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Whole Genome Sequencing: The Way Forward for Molecular Cytogenetics

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Utility of NGS in Prenatally Detected Balanced Chromosomal Rearrangements (Halgren et al., 2018)

Prenatally detected de novo balanced chromosomal rearrangements have been reported to be associated with a 6-9% risk of adverse outcome, but the postnatal long-term morbidity in these antenatally detected cases has not been adequately studied. In this study, Halgren et al. have obtained long term follow-up data, for a mean period of around 17 years, from an existing national registry as well as through clinical follow-up, for 41 individuals who had prenatally detected de novo apparently balanced chromosomal rearrangements (BCRs) but no antenatal ultrasound anomalies (where the pregnancy was continued), and found that as many as 27% of them developed neuropsychiatric or neurodevelopmental disorders. Samples could be obtained from 32 out of these 41 individuals. Chromosomal microarray (CMA) in all these 32 cases was normal. Next generation sequencing (NGS)-based mate-pair sequencing could be done in 29 cases, out of which 21 had intragenic or non-genic disruptions. The findings included disruption of genes (*ARID1B, NPAS3, CELF4*) or regulatory domains of known developmental genes (*ZEB2, HOXC*), or complex BCRs which correlated with the adverse outcomes in these patients. This study demonstrates that NGS outperforms CMA in the characterization of prenatally detected de novo BCRs and can help in more accurate prognostication of these cases. NGS-based mate pair sequencing may soon replace CMA in the evaluation of de novo BCRs, specifically in cases with structurally normal fetuses, where the diagnostic yield of CMA is very low.

Utility of WGS in Copy Number Variation Analysis (Zhou et al., 2018)

Conventionally, sequencing technologies have been stated to be unsuitable for identification of copy number variations (CNVs), and molecular cytogenetic techniques especially chromosomal microarray (CMA) have been recommended for CNV analysis. In their study, Zhou et al. have studied the ability of three Whole Genome Sequencing (WGS) strategies - short insert, 3 kb insert mate pair and 5 kb insert mate pair (each at 1X, 3X and 5X coverages) to detect CNVs. They have investigated how these strategies perform relative to each other and also compared their yield to 17 currently used high-density oligonucleotide arrays. A set of gold standard CNVs generated for the 1000 Genomes Project (CEU subject NA12878) was used as the benchmark. WGS strategies with even low coverage were found to be able to detect significantly more CNVs and gold standard CNVs with validation, when compared to the high-density oligonucleotide array platforms. Thus, WGS appears to be having a higher sensitivity than even the best performing arrays, in detecting CNVs, with a lower percentage of unvalidated CNV calls.

WGS–based NIPT for Prenatal Cytogenetic Analysis (Van Opstal et al., 2018)

A new study from Netherlands by Van Opstal et al. has reported the yield of Whole Genome Sequencing (WGS)- based non-invasive prenatal testing (NIPT) for the detection of chromosomal aberrations other than common chromosomal aneuploidies, among participants of the TRIDENT study (Trial by Dutch laboratories for Evaluation of

Non-invasive prenatal Testing). Out of the 2527 cases where whole-genome shallow massively parallel shotgun sequencing was performed in the cell-free DNA derived from the maternal blood sample, in 78, one of the common trisomies was reported (trisomy 21/13/18) and in 41 (1.6%), some other chromosomal aberration was found. Further cytogenetic evaluation of the chorionic villi/ amniotic fluid/ fetal blood/ fetal skin/ placental samples revealed that out of these 41 chromosomal aberrations detected through NIPT, 10 were fetal, 22 were placental and 1 was a maternal CNV; in 7 cases, the origin of the aberration remained unresolved and in one case, cytogenetic follow-up could not be done. Nine of the 10 fetal chromosomal aberrations were associated with an abnormal clinical phenotype and 13 of the 22 placental aberrations were associated with fetal congenital anomalies and/or poor fetal growth. This study demonstrates the utility of WGS-based NIPT in the detection of chromosomal aberrations other than common trisomies and also in the identification of confined placental chromosomal aberrations that may affect the pregnancy outcome.

WGS as the First-tier Genetic Test for Pediatric Patients (Lionel et al., 2018)

The utility of Whole-genome sequencing (WGS) as a comprehensive testing platform in suspected pediatric genetic disorders was explored in a study by Lionel et al. One hundred and three patients with a clinical phenotype suggestive of an underlying genetic disorder were recruited from pediatric non-genetic subspecialty clinics. The diagnostic yield was compared with that of conventional step-wise genetic testing. Diagnostic variants were identified in 41% of cases. WGS was able to detect all the molecular aberrations detected by conventional genetic testing methods as well as an additional 18 variants, including structural and non-exonic sequence variants. WGS was thus shown to provide a higher diagnostic yield as a primary test, when compared to conventional genetic tests, in a clinically heterogeneous cohort.

References

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