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Perspective

Past, present, and future of rare disease genetics

Musharraf Jelani

Centre for Omic Sciences, Islamia College Peshawar 25120, Khyber Pakhtunkhwa, Pakistan.

A disease is considered rare if it affects less than 1 in 2,000 people in Europe. In the United States, a disease is considered rare if it affects fewer than 2 million people. Pakistani population has its unique structure. The variations in ethnicity, geographical, socio-economic status, cultural customs, and marriage priorities have led this population separated into genetic islands. Online Mendelian Inheritance in Man (OMIM), has updated 6,808 phenotypes and 4,377 genes either causing single or multiple traits (https://www.omim.org/statistics/geneMap). Genetic analysis of these traits was previously restricted to genome-wide linkage analysis through STS markers genotyping [1]. However, this tool had low resolution and some of the genome targets carrying the causative genes had the chance of not being detected. STS markers were replaced by SNP genotyping which had a higher resolution, more accurate, and efficient [2]. Linkage analysis tools were only specific to identify the locus suspected for causative genes. This method although requires Sanger sequencing of potential candidates nonetheless effective and successful in genetic analysis of large families.

During the past two decades, Pakistani scientists either working indigenously or availing the international collaboration opportunity have exceptionally contributed to identifying new genes and novel phenotypes to rare disease genetics. With the advent of next-generation sequencing technologies (NGS), the genetic analysis further refined by establishing customized gene panels, whole-exome sequencing (WES), or whole-genome sequencing (WGS). The advantage of WES analysis over the customized gene panel is to provide a broader picture of human coding genes instead of focusing on only a few provided in gene panels. WES has been widely used as a first-line diagnostic test in single-gene disorders. The key of the successful WES results lies in the availability of data analysis pipelines which should be more population-specific as compared to utilize the general genome projects of other ethnicities. Similarly, the clear clinical picture can only guide the molecular geneticists to look for the precise diagnosis, which though totally rely on the patient's availability to clinical experts and highly equipped hospitals. As most of such patients reside in far long areas and their economic status does not allow them to go for sorting out their problems.

Plenty of international companies are now offering fast and accurate results for molecular diagnostics; however, first, these tests are never affordable by the Pakistani community especially when the affected families belong to below-average income. Second, they use genome sequences of other populations for the primary alignment of the NGS sequencing data. Third, the diagnostics companies require precise clinical data which is only possible if genetic analysts work in a consistent and cooperative environment.

Keeping in view the above realities, Pakistan needs a National Genome Centre to look for solving the local issues. This project has several advantages, (a) the genetic testing money will not go outside the country, (b) the genome sequencing data of such patients would be stored in a national database which could be used further for improving diagnostics and forensic studies, (c) this will also help to identify potential risks of diseases in future generations and provide the basis for genetic counseling and policymakers.

References:

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