Identification of Polyploid Embryos Using a Targeted NGS-Based Preimplantation Genetic Screening Assay

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Background

Polyploid embryos contain more than two sets (n) of chromosomes (e.g. triploid (3n) and tetraploid (4n)) and often lead to miscarriage. Those that survive to term can live no more than a few days. Triploidy accounts for ~1% of all conceptions and ~10% of miscarriages. Tetraploidy is rare.

Types of triploidy include digynic fertilization (2 of 3 sets maternally derived; diploid ovum) or diandric (2 of 3 sets paternally derived; diploid sperm or fertilization by 2 sperms (dispermy)).

Most PGS technologies cannot reliably detect all types of polyploidy, but can detect embryos with unbalanced sex chromosome ratios (69,XXY; 69,XYY; some forms of tetraploidy). Here, we characterize the types of polyploidy we have been able to detect.

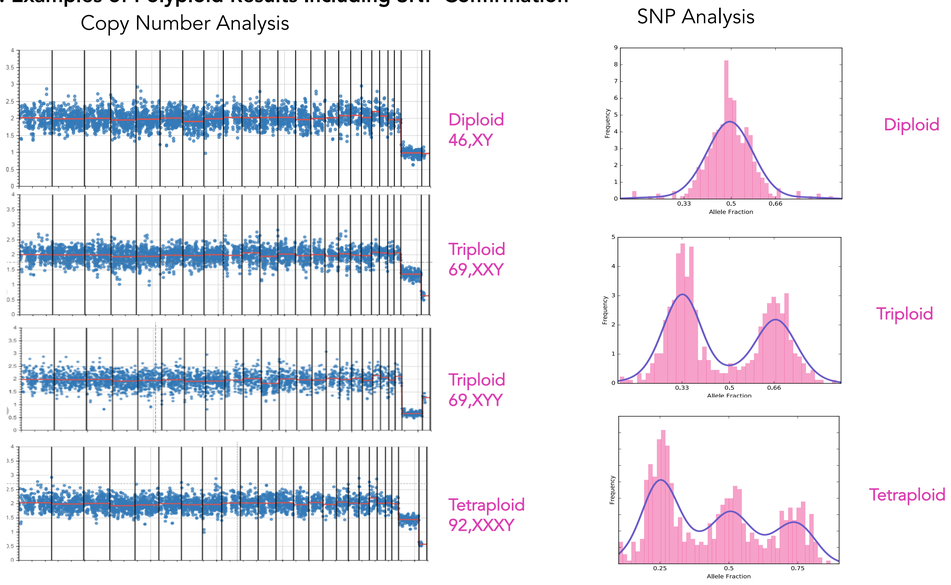
Objective

To report our clinical experience with embryos identified as polyploid via abnormal sex chromosome ratios.

Materials and Methods

Trophectoderm biopsies from >45,000 embryos were analyzed using a targeted NGS-based assay. Utilizing chromosome copy number calls for autosomes and sex chromosomes, we identified embryos expected to be polyploid. Using NGS single nucleotide polymorphism (SNP) information, we confirmed the polyploidy calls and stratified the data by oocyte age, clinical indication, and fertilization type. Figure 1 shows some examples of how we classified likely polyploid embryos via copy number analysis and confirmed them by SNP analysis.

Figure 1. Examples of Polyploid Results Including SNP Confirmation



Results

Using copy number analysis, we identified 318 likely polyploid embryos based on unbalanced sex chromosome ratios; <1% of tested embryos. Likely polyploid embryos were seen in all age groups between 20-45 (ranging from 0.07-1.1% of tested embryos) and does not appear to increase with maternal age (Figure 2). Of interest, nine patient cycles had more than one polyploid embryo, four of which were egg donor cycles. A subset of the likely polyploid embryos were studied using NGS-based SNP analysis and, for embryos with enough informative SNPs, 75% were confirmed as polyploid based on allelic ratios.

Of the 216 confirmed polyploid embryos, the majority were triploid (197) and nineteen were tetraploid. Consistent with previous reports, most triploid embryos were XXY (193). All tetraploids were XXXY (19). About half of all polyploid embryos had another chromosome abnormality (Figure 3). Of the polyploid embryos where fertilization type was known, 85% had undergone ICSI, meaning dispermy can be ruled out.

Figure 2. Age Distribution of Polyploid Embryos

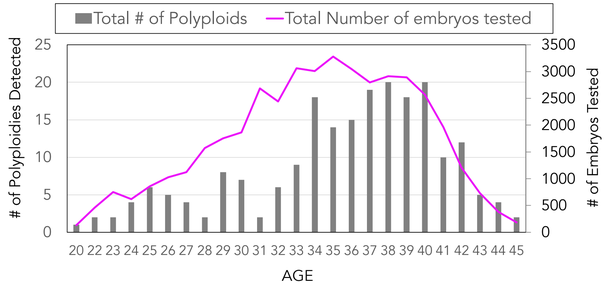
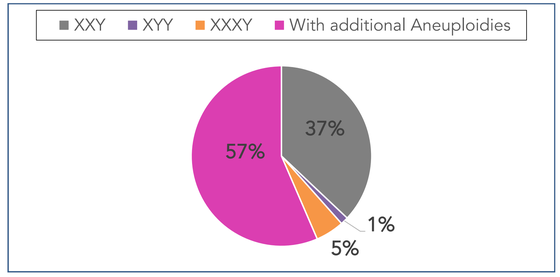


Figure 3. Detected Polyploid Types +/- Other Aneuploidies



Conclusions

Identifying embryos with the greatest chance of implantation and live birth is vital to improve IVF success rates. Detection of polyploid embryos is essential to decreasing miscarriage rates in PGS-derived pregnancies.

In this dataset, the incidence of polyploidy did not correlate with patient age or fertilization type. Given the technical limitations of many PGS assays, some forms of polyploidy routinely go undiagnosed (69,XXX; 92,XXXX; 92,XXYY); however, forms with skewed sex chromosome ratios are likely picked up and correctly diagnosed as aneuploid.

Here we use a combination of sex chromosome ratios and targeted NGS-based SNP analysis to confirm the presence of 69,XXY, 69,XYY and 92,XXXY in a subset of samples. This technology has recently been validated to detect other types of currently undetectable polyploidy (ASRM 2017 Poster #426), increasing the accuracy of NGS-based PGS.

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