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Since completion of the mapping of the human genome in early 2000, tremendous progress has been made in the identification of many different genes associated with our health and across diseases. Although social work researchers are not expected to conduct genetic research at the molecular level, it is imperative that we are able to understand the basic genetic findings related to behavioral problems and are able to translate and integrate this information into psychosocial treatment approaches and program development. This article is an introduction and overview of genetic approaches, using studies of the genetics of alcoholism to exemplify important issues. The literature review is not comprehensive and focuses primarily on the Collaborative Study on the Genetics of Alcoholism project as an example of a multidisciplinary and integrative approach to the genetic study of a major health problem often encountered in social work practice.

Keywords: Alcohol dependence, genetics, social work research

INTRODUCTION

Alcohol use disorder (AUD) is one of the most common psychiatric disorders in the United States and in Europe. A recent epidemiological survey of the U.S. general population found that the lifetime prevalence of alcohol abuse was 17.8% and alcohol dependence was 12.5% among adults (Hasin, Stinson, Ogburn, & Grant, 2007). Alcohol use disorder is associated with high psychiatric and physical comorbidity as well as social and family problems. Although the problems caused by AUD are well known, only 24% of persons with alcohol dependence ever seek treatment (Hasin et al., 2007). Efforts to identify etiological factors leading to chronic alcohol use and abuse have been ongoing for more than 200 years. The search for etiological factors has once again focused on familial (biological as well as environmental) contributions to the risk for developing alcohol dependence.

Clinical observations and empirical evidence suggest that mental disorders including alcohol and other substance use disorders are familial, indicating that a genetic influence plays some

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role in the development and course of these disorders. Basic science and clinical researchers have been attempting to identify a gene or genes that increase the vulnerability for developing alcohol dependence. Recent rapid advances in genetic research technology have been built upon the developments of the National Institutes of Health (NIH) Human Genome Project and related efforts (Li, 2004). These technological advances now permit the direct examination of the entire human genome and the identification of specific genes that are responsible for increased risk for certain conditions and disorders. As more genetic information becomes available, an increasing number of health care researchers and health services providers will be expected to become familiar with how genes influence in human behaviors. The understanding of the mechanisms of genetic influences on different disorders as well as how genes interact with environmental factors to increase or reduce risks for development of disorders will provide important and useful information for studies of the etiology, life course, and outcomes of disorders. Further, genes may be identified that may reduce risk as well as increase resiliency and also make substantial contributions to the health of the population. Currently there is an abundance of literature on genetic studies of a variety of physical and psychiatric disorders. However, this review focuses only on genetic studies of alcohol dependence.

Genetic Research and Social Work Practice?

It is important for social work investigators to become familiar with, and engage in, genetic research for all aspects of human behavior and mental and physical health. Social work has traditionally recognized the importance of biological, psychological, and social factors influencing physical and mental health. Social workers have traditionally understood the importance of assessing not only the person, but also his or her family and the family environment. Furthermore, social worker practitioners have traditionally placed significant importance on the individual person interacting with his or her environment. An understanding of genetics and translational research that lead to the implementation of individualized interventions are consistent with social work tradition and values that focus on the interaction of a person and his or her environment (Germain & Gitterman, 1996), and the importance social workers place on clients' rights to self-determination.

The existing genetic research literature is very broad and diverse, ranging from direct studies of individual genes at the molecular level to studies that focus on the clinical implications of genetic findings. To date, social work research has mainly focused on the translational aspects of genetic findings in their practice, with a focus on implications of the findings for the health of individuals and families, the role of environmental factors for gene expression and/or policy concerns (Werner-Lin, Rubin, Doyle, & Hurley, 2012). *Social Work in Public Health* recently published a special issue (2011) on the Human Genome: Health Care Policy Issues in the Black Community. This issue discussed many important and timely issues concerning the Human Genome Project, ranging from a historical perspective of "genetics" to implications of recent genetic findings for social work practice and education, as an aspect cultural competence for practice as well as the policy implications for working with African Americans. However, to date, social work research has not been involved in studies that are directly working with genes themselves at molecular level, as social workers are typically not trained in biology including genetics. Social work investigators' lack of involvement in genetic studies is understandable as genetic studies are complex and broad and typically beyond the scope of one discipline. For this reason, one practical approach to the study of genetics for social work investigators is to participate as part of an interdisciplinary research team. Currently many of human genetic studies are interdisciplinary in nature, bringing together the necessary tools and knowledge from several disciplines and areas of expertise including basic and social behavioral science. Social work investigators' participation in interdisciplinary genetic research is fairly new. However, there are many advantages of social work investigators being part of an interdisciplinary team as each discipline brings its own perspective, culminating in a

comprehensive approach to research, including development of phenotype measures, assisting in the translation of the findings into clinical practice and, hopefully, implementation of evidence-based interventions. Additional advantages include the sharing of research resources for conducting studies and providing broad-based training for investigators and students. Social work investigators can become involved in genetic research by posing research questions that have a genetic focus and by broadening the conceptual frame work of their study to include genetic factors as a biological component.

Genetics and Behavioral Traits

Genetically influenced traits in humans are generally of two types: simple and complex. Although a single gene controls variations in simple genetic traits, complex genetic traits are influenced by more than one gene, by the interaction of several genes, or by interaction of genetic and environmental factors. Huntington's disease, Duchenne muscular dystrophy, and cystic fibrosis are examples of diseases that result when the function of the gene is altered or destroyed. The prevalence of disorders caused by single gene is quite rare and often observed in less than one in 5,000 individuals (M. Hesselbrock, Hesselbrock, & Chartier, 2012).

Medical and behavioral disorders identified as complex genetic traits are quite common. These disorders are influenced by multiple genes, often interacting with each other or with the environment, resulting in an increased vulnerability for the development of these disorders. Many health conditions such as many cardiovascular and neurological diseases and diabetes among others are examples of complex disorders. Psychiatric disorders are heterogeneous in their etiology and clinical presentation, do not have a clear pattern of inheritance, and affect the client's families in a variety of ways. Alcohol and other drug dependence are good examples of complex genetic trait disorders. Persons with alcohol dependence present with a variety of symptoms and describe many pathways leading to the development of alcoholism, suggesting that this is a complex gene trait, with several genes acting in concert or interacting with the environment that contribute to the individual's susceptibility. Although genes and their action can be studied at several levels and in many medical and psychiatric conditions, this review focuses only on alcohol dependence.

The science of genetics can be approached behaviorally and at the molecular genetic levels. At the behavioral level, the disorder is typically defined by considering the clinically observable features of a disorder; such features are called phenotypes and are theoretically linked to genetic influences. Once a disorder is clinically defined or identified, it is then necessary to establish the genetic basis of the disorder, often by examining the family pedigrees of individuals with the disorder. Once genetic influences are considered to be an important component of familial transmission, studies then focus on how the disorder is transmitted from one generation to the next, considering possible genetic and environmental factors . Several of these approaches are described below. The next step is to identify and map the location of the relevant genes using linkage studies and/or association studies (Nurnberger & Bierut, 2007).

Sources of Evidence for a Genetic Influence

Evidence for genetic influences on the development of alcoholism is derived from a variety of sources, including animal models, the study of multigenerational families, persons who were adopted away from biological parents at birth, half siblings, and twins. At the behavior genetic level, no single source of information can confirm a genetic association or diathesis for a disorder. However, the confluence of findings from studies of extended family pedigrees, of adopted persons reared apart from their biological parents, and studies of monozygotic and dizygotic twin pairs argue persuasively for a genetic contribution to the vulnerability for developing alcohol dependence.

Family Pedigree Studies—Transmission across Generations

Family pedigree studies begin with the indexed case (known as a proband) with an AUD and the assessment of all available close biological relatives; then, the prevalence of AUD in the proband and his or her relatives is compared to that of the general population. First-degree relatives (parents, siblings, offspring) are those with the closest genetic ties to the proband. The extant literature has clearly shown that the increase in risk for developing alcoholism may be four- to sevenfold among the first-degree relatives of persons with an alcohol dependence compared to the general population—regardless of the nationality of the study sample (Bierut et al., 1998; Cotton, 1979; M. Hesselbrock & Hesselbrock, 1992; V. Hesselbrock, Stabenau, & Hall, 1985; Merikangas, 1990; Midanik, 1983; Vanyukov & Tarter, 2000). Further, a positive family history effect extends to other comorbid psychiatric disorders (Merikangas, 1990; Merikangas, Leckman, Prusoff, Pauls, & Weissman, 1985), other substance abuse (Kosten, Rounsaville, Kosten, & Merikangas, 1991), and antisocial personality disorder (Reich, Cloninger, Lewis, & Rice, 1981) associated with alcohol dependence. Walters (2002) conducted a meta-analysis of 22 family studies of alcohol dependence published from 1951 to 1999. Twenty-one of these studies reported an association of alcohol dependence in the proband with a family history of alcohol dependence, even though the size of the effect varied from study to study. Gender and severity of the proband's alcohol dependence were moderating factors of the heritability (Walters, 2002). It was also noted that the heritability increased when a more severe definition of alcohol dependence was used.

Although family pedigree studies are powerful tools to establish the familial nature of alcohol dependence, they cannot separate the genetic from environmental sources of susceptibility. A major methodological limitation of family studies is a concern about the selection of families. To study the generational and familial transmission of disorders, the proband selected for study needs to have one or more siblings with the disorder. Another concern is that selection of the proband is often limited to convenience samples such as through treatment facilities and the advertisements in public media. Even when a family agrees to participate, typically not all family members are available to participate due to living away from the research facility or refusing to participate in the study. Also, it is difficult to determine the level and timing of possible environmental influence contributing to the increased familial risk. Consequently, environmental effects and sample selection factors may contribute to the bias in estimating genetic contributions to the development of alcoholism. To remove the effects of environmental influence, investigators have turned to adoption studies.

Adoption Studies—Separating Genetic and Environmental Influences

Adoption studies are natural experiments that allow for the separation of genetic and environmental factors that contribute to the risk for developing alcohol dependence, thus providing more accurate estimates of genetic effects. Adopted children and their adoptive parents share the same environment but no genes, whereas adopted children and their biological parents share genetic factors but no environmental factors. It is hypothesized that a genetically based trait should be expressed in an offspring regardless of environmental status. In adoption studies, the concordance rates of alcohol dependence between offspring and their biological parents and those of the adoptive parents are compared. If the rates of the offspring and their biological parents are similar, it is suggestive of a genetic influence whereas similarity of rates with their adoptive parents suggests an environmental influence (Agrawal & Lynskey, 2008). An example of an informative adoption study of alcoholism and other psychiatric disorders was derived from the Danish Birth Cohort Study using the adoption registry in Copenhagen, Denmark, by Goodwin et al. (1973). Participants for the study included adoptees placed with nonbiological relatives prior to 6 weeks of age and raised by adoptive parents who were not biologically related. They were between age 22 to 45 at

follow-up, well into the age of risk for developing most psychiatric conditions, including alcohol dependence. Strong associations were found between adoptees and biological parents' alcohol dependence while being reared by an adoptive father with alcohol dependence was not associated with the adoptees' risk for developing alcoholism. Subsequent studies have consistently found higher rates of alcohol dependence among adopted adult offspring of parents who were alcohol dependent as compared to the offspring whose biological parents were not alcohol dependent (Bohman, Cloninger, Sigvardsson, & von Knorring, 1987; Cadoret & Gath, 1978; Cloninger, Bohman, & Sigvardsson, 1981; Cotton, 1979; McGue, Sharma, & Benson, 1996). Most adoption studies have been conducted in Scandinavia including Denmark, Sweden, and Finland. It is difficult to conduct adoption studies in the United States, as no state or national adoption registries exist and adoption records are typically sealed in most states. The longitudinal study of adopted children in Iowa is the only one conducted in the United States (Cadoret, O'Gorman, Troughton, et al., 1985). The findings of the Iowa adoption study are also consistent with those adoption studies conducted in Europe (Cadoret, Troughton, Gorman, & Heywood, 1986). Strict legal limitations make studying adoption very difficult in the United States whereas studies in Europe also have several methodological limitations. Almost all adoption studies use recorded information, such as temperance board registrations, hospital admissions, and so on. Although the records are well kept, the assessment of alcohol dependence recorded in the record may not have been completed by a trained mental health professional and the criteria used for diagnosis may not be comparable to those used in the United States. Another limitation of existing adoption studies is the absence of information about maternal alcohol dependence and/or the small number of female adoptee participants (Cloninger, Bohman, Sigvardsson, & von Knorring, 1987). However, though information on biological mothers can provide important family history data, such information cannot be obtained, by law, from most existing adoption studies as records remain sealed in many states, except in the case of a medical emergency. Cadoret, Yates, Troughton, Woodworth, and Stewart (1996), in a sample of 102 adopted women, reported a similar pathway of genetic transmission as men that began with biological parents who were antisocial influencing the rates of conduct disorder in women, a prime risk factor that often leads to the abuse of drugs and alcohol. Although the number of adoption studies is rare in the United States, investigators have attempted to separate genetic and environmental effects through twin studies.

Twin Studies—Genes Versus Shared Environmental Effects

Studies of twins are also able to separate genetic influences from shared environmental factors. Twin studies compare the rates of similarity of a trait (e.g., a diagnosis or a particular behavior) between identical or monozygotic twins and fraternal or dizygotic twins. Monozygotic twins are genetically identical at every locus and share 100% of their genes, whereas dizygotic twins are genetically similar to any other set of siblings, sharing about 50% of their genetic complement. Twins studies assume that the twins (whether identical or fraternal) are reared in a shared environment; therefore, comparing the degree of concordance of alcohol dependence between the two types of twins provides an estimate of genetic influence. If the level of concordance of alcohol dependence is similar between monozygotic twins and dizygotic twins, a genetic basis cannot be assumed. However, if the degree of concordance is directly related to twin type, with monozygotic twins having greater concordance levels than dizygotic twins, there is a strong probability that a significant portion of the phenotypic variance is genetically influenced.

Monozygotic twins generally show a higher concordance rate of alcoholism compared to dizygotic twins whose concordance rate is similar to the rates of other nontwin siblings (Kendler, Heath, Neale, Kessler, & Eaves, 1992; Pickens, Svikis, McGue, & LaBuda, 1995).

The level of genetic influence estimated by twin studies is expressed in terms of "heritability"—a statistical term indicating the proportion of the total phenotypic variance that can be attributed

to genetic factors (Agrawal & Lynskey, 2008). More recent twin studies have confirmed the importance of the genetic contribution to the development of alcoholism, with the heritability ranging from 50% to 70% (Agrawal & Lynskey, 2008; Heath et al., 1997; Heath, Bucholz, Madden, et al., 1997; R. J. Rose & Kaprio, 2008). There is a consistency of findings of the genetic and environmental contributions to alcohol dependence risk in national twin samples well as in a population-based sample of male twins; similar findings exist with respect to female twins (Kendler & Prescott, 1999; Prescott & Kendler, 1999).

Some cautions are suggested by these authors who extensively reviewed the twin study literature. The twin study methodology assumes that level of shared environment among monozygotic twins is similar to that of dizygotic twins. If not, heritability estimates can be either over- or underestimated. Another assumption is that there is random mating in the general population. If, however, the biological parents of twins under study selected each other based on certain traits (i.e., assortative mating) that carry a genetic predisposition for the same or a related trait (e.g., heavy drinking), concordance rates may be inflated because the genetic predisposition is present in both biological parents. Further, because the twin study design assumes a shared genetic environment, gene-environment interplay is not considered. In reality, however, a person is constantly interacting with his or her environment. Ignoring this aspect of daily life would bias heritability estimates.

Family pedigree studies, adoption studies, and twin studies provide important information of the genetic influences for risk for developing alcohol dependence. However, these types of studies provide estimates of genetic effects only.

Moving from Behavior to Genes

To identify specific genes, the investigations must be done at the molecular genetic level. Because completion of the mapping of the human genome in 2000, tremendous advances in molecular genetics have been made. However, identifying the complement of genes that influence the development of alcohol dependence is quite complex. All genetic studies begin with identifying a particular trait (phenotype) for study. Phenotypes are observable characteristics of the individual and are thought to reflect the action(s) of a gene(s). As mentioned earlier, alcohol dependence is clinically heterogeneous, and there are many pathways leading to the development of the disorder. Thus, the clinical manifestations of the disorder, such as tolerance or withdrawal, may represent different phenotypes of alcohol dependence. The specification of a clearly defined phenotype is vital to identify more homogeneous groups of participants (Dick, Meyers, Rose, Kaprio, & Kendler, 2011). The diagnosis of alcohol dependence is also a commonly used phenotype as are other aspects of the disorder, including the participant's alcohol use history, course of the disorder, co-occurring psychiatric disorders, and so on are considered.

A usual research design to determine genetic effects is to study genetically similar groups such as families in which multiple biologically related members display the trait of interest, such as alcohol dependence. For example, a person seeking treatment for alcohol dependence who meets diagnostic criteria for alcohol dependence and whose family members are willing to participate in the study will be recruited. Once the person meets inclusion criteria to participate in a study, phenotypic measures (severity, associated conditions, etc.) are assessed and DNA samples are obtained from all available family members willing to participate in the study. A chromosomal survey is then used to identify potentially significant stretches or regions of DNA based upon selected chromosomal features known as microsatellite markers that appear more frequently in the affected versus unaffected relatives. The next step is the investigation of a genetic association in which role of the specific gene is investigated by closely mapping the DNA region near the marker and the identification of relevant single nucleotide polymorphisms (SNPs) within the gene of interest (Nurnberger & Bierut, 2007).

Gene and Environment Controversy

Although there have been tremendous advances in genetic research at the behavioral and molecular levels, complex disorders such as alcoholism face the controversy whether genes or environmental factors are the primary vulnerability factors. The issue stems from several factors that derive from empirical observations and studies. It is well known that alcohol dependence is a clinically heterogeneous disorder with alcohol dependence symptoms and related conditions manifested differentially. Further, there are many pathways leading to the development of alcohol dependence. Genetic explanations of findings across studies are inconsistent, and the heritability of alcohol dependence can vary depending on the locale of the studies, sample size, and selection and characteristics of the samples studied. One source of controversy is the lack of agreement regarding the clinical description of alcohol dependence. For example, *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*; American Psychiatric Association, 1994) and International Classification of Diseases (ICD-10; World Health Organization, 2008) capture different groups of persons who are diagnosed as alcohol dependent. This differential identification of "affected" individuals across different diagnostic systems results in variations in the participants' genotypes reducing the explanatory power of genetic factors that may influence the transmission of alcohol dependence.

A second, related point that may cloud the gene-environment issue is the presence of an additional comorbid psychiatric disorder in the proband, in addition to alcohol abuse/dependence. Other psychiatric disorders such as major depressive disorder and antisocial personality disorder are also strongly familial in nature and also have genetic factors contributing to their heritability. Further, there may also be genes that are common across disorders as well as genes that are specific to only one disorder (Kendler, Schmitt, Aggen, & Prescott, 2008). Studies of samples of individuals with alcohol dependence drawn from clinical settings (cf. M. N. Hesselbrock, Hesselbrock, Segal, Schuckit, & Bucholz, 2003; M. N. Hesselbrock, Meyer, & Keener, 1985) and from the community (cf. Dawson, Grant, Stinson, & Chou, 2004; Hasin et al., 2007; Helzer & Pryzbeck, 1988; Li, Hewitt, & Grant, 2004; Regier et al., 1990) have found that a variety of other psychiatric disorders often coexist with alcoholism. Further, the presence of an additional psychiatric condition, such as depression, may complicate the specification of the alcoholic phenotype because symptoms of these disorders often mimic those associated with alcoholism. Failure to distinguish symptoms arising from chronic and heavy alcohol use from those due to a separate psychiatric disorder can lead to diagnostic confusion (Schuckit, 1973) and misspecification of the trait/diagnosis/phenotype. Thus, the inclusion of "false positives" in genetical analyses can lead to an artificial attenuation of the size of genetic effects found.

Major depressive disorder and antisocial personality are frequently found in families with alcoholism, yet both appear to have different etiologies and to be genetically distinct (cf. Cadoret, O'Gorman, Troughton, & Heywood, 1985; Merikangas et al., 1985). Although certain comorbid conditions such as depression or antisocial personality disorder are neither necessary nor sufficient causes of alcoholism, their presence may increase a person's vulnerability for developing alcohol problems.

The ages of the proband and the proband's biological family members at the time of ascertainment may also influence estimates of genetic contributions. The age at which a person is likely to become affected (i.e., the age of "risk") varies across psychiatric disorders. Therefore the age of family members at the time of recruitment will determine the proportion of family members who are either not yet at risk, who are presently in the period of risk, or who have passed through the period of risk at the time of assessment and may attenuate or inflate the estimate of genetic influence. Failure to find genetic effects may arise, for example, when the sample contains a number of youthful probands, showing little or no familial aggregation of alcoholism at the initial assessment due to their age, but the family may show substantial familial aggregation when

followed years later after the majority of the biologically related individuals have passed through the period of risk. In addition, some evidence suggests that the unique environmental influence and the contribution of genes changes over time as people age. van Beek et al. (2012) examined the change in influence of genetic and environmental factors associated with AUD from adolescence into early adulthood and found that the unique environmental influence decreased while genetic influence increased as the subjects moved into adulthood. The findings are also replicated in the study of Danish twins by Rose (2010).

A related complication is that some psychiatric disorders show secular trends in their age of onset and lifetime prevalence rates, both can influence estimates of genetic effects. For example, Reich et al. (1998) and Rice et al. (2003) have found that more recently born cohorts, compared to older cohorts, have higher than expected lifetime prevalence rates of alcoholism and decreased ages of onset. Age corrections can be applied to the rates of alcohol dependence among biological relatives-for example using the Stromgren method (Slater & Cowie, 1971), which involves weighing the number of persons at risk by the proportion of the risk period through which they have passed. Such a correction is often necessary to make accurate comparisons of possible genetic effects of samples spanning several generations or from different populations.

Another source of controversy is sample selections and sources of information. Many published studies of the heritability of alcoholism have used hospital, health service, or registry records to obtain information on the psychiatric status of the proband and/or the family members. Records seldom contain the information necessary to meet formalized diagnostic criteria (e.g., *DSM-IV*, ICD-10), requiring a compromise in the criteria used for the identification of a "case." The use of a reduced diagnostic criteria set often results in reduced sensitivity (i.e., the number of "true" positives) and specificity (i.e., the number of "true" negatives). The inability to accurately identify a "true" case can dramatically reduce the ability of many statistical analytic methods used for prediction of a particular outcome (e.g., survival analyses, regression analyses, structural equation modeling, trajectory, or growth modeling).

Also, an important source of bias in genetic studies can occur due to population stratification. Population stratification is the presence of a systematic difference in allele frequencies between subpopulations of a population possibly due to different ancestry, especially in the context of genetic association studies. It is well known that the frequencies of certain genes do vary by ethnicity (e.g., *ALDH2*2* an alcohol-metabolizing gene found only in subpopulations of Asians (Higuchi et al., 2004) or taste receptor gene *TAS28R* that is more common in African Americans versus persons of northern European ancestry (Hinrichs et al., 2006). *ALDH2** and *TAS28R* have been found to "'protect"' against heavy drinking and alcoholism. In the case of *ALDH2*2*, persons of Asian origin, particularly Japanese and Koreans, with the *ALDH2*2* allele experience a strong "flushing" response that can include facial flushing, tachycardia, headache, sleepiness, and nausea following consumption of a small amount of beverage alcohol, leading to abstinence (cf. Higuchi et al., 2004). Hinrichs et al. (2006) found that some persons of African American ancestry with the minor *TAS28R* allele find the taste of alcohol to be quite bitter, leading to abstinence or very low levels of alcohol consumption. These findings highlight a deficiency in gene-finding studies that do not consider the ethnic background of the proband, and control samples are likely to produce false results.

The Collaborative Study on the Genetics of Alcoholism

As indicated above, the evidence for the genetic basis of alcohol dependence was historically based upon indirect estimates of genetic effects because the methods for identifying specific genes were too expensive or were lacking. However, over the past 10 to 15 years, important technological advances now permit direct examination of the entire human genome and the identification of specific genes responsible for increased vulnerability to alcohol dependence and other conditions.

The best illustration of a family pedigree study that begins with a comprehensive phenotypic assessment of alcohol use behavior including alcohol dependence and searches for genes that are associated with the increased risk for development of alcohol dependence is the Collaborative Study on the Genetics of Alcoholism (COGA), a large-scale, multisite, extended family study that began in 1989. The general aims of the COGA project are to characterize the familial distribution of alcohol abuse and alcohol dependence and related phenotypes, and to identify the genetic linkage and association between the DNA probes and alcohol abuse/dependence and related phenotypes (Begleiter et al., 1999). Approximately 1,800 male and female index cases (probands) have been identified through inpatient and outpatient treatment services for alcohol dependence. At six different sites across the United States, patients and their first-, second-, and third-degree biological relatives were invited to participate in this study; those participating in COGA have completed a structured psychiatric interview (Semi-Structured Assessment of Genetics of Alcoholism [SSAGA]) (Bucholz et al., 1994; M. Hesselbrock, Easton, Bucholz, Schuckit, & Hesselbrock, 1999) several personality tests, a neurophysiological battery, electrophysiological procedure, and provided a blood sample for DNA analysis. To date, more than 1,900 families and over 16,000 family members between age 7 and 103 have been assessed whereas a large number of participants have participated in two follow-up interviews. Using qualitative (i.e., categorical) and quantitative (i.e., numerical) phenotypes, multidisciplinary approaches were used for the search of identifying genetic bases for alcohol dependence. Qualitative clinical phenotypes examined to date have been based on *DSM-III-R* and *DSM-IV* psychiatric diagnoses or on clinically relevant alcohol-related symptoms. Quantitative phenotypes have been derived from symptom counts as well as through multivariate analyses (factor analysis, cluster analysis, latent class analysis) of symptoms. The COGA study has been successful characterizing the genetic vulnerability of persons with and persons without the disorder in the sample using the wealth of phenotypic data, including psychiatric diagnoses, derived from the extensive SSAGA interview and other data that were collected.

Alcohol-Related Phenotypes and the Search for Genes

Several alcohol use behavior patterns and alcohol-related conditions have been examined as phenotypes with promising results. Initial DNA analysis has indicated that genes contributing to the susceptibility for alcohol dependence may be located on several different chromosomes, including chromosomes 1, 2, 4, and 7 (Foroud et al., 2000; Reich et al., 1998). Importantly, two specific neurotransmitter genes, *GABRA2* (Edenberg et al., 2004) and *CHRM2* (Jones et al., 2004; Wang et al., 2004), have been shown to be linked to the vulnerability for alcohol dependence. *GABRA2* is a gene in the gamma aminobutyric acid (GABA) neurotransmitter system, and recent studies have suggested that genetic variants of the GABA-A receptor alpha2 subunit gene (GABRA2) are associated with alcohol dependence, possibly due to increased sensitivity to ethanol. The CHRM2 gene is involved in neuronal excitability, synaptic plasticity, and feedback regulation of acetylcholine release in relation to neuronal activity. It has been associated with higher cognitive processing such as learning, reward and short-term memory. As with the *GABRA2* gene, the association between *CHRM2* and alcohol dependence in the COGA sample was strongest in people who had comorbid alcohol and other drug dependence (Dick et al., 2007). Additional analyses in the COGA sample have suggested that *CHRM2* is also associated with a generally increased risk of externalizing disorders, an additional risk factor for developing drinking problems.

The *GABRA2* finding has now been independently replicated in three separate clinical samples, including two from Europe. Genes responsible for aspects of the electroencephalographic (EEG) wave form, slow beta EEG (Porjesz et al., 2002), P300 amplitude (V. Hesselbrock, Begleiter, Porjesz, O'Connor, & Bauer, 2001), as well as a reduced subjective response to the intoxicating effects of ethanol (Schuckit et al., 2000) also contribute to the susceptibility for alcohol

dependence. Interestingly, there are few other genes that may specifically predispose to alcohol dependence (Kendler, Prescott, Myers, & Neale, 2003). However, these susceptibility genes also likely contribute to other conditions that occur with alcohol dependence such as suicide (Dick et al., 2010; V. Hesselbrock et al., 2004), childhood conduct disorder (Dick et al., 2010), depression (Nurnberger et al., 2004), and tobacco dependence (Bierut et al., 2004). The analysis of additional alcohol dependence phenotypes continues, and several other alcohol-related phenotypes were found to have genetic relevance.

One aspect of drinking behavior, maximum number of standard drinks ever consumed in a 24-hour period (max drinks), has been associated with the risk for the development of alcoholism (Saccone et al., 2000). Similarly, a low level of response (LR) to the intoxicating effects of alcohol has been found to be present among some "at-risk" drinkers long before heavy drinking and alcohol-related problems develop (Schuckit et al., 2009; Schuckit et al., 2000). A low level of response has been thought to be genetically transmitted with heritabilities ranging from 40% to 60% (Schuckit et al., 2001). Traditionally LR has been measured through observations of changes in the subjective feelings of intoxication, standing steadiness or body sway (i.e., static ataxia), as well as electrophysiological changes (EEG and event related potential [ERP]) associated with drinking. A subsample of 100 COGA young adults age 18 to 25 without alcohol dependence participated in an alcohol challenge study. The results indicate that LR is not highly correlated with electrophysiological measures of disinhibition (Schuckit et al., 2000) and, thus, may represent a different, non-neurophysiological mechanism of risk for developing an AUD. An evaluation of the Self Report of Ethanol's Effects (SRE) (Schuckit et al., 2001) a questionnaire measure of LR ($N = 745$) found correlations of SRE scores among first-degree relatives of approximately $r = .20$ compared to $r = .03$ for unrelated individuals. These findings support the potential genetic influences for the SRE performance overall. The results of the study appear to indicate that LR is an important genetically influenced intermediate phenotype related to the risk of developing alcohol dependence and may operate independently of other genetically influenced risk factors such as externalizing behaviors, alcohol-metabolizing enzymes, and other psychiatric disorders.

Linkage analyses have identified four chromosomal regions with logarithm of the odds (LOD) scores ≥ 2, including a finding on chromosome 10 in a region replicated by several other studies (Schuckit, Smith, & Kalmijn, 2004; Wilhelmsen et al., 2003). An LOD score is a statistical test of linkage/association between two genetic loci. By convention, a LOD score greater than 3.0 is considered evidence for a genetic relationship and represents an odds of 1000:1 in favor of linkage.

Two candidate genes currently being investigated from this region with potentially promising results are *KCNMA1* and *CYP2E1*. *KCNMA1*, a potassium channel gene involved in neural activity, has been shown to be related to the initial sensitivity to alcohol (i.e., first exposure) in mice (Wolen et al., 2012) and has been associated with alcohol dependence in humans (COGA). CYP2E1 is an important enzyme in the metabolism of ethanol, along with the two alcohol-metabolizing enzymes ADH1 and ALDH2. Furthermore, preliminary genetic analyses carried out in a family study similar to COGA support the *KCNMA1* finding and the potential importance of the one allele of the serotonin transporter and the possible impact of variants of the GABA gene cluster on chromosome 5. Serotonin is another neurotransmitter that is associated with the regulation of mood, often a factor in determining how much and how often a person may drink.

Drinking Behaviors as Phenotypes

Analyses of the COGA data have demonstrated the importance of examining drinking behaviors as phenotypes. Max drinks has long been established as a risk factor for alcohol dependence (Saccone et al., 2000), two-stage linkage analysis identified several chromosome regions of interest and a subsequent examination of the data showed linkage on chromosomes 2 and 7 (LOD $\geq$ 1.80).

Further, association analyses found multiple traits associated with SNPs in the chromosome 7 linkage region that also contains several bitter taste receptor genes (which may influence preference for beverage type) as well as *CHRM2* (described above).

Other phenotypes related to drinking and drinking problems have shown an association with different genes. Alcohol dependence and age of onset of alcohol dependence have been linked with several SNPs in *NFKB1* (Edenberg et al., 2008), a ubiquitous gene associated with a variety of biological functions. Further Dick, Plunkett et al. (2006) found age of onset of regular drinking and intoxication in association with four GABA receptor genes on chromosome 5.

Craving for alcohol, though not a diagnostic criterion for alcohol dependence in *DSM-IV* (American Psychiatric Association, 1994), (but proposed for *DSM-V*) is an important and relatively common aspect of alcohol dependence. Craving for alcohol was found to be quite common in persons with alcohol dependence in the COGA sample, with 42% of *DSM-IV* individuals with alcohol dependence also reporting alcohol craving, with the rate of craving similar in men and women (43% vs. 38%, respectively). However, only 2% of individuals who did not meet criteria for *DSM-IV* alcohol dependence reported alcohol craving. Animal studies have reported that variations in alcohol consumption are associated with the a-synuclein gene, *SNCA*. *SNCA* is thought to help regulate dopamine, a neurotransmitter involved in the starting and stopping of voluntary and involuntary movements. Foroud et al. (2007) examined "craving" as a phenotype and found no evidence of an association between any of the SNCA SNPs and alcohol dependence ($p \geq 0.13$) in the COGA sample. However, eight SNPs provided evidence of association ($p < 0.05$) with the phenotype of alcohol craving. A haplotype encompassing SNPs in intron 4 through the region downstream of the gene was overtransmitted to cravers and a second haplotype was overtransmitted to noncravers. These results suggest that variation in *SNCA* contributes specifically to alcohol craving, a common, although not uniform, feature of alcohol dependence.

There is considerable variation in the taste sensitivities people have to different types of food and beverages that may affect their preference for, and consumption of, these foods and beverages. An individual's taste sensitivity to ethanol has been found to influence not only the initiation of drinking alcoholic beverages, but also the continued drinking of alcohol containing beverages. Studies have shown genetic variations in sensitivity are linked to bitter tasting compounds. A mutation in the taste receptor gene *TAS2R16* has been found to reduce sensitivity of the receptor to bitter taste stimuli that is associated with the risk of alcohol dependence (Hinrichs et al., 2006). Family-based association methods were used to examine the phenotypes of alcohol dependence, max drinks and age of onset of regular drinking in relation to the *TAS2R38* gene, another taste receptor gene. A positive association between this gene and max drinks was found only among African American–origin high-risk families. A negative correlation between *TAS2R16* and max drinks was found suggesting that *TAS2R16* may offer protection against alcohol dependence for individuals from African American families (Wang et al., 2007). The findings provide another indication for the importance of examining ethnic differences in genetic studies of susceptibility for alcohol dependence as this gene is uncommon in Whites though more common among African Americans (almost one half).

In addition to alcohol-related phenotypes, analyses of COGA data have identified genes that are related to several alcohol-related comorbidities. A number of epidemiological and clinical studies have reported a high rate of comorbidity associated with alcohol dependence. For example, childhood problem behaviors indicative of conduct disorder have been associated with an increased risk for developing of alcohol and other drug dependence. Further these conduct problems often continue well into adolescence as behaviors characteristic of antisocial personality disorder (ASPD). Twin studies have found shared genetic factors between conduct disorder, ASPD, and alcohol dependence (Jacobson, Prescott, & Kendler, 2000). An examination of COGA families has demonstrated an increased prevalence of ASPD and other drug dependence in the relatives of participants who were alcohol dependent (Nurnberger et al., 2004). *GABRA2* was initially

associated with *DSM-IV* alcohol dependence among COGA adults (Edenberg et al., 2004) and has been replicated by other studies (Covault, Gelernter, Hesselbrock, Nellissery, & Kranzler, 2004; Soyka et al., 2008). An association of *GABRA2* with other drug dependence and ASPD has been found in the COGA sample (Agrawal et al., 2006; Dick, Bierut et al., 2006). The relationship between *GABRA2* and childhood conduct disorder was examined in a sample of 7- to 17-year-old children and adolescents in COGA. More adolescents in the high-risk *GABRA2* genotype group had three or more childhood conduct disorder symptoms compared to the low-risk group (17.5% vs. 10%). However, no association was reported between *GABRA2* and alcohol use problems in this sample, suggesting that *GABRA2* may be acting directly through behavior problems to increase vulnerability for developing alcohol use problems.

Another gene associated with alcohol dependence in the COGA sample, *CHRM2* has also been associated with externalizing disorder/conduct problems (Dick et al., 2007). An externalizing disorder such as ASPD appears to increase the heritability within families of an increased prevalence of combined behaviors (alcohol and drug dependence, ASPD behaviors, etc.). In twin studies, these increased heritabilities range from 80% to 85% (Hicks, Krueger, Iacono, McGue, & Patrick, 2004; Krueger et al., 2002); further, a multivariate analysis of a composite score of several externalizing variables and *CHRM2* produced a stronger association than any single symptom of the disorder.

Adolescents who smoke tobacco have been found to have an increased risk of early alcohol use and subsequent development of an AUD compared with nonsmoking teenagers. COGA has identified several chromosomal regions likely to contain genes that specifically contribute to alcohol dependence and habitual smoking vulnerability. These include region within *GABRA2, CHRM2,* and *CHRMA5* (both nicotinic receptors), all important neurotransmitters (Bierut et al., 2004).

Major depressive disorder is common psychiatric disorder frequently associated with alcohol dependence among men and women. Consistent with existing literature, the prevalence of lifetime depressive disorder is much higher among participants who are alcohol dependent compared to participants who are not alcohol dependent in COGA.

SUMMARY

Significant progress is being made in determining and understanding the genetic bases of the susceptibility for alcohol dependence and its related conditions. The familial nature of alcoholism is well documented, and a variety of studies confirm the importance of the roles of genetic and environmental factors in the transmission of heavy drinking behaviors and the pathological use of alcohol within families. Taken together, information from pedigree, twin, and adoption studies strongly support the role of genes in the liability for the development of alcoholism. However, no single study can clearly demonstrate the importance of genetic factors for alcoholism susceptibility for either males or females. Although this is somewhat discouraging, a variety of methodological issues related to identifying a clear phenotype and problems related to the sampling of the proband limit the importance of many studies which fail to demonstrate clear genetic effects. Although the evidence grows that the susceptibility for developing severe forms of alcoholism (such as *DSM-IV*-defined alcohol dependence) has a strong genetic component, it is also clear that other personal factors (such as personality traits) and environmental factors play important roles in the development of different aspects of drinking behavior, including heavy drinking. Further, environmental factors, including comorbid psychopathology and the level of exposure to alcohol, may be responsible for the gender differences in the population prevalence rates of alcoholism. Thus, the interplay of genetic and environmental factors plays an important role in the etiology and transmission of alcohol-related problems. Importantly, several recent

studies have identified specific genes that contribute to alcohol dependence, related psychiatric conditions, and to factors associated with increased consumption of alcohol. Work is now underway to better understand how these susceptibility genes are influenced by the individual's environment and the biological function of the genes. Both will be necessary to effectively use genetic information for the prevention and for the treatment of alcohol dependence and alcohol-related problems.

To answer our original question—The genetics of alcohol dependence and social work research: do they mix? Clearly the answer is *yes*. Addiction problems are common among social work practice clients so it is important for social work investigators to learn as much as possible that can directly and indirectly improve their practice. Although it is unlikely that social work investigators will develop or lead gene-finding studies, social work investigators can play important roles in collaboration with geneticists to examine the role of gene-environment interplay to better understand the developmental course and trajectory of alcohol-related problems and other associated conditions. It is likely that it will be at this interface of genetic and environmental interaction that new treatment approached and new intervention methods will develop.

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