CHAPTER

92

Congenital Central Hypoventilation Syndrome (CCHS) and *PHOX2B* Mutations

Debra E. Weese-Mayer, Pallavi P. Patwari, Casey M. Rand, André Diedrich, Nancy L. Kuntz, Elizabeth M. Berry-Kravis

Congenital central hypoventilation syndrome (CCHS) is characterized by disordered respiratory control (alveolar hypoventilation) and autonomic nervous system (ANS) dysregulation. Diagnosis is made in the absence of primary lung, cardiac, or neuromuscular disease or an identifiable brainstem lesion that might account for the entire phenotype inclusive of ANS dysregulation (ANSD) [1]. Alveolar hypoventilation, as demonstrated by diminutive tidal volumes and monotonous respiratory rates, results in hypoxemia and hypercarbia. Disordered respiratory control, as demonstrated by absent/severely attenuated ventilatory, behavioral, and arousal responses to endogenous/exogenous hypoxemia/hypercarbia occurring at rest or in activities of daily living results in severe physiologic compromise [1]. Mutations in the paired-like homeobox 2B (*PHOX2B*) gene confirm the clinical phenotype of CCHS. Because of the role of *PHOX2B* in early embryologic development of the ANS, it is not unexpected to identify multiple, characteristic features of physiologic ANSD and pathologic abnormalities in CCHS (Fig. 92.1 and table within).

PAIRED-LIKE HOMEOBOX 2B (*PHOX2B*) GENE

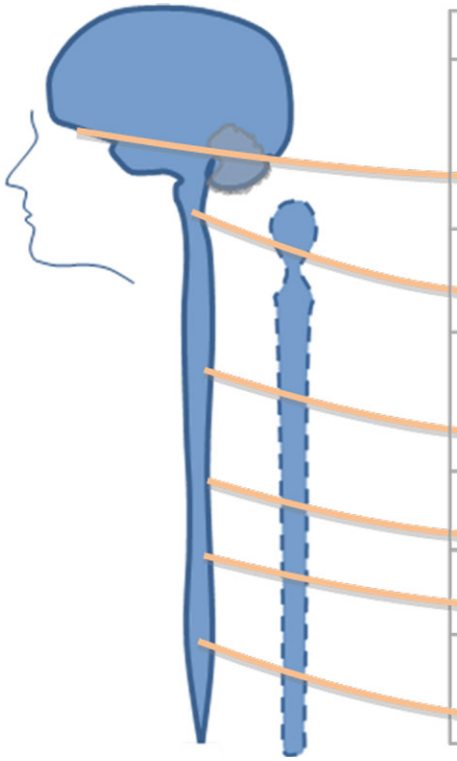
The inheritance pattern and genetic basis of CCHS became more focused after segregation analysis of ANSD symptoms in a case-control family study [2] and demonstration of parent-to-child transmission [1]. Early genetic studies focused on Hirschsprung disease (HSCR)-related genes, but with limited results. In 2003 and 2004, several groups undertaking ANS-focused, candidate gene analysis reported variations in the *PHOX2B* gene [3–5], ultimately confirming *PHOX2B* as the disease-defining gene for CCHS [1]. To clarify, *PHOX2B* encodes a highly conserved homeodomain transcription factor which plays a key role in early embryologic development of ANS reflex circuits in mice [6,7] and has expression in both central autonomic neuron circuits and peripheral neural crest derivatives in the human embryo [3] and in the rodent [6–9].

The *PHOX2B* gene is located at chromosome 4p12 from base pair 41,746,098 to base pair 41,750,986. In the third of three exons, the larger of two polyalanine repeat regions normally has 20 alanines on both chromosomes; thus the *PHOX2B* genotype in a normal subject would be 20/20. Approximately 90% of individuals with CCHS will be heterozygous for a polyalanine repeat expansion mutation (PARM) (Fig. 92.2), with expansions to 24-33 alanine repeats on the affected allele [1]; genotypes of 20/24 to 20/33. The remaining individuals, typically with the most severe CCHS phenotypes, will be heterozygous for a non-PARM (mutation that is not a polyalanine repeat expansion, NPARM) in *PHOX2B*. The 76 reported NPARMs include 78% frameshift, 4% nonsense (resulting in stop codon), 16% missense mutations, and 3% missense with stop codon alteration (Fig. 92.2). Recently, deletions of/or in *PHOX2B* have been identified as CCHS-causing in a small subset (<1%) of patients [10]. Among PARMS, the 20/25, 20/26, and 20/27 genotypes, and among NPARMs, a 38 bp deletion at the site of the polyalanine repeat, remain the most frequently identified. CCHS-related *PHOX2B* mutations have not been found in control populations.

While *de novo* germline mutations cause the majority of CCHS cases, somatic mosaicism has been identified in a subset (5–10%) of parents of CCHS probands [5,11]. An autosomal dominant inheritance from these mosaic parents [5], as well as from probands [5,11], has been established, with stability of the specific *PHOX2B* mutation. This knowledge has led to improved educational efforts and genetic counseling in CCHS families regarding reproductive risks (Fig. 92.3).

PHOX2B GENOTYPE AND CCHS PHENOTYPE ASSOCIATION

In recent years, growing evidence has demonstrated that the type of *PHOX2B* mutation is associated with severity of respiratory control deficit and with type and severity of ANSD features in the CCHS individual. This



System	Physiologic Sign/Symptom	Pathologic Condition
Ophthalmologic	• decreased/absent pupillary light response • anisocoria • esotropia/exotropia • lack of convergent gaze	
Respiratory	• absent perception of dyspnea • alveolar hypoventilation	
Cardiovascular	• altered peripheral perfusion • decreased heart rate variability • prolonged sinus pauses • vasovagal syncope	
Gastrointestinal	• esophageal dysmotility • constipation	Hirschsprung Disease
Neurologic	• decreased anxiety • decreased pain perception	neural crest tumor (sympathetic chain, adrenals)
Sudomotor	• profuse sweating • temperature dysregulation (hypothermia)	

FIGURE 92.1 Signs and symptoms of CCHS-related ANS dysregulation.

allows for anticipatory guidance and an opportunity to provide improved clinical care [1,4,5,12].

Continuous Ventilatory Dependence and Other Studies Pertinent to Respiratory Control

A relationship between the *PHOX2B* genotype and need for continuous ventilatory dependence has been reported [1,4,5,12]. Individuals with the 20/25 genotype have the mildest hypoventilation, typically requiring ventilatory support during sleep only [1]. A subset of patients with the 20/25 genotype and all known patients with the 20/24 genotype present outside of the newborn period, often after exposure to sedation, respiratory depressants or severe pneumonia. Individuals with the 20/26 genotype have variable awake needs depending upon activity level. Individuals with genotypes 20/27–20/33 typically require continuous ventilatory support, though the paucity of cases in the 20/28–20/33 genotype group prevents rigorous analysis. All patients with CCHS will hypoventilate during sleep, necessitating artificial ventilation.

Hirschsprung Disease (HSCR)

HSCR is more prevalent among individuals with NPARMs than PARMs. HSCR is reported in 87–100% of NPARMs in contrast to 13–20% of PARMs [1,11,12]. Notably, HSCR has not been reported in individuals with the 20/25 genotype and only rarely with the 20/26 genotype. A high occurrence of HSCR in individuals with the 20/27 genotype has been found and anecdotally in ~30% of individuals with the 20/27–20/33 genotype.

Tumors of Neural Crest Origin

Extracranial solid tumors of neural crest origin have been reported in CCHS, including neuroblastomas, ganglioneuromas, and ganglioneuroblastomas. These are found in locations with sympathetic nervous tissue such as the chest and abdomen in paraspinal ganglia or the adrenal glands. In individuals with NPARMs, neuroblastoma is the predominant tumor type (~50% are affected). In individuals with PARMs, ganglioneuromas and ganglioneuroblastomas have been reported in children with the 20/29–20/33 genotypes, though the risk for neuroblastoma in PARMs remains unexplored [1].

Cardiac Asystoles

A correlation exists between the most common PARMs and length of longest R-R intervals on Holter monitoring: 0%, 19%, and 83% of individuals with the 20/25, 20/26, and 20/27 genotypes, respectively, had 3-second or longer pauses [1]. Individuals with the 20/25 genotype may be unaffected during childhood, but demonstrate prolonged asystoles in adulthood [1]. Risk of cardiac asystoles to individuals with NPARMs remains unascertained.

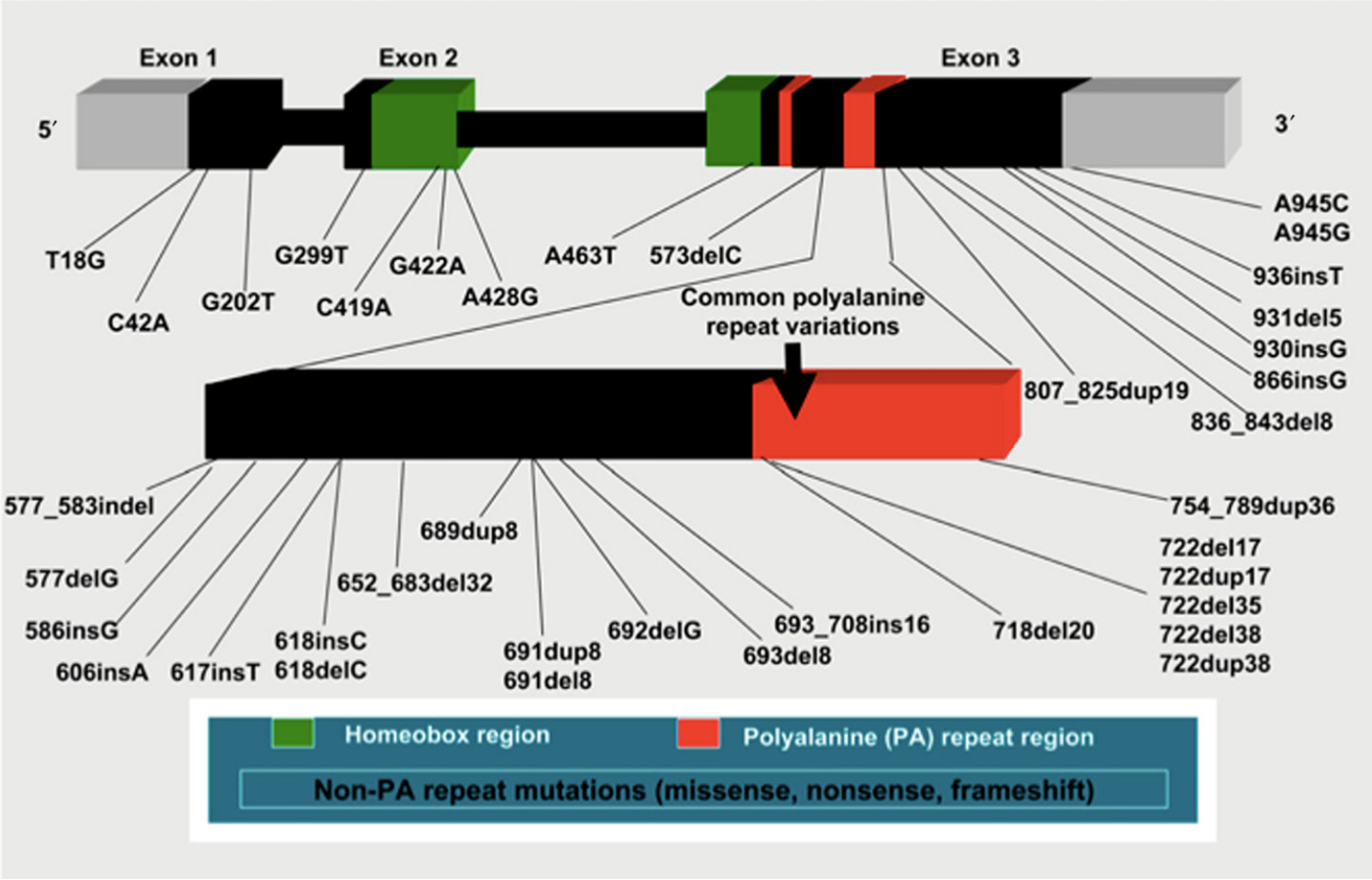


FIGURE 92.2 Schematic of the *PHOX2B* gene with location of all CCHS-associated mutations described to date. All polyalanine repeat expansion mutations (PARMs) are located within the second polyalanine expansion region of exon 3 (shown in red). Nearly all NPARMs identified thus far have been found at the extreme 3′ end of exon 2 or in exon 3. *(Reproduced with permission from reference [14]).*

Facial Dysmorphology

Characteristic features are described for children and young adults with CCHS, primarily those with *PHOX2B* PARMs [1]. The face is not dysmorphic, but is generally shorter and flatter with resulting effect of a boxy-shape. The "lip trait" includes an inferior inflection of the lateral {1/3} of the upper vermilion border. Using five variables to characterize facies (upper lip height, biocular width, upper facial height, nasal tip protrusion and the lip trait), 86% of the CCHS cases and 82% of the controls were predicted.

Phenotype Specific to NPARMs

While there is overlap in all areas of the phenotypic profile of PARMs and NPARMs, disease tends to be more severe in cases with NPARMs**.** However, severity of the NPARM phenotype will be mutation-specific and vary greatly by the effect of frameshift, missense, or nonsense mutations on DNA transcription and, ultimately, on protein formation and function. NPARMs generally occur *de novo* producing severe respiratory and autonomic dysfunction with HSCR and/or extensive intestinal dysmotility, need for continuous ventilatory support, and an increased tumor risk [1,4,5,11,12]. Some NPARMs are associated with a very high incidence of HSCR but a milder physiologic CCHS phenotype, and incomplete penetrance. Most NPARMS causing frameshift in the *PHOX2B* protein, especially recurrent 38- and 35-base pair deletions, produce very severe disease. However, a few frameshift mutations located early in exon 3 of *PHOX2B* have been inherited and are variably penetrant, suggesting that frameshifts in this area may produce a milder functional deficit than other frameshift mutations. Missense mutations in exon 2 have been found in several unrelated cases of CCHS and are the only missense mutations yet identified as causative in CCHS. Some of these, located at the 3′ end of the exon, may exert their effects by altering splicing.

Later-onset CCHS (LO-CCHS)

Individuals presenting later than 1 month of age whose symptoms are otherwise compatible with CCHS and who have a *PHOX2B* mutation, are termed later-onset CCHS

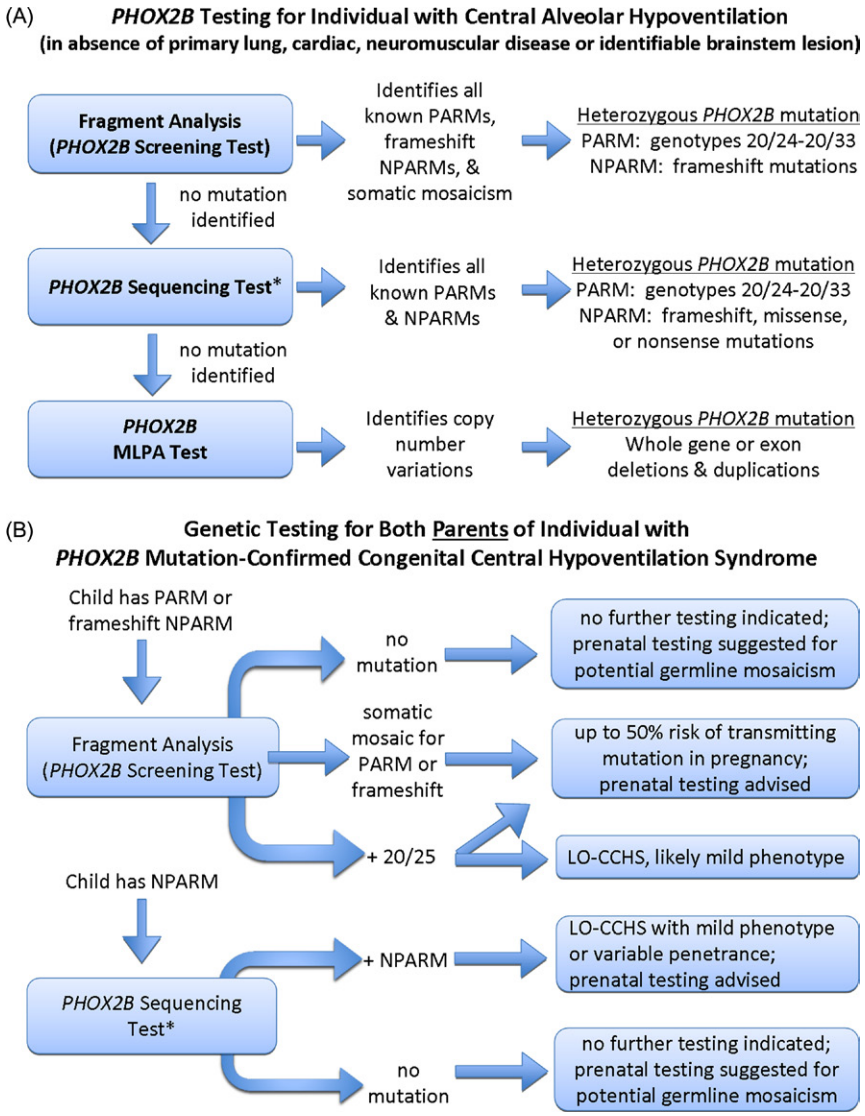


FIGURE 92.3 (A) Algorithm to determine when and what type of *PHOX2B* genetic testing should be performed in various clinical scenarios in which CCHS and LO-CCHS are suspected or confirmed. (B) Algorithm to determine when and what type of *PHOX2B* genetic testing should be performed in parents of CCHS proband. **The PHOX2B Sequencing Test will not identify low level mosaicism [15].*

(LO-CCHS) [1]. LO-CCHS appears to reflect the variable penetrance of the *PHOX2B* genotypes 20/24 and 20/25 or rarely an NPARM; a subset of these mutations may require environmental cofactors to elicit the hypoventilation. LO-CCHS should be considered in the event of centrally mediated alveolar hypoventilation, cyanosis, or seizures following: (i) anesthetics or CNS depressants; (ii) severe pulmonic infection; or (iii) obstructive sleep apnea intervention. The suggested evaluation should commence with *PHOX2B* testing from a peripheral blood sample (Fig. 92.3).

Autonomic function tests are useful to detect early autonomic dysfunction in adult-onset CCHS. Reduced heart rate variability, cardiac baroreflex sensitivity, blunted sympathetic responses to Valsalva maneuver, to hypoxemia, to isometric exercise, and to cold pressor have been reported in adult-onset *PHOX2B* mutation-confirmed CCHS. Abnormal maturation of carotid body and visceral sensory ganglia are hypothesized to be the cause of the observed autonomic dysfunction [13].

COMPREHENSIVE CLINICAL EVALUATION

Annual in-hospital comprehensive physiologic assessment for children three years and older, and bi-annually in the first three years of life, includes assessment of ventilatory needs during varying levels of activity and concentration while awake, ventilatory needs during all stages of sleep, exogenous ventilatory response to hyperoxia, hypoxia, hypercarbia, and combinations of these, along with continuous recording of multiple respiratory and cardiovascular variables [1]. Further, these studies are

accompanied by audiovisual surveillance with continuous recording (at a minimum) of the following variables: respiratory inductance plethysmography (chest, abdomen, sum), ECG, hemoglobin saturation with pulse waveform, end tidal carbon dioxide with waveform, sleep state staging, blood pressure, and temperature.

CCHS is a life-long disease for which early initiation of chronic home ventilator support is essential. For infants and young children, optimal ventilation is provided via tracheostomy with portable home mechanical ventilation. In the older child, non-invasive positive or negative pressure ventilation may be appropriate. Non-invasive positive pressure ventilation is difficult to implement long-term and not optimal in young infants with their pliable and incompletely developed facial structures. Diaphragmatic pacing is useful in patients who are mobile and require daytime ventilatory support in addition to sleep support. All ventilatory support should be accompanied by home pulse oximetry and end tidal carbon dioxide monitoring to allow for precise control of gas exchange, and continuous attendance by a highly trained registered nurse. In CCHS, peripheral and central chemoreception is affected resulting in insufficient modulation of ventilatory response to derangements in O_2 and CO_2. Therefore, individuals with CCHS have monotonous respiratory rates with an attenuated or absent increase in tidal volume and respiratory rate, absence of perception of asphyxia, and potentially devastating consequences in at-risk situations (sedation, swimming, exertion, etc.).

Care for individuals with CCHS is ideally provided through centers with extensive expertise in CCHS, working in close partnership with parents and regional pediatric pulmonologists and pediatricians, to provide consistent, state-of-the-art management guidance and to provide thorough, up-to-date education. The concept of centers is based on an understanding that management of children with CCHS is more time-intensive and complex than the care of other ventilator-dependent children. With modern technology for home ventilation, most children with CCHS can have prolonged survival with a good quality of life. At present, the oldest neonatally-identified patients with CCHS are graduating from college, marrying, and maintaining employment. It behooves the family and medical personnel to provide optimal ventilation and oxygenation to assure maximization of neurocognitive potential. Aggressive educational intervention coupled with careful ventilatory and cardiovascular management is essential to promote favorable neurocognitive and quality of life outcomes [1].

References

[1] Weese-Mayer DE, Berry-Kravis EM, Ceccherini I, Keens TG, Loghmanee DA, Trang H. An official ATS clinical policy statement: Congenital central hypoventilation syndrome: genetic basis, diagnosis, and management. Am J Respir Crit Care Med 2010;181(6):626–44.

[2] Weese-Mayer DE, Silvestri JM, Huffman AD, Smok-Pearsall SM, Kowal MH, Maher BS, et al. Case/control family study of autonomic nervous system dysfunction in idiopathic congenital central hypoventilation syndrome. Am J Med Genet 2001;100(3):237–45.

[3] Amiel J, Laudier B, Attie-Bitach T, Trang H, de Pontual L, Gener B, et al. Polyalanine expansion and frameshift mutations of the paired-like homeobox gene PHOX2B in congenital central hypoventilation syndrome. Nat Genet 2003;33(4):459–61.

[4] Matera I, Bachetti T, Puppo F, Di Duca M, Morandi F, Casiraghi GM, et al. PHOX2B mutations and polyalanine expansions correlate with the severity of the respiratory phenotype and associated symptoms in both congenital and late onset Central Hypoventilation syndrome. J Med Genet 2004;41(5):373–80.

[5] Weese-Mayer DE, Berry-Kravis EM, Zhou L, Maher BS, Silvestri JM, Curran ME, et al. Idiopathic congenital central hypoventilation syndrome: analysis of genes pertinent to early autonomic nervous system embryologic development and identification of mutations in PHOX2b. Am J Med Genet A 2003;123A(3):267–78.

[6] Pattyn A, Morin X, Cremer H, Goridis C, Brunet JF. The homeobox gene Phox2b is essential for the development of autonomic neural crest derivatives. Nature 1999;399(6734):366–70.

[7] Pattyn A, Morin X, Cremer H, Goridis C, Brunet JF. Expression and interactions of the two closely related homeobox genes Phox2a and Phox2b during neurogenesis. Development 1997;124(20):4065–75.

[8] Dubreuil V, Hirsch MR, Pattyn A, Brunet JF, Goridis C. The Phox2b transcription factor coordinately regulates neuronal cell cycle exit and identity. Development 2000;127(23):5191–201.

[9] Stornetta RL, Moreira TS, Takakura AC, Kang BJ, Chang DA, West GH, et al. Expression of Phox2b by brainstem neurons involved in chemosensory integration in the adult rat. J Neurosci 2006;26(40):10305–10314.

[10] Jennings LJ, Yu M, Rand CM, Kravis NS, Weese-Mayer DE. Analysis of PHOX2B gene for whole exon and gene deletion/duplication in 181 cases and controls. Am J Respir Crit Care Med 2010;181(A2282)

[11] Trochet D, O'Brien LM, Gozal D, Trang H, Nordenskjold A, Laudier B, et al. PHOX2B genotype allows for prediction of tumor risk in congenital central hypoventilation syndrome. Am J Hum Genet 2005;76(3):421–6.

[12] Berry-Kravis EM, Zhou L, Rand CM, Weese-Mayer DE. Congenital central hypoventilation syndrome: PHOX2B mutations and phenotype. Am J Respir Crit Care Med 2006;174(10):1139–44.

[13] Diedrich A, Malow BA, Antic NA, Sato K, McEvoy RD, Mathias CJ, et al. Vagal and sympathetic heart rate and blood pressure control in adult onset PHOX2B mutation-confirmed congenital central hypoventilation syndrome. Clin Auton Res 2007;17(3):177–85.

[14] Weese-Mayer DE, Rand CM, Berry-Kravis EM, Jennings LJ, Loghmanee DA, Patwari PP, et al. Congenital central hypoventilation syndrome from past to future: model for translational and transitional autonomic medicine. Pediatr Pulmonol 2009;44(6):521–35.

[15] Jennings LJ, Yu M, Zhou L, Rand CM, Berry-Kravis EM, Weese-Mayer DE. Comparison of PHOX2B testing methods in the diagnosis of congenital central hypoventilation syndrome and mosaic carriers. Diagn Mol Pathol 2010;19(4):224–31.