Mini Review

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Progress in pharmacogenetics: consortiums and new strategies

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Abstract: Pharmacogenetics (PGx), as a field dedicated to achieving the goal of personalized medicine (PM), is devoted to the study of genes involved in inter-individual response to drugs. Due to its nature, PGx requires access to large samples; therefore, in order to progress, the formation of collaborative consortia seems to be crucial. Some examples of this collective effort are the European Society of Pharmacogenomics and personalized Therapy and the Ibero-American network of Pharmacogenetics. As an emerging field, one of the major challenges that PGx faces is translating their discoveries from research bench to bedside. The development of genomic high-throughput technologies is generating a revolution and offers the possibility of producing vast amounts of genome-wide single nucleotide polymorphisms for each patient. Moreover, there is a need of identifying and replicating associations of new biomarkers, and, in addition, a greater effort must be invested in developing regulatory organizations to accomplish a correct standardization. In this review, we outline the current progress in PGx using examples to highlight both the importance of polymorphisms and the research strategies for their detection. These concepts need to be applied together with a proper dissemination of knowledge to improve clinician and patient understanding, in a multidisciplinary team-based approach.

Keywords: next-generation sequencing (NGS) technologies; personalized medicine; pharmacogenetics; standardization; translation.

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Major points

- **Human genomic variation for personalization of drug treatments, from single genes to the genome-wide era**
  Achieves the evolution of pharmacogenetics (PGx) research studies evolving from phenotype testing to candidate gene studies due to the availability of genome-wide and next-generation sequencing studies.
- **Pharmacogenetics and personalized therapeutics networking. Europe: European Society of Pharmacogenomics and Personalized Therapy, ESPT. Latin America: Ibero-American Network of Pharmacogenetics, RIBEF.**
  Highlights the importance of working in consortiums in order to achieve the big targets for personalized medicine (PM) development.

- **Advances in the pharmacogenetics in psychiatry**
  Analyzes the need of prospective validating studies to prove the clinical and economic benefits of using genetic information for drug prescription and dose selection.
- **Strategy of extreme phenotypes to the identification of pharmacogenetics markers**
  Proposes massive sequencing of extreme phenotypes as a way to identify causal PGx variants as a cost-effective approach.
- **Personalized medicine through massive sequencing**
  Remarks the challenges of working with NGS in terms of data storage and interpretation, and highlights the use of a systems biology perspective as a way to understand complex interactions between genes.

Introduction

Pharmacogenetics (PGx) is dedicated to achieving the goal of personalized medicine (PM) in order to ensure that "each patient receives the right drug at the right time at the right dose for the right disease". Adverse reactions to drugs (ADRs) are one of the leading causes of morbidity in developed countries and represent a substantial burden on health care resources encompassing much of the hospitalizations. Together with ADRs, efficacy and dosage determine the clinical outcome of medication. A clinician must evaluate the benefit-risk of prescribing a certain drug to a patient with a particular disease. Clinicians have to be aware of the fact that drug response varies between individuals owing to disease heterogeneity, environmental and genetic factors, and intrinsic patients' aspects such as age, weight, or ethnicity between others [1].

As an emerging field, PGx confronts new challenges such as ensuring its correct standardization and its correct translation into routine clinical practice. This need has enhanced the creation of different multidisciplinary consortiums, such as the European Society of Pharmacogenomics and personalized Therapy (ESPT) [2, 3]. The need of understanding intrinsic patients' aspects related to response to drugs resulted in organizations such as the Ibero-American network of Pharmacogenetics, RIBEF [4, 5].

Regardless of that, one of the major challenges facing researchers working in the field of PM is translating their discoveries into clinical practice. Therefore, identifying and replicating associations of new biomarkers found in recent publications in order to incorporate them into clinical practice is especially interesting. Furthermore, concerted efforts and open and active cooperation with industry are required in order to facilitate translation and commercialization, avoiding to stuck pharmacogenetic biomarkers in the discovery phase [6].

Technologies to analyze pharmacogenetic markers have been evolved over the years. Nowadays, the development of next-generation sequencing (NGS) technologies has enabled investigators to allow a precise and rapid analysis of the whole genome of an individual and identify individual rare and common variants [7, 8]. NGS technologies let the identification of clear candidate genes to study common polymorphisms of minor impact. By selecting extreme phenotypes it is possible to enrich the system with rare variants of low frequency presenting strong effects, and therefore aiming to identify possible causal variants [9]. The final goal is to permit the development of new predictive markers and propose new therapeutic targets.

Nevertheless, given the multigenic nature of most traits, most diseases can only be explained as the set of complex interactions between genes, which make interpretation of results specially challenging. Therefore, illnesses are better understood as failures of functional modules caused by different combinations of mutated genes that can be easily simulated by a systems biology perspective, rather than by unique mutation(s) in one single gene. Therefore, the development of web tools with intuitive interfaces to analyze gene expression and genomic data resulting from high-throughput experiments is required [10].

Despite that PGx research has provided evidence of the potential use of genetic information for the improvement in the treatment outcomes, the use of PGx information to assist drug selection on areas such as psychiatry is still minimal [11]. The main problem is that it requires a precise characterization of the phenotype, which might be difficult since characterization and collection of efficacy and toxicity of a drug is especially complex. In the recent years, cost-effectiveness studies to assess the clinical and economic benefits of using genetic information for drug prescription and dose selection have been published [12, 13], remarking the role of PGx as a valuable tool that could be implemented in the daily life of a hospital in the near future.

Human genomic variation for personalization of drug treatments, from single genes to the genome-wide era

Classical medicine is based on the assumption that each patient's body will handle the drug in the same way, but patients vary in age, weight, ethnicity, dietary habits, alcohol intake, smoking status, and any interacting medications they take. Additionally, classification of most diseases is based on a gross and easily measurable phenotypic marker, which might be, in some cases, obsolete nowadays.

It is therefore not surprising that there is large variability in drug response (both efficacy and toxicity) in current clinical practice between different patients treated with the same drugs for seemingly the same disease. This inter-individual variability in drug response is well known to be a consequence of genetic factors, which have been broadly explored by using pharmacokinetic and pharmacodynamics studies. PGx research studies have rapidly evolved from phenotype testing to candidate gene studies due to the availability of genome-wide and NGS studies. Nevertheless, rather than competitive, phenotyping and genotyping techniques might be considered as complementary. As an example, well known is the *TPMT* evaluation, where phenotyping is the preferred method for routine screening in the UK, and on the other hand the strong association of *HLA-B*57:01* with abacavir hypersensitivity [14].

The clinical outcome of a medication can be determined by three key factors: efficacy, dosage, and ADRs. These three factors influence the use of pharmacogenetic biomarkers: the identification of driver somatic mutations in response to cancer drugs as an example on the efficacy of the drug [15]; the association between *VKORC1* and *CYP2C9* and warfarin dose requirements [16]; and the association of serious immune-mediated ADRs with *HLA* biomarkers [17].

There is a need to join forces to achieve future success in those pharmacogenetic biomarkers stuck in the discovery phase, standardizing phenotyping and genotyping strategies together with collaborative work and multidisciplinary approaches to identify and replicate associations of new biomarkers found in publications, as well as cooperation with industry to facilitate translation and commercialization. Additionally, acceptance of these approaches by clinicians, regulators, patients, and the public will be important in determining future success [18].

Pharmacogenetics and personalized therapeutics networking. Europe: European Society of Pharmacogenomics and Personalized Therapy, ESPT

Partnerships and networks are vital in bringing synergy, new perspectives, and insights, and increase impact and visibility to PGx. Consequently, ESPT [2] was founded with the aim of creating a scientific European organization able to give advice on the new field of pharmacogenomics.

ESPT is now a scientifically recognized society comprising more than 1200 members stratified in individual members, scientific groups, and national societies. ESPT recognizes the needs of both developed and developing countries and establishes collaborations between them.

The main aim of the organization is to facilitate a personalized individual treatment of patients, thus maintaining the health of all citizens through the collection of pharmacogenomics data. Its major issue is based on the principle of transcending boundaries of single nations or corporations to develop the field of PGx and PM. To achieve this goal, ESPT has structured its organization with four specialized divisions: scientific and clinical implementation, education and courses, communication and external relations, and congress and meetings divisions. Through leadership and innovation in science and education, the society will strive to enhance the scientific basis for the pharmacogenomics biomarkers recommended and then the quality of diagnosis and therapy for patients throughout the world.

PM development requires approaching three big targets: (i) patient's stratification of the healthy and sick subjects in function of the molecular targets, (ii) treatment of the big amount of data, and (iii) use of guidelines for clinicians and patients [3]. Therefore, developing databanks, as well as direct access recommendations, clinical decision support tools, and development of guidelines are essential requirements to translate PGx to the clinical use.

Based on the important need to focus on translation, ESPT is concentrated in providing a high-quality education at all levels. There are knowledge barriers among researchers, health professionals, students, and patients that must be overcome. Through promoting summer schools, congresses, symposia, and workshops in PGx and PM, ESPT is perfectly managing educational activities [19].

Pharmacogenetics and personalized therapeutics networking. Latin America: Ibero-American Network of Pharmacogenetics, RIBEF

RIBEF [4], founded in 2006, is an interdisciplinary research group comprising 16 countries and 41 research groups including researchers and health professionals. The RIBEF network promotes collaborative research between Spanish and Portuguese speaking countries, and aims to develop and perform projects focused on the development of PGx and PM whose final goal is to enable the delivery of adequate medical care in Ibero-America.

Under the context of the RIBEF, 13 research groups established the CEIBA Consortium (the acronym for the Spanish name Consorcio Europeo e Iberoamericano de Farmacogenética de Poblaciones). Subsequently, from CEIBA Consortium arises the MESTIFAR project (the acronym for the Spanish name Farmacogenética de Mestizos), founded to determine the variability of polymorphisms in genes involved in response to drugs in populations of different ethnic origin [Native Americans (Ameridian) and Mestizos (the result of post-Columbian admixture)] and the clinical introduction of population-oriented PGx panels. The final goal of the MESTIFAR Project is the promotion of training of Latin American professionals in the handling and safety of drugs, and patient empowerment about the use and risk of pharmaceutical products.

The CEIBA-MESTIFAR project has focused mainly on determined genotyping CYPs genetic polymorphisms and the relationship between ancestry, pharmacogenetic genotypes and pharmacological phenotypes in population of different ethnic origin [5]. In this project, more than 6000 healthy volunteers have been evaluated, which constitutes the largest study of population pharmacogenomics developed to date worldwide.

This project has already produced many interesting and recognized results raising new questions about PGx implementation. The interethnic variability described on *CYP2D6* alleles suggests the possibility of developing pharmacogenetic programs especially dedicated to ethnic groups or regions [20]. Additionally, concerning *CYP2D6* ultra-rapid metabolizers (UM), one study published by RIBEF consortium found that only 40% of the metabolic phenotype from UM was predicted from genotype [21], something that reveals the need of standardization to characterize UM. Furthermore, the recent discovery of a high *CYP2D6* hydroxylation capacity by the presence of -1584G allele in the promoter region of the *CYP2D6* gene [22] emphasizes the need of an improvement in the genetic analysis in order to take into account other factors apart from gen duplication/multiplication. The effect of UM for *CYP2D6* on suicidal behavior has to be highlighted since several studies have found poor response to antidepressant drugs or early dropout from monotherapy treatment with *CYP2D6* antidepressant substrates [23, 24].

Advances in the pharmacogenetics in psychiatry

Recent advances in genome-wide technologies have changed considerably the screening methodologies for searching predictive markers in clinical genetics. Early studies based on linkage analysis requested families in which a disease was segregated to identify the genetic causes of the phenotype. Successful results were obtained for highly penetrant diseases and for some complex traits by sampling the extreme end of the phenotypic distribution [25]. However, especially in psychiatry, such an approach was not sufficient because genetic predispositions to complex traits are more difficult to elucidate and require larger numbers of samples to discern signal from noise. Thus, the development of high-throughput methodologies, cheaper and faster, has enabled genetic advances in the field of psychiatry and in pharmacogenomics [26]. A high number of genes involved in pharmacokinetic and pharmacodynamic processes that contribute to the variability observed in response to pharmacotherapy have been identified. Pharmacogenetic research has identified functional polymorphisms in kinetic genes (i.e. cytochrome P450 enzyme drug-metabolizing system), receptors (i.e. serotonin receptor, HTR2A), and transporters (i.e. serotonin transporter, 5HTTLPR) that directly influence drug-efficacy and drug-induced adverse reactions [11, 27]. Because of these findings, several tests for genetic determination of the metabolic status of patients, prediction of the level of efficacy, and risk of developing side effects are already available in commercial and clinical laboratories.

Although PGx research has provided evidence of the potential use of genetic information in treatment outcomes in psychiatry, its use to assist drug selection on psychiatry is minimal. The main reason lies on the lack of research assessing the benefits of PGx tests. Prospective validating studies are needed to prove the clinical and economic benefits of using genetic information to aid drug and dose selection [28, 29].

On the other hand, during the last decade, epigenetic mechanisms have gained attention in psychiatry, since

they are modulated by environmental stimuli and adaptive to different stages and phases of the disorders. For example, it has been described that olanzapine affects the methylation status of the cadherin gene promoters in rat brain tissue; therefore, epigenetic changes may have an important role in response to olanzapine treatment in psychosis [30]. Furthermore, a study with major depressive disorder patients showed that serotonin transporter gene methylation could predict antidepressant treatment response [31]. Considering these results, epigenetic biomarkers for treatment response comprise a new and interesting field for psychiatry research [32].

Strategy of extreme phenotypes to the identification of pharmacogenetic markers

NGS technologies allow the generation of prodigious amount of knowledge enabling a deeper understanding of the molecular basis of the diseases and the genetic variation of the patients, thus having a direct effect in the genetic diagnostic in terms of rapidness and effectiveness. NGS analysis enables stratifying illnesses and patients that are two of the major challenges of personalized care. Nowadays, illness stratification relies on subjective scales that should be complemented with succinct medical questionnaires.

The pharmacogenomics area has highly benefited from technologies that can be guided towards monitoring disease relapse and response to treatment. Additionally, it has been possible to identify new biomarkers to predict efficacy versus toxicity related to drugs, and possible targets for future applications. Nevertheless, these applications should be always supplemented by cost-effectiveness studies [33].

One possible approach to identify causal variants is the massive sequencing of extreme phenotypes, which will lead to an enrichment of rare variants of low frequency with strong effects, allowing the identification of clear candidate genes to study common polymorphisms of minor impact. Also "extreme-trait" studies, in which only individuals with the most extreme responses to treatment are included, are cost-effective alternatives, with a high power to detect true associations, and do not require large sample sets. Nevertheless, despite its advantages, there might also be limitations since results might not be generalizable to the underlying population and might be sensitive to outliers, sampling bias, and the assumption of normality for the underlying traits. Additionally, if a complex trait is influenced by multiple loci, extreme-phenotype sampling can reduce power to detect loci with small effects [34]. However, by far, the main problem is the need of a precise characterization of the phenotype that might be difficult and expensive since the definition, characterization, and collection of pharmacogenetic data such as the efficacy and toxicity of a drug are complex. Moreover, PGx evolves with time and changes depending on the physiopathology of the patients and the external factors.

According to the above-mentioned approach, suggestions towards whole-exome sequencing as a possible strategy to determine defective variants that can influence the adverse drug reaction effects and that are able to be applied to complex phenotypes are gaining strength [35].

Personalized medicine through massive sequencing

Rapid advances in technology and decreasing cost enable us to bring next-generation technologies into the clinical practice. NGS technologies are high-throughput parallel-sequencing approaches that generate billions of short sequence reads. These short reads are compared against a reference genome; therefore, identification of variations is straightforward. Analysis of DNA or RNA can be performed for variant detection and *de novo* mutations, low or common frequency variants, as well as somatic or germline mutations. The possibility of detecting diagnostic and treatment markers in a single assay contributes to implementing PM.

Given the multigenic nature of most traits, these can only be explained as a result of complex interactions between genes, and, as a consequence, most diseases are better understood as failures of functional modules caused by different combinations of mutated genes rather than by unique mutation(s) in one single gene. In this context the use of a systems biology perspective in the analysis of genomic data is leading to new approaches in biomedical research including diagnostics, drug discovery, as well as pharmacology and toxicology.

For this reason web tools for the functional analysis of gene expression and genomic data in high-throughput experiments are being developed. Such is the case of Babelomics [36], already in its fifth release, encompassing a complete suite of web tools with a user-friendly interface [37]. In its beginning, this tool was composed of six modules and included biological information for

functional annotation coming from different sources, such as Gene Ontology, pathways, Interpro functional motifs, tissues, and chromosomal locations. In this new release, a support for NGS data including gene expression (RNA-seq), exome or genome re-sequencing has been implemented. Besides, it has simplified its interface allowing better visualization options and an interactive network viewer. Additionally, it offers access to a full range of methods from primary data analysis to a variety of tests for different experimental designs and different enrichment and network analysis algorithms for the interpretation of the results in the proper functional context [38]. Moreover, the net allows the possibility of store data and results from exome data, which is one of the main problems from NGS results [39].

Conclusions

Pharmacogenetics (PGx), as an emerging field dedicated to achieving personalized medicine, comprises challenges that need to be overcome to ensure its correct translation into clinical practice. Nevertheless, a lot of efforts have been invested in solving such challenges in the last few years. Standardization and validation of new biomarkers are being achieved with concerted efforts by working in consortiums. Technology drawbacks have been overcome by employing NGS that allow obtaining more information such as rare variation. Moreover, open and active cooperations with industry in order to achieve cost-efficiency tests to ensure clinical translation are being established. Therefore, it is only a question of time that PGx will be a reality into clinical practice.

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