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Genetic Influences on Response to Alcohol and Response to Pharmacotherapies for Alcoholism

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Abstract

Although very many individuals drink alcohol at safe levels, a significant proportion escalates their consumption with addiction as the end result. Alcoholism is a common, moderately heritable, psychiatric disorder that is accompanied by considerable morbidity and mortality. Variation in clinical presentation suggests inter-individual variation in mechanisms of vulnerability including genetic risk factors. The development of addiction is likely to involve numerous functional genetic variants of small effects. The first part of this review will focus on genetic factors underlying inter-individual variability in response to alcohol consumption, including variants in alcohol metabolizing genes that produce an aversive response (the flushing syndrome) and variants that predict the level of subjective and physiological response to alcohol. The second part of this review will report on genetic variants that identify subgroups of alcoholics who are more likely to respond to pharmacotherapy to reduce levels of drinking or maintain abstinence. Genetic analyses of the level of response to alcohol, particularly of the functional *OPRM1* A118G polymorphism and 5' and 3' functional polymorphisms in *SLC6A4*, are beginning to provide insights into the etiology of alcoholism and also genotype-stratified subgroup responses to naltrexone and SSRIs / ondansetron respectively. Because of large inter-ethnic variation in allele frequencies, the relevance of these functional polymorphisms will vary between ethnic groups. However there are relatively few published studies in this field, particularly with large sample sizes in pharmacogenetic studies, therefore it is premature to draw any conclusions at this stage.

Keywords

OPRM1; 5-HTTLPR; rs1042173; GABRA2; ALDH2; ADH1B; level of response to alcohol; naltrexone; SSRIs; ondansetron

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Introduction

Very many individuals derive benefits, social and otherwise, from consuming alcohol throughout their lives at low levels that do not escalate. Unfortunately, a significant proportion becomes addicted. Alcoholism is a common psychiatric disorder that is associated with considerable morbidity, mortality and societal costs. The lifetime prevalence of alcohol use disorders (AUD) (alcohol dependence and abuse) in the USA is 30% (Hasin et al, 2007). Alcohol and nicotine are by far the most common drugs of abuse; the 12 month prevalence for AUD is 8.5%, for nicotine dependence is 12.8%, for cannabis use disorders is 1.5% and for other illicit substance use disorders is 0.1-0.4% (Grant et al, 2004).

The essential features of alcohol addiction are loss of control over consumption, obsessive thoughts about the next drink, and continuation of drinking despite knowledge of negative health and social consequences (American Psychiatric Association, 1994). It is well established from twin studies that the heritability (the genetic component of the variance) of alcoholism is around 50% (Goldman et al, 2005) therefore genetic and environmental influences on vulnerability to this disorder are equally important. In terms of environmental influences, it is becoming increasingly apparent that childhood trauma is a predictor for the development of psychopathology including alcoholism (Enoch, 2011). Variation in the clinical presentation of alcoholism, for example in terms of age of onset, predisposing personalities, psychiatric comorbidity, severity of disease and withdrawal symptoms (Enoch and Goldman, 2001; Moss et al, 2007) suggests inter-individual differences in mechanisms of vulnerability including genetic risk factors. Likewise, inter-individual variation in response to pharmacotherapy for alcoholism may be due in part to genetic variation or pharmacogenetics.

The road leading to alcoholism starts of course with regular alcohol consumption. This review will first of all focus on genetic factors underlying inter-individual variability in response to alcohol consumption, including variants in alcohol metabolizing genes that produce an aversive response (the flushing syndrome) and variants that predict the level of subjective and physiological response. The second focus of this review is on genetic variants that identify subgroups of alcoholics who are more likely to respond to pharmacotherapy to reduce levels of drinking or maintain abstinence. Perhaps not surprisingly, there is a degree of overlap between the functional variants that influence alcohol consumption and influence response to pharmacotherapy.

1 Metabolism of ethanol

Ethanol is metabolized largely in the liver by alcohol dehydrogenases (ADH) to acetaldehyde which is then converted to acetate by aldehyde dehydrogenases (ALDH), primarily by the mitochondrial enzyme ALDH2 but also by the cytosolic enzyme ALDH1. ADH enzymes have been categorized into five classes based on structural similarity and kinetic properties (Edenberg, 2007). The class I enzymes encoded by the *ADH1A*, *ADH1B* and *ADH1C* genes contribute about 70% of the total ethanol oxidizing capacity, and the class II enzyme encoded by *ADH4* contributes about 30% (Hurley and Edenberg, 2012). The class III ADH5 enzyme is the only enzyme detectable in brain. Class IV ADH7 is mainly expressed in the upper digestive tract where it oxidizes ethanol at high concentrations. The

class V ADH6 enzyme catalyzes a widely variety of substrates including retinol but it is less efficient in ethanol metabolism.

2. Inter-individual variability in response to alcohol

2.1 Aversive response to alcohol (flushing syndrome)—Approximately 45% of East Asians (Japanese, Chinese, Koreans) are carriers of the ALDH2*2 allele (Glu504Lys, rs671) that encodes the inactive ALDH2 enzyme. After consumption of small quantities of alcohol by these individuals the toxin acetaldehyde rapidly accumulates, resulting in the very unpleasant flushing syndrome (facial flushing, tachycardia, sweating, headaches, nausea), colloquially called ‘Asian Glow’ or ‘Asian Blush’, that is protective against heavy drinking and therefore alcoholism (Higuchi et al, 2004). Individuals with the combination of the ALDH2*2 allele and the ADH1B*2 allele, encoding higher enzyme activity, have a particularly severe flushing response and low risk for AUD (Chen et al., 1999). The inactive ALDH2 variant is also associated with increased risk of esophageal cancer (Brooks et al, 2009). Anecdotal evidence suggests that some young Asians have now discovered ways to reduce these aversive effects by taking antihistamines or antacids prior to drinking. Since acetaldehyde still accumulates, this environmental modification greatly increases the risk of liver toxicity, cancer and AUD. The ALDH2*2 allele is unique to East Asian populations and in these individuals the ALDH1 cytosolic enzyme is particularly important for acetaldehyde elimination (Bosron et al, 1993).

It should be noted that disulfiram (antabuse), the first medication to treat alcoholics, acts as a deterrent to drinking since it mimics the ALDH2 inactive enzyme by blocking acetaldehyde metabolism, thereby resulting in the very unpleasant flushing syndrome in combination with alcohol.

The higher enzyme activity encoded by the polymorphisms in the class I genes: ADH1B*2 (Arg48His, rs1229984), ADH1B*3 (Arg370Cys, rs2066702) and the ADH1C*1 haplotype (Arg272Ile350) enables more rapid conversion of ethanol to acetaldehyde, thereby also resulting in the flushing syndrome and also being protective against excessive alcohol consumption and AUD (Chen et al, 1999, Edenberg, 2007)..

The ADH1B*2 allele is most abundant (0.75) in East Asians. However, it is also common in Jewish populations with frequencies ranging from 0.20 to 0.31 and is associated with increased alcohol elimination and reduced ethanol consumption (Shea et al, 2001; Carr et al, 2002; Neumark et al, 2004; Meyers et al, 2013). In this regard it is interesting to note that Jewish ancestry has been associated with more intense subjective feelings to alcohol challenge (Monteiro et al, 1991).

The ADH1B*2 allele is uncommon in other populations, occurring at a frequency of 0.01 in Caucasians, African Americans and American Indians (Liu et al, 2011). Nevertheless, studies in large non-East Asian datasets of several thousand individuals have likewise demonstrated a protective effect of ADH1B*2 on AUD (Bierut et al, 2012; Sherva et al, 2009), and a study in 4500 largely Caucasian Australian twins found an association between ADH1B*2, flushing and alcohol consumption (Macgregor et al, 2009).

Finally, the *ADH1B*3* allele occurs at a frequency of 0.22 in individuals of African ancestry and is not found in Caucasians or Asians. This allele has been associated with higher rates of sedation after alcohol challenge and a protective effect on risk for AUD in African Americans (Edenberg et al, 2006; McCarthy et al, 2010).

2.2 Measured subjective and physiological responses to alcohol—Individuals vary considerably in their responses to alcohol. Studies have shown that there is a 3- to 4-fold variation, between- and within-subjects, in breath alcohol concentrations following oral alcohol administration (Ramchandani et al, 2009). Variability factors include sex, age, body size, recent alcohol use, and genetic vulnerability. In addition, even at the same blood alcohol concentrations there is inter-individual variation in subjective and physiological responses to alcohol. Subjective response to alcohol is biphasic, with generally positive responses during the rising breath / blood alcohol curve (BAC) to the stimulant effects of alcohol and negative responses during the descending BAC to the sedative effects. The level of response (LR) to alcohol can be defined in terms of an individual's subjective response and also physiological response such as motor coordination to a given dose and blood level of alcohol (Joslyn et al, 2010). Several other physiological responses to alcohol have been measured including cortisol, ACTH, prolactin, cardiovascular, oculomotor, resting EEG, event related potentials (reviewed in Newlin and Thomson, 1990) and brain imaging

Many studies (Pollock, 1992) have demonstrated that there are individuals who display a lower intensity of response to alcohol that is seen from the time individuals start drinking and is not the result of tolerance (Schuckit, 1994). One of the earliest studies was conducted in a group of 227 social drinking young men with severely alcoholic fathers and 227 young men with a negative family history (FH) of alcoholism. The FH+ group showed lower levels of change in body sway and lower subjective feelings of intoxication, effectively during the declining BAC, compared with the FH- group (Schuckit, 1980; Schuckit and Gold, 1988). This has also been shown in daughters of alcoholics from the same sample (Eng et al, 2005). Longitudinal follow up of the sons of alcoholics showed that a low LR to alcohol at age 20 was associated with a four-fold increased risk of alcoholism (but not other drug use) 10 years later, irrespective of FH (Schuckit, 1994). Men with the 15% highest and 15% lowest scores on a composite z score measure of LR to alcohol were described as low and high responders (Schuckit and Smith, 1996). In this group of two extremes it was shown that, irrespective of FH, LR was a mediator of alcoholism risk. A small alcohol challenge study from COGA, the Collaborative Study on the Genetics of Alcoholism, also found a lower LR to alcohol in FH+ men relative to FH- men in terms of subjective feelings but more robustly in cortisol response (Schuckit et al, 1996).

An intriguing study in a group of 335 Chinese and Korean college students found that the Koreans had a significantly lower LR to alcohol determined by the Self Rating of the Effects of Alcohol (SRE) questionnaire (low LR defined as a total SRE score of ≤ 4.5) controlling for gender, height, weight, recent alcohol consumption, *ALDH2* and *ADH1B* genotypes, country of origin and FH (Duranceaux et al, 2008). This disparity in LR to alcohol that is independent of the key alcohol metabolizing gene variants warrants investigation across different ethnicities.

In contrast, numerous studies have shown a *higher* level of response to acute alcohol in FH+ individuals – that is, in the rising BAC (reviewed in Newlin and Thompson, 1990; Newlin and Renton 2010). A longitudinal laboratory alcohol challenge study in community-derived, high risk, heavy social drinkers and light drinking controls looked at time frames that incorporated both the ascending and descending BAC. The investigators found that in heavy drinkers relative to light drinkers, alcohol produced greater stimulant and rewarding responses as well as lower sedative and cortisol responses. Heightened acute positive responses and diminished negative responses predicted the development of alcoholism (King et al, 2011).

In contrast, a study looking at subjective response to IV alcohol in men over the ascending and descending BAC showed that heavy drinkers reported lower stimulation than light drinkers although, as in previous studies, they also experienced lower levels of intoxication and sedation. Moreover, levels of intoxication were positively correlated with fMRI ventral striatum (VS) activation (Gillman et al, 2012). Thus alcohol activated the VS in light drinkers but not in heavy drinkers although whether this blunted response to alcohol was a trait effect or the result of chronic drinking could not be distinguished. Likewise, positron emission studies (PET) have shown that alcohol-induced dopamine (DA) release in the VS is correlated with subjective response ('high' or intoxication) to IV alcohol infusion (Yoder et al, 2007). However this finding was in men but not women in whom DA release in the VS is lower (Urban et al, 2010). This raises the possibility of sexually dimorphic genetic influences on VS reactivity; indeed, one study of haplotypes in *GAL*, the gene encoding the neuropeptide galanin, suggests that this might be the case (Nikolova et al, 2013).

2.3 Genetic influences on LR to alcohol

2.3.1 Heritability: LR to alcohol appears to have moderate to high heritability. A study in young adult Australian twins showed that a composite alcohol sensitivity measure, combining subjective intoxication and increase in body-sway after alcohol challenge had a heritability of 0.60 (Heath et al, 1999). A sibling study in young adult social drinkers concluded that the heritability of the SRE was 0.67 (Kalu et al, 2012). Since the longitudinal studies described above have shown that a low LR to alcohol predicts the development of alcoholism, a low LR can be considered as an intermediate phenotype to search for candidate genes for alcoholism (Enoch et al, 2003).

2.3.2 Candidate genes for LR to alcohol: With a moderate heritability, genetic influences on LR should be substantial although this may well result from numerous genes, each with a small effect. A genome-wide linkage scan using an alcohol challenge protocol as a direct measure of LR found the strongest evidence on chromosomes 10, 11 and 22 (Wilhelmsen et al, 2003) although no specific genes were identified (Schuckit et al, 2005).

As described below, several subsequent studies have identified associations between genetic variants in candidate genes and LR to alcohol, both in the ascending and descending BAC.

2.3.2.1 *OPRM1* A118G: *OPRM1* is a key candidate gene since β -endorphin and the μ opioid receptor have been shown to play an important role in the rewarding or reinforcing effects of alcohol (Thorsell, 2013). A polymorphism in the μ opioid receptor gene *OPRM1*, A118G

(Asn40Asp) rs1799971 (Bergen et al, 1997) produces a threefold increase in β -endorphin binding affinity and potency (Bond et al, 1998). PET studies have shown that this polymorphism alters μ opioid receptor availability in healthy controls and abstinent alcoholics (Weerts et al, 2013). In an IV alcohol challenge PET [^{11}C]raclopride study, DA release in the VS in men correlated with the *OPRM1* A118G polymorphism such that the carriers of the minor G allele showed greater VS DA release than carriers of the major AA homozygote (Ramchandani et al, 2011). Genotype accounted for 30% of the variance in brain response although genotype did not on the whole correlate with subjective response to alcohol (Ramchandani et al, 2011). In line with these imaging results, an earlier study of male and female students showed that G allele carriers experienced increased levels of subjective intoxication and higher levels of alcohol-induced sedation relative to AA homozygotes (Ray and Hutchison, 2004). In a group of non-treatment seeking alcoholics, G allele carriers reported greater hedonic effects (stimulation and positive mood) in response to IV alcohol (Ray et al, 2013). Moreover, male heavy drinkers who were G allele carriers reported significantly more craving for alcohol in response to alcohol cues (van den Wildenberg et al, 2007). In order to directly establish the causal role of *OPRM1* A118G variation, Ramchandani et al, 2011 generated two humanized mouse lines carrying the respective human sequence variant. Brain microdialysis showed a fourfold greater peak DA response to an alcohol challenge in GG mice compared with the AA mice. Taken together, these genetic studies consistently implicate the G allele with increased DA release and increased subjective effects, both in the ascending and the descending BAC, in response to alcohol. Therefore *OPRM1* A118G variation appears to modulate alcohol reward and, as discussed later, this has relevance for treatment with naltrexone, a μ opioid receptor antagonist.

2.3.2.2 *SLC6A4* 5-HTTLPR: A functional promoter polymorphism 5-HTTLPR in *SLC6A4*, the gene encoding the serotonin transporter (5-HTT) has been associated with changes in neuronal circuitry implicated in negative affect (Hariri et al, 2005; Heinz et al, 2005; Pezawas et al, 2005). 5-HTTLPR is a common polymorphism including a variable number of tandem repeats (44-base pair insertion/deletion) in the promoter region that alters transcription such that the less common, short 'S' allele is associated with an approximately 50% reduction in 5-HTT availability and concomitant increase in synaptic serotonin, reduced neuronal uptake of serotonin and decreased 5-HIAA (Heils et al, 1996). Triallelic genotyping (incorporating the functional SNP rs25531) of 5-HTTLPR identifies the low transcriptional activity S allele but additionally separates the high activity L_A allele from a third allele, L_G which displays low transcriptional activity similar to the S allele (Hu et al, 2006). This is particularly important when studying individuals of African ancestry where the frequency of L_G is comparatively high (Table 1). In a sample of 243 German adolescents who had completed the SRE questionnaire, the LR to alcohol was significantly lower in carriers of the 5-HTTLPR high activity variant (Hinckers et al, 2006), confirming the results from an earlier, smaller oral alcohol challenge study in the US (Hu et al, 2005).

2.3.2.3 *GABRA2*: One of the few robust genetic predictors for alcoholism is *GABRA2* that encodes the GABA $_A$ α_2 subunit that forms the pentameric GABA $_A$ receptor $\alpha_2\beta_1\gamma_1$ found in the mesolimbic dopamine reward pathway. Several studies have associated tightly linked

SNPs in a distal *GABRA2* haplotype block with alcoholism (reviewed in Enoch, 2008). Recently, a few studies have associated *GABRA2* variation within this haplotype block with subjective responses to alcohol. A study of 69 healthy volunteers who participated in a cumulative oral dosing procedure with continuous subjective assessments using a visual analog drug effect scale, the biphasic alcohol effects scale (BAES) and the subjective feeling of high (SHAS) showed that carriers of the minor alleles of SNPs within this haplotype block, previously associated with alcoholism (Enoch, 2008) had lower negative alcohol effect scores than carriers of the major homozygotes (Uhart et al, 2013). Similar results were found in a study of 110 Japanese social drinkers, stratified by *ALDH2**1/*1 and *ALDH2**1/*2 genotype, using an IV alcohol paradigm, the alcohol clamp method (O'Connor et al, 1998) with subjective responses measured by a sensation scale and the BAES; the minor homozygotes of SNPs within the same haplotype block were associated with a lower initial response to alcohol (Roh et al, 2011). Also, similar results were found in a much smaller earlier study in social drinkers (Pierucci-Lagha et al, 2005). Although these are congruent results and the association of *GABRA2* with alcoholism is robust, it should be noted that no functional variant has yet been found, either in *GABRA2* or in the tightly linked, closely adjacent *GABRG1* gene.

2.3.2.4 Chromosome 15q25.1 nicotinic receptor subunit gene cluster: Numerous studies have implicated the chromosome 15 cluster of genes *CHRNA5-CHRNA3-CHRNA4*, encoding nicotinic receptor subunits, with nicotine dependence. In a study of 367 siblings, two sentinel SNPs within the chromosome 15q25.1 region of high linkage disequilibrium associated with LR to alcohol (Joslyn et al, 2008; Saccone et al, 2007). This commonality of genes for both alcohol and nicotine phenotypes is not unexpected since there is considerable comorbidity between the two addictions and overlap in heritability; for example, a heavy smoking - heavy alcohol genetic factor accounts for 45% of the heritable variance in heavy drinking and 35% of the heritable variance in heavy smoking (Swan et al, 1997).

2.3.3 Genome-wide association study: Using a non-hypothesis driven approach to attempt to detect novel genetic influences on LR to alcohol, a sample of 367 self-identified Caucasians were genotyped using a genome-wide association study (GWAS) array (Joslyn et al, 2010). Analyses were performed for association with three alcohol challenge LR phenotypes: body sway (BSA), the SHAS and the SRE. The authors found no SNP associations that had genome-wide significance. In line with the current trend for analyzing GWAS data, the authors then took a systems biology approach using gene set enrichment techniques and identified a gene list that was strongly enriched for cell signaling functions and pathways with an emphasis on neuronal signaling; for example, glutamate receptor signaling, in particular NMDA receptors (Joslyn et al, 2010).

2.3.4 Gene $\times$ Environment ($G \times E$) interactive effects on LR to alcohol: It is well known that stress can affect neuronal plasticity. Early life stress in rats has significant, long-lasting effects on the mesolimbic DA pathway including responsiveness of DA neurons to psychostimulants in adulthood (Brake et al, 2004; Mesquita et al, 2007; Moffett et al, 2007). These findings in rats, supported by a few studies in humans (Dillon et al, 2009; Pruessner et al, 2004), are consistent with the hypothesis that early life stress affects the DA system.

Therefore it is possible that genetic influences on LR to alcohol, in terms of VS DA release, may be modified by early life stress and therefore it will be relevant to look for $G \times E$ interactive effects. No $G \times E$ study for LR to alcohol has been published so far.

3. Pharmacogenetics: inter-individual variability in response to pharmacotherapy

The second half of this review will focus on genetic variants that identify subgroups of alcoholics who are more likely to respond to pharmacotherapy to reduce levels of drinking or maintain abstinence by preventing relapse.

Alcoholism is a chronic disease that has a variable course characterized by periods of remission and relapse. However, a population survey of approximately 43,000 individuals across the USA, the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), has shown that within the community only 26% of alcoholics have ever sought any kind of treatment (including Alcoholics Anonymous) (Dawson et al, 2005). There are four factors that need to be addressed for successful recovery from alcoholism: physiological dependence (symptoms of withdrawal), response to stress and drug related cues, habit (the role alcohol plays in the framework of daily living), and comorbid psychopathology. For those who seek treatment, current therapy relies largely on social support, self-help and behavioral modification therapies such as cognitive behavioral therapy (CBT) (Enoch and Goldman 2002) Although three medications, described below, have been licensed for several years in the USA for treatment of alcoholism, they are not widely used, even in clinical settings, and there is variability in therapeutic response Studies derived from treatment centers show that 40 – 60% of treatment-seeking alcoholics remain abstinent for the first few months post-treatment and only 20 – 30% are still abstinent at the end of one year (Dawson et al., 2007). It is likely that most benefit will be achieved if behavioral or psychosocial therapy is combined with pharmacotherapy, targeted to subgroups most likely to respond, in part identified by genetic stratification.

3.1 FDA approved treatments for alcoholism: disulfiram, naltrexone, acamprosate—Pharmacotherapeutic aims for the treatment of alcoholism are twofold: prevention of future pathology by reducing heavy drinking in problem drinkers and alcoholics unable to abstain, and abolition or reduction of craving in order to prevent relapse. The World Health Organization has described craving as a powerful urge to drink or as intense thoughts about alcohol.

Three drugs have been licensed for several years in the USA for treatment of alcoholism: disulfiram (antabuse) since the 1940's, naltrexone since 1995, and acamprosate since 2004. Disulfiram, rarely prescribed since it has potentially serious side effects, has been used as a drinking deterrent because, by blocking acetaldehyde metabolism in the alcohol metabolic pathway, it produces the very unpleasant flushing syndrome, described earlier, in combination with alcohol. Naltrexone, a μ opioid receptor antagonist, has been shown to have a modest effect on drinking outcomes (Ray et al, 2010; Setiawan et al, 2012). A review of 29 US studies involving naltrexone that included nearly 6000 alcohol dependent patients found that 70% of 27 trials that measured reduction in heavy drinking demonstrated an advantage for prescribing naltrexone over placebo in contrast to only 36% of 25 clinical

trials measuring abstinence (Pettinati et al, 2006). Among alcoholics who chose to be abstinent at the initiation of the study, a long-acting formulation of naltrexone maintained abstinence for 6 months in 32% of alcoholics compared with 11% who received placebo (O'Malley et al, 2007). Acamprosate, a weak NMDA antagonist, is largely used in Europe where many centers routinely offer it to newly detoxified patients aiming for abstinence. Results from three major European studies showed that the rate of complete abstinence in the acamprosate group was 3 times that of the placebo group at 3 months and 1.8 times that of placebo treatment at one year (Kranzler and Gage, 2008). Both acamprosate and naltrexone are safe and generally well-tolerated and, as described above, both have shown modest effects on drinking reduction and relapse prevention in some but not all alcoholics.

In addition, selective serotonin re-uptake inhibitors (SSRIs) are used in the treatment of depression comorbid with alcoholism, since depression is common amongst recently abstinent alcoholics.

3.2 Potential pharmacotherapies for treatment of alcoholism—Several other medications are being investigated for efficacy in the treatment of alcoholism. Examples include nalmefene, an opioid antagonist, topiramate, an anticonvulsant, ondansetron, a selective 5-HT₃ antagonist currently used as an anti-emetic, baclofen, a GABA-B receptor agonist used to treat spasticity and varenicline, a partial nicotine agonist (for further details see Edwards et al, 2011; Heilig and Egli 2006; Franck and Jayaram-Lindstrom, 2013).

3.3 Pharmacogenetics: functional gene variants—The modest results for the efficacy of current pharmacotherapeutic agents, despite usually being provided in combination with behavioral therapies, may be due in part to the heterogeneity of the disorder and the complexities of the holistic approach. It is encouraging that a few recent studies have shown that the identification of subgroups by genetic stratification might improve treatment outcomes. Pharmacogenetic effects of functional gene variants have thus far been demonstrated for naltrexone, SSRIs and ondansetron.

3.3.1. Pharmacogenetics of naltrexone: the functional *OPRM1* polymorphism A118G Asn40Asp, rs1799971: Naltrexone is a nonselective opioid receptor antagonist that acts primarily at the μ opioid receptor. In G allele carriers compared with AA homozygotes, naltrexone has been shown to decrease ethanol induced euphoria in social drinkers (Setiawan et al, 2011) and blunt alcohol-induced 'high' in non-treatment seeking heavy drinkers (Ray and Hutchison, 2007). In a 12 week, randomized clinical trial of naltrexone to reduce drinking in 158 problem drinkers, G allele carriers were at greater risk of drinking more when the desire to drink was relatively high, and this was attenuated by naltrexone (Kranzler et al, 2013). However another study did not find an effect of the A118G polymorphism on drinking reduction in non-treatment seeking alcoholics (Anton et al, 2012).

It is worth taking a detailed look at the results of the Combining Medications and Behavioral Interventions for Alcoholism (COMBINE) study. This was a large study of recently abstinent alcoholics that was conducted across 11 academic sites; 301 (67 G allele carriers) were treated with naltrexone and 303 (68 G allele carriers) with placebo for 16 weeks and

had either medical management (MM) alone or CBT (Anton et al, 2008). The impact of genotype was modest, perhaps due to the small sample sizes of G allele carrier groups. G allele carriers treated with naltrexone and MM alone had a decreased percentage of heavy drinking days while AA homozygotes showed no medication differences. Of the G allele carriers, 87% of those treated with naltrexone had a good clinical outcome compared with 49% of those treated with placebo and of the AA homozygotes, 55% had a good clinical outcome whether they were treated with naltrexone or placebo (Anton et al, 2008). Finally, a haplotype-based approach using the COMBINE data confirmed that A118G was the single predictor in the *OPRM1* gene for response to naltrexone (Oroszi et al, 2009).

Naltrexone administration results in HPA axis activation and higher cortisol levels that are negatively correlated with intensity of alcohol craving (O'Malley et al, 2002): G allele carriers show greater HPA activation, increased baseline cortisol levels and larger cortisol responses than AA homozygotes (Hernandez-Avila et al, 2003; Wand et al, 2002). In general, alcoholics show reduced central dopaminergic sensitivity that is also associated with poor treatment outcome, however, alcoholics carrying the G allele have significantly greater central dopaminergic receptor sensitivity after one week of abstinence that is not seen before detoxification or at 3 months of abstinence (Smolka et al, 1999). These findings are in line with another study showing that G allele carrying naltrexone-treated alcoholics had significantly lower relapse rates and took longer to return to heavy drinking than AA homozygotes (Oslin et al, 2003). Likewise, a meta-analysis using a random-effects model of six studies published between 2002 and 2009 that investigated the association between A118G and response to naltrexone in alcoholics determined that G allele carriers had modestly lower relapse rates than AA homozygotes (OR = 2.02, 95% CI = 1.26 – 3.22) but there was no difference in rates of abstinence (Chamorro et al, 2012).

In summary, studies to date appear on balance to show a modestly greater therapeutic response of *OPRM1* A118G G allele carriers to naltrexone. It should be noted that Asian alcoholics are likely to derive the most benefit from naltrexone since the G allele is common in this population whereas the G allele is virtually absent in individuals of African ancestry (Table 1).

3.3.2 Pharmacogenetics of SSRIs: SSRIs are thought to interact with the 5-HTT and increase intrasynaptic serotonin (5-HT) levels, however eventually feedback mechanisms result in decreased 5-HT synthesis and turnover but enhanced DA function, and this may substitute for some of ethanol's rewarding effects.

3.3.2.1 The 5-HTT gene (SLC6A4) functional promoter polymorphism 5-HTTLPR:

Several studies have shown that in the treatment of depression with SSRIs, the 5-HTTLPR low activity S allele, and particularly the SS genotype, is associated with poorer therapeutic response and more serious adverse events, at least in Caucasians (Murphy et al, 2004). There have been mixed results for SSRI treatment of alcoholics although a meta-analysis of data from 17 published studies (3489 alcoholics, 2325 controls) found a modest association between the low activity S allele and AD (OR = 1.18, 95% CI = 1.03 – 1.33) (Feinn et al, 2005). Fluoxetine and sertraline, in combination with CBT, have been found to be effective in decreasing both depressive symptoms and the level of alcohol consumption in depressed

alcoholics (Cornelius et al, 2000; Moak et al, 2003) although SSRIs have actually been shown to worsen the treatment gains of CBT among early onset (EOA) alcoholics (Kranzler et al, 1996). In contrast, sertraline was shown to be effective in improving drinking outcomes in late onset (LOA) male alcoholics (Moak et al, 2003) but only in carriers of the 5-HTTLPR high activity genotype (LL homozygotes) (Kranzler et al, 2011; Kranzler et al, 2012b). In contrast, EOAs had a better response to placebo (Kranzler et al, 2011), particularly in carriers of the 5-HTTLPR high activity genotype (Kranzler et al, 2012a).

The 5-HTTLPR results to date for response to SSRIs are somewhat complex in that LL genotype predicts a better outcome only in late onset alcoholics who are more likely to have comorbid depression and anxiety than in early onset alcoholics who are more likely to have comorbid antisocial personality disorder. Clearly further studies are warranted.

3.3.2.2 *SLC6A4* 3'UTR functional SNPs: rs1042173 and rs3813034: Recent studies have suggested that there may also be a functional variant or variants (rs1042173 and rs3813034) at the distal end of *SLC6A4* in the 3' untranslated region (UTR) (Battersby et al, 1999; Gyawali et al, 2010) that may be implicated in response to fluoxetine (Hartley et al, 2012) and alcohol craving and drinking intensity (Ait-Daoud et al, 2012; Seneviratne et al, 2009). The 5-HTTLPR polymorphism and these two distal SNPs are not in linkage disequilibrium and have independent effects on behavior (Enoch et al, 2013). Therefore both the 5' and 3' functional variants are likely to be implicated in the response to SSRIs, although since frequencies vary considerably between ethnicities (Table 1), so too will response rates in different ethnic groups.

3.3.3 Pharmacogenetics of ondansetron: Ondansetron is currently FDA-approved for the treatment of chemotherapy-induced and postoperative nausea but it is under investigation for the treatment of alcoholism. Ondansetron is a selective antagonist of 5-HT₃ receptors, encoded by the *HTR3A* and *HTR3B* genes, that are ligand-gated ion channels which when bound to 5-HT produce fast activation of neurons and play a role in reward by modulating DA release in the mesolimbic pathway (Liu et al, 2006; McBride et al, 2004). Ethanol potentiates the effect of 5-HT on 5-HT₃ receptors. Ondansetron, together with CBT, has been shown to reduce overall craving and alcohol consumption and increase abstinence in EOAs but not in LOAs (McBride et al, 2004).

3.3.3.1 *SLC6A4* functional polymorphisms 5-HTTLPR and SNP rs1042173: A trial of ondansetron plus CBT in alcoholics found no overall significant difference between treatment groups until *SLC6A4* genotypes were entered into the equation. It then became apparent that 5-HTTLPR LL homozygotes drank less per drinking day and had more (11%) abstinent days relative to treatment with placebo and of those individuals treated with ondansetron, LL homozygotes drank less and had more abstinent days (10%) than the LS/SS genotype groups combined (Johnson et al, 2011). Furthermore, the strongest finding was in the alcoholics who were both 5-HTTLPR LL homozygotes and rs1042173 TT homozygotes. These individuals showed a reduction of -2.63 drinks/day and a 17% increase in abstinent days (Johnson et al, 2011). Although these results are intriguing, they should be put into the context of a small sample size for genotype group combinations and await replication.

3.3.3.2 *HTR3B* functional polymorphism rs1176744 Tyr129Ser: A recent study has shown additive effects of a functional *HTR3B* rs1176744 SNP and the 5-HTTLPR polymorphism on alcohol and drug dependence (Enoch et al, 2011), predicting that genotype combinations of *HTR3B* variants and the 5-HTTLPR polymorphism may identify subgroups of alcoholics with varying response to ondansetron. Evidence that this may be the case comes from a study showing that genotype combinations across *SLC6A4*, *HTR3A* and *HTR3B* predicted the response of alcoholics to ondansetron (Johnson et al, 2013). Although exploratory at this stage and requiring very large sample sizes for validation, this kind of biologically relevant pharmacogenetic approach might have practical applications for improving therapeutic response.

3.3.4 Pharmacogenetics of other pharmacotherapies for alcoholism: Thus far, no functional genetic variants have been shown to identify subgroups for response to other pharmacotherapies, including for acamprosate. There is one intriguing preliminary finding in the *GRIK1* gene that encodes the glutamate receptor GluR5 that selectively binds topiramate. A non functional intronic SNP was associated with the severity of topiramate induced side effects which is relevant since adverse responses to this drug have thus far limited its use in the treatment of alcoholism (Ray et al, 2009).

Conclusion

Much has been learnt about the aversive effects of alcohol in individuals of Asian and Jewish ancestry who have functional variants in genes encoding alcohol metabolizing enzymes and also from very large studies in other ethnicities amongst whom these gene variants are uncommon. The LR to alcohol, in terms of subjective and physiological responses to alcohol, can be regarded as an intermediate phenotype for alcoholism. Genetic analyses of LR to alcohol, particularly of the functional *OPRM1* A118G polymorphism, are providing insights into the etiology of alcoholism and also subgroup responses to naltrexone. The G allele has been associated with increased VS DA release and subjective intoxication in social drinkers and might therefore be regarded as protective against alcoholism yet on balance studies have shown no relationship between this polymorphism and alcoholism per se (Bergen et al, 1997). In alcoholics the G allele is associated with increased hedonic effects in response to alcohol and increased craving in response to alcohol cues and it is this group, rather than the group of AA homozygotes, that benefits most from naltrexone in terms of blunted alcohol induced euphoria, reduction in problem drinking and lower relapse rates. Evidence is emerging that genotypes of the *SLC6A4* 5-HTTLPR polymorphism and the 3'functional SNPs rs1042173 / rs3813034 can be stratified for response to SSRIs and also ondansetron. Many and much larger clinical studies are required to identify potential genetic variation in response to pharmacotherapeutic agents. Also, it should be noted that since allele frequencies can vary considerably between ethnicities (Table 1), group effectiveness of medications may relate to ethnicity. On the other hand, studies to date have shown that differences between genotype groups in response to pharmacotherapy are quite modest. It may be that more refined measures of medication response in clinical trials are required or that genetic stratification is required for other elements of the holistic treatment

package, for example as has recently been reported for response to behavioral therapy (Felmingham et al, 2013).

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Highlights

- Genetic variants producing the alcohol flushing syndrome protect against alcoholism
- Low level of response to alcohol increases risk for alcoholism
- The functional OPRM1 A118G polymorphism predicts response to alcohol and naltrexone
- The functional *SLC6A4* polymorphisms predict response to SSRIs and ondansetron

Table 1
Minor allele frequencies in Caucasians, Africans and Asians of common functional polymorphisms that have been shown, or have the potential, to influence response to alcohol

Functional Polymorphism	Caucasians	Africans	Asians
ALDH2*2: Glu504Lys, rs671	0	0	0.20
ADH1B*2: Arg48His, rs1229984	0.01 0.20 – 0.31 ¹	0	0.75
OPRM1 A118G: Asn40Asp, rs1799971	0.17	0.01	0.42
SLC6A4: 5-HTTLPR + rs25531	S = 0.40 ² L _G = 0.09 L _A = 0.51	S = 0.25 ² L _G = 0.24 L _A = 0.51	S = 0.75 ³ L _G = 0.11 L _A = 0.14
SLC6A4: rs3813034 / rs1042173	0.58	0.82	0.20
HTR3B: Tyr129Ser: rs1176744	0.29	0.43	0.25

The frequency data is taken from HapMap unless otherwise specified.

The frequency for Asians is the average of the HapMap Chinese and Japanese samples

¹ Jewish samples: Carr et al, 2002; Neumark et al 1998, 2004; Shea et al, 2001

² Hu et al, 2006;

³ Kang et al, 2008

5-HTTLPR alleles are grouped as low activity (SS, SL_G, L_GL_G), medium activity (SL_A, L_AL_G) and high activity (L_AL_A) variants.