

Title: Congenital Central Hypoventilation Syndrome *GeneReview* – Molecular Genetics  
Authors: Weese-Mayer DE, Marazita ML, Rand CM, Berry-Kravis EM  
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Several lines of evidence support a possible dominant-negative mechanism for *PHOX2B* mutations in CCHS:

- Other polyalanine repeat mutations in homeodomain proteins associated with human disease are thought to act in a dominant-negative fashion (syndactyly and *HOXD13* [Goodman et al 1997]; [hand-foot-genital syndrome](#) and *HOXA13* [Utsch et al 2002]).
- Transcriptional activity of *PHOX2B* deletion variants (deleted for 1- to 13-alanine residues), was decreased to roughly 50%-70% of wild-type activity, while a disease-associated five-repeat expansion reduced transcriptional activity to about 20% of wild type [Toyota et al 2004].
- Deletion variants and alleles with nine, 13, 14, and 15 alanine repeats as well as an expansion with 22 repeats appear to be population variants not associated with CCHS, while individuals with five or more repeat expansions uniformly have CCHS [Amiel et al 2003, Weese-Mayer et al 2003b, Toyota et al 2004].
- Weese-Mayer et al [2003a] and Matera et al [2004] have shown correlations between polyalanine repeat length in CCHS and severity of autonomic symptoms.

Both polyalanine repeat expansion mutations and non-polyalanine repeat expansion mutations in *PHOX2B* have been shown to impair transcriptional function; and transcriptional impairment increases with expansion length for polyalanine repeat expansion mutations [Matera et al 2004, Bachetti et al 2005]. For non-polyalanine repeat expansion mutations, the least impairment of transcriptional function, comparable to activity from the smallest at the time (5-repeat) polyalanine expansion, was seen with the 618delC and the 577delG frameshift mutations [Bachetti et al 2005], both of which are -1 frameshifts occurring in the same area of the protein. This is consistent with incomplete penetrance for a small subset of non-polyalanine repeat expansion mutations and the 20/25 genotype (i.e., 20 CGN repeats on one allele and 25 CGN repeats on the other allele). Thus, specific types and locations of mutations may be more likely to present with variable expressivity and reduced penetrance, based on a relatively smaller effect on *PHOX2B*-mediated transcription than is seen for fully penetrant mutations.

Given the data available from mouse models and humans with CCHS, it is likely that a threshold effect for *PHOX2B* activity exists, below which the CCHS phenotype is manifest. Thus, loss of an allele is likely insufficient to cause disease in most cases, but activity is likely reduced below the disease threshold in individuals with all but the smallest polyalanine expansion mutations or distal truncating mutations because of a dominant-negative effect on function of the wild-type protein, reducing *PHOX2B* activity to less than 50%. As intranuclear and intracellular protein aggregates are also seen with

certain mutations including longer polyalanine repeat mutations and many non-polyalanine repeat mutations, a gain of function mechanism may also play a role in the CCHS phenotype.

## References

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