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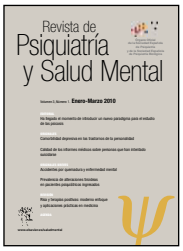

EDITORIAL

Strategies, strengths and limitations in pharmacogenetic studies of antipsychotics

Estrategias, fortalezas y limitaciones en estudios de Farmacogenética con antipsicóticos

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When pharmacogenetics burst onto the scene in the 1950s, it opened up great prospects for individualised therapy with safer and more effective treatment alternatives.[1] However, the application of pharmacogenetics in routine clinical practice is still far from becoming a reality, although psychiatry's interest in this discipline has increased exponentially over the last decade. Analysis of the characteristics of pharmacogenetic studies published during the last 10 years shows that there has been not only an increased number of genetic polymorphisms and genes analysed but also a change in the design and execution of these studies, with a transition from candidate gene strategies to genome-wide association (GWA) studies.[2]

From candidate gene strategies to GWA

Pharmacogenetic studies are benefiting greatly from rapid advances in genotyping technologies. There are currently platforms for analysing multiple genetic polymorphisms—basically, polymorphisms from a single nucleotide or SNP (single nucleotide polymorphisms)—in large populations at very competitive prices.[3]

These advances in genotyping techniques are also linked to an expanded knowledge of the human genome's global architecture and the distribution and location of the genetic polymorphisms along it. As a result of the International Haplotype Mapping Project (International HapMap Consortium),[4] public databases contain information on the verified frequencies of more than 2 million SNPs. The intention is to characterize the linkage disequilibrium (LD) pattern along the genome to facilitate the selection of SNPs that have more information (*tag SNP*) for inclusion in genetic studies.[5] These tag SNPs enable the variability of each haplotype block to be captured without having to genotype all the SNPs that make it up, and this permits the study of genetic variability across wide portions of the genome.

The results of these studies with a multitude of genetic polymorphisms require statistical tools to analyse them. In this regard, appropriate algorithms are being developed to analyse the data taking into account crucial factors such as the proportion of LD, the Hardy-Weinberg equilibrium (HWE), and corrections for multiple comparisons.[6]

GWA in pharmacogenetic studies with antipsychotics

gWA studies are still not very common in the field of pharmacogenetics for antipsychotics in schizophrenia. The

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results of 12 GWA studies have been published to date.[7-18] A similar number of GWA studies has been published in connection with the risk of schizophrenia.[19] However, of the 12 GWA in pharmacogenetics, 7 of them[10-16] were conducted in the population of patients participating in the CATIE study and 2 of them[8,9] with patients participating in a phase III clinical trial with iloperidone. This situation arises because pharmacogenetics studies experience recruiting limitations, especially in the area of psychiatry, which conditions the attainment of large cohorts.

Limitations of pharmacogenetic studies

There is a wide variety of antipsychotics that may be used in the treatment of schizophrenia. Proof of this lies in the heterogeneity observed in pharmacogenetic studies with these drugs over the last 5 years. Most of the studies use groups of patients treated with different antipsychotics, in many cases, not only the typical or first generation antipsychotics but also the atypical or second generation antipsychotics. This pharmacological heterogeneity is rarely taken into account in analysing the results because only one-third of the studies include this variable in the statistical analysis.[20-26]

There are also significant differences in the way these different treatments are assigned to participants. In studies like the CATIE or in clinical trials, the drug is randomly assigned. However, the design of most pharmacogenetic studies, whether prospective or retrospective, follows a naturalistic recruitment where the antipsychotic is assigned by clinicians on the basis of the patient's medical record, the symptomatology, and the clinical guidelines. Heterogeneity occurs not only in the type of antipsychotic used but also the concomitant medications and the dosage range for each antipsychotic administered. Bearing in mind that many pharmacological properties of the antipsychotics are dose-dependent, this is a variable of major importance in pharmacogenetic studies. However, not all studies take the existence of this variable into account in their analysis, nor is it always incorporated as a covariable in the statistical analysis.

All these limitations characterize recruiting for pharmacogenetic studies with antipsychotics, which translates to reduced cohorts being obtained. To these difficulties must be added others which, although they may not condition the recruiting, do make it difficult to compare different studies, to conduct meta-analyses, to replicate results, and to design multi-centre studies. These difficulties lie mainly in measurement of the primary variable and in the heterogeneity of the diagnosis. With regard to the primary variable, there are multiple approximations for assessing not only efficacy (for example, PANSS, BPRS, CGI, SANS, SAPS) but also the different adverse effects, and not only metabolic changes (for example, metabolic syndrome, BMI, lipid markers) but also motor changes (for example, AIMS, BARS, SA, UPDRS). Sometimes the diagnosis is not clearly defined or identified by the clinical tests or there is no molecular characterisation. In this regard, the search for endophenotypes may simplify these studies, especially in the field of psychiatry and mental illness. Supposedly, a genetic polymorphism will have more influence on an endophenotype than on a complex pathology such as the neuropsychiatric disorders. However, doubt has been cast upon this possible simplification, which would translate to even smaller sampling sizes.

Future challenges: the translation to clinical practice

the candidate gene and GWA strategies are necessary and complementary. Candidate gene strategies seem better adapted to pharmacogenetic studies, but they may appear to be favoured because of the results obtained in GWA studies and because of technological advances and the genome knowledge they apply. Moreover, GWA strategies can select markers, not only basing it on tag SNPs and the proportion of LD among them but also incorporating functional markers or other SNPs identified through gene or candidate SNP strategies.

However, there is no regulation stipulating the requirements for validating a pharmacogenetic test, analytically and clinically, which makes it difficult to apply in clinical practice. The credibility of both GWA strategies and gene or candidate SNP strategies depends largely upon the replication of results in different populations or in large-size cohorts. This replication is not a simple matter, however, because there are many factors involved, such as differences in the allelic frequencies and the proportion of LD among different populations, or differences in diagnosis and treatment among different Centres or organisations. There are also the limitations to recruiting a large cohort for pharmacogenetic studies, as mentioned above.

The different strategies addressed here (candidate gene and GWA) are different but equally valid approximations for achieving the ultimate objective of pharmacogenetics—individualised therapy.

Conflict of interest

The author declares no conflict of interest.

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