Are We Ready to Implement Gwas and Ngs in Diseases Risk Assessment?

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Introduction

Today, Genome Wide Association Studies (GWAS) had been broadly utilized to identify disease risk genes and gene variants, for many disorders in different ethnic backgrounds world-wide. Various uncertainties exist as to how we may interpret the genetic data resulting from such studies, and how to implement genetic information for prognosis or prevention and treatment decisions. Reasons for uncertainties are for instance due to clinical heterogeneity of diseases, diverse ethnicities underlined by genetic variability, differences in diseases minor alleles' frequencies across populations, linkage disequilibrium between nearby genetic markers, and the penetrance of the associated genes and their variants.

Published gene markers that reached a high enough GWAS significance level need external validation, since they may not necessarily become universal disease markers according to the above reasons. Hence, the question remains whether these markers are applicable to individuals elsewhere in the same way they are to the population from which they were originally derived. In the search for common grounds in disease genetics, perhaps we at the very minimum need to accept the pathways through which these disease-associated gene markers are dysregulated.

These arguments may be illustrated by the complexity associated with the globally prevalent diabetes and obesity, where combinations of genes variations act synergistically, via dysregulated metabolic and endocrinological systems. Insulin resistance in peripheral tissues and disturbed pancreatic beta cell function remain the central players in both these disorders. A consensus is lacking today in trying to replicate the effects of known risk genes for these disorders in diverse ethnic backgrounds. However, it is yet to be demonstrated whether biology can link all views in context of a pathway-based disease pathogenesis, where biology is the common ground tethering the many genes suggested to contribute to such complex disorders.

Another dimension of genetic complexity, although cannot be generalized but may be applicable to some individuals, is the hypothesis that rare but highly penetrant genetic variations are responsible for these disorders. Owing it to the new next generation sequencing (NGS) technology, it is becoming within reach to test such likelihoods. Lastly, we should not forget that penetrance of susceptibility genes in complex diseases is also regulated by environmental factors (e.g. lifestyle) and epigenetic effects. However, it remains to be seen how to implement such tools in the clinical practice, as the need for standardization is a must, and calls for careful establishment of a consensus in this era of data globalization.