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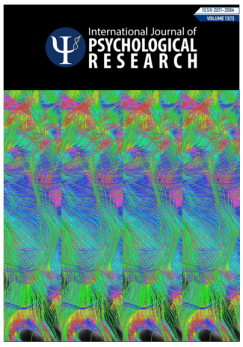
EDITORIAL



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The Mendelian Legacy to Mental and Behavioral Disorders

El legado mendeliano a los trastornos mentales y comportamentales

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During the last four decades it became clear that genetics together with environmental forces play a major role in shaping psychiatric syndromes. A compelling evidence to back this preposition up is the significant estimated parameter of heritability for Schizophrenia (EQZ), Bipolar Disorder (BD), Major Depression (MD), Attention Deficit/ Hyperactivity Disorder (ADHD), among other operative taxonomic clinical units (OTCU), as defined by the saga of DSMs (DSM-I to 5) (Pettersson et al., 2019).

Heritability symbolizes the amount of phenotypic variance explained by inheritance in a linear equation that parallels genetics + environment + error (noise) to the whole complexity of the trait (phenotype) (Vinkhuyzen, Wray, Yang, Goddard, & Visscher, 2013). Estimated heritability for different psychiatric disorders range from 0.30 to 0.80, being MD the lower and ADHD the higher one (Pettersson et al., 2019). These results have been replicated by different studies using different schemes of ascertainment, type of cohorts (family based, case-control), populations under study, diagnostic tools, and sets of molecular genotyping data from the outburst of genome-wide association (GWA) studies (Acosta, Arcos-Burgos, & Muenke, 2004; Acosta et al., 2011; Arcos-Burgos & Acosta, 2007; Feldman & Ramachandran, 2018; Pettersson et al., 2019; Ruiz, Blanco, Arcos, Santander, & San Martin, 1997).

In the case of the heritability estimated by the GWA studies, the amount of variance attributable to genetic differences in the measured trait is less than the one based on correlations between relatives, and to this difference the term 'missing heritability' has been coined (Feldman & Ramachandran, 2018). As pointed by Feldman and Ramachandran (Feldman & Ramachandran, 2018), in this case, missing heritability refers to a genetic variation that cannot account for much of the heritability of diseases. In addition, the term 'heritability' has several limitations:

> Heritability estimated from linear models for variance analysis still depends on the environment in which it is measured, and an increase in SNP-based heritability… cannot provide useful information as to whether cultural, social context or environmental intervention is likely to have an effect (Feldman & Ramachandran, 2018, p. 7)

Even knowing the limitations of the concept of heritability, let us assume that hidden and unexplained cultural vertical transmission, epigenetic mechanisms, and epistatic interactions are not underpinning this 'missing heritability'. The reason for this assumption is that mental disorders, in contraposition to behavioral traits, are less likely to be affected by vertical transmission, and it is challenging to build a paradigm of cultural transmission in the case of devastating psychiatric diseases. Further, while epistatic effects underpins susceptibility to mental disorders, as for example ADHD, ASPD and MD, the real contribution of epigenetic effects is yet under research (Acosta et al., 2011; Arias et al., 2011; Jain et al., 2012; Valencia & Cuartas Arias, 2016; Wong, Dong, Andreev, Arcos-Burgos, & Licinio, 2012).

Following this vein, one of the main concerns emerging from these high estimates of heritability for psychiatric syndromes is that such significant genetic apportionment to a phenotypic trait can be explained, at least partially, by the existence of major genetic loci (also known as major effect loci, quasi-mendelian effect loci) instead of polygenes of minor effect. In other words, these major loci will be the main cause predisposing to mental disorders (Arcos-Burgos & Acosta, 2007; Arcos-Burgos & Muenke, 2010). This concept is not trivial, as the definition of major genes is consequently linked to best precision and reliability of the clinical diagnosis, disease follow up, prediction of natural history, and eventual prevention, and/or the finding of potential targets for therapeutics. The main limitation associated to these loci of major effect is that their harbored disease predisposing alleles are rare and heterogeneous.

Two of the most replicated loci exhibiting features of major genes, which predispose to EQZ, are harbored in the long arm of chromosome 22 (22q12-q13.1) and on the short arm of chromosome 6 (6p24-22). Initial reports of this association and linkage of these chromosome regions to EQZ date since 1994 (Pulver et al., 1994). These findings have been supported by additional studies of linkage and during the last decade by GWA studies, i.e., one seminal manuscript, involving thousands of cases and controls from European ancestry, showed that the most associated genotyped SNP was located in the first intron of myosin XVIIIB (MYO18B) on chromosome 22; the second strongest association comprised more than 450 SNPs on chromosome 6p spanning the major histocompatibility complex (MHC) (International Schizophrenia Consortium et al., 2009). Additional studies from populations with different ancestral origins showed that loci heterogeneity is highly plausible (Lam et al., 2019)

As a whole, we can recapitulate several points: i) the linkage results fitting dominant-codominant models of Mendelian inheritance to the segregation of the EQZ phenotype; ii) the definition of minimal critical regions containing the potential causal genes; iii) the characterization of potential causal mutations with the new state of the art techniques of genome sequencing; iv) the definition of the 'final cause' gene or genes predisposing to EQZ that are harboured in these to chromosomal regions; v) the possibility of modelling the effect of this mutations in advanced systems of cell culture (neuronal) to evaluate the effect on gene transcription, translation, genome regulation, cell and organ development, and metabolomics effects.

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