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Abstract Topic:- Molecular and cytogenetic diagnostics

Abstract Title:- Importance of PGT-M in cases of VUS findings on whole exome sequencing

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Aims:-To offer preimplantation genetic testing for monogenic disorders (PGT-M) where one or both the partners are carriers of variant of unknown significance (VUS) in the same gene.

Methods:- Whole exome sequencing (WES) was carried out to check for presence of autosomal dominant, recessive or X-linked disorders. The pathogenic or VUS variants found were confirmed by Sanger sequencing. PGT for aneuploidy (PGT-A) and PGT-M was offered to the couples carrying pathogenic variations and/or VUS in the same gene through in vitro fertilization (IVF) technology. The euploid unaffected embryo was used for frozen embryo transfer. PGT-M was offered for couples where one of the partners carries VUS in genes like CFTR (cystic fibrosis), GJB2, ADGRV1 (hearing loss), PDE6B (retinitis pigmentosa), RELN (lissencephaly 2 – Norman-Roberts type), multiple variations in HYDIN gene (primary ciliary dyskinesia, 5) where the mode of inheritance was autosomal recessive and the couple had previous history of miscarriages or intrauterine/neonatal death.

Results:- The female partners were pregnant in the first attempt using euploid unaffected embryos for implantation and delivered healthy children free of disorder tested.

Conclusions:- The WES findings are classified as pathogenic, likely pathogenic or variant of unknown significance (VUS) where sufficient data is not available worldwide at the time of reporting, to classify the variant as pathogenic or benign. These VUS may be reclassified in future as pathogenic after the database grows. Preimplantation genetic testing for a monogenic disorder (PGT-M) is generally not offered to the couple if the WES finds a VUS. But if one of the partners is found to be carrier of a pathogenic variation and the other partner has VUS for the same disorder, or both the partners are carriers for VUS in the same gene, we advise carrying out PGT-M in such cases as the outcome of the homozygous or compound heterozygous status of those variants is unknown. It is possible that a future child carrying those variants may be affected. A father carrying ΔF508 variation in CFTR gene may transmit the congenital absence of vas deference (CAVD) condition to his son who also will have azoospermia. After PGT-A and PGT-M, the couples could choose the embryos which were euploid and free of ΔF508 variation in CFTR gene. This shows the importance of PGT-M in cases of VUS findings on WES.

Keywords:- PGT-M, VUS, variant of unknown significance, IVF, CFTR