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MARC Project 5:

MOLECULAR EPIDEMIOLOGY OF ALCOHOLISM AND COMORBID DISORDERS

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ABSTRACT

- This MARC research project, project 5, seeks to build upon gene-discovery projects such as COGA (Collaborative Study on the Genetics of Alcoholism: PIs Begleiter and Reich) and similar projects (e.g. PIs Hill, Kendler) which are studying treatment-ascertained alcoholics and their relatives, and the MARC-affiliated Alcohol-QTL IRPG consortium (PIs Heath, Martin, Madden, Todd), which is studying community-ascertained alcoholics and heavy smokers and their adult relatives, by incorporating a molecular genetic component into 4 mature, prospective longitudinal studies (PIs Chassin, Cooper, Heath, Sher) spanning the age-range from early adolescence into young adulthood, with 3-7 waves of prospective assessment.

ABSTRACT (continued)

- In addition to collecting DNA from the target samples (years 1-3), this research project will combine secondary data-analysis and genotyping, proceeding in 4 stages: (i) longitudinal and other phenotypic analyses to establish consistent phenotype definition across informative data-sets (not all data-sets will be informative for all phenotypes of interest) (years 1-3); (ii) behavioral genetic analyses using existing twin data sets (MOAFTS, the former MARC Project 1, or other U.S. and Australian data-sets to which we have access through the MARC) to confirm heritability of phenotypes defined at stage (i), and where possible determine whether that phenotypic operationalization is optimal for understanding genetic effects (which may not be the case if the structures of genetic and environmental influences are very different) (years 1-3); (iii) genotyping for a limited number of candidate genes (years 3-5); and (iv) genetic association analysis (years 4-5).

ABSTRACT (continued)

- This carefully staged approach is necessary to minimize the dangers of multiple testing when combining candidate gene data and rich longitudinal data sets. For the same reason, we focus on a limited number of candidate phenotypes where prospective data are expected to be informative for understanding the etiology of alcoholism, as justified under Background and Preliminary studies. Selection of candidate phenotypes and candidate genes is guided by the MARC focus on the roles of overlapping mechanisms of behavioral under control, negative affect regulation and pharmacologic vulnerability in the etiology of alcohol use disorders (AUDs), emphasizing AUD phenotypes associated with (a) externalizing symptoms, (b) tolerance and quantitative consumption indices, (c) cognitive aspects of alcohol use (expectancies), (d) co-occurrence with tobacco dependence, and (e) negative affect (depression, suicidality).

Specific Aims

- **Project Goals**
  - **1.1. To obtain blood samples for DNA extraction, from participants in 4 prospective longitudinal studies (PI-s Chassin, Cooper, Heath, Sher).**
  - **1.2. To derive phenotypes of alcohol involvement (use and problems) and co-occurring features based on longitudinal course, that can be operationalized across two or more data-sets, focused on four domains: (i) externalizing symptoms; (ii) consumption, as well as cognitive aspects of alcohol use (expectancies); (iii) co-occurrence with tobacco dependence; (iv) co-occurrence with early trauma and depression, from the databases of these 4 studies. Two approaches will be emphasized for phenotype identification – developmental (e.g. using mixture modeling to identify trajectories through time); and state/trait modeling (e.g. modeling chronicity of effects).**

Specific Aims

- Project Goals (continued)
  - 1.3. To conduct secondary analyses of existing twin and children-of-twins data sets to confirm heritability of the variables thus defined, excluding non-genetic phenotypes from further analysis, and further refining phenotypes where necessary.
  - 1.4. Following these two stages of secondary data-analysis, to test for candidate gene effects on these phenotypes (however, choice of candidate gene is expected to need revision in the light of emerging findings from ongoing gene-discovery efforts, including MARC-affiliated projects, by the time the genotyping phase of the project begins):

Specific Aims

- Project Goals (continued)
  - 1.4
    - (i) AUDs and externalizing symptoms (DRD4, DRD5, SLC6A3 (DAT1 in old notation));
    - (ii) AUDs, alcohol consumption and alcohol expectancies (ALDH2 promoter polymorphism, ADH1B (ADH2 in old notation), ADH1C (ADH3 in old notation);
    - (iii) AUDs and tobacco consumption (CHRNA4, CHRNA7, CHRNB2);
    - (iv) AUDs and early trauma and other high-risk environmental exposures associated with parental alcoholism (CRF, NPY, SLC6A4 (HTT in old notation)).

Specific Aims

- **Project Goals (continued)**
  - **1.5 Through the availability of DNA from the participants in these longitudinal studies, to encourage future coordinated genotyping efforts by the principal investigators of the original studies, beyond the 5-year funding period of this center project, to take full advantage of the information about alcoholism etiology that has been gathered in these studies.**

Preliminary Results

- Our efforts over the 1st year have been devoted to organization of d data sets and analytic approaches for the determination of phenotypes of interests for genetic analysis and the completion of an initial screening project to determine interest of subjects participating in this project. Current progress for this study has occurred on two fronts.
- First, three meetings of key investigators and biostatisticians have been held over the last year to discuss analytic approaches to the development of phenotypes across data sets and to begin joining data sets. The consensus is that phenotypes will be initially developed in the two University of Missouri data sets then tested for heritability in the MOAFTS (Missouri Adolescent Female Twin Study) data set. Common items and constructs are being developed.

Preliminary Results (continued)

- Second, a test of how to approach subjects for blood collection is underway in the Sher et al. study. At the time of our first progress report, 257 individuals (approximately ½ of the target sample) had been contacted to assess interest in the study, and 249 agreed to participate (a 96.9% initial cooperation rate). Materials for blood collection are being mailed to potential participants. The participants are asked to go to local clinics or laboratories for blood drawing and samples are then express shipped to the laboratory at Washington University. The next wave of interviews with the MOAFTS sample has begun, and blood collection efforts with cooperative twins is being conducted with these.

Preliminary Results (continued)

- **Progress to Date on Sample Collection and Genotyping**
  - Blood and buccal swab samples are now being collected for DNA isolation from all four prospective studies populations.
  - To date a total of 1,332 specimens have been received in the lab. Of these, DNA has been prepared and under gone quality control checks for 1,102 individuals. Functional repeat polymorphism genotypes have been produced for DRD_4, DRD_5 , $SLC6A_3$ (DAT1) and $SLC6A_4$ (HHT) loci on 971 samples.

Preliminary Results (continued)

- **Immediate Plans**
  - During the next year we anticipate completing sample collection, repeat polymorphism genotyping and most single nucleotide polymorphism (snp) genotyping as well as developing phenotypes for joint samples.