Global Approach to Prenatal Testing

Akanchha Kesari[1], Shruti Sureshkumar[2], Rajiv Rose[2], Babi Nallamilli[1], Christin Collins[1], Madhuri Hegde[1].
[1]Revvity Omics, Duluth, GA, USA, [2]Revvity Health Sciences Pvt.Ltd., Chennai, India

BACKGROUND

- Prenatal testing is the best strategy for reducing the burden of genetic disorders and congenital disabilities that cause significant postnatal functional impairment.
- In most countries no nation-wide consensus or protocols are available. Due to the absence of any definite guidelines regarding the appropriate prenatal screening/ testing in the country, the optimum benefits of these screening/ testing protocols are not reaching the population.
- Most of the patients with genetic disorders are not investigated, especially if the underlying genetic condition appears to be untreatable.
- In addition to the lack of availability of affected individuals for molecular diagnosis, other problems like late referrals due to inadequate awareness about prenatal diagnosis amongst the primary care physicians and obstetricians and the psychosocial issues involved in prenatal diagnosis and termination add to the complexities of prenatal diagnosis in India.
- Here we present our experience in a of prenatal testing in a cohort of Indian patients between the period January 2020 to December 2020 and the use of carrier detection prior to offering prenatal diagnosis.

RESULTS

- During one-year period we have tested 63 prenatal samples in our laboratory, of which 71.4% (45 cases) molecular testing was previously performed in our laboratory or externally.
- Of these 45 cases, in about 26.6% (12 fetuses) carrier testing in parents were offered before prenatal testing. Whereas 28.5% (18 fetuses) molecular workup was not previously done, so carrier testing was performed in parents, followed by prenatal testing.
- Our result showed ~20% (12 fetuses) had a homozygous variant, while 55.56% (35 fetuses) had a heterozygous finding, consider to be carrier for the autosomal recessive condition.
- Pathogenic and likely pathogenic variants detected in these cases were identified in a variety of rare genes including (but not limited to) *ATRX, CFTR, GAA, GALNS, GALT, GBA, GLB1, HBB, IDS, IDUA, PKHD1, SGSH* etc.

CASE STUDIES

- **Scenario 1: Proband workup followed by Parental sample testing and PND in future pregnancies**
- Male with molar tooth sign, frontal bossing, nystagmus and clinical suspicion of Joubert Syndrome
- Proband testing via Focused exome sequencing: Homozygous for c.1094dup *AHI1* pathogenic variant
- Parental testing via sanger sequencing: Both parent's carriers for *AHI1* pathogenic variant
- Prenatal testing via sanger sequencing: Homozygous for c.1094dup *AHI1* pathogenic variant

- **Scenario 2: X-Linked with family history**
- Female with developmental delay, patchy pigmentation, facial dysmorphism, oligodactyly and coloboma
- Proband testing via Focused exome sequencing: Heterozygous for c.946+2_946+3del *PORCN* pathogenic variant
- Sibling testing via sanger sequencing: Carrier for the *PORCN* pathogenic variant
- Prenatal testing via sanger sequencing: c.946+2_946+3del pathogenic variant in the *PORCN* gene in the fetus

- **Scenario 3: Affected child not tested; parental carrier testing followed by prenatal testing**
- Female with history of children loss due to suspicion of agenesis of corpus callosum, ventriculomegaly
- Carrier testing in mother via Focused exome sequencing: Heterozygous for c.121C>T p.Arg41Ter *ERCC1* pathogenic variant
- Father's testing via sanger sequencing: Heterozygous for c.121C>T p.Arg41Ter *ERCC1* pathogenic variant
- Prenatal testing via sanger sequencing in Twin pregnancy: Both fetuses were heterozygous for c.121C>T p.Arg41Ter *ERCC1* pathogenic variant

CONCLUSION

- The ideal scenario to offer prenatal diagnosis involves completing the proband workup and subsequent parental testing prior to the testing of the prenatal sample, however this is not always possible due to lack of molecular testing and cost of testing in affected individuals.
- Advancement in sequencing technology and carrier testing options to prospective parents help in reducing the incidence of disease and anxiety.
- Pretest and posttest genetic counseling should be offered to every prospective parent undergoing prenatal diagnosis to help them make informed decisions and navigate through the impact of the results from the prenatal testing.
- Continued genetic education and communications with referring physicians will support in providing better genetics services and which will help to lessen social psychological, financial burden of rare genetic disorders.