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A Brief History of Research on the Genetics of Alcohol and Other Drug Use Disorders

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ABSTRACT. Objective: This article reviews developments in research on genetic influences on alcohol and other drug use and disorders over the past 7 decades. **Method:** The author began with a review of the flow and content of articles published in the three iterations of the journal since 1940 and then used a PubMed search of genetics of alcohol and other drug-related topics to gain a broad overview of developments in this field. **Results:** The literature demonstrates the rapid metamorphosis of genetic research from the ideas of Mendel to an understanding that the substance use disorders are complex, genetically influenced conditions where genes explain up to 60% of the picture. Most genes operate through additional intermediate characteristics, such as impulsivity and a low sensitivity to alcohol, some of which are substance specific and others related to substances in general. Using linkage, association, genome-wide association, and other modern methods, investigators have identified a diverse range of genetic variations that affect substance-related phenomena. **Conclusions:** Genetic studies regarding alcohol and other drug use and problems have grown dramatically in the past 75 years. We currently have a much more sophisticated understanding of these influences, and the rapid development of new methods has the promise of continuing what has been a solid contribution of important findings in recent years. (*J. Stud. Alcohol Drugs, Supplement 17,* 59–67, 2014)

IN 1940, THE YEAR THAT THE *Quarterly Journal of the Studies on Alcohol* (QJSA) was first published, Europe was at war, Asia was facing chaos, and the United States was less than 2 years from entering World War II. Fascist governments held sway in much of the world, the modern computer had not yet been imagined, and funding for health-related research was very limited. More directly relevant to this review, the bases for modern genetic approaches had been developed, but few results had been published regarding substance-related problems.

Although the science of genetics was reflected in earlier farming and ranching practices, the modern basis for genetics research had been established 150 years previously through Gregor Mendel's work with plants. His discoveries were quickly expanded to studies of a range of organisms, which led to the beginning steps in the recognition of the existence of DNA and chromosomes (Crow and Crow, 2002; Griffiths et al., 2000). The subsequent development of more powerful statistical methods along with increasing interest in genetic questions contributed to a more sophisticated understanding of genes and chromosomes and the isolation of DNA by the early 1940s (Avery et al., 1944).

Since then, the double helix structure of DNA was identified (Watson and Crick, 1953), gene-sequencing approaches were established (Min Jou et al., 1972), and the methods needed to better understand gene structure and their functioning were developed. These series of events contributed to the successful mapping of the human genome in 2003 (McElheny, 2010).

Although the tenets of genetic influences were sometimes misunderstood or deliberately twisted to justify malevolent goals (McLaren, 1990), these earlier findings led to a better understanding of health and behavior. This contributed to a persistent push toward better research approaches and the rapid accumulation of new data and unique ideas, including those related to problematic drinking and other drug use. These issues were reflected in what was QJSA, which grew into the *Journal of Studies on Alcohol* (JSA) in 1975, and then the *Journal of Studies on Alcohol and Drugs* (JSAD) in 2007. Over the 75 years of its existence, the journal published about 350 articles regarding genetic issues related to alcohol and other drug use and disorders and addressed a wide range of questions that reflected the state of the art for genetic research in our field.

Method

The broad and complex issues covered in a multitude of articles in the field of genetics of alcohol and other drug disorders overall cannot be reviewed in detail in any single manuscript (Gonzales-Alcaide et al., 2013). This review began with those 350 articles as noted above. Those findings were then placed into context through a PubMed search of genetics of alcohol and other drug–related topics to ensure that the comments offered here represent a broad overview of developments in this field. In this process, guidelines

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were needed to determine what to include or exclude and the depth in which the material could be covered. Those decisions were guided by considering the likely readers of what has become JSAD. Thus, this review is directed at researchers across the fields of alcohol and other drugs from a broad range of disciplines including epidemiologists, social scientists, clinician researchers, and those engaged in basic science and studies of animal models. The article first briefly reviews how JSAD has contributed to the field of genetics research on substance use and problems over the years, followed by a broad overview of where the field of genetics is today. References are used as examples reflecting a "population of convenience" that represents the types of research that have developed over the past three quarters of a century, with an emphasis on areas of genetics research that were known in greatest depth by the author.

Results

The Quarterly Journal of Studies on Alcohol (1940–1974), the Journal of Studies on Alcohol (1975–2006), and the Journal of Studies on Alcohol and Drugs (2007–present)

Since 1940, the three iterations of what has become JSAD published diverse articles on a broad list of topics. Despite this eclecticism, studies related to familial and genetic contributions to alcohol use disorders (AUDs), along with some focusing on other substance use disorders (SUDs), have been moderately well represented since the mid-1970s. Reflecting the predominance of alcohol research in the journal until 2007, studies of genetic influences for alcohol dominate this review, although other drug-related issues are also covered.

A scan of articles published in the journal since 1940 identified more than 335 manuscripts that touched directly or indirectly on issues related to genetics of substance-related problems. In 1947 and 1953, the first papers that directly addressed genetic influences in our journal evaluated the heritability (proportion of the risk explained by genes) for alcohol preference in humans and rats (Mardones et al, 1953; Williams, 1947). Articles related to genetic issues began to increase in 1968 with discussions of family histories of AUDs among alcoholics, teetotal relatives of patients with alcohol problems, and a 1973 commentary on recent twin and adoption study findings that documented the role of genetic influences in alcoholism.

By the mid-1970s, articles in our journal began to speculate about specific genetic factors that contribute to heavy drinking and alcohol problems. From 1975 on, an average of four to eight articles per year discussed many of the genetic questions raised in the alcohol and other drug field in general. These comprised comorbidity between alcohol, other drug, and psychiatric conditions; the potential impact of assortative mating (nonrandom selection of spouses); animal models of heavy drinking and alcohol-related problems; and the recognition of the potential types of risk factors through which the genetic influences operate, as discussed below. During the most recent 2 years of JSAD, articles have evaluated ethnicity and the risk for both alcohol and other drug use disorders, comorbidity between alcohol and psychiatric problems, variations in specific genes that relate to the sensitivity to alcohol, twin studies, the relationships between the age at onset of substance use and specific gene variations related to the development of substance-related problems, and gene/environment interactions.

In summary, the publications in the iterations of JSAD have paralleled developments in studies of genetics of substance-related problems overall. This offers an opportunity to contemplate the specific genetically related topics that are likely to appear in the journal in the future. To accomplish that, this review now turns to a presentation of findings leading up to the most recent years and an overview of the current state of the art regarding genetic influences in alcohol and other drug use and problems.

Developments from ~1970 to ~2000: The foundation for where the field is today

As briefly alluded to above, so much progress has been made regarding the search for genes relating to alcohol and other drug use disorders that it is difficult to choose which specific findings are relevant to cite in this broad overview. Therefore, reflecting the history of the journal and because the genetic influences for these disorders were easier to identify (AUDs are more prevalent than SUDs and have been seen across multiple generations for many years), the focus will be primarily on alcohol. For other drugs, the shortage of space contributed to the decision to focus more on illicit substances rather than on nicotine and caffeine. More detail regarding genetic influences for specific substances of abuse, as well as more in-depth presentations of genetic methods, are offered in several recent articles (Bierut, 2011; Edenberg, 2011; Lessov-Schlaggar et al., 2012; Mayfield et al., 2008; Olfson and Bierut, 2012; Schuckit, 2009; Xian et al., 2008; Yan et al., 2013).

The modern era of genetic studies regarding alcohol and other drug-related problems was built on many years of observations that alcohol problems cluster in families (reviewed by Cotton, 1979; Goodwin, 1979, 1985, 1989). However, a familial influence, although a key first step in considering whether genetic factors might be important, does not demonstrate whether the familial link relates to genes, environment, or their combination.

The distinction between genes and/or environment for these conditions was next addressed primarily through two approaches. First, having established a three- to four-fold increased risk for AUDs in relatives of alcoholics (Goodwin, 1989), studies evaluated if this enhanced risk for alcohol problems observed in children of alcoholics was seen even if

the offspring had been separated from their parents early in life. The first effort in this area evaluated a small sample of children of alcoholics and controls who became foster children at various ages and who were studied in their 20s; the author reported few notable differences between the groups (Roe, 1944). However, the small sample and methodological problems did not allow for definitive conclusions. Later, a larger study focusing on half-siblings from families of alcoholics and controls reported on 154 subjects, finding that adverse alcohol outcomes in offspring related more closely to alcoholism in a biological parent than alcohol problems in the parents of upbringing (Schuckit et al., 1972). This article was published at about the same time as several large adoption studies from the United States, Denmark, and Sweden, which confirmed the three-fold or higher increased risk for alcoholism in sons of alcoholics adopted away and raised by nonalcoholics, although less conclusive evidence was found for daughters of alcoholics (Goodwin et al., 1973, 1974, 1977). One investigation compared alcohol-related outcomes in sons of alcoholics raised in their original families with outcomes for their brothers who had been adopted out, finding similar rates of alcohol problems in both brothers (Goodwin et al., 1974).

Studies of twins were also useful in distinguishing between genetic and environmental influences in alcoholism. This approach takes advantage of the fact that although identical twins share 100% of their genes, fraternal twins share only 50% (the same as any full siblings). Because twin pairs are usually raised together in the same homes and experience the same childhood life events at the same ages, a higher level of similarity for a diagnosis among identical compared with fraternal twins indicates that genetic factors were likely to have contributed to the development of the disorder, not just childhood environment. Twin studies were carried out in the United States, Finland, Sweden, and the United Kingdom (Gurling et al., 1984; Hrubec and Omenn, 1981; Kaji, 1960; Kendler et al., 1994; Murray et al., 1983; Partanen et al., 1977), and almost all supported a genetic influence in alcoholism with an estimated proportion of the risk explained by genes of about 60% (Edenberg, 2011; Kendler et al., 2012). Similar studies with similar results were seen for other drug-related problems (Bierut, 2011; Tsuang et al., 1996).

Investigators next turned to methods for identifying specific genes that contribute to the risk for these conditions. An important step was to identify some genetically influenced characteristics, or phenotypes, through which the genes were likely to operate. One such intermediate phenotype was associated with a decreased risk for AUDs but was unrelated to SUDs: an intense skin flush after drinking related to several variations in alcohol metabolizing enzymes that were associated with an enhanced sensitivity to alcohol. This phenomenon had been observed for centuries in Asian drinkers (Japanese, Chinese, and Koreans), and the enzymes involved were identified in the 1970s (Bosron et al., 1980; von Wartburg, 1980). The second intermediate phenotype, one that related to an enhanced risk for both AUDs and SUDs, was the long-known association between substance-related problems and impulsive behaviors (Dick et al., 2006; Schuckit et al., 1970; Slutske et al., 1998). The underlying characteristics include sensation seeking and behavioral/physiological disinhibition that contribute to what was described as Type 2 and Type B subtypes of alcoholism that are associated with an early onset of alcohol and other drug problems and a severe clinical course (Babor et al., 1992; Cloninger, 1987). The third genetically related intermediate characteristic affects the risk for AUDs but not SUDs and relates to a low level of response (low LR or low sensitivity) to the effects of alcohol (Schuckit, 1980). A fourth intermediate phenotype, one related to both AUDs and SUDs, operates through several additional major psychiatric conditions, such as schizophrenia and bipolar disorders (Schuckit, 2009; Yip et al., 2012).

The search for specific genes potentially related to alcohol and other drug problems between 1970 and 2000 often used linkage and association (candidate gene) studies (Agrawal et al., 2008). Linkage evaluates inheritance of a trait (or disorder like AUDs) within families by determining whether some gene markers (i.e., signpost) spaced across the 23 pairs of human chromosomes are inherited together with the trait. This approach identifies regions of chromosomes that may contain genetic variations affecting the risk for the trait and that are potentially fruitful areas to evaluate for specific genes. Association studies work to identify markers (or genes) that are more (or less) common in people with a trait than in those without. These studies sometimes begin by searching for genes that might be related to the trait (e.g., AUDs) by looking at genes that lie in chromosomal regions of interest highlighted in linkage analyses. More recently, additional approaches have become the prominent mode for searching for gene variations related to conditions like AUDs and SUDs (e.g., Edenberg et al., 2010; Ehlers et al., 2010; Gelernter et al., 2009). These newer protocols as well as results from linkage and association studies form the basis for the current state of the art in genetic investigations into substance-related conditions, as described in the next section.

Current studies of genetic and environmental contributors to AUDs and SUDs

Alcohol and other drug use disorders are typical of most complex genetically influenced medical and psychiatric conditions. Genes contribute to the risk, usually by operating in the context of important environmental and attitudinal characteristics (e.g., Schuckit et al., 2011, 2012b). The genetic influences for complex disorders do not follow the rules proposed by Mendel but operate through a series of mechanisms with many genes contributing to a range of genetically influenced intermediate characteristics (or phenotypes).

Therefore, as briefly noted earlier, the search for genes can be simplified if the focus is on the intermediate phenotypes. This section briefly outlines data supporting the range of different intermediate phenotypes associated with the risk for AUDs and SUDs, defines some recent approaches applied to the field of substance-related disorders, and offers examples of results that represent the major current approaches.

Genes from association studies regarding intermediate phenotypes for AUDs and SUDs. The protective effects for AUDs (but not SUDs) from some variations in genes that produce the major alcohol-metabolizing enzymes have long been known (Bierut et al., 2012; Eng et al., 2007; Hubacek et al., 2012; Li et al., 2011; Luczak et al., 2011). One example is a mutation seen in about 40% of Asians in the gene producing the enzyme aldehyde dehydrogenase (ALDH) that is responsible for the metabolism of the first breakdown product of alcohol, acetaldehyde. If both copies of that gene have the mutation (i.e., the individuals are homozygotes for *ALDH2-2*), even low doses of alcohol produce severe nausea and vomiting and an intense skin flush, with the result that the AUD risk is close to zero. If the person has only one genetic copy of the mutation (i.e., they are heterozygotes), his or her reaction to alcohol involves more minor symptoms such as a skin flush. Although many *ALDH-2* heterozygotes are drinkers, they tend to consume less per occasion and have a diminished AUD risk. Additional mutations can occur in the major genes that metabolized alcohol to acetaldehyde (forms of alcohol dehydrogenase or *ADH*) with resulting enzyme forms known as ADH1B-2 and ADH1C-1 that produce a modest flush in a reaction that is sufficient to also relate to a lower AUD risk. The roles for these gene variations were originally studied using linkage and association (candidate gene) approaches, as defined in the prior section.

Variations in genes that enhance impulsivity, sensation seeking, and disinhibition (examples of externalizing behaviors) increase the risk for both AUDs and SUDs. Multiple genes have been identified as related to this enhanced risk through linkage and association studies, including several variations of the receptors for the brain chemical (neurotransmitter) gamma aminobutyric acid (e.g., the *GABRA2* receptor gene), genes related to cholinergic receptors (e.g., *CHARNA5*), several genes relating to dopamine metabolism and receptors, and an *ADH* form that operates on high blood alcohol levels (*ADH4*) (Derringer et al., 2010; Dick et al., 2010, 2011, 2013; Edenberg et al., 2006; Gelernter et al., 2007). Genes related to disinhibition have also been identified through studies of related electrophysiological characteristics including gene variations for the GABRA2 receptor, a receptor for a more stimulating brain chemical, glutamate (GRM8), a receptor for muscarinic cholinergic brain activity (CHRM2), and a gene that influences how a potassium channel in brain cells relates to stimuli such as alcohol (*KCNJ6*) (Chen et al, 2012; Edenberg et al., 2004; Wang et al, 2004).

Recent association studies have highlighted gene variations potentially related to the low LR to alcohol, the most thoroughly studied of several different phenomena related to the reaction to this substance (Newlin and Renton, 2010). LR can be measured through direct observations of the response to alcohol at a given blood alcohol concentration or through a retrospective questionnaire; LR can be documented very early in a person's drinking career; it predicts later heavy drinking and alcohol problems but not SUDs; and is itself 40%–60% genetic (Chung and Martin, 2009; Quinn and Fromme, 2011; Schuckit and Smith, 2013; Schuckit et al., 2012b). Studies have described the association of this lower sensitivity to alcohol with a variation in an alcohol-metabolizing enzyme active in the brain, CYP2E1 (Webb et al., 2011), a gene that affects how potassium channels in cells respond to alcohol (*KCMNA1*), variations in the gene for the protein that affects how the brain transports the chemical serotonin back into cells (*SLC6A4*), as well as additional gene variations from the cholinergic receptor complex on chromosome 15 (Choquet et al., 2013; Joslyn et al., 2008; Schuckit et al., 2001, 2005; Wilhelmsen et al., 2003). The effects on heavier drinking for genes that contribute to the low LR operate partly through several environmental events (e.g., drinking in peers and reactions to stress), and the underlying mechanism may relate to a mild inefficiency in the amount of brain effort required to process some cognitive tasks (Paulus et al., 2012).

Specific genes related to psychiatric disorders associated with a high risk of both alcohol and other drug-related problems are best reviewed through further reading regarding genetic contributors to schizophrenia, bipolar disorder, and several additional psychiatric conditions. Details about these complex relationships are beyond the scope of this review. However, recent results have highlighted a range of genetic variations likely to be related to the risk for alcohol and other drug use disorders and some psychiatric conditions. These include variations affecting the dopamine 2 receptor (DRD2), the dopamine transporter (SLC6A3), additional serotonin-related genes, the enzyme Catechol-O-Methyl Transferase (COMT) responsible for the metabolism of several brain chemicals, and gene variations that affect the opioid receptors (e.g., OPRM1) (Bierut, 2011; Dick et al., 2007; Olfson and Bierut, 2012).

Genome-wide association studies related to AUDs and SUDs. Genetic association studies discussed thus far focus on one or a very limited number of gene variations. In contrast, genome- (i.e., related to the complete set of genetic material for an individual) wide association studies (GWASs) evaluate variations in genes across all chromosomes at once in an attempt to identify variations that are more (or less) common in people with a trait than in those without (Manolio, 2010). These studies begin without hypotheses regarding which genes are likely to prove to be important,

and the analyses use single nucleotide polymorphism (SNP) variations in single positions (base pairs) in the large DNA sequences of base pairs. In this approach, more than 100,000 (sometimes more than a million) SNPs are evaluated for large groups of individuals (often tens of thousands) composed of people with and without the characteristic being studied. A downside of simultaneously evaluating the relationship of so many SNPs with a characteristic (e.g., externalizing attributes, LR, or AUDs) is the level of statistical significance required for a finding to be considered as highly likely to be meaningful. Instead of the probability (p) that a single finding is meaningful of 5 in a 100 (i.e., $p < .05$), in a GWAS a meaningful finding must have less than 1 chance in 100 million of being wrong (i.e., 5×10^{-8}). Some studies will report findings of potential interest with probabilities of 10^{-5} to 10^{-7}, but those are considered as potentially spurious and not definitive.

Although a few GWAS results have been impressive (e.g., the discovery of a gene variation related to a degeneration of the eye, macular degeneration; Klein et al., 2005), few results in the substance-related disorders field have been as impressive. One prominent finding from a GWAS reported an association of alcohol intake levels with a variation in the autism susceptibility *candidate 2* (*AUTS2*) gene, with a p value of 10^{-8} (Schumann et al., 2011). Another large GWAS reported a finding on chromosome 2 in a region that other studies had suggested as potentially related to the LR to alcohol, some electrophysiological measures, and alcohol dependence ($p < 10^{-8}$), although the specific gene responsible for the finding has not been determined (Treutlein et al., 2009). Several other GWAS have highlighted a potential (i.e., ~10^{-6}) relationship to AUDs and SUDs for several gene variations originally cited in association studies, including several potassium channel genes, the μ opioid1 receptor (OPMR1), the dopamine 2 receptor (DRD2), an alcohol-metabolizing gene, and the cholinergic receptor cluster on chromosome 15 (Agrawal et al., 2011; Biernacka et al., 2013; Bierut, 2011; Olfson and Bierut, 2012). On the other hand, this non-hypothesis-driven and broad brush approach has also highlighted some potentially promising genes that have not been identified in prior linkage or association work and that have little, if any, logical relationship to alcohol and other drug use disorders.

A variation of the GWAS approach is to center the work on a limited set of brain pathways that might logically be related to the development of AUDs or SUDs. These approaches, referred to as Gene Set Analyses or Gene Set Enrichment Analyses, are more focused than the usual GWAS approach but still incorporate SNPs from a wide range of genes (Biernacka et al., 2013; Joslyn et al., 2010). Such analyses have highlighted the potential importance of genes related to the more excitatory brain receptors (*N*-methyl-D-aspartate [NMDA] receptors), as well as the potential impact of genes relating to ketone bodies that are involved with an adverse reaction to alcohol, and gene sets representing a wide range of brain receptor systems.

In summary, GWAS and related approaches that incorporate a large number of chromosomal elements (SNPs) hold promise for adding useful information regarding specific genes that might contribute to both alcohol- and other drug-related problems. However, to be identified by the GWAS approach, the impact of the gene must be relatively strong, the statistical level of significance required is demanding, and it is likely that some important gene variations seen in a relatively small number of families are overlooked.

Searching for rare gene variants potentially related to alcohol and other drug problems. Because GWAS approaches only identify relatively common gene variations with relatively small effects, some studies have included an approach with the opposite profile of assets and liabilities. The more rare genetic variations with more powerful effects are more difficult to find but could be worth the effort (Bodmer and Bonilla, 2008; Edenberg, 2011).

One approach to finding these rare variants is to focus on promising genes from prior association and linkage studies. The relevant gene is then evaluated in depth, looking for variations in the entire sequence of base pairs across the gene. In effect, the approach is based on a hypothesis that genes relevant to a specific trait or condition are likely to have many variations that occur relatively rarely in the population but that have a large impact within the family being studied. Although this procedure has great promise and detailed sequencing of genes is now being carried out in many laboratories, it is too early to highlight specific and reliable results related to the SUDs.

Searching for genes by observing similarities in characteristics across species. Many of the association studies and several of the more focused variations of GWAS chose the specific genes or neurotransmitter systems on which to focus by looking at results across species. This approach has been particularly useful regarding the low LR to alcohol, as multiple animal species (worms, rats, mice, and monkeys) are likely to have subgroups that differ dramatically on the intensity with which they respond to alcohol (e.g., Barr et al., 2003; Davies et al., 2003). One relevant study began with mouse and human data indicating that a variation in a glypican gene (*GPC5*) related to the low LR to alcohol (Joslyn et al., 2011). The investigators then found that the similar gene in Drosophila (fruit flies) had a similar relation to LR. *GPC5* affects how a cell modulates its electrical activity and variations in *GPC5* are implicated in the effects of alcohol (Joslyn et al., 2011). Another example of a similar cross-species approach identified a possible link of the *anaplastic lymphoma kinase* (*ALK*) gene to the sedating effects of alcohol across Drosophila, mice, and humans (Lasek et al., 2011). The cross-species approach for identifying genes potentially relevant to alcohol and other drug use disorders is still relatively new, but it holds promise.

Some additional approaches used in recent genetic studies. Other approaches being applied to enhance the understanding of genetic influences in the substance-related field include studies of copy number variants (CNVs). These represent duplications or deletions of runs of base pairs as part of an individual's genetic makeup (Lin et al., 2012). Although the clinical significance of CNVs has been debated in the alcohol and other drug field, studies are searching for particular CNVs that might be associated with alcohol dependence or related phenomena.

Another approach that is essential for optimal understanding of gene effects is referred to as functional genetic studies. These offer important insights into how gene variations affect the development of traits or disorders, including those related to alcohol and other drug use. Such investigations get down to the molecular level of determining how gene-based variations in the proteins made by genes, including enzymes and receptors, operate and, thus, offer great promise regarding potential future evaluations of new treatments and potential prevention approaches (Pochareddy and Edenberg, 2011).

A third important approach that is in its relative infancy regarding alcohol and other drugs includes a focus on factors that affect whether a gene is active or dormant. The phenomenon involved is known as epigenetics and occurs, at least in part, through a process of adding a chemical unit, a methyl group, to specific pairs of the DNA, which then affects gene expression (Bohacek et al., 2013). Such studies may give key insights into the functioning of the nervous system, memory formation, and how genes react to life events, including exposure to alcohol or other drugs (Franklin and Mansuy, 2010; Robinson and Nestler, 2011).

Optimal understanding of genetic influences requires evaluating environmental and attitudinal factors. At least 40% of the variance in developing substance-related problems rests with the environment and gene–environment relationships. Using the low LR to alcohol as an example, the genes can only contribute to alcohol-related problems if a person drinks, and about half the genetic effect is mediated through selecting heavy drinking peers, positive expectations of the effects of alcohol, life stresses, and using alcohol to deal with stress (Schuckit et al., 2011, 2012b). Knowing the mechanisms through which the predisposition operate can lead to programs to prevent the adverse alcohol outcomes associated with LR by addressing the environmental components related to that specific risk (Schuckit et al., 2012a).

Discussion

When the *Quarterly Journal of Studies on Alcohol* was first published in 1940, the field of modern studies of genetics was still relatively young and had not paid much attention to alcohol and other drug use and problems. Over the subsequent 75 years, our field has developed methods and concepts that Mendel had probably never dreamed about, and these advances have had a major impact on our understanding of the complexities involved in the ~60% of the risk for alcohol and other drug use disorders explained by genes. This review gives a bird's eye view of where the field of genetic influences in substance use disorders has been and our likely future directions. Research in this area has progressed through linkage and association genetic studies, participation in a range of GWAS, and current involvement in Gene Set Enrichment Analyses, sequencing genes to search for rare gene variants with potentially robust effects, studies of CNVs in the base pairs that are the building blocks of genes, evaluations of epigenetic phenomena that turn genes off and on, and a host of other recently developed methods. It is hoped that this brief review has helped alcohol and drug researchers who work outside the genetics field to gain a useful understanding of the current developments and exciting future work likely to accrue in our field.

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