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Abstract Topic:- Molecular and cytogenetic diagnostics

Abstract Title:- Duplication of one nucleotide at position c.1164 of the ATP9A gene causes a novel neurodevelopmental disorder involving progressive pes cavus, severe intellectual disability with behaviour problems

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Aims:-Genes implicated in endosomal trafficking machinery are crucial for brain development and are critical for maintaining neuronal communication, as well as for normal cellular physiology. The motor axons due to their length may be particularly susceptible to disruptions in the pathway leading to pes cavus.

Methods:- Exome sequencing was performed in the affected individual and his parents (non-consanguineous). Proband is a 14 yr old who presented with delayed neurodevelopment, severe intellectual disability and behavior problems. He had progressive pes cavus with no evidence of peripheral sensory neuropathy on nerve conduction study

Results:- We detected homozygous duplication of one nucleotide at position c.1164 of the ATP9A gene. This variant has not been reported in literature as causative of disease. The c.1164 dup variant results in duplication of one nucleotide at position c.1164 of the ATP9A gene causing a frameshift in the protein reading frame. It has been shown previously that ATP9A localizes to early and recycling endosomes. ATP9A pathogenic mutants have aberrant subcellular localization and cause abnormal endosomal recycling. These findings provide strong evidence that ATP9A deficiency leads to neurodevelopmental disorders and synaptic dysfunctions and establishes novel regulatory roles for ATP9A in RAB5 and RAB11 activity-dependent endosomal recycling pathway and neurological diseases

Conclusions:- Our findings show that pathogenic variants in ATP9A cause a novel autosomal recessive neurodevelopmental disorder with pes cavus. Ras superfamily of small GTPases is a master regulator of early to late endocytic membrane transport and mutations in this have been described in CMT2 which may explain the development of pes cavus in our patient. Further functional studies will help us understand the effect of this novel mutation in endosomal trafficking

Keywords:- Pes Cavus, ATP9A mutation, endocytic membrane transport