

Issues with genetic carrier screening revealed through couples seeking PGT-M

Yoshiharu Nakaoka, Michiko Ammae, Tatsuya Nakano, Naoya Tsuji, Haruhisa Konishi, Shou Fujiwara, Hiroko Yamauchi, Naoharu Morimoto, Kanako Katsu, Yoshiharu Morimoto

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Introduction: Genetic carrier screening for hereditary diseases (hereafter, carrier screening) is becoming increasingly common in fertility clinics in the United States. These screenings aim to identify individuals carrying recessive genetic conditions, with the specific genes and variants tested varying based on the testing company and associated costs. This paper explores the limitations of carrier screening through the case of a Japanese couple who, despite receiving a negative result from carrier screening in the US, delivered a child with Fukuyama congenital muscular dystrophy.

Case Presentation: A 36-year-old woman and her 37-year-old husband, with a reproductive history of Gravida 1, Para 1 and no significant medical background, underwent carrier screening in the US using the Horizon 274 panel by Natera, which revealed no genetic abnormalities. Subsequent non-invasive prenatal testing (NIPT) also showed no anomalies. However, their male infant, born at 36 weeks weighing 2865g, displayed reduced suckling and muscle strength. After an initial lack of diagnosis in the US, the child was diagnosed with Fukuyama congenital muscular dystrophy in Japan, characterized by homozygous retrotransposon insertion mutations in the FKTN gene. While the wife cared for their child undergoing therapy in Japan, they sought PGT-M (preimplantation genetic testing for monogenic disorders). Genetic testing revealed both parents to be heterozygous carriers of the FKTN gene mutation. Following approval from the Japan Society of Obstetrics and Gynecology, the couple's PGT-M treatment led to a successful and ongoing pregnancy.

Conclusions: This case highlights the potential shortcomings in comprehensive genetic counseling in the US regarding the limitations and accuracy of hereditary disease tests offered during carrier screening at fertility clinics. Notably, the utilized panel did not include the FKTN gene, a common

genetic anomaly in the Japanese population. Future genetic screening practices in Japan must prioritize thorough counseling on the scope and implications of offered tests, particularly regarding the identification of pathogenic variants associated with genetic disorders. Additionally, considering the restrictions on freely performing PGT-M in Japan, open and informed discussions on pregnancy management for couples carrying such variants become crucial.