Importance of reviewing previous NGS data and variants reported in genetic reports before making a reproductive decision.

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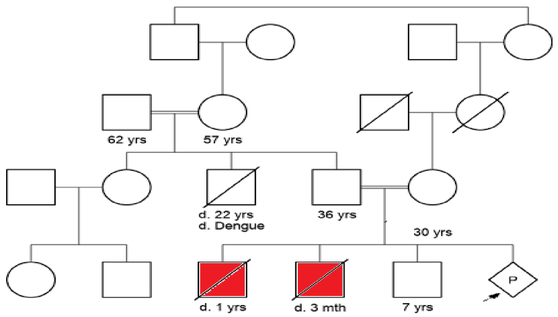
What is known?

- Prenatal testing is advisable upon detection of **phenotypically relevant** pathogenic and likely pathogenic variants in a zygosity which correlates with established inheritance pattern.
- A strong correlation of all phenotypic features with the detected variants is important to identify presence of outlier symptoms, which when present questions the confirmation of diagnosis.
- Variant classification is subject change with variants more commonly being downgraded over time (Xiang J, et al., 2020).
- NIPT is a screening test which is used to identify the risk of common aneuploidies in the fetus.
- This case entails the diagnostic odyssey in a couple who had approached NCGM for NIPT and prenatal testing for galactosemia.

Pedigree



Clinical details of previous children

	Child 1	Child 2
Clinical features	- Bilateral cataract - Feeding difficulties	- Bilateral cataract - Feeding difficulties - Seizures - CT scan was s/o Leukodystrophy

Their diagnostic journey in the third conception

- Couple had contacted a genetic centre (other than NCGM) in their third pregnancy

TRIO GALT Sanger sequencing (2017):

GALT variant	Father	Mother	CVS (3rd pregnancy)
c.940A>G (p.N314D)	✓	✓	✓

➢ **They were informed that child was unaffected:** Child delivered and currently asymptomatic at 7 years

Fourth conception

- **Referred for an NIPT test to NCGM.**
- Upon history taking, they were counseled that NIPT would not detected single gene disorders and dissuaded to pursue the same.
- Variant review:

Benign (Jul 15, 2021)	★☆☆☆ (GeneDx Variant Classification Process June 2021) Method: clinical testing	Not Provided Affected status: yes Allele origin: germline	GeneDx Accession: SCV000238875.12 First in ClinVar: Jul 18, 2015 Last updated: Mar 04, 2023	Comment: Observed on 25366/282804 (9%) alleles including multiple unrelated homozygous individuals in large population cohorts (Lek et al., 2016); This variant is associated with the following ... (more)

Duarte variant: currently classified as well known polymorphism
Did not explain MRI findings
BACK TO SQUARE ONE: The couple were informed that the familial disorder had not yet been ascertained genetically.

Couple carrier screen by NGS performed

Gene: EIF2B2 (NM_014239.4),c.871C>A (p.Pro291Thr)

Type of variant	gnomAD frequency	Computational evidences	Amino acids conserved by	ClinVar	Previously reported	Variant references
Missense variant	Absent	**REVEL score:** 0.8050 **Polyphen**: Possibly damaging **MutationTaster**: Disease causing **CADD Phred**: 23.6000	GERP++ PhyloP	No	No	NA

Previously detected GALT variant was also detected in our analysis. It is a well defined polymorphism which in homozygous state does not cause disease.

EIF2B2 gene: Novel; Another missense reported (c.871C>T; p.Pro291Ser); Absent in gnomad; Damaging by prediction
Classification: Likely Pathogenic
Phenotypic correlation : Cataracts (early-onset), Seizures, Feeding difficulties (early-onset), Impaired intellectual development (mild), Deterioration of motor development.

Prenatal testing

Gene & Transcript	Variant Nomenclature	Zygosity	Classification	OMIM phenotype	Inheritance
EIF2B2 (NM_014239.4)	c.871C>A p.(Pro291Thr)	Heterozygous	Likely pathogenic	Leukoencephalopathy with vanishing white matter 2, with or without ovarian failure	Autosomal recessive

The EIF2B2 (NM_014239.4), c.871C>A p.(Pro291Thr) variant was detected to be heterozygous in the analyzed AF sample, this suggests that the fetus is likely to be a carrier of the variant detected in the parents.
Couple also wanted additional testing for GALT. Should it be performed?
Would love to know your opinion. Hit me up at 9624707253.

Learning points

- Significance of detailed history taking in all cases even when referred for tests like NIPT.
- Re-visiting previously classified variants for changes in variant classification
- Correlating all clinical features of proband to detect outliers leading to the need of further investigations.
- Highlights the level of care required before recommending prenatal testing.
- Biggest challenge in this case: Convincing the couple that GALT was not important as their third child wherein CVS was performed is asymptomatic.
- Testing for the c.871C>A (p.Pro291Thr) variant in EIF2B2 gene in third child has been recommended.

References

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Acknowledgement

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