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## *Identification of a Mutation in CNNM4 by Whole Exome Sequencing in an Amish Family and Functional Link between CNNM4 and IQCB1*

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# Abstract

We investigated an Amish family in which three siblings presented with an early-onset childhood retinal dystrophy inherited in an autosomal recessive fashion. Whole exome sequencing was performed and identified a homozygous nonsense mutation (c.C1813T, p.R605X) in the cyclin and CBS domain divalent metal cation transport mediator 4 (*CNNM4*). Here we show that CNNM4 interacts with IQCB1, which causes Leber Congenital Amaurosis (LCA) when mutated. A truncated CNNM4 protein starting at R605 significantly increased the rate of apoptosis, and significantly increased the interaction between CNNM4 and IQCB1. Mutation p.R605X may cause Jalili syndrome by a nonsense-mediated decay mechanism, affecting the function of IQCB1 and apoptosis, or both. Our data, for the first time, functionally link Jalili syndrome gene CNNM4 to LCA gene IQCB1, providing important insights into the molecular pathogenic mechanism of retinal dystrophy in Jalili syndrome.

# Results

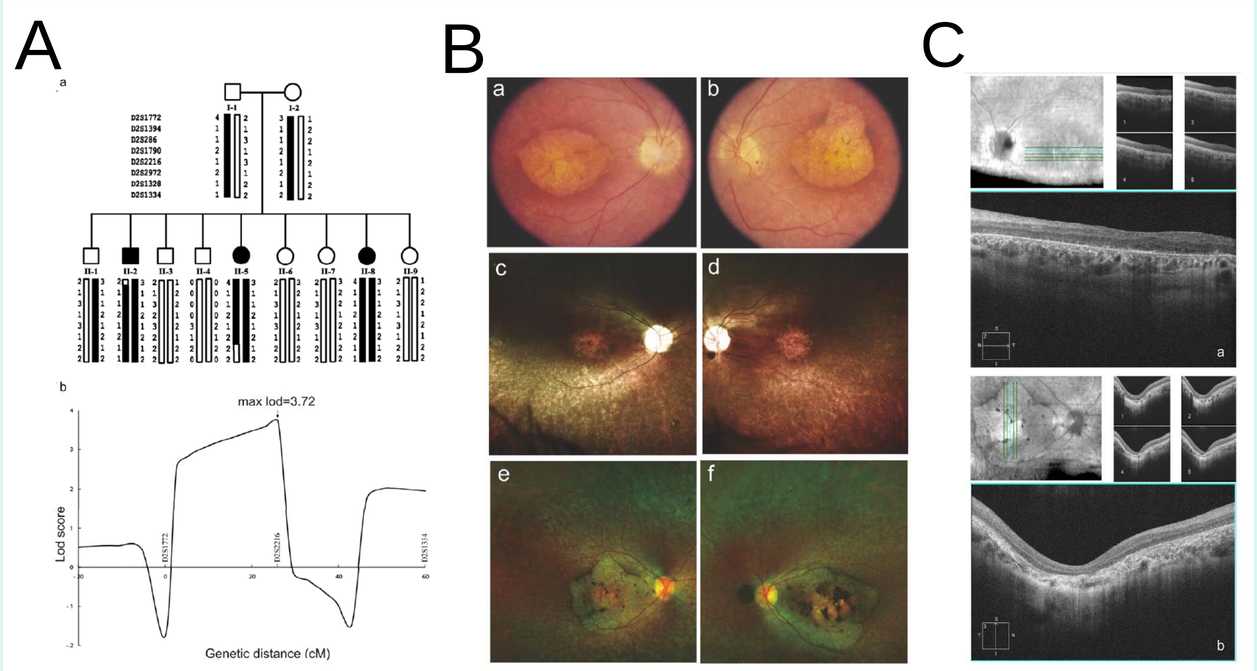


**Figure 1** (A)Linkage analysis. (B) Fundus photos of three siblings with Jalili syndrome. (C) Representative OCT.

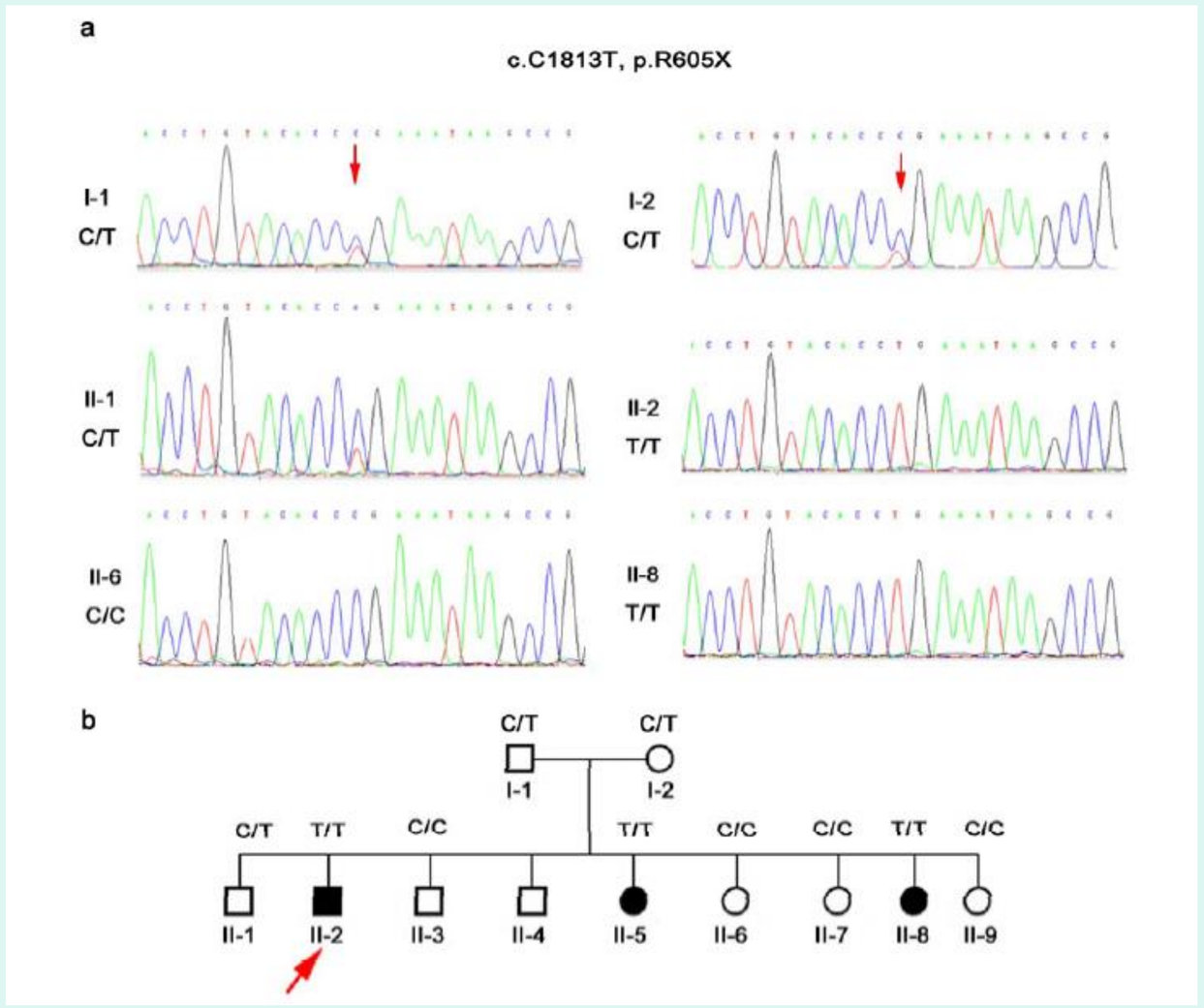


**Figure 2** Identification of a CNNM4 mutation co-segregating with the disease in the Amish family.

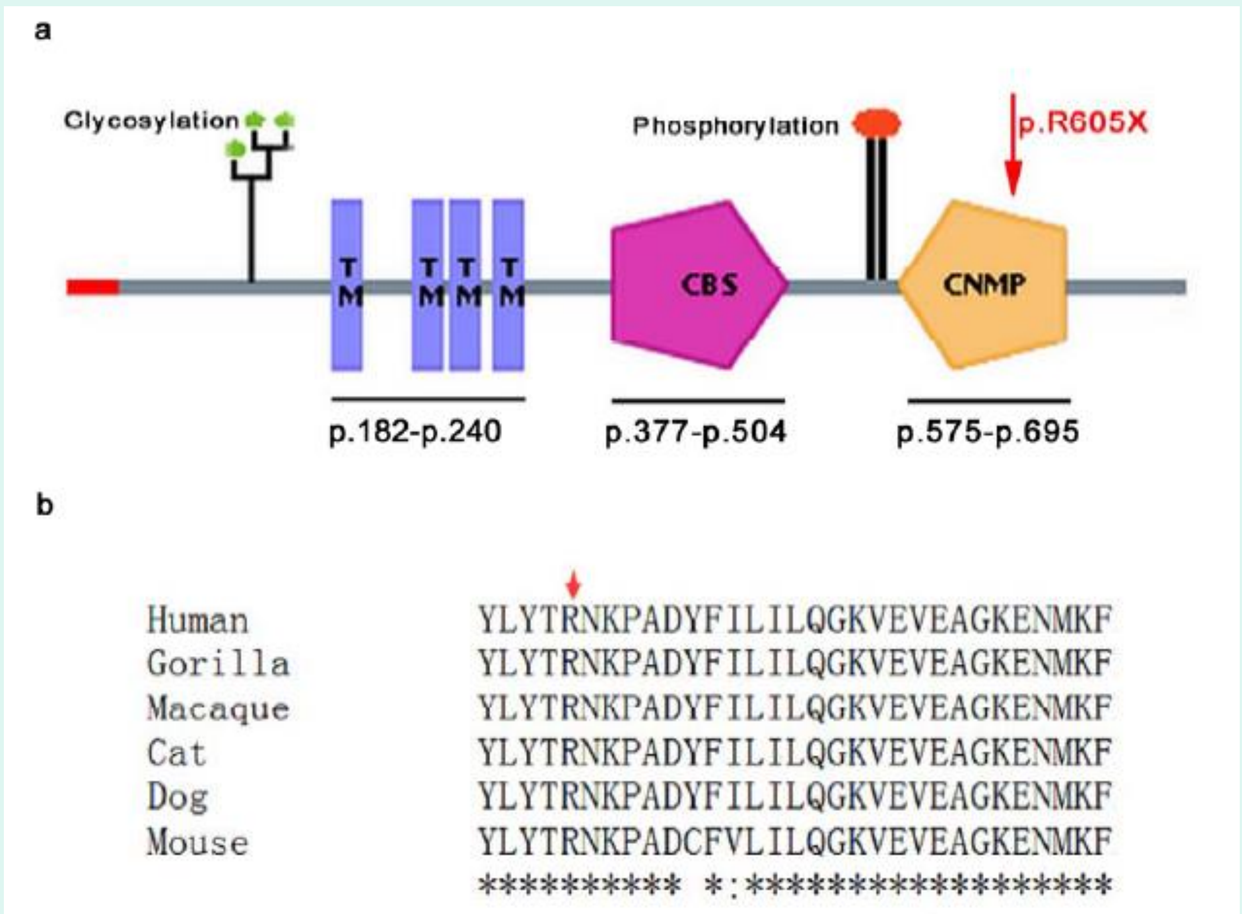


**Figure 3** Schematic drawing and multiple sequence alignment of the CNNM4 protein.

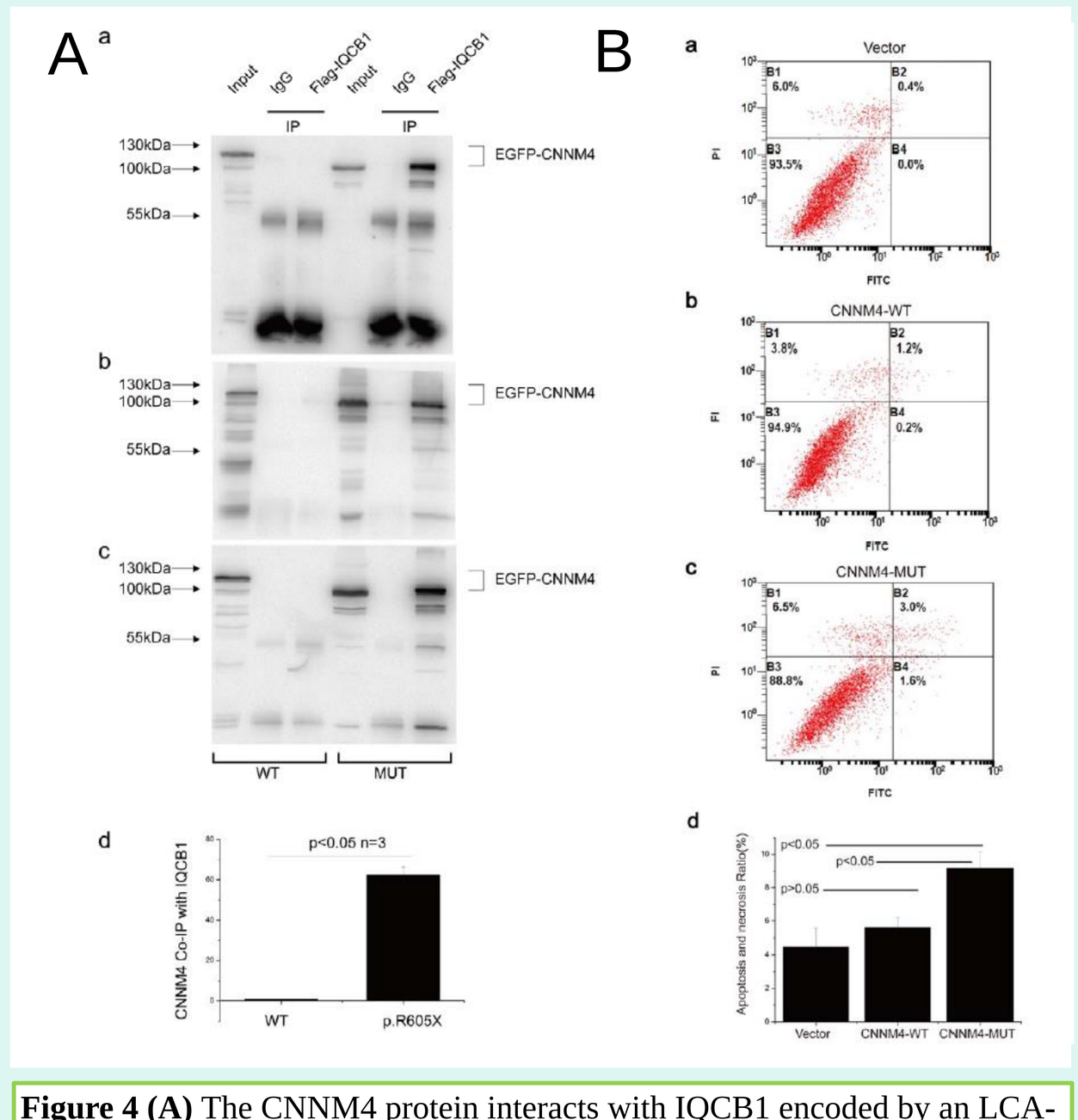


**Figure 4 (A)** The CNNM4 protein interacts with IQCB1 encoded by an LCA-causing gene. (B) The CNNM4 protein interacts with IQCB1 encoded by an LCA-causing gene.

# Acknowledgements

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