An attractive alternative to prenatal diagnosis: a case report of preimplantation genetic testing in familial cardiomyopathy

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Familial hypertrophic cardiomyopathy is an autosomal dominant familial inherited heart disease caused by mutations in the sarcomere protein that affects nearly 1 in 500 people. Genetic testing is of immense importance for familial inherited diseases. This study aimed to determine a way to allow couples with either partner or both partners with familial disease to achieve a healthy biological child. Preimplantation genetic testing for monogenic disorders of the embryos is a new technique that identifies the causative mutation in the genome of family members. The embryo trophectoderm is biopsied at the blastocyst stage of development. Subsequently, embryos are made via in vitro fertilization, and 6 to 8 cells are biopsied from the trophectoderm of the day 5 blastocyst. A couple in their early 20s consulted the hospital for preconceptional counseling for a second child. Their first child was a girl who had a heterozygous variant of chr7:128844078C>T; (HET); c.3004C>T; p.Arg1002Trp on Exon 20 with a gene transcript of filamin C (+) ENST00000 325888.13. Preconceptional pretest genetic counseling of the couple regarding the genetic aspects of the severity of the mutation and its inheritance was conducted. A heterozygous missense variation was present in the asymptomatic father, whereas the mother was normal. Posttest genetic counseling was conducted using a multidisciplinary approach, and the parents were informed about the clinical implications and the possibility of risk of transmission. Preimplantation genetic testing for monogenic disorders was performed, and 6 of 10 embryos were abnormal. A frozen-thawed embryo transfer was performed that resulted in a singleton pregnancy and the term delivery of a healthy male child. Genetic testing of embryos assists clinicians in managing couples at risk of transmission of serious genetic disorders. For couples with familial disease in either partner, medically assisted reproduction with preimplantation genetic testing for monogenic disorders is a promising strategy to achieve a healthy biological child.

Key words: familial hypertrophic cardiomyopathy, preimplantation genetic testing, familial disorders, healthy child, preimplantation genetic testing for monogenic disorders

Introduction

Familial hypertrophic cardiomyopathy (FHC) is an autosomal dominant inherited heart disease that affects nearly 1 in 500 people.[1] It has a variable onset and progression, and sudden death occurs in 1% to 2% of the cases.[2]

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No ethical approval was required as the study was retrospective and noninterventional.

Written informed consent was obtained from the patient for participation and publication of this case report.

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The diagnosis is usually incidental or after sudden cardiac death of a family member. The disease goes unnoticed as most individuals are asymptomatic.[2] However, the presenting symptoms include chest pain, breathlessness, impaired consciousness, and unexpected sudden death.[3] The diagnosis can be established clinically using electrocardiogram and echocardiogram[4] or histopathologically by the presence of sarcomere disorganization, myocyte disarray, and fibrosis.

Genetic testing is of immense importance for familial inherited diseases. A series of studies in the 1980s and 1990s showed the genetic basis of hypertrophic cardiomyopathy[5] to be autosomal dominant mutations in sarcomere proteins. To date, more than 450 mutations have been identified in 20 genes.[6]

Preimplantation genetic testing (PGT) of the embryo is a new technique that was first performed in the United Kingdom in the early 1990s.[7] The causative variant mutation in the genome of the family members is identified. Embryos are biopsied from the trophectoderm at the blastocyst stage (day 5 or 6). The advantage of this approach is the presence of an intact inner cell mass from which the baby develops.[8]

There are 3 main types of PGT: preimplantation genetic testing for aneuploidy (PGT-A), which screens for aneuploidy; preimplantation genetic testing for monogenic disorders (PGT-M), which determines whether the embryo carries any genetic abnormality in a specific inherited gene; and preimplantation genetic testing for structural rearrangements (PGT-SR), which precisely screens for structural rearrangement of the chromosomes.

Case

A nonconsanguineous couple in their early 20s consulted the hospital for preconceptional counseling to plan for their second child. The mother was a gravida 1 para 1 who had regular menstrual cycles at an interval of 28 to

30 days with 5 days of bleeding that required 2 pads per day but without pain. Neither parent had a significant medical history.

First pregnancy

The mother was a 23-year-old primigravida who naturally conceived and underwent all recommended antenatal tests. Morphologic imaging in the first trimester of pregnancy revealed normal nuchal translucency and visible nasal bone. Screening indicated a low risk of chromosomal aneuploidies (13, 18, and 21). There was no exposure to any harmful factors that would justify placing the pregnancy in the high-risk category.

However, an anomaly scan at 22 weeks of gestation revealed a ventricular septum defect (VSD) in the baby. The parents decided to proceed with the pregnancy, which was assumed to be a sporadic change that was correctable after birth. The growth scan performed at 33 weeks of gestation showed a decreased growth of the head corresponding to the gestational age, which was suggestive of microcephaly.

At 38 weeks of gestation after spontaneous labor for 18 hours, a live female child weighing 2.34 kg was delivered. The delivery was uncomplicated, and the mother made a rapid postpartum recovery.

The neonate had impaired breathing and swallowing capacity. The neonate was unable to sustain spontaneous breathing, and assisted mechanical ventilation was constantly needed.

Initial diagnosis of the first newborn

Based on the clinical signs and investigations, it was established that the neonate had microcephaly, cleft palate, VSD with congestive cardiac failure, and viral pneumonia. The pediatrician conducted several tests, such as toxoplasmosis, rubella cytomegalovirus, herpes simplex, and HIV screening test; neonatal metabolic panel (normal thyroid stimulating hormone levels and normal metabolic markers); echocardiography (confirming hypertrophic cardiomyopathy and ruling out myocarditis-induced dysfunction); magnetic resonance imaging of the brain (checking for structural malformations); and neonatal screening test (evaluating for metabolic/endocrine disorders), to rule out nongenetic causes. A genetic cause was suspected. The neonate had a normal karyotype of 46XX, and whole-exome sequencing was performed.

The process involved selective capture and sequencing of the protein-coding regions of the genomes. DNA was used for targeted gene capture via exome capture. The identification of variants in the samples was performed using Sentieon (version 201808.07, Sentieon Inc, San Jose, CA). The sequences obtained were aligned to the human reference genome (GRCh38.p13) using a Sentieon aligner and were analyzed using Sentieon for removing duplicates, recalibrations, and realignment of indels (insertion deletion). In addition, the Sentieon haplotype was used to identify variants that were relevant to clinical indications. Gene annotation of the variants was performed using the Variant Effect Predictor program against the Ensembl release 99 human gene model.

The resulting profile showed presence of a heterozygous variant of chr7:128844078C>T; (HET); c.3004C>T; p.Arg1002Trp on Exon 20 with a gene transcript of filamin C (FLNC [+]) ENST00000 325888.13 that was suggestive of Familial Hypertrophic Cardiomyopathy-26/Familial Restrictive Cardiomyopathy-5 that is inherited in an autosomal dominant manner.

Pretest counseling

The couple was informed about the specific type of test, that is, whole-exome sequencing, that will be performed on the DNA sample for testing for the FLNC gene for a specific variation using next-generation sequencing (NGS). The importance of this test was to identify other clinically affected family members, patterns of disease transmission, consanguinity within the family, and history of sudden cardiac death in a relative. After a thorough discussion, written informed consent and blood samples were collected from the parents.

Furthermore, both partners were tested for the FLNC gene on Exon 20 for a variation of chr7:128844078C>T; (HET); c.3004C>T; p.Arg1002Trp using NGS.

A heterozygous missense variation of uncertain significance was detected in a heterozygous condition in the asymptomatic father, but it was not detected in the mother. The variant was confirmed using Sanger sequencing. Specific primers were designed manually according to mutations and were tested using blood samples from the parents. The parents were informed regarding the confirmation of PGT via chorionic villus sampling or amniocentesis.

Posttest counseling

The results of the whole-exome sequencing were conveyed to the couple. A multidisciplinary approach was adopted involving a trained genetic counselor, an in vitro fertilization (IVF) specialist, and a cardiologist to explain the clinical implications and risk of transmission to the next generation. After a detailed discussion, a cumulative decision was reached for the benefit of the patient. The couple decided to proceed with IVF using intracytoplasmic sperm injection (ICSI) with PGT-M for the purported gene of interest to prevent transmission in the next child.

Successful second pregnancy

Using age, weight, antral follicle count, and antimüllerian hormone levels, the antagonist protocol was given using 300 IU of follicle-stimulating hormone (follitropin beta) for 10 days and cetrorelix (gonadotropin-releasing hormone antagonist) for 4 days with a recombinant human chorionic gonadotropin (hCG) trigger. After 12 days, 28 oocytes were retrieved through transvaginal puncture and fertilized using ICSI, resulting in 17 blastocysts (day 5).

In addition, 10 of 17 embryos were biopsied on day 5 (N1−N10) and were submitted for PGT-M and PGT-A analyses. For the PGT-M workup, all 10 biopsy samples were subjected to whole-genome amplification, followed

TABLE
Phenotype and genotype features of the family members

Family member	Phenotype	Genotype
First child is a girl	At 22 wk of gestation: ventricular septum defect At 33 wk of gestation: microcephaly At birth: microcephaly, cleft palate, viral pneumonia, ventricular septal defect, and congestive cardiac failure	Heterozygous variant of chr7:128844078C>T; (HET); c.3004C>T; p.Arg1002Trp on Exon 20 with a gene transcript of FLNC (+) ENST00000 325888.13
Mother	Asymptomatic	Variant not detected
Father	Asymptomatic	Heterozygous variant of chr7:128844078C>T; (HET); c.3004C>T; p.Arg1002Trp on Exon 20 with a gene transcript of FLNC (+) ENST00000 325888.13
First euploid embryo (N2)	Healthy embryo	Variant not detected (wild type)
Second euploid embryo (N4)	Healthy embryo	Variant not detected (wild type)
Second child is a boy	Asymptomatic	Variant not detected

FLNC, filamin C.

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by targeted polymerase chain reaction amplification for the region covering the FLNC variant: chr7:128844078C>T; (HET); c.3004C>T; p.Arg1002Trp.

These samples were processed for bidirectional Sanger sequencing, and the data were further analyzed using the Sequencher software (version 5.4.6; Gene Codes Corporation, Ann Arbor, MI). Of 10 blastocysts (N1−N10). The c.3004C>T variant was not detected in 7 blastocysts (N1−N5, N8, and N10), which were recommended for the transfer. However, 3 blastocysts were carriers of the father's mutation, 2 in the homozygous state (N6 and N7) and 1 in the heterozygous state (N9), and were not recommended for transfer.

Furthermore, all embryos were subjected to PGT-A using NGS, and the genetic information was evaluated to determine the occurrence of chromosomal aneuploidies. Aneuploidy was detected in 5 embryos (N5 and N7 −N10). Hence, 4 healthy embryos (N1 −N4) were recommended for transfer after PGT-M and PGT-A.

A frozen-thawed embryo transfer was performed in the following cycle, transferring the 2 euploid noncarrier blastocysts on day 5 after endometrial preparation with exogenous estrogen. The result was confirmed with beta-hCG being positive, and the viable singleton pregnancy was confirmed via ultrasound at 6 weeks.

Outcome

The pregnancy was uncomplicated. A noninvasive double prenatal test revealed a low risk of aneuploidy. Obstetrical ultrasound showed a normal growth rate and organ development in the baby. At 38 weeks of gestation, delivery via cesarean delivery was performed, and a healthy male child weighing 4.160 kg was born. Upon testing, the variant of interest was not detected in the child.

Discussion

The primary role of the FLNC gene is to maintain the structural integrity of the sarcomere—the structural protein that cross-links actin filaments and anchors sarcolemmal proteins to the cytoskeleton.[9] Mutations in this gene have been related to dilated cardiomyopathy,[9] hypertrophic cardiomyopathy, and other cardiac phenotypes, such as arrhythmias, congenital heart disease, restrictive cardiomyopathy,[10] and noncompaction cardiomyopathies.[11]

FHC is mainly associated with missense variants that result in abnormal protein structures, as described by Gómez et al[12] and Ader et al.[11] It was confirmed through genetic investigations as a likely pathogenic variant with an alteration in the FLNC gene.

As seen in this case, IVF using PGT-M seems to be a strategy that increases the chance of a healthy pregnancy when 1 partner or both partners carry potentially lethal mutation or mutations. In addition to PGT-M, PGT-A has a role in preventing the risk of aneuploidy even in young patients, as highlighted in the case. Oates et al[13] described a case in which the disease was inherited through the mutation in the father's genotype, similar to our case. For a conclusive overview, the phenotype and genotype findings of all family members are presented in the Table.

A combined methodology was suggested by Rees et al[14] with the aim of improving the diagnosis efficiency from 4 distinct perspectives (genetic, biophysical, pathologic, and clinical) and the associated pathogenicity of missense variants. Jarcho et al[15] mapped the FHC to locus D14S26 on chromosome number 14q1, which differed from our case in which it was found on the FNLC gene on chromosome 7.

Conclusion

Genetic testing is an integral part of clinical practice because of its role in both diagnosis and prognosis. Genetic testing assists clinicians in decision-making on management and therapies for high-risk individuals. For couples with familial disease in either partner, IVF with PGT is a promising strategy to achieve a healthy biological child. ■

CRediT authorship contribution statement

Shubhra Pandey: Writing – review & editing, Validation, Supervision, Project administration, Methodology, Conceptualization. **Parth Khandhedia:** Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

REFERENCES

1. Richardson P, McKenna W, Bristow M, et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the definition and classification of cardiomyopathies. Circulation 1996;93:841–2.

2. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. JAMA 2002;287:1308–20.

3. Elliott PM, Gimeno JR, Thaman R, et al. Historical trends in reported survival rates in patients with hypertrophic cardiomyopathy. Heart 2006;92:785–91.

4. Maron BJ, Towbin JA, Thiene G, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation 2006;113:1807–16.

5. Geisterfer-Lowrance AA, Kass S, Tanigawa G, et al. A molecular basis for familial hypertrophic cardiomyopathy: a beta cardiac myosin heavy chain gene missense mutation. Cell 1990;62:999–1006.

6. Keren A, Syrris P, McKenna WJ. Hypertrophic cardiomyopathy: the genetic determinants of clinical disease expression. Nat Clin Pract Cardiovasc Med 2008;5:158–68.

7. Handyside AH, Kontogianni EH, Hardy K, Winston RM. Pregnancies from biopsied human preimplantation embryos sexed by Y-specific DNA amplification. Nature 1990;344:768–70.

8. McArthur SJ, Leigh D, Marshall JT, Gee AJ, De Boer KA, Jansen RP. Blastocyst trophectoderm biopsy and preimplantation genetic diagnosis for familial monogenic disorders and chromosomal translocations. Prenat Diagn 2008;28:434–42.

9. Verdonschot JAJ, Vanhoutte EK, Claes GRF, et al. A mutation update for the FLNC gene in myopathies and cardiomyopathies. Hum Mutat 2020;41:1091–111. https://doi.org/10.1002/humu.24004.

10. Brodehl A, Ferrier RA, Hamilton SJ, et al. Mutations inFLNCare associated with familial restrictive cardiomyopathy. Hum Mutat 2016;37:269–79. https://doi.org/10.1002/humu.22942.

11. Ader F, de Groote P, Réant P, et al. FLNC pathogenic variants in patients with cardiomyopathies: prevalence and genotype-phenotype correlations. Clin Genet 2019;96:317–29. https://doi.org/10.1111/cge.13594.

12. Gómez J, Lorca R, Reguero JR, et al. Screening of the filamin C Gene in a large cohort of hypertrophic cardiomyopathy patients. Circ Cardiovasc Genet 2017;10:e001584. https://doi.org/10.1161/CIRCGENETICS.116.001584.

13. Oates EC, Jones KJ, Donkervoort S, et al. Congenital Titinopathy: comprehensive characterization and pathogenic insights. Ann Neurol 2018;83:1105–24.

14. Rees M, Nikoopour R, Fukuzawa A, et al. Making sense of missense variants in TTN-related congenital myopathies. Acta Neuropathol 2021;141:431–53.

15. Jarcho JA, McKenna W, Pare JAP, et al. Mapping a gene for familial hypertrophic cardiomyopathy to chromosome 14q1. N Engl J Med 1989;321:1372–8.