics. Congenital central hypoventilation syndrome (CCHS) is a rare disorder of respiratory and autonomic regulation. It is typically characterized by a classic presentation in newborns and, rarely, a milder later-onset (LO-CCHS) presentation in toddlers, children, and adults.

Classic CCHS presents in newborns as:

- Apparent hypoventilation with monotonous respiratory rates and shallow breathing either during sleep only or while awake as well as asleep;
- Autonomic nervous system dysregulation (ANSD); and
- In some individuals, altered development of neural crest-derived structures (i.e., Hirschsprung disease) and/or tumors of neural crest origin (neuroblastoma, ganglioneuroma, and ganglioneuroblastoma).

Individuals with CCHS who have been diagnosed as newborns and ventilated conservatively and consistently throughout childhood have now reached the age of 20 to 30 years; they are highly functional and live independently. LO-CCHS manifests as nocturnal alveolar hypoventilation and mild ANSD. Individuals with LO-CCHS who were not identified until age 20 years or older have now reached the age of 30 to 55 years.

Diagnosis/testing. Diagnosis of CCHS is established based on:

- Clinical findings of alveolar hypoventilation and ANSD in the absence of primary pulmonary, cardiac, or neuromuscular disease, or a causative brain stem lesion that can account for the entire phenotype; and
- Identification of a disease-causing mutation in *PHOX2B*. *PHOX2B* is the only gene in which mutations are known to cause CCHS.

Management. *Treatment of manifestations:* Tracheostomy and home ventilator for individuals requiring ventilatory support 24 hours per day and for infants/children/adults requiring ventilatory support during sleep only. Diaphragm pacing by phrenic nerve stimulation can be considered in ambulatory children requiring mechanical ventilation 24 hours a day and potentially in older children and adults requiring nocturnal ventilation only, though tracheostomy removal for nocturnal diaphragm pacing is not assured. Mask ventilation or negative-pressure ventilation is a consideration in cooperative older children requiring ventilatory support during sleep; however, during intercurrent illnesses more aggressive ventilatory support such as intubation with continuous mechanical ventilation in an intensive care setting may be needed. A cardiac pacemaker may be required for prolonged sinus pauses. Hirschsprung disease is treated in the usual manner. Neuroblastomas are removed surgically; those beyond Stage 1 are treated with chemotherapy. Treatment of other tumors of neural crest origin is based on location and type, though surgical removal is typically recommended.

Prevention of secondary complications: Mask ventilation in the infant and young child is strongly discouraged because it is not adequately stable as a life-sustaining support, with risk for repeated hypoxemia and neurocognitive compromise.

Surveillance: For all individuals with CCHS: at least yearly (every 6 months until age 3 years) comprehensive, multiple-day in-hospital physiologic evaluation to optimize ventilatory support awake and asleep and in varied levels of activity and concentration simulating activities of daily living; yearly 72-hour Holter recording to identify any prolonged sinus pauses; yearly echocardiogram to identify right ventricular hypertrophy or cor pulmonale; yearly hemoglobin, hematocrit, and reticulocyte counts to identify polycythemia; and yearly neurocognitive testing to evaluate the success of artificial ventilation. For children with specific *PHOX2B* mutations placing them at higher risk: evaluate for Hirschsprung disease and tumors of neural crest origin.

Agents/circumstances to avoid: Swimming (asphyxia; death); breathholding contests (asphyxia; death); alcohol (respiratory depression), recreational drugs (varied effects including death), and prescribed as well as non-prescribed medications/sedatives/anesthetics that could induce respiratory depression.

Evaluation of relatives at risk: Both parents of children with a known *PHOX2B* mutation should be tested for the family-specific mutation to determine their risk for later-onset CCHS or mosaicism.

Genetic counseling. CCHS is inherited in an autosomal dominant manner. Most individuals with CCHS are heterozygous for a *de novo PHOX2B* mutation; some have an affected parent and up to 25% have an asymptomatic parent who has mosaicism for a *PHOX2B* mutation. Each child of an individual with CCHS has a 50% chance of inheriting the *PHOX2B* mutation; the risk to the offspring of an individual with mosaicism is 50% or lower. Prenatal testing for pregnancies at increased risk is possible if the causative mutation has been identified in an affected family member. Some families choose to pursue prenatal testing in order to make informed decisions about the pregnancy and, if the pregnancy is continued, allow for a smooth transition to extrauterine life for the affected infant.

Diagnosis

Clinical Diagnosis

Guidelines. The American Thoracic Society has issued both an updated statement on the diagnosis and management of congenital central hypoventilation syndrome (CCHS) [Weese-Mayer et al 2010 (full text)] and a lay summary [Patwari et al 2010b (full text)].

CCHS is diagnosed in newborns with the following:

- Hypoventilation with absent or attenuated ventilatory response to hypercarbia and/or hypoxemia when awake and asleep
- Generally adequate ventilation while awake and at rest and apparent hypoventilation with monotonous respiratory rate and shallow breathing (diminished tidal volume) during sleep OR apparent hypoventilation while both awake and asleep
- Absent perception of asphyxia (i.e., absent behavioral awareness of hypercarbia and/or hypoxemia) and absent arousal from sleep with development of physiologic compromise secondary to hypercarbia and/or hypoxemia
- No evidence of primary neuromuscular, lung, or cardiac disease or identifiable brain stem lesion that could account for the full constellation of signs and symptoms including autonomic nervous system dysregulation (ANSD)

- Presence of a CCHS-related *PHOX2B* mutation
- Symptoms of ANSD including but not limited to severe breath-holding spells; lack of physiologic responsiveness to the challenges of exercise and environmental stressors; diminished pupillary light response; esophageal dysmotility; severe constipation even in the absence of Hirschsprung disease; profuse sweating; reduced basal body temperature; and altered perception of anxiety

Later-onset CCHS (LO-CCHS) is diagnosed in individuals with the following:

- Same criteria as described above for CCHS of the newborn but with presentation after one month of life, often occurring in later childhood or adulthood

Molecular Genetic Testing

Gene. *PHOX2B* is the only gene in which mutations are known to cause CCHS.

The two major types of *PHOX2B* mutations observed in CCHS are polyalanine repeat expansion mutations (PARMs) and non-polyalanine repeat expansion mutaitons (NPARMs).

Polyalanine repeat expansion mutations (PARMs)

PHOX2B has two polyalanine repeat regions in exon 3, the second of which is the region of primary importance in CCHS. This polyalanine repeat comprises any one of four codon combinations — GCA, GCT, GCC, or GCG — as each one encodes the amino acid alanine. The term "GCN" has been used to designate these four codons.

Allele sizes. Allele sizes and categories are summarized here; see also Weese-Mayer et al [2010].

- **Normal alleles.** The unaffected individual has 20 alanines (GCN repeats) on both *PHOXB* alleles in the repeat region of exon 3.Though benign variants of 9, 13, 14, and 15 GCN repeats have been reported [Amiel et al 2003, Weese-Mayer et al 2003, Toyota et al 2004], individuals with alleles of this length have not been studied systematically to confirm they are entirely normal without any control of breathing deficit or autonomic dysregulation.
- **Mutable normal alleles.** Currently, this category of alleles is not known to occur in this disorder
- **Reduced penetrance alleles.** Individuals heterozygous for 24 alanine repeats (e.g., genotype 20/24) and a subset of individuals heterozygous for 25 alanine repeats (e.g., genotype 20/25) may have a very mild phenotype such that diagnosis is delayed and/or not manifest except when exposed to respiratory depressants or severe intercurrent pulmonary illness [Repetto et al 2009]. Rarely a small NPARM will also have variable penetrance [Berry-Kravis et al 2006].
- **Full penetrance alleles.** Individuals with 25 alanine repeats who present in the newborn period (e.g., genotype 20/25), and those heterozygous for 26 to 33 alanine repeats (e.g., genotype 20/26 to 20/33) [Weese-Mayer et al 2003, Weese-Mayer et al 2010]. The largest known repeat length is 33 alanines.
- **Alleles of uncertain significance.** Only one individual with such a small expansion allele has been described [Toyota et al 2004], in a study on schizophrenia; no clinical information relevant to CCHS phenotype is known about the individual.

Non-polyalanine repeat expansion mutations (NPARMs)

PHOX2B mutations that are not specifically polyalanine expansions, including sequence alterations outside of the polyalanine repeat and frameshift mutations affecting the region encoding the polyalanine repeat, are typically small out-of-frame deletions or duplications of approximately one to 38 nucleotides.

Note: Details of these mutations from many published reports are summarized in Berry-Kravis et al [2006] and Weese-Mayer et al [2010].

Though individuals with NPARMs typically have a more severe phenotype than most individuals with PARMs, on rare occasion a small frameshift mutation could have reduced but variable penetrance in a given family [Berry-Kravis et al 2006].

PHOX2B deletions ranging from 6,216 base pairs (involving only *PHOX2B* exon 3) to 2.6 megabases (involving all of *PHOX2B* and 12 other genes) have been observed in a small cohort of individuals with clinical findings that may include alveolar hypoventilation or Hirschsprung disease [Jennings et al 2011]. Further study is necessary to elucidate the relationship between *PHOX2B* haploinsufficiency and the CCHS phenotype [Jennings et al 2011].

Clinical testing

- **Targeted mutation analysis (fragment length analysis).** This test, referred to as the ***PHOX2B* Screening Test** [Weese-Mayer et al 2010, Weese-Mayer et al 2012], amplifies the region encoding the polyalanine repeat and determines the polyalanine repeat length. Specifically, it detects the polyalanine repeat expansion mutations (PARMs) observed in 92% (185/201) of individuals with CCHS as well as the large (35- and 38-bp) deletions, and some of the small out-of-frame deletions or duplications [Berry-Kravis et al 2006]. Thus, the *PHOX2B* Screening Test identifies mutations in approximately 95% of individuals with CCHS. In addition, it is the only clinically available test to identify low-level somatic mosaicism [Jennings et al 2010].

  Note: Small out-of-frame deletions or duplications change the expected length of the PCR fragment and, thus, can also be detected by fragment length analysis; however, the identification of the precise nucleotide changes and confirmation of a frameshift require subsequent (sequel) sequence analysis.
- **Sequence analysis.** Approximately 8% (16/201) of individuals with CCHS have a *PHOX2B* missense, nonsense, frameshift, or stop codon mutation, including frameshifts in the polyalanine region described above. As noted above, a subset of these NPARMs are detected by the *PHOX2B* Screening Test.
- **Deletion/duplication analysis.** MLPA analysis can be used to detect deletions of the entire *PHOX2B* gene (although the clinical significance of these whole-gene deletions is unclear), or a single or multiple exons (expected to cause CCHS). These mutations can be missed with sequencing and targeted mutation analysis.

Table 1. Summary of Molecular Genetic Testing Used in Congenital Central Hypoventilation Syndrome

Gene [1]	Test Method	Mutations Detected [2]	Mutation Detection Frequency [3]	Test Availability
PHOX2B	Targeted mutation analysis (fragment analysis; Screening Test [4])	PARMs [5]; other out-of-frame NPARMs [6]; nucleotide deletions and duplications in the polyalanine repeat region; 35- to 38-bp deletions; low level mosaicism for PARMs and for NPARMs [7]	~95%	Clinical
	Sequence analysis	PARMS detected with targeted mutation analysis	92%	
		All NPARMS (i.e., sequence variants not within the polyalanine repeat region) [8]	8%	
	Deletion/duplication analysis [9]	Deletion of exon 3 or whole-gene deletion plus other nearby genes [7]	<1% [10]	

1. See Table A. Genes and Databases for chromosome locus and protein name.
2. See Molecular Genetics for information on allelic variants.
3. In individuals with the confirmed CCHS phenotype [Berry-Kravis et al 2006]
4. "Screening Test" refers to the test first described by Weese-Mayer et al [2003] and developed by Weese-Mayer et al [2010].
5. PARMs= polyalanine repeat expansion mutations
6. NPARMs= non-polyalanine repeat expansion mutations
7. Jennings et al [2011]
8. Examples of mutations detected by sequence analysis may include small intragenic deletions/insertions and missense, nonsense, and splice-site mutations. Constitutional polyalanine expansions can be detected, but not low-level mosaicism or deletion of most but not all of exon 3.
9. Testing that identifies deletions/duplications not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA; included in the variety of methods that may be used are: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.
10. True prevalence of whole-gene deletion of *PHOX2B* is unknown. Based on Jennings et al [2011], prevalence is likely very, very low (<1% of individuals with the CCHS phenotype). The phenotype of individuals with the whole-gene deletions is variable and not fully characterized at present.

Testing Strategy

To confirm/establish the diagnosis in a proband, the American Thoracic Society Statement on CCHS suggests step-wise *PHOX2B* testing in persons meeting clinical diagnostic criteria (see Figure 1) [Weese-Mayer et al 2010 (full text), Weese-Mayer et al 2012].

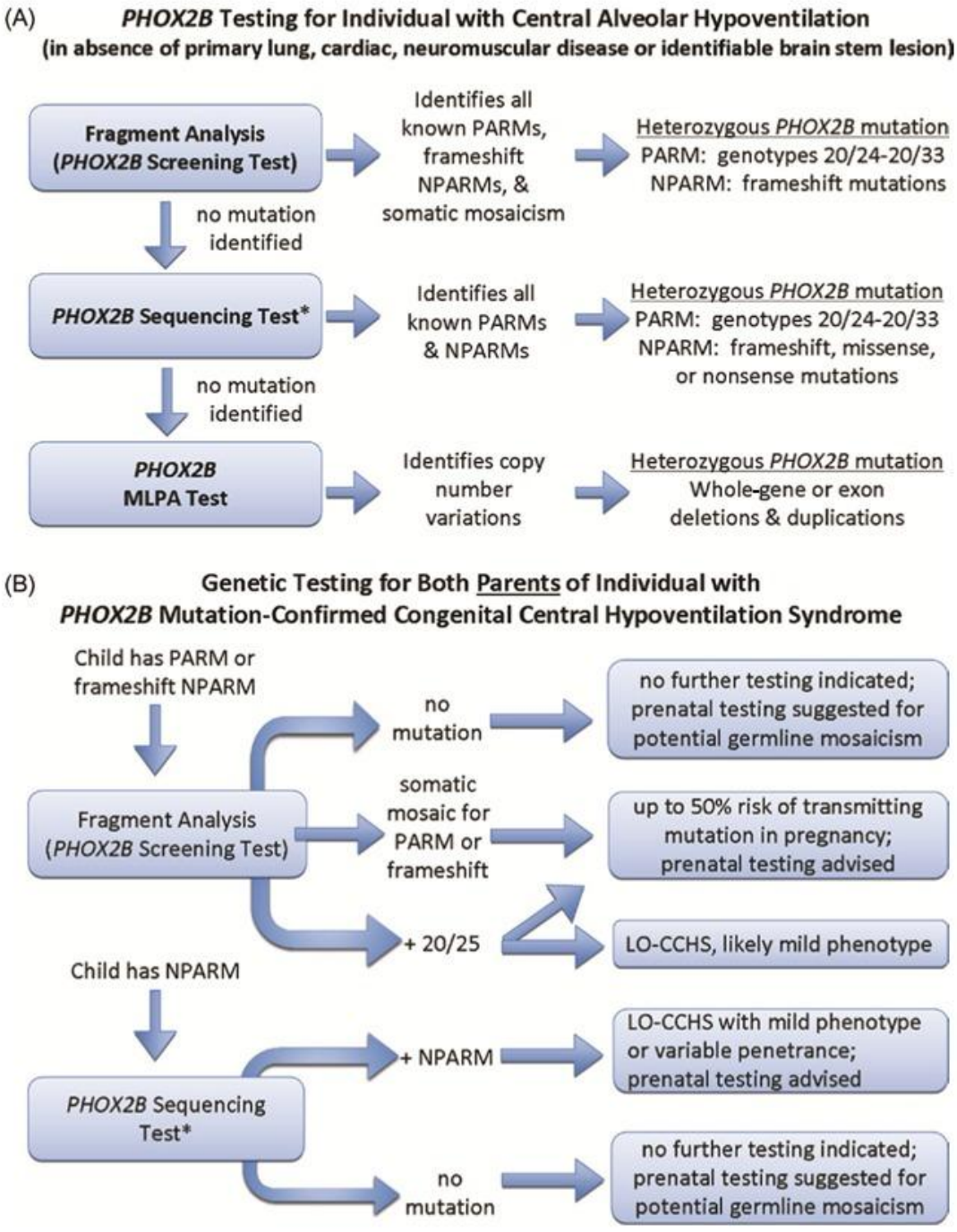

Figure 1

(A) Algorithms to determine when and what type of *PHOX2B* genetic testing should be performed in various clinical scenarios in which CCHS and LO-CCHS are suspected or confirmed

(B) Algorithm to determine when and what type of *PHOX2B* genetic testing should be performed in the parents of a proband with CCHS

*The *PHOX2B* Sequencing Test will not identify low-level mosaicism [Jennings et al 2010]

Weese-Mayer et al [2012]; used by permission of Elsevier

1. Targeted mutation analysis (fragment analysis; Screening Test) should be performed to identify the following [Weese-Mayer et al 2003, Berry-Kravis et al 2006, Weese-Mayer et al 2010, Bachetti et al 2011, Jennings et al 2011, Weese-Mayer et al 2012]:
   - All the CGN polyalanine repeat expansion mutations (PARMs)
   - The 35-bp and 38-bp NPARM recurrent out-of-frame deletions in the coding region involving the polyalanine repeat region, which cause a frameshift and obliteration of the polyalanine repeat sequence
   - Low-level mosaicism for both PARMs and NPARM deletions
2. If no mutation is identified with the Screening Test, perform sequence analysis of the entire PHOX2B coding region and intron-exon boundaries.
3. If no mutation is identified and if clinical suspicion is high, perform deletion/duplication analysis to determine if an exonic or whole-gene deletion is present.
   Note: This third step of testing became available after the American Thoracic Society Statement of 2010 was published [Weese-Mayer et al 2010].

Predictive testing for at-risk asymptomatic adult family members requires prior identification of the disease-causing mutation in the family.

- Parents of a proband who has the 20/24 genotype or the 20/25 genotype (i.e., 20 CGN repeats on one allele and 25 CGN repeats on the other allele) should be tested for the *PHOX2B* mutation with the Screening Test to determine if they are at risk for later-onset CCHS (LO-CCHS).
- Parents of a proband with a longer PARM (genotypes 20/26-20/33) should be tested for a *PHOX2B* mutation with the Screening Test to determine if they have somatic mosaicism for their child's identified mutation.
- Parents of a proband with a 35 bp or a 38 bp deletion (NPARM) should be tested for a *PHOX2B* mutation with the Screening Test to determine if they have somatic mosaicism for their child's identified mutation.

Note: Germline mosaicism in a parent of a proband is rare and cannot be identified with molecular genetic testing of leukocytes or tissues other than germ cells [Rand et al 2012].

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutation in the family.

Genetically Related (Allelic) disorders

No other phenotypes are known to be associated with CCHS-related mutations in *PHOX2B*.

Allelic *PHOX2B* variants in intron 2 and in exon 3 have been reported in sudden infant death syndrome (SIDS) [Rand et al 2006] and Hirschsprung disease (HSCR) [Garcia-Barcelo et al 2003]. The significance of these variants in causation of these diseases is unknown at this time, though they are clearly not disease defining in terms of the CCHS phenotype.

Schizophrenia and strabismus have been associated with the polyalanine repeat contraction variants in the *PHOX2B* polyalanine repeat tract observed in control populations without CCHS [Toyota et al 2004].

Clinical Description

Natural History

Congenital central hypoventilation syndrome (CCHS) represents the extreme manifestation of autonomic nervous system (ANS) dysregulation (ANSD), with a hallmark of disordered respiratory control [Weese-Mayer et al 2010].

Classic CCHS is characterized by adequate ventilation while the individual is awake and apparent hypoventilation with monotonous respiratory rates and shallow breathing (diminished tidal volume) during sleep. More severely affected individuals with CCHS hypoventilate both when awake and when asleep [Weese-Mayer et al 2010]. Children who hypoventilate both when awake and when asleep typically present in the newborn period, as do the vast majority of children who hypoventilate only when asleep. The salient respiratory and cardiac findings of CCHS are summarized in Table 2.

Table 2. Published Clinical Features of Congenital Central Hypoventilation Syndrome (CCHS)

Clinical Feature		References
Cardiac	Decreased heart rate beat-to-beat variability	Woo et al [1992], Ogawa et al [1993], Silvestri et al [2000], Trang et al [2005]
	Increased ratios of low frequency-band to high frequency-band spectral power and transient prolonged asystoles	Woo et al [1992], Ogawa et al [1993], Silvestri et al [2000]
	Attenuated heart rate response to exercise	Silvestri et al [1995]
	Attenuated pulse arterial tonometry signal magnitude following sigh and with cold hand pressor test	O'Brien et al [2005]
	Blood pressure values lower during wakefulness and higher during sleep (vs controls), indicating attenuation of the normal sleep-related blood pressure decrement	Trang et al [2003]
	Increased length of PARM associated with increased risk of prolonged sinus pauses and cardiac pacemaker placement among the 3 most common PARMs (20/25, 20/26, 20/27)	Gronli et al [2008]
	Capacity to elevate blood pressure on standing and head-up tilt positions is limited. Normal standing-related blood pressure overshoot is absent. Affected individuals may have absence of symptoms despite profound orthostatic hypotension with reduced cerebral regional blood flow.	Trang et al [2005], Carroll et al [2013a]
Dermatoglyphics	See footnote 1	Todd et al [2006a]
Facies	See footnote 2	Todd et al [2006b]

Clinical Feature		References
Gastrointestinal	Hirschsprung disease (~16%-20% of individuals)	Trochet et al [2005b], Berry-Kravis et al [2006], de Pontual et al [2006]
	Severe constipation even in absence of Hirschsprung disease	Weese-Mayer et al [1993], Weese-Mayer et al [2001]
	Esophageal dysmotility/dysphagia	Weese-Mayer et al [1999], Weese-Mayer et al [2001], Faure et al [2002], Gordon et al [2013]
Neural crest tumors	Tumors of neural crest origin (e.g., neuroblastoma, ganglioneuroblastoma, and ganglioneuroma)	Trochet et al [2005b], Berry-Kravis et al [2006]
Ophthalmologic	Pupillary abnormalities Altered accommodation Positive correlation between length of PARM and alteration in pupillary response to light among the 3 most common PARMs	Weese-Mayer et al [1992], Goldberg & Ludwig [1996], Patwari et al [2012]
Psychological	Decreased perception of anxiety	Pine et al [1994]
Respiratory	Alveolar hypoventilation	Weese-Mayer et al [2010]
	Lack of normal ventilatory and arousal responses to hypercarbia and hypoxemia	Weese-Mayer et al [2010], Carroll et al [2010], Carroll et al [2013b]
	Limited breath-to-breath variability	Weese-Mayer et al [2003], Weese-Mayer et al [2010]
Sudomotor	Sporadic profuse sweating Decreased basal body temperature	Weese-Mayer et al [1999], Weese-Mayer et al [2001], Saiyed et al [2011], Gordon et al [2013]

PARM = polyalanine repeat expansion mutation

1. Dermatoglyphic pattern type frequencies are altered in individuals with CCHS compared to controls. In particular, an increase of arches was observed in females, and an increase of ulnar loops in males. The largest differences were noted for the left hand and for individuals with both CCHS and Hirschsprung disease [Todd et al 2006a].

2. A characteristic facial phenotype has been described in CCHS [Todd et al 2006b]. The facies are generally shorter and flatter and typically show an inferior inflection of the lateral segment of vermillion border on the upper lip. The significantly decreased facial index and decreased upper facial index (such that the face is short relative to its width) results in the characteristic box-shaped face. The results also suggest that males with CCHS are more significantly affected than females. Using five variables to characterize facies (upper-lip height, biocular width, upper facial height, nasal tip protrusion, and the lip trait), 85.7% of individuals with CCHS and 82.2% of controls were correctly predicted.

Autonomic nervous system dysregulation (ANSD) [Marazita et al 2001, Weese-Mayer et al 2001]. As would be expected in consideration of the key role of *PHOX2B* in development of the autonomic

nervous system [Howard et al 2000], children with CCHS have manifestations of ANSD (Table 2). Table 3 highlights neuropathologic and neuroimaging findings of individuals given a clinical diagnosis of CCHS (many of whom unfortunately did not undergo confirmatory *PHOX2B* molecular genetic testing).

Table 3. Neuropathologic and Neuroimaging Findings

Finding	References
Neuronal loss of reticular nuclei and nearby cranial nerve nuclei (1 case)	Liu et al [1978]
Absent arcuate nucleus (1 case)	Folgering et al [1979]
Hypoxia-induced posterior thalamic, cerebellar, midbrain, and limbic deficits	Macey et al [2005b]
Multiple areas of white matter abnormality on brain MRI	Kumar et al [2005]
Abnormal functional MRI (fMRI) brain responses to cold pressor challenge, hypoxia, and hyperoxia	Macey et al [2005a] Macey et al [2005b] Woo et al [2005]
MRI changes [1] in: • Hypothalamus (responsible for thermal drive to breathing) • Posterior thalamus and midbrain (mediating O_2 and oscillatory motor patterns) • Caudal raphé and locus coeruleus (regulating serotonergic and noradrenergic systems) • Lateral medulla, parabrachial pons, and cerebellum (coordinating chemoreceptor and somatic afferent activity with breathing) • Insular and cingulate cortices (mediating shortness of breath perception)	Patwari et al [2010a]

1. Structural and functional alterations in these sites may be caused by *PHOX2B* mutations or result from hypoxia/perfusion alterations related to suboptimal management/compliance. Note that subjects in this publication and other publications referenced in the above table were diagnosed with CCHS clinically and did not necessarily have confirmatory *PHOX2B* molecular genetic testing.

Many successfully ventilated individuals with CCHS are now in their 20s, suggesting the potential for a normal life span. The cause of death in individuals with CCHS is usually related to suboptimal ventilatory support or involvement with substances that could affect judgment or ventilation [Chen et al 2006]. Development of asystoles is another potential cause of sudden death in CCHS [Gronli et al 2008] among individuals with a prolonged R-R interval who have not received a cardiac pacemaker [Antic et al 2006] or in individuals who are not rigorous about monthly cardiac pacemaker assessment (e.g., the battery life is depleted or the pacemaker malfunctions).

Neurocristopathy (i.e., maldevelopment of neural crest-derived structures) including Hirschsprung disease and congenital absence of parasympathetic intrinsic ganglion cells of the distal hindgut are present in 16%-20% of individuals with CCHS. The risk of Hirschsprung disease is highest in children with NPARMs and with the longer PARMs. Hirschsprung disease typically presents in the newborn period, although it has been diagnosed later in infancy and early childhood (see also Genotype-Phenotype Correlations).

Tumors of neural crest origin including neuroblastoma, ganglioneuroma, and ganglioneuroblastoma, are observed overall in 5%-6% of children with CCHS [Trochet et al 2005b, Berry-Kravis et al 2006]. The risk of a neural crest tumor is highest in children with NPARMs (~50% will develop a neuroblastoma), and rare among children with PARMs (low but apparent risk is in those with 20/29-20/33 genotypes). The tumors can present at variable ages: neuroblastoma typically before age two years; ganglioneuromas later as incidental findings. Tumor-related deaths are uncommon (see also Genotype-Phenotype Correlations).

Later-onset CCHS (LO-CCHS) with *PHOX2B* mutations is characterized by alveolar hypoventilation during sleep and symptoms of autonomic nervous system dysregulation (ANSD); however, onset is after the first month of life with diagnosis in later infancy, childhood, or adulthood.

LO-CCHS results from reduced penetrance of certain *PHOX2B* mutations: for example, compound heterozygosity for the normal 20 CGN and the abnormal 24 CGN alleles, compound heterozygosity for 20 CGN and 25CGN, and (rarely) a small NPARM or homozygosity for an allele coding for 24 CGN alanine repeats.

LO-CCHS needs to be considered in:

- Individuals who do not necessarily have the characteristic CCHS phenotype, but do have the following:
    - Apparent life-threatening events and cyanosis during sleep
    - Recurrent severe pulmonic infections with related hypoventilation
    - Unexplained seizures
    - Respiratory depression after anti-seizure medication, sedation, or anesthesia
    - Unexplained neurocognitive delay with any history of prior cyanosis
    - Unexplained nocturnal hypercarbia and hypoxemia
    - Unresolved central alveolar hypoventilation after treatment for obstructive sleep apnea
    - Seeming unresponsiveness to conditions of apparent hypercarbia or hypoxemia (prolonged underwater swimming, pneumonia)
- Infants and children who die suddenly and unexpectedly ("SIDS" and "sudden unexplained death of childhood [SUDC]"), especially if there is a family history of CCHS

See ATS Statement for more details.

A growing number of individuals have been reported in the literature with LO-CCHS and a confirmed *PHOX2B* PARM or NPARM. On occasion only one family member is described, but more typically several family members in multiple generations are described. These studies emphasize the importance

of adult care providers obtaining a family history which includes whether the individual has a child with a genetic disorder (e.g., CCHS).

The physician with a heightened clinical suspicion of LO-CCHS who orders prompt molecular genetic testing of*PHOX2B* will quickly make the diagnosis and avert potentially life-threatening decompensation as well as the risk for neurocognitive compromise. The clinician should inquire about whether the individual has a history of hypoventilation temporally related to past anesthesia or sedation exposure, delayed "recovery" from a severe respiratory illness, and/or unexplained seizures or neurocognitive impairment.

Genotype-Phenotype Correlations

Respiratory. A correlation between the *PHOX2B* polyalanine repeat expansion mutation (PARM) length and the severity of the respiratory phenotype and associated symptoms has been observed [Weese-Mayer et al 2003, Matera et al 2004, Berry-Kravis et al 2006].

ANSD. Association between the PARM length and quantitative ANSD traits (i.e., number of ANSD symptoms and number of affected systems as described in Weese-Mayer et al [2001] and Marazita et al [2001]) has been investigated [Weese-Mayer et al 2003].

A significant association was observed between:

- PARM length and number of ANSD symptoms (p=0.02), but not number of ANSD-affected systems (p=0.13);
- PARM length and daily duration of required ventilatory support (p=0.003).

The type of *PHOX2B* mutation and the length of PARMs determine severity of ANSD. Increasing PARM length is associated with increasing frequency of organ system-specific physiologic ANSD.

Hirschsprung disease. Individuals who are heterozygous for 20/27 genotype or longer PARMs are at greatest risk for Hirschsprung disease. Nearly all individuals with NPARMs have Hirschsprung disease [Trochet et al 2005b, Berry-Kravis et al 2006].

Tumors of neural crest origin. Individuals with NPARMs have a greater risk of developing a tumor of neural crest origin than those with PARMs. Likewise, individuals with the longest PARMs are at an increased risk (albeit lower than the risk of those with NPARMs) of developing a tumor of neural crest origin [Trochet et al 2005b, Berry-Kravis et al 2006]. Prevalence of tumors of neural crest origin varies by type of *PHOX2B* mutation with report of individuals with PARM genotypes of 20/29 and 20/33 only and in NPARMs [Amiel et al 2003, Weese-Mayer et al 2003, Trochet et al 2005b, Weese-Mayer et al 2010].

Cardiac arrhythmia. A positive correlation between longest R-R interval and PARM length was identified in individuals with the three most common *PHOX2B* genotypes: compound heterozygosity for the following number of GCN repeats (20/25; 20/26; 20/27).

Specifically, the risk for prolonged sinus pauses and the need for a cardiac pacemaker are increased in individuals with PARMs of 20/26 and 20/27 as compared to 20/25 [Gronli et al 2008]. Likewise, a positive correlation between number of children for whom a cardiac pacemaker was recommended and PARM length was identified [Gronli et al 2008].

Facial features. The significant negative correlation between PARM length and four anthropometric measures (mandible breadth, nasolabial angle, lateral lip height, and mandible-face width index) decreases as the PARM length increases [Todd et al 2006b].

Dermatoglyphic pattern. No significant association was found between the PARM length and dermatoglyphic patterns [Todd et al 2006a]. However, an increase in arches among girls and an increase in ulnar loops among boys were reported.

Pupillary response to light. See information in Table 2.

Penetrance

Penetrance for the *PHOX2B* polyalanine repeat expansion mutation appears to be high. Amiel et al [2003], Sasaki et al [2003], Weese-Mayer et al [2003], Matera et al [2004], and Berry-Kravis et al [2006] found no controls with a *PHOX2B* polyalanine repeat expansion mutation.

However, the recent identification of CCHS in adults and young children (but not infants) with the 20/24 genotype and the 20/25 genotype indicates reduced penetrance in early childhood for this specific genotype. This also appears to be true for a small subset of the NPARMs [Berry-Kravis et al 2006].

Anticipation

Limited data suggest that the polyalanine expansion in *PHOX2B* is meiotically stable. Many reports have consistently documented a stable number of repeats during parent-to-child transmission, including instances of parental mosaicism for the expansion [Weese-Mayer et al 2003, Trochet et al 2005b, Weese-Mayer et al 2005, Antic et al 2006]. In all instances in which the *PHOX2B* polyalanine repeat expansion mutation was transmitted from a parent with CCHS to a child with CCHS or from a mosaic parent to a child with CCHS, no change was observed in the number of repeats (i.e., parent and child had mutated alleles of the same size).

Nomenclature

The appropriate nomenclature for this disorder is congenital central hypoventilation syndrome (CCHS).

A literary misnomer, "Ondine's curse," has been used in the past. In the German folk epic [Sugar 1978], the nymph Ondine falls in love with a mortal. When the mortal is unfaithful to Ondine, the king of the nymphs places a curse on the mortal that makes him responsible for remembering to perform all bodily functions, even those that occur automatically such as breathing. When the mortal falls asleep, he “forgets” to breathe and dies. Because Ondine was not the one who cursed the mortal, individuals with CCHS do not forget to breathe, and individuals with CCHS are not “cursed,” the term “Ondine's curse” is a misnomer and should be discouraged.

Haddad syndrome refers to the co-occurrence of CCHS and Hirschsprung disease; the term is not widely used.

Prevalence

With the introduction of clinically available molecular genetic testing for *PHOX2B* in 2003, it has become apparent that CCHS is no longer as rare as previously considered. Current estimates of at least 1,000 individuals worldwide [Weese-Mayer et al 2009, Weese-Mayer et al 2010] are likely an underestimate because of the variable severity observed in later-onset CCHS (LO-CCHS).

The only population study in the literature thus far was performed in Taiwan [Hung et al 2007]. To date no prospective study has ascertained the incidence of CCHS in an ethnically diverse cohort. Consequently, estimates of the incidence of CCHS should be discouraged.

From 2005 to 2011, more than 160 additional individuals with a *PHOX2B* mutation were identified [Authors, personal experience] — an average of 25 new cases per year [Rand et al 2011]. Further, testing of children with atypical presentations (LO-CCHS) who are found to have the 20/24 genotype and the 20/25 genotype continues to be delayed beyond the neonatal period and first year of life [Rand et al 2011]. With the 2013 introduction of the first International CCHS REDCap Registry (Lurie Children's Hospital, Chicago, IL), a more clear determination of the number of cases of CCHS worldwide will be determined and further delineation of the *PHOX2B* genotype/CCHS phenotype relationship with advancing age will be described.

Differential Diagnosis

Children with congenital central hypoventilation syndrome (CCHS) typically present in the newborn period. Studies should be performed to rule out primary neuromuscular, lung, or cardiac disease or an identifiable brain stem lesion that could account for the full constellation of symptoms characteristic of CCHS, including the autonomic nervous system dysregulation (ANSD). *PHOX2B* genetic testing (which became available in 2003) allows for distinction between CCHS and other disorders in the differential diagnosis including severe prematurity [Bajaj et al 2005], identifiable brain stem findings that could (but do not) account for the hypoventilation [Bachetti et al 2006], asphyxia, infection, trauma, tumor, and infarction.

Because it is anticipated that a growing number of children and adults with a mild CCHS phenotype will be heterozygous for a *PHOX2B* mutation, the differential diagnosis for unexplained childhood and adult alveolar hypoventilation or adverse event (cyanosis or seizures) secondary to sedation, severe pulmonary infection, or treated obstructive sleep apnea must include CCHS and complete step-wise *PHOX2B* testing.

ROHHAD (*r*apid-onset *o*besity with *h*ypothalamic dysfunction, *h*ypoventilation, and *a*utonomic *d*ysregulation) is distinct from CCHS. ROHHAD was first described more than 45 years ago as "late-onset central hypoventilation syndrome with hypothalamic dysfunction" [Fishman et al 1965]. In 2000, Katz et al [2000] suggested that it was distinct from CCHS. In 2007, Ize-Ludlow et al [2007] coined the acronym ROHHAD and demonstrated the absence of CCHS-related *PHOX2B* mutations. ROHHAD is a

rare disorder characterized by dramatic weight gain over a six- to 12-month period between ages 1.5 and 10 years (most often age 3-7 years), which is typically followed by:

- Hypothalamic dysfunction (altered water balance, hyperprolactinemia, hypothyroidism, altered onset of puberty, growth hormone deficiency, and ACTH insufficiency) [Ize-Ludlow et al 2007, Bougnères et al 2008];
- Central alveolar hypoventilation (often preceded by obstructive sleep apnea); and
- ANSD (altered thermoregulation, diaphoresis, pupillary response, vasomotor function, and bradycardia).

The acronym was developed to reflect the most characteristic sequence of phenotypic manifestations. Affected children can also have mild to severe behavioral problems; many of the children have tumors including ganglioneuromas and ganglioneuroblastomas. Although ROHHAD is suspected to be genetic in origin, candidate gene investigations have not identified a genetic association with any of the following genes: *PHOX2B, TRKB, BDNF* [Ize-ludlow et al 2007], *ASCL1*, *NECDIN* [DePontual et al 2006], HTR_{1A}, *OTP*, or *PACAP* [Rand et al 2011]. Ongoing investigation has focused on copy number variation, methylation, and most recently exome sequencing.

Note to clinicians: For a patient-specific 'simultaneous consult' related to this disorder, SimulConsult®, an interactive diagnostic decision support software tool that provides differential diagnoses based on patient findings (registration or institutional access required).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with congenital central hypoventilation syndrome (CCHS) or later-onset CCHS (LO-CCHS), the following evaluations are recommended:

- Assessment in a pediatric respiratory physiology laboratory, with:
  - Clinical study of spontaneous breathing awake and asleep including (at a minimum) tidal volume, respiratory inductance plethysmography of the chest and abdomen, hemoglobin saturation with pulse waveform, end-tidal carbon dioxide level with visible waveform, and electrocardiogram; and
  - Evaluation of the awake and asleep responses to exogenous and endogenous challenges of hypercarbia and/or hypoxemia.
- Venous or arterial blood gas or serum bicarbonate level to look for elevated carbon dioxide content at the time of presentation
- Hemoglobin, hematocrit, and reticulocyte count to assess for polycythemia
- 72-hour Holter recording to assess for abrupt, prolonged asystoles
- Echocardiogram to assess for changes consistent with right ventricular hypertrophy and cor pulmonale
- Neurocognitive assessment to determine baseline function
- Comprehensive autonomic testing of all organ systems regulated by the ANS, including but not limited to pupillometry, head up-tilt testing, thermoregulatory chamber sweat testing, Q-Sweat

testing, heart rate deep breathing, Valsalva maneuver, and measures of regional blood flow in activities of daily living as well as orthostatic testing.
- Medical genetics consultation

See Table 4 for additional details.

Treatment of Manifestations

Ventilatory support. The treatment goals for classic CCHS are to secure the airway and to use chronic ventilatory support at home to compensate for the altered/absent ventilatory responses to hypoxemia and hypercarbia. Of note, although oxygen administration without artificial ventilation improves the PaO_2 (partial pressure of oxygen in arterial blood) and relieves cyanosis, it is not an adequate treatment of hypoventilation.

Because individuals with CCHS may experience complete respiratory arrest or severe hypoventilation and, thus, the sequelae of hypoxemia, they require monitoring of objective measures of oxygenation (i.e., pulse oximeter) and ventilation (i.e., $P_{ET}co_2$ monitor) continuously during sleep and at regular intervals while awake. They also require observation and continuous care, especially during all sleep, by an RN trained and experienced in ventilator management.

For each of the options listed below, the goal is to provide the affected individual with the technology optimal for her/his life style needs.

Typically, the infant needing ventilatory support 24 hours per day is most safely and effectively supported via tracheostomy and use of a home mechanical ventilator. Tracheostomy is also recommended for children and adults who require ventilator support during sleep only.

As children who require continuous ventilatory support become ambulatory, diaphragm pacing by phrenic nerve stimulation can be considered to allow for increased mobility and improved quality of life. Diaphragm pacing is not typically recommended for the young child who requires only nighttime ventilatory support because the benefits do not outweigh the risks; however, for older adolescents and young adults, this could be an appropriate consideration. Tracheal decannulation is not assured in affected individuals who use diaphragm pacing during sleep.

- Diaphragm pacers for the active child with CCHS should be implanted at each phrenic nerve in the chest, ideally by thoracoscopic technique [Weese-Mayer et al 1996, Shaul et al 2002, Chin et al 2012].
- Older infants, toddlers, and children with diaphragm pacers should be assessed for use of a Passy-Muir one-way speaking valve while awake, allowing for vocalization and use of the upper airway on exhalation.
- Children with diaphragm pacers may be assessed for capping of the tracheostomy tube while awake and paced, thereby allowing for inspiration and exhalation via the upper airway; tracheostomy is typically still required for mechanical ventilation during sleep to avoid upper airway obstruction and physiologic compromise.
- Although not yet accomplished, the older child with an entirely normal airway may be able to eliminate the need for a tracheostomy by relying on diaphragm pacing while awake and on mask

ventilation while asleep; however, such a child may require interim endotracheal intubation to allow for optimal oxygenation and ventilation during acute illness that requires more aggressive ventilatory management.

Cooperative older children with CCHS who consistently require ventilatory support only while sleeping may be candidates for noninvasive support with either mask ventilation or negative-pressure ventilation; however, this must be done with careful consideration of each child's needs. If successful, tracheal decannulation can be considered (with the caveat that in the event of severe illness, interim endotracheal intubation may be required in a pediatric intensive care unit). The child who normally requires ventilatory support during sleep only may, during an intercurrent illness, also require artificial ventilation both awake and asleep.

Note: Straus et al [2010] reported that the ventilatory response to hypercarbia seemed to improve with the use of oral contraceptives in two young women heterozygous for 20/25 and 20/26 genotypes. Ongoing studies have not confirmed this report.

Cardiac. Prolonged transient asystoles may present as syncope and/or staring spells, and may be of such significant duration (≥3.0 seconds) as to warrant placement of a cardiac pacemaker for management [Silvestri et al 2000, Gronli et al 2008].

Hirschsprung disease. See Hirschsprung Disease Overview.

Tumors of neural crest origin. Neuroblastomas are removed surgically and followed by chemotherapy if they have advanced beyond Stage 1. Other tumors of neural crest origin are treated individually by location and type, though surgical removal is typically recommended.

Prevention of Secondary Complications

Mask ventilation in the infant and young child is strongly discouraged. Mask ventilation is not adequately stable as a life-sustaining support, with risk for repeated hypoxemia and neurocognitive compromise in the infant and young child. If mask ventilation is used, an actual ventilator is needed as the traditional Bi-PAP machine is not approved for life-sustaining support. Also, close longitudinal follow up by specialists with craniofacial and dental expertise is essential as the potential for doing harm with facial deformation is an important consideration and may necessitate midface advancement in the teen years.

Surveillance

For all individuals with CCHS, the following evaluations are recommended:

- At least yearly (every 6 months until age 3 years) comprehensive, multiple-day in-hospital physiologic evaluation (see Table 4)
- Yearly echocardiogram to identify right ventricular hypertrophy and/or cor pulmonale
- Yearly hemoglobin, hematocrit, and reticulocyte counts to identify polycythemia

Table 4 summarizes the recommended clinical evaluations for affected individuals with CCHS based on the *PHOX2B* mutation present.

Table 4. Clinical Evaluations to Characterize CCHS Phenotype Based on *PHOX2B* Mutation

***PHOX2B* Mutation**	**Annual In-Hospital Comprehensive Testing [1]**	**Annual Neurocognitive Assessment**	**Annual 72-hr Holter and ECG**	**Hirschsprung Disease Assessment**	**Tumors of Neural Crest Origin Assessment**
PARM genotype: 20/24, 20/25	X	X	X		
PARM genotype: 20/26, 20/27	X	X	X	X	
PARM genotype: 20/2820/33	X	X	X	X	X [2]
NPARM	X	X	X	X	X [3]
Deletion/ duplication [4]	X	X	X	X	X [2]

Adapted from Weese-Mayer et al [2010]
PARM = polyalanine repeat expansion mutation with number of repeats on each allele, e.g., 20/24
NPARM = non-polyalanine repeat expansion mutation (i.e., missense, nonsense, frameshift, stop codon)
Note: In infants and those newly diagnosed with LO-CCHS the recommendation is for above-described evaluation every 6 months until age 3 years (or 3 years from the LO-CCHS diagnosis).
1. Awake and asleep physiologic testing in varying levels of concentration and activity simulating activities of daily living; exogenous and endogenous gas challenges; comprehensive age-appropriate clinical autonomic testing
2. Annual chest and abdominal imaging to identify ganglioneuromas and ganglioneuroblastomas and potentially neuroblastomas
3. Chest and abdominal imaging and urine cathecholamines every 3 months in the first 2 years, then every 6 months until age 7 years to identify neuroblastomas
4. Exonic or whole-gene deletion or duplication

Agents/Circumstances to Avoid

Ideally, children with CCHS should not go swimming. If they do, they should be carefully supervised, regardless of the presence or absence of a tracheostomy. Children with CCHS should not compete in underwater swimming contests as they cannot perceive the asphyxia that occurs with drowning and breath-holding and, therefore, are likely to swim longer and farther than children without CCHS, thereby increasing the risk of drowning. Furthermore, breath-holding contests can lead to asphyxia and/or death.

Alcohol (respiratory depression), recreational drugs (varied effects), and prescribed as well as non-prescribed medications/sedatives/anesthetics that could induce respiratory depression should be avoided [Chen et al 2006].

Evaluation of Relatives at Risk

The molecular genetic test method used to evaluate parents, children, and at-risk sibs of individuals with CCHS depends on the mutation identified in the proband (see Testing Strategy). Parents of children with a known *PHOX2B* mutation should be tested for the family-specific mutation to determine their risk for later-onset CCHS or mosaicism.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Though not prospectively evaluated, the ventilatory needs of a pregnant woman with CCHS warrant careful consideration by the obstetrician.

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.

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. —ED.

Mode of Inheritance

CCHS is inherited in an autosomal dominant manner [Weese-Mayer et al 2003].

Risk to Family Members

Parents of a proband

- Most individuals with CCHS are heterozygous for a *de novo* mutation in *PHOX2B*.
- Some individuals with CCHS have a parent with CCHS [Weese-Mayer et al 2003, Trochet et al 2005b, Weese-Mayer & Berry-Kravis 2004, Antic et al 2006].
- Germline mosaicism with or without somatic mosaicism for a *PHOX2B* mutation is present in about 25% of asymptomatic parents of individuals with CCHS [Weese-Mayer et al 2003,

Trochet et al 2005b, Berry-Kravis et al 2006]. Parents with mosaicism should have comprehensive physiologic assessment to determine if features of the CCHS phenotype are present.

- Germline mosaicism (without somatic mosaicism) for a *PHOX2B* mutation is present in a very limited number of asymptomatic parents of individuals with CCHS [Rand et al 2012] and should be considered as an explanation if no evidence for somatic mosaicism is present in families with recurrence of CCHS in offspring.
- Recommendations for the evaluation of parents of a proband with a presumed *de novo* mutation include testing of both parents for the *PHOX2B* mutation present in the proband including methods known to detect low-level mosaicism [Jennings et al 2011].

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs is 50%.
- If a parent of the proband has mosaicism for the *PHOX2B* mutation observed in the proband, the recurrence risk to the sibs of the proband is 50% or lower.
- When the parents are clinically unaffected, the sibs of the proband may still be at risk, as mosaicism in asymptomatic parents has been reported [Weese-Mayer et al 2003].

Offspring of a proband. Each child of an individual with CCHS has a 50% chance of inheriting the mutation.

Other family members. The risk to other family members depends on the status of the proband's parents. If a parent is affected, her or his family members are at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

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.

Prenatal Testing

If the disease-causing mutation has been identified in the family, prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis

(usually performed at ~15-18 weeks' gestation) or chorionic villus sampling (usually performed at ~10-12 weeks' gestation).

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

Preimplantation genetic diagnosis (PGD) may be an option for some families in which the disease-causing mutation has been identified.

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.

- **CCHS (Congenital Central Hypoventilation Syndrome) Family Network**
  www.cchsnetwork.org
- **Children's Neuroblastoma Cancer Foundation**
  PO Box 6635
  Bloomingdale IL 60108
  Phone: 866-671-2623 (toll-free)
  Fax: 630-351-2462
  Email: info@nbhope.org
  www.cncfhope.org
- **Pull-thru Network (PTN)**
  2312 Savoy Street
  Hoover AL 35226-1528
  Phone: 205-978-2930
  Email: PTNmail@charter.net
  www.pullthrunetwork.org
- **RADICA-FRE**
  Respiratory and Autonomic Disorders of Infancy, Childhood, and Adulthood Foundation for Research and Education
  www.radicafre.com
- **ROHHAD Fight, Inc.**
  3 Surrey Lane
  Hempstead NY 11550
  Phone: 516-642-1177
  Fax: 516-483-0566
  Email: rohhadfight@aol.com
  www.rohhadfight.org
- **International CCHS REDCap Registry**
  Phone: 312-227-3300
  Email: sagordon@luriechildrens.org
  www.luriechildrens.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. Congenital Central Hypoventilation Syndrome: Genes and Databases

Gene Symbol	Chromosomal Locus	Protein Name	Locus Specific	HGMD
PHOX2B	4p13	Paired mesoderm homeobox protein 2B	PHOX2B homepage - Mendelian genes	PHOX2B

Data are compiled from the following standard references: gene symbol from HGNC; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from UniProt. For a description of databases (Locus Specific, HGMD) to which links are provided, click here.

Table B. OMIM Entries for Congenital Central Hypoventilation Syndrome (View All in OMIM)

209880	CENTRAL HYPOVENTILATION SYNDROME, CONGENITAL; CCHS
603851	PAIRED-LIKE HOMEOBOX 2B; PHOX2B

Molecular Genetic Pathogenesis

Click here for information on polyalanine expansion (pdf).

Mutations in genes other than *PHOX2B* have been identified in persons with CCHS (Table 5); their significance is not known.

Table 5. Other Genes with Mutations Reported in Individuals with Clinically Determined CCHS

Gene	# Individuals Reported with a Mutation in the Gene	# Individuals with Mutation in Specified Gene AND *PHOX2B* Polyalanine Expansion Mutation	Reference
RET	8	3	Amiel et al [1998] Sakai et al [1998] Sakai et al [2001] Fitze et al [2003] Sasaki et al [2003]
GDNF	1	1	Amiel et al [1998]
EDN3	1	1	Bolk et al [1996]
BDNF	1	1	Weese-Mayer et al [2002]
ASCL (HASH1)	5	3	de Pontual et al [2003] Sasaki et al [2003]
PHOX2A	1	-	Sasaki et al [2003]
GFRA1	1	1	Sasaki et al [2003]
BMP2	1	1	Weese-Mayer et al [2003]
ECE1	1	1	Weese-Mayer et al [2003] Berry-Kravis et al [2006]

The *PHOX2B* repeat expansion mutation segregated with CCHS in families from which parental samples were analyzed, while the *RET, GDNF*, *BDNF*, and *HASH1* mutations did not. It is unknown to the authors whether all individuals with these mutations have been tested for *PHOX2B* mutations. Therefore, the role of mutations in genes other than *PHOX2B* in disease causation is unclear; they could be pathogenic or benign polymorphisms. See Weese-Mayer et al [2003] for a complete discussion.

PHOX2B

Gene structure. *PHOX2B* has a "GCN" repeat in exon 3 that comprises any one of four codon combinations GCA, GCT, GCC, or GCG — each encoding the amino acid alanine. (The term "GCN" has been used to designate these four codons). For a detailed summary of gene and protein information, see Table A, **Gene Symbol**.

Benign allelic variants. A 20-repeat length is benign; benign variants of 7, 13, 14, and 15 repeats have been reported [Amiel et al 2003, Weese-Mayer et al 2003, Toyota et al 2004]

Pathogenic allelic variants. GCN tract of 24-33 repeats (For more information, see Table A.) More than 75 individuals with a non-polyalanine repeat expansion mutation have been identified thus far [Amiel et al 2003, Sasaki et al 2003, Weese-Mayer et al 2003, Matera et al 2004, Trochet et al 2005a, Berry-Kravis et al 2006, Weese-Mayer et al 2010].

Mutation information is summarized in the ATS statement [Weese-Mayer et al 2010 (full text)].

Normal gene product. *PHOX2B* encodes a highly conserved homeobox domain transcription factor (314 amino acids), with two short and stable polyalanine repeats of nine and 20 residues encoded by the GCN repeat in exon 3 [Amiel et al 2003].

Abnormal gene product. Disorders caused by triplet repeat expansions can cause disease through either gain-of-function or loss-of-function mechanisms. There is no CCHS phenotype in mice haploinsufficient for *Phox2b* (although these mice have dilated pupils and atrophy of the ciliary ganglion) [Cross et al 2004] and nearly all individuals with CCHS have mutations that alter the protein downstream from the homeodomain [Amiel et al 2003, Sasaki et al 2003, Weese-Mayer et al 2003, Matera et al 2004], suggesting that mutations causing CCHS result in a change in function as opposed to simply reducing the amount of the PHOX2B protein. Because paired-homeodomain proteins such as PHOX2B bind to their target sites on DNA as dimers, PHOX2B mutant proteins that have the binding site intact could potentially act in a dominant-negative manner by interfering with the function of the wild-type protein when it dimerizes with a mutant protein.

Several lines of evidence support a possible dominant-negative mechanism for *PHOX2B* mutations in CCHS. Click here for more information (pdf).

Somatic mutation of *PHOX2B* in cancer. *PHOX2B* mutations have been reported in apparently sporadic neuroblastoma [van Limpt et al 2004]. In this case, it is unclear how comprehensively the affected child was evaluated for breathing issues.

References

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

Published Guidelines/Consensus Statements

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Suggested Reading

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