Challenging PGT-M Cases Resolved with Whole Genome Sequencing (WGS) Of Embryos

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ASRM 2024
Equity, Access, and Innovation
Denver, Colorado
October 19-23, 2024

PURPOSE & OBJECTIVES

This study presents case examples that showcase the capability of whole genome preimplantation genetic testing (PGT-WGS) to address challenging scenarios in PGT for monogenic conditions (PGT-M) without the necessity of probes.

Two couples sought PGT-WGS after being rejected from other PGT labs due to the complexities of their PGT-M requests. In the first case, the couple discovered that their anonymous egg donor, with whom they had created frozen embryos, screened positive for two conditions: Prothrombin Deficiency (*F2* gene) and Factor V Leiden Deficiency (*F5* gene), which the male partner also tested positive for. Additionally, the egg donor was identified as a carrier for Glucose-6-Phosphate Dehydrogenase (*G6PD*) Deficiency. Although the couple desired to re-biopsy their frozen embryos and test for all three conditions, they did not have access to donor DNA.

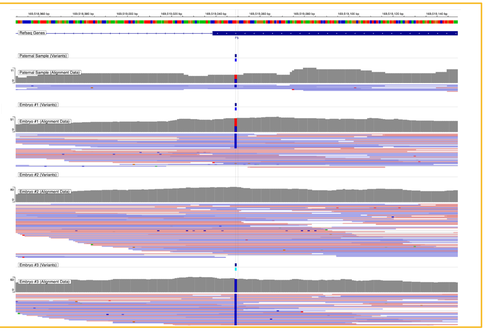
In the second case, the couple aimed to screen embryos for a ~412kb duplication on chromosome 10 associated with split-hand-foot syndrome, as harbored by the affected male partner. Since the duplication had originated de novo in him, the patient lacked informative family members for traditional PGT-M probe development.

Whole genome embryo screening provides a solution for mitigating the risk of monogenic diseases among patients facing challenging scenarios where traditional PGT for monogenic conditions falls short.

RESULTS

Figure 1:

IGV plots demonstrating direct detection of a familial c.1601A>G *F5* Variant. Three embryos sequenced at 30x are shown around the locus associated with the *F5* variant, with the paternal sample show at the top. For each sample, variant calls from the output VCF files are presented alongside read depth and raw read data from the output BAM files.



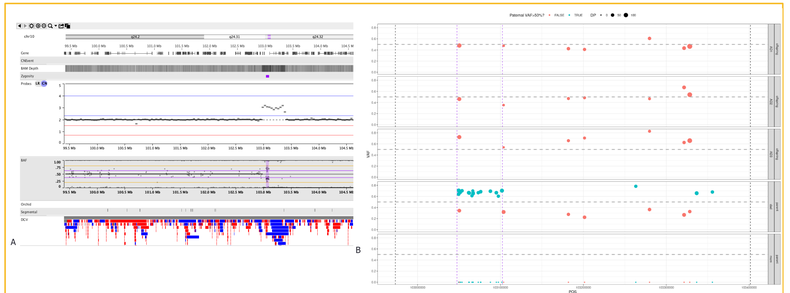


Figure 2: A) Paternal duplication B) Informative paternal SNPs in the duplicated region showing allelic imbalance

MATERIAL & METHODS

Embryos created using donor eggs were biopsied by trained embryologists at their respective In-vitro Fertilization (IVF) centers and sent to Orchid laboratory for testing. Each embryo biopsy underwent whole genome amplification using a lab-developed protocol followed by next-generation sequencing (NGS). Euploid embryos underwent PGT-M for the requested variants, and findings were confirmed via Sanger sequencing. A saliva sample was collected from the male individual carrying the chromosome 10 duplication, underwent NGS, and was analyzed using the PGT workflow to verify the identification.

RESULTS

PGT-WGS was able to successfully call combinations of homozygous, heterozygous, and hemizygous embryos for the *F2*, *G6PD* and *F5* variants (figure 1). This outcome provided the couple with confidence to choose an embryo with the most desirable results for transfer. Similarly, the PGT workflow was used to confirm the chromosome 10 duplication case could be accepted for an upcoming IVF cycle. First, historical biopsy samples were reviewed to ensure that microdeletion/microduplication calls within the region of interest were clean. Next, the duplication was identified in the affected parent and then high-confidence marker SNPs within the duplication region were identified for orthogonal confirmation alongside direct detection (figure 2a and 2b).

CONCLUSIONS

PGT-WGS offered a viable option for PGT-M for two families that faced rejection from other labs due to technical limitations. It serves as an alternative pathway for families encountering challenging PGT-M requests, attributed to a variety of factors including lack of informative familial samples due to use of a gamete donor and/or de novo variants.

CONTACT INFORMATION

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