Big leaps in diagnostics, small steps in therapeutics

Editorial

Correct diagnosis is the first step to treatment. Treatment is aimed at cure. DNA based diagnosis of monogenic disorders has been established and more diagnostic tests are being added rapidly. Gone is the era of linkage based diagnosis; today, in most centers DNA-based diagnosis is done by mutation detection only. This is due to improvement in the technology of sequencing as well as the development of newer techniques like multiplex ligation probe amplification (MLPA), etc. The problem with large sized genes and genetically heterogeneous disorders has been tackled by the high throughput technique of next generation sequencing (NGS). NGS technology has also been instrumental in identifying causative genes of many rare disorders. Though the pace of diagnostics is far more as compared to that of development of novel treatments and cures, research in the area of treatments is showing great promise. Duchenne muscular dystrophy (DMD) is one such example of a genetic disorder for which many novel therapeutic strategies are being explored and the review article in this issue discusses many of the conventional as well as newer diagnostic and therapeutic aspects related to Duchenne muscular dystrophy. One of the latest treatment strategies showing promise is use of an internal ribosome entry site (IRES), the article about which is mentioned in the Genexpress of this issue. The treatment strategies being innovated and tried are novel and varied. But all of them depend on better understanding of the pathophysiology based on the function of the causative gene and the different degrees of effects of various mutations on protein expression and function.

The story of most of the monogenic disorders e.g. cystic fibrosis, Marfan syndrome, etc., is the same. Identification of the causative gene and understanding of its function and of the pathophysiology of the disease has lead to development of novel treatment strategies for each of them, gene therapy being the common final goal for all. It is becoming obvious that though gene therapy may take longer than was expected, other strategies to manipulate other genes, proteins or pathways may be equally successful in ameliorating symptoms of diseases as has been seen for some diseases like Marfan syndrome, RASopathies, etc. Early diagnosis becomes important for timely intervention for such treatable disorders. For early diagnosis of these disorders newborn screening by sequencing the exome or whole genome of a neonate is an option and technically feasible today. It is being done in clinical settings in patients with difficult clinical diagnoses. One of the articles mentioned in Genexpress of this issue has reported the diagnostic yield of whole exome sequencing to be 25%. Of course analysis of sequence data and interpretation regarding the pathogenic nature of sequence variations are demons arising from the huge NGS data and the bioinformatician's fight against these demons has begun. The tools used in this war are discussed in the article on 'Prediction of Pathogenicity of Sequence Variations' in this issue. Not only laboratory personnel and geneticists but clinicians will need to be well conversant with these tools as they now need to participate in the analysis and interpretation of result data and not limit themselves to only communication of the results to the patients / families. The size of the demon of "variations of uncertain significance" will continue to shrink and whole genome / exome sequencing will become a technique for presymptomatic diagnosis; genetic medicine may then take the form of preventive medicine in the real sense. And, embryonic diagnosis and nonsurgical treatment of congenital malformations such as duodenal atresia or transposition of great vessels or cure for major defects such as holoprosencephaly may not remain just a science fiction.

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