GeNeXpreSS

Tradition with a Twist: New Avenues for Genetic Tests

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Prenatal Arrays [Srebniak et al., 2016]

Fetuses with ultrasonographically detected abnormalities are known to carry a high percentage of submicroscopic aberrations in addition to microscopically visible chromosome abnormalities. These could only be detected by targeted testing in case of specific ultrasound anomalies, for example, 22q11 deletion in fetuses with cardiac defects. However, prenatal phenotyping based on ultrasonographic evaluation is difficult. The whole genome cytogenetic microarray is a solution to this problem. Srebniak et al. studied the microarray findings in 1033 fetuses. In 7.4% fetuses a pathogenic array finding was detected of which 75% were submicroscopic aberrations. More importantly, in 0.5% an unexpected diagnosis of a known syndrome (often severe, early onset, untreatable) was made that did not explain the abnormal ultrasound findings. So, karyotyping as a stand-alone test is no longer adequate and genomic SNP array should be the preferred first-tier technique to detect causative chromosome aberrations in fetuses with ultrasonographic anomalies.

New rays with arrays [Nevado et al., 2014]

The advances in the use of microarrays for diagnosis and research in genomic disorders has permitted the discovery of infrequent genomic rearrangements in a variety of diseases and the reports of several microdeletion and microduplication syndromes. The dilemma often encountered in classifying the variants and the compilation of clinical and genetic information in various databases cannot be overemphasized. Nevado et al. have systematically reviewed the novel microdeletion and microduplication syndromes described in the past five years and grouped these 96 microdeletion and 20 microduplication syndromes by chromosome location. This is a quick and useful source of information for clinicians and researchers.

Variants in Resilients [Chen et al., 2016]

Genetic studies of human disease have traditionally focused on the detection of disease-causing mutations in afflicted individuals. A complementary approach is to identify healthy individuals resilient to highly penetrant forms of genetic childhood disorders. Chen et al. performed a comprehensive screen of 874 genes in 589,306 genomes which led to the identification of 13 adults harboring mutations for 8 severe Mendelian conditions, with no reported clinical manifestation of the indicated disease. These conditions include Smith –Lemli –Opitz syndrome, cystic fibrosis, familial dysautonomia, epidermolysis bullosa simplex, Pfeiffer syndrome, autoimmune polyendocrinopathy syndrome, acampomelic campomelic dysplasia and atelosteogenesis which have early onset (<18yrs), severe phenotype and complete penetrance. This "Resilience Project" demonstrates the promise of broadening genetic studies to systematically search for well individuals who are buffering the effects of rare, highly penetrant, deleterious mutations. This may provide the first step towards uncovering protective genetic variants that could help elucidate the mechanisms of Mendelian diseases and new therapeutic strategies.

NIPD of Duchenne muscular dystrophy (DMD) [Parks et al., 2016]

The non-invasive prenatal diagnosis for single gene disorders (NIPSIGEN) project (UK), aims at developing an affordable NIPD test for single gene disorders using cell free fetal DNA from maternal blood. Success has already been reported for beta thalassemia and congenital adrenal hyperplasia. Recently, DMD has also been added to the list. Massively parallel sequencing by targeted capture enrichment of SNPs was performed across the dys-

trophin gene followed by relative haplotype dosage (RHDO) analysis. This showed a test accuracy of 100%, when the calculated fetal fraction was >4% and correlated with known outcomes.

References

1. Chen R, et al. Analysis of 589,306 genomes identifies individuals resilient to severe Mendelian childhood diseases. Nat Biotechnol 2016; 34: 531-538.
2. Nevado J, et al. New microdeletion and microduplication syndromes: A comprehensive review. Genet Mol Biol 2014; 37(1 suppl): 210-219.
3. Parks M, et al. Non-invasive prenatal diagnosis of Duchenne and Becker muscular dystrophies by relative haplotype dosage. Prenat Diagn 2016; 36: 312-320.
4. Srebniak MI, et al. Prenatal SNP array testing in 1000 fetuses with ultrasound anomalies: causative, unexpected and susceptibility CNVs. Eur J Hum Genet 2016; 24: 645-651.

GeNeEvent - Workshop on Rare Diseases

The workshop on Rare diseases titled "To Develop a Scientific Program for Research on Rare Diseases" was held on April 22-23, 2016 at the Indian National Science Academy, New Delhi. The conference focused on the current status and future directions in rare disease research, treatment and diagnosis. Participants of the conference and the faculty debated on need for development of a national policy for rare/orphan disorders relating to awareness, research, treatment, orphan drug development etc. Various stakeholders including clinical geneticists, researchers, representatives from non-governmental organisations working in this field, government representatives , members from pharmaceutical companies, parent support groups presented their views on the existing status of rare disorders in India and the vision for the route ahead.