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Letter to the Editor

Whole Exome Sequencing as a Diagnostic Tool for Genetic Disorders in Pakistan

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The term consanguineous is derived from the Latin words (con means "shared" and sanguis means "blood"). Each partner in such a marriage shares genes of a common ancestor (grandparent).[1] Approximately 40% of all the marriages in the Middle East and South Asian countries are consanguineous.[2] According to a report, about 82.5% of Pakistani parents are blood relatives due to economic, social and cultural reasons in different regions of Pakistan.[3] Several studies carried out from different regions of Pakistan such as Bhimber district of Mirpur division (AJK), Sargodha, Rahim Yar Khan District, Khyber Pakhtunkhwa and Federally Administered Tribal Areas (FATA) showed 62%, 56.72%, 58.46%, 58.3% and 22.34% consanguineous marriages respectively.[4-8]

Over the past several years, molecular genetic tests such as linkage analysis and candidate gene sequencing have been widely used in Pakistani research institutes to identify the disease-causing variants responsible for several severe genetic disorders. The research methods such as linkage analysis using sequence-tagged sites (STS) markers, Sanger sequencing, and whole genome single nucleotide polymorphism (SNP) array are time-consuming and costly, particularly when several genes are known to cause a particular disorder. Recently, the landscape of human genetics and medicine has been revolutionized by the use of next-generation DNA sequencing (NGS) technologies. Whole exome sequencing (WES) as a diagnostic tool can uncover and identify the causative genes in different heterogeneous disorders having complex phenotypes (multifactorial, syndromic cases), since it allows getting the mutational screening of nearly all coding regions. However, interpretation of the data obtained after WES is a great challenge, since identification of the candidate variants associated with the disease phenotype is difficult to pinpoint due to high polymorphisms.[9,10] The arduous data analysis issue is being solved by the bioinformatics tools, assisting to narrow down the variants (rejecting/prioritizing variations) and selecting the disease causing variant based on (i) inheritance, (ii) pathogenicity, (iii) frequency in the public databases, (iv) association with specific pathways and (v) protein-protein interactions.

In Pakistan, diagnosing human genetic disorders conventionally depend on clinical phenotype examination with several other diagnostic tests. Still, such diagnosis methods are a challenge for clinicians due to high genetic and clinical heterogeneity of different genetic disorders. Different syndromic disorders presenting overlapping or atypical phenotypes sometimes lead to improper clinical diagnosis and thus resulting in unsatisfactory genetic counseling and treatment. Many of the rare variants are limited to certain ethnic or topographical populations. These population-specific variants (polymorphisms) are absent from public databases which also makes discovery and diagnosis difficult.

NGS technologies, especially WES has emerged as an effective and powerful diagnostic tool when traditional genetic screening has failed. Particularly in Pakistan, NGS technology should be implemented in research institutes and hospitals, which will result in the establishment of NGS analysis pipelines and in-house database. WES, facility should be introduced in the major hospitals of Pakistan, where the physicians and the exome analysis team can work in collaboration. It will not only facilitate the physicians to make cost-effective genetic diagnosis in case of rare genetic disorders but also help to decrease the time of diagnosis, thus help on supportive care, genetic counseling, and treatment of the patient.

In Pakistan, premarital and preconception counseling should be organized to assist the couple in decision making. Premarital screening tests

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should be arranged for all consanguineous marriage couples in health facilities. If the test results are positive, the couple should be evidently well-versed of the consequences. Applications of WES is not only limited to premarital testing, it is currently used in different fields such as DNA profiling, pharmacogenomics, personalized medicine, transcriptomics, cancer genetics and genetic counseling. Health professionals should promote the current policies and regulations of premarital screening for diseases like thalassemia and other syndromic and non-syndromic genetic disorders in Pakistan.

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