The Complexity of Mental Disorders

Ayla Arslan

International University of Sarajevo, Faculty of Engineering and Natural Sciences, Department of Genetics and Bioengineering, HrasnickaCesta 15, Ilidža 71210 Sarajevo, Bosnia and Herzegovina

Abstract

Upon completition of human genome project, there has been a huge effort to identify genes that have been associated to mental disorders like schizophrenia or depression. However, these investigations still remain at theoretical level. Thus, psychiatry does not seem to benefit from postgenomic era as desired. This paper will briefly discuss the reasons for this bottleneck in terms of the complexity of mental disorders.

Keywords: Genetic variation, gene-environment interactions, neuropsychiatric disorders

1.Introduction

Mental disorders are brain diseases that arise from the complex interplay of nature and nurture. In comparison to other complex disorders however, the effect of nature appears to be quite strong: the susceptibility for major psychiatric disorders show a strong degree of heritability (Moldin and Gottesman, 1997). Thus, following the completition of human genome project (HGP), there has been a huge effort to identify genes that have been associated to mental disorders like schizophrenia or depression. However, these investigations still remain at theoretical level.

This problem is already well reflected in the lack of validated drug targets. For example, a careful observation of scientific studies between the years of 1990-2001 will show the dramatic increase in the total number of research papers related to cognition and schizophrenia but, this progress was not translated to drug research as the clinical trials during the same period remained unchanged (Hyman and Fenton, 2003). Thus, considering the potential of new genetic approaches (see below), psychiatry does not seem to benefit from postgenomic era as desired. This paper will briefly discuss the reasons for this problem in terms of the complexity of mental disorders.

2. The Human genome project and new opportunities

The completition of Human Genome Project (HGP) in 2001 has had big impact in the society both economically and medically. According to a study published by Battelle Technology Partnership Practice

(2011), $3.8 billion investment on the HGP by the US government has led to a drive of $796 billion in the U.S. economy between the years 1998-2003. Besides, medical diagnosis, treatment and disease prevention have been innovated. For instance, EGFR mutation in lung cancer, KRAS mutation in colon and lung cancers, BRAF mutation in colon cancer have led to the identification of molecular markers to be used for diagnosis (McLeod, 2013).

Although genomic approaches increasingly provide new answers in medical practice, much basic research remains to be done for an effective application of genomics especially for a translational psychiatric research. The HGP has led to the emergence of new approaches for the utilization of new genetic data. Among these approaches, analysis of genetic variations, i.e., single nucleotide polymorphisms (SNPs), analysis of gene expression and gene function have been especially powerful (Tang et al., 2009). As a result of these methodologies many candidate genes have been identified in relation to mental disorders like schizophrenia or depression but these investigations still remain at theoretical level (Ptacek et al., 2011). Why does not psychiatry seem to benefit from genomic revolution as desired ? This problem is likely a factor of complex nature of psychiatric diseases.

3. Genotype, phenotype and environment

Mental disorders are not caused by a single gene, rather by multiple genes (Arslan, 2015). The multiple genetic factors will not be discussed here in detail as it is rather a better known phenomenon. The genetic complexity of mental disorders is further increased by

gene×environment (G×E) interactions in between the genotype and phenotype (Caspi and Moffitt, 2006). Regarding this, a good example comes from a study of 2002 by Caspi et al. who published a research paper showing the role of the monoamine oxidase A gene (*MAOA*) in the development of antisocial behaviors. Utilizing the data from the Dunedin Multidisciplinary Health and Development Study (DMHDS), Caspi et al. showed the effect of G×E interactions between childhood maltreatment and the variations in the MAOA gene in the development of antisocial behaviors. Thus, the associations between childhood maltreatment and antisocial behavior have been found to be modified by the variations of MAOA gene. The gene encodes the Monoamine oxidase A (MAOA), an enyzme, which catalyzes the oxidative deamination of biogenic amines, including serotonin (5-HT), norepinephrine (NE), and dopamine (DA) and the neuromodulator phenyl ethylamine (PEA). There are several variations in the MAOA gene and these polymorphisms have already been shown to be associated with behavioral phenotypes such as aggression and substance abuse besides to affective disorders like bipolar disorder and panic disorder (reviewed in Shih and Thompson, 1999). Among these variations, a well-characterized upstream variable number tandem repeat (uVNTR) polymorphism in the promoter region of the MAOA gene that is known to affect gene expression causing high activity or low activity MAOA variants. Caspi et al (2002) found that the carriers of the low activity variant are more responsive to the effects of childhood maltreatment associated with the development of antisocial personality disorder than the carriers of high-activity variant. Since then, this paper has been well replicated Enoch et al., 2010 Prom et al., 2009Sjoberg 2007, Nilsson et al/. 2006 despite some negative results (Huang et al., 2004). Nevertheless the results were further supported by a study of meta-analysis (Taylor and Kim-Cohen, 2007). While the effect of the GxE is evident, it remains unclear how to incorporate this parameter in to genetic analysis as multiple genetic variations needs to be assessed in terms of environmental factors.

Besides to the complexity of genetic factors, and gene-environment interactions, a further complexity is the lack of biologically defined diagnostic criteria: psychiatric disorders are diagnosed on clinical grounds. According to the current version of the Diagnostic and Statistical Manual of Mental Disorders-V, (DSM-V), there are over 300 different types of mental disorders. One problem is the problem of objectivity: the main source of information about the symptoms come from the patients so they may not be objective. Still, many psychiatric illnesses can be diagnosed reliably according to the Diagnostic and Statistical Manual (DSM) and the International Classification of Diseases (ICD) the standard diagnostic guidelines. But these guidelines often does not provide the objective tests to draw boundaries around a particular clinical state (Tandon 2012). Another problem is that sometimes patients may show a combination of such phenotypes (symptoms) that overlap across these disease boundaries defined by DSM (Arslan, 2015). Since the classical psychiatric genetic research has been directed to genetic effects on disease, it is likely that gene-discovery studies in psychiatric research still remains at the theoretical level, because disease diagnosis is not based on biological criteria so it interferes with the top-down research (Arslan, 2015).

4. Conclusion

Despite the opportunities of genomic revolution, there is a lack of genetic markers that reliably guide the diagnosis of psychiatric disorders (Hyman and Fenton, 2003). This problem seems to derive from the complex nature of psychiatric disorders. These complexities are multiple genetic factors, gene-environment interactions, subjective nature of psychiatric phenotypes and the lack of biologically defined diagnostic criteria that interferes with the top-down research. Recognition of these complexities however will lead to the emergence of new approaches. Among these approaches, integration of environmental factors into functional neuroimaging studies have good implications (Lederbogen, F., et al., 2011; Meyer-Lindenberg and Tost, 2012). Moreover, there is a growing literature addressing the complexity problem of psychiatric phenotypes by the use of intermediate phenotypes since 2000s (Bookheimer, et al., 2000). With the support of new statistical developments, a further progress will be the accumulation of data collected by multivariate, large-scale analysis of genetics and intermediate phenotypes that eventually leads to the analysis of psychiatric phenomenon in terms of neural activity, genetic variation, environmental context together.

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