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## Central Hypoventilation Syndrome, Congenital

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### Synonyms of Central Hypoventilation Syndrome, Congenital

- autonomic control, congenital failure of
- CCHS
- CCHS with Hirschsprung disease, included
- Haddad syndrome
- OHD
- Ondine curse, congenital
- Ondine-Hirschsprung disease, included

### Disorder Subdivisions

## **General Discussion**

Congenital central hypoventilation syndrome (CCHS) is a rare disorder of autonomic nervous system dysregulation (ANS/D). The autonomic nervous system is the portion of the nervous system that controls or regulates certain involuntary body functions including heart rate, blood pressure, temperature regulation, breathing, and bowel and bladder control. Impaired breathing (respiratory control) is the main finding associated with CCHS. Individuals with CCHS typically present in the newborn period with inadequate breathing (alveolar hypoventilation) during sleep and, in more severely affected individuals, during wakefulness and sleep. Breathing complications occur despite the lungs and airways being normal. A growing number of individuals are now being identified who present in later infancy, childhood, or even adulthood.

All individuals with CCHS have a mutation in the PHOX2B gene. The vast majority of individuals (90%) with CCHS have a polyalanine repeat expansion mutation (PARM) in PHOX2B. The remaining individuals with CCHS have a non-polyalanine repeat expansion mutation (NPARM) in the PHOX2B gene.

## **Symptoms**

The symptoms and severity of CCHS vary from one individual to another. The type of mutation in the PHOX2B gene and the repeat length are related to disease severity. A rapidly expanding understanding of the risks specific to the PHOX2B mutation is allowing physicians and parents to anticipate risks and potentially neurocognitive outcome and risk for sudden death in children with CCHS.

The hallmark of CCHS is duskiess or a bluish discoloration of the skin and mucous membranes (cyanosis), resulting from very shallow breathing, and a general decrease in respiratory function (hypoventilation) during sleep (nap and night). Breathing is not increased and arousal is unsuccessful even with physiological stimuli such as low oxygen and elevated carbon dioxide. This same lack of responsivity to low oxygen and elevated carbon dioxide occurs during wakefulness as well, even when awake breathing is adequate.

Some individuals with CCHS have structural malformations including Hirschsprung disease. Overall, 16-20% of individuals with CCHS have Hirschsprung disease but the risk is higher for those who have large repeat expansions or NPARMs. Likewise, only individuals with large repeat expansions and NPARMs have been identified with tumors of neural crest origin, including ganglioneuromas and ganglioneuroblastomas for the PARMs and neuroblastoma for the NPARMs.

Individuals with CCHS may also have a characteristic facies, heart rhythm abnormalities such as brief episodes when the heart stops beating (cardiac asystole), abnormalities affecting the normal contractions of the digestive system that pushes food through the digestive tract (altered gut motility) even in the absence of Hirschsprung disease, altered temperature regulation and pain perception, decreased anxiety and eye abnormalities.

## Causes

PHOX2B, the disease-defining gene for CCHS, is located on chromosome 4 at 4p12. Chromosomes, which are present in the nucleus of human cells, carry the genetic information for each individual. Human body cells normally have 46 chromosomes. Pairs of human chromosomes are numbered from 1 through 22 and the sex chromosomes are designated X and Y. Males have one X and one Y chromosome and females have two X chromosomes. Each chromosome has a short arm designated "p" and a long arm designated "q". Chromosomes are further sub-divided into many bands that are numbered. For example, "chromosome 4p12" refers to band 12 on the short arm of chromosome 4. The numbered bands specify the location of the thousands of genes that are present on each chromosome. Genes contain the instructions for creating proteins which perform vital functions in the body.

The vast majority of individuals (90%) with CCHS are heterozygous for a polyalanine repeat expansion mutation (PARM) in exon 3 of the PHOX2B gene from the normal 20 repeats to 24-33 repeats. The remaining individuals with CCHS have a non-polyalanine repeat expansion mutation (NPARM) typically between the end of exon 2 and into exon 3 of the PHOX2B gene. The altered DNA sequences resulting in the PARMs and NPARMs cause the protein resulting from the PHOX2B gene to function improperly.

The PHOX2B mutation results in malregulation of involuntary or automatic body functions (autonomic nervous system) primarily by abnormal development of early embryonic cells that form the neural crest. Individuals with the NPARMs will typically be more severely affected than individuals with the PARMs, and individuals with the greater number of repeats will typically be more severely affected than those with the fewer number of repeats.

Genetic diseases are determined by the combination of genes for a particular trait that are on the chromosomes received from the father and the mother. CCHS and the PHOX2B mutations are inherited in an autosomal dominant manner. Autosomal dominant genetic disorders occur when only a single copy of an abnormal gene is necessary for the appearance of the disease. The abnormal gene can be inherited from either parent, or can be the result of a new mutation (gene change) in the affected individual. Though 90-95% of the CCHS-related PHOX2B mutations are not inherited (so new or de novo), 5-10% of parents of children with CCHS are mosaic for the same mutation. That means that these mosaic parents have the PHOX2B mutation in some of their cells, but presumably not in their brains as they do not appear to have the CCHS phenotype.

The risk of passing the abnormal gene from affected parent to offspring is 50% for each pregnancy regardless of the sex of the resulting child. The risk of passing the abnormal gene from mosaic parent to offspring is up to 50% for each pregnancy regardless of the sex of the resulting child. An individual with CCHS can have either a totally healthy normal child or a child with CCHS. Likewise, a mosaic parent can have either a totally healthy normal child or a child with CCHS. A mosaic parent can not have a mosaic child. When inherited, the PHOX2B mutation (repeat number in the PARMs or the specific NPARM) will be identical in the parent and the child.

Some individuals affected with CCHS have been found to have mutations in other genes, but

these mutations do not cause CCHS.

### **Affected Populations**

Congenital central hypoventilation syndrome is a rare disorder that affects males and females in equal numbers. Though the mutation is already present at birth, in milder cases the diagnosis may be missed. Some affected individuals will not be identified until after receiving sedation, anesthesia, or anticonvulsants. As of 2009 approximately 1,000 cases are known worldwide with the vast majority diagnosed in the U.S. in the Chicago laboratories. The birth prevalence of CCHS is unknown as culturally diverse large population based studies have not been reported. Because the milder cases of CCHS may go unrecognized or misdiagnosed, it is difficult to estimate the true frequency of CCHS in the general population.

### **Related Disorders**

Before the opportunity for genetic testing to confirm CCHS, and the description of the characteristic facies in CCHS, the diagnosis was essentially one of exclusion. CCHS was diagnosed in the absence of primary lung, cardiac, neuromuscular, or causative brainstem abnormalities. Even those diagnoses listed below do not have the anticipated phenotype of autonomic dysregulation nor will they have a PHOX2B mutation.

Congenital myopathy is a term for any muscle disorder present at birth. By this definition the congenital myopathies could include hundreds of distinct neuromuscular syndromes and disorders. In general, congenital myopathies cause loss of muscle tone and muscle weakness in infancy and delayed motor milestones, such as walking, later in childhood. Three distinct disorders are definitively classified as congenital myopathies: central core disease, nemaline rod myopathy, and centronuclear (myotubular) myopathy.

Congenital myasthenia usually occurs in infants but may become evident in adulthood. Associated features may vary in severity from case to case. Such abnormalities may include feeding difficulties, periods with absence of spontaneous breathing (apnea), failure to grow and gain weight at the expected rate, muscle weakness and fatigue, weakness or paralysis of eye muscles (ophthalmoplegia), and/or other abnormalities.

Moebius syndrome is a rare developmental disorder that may have a number of different causes and is characterized by facial paralysis present at birth (congenital). Facial nerve development is absent or diminished causing abnormalities of the facial muscles and jaw. Additional symptoms may include numerous abnormalities of the mouth and face (orofacial region) and potentially malformations of limbs. Mental retardation occurs in approximately 10 percent of cases. (For more information on this disorder, choose "Moebius" as your search term in the Rare Disease Database).

When central hypoventilation syndrome occurs in adults it may be confused with other more common respiratory diseases such as obstructive sleep apnea unresponsive to traditional management. Notably individuals with CCHS will not have dyspnea as they do not perceive low oxygen or elevated carbon dioxide.

Rapid onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic

dysregulation (ROHHAD) is a related but separate disorder. Children with ROHHAD typically present between the ages of 3 and 10 years of age with a rapid weight gain of 20 or more pounds over a 6 month period. They are then noted to have symptoms of hypothalamic dysfunction such as growth insufficiency, hypothyroidism and water imbalance. A subset of the cases will experience a respiratory arrest subsequent to an intercurrent illness, and all will be noted to have some element of obstructive sleep apnea. Once the obstructive sleep apnea is treated the children will be noted to have hypoventilation, even among those who did not endure a cardiorespiratory arrest. Soon thereafter the children will be noted to have other symptoms of autonomic nervous system dysregulation including dramatically low body temperatures and very slow heart rates. A subset of the children will have tumors of neural crest origin. Children with ROHHAD do not have mutations in the PHOX2B gene.

The following disorders may be associated with congenital central hypoventilation syndrome as secondary characteristics. They are not necessary to confirm a diagnosis of CCHS.

Hirschsprung disease is a rare gastrointestinal disorder characterized by absence at birth of certain cells (autonomic ganglia) in the lower segment of the large bowel. The ability of the colon to push intestinal contents along the length of the bowel (peristalsis) is absent or impaired. The lower bowel is typically in continuous spasm and is abnormally large (megacolon). The symptoms of Hirschsprung disease appear soon after birth and may include constipation, abdominal distention and vomiting. Older infants may have a profound loss of appetite (anorexia), failure to thrive and severe constipation. (For more information about this disease, choose "Hirschsprung" as your search term in the Rare Disease Database.)

Epilepsy is a group of disorders of the central nervous system characterized by repeated convulsive electrical disturbances in the brain. In CCHS the cause of seizures is most often due to suboptimal ventilatory management, resulting in low oxygen. The major symptoms may include loss of consciousness, convulsions and spasms. The symptoms of a grand mal seizure may include loss of consciousness, violent muscle spasms, gnashing of teeth, loss of bladder and/or bowel control, confusion, and/or drowsiness. (For more information on these disorders, choose "epilepsy" as your search term in the Rare Disease Database).

## **Standard Therapies**

### **Diagnosis**

The diagnosis of CCHS is based on the clinical presentation, the related clinical features, documentation of an absence of other potentially confounding diagnoses, and confirmation with clinically available PHOX2B testing. The PHOX2B screening test is the first step in making the genetic diagnosis of CCHS. This test will diagnose all of the polyalanine repeat expansion mutations (PARMs), mosaicism, polyalanine repeat contraction mutations, and the large deletion non-polyalanine expansion mutations (NPARMs). If the PHOX2B screening test is normal and the subject has the clinical presentation of CCHS then the sequel PHOX2B sequencing test should be performed. The PHOX2B sequencing test will detect the PARMs, the contractions, and the NPARMs but it will not detect mosaicism, so this test is rarely useful in parents of children with CCHS. Because the PHOX2B screening test is less expensive with a more rapid turnaround time than the PHOX2B sequencing test, the two-step testing process is most efficient, least costly, and most expeditious for nearly all

patients in whom CCHS is considered.

Physiologic evaluation should include annual comprehensive physiologic assessment during spontaneous breathing awake (in varying levels of concentration and activity) and during sleep in a pediatric respiratory physiology laboratory with extensive expertise in CCHS. Responses to endogenous and exogenous hypercarbia, hypoxemia, and hyperoxia should be assessed, ideally awake and asleep. 72 hour Holter recording should be performed annually to evaluate for asystoles that might require a cardiac pacemaker. A tilt test should be performed annually to better understand the relationship between syncope and the asystoles. An echocardiogram should be performed annually to rule out cor pulmonale or right ventricular hypertrophy. Gastrointestinal motility studies and, if indicated, a rectal biopsy should be performed in the event of severe constipation. Neurocognitive testing should be performed annually to determine the effectiveness of the ventilatory management. All of the above described tests are part of routine standard of care. Efforts are underway to create a comprehensive testing profile for autonomic regulation in children which will also be considered standard of care for children with CCHS.

#### Treatment

Infants with CCHS are usually treated by surgically creating a temporary opening in the throat (tracheostomy) into which a small tube (cannula) is inserted, and the baby is then mechanically ventilated. The baby requires a mechanical ventilator at home (with a back-up ventilator, pulse oximeter, end tidal carbon dioxide monitor, generator) as well as experienced nursing care 24 hours/day. In select cases, other assistive breathing apparatus and/or techniques may be used such as diaphragm pacing. In older children and adults, mask ventilation may be considered. This technique is discouraged in infants and young children because of the risk of facial deformation from the mask and inadequate stability of mask ventilation at a time of rapidly progressing neurodevelopment. The goal is to optimize oxygenation and ventilation. Children with CCHS require artificial ventilation during sleep. Ventilatory needs will vary with the specific PHOX2B mutation. For example, individuals with small repeat expansions will typically require ventilator support during sleep only, whereas individuals with large repeat expansions and those with an NPARM will typically require artificial ventilation 24 hours/day.

Some individuals with CCHS and transient abrupt asystoles require a cardiac pacemaker to correct the rhythm. The risk for asystoles varies with the specific PHOX2B mutation.

Treatment of Hirschsprung disease usually consists of surgery to relieve the obstruction. A temporary bowel opening of the colon in the abdominal wall (colostomy) is usually performed. The second operation consists of removing the diseased parts of the colon and rectum and connecting the normal bowel to the anus.

Neuroblastomas are removed surgically followed by chemotherapy in some cases. Treatment for other tumors originating from the neural crest depends on the type and location of the tumor. These other neural crest tumors are often detected anecdotally.

Multidisciplinary care from a Center of Excellence with long-term comprehensive experience

in the care of children and adults with CCHS is key to the successful management of these patients. This team may include pediatricians, med-peds physicians, pulmonologists, cardiologists, intensivists, ENT physicians, surgeons, gastroenterologists, neurologists, ophthalmologists, psychologists, psychiatrists, respiratory therapists, nurses, social workers, speech and language therapists, special education teachers, and more.

A high index of suspicion, early detection, and aggressive conservative intervention are critical to optimizing neurocognitive outcome. If inadequately treated, the affected individuals will likely suffer neurocognitive compromise and potentially sudden death. If treated conservatively and followed comprehensively individuals with CCHS can have a good quality of life and an anticipated normal life span.

### **Investigational Therapies**

Information on current clinical trials is posted on the Internet at [www.clinicaltrials.gov](http://www.clinicaltrials.gov). All studies receiving U.S. Government funding, and some supported by private industry, are posted on this government web site.

For information about clinical trials being conducted at the NIH Clinical Center in Bethesda, MD, contact the NIH Patient Recruitment Office:

Tollfree: (800) 411-1222  
TTY: (866) 411-1010  
Email: [prpl@cc.nih.gov](mailto:prpl@cc.nih.gov)

For information about clinical trials sponsored by private sources, contact:  
[www.centerwatch.com](http://www.centerwatch.com)

For more information on Congenital Central Hypoventilation Syndrome and/or PHOX2B Testing, please contact:

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web information on CCHS: [www.genetests.org](http://www.genetests.org)

### **Organizations related to Central Hypoventilation Syndrome, Congenital**

- Congenital Central Hypoventilation Syndrome (CCHS) Family Support Network

71 Maple Street  
Oneonta NY 13820  
Phone #: 6074328872  
800 #:  
e-mail: VanderlaanM@Hartwick.Edu  
Home page: <http://www.CCHSNetwork.org>

- International Foundation for Functional Gastrointestinal Disorders

P.O. Box 170864  
Milwaukee WI 53217  
Phone #: 4149641799  
800 #: 8889642001  
e-mail: [iffgd@iffgd.org](mailto:iffgd@iffgd.org)  
Home page: <http://www.iffgd.org>

- MUMS (Mothers United for Moral Support, Inc) National Parent-to-Parent Network

150 Custer Court  
Green Bay WI 54301-1243  
Phone #: 9203365333  
800 #: 8773365333  
e-mail: [mums@netnet.net](mailto:mums@netnet.net)  
Home page: <http://www.netnet.net/mums/>

- National Institute of Neurological Disorders and Stroke (NINDS)

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