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REVIEW ARTICLES

The Genetics of Childhood Disease and Development: A Series of Review Articles

This review is the tenth this series. In it Dr. Gaultier and her colleagues describe the genetic mutations responsible for the congenital central hypoventilation syndrome. These studies are important not only for an understanding of the genetics of this syndrome but also for investigation of clinical disturbances of breathing, such as the apnea of prematurity and sudden infant death syndrome. Animal models of these genetic defects further the exploration of the physiology of respiratory control.

Genetics and Early Disturbances of Breathing Control

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ABSTRACT

Early disturbances in breathing control, including apneas of prematurity and apparently life-threatening events, account for some cases of sudden infant death syndrome and for a rare disorder called congenital central hypoventilation syndrome (CCHS). Data suggesting a genetic basis for CCHS have been obtained. Recently, we found heterozygous *de novo* mutations of the *PHOX2B* gene in 18 of 29 individuals with CCHS. Most mutations consisted of five to nine alanine expansions within a 20-residue polyalanine tract, probably resulting from nonhomologous recombination. Other mutations, generally inherited from one of the parents, in the coding regions of genes involved in the endothelin and RET signaling pathways and in the brain-derived-neurotrophic factor (*BDNF*) gene have been found in a few CCHS patients. Interestingly, all these genes are involved in the development of neural crest cells. Targeted disruption of these genes in mice has provided information on the pathophysiological mechanisms underlying CCHS. Despite the identification of these genes involved in breathing control, none of the genetically engineered mice developed to date replicate the full human CCHS respiratory phenotype. Recent insights into the genetic basis for CCHS may shed light on the genetics of other early disturbances in breathing control, such as apnea of prematurity and sudden infant death syndrome. **(*Pediatr Res* 55: 729–733, 2004)**

Abbreviations

CCHS, congenital central hypoventilation syndrome
SIDS, sudden infant death syndrome
ALTE, apparently life-threatening event
HSCR, Hirschsprung's disease
***RET*,** rearranged after transfection gene
***GDNF*,** glial-derived neurotrophic factor gene
***GDNFR*,** glial-derived neurotrophic factor receptor gene
***MASH1*,** mammalian achaete-scute homologous 1 gene
***HASH1*,** human achaete-scute homologous 1 gene
***EDN1*,** endothelin 1 gene
***EDN3*,** endothelin 3 gene
***ECE1*,** endothelin-converting enzyme gene
***BDNF*,** brain-derived neurotrophic factor gene
***PHOX2A*,** paired-like homeobox 2a gene
***PHOX2B*,** paired-like homeobox 2b gene

Early disturbances in breathing control, including apneas of prematurity and apparently life-threatening events, account for some cases of SIDS and for a rare disorder called CCHS (1). Data suggesting a genetic basis for CCHS have been obtained. Heterozygous gene mutations have recently been identified in patients with CCHS (2–11). Mice are the preferred mammalian species for manipulating genes, and the respiratory phenotypes of knockout newborn mice may help to unravel potential links between the CCHS phenotype and gene mutations. This minireview summarizes the main clinical features and genetic factors in CCHS and describes the respiratory phenotypes of newborn mice with loss of function of genes that are involved in brainstem development and/or mutated in CCHS patients.

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CLINICAL FEATURES AND GENETIC FACTORS IN CCHS

CCHS, first described in 1970 (12), is defined as failure of the metabolic (autonomic) control of breathing responsible for central alveolar hypoventilation in the absence of pulmonary, cardiac, or neuromuscular disorders, and without patent brainstem lesions (1, 13). Although neonatal respiratory failure is the most common clinical picture, apneas and episodes of cyanosis are inaugural in some patients (1, 13). Polysomnographic recordings show that hypoventilation is most marked during slow-wave sleep. In the most severe cases, hypoventilation is present during other nonrapid eye movement sleep stages and even wakefulness (1, 13). Worldwide, about 200 children with CCHS are being managed with various types of ventilatory support during sleep or throughout the 24-h period (14). Congenital lack of central chemosensitivity with absence of the ventilatory response to hypercapnia is the main characteristic of CCHS (1, 13, 15). In addition, CCHS patients have no ventilatory responses to sustained hypoxia (1, 13). Nevertheless, some remnant peripheral chemosensory input to breathing is present in less-affected CCHS patients (1, 16). The pathophysiological mechanisms of CCHS are unknown. Failure of mechanisms that integrate chemoreceptor inputs to the respiratory centers is the current hypothesis (16, 17). Moreover, CCHS is a multi-system disorder: some patients have a broader dysfunction of autonomic control, including heart rate dysregulation, esophageal dysmotility, excessive sweating, ocular abnormalities, HSCR, which is a condition of defective enteric nervous system development, and/or neural crest-derived tumors, suggesting that CCHS may be a neural crest disorder (1, 13).

A genetic basis for CCHS is supported by several lines of evidence: (i) although CCHS is usually a sporadic disorder, familial cases have been reported in monozygotic twins, female siblings, and male-female half-siblings (1, 13); (ii) about 20% of CCHS cases are associated with HSCR (1, 13); and (iii) investigations in parents of CCHS patients have found a high prevalence of dysautonomic symptoms, suggesting that CCHS may be the most severe manifestation of a general autonomic system dysfunction with low penetrant Mendelian transmission (18). More importantly, vertical transmission of CCHS has been reported: among babies born to five women with CCHS but no HSCR (19, 20), two had CCHS, suggesting autosomal dominant inheritance (19, 20). A third infant exhibited recurrent episodes of ALTE consistent with a link between CCHS and ALTE (20). The fourth infant was born prematurely and had severe bronchopulmonary dysplasia. Finally, one child was apparently healthy (20). In addition, a child with CCHS was born to a mother who had a neural crest tumor, suggesting differences in the clinical expression of neural crest disorders (21). So far, no sex bias has been reported (1, 13, 14).

CANDIDATE GENES AND THEIR INVOLVEMENT IN FUNCTIONAL TRANSDUCTION PATHWAYS

Candidate genes in CCHS could be regarded as genes involved in neural crest stem cell development, which act mainly on the endothelin and RET signaling pathways (Fig. 1).

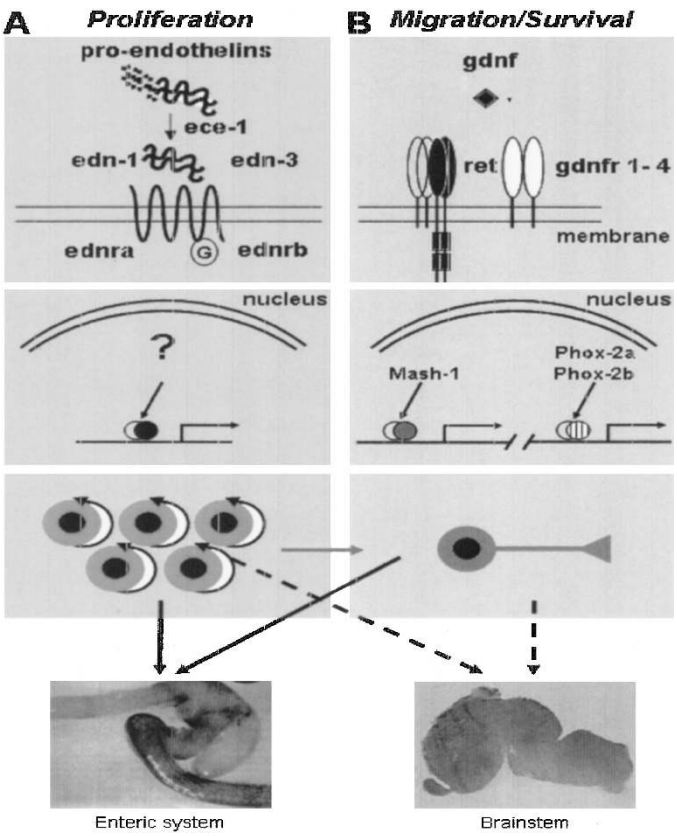

Figure 1. Schematic representation of the endothelin and RET signaling pathways. (*A*) Proliferation of neural crest stem cells involves the endothelin pathway. The converting enzyme ECE1 catalyzes the conversion of pro-endothelins to EDN1 and EDN3, respectively. EDNRA and EDNRB are G-protein transmembrane receptors for EDN1 and EDN3. (*B*) Migration and survival of neural crest derivatives. GDNF is the ligand for the RET tyrosine kinase receptor. GDNFR 1–4 are RET co-receptors. Nuclear signaling pathways related to neural crest cell development are not known for the endothelin pathway. In contrast, *MASH1*, *PHOX2A*, and *PHOX2B* are transcription factors known to be involved in the neuronal determination of neural crest derivatives. *Double circles* represent two distinct transcription factors. Progenitors are first cycling (*left panel*) and later differentiate (*red arrow*) into postmitotic derivatives as indicated on *right panel*. The involvement of endothelin and RET signaling pathways is established in the enteric nervous system (*plain arrows*) and hypothesized in the brainstem (*dotted arrows*).

The endothelin pathway involves two G protein–coupled membrane receptors, EDNRA and EDNRB, which transduce signals through the endothelins (EDN1, EDN3) (22) and ECE1, a membrane-bound metalloproteinase that processes only EDN1 and EDN3. This pathway is involved in the proliferation of neural crest cells (23). A second pathway involves the transcription factor Mash1, diffusible factors such as GDNF and its receptor the RET membrane tyrosine kinase receptor (24, 25). *MASH1* is a master gene that induces neuronal differentiation of neural-crest stem cells (26). *PHOX2A* and/or *PHOX2B*, depending on the neuronal stem cells, is needed for the expression of the GDNF-receptor subunit RET and for maintaining *MASH1* gene expression (27, 28). Other molecules similar to GDNF, such as neurturin, artemin, or persephin, bind to the RET membrane receptor and are crucial for the development and maintenance of distinct sets of central and peripheral neurons (29). Furthermore, mouse studies have

demonstrated that this signaling pathway is also involved in the migration of neural crest cells (30). Both the RET and endothelin signaling pathways appear to interact with each other, as recently suggested by studies of *RET*-null and *EDNRB* hypomorphic piebald alleles (31–33). Studies of *PHOX2A* and *PHOX2B* knockout mouse embryos showed unexpected ontogenetic similarity among the sympathetic, adrenal, parasympathetic, and enteric derivatives, as well as the placode-derived visceral sensory neurons and brainstem neurons (34, 35). Based on these similarities, it is tempting to suggest that both the endothelin and the RET signaling pathway are involved in brainstem neuronal progenitor proliferation and migration, as well as in survival of their neuronal derivatives.

MUTATIONS IN CANDIDATE GENES

Table 1 shows the identified gene mutations and main characteristics in CCHS patients. Recently, we found heterozygous *de novo* mutations of *PHOX2B* gene in 18 of 29 individuals with CCHS (11).* Most mutations consisted of five to nine alanine expansions within a 20-residue polyalanine tract, probably resulting from nonhomologous recombination. Other mutations, generally inherited from one of the parents, affecting the coding regions of genes involved in the RET and endothelin signaling pathways (2–6) and the *BDNF* gene (7) have been found in a few CCHS patients and appear to be neither necessary nor sufficient to cause CCHS. Interestingly, three patients each had mutations in two genes, *PHOX2B* plus *RET* and *PHOX2B* plus *GDNF*. Taken together, these genetic studies suggest that CCHS may be an autosomal dominant disease with *PHOX2B* as a master gene. However, one cannot exclude mutations in other genes as responsible for the wide variability in CCHS phenotypes. Animal models have proved useful for determining causal relationships between mutations at specific loci in CCHS patients and the development of breathing control. Findings in humans have prompted studies of the respiratory phenotype of mice with loss of function of genes in the RET and endothelin pathways or of the BDNF genes.

* Our findings were confirmed by recent publications from Sasaki A et al. Hum Genet 2003; 119:22–25, and Weese-Mayer et al. Am J Hum Genet 2003; 123:267–278.

TENTATIVE MURINE MODELS OF CCHS

Respiratory studies in newborn mice are still scarce, due to technical problems raised by the small size (weight, 1.5 g; tidal volume, 4 μL) and rapid breathing control maturation of these animals. The ventilatory response to hypercapnia is present 1 h after birth, whereas the ventilatory response to hypoxia is weak during the first 12 h, *i.e.* before peripheral chemoreceptor resetting (36). Studies have used head-out plethysmography

Table 1. *Gene mutations in CCHS patients*

Gene mutation	No.	Nucleotide	Predicted protein	Sex	HSCR	Inheritance from an unaffected parent	Investigators (ref)
RET	1*	Point mutation	Modified protein (P10391)	F	L-segment	Father	Amiel *et al*. (3)
RET	1	Point mutation	Modified protein (T706A)	F	L-segment	?	Sakai *et al*. (4)
RET	1	Point mutation	Modified protein (R114H)	F	No	Father	Kanai *et al*. (8)
GDNF	1	Point mutation	Modified protein (R93W)	M	No	Mother	Amiel *et al*. (3)
GDNF	1*	Point mutation	Modified protein (R93W)	F	No	?	de Pontual *et al*. (6)
HASH1	1*	Point mutation	Modified protein (P18T)	F	No	No	de Pontual *et al*. (6)
HASH1	1	In-frame deletion	Modified protein (A_{37}-A_{41}del)	F	No	Father	de Pontual *et al*. (6)
HASH1	1	In-frame deletion	Modified protein (A_{36}-A_{43}-del)	F	L-Segment	?	de Pontual *et al*. (6)
PHOX2B	18			8 M, 10 F	10/18 (6 L-segments)	*De novo* mutation validated in 8/18	Amiel *et al*. (11)
	16/18	Triplet expansion of 15–27 nucleotides	Polyalanine expansion				
	2/18	Insertion or deletion	Frameshift downstream of homeobox				
EDN1	1	Insertion	Modification of transcript 3′ UTR	M	No	?	Swensson (5)
EDN3	1	Point mutation	Frameshift followed by a premature stop in exon 5	F	No	?	Bolk *et al*. (2)
BDNF	1	Point mutation	Modified protein (I2T)	F	No	Father	Weese-Mayer *et al*. (7)

L-segment, long aganglionic segment; ?, no genetic analysis in parents, modified protein, the aminoacid changes induced by point mutation in nucleotide sequence are indicated.

* Plus *de novo* PHOX2B mutation.

Table 2. *Respiratory phenotypes in knock-out newborn mice*

Newborn mice	Other birth defects	Age at study	Respiratory frequency	Apneas	Hypercapnic VR	Hypoxic VR	Investigators (ref)
Ret−/−	HSCR	A few hours	NS	+	Decreased*	NS	Burton *et al*. (37)
Ret+/−		12 h	NS	+	NS	NS	Aizenfisz *et al*. (47)
Gdnf−/−	HSCR	First day	Decreased				Erickson *et al*. (43)
Mash−/−		A few hours	Increased*	No			Dauger *et al*. (42)
Mash+/−		A few hours	Increased*	No	Decreased†	NS	Dauger *et al*. (38,42)
Phox2b+/−		48 h	NS	+	Decreased		Dauger *et al*. (46)
Edn1−/−	Cardiac, craniofacial	First day			Decreased	Decreased	Kuwaki *et al*. (40)
Ednra−/−	Cardiac, craniofacial	First day			Decreased	Decreased	Kuwaki *et al*. (40)
Ednrb−/−	HSCR	First day	NS		NS	NS	Kuwaki *et al*. (40)
Ece1+/−		A few hours	NS	No	NS	Decreased	Renolleau *et al*. (49)
Bdnf−/−		First day	Decreased	+	Present		Erickson *et al*. (44)
Bdnf+/−		First day	Decreased	+			Erickson *et al*. (44)

VR, ventilatory response; NS, not significantly different from wild-type littermates.
* Significantly decreased, increased as compared with wild-type littermates.
† Significantly decreased in males.

(37) or whole-body plethysmography (38); with this last method, there is no need to restrain the animal. Baseline breathing patterns and ventilatory responses to chemical challenges have been investigated in studies that did not characterize sleep states. One study examined behavioral arousal (39). Currently, no blood gas or cardiovascular variables are available in newborn mice, in contrast to adult mice (40).

Table 2 lists the homozygous and heterozygous knockout newborn mice studied to date and their age at the time of investigation. Survival differed across knockout mice. *ECE1*−/− and *PHOX2B*−/− embryos died *in utero* (34, 41), *RET*−/− and *MASH1*−/− newborn mice died soon after birth from respiratory failure (37, 42), and *EDN1*−/− and *EDNRA*−/− newborn mice survived 24 h provided they were delivered by cesarean section and tracheotomized (40). All knockout newborn mice except *EDNRB*−/− (40) exhibited one or more breathing control abnormalities. Baseline respiratory frequency was decreased in both *GDNF*−/− and *BDNF*−/− newborn mice (43, 44). Recordings of brainstem–spinal cord preparations from *BDNF* mutant mice showed discharge frequency attenuation, which was more marked in homozygous than in heterozygous newborns (45). *MASH1*−/− and *MASH1*+/− newborns had an abnormally fast respiratory rate (42), a finding that has never been reported in CCHS patients. Numerous apneas occurred in *RET*+/− (46), *GDNF*−/− (43), *BDNF*−/−, and *BDNF*+/− newborn mice (44, 45). In *PHOX2B*+/− newborn pups, the ventilatory response to hypercapnia was substantially weaker than in wild-type pups, and hypoxia resulted in a striking increase in apnea duration after a normal initial increase in ventilation (46). Decreases have been found in hypercapnic and hypoxic ventilatory responses of *EDN1*−/− and *EDNRA*−/− newborn mice (42) and in hypercapnic responses of *RET*−/− (38) and male *MASH1*+/− newborn mice (38). *RET*+/− newborn mice had normal arousal and ventilatory responses to hypercapnia and hypoxia (47). Conversely, *BDNF*−/− mutants had loss of afferent neurons supporting the arterial chemoreflex and baroreflex (48) and exhibited a deficient ventilatory response to hyperoxia (44). Finally, *ECE1*+/− newborn mice showed blunting of hypoxic responses (49), possibly related to low *EDN1* levels (41). Despite the identification of these numerous genes involved in breathing control, none of the genetically engineered mice developed to date replicate fully the human CCHS respiratory phenotype.

PERSPECTIVES

The identification of *PHOX2B* mutations in most patients with CCHS is an important milestone in our quest to unravel the pathophysiological mechanisms of this disease. One key issue is to determine the functional consequences of the polyalanine expansion generated by the mutated *PHOX2B* alleles in CCHS patients. The development of genetically modified mice with *PHOX2B* alleles having similar mutations will be instrumental in this respect.

The finding of heterozygous *PHOX2B* polyalanine expansions in the vast majority of CCHS patients allows genetic counseling for a disease with an unexpected autosomal dominant mode of inheritance. These studies fully warrant a dedicated genetic consultation, especially as prenatal diagnosis may be relevant in some families. It is also essential to disseminate information on the potential transmission of CCHS to CCHS families, obstetricians, and pediatricians. Moreover, meticulous attention should be paid to infants whose mothers or fathers have CCHS (20). An international database including clinical data and genetic specimens from CCHS patients and their parents and relatives is needed. Future research into the genetic basis of CCHS may improve our understanding of early breathing control disturbances such as SIDS. The prevalence of SIDS is high in CCHS families, suggesting that these two disorders may share developmental breathing control abnormalities (50). Finally, it can be speculated that the well-described interindividual variability in apneas in preterm infants may be related to genetic variation.

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