Clinical Experience Utilizing Single-Nucleotide Polymorphism Data Captured by FAST-SeqS to Reduce the Transfer of Polyploid Embryos

INVITAE

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BACKGROUND

Our FAST-SeqS NGS aneuploidy screening (PGT-A) platform analyzes single-nucleotide polymorphisms (SNPs) in addition to long interspersed nucleotide elements (LINE-1s).

The SNP enhancement permits the detection of all forms of triploidy (e.g., 69,XXX), other forms of polyploidy (e.g., 92,XXXX), haploidy/whole genome uniparental isodisomy (WG-UPiD), and many instances of single-chromosome UPiD, in addition to whole-chromosome and segmental aneuploidy.

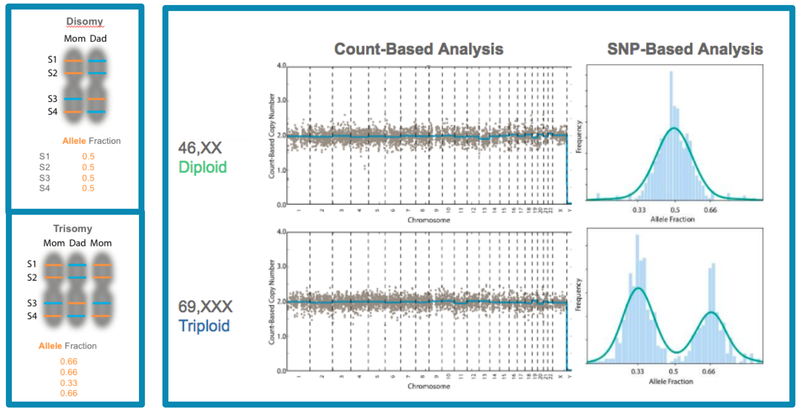
These FAST-SeqS enhancements allow for correct classification of abnormalities potentially misclassified previously, which is essential for decreasing molar pregnancy and miscarriage rates.

Here, we report our clinical experience with polyploidy and UPiD since the addition of SNPs to our PGT-A offering.

OBJECTIVE

To report the prevalence of polyploid and haploid/WG-UPiD embryos as detected by FAST-SeqS.

Figure 1. FAST-SeqS analyzes SNPs to determine ploidy and UPiD



METHODS

Trophectoderm biopsies from >67,000 embryos were analyzed using our refined PGT-A pipeline. FAST-SeqS, an NGS platform, has been validated to detect whole-chromosome and segmental aneuploidies (≥10 MB) and more recently, to analyze data from ~10,000 polymorphic sites to accurately identify WG-UPiD, all forms of triploidy, and many instances of single-chromosome UPiD.[1-3]

For this study, ploidy and UPiD results were stratified by oocyte age, clinical indication, and fertilization type.

RESULTS

Over a 14 month period, 67,847 embryos were analyzed. We identified 1,090 polyploid and haploid/WG-UPiD embryos (1.6%) across all age groups (20-48 years old) and clinical indications. Table 1 shows the ploidy types.

Table 1: Ploidy Types

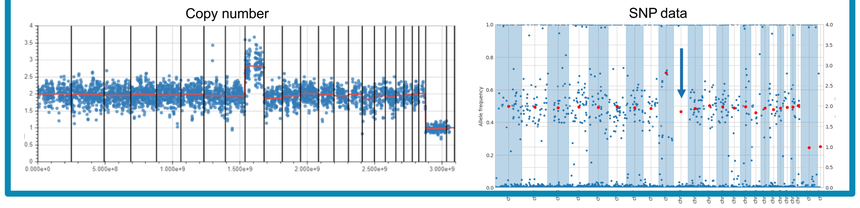
Type	# Detected
Triploidy	805 (74%)
Haploidy/ WG-UPiD	148 (14%)
Tetraploidy	137 (13%)
Total	1,090

Of those cases where fertilization method was indicated, intracytoplasmic sperm injection (ICSI) was performed at a similar rate (90%) in both the polyploid and non-polyploid groups. Additionally, ninety-four patient cycles had more than one polyploid/WG-UPiD embryo, seven of which were egg donor cycles.

RESULTS

In this dataset, 22 single-chromosome UPiD abnormalities were detected involving chromosomes 1,3,4,8,10,11,14,15,16,18 & X, with UPiD 15 being the most frequent (n=6). Figure 2 illustrates an example of whole chromosome UPiD 10 (in addition to trisomy 9).

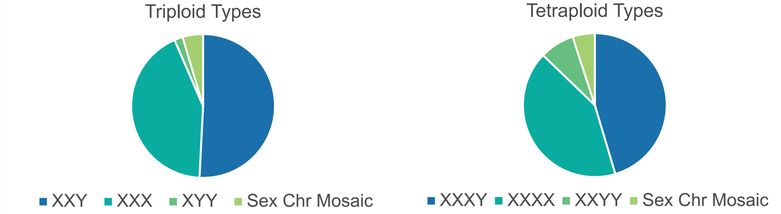
Figure 2: Example of whole chromosome UPiD detected by SNP data



RESULTS

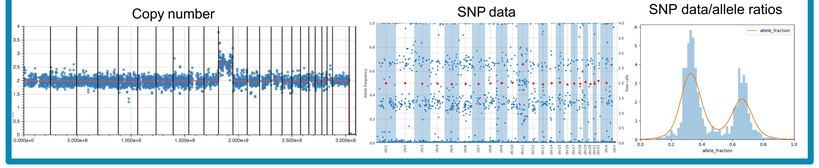
Of 805 triploid embryos, 50.8% were XXY, 42.7% were XXX, 1.9% were XYY, and 4.6% were sex chromosome mosaics. Of the tetraploid embryos, 46% were XXXY, 43.1% were XXXX, 5.8% were XXYY, and 5.1% were sex chromosome mosaics (Figure 3).

Figure 3: Frequency of Polyploid Types



Forty-four percent (482/1,090) of the polyploid embryos had one or more additional copy number abnormality. Without our SNP-based ploidy calls, these additional aneuploidies would have likely been classified as mosaic (Figure 4).[4]

Figure 4: Example of Triploidy with an Additional Copy Number Abnormality



CONCLUSIONS

In 14 months, this SNP enhancement has identified 570 embryos that otherwise may have been incorrectly classified as euploid or mosaic using traditional NGS-based technology. If transferred, those embryos may have resulted in a miscarriage or molar pregnancy.

Preventing transfer of chromosomally abnormal embryos is essential to improving PGT-derived pregnancy outcomes.

Disclosures: All authors are employees and stockholders of Invitae.

References: 1) Gole J *et al. Fertil Steril.* 2016;105(2):e25. 2) Umbarger MA *et al. Fertil Steril.* 2016;106(3): e152. 3) Kosheleva K *et al. Fertil Steril.* 2018;109(3):e54. 4) Marin D. *et al. Curr Opin Obstet Gynecol.* 2017; 29(3):168-174.