Use of PGT-M to avoid deafness in the future child through proper genetic counseling.

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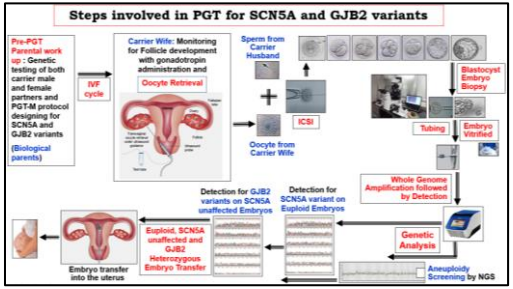
Introduction: Heterozygous variant in the ***SCN5A* gene** on chromosome 3p21 leads to Atrial fibrillation, familial, 10/ Brugada syndrome 1/ Cardiomyopathy, dilated, 1E/ Heart block, nonprogressive or progressive/ Long QT syndrome 3 (autosomal dominant inheritance).
Autosomal recessive deafness-1A (DFNB1A) is caused by homozygous or compound heterozygous variants in the ***GJB2* gene**, which encodes the gap junction protein connexin-26 (CX26), on chromosome 13q12.

Case History: A non-consanguineously married couple approached our IVF clinic with history of 2 miscarriages and 1 IUI failure. The husband also had a history of cardiological issues on the maternal side of his family. He was diagnosed with ventricular bigeminy and has S/P ICD (Medtronic), Arrhythmogenic right ventricular cardiomyopathy (ARVC). Husband's brother had died at 22 years of age due to cardiac issues.
There was no family history of deafness.

Materials and Methods:
Couple karyotype, whole exome sequencing (WES) and FISH test for DiGeorge Syndrome for husband were carried out. Based on WES results, Pre-PGT-M workup was carried out for SCN5A gene variant (cardiomyopathy) in husband and GJB2 gene variants (deafness) found in couple. From 2 IVF-ICSI cycles, 10 blastocyst embryos were biopsied and subjected to preimplantation genetic testing for aneuploidies (PGT-A) followed by PGT-M (monogenic disorder) for SCN5A on 5/10 euploid embryos and GJB2 variants on 4/5 embryos (SCN5A variant absent). The couple underwent 3 frozen embryo transfer (FET) cycles. Pregnancy test done for confirmation.



Results:
- Couple karyotype and husband's FISH for DiGeorge syndrome was normal.
- On WES husband was heterozygous for autosomal dominant (AD) SCN5A pathogenic variant (Exon 6: c.665G>A) and GJB2 autosomal recessive (AR) pathogenic variant (Exon 2: c.71G>A). Wife was heterozygous for GJB2 (AR) variant with uncertain significance (VUS) (Exon 2: c.380G>A).
- On PGT-A 5/10 embryos were euploid.
- After PGT-M, 4/5 embryos were unaffected for SCN5A pathogenic variant.

PGT-M for GJB2: Of 4 SCN5A unaffected embryos, 1 was compound heterozygous. 2 were heterozygous and 1 was normal for GJB2 variants. The lady got pregnant in 3rd attempt using a GJB2 carrier embryo with singleton pregnancy which is ongoing.

Cycle 1

Cycle 2

Sr. No.	Sample ID (Label On Vial)	Result			Interpretation
		Aneuploidy of chromosome 3.			
1	MI-3723-Embryo-1 (MS1)	Chromosome	SOS 3429	Deletion	ABNORMAL

Result Summary (PGS + PGD)

Sample ID	Result (PGS)	Mutation Analysed in SCN5A gene	Result (PGD)	Mutation Analysed in GJB2 gene	Result (PGD)	Combined (PGD + PGS) Interpretation
MI-3973-Embryo-1 (MS1)	Aneuploidy of Chromosome 14.	NA	NA	NA	NA	ABNORMAL
MI-3973-Embryo-2 (MS2)	Cytogenetically normal chromosome complements.	c.665G>A Ex-6	Normal	c.380G>A Ex-2	Normal	CARRIER
				c.71G>A Ex-2	Heterozygous	
MI-3973-Embryo-3 (MS3)	Cytogenetically normal chromosome complements.	c.665G>A Ex-6	Normal	c.380G>A Ex-2	Heterozygous	CARRIER
				c.71G>A Ex-2	Normal	
MI-3973-Embryo-4 (MS4)	Cytogenetically normal chromosome complements.	c.665G>A Ex-6	Normal	c.380G>A Ex-2	Compound Heterozygous	ABNORMAL
				c.71G>A Ex-2		
MI-3973-Embryo-5 (MS5)	Cytogenetically normal chromosome complements.	c.665G>A Ex-6	Heterozygous	c.380G>A Ex-2	NA	ABNORMAL
				c.71G>A Ex-2		
MI-3973-Embryo-6 (MS6)	Aneuploidies of Chromosome 7 and 22.	NA	NA	NA	NA	ABNORMAL
MI-3973-Embryo-7 (MS7)	Aneuploidy of Chromosome 16.	NA	NA	NA	NA	ABNORMAL
MI-3973-Embryo-8 (MS8)	Aneuploidy of Chromosome 4.	NA	NA	NA	NA	ABNORMAL
MI-3973-Embryo-9 (MS9)	Cytogenetically normal chromosome complements.	c.665G>A Ex-6	Normal	c.380G>A Ex-2	Normal	NORMAL
				c.71G>A Ex-2	Normal	

Discussion/ Conclusion:
Couple's WES was advised to check for any other common disorder along with any pathogenic variant for cardiomyopathy. WES showed presence of GJB2 variants (1 pathogenic and 1 VUS) causative of deafness in AR manner. The classification of VUS may change in future to pathogenic hence PGT-M was advised. Without WES of wife and PGT-M for VUS, there was a high risk of having future child with deafness. PGT-A helped to select euploid embryo for successful implantation. This showed the importance of experienced genetic counseling and targeted genetic testing.

Acknowledgment:
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