Neuroanatomic lesions in murine models of central congenital hypoventilation syndrome

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Mutations in the neuron type-specific homeogene Phox2b are causative for central congenital hypoventilation syndrome (CCHS). We have shown that introducing one of the most common human mutations in mouse leads to a CCHS-like respiratory syndrome, including apneas, arythmia, and unresponsiveness to a hypercapnic challenge —and neonatal death. While the mutation preserves many Phox2b-positive neural structures, it destroys the retrotrapezoid nucleus (RTN), a group of neurons at the ventral surface of the facial motor nucleus. Electrophysiological studies have implicated the RTN in central CO2 sensitivity and perinatal entrainment of the main respiratory pacemaker. Altogether, these data point to the RTN as a major culprit in CCHS pathogenesis. However, we recently found that spatially limited expression of the Phox2b27Ala allele can be compatible with life, while nevertheless destroying the RTN and the perinatal hypercapnic response. Thus, other defects in Phox2b-expressing neurons contribute to the full CCHS-like syndrome in mouse, whose discovery will likely improve our understanding of the human condition.