CARRIER SCREENING BY EXOME SEQUENCING (NGS) IN HIGH RISK COUPLES FOR PREVENTING CONGENITAL ANOMALIES

Sherrin T Alex[1], Santhi Sarojam[1], Aswathy C G[1], Sankar V H*[1],

[1]Department of Pediatrics, SAT Hospital, Government Medical College and*
[1]Genetic Lab, Child Development Centre, TVPM

INTRODUCTION

Congenital anomalies (CA) also commonly known as birth defects which is a more comprehensive term including both structural and functional abnormalities that occur during intrauterine life. The etiology in most situations is multifactorial where there is an interplay of genetic and environmental factors but it can also be monogenic or chromosomal disorder. Birth defects are a significant cause of mortality and disability among infants and children under five years of age. They can be life-threatening, result in long-term disability, affect families both psychologically and financially, health-care systems and society.

Carrier screening is used to investigate whether a couple has an increased risk of having children with a severe Autosomal Recessive(AR) and X-linked Recessive(XLR) genetic disorder in order to facilitate reproductive decision making. Next generation sequencing (NGS) is a robust technology which simultaneously screen for many different diseases at a faster turnaround time without significantly increasing costs. We are presenting the utility of carrier screening by NGS in high risk couples to prevent congenital anomalies.

AIM

To highlight the importance of doing carrier screening by NGS in high risk couples to prevent congenital anomalies.

MATERIALS AND METHODS

The study is a retrospective data analysis conducted at Genetic Clinic, SAT Hospital & Genetic Lab, Child Development Centre, Government Medical College Campus, Thiruvananthapuram. The period of study was five years from 2017 to 2021. Carrier screening was done in 36 couples by NGS platform and the data were used for clinical diagnosis and genetic counseling. Only selective couples who had history of previous child with congenital anomalies/Family History of any monogenic disorders/ Consanguinity were included (as per our protocol) in the study.

The detailed pre-test genetic counseling was done in all cases where necessity of doing carrier screening as well as sensitivity and limitations of the specific NGS test was explained. Peripheral blood samples (3 ml) were collected in EDTA vaccutainer after getting the written informed consent. The NGS testing was outsourced in standard laboratory in India. Indication for testing and the clinical utility of the test was analyzed. Prenatal testing was also offered for a few cases.

RESULTS & DISCUSSION

The test will be considered significant if both couple carriers a pathogenic/likely pathogenic variant in the same gene causing AR Disease or mother is having a heterozygous pathogenic/likely pathogenic variation in case of XLR disease. Consanguinity increases the

prevalence of rare genetic congenital anomalies and nearly doubles the risk for neonatal and childhood death, intellectual disability, and other anomalies. In our study out of 36 cases, 15 cases (41%) were consanguineous couples.

Of the 36 cases analyzed in this study with NGS results, reports of 22 cases were contributory which included 18cases (50%) of pathogenic mutation and 4 cases (11%) of likely pathogenic mutations. The result was non-contributory in 14 cases which included 11 cases (33%) of variant of unknown significance (VUS) and 3 cases were negative.

Carrier status of the couples were revealed in 16 cases of AR Disorders and in six cases mothers' were found to be carrier for XLR disorder [Hemophilia, X-linked SCID, OTC Deficiency(2 cases), X-linked Chronic Granulomatous Disease, Hydrocephalus Partial agenesis of corpus callosum]. The interesting cases will be illustrated. We were also able to provide prenatal diagnosis in nine cases which includes both AR and XLR Disorders. Prenatal testing by Chorionic Villus Sampling (CVS) revealed 7 fetuses unaffected and 2 fetuses affected.

Overall clinical utility of carrier screening by NGS platform was helpful in diagnosis and genetic counseling in 22 cases out of 36 cases (61%).

CONCLUSION

Carrier screening of couples would not only help them to know their carrier status for diagnosed genetic disorders but also paves the way to know the carrier status and predict recurrent risk in extended family members, especially in cases of XLR disorders as well as AR disorders. In our study we could able to render genetic counseling and prenatal diagnosis to few extended family members. Carrier screening by NGS would aid in reducing the burden of congenital anomalies globally.