ELSEVIER SCIENCE IRELAND

Drug and Alcohol Dependence 34 (1994) 161–162

DRUG and ALCOHOL DEPENDENCE

Commentary

Meeting report: collaborative approaches in drug abuse genetics

George R. Uhl*[b], Antonio Persico[a]

[a]*Molecular Neurobiology Branch, Addiction Research Center, National Institute on Drug Abuse, NIH, Box 5180, Baltimore, MD 21224, USA*
[b]*Departments of Neurology and Neuroscience, Johns Hopkins School of Medicine, Baltimore, MD 21224, USA*

(Received 1 November 1993; revision received 29 November 1993; accepted 1 December 1993)

Key words: Association; Addiction; Twin; Cocaine; Heroin

A workshop on Collaborative Networks in Substance Abuse Genetics was held on October 2, 1993 as part of the World Congress on Psychiatric Genetics. Workers from several international and US centers discussed means whereby progress in defining genetic components to drug abuse vulnerability could be enhanced by collaborative work.

These workers reached substantial agreement that collaborative effort to provide DNA from well-characterized affected siblings and twin pairs with defined substance histories for molecular genetic studies would provide one of the most exciting collaborative possibilities that could yield power in approaches to the difficult problems raised by drug abuse genetics.

Attendees provided substantial consensus concerning a number of considerations in reaching this conclusion:

- Current evidence from family, adoption, and twin studies provides fairly strong support for genetic components to interindividual differences in vulnerability to drug abuse. However, no current evidence absolutely excludes the possibility that some of the findings of genetic components could arise from inheritance of genetically-determined disorders that are commonly comorbid with drug abuse, such as alcohol abuse or antisocial personality.
- Genetic influences on several features of the drug/human interaction are possible. Drug metabolism, mechanisms of drug-induced behavioral reward, motivation to initiate drug use and the extent of addiction are each possible features susceptible to interindividual genetic differences.
- Not all of the genes that contribute to interindividual differences in drug abuse are necessarily identical to each of the genes that contribute to interindividual differences in vulnerability to alcoholism.
- Because of the striking secular trends in substance abuse, studies in individuals from the same generation, such as twin and sibling pair, are more likely to be successful than detailed family pedigree studies.
- Defining genetic influences in drug abuse will facilitate definition of environmental influences in this disorder.

Many open questions were clearly recognized. Different genes could contribute differentially to different features of drug abuse vulnerability and consequences. Interindividual differences in initiation of use, experimentation with drugs, pharmacological effects of individual drugs, continuation of use, patterns of use, development of tolerance, withdrawal, physical complications, and comorbidity with antisocial personality and/or alcoholism were each mentioned as possible behavioral and pharmacologic substrates for interindividual differences. Longitudinal studies could help to assess some of these variables. Population-based approaches, studies of subjects who do not respond to drugs, and quantitative trait locus approaches in animal models could aid in identifying important genes contributing to specific features of substance abuse

* Corresponding author.

0376-8716/94/$07.00 © 1994 Elsevier Science Ireland Ltd. All rights reserved.
SSDI 0376-8716(94)00986-P

vulnerability. Realization was strong that careful clinical characterization of drug users is a key to the ability to identify genetic predispositions. Recognition that the most frequent phenotype in the community may be the polysubstance abuser was also noted.

Attention of this group focused on means whereby specific gene contributions could be identified through candidate gene or even positional cloning strategies. Molecular genetic strategies were focused on association by the lack of pedigrees manifesting pure, multigenerational drug abuse. Linkage method application to sibling pairs also received substantial support. The availability of large clinically-characterized twin samples through the Vietnam Era Twin Study, as well as Minnesota, Virginia, St. Louis, and Australian twin samples, and smaller numbers of affected sibling pair samples from other genetics studies, provides potential populations of drug-abusers and non-abusers. Studies of dizygotic twin pairs discordant for substance abuse phenotype would eliminate the confounding possible effects due to ethnic variability in gene markers that can provide false-positive effects in small association studies. Studies of monozygotic twin pairs concordant for substance abuse phenotype would significantly enhance confidence that the studied phenotype was genetically mediated, since much of the environmental impact on drug abuse phenotype appears to derive from environmental influences not shared between members of twin pairs. Twin samples provide control even for some of the rapidly-changing drug abuse demographics and epidemiology. The availability of these clinical populations will be likely to coincide with other developments:

- Improvements in understanding association strategy application to studying disorders likely to be polygenic.
- Identification of more numerous markers for more candidate genes, and for more closely-spaced anonymous chromosomal loci.
- 'Multiplex' approaches to allow more rapid comparisons of marker frequencies in DNA samples from groups of substance abusers and controls. Availability of polymerase-chain reaction based methods for detecting simple sequence repeat polymorphisms, for example, makes the possibility of examining marker frequencies in pools of abusing and pools of non-abusing individuals in two reactions.

There was thus broad consensus that collaborative efforts in drug abuse genetics are now warranted by the possibility of producing exciting results. Such collaborations could provide DNA from well-characterized monozygotic and dizygotic twin pairs with and without substance histories in themselves and their families for association and linkage studies. Availability of these DNAs would greatly expand the number of candidate genes that could be tested in these individuals, and would allow validation of methods for testing samples from pools of affected and unaffected subjects. Participants recognized that this work would result in data that should stimulate improved mathematical means for theoretical and practical analyses of association data. These studies could provide an exciting collaborative array that could yield power in approaches to the difficult problems raised by drug abuse genetics.