

The role of genetics in alcohol dependence

Guilherme Peres Messas^a e Homero Pinto Vallada Filho^b

^aUNIAD (Unidade de Pesquisa em Álcool e Drogas) da UNIFESP

^bInstituto de Psiquiatria do HC da FMUSP

Abstract

In this article we examined the heritability of alcohol dependence. A review of family, twin and adoption studies, allowed us to support the thesis of an important genetic component in this dependence. The transmission of this heritability occurs through a biological vulnerability associated to environmental factors, in a model called epigenetic. We also discussed the relationship between biological vulnerability and high-risk phenotypes for alcohol dependence. In the end, we briefly comment on the molecular genetic studies associated with this disorder.

Keywords: Substance-related disorders. Genetic predisposition to disease. Vulnerability.

Introduction

The study of the genetic component in the chemical dependences in general have the same difficulty experienced by the other psychiatric disorders: phenotypic indefiniteness, that is, the difficulty of delineating clear borders for the diagnostic categories. However, several studies have examined the issue, with significant results, which will be discussed below. Studies will be divided in two groups: epidemiological and molecular. The former provide the empirical basis for the performing of the latter, suggesting which phenotypes could be more genetically influenced and, therefore, more fertile for molecular analysis. In this article we will present the main results regarding the genetic factors on alcohol dependence. However, as there is a considerable overlap between the categories of the several dependences, in some moments, along the exposition, the presentation of some data related to dependence on other drugs will be unavoidable.

Epidemiological studies

Epidemiological studies are divided in three modalities: family, twin and adoption studies. Family studies demonstrate family aggregation suggesting some genetic component. However, they are not able to decide per se if the aggregation is mainly genetic or through the shared environment. In order to enhance the exam of this distinction twin and adoption studies are employed. The first ones are based on that monozygote twins (MT) share almost 100% of their genes, whereas dizygote twins (DT) share nearly 50% of them, being both subjected to similar environmental influences. Distinct prevalence of a trait or disorder between both types of twins could originate in their genetic difference. As the fundamental supposition that twins are submitted to similar environmental influences cannot be determined a priori, adoption studies are needed to reinforce the genetic thesis. These studies examine populations at genetic risk (e.g., children of alcohol-dependent subjects) reared in environments distinct from their original family (e.g., in the case of alcohol dependence, adoptive twins

reared since a few days or weeks of age in households without history of alcohol problems). Decades after the adoption, in case of a high prevalence of this disorder in these children, compared to the prevalence in other children adopted by biological parents without the problem (in this case, chemical dependence), we may state the importance of the genetic factors for this disorder. The assembling of all these modalities of studies provides solid evidence for the acceptance or refusal of the importance of genetics for the studied trait or disorder.

1. Family studies

Family studies have surely demonstrated the family aggregation of alcohol dependence, finding a three- to four-fold prevalence of this dependence among first-degree relatives when compared to subjects of the general population. However, the relationship between the aggregation of dependence on alcohol and other drugs show a less defined scenario. Some studies found a combined transmission pattern of dependence on alcohol and on other drugs, such as cocaine and heroin, in which the risk of alcohol dependence in first-degree relatives is increased among relatives of cocaine- and heroin-dependent subjects, whereas others found specific aggregation patterns for each drug: for opioids, alcohol, cannabis, cocaine and tobacco. In these cases, first-degree relatives have a significantly higher risk of developing a specific dependence on each drug, compared to the risk for any other drug. In a recent study, Merikangas et al.¹ found evidence for two transmission patterns: one, specific, for each dependence and other, general, for all of them, in a synthesis that seems to be the best summary of family studies, in which the hereditary transmission should occur within a spectrum which, at one end, causes a general vulnerability for any dependence and, at the other, provides conditions for the development of a specific form of dependence.

2. Twin studies

Several studies have found moderate or high genetic influences on alcohol dependence among males, with heritability estimates varying from 40% to 60%. Heritability is an epidemiological concept which assesses, within a population, the amount of variance of a trait or of a disorder which is due to genetic factors: therefore, it does not provide precise information regarding the way in which the genetic transmission occurs. Regarding females, more controversial results were found, with some studies showing an important genetic contribution; however, in one study this finding was not confirmed. However, this sole study was based on a relatively small sample (31MZ and 24 DZ), and its results may be interpreted as consequence of a selection bias. Studies about dependence on other drugs differed on heritability values found, having at one extreme the lowest specific heritability for sedatives among women (30%) and the highest for cocaine abuse among women (79%).³ In general it may be stated the presence of a genetic component on all drug dependences. One study found evidence of a common vulnerability for alcohol and tobacco dependence among males.

3. Adoption studies

Due to their capability of separating genetic from environmental influences, these studies are the most relevant for the exam of a genetic influence within a disorder. Nevertheless, the difficulties proper to the accomplishment of such studies explain their scarcity. The studies which examined the issue of alcohol dependence or dependence on other drugs, as a rule, found a significantly higher prevalence of alcohol or drug dependence among children of biological parents with similar diagnosis than among controls, for both genders. Using a more complex data modeling, Cadoret et al.⁴ demonstrated two genetic pathways that would lead to dependence on alcohol or on other drugs: one directly stemming from a father with a similar diagnosis and the other from a paternal/maternal diagnosis of anti-social personality disorder; these findings provide important input for the exam of different vulne-

rabilities for the disorders, being fundamental to guide molecular studies.

The complexity of transmission and the epigenetic model

If the studies above allow us to conclude, generically, for the importance of the hereditary factors as a cause of chemical dependences, they have little to say about the hereditary modes of transmission. The great heterogeneity of the results found practically dismisses a Mendelian mode of transmission for the issue of chemical dependence, with only one gene being responsible for the appearance of the disorder. On the contrary, the variation of results includes chemical dependence in the model of the so-called complex diseases, such as diabetes or arterial hypertension, which have been receiving special attention in the last years. In these diseases the genetic effect stems from several genes which act together to produce a situation of vulnerability which, as a whole, and in combination with the environment, produce the final phenotype. That is, what is effectively inherited are the conditions of vulnerability, rather than the disease or the disorder proper. Regarding chemical dependence, therefore, we should speak, for the sake of linguistic accuracy, of the genetics of the conditions of vulnerability or susceptibility. This model, encompassing the genetic inheritance of the vulnerabilities and its modulation along the years by the environmental effects, is called epigenetic model. For a solid support of this model the studies should demonstrate the genetic component of other phenotypes associated with dependence: vulnerability or high-risk, which will be presented below.

1. Alcohol and vulnerability phenotypes

Several conditions of susceptibility have been demonstrated for alcohol dependence and may be roughly divided in two sub-groups: those related to the personality trait and those related to the biochemical action of the drug in the body.

Five personality traits have been related to vulnerability to alcoholism. Level of behavioral activity: Evidence from several sources correlated this variable with increased risk for the development of alcoholism. Longitudinal, retrospective and even adoption studies found this association. Besides, one study observed significantly higher scores of behavioral activity among children of alcohol-dependent subjects compared to children of non-dependent subjects. More recently, in the only study in which the level of activity was directly assessed (and not by means of scales) through an actigraph bound to the patients' wrist, Moss et al.⁵ have confirmed the result above for children of alcohol-dependent or drug-abuser subjects regarding non-dependent subjects. Emotivity: Defining this trait as the propensity for a great emotional reaction to environmental stimuli, Sher et al.⁶ found higher emotional response among children of alcohol-dependent subjects regarding non-dependent ones, measured as neuroticism scores. In the same sense, Finn et al.⁷ found increased susceptibility to the activation of the autonomous nervous system among subjects at high-risk of developing alcohol-dependence.

Soothability: Only one study found a higher difficulty, among young male subjects at high-risk of alcohol-dependence, to return to the emotional baseline after autonomic activation, indicating the possibility of this trait being involved in the vulnerability for dependence.

Persistency of attention: Studies have demonstrated a higher prevalence of attention disorders among populations at high-risk of developing alcohol dependence, indicating this factor as a vulnerability factor. Besides, one neurophysiological investigation found alterations of the P300 wave in children of alcohol-dependent subjects, a physiological marker related to attention mechanisms.

Sociability: Some prospective studies of people who ended developing alcoholism show variations in the mode of socialization, which could be summed up under the name of behavioral lack of inhibition, be it as

aggressiveness, search for sensations, impulsivity or social incoformism.

Along with personality traits associated with vulnerability, the most studied biochemical component is the variation of alcohol-metabolizing enzymes. Alcohol-dehydrogenase enzyme is responsible for the metabolism of alcohol into acetaldehyde, which, in high blood levels, provokes unpleasant reactions such as nausea and vomiting. However, acetaldehyde levels remain low due to the activity of other enzyme, aldehyde-dehydrogenase (ALDH). This enzyme has at least two genetically-controlled variants (ALDH1 and ALDH2), ALDH2 being biologically inactive, what makes that 10% of the Asian population, which is homozygotic for this gene, have intense adverse effects, becoming protected for the development of alcohol-dependence. Other phenotype, which has been recently studied, the level of response to alcohol, brings promising perspectives for this area. Schuckit⁸ found association between a lower level of response to alcohol with the development of alcohol-dependence, making room to start studies on the biochemical pathways involved in the effects of alcohol, besides aldehyde-dehydrogenase.

Other strategy which has found interesting results is the search for common vulnerabilities between dependence on alcohol, drugs and other behavioral phenotypic traits. Therefore, Comings et al.⁹ found evidence for a common genetic vulnerability for attention deficit and hyperactivity, stuttering, tics, conduct disorder, obsessive-compulsive disorder, mania, generalized anxiety and alcohol abuse. In this model, several psychiatric disorders would have a genetic common basis, being the epigenetic development in charge of the production of one or other phenotype. We will return to this study when dealing with molecular studies.

Molecular studies

Guided by the strength of epidemiological studies which prove the existence of genetic participation in dependence disorders and stimulated by the progress of molecular genetics techniques, researchers have been strongly investing on molecular studies of alcohol abuse or dependence. The first article published with a positive finding by Blum et al., in 1990,¹⁰ had a great international repercussion and raised early optimism about the finding of the gene for alcohol dependence. These authors found an association of a variant of subtype 2 dopaminergic receptor (DRD2 – allele A1) with alcoholism. However, the initial optimism was soon attenuated by the incapability of other centers to replicate the result,^{11 12} suggesting that the solving of the problem could not be restricted to the search of sole genes. Within this atmosphere of increasing complexity, several studies on molecular genetics were and are being performed, as we will describe below.

Before that, nevertheless, we will describe two types of performing studies on molecular genetics: linkage and association studies. In the former, the gene's major effect is sought, i.e., for a determined disorder it is sought a gene which could be capable per se of causing the development of the disturbance. Association studies investigate the participation of candidate genes within the disorder, that is., they verify at which percentage a determined gene has an influence. It is, therefore, the most appropriate design for the study of complex phenotypes, such as alcohol-dependence, although linkage studies in the field of chemical dependence should not be fully discarded, moreover in the investigation of conditions in which there is great family aggregation. We will limit ourselves to present here the studies of association relevant to this field. As these studies mostly investigate simultaneous dependence on several drugs at the same time, we will deal with them together, always indicating, whenever possible, the differences found for the singularities of each drug. For the sake of clarity in the exposition, we will divide the studies according to the neurophysiolo-

gical system studied.

1. Dopaminergic system

It is the most studied among the pathways involved in the brain reward system, specially the investigation of polymorphic variations in the genes of its five receptors types (DRD1; DRD2; DRD3; DRD4 and DRD5). Polymorphisms are variations in the sequence of the bases in a gene, which may lead to differences in its expression and, consequently, to functional variations of each protein generated by it. Associations are found between certain polymorphisms with drug dependence for all receptors.

DRD1 – Comings et al.¹³ found an association of one gene variation for this receptor with several impulsive behaviors, including drug abuse.

DRD2 – due to its originality as the first positive finding in the field of alcohol-dependence, the association of alleles of this gene with drug dependence has been much studied, providing the most consistent results of all this research field. In one metanalysis encompassing 15 American and European studies, totaling 1,015 alcoholics and 898 controls, Noble¹⁴ has found a three-fold prevalence of the allele A1 of this gene in subjects severely dependent on alcohol compared to controls, whereas no difference was found between controls and subjects with mild alcohol dependence. He has also found association of other variant, allele B1, with alcohol dependence. These associations were also found by other authors for cocaine dependence and polydrug use.

More recently, Ponce et al.¹⁵ have found an association of the allele A1 with anti-social personality disorder, in a sample of alcohol-dependent subjects. There are also negative results observed in some studies. However, we may conclude that functional variations produced by polymorphisms may occur. Three studies reinforce this hypothesis: Noble et al.¹⁶ found an association of DRD2-A1 and increased latency time for P300 waves in children of alcohol-dependent subjects, regarding controls, indicating a physiological pathway for the activity of the dopaminergic inheritance. Pohjalainen et al.,¹⁷ studying healthy volunteers in a Finish population, found association between DRD2-A1 and low availability of D2 receptors. As the low availability of D2 receptors has already been associated with certain personality traits, this finding reinforces the hypothesis of transmission of heritability through personality traits. Noble et al.¹⁸ also analyzing subjects without diagnosis of alcohol or drug abuse, found reduced glucose brain regional metabolism in subjects with the allele A1 of this receptor for the areas involved in the brain reward system, such as the nucleus accumbens, or regulators of the frontal function, such as the pre-frontal cortex. This original study provides important collaboration for the recognizing of individual differences in the susceptibility to alcoholism.

DRD3 – despite its predominant presence in limbic regions and, therefore, the possible role in the regulation of emotions, the gene for this receptor has not received yet much attention from researchers. Thome et al.¹⁹ found a significantly higher presence of the allele 1 in alcohol-dependent subjects regarding controls, whereas Parsian et al.²⁰ have not found any association.

DRD4 – the interest in this gene stems from the observation of its influence in the genesis of attention/hyperactivity disorder of children, a trait involved in the vulnerability to dependences. The few studies which directly investigated dependences are controversial, with negative²⁰ and positive associations²¹ of long alleles (seven repetitions) of the alcohol dependence gene, in the first study, with dependence on opiates, in the second one. More recently, evidence has appeared that long alleles could be involved in the modulation of the intensity of alcohol craving.

DRD5 – the only study²² which examined polymorphisms on this gene found interesting results. DRD5 is expressed particularly on the hippocampus, a region apparently involved in responses to new stimuli, and the authors tested a possible association of a polymorphism of the

gene with substance abuse, mediated by the personality trait of novelty searching. They found this positive finding for females, being the first molecular study highlighting the different pathways of vulnerability between genders.

2. Other systems

The scarcity of studies on other brain systems potentially involved in drug dependence leads us to situate them all, transiently, in only one category. Kranzler et al.²³ found a modest association ($p=0.03$) of the alleles of the opiate receptor gene with alcohol/drug dependence. Other three studies were unable to find any association. The gabaergic system, the main brain inhibitory system, has received attention in two studies: one with negative results and other having a positive association of polymorphism in the subtype alpha3 with alcohol dependence. Preliminary evidence of the association of variants of the adrenergic, serotonergic systems and the monoaminooxidase gene with alcohol or drug dependence, or of the gene of catechol-O-methyltransferase gene with risk behaviors for drug abuse, are waiting for further investigation in order to confirm these associations.

3. Genes Interaction

The so-called complex diseases have as their characteristic the intervention of more than one gene for the transmission of their heritability. One of the mechanisms by means of which this combined action of genes occurs is the so-called interaction. In this mechanism, the collection of some specific genes is capable of producing one phenotype, which, alone, would not be possible. The sum of the action of these genes characterizes less a qualitative activity, in the sense of the existence or not of some trait, but rather a qualitative functioning, in which the effect (non-pathological per se) of genes favors the development of the disorder. Some studies have examined this effect for dependences. Noble et al.²⁴ investigated the prevalence of polymorphic variations of the genes for dopaminergic (DRD2) and gabaergic (subunit beta 3 – GABRB3) receptors: they found a higher prevalence of the allele DRD2-A1 (already presented in the studies above) and a lower prevalence of the allele GABRB3-G1 among severe alcohol-dependent subjects, when compared to controls without the phenotype, in separate analyses. However, when analyzing the combination of both variants, the effect of the risk of alcohol-dependence was more robust, indicating the presence of interaction.

In a very creative study, Schuckit et al.²⁵ investigated the interaction of different systems in the genesis of one vulnerability trait of alcohol dependence, the level of response (LR) to alcohol. For the allele LL of the serotonin transporter (5-HTT) gene and for the Pro/Ser of the GABA alpha6 receptor (GABRA6) gene, they found association with low LR and higher prevalence of alcohol dependence. Analyzing the bearers, both polymorphisms found lower LR and 100% ($n=4$) of history of alcohol dependence, indicating again the effect of interaction in the intensity of the phenotype. One study⁹ found evidence of interaction between alcohol dependence and traits possibly involved in the susceptibility to the development of dependences. The authors observed an additive effect between polymorphism of three dopaminergic genes (DRD2, dopamine beta-hydroxylase, and dopamine transporter) and stuttering, child attention/hyperactivity disorder, conduct disorder and alcohol dependence.

Conclusions

The strongest conclusion of epidemiological and molecular studies, taken as a whole, is the presence of hereditary factors in the genesis of alcohol abuse or dependence.

The heterogeneity of the results in terms of defining the boundaries of phenotypes and hereditary transmission mechanisms indicates that alcohol abuse or dependence are a result of a complex interaction of genetic, psychosocial and cultural factors, better understood within a developmental model of psychopathology.

The pathways for the genesis of abuse/dependence of alcohol and other drugs are multiple, comprising specific pathways for each drug and general ones for all drugs: the individual cases are possibly combinations, in diverse proportions, of these different pathways.

Besides the general and specific pathways for the hereditary transmission of vulnerability to drug dependence or abuse, common susceptibilities to all psychiatric phenotypes coexist; in some cases, it is not possible to reject the hypothesis of transmission of a trait common to all psychiatric disorders.

There are no unique genes for alcohol abuse or dependence, as well as there is no evidence of exclusive genes for this phenotype. On the contrary, molecular studies point to a genetic transmission (mediated by different personality and individual characteristics to the effects of drugs) of variations in the balance of systems of neurotransmission and biochemical metabolism of drugs. The action of the environment on these biological conditions produces the phenotypic expression.

The lower variant of the gene of the DRD2 dopaminergic receptor, known as DRD2-A1 seems to have an important role in the transmission of vulnerability to alcohol dependence, as well as to other phenotypes. This heritability occurs probably through neurophysiological mechanisms which produce functional variations in the brain systems, causing affective and neuropsychological patterns vulnerable to the appearance of the disorder.

Preliminary evidence indicates a role for other genes of the dopaminergic, serotonergic, gabaergic and opioid systems which, acting combined, may increase the individual susceptibility of their bearers to dependences.

The power of the results reviewed above leads directly, by two ways, to the issue of the treatment of alcohol dependence. Initially, the gradual recognition of the biochemical pathways involved in the genesis and maintenance of dependence enables the improvement of psychopharmacs which, acting punctually in sites of specific action (e.g., receptors and transporters which are fundamental to the process), may act more efficiently on the disorder. Secondly, the molecular recognition of vulnerability conditions for the disorder allows preventive actions on at-risk populations, be they to prevent the contact with drugs or to reduce the susceptibility traits.

Future perspectives

The studies on the genetic of chemical dependences promise more solid results in the next years, progressing by means of studies with more complex methodologies, in a synergistic action. On the one hand, the more detailed investigation of subphenotypes, i.e., of neuropsychological and neurophysiological conditions (including subjective states) associated with vulnerability; these subphenotypes stem more directly from biological functions, making more reliable the findings associated with them, differently from the complex nosographic constructs of psychiatry which, considering the continuous action of the environment on biology, have not much to say about the biological basis of psychiatric disorders in general. On the other hand, the investigation of the effects of interaction of some environmental aggressors acting on specific conditions of vulnerability, generating the disorder. In other words, as the researchers of the area abandon the strict diagnostic categories of psychiatry and investigate the phenomenon of mental disorders as a composition of neuropsychophysiological trends and ecopsychosocial factors, the researching strategies will facilitate the elucidation of several enigmas of the sector, surely including alcohol dependence. Finally, the development of pharmacogenetics, that is, genetic determinants for a good or bad response to the pharmacological treatment, which include the verification of interindividual differences in the pharmacokinetic (studies which inves-

tigate the genetic variants of the enzymes which metabolize these drugs) and pharmacodynamic mechanisms (studies about the functional variants of the genes which codify the sites involved in the mechanism of action of these medications/drugs).

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Correspondence

Guilherme Peres Messas
 Instituto de Psiquiatria
 Rua Dr. Ovídio Pires De Campos, s/n, 3º andar, sala 4051
 05403-010 São Paulo, SP, Brasil
 E-mail: messas@netpoint.com.br_