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Description of the Genetic Analysis Workshop 11 Collaborative Study on the Genetics of Alcoholism

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Problem 1 of Genetic Analysis Workshop 11 consists of data from a family study of the genetics of alcoholism and related traits contributed by the six centers making up the National Institute for Alcohol Abuse and Alcoholism sponsored by the Collaborative Study on the Genetics of Alcoholism (COGA). The family data included 1,214 members of 105 pedigrees ascertained for having three or more individuals affected with alcoholism. Data available to workshop participants included clinical phenotypes, personality measures, smoking behavior, event-related potentials, platelet monamine oxidase B activity, and a genome scan of 296 markers. © 1999 Wiley-Liss, Inc.

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INTRODUCTION

The goal of the Collaborative Study on the Genetics of Alcoholism (COGA) is the elucidation of genetic mechanisms that influence susceptibility to alcohol abuse and

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dependence and related phenotypes. To accomplish this, many researchers from different domains have been collaborating so that comprehensive, multidimensional, phenotypic family assessment is conducted and correlated with measurements at the genetic level. Genetic association studies with candidate genes and linkage studies are included. Because no single group in the field of Alcohol Studies has the expertise and experience necessary for a comprehensive study, we have formed a consortium of investigators who have designed and implemented the genetic program.

The long-range goal of COGA is the creation of an archival database of families that includes comprehensive phenotypic assessments in many relevant domains that are suitable for genetic linkage and association studies. Control families are included so that non-diagnostic variables that are correlated with susceptibility to develop alcoholism, are measured in a normative population and integrated with data from the families of alcohol dependent probands. Lymphoblastoid cell lines have been cryopreserved to provide an inexhaustible supply of DNA, assuring wide distribution and the continued utility of this sample for many years. The archival database including phenotypes, genotypes, and DNA will be available to the entire scientific community by the end of this grant period (September 1999).

The sampling frame in COGA has been carefully designed to permit the replication of genetic findings. This has been accomplished by dividing the sample of families that are suitable for genetic studies into two separate, but identically ascertained, groups. In addition, an ongoing quality assurance program has been in place to ensure the data are of the highest quality. A five-year follow up reinterview study is in progress to add incident cases to the sample of affected individuals and to reduce errors of diagnosis. Thus, phenotypic assessments in this study are as reliable, valid, and stable as possible. Improving the quality of measurement decreases error, increases estimates of heritability of susceptibility genes, and therefore increases the power of our genetic studies. During the first five years (1989 to 1994) of COGA, a comprehensive, multidimensional assessment protocol was developed and implemented. Polydiagnostic clinical assessment of adults was included, along with assessments in many non-diagnostic domains. Semi-structured direct lifetime interview schedules for children and adolescents were developed along with a companion assessment schedule of the parents to discuss the offspring. Non-diagnostic assessments were chosen based on their correlations with the susceptibility to develop alcohol dependence. Personality trait measures were also included. For a subset of genetically informative families, a neuropsychological test battery was administered along with neurophysiological measures including EEGs (electroencephalograph) and ERPs (auditory and visual event-related potentials). Blood samples were taken from informative individuals and used for biological marker studies and for the manufacture and cryopreservation of lymphoblastoid cell lines. These have been used to produce DNA for ongoing genetic studies.

METHODS

Overview of Ascertainment Strategy

A two-stage ascertainment protocol was begun during the first five-year grant period and has remained in place since then. Briefly, potential probands are identified by random consecutive sampling of inpatient and outpatient alcoholism treatment facilities. Inclusion criteria for probands are: a lifetime diagnosis of alcohol dependence by DSM-III-R criteria and definite alcoholism by Feighner criteria. The co-occurrence of these diagnoses is

called the "COGA criteria" and is used throughout the study for ascertainment and analysis. Other inclusion criteria are: age 18 or greater, English speaking, living in the catchment area of a center, giving informed consent (assent for minors), and having two or more first degree relatives living in the catchment area of any of the six COGA centers. Exclusion criteria are having a fatal illness that is not alcohol related, being unable to participate in the protocol, significant intravenous drug use, or being infected with the HIV virus. Potential probands are required to have at least three full sibs and two parents available for study, or if one or more parents are dead or missing, a larger sibship is required. If the proband is a parent and his/her family does not meet the sibship requirements, then we require the potential proband to have an available mate and at least three children greater than 18 years (13 in New York). If the mate is missing then more offspring are required. Probands and families meeting these criteria are designated Stage I and all available first-degree relatives are personally interviewed with a semi-structured interview developed specifically for COGA (SSAGA for ages 18 year or older, the C-SSAGA-C for children ages 7 to 12 and the C-SSAGA-A for adolescents age 13 to 17). In addition to the COGA criteria for diagnosis of alcohol dependence, a very close approximation to the World Health Organization diagnosis (ICD-10) of alcohol dependence is also given to all interviewed subjects. The ICD-10 diagnosis is more severe, less common, and has a higher sibling relative risk than the COGA diagnosis. Almost all individuals who are affected by the ICD-10 criteria are also affected by the COGA criteria. Besides classifying individuals as affected or not, those with some symptoms of alcohol dependence who did not meet criteria for "affected" are classified as "unaffected with some symptoms." A test-retest reliability study conducted between and within COGA sites attested to the reliability of the lifetime diagnosis of alcohol dependence. Subjects also completed two paper and pencil personality trait questionnaires (TPQ/TCI [Cloninger, 1987]; and the Zuckerman Sensation Seeking Scale (v5) [Zuckerman et al., 1964]). Children 7 years or older are included in the study. A Pedigree Structure Form (PSF) is reviewed with all family members to collect and codify family structure information. The Family History Assessment Module (FHAM), a structured family history schedule developed expressly for this study, is administered to all family members.

Families with three or more first-degree alcohol-dependent relatives (by COGA criteria) are designated Stage II families. They are invited for more extensive testing, including neurophysiology test (ERPs and EEGs) and a battery of neuropsychological assessments. Blood is also obtained for biological marker studies and the production of lymphoblastoid cell lines (adults) or DNA (juveniles). Pedigrees are extended into second and third degree branches if family history assessment reveals the presence of other affected relatives. Families with evidence of bilineal alcohol dependence are not included in the extended assessment protocol. The assessment of relatives in the extended pedigrees is the same as that used for member of the nuclear families.

Assessment of Multiplex (Stage II) Families

Neurophysiology Component. The neurophysiology component of COGA measures probands electrical brain activities with noninvasive scalp electrodes using two techniques: the EEG and event-related potentials (ERPs). ERPs are brain waves that are elicited in response to specific stimuli (e.g., a light or sound) and provide sensitive measures of cognitive brain activity. ERPs consist of several waves, or components. The component most frequently studied in alcohol research is P300, a positive wave that

occurs about 300 milliseconds after the stimulus. The height of the wave (i.e., the amplitude) is related to the significance of a stimulus.

Several studies have found that among other ERP aberrations, abstinent alcoholics exhibit a reduced P300 amplitude in response to a stimulus (for review, see Porjesz and Begleiter [1996]). In addition, subjects at risk for alcoholism, particularly sons of alcoholic fathers, exhibit low P300 amplitudes even prior to alcohol exposure [Begleiter et al., 1984; Berman et al., 1993; for review, see Polich et al., 1994]. A recent meta-analysis of the entire literature on P300 in high-risk individuals concluded that "the P300 component is a useful investigative tool in this context but also that it may have predictive value as an index of vulnerability for alcoholism when well-designed paradigms are used to elicit ERPs" [Polich et al., 1994].

The reduced P300 amplitude is a consistent finding that seems to characterize people at risk for alcoholism and which may serve as a phenotypic marker for alcoholism. Furthermore, twin studies have provided evidence that P300 characteristics are heritable [Polich and Burns, 1987; O'Connor et al., 1994]. COGA provides a unique opportunity to assess the value of P300 as a phenotypic marker for alcoholism.

Laboratories at all six COGA centers collect EEG and ERP information on member of the Stage II and Control families. The experiments also assess P300 characteristics. The Control families are randomly selected and represent the population at each COGA site. Control subjects with alcoholism or other psychiatric illnesses are not excluded so that the prevalence of these disorders corresponds to that in the general population.

For each of the ERP-related experiments, researchers have examined the consistency of the findings across the six COGA sites. For example, in experiments measuring P300 in response to light stimuli, the wave forms and the P300 amplitudes did not differ significantly among sites [Cohen et al., 1994]. Similar results were obtained for a number of other experiments [Alexander et al., 1994; Kuperman et al., 1995]. Because of these similarities, data from all study sites can be analyzed together. Results of P300 analyses in the COGA sample are consistent with other findings [Porjesz and Begleiter, 1998]. A genome screen to find the underlying genetic determinants of the ERP P300 has recently been reported [Begleiter et al., 1998].

Other Available Measurements

Personality traits are assessed with the TPQ developed by Cloninger [1987]. The TPQ has been found to be heritable and its scales have been correlated with the lifetime diagnosis of alcohol dependence.

Eleven diagnostic symptoms of alcohol dependence scored on a two- or three-point scale were selected from a list of 32 symptoms to create a quantitative measure of dependence. Latent class analysis of these symptoms has been used to identify a more homogeneous phenotype, which is largely characterized by physical dependence and severity.

Tobacco addiction is extremely common in alcohol-dependent individuals and evidence from twin studies has supported a strong genetic correlation between alcohol dependence and nicotine addiction. Accordingly, data on habitual smoking is included in the GAW data set. Monoamine oxidase B (MAOB) activity has been related to alcohol dependence and smoking behavior and is also included in the data set.

Genotype Data

Stage II families are reviewed to select those that are suitable for genetic linkage and candidate gene analyses. These families are also pruned to eliminate uninformative individuals and branches. Two separate samples are selected for genetic studies. The first included genome-wide genetic linkage studies and candidate gene studies of alcohol dependence and related phenotypes in 105 multigenerational pedigrees (983 individuals). The second study offers an opportunity for replication of positive findings, in a separate, but identically ascertained sample.

The data set distributed to GAW11 participants included 105 pedigrees with 1,214 members. Nine hundred and ninety-two members have been genotyped and of these, 970 have been interviewed using the adult assessment protocol. A subset of the interviewed adults also successfully completed the personality trait assessement. Twenty-two individuals have been genotyped and did not receive the adult assessment protocol and 13 individuals have been assessed but were not genotyped. Two hundred and ninety-six markers, with an average heterozygosity of 0.73 have been typed at an average intermarker distance of 13.6 cM. Allele frequencies were estimated with the USER M13 program [Boehnke, 1991] and the CRIMAP program [Lander and Green, 1987] was used to estimate marker order and distances. The allele frequencies and map information was distributed to participants. Results of the intial genome scan of these data have been published [Reich et al., 1998]. The second study is ongoing and includes 157 multigenerational pedigrees (1,219 individuals). Six hundred and seven individuals in 103 families were assessed in COGA neurophysiology laboratories. The control sample and the replication sample of multiplex pedigrees were not available for analysis by GAW11 participants.

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