Pathogenic study of Fgf13 gene mutation in Chinese intellectual disability patients

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Abstract: Objective Congenital intellectual disability (ID) is usually caused by the abnormality of genes or chromosomes. The ID-related gene mutations of Chinese population which are different from others need systematic investigations. We screened the ID-related gene mutations from Chinese ID children by sequencing, and identified some novel mutations of genes including fibroblast growth factor 13 (FGF13), which is a candidate gene for a syndromal X chromosome linked ID (XLID). The genetic deletion of Fgf13 in mice results in neuronal migration defects and weaken learning and memory in our previous study. We studied the pathogenicity and related mechanisms of the mutations of Fgf13 in influencing ID phenotypes. Methods Whole genome sequencing and genetic analysis of family trees were performed to screen mutation sites. Cultured iPSCs-derived neural stem cells and neurons were
used to investigate the molecular mechanisms. The construction of gene mutation transgenic mice and related behavioral tests were used to test the pathogenic phenotypes at various levels. **Results** (1) A single base mutation was occurred in *Fgf13* gene of 3 ID boys, which caused down-regulation of the protein but not the mRNA expression of FGF13 in HEK293 cells. (2) iPSCs-derived neural stem cells from those mutation-carrying ID children further confirmed down-regulation of the protein but not the mRNA expression of FGF13, and a rescued single base mutation reversed those alterations. (3) Behavior tests showed that the knock-in mice carrying the point mutation of *Fgf13* gene resulted in the learning and memory defects similar with those in ID patients, and exhibited delayed migration and increased axonal branching of neurons in the developing brains. **Conclusion** Our study provides ID-related pathogenic genes and related mechanisms of Chinese population.

**Keywords:** intellectual disability; fibroblast growth factor 13; whole genome sequencing; iPSCs-derived neural stem cells; single base mutation transgenic mice