Seminarios internos del IBFG

A novel human Cdh1 mutation impairs APC/C activity resulting in microcephaly

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The Fizzy-related protein 1 (Fzr1) gene encodes Cdh1 protein, a coactivator of the E3 ubiquitin ligase anaphase-promoting complex/cyclosome (APC/C). Previously, we found that genetic ablation of Fzr1 promotes neural progenitor cell death, leading to neurogenesis impairment and microcephaly in mouse. To ascertain the possible translation of these findings in humans, we investigated a novel missense (p.Asp187Gly) Fzr1 gene mutation (c.560A>G) in a 4-year-old boy, born from non-consanguineous Spanish parents, who presents with severe antenatal microcephaly and psychomotor retardation. Cdh1 protein levels in leucocytes isolated from the patient were significantly lower than those found in his parents. Expression of the Asp187Gly mutant form of Cdh1 in human embryonic kidney 293T cells produced less Cdh1 protein and APC/C activity, resulting in altered cell cycle distribution when compared with cells expressing wild-type Cdh1. Furthermore, ectopic expression of the Asp187Gly mutant form of Cdh1 in cortical progenitor cells in primary culture failed to abolish the enlargement of the replicative phase caused by knockout of endogenous Cdh1. These results indicate that the loss of function of APC/C-Cdh1 caused by Cdh1 Asp187Gly mutation is a new cause of prenatal microcephaly.

Bibliography

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