GeNeDit

Genotype-Phenotype Correlation in the True Sense of the Word!

Editorial

Diagnostic testing for genetic disorders is undergoing a paradigm shift from targeted testing to genomic testing. With availability of genomic techniques like microarray and high through-put sequencing of the exome or whole genome sequencing, one does not have to decide what genetic abnormality one is looking for, before ordering the test. From the data generated from these genome analysis techniques one needs to filter out the likely pathogenic or causative genetic changes and make the decision about the causative nature of the genetic variation mainly based upon the correlation between the clinical picture of the patient and available information about the phenotypes known to be associated with that specific gene or genetic variation and /or available information about the function of the gene. These techniques of genome analysis can be compared with whole body clinical examination, after which the clinician has to decide what are the abnormal findings and which ones explain the symptoms in the patient. So on the one hand we have the clinical examination findings which may include features detected on imaging of internal organs and on the other hand we have the sequence data of the whole genome or exome. While in most situations we can be sure of abnormal and significant clinical findings, at present we have very limited information about definitely abnormal genetic variations in the whole genome. This makes interpretation of genome data obtained by next generation sequencing or microarray a challenging task.

Important ways to interpret genomic data include search into databases of known pathogenic variants and polymorphic variations, knowledge of the function of genes and softwares to predict the functional effects of the genetic change. These have been successfully used in many cases but fail to provide causative genetic variation in a number of cases. This has lead to the concept of search for causative genetic variation based on the phenotype information. Softwares like Phenomizer and Phevor have been designed for this purpose. Phenotype information can be used as the tool to dig into the mountain of genomic data generated by next generation sequencing techniques and hence, is very important. Thus, clinical examination and documentation of the phenotype in the appropriate format and use of consistent nomenclature are very important. This issue has an article providing information about the various phenotyping databases and search tools. The search tools not only use known human phenotypes of genetic disorders but also naturally occurring or knock out mouse phenotypes, information about gene functions and their role in molecular pathways, etc. The initial publications using these tools are showing very high diagnostic yields. This appears quite natural as explanation of the phenotype is the objective of the whole process of genetic diagnosis. It sounds logical as one is not looking only at rare genetic variants in the data which are many, but is looking for clinically relevant variations. Of course this scenario reinforces the clinician's responsibility to conduct detailed clinical examination and clearly document the phenotype and use the Human Phenotype Ontoloy (HPO) for the purpose. The massive effort that has gone into the HPO project to develop a standard nomenclature for phenotype information is commendable. So, it appears that in the era of genomic medicine, the clinician would do the clinical examination, the laboratory would do the genome sequencing and the purpose of the test would be to 'search for genetic variation which correlates with the clinical findings'.

Genomic tests are here to stay and are gradually becoming first line investigations as they take care of large genes, genetic heterogeneity and novel phenotypes of unknown origin. As more and more components of the genome get annotated, the task of interpreting each and every genetic variant may become simpler. But as we know that no gene functions in isolation and there is great deal of phenotypic variability for most of the genetic disorders, interpretation of variations in modifier genes will pose new challenges and correlation

with clinical findings will continue to take the prime seat even in the molecular era. The science and art of clinical examination and documentation of phenotypes needs to be sharpened and clinical skills will certainly not take a back seat in the era of DNA, computers and bioinformatics. I am sure medical geneticists will find this new form of genetic medicine and the work of 'genotype-phenotype correlation' far more enjoying and exciting than anything until now.

Happy New Year!

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