GeNeDit

Genetics, Genomics and Clinical Geneticists: What's ahead?

Editorial

As one walks towards the horizon, distant pictures start becoming clearer while new blurred images appear on the horizon. We need to walk further to get a clearer view of them. Same thing happens in genetic diagnostics. The techniques to evaluate genes and the genome have improved greatly but one investigation for all genetic diagnostics keeps on evading the clinicians. More than three decades ago, clinical diagnosis had a lot of limitations as cases with signs and symptoms overlapping with two genetic disorders or novel phenotypes were a common experience. And young minds like me were waiting for identification of causative genes for all genetic disorders especially for malformation syndromes with the expectation that we shall be able to put cases in bins with the right diagnosis. As per current OMIM statistics, more than 7500 phenotypes with known causative genes and about 5000 genes with known phenotypes are documented. It is obvious that there are some genes with multiple phenotypes. About 1500 genes are associated with 2, 3, 4 or more phenotypes each. Also, we know many phenotypes are genetically heterogenous. Hence, one gene for one phenotype does not work either way!

Next generation sequencing has made diagnosis easy for most of the monogenic disorders and presentations with possible genetic diagnosis. Whole genome sequencing is taking care of intronic variants, copy number variations, structural variants and balanced rearrangements in one go. The technique of long read sequencing appears to be very powerful for novel types of variants including triplet repeats. It is especially helpful in identifying structural variants as exemplified by publications referred to in the GenExpress of this issue. One has been waiting for whole genome sequencing to get cheaper so that one investigation for every patient or genomic data in everyone's pocket even before symptoms appear will be the reality soon. It now seems that there is a choice of technology for sequencing the genome. Analyzing strategies also vary and may have different detection abilities.

As exome sequencing has made genetic diagnosis easy and there is awareness about presentations of genetic disorders amongst clinicians, many diagnoses are made in settings outside medical genetics departments. This is good in a way as not even developed countries have enough medical / clinical geneticists to take care of ever-expanding numbers of patients and families with genetic disorders. But it also calls for genomic education amongst non-genetics clinicians and complementary services of genetic counsellors. The judicious and cost-effective use of diagnostic techniques requires good knowledge of basic genetics, molecular genetics and principles of genomic testing and if there is lack of this there is a fear of over testing or missing a simple diagnosis. Interpretation of reports and communication of these high-end reports with lifelong implications to the patient and the family needs medical doctors with training in medical genetics. The increasing market of genomic diagnostics calls for urgent short-term, long-term, offline, and online courses in medical genetics for clinicians at various stages of their careers and incorporation of genomics in the undergraduate and postgraduate medical curriculum.

Genomics-related education is not only required to understand the power of genomics and genomic tools but also to know the limitations of these various technologies for high throughput sequencing. The power of knowing each nucleotide of the genome gives a bit of overconfidence about diagnosing all disorders pre-symptomatically in patients, and carrier screening for the purpose of reproductive decisions. Without clinical clues and suspicion of disorders with different disease mechanisms, the choice of exome sequencing and analysis of the data may be incorrect. The implications of results of uncertain significance, inability to predict phenotypes, non-penetrance, etc. are some of the many issues which need inputs of clinical/ medical geneticists for preventing harm to the individual,

as non-maleficence is the obligation of a clinician.

One more important role of clinical geneticists in genetic diagnostics is phenotyping including reverse phenotyping which has been highlighted in both the case reports in this issue. Now also, some clinical diagnoses are possible, especially with experienced clinical geneticists. If not possible, clinical phenotype-based classification and reverse phenotyping are very important parts of genetic diagnosis even in the era of high throughput sequencing and need an astute clinical geneticist. It is equally important for ordering the right test. In spite of all clinical expertise and access to advanced genetic tests still many cases remain undiagnosed. Research may identify novel genomic mechanisms unknown to date for disease pathogenesis and the search for one comprehensive test for every genetic disorder, without reliance on clinical data, will continue to be at the far away horizon. Genomics has to keep on marching ahead and clinical geneticists will have to play a major role in the second level of approach to diseases undiagnosed or misdiagnosed at the level of our non-geneticist clinical colleagues.

Dr. Shubha Phadke
1st October, 2024