GENETICS OF ALCOHOL USE DISORDER

Maria Bonea¹, Ioana V. Micluția²

Abstract: Contrary to the stigmatizing perception, alcohol dependence is not a mark of moral decay, but the result of combining environmental, social, cultural and especially biological factors, family studies finding that about 50% of the risk is due to heredity. Genetic linkage and association studies have failed to identify significant risk alleles, except for the alcohol-metabolizing enzyme genes. Thus, a new approach was needed - genome wide association studies (GWAS) that do not depend on a pre-existing hypothesis and highlighted new polymorphisms associated with susceptibility to alcoholism. A review of family, twin, linkage, candidate genes and GWAS will be briefly presented. Keywords: alcoholism, gene, polymorphism, genetic study

INTRODUCTION

According to the World Health Organization (WHO), harmful alcohol consumption is responsible for 5.9% of the global mortality, with a 3-4 times higher risk of premature death for alcoholics compared to the general population. The association with behavioral and psychiatric disorders is well known, alcohol dependence has become one of the most important public health problems through its social and economic impact and strong functional and quality of life impairment, even at a young age. (1) It is estimated that in developed countries, up to 80% of male and 60% of female adults use alcohol at some time in their lives, the prevalence of dependence for men reaching, according to some studies, even 10%. (2)

Current diagnostic criteria, established by the International Classification of Diseases, 10th edition (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), do not match perfectly on this topic. If DSM-IV-TR describes two distinct disorders, alcohol abuse and dependence, DSM-5 integrates these two entities into a single one Alcohol Use Disorder (AUD). (3) At the more severe end of the spectrum, the dependence implies tolerance, withdrawal, loss of control, compulsion ("craving") to drink daily or almost daily, despite significant disability. The disorder may be underdiagnosed, some studies revealing that only a quarter of addicts receive treatment. (4) By applying DSM-5 criteria, in the US, 36% of men and 22.7% of women develop AUD during their lifetime, in the younger population, gender differences have narrowed. (5)

In the “Alcohol related disorders” chapter, ICD-10 differentiates between harmful use (assuming physical or mental impairment) and alcohol dependence, that requires three out of six positive criteria: strong desire or compulsion to drink, difficulties in avoiding initial use, in discontinuing and controlling the consumed quantity, withdrawal or alcohol use to avoid its symptoms, tolerance, neglecting other activities / interests to obtain, use or recover after consumption, continued use despite physical, psychological or cognitive problems. (6) Besides several types of genetic studies, another argument for the role of genetics in the development of alcoholism are laboratory animals genetically manipulated to present features such as the preference for alcohol, sensitivity to the sedative effects or withdrawal symptoms. (7)

FAMILY AND TWIN STUDIES

Cognitive tests applied during functional MRI revealed inappropriate activation of long neural pathways that connect temporo-parietal regions to prefrontal areas. These brain disturbances occur in families with a strong history of alcohol dependence, supporting a biological basis, genetically determined. The impairment of cognitive functions and work memory required to resolve conflicts generates the disinhibited, even antisocial behavior. (8)

Twin studies report that 50-70% of the risk of developing an AUD is given by genetic factors. The strongest association was with the reducing risk genotype, the allele ALDH2 *2 (the gene encoding the mitochondrial hepatic enzyme aldehyde dehydrogenase). The polymorphism, common in Asians, but rare in Europeans, leads to altered alcohol metabolism with the development of facial erythema, tachycardia, sweating and gastrointestinal symptoms, creating aversion. (9)

LINKAGE STUDIES

The COGA study (Collaborative Study on the Genetics of Alcoholism) identified regions of interest on chromosomes 1, 2, 10, 13. (10) Depending on the components of alcoholism, regions on chromosomes 1 and 11 were associated with the initial response to alcohol, the age of onset with areas on chromosome 9, while a maximum alcohol use, with regions on chromosomes 12 and 18. Signals from the chromosomes 1, 6 and 22 were correlated with tolerance, while the severity of the withdrawal was linked to a region on chromosome 2. (11) Likewise, regions encoding the structure of the Gamma-Aminobutyric Acid Type A Receptor, Alpha2 Subunit (GABRA2), located on chromosome 4 were correlated with addictions in

¹Psychiatry Resident, PhD student, Children's Emergency Hospital, Cluj Napoca. Correspondence: Bonea Maria, Psychiatry Clinic, Victor Babeș Street no. 43, Cluj-Napoca, România. E-mail: Bonea.Maria@umfcluj.ro; Phone: 0604 0727 187 292
²Professor Doctor, Head of Psychiatry Department, University of Medicine and Pharmacy "Iuliu Hațieganu" Cluj-Napoca

Received January 29, 2017. Revised February 29, 2017. Accepted March 17, 2017

Corresponding author:
Maria Bonea
E-mail: Bonea.Maria@umfcluj.ro

Article History:
Received: 29 January 2017
Accepted: 17 March 2017

DOI: 10.37897/RJPP.2017.219
Ref: Ro J Psychiatry Psychother. 2017;19(2)
general. In the same way, the muscarinic acetylcholine M2 (CHRM2) genes, located on chromosome 7q were found to affect cognitive functions, depressive symptoms and the development of alcohol dependence. Association studies, that test candidate genes in regions discovered through linkage studies, confirmed the protective effect of Alcohol Dehydrogenase 1B (Class I), Beta Polypeptide alleles ADH1B*2 (found in Asian populations) and ADH1B*3 (more specific for African Americans) and also of the Alcohol Dehydrogenase 1C (Class I), Gamma Polypeptide allele ADH1C*2, which stimulating the metabolism of alcohol to acetaldehyde. A similar lower risk of dependence was associated with the Aldehyde Dehydrogenase 2 Family (Mitochondrial) allele, ALDH2*2 (that hampers acetaldehyde metabolism). Polymorphisms of the genes encoding type A GABA receptor (GABRA2, the most widespread class of cerebral inhibitory receptors that influences the subjective response to ethanol) and of the type B GABA receptor correlate with alcohol dependence. Other studies refute the relationship between GABAergic system genes and alcoholism, limiting it only to specific situations such as poly substance abuse or a particularly strong family history.

Neuropeptide Y (NPY), with the G1258A single nucleotide polymorphism (SNP) and the NPY Pro7 allele, could have a role in the pathogenesis of alcoholism, and also to cocaine and heroin abuse, associated, found SNPs near the Microtubule Affinity Regulating Kinase 1 gene (MARK1, that influences the development and differentiation). Changes in the pre synaptic 1B serotonin autoreceptor gene may determine the susceptibility to alcohol dependence, and also to cocaine and heroin abuse, some studies suggesting that the polymorphisms HTR1B A-161 could represent a genetic marker for alcoholism. The gene for the serotonin receptor 4 (HTR4), located in the limbic system, specifically in the hippocampus, involved in the development of depression by generating anhedonia, could have a role in the pathogenesis of alcohol dependence. The polymorphism of the serotonin receptor and transporter. Genomics is constantly developing techniques for sequencing the entire genome, with the cheaper version of the whole exome sequencing (WES) becoming increasingly more affordable. In this way, rare recessive mutations can be identified in exonic regions (areas that encode proteins). These techniques found point mutations in autism spectrum, affective and psychotic disorders, so favorable results in connection to addiction could be expected.
REFERENCES


***

Conflict of interest: none declared

Financial support: none declared