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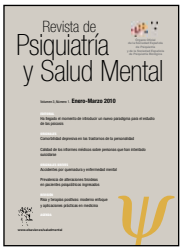

EDITORIAL

A Genetic signature for complex psychiatric diseases

Una firma genética para las enfermedades psiquiátricas complejas

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The past decade experienced a genomic revolution with the identification of associations between thousands of genes and a range of common complex disorders. Psychiatric diseases, such as schizophrenia, bipolar disorder, Alzheimer's and Parkinson's disease, major depression and autism fall within this category of common complex disorders. The identification of genes increasing risk to these brain disorders affecting mental function and behavior, potentially presents an opportunity to further understanding their pathophysiology and to predict high-risk individuals or risk for their offspring. This may also lead to strategies that reduce the burden of psychiatric disease through intervention at a presymptomatic stage.

Genes in complex disorders

One of the first mental disease genes identified by positional cloning was the gene that harbors the mutation responsible for the classical Mendelian disorder of Huntington's disease[1]. One copy of the altered gene causes an individual to be 100% likely to develop Huntington's disease. To date, thanks to the Human Genome Project, the HapMap Project and modern genomic, molecular and statistical tools, we know the genes responsible for over 4000 Mendelian diseases[2]. Huntington's disease and other Mendelian diseases are caused by single gene mutations and are relatively rare in the population. In contrast, common complex diseases are usually present in the population with a prevalence of 1 % or more and, so far, gene-finding has not been as successful as with Mendelian diseases. Common diseases as schizophrenia have a complex inheritance and are believed to result from a combination of multiple genetic and environmental factors that act together to cause the disease. Each genetic factor in itself does not have a major effect on the pathophysiology of the disease and thus can exist in high frequency in the general population. Demonstrating genetic causation on complex diseases is, therefore, a difficult task given the their complex nature. Individual genetic variants are generally neither necessary nor sufficient to cause the disease and they are present in both affected and non-affected individuals, which makes difficult to unequivocally assign them to the disease. Functional studies aimed at finding the specific role of those genes in the disease may not give positive results, since the effect of each individual variant on the disease is small and might not be reflected as an observable change in the physiological function.

Despite the difficulties of gene-finding in complex diseases, many genetic variants that increase risk to some complex psychiatric diseases have been identified. Although the increase in risk for the majority of the common genetic variants is low, all of them taken together have a substantial effect on the disease in the population at risk. In schizophrenia, for instance, heritability goes up to 80% and first-degree relatives of affected individuals have 5 to 10-fold increase in risk compared to the general population; which points to a strong genetic component for this disorder. In the past few years, linkage and association

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studies have uncovered hundreds of genetic variants that increase the risk for schizophrenia[3]. The current view of the genetic architecture of schizophrenia is that multiple common and a few rare genetic variants contribute to the susceptibility to schizophrenia. Linkage and candidate gene association studies have led to the identification of a few genes implicated in schizophrenia, including among others, neuregulin 1 (NRG1), dysbindin (DTNBP1), G72/G30 locus, and the DISC1 gene[4-7].

In the past decade genome-wide association studies (GWAS) have taken the lead in gene-finding for genetic diseases. With this approach one can look for genetic variants associated with the disease (i.e. Single Nucleotide Polymorphisms or SNPs that are changes in one nucleotide of the DNA sequence) localized throughout the genome. The results of ten GWAS have been published so far. These show an association of schizophrenia with several genetic variants or SNPs[8-18]. In addition to SNP association studies - where the associated genetic variants are common in the population and usually have a low effect on the individual carrier - Copy Number Variants (CNVs), which are small chromosomal aberrations (microdeletions and microduplications), have been found more frequently in patients than in controls, and to be associated with a high increase of risk to develop the disease. CNVs have been found implicated in schizophrenia and other neuropsychiatric diseases including bipolar disorder and autism[14,15,19-24]. Support for the implication of microdeletions on the etiology of schizophrenia comes from the 22q11.2 deletion syndrome or DiGeorge syndrome. These patients harbor a deletion typically of 3 Mb in chromosome 22, and patients present with a high risk for developing schizophrenia[25].

Genetic studies and direct-to-consumer tests

We are still far from explaining all the heritability observed in schizophrenia. Clearly, there are many more variants implicated in schizophrenia as well as in other neuropsychiatric disorders, and we are probably only seeing the tip of the iceberg. New technologies as next-generation sequencing in the next few years may bring us many more genetic variants that help explaining the heritability of complex neuropsychiatric disorders[26], and may provide a more comprehensive view of the already identified variants. In the meantime, scientific publications are accumulating data on genetic variants associated with complex diseases that may be useful for translational research in this early stage. Is it too early to apply this knowledge to the clinic? Do we have all the pieces to complete the puzzle and develop intervention strategies for patients with genetic variants associated with increasing risk for psychiatric diseases? We may not have the answers for these questions, however, in the last few years, companies offering genetic testing services on the Internet (the so-called, Direct-To-Consumer tests, DTC) are using the same common genetic variants used in genome-wide association studies to provide patients with measures of risk assessment for complex diseases after testing them for a battery of genetic variants. Commercialization of these tests is driven by strong financial incentives to bring them to the public market including via Internet. Early tests, however, may be poorly predictive due to variants still to be found and the little knowledge of gene-gene and gene-environment interactions. Other questions remain to be answered as for example how the genetic susceptibility to certain diseases changes depending on the ethnic background of the individuals and how much weight epigenetic changes have in determining the gene expression pattern of one person's genome throughout life.

It is, then, arguable whether it is currently worthwhile pursuing common genetic variants given that they have a low effect on the disease, and intervention strategies in patients with these individual variants may not have a considerable benefit and may not reduce the burden of disease in the population at large. But should we ignore the scientific information since it is not yet 'complete'? We may want to start developing strategic interventions based on what we already know, provided the information has been contrasted in independent studies, so we can keep improving them as we accumulate new and useful scientific data leading to translational research.

In the past, only medical institutions offered genetic testing, as part of the genetic counseling upon referral of a medical doctor. In words of the US National Society of Genetic Counselors "Genetic counseling is a medical service that helps people understand and adapt to medical, psychological and familial implications of genetic contributions to disease". Now, individuals seeking to know about their genetic risk to develop a range of diseases can obtain information via DTC tests "bypassing" the medical sector, i.e., without counseling[27,28].

Regulation of genetic testing in complex disorders

Questions have arisen along the commercialization of these tests, mainly among patients and physicians that may not be ready to enter this still fussy complex disease genomics world, avoiding fear and misconceptions. It is important to bear in mind that even if any given individual does not carry the risk variant he/she could still develop the disease[26]. The availability of such information could be misleading to patients who might think they will never get the disease. On the contrary, carrying a risk variant does not mean that the patient must develop the disease (because of the low risk associated with each variant). This situation may be different in a few years when the effect of more genetic variants associated with common diseases will be better described. Other issues on the sensitivity and specificity of the test[29] and confidentiality, employment and life insurance need clarification. It is important, therefore, to ensure transparency and to provide accurate information to consumers so they can make informed decisions on their health. We also need appropriate guidelines to help physicians advise their patients, who are considering this form of genetic testing, to inform them about the limitations of the currently commercially available tests, and to develop strategic interventions when possible[30,31]. The US Food and Drug Administration (FDA) agency is

now on the way to regulate the Direct-To-Consumer tests as 'devices'. The Medical Device Amendments to the Act require premarket review and approval by the FDA of medical devices intended for human use, to ensure that they are analytically and clinically accurate "so that individuals are not misled by incorrect test results or unsupported clinical interpretations". The Act aims to "protect the public from medical products that may pose an unreasonable risk of harm" (http://www.phgfoundation.org). In the EU, however, the European Medicines Agency (EMEA) does not intervene in these issues. Although the "European Directive on in vitro diagnostics medical devices (98/79/EC)" regulates in vitro diagnostics, everything that is 'predictive' is not included, which is the case for DTC tests. Therefore, the market of DTC tests is open in the EU and companies do not need to do any pre- or post- market analysis to commercialize these tests. The scientific and medical community should become involved with this issue and advise the institutions to regulate companies offering DTC tests, as it will certainly be an expanding field.

There are many studies that have examined the issue of genetic counseling in schizophrenia and other complex psychiatric diseases among the general population and among physicians. Most of these studies conclude that genetic counseling is well received especially by families of affected patients that want to know their risk to develop the disease, or their risk to transmit the associated genetic variants to their offspring. Nevertheless, access to genetic counseling services is not widely available and physicians do not routinely offer the option of genetic counseling[32-35]. Some patients and their relatives also believe that knowing their genome could help them psychosocially, maybe eliminating feelings of guilt and or shame[36]. Some studies showed that genetic testing can cause increased anxiety, but that it tends to be transient[37].

We are approaching a new era in genetic testing that has a great deal to offer clinicians and patients. However, as we pursue greater knowledge of genomics and its application to clinical medicine we should proceed carefully and with caution. Patients will want to know the risk for the development of certain diseases, however, this is not an easy subject when talking about complex psychiatric diseases. Information about how much more risk a person has, compared to the general population must be provided with educational strategies about how to accurately interpret the results of genetic tests. Special legislation for the DTC tests may be needed and guidelines for how such information should be interpreted and applied including as regards intervention strategies based on risk assessment.

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