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Chapter 1

TOWARD INCORPORATION OF CLINICAL GUIDELINES OF PHARMACOGENOMICS IN LATIN AMERICA

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ABSTRACT

In Latin America the Pharmacogenetics and Pharmacogenomics areas are recently emerging fields and the main focus of the research is to evaluate ethnic differences to apply adapted guidelines to manage personalized pharmacotherapy. Large differences between countries in the awareness and in the use of pharmacogenomic testing are presumed, but are not well assessed to date. In this chapter, we present the efforts to investigate variability in drug response using the molecular approaches and the limitations to apply pharmacogenomics test in clinical centers and hospitals.

Keywords*: pharmacogenomics, pharmacogenetics, guidelines, Latin America, ethnicity.*

INTRODUCTION

Pharmacogenomics is an emergent field and currently this discipl[1]ine is addressed to personalization of patient therapy being an important tool of the personalized medicine. In this respect, it´s a well known fact that patients respond differently to drug therapy and no drug is completely effective in all patients. This variability in response, largely due to genetic, epigenetic, biological, physiological, physiopatological and environmental factors affecting proteins that metabolize or transport drugs, their therapeutic targets (receptors) or both, influence its effectiveness and safety (Ma *et al*., 2011). The contribution of each factor varies among drugs (Evans & McLeod, 2003; Wijnen *et al*., 2007; Zhou *et al*., 2008; EMA, 2015; Quiñones *et al*, 2016). Table 1 summarizes the factors influencing the interindividual variation in drug response.

On the other hand, the development of non-invasive techniques of genetic engineering and the necessity to find explanations for the variations in response to the action of drugs have posed pharmacogenomics as a very important area in drug research. Important substrates for pharmacogenomic development have been several genomic projects as for example the human Genome project (HUGO, 2016), the International HapMap project (2016), 1000 Genomes project (2016), the SNP consortium (2016) and the GWAS (Genome-Wide Association studies) (2016). Together, the results of this initiatives have significantly contri[2]buted to our understanding of human genetic variation (Deenen *et al*., 2011; Innocenti *et al*., 2011; Simon & Roychowdhury, 2013). Thus, It is now known that there are 20,296 coding genes, 148,892,479 SNPs (single nucleotide polymorphisms) and 4,363,564 structural variants (insertions, deletions, duplications, translocations, complex chromosomal rearrangements, etc.) (Ensembl, 2016). Therefore, their results have been important inputs for customization of drug therapy and for the development of the first 35 pharmacogenomic clinical guidelines (CPIC, 2016).

Genetic Polymorphisms

Genetic polymorphisms can modify expression and function of enzymes and proteins involved in drug metabolism, affecting absorption, distribution, biotransformation and excretion as well as the drug-target interaction. Therefore, the presence of allelic variants will define to people as poor, extensive, intermediate or rapid/ultrarapid metabolizers, giving rise to differences in efficacy and safety.

Accordingly, the current practices for the dosing of therapeutic agents should be improved through the understanding of gene variation associated with “drug life” inside the human body. Therefore, in order to be able to predict patient’s predispositions to treatment complications and poor outcome it is essential to examine all candidate loci influencing response to drugs. We should also investigate metabolic pathways for activation or inactivation of drugs, the interaction between drugs, age and gender sensitivities, the impact of ethnicity and environmental factors to understand the individual and population variability

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in drug response. This is particularly important in Latin America, where there is a very heterogeneous profile of ethnicity and also different environmental conditions.

As we mention before, it is well known that the efficacy and safety of drug therapy show substantial inter-individual variability which is based on genetic variations affecting pharmacokinetic and/or pharmacodynamic factors (Evans, 2003). However, it is also known that there are non-genetic factors affecting drug response, for example age, sex, organ function, concomitant therapies, drug interactions, evolution of disease, nutritional factors, smoking habit, alcohol consumption, the presence of virus, among others. Therefore failure in efficacy or toxicity of drug therapy is due to the interaction of genes with environmental factors. A drug that is well tolerated and causes a strong response in some patients may be ineffective, toxic or may cause adverse drug reactions in other patients. In fact, it has been reported that 1 in 15 hospital admissions in the United Kingdom are due to adverse drug reactions (Pirmohamed *et al.*, 2004) and that adverse drug effects in hospitalized patients are the fifth leading cause of death in the United States (Mancinelli *et al*., 2000). It has been reported that approximately 2 millions adverse drug reactions lead to an spending of U$100 billion annually (Ross *et al*., 2011).

The pharmacogenomics/pharmacogenetics development in Latin America

From the academic point of view, there has been an increase in the number of research articles and clinical trials of pharmacogenomics/pharmacogenetics studies since 1961, just after the German pharmacologist Friedrich Vogel (1959) coined the term pharmacogenetics. As it is observed in Figure 1 from Vogel's definition, the number of publications has constantly increased, especially in the last 15 years, concomitantly the development of pharmacogenomics has evolved. Moreover an important number of Journal addressed to the pharmacogenomic field has appeared.

While the most conservative use of pharmacogenomics aims to stratify patient populations into poor, extensive, intermediate and rapid/ultrarapid metabolizer testing could be more useful in outlier patients.

In Latin America efforts to address pharmacogenetics/pharmacogenomics discipline starting from 1988 in Mexico and 1995 in Chile, together with the first study of genetic polymorphisms in CYP enzymes. In 1998 the frequencies of genetic variants of CYP1A1, GSTM1 and CYP2E1 were published in the amerindian "Mapuche" population (Muñoz et al, 1998) and later, in Chilean general population, frequencies were reported comparatively in relation to other populations (Quinones *et al.*, 1999). Lares Asseff *et al* performed clinical pharmacokinetic studies in pediatric mexican patients, showing a great interindividual variability which should be explained by pharmacogenetics and environmental factors as a modifier factor. In a study conducted by the same group (Lares-Asseff *et al*., 2005) included 55 Tepehuano amerindian subjects, all were extensive metabolizers (metabolic ratio MR <0.3). Moreover, they found a monoexponential relationship between the metabolic ratio of DM and DX (Dextrometorphan/Dextrorphan), and their oncentrations respectively, which can have clinical applications, since metabolic ratio can be predicted from a known DM or DX concentration.

In parallel, a number of studies on the ethnic distribution of these genetic polymorphisms were developed by a joint effort of several Latin American researchers supported by Spanish leading researchers in this field, so in 2006, borned the Latin American Network of

pharmacogenetics and Pharmacogenomics (RIBEF), which originates from a call of the Ibero-American Science and Technology CYTED, a Project with great Impact on Public Health, leaded by Dr. Adrián Llerena. This entity celebrated in 2008 its first conference in Cartagena de Indias on "Pharmacogenetics, Pharmacovigilance and Clinical Trials" with a broad representation of the Latin American Scientific Community and Professionals. This conference lead to the "Declaration of Cartagena" which set out the principles of the network. Currently, the RIBEF is a scientific society comprised of professionals whose regular work pharmacogenetics and pharmacogenomics is a main tool. The "Mission" of the RIBEF is the promotion of teaching, research and clinical care implementation of pharmacogenetics and pharmacogenomics in humans.

Recenlty, in 2014, begins the creation of a new Latin American network that brings together the highlights of the pharmacogenomic researchers and the study of the limitations of pharmacogenomics to be included in clinical (Quinones *et al*., 2014). This network is consolidated in the "I Latin American Congress of Pharmacogenomics and personalized Medicine" in Viña del Mar, Chile (May 21 to 23), which was carried out with participation of the majority of the Latin American pharmacogenomics researchers, one of the main world exponent of the discipline Dr. Magnus Ingelman-Sundberg and the Coordinator of Clinical Pharmacogenetics Implementation Consortium (CPIC), Mrs. Kelly Caudle. From that conference it was created the Latin American Society of Pharmacogenomics and Personalized Medicine (SOLFAGEM) entity that aims to strengthen the development of pharmacogenomics scientific research, both theoretical and experimental, in order to lead to progress and dissemination of creating discipline, clinical tools search and find products or biomarkers that can improve current treatments of diseases that afflict humans, as well as any other initiative aimed at maximum utilization of this scientific discipline for the benefit of the Latin American and global public health. In August of 2015 the president of SOLFAGEM (Dr. L. Quiñones) is included to CPIC as the first representative of a Latin American countries. Nowadays SOLFAGEM is looking for the adaptation of more than 30 clinical guidelines already implemented by the CPIC (2016) to the Latin American ethnic and socioeconomic reality.

In the work of the Quiñones *et al* (2014) there was reported the perceived importance of barriers for implementing the use of pharmacogenomics testing in clinical practice for Latin American countries, showing three major closely related groups of barriers: a) the necessity of clear guidelines for the use of pharmacogenomics in clinical practice, b) the insufficient awareness about pharmacogenomics among clinicians and c) the absence of a regulatory institution that facilitates the use of pharmacogenetic tests. Moreover, in this work it was included a survey for the analysis of the perceived relevance of the usefulness for 51 gene/drug pairs. As a result the Latin American health professionals considered relevant the TPMT/thioguanine, TPMT/azathioprine, CYP2C9/warfarin, UGT1A1/irinotecan, CYP2D6/amitriptiline, CYP2C19/citalopram and CYP2D6/clozapine pairs, however none pair received a higher than 50% of importance. The higher ranks for psychiatric drugs give rise to the idea that in the Latin American countries the variability in the response to these drugs (e.g. antidepressants) is fairly important. These results were considered as preliminary because the pharmacogenomic is poor developed in the region and due to that the importance of the gene/drug pairings in different countries could be evaluated differently because of the absence of some drugs in each market according to drug acquisition policies of each Ministry of Health.

CONCLUDING REMARKS

In conclusión, In Latin America the Pharmacogenetics and Pharmacogenomics areas are recently emerging fields and the main focus of the research is to evaluate ethnic differences to apply adapted guidelines to manage personalized pharmacotherapy. Large differences between countries in the awareness and in the use of pharmacogenomic testing are presumed, but are not well assessed to date.

Table 1: Factors conditioning interindividual variation in response to drugs *(Adapted from Quiñones et al, 2016, Rev Med Chile, In press)*

Drug
Quality Physicochemical, pharmacokinetic and pharmacodynamic properties Type of excipients used Posology Route of administration Interaction with other drugs
Patient
Genetic factors: Transporters efficacy, metabolic activity enzyme, receptor sensitivity. Epigenetic factors: CpG islands methylation, histone acetylation, expression of miRNAs and others. Physiological factors: Pregnancy-lactation age, sex, renal and hepatic function: Pathological factors: kidney disease, liver or another. Psychological factors: placebo effect
Environment
Diet: caffeine, meat, vegetables. Alcohol intake Cigarette smoke Pollutants

CpG: Citosine and Guanine rich sites. miRNA: micro RNA

FIGURE 1: Variation in number of publications [Scopus] and clinical trials including pharmacogenomics/pharmacogenetics studies from 1961 (extracted from Curr Drug Metab, 15(2): 202-8).

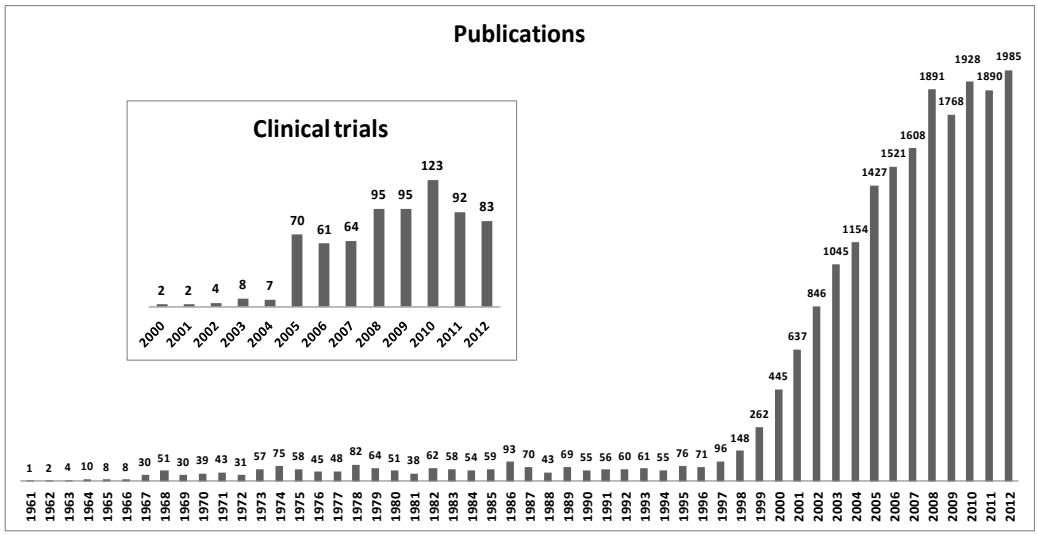

Table 2. Dosing Guidelines - CPIC (Available in https://www.pharmgkb.org/view/dosing-guidelines.do?source=CPIC)

	Drug	Guidelines	Updated
1	abacavir	CPIC Guideline for abacavir and HLA-B	*10/18/2016*
2	allopurinol	CPIC Guideline for allopurinol and HLA-B	*10/18/2016*
3	amitriptyline	CPIC Guideline for amitriptyline and CYP2C19,CYP2D6	*10/18/2016*
4	atazanavir	CPIC Guideline for atazanavir and UGT1A1	*10/18/2016*
5	azathioprine	CPIC Guideline for azathioprine and TPMT	*10/18/2016*
6	capecitabine	CPIC Guideline for capecitabine and DPYD	*10/18/2016*
7	carbamazepine	CPIC Guideline for carbamazepine and HLA-B	*10/18/2016*
8	citalopram	CPIC Guideline for citalopram,escitalopram and CYP2C19	*10/18/2016*
9	clomipramine	CPIC Guideline for clomipramine and CYP2C19,CYP2D6	*02/07/2014*
10	clopidogrel	CPIC Guideline for clopidogrel and CYP2C19	*10/18/2016*
11	codeine	CPIC Guideline for codeine and CYP2D6	*10/18/2016*
12	desipramine	CPIC Guideline for desipramine and CYP2D6	*09/15/2016*
13	doxepin	CPIC Guideline for doxepin and CYP2C19,CYP2D6	*09/15/2016*
14	escitalopram	CPIC Guideline for citalopram,escitalopram and CYP2C19	*10/18/2016*
15	fluorouracil	CPIC Guideline for fluorouracil and DPYD	*10/18/2016*
16	fluvoxamine	CPIC Guideline for fluvoxamine and CYP2D6	*10/18/2016*
17	imipramine	CPIC Guideline for imipramine and CYP2C19,CYP2D6	*09/15/2016*
18	ivacaftor	CPIC Guideline for ivacaftor and CFTR	*10/18/2016*
19	mercaptopurine	CPIC Guideline for mercaptopurine and TPMT	*10/18/2016*
20	nortriptyline	CPIC Guideline for nortriptyline and CYP2D6	*10/18/2016*
21	paroxetine	CPIC Guideline for paroxetine and CYP2D6	*10/18/2016*
22	peginterferon alfa-2a	CPIC Guideline for peginterferon alfa-2a,peginterferon alfa-2b,ribavirin and IFNL3	*10/18/2016*
23	peginterferon alfa-2b	CPIC Guideline for peginterferon alfa-2a,peginterferon alfa-2b,ribavirin and IFNL3	*10/18/2016*
24	phenytoin	CPIC Guideline for phenytoin and CYP2C9,HLA-B	*10/18/2016*
25	rasburicase	CPIC Guideline for rasburicase and G6PD	*10/18/2016*
26	ribavirin	CPIC Guideline for peginterferon alfa-2a,peginterferon alfa-2b,ribavirin and IFNL3	*10/18/2016*
27	sertraline	CPIC Guideline for sertraline and CYP2C19	*10/18/2016*
28	simvastatin	CPIC Guideline for simvastatin and SLCO1B1	*10/18/2016*
29	tacrolimus	CPIC Guideline for tacrolimus and CYP3A5	*10/18/2016*
30	tegafur	CPIC Guideline for tegafur and DPYD	*10/18/2016*
31	thioguanine	CPIC Guideline for thioguanine and TPMT	*10/18/2016*
32	trimipramine	CPIC Guideline for trimipramine and CYP2C19,CYP2D6	*09/15/2016*
33	warfarin	CPIC Guideline for warfarin and CYP2C9,VKORC1	*06/19/2014*

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