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Case Study on Rare Disease: Muscle Brain Eye Disease (Congenital Muscular Dystrophy-Dystroglycanopathy with Brain and Eye Anomalies, Type A3)

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Abstract: ***A case of Congenital muscular dystrophy-dystroglycanopathy which is Likely Compound Heterozygous in Nature. Including 3 types of Congenital muscular Dystroglycanopathy. Includes Type A3 With Muscle, Brain and Eye, Type B3 with intellectual Disability, Type C3 with Limb Girdle type of Muscular disability. This Patient Having prominent Clinical Features of Type A3 (Muscle brain Eye Disease). This Disorder associated with POMGNT1 mutation with some Pathogenic mutant variant (PVS1, PM2, PP5) lead to A rare autosomal recessive disorder with clinical outline of global developmental delay, midbrain atrophy, cerebral and cerebellar atrophy, cerebellar vermal and pontocerebellar hypoplasia, central hypotonia, distal muscle weakness in upper and lower limbs, and abnormal USG. So, basically this disorder characterized by muscle weakness (hypotonia), severe nearsightedness (myopia), glaucoma and brain abnormalities. They also have developmental delay and intellectual disability, a buildup of fluid in the brain (hydrocephalus), and distinctive facial feature. Multiple Neurological abnormalities.***

Keywords: Muscle Brain Eye Disease, Limb-girdle muscular, Intellectual Disability, Global Developmental Delay, Hypotonia, Myopia, Glaucoma.

1. Introduction

Muscle Brain Eye Disease is a recessively inherited disease with faulty product of the POMGNT1 gene (protein O-mannose beta-1, 2-N-acetylglucosaminyltransferase) participates in O-mannosyl glycan synthesis by transferring N-acetylglucosamine residues to O-linked mannose. O-mannosyl glycan synthesis is essential for the proper functioning of dystroglycan, the central element of the Dystrophin-Glycoprotein Complex (DGC). Dystroglycan complex works as a transmembrane linkage between the extracellular matrix and the cytoskeleton. Dystrophin-Glycoprotein Complex which links the extracellular matrix to the intracellular actin cables, is thought to provide structural integrity in muscle tissues.

2. Case Report

A 2 year old male child born of non-consaguineous marriage presented to paediatrics OPD with complain of Not able to sit at 2 year of age, Not following light,. No other complaints at present.

Associated with Birth History of Didn't Cry immediately after birth, Patient has been put under oxygen Hood in NICU at the time of initial Hours of Life. antenatal USG s/o Large both kidney with B/L Hydronephrosis. Which was correlate Postnatally with Finding s/o Vesico ureteric reflex.

On detailed history the child did not sitting without support. In addition patient has Not attained neck holding at 2 year of age and patient was having intellectual disability and Druling of Saliva. On fine motor pincer grasp not achieved. On CNS examination tone of both upper limb was decreased, deep tendon reflex was brisk and ankle clonus +++. Other skeletal, ear examination was normal. Head Circumference at birth was 36.5 cm, Patient Having no sign of Cranial nerve involvement

All routine investigations (blood) was within normal limit's, chest x-ray was NAD, Usg abdomen was Suggestive of Vesico ureteric reflex.

MRI Brain done, which Suggestive of

1) Abnormal shape of the pons and brainstem with marked hypoplastic and flattened pons. Thickening of the midbrain tectal plate
2) Dysplastic cerebellum with multiple small cysts in the bilateral superior cerebellum. Abnormal bilateral cerebellar folia with polymicrogyria. Hypoplasia of the cerebellarvermis
3) Prominent cisterna magna in the posterior fossa.
4) Mild to moderate dilatation of both the lateral, third and fourth ventricles.
5) Diffuse altered signal in the bilateral cerebral white matter (periventricular, deep and Subcortical white mattermay represent hypomyelination.

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6) Abnormal cortical gyri pattern in the bilateral fronto-parietal region with polymicrogyria / thick cortex.
7) Thinning/dysplastic splenium of corpus callosum. Non-visualization of the septum pellucidum, may representabsent septum pellucidum. These findings most likely represents congenital Muscular Dystrophy.

Whole Genome sequencing Done finding S/O POMGNT1mutation with Compound Heterozygous Variety of Congenital muscular dystrophy-dystroglycanopathy with brain and eye anomalies (type A3) with Congenital muscular dystrophy-dystroglycanopathy with impaired intellectual development (type B3) and Limb-girdle muscular (type C3)

Treatment and prognosis
No curative treatment is available. Management is supportive

3. Discussion

According to Clinical Presentation and Detail History taking and Investigation This Patient was suffering from Heterozygous Variety of congenital muscular Dystroglycanopathy with Prominent symptoms of Type A3 (Muscle Brain Eye Disease).

MEB was first discovered in Finland. In 1978, a patient from Finland showed symptoms including congenital muscular weakness, severe myopia, glaucoma, optical malformation, intellectual disability, retinal hypoplasia, etc.1

MEB is phenotypically similar to the Walker–Warburg syndrome (WWS), both disorders are congenital muscular dystrophy. In 1990, Santavuori argued to distinct MEB from WWS, since MEB is specifically involving muscle weakness and there is a relatively long survival for MEB patients.2

In 2001, the cause of MEB was first demonstrated as the mutations in the POMGNT1 gene, causing loss of its function.3

In Conclusion Muscular hypotonia associated with eye disease (myopia/Glaucoma) with Radiological finding we can suspect muscular Dystrophy. whole genome sequencing is Confirmatory.

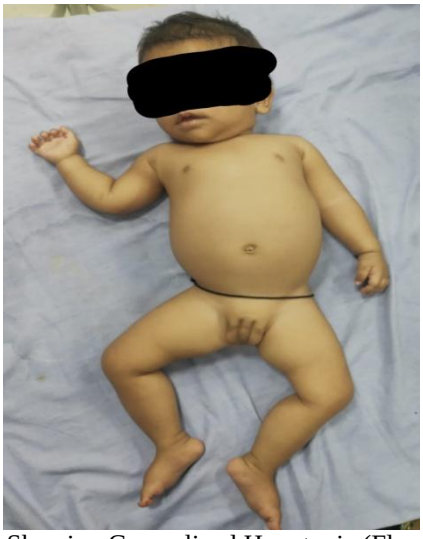

Figure 1: Showing Generalized Hypotonia (Floppy Baby)]

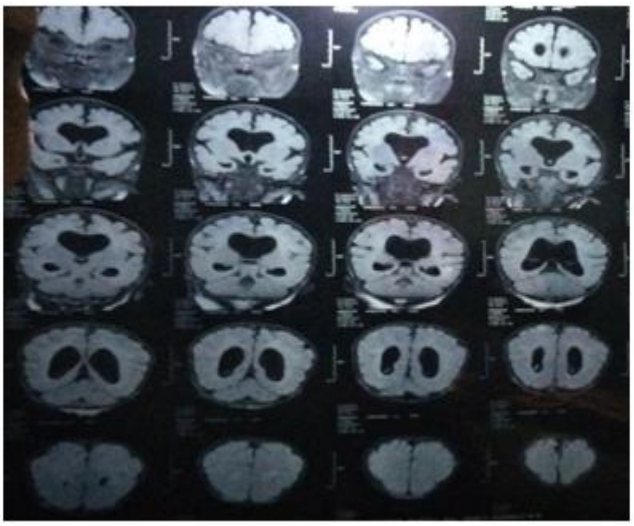

Figure 2: Showing MRI findings s/o Dilated Both [Lateral ventricles]

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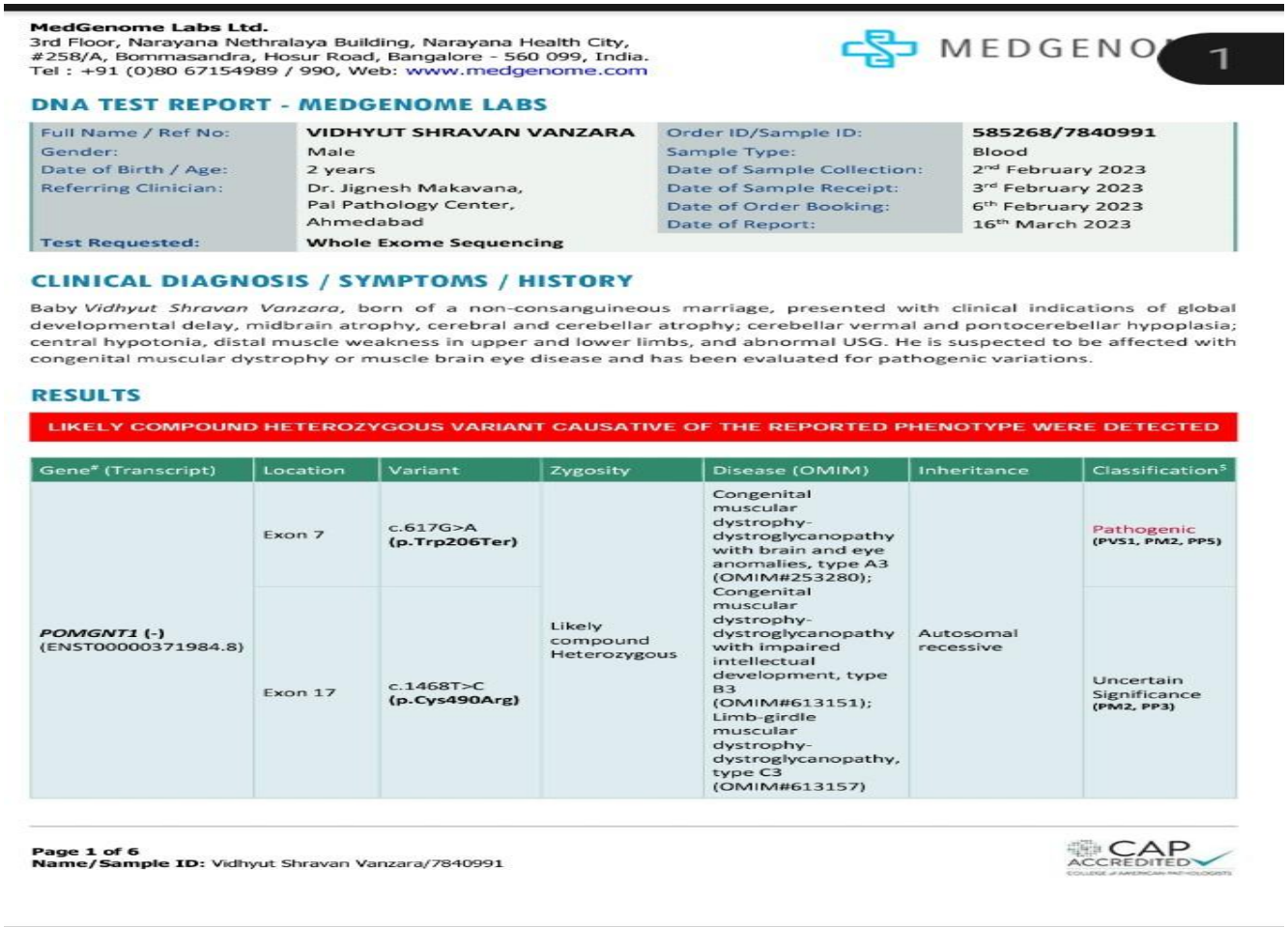

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MEDGENO 1

DNA TEST REPORT - MEDGENOME LABS

Full Name / Ref No:	VIDHYUT SHRAVAN VANZARA	Order ID/Sample ID:	585268/7840991
Gender:	Male	Sample Type:	Blood
Date of Birth / Age:	2 years	Date of Sample Collection:	2nd February 2023
Referring Clinician:	Dr. Jignesh Makavana, Pal Pathology Center, Ahmedabad	Date of Sample Receipt:	3rd February 2023
		Date of Order Booking:	6th February 2023
		Date of Report:	16th March 2023
Test Requested:	Whole Exome Sequencing		

CLINICAL DIAGNOSIS / SYMPTOMS / HISTORY

Baby *Vidhyut Shravan Vanzara*, born of a non-consanguineous marriage, presented with clinical indications of global developmental delay, midbrain atrophy, cerebral and cerebellar atrophy; cerebellar vermal and pontocerebellar hypoplasia; central hypotonia, distal muscle weakness in upper and lower limbs, and abnormal USG. He is suspected to be affected with congenital muscular dystrophy or muscle brain eye disease and has been evaluated for pathogenic variations.

RESULTS

LIKELY COMPOUND HETEROZYGOUS VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WERE DETECTED

Gene# (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification$
POMGNT1 (-) (ENST00000371984.8)	Exon 7	c.617G>A (p.Trp206Ter)	Likely compound Heterozygous	Congenital muscular dystrophy-dystroglycanopathy with brain and eye anomalies, type A3 (OMIM#253280); Congenital muscular dystrophy-dystroglycanopathy with impaired intellectual development, type B3 (OMIM#613151); Limb-girdle muscular dystrophy-dystroglycanopathy, type C3 (OMIM#613157)	Autosomal recessive	Pathogenic (PVS1, PM2, PP5)
	Exon 17	c.1468T>C (p.Cys490Arg)				Uncertain Significance (PM2, PP3)

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Name/Sample ID: Vidhyut Shravan Vanzara/7840991

CAP ACCREDITED

Figure 4: Whole genome sequencing study

References

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