GeNeDit

Mirror, Mirror on the Wall – Show the Complete Picture to Us All!

Editorial

The Human Genome Project was an ambitious dream. Reading all our genomes became a reality in 2003! The gaps were filled and now we know the 'telomere to telomere' ATGC sequence of Homo sapiens. Now almost anyone and everyone can get their genome sequenced any time- before birth, at birth or after birth. The power of this technology is being harnessed by clinicians not only in diagnostics but also for developing treatments based on the understanding of genetic pathogenesis. Examples include personalized treatment for cystic fibrosis based on the disease-causing variants and antisense oligonucleotide therapies for various monogenic diseases as discussed in the review article in this issue. Curative treatment in the form of gene therapies for beta thalassemia, hemophilia, retinitis pigmentosa, and spinal muscular atrophy is a major milestone in the history of genetic disorders. At the same time the utilization of this technology has caused a paradigm change in the diagnosis of monogenic disorders. Diagnosis of rare disorders has become easier and more definitive than that of tuberculosis. Short-read/long-read whole genome sequencing and optical genome mapping have made the diagnosis of all types of genomic variations possible. At present these techniques are complementary to each other and can be enhanced by RNA-based studies to make the diagnosis of exonic and intronic variants, triplet repeat expansions, copy number variations, structural variants, and imprinting abnormalities in one go. We are close to a one-stop diagnostic solution for all genetic disorders. However, the development of disease-modifying treatments is still moving at a slow pace. Hence, prevention of disorders by prenatal diagnosis is an acceptable option and is being offered in a big way. Here, termination of the fetus affected with the disorder is the option if it is acceptable to the family. This puts a lot of responsibility on medical geneticists to give a definite answer as to whether the fetus carrying a variant will develop serious disease, and to predict the severity of the phenotype. This is very challenging as we continue to face the complexities of interpretation of genetic variants.

Technical marvels will keep on increasing the diagnostic yield of possible genetic disorders and may identify novel genes and maybe novel mechanisms for still-enigmatic genetic disorders. Though these technological advances provide accurate genetic diagnosis to many patients and shorten the diagnostic odyssey, many genetic mysteries continue to remain unsolved. Though the identification of a variant for a Mendelian disorder has become an easy job, the previously known issue about modifying factors, especially genetic modifiers, is confronting us in a big way. Why do some patients with the L444P (p.Leu483Pro) mutation in the *GBA* gene develop neurological manifestations of Gaucher disease and others do not? Among those with this *GBA* mutation who do not have oculomotor involvement during childhood, we cannot predict who will go on to develop neurological involvement later and when. The modifiers for thalassemia intermedia and spinal muscular atrophy are known but do not explain all the phenotypic variability. A large volume of data has confirmed that there is no genotype-phenotype correlation for most of the genetic disorders. There is great degree of intrafamilial phenotypic variability for autosomal dominant disorders. Exome sequencing has expanded the phenotypic spectrum of many monogenic disorders. Late-onset variants for many serious neurogenetic disorders like Krabbe disease, metachromatic leukodystrophy, and other inborn errors of metabolism have been observed. Many of these disorders, which we usually consider to be lethal, are being diagnosed in adults and some may present even after 50 years of age. Some of the individuals might have led fulfilling lives and contributed to society by then. Many of the genes like *LMNA* and collagen-encoding genes are associated with numerous phenotypes of varying severity. We can correlate the phenotype with the genotype and use it as supportive evidence for prediction of the pathogenicity of a genetic variant.

But can we always accurately predict the phenotype of a known pathogenic variant if it is detected in an asymptomatic carrier parent, in the fetal DNA in maternal plasma, or in the amniotic

fluid sample? No, in many cases we cannot! If we identify a de novo pathogenic variant in the *FBN1* gene in the fetal DNA from maternal plasma, will we be able to explain the life of an individual with Marfan syndrome to the would-be parents from a non-medical background? Can they decide whether to give birth to a child with Marfan syndrome or not? Is termination justified for a disease where the life expectancy is likely to be normal/ near normal? If we feel the answers to all these questions are 'No', is screening of all couples for carrier status, of asymptomatic fetuses for pathogenic variants, of de novo mutations in fetal DNA from the mother's plasma justified at this point? For families with a child or an individual with a serious disorder with a poor outcome, prevention of recurrence appears to be justified at this time. The family is aware of the disorder, its clinical presentation and outcome. Prenatal diagnosis in this scenario will not have any significant error rate related to an uncertain outcome. But prenatal diagnosis for a likely pathogenic variant in a family without previous history of the disorder cannot give an idea about the outcome with certainty. We know this from our experience of counseling, for example in the case of a female fetus with a full mutation in the *FMR1* gene. How difficult is counseling and the decision! In fact, some pathogenic variants and homozygous loss-of-function variants are seen in databases of normal populations also.

The desire to have a normal, healthy, and beautiful child is normal. As clinicians we know that a 'normal child' free of disease cannot be guaranteed. Even when we do whole genome sequencing of the fetus, there is still a lot which cannot be seen and most importantly, much cannot be definitely interpreted. We, the clinicians and scientists, need to be aware of the limitations of interpretation of the currently available powerful sequencing technologies. Genome sequencing ability is a technological marvel, but we still do not know the interpretation of many variants and the role of modifying variants. These powerful technologies should be used for efficient postnatal diagnosis and research in understanding genotype-phenotype correlations, so that new therapeutic strategies can emerge. Along with these genome sequencing strategies we need to develop strong supporting knowledge of gene functions and a more in-depth understanding of protein-protein interactions, etc. Till we are able to definitely predict the phenotype based on the genotype, it may not be wise to take decisions about termination of pregnancies or even preimplantation diagnosis, based entirely on variants detected through carrier screening of couples or broad-spectrum testing of fetal DNA, without history of the disease in the family. Without foolproof evidence even a murderer cannot be hanged and here, a child who may not have a serious disease and who might have been able to live a long life might be terminated. Even preimplantation diagnosis increases the risk of birth defects and poor outcomes. Excessive parental control over the genome of the unborn baby, with blind faith in the power of genomic techniques and the ambitious confidence of scientists in prevention of genetic disorders by screening through next-generation sequencing (NGS) technology, is frightening. Though the intentions of geneticists are good, they may cause termination of normal fetuses. And what effect such population-based screening will have on the gene frequencies, if carried out on a large scale, cannot be foreseen. It is time to tell the parents that a disease-free 'normal baby' cannot be guaranteed and that though technology can read the genome completely, at present we are able to understand the meaning only partially. Half knowledge can be dangerous.

The mirror of genomic technology needs to be able to show multiple dimensions of interpretations of ATGC variants before it can be applied for prenatal or pre-conceptional screening of a normal population and of low-risk pregnancies.

Mirror-mirror on the wall
Please show the correct multi-dimensional picture to us all.
The ATGC story is ready to be read,
But a lot needs to be deciphered.
Show us not only the exterior image,
Not just the variants but also the mechanism causing the damage.
Based on which we can do correct interpretation,
And help families come to a meaningful conclusion.

(The views expressed here do not represent the views of the Indian Academy of Medical Genetics or of the Editorial Board of Genetic Clinics. These are the personal views of the author to open the minds of geneticists and clinicians to the complexities of the issue.)

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