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SHORT COMMENTARY

Genetic Evaluation of the Parents Following Demise of the Index Case: Report of a Family with Fucosidosis

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Abstract
It is common in obstetric practice to encounter couples who seek prenatal genetic counseling and testing in view of history of known or suspected genetic disorders in the previous offspring or in other family members. Recent advances in genetic testing techniques, especially the availability of the next-generation sequencing (NGS) technology, have greatly facilitated genetic evaluation of the proband and/or the consultand couple and enabled provision of accurate genetic counseling and prenatal genetic testing in such clinical scenarios. However, even in this era of NGS, comprehensive clinical history taking and detailed phenotype characterization through clinical examination and thorough perusal of available medical records, are very important and essential for accurate diagnosis, as reiterated by this report of a 30-year-old third gravida, who was referred for prenatal genetic counseling and testing, in view of history of death of the first offspring due to a suspected neurogenetic disorder. Retrospective clinical diagnosis for the deceased index child with the help of available medical records and reports, followed by relevant NGS-based clinical exome sequencing of the couple, helped to arrive at a definitive diagnosis of fucosidosis, based on which accurate prenatal genetic testing could be done.

Keywords Prenatal genetic counseling · Next-generation sequencing · Exome sequencing · Fucosidosis

Short Commentary

Prenatal genetic diagnosis is currently the most effective strategy for preventing the birth of children affected with debilitating genetic disorders [1]. Establishment of the accurate genetic diagnosis and identification of the exact disease-causing gene mutation(s)/ chromosomal anomaly, are important prerequisites for definitive prenatal genetic testing, to prevent recurrence of a serious genetic disorder present in the previous offspring, in either partner, or in another family member. Prenatal genetic testing done based on a presumed diagnosis, without prior knowledge of the exact disease-causing mutation(s) present in the affected family member and/or carrier partners, is prone to errors of interpretation.

In obstetric practice one often encounters couples seeking prenatal genetic counseling and testing, in view of history of a previous child (or children), affected with known or suspected genetic disorders. In such scenarios, wherever feasible, complete evaluation of the proband or index case should be done first, through detailed clinical examination, relevant laboratory investigations and imaging studies, and confirmatory genetic testing. The gene mutation(s) or chromosomal anomaly identified in the index child should then be tested in the couple to look for their carrier status for the same. This evaluation should preferably be completed prior to the next conception or at least in the first trimester of the next pregnancy. Based on the identified genetic defect, the risk of recurrence can be accurately ascertained and definitive targeted prenatal genetic testing for the same can be offered, for each subsequent pregnancy of the couple. If the index patient is no

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longer alive, available photographs, clinical records, radiographs and neuroimaging films, and other reports should be thoroughly reviewed to narrow down the diagnostic possibilities. Based on this, genetic evaluation of the couple can be done and accurately interpreted, as illustrated by the following example of a couple referred in view of history of neuroregression and death in early childhood, of the first offspring.

This third-degree consanguineous couple was referred for prenatal genetic counseling and testing of the third pregnancy, at 8 weeks of gestation. The first offspring of the couple, a male child, was noted to have global developmental delay since early infancy, developed neuroregression from 2 years and died at the age of 5 years. Unfortunately, the child had succumbed to the illness before the diagnostic evaluation could be completed, and the exact genetic etiology could be established. The second child of the couple, a four years-old girl, was normal. The couple were asked to bring the photographs and all available medical records and reports of the affected deceased child. Mildly coarse facies, microcephaly, and kyphosis of the dorsal spine were noted in the photographs. Mild hepatomegaly, moderate bilateral hearing loss, and spasticity with brisk deep tendon reflexes, were documented in the treating pediatrician's records. Skeletal radiographs showed features suggestive of dysostosis multiplex. Brain MRI images showed diffuse hypomyelination, mild cerebral atrophy, and T2 hyperintensities in the globus pallidus and basal ganglia. Bilateral spike and wave discharges were noted in the electroencephalogram (EEG). Enzyme assays for mucopolysaccharidosis (MPS) types I, II, III B, IV A and IV B and GM1 gangliosidosis were normal. Based on all the available information, a presumptive diagnosis of a rare lysosomal storage disorder, most likely an oligosaccharidosis, was made.

As the deceased index child's blood or DNA sample had not been preserved, clinical exome sequencing was performed in the DNA extracted from the peripheral blood samples of the couple, using the Illumina sequencing platform. The data were analyzed, with the help of standard bioinformatics algorithms, variant databases and in silico prediction software, for pathogenic variants in genes known to be associated with the clinically delineated phenotype. A novel heterozygous pathogenic 3′ splice variant c.1161-1G > C in intron 6 of the *FUCA1* gene (NM_000147) was identified in both partners. Biallelic pathogenic variants in the *FUCA1* gene cause fucosidosis, the clinical features of which are consistent with the phenotype of the deceased child. Fucosidosis is a rare disorder, which belongs to the oligosaccharidosis group of lysosomal storage disorders, with very few mutation-confirmed and/or enzymatically proven patients reported from India till date [2, 3]. The homozygous splice variant identified in this family is a novel, hitherto unreported, pathogenic variant.

The couple were counseled about the autosomal recessive pattern of inheritance of the disease and about the recurrence risk of 25% in each of their offspring. Prenatal testing through amniocentesis was done for the third pregnancy at 16 completed weeks of gestation, fetal DNA was extracted from the amniocytes, and maternal cell contamination was ruled out. Targeted Sanger sequencing for the identified *FUCA1* gene variant was done in the fetal DNA. The fetus was found to be a heterozygous carrier for the *FUCA1* gene variant. Additionally, the couple also opted to get chromosomal microarray analysis (CMA) done in the fetal DNA. CMA done through the Affymetrix CytoScan TM 750 K Array platform (Affymetrix, Thermo Fisher Scientific, USA) was normal and ruled out clinically significant chromosomal anomalies. The couple were reassured that the fetus was not affected with fucosidosis disease, based on which they opted to continue the pregnancy.

Next-generation sequencing (NGS) is the term used for any one of different 'massively parallel' DNA sequencing methodologies. Different customized testing platforms that use NGS technology, such as multigene panels, clinical exome sequencing (CES), whole exome sequencing (WES), and whole genome sequencing (WGS), are now available for clinical use. WES covers the coding portions, i.e., the exonic regions of all the genes in the genome, CES covers the exons of only the genes known to be associated with human genetic disorders, multigene panels include specific sets of genes associated with a particular disease phenotype (e.g., deafness panel, neuromuscular disorder panel, cardiomyopathy panel, etc.), and WGS covers the entire genome. Availability of these NGS-based testing platforms has greatly facilitated molecular genetic testing and accurate identification of the pathogenic gene variant(s) in the index patient and/or carrier parents [4]. However, in spite of the availability of these advanced testing techniques, detailed clinical phenotyping retains its significance as an important step toward accurate diagnosis, because these high-throughput technologies identify large numbers of variants, and phenotypic match is one of the most important parameters taken into consideration when sifting through these variants, to sort and filter out the exact disease-causing variant(s) from the other incidentally detected, thousands of variants. Another important issue related to these tests is their cost. Though the costs have considerably come down in recent years making these tests more accessible, they still remain beyond the reach of patients from the lower socioeconomic strata. Certain modifications in the testing protocols can be made in resource-poor settings to reduce the costs. For example, in a scenario like the family reported here, CES can be performed for one partner first to ascertain the carrier status for a genetic mutation related to the expected autosomal recessive condition, and the other partner's carrier status can thereafter be evaluated through targeted analysis of that mutation or gene only.

Appropriate and effective pretest and post-test genetic counseling are essential to deliver important elements of complex genetic information, to assist couples to understand and assimilate this information, and thereby to help them make informed reproductive choices.

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Compliance with Ethical Standards

Conflict of interest None.

Research Involving Human Participants and/or Animals Clinical case report of human subject.

Informed Consent Signed informed consent form was obtained (attached as Supplementary Material).

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