P-554 Reproductive risks and preimplantation genetic testing intervention for X-autosome translocation carriers

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Study question: For X-autosome translocation [t(X-A)] carriers, is it a more applicable preimplantation genetic testing (PGT) strategy, that distinguishing non-carrier from euploid/ balanced embryos and prioritized transfer?
Summary answer: Noncarrier and carrier embryos discrimination in PGT is an applicable strategy to avoid transferring genetic and reproductive risks to the offspring of t(X-A) carriers.
What is known already: Balanced t(X-A) is a specific reciprocal translocation, with a higher risk of detrimental phenotype and fertility issues compared to individuals with autosomal translocation. Alternative X-chromosome inactivation (XCI) is a specific pathogenic mechanism in this population. For carrier offspring of couples with t(X-A), the genetic counseling is challenged in both the prenatal and postpartum stages, because of the complexity and severity of phenotype outcomes that are unpredictable and associated with the complex XCI mechanism. Therefore, caution is necessary when designing a PGT strategy for couples with t(X-A).
Study design, size, duration: A retrospective study. We collected a 3-year-old girl with maternal translocation 46,X,t(X;1)(q28;p31.1) presenting with multiple congenital disabilities. Three couples with female t(X-A) carrier requesting for PGT.
Participants/materials, setting, methods: Karyotype analysis, whole-exome sequencing (WES), and X inactivation analysis were performed for the girl with congenital cardiac anomaly, language defect, and mild neurodevelopmental delay. PGT based on next-generation sequencing following the microdissecting junction region to distinguish noncarrier and carrier embryos were used in three couples with female t(X-A) carrier (Cases 1-3).
Main results and the role of chance: The girl carried a maternal balanced translocation 46,X,t(X;1)(q28;p31.1). WES revealed none monogenic mutation related to her phenotype, but she carried a rare skewed inactivation of the translocation X chromosome and spread to the adjacent interstitial 1p segment, contrary to her mother. All translocation breakpoints of Cases 1-3 were successfully identified and each couple underwent one PGT cycle. Thirty oocytes were retrieved, and 13 blastocysts were eligible for biopsy, of which 6 (46.15%) embryos were balanced and only 4 were noncarriers. Three frozen embryo transfers with noncarrier embryos resulted in the birth of two healthy children (one girl and one boy), who were subsequently confirmed to have normal karyotypes. We reported a girl with multiple congenital disabilities resulting from maternally balanced t(X-A) and validated that noncarrier and carrier embryo discrimination is an effective and applicable strategy for avoiding transferring genetic and reproductive risks to the offspring from t(X-A) carriers.
Limitations, reasons for caution: Here, we reported a girl with multiple congenital disabilities resulting from maternally balanced t(X-A) found different XCI patterns, while we did not further determine the mechanism causing the different XCI patterns between the girl and her mother.
Wider implications of the findings: We demonstrated passing on a balanced t(X-A) may result in clinical manifestations associated with the X-inactivation, and verified the PGT strategy, that distinguishing normal and carrier embryos in can widely applied in t(X-A) carrier couples to avoid the genetic and reproductive risk of transferring t(X-A) to the next generation.
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