Loss-of-function mutation in RUSC2 causes ntellectual disability and secondary microcephaly

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Intellectual disability is seen in up to 1% to 3% of the general population, and is often dichotomized into syndromic and non-syndromic forms. A genetic aetiology accounts for about 25% to 50% of cases, with up to 700 monogenic mutations identified so far. Recent advances in genetic testing have allowed the identification of an ever-increasing repertoire of genes causing intellectual disability. Characterization of their protein products has shed light onto the diverse biological pathways affected in this important neurological disease that results in significant impairment in cognitive and adaptive behaviour, and which has important medical and social implications. Aberrancies in synaptic vesicular transport and intracellular protein trafficking have been highlighted among the various biological pathways reported to cause intellectual disability. Included in these are mutations in genes coding for Rab proteins (rabaptins), a group of small Ras GTPases that have been shown to play an important role at different levels of the cellular trafficking pathway. Although over 60 Rab proteins have been identified so far, only a few have been implicated in human disease, including in patients with intellectual disability with or without associated brain malformations. RUSC2, officially known as RUN and SH3 domain containing a gene found on chromosome 9p13.3 (gene identifier [ID] 9853, Mendelian Inheritance in Man [MIM] 611053). RUSC2 codes for iporin, a ubiquitous protein with moderate to high expression in the human brain. The literature on the functions of iporin remains sparse, but there is some evidence that it interacts with Rab1b and Rab1-binding protein GM130,10 both of which are also expressed in the brain, with highest expression in dendritic spines where they appear to play an important role in synaptogenesis. So far, no mutations in RUSC2 have ever been shown to cause human disease, and no animal models disrupting this gene have been described. However, to our knowledge for the first time, we describe the clinical presentations of three patients (two male siblings and one unrelated female) with severe intellectual disability and microcephaly. Through whole-exome sequencing, all three were found to have inherited homozygous nonsense mutations in RUSC2.

Speaker Biography

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