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Critical Review

A Critical Review of Methods and Results in the Search for Genetic Contributors to Alcohol Sensitivity

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Attributes of alcohol sensitivity are present before alcohol use disorders (AUDs) develop, they predict those adverse alcohol outcomes, are familial in nature, and many are heritable. Whether measured by alcohol challenges or retrospective reports of numbers of drinks required for effects, alcohol sensitivity reflects multiple phenotypes, including low levels of alcohol response and alcohol-related stimulation. Identification of genes that contribute to alcohol sensitivity could help identify individuals carrying risks for AUDs through their alcohol responses for whom early intervention might mitigate their vulnerability. Such genes could also improve understanding of biological underpinnings of AUDs, which could lead to new treatment approaches. However, the existing literature points to a wide range of genetic mechanisms that might contribute to alcohol responses, and few such genetic findings have been widely replicated. This critical review describes the potential impact of the diverse methods used to study sensitivity on the diversity of genetic findings that have been reported, places the genetic variants mentioned in the literature into broader categories rather than isolated results, and offers suggestions regarding how to advance the field by interpreting findings in light of the methods used to select research subjects and to measure alcohol sensitivity. To date, the most promising results have been for GABA, glutamate, opioid, dopamine, serotonin, and cholinergic system genes. The more gene variants that can be identified as contributors to sensitivity the better future gene screening platforms or polygenic scores are likely to be.

Key Words: Level of Response, Alcohol Stimulation, Alcohol, Genes, Research Methods.

PREDICTING THE DEVELOPMENT of complex genetically influenced disorders is complicated. Each condition (e.g., an alcohol use disorder [AUD]) is likely to encompass multiple phenotypes (e.g., for AUD: externalizing behaviors and a person's alcohol response), each of which could explain part of the genetic contribution (e.g., Goldman et al., 2005; Reilly et al., 2017; Schuckit, 2014). Those phenotypes themselves are likely to reflect multiple genetically influenced subcomponents that interrelate with the environment. The search for genes that underlie these complex genetically influenced conditions requires recognizing potential differences across phenotypes being studied. This critical review briefly addresses phenotypes related to how a person responds to alcohol, with an emphasis on specific gene variants potentially impacting alcohol sensitivity.

Alcohol challenges have identified multiple characteristics that contribute to a person's intensity and type of alcohol responses. Such responses might differ depending on the leg of the blood alcohol concentration (BAC) curve evaluated, attributes of study participants, and alcohol administration protocols. The phenotypes include low levels of alcohol responses (low LRs), most prominent at peak and falling BACs, and high alcohol-related stimulation, typically observed at rising BACs (King et al., 2014; Quinn and Fromme, 2011). These different findings have led to questions regarding whether low LRs can stand alone in predicting later problematic drinking or if the combination of low LR with high stimulation (i.e., a Differentiator Model) is more important (e.g., Newlin and Renton, 2010). I believe both models are correct, with results differing depending on research protocols used. Therefore, this review of genetic variants potentially related to alcohol responses includes data regarding low LR, high stimulation, and their combination.

The low LR, or low sensitivity, focuses more on depressant effects of alcohol, but extends beyond sedation. This is indicated by items used to measure alcohol-induced subjective feelings in our own work (e.g., feeling high, intoxicated, or drunk) and through the first of 4 questions in a retrospective measure of alcohol sensitivity (i.e., standard drinks needed to first feel any alcohol effect) (Schuckit and Gold, 1988; Schuckit et al., 1997). Low LR goes beyond subjective feelings and also measures dampened alcohol-related changes in hormones, electrophysiologic measures, and patterns of

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functional magnetic resonance imaging (fMRI; Paulus et al., 2012; Schuckit et al., 2016b; Tapert et al., 2004). Enhanced alcohol stimulation might also relate to cortisol responses to alcohol. Low LR and enhanced stimulation with alcohol have sometimes been observed in the same individuals (e.g., King et al., 2011; Roche et al., 2014; Schuckit et al., 2002), although it is possible that factors that contribute to a low LR and to more intense stimulation might not be identical.

This article reviews the current state of the search for genes that contribute to alcohol sensitivity. The goal is to help investigators prepare for future efforts to identify reliable genetic variants. Studies are described from a phenotypic perspective, but diversity in genotypic methodology is likely to be equally challenging. The relative ease of measuring aspects of alcohol sensitivity in animals has resulted in important leads from animal studies that are also referenced.

A BRIEF REVIEW OF MAJOR METHODS USED TO EVALUATE ALCOHOL REACTION PHENOTYPES

As demonstrated in Fig. 1, across studies evaluations of alcohol sensitivity can flow from alcohol reaction phenomena in animals, to testing reactions in several types of non-AUD drinkers, using at least 4 ways to establish reactions by administering alcohol or using retrospective questionnaires, with protocols incorporating any of at least 6 different sensitivity measures, and at least 2 outcome time frames (short term or long term). This pattern of approaches produces a wealth of information about alcohol responses, but creates hundreds of combinations of sensitivity measures that could possibly reflect different sets of genes. This suggests that it might be prudent to evaluate genetic contributors to each major method separately before combining results into a single genetic analysis.

Examples of Measures of Alcohol Reactions Across Different Populations

Our group focuses on identifying genetically influenced characteristics that predict future binge drinking and alcohol problems in young, relatively light drinkers. We usually administer 0.75 ml ethanol/kg over 10 minutes as a single drink, with doses adjusted for height, weight, and sex, producing peak BACs of ~0.06 gm/dl at about 60 minutes. Alcohol responses are measured every 15 to 30 minutes at rising, peak, and falling BACs using the Subjective High Assessment Scale (SHAS) and body sway. Some paradigms also include changes in prolactin, cortisol and/or adrenocorticotropin hormone (ACTH), electroencephalographic measures (EEGs), and/or fMRI (e.g., Paulus et al., 2012; Schuckit, 1998). Other laboratories have used the Biphasic Alcohol Effects Scale (BAES) questionnaire instead of the SHAS. The BAES is a reliable 24-item self-report measure with good internal consistency that evaluates 7 items each regarding sedation and stimulation during alcohol challenges.

A different oral alcohol paradigm that focuses on predicting future alcohol-related problems in drinkers who have already developed alcohol binges uses a "peak and plateau" drinking schedule where subjects consume 1 drink, wait, and then take a second drink (e.g., Arias et al., 2013), allowing the body to react/adjust/react/adjust to alcohol. Because different gene sets might contribute to alcohol sensitivity measured by different paradigms, it may be useful to first carry out separate genetic analyses for single dose and multiple dose paradigms before combining genetic samples into a single overall analysis. Similar considerations apply to potentially different gene sets for intravenous (IV) vs. oral paradigms and retrospective questionnaires versus alcohol-challenge-based measures. Note that oral alcohol challenges evaluate how a person responds to alcohol over several hours at a specific time of day and in a laboratory setting.

Other alcohol paradigms infuse IV alcohol at constant rates to reach peak BACs in ~20 minutes and then maintain constant BACs (e.g., Ramchandani et al., 1999; Roh et al., 2011). This rapid BAC increase might contribute to stimulation effects of alcohol early in the experiment (Schuckit et al., 2002), and maintaining constant BACs produces intrasession tolerance.

Alcohol sensitivity can also be measured by retrospective questionnaires that record usual numbers of standard drinks

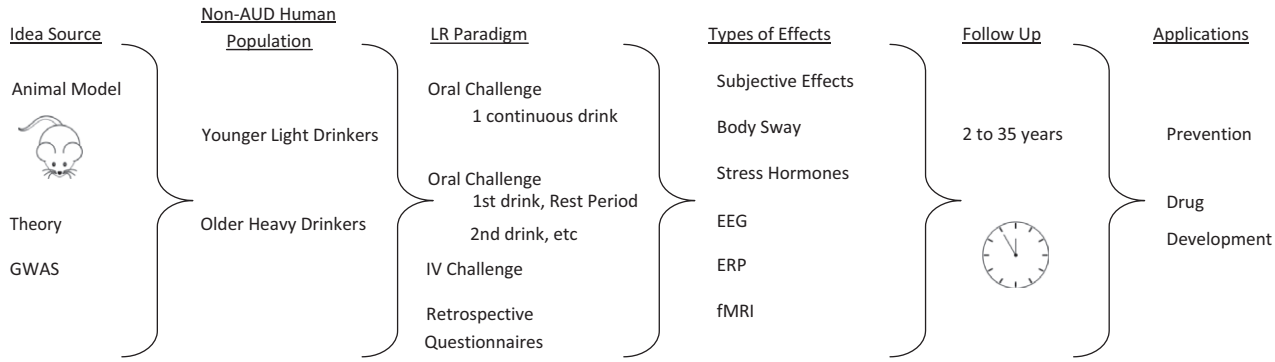

Fig. 1. Description of potential pathways across studies working to identify genes related to alcohol sensitivity.

required for various effects (e.g., Fleming et al., 2016; Schuckit et al., 1997, 2007, 2008). A higher number of drinks required across effects indicates a lower sensitivity per drink, and vice versa. The 12-item Self-Report of the Effects of Alcohol (SRE) questionnaire asks the same 4 questions regarding drinks required to first feel any effect, slur speech, feel unsteady on your feet, and unwanted falling asleep for the first 5 times of drinking, the period of heaviest drinking, and recent 3-month drinking. The 15-item Alcohol Sensitivity Questionnaire includes items constructed to separately measure stimulation and sedation, asking participants if they *ever* experienced the effect and, if so, the minimum or maximum drinks associated with the item. The 2 retrospective measures compare favorably, and each generates scores relating to alcohol sensitivity (Fleming et al., 2016). The SRE value has been adjusted for sex, age, weight, and/or the number of effects experienced, but the raw score without adjustments appears to work well. Note that, in contrast to alcohol challenges, these questionnaires ask participants to consider alcohol's overall effects across several hours.

SRE and alcohol oral single dose challenge-based low LRs predict heavy drinking up to 35 years later in men and women in most studies in the United States, Australia, the United Kingdom, and Germany (e.g., Daeppen et al., 2000; Ehlers et al., 1999; Gonçalves et al., 2017; Heath et al., 1999; Quinn and Fromme, 2011; Schuckit et al., 2007, 2008). High stimulating effects of alcohol on alcohol challenges robustly predict increases from baseline in heavy episodic (binge) drinking and alcohol problems at 2- and 6-year follow-ups (e.g., King et al., 2011, 2014, 2016).

SRE scores have validities and retest reliabilities of 0.70 to 0.80 or higher (Kalu et al., 2008; Ray et al., 2011; Schuckit et al., 1997), while repeat reliabilities of alcohol-challenge-based stimulation are also high (King et al., 2014, 2016). Using data from 5-year follow-ups of 66 men who had participated in both alcohol challenges and completed SRE questionnaires at baseline, a series of regression analyses predicting later alcohol quantities revealed that 60.3% of the ability of alcohol-challenge-based LR to predict alcohol outcomes overlapped with the ability of the SRE-based LR to predict the same outcome (e.g., Schuckit et al., 2009).

Two Relevant LR Phenotypes

Low LR. The emphasis in studies of low LR is on predicting onsets of heavy drinking and multiple alcohol problems. Therefore, subjects typically do not yet have the outcomes being predicted and have not already passed through ages of risk for developing repetitive alcohol problems (the latter is to avoid selecting older participants who despite drinking have not developed problems and are less likely to carry the high-risk phenotype being studied). AUD risk is usually defined by an alcohol-dependent relative or an ethnic group membership with high or low AUD risk (e.g., Ehlers et al., 2010; Monteiro et al., 1991).

The major source of prospective data on low LR comes from the 35-year-long San Diego Prospective Study (SDPS) with single dose oral alcohol challenges in 453 drinking men (usual past consumption 3 drinks per occasion) at about age 22 (range 18 to 25). Half of the participants (probands) had an alcohol-dependent father and half had no relatives with AUDs, with the 2 groups matched on age, race, education, drinking, and other substance use histories (Schuckit and Gold, 1988; Schuckit et al., 2000). Over time, SRE data were gathered from drinking spouses and offspring, generating information on ~1,620 individuals. Relationships of SRE-based low LR to heavier drinking and future alcohol problems were also prospectively documented in the Avon Longitudinal Study of Parents and Children, the Collaborative Study on the Genetics of Alcoholism, and other investigations (e.g., Daeppen et al., 2000; Schuckit et al., 2001, 2008). Sibling-pair, twin, and family studies indicate low LR heritabilities of 40 to 60% (e.g., Heath et al., 1999; Joslyn et al., 2008; Kalu et al., 2012; Schuckit et al., 2001; Viken et al., 2003).

Beginning in 1988, 99% of the probands from the SDPS were followed up at about age 30, when the low LR was found to relate to later heavy drinking, alcohol problems, and AUDs, but not to dependence on other substances or to major psychiatric disorders (Schuckit and Smith, 1996; Schuckit et al., 2014). Subsequent every 5-year follow-ups of >90% of original subjects documented that the relationships of low LR to future alcohol problems were partially mediated by heavy drinking friends, overly optimistic expectations of the effects of alcohol, and using alcohol to cope with stress, characteristics that became the focus of a successful program to decrease the heavy drinking risk for five hundred 18-year-old university students (Gonçalves et al., 2017; Savage et al., 2015; Schuckit et al., 2016a).

High Stimulation with Alcohol. Studies of high stimulation effects of alcohol often begin with nonalcohol-dependent heavy drinkers and light drinkers, attempting to predict escalations in preexisting heavy episodic drinking and increases in alcohol problems. Consistent with those goals, some subjects are in their 30s and include individuals already engaged in heavy drinking. The stimulation effects have included higher subjective feelings of stimulation, especially in early phases of the rising BAC, greater liking and wanting more alcohol during challenges, and lower sedation and lower salivary cortisol later in the alcohol challenge. The more recent work indicated that both elevated stimulation and dampened sedation might be seen in heavier drinkers even earlier in alcohol administration.

The primary source of these data involved 190 subjects who consumed oral alcohol during two 5-minute periods separated by 5 minutes rest (e.g., King and Byars, 2004; King et al., 2006, 2011, 2014, 2016). Similar results were seen in a separate sample of 104 individuals (Roche et al., 2014). At study entry, the 190 participants were on average age 26 (range 21 to 35), 104 of whom habitually engaged in weekly

binge drinking, consuming 5+ drinks for men and 4+ for women 1 to 4 times per week, with between 10 and 40 drinks per week for at least the prior 2 years (King et al., 2006, 2011, 2016). The 86 light drinkers consumed ≤5 drinks per week with ≤5 binges per year. In a 2-year follow-up of almost all the subjects, greater alcohol-induced stimulation and lower sedation predicted increases over baseline binge drinking (King et al., 2011), a finding confirmed for stimulation in a 6-year follow-up of 156 subjects (83%) (King et al., 2014). The heavy drinkers were more likely to have alcoholic relatives, and animal studies have confirmed stimulation effects of alcohol in some genetic lines of alcohol preferring rodents (e.g., Cunningham and Noble, 1992; Masur et al., 1986).

Studies documenting alcohol-related low LR and/or high stimulation are the focus of this review of gene variations related to the intensity of response to alcohol. As suggested above, researchers should consider differences across the various paradigms before combining results into a single analysis when searching for genes related to alcohol sensitivity.

THE SEARCH FOR GENE VARIANTS RELATED TO ALCOHOL SENSITIVITY (SEE TABLE 1)

While no receptors are dedicated specifically to alcohol, this drug has prominent effects on gamma-aminobutyric acid (GABA), glutamate, opioid, dopamine, serotonin (5-HT), and acetylcholine systems and on the hypothalamic–pituitary–adrenal (HPA) axis, each of which could contribute to alcohol sensitivity (Koob and Volkow, 2010). Each effect relates to sets of genes and environmental forces, and thus, evaluations of gene × gene (G × G) and gene × environment (G × E) interactions are important in understanding how genes relate to how a person responds to alcohol (Goldman, 2010). Few gene effects are likely to follow Mendelian patterns; some gene variants are rare across families, but common within relatives (Choquet et al., 2013); and most are relatively common but explain small proportions of sensitivity phenomena (Joslyn et al., 2010, 2011; Manolio et al., 2009; McCarthy and Hirschhorn, 2008; Wang et al., 2005).

The following material reviews gene variants that might relate to alcohol sensitivity and are worth considering in future investigations. These text descriptions are briefly summarized in the broader overview in Table 1, including the predominant pattern of phenotypes that have been evaluated for each variant, and the number of relevant references cited in this section.

Alcohol Metabolizing Enzymes

Variants of the genes for ALDH2 on chromosome 12q24.12 (e.g., rs671), ADH1B on chromosome 4q23 (e.g., rs1229984), and CYP2E1 on chromosome 10q26.3 (e.g., rs10776687) (Webb et al., 2011) are associated with increased alcohol responses and decreased AUD risks (Bujarski et al., 2015; Jaime et al., 2014; Kuo et al., 2008; Sartor et al., 2015). Those actions could interfere with identification of other genetic variants related to low sensitivity. The relationships of these gene variants to alcohol sensitivity have been supported by animal and human alcohol studies (e.g., Cook et al., 2005; Dickson et al., 2009; Fischer et al., 2007; McCarthy et al., 2010; Wall et al., 2005; Weng et al., 2009).

Gene Variations Related to Stress Responses

The stress response system is of interest for drug reactions (Koob and Kreek, 2007), but has rarely been studied regarding alcohol sensitivity. Individuals with low LR or high stimulation demonstrate less intense increases in cortisol, ACTH, and/or prolactin during oral and IV alcohol challenges (King et al., 2006; Schuckit, 1998). Also, homozygotes for C-alleles of corticotropin-releasing hormone (CRH) receptor 1 (chromosome 8q13.1) rs1876831 and/or carriers of the rs242938 A-allele have histories of higher maximum drinks per occasion (perhaps reflecting a lower LR per drink), more binge drinking, higher prevalence of drunkenness (e.g., Hansson et al., 2006; Hayes et al., 2005; Treutlein et al., 2006), and heavier drinking in response to negative life events (Blomeyer et al., 2008). More definitive studies of possible relationships of sensitivity to aspects of the alcohol effects on the HPA axis are needed.

GABA-Related Genes

Alcohol has prominent effects on GABA-A receptors (e.g., Korpi et al., 1993; Ray and Hutchison, 2009), variants of which may relate to AUD risks (e.g., Covault et al., 2008; Kareken et al., 2010; Kosobud et al., 2015; Krystal et al., 2006), and perhaps to sensitivity. Beginning with GABRA2 (chromosome 4p12), oral and IV alcohol challenges indicate relationships to sensitivity and heavier drinking for G-alleles of rs279858 (e.g., Arias et al., 2013; Covault et al., 2004, 2008; Kosobud et al., 2015; Lappalainen et al., 2005; Pierucci-Lagha et al., 2005; Roh et al., 2011; Uhart et al., 2012); rs279869 and rs279837 (Roh et al., 2011); rs279871 AA genotype (Kareken et al., 2010); the minor allele (T) for rs279844 (Uhart et al., 2012); and for a haplotype block of minor alleles for rs279858 (C-allele), rs279844 (T-allele), rs279845 (A-allele), rs279826 (G-allele), rs279828 (C-allele), and 279836 (A-allele) (Uhart et al., 2012).

The potential relevance to alcohol responses of GABRA1 (chromosome 5q34) variants comes from animal knockout, gene expression, and between-strain animal studies (e.g., Hanchar et al., 2005; Loh and Ball, 2000), as well as a human genomewide association study (GWAS) using single dose oral alcohol (Wilhelmsen et al., 2003). Dick and colleagues (2006) reported that SRE-based low LR was related to rs1037715.

Several animal studies implicated GABRA6 (chromosome 5q34) regarding lower LRs for cerebellar and movement-related effects (Korpi et al., 1993; Sander et al., 1999). Oral alcohol challenges indicated that GABRA6 Pro385Ser

Table 1. Gene Variants Potentially Related to Alcohol Sensitivity Presented in the Text by Category, Listing Human Genetic Location, Phenotype, and Number of Cited Studies

Gene	rs (or other ID)	Phenotype	Citations
Alcohol metabolizing enzymes*		AL-O	12
ALDH 2*2	671	AN	
ADH1B	1229984	SO	
CYP2E1	10776687	SRE	
Stress hormones		AN	7
CRH1	1876831	AL-I	
	242938	AL-O	
		AL-C	
GABA			
GABRA2	279858	AL-O	9
	279869	AL-I	
	279837	AN	
	279871		
	279844		
	279845		
	279826		
	279828		
–	279836		
GABRA1	1037715	AN	4
		SRE	
GABRA6	Pro385/Ser	AL-O	4
		AN	
		GW	
GABRG1	1391166	AL-C	1
	1497571	SRE	
SLC6A11	10913738	GW	1
		SRE	
Glutamate/NMDA			
GRLK1 (GluR5)	2832407	AD	1
		AN	
GRM3	6465084	AD	2
		AL-O	
		BS	
GAD1	2241165	SRE	1
	2058725		
	379185		
FYN (PTK)	T137346C	AL-C	3
		AN	
Opioid and dopamine			
OPRM1	1799971	AD	9
	3778150	AL-I	
		AL-O	
		SO	
		SRE	
OPRK1	963549	AL-C	5
	997917	AL-I	
		AN	
DAT	28363170	AD	3
		AL-C	
		AL-I	
		AL-O	
Serotonin			
SLC6A4 (5-HTTLPR L allele)		AD	4
		AL-O	
		SRE	
CHRNA5/CHRNB2 cluster			
	749132306	AL-O	2
	2229961	SO	
	55863434	SRE	
	80087508		
	2072658		
	051730 (A/A)		
	8034191 (C/C)		
Potassium and calcium channel			
KCNMA1	Chromosome 10q22.3	AD	4
		AN	
		SRE	
NPY			
	16147	AD	7
	Leu/7Pro	AL-C	
		AN	
Additional genes			
PRMT3	74761974	SRE	1
ZNF699	7254880	AD	5
		AN	
ALK	17004646	AL-O	2
		AN	
GPC5	1330469	AL-O	2
		AN	
KLF-3/KLF-12	—	AN	3
COL6A3	—	AN	1
RYR3	—	AL-O	2
		AN	
DLGAP1	146298733	GW	4
		SRE	
Per2, Per3	—	AN	3

The table offers basic descriptions of gene variants identified in the literature as potentially related to alcohol sensitivity, as described in greater detail in the text of this review. Whenever possible the genes are listed as they relate to neurochemical systems with columns offering the gene name as spelled out in the text, gene variant identifiers (usually rs numbers, if known), the type of alcohol sensitivity measure involved and the number of relevant citations for that gene variant offered in the text. The latter is offered as a guide of how often the variant has been potentially linked to a sensitivity measure. The abbreviations offered for phenotypes include: AD = alcohol use disorder; AL-C = alcohol consumption measures; AL-I = IV alcohol challenges; AL-O = oral alcohol challenges; AN = animal models; BS = body sway; GW = genomewide association studies; SO = subjective alcohol response measures other than the SRE; SRE = Self-Report of the Effects of Alcohol retrospective measure. Studies involve human subjects unless noted by AN.

related to lower LRs (Hu et al., 2005; Schuckit et al., 1999), especially in combination with L variants of the serotonin transporter gene (5-HTTLPR).

GABRG1 (chromosome 4p12) variants in rs1391166 and rs1497571 are potentially related to low SRE-based alcohol sensitivity. Subjects with rs1497571 CC genotype had lower LRs per drink, higher drinks per occasion, and more alcohol problems (Ray and Hutchison, 2009).

Finally, regarding GABA, a GWAS and meta-analysis using SREs highlighted possible sensitivity relationships for rs10913738 in a GABA transporter, SLC6A11 (chromosome 3p25.3) (Edwards AC, Deak JD, Gizer IR, Chatzinakos C, Wilhelmson KP, Heron J, Hickman M, Webb BT, Bacanu A-A, Kendler KS, Dick DM, Schuckit MA, submitted for publication).

Glutamate and NMDA Receptors

Glutamate receptors, including NMDA, are important for alcohol intoxication, sensitivity, and withdrawal. Some aspects of this system are different in individuals with alcohol-dependent relatives and drinkers with low LR (Bell et al., 2016; Joslyn et al., 2010; Krystal et al., 2003; Schumann et al., 2008). Specific variants include rs2832407 in GRLK1 (GluR5) (chromosome 21q21.3) (Kranzler et al., 2009), the homolog of which is related to low alcohol consumption and high sensitivity in rodents (Bird et al., 2008); GRM3 (chromosome 7q21.11) rs6465084 (Xia et al., 2014) which might relate to oral alcohol-induced body sway and to alcohol dependence (e.g., Wilhelmsen et al., 2003); and GAD1 (chromosome 2q31.1) for SRE-based alcohol sensitivity regarding rs2241165, rs2058725, and rs379185 (Kuo et al., 2009). Sensitivity might also relate to the FYN gene (chromosome 6q21), also known as protein tyrosine kinase [PTK] fyn, especially for T137346C regarding higher maximum drinks (a possible marker for a low sensitivity per drink) (Ishiguro et al., 2000; Schumann et al., 2003). PTK fyn knockout mice have a lower sensitivity to alcohol (Miyakawa et al., 1997). Effects of PTK fyn are likely to occur through NMDA receptors NR2A and NR2B that partially mediate glutaminergic effects of alcohol (Fink and Gothert, 1996).

Opioid Receptors and Dopamine

Alcohol affects release of beta-endorphin and impacts on ventral tegmentum and nucleus accumbens activity, with feelings of reward operating in part through mu-opioid receptors (Koob and Kreek, 2007; Mague and Blendy, 2010; Otto et al., 2017). Dopamine has also been linked to craving and heavy drinking (e.g., Cloninger, 1987; Parsian and Zhang, 1997). These effects could relate to alcohol sensitivity as well.

A nonsynonymous SNP rs1799971 of OPRM1 (chromosome 6q25.2) relates to IV alcohol subjective effects and cue reactivity from alcohol (Courtney et al., 2015; Ray and Hutchison, 2004; Ray et al., 2012) and might be associated with both decreased receptor glycosylation and half-life (Weerts et al., 2017). G-allele carriers of rs1799971 exhibit decreased mu-opioid receptor binding compared to those with AA genotypes (Weerts et al., 2013), and the former may relate to increased responses to oral and IV alcohol and on a retrospective questionnaire, as well as lower AUD risks (Ehlers et al., 2008; Ray and Hutchison, 2004; Schwantes-An et al., 2016). The same SNP might relate alcohol dependence risks and higher alcohol self-administration (Hendershot et al., 2014; Otto et al., 2017; van der Zwaluw et al., 2007, 2009). C-allele carriers of a SNP in linkage disequilibrium (LD) with rs179971 rs3778150 demonstrate decreased intensities of response to oral alcohol. (Hancock et al., 2015; Otto et al., 2017).

Kappa opioid receptor, OPRK1 (chromosome 8q11.23), its endogenous ligand, dynorphin, and the ligand's precursor, prodynorphin, affect substance-related phenomena (e.g., Anderson and Becker, 2017; Gilpin et al., 2014; Walker and Koob, 2008), but have not been adequately evaluated regarding alcohol sensitivity. Acute alcohol increases dynorphin in the nucleus accumbens and frontal cortex, and a kappa receptor antagonist decreases alcohol self-administration in animals with alcohol-dependent-like syndromes (Anderson and Becker, 2017; D'Addario et al., 2011; Gilpin et al., 2014; Walker and Koob, 2008). Rs963549 and rs997917 might relate to sedating effects of alcohol as measured by drinks consumed per day and IV alcohol challenges, at least in the context of naltrexone (Ashenhurst et al., 2012; Gelernter et al., 2007).

The dopamine transporter (DAT) gene (chromosome 5q15.3) has a common variable number of tandem repeat (VNTR) polymorphism (rs28363170) with 10-repeat alleles (A10) associated with higher DAT expression in the striatum (i.e., lower synaptic dopamine). The A9 allele produces higher synaptic dopamine. Individuals with the A9 DAT VNTR and the G-allele for the OPRM1 rs1799971 have higher sensitivity with oral and IV alcohol and lower AUD risks (Anton et al., 2012; Heinz et al., 2000; Ramchandani et al., 2011; Weerts et al., 2017).

5-HT Systems

Low synaptic 5-HT in humans and animals is associated increased drinking; medications that increase synaptic serotonin decrease alcohol intake; 5-HT-like drugs mimic alcohol intoxication; and higher platelet 5-HT reuptake is associated with developing AUDs (Ernouf et al., 1993; George et al., 1997; LeMarquand et al., 1994; Pandy et al., 1992; Rausch et al., 1991). A variant in the promoter region (5-HTTLPR) in the serotonin transporter gene (SLC6A4; chromosome 17q11.2) might relate to a lower LR (e.g., Cope et al., 2017; Hu et al., 2005) for a long (L) repeat length polymorphism associated with faster 5-HT re-uptake (Hu et al., 2005). The L_A variant might be associated with single dose oral alcohol-

challenge- and SRE-based low LR and higher rates of future AUDs (Hinckers et al., 2006; Hu et al., 2005; Schuckit et al., 1999).

Cholinergic Systems

Alcohol- and nicotine-related disorders often co-occur (e.g., Hopfer et al., 2001), the presence of either disorder relates to increased severity of the other (Ehringer et al., 2007), both alcohol and nicotine conditions are genetically influenced, and some gene variants might predispose individuals toward both disorders (Froehlich et al., 2017; Hettema et al., 1999; Hopfer et al., 2001; Steensland et al., 2007; Swan et al., 1997). Nicotinic receptors might contribute to this overlap (Sherva et al., 2010; Wang et al., 2009) in that the nicotinic receptor partial agonist, varenicline, might also attenuate alcohol consumption (Froehlich et al., 2017; Steensland et al., 2007). Oral alcohol challenges and SRE data have highlighted rs1051730 (A/A) and rs8034191(C/C) in the cholinergic gene cluster on chromosome 15q2 as potentially related to lower LR (Joslyn et al., 2008). A rare missense variant of CHRNA5 might relate to more intense oral alcohol challenge responses, including rs749132306, rs2229961, rs55863434, and rs80087508. Data also support possible relationships to alcohol sensitivity for rs2072658 in the CHRNB2 receptor (chromosome 1q21.3) (Ehringer et al., 2007).

Potassium and Calcium Channel-Related Genes

Animal homologs of human KCNMA1 (chromosome 10q22.3) might relate to the intensity of alcohol responses in Drosophila and *Caenorhabditis elegans* (Davies et al., 2003; Wang et al., 2001). In humans, a locus on chromosome 10 near KCNMA1 related to low LRs on the SRE (Ehlers et al., 2010; Wilhelmsen et al., 2003). A similar chromosome 10 region related to smoking, and to AUDs (Agrawal et al., 2008; Gelernter et al., 2009; Li et al., 2006).

NPY

This inhibitory neuropeptide affects appetitive behaviors and emotion (Foroud et al., 2000; Hayes et al., 2005; Heilig and Widerlov, 1995; Hwang et al., 1999; Levine and Morley, 1984). Mice deficient in NPY demonstrate higher alcohol intake and lower sensitivity, rodents with high NPY have lower alcohol intake (Badia-Elder et al., 2003; Ehlers et al., 1998; Gilpin et al., 2003; Tecott and Heberlein, 1998; Thiele et al., 2000; Zhu et al., 2003), and a QTL related to alcohol consumption in rats might involve NPY (Carr et al., 1998). A relevant variant is rs16147 in the promotor region in the NPY gene (7p15.3), and another chromosomal region is a Leu7Pro missense variant in the signal peptide of human NPY where sensitivity is lower with the Leu allele (Lappalainen et al., 2002). The latter genotype is also related to heavier alcohol intake and AUDs in some studies (Hu et al., 2005; Kuhanen et al., 2000; Zhou et al., 2008).

Additional Genes of Potential Interest

Protein arginine methyltransferase 3, PRMT3 (chromosome 11p15.1) variant rs74761974 (A-allele) related to SRE measures in a preliminary analysis of a recent GWAS (1.4×10^{-8}) (Wetherell, 2017). A nearby gene of interest is the glycine neurotransmitter transporter, SLC6A5.

Zinc-finger gene ZNF699 (chromosome 19p13.2) is related to Drosophila gene "hang," which is associated with increased alcohol tolerance (Scholz et al., 2005) and to QTLs involved in alcohol sedation in mice (e.g., Bennett and Johnson, 1998; Ehringer et al., 2002; Markel et al., 1997; Riley et al., 2006). In humans, several gene variants (e.g., rs7254880) might relate to alcohol dependence (Riley et al., 2006).

Homologues of human anaplastic lymphoma kinase (ALK) (also known as ALK tyrosine kinase; chromosome 2p22.3) may be associated with resistance to alcohol's sedative effects in Drosophila, alcohol-induced ataxia in recombinant inbred mice, and with longer alcohol sedation in ALK knockout mice (Lasek et al., 2011a,b). Sequencing of human ALK indicated several variants (e.g. rs17004646) potentially associated with low sensitivity (Lasek et al., 2011b).

Glypican 5 (GPC5) (chromosome 13q31.3) modulates cellular signaling in the caudate nucleus, putamen, and hippocampus. Variant rs1330469 is potentially related to alcohol-induced ataxia in mice, locomotion in Drosophila, and single dose oral alcohol-induced ataxia in humans (Joslyn et al., 2011; Kong et al., 2010; Saunders et al., 1997).

Krueppel-like factor 12 (KLF-12) (chromosome 13q22.1) potentially relates to acute functional tolerance to alcohol in *C. elegans* and to effects of alcohol in the nucleus accumbens and the ventral tegmentum (Adkins et al., 2017; Wolen et al., 2012). This gene has not been directly evaluated in humans regarding alcohol sensitivity.

A mouse homolog of Collagen alpha-3 (COL6A3) (chromosome 2q37.3) is of potential interest to sensitivity because of a QTL related to sensitivity to alcohol withdrawal handling-induced seizures and 2-bottle alcohol-related preference in mice (Adkins et al., 2017).

Ryanodine 3 receptor-related genes (RYR, chromosome 15q13.3) potentially relate to single dose oral alcohol responses in humans, and homologs of this gene may relate to alcohol sensitivity in *C. elegans* (unc-68) and to tolerance development in Drosophila (Adkins et al., 2017; Joslyn et al., 2010). Ryanodine gene effects might operate, at least in part, through calcium channels and dopamine 1 receptors (Kurokawa et al., 2013).

Clock genes involved in circadian rhythms have also been reported to relate to depression and AUDs, and to glutaminergic systems (Huang et al., 2010; Kovanen et al., 2010;

Spanagel et al., 2005). Most salient to the current review are animal studies that have highlighted the impact of mutations in Per2 (human chromosome 2q37.3) and Per3 (human chromosome 1p36.23) on how the time of day relates to the intensity of alcohol reactions, including alcohol sensitivity and alcohol consumption (Perreau-Lenz et al., 2009; Wang et al., 2012). No specific human gene variations have been highlighted for these effects, but the existing data support the need for genetic studies regarding these and other clock genes in human alcohol responses (Edwards AC, Deak JD, Gizer IR, Chatzinakos C, Wilhelmson KP, Heron J, Hickman M, Webb BT, Bacanu A-A, Kendler KS, Dick DM, Schuckit MA, submitted for publication).

Finally, a SRE-based GWAS and meta-analysis highlighted rs146298733 in DKGAP1 (DLG-Associated Protein 1) on chromosome 18p11.31 as potentially related to alcohol sensitivity. Variations in this gene are also associated with obsessive-compulsive disorder and retinitis pigmentosa (Edwards AC, Deak JD, Gizer IR, Chatzinakos C, Wilhelmson KP, Heron J, Hickman M, Webb BT, Bacanu A-A, Kendler KS, Dick DM, Schuckit MA, submitted for publication).

SOME CONCLUSIONS AND FUTURE DIRECTIONS

This review is the first to summarize gene variants potentially related to the alcohol response while emphasizing the diversity of paradigms evaluating alcohol sensitivity. There is no single best approach for evaluating alcohol sensitivity, and the existing variety of methods has the benefit of describing multiple aspects of the alcohol response. However, the information offered above highlights the complexities among the various measures of alcohol responses, and it might be important to consider differences in research methods before combining results from different approaches into a single meta-analysis or GWAS.

For example, investigations, using oral alcohol challenges where alcohol is consumed in 1 continuous drink and paradigms giving alcohol in several servings with interspersed rest periods when alcohol plateaus, might not evaluate identical phenomena with identical genetic contributors. The same reservations apply to combining results from oral and IV alcohol paradigms, because in the latter BACs rise more rapidly, subjective responses tend to be more intense, and some IV paradigms included a phase where the BAC is maintained, with results that might reflect intrasession tolerance. Furthermore, alcohol challenges measure reactions over a relatively short laboratory session, but retrospective self-reports of drinks needed across effects relate to reactions during entire evenings of real-life drinking. It might also be difficult to combine sensitivity results from studies of younger relatively alcohol-problem-free modest drinkers (e.g., Schuckit et al., 2008) with the older heavy drinkers used to predict the escalation of baseline heavier drinking and binges (e.g., King et al., 2014). While it is possible that different methodologies to evaluate alcohol sensitivity might identify identical genes, researchers must consider that different combinations of genes might contribute to sensitivity measured through different approaches. This phenomenon might diminish the ability of meta-analyses and GWAS to consistently identify genes with small effects on how a person responds to alcohol. The optimal approach might be to first evaluate potentially associated genes separately for oral alcohol administrations, IV dosing, and retrospective questionnaire-based measures before combining them into a single analysis.

Despite methodological differences, this review highlighted multiple gene variants that might contribute to alcohol responses. The most promising results are in the GABA, glutamate, opioid, dopamine, serotonin, and cholinergic systems. Finding a wide range of genetic variants likely to contribute to alcohol responses was predictable based on the characteristics of most complex genetically influenced conditions and the range of ethanol-based brain effects.

Low LR heritabilities are 40 to 60% and animal studies have confirmed alcohol stimulation in some genetic lines of alcohol preferring rodents (e.g., Cunningham and Noble, 1992; Masur et al., 1986). Several studies confirm that lower and higher alcohol responses that may operate at different phases of the BAC curve or relate to the rapidity of rise of alcohol blood levels may be related to each other (e.g., King et al., 2016; Ray et al., 2016; Schuckit et al., 2002) and thus both types of measures have been included in this review of gene variants that potentially relate to alcohol sensitivity.

This review has several implications for my own future work. With my interest in evaluating why only some relatively problem-free lighter drinkers escalate their intake and problems, I will continue to include both single dose oral alcohol challenges and retrospective self-reports of drinks needed for effects. While higher stimulation early in the alcohol challenge has rarely been observed using our own paradigms, in future work I will add stimulation measures to our current measures of overall feelings of alcohol intoxication. Our own findings might reflect the fact that my testing paradigm involves slowly rising BACs and the major subjective measure used, the SHAS, is not as likely to pick up stimulation as the BAES that was developed years after my research began (Rueger and King, 2013).

My collaborations with geneticists will continue to combine results across different measures of alcohol responses, but analyses will begin with preliminary evaluations of trends for variants in individual genes and gene systems (e.g., for GABA, glutamate, or clock genes) before combining results from different approaches in genetic analyses. We will work to establish whether the same or similar genes relate to stimulant, depressant, and overall intoxication effects of alcohol as risk factors for future heavy drinking and AUDs.

Improving understanding of how low LRs and alcohol-related stimulation relate to future alcohol problems has

implications for prevention of AUDs. Using low LR as an example, this characteristic is relatively common in individuals from a wide range of socioeconomic strata, and relates to the AUD risk across the sexes and racial or ethnic groups (e.g., Hinckers et al., 2006; Schuckit et al., 2000, 2007, 2017). For low LR, several environmental and attitudinal attributes that partially mediate the risk for adverse alcohol-related outcomes have been identified. Two investigations have shown that these mediators could be addressed through relatively inexpensive Internet-based education programs to decrease heavy drinking (e.g., Savage et al., 2015; Schuckit et al., 2016a). Similar programs might be used in high schools, the military, or industry to identify drinkers with high AUD risks through low alcohol LRs and to help them mitigate future alcohol-related problems. Similar results might be seen for measures of alcohol-related stimulation. Finding genes that contribute to lower LRs and higher alcohol stimulation as risk factors for future heavy drinking and alcohol problems could help with early identification and intervention in those at risk for future alcohol problems through their alcohol sensitivity. Greater understanding of the biological bases for the alcohol reaction phenotypes might also facilitate developing medications to help treat individuals who developed their AUD in the context of low LRs or higher alcohol stimulation.

It is important to consider several additional guidelines for efforts to increase our knowledge of specific gene variants that relate to alcohol sensitivity. First, studies of high stimulation or low LR need to control for the strong effects of ALDH2*2 and ADH1B genotypes, as these could obscure the effects of other genetic contributors to alcohol responses. Second, the impact of any phenotype on adverse alcohol outcomes is likely to operate through many genes and through environmental and attitudinal characteristics. Thus, whenever possible, studies should evaluate more than 1 gene variant at a time and search for G × G and G × E additive and mediational interrelationships (Olfson et al., 2014; Schuckit and Smith, 2017; Schuckit et al., 2017). Third, in light of the likely small effect for any 1 variant when studied across families, investigators should consider evaluating gene effects vertically within families, as some variants might be seen in a third or more of members of any 1 family (Choquet et al., 2013) but be observed in a small proportion of the general population. Fourth, for most gene variants few, if any, specific variants will be consistently identified across almost all studies, and thought might be given to developing a standard for determining which variants are worth emphasizing in additional work (e.g., Joslyn et al., 2011). Fifth, until the national alcohol and drug institutes suggest guidelines for standardizing approaches across studies, investigators should take steps to use the same measures that are already incorporated in the recent literature in an effort to minimize the variance likely to occur when study results are combined.

There are also several caveats for this review that readers should consider. There was not sufficient space or appropriate expertise to critically review specific genetic analytic techniques. Space limitations also precluded a much-needed detailed comparison of specific phenotypic approaches, a deficiency I hope to address in the future with a review carried out jointly with researchers who study different types of participants and those who use different alcohol administration protocols.

In summary, finding gene variants that contribute to complex genetically influenced phenotypes is challenging, and alcohol sensitivity is no exception. The genes associated with such characteristics might vary depending on the population studied and test paradigms used, and such across-study differences might contribute to divergent results. This review highlighted results of studies to date, suggested options for standardizing research paradigms, and discussed issues that should be considered before combining results across studies when searching for genes that might contribute to how a person reacts to alcohol.

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