Congenital Central Hypoventilation Syndrome

A Neurocristopathy with Disordered Respiratory Control and Autonomic Regulation

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KEYWORDS

• *PHOX2B* • Autonomic • Respiratory • CCHS • Hirschsprung • Neuroblastoma

KEY POINTS

- Congenital central hypoventilation syndrome (CCHS) is a rare neurocristopathy with disordered respiratory control and autonomic nervous system regulation.
- CCHS is caused by mutations in the *PHOX2B* gene, and the *PHOX2B* genotype/mutation anticipates the CCHS phenotype, including the severity of hypoventilation, risk of sinus pauses, and risk of associated disorders including Hirschsprung disease and neural crest tumors.
- It is important to maintain a high index of suspicion in cases of unexplained alveolar hypoventilation, delayed recovery of spontaneous breathing after sedation or anesthesia, or in the event of severe respiratory infection, and unexplained seizures or neurocognitive delay. This will improve identification and diagnosis of milder CCHS cases and later onset/presentation cases, allowing for successful intervention.
- Early intervention and conservative management are key to long-term outcome and neurocognitive development.
- Research is underway to better understand the underlying mechanisms and identify targets for treatment advances and drug interventions.

INTRODUCTION

Congenital central hypoventilation syndrome (CCHS) is a rare disorder of respiratory control with autonomic nervous system dysregulation (ANSD), and a result of maldevelopment of neural crest-derived cells (neurocristopathy). The first reported description of CCHS was in 1970 by

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Robert Mellins and colleagues.[1] Despite a multitude of case reports, large series were not published until 1992.[2] As of early 2014, laboratories from the United States, France, Italy, Japan, Germany, China, The Netherlands, and Australia have now collectively diagnosed approximately 1200 cases with *PHOX2B* mutation-confirmed CCHS. However, the birth prevalence of CCHS is unknown, because demographically diverse, large, population-based studies have not been reported. Because the milder cases of CCHS and later-onset (LO) CCHS may go unrecognized or misdiagnosed, it is difficult to estimate the true frequency of CCHS in the general population at this time.

CCHS is characteristically diagnosed in the newborn period. However, individuals can also be diagnosed in childhood[3–6] or adulthood,[5,7–13] depending on the severity of symptoms and the inquisivity of the patient, family, and medical team. Impaired breathing regulation (respiratory control) is the hallmark of CCHS. Individuals with CCHS typically present with shallow breathing (alveolar hypoventilation) during sleep and, in more severely affected individuals, during wakefulness and sleep. These breathing complications occur despite the lungs and airways being anatomically and physiologically normal. Conditions associated with CCHS reflecting anatomic ANSD include Hirschsprung disease (HSCR) and tumors of neural crest origin, in addition to a spectrum of symptoms compatible with physiologic ANSD. CCHS is a life-long disease.

PHOX2B Gene Mutations

Individuals with CCHS have a mutation in *PHOX2B*, a gene that plays an important role in the development of the ANS. The normal *PHOX2B* gene has 20 repeats of the amino acid alanine. Approximately 90% of individuals with CCHS are heterozygous for a *PHOX2B* polyalanine repeat expansion mutation (PARM), with expansions to 24 to 33 alanine repeats on the affected allele,[14] genotypes of 20/24 to 20/33 (normal genotype is 20/20; **Fig. 1**). The remaining 9% to 10% of

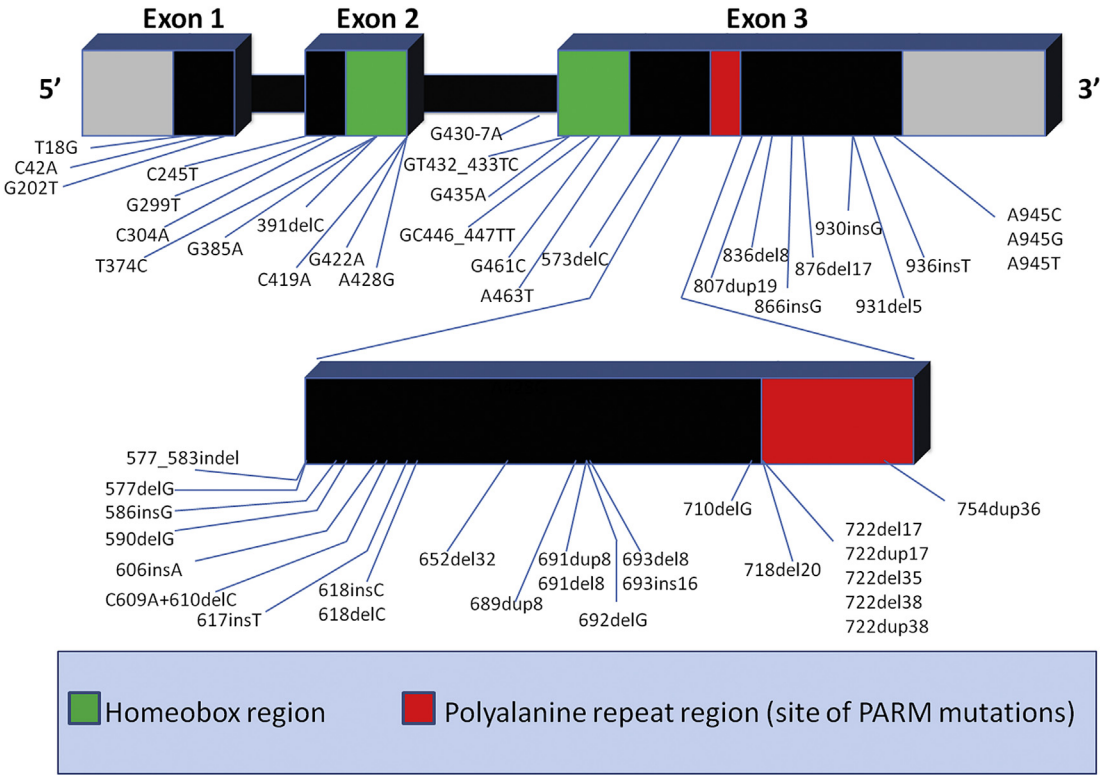

Fig. 1. *PHOX2B* gene with location of all CCHS-associated mutations identified to date. Nearly all polyalanine repeat expansion mutations (PARMs) are located within the second polyalanine expansion region of exon 3 (shown in *red*). Nearly all NPARMs identified thus far have been found at the extreme 3′ end of exon 2 or in exon 3. (*Adapted from* Weese-Mayer DE, Rand CM, Berry-Kravis EM, et al. Congenital central hypoventilation syndrome from past to future: model for translational and transitional autonomic medicine. Pediatr Pulmonol 2009;44:526; with permission.)