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Abstract Topic: - Molecular effects of genetic variation

Abstract Title: - Factors determining the severity of neurodevelopmental phenotypes in Lowe Syndrome.

Presenting author name: - Ron Philip

Presenting author institute: - National Centre for Biological Sciences, TIFR

Co-authors name: - Husayn Ahmed, Yojet Sharma, Priyanka Bhatia, Shubra Acharya, Padinjat Raghu, , , ,

Co-authors institute: - Cancer Dynamics Laboratory, The Francis Crick Institute, London, United Kingdom, National Centre for Biological Sciences, TIFR, Bangalore, India, Technische Universität, Dresden, Center for Molecular and Cellular Bioengineering (CMCB) Center for Regenerative Therapies TU Dresden (CRTD) Cluster of Excellence, Fetscherstr, Dresden, Luxembourg Institute of Health Department of Precision Health, Strassen, Luxembourg, National Centre for Biological Sciences, TIFR, Bangalore, India, , , ,

Aims: - Lowe syndrome (LS) is a rare X-linked recessive genetic disorder characterised by ocular, cerebral and renal manifestations. Its prevalence is estimated to be between 1 and 10 in 1,000,000 people worldwide. The disease most commonly presents as congenital cataract, neurodevelopmental delay and renal tubular dysfunction. However, despite being a monogenic disorder, clinical features in individual patients show wide variability; some patients present with severe neurodevelopmental delay while others present with renal tubular dysfunction and minimal cerebral symptoms. This project focuses on deciphering the genetic and cellular mechanisms underlying the neurodevelopmental phenotype of LS and the basis of its inherent phenotypic variability.

Methods: - We address this problem using a combination of Whole Genome Sequencing and various cellular and imaging-based assays on iPSC-derived neural stem cells and neurons from a Lowe syndrome family.

Results: - The causative gene, OCRL1, encodes for a 5-phosphatase enzyme which regulates the phosphatidylinositol-4,5-bisphosphate (PIP_2) and phosphatidylinositol-4-phosphate (PI4P) levels at various sub-cellular locations in eukaryotic cells. One of these locations is the primary cilia, a sub-cellular organelle widely known to play an important role during neurodevelopment. We show that the loss of the OCRL1 enzyme from the primary cilia can potentially dysregulate some of the developmentally significant functions performed by this organelle.

Conclusions: - The functional relevance of the OCRL1 enzyme within the primary cilia along with the clinical presentation that resembles ciliopathies has led to the suggestion that OCRL1 be known as a ciliopathy-associated gene. I will present my data, using patient-derived iPSC lines, on the potential role of OCRL in regulating cilia function in the developing brain, thus contributing to the neurodevelopmental phenotype.

Keywords: - The causative gene, OCRL1, encodes for a 5-phosphatase enzyme which regulates the phosphatidylinositol-4,5-bisphosphate (PIP_2) and phosphatidylinositol-4-phosphate (PI4P) levels at

various sub-cellular locations in eukaryotic cells. One of these locations is the primary cilia, a sub-cellular organelle widely known to play an important role during neurodevelopment. We show that the loss of the OCRL1 enzyme from the primary cilia can potentially dysregulate some of the developmentally significant functions performed by this organelle.