

Basonuclin 1 deficiency is a cause of primary ovarian insufficiency

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Abstract

Primary ovarian insufficiency (POI) leads to infertility and premature menopause in young women. The genetic etiology of this disorder remains unknown in most patients. Using whole exome sequencing of a large Chinese POI pedigree, we identified a heterozygous 5 bp deletion inducing a frameshift in *BNC1*, which is predicted to result in a non-sense-mediated decay or a truncated BNC1 protein. Sanger sequencing identified another *BNC1* missense mutation in 4 of 82 idiopathic patients with POI, and the mutation was absent in 332 healthy controls. Transfection of recombinant plasmids with the frameshift mutant and separately with the missense mutant in HEK293T cells led to abnormal nuclear localization. Knockdown of *BNC1* was found to reduce BMP15 and p-AKT levels and to inhibit meiosis in oocytes. A female mouse model of the human *Bnc1* frameshift mutation exhibited infertility, significantly increased serum follicle-stimulating hormone, decreased ovary size and reduced follicle numbers, consistent with POI. We report haploinsufficiency of *BNC1* as an etiology of human autosomal dominant POI.