Commentary: Three Approaches to Drug Abuse Genetics

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Several different lines of evidence now suggest substantial genetic influences on inter-individual differences in vulnerability to drug abuse (Uhl et al. 1994). The three proposed studies described by Comings, by Tsuang and Lyons, and by McGue, Lykken, and Iacono each approach issues relating to genetics of drug abuse vulnerability in ways that are distinctive and interesting. Moreover they appear to represent several of the major perspectives in this emerging and exciting area of human genetics.

OVERVIEW

Each of these groups of researchers, at least implicitly, agrees that current evidence suggesting genetic influences on interindividual differences in vulnerability to drug abuse is reasonably strong, although McGue and colleagues are the most circumspect about accepting such evidence. Nevertheless, they conclude that "The challenge to the present generation of behavioral genetics researchers is not so much in establishing whether genetic factors influence behavior, but rather how" (McGue et al., this volume). The behavioral emphases of these groups are evident in their focus on mechanisms by which gene and environment might interact to produce a coherent picture of drug abuse vulnerability.

Tsuang and Lyons use their own Vietnam Era Twin Study data to provide one of the principal supports for accepting the notion of substantial genetic influences in drug abuse vulnerability. They seek biological and psychological vulnerability indices reflecting possible differences in genetic and environmental factors contributing to individual vulnerability to abuse of different classes of psychoactive substances. This approach is consonant with the background of these workers in assessing the genetic and biological marker status of other major psychiatric disorders.

Comings has included consideration of substance abuse in broader thinking about impulsive disorders, defense-style personality, and other behavioral components that largely originate from extensive studies in the genetics of Tourette syndrome (TS) and attention

deficit-hyperactivity disorders (ADHD). Comings' laboratory has also applied single, candidate gene marker association studies to samples of substance abusers; the work proposed here reflects and extends this approach.

COMMENTARY AND ALTERNATE IDEAS

A major feature of the clinical nosology of substance abuse is the frequent comorbidity observed between substance abuse and psychiatric diagnoses, including antisocial personality disorder (ASPD) and depression. Each of these three genetics proposals includes assessment of this feature in substance abusers in search of a common or defining mechanism. However, each stops short of asking more sharply defined questions that may now be appropriate to pose. Can substance abusers in general be considered to display these comorbidities, or do those with ASPD represent a more homogeneous subgroup of substance abusers than would be obtained by mixing them with those without this comorbid condition? If so, is explicit analysis of substance abuser subtypes, defined by these comorbidities, likely to improve the power of other genetic assessments? Are there other means of defining, a priori, better approaches to constructing and evaluating substance abuser subtypes that may provide better clinical and experimental focuses for analyses? Segregation of such comorbid conditions with substance abuse in multigenerational pedigrees would provide an improved rationale for such subtypes. Unfortunately, the drugs that are available and fashionable in most communities change with time. These striking secular trends in abusing illegal substances make such analyses difficult.

Many of the suppositions and perspectives revealed by the three distinctive lines of approach reveal more particular research directions, however. McGue, Lykken, and Iacono describe one such conceptual framework when they suggest that genetic factors "necessarily exert a remote. . . influence," while behavioral influences are "more proximal determinants of behavior." One could easily argue the converse. Many genetic influences on behavior are present continually, so that their impact is likely to be felt much less remotely than the environmental influences, and may largely have been laid down at much more distant times. Genetics may be also more readily controlled in human studies. Twin studies, including the work of Tsuang's group, emphasize the importance of nonshared environment as dominant among the environ-mental determinants of interindividual differences in substance abuse vulnerability. Twin, sib-

pair, and other genetic methods may also make it much easier to control for genetics in many human studies than to control for many of these sorts of environmental influences.

McGue, Lykken, and Iacono focus on the distinction between genotype-environment correlation and genotype-environment interaction as well as the above-mentioned substance abuse-related comorbidities. They note that certain genetic influences may be manifest because individuals of a specific genotype are more likely to experience a unique kind of environ-ment. If the genotype elicits the environment in question, the term "evocative genotype-environment correlation" is used. When the individual seeks a different environment due to the genotype, "active genotype-environment correlation" is manifest. The work on peer group affiliation described by McGue and colleagues provides a direct example of the possibility that genotype could lead to differential acquisition of environmentally derived stimuli. Since abused substances are environ-mental in nature, this sort of pathway could plausibly provide major influences on drug abuse vulnerability. Genotype-environment inter-actions, in which individuals of specific genotypes are more vulnerable to environmental factors, could also play a substantial role in substance abuse vulnerability.

STRENGTHS AND WEAKNESSES OF THE PROPOSED STUDIES

McGue, Lykken, and Iacono propose to study drug abusers to test the idea that environmental factors will be more influential in development of substance abuse and that genetic factors will affect "the psychological and physiologic factors that mediate the expression of this disorder." They then propose to separate genotype-environment correlations from genotype-environment interactions. The strength of such an approach appears to depend on the robustness of assumptions about the primacy of environ-mental factors in the development of substance abuse. Currently, available evidence of strong genetic influences on, for example, age of onset of initiation of alcoholism suggests that key features of the "establishment" of at least some addictive disorders are likely to be genetic. Were this the case for drug abuse, the rationale for seeking genetic influences chiefly in later-developing features of substance abuse would be less compelling.

Tsuang and Lyons propose to evaluate whether differences in event-related evoked electroencephalogram (EEG) potentials, specific

neuro-psychological deficits, specific personality traits, and higher rates for ASPD will mark individuals at higher risk for abuse of one or many psychoactive substances. They propose to use the powerful genetic twin method and to employ the relatively robust findings concerning ASPD-drug abuse comorbidity. However, these investigators are in some sense compelled by the state of development of the field, to use other much less well-established or less-robustly established biologic paradigms to seek correlation with monozygotic/dizygotic twin differences. One conclusion might be that the robust and substantial power of the twin method that Tsuang's group has so carefully used may dwarf the more modest extent to which robust biobehavioral markers for drug abuse are now available.

Tsuang and Lyons also propose to utilize the power of their twin sample to separately examine genetic influences in abusers of different substances. Abusers of only a single drug class may not represent the modal form of substance abuse; the polydrug abusers clinical phenotype is exceedingly common. Moreover, neurobiologic studies suggest that many abused substances, while working at different primary receptors in the brain, nevertheless share abilities to activate common brain reward circuits. From both of these perspectives, it is possible that many genetic influences on abuse of different drug classes might be similar. However, the ability to test this idea would be of substantial utility in exploring the drug-class specificity of genetic and environmental influences on vulnerability.

Comings proposes a more descriptive correlation study, testing whether variants at the dopamine (D) types 1, 2, 3, 4, or 5 (D1, D2, D3, D4, or D5) gene loci will correlate with results from items found in several diag-nostic and behavioral assessment instruments, including the Diagnostic Interview Schedule (DIS), Addiction Severity Index (ASI), the Minnesota Multiphasic Personality Inventory (MMPI), a defense-style questionnaire, and other personality indices. Comings' perspective is broad, with a working hypothesis that variant forms of specific major and modifying genes contribute to groups of symptoms characterizing a number of impulsive disorders. Comings postulates that a small number of major genes and a large number of modifying genes may play a role in a lifelong spectrum of "impulsive, compulsive, addictive, affective and anxiety disorders."

These broad and interesting ideas need to be balanced by studies that emphasize precision in identification of genetically driven syndromes, precision in application of linkage disequilibrium/association methods so that ethnic factors and other confounding features do not provide

false positive or false negative results, precision in separating working hypotheses from well-supported data (e.g., concerning the numbers of "major and modifying genes"), and precision in suggesting whether the genes involved in antisocial personality "can play a role in susceptibility to drug abuse," generally, or if antisocial personality/substance abuse comorbidity defines the substance abuse subtype with, perhaps, its own discrete genetics. Attention to each of these features (and many more) is essential to make sense of what is likely to be complex, non-Mendelian genetics of drug abuse vulnerability. Controls for multiple statistical tests and clean separation of hypothesis-generating from hypothesis-testing research are other important features. It is likely that the kind of broad searches that Comings' group is pursuing will yield positive correlations between gene markers, drug use, and/or other personality factors. However, it is important to be able to state a priori the hypotheses that are being tested and to define the rest of the work as hypothesis generating.

CONCLUSION

The three proposals presented here thus provide an interesting snapshot of the genetics of substance abuse vulnerability. This field is in transition from its initial stage of identification of the presence of genetic influences in drug abuse vulnerability to the beginning of an era in which identifi-cation of the particular genes involved and particular genetically driven substance abuse nosologic subtypes should allow increasingly precise identification of the nature of the genetics and genetic/environment interactions that produce vulnerability to this widespread, common, and debilitating condition.

REFERENCES

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