Review Article

Relevance of pharmacogenomics for developing countries in Europe: implementation in the Maltese population

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Abstract

Pharmacogenomics is a promising new discipline that can realize personalized treatment for patients suffering from many common diseases, particularly those with multiple treatment modalities. Recent advances in the deciphering of the human genome sequence and high throughput genotyping technology have led to the reduction of the overall genotyping costs and enabled the inclusion of genotype-related dosing recommendations into drug package inserts, hence allowing the integration of pharmacogenomics into clinical practice. Although, pharmacogenomics gradually assumes an integral part in mainstream medical practice in developed countries, many countries, particularly from the developing world, still do not have access either to the knowledge or the resources to individualize drug treatment. The PharmacoGenetics for Every Nation Initiative (PGENI) aims to fill in this gap, by making pharmacogenomics globally applicable, not only by defining population-specific pharmacogenomic marker frequency profiles and formulating country-specific recommendations for drug efficacy and safety but also by increasing general public and healthcare professionals' awareness over pharmacogenomics and genomic medicine. This article highlights the PGENI activities in Europe and its implementation in the Maltese population, in an effort to make pharmacogenomics readily applicable in European healthcare systems.

Keywords

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Introduction

The genomic revolution promises to lead to better diagnosis of disease and selection of therapy.[1,2] In the recent years, we have witnessed a significant increase in the amount of DNA variation data that are predictive for risk of toxicity or lack of effectiveness for commonly used treatment modalities. Pharmacogenomics can enhance the assessment of drug efficacy and safety to the current systematic process for rational drug use and may play a significant role in the evaluation of the overall cost-benefit for competing therapies.[3] Consequently, genome-based therapy is gradually being introduced in developed countries to a greater or lesser extent and several national pharmacogenomic networks are being formed, e.g. in the United Kingdom, the Netherlands, as so on. At the same time, genomic information may be equally useful to other countries around the world to enable integration of medications into national formularies in a safe and effective manner.

However, despite much research over the last decade, the clinical application of pharmacogenomics is still poorly integrated in the majority of the underdeveloped and developing countries, where genetic testing and pharmacogenomics may be considered as luxury items, since supply of electricity and fresh water is not guaranteed and modern healthcare infrastructure is missing. This, notwithstanding, does not imply that the application of genetics is not useful for the developing world to stratify public healthcare decisions.

Availability of drugs in countries around the world is overseen by national health authorities, often based on recommendations issued by regional agencies, such as the European Medicines Agency (http://www.ema.europa.eu), or international authorities, such as the World Health Organization (http://www.who.int). In most cases, however, drug safety, efficacy and dosing information is based on White European-based studies that involve subjects from e.g. the United States, Europe or Canada and hence very little is known about how these drugs function in other populations worldwide.

This article aims to outline the various steps that need to be undertaken for implementing pharmacogenomics in developing countries in Europe, using the Maltese population as an example, and the various obstacles that should be overcome to reach the maximum benefit in national healthcare systems.

Pharmacogenomics and developing countries

The PharmacoGenetics for Every Nation Initiative (PGENI; http://www.pgeni.org) is an international project aiming to incorporate pharmacogenomics into the national medication selection decision-making process in developing countries, providing improved rational drug selection.[2] PGENI aims to: (a) promote the integration of genetic information into the public health decision-making process, (b) enhance the understanding of pharmacogenomics in developing countries, (c) increase awareness over pharmacogenomics and genomic medicine in the general public and healthcare professionals in developing countries, (d) provide guidelines for medication prioritization for developing countries using pharmacogenomic information, and (e) help to establish infrastructure for future pharmacogenomic research studies.[2]

There are several drugs whose efficacy and/or toxicity is correlated with genomic variants, for which the relevant pharmacogenomic information is available in the drug label (http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm). For example, HLA-B*5701 screening is highly recommended prior to treatment with Abacavir to prevent drug-related hypersensitivity reaction. The allele frequency of this marker is highly variable, *i.e.* from less than 1% in sub-Saharan Africa to up to 20% in India, while in European populations HLA-B*5701 frequency varies between 1% and 7% .[4] The same is true for the allele frequency of many other pharmacogenomic markers, that are documented in dedicated repositories, such as the Frequency of Inherited Disorders database (FINDbase; http://www.findbase.org).[5,6] The main PGENI study plan includes screening for the commonest pharmacogenomic markers in 50-500 healthy volunteers from various populations and ethnic groups worldwide and the formulation of recommendations for genome-based prioritization of medication selection. Selection of participating countries is mainly based on the existence of a moderate to good healthcare system infrastructure, which is nevertheless insufficient to integrate individual patient genotyping into routine clinical practice. Pharmacogenomic markers include variants in CYP450 enzymes (e.g. CYP2D6, CYP2C9, CYP2C19, CYP4F2, etc), phase II enzymes (e.g. NAT1, NAT2, DPYD, UGT1A1, etc), drug transporters (e.g. MDR1, ABCC1, SLCO1A1, etc), transcription regulators and other enzymes that have been shown to be relevant to drug metabolism (e.g. RXRA, AHR, PPARD, PPARG, etc.).[7] The PGENI project is coordinated by the Institute of Pharmacogenomics and Individualized Therapy of the University of North Carolina (Chapel Hill, NC, USA) and 8 Regional Centers in the Americas (Mexico, Brazil), Africa (Ghana, South Africa), Asia (China, Jordan, India) and Europe (Greece). These entities are established Centers of Excellence to promote pharmacogenomics education and research, integrate pharmacogenomics into healthcare professional education that would potentially serve as a resource to the respective Ministries of Health. Also, these

regional centers will be responsible to advance the research capabilities in developing nations with regional experts, so that the necessary research infrastructure for advancing pharmacogenomics research in these populations is established. Ultimately, the population- and ethnic group-specific pharmacogenomic marker allele frequency information will assist the development of country- and population-specific national recommendations for various therapeutic modalities.[8]

Pharmacogenomics in Europe: challenges and pitfalls

The extent of implementation of pharmacogenomics in the various European healthcare systems may be hindered by several factors. First of all, not all European countries are European Union (EU) member-states, indicating that they are not subject to EU guidelines and directives, e.g. European Medicines Agency recommendations. Also, even among the 27 EU member states, the implementation of the various EU directives, particularly related to healthcare and education, is not uniform and relies on the national legislation. Furthermore, even though certain countries belong to the EU, they are likely to resemble more (e.g. culturally, religiously) with others that are not EU member states. Last, but not least, the Eurozone member states differ substantially in fiscal terms, which directly impacts the available healthcare and national insurance spending. These factors make the implementation of pharmacogenomics in developing European countries an even more challenging task.

The European Regional center of the PGENI initiative is the Golden Helix Institute of Biomedical Research (http://www.goldenhelix.org)[9], an international non-profit scientific organization with interdisciplinary research and educational activities in the field of genome medicine. Briefly, the PGENI-related activities of the Golden Helix Institute of Biomedical Research are:

a) Coordination of sample collection from healthy volunteers originating from various developing European countries that participate in the PGENI project. So far, DNA samples from over 20 European countries have been collected and processed (http://www.goldenhelix.org/index.php/research/the-pgeni-project).

b) Documentation of the pharmacogenomic markers allele frequencies in the FINDbase database (http://www.findbase.org),[5,6] as part of the Golden Helix Server.

c) Organization of education activities in the PGENI European countries to disseminate information pertaining to pharmacogenomics to achieve knowledge transfer to society. These educational activities, known as the Golden Helix Pharmacogenomics days

(http://www.goldenhelixsymposia.org)[10,11] are organized in major cities with large academic hospitals, aiming to (i) provide timely updates on the field of pharmacogenomics and personalized medicine to the local biomedical scientists and healthcare professionals, (ii) increase awareness over pharmacogenomics and their application in various areas of medical practice, and (iii) network faculty members from universities and research institutes from the local scientific arena working in the field of pharmacogenomics in order to initiate collaborative projects in this field.

d) Evaluation and critical assessment of the pharmacogenomic environment in PGENI European countries, particularly pertaining to genetic laboratories, the general public and healthcare professionals.

e) Establishment of guidelines and recommendations for integrating pharmacogenomics in developing countries' healthcare systems (Table 1).

Establish national networks of clinicians and researchers involved in pharmacogenomics in developing countries.
Encourage communication and research interactions with healthcare systems and pharmacogenomics networks in developed countries.
Create international networks between (closely related) developing countries to enhance communication, interaction, pursue funding and initiate joint research projects.
Develop a framework to catalyze knowledge transfer between the regional centre, national healthcare authorities and international agencies.
Ensure that all legal, ethical, social and religious issues are thoroughly addressed.

*Table 1. **Proposed recommendations for integrating pharmacogenomics in developing countries' healthcare systems.***

Considering the fact that genome-based rationalization of drug treatment can contribute towards the reduction of the National Healthcare spending, mostly by reducing hospitalization due to the various adverse drug reactions, this need is more than ever urgent, particularly in South European countries who have a vast fiscal deficit. In Germany, adverse drug reactions cause the death, hospitalization, or serious injury of over 2 million people each year, of which up to 30% of cases are preventable. Direct

treatment costs of adverse drug reaction in internal medicine total €434 million annually; base models including all medical specialties have extrapolated this figure to be more than €816 million.[8,12,13]

These activities contribute to the generation of new knowledge and its dissemination to the various stakeholders, which address, in part or fully, several of the issues that are currently considered as hurdles that hold this field back, such as, healthcare costs, education of healthcare professionals, proper regulation of (pharmaco)genomic tests, data collection, storage and retrieval.[14]

Implementation of pharmacogenomics in Malta

Malta joined the PGENI project in July 2011 and, together with Greece, Serbia and Poland, was among the first countries to express their interest to participate in this multinational initiative. The PGENI project in Malta is overseen by Drs. Fenech, Grech and Borg from the University of Malta. During Phase I of the project, 45 DNA samples from healthy volunteers were analyzed during the DMET+ platform (Affymetrix, Santa Clara, CA, USA). Principal component analysis indicates that the Maltese population nicely clusters together with the Caucasian population, as expected (Figure 1). However, for several pharmacogenomic markers, the allele frequencies in the Maltese population are significantly different compared to those observed in the Caucasian population. For example, the allele frequencies observed for several *CYP2D6* alleles in the Maltese population are different compared to those observed in the Caucasian population, while although the TPMT*3C allele frequency is 3% in the Caucasian population, this allele is completely absent in the Maltese population (data not shown). These findings warrant further investigation during the Phase II of the project that will soon commence.
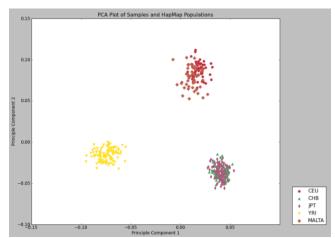

*Figure 1. **Principal component analysis, depicting that the Maltese population nicely clusters with the Caucasian population.***

Also, consistent with the efforts of increasing awareness over pharmacogenomics in the healthcare professionals and Bioscientists in the Maltese population, a Golden Helix Pharmacogenomics Day was organized on December 3rd, 2011, in the University of Malta in Msida, by the Golden Helix Institute of Biomedical Research and the Faculty of Medicine and Surgery, University of Malta. This event was supported by the Foundation of Medical Sciences, Affymetrix, Illumina, QIAGEN, and the Mediterranean bank and was attended by over 160 registered participants. The lectures from the European Commissioner for Health and Consumer Policy John Dalli, Professor Marisa Papaluca-Amati from the European Medicines Agency, Professor Ron van Schaik from Erasmus MC in Rotterdam, the Netherlands and several other leading scientists further emphasized the impact of this event towards informing the healthcare professionals over the importance of pharmacogenomics.[10]

These are some of the PGENI-related activities, which will undoubtedly positively impact on the pharmacogenomics community in Malta.

Conclusions

As more pharmacogenomic information becomes available from data collection and analysis from the various PGENI countries in Europe, this will not only accelerate the integration of pharmacogenomics in healthcare decision-making at the country level but will also support new pharmacogenomics research initiatives in areas with low research potential. Also, targeted educational efforts will also prepare the Ministry of Health staff from participating countries to better integrate genetic information into many areas of healthcare, including disease management and therapeutic interventions.

Overall, individualization of drug therapy is the ultimate goal, providing the rationale for implementing pharmacogenomics in healthcare provision in developing countries in Europe and worldwide.

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