Diagnosing Monogenic Conditions Through Whole Genome Embryo Screening Without Parental DNA

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PURPOSE & OBJECTIVES

Two clinical case studies demonstrate the capacity of whole genome preimplantation genetic testing (PGT-WGS) in detecting inherited monogenic variants within an embryo, without prior knowledge of the genetic status of the affected parent.

MATERIAL & METHODS

Embryos from two separate couples 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 method followed by a whole genome sequencing on Illumina platform. Euploid embryos received monogenic screening for ~1,300 genes without parental saliva or probe development. Sanger sequencing was performed to confirm positive findings.

RESULTS

In one couple's cycle, an embryo was identified as having a pathogenic genetic variant within the *TTN* gene associated with dilated cardiomyopathy, even in the absence of parental genetic information or any known disease history (see Figure 1 and 1b). Subsequent investigation revealed that the father was indeed known to be affected by the condition and was confirmed to harbor the same genetic mutation.

In the other couple's cycle, 8 embryos were identified as having a pathogenic *GCK* variant associated with maturity-onset diabetes of the young (see Figure 2a). The variant was subsequently confirmed in the maternal saliva, consistent with her family history of atypical diabetes (see Figure 2b).

PGT-WGS successfully identified monogenic disease in embryos with significant clinical implications, without the need for prior information from the IVF center or the use of PGT-M probes.

PGT-WGS emerges as a valuable tool in identifying unsuspected familial risk and preventing the transmission of genetic disorders during IVF cycles.

RESULTS

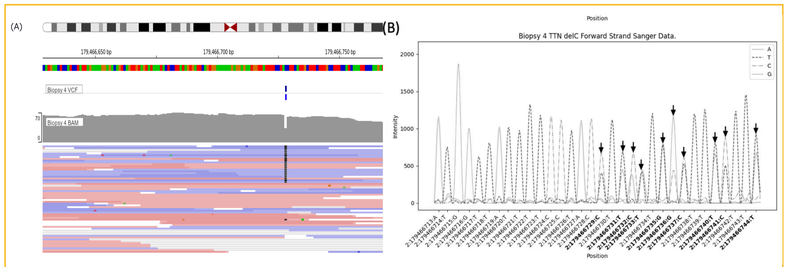


Figure 1A Integrative Genomics Viewer (IGV) plots for embryo biopsy with heterozygous status for *TTN* NM_001267550.2:c.55269+1del.

Figure 1B: Sanger chromatograms confirming the *TTN* variant is present in embryo biopsy #4 as visualized by the peak shift patterning in matching a 1-bp deletion. The x-axis denotes genomic coordinates and the y-axis denotes the intensity of the signal produced by the nucleotide.

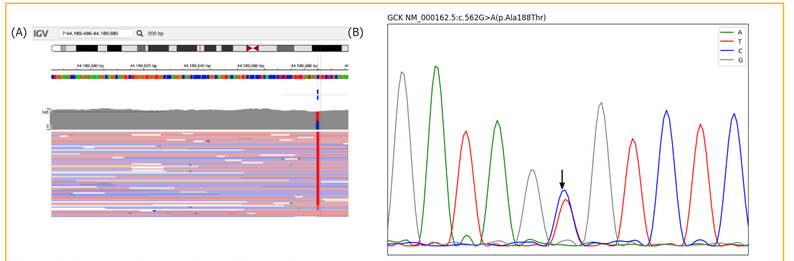


Figure 2A Integrative Genomics Viewer (IGV) plots for embryo biopsy with heterozygous status for *GCK* NM_000162.5:c.562G>A*p.Ala188Thr)
Figure 2B: Sanger chromatogram confirming the GCK variant in the mother

CONCLUSIONS

The findings from these case studies emphasize the capabilities and clinical utility of employing PGT-WGS for detecting mutations beyond the scope of conventional carrier screening. The *TTN* finding in the embryo provided molecular confirmation of a known parental clinical diagnosis. The *GCK* finding provided a family with a monogenic diagnosis for a family history of diabetes - a condition typically attributed to multifactorial inheritance.

In both instances, the genetic basis of the diseases had not been previously disclosed, therefore traditional PGT for monogenic conditions (PGT-M) was not available. PGT-WGS provided these families with the opportunity to prevent the inheritance of genetic diseases in subsequent generations by selecting unaffected embryos for transfer.

CONTACT INFORMATION

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