The Eyes See What the Mind Knows!

Editorial

Clinical acumen had and will continue to have a very important role in the diagnosis of patients. This was a matter of pride for senior clinicians and as students we used to admire teachers for diagnosing rare disorders and rare clinical presentations. Investigations were done to confirm the diagnosis and stamp the clinical expertise of an experienced physician. This clinical expertise was very important especially in the practice of medical genetics where there are more than 5000 phenotypes and most of the disorders are extremely rare. Then the databases of genetic disorders like LMD (London Medical Database), POSSUM (Pictures of Standard Syndromes and Undiagnosed Malformations) and OMIM (Online Mendelian Inheritance in Man) came to the aid of clinical geneticists. It is said that these databases are not experts but they are for the experts. These were very useful to get a list of possible phenotypes which a clinical geneticist could consider in differential diagnosis. Review of literature and comparison of photographic images were required before coming to the logical conclusion about diagnosis. This would pave way for confirmatory test like Sanger sequencing of a candidate gene.

We were looking at a future where causative genes for all disorders would be known and one gene for each phenotype would take care of all phenotypic overlapping syndromes and classification of disorders. Next generation sequencing (NGS) ushered in a new era where all genes can be sequenced in one go and a lot is now known about monogenic disorders. This has increased the diagnostic rates but still more than 30 to 50% cases remain undiagnosed. These need clinical revaluation, reanalysis of NGS data and review of latest literature. The improved diagnostic yield of cases by relooking at the data as the new information of genes and phenotypes keeps on pouring in every month is emphasized in the articles discussed in the GenExpress of this issue. Clinical re-evaluation of each patient after a positive result of a pathogenic / likely pathogenic sequence variation has also become very essential with NGS-based diagnosis as most of the sequence variations identified are novel and correlation with phenotype is an important supportive evidence for deciding the pathogenic nature of the sequence variation. Post NGS result, clinical re-evaluation is also needed due to a great degree of phenotypic and genetic heterogeneity and overlapping phenotypic features. This is the message of the review article on approach to congenital myopathies; the diagnosis of such a homogeneous phenotype was very challenging and tedious in the preNGS era.

Hence re-evaluation after identification of likely pathogenic variation, relooking at NGS data for re-mining for cases without a genetic diagnosis, and re-evaluation of patients as they grow and the phenotype evolves needs to be reiterated. There may be debates about the responsibility of re-contacting the patient; it is important to educate patients with rare disorders about the need for regular follow up. Keeping the families with untreatable and undiagnosed disorders under follow up is a challenge and needs a good rapport. Uncertainty of diagnosis and uncertainty of the pathogenic nature of the test result may be seen as failure of the geneticist and may be also a failure of science by the patient's family. Regular follow up is essential not only for reaching a diagnosis but also for informing them about emerging new treatments which is a true hope, though of unknown magnitude. Also one should be on guard while following patients with novel likely pathogenic sequence variations. Some of them might get reported in other patients with similar phenotype while the possibility of some changing to benign variants over the next few years cannot be entirely ruled out. In that case one has to start from point zero [back to square one].

The eyes see what the mind knows and the physician can diagnose what medical science knows! Genetic science is progressing fast and medical geneticists need to be on their toes. Rejuvenate and re-energise yourself for the additional clinical acumen demanded by the NGS era.

Dr. Shubha Phadke
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