Psychiatria Danubina, 2017; Vol. 29, Suppl. 3, pp 476-480 *Conference paper*

GENETICS AND PSYCHIATRY: MYTH OR REALITY?

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SUMMARY

Greek mythology and philosophical speculations were the first human productions on madness and psychiatry. Likewise, the origins of genetics sink their roots in a very remote and difficult time. This work tries to give an idea of the relationship between genetics and psychiatry through the myth and reality.

Key words: *genetics – psychiatry - genetic factors*

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INTRODUCTION

The myth is a tale that describes events whose understanding is difficult for the ancient man and it is a simplified representation of complex phenomena. In ancient Greece, morbid processes were considered as the result of divine punishment; if the man had offended the God or had not sacrificed sacrificial rites to the extent necessary to overcome the wrath, God sent suffering, illness, and death. The healing process was not contemplated, also because very often the man died due to the morbid processes themselves. The Gods of Olympus were immortal, immune from illness and suffering; they were quarrelsome, vindictive, prone to vices, often devoted to extramarital affections and betrayal. If man were mortal, not worshiping the gods properly, or if he was slandered, he was punished by invisible and infallible darts or by the lightning of Zeus.

But how did the illnesses arise?

Originally, in the mythical golden age, man did not become sick and above all did not work because the earth spontaneously produced all sorts of fruit.

One day, the tithe Prometheus decided to steal fire to the gods to give them a gift to men.

Zeus (Jupiter) punished the entire human race by sending a woman named Pandora along with a sealed vessel in the bottom of which was all forms of illness and suffering.

Pandora, taken by curiosity, opened the lid and every form of evil came out of the pot. From that moment the disease spread and men carried a tough and tiring life that culminated with death; from that situation on was also said the "curiosity is woman"!

Not even homo sapiens was able to give answers to phenomena such as the transmission of hair color and eyes or secondary sexual characters; it will be necessary to wait two millennia for rationally explaining phenomena and formulating laws that govern the existence of living beings.

Psychological disorders and mental illnesses were considered to be prejudiced by the public and public opinion as incomprehensible, difficult to understand and rationalize, or belonging to the irrational sphere, even for bizarre behaviors and deviations from the common sense put in place from the sick. With the advancement of psychiatry and psychology, from the Middle Ages onwards, considerable progress has been made in understanding and treating psychological disorders, considered to increase incidence in the contemporary era. To better understand the nature of psychiatric illnesses, man has increasingly considered the possible role of genetics in these pathologies.

THE REALITY OF GENETICS AND PSYCHIATRY

Although the myth of genetics and psychiatry is still undefined, the reality is well established. In the past 30 years, human genetic studies have identified more than 1000 genes responsible for human diseases among which there are psychiatric illnesses. In particular, using molecular genetic studies such as linkage and association studies (Juli 2012), it has been evaluated the possibility that genetics also plays a critical role in the vulnerability of psychiatric disorders.

The first consideration can be made for bipolar disorder: in this contest, linkage studies have showed significant results concluding that the regions with the best evidence for linkage include areas on chromosomes 1q (Detera-Wadleigh., 1999; Millar 2004), 2p (Liu 2003), 4p (Blackwood 1996), 4q (Badenhop 2003; Liu 2003), 6q (Dick 2003), 8q (Segurado 2003), 11p (Engelad 1987; Zandi 2003), 12q (Morissette 1999), 13q (Stine 1997; Detera-Wadleigh 1999; Kelsoe 2001), 16p, 16q (Dick 2002), 18p, 18q (Berrettini 1994; Garner 2001), 21q (Straub 1994; Detera-Wadleigh 1996, Liu 2001), 22q (Kelsoe 2001; Potash 2003), and Xq (Mclnnis 1999; Ekholm 2002). In addition, association studies identified different candidate genes in bipolar disorder such as serotonin transporter (Zammit 2006), catechol-o-methyl transferase (Craddock 2006; Shifman 2004), brain-derived neurotrophic factor (Sklar 2002,

Neves-Pereira 2005; Okada 2006; Kremeyer 2006), tyrosine hydroxylase (Leboyer 1990), G72/G30 (Hattori 2003; Schumacher 2004), neuregulin (Green 2005), disrupted in schizophrenia genes (Millar 2004). On the other hand, family and twin studies have been recognized that bipolar disorder tends to run in families (Juli 2012).

The influence of genetic factors has been evaluated by different research groups also in Eating Disorders (EDs) such as Anorexia Nervosa, Bulimia Nervosa, Binge Eating Disorder, Feeding Eating Disorders Not Elsewhere Classified and Night Eating Disorder (Juli 2014). As regards linkage studies, a significant linkage has been found on chromosome 1 for classic Restricting Anorexia Nervosa (Bergen 2003) and when the linkage analysis were performed considering not only the illness but other phenotypic characteristics related to it, a significant number of signals were observed such as obsessionality at 6q, anxiety at 9p, body mass index at 4q, concern over mistakes at 11p and food-related obsessions at 17q and 15q (Bulik 2003); a significant linkage between Bulimia Nervosa and 10p chromosomal region has been identified too (Blundell 1987). A number of association studies have been performed to identify candidate genes for EDs: central and peripheral neurotransmitters, hormones and peptides that have been shown to regulate eating behavior, shown polymorphisms that appeared of particular interest. Among them there are serotonergic system (Heils 1999; Fumeron 2001; Matsushita 2004; Di Bella 2000; Monteleone 2008), dopamine (Bachner-Melman 2007; Levitan 2004; Bergen 2005), catechol-o-methyl transferase (Frisch 2001) even if some studies did not confirm this data (Gabrovsek 2004, Bergen 2005), brain-derived neutotrophic factor (Ribasés 2003; Monteleone 2006; Ribasés 2005), endocannabinoid system (Monteleone 2005) and estrogen receptors because of the female predominance in EDs (Rosenkranz 1998, Eastwood 2002) and other candidate genes (Juli 2014). As well, family and twin studies suggest that a strong genetic contribution is believed to be involved (Juli 2014).

The relationship between genetics and psychiatry has been evaluated also in addictive disorders, including vulnerability to initiation, continued use, and propensity to become dependent. Most of the studies have analyzed alcohol dependence but the genetic influence have been evaluated also for the susceptibility of nicotine dependence, drug addiction and gambling disorder (Juli 2015). More in detail, for alcohol dependence it has been estimated that genetics contributes to it for about 50% for men and 25% for women (Reich 1998); on the other hand, glutamatergic system, NMDA, aldehyde dehydrogenase , gamma-aminobutyric acid A receptor, neuronal acetylcholine receptor genes are involved too (Cohen-Gilbert 2015; Petrakis 2004; Saccone 2000; Li 2009; Wang 2008). For nicotine dependence the contribution of genetics is around 28%-84% and the major candidate genes involved in this pathology are nicotinic acetylcholine receptors because of the direct binding that nicotine exerts to them (Li 2009). Heritability of the use/dependence on stimulants, sedatives, and heroin in males is 33%, 27% and 54% respectively (Tsuang 1996) with similar values observed in females (Kendler 1998). Linkage peaks have been identified in the regions on chromosomes 2-5, 7, 9-11, 13, 14 and 17 (Li 2009) and genes studied in this kind of addiction are extracellular signal-regulated kinase (ERK) pathway (Cahill 2014), the zinc finger family of genes (Minică 2014) and others. Gambling disorder has been defined as a new kind of behavioral addiction (DSM 5, May 2013) and it has been recognized that it runs in families (Black 2006). Regarding association studies, most of them have been performed on dopamine receptor transporter genes (Comings 1996, da Silva Lobo 2007). However, all these addiction disorders share different common genes (Juli 2015).

The overwhelming proof that the relationship between genetics and psychiatry, or more in general between genetics and medicine is a reality, it comes up in the 1959 when it was introduced the concept of pharmacogenetics. Pharmacogenetics is the study of specific polymorphisms in distinct genes with known functions that are plausibly connected to drug response (Ventola 2013); moreover, the observation that individual variation of a drug response is often larger among members in a population (population variability) than within the same person at different times (intrapatient variability) further supports inheritance as a major determinant of drug response (Juli 2016; Vesell 1989; Kalow et al., 1998; Ma 2011). Actually, the majority of medicines are taken in dosages determined by different clinical factors (i.e. patient age, body weight) that do not directly consider genetic factors which can account for 20% to 40% of inter-individual differences in drug metabolism and response (Karczewski 2012). On the other hand, genetic mutations of proteins involved in drug targeting and drug metabolism and transport are likely to be the most important sources of individual variability in drug efficacy (Juli 2016). In the last years, several studies have evaluated genetic variants and their influence in the response to different drugs such as opioid drugs (Ma 2012; Ventola 2013;), psychotropic drugs (Ventola 2013; Reynolds 2012), cardiovascular drugs (Ma 2011; Ventola 2013), anticancer drugs (Salari 2012; Ventola 2013; Ni 2013), proton pump inhibitors, anti-infective and anticonvulsant drugs (Ventola 2013).

CONCLUSIONS

From today it can be stated that there is a close bond between genetics and psychiatry with a mutual influence and ability to interact as demonstrated by the great amount of scientific data. However, the scientific rigor of genetics will allow further discoveries on the causes, evolution and maintenance of psychodynamic processes underlying pathologies and psychological disorders.

Acknowledgements: None

Conflict of interest: None.

Contribution of individual authors:

All Authors contributed equally to the conception, design and drafting of the project.

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