Novel interdisciplinary approaches to molecular pathogenesis of Congenital Central Hypoventilation Syndrome: from basic to drug discovery

Congenital Central Hypoventilation Syndrome (CCHS, MIM 209880) is a rare neonatal disease characterized by abnormal ventilatory response to hypoxia and hypercapnia, owing to failure of autonomic respiratory control. Frameshift mutations (5%) and polyalanine triplet expansions (95%) have been detected in the coding region of the transcription factor PHOX2B gene, responsible for the proper development and function of the autonomic nervous system.

Transcriptional dysregulation, dominant negative effect and toxic effects by mutated and misfolded PHOX2B protein contribute to CCHS pathogenesis. No pharmacological intervention are available so far, and the only options for the patients relies on mechanical support for ventilation.

Our aim is to provide new insights into disease pathophysiology, and to provide therapeutic strategies. By generating autonomic nervous system neurons, starting from CCHS patients derived induced pluripotent stem cell (iPSC), we will monitor their development to search for developmental defects, and identify possible pharmacological targets.

References:

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