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Expanding the Phenotype of Congenital Central Hypoventilation Syndrome Impacts Management Decisions

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Abstract

Congenital Central Hypoventilation syndrome (CCHS) is a neurocristopathy caused by pathogenic heterozygous variants in the gene paired-like homeobox 2b (*PHOX2B*). It is characterized by severe infantile alveolar hypoventilation. Individuals may also have diffuse autonomic nervous system dysfunction, Hirschsprung disease and neural crest tumors. We report three individuals with CCHS due to an 8-base pair duplication in *PHOX2B*; c.691_698dupGGCCCGGG (p.Gly234Alafs*78) with a predominant enteral and neural crest phenotype and a relatively mild respiratory phenotype. The attenuated respiratory phenotype reported here and elsewhere suggest an emergent genotype:phenotype correlation which challenges the current paradigm of invoking mechanical ventilation for all infants diagnosed with CCHS. Best treatment requires careful clinical judgment and ideally the assistance of a care team with expertise in CCHS.

Keywords

CCHS; PHOX2B; central congenital hypoventilation syndrome; respiratory; genetic

INTRODUCTION

Congenital Central Hypoventilation Syndrome (CCHS, OMIM 209880) is an autosomal dominant neurocristopathy due to pathogenic heterozygous variants in the gene, paired-like homeobox 2b (*PHOX2B*) and characterized by an altered chemosensory response to hypercapnia and hypoxia, typically most pronounced during sleep (Dubreuil V et al, 2008;

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Dauger S et al, 2003). Individuals with CCHS may variably manifest autonomic nervous system dysfunction, Hirschsprung disease (HSCR) and neural crest tumors (Trochet D et al, 2004; Trochet D et al, 2005; Amiel J et al, 2003; Berry-Kravis EM et al, 2006; Trang H et al, 2014; Heide et al, 2016).

The vast majority of pathogenic variants in *PHOX2B* are +5 to +13 polyalanine repeat expansions (PARMs) of the conserved 20-alanine tract (Figure 1) (Weese-Mayer D et al, 2010; Matera I et al, 2004). Less than 10% of patients have a non-repeat expansion variants, including small insertion-deletions, frameshift and missense variants, collectively referred to as non-polyalanine repeat expansions (NPARMs) (Weese-Mayer D et al, 2010).

Patients with *PHOX2B* NPARMs typically have a severe respiratory phenotype, near universal HSCR and higher rates of malignancy, although a small number of case reports support phenotypic variability (Lombardo R et al, 2017; Magalhães J et al, 2015; Low KJ et al, 2014; Unger SA et al, 2017; Cain JT et al 2017; Kasi AS et al, 2017). Herein, we describe three individuals with CCHS associated with milder than expected respiratory outcomes. Their heterozygous 8-base pair duplication NPARM, *PHOX2B* (NM_003924.3) c.691_698dupGGCCCGGG (p.Gly234Alafs*78) results in a +2 frameshift variant leading to a premature stop codon (hereafter, referred to as *PHOX2B* c.691_698dup8) (Figure 1). Clinically, respiratory presentation was atypically mild and responded well to minimal intervention. These patients seemed to challenge the consensus recommendation for mechanical ventilation for all patients diagnosed with CCHS within the first years of life. With the emergence of a phenotypic expansion of CCHS to include those with a milder respiratory phenotype, a large clinical trial investigating less invasive approaches to respiratory management is warranted.

CLINICAL REPORTS

CASE 1

Case 1 was the second child born at term to 33-year-old Caucasian parents. By day of life (DOL) 3, lethargy, poor feeding and delay in meconium passage raised concern for Hirschsprung disease (HD). The presence of ganglion cells on two rectal biopsies (separated by 48 hours) seemingly negated a diagnosis of HD. Incidentally, several episodes of oxygen desaturations to the 60s were noted during routine inpatient monitoring, prompting a workup for hypoventilation. After extensive investigation, molecular testing of *PHOX2B* revealed a heterozygous, translational frameshift pathogenic variant in *PHOX2B* c.691_698dup8 confirming the diagnosis of CCHS. The patient was transferred for access to clinical expertise in CCHS and specialized evaluation (Tables 1, 2) (Weese-Mayer et al, 2010).

Initial polysomnogram (PSG) at age 7weeks showed an elevated apnea-hypoxia index (AHI) of mixed central and obstructive respiratory disturbances, most concerning for obstructive sleep apnea (OSA) (Table 1). At age 3months, her PSG showed worsened OSA but marked attenuation of associated desaturations with supplemental oxygen (Table 1). Importantly, supplemental oxygen did not worsen ventilation. Comprehensive treatment options were considered and presented to the family. Given her normal ventilation, normal serum bicarbonate, lack of pulmonary hypertension, and palliation with supplemental oxygen

alone, the standard recommendation of tracheostomy with positive pressure ventilation was deferred and the patient was discharged on low-flow supplemental oxygen. The patient tolerated three major surgeries under general anesthesia without complication, post-operative desaturations or episodes of respiratory depression in her first year. PSG showed spontaneous near-normalization of AHI with excellent oxygen saturations at 2.75 years, albeit with the emergence of mild hypercapnia (Table 1).

Initial abdominal ultrasound screening at age 3months showed a mass on the right kidney. This was surgically resected and confirmed to be a poorly differentiated neuroblastoma (Table 2). Although the presence of ganglion cells on multiple (N=3) rectal biopsies and indeterminate rectal manometry findings seemingly ruled out HD, severe constipation requiring manual disimpactation persisted until age 8months. Esophageal dysmotility and fatigue with oral swallowing dictated placement of a gastrostomy tube (G-tube) at age 2weeks. She was exclusively G-tube fed until age 14months but has tolerated oral feeding thereafter.

The proband had everted lower eyelids and hypoplastic nasal alae (Figure 2). She had numerous signs of autonomic nervous system (ANS) dysfunction that evolved with age, including profuse, intermittent sweating that resolved by age 3months. She had a subjectively high tolerance for pain and was never upset during any of her long hospitalizations -- parents described her as a “dream baby”. Her pupils reacted sluggishly to light and her peripheral extremities were persistently cooler than her trunk to touch. Blood pressure and heart rate remained unremarkable with no signs of orthostatic hypotension. No hypothermic episodes were observed. She had no reported breath holding spells or cardiac arrhythmias (Table 1). Now 3.5years old, the proband has achieved age-related developmental milestones and is thriving.

CASE 2

Case 2 is the healthy, 33-year-old mother of Case 1, who came to medical attention after the diagnosis of CCHS in her daughter. Diagnosis was suspected based on her past medical history of HD and confirmed on targeted, parental DNA testing. The variant allele fraction was 50%. She reported no history of breath-holding episodes, apnea, near-death experiences, seizures or feeding difficulty. HD was surgically corrected as an infant with diverting colostomy and delayed reanastomosis without respiratory complication. She graduated from college. She had 3 uncomplicated pregnancies and deliveries; her other two children do not harbor the familial *PHOX2B* variant. On physical examination, pulse and blood pressure were within normal limits with no orthostatic hypotension. Her demeanor was calm. She has a narrow face, wide-spaced eyes, and left ptosis (Figure 3). Overnight PSG and Holter monitoring were normal (Table 2).

CASE 3

Case 3 was born at term after an uncomplicated pregnancy and delivery to his 32-year-old Caucasian parents. Delayed passage of meconium, a distended abdomen and bilious emesis on DOL2 prompted suction rectal biopsy, which confirmed the absence of ganglion cells, consistent with HD. On DOL11, a loop ileostomy was performed after inter-operative

biopsies confirmed absent transition zone and ganglion cells from the entire colon. No respiratory disturbances were recorded during this procedure under general anesthesia.

At age 6weeks, he contracted an upper respiratory infection with deteriorating respiratory status, ultimately prompting hospital admission. At intake, he was placed on continuous positive airway pressure (CPAP), followed by bi-level positive airway pressure (BiPAP) and intubation as respiratory effort declined and CO2 increased. He was extubated on hospital day (HOD) 4. Attempt to wean to room air failed repeatedly due to persistent oxygen desaturations to the 80s. He was successfully weaned to room air on HOD15 and discharged on supplemental oxygen via NC and a Masimo Root pulse oximeter (Irving, CA) for home monitoring.

After discharge, he continued to have oxygen desaturations during sleep and CCHS was considered. Molecular testing of *PHOX2B* revealed a heterozygous, pathogenic variant *PHOX2B* c.691_698dup8 confirming CCHS. Initial PSG at age 3months showed significant abnormalities (Table 1). Desaturations were attenuated with supplemental oxygen, although there was no change in AHI. As with Case 1, comprehensive treatment options were reviewed with the family. Given his relative stability on supplemental oxygen alone, the decision was made to remain on supplemental oxygen.

Repeat PSG at 6months demonstrated profound central and obstructive sleep apnea with associated hypoxemia and hypercapnia (Table 1). Given his mean oxygen saturation, frequency of desaturations, and hypoventilation, it was felt that he was not optimally ventilated during sleep and tracheostomy and mechanical assisted ventilation were recommended. However, the family declined and advocated for a trial of non-invasive mask ventilation with BiPAP and close monitoring, which was initiated. Given the rarity of CCHS, the family was encouraged to seek evaluation at a center with expertise in CCHS, which occurred at 16months of age. Again, BiPAP was recommended during all periods of sleep, illness and respiratory distress. Twenty-four-hour nursing care was recommended for facemask adjustments; family declined.

At age 11months, he underwent a total colectomy and Duhamel procedure using the terminal ileum. Surgery was well tolerated with aggressive use of BIPAP in the peri-operative period. Although he had difficulty gaining weight in infancy, his weight is now at the 50th percentile. Screening abdominal ultrasounds were all normal (Table 2). At age 2-years, his development is within normal age-related parameters (Table 1).

DISCUSSION

In CCHS, the goal of rapid diagnosis and respiratory intervention is to prevent recurrent hypoxic episodes that may lead to long-term cardiopulmonary disease, neurocognitive compromise and/or untimely death (Weese-Mayer DE et al, 2010). Countering this is the awareness that mechanical ventilation has enormous medical, psychosocial, family, and economic implications. Current consensus recommendations advocate for lifelong mechanical-assisted ventilation, either continuously or during sleep, initiated within the first few years of life (Weese-Mayer DE et al, 2010). Indeed, for most patients with CCHS due to

PHOX2B NPARM, the need for ventilatory support is straightforward and clearly indicated. However, as recognition of CCHS has increased and availability of molecular testing expanded, several case reports have identified individuals with milder respiratory phenotypes, including those with the same *PHOX2B* variant as reported in this case series (Table 3) (Lombardo R et al, 2017; Magalhães J et al, 2015; Williams P et al, 2014; Trochet D et al, 2004; Heide S et al, 2016; Raabe EM et al, 2008; Low KJ et al, 2014; Nobuta H et al, 2015; Unger SA et al, 2017). This phenotypic expansion introduces uncertainty about the expected medical outcomes of a diagnosis of CCHS and the absolute need for long term mechanical ventilation.

The patients in this report (albeit of low number) challenge the paradigm that every infant with *PHOX2B* CCHS requires mechanical assisted ventilation early in life (Weese-Mayer DE et al, 2010). Although congenital respiratory abnormalities were clearly present in Cases 1&3 (Table 1), respiratory disturbances were central and obstructive in origin and both infants initially thrived on low-flow supplemental oxygen, a treatment often cautioned against as inadequate in CCHS (Weese-Mayer DE et al, 2010). If conservative respiratory support is elected, close follow-up is mandated as the full spectrum of the natural history of *PHOX2B* NPARM patients is not yet known. A formal, larger clinical trial comparing clinical outcomes for mechanical ventilation and less invasive therapies is warranted.

Several factors influenced our decision to defer mechanical ventilation. In Case 1, obstructive disturbances were confounded by laryngomalacia, a self-limited condition that an infant typically outgrows with age. Indeed, most PSG indices improved as she grew, confirming our decision to opt for conservative management (Table 2). Second, abnormal indices showed dramatic improvement with minimal oxygen supplementation alone with no worsening of ventilation, making the benefit of additional incremental improvements from mechanical ventilation seem marginal. Finally, Case 1 demonstrated adequate endogenous ventilation through repeated tolerance of general anesthesia (Weese-Mayer DE et al, 2010). Lastly, family preference, particularly in light of mother's ongoing normal health, intellect and ventilation despite no ventilatory assistance, was to continue close clinical observation alone.

CCHS due to *PHOX2B* c.691_698dup8 has been reported in 11 other patients in the literature, all presenting with enteral and neuronal crest abnormalities and most (9/14) manifesting mild or no respiratory symptoms (Table 3) (Williams P et al, 2014; Trochet D et al, 2004; Heide S et al, 2016; Raabe EM et al, 2008; Low KJ et al, 2014; Nobuta H et al, 2015). These subjects potentially illustrate an important genotype-phenotype correlation for *PHOX2B* c.691_698dup8 of a milder respiratory phenotype that may evolve with age along with prominent enteric and/or neural crest findings. Larger cohort and longitudinal studies are required before definitive conclusions about a genotype-phenotype correlation can be made and recommendations for genotype-specific respiratory interventions can be generated.

Non-respiratory aspects of the clinical courses of Cases1–3 support the importance of all other CCHS consensus recommendations, including regular comprehensive physiologic evaluation and tumor screening (Weese-Mayer DE et al, 2010). Enteric nervous system or

neural crest abnormalities may be the presenting sign of CCHS when the respiratory phenotype is attenuated; routine but vigilant respiratory monitoring should be considered in all infants presenting with HD and/or neuroblastoma (Table 3).

The pathogenic mechanism in CCHS is not fully understood, but is predicted to be dominant negative and/or gain-of-function (Trochet D et al, 2009; Trochet D et al, 2005; Amiel J et al, 2003; Bachetti T et al, 2005; Di Lascio S et al, 2016; Di Lascio S et al, 2013; Parodi s et al, 2012). To date, all NPARM functional studies have resulted in stable mutant proteins – likely leading to protein misfolding, oligomerization and aggregation with the potential to interfere with the wild-type protein (Trochet D et al, 2005; Bachetti T et al, 2005; Trochet D et al, 2009; Nobuta H et al, 2015). Haploinsufficiency was previously considered an unlikely pathogenic mechanism in CCHS, given the lack of a respiratory phenotype in individuals with whole-gene deletions. However, haploinsufficiency has more recently been reported with a milder respiratory phenotype and more prominent ANS and enteric nervous system (ENS) involvement (Trochet D et al, 2005; Trochet D et al, 2009; Lombardo R et al, 2017; Jennings LJ et al, 2012; Cain JT et al, 2017). Interestingly, mice with *Phox2b* haploinsufficiency have prominent ANS and ENS dysfunction and a respiratory phenotype of hypoxic apnea and reduced hypercapnic response that resolves after the immediate newborn period (Dubreuil V et al, 2008; Dauger S et al, 2003; Cross SH et al, 2004; Pattyn A et al, 1999).

In closing, improved clinical recognition of CCHS and access to *PHOX2B* molecular testing has both facilitated earlier diagnosis and generated an expanded phenotypic spectrum for *PHOX2B*-related disorders. As reported here, these cases illustrate an expanding phenotypic spectrum for *PHOX2b* NPARMs to include individuals with sufficiently mild respiratory abnormalities that infants may first present with seemingly isolated HD and/or neuroblastoma (Cain JT et al, 2017; Kasi AS et al, 2017; Unger SA et al, 2017). From these cases and collation from the literature, we suggest that initiation of mechanical-assisted ventilation should not be a forgone conclusion in all patients diagnosed with CCHS in infancy. With increasing support for the emergence of a mild respiratory phenotype in CCHS, a formal clinical investigation to compare less invasive methods of respiratory support to currently recommended mechanical ventilation is warranted. Revision of consensus guidelines to include the widening spectrum of CCHS could be considered. This report and collation of preceding reports suggest an emergent specific genotype: phenotype correlation for *PHOX2B* c.691_698dup8 may exist, although sustained natural history studies and ascertainment of greater numbers of patients are required. Given the challenging clinical judgment required to manage atypical CCHS presentations, patients will likely continue to benefit from evaluation in centers with extensive expertise in CCHS.

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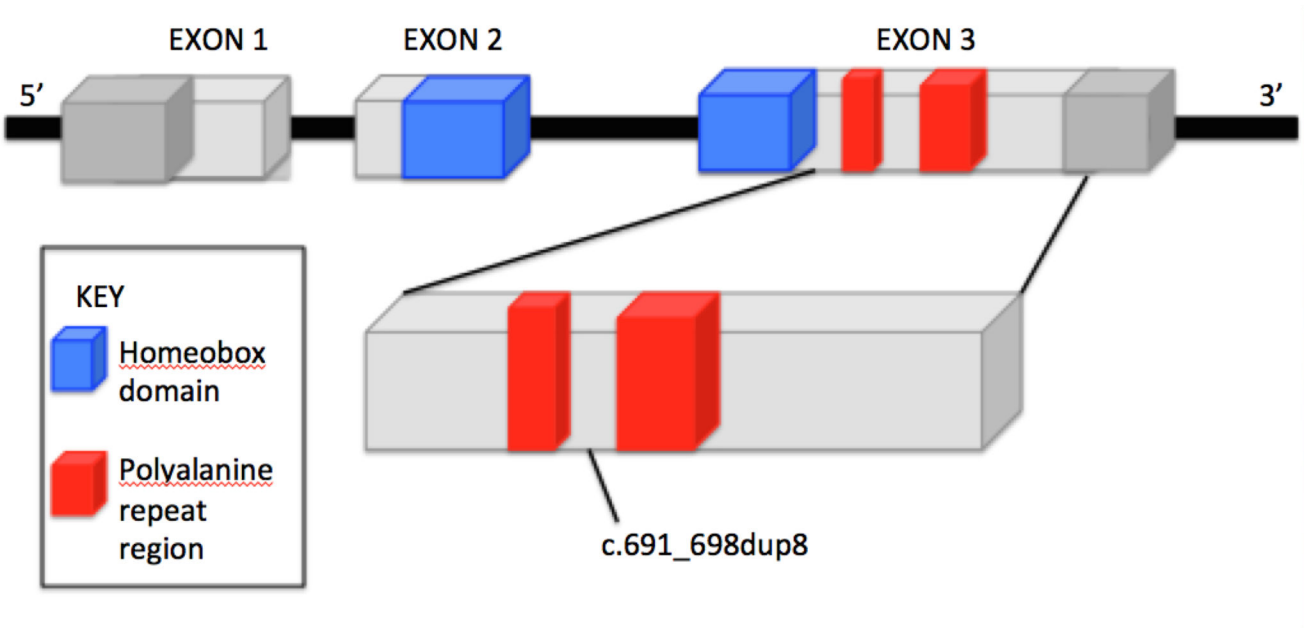

Figure 1.

PHOX2B, the only known disease-causing gene in isolated and syndromic cases of CCHS, is comprised of a homeodomain and two stable, highly conserved polyalanine tracts. *PHOX2B* c.691_698dup8 is located between the 9- and 20-alanine tracts.

Figure 2.

Case 1 at age 3 months (a, b) 13-months (c, d), 18-months (e,f), 2-years (g) and 3-years (h). Note the telecanthus, inverted lower eyelids, hypoplastic nasal alae.

Figure 3.
Case 2 at birth (a), 1yo (b), 2yo (c), 4yo (d), 5yo (e) and 33yo (f). Note Hypoplastic nasal alae, inverted ectroprion and left ptosis.

Table 1

CCHS screening results for Cases 1–3.

CCHS screening and/or intervention	CASE 1	CASE 2	CASE 3
Respiratory management	0–8mo: Continous 0.25L/min supplemental O2. 8mo-current: close monitoring	0–33yo: No intervention. 33yo-current: Close monitoring. No intervention	Age 0–6mo: 0.25L/min (with sleep); 6mo-current: BiPAP 16/7 (with sleep) 16mo: Plus home nursing care
Abdominal ultrasound	Poorly differentiated neural crest tumor	Normal	Normal
72-holder monitoring	NSR. Normal circadian variability	NK	NSR
Echocardiogram	Normal	NK	Normal
ANS evaluation	Abnormal	NK	Abnormal
Neurocognitive assessment	NCI	NCI. College graduate.	Bayley, low-average (16mo)
Gastrointestinal involvement	Severe constipation	HD	Total colon HD
Swallow study	4mo: Fatigue with swallowing. No aspiration. 14mo: Cleared for oral feeding	NCI	NCI

KEY: ANS=Autonomic nervous system. Bayley: Bayley Scales of Infant & Toddler Development - 3rd edition; BiPAP=bilevel positive airway pressure; CCHS=congenital central hypoventilation syndrome. HD=Hirschsprung Disease. L/min=litres per minute. NSR=Normal sinus rhythm. NCI=no clinical indication or concern. NK= results not available and/or test not performed; mo=months. O2= oxygen. PFO=patent foramen ovale. RA=room air.

Table 2

Respiratory markers, Cases1–3.

SUBJECT	Age	Respiratory support	Apnea-Hypopnea Index (AHI)	Nadir SpO2	Mean O2 saturation	Mean end-tidal or transcutaneous CO2
CASE 1	7 weeks	RA	48.6/hr	NK	94%	not obtained
	3-mo	RA	93/hr	71%	98%	44
	3-mo	0.1L/min NC	34/hr	94%	99%	49
	15-mo	RA	98/hr	88%	98%	44
	15-mo	0.1L/min NC	12/hr	95%	99%	49
	2y, 9mo	RA	7.3/hr	92%	98%	55
	2y, 9mo	0.2L/min NC	6.7/hr	95%	99%	55
CASE 2	33-yo	RA	0.7	NK	97%	NK
CASE 3	3-mo	RA	53	65%	94%	NK
	3-mo	oxygen	53.2	88%	99%	NK
	6-mo	RA	142	75%	92%	52
	6-mo	0.25L/min NC	73	78%	93%	52
	6-mo	BiPAP 14/8	NK	NK	NK	NK
	11-mo	RA	11	77%	90%	41
	11-mo	BiPAP 16/7	6.1	81%	92%	41
	16-mo	NK	NK	NK	NK	NK

Key: AHI=Apnea-Hypopnea Index; mo=months; y=years; min=minutes; hr=hour; NC=nasal cannula; O2=oxygen; SpO2= oxygen saturation index; RA=room air; NK=not known

Table 3

Literature review of all reported cases of patients with *PHOX2B* c.691_698dup8

Patient	Age of Diagnosis	Presenting Phenotype	CCHS Respiratory Phenotype (+/−)	Neural Crest Tumor (+/−)	Gastrointestinal involvement	ANS Dysfunction	Inheritance	Reference
1	3 mo	Desaturations, severe constipation	+ (mild)	+	Severe constipation (birth to 8 months)	+	Maternal	this paper
2	33 y	FHx	None	−	HD	+	Unknown	this paper
3	Birth	HD	+ (mild)	−	long-segment HD	NR	*de novo*	this paper
4	4.3 y	NR	−	+	HD	NR	Unknown	Hilde S et al, 2016
5	NR	NR	+ (severity NR)	NR	−	NR	Paternal	Trochet et al, 2005
6	35 y	FHx	−	−	−	NR	Unknown	Trochet et al, 2004
7	10 mo	Neuroblastoma	−	+ (multifocal disease)	HD	NR	*de novo*	Williams P et al, 2014
8	NR	NR	+	+	HD	NR	Maternal	Raabe et al, 2008
9	NR	FHx	−	+	NR	NR	Unknown (but brother also affected)	Raabe et al, 2008
10	NR	FHx	−	+	NR	NR	Unknown (but sister also affected)	Raabe et al, 2008
11	4w	HD & FHx	+ (rx assisted ventilation during sleep)	NR	HD	NR	Maternal	Low KJ et al, 2014
12	Adult, age NR	FHx	+	NR	NR	NR	Maternal	Low KJ et al, 2014
13	Adult, age NR	FHx	+ (mild)	NR	NR	+	Unknown	Low KJ et al, 2014
14	Birth	Hypoventilation	+ (severe)	NR	HD, total intestinal aganglionosis	+	Unknown	Nobuta H et al, 2015

Key: ANS=autonomic nervous system; mo=months; w=weeks; y=years; NR=not reported; HD= Hirschsprung disease; FHx= family history; rx=treated