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Preimplantation Genetic Testing for Monogenic disorder (PGT-M) Case Report

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Preimplantation Genetic Testing for Monogenic Disorders (PGT-M) is an advanced reproductive technology used to test embryos for specific genetic conditions before implantation. This process is designed to help couples at risk of passing on inherited genetic disorders conceive a healthy child. PGT-M allows for the selection of embryos free from the specific genetic mutation, thereby reducing the risk of the child being affected by the disorder.

PGT-M is recommended for couples with a known risk of passing on single-gene disorders. These conditions are typically severe, with significant health impacts. Common conditions tested through PGT-M include: Cystic fibrosis, Huntington's disease, Sickle cell anemia, Thalassemia, Duchenne muscular dystrophy, Hemophilia and can also be applied to rare genetic disorders.

The PGT-M Process includes the following steps

1. **Genetic Counseling**

- **Initial Consultation**: Couples meet with a genetic counselor to discuss their medical history, the genetic disorder in question, and the likelihood of passing it on to their offspring.
- **Risk Assessment**: A thorough risk assessment is performed to understand the genetic makeup of both partners and the probability of the disorder manifesting in their children.

2**. Pre-PGT Workup:**

- Carrier Screening: Both partners undergo genetic testing to confirm their carrier status for the specific disorder. This involves a blood sample to analyze their DNA.
- Informativity analysis for Mutation: Detailed genetic analysis is performed to identify the exact mutation(s) causing the disorder. Informativity testing evaluates for STR markers linked to the gene regions involved by mutation, used to avoid a possible misdiagnosis due to the well-known allele drop-out (ADO) phenomena This step is crucial for designing the embryo testing protocol.

3. Assisted Reproduction cycle with embryo biopsy

- Ovarian Stimulation: The female partner undergoes ovarian stimulation to produce multiple eggs. This process involves hormone injections and close monitoring.
- Egg Retrieval: Mature eggs are retrieved from the ovaries through a minor surgical procedure.

- Fertilization: The retrieved eggs are fertilized with the male partner's sperm in the laboratory to create embryos.

- Embryo Biopsy: A few cells (6-8 cells) are carefully removed from each embryo. This procedure is typically performed on day 5 or 6 of embryo development (blastocyst stage) and does not harm the embryo.

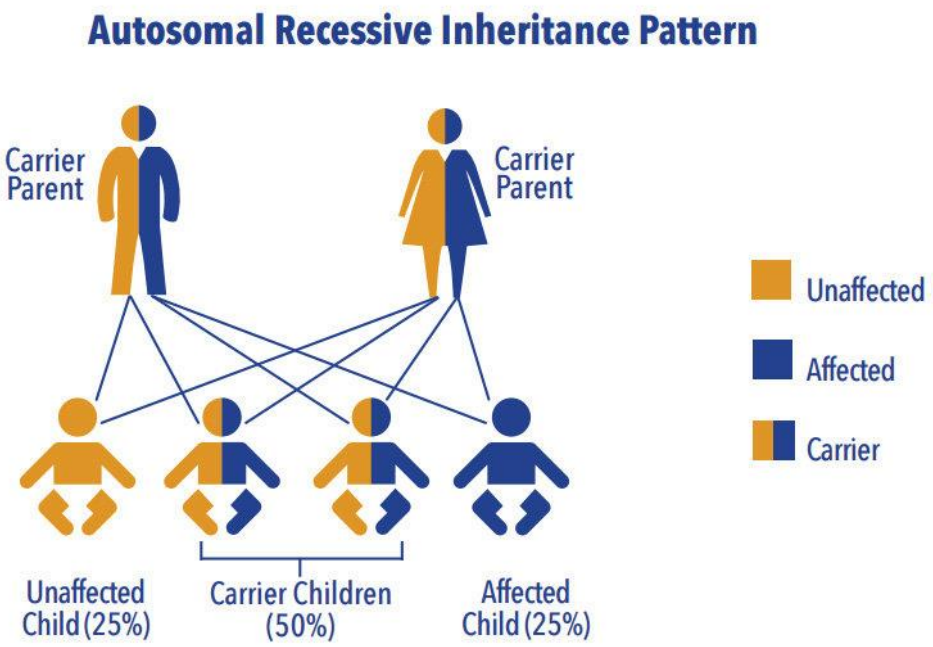
- Genetic Analysis: The biopsied cells are sent to a specialized laboratory where they are tested for the specific genetic mutation. Only embryos free from the mutation are considered for transfer.

Case report:

Mrs. X (33 years) and Mr. Y (40 years) are a non-consanguineous endogamous couple married for 9 years. Their first-born female child presented with nystagmus, difficulty in neck holding, dystonia, sensory issues, spasticity, Global Developmental delay and MRI showed diffuse supra and infratemporal white matter abnormalities suggestive of Pelizaeus-Merzbacher like disease (PMLD). Trio - Whole exome sequencing (done elsewhere) revealed index child harbors a **homozygous likely pathogenic variant**, c.565A>G in *DEGS1* gene causative of **Hypomyelinating leukodystrophy-18 (Autosomal Recessive)** and both partners are heterozygous carriers for the same variant. There was no significant family history. The couple was anxious to understand the recurrence risk and wished to have a healthy child.

Hypomyelinating leukodystrophy-18 (OMIM#618404) is caused by homozygous or compound heterozygous mutations in the *DEGS1* gene (OMIM*615843). It is an autosomal recessive neurologic disorder characterized by onset of global developmental delay usually in early infancy. Affected individuals have very poor psychomotor development, including inability to sit or walk independently in the more severe cases, as well as poor or absent speech, dystonia, and spasticity. A subset of patients may develop seizures. Brain imaging shows hypomyelinating leukodystrophy affecting various brain regions; some patients may also have progressive atrophy of the corpus callosum, thalami, and cerebellum.

For parents who are carriers of an abnormal gene for an autosomal recessive condition there is **25% probability** that the child is born with two abnormal genes hence would be **affected** with the condition.



Therefore, the couple was counseled and choose to undergo IVF using self-gametes and their day 5 trophectoderm biopsies were sent for chromosomal aneuploidy screening by PGT-A and mutation testing in *DEGS1* gene by **Preimplantation Genetic Testing for Monogenic disorder (PGT-M)**. Results:

Embryo	PGT-A status	Mitoscore	PGT-M status (*DEGS1*, c.565A>G)	Interpretation
ADP1	Euploid	0.0022	Homozygous wild type	*DEGS1* mutation is absent
ADP2	Euploid	0.0013	Heterozygous	Carrier for hypomyelinating leukodystrophy-18

Embryo ADP1 embryo was transferred after PGT-M and the couple gave birth to healthy baby.

Conclusion

PGT-M is a powerful tool for couples with a high risk of transmitting genetic disorders. Through a combination of genetic counseling, advanced genetic testing, and IVF, PGT-M offers hope and reassurance to couples striving to build healthy families.

PGT-M Provides valuable information for couples to make informed decisions about their reproductive options. Incorporating PGT-A alongside the PGT-M testing gives higher confidence in embryo selection, reduces risk of miscarriage and improves the chances of a successful pregnancy and the birth of a healthy child.

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If you are considering PGT-M, consulting with a fertility specialist and a genetic counselor is the first step towards understanding and navigating this advanced reproductive technology

Reference: Pant D.C. et al., Loss of the sphingolipid desaturase *DEGS1* causes hypomyelinating leukodystrophy. The Journal of clinical investigation (2019): 1558-8238