NOVEL COPY NUMBER VARIATION INVOLVING 5´UTR AND EXON 1 IN ABDH12 GENE ASSOCIATED WITH PHARC SYNDROME: CASE REPORT AND LITERATURE REVIEW

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INTRODUCTION

PHARC syndrome is an ultra-rare phospholipid catabolism disorder characterized by demyelinating polyneuropathy, sensorineural hearing loss, cerebellar ataxia, retinitis pigmentosa, and cataracts. It is caused by homozygous or compound heterozygous variants in ABDH12 gene and autosomal recessive inheritance pattern. Nonsense, frameshift and missense variants have been reported in literature with known causative haploinsufficiency and loss of function related to the phenotype. We present a case of PHARC with a novel 5kb CNV variant involving exon 1. Other variants involving exon 1 have already been described.

CASE REPORT

A 26-year man with a slowly progressive cerebellar ataxia that started with gait abnormalities, dysarthria, motor incoordination and falls associated with early onset bilateral sensorineural hearing loss and bilateral cataracts with initial clinical suspicion of Refsum disease, Charcot Marie Tooth and mitochondrial disorders. Physical examination evidenced global areflexia, ataxic gait, scoliosis, dysarthria, visual impairment, pes cavum and motor incoordination, slow saccadic movements, vertical ophthalmoparesis and ocular myokymia. He presented no biochemical or metabolic abnormalities, normal levels of vitamin E and phytanic acid. Brain MRI evidenced cerebellar atrophy, and electroneuromyography evidenced a demyelinating polyneuropathy in all 4 limbs. No mutations were found associated with Charcot Marie Tooth. Whole Genome Sequencing analysis evidenced a biallelic pathogenic 5kb CNV involving the 5'UTR and exon 1 of ABDH12 [del(20)(p11.21p11.21)] confirming the molecular diagnosis of PHARC syndrome.

DISCUSSION AND CLOSING COMMENTS

ABDH12 encodes a 45kDa glycoprotein serine hydrolase member family important in maintaining the levels of oxidized phosphatidyl serine during oxidative stress. Loss of function variants impairs phosphatidyl serine hydrolysis inducing inflammation and apoptosis. This lipid signaling pathway is responsible for neurological and extra neurological degeneration and is associated with the PHARC phenotype. Although Large deletions and intra-genic CNVs involving the 5'UTR and exon 1 of ABDH12 have already been reported, this 5kb CNV is absent in DECIPHER database, suggesting a possible recombination locus in this region.

We report a novel large intragenic deletion involving the 5'UTR and exon 1 of *ABDH12* associated with PHARC phenotype. Whole Genome Sequencing is an essential tool for the diagnosis of this ultra rare disease.

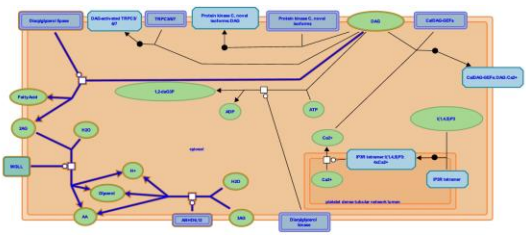

Figure 1: Schematic biochemical pathway of ABDH12/6 function in phospholipid metabolism. ABDH12 encodes a serine hydrolase involved in the hydrolysis of 3-acyl isomer of arachidonoylglycerol (3AG) generating arachdonic acid (AA) and glycerol. Image generated from REACTOME, avaiable online in: PB | ABHD6,12 hydrolyse 3AG (UniProt:Q8N2K0)

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