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Genome-wide association studies of alcohol intake—a promising cocktail?[1–3]

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Excessive alcohol consumption is the third leading contributor to preventable death worldwide, contributing to 2.5 million deaths per year (1–3). Casual drinking is an aspect of the typical diet in many parts of the world. Yet, excessive alcohol consumption has a devastating effect on public health. Excessive drinking, which is correlated with alcoholism (4), is a serious concern and levies a profound economic and social burden (2).

That alcohol consumption is heritable is well recognized (5, 6). Nearly 50% of the variation in excessive alcohol consumption and problem drinking is attributable to genetic influences (7). As reported in this issue of the Journal, in an effort to delineate the genetic variants that comprise this genetic variance Baik et al (8) embarked on an exploration of the human genome. In a sample of 1721 Korean adult male drinkers, they identify and replicate several loci that are associated with more frequent alcohol consumption. The most promising results, which easily surpass thresholds for genome-wide significance, were observed on chromosome 12 for rs2074356 and rs11066280, which are highly correlated with a functional polymorphism in the aldehyde dehydrogenase (*ALDH2*) gene, rs671. These results are consistent with past studies that have linked specific functional polymorphisms in *ALDH2*, particularly rs671, with both alcohol intake and the flushing response. The less common and protective form of this variant induces a change from the amino acid glutamic acid to lysine in the 12th exon of the gene, leading to reduced alcohol tolerance (9, 10).

Associations between single nucleotide polymorphisms (SNPs) in *ALDH2* with alcohol intake reconcile well with the known biology of alcohol metabolism (11). After intake, alcohol is metabolized into acetaldehyde by alcohol dehydrogenase enzymes (*ADH*); the *ALDH2* enzyme metabolizes acetaldehyde into acetic acid, which is nontoxic. In addition to being an International Agency for Research on Cancer class 1 carcinogen, accumulating acetaldehyde causes flushing and the unpleasant symptoms associated with a hangover (12). Intriguingly, genome-wide association studies (GWAS) have shown that these same SNPs are associated with increased risk of esophageal squamous cell carcinoma—a cancer partly caused by alcohol intake (13).

The genetic etiology of alcohol consumption holds considerable intrigue for a number of fields, including nutrition, psychiatry, and chronic diseases such as cancer. Thus, the study by Baik et al (8) bears promise. However, the functional rs671 *ALDH2* SNP is not polymorphic in non-Asian populations, and in fact the genetic architecture underlying polymorphisms in the alcohol and aldedehyde dehydrogenase family of genes is complex and shows considerable variation across ethnic groups (14). This begs the critical question of why existing and ongoing GWAS of alcohol involvement in non-Asian populations have failed to identify polymorphisms in additional regions besides 12q24.

The lowest *P* value reported by Baik et al (8) exceeds 10×10^{-50}, and the study identified variants with a substantial effect on alcohol intake. For example, the mean intake of participants with the common homozygote of rs2074356 was 32.4 g, whereas those homozygous for the protective allele had a mean daily intake of only 4.9 g. The authors also report dramatic associations with the flushing response—for instance, carriers of the less common/protective allele of rs11066280 were >13 times as likely to experience alcohol-related flushing than those homozygous for the common allele. In addition, there was evidence for association with alcohol problems consistent with alcoholism. Although the same protective effects were noted, the effect sizes were smaller and did not reach similar levels of genome-wide significance, which was likely due to the reduced sample size available for those analyses.

Due to the infrequent presence of the protective form of rs671 and correlated variants (eg, rs2074356 and rs11066280) in other populations (eg, European Americans), it is likely that other genetic variants exert an influence on alcohol intake in these pop-

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ulations. This might reflect genetic heterogeneity in the etiology of alcohol intake (6). A related possibility is that the long history of alcohol consumption in certain populations produced nutritional adaptation via preferential selection of the more common variant of these genes. This natural selection may allow individuals in these populations to efficiently metabolize and tolerate alcohol (15–17). Conversely, an intriguing theory suggests that the presence of the protective forms of alcohol and aldehyde dehydrogenase variants in Asian populations may reflect adaptation to diet, food toxins, and infectious agents previously indigenous to this population (15).

Regardless of the evolutionary basis of *ALDH2* variants, polymorphisms in other genes are likely to gain prominence in studies in non-Asian populations. Currently, there are 3 published GWAS of alcoholism (18–20), with others forthcoming. Across these efforts, not surprisingly, few loci have reached statistical significance, and there has been a near absence of replication, despite sample sizes in those studies well exceeding the pooled sample ($n = 2834$) used by Baik et al (8). Several consortia have also embarked on meta-analytic GWAS of alcohol consumption. Energized by the recent successes of smoking-related phenotypes, these consortia have amassed enviable sample sizes; however, these meta-analyses are challenged by differences in the assessment of alcohol intake across the different studies (21). It is likely that those genes that robustly correlate with a general vulnerability to alcohol use and misuse will skim to the top. Understanding the biological pathways that underlie these ''top hits'' will provide new insights into its etiology.

Where can investigators look to maximize the most genomic bang for their (millions of) bucks? Collaboration across multiple samples is the immediate and obvious requirement. However, within their own samples, investigators may wish to consider the role of gene-environment interplay. For instance, a wealth of epidemiologic literature suggests that those who begin drinking at an early age may be at greater risk for a maladaptive and more genetically pronounced form of alcohol consumption (22, 23). Other well-documented interactions with socioregional characteristics (eg, living in an urban environment) (24), low religious affiliations (25), and marital status (26) indicate that, in certain environmental milieus, the heritability of alcohol consumption is higher (27). Much like Baik et al who reported on a subpopulation of middle-aged male drinkers, analyses that either focus on subgroups of individuals (eg, older men) or capture the interactions between genotype and sex, birth cohort, age, and environmental covariates may identify alleles with a larger effect size.

Alcohol intake has often been considered to be the environmental background against which other physiologic processes occur. As environmental factors modify genetic vulnerability to alcohol intake, alcohol itself modifies the action of genetic influences on cardiovascular (28) and other disease outcomes (29). For instance, those with the less common allele of rs671 who also drank were at a nearly 9-fold increased risk of esophageal squamous cell carcinoma when compared with those with the risk genotype alone. This partly reflects a genotype-environment correlation, whereby rs671 modifies risk of esophageal cancer and for likelihood of exposure to alcohol (13). It also represents a gene-environment interaction, whereby exposure to alcohol exacerbates the genetic risk of esophageal cancer. Hence, as supported by an extensive literature and shown by Baik et al (8) in this issue, alcohol is an important environmental factor with a strong genetic basis and studying it in both of these contexts will be vital to understanding its role in public health.

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