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Congenital Central Hypoventilation Syndrome

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Summary

Clinical characteristics

Congenital central hypoventilation syndrome (CCHS) represents the extreme manifestation of autonomic nervous system dysregulation (ANSD) with the hallmark of disordered respiratory control.

The age of initial recognition of CCHS ranges from neonatal onset (i.e., in the first 30 days of life) to (less commonly) later onset (from 1 month to adulthood).

- **Neonatal-onset CCHS** is characterized by apparent hypoventilation with monotonous respiratory rates and shallow breathing either during sleep only or while awake as well as asleep; ANSD including decreased heart rate beat-to-beat variability and sinus pauses; altered temperature regulation; and altered pupillary response to light. Some children have altered development of neural crest-derived structures (i.e., Hirschsprung disease, altered esophageal motility/dysphagia, and severe constipation even in the absence of Hirschsprung disease) and/or tumors of neural crest origin (neuroblastoma, ganglioneuroma,

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and ganglioneuroblastoma). Neurocognitive delay is variable, and possibly influenced by cyanotic breath holding, prolonged sinus pauses, need for 24-hour/day artificial ventilation, and seizures.

- **Later-onset CCHS** is characterized by alveolar hypoventilation during sleep and attenuated manifestations of ANSD.

Diagnosis/testing

The diagnosis of CCHS is established in a proband with suggestive findings and a heterozygous *PHOX2B* pathogenic variant identified on molecular genetic testing.

Management

Treatment of manifestations: Management by multidisciplinary specialists, including pediatric pulmonology, sleep medicine, cardiology, oncology, ophthalmology, gastroenterology, neurodevelopmental psychology, and neurology, is recommended. The treatment goals for CCHS are to secure the airway and to use chronic artificial ventilatory support at home to compensate for the hypoventilation and the altered/absent ventilatory responses to hypoxemia and hypercarbia. Prolonged transient asystoles that may present as syncope and/or staring spells and are of significant duration (≥3.0 seconds) may warrant placement of a cardiac pacemaker; abnormal pupillary reactivity may necessitate protective eye wear given the amount of light exposure in daily life from LED lights, and screen time in educational settings, computer-based work environments, and mobile devices. Other findings treated as per standard practice include Hirschsprung disease and other gastrointestinal motility issues; tumors of neural crest origin; and cognitive impairment/delay.

Surveillance: Assess every six months for the first three years, then annually thereafter: (1) in a pediatric respiratory physiology laboratory spontaneous breathing awake (in varied age-appropriate activities of daily living during the daytime and before sleep) and asleep, with recording of respiratory inductance plethysmography of the chest and abdomen, hemoglobin saturation with pulse waveform, end-tidal carbon dioxide level with visible waveform, electrocardiogram, blood pressure, cerebral regional blood flow/oxygenation, and appropriate sleep state staging measures; (2) hemoglobin/hematocrit and reticulocyte count for polycythemia; (3) 72-hour Holter recording for abrupt, prolonged asystoles; (4) echocardiogram changes consistent with right ventricular hypertrophy and *cor pulmonale*; (5) neurocognitive assessment/educational needs; and (6) comprehensive age-appropriate noninvasive autonomic testing.

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

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of parents, sibs, and offspring of an individual with CCHS in order to identify as early as possible family members who would benefit from prompt initiation of treatment, surveillance, and awareness of agents/circumstances to avoid.

Genetic counseling

CCHS is typically inherited in an autosomal dominant manner (CCHS caused by biallelic reduced penetrance *PHOX2B* pathogenic variants has been reported in two families). The majority of affected individuals have the disorder as the result of a *de novo* pathogenic variant. Somatic/germline mosaicism is present in 5%-25% of asymptomatic parents. If a parent of the proband is known to be heterozygous for the *PHOX2B* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. Once the *PHOX2B* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible (because of the high frequency of parental mosaicism in CCHS, a fetus should be considered at risk for CCHS even if the *PHOX2B* pathogenic variant detected in the proband was not identified in either parent).

Diagnosis

The 2010 American Thoracic Society Statement on congenital central hypoventilation syndrome (CCHS) presents the current consensus clinical diagnostic criteria for CCHS (neonatal-onset and LO-CCHS [later-onset CCHS]) [Weese-Mayer et al 2010] (full text). A version for affected individuals and their families is also available [Weese-Mayer et al 2018] (full text).

Suggestive Findings

CCHS **should be suspected** in newborns, children, or adults with the following clinical findings and family history.

Neonatal-onset CCHS (first 30 days of life) clinical findings

- **Unexplained shallow breathing**
  - 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 both while awake and while asleep
- **Abnormal ventilatory drive**
  - Absent or attenuated endogenous and exogenous physiologic ventilatory response to hypercarbia and/or hypoxemia when asleep or awake and asleep
  - Absent arousal from sleep despite physiologic compromise secondary to hypercarbia and/or hypoxemia
  - Absent perception or behavioral awareness of asphyxia with severe hypercarbia and/or hypoxemia
  - Absence of shortness of breath
- **Autonomic nervous system dysregulation (ANSD)** including, but not limited to, the following:
  - Severe typically cyanotic breath-holding spells
  - Lack of physiologic responsiveness or behavioral perception to the challenges of exercise and environmental stressors
  - Altered perception of anxiety
  - Esophageal dysmotility
  - Severe constipation even in the absence of Hirschsprung disease
  - Profuse sweating
  - Reduced basal body temperature and peripheral skin temperature
  - Diminished pupillary light response
- No evidence of primary neuromuscular, lung, or cardiac disease or identifiable brain stem lesion that could account for the **FULL** constellation of manifestations including hypoventilation, abnormal ventilatory drive, and ANSD

Later-onset CCHS (LO-CCHS; age 1 month to adulthood) clinical findings

- **Unexplained shallow breathing**
  - Generally adequate ventilation while awake and at rest, and apparent hypoventilation with monotonous respiratory rate and shallow breathing (diminished tidal volume) during sleep
  - Apparent life-threatening events and cyanosis during sleep with 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, breath holding, severe pneumonia)
- Delayed "recovery" from a severe respiratory illness or recurrent severe pulmonic infections with related hypoventilation, such that the individual without intrinsic lung disease cannot be weaned from the ventilator
- Hypoventilation (unexplained marked elevation in end tidal carbon dioxide level) temporally related to antiseizure medication, sedation, anesthesia, or severe intercurrent illness
- Infants and children who die suddenly and unexpectedly ("sudden infant death syndrome [SIDS]" and "sudden unexplained death of childhood [SUDC]"), especially if there is a family history of CCHS or sudden death at any age

- **Neurologic findings**
  - Unexplained seizures
  - Unexplained neurocognitive delay with any history of prior cyanosis
  - Unexplained neurocognitive impairment
- **Autonomic nervous system dysregulation**
- **Characteristic facial features** (See Todd et al [2006].)

Family history. Affected individuals typically represent simplex cases (i.e., a single affected family member). The family history may be consistent with autosomal dominant inheritance (e.g., affected males and females in successive generations) in families with typically milder phenotypes.

Establishing the Diagnosis

The diagnosis of congenital central hypoventilation syndrome (CCHS) **is established** in a proband with suggestive findings and a heterozygous *PHOX2B* pathogenic variant (or likely pathogenic variant) identified on molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *PHOX2B* variant of uncertain significance does not establish or rule out the diagnosis. The authors of this chapter have offered to review with clinicians *PHOX2B* variants of uncertain significance; see Chapter Notes.

PHOX2B Pathogenic Variants

The three types of *PHOX2B* pathogenic variants:

- Polyalanine repeat expansion mutations (PARMs)
- Non-polyalanine repeat expansion mutations (NPARMs)
- Whole-gene or exon 3 deletions (a subset of the NPARMs that will not be detected with sequence analysis)

Polyalanine repeat expansion mutations (PARMs). *PHOX2B* has two polyalanine repeat regions in exon 3. Expansion of the second polyalanine repeat region causes CCHS.

Note: The N in GCN represents any nucleotide (A/C/G/T). All four possible sequences have been observed in the complex repeat.

Repeat sizes and genotypes are as follows [Weese-Mayer et al 2010, Weese-Mayer et al 2017]:

- **Normal.** 20 GCN (alanine) repeats
  - 20 GCN repeats is most common in the population.

    - 9, 13, 14, and 15 GCN repeats have been reported but not associated with either neonatal-onset CCHS or LO-CCHS phenotype [Amiel et al 2003, Weese-Mayer et al 2003, Toyota et al 2004].
- **Uncertain significance.** Individuals with 21-23 GCN repeats have not been described with CCHS to date; therefore, the clinical significance of GCN repeats of these sizes is not known.
- **Full penetrance**
    - **Later onset.** Individuals with 24 GCN repeats and a subset of individuals with 25 GCN repeats may have a very mild phenotype with delayed onset of the disorder and/or manifestations only when the individual is exposed to respiratory depressants and/or has severe intercurrent pulmonary illness [Repetto et al 2009].
    - **Neonatal onset.** Individuals with 26-33 GCN repeats, as well as most with 25 GCN repeats, present in the newborn period [Weese-Mayer et al 2003, Weese-Mayer et al 2010, Weese-Mayer et al 2017]. The largest known repeat length is 33 GCN repeats.

Note: Given the high frequency of the 20-GCN allele relative to other non-disease-causing repeat variants, all affected individuals with expanded alleles are said to have a 20/N genotype (e.g., genotype 20/25) unless otherwise specified.

Non-polyalanine repeat expansion mutations (NPARMs). NPARMs include missense, nonsense, splice site, stop codons, and frameshift variants. Note: Frameshift variants can be found either outside of the polyalanine repeat region or (more frequently) within the polyalanine repeat, and are typically small out-of-frame deletions or duplications [Berry-Kravis et al 2006, Weese-Mayer et al 2010, Weese-Mayer et al 2017].

***PHOX2B* partial and whole-gene deletions** have also been reported [Jennings et al 2012, Weese-Mayer et al 2017].

Molecular Genetic Testing Approach

Single-gene testing is the only molecular genetic testing approach. The American Thoracic Society Statement on CCHS suggests step-wise *PHOX2B* testing in persons meeting clinical diagnostic criteria; see Weese-Mayer et al [2010] (full text), Weese-Mayer et al [2012].

Note: Currently no multigene panel exists for the diagnosis of CCHS. Most multigene panels are next-generation sequencing (NGS)-based assays that are unable to detect polyalanine repeat expansions, the most common disease-causing *PHOX2B* variants.

Molecular genetic testing may proceed in the following order, based on the likelihood of detecting the most common disease-causing *PHOX2B* variants (see Figure 1):

- **Step 1.** Fragment analysis by gel electrophoresis targeted on the polyalanine repeat region will detect the following:
    - GCN repeat expansions (PARMs), the most common type of disease-causing *PHOX2B* variants
    - The 35-bp and 38-bp NPARM recurrent out-of-frame deletions within the GCN repeat region
    - Low-level mosaicism (see Molecular Genetics), which is pertinent for parental testing (see Genetic Counseling)
- **Step 2.** Sequence analysis of *PHOX2B* will detect NPARMs and PARMs but not low-level mosaicism.

  Note: Low-level mosaicism for both PARMs and NPARM deletions has been observed. A protocol to detect low-level somatic mosaicism, not detectable by routine Sanger sequencing, has been developed (see Molecular Genetics).
- **Step 3.** *PHOX2B* targeted deletion/duplication analysis to detect exon 3 and whole-gene deletions or duplications should be considered when PARMs or NPARMs are not detected by Step 1 and Step 2 testing.

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

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
PHOX2B	Targeted analysis for GCN [3] expansions [4, 5]	~90%-92% [6]
	Sequence analysis [7]	~8%-10% [6]
	Gene-targeted deletion/duplication analysis [8, 9]	<1% [9]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. This polyalanine repeat comprises any one of four codon combinations – GCA, GCT, GCC, or GCG – and is referred to as GCN.
4. See Molecular Pathogenesis, ***PHOX2B*-specific laboratory technical considerations** to characterize the number of GCN repeats in *PHOX2B*.
5. Referred to in the literature as PARMS (polyalanine repeat expansion mutations) and NPARMs (non-polyalanine repeat expansion mutations)
6. Weese-Mayer et al [2003], Matera et al [2004], Trochet et al [2005]
7. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
8. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene.
9. Breakpoints of large deletions and/or deletion of adjacent genes may require special methods [Jennings et al 2012].

Clinical Characteristics

Clinical Description

Congenital central hypoventilation syndrome (CCHS) represents the extreme manifestation of autonomic nervous system dysregulation (ANSD) with a hallmark of disordered respiratory control [Weese-Mayer et al 2017].

Classic CCHS is characterized by adequate ventilation when the individual is awake and apparent hypoventilation with monotonous respiratory rates and shallow breathing (diminished tidal volume) when asleep. More severely affected individuals hypoventilate both when awake and when asleep. Children who hypoventilate both when awake and when asleep typically present in the neonatal period (i.e., first 30 days of life), as do the vast majority of children who hypoventilate only when asleep.

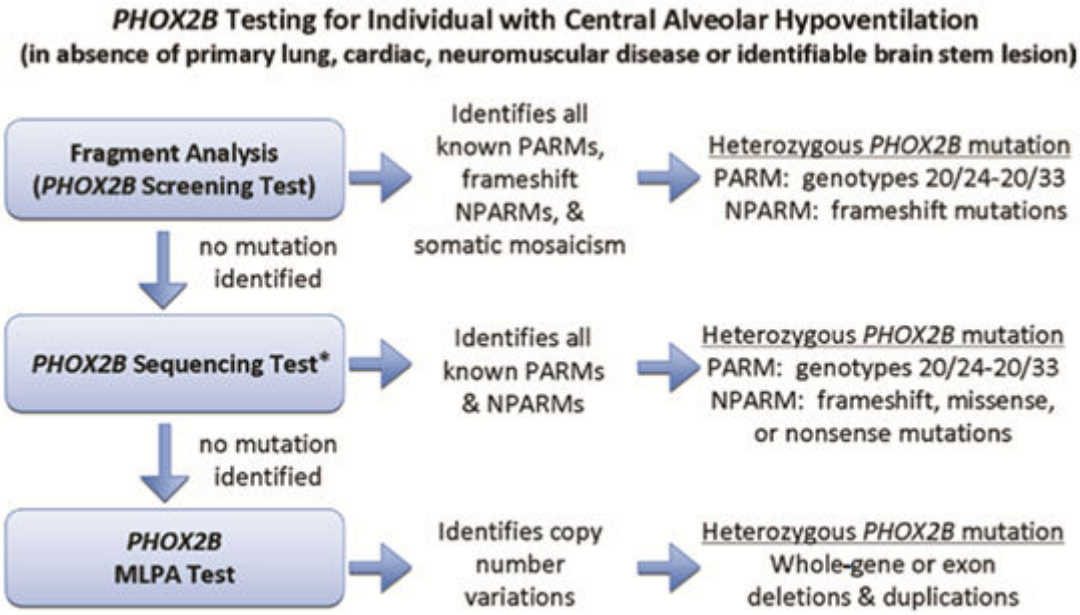

Figure 1. Algorithm to determine when and what type of *PHOX2B* genetic testing should be performed in various clinical scenarios in which neonatal-onset CCHS and later-onset CCHS are suspected or confirmed

NPARMs = non-polyalanine repeat expansion mutations; PARMs = polyalanine repeat expansion mutations

* The *PHOX2B* sequencing test will not identify low-level mosaicism [Jennings et al 2010].

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

Table 2. Select Features of Congenital Central Hypoventilation Syndrome by PARM vs NPARM and PARM Genotype

Feature	Genotype				
	PARM genotype			NPARMs	
	20/24, [1] 20/25	20/26	20/27	NPARM in general	38-bp deletion
Respiratory (hypoventilation)	Asleep only	Awake w/ exertion & eating & asleep	Awake & asleep	Awake & asleep	Awake & asleep
Cardiac arrhythmia: Abrupt sinus pauses ≥3 sec warranting cardiac pacemaker	Variable: none w/childhood onset; subset will have prolonged sinus pauses in adulthood	19%	>80%	None w/childhood onset to date	
Hirschsprung disease	<0.1%	20%-30%		80%-90%	95%-100% severe long segment disease (i.e., entire colon & some small intestine)
Severe constipation		~≥50%			
Esophageal dysmotility/dysphagia		1st yr of life			

Table 2. continued from previous page.

Feature		Genotype				
		PARM genotype			NPARMs	
		20/24, [1] 20/25	20/26	20/27	NPARM in general	38-bp deletion
Neural crest tumors	Neuroblastoma	0%	0%	See footnote 2.	50%	
	Ganglio-neuroblastoma	0%	0%	0%	<5%	
	Ganglioneuroma	0%	0%	0%	<5%	
ANSD: Pupillary response to light		Normal response	Midsize pupils w/attenuated response to light	Small pupils at rest; nearly absent response to light	Large pupils at rest; negligible response to light	

Based on Weese-Mayer et al [2017] (full text)
ANSD = autonomic nervous system dysregulation; NPARM = non-polyalanine repeat expansion mutation (i.e., missense, nonsense, frameshift, stop codon, splice site); PARM = polyalanine repeat expansion mutation
1. Genotype 20/24 would be considered a susceptibility allele (needs another factor to manifest) or a low- or variable-penetrance allele with features that can be triggered by pharmacologic agents (a pharmaco-genetic phenomenon), or a gene x environment interaction (without main effects).
2. Generally 0%; however, an infant with the 20/33 genotype had metastatic neuroblastoma [Armstrong et al 2015].

Respiratory. Individuals with CCHS have shallow breathing during sleep such that they develop hypoxemia and hypercarbia. These individuals do not increase their rate or depth of breathing in response to these endogenous physiologic "challenges" (altered O_2 and CO_2 values). Individuals with the more severe respiratory phenotype additionally have shallow breathing awake with exertion and eating, and often with quiet sedentary activities. With exogenous ventilatory challenges to simulate the level of physiologic compromise encountered in age-appropriate activities of daily living, children and young adults with CCHS will have absent or attenuated changes in spontaneous ventilation. Only the younger infants may maintain some level of carbon dioxide responsiveness [Carroll et al 2014].

Cardiac arrhythmia. All individuals with CCHS have decreased heart rate beat-to-beat variability [Woo et al 1992, Ogawa et al 1993, Silvestri et al 2000, Trang et al 2005]. This is most apparent when reviewing traditional measures of heart rate variability as well as visualizing a Poincaré plot of R-R+1 vs R-R from continuous EKG recording obtained during physiologic testing or Holter recording ("cigar" pattern in contrast to the normal "ice cream cone" pattern). The Poincaré plot characteristically demonstrates dramatically decreased heart rate variability awake and in REM sleep, and in some instances during all awake and asleep time. Notably, prolonged sinus pauses in individuals with CCHS have consistently occurred when the person is awake.

Neurocristopathy (i.e., maldevelopment of neural crest-derived structures), including Hirschsprung disease:

- **Hirschsprung disease** (congenital absence of parasympathetic intrinsic ganglion cells of the distal hindgut) typically presents in the newborn period, but has been diagnosed later in infancy and early childhood. The *PHOX2B* genotype will determine the risk for Hirschsprung disease (see Table 2). Total aganglionosis of the intestine is rare but has been reported in CCHS.
- **Severe constipation** is a hallmark of the gastrointestinal phenotype among individuals with CCHS who do not have Hirschsprung disease. The prevailing theory is that ganglion cells are present (hence no diagnosis of Hirschsprung disease) but their function may not be entirely normal.
- **Esophageal dysmotility/dysphagia.** Individuals with Hirschsprung disease have altered esophageal motility in the first year of life which subsequently improves.

- **Tumors of neural crest origin** including neuroblastoma, ganglioneuroma, and ganglioneuroblastoma are observed overall in fewer than 5% of individuals with CCHS and PARMs with the 20/30-20/33 genotypes, and in 50% of individuals with NPARMs [Trochet et al 2005, Berry-Kravis et al 2006].

  The tumors can present at variable ages – neuroblastoma typically before age two years, ganglioneuromas and ganglioneuroblastomas later as incidental findings.

  Tumor-related deaths in individuals with CCHS are rare.

Autonomic nervous system dysregulation (ANSD) [Marazita et al 2001, Weese-Mayer et al 2001]. In considering all of the organ systems affected by the autonomic nervous system, individuals with CCHS will have variable manifestations with varied severity.

- **Ophthalmologic**. An altered pupillary response to light is apparent from early infancy but will vary by genotype (see Table 2). Other possible ophthalmologic findings include anisocoria, strabismus, lack of convergent gaze, and Marcus Gunn jaw winking [Bishara et al 2018].
- **Other ANSD** can include hypothermia, poor heat tolerance, sporadic diffuse sweating, decreased pain perception, and endocrine findings (hyperinsulinism, hypoglycemia, and hyperglycemia) [Bishara et al 2018].

Other

Cognition. Individuals with CCHS have consistently been reported to have variably reduced IQ at school age with a mean IQ of 85 and standard deviation of 15, and without genotype/phenotype relationship [Zelko et al 2010, Zelko et al 2018].

Charnay et al [2016] demonstrated that preschool-age children with the *PHOX2B* PARM genotype 20/25 have normal IQs, whereas those with *PHOX2B* PARM genotypes 20/26 and 20/27 already have reduced IQs. They also demonstrated that CCHS-related cyanotic breath holding, prolonged sinus pauses, need for 24-hour/day artificial ventilation, and seizures negatively affect the neurodevelopmental testing scores.

Taken together, these results raise the concern that decreased cognitive performance is more pronounced in children with suboptimal ventilatory management and more severe phenotypic features (i.e., intermittent hypoxemia and altered cerebral autoregulation).

Seizures. While seizures could result from a primary neurologic problem, asystole-induced hypoxemia, and/or hypoglycemia, they are more often due to complications in management of hypoventilation [Author, personal observation].

Psychological. This has not been objectively explored since Pine et al [1994] reported decreased anxiety.

Later-onset CCHS, in which onset is in infancy (after age 30 days), childhood, or adulthood is characterized by alveolar hypoventilation during sleep and manifestations of ANSD.

Prognosis

Many individuals with CCHS are living with successful artificial ventilation into their third and fourth decades, suggesting the potential for a normal life span. The cause of death when it has occurred has been related to suboptimal ventilatory support leading to recurrent hypoxemia and hypercarbia or lack of compliance with artificial ventilation. A limited number of individuals have engaged in substance use, a lethal combination for unsupervised ventilator-dependent adolescents or young adults [Chen et al 2006].

Among individuals with a prolonged R-R interval, development of asystoles is a potential cause of sudden death [Gronli et al 2008], including those who do not have a cardiac pacemaker [Antic et al 2006] or who are not

sufficiently rigorous about monthly cardiac pacemaker assessment (e.g., the battery life is depleted or the pacemaker malfunctions).

Neuropathologic and Neuroimaging Findings

Neuropathologic and neuroimaging findings of individuals given a clinical diagnosis of CCHS (many of whom did not undergo confirmatory *PHOX2B* molecular genetic testing) are detailed in Table 3.

Table 3. Congenital Central Hypoventilation Syndrome: Neuropathologic and Neuroimaging Findings (See footnote 1.)

Finding	References
Neuronal loss of reticular nuclei & 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, & limbic deficits	Macey et al [2005b]
Multiple areas of white matter abnormality on brain MRI	Kumar et al [2005]
Abnormal fMRI brain responses to cold pressor challenge, hypoxia, & 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 & midbrain (mediating O_2 & oscillatory motor patterns) • Caudal raphé & locus coeruleus (regulating serotonergic & noradrenergic systems) • Lateral medulla, parabrachial pons, & cerebellum (coordinating chemoreceptor & somatic afferent activity w/breathing) • Insular & cingulate cortices (mediating shortness of breath perception)	Patwari et al [2010a]

1. Structural and functional alterations in these sites may be caused by pathogenic variants in *PHOX2B* or result from hypoxia/perfusion alterations related to suboptimal management/compliance. Note that individuals in this publication and other publications referenced in Table 3 were diagnosed with CCHS clinically and did not necessarily have confirmatory *PHOX2B* molecular genetic testing.

Genotype-Phenotype Correlations

See Table 2.

Nomenclature

Later-onset *congenital* central hypoventilation syndrome. The term "congenital" in the name of a condition that may not manifest until adulthood may seem like a misnomer; however, it is apparent when reviewing the histories of older affected individuals that mild manifestations were present from an early age, but their significance was not recognized [Author, personal observation].

Ondine's curse. 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

Until a large screening study is performed in a racially/ethnically diverse cohort, the prevalence of CCHS will remain an estimate. Investigators in France [Trang et al 2005] have proposed an incidence of 1:200,000 live births, and investigators in Japan [Shimokaze et al 2015] have proposed an incidence of 1:148,000 live births. However, if one considers these proposed incidences relative to the world births in the 50 years since the first description of CCHS [Mellins et al 1970], 33,000-45,000 individuals with neonatal-onset CCHS or LO-CCHS should have been diagnosed, which is in sharp contrast to the estimated 3,000 individuals identified since 1970. Consequently, thousands of undiagnosed individuals with neonatal-onset CCHS and LO-CCHS have either died without a CCHS diagnosis or their hypoventilation is so mild they are yet to be identified. Alternatively, the incidence figures provided from France and Japan may be an overestimate when applied worldwide.

Genetically Related (Allelic) disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *PHOX2B*.

Differential Diagnosis

Neonatal-onset congenital central hypoventilation syndrome (CCHS). In addition to CCHS, the differential diagnosis in a newborn with hypoventilation alone includes:

- Primary neuromuscular, pulmonary, or cardiac disease or an identifiable brain stem lesion that could account for the full constellation of CCHS findings, including the autonomic nervous system dysregulation (ANSD) [Bachetti et al 2006, Weese-Mayer et al 2010];
- Hypoxic ischemic encephalopathy, asphyxia, infarction, infection;
- Severe prematurity [Bajaj et al 2005].

Later-onset congenital central hypoventilation syndrome (LO-CCHS)

ROHHAD (*r*apid-onset *o*besity with *h*ypothalamic dysfunction, *h*ypoventilation, and *a*utonomic *d*ysregulation), a rare disorder distinct from LO-CCHS, is characterized by dramatic weight gain over a three- to 12-month period between ages 1.5 and ten years (most often age 2-7 years) in a healthy child with normal body habitus, 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) asleep and later awake and asleep; and
- ANSD (altered thermoregulation, diaphoresis, pupillary light response, peripheral vasomotor function, and bradycardia).

Affected children can also have mild-to-severe behavioral problems if ventilatory support is inadequate; about 40% of the children have tumors including ganglioneuromas and ganglioneuroblastomas (rarely neuroblastomas). The ROHHAD phenotype "unfolds" with advancing age as additional features of the phenotype become apparent. With pristine management, awake spontaneous breathing has recovered [Author, personal observation]. Although a genetic cause is suspected, candidate gene investigations have not yet identified a molecular cause of ROHHAD [Barclay et al 2015, Barclay et al 2016].

Management

Clinical practice guidelines for congenital central hypoventilation syndrome (CCHS) have been published in the ATS Statement on CCHS [Weese-Mayer et al 2010] (full text). Weese-Mayer et al [2017] (full text) also provides management information.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with CCHS, the evaluations by phenotype summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) and text that follows are recommended to be performed every six months until age three years, then annually thereafter at a minimum.

Table 4. Congenital Central Hypoventilation Syndrome: Recommended Evaluations by Genotype Following Initial Diagnosis

PHOX2B Variant		Comprehensive Physiologic Testing [1]	Neuro-cognitive Assessment	72-hr Holter & Echo-cardiogram	Hirschsprung Disease [2, 3]	Neural Crest Tumors
PARM genotypes	**20/24-20/25**	X	X	X		
	20/26	X	X	X	X	
	20/27	X	X	X	X	
	20/28-20/33	X	X	X	X	X [4]
NPARM		X	X	X	X	X [4]
Deletion/duplication [5]		X	X	X	X	X [4]

Adapted from Weese-Mayer et al [2010] and Weese-Mayer et al [2017]
NPARM = non-polyalanine repeat expansion mutation (i.e., missense, nonsense, frameshift, stop codon, splice site); PARM = polyalanine repeat expansion mutation with number of repeats on each allele (i.e., 20/24-20/33)
1. Evaluations asleep and awake during age-appropriate activities of daily living with exogenous and endogenous ventilatory challenges and autonomic testing
2. Evaluation as per standard protocols
3. A punch biopsy in the neonatal period or a full thickness biopsy later should be considered based on symptoms and *PHOX2B* variant/genotype (see Table 2).
4. Chest and abdominal imaging to detect ganglioneuroblastomas and ganglioneuroma; chest and abdominal imaging and urine catecholamines to detect neuroblastomas
5. Exon or whole-gene deletion or duplication

Evaluations should also include **assessment in a pediatric respiratory physiology laboratory** experienced in the diagnosis and care of individuals with CCHS, including the following:

- 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, electrocardiogram, blood pressure, cerebral regional blood flow/oxygenation, and appropriate sleep-state staging measures
- Evaluation of the awake and asleep physiologic responses to exogenous and endogenous challenges of hypercarbia and/or hypoxemia in varied age-appropriate activities of daily living
- 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 autonomic nervous system, 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 cerebral regional blood flow and blood pressure in activities of daily living as well as orthostatic testing

Consultation with a genetics professional (e.g., medical geneticist, certified genetic counselor, or certified advanced genetic nurse) is recommended to inform affected individuals and their families about the nature, mode of inheritance, and implications of CCHS in order to facilitate medical and personal decision making.

Treatment of Manifestations

Management by multidisciplinary specialists including pediatric pulmonology, sleep medicine, cardiology, oncology, ophthalmology, gastroenterology, neurodevelopmental psychology, and neurology is recommended.

Ventilatory support. The treatment goals for neonatal-onset CCHS are to secure the airway and to use chronic artificial ventilatory support at home to compensate for the hypoventilation and 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 may worsen the hypoventilation. Supplemental oxygen alone is NOT a treatment of hypoventilation.

Because individuals with CCHS may experience severe hypoventilation or complete respiratory arrest and, thus, the sequelae of hypoxemia, they require monitoring of objective measures of oxygenation (i.e., peripheral pulse oximeter SpO_2) and ventilation (i.e., $PETCO_2$ monitor) continuously during sleep and at regular intervals while awake regardless of mode of ventilatory support in-hospital and in-home. They also require observation and continuous care – especially during all sleep – by an RN trained and experienced in ventilator management and life support.

For each of the options listed below, the goal is to provide the affected individual with the technology optimal for the individual's lifestyle needs.

Typically, the infant needing ventilatory support 24 hours/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 artificial ventilation during sleep only, though transition to mask ventilation is a consideration in a subset of individuals after maturation of the facial configuration.

As toddlers 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 a subset of 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, especially young children [Valika et al 2019].

- Diaphragm pacers for the active child with CCHS should be implanted at each phrenic nerve in the chest, ideally by thoracoscopic technique by highly experienced surgeons and phrenic nerve-diaphragm pacer teams [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 speaking valve (Tracoe or 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 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 the individual 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: While Straus et al [2010] reported that the ventilatory response to hypercarbia appeared to improve with the use of oral contraceptives in two young women heterozygous for PARM genotypes 20/25 and 20/26, ongoing studies have not confirmed this report.

Cardiac. Prolonged transient asystoles may be asymptomatic or present as syncope and/or staring spells and may be of such significant duration (≥3 seconds) as to warrant placement of a cardiac pacemaker for management [Silvestri et al 2000, Gronli et al 2008].

Hirschsprung disease, altered esophageal motility/dysphagia, and severe constipation are treated in the standard manner.

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 even for benign tumors.

Abnormal pupillary reactivity. With so much light exposure in daily life from LED lights and screen time in educational settings, computer-based work environments, and mobile devices, abnormal pupillary reactivity may necessitate protective eye wear.

Because individuals with CCHS may receive medications expected to alter pupillary light response or because of potential use of illicit drugs, it is essential that medical personnel appreciate the innate abnormalities of pupillary reactivity to light. Use of pupillometry at the time of each clinical evaluation allows reliable objective documentation of the individual's signature pupillary light response relative to an established clinical baseline and published norms**.**

Neurocognitive. The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

- **Ages 0-3 years.** Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.
- **Ages 3-5 years.** In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition.

Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

- **All ages.** Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life.

Surveillance

Every six months for the first three years, then annually thereafter, assessment of the following in a pediatric respiratory physiology laboratory experienced in the diagnosis and care of individuals with CCHS is recommended:

- 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, blood pressure, cerebral regional blood flow/oxygenation, and electrocardiogram, and appropriate sleep state staging measures
- Evaluation of the awake and asleep responses to exogenous and endogenous challenges of hypercarbia and/or hypoxemia in varied age-appropriate activities of daily living
- 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/educational needs
- Comprehensive autonomic testing of all organ systems regulated by the autonomic nervous system, 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 cerebral regional blood flow and blood pressure in activities of daily living as well as orthostatic testing

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.

Breath-holding contests may 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 parents *, sibs, and offspring of an affected individual are at risk for CCHS. It is appropriate to clarify the genetic status of these individuals in order to identify as early as possible family members who would benefit from prompt initiation of treatment (see Evaluations Following Initial Diagnosis), surveillance, and preventive measures.

* Evaluation of the parents of a child with CCHS should include testing capable of detecting low-level somatic mosaicism (see Molecular Pathogenesis, ***PHOX2B*-specific laboratory technical considerations**). Parents with mosaicism should have comprehensive physiologic assessment to determine if features of the later-onset CCHS phenotype are present and to alert them to their reproductive risk.

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 in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Congenital central hypoventilation syndrome (CCHS), i.e., neonatal-onset CCHS and later-onset CCHS (LO-CCHS), are typically inherited in an autosomal dominant manner.

CCHS caused by biallelic reduced penetrance *PHOX2B* pathogenic variants has been reported in two families: in one family the proband had biallelic 20/24 PARM pathogenic variants (24/24) [Trochet et al 2008] and in one family an infant had the 20/24 PARM and the NPARM (c.785G>T, p.Gly262Val), with each parent heterozygous for one of the variants [Sivan et al 2019]. The parents of the two probands identified in these publications were not overtly symptomatic for CCHS.

Risk to Family Members (Autosomal Dominant Inheritance)

Parents of a proband

- The majority of individuals diagnosed with CCHS have the disorder as the result of a *de novo* pathogenic variant.
- Some individuals diagnosed with CCHS have an affected parent [Weese-Mayer et al 2003, Matera et al 2004, Weese-Mayer & Berry-Kravis 2004, Trochet et al 2005, Antic et al 2006, Bachetti et al 2011].
- Molecular genetic testing for the *PHOX2B* variant present in the proband (including methods known to detect low-level mosaicism; see Molecular Pathogenesis, ***PHOX2B*-specific laboratory technical considerations**) is recommended for both parents of a proband. Confirmation of parental genetic status allows reliable recurrence risk assessment and may identify a parent at risk for LO-CCHS.
- Germline mosaicism (*without* somatic mosaicism) for a *PHOX2B* pathogenic variant 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. Note: Germline mosaicism in a parent of a proband cannot be identified with molecular genetic testing of leukocytes or tissues other than germ cells.
- Germline mosaicism *with or without* somatic mosaicism for a *PHOX2B* pathogenic variant is present in about 5%-25% of asymptomatic parents of individuals with CCHS [Weese-Mayer et al 2003, Bachetti et al

2011]. Parents with mosaicism should have comprehensive physiologic assessment to determine if features of the LO-CCHS phenotype are present (see Evaluations Following Initial Diagnosis).

- The family history of some individuals diagnosed with CCHS or LO-CCHS may appear to be negative because of reduced penetrance or variable expressivity in a heterozygous parent. Therefore, an apparently negative family history cannot be confirmed unless the appropriate molecular genetic testing (see Figure 2) has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband and appropriate physiologic testing has been completed.

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 and/or is known to be heterozygous for the *PHOX2B* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. A sib who inherits a *PHOX2B* pathogenic variant will have clinical manifestations of the disorder similar to those observed in the proband (a range of clinical severity may be observed only in association with a limited number of the NPARMs or the 20/24 genotype PARM).
- If a parent of the proband has mosaicism for the *PHOX2B* pathogenic variant identified in the proband, the recurrence risk to the sibs of the proband is up to 50%.
- If the parents have not been tested for the *PHOX2B* pathogenic variant but are clinically unaffected, sibs are still presumed to be at increased risk for CCHS because of the significant possibility of parental mosaicism and the possibility of reduced penetrance or variable expressivity in a heterozygous parent [Weese-Mayer et al 2003].

Offspring of a proband. Each child of an individual with CCHS has a 50% chance of inheriting the *PHOX2B* pathogenic variant.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent has the *PHOX2B* pathogenic variant, the parent's 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/preimplantation genetic 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.

Prenatal Testing and Preimplantation Genetic Testing

Once the *PHOX2B* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible. Note: Because of the high frequency of parental mosaicism in CCHS, a fetus should be considered at risk for CCHS even if the *PHOX2B* pathogenic variant detected in the proband was not identified in either parent.

Delivery of a fetus known to have a CCHS-causing pathogenic variant should be managed by a high-risk obstetrician. A neonatology team should be present at delivery, and delivery should occur in a quaternary care medical center so that the newborn's transition to extrauterine life, prompt intubation, and mechanical ventilation can be smoothly achieved and transfer to the neonatal intensive care unit can be expedited.

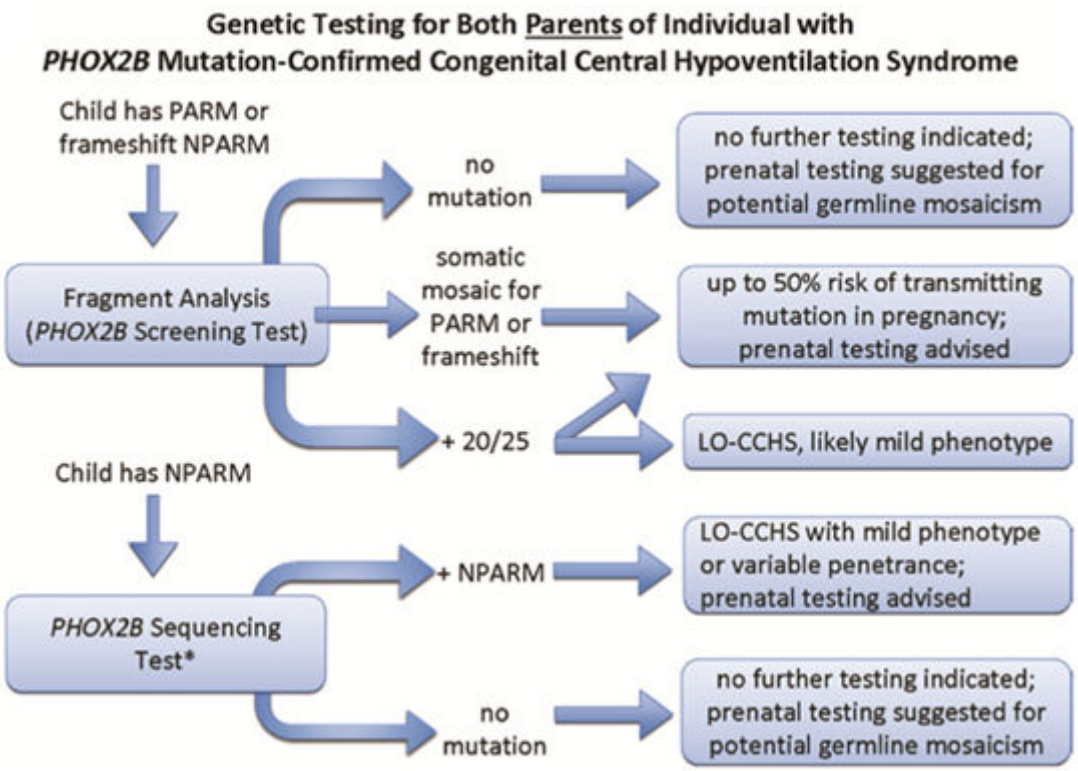

Figure 2. Algorithm to determine when and what type of *PHOX2B* genetic testing should be performed in the parents of a proband with CCHS

NPARMs = non-polyalanine repeat expansion mutations; PARMs = polyalanine repeat expansion mutations

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

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

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

Resources

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

- **American Thoracic Society: Patient Education | Information Series**
  Congenital Central Hypoventilation Syndrome (CCHS)
- **ROHHAD Association**
  11A Lomond Crescent
  Scotland G83 0RJ
  United Kingdom
  Phone: 44 7917-225-276
  Email: rohhadassociation@gmail.com

- **ROHHAD Association Belgium**
  Rimière Street 22
  Neupre
  Belgium
  Phone: 32 (0)4 223 75 52
  Email: association@rohhad.be
- **CCHS (Congenital Central Hypoventilation Syndrome) Network**
  www.cchsnetwork.org
- **Children's Neuroblastoma Cancer Foundation**
  Phone: 630-380-4058
  Email: info@cncfhope.org
  www.cncfhope.org
- **Pull-thru Network**
  Phone: -309-262-0786
  Email: info@pullthrunetwork.org
  pullthrunetwork.org
- **ROHHAD Fight, Inc.**
  3 Surrey Lane
  Hempstead NY 11550
  Phone: 516-642-1177
  Fax: 516-483-0566
  Email: rohhadfight@aol.com
  www.rohhadfight.org
- **National Institutes of Health (NIH) ClinicalTrials.gov Registry**
  International CCHS Registry
  International Congenital Central Hypoventilation Syndrome (CCHS) Registry
- **National Institutes of Health (NIH) ClinicalTrials.gov Registry**
  International ROHHAD Registry
  International Rapid-onset Obesity With Hypothalamic Dysfunction, Hypoventilation & Autonomic Dysregulation (ROHHAD) Registry

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	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

PHOX2B	4p13	Paired mesoderm homeobox protein 2B	PHOX2B database	PHOX2B	PHOX2B

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

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

209880	CENTRAL HYPOVENTILATION SYNDROME, CONGENITAL, 1; CCHS1
603851	PAIRED-LIKE HOMEOBOX 2B; PHOX2B

Molecular Pathogenesis

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 a GCN repeat in exon 3 [Amiel et al 2003]. GCN refers to any one of four codon combinations GCA, GCT, GCC, or GCG – each encoding the amino acid alanine.

A 20-GCN repeat is the most common normal allele. Normal alleles with 7, 13, 14, and 15 repeats have been reported [Amiel et al 2003, Weese-Mayer et al 2003, Toyota et al 2004].

Polyalanine repeat expansion mutations (PARMs) and non-polyalanine repeat expansion mutations (NPARMs) cause congenital central hypoventilation syndrome. NPARMs, including frameshift variants within the polyalanine repeat, are typically small out-of-frame deletions or duplications [Berry-Kravis et al 2006, Weese-Mayer et al 2010]. *PHOX2B* partial and whole-gene deletions have also been reported [Jennings et al 2012].

Further study is necessary to elucidate the relationship between *PHOX2B* haploinsufficiency, whole-gene deletion, and the CCHS phenotype [Jennings et al 2012].

Mechanism of disease causation. Disorders caused by triplet repeat expansions can cause disease through either gain-of-function or loss-of-function mechanisms.

Several lines of evidence support a possible dominant-negative mechanism for *PHOX2B* pathogenic variants in congenital central hypoventilation syndrome.

All individuals with CCHS have pathogenic variants that alter the protein downstream from the homeodomain, potentially producing altered proteins [Amiel et al 2003, Sasaki et al 2003, Weese-Mayer et al 2003, Matera et al 2004]. Because paired-homeodomain proteins such as *PHOX2B* bind to their target sites on DNA as dimers, abnormal *PHOX2B* proteins could potentially act in a dominant-negative manner when dimerized to a normal protein.

***PHOX2B*-specific laboratory technical considerations.** Typically, the number of GCN trinucleotide repeats is determined by Sanger sequencing. Low-level mosaicism for both PARMs and NPARM deletions has been observed. Fragment analysis to detect low-level somatic mosaicism, which may be too low to detect by routine Sanger sequencing, has been developed [Weese-Mayer et al 2003, Jennings et al 2010, Weese-Mayer et al 2010, Weese-Mayer et al 2017].

For other technical considerations see Table 5.

Table 5. *PHOX2B* GCN Expansion Technical Considerations

Technical Issue	Comment [Reference]
Sequence of repeat	The polyalanine repeat comprises any 1 of 4 codon combinations — GCA, GCT, GCC, or GCG – & is referred to as GCN.
Methods to detect expanded allele	Sanger sequencing
Repeat interruptions	None reported. See Sequence of repeat **Comment** (above) for variability in codon sequence.
Somatic instability	Not reported
Germline instability	Repeat stability during parent-to-child transmission, incl instances of parental mosaicism for the expansion, has been consistently observed [Weese-Mayer et al 2003, Trochet et al 2005, Weese-Mayer et al 2005, Antic et al 2006].

Table 6. Notable *PHOX2B* Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
NM_003924.3 NP_003915.2	c.721_723[7_20]	p.Ala241[7_20]	Normal GCN repeat size range
	c.721_723[21_23]	p.Ala241[21_23]	GCN repeat size range of uncertain significance
	c.721_723[24_33]	p.Ala241[24_33]	Abnormal GCN repeat size range

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

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