GeNeDit

Deciphering Clues to Genotype-Phenotype Correlation

Editorial

The beginning of the era of mutation detection in clinical practice was very exciting. Some 'lumped' phenotypes got separated while some disorders with great phenotypic similarities were either found to be allelic or disorders sharing a common pathway. One gene and multiple phenotypes was found to be not uncommon. Incomplete penetrance and variable expression did not remain concepts and observations but had molecular evidence to support them. Intrafamilial variability more common with autosomal dominant disorders but also seen in autosomal recessive disorders led to the search for modifier genes. Interaction between alpha and beta globin genes provided some insights into the genotype-phenotype correlations of thalassemia intermedia. Null alleles, specific locations of mutations and gain-of-function mutations provided some genotype-phenotype correlations in beta thalassemia, osteogenesis imperfecta, etc. Specific single causative mutation responsible for the disease in concern has been observed in very few disorders such as sickle cell disease, type V osteogenesis imperfecta, and Caffey disease. In certain others such as achondroplasia, Apert syndrome and Hutchinson-Gilford progeria syndrome, one or a few mutations have been found to account for majority of the cases. Some correlation based on the nature and position of the mutation is understood, such as out-of-frame/ frameshifting deletions in the dystrophin gene leading to the more severe phenotype of Duchenne muscular dystrophy versus the in-frame deletions causing the less severe phenotype of Becker muscular dystrophy. However, this alone cannot explain the phenotypic variation in all cases. In general, for most of the disorders no genotype-phenotype correlation is observed.

Genetic heterogeneity and phenotypic heterogeneity are challenges in clinical practice. Next generation sequencing-based diagnostics have provided solutions to some extent to the genetic heterogeneity. However, prediction of phenotype continues to remain a big question even for known pathogenic variations. One of the most important causes of marked phenotypic variability observed in females with fragile X syndrome is lyonization leading to mosaicism for the mutated and fully methylated allele of *FMR1* gene. Mosaicism for number of repeats and mosaicism for methylation of *FMR1* promoter has been observed in males. The methylation status of *FMR1* gene promoter has shown correlation with *FMR1* mRNA and neurodevelopmental dysfunction. The GenExpress of this issue discusses the use of methylation of *FMR1* gene promoter in samples of newborn screening, for diagnosis and prognostication. Many genes involved in chromatin modelling influence the expression of many other genes, and mutations in these genes thus cause phenotypic abnormality due to changes in the expression of genes under their control. The modification of methylation of many genes in the genome by pathogenic sequence variations in genes for monogenic syndromes like Coffin-Siris syndrome, Rubinstein-Taybi syndrome, etc. has been reported in recent literature. Research in this area has successfully provided specific methylation signatures of these monogenic disorders. Studies of correlation of the expression of genes with modified methylation, sequence variation in concern and the phenotypes, will be useful in classifying novel sequence variations as pathogenic or non-pathogenic, and also may provide insights into genotype-phenotype correlations. The GenExpress in this issue also mentions another interesting study on differentially methylated regions (DMRs) that undergo demethylation in late gestational age in cord blood cells, which can be used to correctly assess the gestational age of a neonate.

As next-generation sequencing is coming into clinical practice for population-based screening for carriers of recessive disorders and for newborn screening for early-onset serious genetic disorders, there is a strong need to find out genetic modifiers so as to go into the depth of genotype-phenotype correlation. Not only sequence variations in the genome and genes of the pathway or protein complexes but the various epigenetic mechanisms affecting gene expression may provide clues to the unanswered questions of genotype-phenotype correlations.

Dr. Shubha Phadke
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