GeNeXpreSS

Next Generation Sequencing Facilitates Disease Discoveries

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Whole Genome Sequencing for New Born screening

Next generation sequencing (NGS) has covered a long way from the lab to the clinic, especially with respect to new born screening (NBS). Whole genome sequencing (WGS) may help in detecting or ruling out not only disorders currently detected through NBS assays, but also help in pinpointing the molecular diagnoses and in detecting conditions not detectable with the presently done NBS assays [Bodian et al., 2015]. Some recent studies have focused on the feasibility of implementing this technology in routine newborn screening. One study suggested that, at baseline, parents have a substantial level of interest in WGS for their newborn, with little dilemma. There are so many ethical, social, and practical issues for parents and providers like concerns about the potential psychosocial harms associated with unexpected genomic results, as well as how to interpret complex or ambiguous results. Inspite of this, almost 60% of the participants were either definitely or somewhat interested in having a potential future newborn's whole genome sequenced [Goldenberg et al., 2015]. Another study which involved a survey among genetics professionals regarding this issue showed that the survey participants were in favour of disclosing most types of results of NGS at some point in the lifetime. However, the majority (87.3%) also indicated that parents should be able to choose what results are disclosed [Ulm et al., 2015]. There are many practical challenges to the use of WGS in NBS especially regarding the communication of results and their interpretation for the family. These studies can help health-care providers to make more informed choices about when and how to utilize this WGS technology in the newborn period.

New type of physiological maternal inheritance: Skewed inheritance

The maternal genome is known to have a stronger effect on offspring as compared to the paternal genome. This is attributed to maternal RNA, maternal mitochondrial genome and imprinting. But in one recent study, mutations in the *RBP4* gene causing congenital eye malformations have been shown to result in altered biochemistry that disrupts Vitamin A delivery both within the fetus and in the placenta [Chou et al., 2015]. Skewed inheritance due to a functional restriction of placental vitamin A transport has been found for this condition and it defines a new type of physiological maternal inheritance. Genetic vitamin A deficiency has been previously suggested as a potential factor for eye malformations. The dominant-negative effect of the mutant retinol binding protein results in disruption of vitamin A delivery from wild-type proteins within the fetus, as well as, in the case of maternal transmission, at the placenta. This effect of the *RBP4* mutant alleles provides a further example of gene-environment effects. The mutation in the mother and the same mutation in the fetus interact together and define the phenotype. These findings further highlight the importance of maternal-fetal nutrition and may apply broadly to congenital malformations in general.

Refining Non-invasive Prenatal Diagnosis with Single-Molecule Next-Generation Sequencing

Accurate prenatal diagnosis can be challenging and has conventionally been based on invasive procedures. The gradual elimination of risky proce-

dures used for sampling fetal material for prenatal diagnosis has been an important objective of fetal medicine. Definitive diagnosis of aneuploidy using cell-free fetal DNA (cffDNA) is still not possible because of the small percentage of discrepant results which occur because the cffDNA is derived from the placenta. There is a large market opportunity for the development of aneuploidy testing and also for testing for monogenic disorders in cffDNA. Noninvasive prenatal diagnosis (NIPD) using next generation sequencing (NGS) provides a promising approach which can be applied in the detection of multiple mutations in a single assay as well as for screening a gene with multiple pathogenic mutations. For the very first time, Chitty et al. demonstrated that through NGS-based testing in cffDNA, non-invasive prenatal diagnosis could be done for pregnancies at risk of achondroplasia and thanatophoric dysplasia [Chitty et al., 2015], thereby documenting the utility of NIPD for single gene disorders. Another recent study used whole genome amplification (WGA) of DNA from single fetal nucleated red blood cells (FNRBCs), followed by massively parallel sequencing to detect trisomy of chromosomes 21, 18 and 15, showing the potential utility of this technique for definitive NIPD for fetal aneuploidy[Hua et al., 2015].

What happens with Loss of function mutations in the genome: Real implications for opportunistic screening

Putative loss-of function (pLOF) variants are common in genomes and understanding their contribution to disease is very important for predictive medicine. Genome sequence analysis can generate up to 800 pLOF mutations in a single genome. With the increasing use of NGS for predictive medicine, it is critical to be able to predict the consequences of pLOFs, especially in individuals without pre-existing clinical diagnoses. The study by Johnston et al. (2015) focused on the practical detection of phenotypes associated with these pLOF variants. An average human typically contains some pLOF variants. On clinical evaluation, few of them are found to be disease-causing (the phenotype having been missed or hidden by the patient in the initial examination), but some of them (about 30%) do not have any phenotypic manifestation, indicating incomplete penetrance. For individuals without a clear family history of disease, variant identification and interpretation is more difficult because it is possible that the identified variant is not causative, and non-penetrance must always be considered. Johnston et al. took the exome data of 951 participants and filtered for pLOF variants in genes likely to cause a phenotype in heterozygotes. They performed a customized clinical evaluation of the participants with these variants to identify phenotypic characteristics in them or their close family members that could be attributable to the pLOF variant [Johnston et al., 2015]. They concluded that 1/30 unselected individuals harbor a pLOF mutation associated with a phenotype either in themselves or their family. This study gives a new approach i.e. iterative phenotyping or hypothesis-generating clinical research.

References

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