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The Next Challenge for Psychiatric Genetics: Characterizing the Risk Associated with Identified Genes

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Abstract

Background—As advances in genetics further our ability to identify genes influencing psychiatric disorders, the next challenge facing psychiatric genetics is to characterize the risk associated with specific genetic variants in order to better understand how these susceptibility genes are involved in the pathways leading to illness.

Methods—To further this goal, findings from behavior genetic analyses about *how* genetic influences act can be used to guide hypothesis testing about the effects associated with specific genes.

Results—Using the phenotype of alcohol dependence as an example, this paper provides an overview of how the integration of behavioral and statistical genetics can advance our knowledge about the genetics of psychiatric disorders. Areas currently being investigated in behavior genetics include careful delineation of phenotypes, to examine the heritability of various aspects of normal and abnormal behavior; developmental changes in the nature and magnitude of genetic and environmental effects; the extent to which different behaviors are influenced by common genes; and different forms of gene-environment correlation and interaction.

Conclusions—Understanding how specific genes are involved in these processes has the potential to significantly enhance our understanding of the development of psychiatric disorders.

Keywords

behavior genetics; twin studies; genetics; gene-environment interaction

INTRODUCTION

Despite strong evidence that genetic effects contribute to psychiatric phenotypes, detecting the specific genes involved has proven difficult. Early studies were plagued by small sample sizes and the use of statistical methods developed for single gene disorders that did not take into account the complexities introduced by multifactorial, polygenic disorders [1,2]. Many of the factors that contributed to the failure of early studies aimed at gene identification have now have been addressed. The sample sizes used in studies aimed at gene identification have

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dramatically increased, and nonparametric, allele-sharing methods more appropriate for the analysis of complex phenotypes have been developed [3]. In conjunction with advances in genotyping technology and knowledge acquired from the Human Genome Project, there is reason to be enthusiastic about emerging successful gene identification efforts in complex disorders. Large, systematic collections of affected families informative for linkage and association analyses aimed at gene identification are on-going for most major psychiatric problems, including schizophrenia [4], bipolar disorder [5], autism [6], major depression [7], attention deficit hyperactivity disorder [8], alcoholism [9], and nicotine and other drug dependence [10]. These large collaborative projects promise a new era of gene discovery in relation to psychiatric disorders. Several reports of specific genes influencing psychiatric disorders, including alcohol dependence [11] and schizophrenia [12] have recently been published. The next challenge is to characterize the risk associated with these genetic variants in order to better understand how these susceptibility genes are involved in the pathways leading to illness. To further this goal, findings from behavior genetic analyses about *how* genetic influences act can be used to guide hypothesis testing about the effects associated with particular genes.

Using the phenotype of alcohol dependence as an example, this paper provides an overview of how the integration of behavioral and statistical genetics can advance our knowledge about the genetics of psychiatric disorders. Alcohol dependence provides a particularly relevant example, as this disorder embodies many of the complexities entailed in psychiatric disorders: multiple genes are thought to be involved, each of small effect; the environment plays an important role in the development of the disorder, as does gene-environment interaction [13]; genetic heterogeneity is thought to be involved; and there are multiple systems that have been suggested for defining the phenotype of alcohol dependence and related subtypes [14]. Despite these complications, this year has been witness to the publication of several reports of genes associated with alcoholism (*GABRA2* [11], *GABRG3* [15], *CHRM2* [16]), accompanied by preliminary reports of replication for *GABRA2* [17,18], providing a timely context to discuss further characterization of risk associated with specific genes.

BEHAVIOR GENETIC CONTRIBUTIONS TO THE GENETICS OF SUBSTANCE USE

Behavior genetic (BG) research has convincingly demonstrated that genetic variation contributes to individual differences in virtually all behavioral domains [19–21]. Traditional twin analyses now have expanded to address questions about *how* genetic influences act [22]. Areas currently being investigated include careful delineation of phenotypes, to examine the heritability of various aspects of normal and abnormal behavior; developmental changes in the nature and magnitude of genetic and environmental effects; the extent to which different behaviors are influenced by common genes; and different forms of gene-environment correlation and interaction. Accordingly, findings emerging from behavior genetics can be used to develop and test hypotheses about the risk associated with specific genes identified through statistical and molecular genetic studies.

Refining Phenotypes

In relation to substance use, twin studies provide unambiguous evidence that genes play an important role in the development of alcohol dependence [23]. Genetic influences account for approximately 50–60% of the population variance in alcohol dependence [23]. Twin studies have also demonstrated that dimensions of alcohol use, such as quantity of alcohol consumed on a typical drinking occasion, frequency of use, frequency of intoxication, and alcohol metabolism measures, including time to peak blood alcohol concentration and rate of elimination, are under substantial genetic influence [24]. Although genes are known to

influence both dependence and related substance use phenotypes, it is not clear to what extent these genes overlap [24]. As specific genes influencing alcohol dependence are identified, researchers will need to more explicitly demarcate the relationship between identified susceptibility genes and outcome. One question that needs to be addressed is the extent to which the effects of susceptibility genes influencing substance dependence also impact population variation in related behavioral phenotypes, such as indices of frequency/quantity of alcohol use among both affected and unaffected individuals: Do susceptibility genes contributing to clinically diagnosable dependence also contribute to problematic use at sub-clinical levels, to continuous variation in substance use across the population, and to the initiation and cessation of use?

In addition, alcohol dependence is a clinically heterogeneous disorder, with diagnoses based upon numerous behavioral components and symptoms that can vary between individuals. More complete understanding of the underlying processes contributing to dependence will arise from determining how susceptibility genes influence the characteristics that lead to a dependence diagnosis. For example, some susceptibility genes may be more related to loss of control when drinking, whereas others may be more closely related to the development of tolerance or withdrawal. It will be important to identify phenotypic subtypes that are related to susceptibility genes. Some susceptibility genes may be more closely linked to drinking that is accompanied by antisociality and criminality, whereas other susceptibility genes may be more involved in alcohol abuse related to anxiety and depression.

Evidence exists suggesting that genes may be more important in certain subtypes of alcoholism [25]. One classification system proposes two types of alcoholism: one characterized by early onset and comorbid antisociality and poor impulse control, and a second characterized by a later age of onset, and enhanced guilt and anxiety about drinking problems [26]. Preliminary genetic analyses support the hypothesis that susceptibility genes may differ for these subtypes of alcohol dependence. Genetic variation associated with the serotonin system appears to be particularly important in early-onset alcoholism accompanied by antisocial behavior and poor impulse control [27,28]. An increased frequency of the short allele of the serotonin transporter gene was found among habitually violent, early onset alcoholics, compared to later onset alcoholics and controls [29]. Another serotonin receptor gene, HTR1B, has also been associated with antisocial alcohol dependence [30]. Other candidate genes for alcohol dependence, such as neuropeptide Y (NPY), also show more significant association with early onset alcohol dependence [31].

Developmental Genetic Analyses

Behavior genetic analyses have demonstrated that the effect of genes can vary dramatically across development. For example, there is evidence of genetic effects on patterns of alcohol use as early as adolescence, and these effects appear to increase over time [32]. Figure 1 combines data from two population-based longitudinal Finnish twin studies to show the relative importance of genetic and common environmental influences at ages 14, 16, 17, and 18.5. This figure demonstrates the significant increase in the importance of genetic influences across adolescence, and the corresponding decline in the importance of common environmental influences on drinking patterns across this developmental period. Genetic influences accounted for only 18% of the variance in drinking initiation at age 14, and this was significant only in girls [33]. There was no evidence of genetic influence on drinking patterns in boys yet at this early age. However, there is a steady increase in the relevance of genetic factors across adolescence, with genes accounting for a third of the variation in drinking patterns in both sexes by age 16, and half of the variation by age 18 [32]. Thus, as drinking patterns develop, differentiate, and stabilize across adolescence, genetic factors assume increasing importance

on drinking patterns; however, alcohol use early in adolescence appears to be almost entirely influenced by family, school, and neighborhood influences [34].

This is also true of alcohol dependence symptoms. Although alcohol dependence in adults is largely influenced by genetic factors, alcohol dependence symptoms in early adolescence appear to be largely influenced by environmental factors. In the same Finnish twin sample, 12% of the adolescents showed alcohol problems by age 14 (as indicated by the endorsement of DSM alcohol dependence symptoms); however, genetic analyses of alcohol dependence symptoms found no evidence of genetic effects in either males or females [35]. Alcohol dependence symptoms were entirely environmentally influenced at this age. Lack of evidence for genetic influence on alcohol dependence in early adolescence has been reported in other samples as well [36].

Thus, one developmental change that can occur is that the magnitude of genetic influence on a trait may vary across time. Another developmental change involves genetic influences being expressed as different phenotypes at different developmental stages. For example, childhood conduct disorder shows significant evidence of genetic influence across multiple samples, regardless of whether it is assessed retrospectively in adulthood [37,38], prospectively in adolescence [35], or by child or parent report [39]. This finding is of particular interest because conduct disorder is a robust predictor of both concurrent and future alcohol problems, as demonstrated in both school-based and clinically-ascertained samples [36,40–43]. However, the overlap between conduct disorder and *adolescent* alcohol problems appears to be entirely environmentally mediated (as no genetic effects are evident on alcohol dependence symptoms in early adolescence) [35], while the overlap between conduct disorder and *adult* alcohol dependence is largely attributed to shared genes [44]. A genome scan of retrospectively reported childhood conduct disorder identified linkage to a chromosomal region (2p) that also shows linkage to adult alcohol dependence [45]. These findings suggest that conduct disorder may be an adolescent manifestation of genes that later predispose to adult alcohol dependence. And further, these studies suggest that genes impacting adult alcohol dependence may be more closely related to conduct disorder in adolescence than to early adolescent problems and symptoms diagnosed as alcohol dependence, which appears to be largely caused by environmental factors. Only a small fraction of those who will receive a lifetime diagnosis of alcohol dependence fulfill criteria for alcohol dependence in early adolescence (and some do not even drink regularly). In short, this early onset form of alcohol dependence appears to have different determinants.

Interestingly, preliminary analyses of a subset of children who have been genotyped as part of the Collaborative Study on the Genetics of Alcoholism (COGA) sample, in which the *GABRA2* association with adult alcohol dependence was first established [11], suggest that there are developmental changes in the risk associated with this gene. Although *GABRA2* is associated with alcohol dependence in the adult sample, it does not appear to be significantly associated with alcohol dependence symptoms in the child sample. Rather, there was a significant association between *GABRA2* and conduct disorder symptoms in the child COGA sample. These analyses support the suggestion from twin studies that conduct disorder may be an early adolescent manifestation of the genes that later influence adult alcohol dependence. Follow-up survival analyses examining the association between alcohol dependence and the *GABRA2* genotype suggest that this relationship does not begin to emerge until later in adolescence, with the survival curves for alcohol dependence for individuals with different genotypes at *GABRA2* not diverging until after age 15 (Figure 2) [46]. These analyses support twin studies finding that genetic influences on drinking behavior are not significant in early adolescence, but increase across adolescence and into adulthood.

Comorbidity Among Disorders

It is well known that many psychiatric disorders tend to co-occur. This is particularly true of alcohol dependence, which shows significant overlap with many other problems, including nicotine dependence [47], childhood externalizing disorders [42,48], anxiety and mood disorders [49], and antisociality [50]. Behavior genetic models have investigated the degree to which covariation of different disorders or behaviors is due to common genetic influences, common environmental influences, or both. As an example, data from the Virginia Twin Registry was used to investigate genetic and environmental risk factors contributing to the pattern of comorbidity among 10 lifetime psychiatric disorders, including major depression, generalized anxiety disorder, phobia, alcohol dependence, drug abuse/dependence, adult antisocial behavior, and conduct disorder. It was concluded that "the pattern of lifetime comorbidity of common psychiatric and substance use disorders results largely from the effects of genetic risk factors" [51]. These findings suggest that some genes that are identified will contribute to multiple behavioral problems, whereas others will be more specific to a particular outcome. The term "co-morbidity" in itself may be misleading, as it implies the co-occurrence of independent disorders, whereas many psychiatric phenotypes, such as alcohol dependence, conduct disorder, and antisocial personality disorder, may represent alternative manifestations of behavioral disinhibitory processes [52,53].

Data from specific gene studies are also accumulating to support these findings of significant genetic overlap suggested by twin data. As an example, the neurotransmitter dopamine is believed to play an important role in reward behavior [54]. An association between a particular dopamine receptor, *DRD2*, and alcoholism was first reported in 1990 [55], and subsequently has been replicated by several groups [56–64], although not others [65–84]. It has been suggested that *DRD2* may contribute to a "reward deficiency syndrome", a collection of addictive, impulsive, or compulsive behaviors, including alcoholism, polysubstance abuse, smoking, obesity, attention-deficit disorder, and gambling [85]. In addition, the CHRM2 gene, recently investigated in the COGA sample under a linkage peak, shows significant association with both alcohol dependence and major depressive disorder [16]. Many genes are likely to be involved in multiple psychiatric disorders, contributing to their co-occurrence. Once specific genes are identified, twin results suggesting that particular disorders/phenotypes overlap due to shared genes can be used to guide tests of the effects associated with any particular gene.

Gene-Environment Interaction and Correlation

Both genetic and environmental risk factors are known to contribute to the development of alcohol use and dependence, and more recent studies have examined the degree to which genetic and environmental influences may vary according to the environmental context. Data from the Australian twin registry provided early evidence of gene-environment interaction: genetic influences on alcohol use were attenuated among women who were married [86]. Religiosity also has been found to have a moderating effect on alcohol use among females [87]: in subjects without a religious upbringing, genetic effects played a large role, dwarfing the influence of shared environment; however, in individuals with a religious upbringing, there was no evidence of genetic influence, with the environment playing a large role instead. In adolescent data from the Finnish twin studies we have demonstrated dramatic changes in the importance of genetic influences in different environments. Genetic influences were found to have a stronger impact on alcohol use at age 16 among adolescents residing in urban environments, as compared to adolescents from rural environments [32]. This finding has been replicated in Minnesota twin data [88]. When we expanded our gene-environment interaction models to incorporate more continuous, descriptive measures of the environment, such as indices of neighborhood stability and regional alcohol sales, we found dramatic moderating effects, with more than five-fold differences in the degree of genetic influence evident across

environmental extremes [13]. Adoption studies have also been particularly informative in delineating gene-environment interaction processes [89].

Genetic and environmental influences can also be related by gene-environment correlation. While gene-environment interaction can be conceptualized as genetic control of *sensitivity* to the environment (or environmental control of genetic expression), gene-environment correlation involves genetic control of *exposure* to the environment. An individual's genotype can alter the probability that an individual will experience various environmental events. As an example, certain types of stressful life events have been shown to be moderately heritable [90]. Some individuals are more prone to experiencing stressful life events than others, and to the extent that individual dispositions influence an individuals' exposure to certain events, these events show a degree of genetic influence. This represents gene-environment correlation: an individuals' genotype is correlated with the likelihood of exposure to a particular environment. One could imagine that these processes may be particularly relevant to alcohol use, as individuals actively select peer groups [91] and other environmental settings that can differ in the availability of alcohol and/or acceptance of substance use. To the extent that genes influence individual predispositions and personality characteristics, these genes could be associated with the likelihood that individuals will select high risk environments that impact the subsequent development of problems.

Once specific genes begin to be identified we will be able to test specific gene-environment interaction and correlation processes. For example, preliminary analyses of the COGA sample suggest both gene-environment correlation and interaction between the *GABRA2* genotype, marital status, and alcohol dependence. Marital status has consistently been related to alcohol use in the epidemiological literature, with married individuals consuming less alcohol than single or divorced individuals [92–94]. In the COGA sample, individuals who carry the high risk genotype at *GABRA2* are more likely to be unmarried, providing an example of gene-environment correlation. Interestingly, this is not due simply to the association between *GABRA2* and alcohol dependence, as the association between *GABRA2* and marital status is more significant among nonalcoholic individuals. Instead, it appears to be mediated in part by an association between *GABRA2* and reduced reward dependence and increased rates of antisocial personality disorder among individuals who carry the high risk genotype but are not alcoholic.

There is also evidence that marital status moderates the importance of the *GABRA2* genotype (Figure 3). Among individuals who are not married, there is no difference in rates of alcohol dependence according to genotype; however, among individuals who are married, the effect of *GABRA2* is magnified (an OR of 1.7 compared to 1.4 in the full sample). This interaction remains significant after controlling for age and gender. These analyses provide evidence of gene-environment interaction. The data suggest that being unmarried is a sufficiently potent environmental risk factor for individuals from these high risk families that the effect of the *GABRA2* gene on alcohol dependence becomes negligible. The environment alone (or perhaps the cumulative consequences of a lifestyle) appears to be sufficient to drive individuals across the threshold for alcohol dependence. However, among individuals in the lower risk environment of being stably married, genetic factors become more apparent in the susceptibility for alcohol dependence; accordingly, the importance of *GABRA2* on alcohol dependence is magnified in this environment [95].

CONCLUSIONS

Behavior genetic studies have been pivotal in demonstrating genetic influence on a variety of behavioral dimensions and in advancing our understanding of the dynamic nature of genetic influence. But traditional studies have modeled genetic influence latently, inferring genetic

effects most often via comparisons of monozygotic and dizygotic twins, but also through family and adoption designs. Statistical and molecular genetic studies are making rapid progress in identifying genes involved in psychiatric disorders. The next step in advancing our understanding of genetic contributions to behavioral development must be to integrate these research traditions, incorporating knowledge from behavior genetics about the various heritable dimensions of behavior and how genetic influences act, in order to develop hypotheses to further delineate the risk associated with specific genes. For research on alcohol dependence, this will involve studying how genes identified as contributing to alcoholism also influence related behavioral traits, such as quantitative dimensions of alcohol use and smoking; what aspects of substance dependence these genes are most directly influencing; what related behavioral phenotypes these genes may also be involved in; how the influence of these specific genes changes across development; whether these genes are involved in different behaviors at different developmental stages; and how these genes are correlated with environmental risk factors and/or how the risk associated with these genetic variants may change in the presence or absence of particular environments.

More careful characterization of the risk associated with specific genes may also help resolve inconsistencies in association findings reported by different studies. Failure to consistently replicate genetic effects may result, in part, from differences in sample compositions between studies. Alcohol dependence is a heterogeneous disorder, diagnosed in the DSM-IV by the presence of any three of seven possible symptoms [96]. Accordingly, by definition, alcoholic individuals often have varying symptomatic profiles. If, for example, a particular gene is related most directly to alcohol withdrawal, study of a sample characterized by many alcoholics with withdrawal symptoms may detect an association between the gene and alcohol dependence, but a second sample with a smaller number of alcoholics who experienced withdrawal may fail to detect an association. More accurate characterization of the phenotypes most closely related to the gene could help clarify inconsistent findings. Similarly, if the effect of a particular gene is magnified or diminished in the presence of other environmental risk factors, studies that fail to measure and take into account the relevant environmental factors may differ in their ability to detect an association with the gene due to differences in the presence of the relevant environment among their study participants. Better characterization of the risk associated with specific genes would help reduce these problems as studies could be designed taking into account these other important variables.

In summary, delineating the risk specifically tied to particular genes across development, and in conjunction with environmental risk factors, has the potential to significantly enhance our understanding of the development of psychiatric disorders. The integration of behavioral and statistical genetics provides a promising framework within which to elucidate pathways of risk associated with genetic influences on psychiatric phenotypes.

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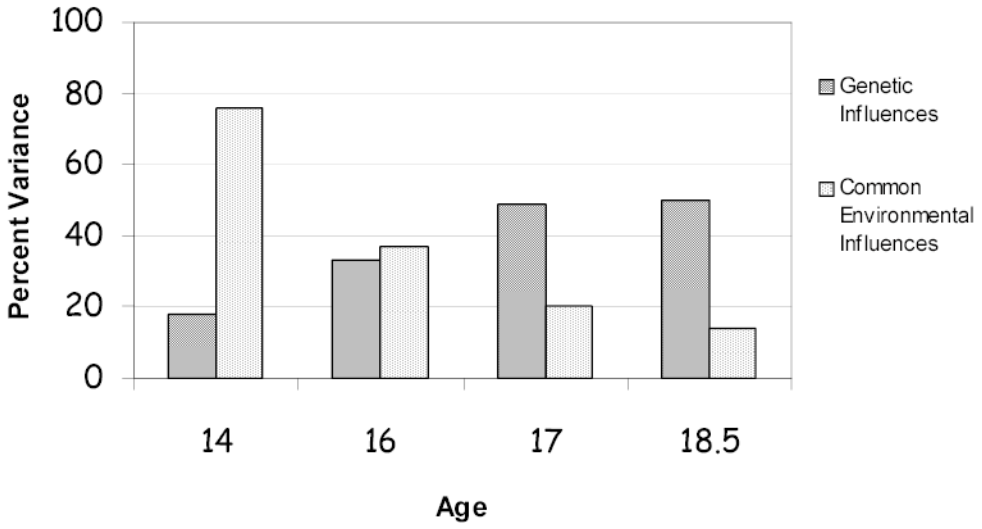

Figure 1.
Data from the Finnish Twin Studies demonstrate the changing importance of genetic and common environmental influences across adolescence.

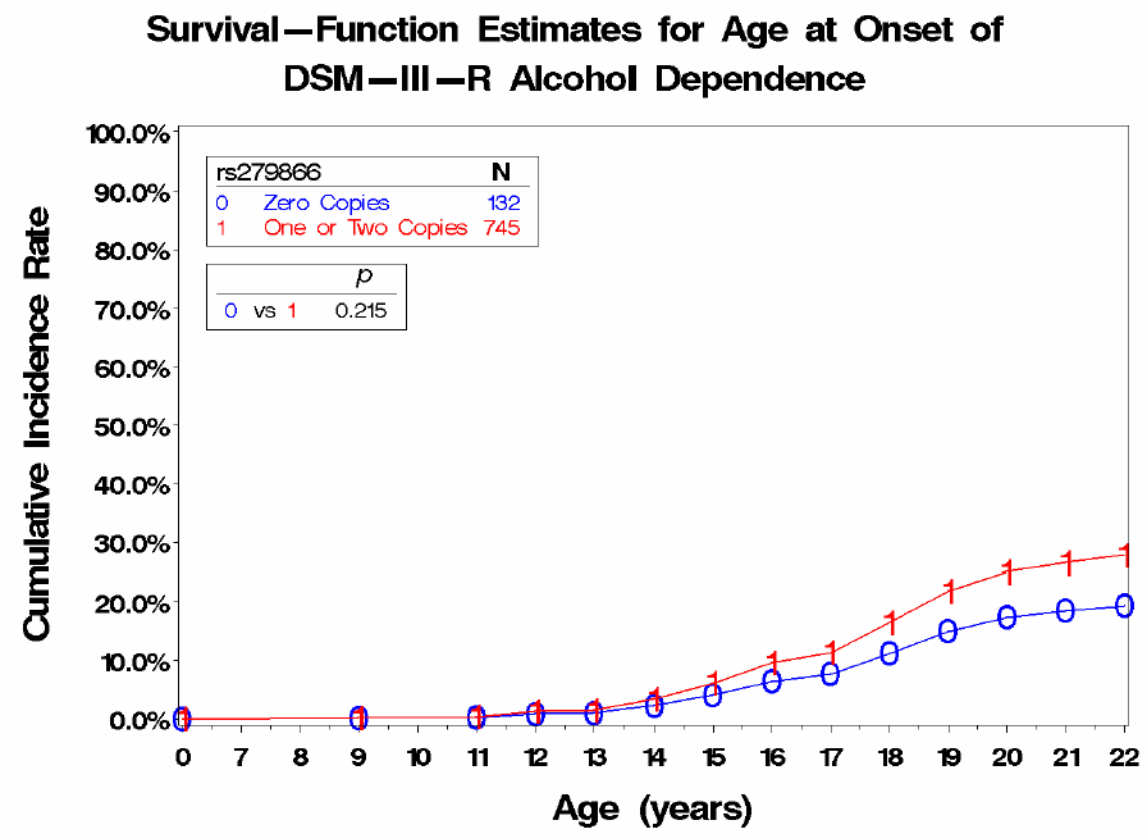

Figure 2.
Survival–Function Estimates for Age at Onset of DSM–III–R Alcohol Dependence

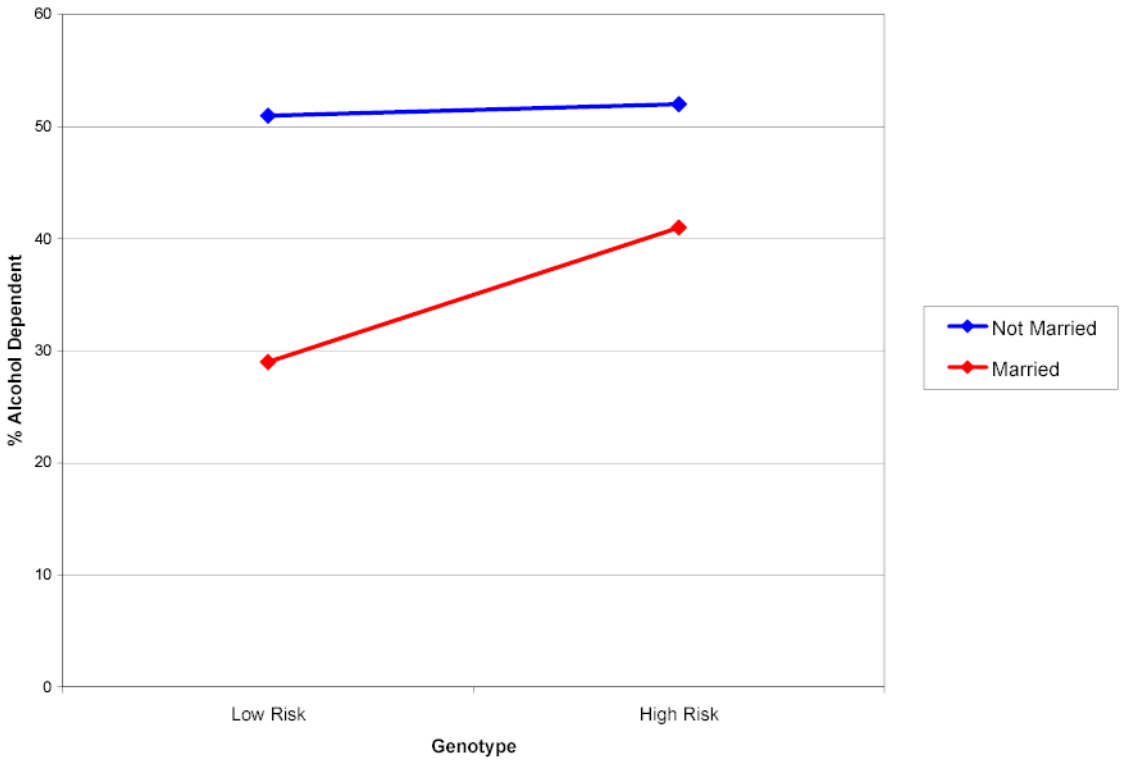

Figure 3.
Rates of Alcohol Dependence as a Function of *GABRA2* Genotype and Current Marital Status