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One suggestion of the method to prevent a misdiagnosis of PGT-M

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Introduction

Guidelines for preimplantation genetic testing (PGT-M) to detect single gene disorders that were developed by the Japan Society of Obstetrics and Gynecology (JSOG) recommend a combination of direct and indirect methods for diagnosis using biopsy specimens. We have analyzed for the presence of pathogenic variants as a direct method and for the presence of informative short tandem repeats (STRs) closely associated with pathogenic variants as an indirect method. We present here a case in which the results of the direct and indirect methods did not agree at the time of the initial testing, and the results of the direct method in the retest differed from the initial results.

Material & methods

The couple in this case had two children, both of whom were diagnosed with Zellweger spectrum disorder (ZSD), a disorder in which brain malformations were noted from prenatal period and died after the first year of life. Genetic testing revealed that ZSD was caused by a dual pathogenic mutation of PEX1 c.2633T>C and c.2T>G, and that each of the couple was a carrier of one of the PEX1 pathogenic mutations. After genetic counseling, the couple requested PGT-M application based on JSOG implementation guidelines. Four oocyte retrievals and IVF resulted in the development of 4 blastocysts, and biopsies of these were performed.

Results

Three of the four blastocysts were genetically transferable. In the remaining one, none of the pathogenic variants were detected by the direct method. However, informative STRs associated with pathogenic variants were amplified by the indirect method. Therefore, a second biopsy was performed and analyzed, and this blastocyst was shown to have pathogenic variants by the direct method, and the informative STRs involved in pathogenic variants were amplified again by the indirect method. These findings indicated that the first analysis was a misdiagnosis and that the fourth sample was genetically inapplicable.

Conclusions

No pathogenic variants were detected in the first direct method analysis, but pathogenic variants were detected in the second analysis. On the other hand, both of the two STR marker tests showed alleles with pathogenic variants; it was pointed out that allele drop out (ADO) could lead to false positive diagnosis since the early stage when PGT-M was introduced into clinical practice. Although it is not possible to determine whether ADO caused the discrepancy in the direct method test results from our data, it is highly likely that ADO was the cause of the discrepancy. We believe that the difference between the direct and indirect methods is indicative of the occurrence of ADO; an important measure to detect ADO is to include the detection of closely linked, informative STR markers in the inspection. We believe that finding informative SRTs is an economic burden for couples, but it can help prevent misdiagnosis.