
Editor's Corner: Keep It Simple

SEVERAL HUNDRED years ago, William of Occam proposed the philosophy that the more simple explanation is likely to be the best. Although no rule of thumb is perfect, "Occam's razor" might have some benefits in rapidly growing fields where large numbers of diverse bits of information accumulate in a short period of time. When this occurs, it might be worthwhile to step back and search for more simple patterns.

A case in point might have developed in the search for genetic influences in alcohol abuse and/or dependence (alcoholism). As is typical of many complex disorders, a variety of genetic influences explain about 40% to 60% of the risk (Hyman, 1999; Kendler et al., 1995; McGue, 1999). It is likely that there are multiple avenues for an enhanced or diminished probability of developing heavy and repetitive drinking, and the picture is further complicated by the likelihood that multiple genes contribute to many of the phenomena.

Even a cursory reading of the recent literature reveals a large variety of possible genetic markers for repetitive heavy drinking (Farren and Tipton, 1999; Hill, 2000; Li, 2000). This panoply of findings is not surprising in light of the number of neurochemical systems directly affected by alcohol, as well as the complex changes in these frameworks that ensue as acute exposure changes to chronic, and as these conditions give way to withdrawal. Our field does not suffer from a lack of ideas or correlates of risk, but we might have developed a situation where so many different potential markers have been identified that it is hard to see the global picture.

For obvious reasons, it was easiest for me to begin the search for themes by working with a group of markers that might relate to a person's intensity of response to alcohol. In brief, the level of reaction to this drug appears to be genetically influenced, and a low reaction is observed more often in children of alcoholics and predicts future alcohol-related life problems and alcoholism (Heath et al., 1999; Schuckit and Smith, 1996; Volavka et al., 1996). The level of response to alcohol correlates with a number of other characteristics including an allele of the serotonin transporter, some GABA receptors, neuropeptide *Y* functioning, several background cortical EEG characteristics, and some components of intracellular signaling, including adenylyl cyclase, protein kinase and *G* proteins. Thus, different genetic markers might con-

tribute through different mechanisms to the intensity of response to alcohol as a potential risk factor for alcoholism.

A second category of influence might be subsumed under the heading of behavioral impulsivity or neuronal disinhibition (Bauer and Hesselbrock, 1999; Begleiter and Porjesz, 1999). This potential family of characteristics involves a series of overlapping (but not perfectly concordant) phenomena. They might reflect brain processes that result in varying degrees of impulsiveness or sensation seeking which might diminish a person's ability to control his or her drinking. In the extreme form, disinhibition is probably represented as conduct disorder in childhood and antisocial personality disorder in adults, phenomena tied to early onset and more severe alcohol- and other substance-related life problems (Bauer and Hesselbrock, 1999; Hill et al., 1999). Several findings are likely to fit together in this domain, including a low amplitude of the *P3* wave of the event-related potential, low overall levels of serotonin, some alleles of the *D2* and *D4* dopamine receptors, as well as alleles for the dopamine transporter (Hill, 2000). Most data indicate that the disinhibition domain is relatively independent of genetic influences that have an impact on the intensity of response to alcohol.

A third category, one especially relevant to Asian men and women, relates to some alleles for the two major alcohol-metabolizing enzymes, alcohol (ADH) and aldehyde dehydrogenase (ALDH). This domain reflects gene forms that lower the alcoholism risk through two potential mechanisms. The ALDH2-2, 2-2 homozygotes have such high levels of acetaldehyde after consuming alcohol that the aversiveness of the drug is associated with almost no alcoholism risk (Li, 2000). ALDH2-1, 2-2 heterozygotes, as well as individuals carrying the alleles for ADH2-2, 2-3 and 3-1, have significantly lower levels of risk for alcoholism, perhaps related to a higher intensity of response to the drug (Wall et al., 1999).

There are, of course, additional genetically controlled markers that operate through other avenues. These might include an enhanced risk for severe alcohol-related life problems through genes that predispose a person to any of several different psychiatric disorders (e.g., schizophrenia or bipolar manic depressive disease). Other markers might operate through genes that have an impact on the pattern of opioid receptors or reaction to endogenous opioids (Gianoulakis et al., 1996; Wand et al., 1998). Perhaps these might reflect levels

of reinforcement. I am sure there are additional potential categories that are worthy of discussion.

The purpose of this brief editorial is not to offer an exhaustive review of all potential markers and every possible category of influence. Rather, the central message is that the field of study of genetic influences in alcoholism has grown and matured. We now face the enviable situation of having identified so many potential markers of risk that it makes sense to take time to step back and search for commonalities as well as distinctions. Occam might have predicted that for any complex situation there is likely to be a huge number of potential correlates, with the next logical stage of thinking being to focus on themes as well as individual building blocks.

As editor of the *Journal of Studies on Alcohol*, I hope these thoughts will stimulate debate and foster additional research in the genetics field. We at the *Journal* welcome opinions on this matter and invite scientists to submit other potential editorials on any topic of interest to our readers.

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