Title: Congenital Central Hypoventilation Syndrome *GeneReview* – Molecular Genetics
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Polyalanine Expansion

Mutations that result in polyalanine expansion have been described as a cause of disease in a number of homeodomain- and non-homeodomain-containing transcription factors including:

- *HOXD13* (synpolydactyly)
- *HOXA13* (see Hand-Foot-Genital Syndrome)
- *RUNX2* (see Cleidocranial Dysplasia)
- *ZIC2* (see Holoprosencephaly Overview) [Goodman & Scambler 2001]

There is precedent for polyalanine repeat tract expansion in a homeobox gene as a cause of neurologic disease resulting from presumed failure of specification and/or migration of a specific neuronal cell type. *ARX*, (the aristaless-related homeobox gene) has been associated with XLAG (X-linked lissencephaly and ambiguous genitalia) [Kitamura et al 2002], X-linked intellectual disability [Bienvenu et al 2002], X-linked and sporadic infantile spasms, and other developmental disorders with intellectual disability and epilepsy [Stromme et al 2002]. *ARX* contains a polyalanine tract that is expanded in some affected individuals, particularly those with infantile spasms or myoclonic epilepsy. Other affected individuals have missense or truncating mutations that likely result in loss of function.

Mice with mutations in *Arx* show aberrant differentiation and migration of GABA-ergic neurons in neocortex [Kitamura et al 2002]. Given the expression patterns of *PHOX2B* in central autonomic structures and peripheral neural crest derivatives and the wide range of ANS dysfunction seen in CCHS, it seems likely that a similar mechanism of aberrant differentiation and/or migration of central and peripheral noradrenergic sympathetic and parasympathetic neurons results from the polyalanine tract expansion in *PHOX2B*.

Role of *PHOX2B* in embryogenesis. *PHOX2B* has an early embryologic action as a transcriptional activator in:

- Promotion of neuronal differentiation including upregulation of expression of proneural genes (including *MASH1*); and
- Expression of motor neuron differentiation [Dubreuil et al 2002].

PHOX2B has a separate role via a different pathway, in which it represses expression of inhibitors of neurogenesis [Dubreuil et al 2002]. *PHOX2B* is required for expression of tyrosine hydroxylase (see GTP Cyclohydrolase 1-Deficient Dopa-Responsive Dystonia),

dopamine beta hydroxylase (see Dopamine Beta-Hydroxylase Deficiency) [Lo et al 1999], and RET (see Multiple Endocrine Neoplasia Type 2 and Hirschsprung Disease Overview) and for maintenance of *MASH1*, suggesting that *PHOX2B* regulates the noradrenergic neuronal phenotype in vertebrates [Pattyn et al 1999]. The importance of *PHOX2B* early in the embryologic origin of the ANS – with a role in determining the fate of early neuronal cells and a role in disinhibition of neuron differentiation – could account for the seeming imbalance in the sympathetic and parasympathetic nervous system and dysfunction in the enteric nervous system seen in children with CCHS. Studies by Pattyn et al [1997] and Pattyn et al [1999] indicate an early expression pattern of *PHOX2B* in rhombencephalon, suggesting a link to early patterning events for later neurogenesis in the hindbrain.

In the mouse, *Phox2b* is expressed in the neonatal CNS, specifically in the area postrema, nucleus tractus solitarius, dorsal motor nucleus of the vagus, nucleus ambiguus, ventral surface of medulla, locus coeruleus (until embryonic day 11.5), and cranial nerves III (oculomotor), IV (trochlear), Vll (facial), IX (glossopharyngeal), and X (vagus). Until mid-gestation in the mouse, *Phox2b* is expressed in the Vth (trigeminal) cranial nerve. In the mouse peripheral nervous system, *Phox2b* is expressed in the distal VIIth, IXth, and Xth cranial sensory ganglia from embryonic day 9.5 and in all autonomic nervous system ganglia from the time these are formed until at least mid-gestation. Finally, by embryonic day 9-9.5, the Phox2b protein is detected in enteric neuroblasts invading the foregut mesenchyme. It is expressed in the esophagus, small intestine, and large intestine [Pattyn et al 1997, Pattyn et al 1999] and in all undifferentiated neural crest-derived cells in the gut with a rostrocaudal gradient [Young et al 1999]. In the *Phox2b* knockout mouse, the gut has no enteric neurons and even the neural crest-derived cells that are found in the foregut at E10.5 do not survive or migrate further [Young et al 1999].

The phenotypic findings of CCHS (symptoms of ANSD in the respiratory control system, cardiovascular system, ophthalmologic system, neurologic system, and gastrointestinal system) follow logically from the embryologic distribution of *PHOX2B*. It remains unclear how the distribution and actions of *PHOX2B* account for involvement of other systems often included in the ANSD profile of the child with CCHS, including the sudomotor, psychological, and renal systems.

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