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GENETIC DISORDERS (W BERRETTINI, SECTION EDITOR)

Genetics of Alcoholism

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Abstract Alcohol use and alcohol use disorders are substantially heritable. Variants in genes coding for alcohol metabolic enzymes have long been known to influence consumption. More recent studies in family-based samples have implicated GABRA2, nicotinic receptor genes such as CHRNB3, and a number of other specific single genes as associated with alcohol use disorders. The growing use of genetic analyses, in particular studies using polygenic risk scores; neurobiologic pathways; and methods for quantifying gene × gene and gene × environment interactions have also contributed to an evolving understanding of the genetic architecture of alcohol use disorders. Additionally, the study of behavioral traits associated with alcohol dependence such as impulsivity and sensation seeking, and the influences of demographic factors (i.e., sex and ethnicity) have significantly enhanced the genetics of alcoholism literature. This article provides a brief overview of the current topically relevant findings in the field to date and includes areas of research still requiring attention.

Keywords Alcohol · Genetics · Epidemiology · Genetic analysis · Linkage analysis · GWAS · Candidate genes · Gene networks · G×E · Behavioral traits · Social and cultural influences

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Introduction

Alcohol is one of the oldest psychoactive substances in current use in human populations. As of 2013, excess alcohol use constituted the third leading modifiable cause of death in the USA [1]. Approximately 65 % of the US population drinks alcohol. However, 73 % of alcohol consumed in the USA is imbibed by only 10 % of the population [2]. Those engaging in large quantities of alcohol consumption may meet criteria for alcohol use disorders (AUDs) as defined by the *Diagnostic and Statistical Manual of Mental Disorders* [3, 4].

After briefly reviewing epidemiological research designs, specifically twin, adoption, and family studies, this article will introduce genetic analyses that have been used and are currently being used to explore the genetics of AUDs (i.e., linkage analysis, candidate gene analysis, genomewide association studies, copy number variations, sequencing studies, gene network analysis, and polygenic risk score analysis). Additionally, behavioral traits associated with AUDs will be discussed, as well as sex and ethnic influences that may impact the heritability of drinking and alcohol-related problems.

Genetic Epidemiology

AUDs have been shown to have a heritability of 40–50 % [4, 5]. Research establishing the heritability of AUDs primarily utilizes three research designs: twin studies, adoption studies, and family studies.

Traditional twin studies use identical/monozygotic (MZ) and fraternal/dizygotic (DZ) twins. The basic research premise relies on shared and unshared genetic and environmental factors. Research has documented a greater concordance in rates of alcohol dependence between identical twins (who

share all of their genes) than in fraternal twins (who share close to half of their genes) [6, 7].

Adoption studies compare affected adoptees to unaffected adoptees to explore the genetic versus environmental influences on a behavior. Most classic adoption studies occurred 20–30 years ago and generally demonstrated that adoptees more closely resemble their biological parents than their adoptive parents in terms of risk for developing AUDs [8–10].

The heritability of alcoholism can be further studied using family-based research designs. This allows researchers to trace alcohol drinking behavior and AUD symptomatology within multiple familial generations [11]. Family studies of alcohol use disorders have clearly demonstrated familial aggregation for alcohol dependence and for comorbid disorders such as drug use disorders and mood and anxiety disorders [12].

Current Genetic Analysis/Molecular Genetic Studies

There are several approaches that are used to identify specific genetic contributions that may affect AUDs: linkage analysis, candidate gene association studies, genomewide association studies, and sequencing studies. Recently, researchers have also focused on gene networks and polygenic risk scores to assess additive influences of multiple genes relating to the vulnerability of AUDs.

Linkage Analysis

Linkage studies are a type of genomewide analysis used to identify specific chromosomal regions implicated in a disease or trait of interest. The first entire-genome linkage study in a largely European ancestry population was conducted using families who were recruited as part of the Collaborative Study on the Genetics of Alcoholism (COGA) project. Initial results indicated a linkage between alcohol-related phenotypes and chromosomes 1, 4, and 7 [13]; a separate study in a Native American sample identified linkage at 11p, 4p, and 4q [14].

More recently, Gizer and colleagues [15] conducted a linkage scan for alcohol dependence (AD), which revealed four peaks of interest in chromosomes 1, 2, 8, and 18. Follow-up linkage analyses using the 12 items used to classify AD symptoms as assessed via the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) indicated that the peaks in chromosomes appeared to be linked to particular Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. In the past decade, association strategies have largely replaced traditional linkage studies [16]. Although an important first step, linkage studies lack the power necessary to identify non-robust effects in comparison to association studies [17].

Candidate Gene Associations

This type of approach is beneficial in establishing specific single genes that contribute to the risk of development of AUDs [18]. Candidate genes are usually assessed both by their chromosomal location near prior identified linkage signals (i.e., positional candidates) and by their properties (i.e., neurobiological candidates) [19].

Several prominent candidate genes have consistently appeared within the genetics of alcoholism literature; an abbreviated list of some of these genes will be discussed here individually:

ADH and ALDH The initial candidate gene studies on alcoholism focused on genes that metabolized alcohol [16]. Research indicated that variations in ALDH2 were associated with aversive reactions (i.e., flushing, tachycardia, and nausea) when alcohol was consumed. Similar effects were also found with some ADH variants. These reactions strongly curbed consumption of alcohol in some individuals, leading researchers to conclude that these gene variants were protective factors in developing alcoholism [16, 20, 21]. Edenberg et al. [22] found strong evidence that variations in ADH4 and ADH1B were implicated in alcohol risk. More recently, these results have been extended and replicated in a Korean sample [23]. The aversive reactions noted, primarily in Asian populations, are thought to be related to accumulation of the toxic metabolite acetaldehyde. Similar but subtler variations in metabolism would be expected to characterize subjects with lower vulnerability to alcohol use disorders based on variations in ADH4 or ADH1B.

GABRA2 Edenberg et al. [24] found an association between GABRA2 and adult AD within the COGA population. This finding has since been replicated by several independent investigative groups [25–28]. More recently, variations in GABRA2 were related to increased drunkenness during the transition between adolescence and adulthood [29, 30]. Further research has been found to indicate that the initial risk pathway for GABRA2 association with alcohol problems may actually begin with a predisposition to conduct problems and sensation-seeking behaviors in early adolescence [31, 32•]. Along these lines, Trucco et al. [33•] found that the effect of GABRA2 on problematic drinking appears to be mediated by increased rule breaking in mid-adolescence.

CHRM2 CHRM2 encodes the muscarinic acetylcholine receptor M2. The activation of the CHRM2 receptor has been found to alter neural signaling associated with decision-making. COGA investigators found an association between CHRM2 gene variants and AD as well as major depressive syndromes [34]. CHRM2 has also been linked to the electrophysiological evoked potential measure, P300, a biomarker

shared across externalizing disorders [35]. Dick et al. [36] later found that CHRM2 was related not only to externalizing disorders but also to specific symptoms associated with both drug and alcohol dependence.

DRD2 The dopamine D2 receptor, DRD2, found on chromosome 11, has been proposed to regulate reward and reinforcement, including reward processes related to alcohol use [37]. At present, the DRD2 literature includes a mixture of positive and negative findings with regard to association with AD. The difference in results could be indicative of DRD2 being a marker leading to an increased propensity to develop an AUD among other disorders, or it may be a false-positive finding. There are ambiguities in the interpretation of the marker data as well [38]. Although further research is still necessary to parse out this relationship, many promising findings have been reported. Mota et al. [39] investigated whether the relationship between DRD2–DRD4 and adult AD was actually mediated by childhood conduct disorder (CD). They found that the presence of the DRD2 T allele was related to an increased risk of CD for individuals who did not have the DRD4 7R allele. The authors suggest that although further replication is necessary, their study may indicate that the interaction between DRD2 and DRD4 could influence the development of behavioral disorders in childhood (i.e., conduct disorder), and subsequently adult AD.

5HTT (SLC6A4) The serotonin transporter protein may be implicated in alcohol craving and dependence. Hammoumi et al. [40] found a higher instance of the S allele in 5-HTTLPR (i.e., the promoter polymorphism in the gene *SLC6A4*) among subjects diagnosed with AD. Dick et al. [41] noted that individuals who had the S/S genotype were at an increased risk for depression after experiencing stressful life events compared to those who had the L/L genotype. They did not however identify a relationship between 5HTT and AD. Identification of a relationship between life stress and alcoholism may require a more complex genetic model.

The discussion above describes several examples of candidate genes in alcohol use disorders. Many others have been investigated. A table highlighting the 55 most studied candidate genes in COGA and Study of Addiction: Genes and Environment (SAGE) is included (Table 1) [34, 35, 41–43, 45•, 46–70, 73–80, 82–91].

Gene × Environment (G×E) Interactions

The likelihood of one gene fully accounting for the genetic liability for an AUD in an individual is highly unlikely given our current understanding of this complex genetic disorder. Indeed, genetic effects relating to health, behavior, and disease states do not operate in isolation but are subject to environmental influences that can profoundly affect the trajectory of disease progression. Studying G×E interactions is crucial to understanding the course and etiology of alcohol problems, as well as the response to treatment for AUDs. There however remains a significant complexity in studying these interactions. Sher et al. [72] highlight many promising approaches to take when considering G×E research. Belsky, Pluess, and Widaman [81] further suggest the increased need for hypothesis-informed statistical tests as opposed to simply exploratory G×E studies. Specifically, their suggestion of a new regression technique to conduct direct testing of theory-derived predictions deserves further assessment in the alcohol literature.

The National Human Genome Research Institute has created a database archiving all National Institutes of Health (NIH) present-day initiatives committed to studying the interplay of genetics and environment in understanding health and disease progression. The information regarding these Gene Environment Association Studies (GENEVA) can be accessed at https://www.genome.gov/27541319.

Genomewide Association Studies

Genomewide association studies (GWAS) compare DNA markers across the genome to identify common genetic variants expressed by individuals with a specific trait or disease of interest [92]. Typically, several hundred thousand to several million markers are used. Because the entire genome is tested in a single experiment, the number of independent tests requires stringent correction (generally a p value of 5×10^{-8} is required for statistical significance). Treutlein et al. [93] conducted the first GWAS study on AD. Their study identified two closely linked SNPs in chromosome region 2q35 that met genomewide significance (rs7590720 and rs1344694).

Noting the strong association between the number of alcoholic drinks consumed in a 24-h period and AD, a group of researchers conducted a GWAS looking at the phenotype of number of drinks consumed (i.e., max drinks) [94]. Conducting two separate GWAS, one from COGA (N=2322) and the second from the SAGE (N=2593), they found associations for rs9523562 located on chromosome 13q31.1 and rs67666182 located on chromosome 8 in the COGA and SAGE study samples, respectively. Further, gene-based meta-analyses were conducted between the two GWAS studies and the outcome variable of max drinks. Results revealed associations for the LMO1 and PLCL1 genes and max drinks in both studies. Additionally, associations were found for variants of AUTS2, INADL, C15orf32, and H1P1.

Heath and colleagues [95] also assessed alternative phenotypic outcome variables in their GWAS study. They created a heaviness of drinking (HOD) measure composed from items measuring lifetime max drinks, consumption during the three heaviest periods of drinking, frequency of drinking to intoxication, and average weekly consumption. Using the

Table 1 List of most studied candidate genes in COGA and SAGE

Pathway	Gene	Associated phenotypes	Reference
GABA	*GABRA2*	Alcohol dependence	Edenberg et al. [25]
		EEG beta power	Porjesz et al. [42]
		EEG coherence (theta 2)	Rangaswamy & Porjesz [43]
		Drug dependence	Agrawal et al. [44]; Dick et al. [31, 38, 41, 52]
		Conduct disorder	Dick et al. [31, 52]
	GABRG3	Alcohol dependence	Dick et al. [46]
	GABRA6	Alcohol dependence	Kimura & Higuchi [85]
	GABRB1	Alcohol use disorder	Li et al. [47]
		Alcohol dependence	Kimura & Higuchi [85]
	GABRB2	Alcohol dependence	Loh et al. [48]
		Alcohol dependence with Korsakoff's syndrome	Loh & Ball [49]; Sander et al. [50]
	GABRB3	Severe alcoholism	Noble et al. [51]
	GABRA1	Drinking patterns	Dick et al. [52]
Muscarinic receptor	*CHRM2*	Alcohol dependence	Wang et al. 2004a, b
		Major depressive disorder	Wang et al. 2004a, b
		IQ	Dick et al. [38]; Dick et al. [41]
		Illicit drugs	Dick et al. [38, 41]
		Theta ERO	Agrawal et al. [44]
		EEG coherence (theta)	Jones et al. [35, 53]
		Externalizing psychopathology	Porjesz & Rangaswamy [54]
Taste receptors	*TAS2R38*	Max drinks	Wang et al. [55]
	TAS2R16	Alcohol dependence	Hinrichs et al. [56]
		Max drinks	Wang et al. [55]
Nicotinic receptors	*CHRNA5*	Alcohol dependence	Wang et al. [57]
		Nicotine dependence	Wang et al. [57]
		Cocaine dependence	Grucza et al. [58]
	CHRNA3	Nicotine dependence	Saccone et al. [59]
Opioid	*OPRK1*	Alcohol dependence	Xuei et al. [60]
	PDYN	Alcohol dependence	Xuei et al. [60]
	PDYN	Alcohol dependence	Xuei et al. [60]
	POMC	Opioid dependence	Xuei et al. [61]
	PENK	Opioid dependence	Xuei et al. [61]
	OPRM1	Alcohol dependence	Wang et al. [62]
		Development of alcoholism	Enoch [63]; Olfson & Bierut [66]
	OPRD1	Alcohol dependence	Zuo et al. [64]
		Alcoholism	Zuo et al. [64]
		Opioid dependence	Olfson & Bierut [66]
	OPRL1	Opioid dependence	Xuei et al. [61]
Drug metabolism	*ADH4*	Alcohol dependence	Edenberg & Foroud [23]
	ADH1C	Alcoholism	Olfson & Bierut [66]
		Alcohol dependence	Frank et al. [67]
	ADH5	Alcohol dependence	Gelernter et al. [65]
		Alcoholism	Olfson & Bierut [66]
	ADH7	Alcoholism	Olfson & Bierut [66]
	ALDH1A1	Drug addiction	Guo et al. [68]
		Alcoholism	Olfson & Bierut [66]
	ALDH2	Alcohol dependence	Zuo et al. [64]
		Alcoholism	Olfson & Bierut [66]

Table 1 (continued)

Pathway	Gene	Associated phenotypes	Reference
	CYP2E1	Alcoholism	Olfson & Bierut [66]; Morozova et al. [87]
	ADH1A	Substance use disorders	Meyers and Dick [69]
		Alcohol dependence	Edenberg & Foroud [23]
	ADH1B	Substance use disorders	Meyers and Dick [69]
		Alcohol dependence	Edenberg & Foroud [23]
HPA	*CRHR1*	VP3 amplitude alcohol dependence	Chen et al. [70]
Other	*SNCA*	Alcohol craving	Foroud et al. [88]
	TACR3	Alcohol dependence DSM3R cocaine dependence	Foroud et al. [73]
	ACN9	Alcohol dependence VP3 theta ERO	Dick et al. [38, 41]
	NPY	Alcoholism	Olfson & Bierut [66]
		Alcohol dependence	Wang et al. [62]
	NFKB1	Alcohol dependence VP3 delta ERO	Edenberg et al. [74]
	AKAP9	Alcohol dependence	Kendler et al. [75]
	RELN	Drug addiction	Guo et al. [68]
Stomach/gastrointestine	*CCK*	Alcoholism	Olfson & Bierut [66]
	CCKAR	Alcoholism	Olfson & Bierut [66]
	CCKBR	Alcoholism	Olfson & Bierut [66]
Dopamine	*DRD2*	Alcohol dependence	Dick et al. [38, 41]; Samochowiec et al. [76]
		Sensation seeking	Derringer et al. [77]
		Alcoholism	Edenberg et al. [78]
	DRD3	Sensation seeking	Derringer et al. [77]
		Alcohol dependence	Derringer et al. [77]
		Cocaine dependence	Derringer et al. [79]
	DRD4	Substance abuse	Vandenbergh et al. [89]
		Sensation seeking	Derringer et al. [77]
Glutamate	GAD1	Alcohol dependence	Dick et al. [32•]; Zuo et al. [90]
	GAD2	Substance dependence	Agrawal et al. [82]
	GRM8	Alcohol dependence EEG coherence (theta)	Chen et al. [83]
		VP3 theta ERO	
	GRIN1	Alcohol dependence	Kendler et al. [75]; Karpyak et al. [84]
	GRIN2B	Alcohol dependence	Gelernter et al. [65]; Kendler et al. [75]; Karpyak et al. [84]
Serotonin	HTTLPR	Depression	Dick et al. [41]
	HTR1A	Alcohol dependence	Zuo et al. [64, 86]
	HTR1B	Alcohol dependence	Hesselbrock et al. [91]; Zuo et al. [64]
	HTR2A	Alcohol dependence	Zuo et al. [90]
	TPH1	Alcohol dependence	Olfson & Bierut [66]
	TPH2	Alcohol dependence	Olfson & Bierut [66]
	SLC6A4	Depression	Dick et al. [38, 41]
		Alcohol dependence	Zuo et al. [90]

Table modified from Olfson & Bierut [66]; Hodgkinson et al. [71]

Australian Twin Registry, they conducted SNPs on 8754 (2062 AD) individuals. Their results for HOD did not reveal any genomewide significant associations. However, a SNP on chromosome 3 (rs12369955) showed a suggestive association with the composite HOD measure ($p=1.6\times10^{-6}$), as well as with consumption during the heaviest period of heavy drinking ($p=4.7\times10^{-6}$), frequency of getting drunk ($p=3.9\times10^{-5}$), frequency of any alcohol use ($p=4.9\times10^{-5}$), and weekly alcohol consumption ($p=2.7\times10^{-6}$). The authors concluded that hundreds of genetic variants, through modest contributions, are involved in the risk for heavy drinking.

As of 2014, a total of seven GWAS studies concentrating on alcohol dependence have been published (see Table 2 for a complete list) [67, 93, 96–100]. Increases in sample sizes are necessary in order to replicate and extend current GWAS findings on alcoholism [16]. Currently, the National Human Genome Research Institute has an exhaustive online catalog of all published genomewide association studies (www.genome.gov/gwastudies/). Just as important as online databases are the implementations of consortia (i.e., putting large samples together for meta-analysis or mega-analysis). The National Institute on Alcohol Abuse and Alcoholism (NIAAA) has sponsored a large consortium, spearheaded by COGA, that is preparing its initial GWAS manuscript with all AUD research data available at present. Additionally, the Psychiatric Genomics Consortium (PGC), which has pioneered expansive successful GWAS in schizophrenia and other disorders, has now opened a section on Substance Use Disorders (SUDs). Yu et al. [101] created the GWAS Integrator, which "is a bioinformatics tool that integrates information on GWAS associations from the National Human Genome Research institute (NHGRI) Catalog, SNAP (SNAP Annotation and Proxy Search), and the Human Genome Epidemiology (HuGE) Navigator literature database." Significant associations from GWAS and alternative SNPs can be quickly identified using the tools search and data mining functions.

Such resources are crucial to facilitate cross-collaboration and expansion of sample sizes necessary to appropriately utilize GWAS results. The major limitation of GWAS is the large sample sizes necessary to identify gene variants of modest effect (RR<2), which characterizes the bulk of findings in psychiatric illness. Nevertheless, there have been groundbreaking advances in our understanding of a number of complex disorders using GWAS, including dramatic recent progress in the genetics of schizophrenia.

Copy Number Variants

Copy number variants (CNVs) are small chromosomal insertions and deletions. The CNVs commonly studied in today's literature are generally too small to be detected by classical cytogenetic methods but may be deduced from microarray data and confirmed with direct sequence information. Located on particular chromosomal segments, CNVs expose organizational instability in the DNA. They are a genetic variation that has considerable impact on levels of gene expression [102, 103]. Although a strong association has been found between CNVs and some neuropsychiatric disease outcomes (e.g., Williams-Beuren syndrome, Charcot-Marie-Tooth neuropathy type 1A, autism, intellectual disability, schizophrenia (see Malhotra and Sebat [104])), little research has been conducted to assess the link between CNVs and AD.

A recent study by Lin et al. [102] found that CNVs in 6q14.1 and 5q13.2 were significantly related to AD. These regions have been linked to neurological disorders (specifically intellectual disability and language delay) in prior literature. The relationship between CNVs and AD warrants further research investigation.

Sequencing Studies

Through the use of sequencing, researchers have been able to identify rare variants (i.e., mutations). Unlike with GWAS, which uses chips or arrays featuring discrete markers spaced at intervals on each chromosome, sequencing studies look at each base pair across the entire genome or across portions of the genome. In this way, rare variants (by definition, variants found in <1 % of the population) can more easily be uncovered. Typically, rare variants are found by one of two systematic means of study: (1) pooled sequencing (i.e., within pools

Table 2 List of currently published GWAS studies concentrating on AD

Study	Sample size	Chromosome region	SNP	Candidate genes
Treutlein et al. [93]	Study 1: 487 cases, 1358 controls; Study 2: 1024 case, 996 controls	2q35	rs7590720, rs1344694	CDH13, ADH1C
Bierut et al. [96]	1897 cases, 1932 controls	n.s	n.s	n.s
Edenberg et al. [97]	792 cases, 692 controls	n.s (nearby region 11)	n.s (nearby rs4758533)	n.s (nearby SLC22A18, PHLDA2, NAP1L4, SNORA54, CARS, OSBPL5)
Zlojutro et al. [98]	1192 cases, 692 controls	2q11, 10q23	rs4907240, rs7916403	ARID5A, HTR7
Wang et al. [99]	1638 cases, 964 controls	15q14	rs12912251	C15orf53
Edwards et al. [100]	467 cases, 407 controls	n.s	n.s	n.s
Frank et al. [67]	487 cases, 1358 controls	4	rs1789891	ADH1B, ADH1C

of DNA from multiple persons, giving quantitative allele frequencies) or (2) individual "next-generation" sequencing (i.e., giving the specific base pair sequence from each individual tested).

A recent study assessed rare variants in CHRNB3 from the COGA study population. Among European Americans, carriers of missense variants in CHRNB3 had increased DSM-IV AD symptoms [105•].

Gene Networks

With the known 50 % heritability and the numerous candidate genes, each with a small effect size, contributing to AUDs, it is important for researchers to find ways to organize the information from these complex genetic relationships. One current method utilized by investigators to address this issue is the study of gene expression in gene networks. With enough sources of information, a neurobiologically informed causal network can be constructed. Manifestations of this network can then be used to test mechanistic relationships responsible for phenotypes related to alcoholism [106–108].

Farris and Miles [106] examined the newest methods currently used to construct gene networks and assessed current studies applying these analytic methods. They recommended using gene expression data derived from targeted or whole-genome arrays. For alcohol use disorders, gene expression may be assessed in animal models, human lymphocytes or transformed peripheral cells, or autopsy brain samples. They also suggest the construction of co-expression networks, that is, the study of genes with correlated expression patterns.

A very promising application of gene expression analysis has been found in the field of cancer research. Yang et al. [109] noted the importance of prognostic gene expression in the global understanding of an individual's cancer disease advancement. The authors used gene network expression analysis to examine the co-expression properties of prognostic genes. Through their analyses, they actually found that prognostic genes were not actually hubs (i.e., genes with an individual high level of connectivity) but rather were enriched in modules (a part of a group of highly interconnected genes).

At present, there is no accepted best practice for the definition and description of gene networks. Farris and Miles [106] suggest that the most informative gene networks will emerge from the results of both human and animal models, and the future substantive use of gene networks relies on the continued development of large-scale bioinformatics resources that can outline temporal and spatial patterns of gene expression.

Polygenic Risk Scores

Another way to look at the additive influence of multiple genes on alcoholism is by creating polygenic risk scores. A simple method of doing this is to sum the number of genetic risk markers associated with a trait of interest and, by doing so, create a genetic sum score, which can then be used in analyses. Yan et al. [110] created genetic sum scores for SNPs associated with AD to test whether they could be used to distinguish among case and controls in validation samples. They found that genetic sum scores using the SNPs in their sample were unable to discriminate between case and control samples. The authors concluded based on their results that such sum scores have a restricted clinical value for AD at present. However, they are hopeful that with increased information about specific variants contributing to AD, genetic sum scores will become an important predictive tool to evaluate risk.

Many substance use disorders are comorbid. Taking into account the known associations between cigarette smoking and alcohol consumption, Vink and colleagues [111] used polygenic risk scores to investigate the possible overlapping genetic factors involved in this relationship. Using a subset from the Netherlands Twin Register (N=1583), they created a risk score for "cigarettes per day" and found a significant association with "number of glasses of alcohol consumed per week." The polygenic scores for "age at onset of smoking" were also significantly associated with "age at regular drinking." These results highlight the idea that genetic risk factors may be shared between different substances of abuse. More importantly, both of these studies highlight the continued complexity of studying the genetic causes of AD.

Behavioral Traits Associated with AUDs

In addition to current genetic analyses being used, the explorations of behavioral traits related to AUDs may be a crucial step to further explore the genetics of alcoholism. Some of these traits may fulfill criteria for a genetic biomarker for AUD or an endophenotype (see Gottesman and Gould [112] or Begleiter and Porjesz [113]).

Impulsivity Impulsivity is a personality trait characterized by a lack of behavioral inhibition or control. Individuals who are impulsive tend to engage in reckless acts without much thought or consideration. An association between impulsivity and AUDs has been supported in the literature [114, 115]. However, there is a complexity in studying this association. Dick et al. [116] outline many of the reasons for this difficulty and discuss current measures to study impulsivity in the association with AUDs.

In a family-based sample (173 families, 449 subjects) screened for alcoholism, Villafuerte et al. [117] found that increased impulsivity and insula activation during an anticipated reward task was related to variants of GABRA2 being associated with AUD. Specifically, the authors suggested that

the relationship between impulsiveness and GABRA2 is mediated via changes in insula activity. They suggest that GABRA2 impacts underlying neural mechanisms that affect different aspects of risk over time, as well as subsequent AD.

Sensation Seeking Dick et al. [32•] further studied the relationship of sensation seeking over time to AD. They found that similar to the hypothesized mechanism of Villafuerte et al. [117], GABRA2 shared associations with both AD and sensation seeking. Specifically, their study suggests that the risk pathway for AD by GABRA2 actually begins with a predisposition to sensation seeking in early adolescence.

Based on the above findings, certain behavioral traits (i.e., impulsivity and sensation seeking) not only may be related to AD and AUDs but also may mediate or exacerbate the relationship between genetic predisposition and subsequent future development of alcoholism.

Sex/Ethnic Influences on the Heritability of Alcoholism

Many individual social/biological factors can profoundly modify the genetic risk for AUDs as well as the course of development of these disorders [118, 119].

Sex Differences

In virtually all studies of alcohol dependence in populations or in families, men have 2× or greater risk for the condition compared to women. Is this related to genetic factors, social-cultural differences, or both? Agrawal et al. [82] noted that there is little difference between men and women in genetic factors responsible for AD. It is possible that the environmental triggers for developing alcohol dependence may vary for men and women.

Added complexity occurs in G×E relationships when assessing differences in sex. For example, Perry et al. [120] found that the impact of daily hassles on the relationship between GABRA2 and alcohol dependences differs between men and women. Specifically, attitudes toward increased positive life events served as a protective factor for men with the high-risk GABRA2 genotype, but not for men with the low-risk genotype. These results were not noted in women (who did not show a significant GABRA2 effect on alcohol dependence), thus suggesting that an individual's gender may expose them to different social norms, constraints, or opportunities, which can ultimately effect differences in G×E interactions.

Ethnic Differences

There is substantial genetic variability in AD among different ethnic groups.

We have noted above the genetic variations in alcohol metabolic enzymes affecting alcohol response and subsequent patterns of drinking. This is particularly true in East Asian populations, in which these variants are common. Quillen and colleagues [121] found associations between the gene ALDH2 and "daily maximum drinks" in their GWAS study of 313 males from Northern China. Park et al. [23] extended GWAS studies on the genetic associations between ADH cluster genes and AD to include Korean Americans. Further, Han, Gelernter, Kranzler, and Yang [122•] conducted an ordered subset linkage analysis in a sample of 384 African American (AA) families. By using admixture proportion as a covariate, they were able to decrease genetic heterogeneity and increase the discovery of linkage for AD in an admixed population that included AA subjects. Differences in AA subjects have also been found in the frequency of variants of GABRAG1 and GABRA2 and their association with AD [123•]. In summary, there is compelling research to suggest that persons with different ethnic backgrounds may have different genetic vulnerability factors for AD. Since ethnicity is an anthropological concept that combines the effect of the biological origin of populations with the effects of culture on human behavior, the analysis of observed differences between study groups of different ethnicities is necessarily complex. It is prudent to include control groups of similar ethnic backgrounds without the condition in question (i.e., alcohol use disorders) in any such investigation.

Conclusions

Over the past several years, great progress has been made in our understanding of the genetics of alcoholism. The current literature continues to support the idea of alcoholism being a complex, multifaceted disorder. The contribution of genetics and its associations with behavioral traits and sex and ethnic influences serves to increase the complexity of the condition. Nevertheless, exceptional strides have been made. Specifically, the tools available to pursue lines of genetic analysis (i.e., sophisticated genetic analysis programs, consortia, and online databases) increase the accuracy of reported results, enhance the ability to synthesize the findings into a shareable format, and drastically expand the likelihood of generating the large sample sizes necessary to appropriately conduct genetic research in the field of alcoholism.

Clearly, we cannot truly understand the influence of genetics without understanding G×G and G×E interactions. For instance, a person's ethnicity and gender may significantly, and differentially, contribute to or interact with the genetic pathways responsible for the risk of developing AUDs. The future study of the genetics of alcoholism is extremely promising given the advances (i.e., influential candidate genes,

creation of polygenic risk scores, GWAS studies, sequencing studies, and understanding sex and ethnic influences) that have been made in the last few years. Variations in genes like ADH, ALDH, and GABRA2 continue to highlight the very strong genetic risk and differential susceptibility that exist in developing AD and AUDs. The progress in the study of the interplay between environmental, individual, and genetic influences in the progression of alcoholism may make it possible to one day create personalized treatments based on an individual's specific needs. In fact, such a trial is in progress, testing response to naltrexone in groups defined by variants in the OPRM1 gene (which codes for the mu opioid receptor). Preliminary data in this area have been promising [124].

Compliance with Ethics Guidelines

Conflict of Interest Priya A. Iyer-Eimerbrink and John I. Nurnberger, Jr., declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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