Pharmacogenetics of alcoholism: a clinical neuroscience perspective

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Twin and adoption studies have shown that the heritability of alcoholism may be as high as 50–60% [1]; however, the neuropathophysiology of alcoholism and its underlying genetic architecture is complex and remains largely elusive to scientists in the field. Pharmacogenetics has the potential to aid in the identification of genetic markers for alcoholism risk and treatment response in that the introduction of a CNS drug narrows the genetic focus to those systems involved in the drug's metabolism and efficacy (pharmacokinetics and pharmacodynamics). In this editorial, we briefly discuss the pharmacogenetics of alcohol as a drug, the pharmacogenetics of alcoholism treatment, and provide a series of recommendations for future research.

Pharmacogenetics of alcohol response

The neuropharmacological and behavioral effects of alcohol include both stimulant and sedative properties. The stimulant effects of alcohol are predominant during the ascending limb of the blood alcohol curve, while the sedative effects are more salient during the descending limb of alcohol intoxication. Individual differences in subjective responses to alcohol, including higher sensitivity to the rewarding stimulant effects and lower response to the primarily aversive sedative effects represent biobehavioral risk factors for alcoholism [2,3]. These biobehavioral phenotypes can in turn inform the search for genetic determinants of alcoholism [4]. To that end, a number of molecular genetic studies have examined variation in four primary neurotransmitter systems underlying acute subjective responses to alcohol, namely opioidergic, dopaminergic, GABAergic and glutamatergic systems (for a review, see [5]).

In brief, while genetic variation in the opioidergic and dopaminergic systems are primarily implicated in the rewarding and positive reinforcing effects of alcohol, GABAergic and glutamatergic systems are thought to underlie acute tolerance and sensitivity to the sedative and unpleasant effects of the drug. Using the intermediate phenotype framework [6], a number of candidate genes have been advanced within these systems [5]. Likewise, studies of alcohol metabolism have been fruitful in identifying genetic variants in alcohol-metabolizing enzymes associated with an aversive neurobehavioral response to alcohol, hence serving as protective factors against the development of alcoholism [7]. Together, studies of the pharmacogenetics of alcohol response have helped elucidate genetic risk factors for the disorder as well as potential treatment targets. Notably, however, no genome-wide association studies to date have been conducted on subjective responses to alcohol. While meeting sample size requirements for genome-wide association studies represents an arduous task, given that an alcohol challenge (i.e., controlled alcohol administration in the laboratory) is the gold standard in the assessment of subjective responses to alcohol, large-scale studies of the pharmacogenetics of alcohol response are clearly warranted.

Pharmacogenetics of alcoholism treatment

Three pharmacotherapies are currently US FDA-approved for the indication of alcoholism, naltrexone (oral and injectable), acamprosate and disulfiram. Naltrexone is an opioid antagonist, with highest affinity for the μ-opioid receptor. The endogenous opioid system has been implicated in the pathophysiology of alcoholism as it modulates the reinforcing effects of alcohol via activation of μ-opioid receptors in the ventral tegmental area and nucleus accumbens, which in turn enhances extracellular concentrations

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of dopamine in the mesolimbic pathway [8]. Through the blockade of μ-opioid receptors, naltrexone is thought to blunt the reinforcing effects of alcohol, which is supported by behavioral pharmacology studies [9]. Recent pharmacogenetic studies have implicated a SNP of the *OPRM1* gene, the A118G SNP (rs17799971) as a moderator of naltrexone response. The A to G nonsynonymous mutation results in an amino acid change from asparagine to aspartic acid, which in turn is thought to change the chemical properties of these receptors increasing their binding affinity for β-endorphin [10]. The G-allele has been associated with stronger alcohol-induced reinforcement [11] and with greater dopaminergic output in the striatum during alcohol administration [12].

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Some clinical studies of naltrexone have suggested improved clinical outcomes among G allele carriers [13,14], with noted exceptions [15], and the purported mechanism of action is greater naltrexone-induced blunting of alcohol 'high' among these individuals [9]. While the literature on naltrexone pharmacogenetics is far from conclusive, a clinical neuroscience perspective suggests that since reinforcement drinking is more salient during early stages of alcoholism, naltrexone and its *OPRM1*-based pharmacogenetics may be in fact capturing genetic vulnerability associated with alcohol-induced reward and may be most effective at the earlier stages of the disorder [16]. This is consistent with the notion that phenotypic heterogeneity in alcoholism may be used to develop and refine clinical interventions [17]. In addition to naltrexone pharmacogenetics, a recent study has found that genetic markers in the serotonin transporter gene were associated with improved clinical response to ondansetron for alcoholism [18]. These studies highlight opportunities for personalized medicine in alcoholism treatment, which is critical in light of the overall modest effect sizes for the FDA approved, and experimental, pharmacotherapies.

Recommendations for future research

Recent progress in the pharmacogenetics of alcohol response and alcoholism treatment is met with cautious optimism. A number of unresolved methodological and conceptual issues must be carefully considered and addressed in order to advance the field. To that end, the following recommendations are provided.

Neuroscience-based clinical phenotypes can advance genetic studies of alcoholism etiology and treatment. The last decade in psychiatric genetics has been marked by increasing recognition of the limitation of diagnostic phenotypes, including alcoholism [6]. Intermediate phenotypes, or endophenotypes, have been advanced as an alternative to diagnostic phenotypes. However, in order for these alternative phenotypes to be useful, it is critical that they be informative about the underlying neurobiology of alcoholism. While the basic neuroscience of addiction has progressed rapidly, there is a clear need to translate these findings to clinical samples. The examples of translational and reverse translational approaches to alcoholism pharmacogenetics are few (see [17]), yet their results are encouraging and provide a model for future efforts. Clinically meaningful neuroscience-based phenotypes capturing reward-based drinking and withdrawal-relieving drinking, for example, may be particularly useful as they can be traced to specific neurobiological substrates that can in turn help 'hone in' genetic and pharmacogenetic inquiry. Much like the literature on the subjective responses to alcohol where positive and negative reinforcing effects are at play simultaneously, clinical instruments that can capture the dynamic interplay between these systems are most pressing. Determining the validity of such clinical neuroscience measures represents a critical limitation to their development. To that end, recent advances in neuroimaging techniques may be particularly useful in establishing clinical instruments that can capture meaningful neurobiological substrates of alcoholism in humans.

Allele frequency imbalance across ethnic groups may lead to health disparities in the era of personalized medicine. There is a strong need for replication and extension of personalized medicine findings to diverse patient populations. Given that Caucasian is the predominant racial group in research samples, genetic studies are often unpowered to address whether the findings can be extended to other ethnic groups. Moreover, allele frequency imbalance may indicate underlying differences in allelic function, furthering the argument for careful consideration of ethnicity issues beyond genomic controls for ancestry informative panels, which are uninformative about the applicability of the

findings across ethnicities [19]. For example, a recent study found that while the *OPRM1*-based naltrexone pharmacogenetics were supported in Asian–Americans, the operative mechanisms of action may be distinct [20].

Practical issues in the implementation of personalized medicine must be considered. A number of practical issues have been noted with regard to the implementation of personalized medicine in clinical settings, including provider training, feasibility of genetic testing, as well as privacy and confidentiality concerns surrounding genetic testing, to name a few. The effective resolution of these issues will ultimately determine whether pharmacogenetic findings can in fact improve clinical care. These issues also raise the important question of what information is unique to genetic testing that cannot be captured by clinical variables alone. First, it is plausible that pharmacogenetic studies are in fact capturing meaningful phenotypic variation in the disease profile that is accessible at the behavioral and clinical levels, albeit in more opaque form. If that is the case, then a proper cost–effectiveness analysis must be considered in order to inform the use of clinical versus genetic markers. Second, pharmacogenetic findings may inform reverse translational studies that can help elucidate the underlying mechanisms of action and in turn inform the development of clinical algorithms beyond genetic testing. In either case, the clinical utility and application of the findings should guide the decision to pursue clinical and/or genetic markers to personalize treatment for alcoholism, as well as other complex neuropsychiatric disorders.

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On balance, the field of alcoholism pharmacogenetics has progressed rapidly over the past decade. While the results are encouraging, the path to translating these findings into clinical advancements is long and will require extensive research. A clinical neuroscience perspective has been called to facilitate the translation of clinical research that is informed by basic neuroscience findings. To that end, there is a clear need for translational phenotypes for alcoholism that can bridge the gap between the neurobiology of the disorder and its clinical manifestations. Recent research integrating the neural, genetic, and pharmacological bases of alcohol-induced reward has proven fruitful [17] and provides a roadmap for future investigations.

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