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GPI-Anchor pathway defects: Implications for neurodevelopmental morbidity, congenital disorder of glycosylation, Mabry syndrome and Fryns syndrome

Cyndromic intellectual disability (ID) is predominantly genetic in origin. Currently, with the advent of next generation Osequencing, an increasing number of novel genes and genetic developmental pathways causing syndromic ID are being identified; the GPI-anchor pathway is one such pathway. In mammalian cells, there are thought to be over 150 different proteins that are attached to the plasma membrane using a glycosylphosphatidylinositol (GPI) anchor. This diverse family comprises receptors, adhesion molecules and enzymes and is critical for normal neuronal and embryonic development. The GPI anchor is synthesised and remodelled in a complex series of biochemical reactions that occur either in the endoplasmic reticulum or golgi apparatus, and at least 30 genes are known that encode components of this pathway. The clinical significance of this pathway was first demonstrated in 1993 when somatic mutations in PIGA were shown to be the underlying cause of paroxysmal nocturnal haemoglobinuria. Recessive mutations in genes in the early part of this pathway are associated with multiple congenital abnormalities, developmental delay and sometimes a reduced life span. Recessive mutations in the later part of the pathway result in global developmental delay, intellectual disability, seizures, microcephaly, facial dysmorphism and brachytelephalangy. This is often accompanied by raised levels of serum alkaline phosphatase and has been termed 'Hyperphosphatasia Mental Retardation syndrome (HPMRS)' or Mabry syndrome. Recently, several genes within this pathway including PIGV, PIGO. PGAP2, and PIGY have been shown to cause these phenotypes. Biallelic PIGN mutations have been shown to cause Fryns syndrome - a multiple congenital anomaly syndrome associated with a reduced life span. Genotypephenotype correlation and the contribution of GPI-anchor biogenesis towards developmental disorders is under further investigation.

Biography

Usha Kini is a Consultant Clinical Geneticist working at the Oxford Centre for Genomic Medicine in Oxford, UK. She also holds the position of Honorary Senior Clinical Lecturer in Clinical Genetics at the University of Oxford. Her research interest is in the genetics of birth defects such as congenital brain anomalies and orofacial clefting. She is the Chief investigator of the Genetics of Structural Brain abnormalities and learning disabilities study and is also the Clinical lead of the Oxford Brain Abnormlaties Research Group. Her group has successfully described several novel genes implicated in causing congenital brain anomalies.

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