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The limits of association studies in behavioral genetics: a revenge of sexual reproduction?

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Abstract

Genetic testing is showing its limits in assessing the hereditary risk for complex diseases as well as for psychic/psychiatric normal and pathological conditions. Genetic associations studies have revealed unable to produce consistent data on major disorders and more recent genome-wide association studies (GWAS) have provided more promising results identifying several genetic markers for individual risk of genetic diseases, but these generally consist of common variants that explain a small fraction of the overall genetic contribution to such risk. Even the mapping of copy number variations (CNVs) has so far produced inconsistent results. The future is thus to investigate how the alleles carried by our cells are expressed, and this is being pursued by two approaches: the study of our non-coding DNA, which is known to have an important role in the regulation of gene expression, and that of epigenetic mechanisms that represent the interface of gene x environment interactions and may allow us to better understand how neuronal populations direct behavior. As of now, the complex, multifactorial nature of our behavior and the continuous genotypic variation of human populations appear to represent the premise for such limits. Since sexual reproduction is the source of allelic assortment that makes our genetic variation continuous, it represents a strong restraint for geneticists.

Keywords: SNP, GWAS, CNV, psychiatry, epigenetics, sexual reproduction

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1. Introduction

A growing number of studies is revealing the limits of genetic testing to assess the hereditary risk for our diseases. The reason is easy to understand: apart from a few rare alleles the presence of which is the direct cause of genetic diseases, see for example cystic fibrosis, sickle-cell anemia, phenylketonuria, determining an individual's specific genotype does not predict the chance of getting sick. In fact, when analyzing complex diseases, it is important to consider their multifactorial nature, by which the phenotypic variance relative to a single gene is difficult to express. This is particularly true for behavioral genetics. When phenotypic traits, including behavior, are the product of the action of genes that do not control vital cellular processes so to not substantially influence one's fitness, it is hard to unveil their genotypic dependence.

2. Genetic association studies of behavior

There are now thousands of genetic association studies of psychic and psychiatric disturbances, personality traits and cognitive functions, but still there is absence of clear results revealing that this or that genetic symptom or behavioral disposition or personality disorder is associated to a gene or another, or that bearing a certain allele represents a risk factor for a disease. In other words, we are still searching a genetic marker

that could help identify a specific psychiatric disorder (Li, 2013).

Genetic differences among individuals sum up to approximately one every thousand base pairs, that is various million nucleotides per individual genome. Even so, considering that, for where single nucleotide polymorphisms (SNP) are concerned, many of them fall within gene coding regions, phenotypic differences among humans are not so pronounced. Genetic polymorphisms are so widespread that for most chromosomal loci, bearing one allele or another does not make a substantial difference.

Let's take the example of eating disorders (ED). A meta-analysis by Lee and Lin (2009) of data relative to more than 2,000 participants from eight independent case–control association studies of a functional polymorphism of the serotonin transporter gene promoter (5-HTTLPR) with EDs, found that anorexia nervosa (AN) but not bulimia nervosa (BN) is associated with *s* allele carriers (*ss* and *ls* genotypes). Despite this result, however, many studies have produced inconsistent data or found no significant association. In general, the association of genes to EDs is still to be fully understood (Boraska et al., 2014).

Based on the efficacy of serotonin reuptake inhibitors in treating, among other psychic conditions, obsessive-compulsive disorder (OCD), the 5-HTTLPR polymorphism, which was found to have a significant functional effect on extracellular serotonin concentration (Lesh et al., 1996), has been largely studied in OCD patients. So far, however, contrasting results have been produced and a meta-analysis by Mak et al. (2015) describes no association of this polymorphism with OCD. In general, association studies examining candidate genes functioning within the serotonergic and dopaminergic systems, based on pathophysiological and pharmacological information of OCD, have been inconsistently replicated.

My group has investigated association of the 5-HTTLPR polymorphism with OCD symptoms, personality traits or perfectionism, in one study (Di Nocera et al., 2014) and with procrastination in another study (Di Nocera et al., 2017), obtaining negative results. A meta-analysis by Risch et al. (2009) also found no evidence that this polymorphism alone or in interaction with stressful life events is associated with elevated risks of depression.

3. The impact of genome-wide association studies

Since 2005, genome-wide association studies (GWAS) have provided a new powerful tool in the genetic field, being able in a single shot, to tests hundreds of thousands of single-base genetic variants carried by one subject. GWAS identify markers for individual risk of genetic diseases: as of now more than a million have been described in hundred thousand individuals. Thus, from a few genetic associations truly identified in various medical fields before the introduction of GWAS, today there are hundreds of regions of our genome displaying replicated associations with dozens common diseases or complex traits.

However, markers identified in GWAS are common variants that generally explain a small fraction of the overall genetic contribution to the risk for a disease. Since genetic diseases usually affect a small percent of the population, it appears that carrying one of the "enemy" markers found, increases the risk for any disease of an insignificant amount. As a matter of fact, even for widely approached diseases, markers identified so far typically explain less than 20% of the heritable risk variance (for a thorough review, see Gibson, 2012).

Paradoxically, as underlined by Daniel Goldstein (Goldstein, 2009), if sample sizes were increased to reveal variants covering the entire genetic risk, the number of common markers identified would be so high that very little knowledge would be provided into the biology of a disease and its medical approach. So, the search should move towards variants with larger effect sizes. However, these variants would have a substantial role in any disease and natural selection is known to reduce the frequency of disease-associated variants in the population. In other words, these markers are necessarily rare and very difficult to identify.

This search would be particularly indicated for psychiatric diseases, such as schizophrenia, the genetic risk of which should be pursued in extremely rare gene variants that are not shared by large populations, but are limited to families and single individuals. Going to a conclusion, what progress have we recorded in the psychiatric field? Little if any. From the one side, association studies have told us that we have probably been looking at the wrong genes, from the GWAS side, many genetic markers have now been identified that still tell us little of the biology of any condition.

4. Copy number variations

In 2006 an additional research topic, also pursued by GWAS, has initiated the mapping of copy number variations (CNVs), or chromosomal loci that contain either duplicated or deleted genes (Redon et al., 2006). These studies have identified thousands of these variation, show that they are common, they may be large, with several duplications, and cover more than 10 percent of our genome. Sixteen percent of known disease-related genes, including a few psychiatric disorders, have been mapped in the CNVs. However, as of now this search has produced inconsistent results (see for example, Velinov et al., 2019).

3. What's next?

If we look from a truly biological perspective, what counts for any of our cells is how and when the alleles they carry are expressed, and how their expression can depend on the environment. Something new we have learned from the complete sequencing of our genome is that only 2 percent of our DNA contains the "coding genes", genes that carry information needed to synthesize proteins. The remaining 98 percent is known to have an important role in the regulation of gene expression but does not participate directly to biosynthetic activities. To locate pathogenic mutations in the non-coding genome, Gussow and colleagues have developed a new technique called Orion (Gussow et al., 2018), designed to pinpoint regions that are likely to contain genetic changes responsible for diseases. This approach may also be helpful in the psychiatric field. On the other hand, gene x environment interactions can be now investigated based on known epigenetic mechanisms. Epigenetic studies may unveil specific mechanisms that influence gene expression and control neuronal activity, representing the cellular basis for behavior.

Besides the need to search for more candidate genes and gene regulation data, what have we learned from the genetic studies of behavior, taken for granted that they concern a field with relatively low biological significance? We are surely more aware that given the genetic variation produced by mutations, meiosis and sexual reproduction make such a wide assortment of chromosomal sequences, that resulting individuals are much less different than they should be. This sharing of genetic variation is continuous and widespread, so that all sorts of alleles are mixed up in an enormous container, a sort of Pandora's jar (which, however, contained all the evil of humanity), and picked up, two at a time, at every new recruiting of gametes to produce a new individual. The complex, multifactorial nature of our behavior, together with the continuous genotypic variation of human populations, produces a genetic stalemate, an impasse. So, there is one real conclusion in this historic phase of genetic studies. What we are observing is partly due to the fact that we are diploid and reproduce sexually, so it confirms the evolutionary success of sexual reproduction, that is why we reproduce sexually and not budding kids from our bodies.

Sex can make us happy, it sometimes makes geneticists a little less happy.

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