The Journal of Obstetrics and Gynecology of India (November–December 2022) 72 (S2):S409–S411
https://doi.org/10.1007/s13224-022-01715-x

CASE REPORT

Exome Sequencing, whom to Test? A Case Report of Rare Genetic Findings in Consanguineous Couple with Two Neonatal Deaths

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Received: 9 June 2022 / Accepted: 14 September 2022 / Published online: 29 September 2022

Keywords Consanguinity · Exome sequencing · Genetic counseling · Genetic variations · Karyotype

Introduction

Consanguineous marriage is defined as marriage between two close blood relatives who have at least one common ancestor or second cousins or closer. History suggests that the tradition of consanguineous marriages (CM) is long-standing. In India marriages between 1st cousins are commonly seen. It is reported that in CM the chances of having child with autosomal recessive disorder increase [1]. The problem is seen in child of consanguineous couples who usually have one gene affected in the family and both have the same affected copy of that particular gene. Rarely there could be involvement of more than one gene as well. The availability of advanced genetic techniques has well established that certain deleterious genetic conditions leading to congenital malformation in the offspring have a genetic etiology in CM. These usually are associated with increased mortality in neonates and childhood. The evaluation of the index case and subsequently parental evaluation for carrier status followed by extended genetic counseling is very important, especially for offering the prenatal diagnosis [2]. Additionally, parental testing helps in confirming the mode of inheritance as well as understanding the status of other genes sharing if any which are not seen in the affected fetus but can be present in mutated form in the couple (carrier stage). In this case report we are explaining the association of deleterious effects of consanguinity leading to neonatal mortality. Additionally, this report will help in knowing the importance of parental evaluation for genetic carrier status in CM for genes other than found in neonates and which could have been the independent cause of fetal genetic abnormality in subsequent pregnancies. Which otherwise also had led to psychological, physical trauma and increase expenditure of ART in view of two LSCS. Our study also shows very rare findings of pathogenic variations in four different genes in a couple which all were not present in neonates.

Case

An Indian couple presented with history of consanguinity (maternal uncle's daughter) for genetic counseling in view of previous two neonatal deaths both males with suspicion of some metabolic condition. Both deliveries were preterm around 8.5 months, low birth weight (LBW) and lower segment cesarean section (LSCS) done for heaving bleeding. The first baby died at the age of 6 days with septic shock, severe metabolic acidosis and clinical suspicion of inborn error of metabolism (IEM). No genetic testing was done that time; however, the DNA was stored. After one year and 4 months, she delivered a baby boy, and the baby had neonatal hepatitis, hypoglycemia and again suspicion of some IEM. The baby expired at the age of 1 month; however, this time the exome sequencing (ES) was done. The couple was interested in planning the next pregnancy. Trio ES (couple and the stored DNA from first pregnancy) was carried out in view of consanguinity and previous neonatal losses with reported genetic abnormality [3]. Additionally, couples karyotype was done to rule out chromosomal factor if any as karyotype of both the neonates was not done. Details of the investigation carried out and results are mentioned in Table 1

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Table 1 Investigations performed and results of genetic tests

Sr no	Test conducted	Findings
1	*Chromosomal karyotyping*	
	Mother	Apparently normal
	Father	Apparently normal
2	*Clinical exome*	
	First baby (stored DNA-blood)	DGUOK, CFTR and NPC1 gene variation (homozygous)
	Second baby (blood)	DGUOK, CFTR and NPC1 gene variation (homozygous)
	Mother (blood)	DGUOK,CFTR,NPC1 and BBS12 gene variation (heterozygous)
	Father (blood)	DGUOK,CFTR,NPC1 and BBS12 gene variation (heterozygous)

Results

This study presents a retrospective analysis of a consanguineous family who attended the genetic counseling center at GRC. In view of consanguinity and two neonatal losses couples karyotype was done which was apparently normal. The ES of second baby done was suggestive of likely pathogenic variant. Homozygous missense variation in exon 3 of the *DGUOK* gene (chr2: g,74173942C > T) was reported to be seen in mitochondrial DNA depletion syndrome. Additionally, in-silico predictions and MAF of variants detected *CFTR*, chr7:117,251,692: G > A (ENST00000003084.6) c.3197G > A (p. Arg1066His) and *NPC1*, chr18:21,115,444: T > C (ENST00000269228.5) c.3466A > G (p. Asn1156Asp) probably damaging or damaging variants by using PolyPhen and Mutation Taster software, respectively, were also found. However, there was similar presentation in first baby as well, to confirm and to make it cost-effective trio testing that includes testing of stored DNA of first baby and parental testing by clinical exome. The stored DNA of first baby showed same variations that of second baby, whereas in the parents along with the variation in the two babies additional variations in the form of carrier status for Bardet–Biedl syndrome 12 (BBS 12) were seen in both the partners. The variation found in both the partners for BBS 12 is pathogenic (BBS12, Exon 3, c.1063C > T, p. Arg3555ter, heterozygous) was in heterozygous form and was not seen in both the babies.

Discussion

Here, in our case study we present the importance of doing parental ES additionally instead of doing only duo (two affected babies) ES in CM. In this study we have detected four independent monogenic conditions in a couple. Diagnostic ES is gaining importance as a most comprehensive genetic test available for ruling out genetic factors in malformed babies. It can detect abnormality in 30–50% of patients tested with congenital anomalies. In addition, 4.6–7% of patients can be diagnosed with two independent monogenic conditions. Our study highlights the importance of parental ES (index cases and parents) as additional genetic information was obtained in the form of pathogenic carrier status of parents for BBS 12 which was not detected in both the neonates [3]. Since this pathogenic mutation for BBS 12 was seen in parents although not in the two neonates, the risk of them having the next baby with BBS 12 will be high (50%). If only index case evaluation would have done and not the trio genetic testing or parental genetic testing, an important additional information of BBS 12 would have been missed and the couple next time would have given birth to BBS 12 baby. Preconceptional prenatal genetic counseling is very important in such cases, as if the same would have been done before first or second pregnancy in this case, the couple would not have gone through the financial, physical and psychological trauma. Additionally, the risk was associated in the next pregnancy because of previous two LSCS and costly option of artificial reproductive techniques (ART) the couple would not have gone through.

Conclusion

Genetic counseling plays very crucial role in consanguineous couple. In recurrent pregnancy losses or neonatal deaths, the importance is always given to traditional way of evaluation of the index case or abortus material. However, in families with history of consanguinity trio ES testing have can ravel additional genetic information. Trio ES can provide additional information as compared to traditional way of index case evaluation. Additionally, in couples having two affected babies with the same condition duo ES is currently test of choice. However, along with duo if parental ES is done, additional genetic information can be obtained and same is suggested in consanguinity.

Acknowledgements We acknowledge the encouragement from the Director. We acknowledge all the institutional staff members for their support.

Funding The study was funded by ICMR-NIRRH (institutional support).

Data availability Not applicable.

Code availability Not applicable.

Declarations

Conflict of interest The authors declare there is no conflict of interest.

Ethical approval The study was approved by the Institutional Ethics Committee.

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