39, 326 between 40-42 and 192 were ≥43. For the untested group, 434 patients were <35, 182 between 35-37, 79 between 38-39, 92 between 40-42 and 64 were ≥43. Chi-square test was applied for categorical group comparisons. PGT-A was done by NGS ReproSeq on Ion Torrent S5 (ThermoFisher) following trophectoderm biopsy.

RESULTS: In the <35 age group, ongoing pregnancy rates (OPRs) per transfer were 58.8% and 36.8% in the tested and untested group, respectively (p= 0.0672). In the 35-37 age group, OPRs were 64% and 32.9% (p= 0.0026); in the 38-39 age group 36.3% and 13.9% (p= 0.0076); in the 40-42 age group 57.1% and 6.5% (p<0.0001), in the ≥43 age group 80% and 5% (p <0.0001), with and without PGT-A, respectively.

In the group without PGT-A, under 35 years of age, OPRs per initiated cycle were found to be higher than the group with PGT-A (20.6% vs. 11%; p<0.0001), showing that the underlying cause for infertility may not be directly related with aneuploidy but other clinical factors may be in play. For the 35-37 age group, OPRs per initiated cycle were 15.6% and 17.2% (p=0.0058), for the 38-39 age group 4.3% and 6.5% (p=0.0502), for the 40-42 age group 1.6% and 5% (p=0.5409) and for the ≥43 age group 1.1% and 2% (p=0.2695), in the untested and tested groups, respectively.

CONCLUSIONS: Above 35 years of age, OPRs per embryo transfer and per initiated cycle are higher in the PGT-A group when compared to the untested group. Therefore, PGT-A is a good option for women who are above 35 years of age and have low number of blastocysts.

SUPPORT: No financial support needed for the study.

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PGT-A INCIDENTAL FINDING: RECURRENT MOSAIC SEGMENTAL ANEUPLOIDY INDICATIVE OF BENIGN FAMILIAL VARIANT.

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OBJECTIVE: To describe the first known cases of recurring mosaic segmental aneuploidy (RMSA) identified through PGT-A and present the results of subsequent genetic testing.

DESIGN: Case report.

MATERIALS AND METHODS: At a single clinic, results of 396 PGT-A cases were reviewed from February 2019 to December 2019 for RMSA. RMSA was defined as 3 or more embryos with the same mosaic deletion or duplication with the same breakpoints.

RESULTS: Two cases were identified.

Case 1: A G0, 37-year-old female with a history of primary infertility and male factor (oligospermia) underwent IVF with PGT-A. PGT-A results identified 3 out of 14 embryos with a mosaic dup(22)(pter-q12.1).

Case 2: A G0, 34-year-old female with a history of primary infertility and male factor (oligospermia). The family history was suggestive of a chromosomal translocation and parental karyotype results were consistent with 45,XX,der(13;14)(q10;q10) and 46,XY. IVF with PGT-SR was recommended. PGT-A results from the first cycle were abnormal and identified 2 out of 4 embryos with a mosaic dup(12)(q24.32-qter). PGT-A results from the second cycle identified 2 out of 2 embryos with the same mosaic duplication.

These results can suggest an underlying parental translocation, so all parents underwent karyotype analysis. Results of all karyotypes were normal except for the patient previously identified with a robertsonian translocation.

In our second case, parental fluorescence in situ hybridization (FISH) for the distal 12q arm and SNP microarray were performed. Results of both tests were normal. However, the lab commented that the female patient had a 1.7Mb interstitial triplication of 12q24.32 in all cells. The triplication did not contain any genes of clinical significance.

CONCLUSIONS: To our knowledge, these are the first descriptions of RMSA identified through PGT-A. By definition, mosaic abnormalities occur at random, yet we identified two cases of recurring mosaic duplications that were suggestive of dominant inheritance.

In our first case we did not identify an inheritable cause. In the second, a parent was found to carry a benign 12q24.32 triplication in all cells that explained the recurring finding in her embryos. A 1.7Mb interstitial triplication is below the resolution of NGS which may explain why the embryos were classified as mosaic and highlights the limitations of NGS.

RMSA may be indicative of a uniform copy number variation (CNV) in a parent and follow up testing should be considered to determine the clinical significance and true breakpoints. Embryos reported with benign CNV can be suitable for transfer and may help couples undergoing IVF pursue less treatment.

Although we did not identify an inheritable cause in our first case, it is unlikely that the recurrent mosaic duplication occurred by chance alone. One hypothesis is that these findings may be suggestive of an inherited benign autosomal fragile site. 22q12.2 is a known common fragile site (FRA22B).

As clinics continue to consider mosaic embryo transfer, it will be important to investigate the clinical significance of RMSA and this may warrant additional parental follow up testing.

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GENOMICS ANALYSIS OF MATERNAL EXOMES REVEALS NEW CANDIDATE GENES AND PATHWAYS FOR THE DIAGNOSIS AND PREDICTION OF RECURRENT PREIMPLANTATION EMBRYO ARREST IN IVF CYCLES.

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OBJECTIVE: The aim of our study was to discover whether genomic analysis of maternal exomes is capable of identifying new target genes to improve infertility diagnosis in cases with recurrent preimplantation developmental embryo arrest.

DESIGN: Genetic analysis.

MATERIALS AND METHODS: The study was conducted at Istanbul Memorial Hospital ART and Reproductive Genetics Unit between December 2018-November 2019 in cooperation with Igenomix, Italy. Ten women, five with consanguinity history, four being the offspring of first-cousin marriage with a history of recurrent embryo developmental failure in multiple IVF cycles were recruited. WES was performed *(Agilent SureSelect whole-exome capture and Illumina sequencing technology).* Variant calling against the reference genome GRCh38 was done using Freebayes and identified on average 436k high quality variants per samples. According to Ensembl classification 2.8% are expected to have high (0.25%) or moderate (2.56%) disruptive impact in the gene product. Variants were filtered on a per-individual base using a number of criteria (frequency <0.05% in the 1000 Genomes and gnomeAD; severity as estimated by Ensembl; the functional effect using the CADD score above the 90 percentile and variants location in genes highly intolerant to loss of function, pLI>0.9. Finally variants retained had to be in genes relevant to the early embryonic development (3600 gene list). To control for false positives, we run the same filtering on 100 replicates of 10 random samples from the publicly available Human Genome Diversity Project data set, and we filtered out variants falling in genes showing up in 50% of the hundred replicates, controlling for random occurrence of hits.

RESULTS: Overall, 1700 unique variants in 1281 unique genes were retained after filtering, most involved in lethal embryonic pathways. Thirty-one unique retained variants have high impact and among them sixteen are splice variants and nine are stop-gains. Each sample carries on average 185.9 (10.0 s.d.) potentially detrimental variants. Of particular relevance two individuals had pathogenic variants in SPAG5, an essential component of the mitotic spindle required for normal chromosome segregation and progression into anaphase. Furthermore, two individual showed pathogenetic variants in the zinc finger protein 91 (ZFP91). The knockdown of ZFP91 reduces FOXA1 polyubiquitination and cellular progression in embryonic and cancer cells. Finally, three samples share the G allele of the rs1217009744 variants in homozygosis in the *SHANK3* gene.

CONCLUSIONS: Exome analysis of women with recurrent embryo arrest successfully identifies genomic variants lethal at the embryonic stage, thus providing a diagnostic tool. However, functional genomics studies and validation in an independent cohort of patients with preimplantation embryo arrest phenotype and of different ethnicity is required to corroborate these findings. The generation of polygenic models will also further contribute to increasing discovery rate and to the development of more general and powerful predictive models for this phenotype.

SUPPORT: None