e - ISSN - 2349 - 8005

INTERNATIONAL JOURNAL OF ADVANCES IN CASE REPORTS

Journal homepage: www.mcmed.us/journal/ijacr

PERSONALIZED MEDICINE AND GENETIC TESTING: THE NEED FOR PERSONALIZATION

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Article Info
Received 15/01/2015
Revised 27/01/2015
Accepted 02/03/2015

Key words:
Genetics, molecular diagnosis, personalized medicine, pharmacogenomics.

ABSTRACT
Genetics and genomics both play critical roles in human health and diseases. Although all human beings are believed to be 99.9% identical in their genetic makeup, the remaining 0.1% genetic variability provides certain uniqueness to each incidivdual and holds important keys to the human appearance (e.g. color of the hair or eyes), personality and behavioural traits, health, and causes of nearly all diseases. In addition, these genetic variabilities can also reflect therapeutic response of an individual to medications from being responsive to non-responsive or even resulting in adverse drug reaction, often referred to as 'pharmacogenetics or pharmacogenomics'. A careful matching of these variable genetic makeup and tailor-made medical care is the specific goal of personalized medicine.

INTRODUCTION

Personalized medicine is already being used by numerous health care providers worldwide. The advent of genetic technologies such as whole genome sequencing paired with increased accessibility to the sharing and reporting of scientific data has made it possible to identify clinically actionable genetic variation(s) warranting early medical interventions specifically tailored to the genetic makeup of an individual. Personalized medicine aims at identifying the two types of genetic sequence changes that an individual might usually carry: mutations (disease causing), which are usually harmful, and single nucleotide polymorphisms (SNPs), which are usually harmless. SNPs can be further divided into two types, those which are totally benign and those which have been shown to be a genetic risk factor for certain medical conditions. Personalized medicine genetic testing (PMGT) generally involves the testing of a few thousand SNPs that are known as risk factors for various diseases and conditions. Following testing, a report is issued detailing which SNP(s) an individual tested positive for and what disease(s) and condition(s) are linked to these SNP(s).

The American College of Medical Genetics (ACMG) have proposed an updated recommendations for standards for interpretation and reporting of sequence variations [1]. Despite these recommendations, however, a careful reviewing of 5 reports from 5 different major PMGT service providers worldwide, brought forth some apparent shortcoming in the current practice. We realized that the PMGT reporting was falling short in the area of personalization of gene test results.

The limitations and shortcomings we noticed in these reports are summarized in the following points:

i) The *ethnicity* of the tested individual is not taken into consideration when assessing the risk factor associated with a particular SNP. Particular SNPs have been documented with associated genetic risk in certain ethnicities while they may be harmless or untested in others.

ii) *Personal and family medical history* are not taken into consideration when evaluating the importance of a SNP which was tested positive for. E.g., the risk factor of an individual with a family history of diabetes who is found to be a carrier of a SNP associated with diabetes should be different than that of someone who tested positive for the same SNP and does not have a family history of diabetes.

iii) As pointed out earlier, most current reports give the same weight, in terms of seriousness, to SNPs reported in a single study and in one ethnicity to SNPs reported in many studies and in *multiple ethnicities.* Clearly, SNP proven to be a risk factor in multiple studies and in more than one ethncity will be more important in term of its relationship with a disease/condition.

iv) Most current reports do not take into consideration the potential *pathogenicity* of the SNP (i.e, does the SNP changes an amino acid?, does the SNP have a profound effect on the protein structure and/or function?).

v) Some current PMGT reports do not factor in the *genotype status* i.e., whether an individual is homozygous, carrying two affected alleles from both parents, or heterozygous, carrying one affected allele from one parent, for a particular SNP. A homozygous status is expected to have heightened risk as compared to a heterozygous status.

CONCLUSION

The body of knowledge now available with PMGT can only be used efficiently if the reporting is improved upon to deliver on personalization. Currently, there is no consensus to communicate the knowledge of novel genetic variant of uncertain clinical significance effectively between genetic testing laboratories and clinicians. A standardized framework has been reported to evaluate such variants in an objective manner [2] and which can be utilized. The service can be further customized by offering pre-assesssment and post-report counselling by a genetic counselor followed by consultation with a health care provider. Through genetic counselling, individuals completing PMGT will receive accurate genetic information and the SNPs most relevant to the individual's health will be highlighted without relying on the patient's interpretation of the report. Following genetic counselling, health care providers can advise on lifestyle and dietary changes that should be made to achieve better health and well-being. By moving away from the "one size fits all" approach and taking the above points into consideration to create a risk-algorithm, PMGT can provide more meaningful results for the individual and the health care providers, ultimately improving patient outcomes and reducing the overall medical economic burden.

ACKNOWLEDGEMENTS

Drs Khaled K. Abu-Amero and Altaf A. Kondkar are supported by the Glaucoma Research Chair at Department of Ophthalmology (Supervisor: Dr. Saleh A. Al-Obeidan), College of Medicine, King Saud University, Riyadh - 11411, Saudi Arabia.

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