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Midwest Alcoholism Research Center: An overview

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MIDWEST ALCOHOLISM RESEARCH CENTER: AN OVERVIEW

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GOAL

- To conduct a collaborative program of community-based research on the etiology of alcohol dependence, and associated psychiatric and substance use disorders, to address three etiologic models and five major research questions.

- **Etiologic Models for Alcohol Dependence**
  - **Behavioral undercontrol** – what is the role of impulsive traits, attentional problems, and adolescent conduct problems (or problem behaviors) in the etiology of alcohol dependence?
  - **Negative affect regulation** – what is the role of negative affect, depression and anxiety disorders and early onset suicidality in the etiology of alcohol dependence?
  - **Pharmacologic vulnerability** – what is the role of innate differences in metabolic, subjective, psychomotor and physiologic responses to alcohol, and to nicotine, in the etiology of alcohol dependence?

Major Research Questions

- **Mediating variables**
  What sociodemographic, personality, psychiatric, or other individual difference variables account for genetic (or environmental) influences on risk of alcohol dependence?
- **Risk Modifiers**
  What modifiers/vulnerability factors, genetic or environmental, interact with known risk factors to exacerbate or diminish risk (e.g., under what environmental conditions is the effect of genetic risk increased or diminished – genotype x environment interaction)?
- **Developmental course/natural history**
  Can we identify stage-specific risk factors (genetic or environmental), e.g., different risk or protective factors for initiation of adolescent drinking versus transition to problem drinking versus remission of alcohol problems?
- **Outcomes**
  What are the consequences of adolescent problems with alcohol?
- **Gene discovery**
  Can we use genetic linkage or association approaches to identify novel genetic risk factors for alcohol dependence or associated substance use disorders (e.g., tobacco dependence)?

Approach

- Bring together expertise in diverse areas of alcohol research, represented principally at the three major research universities of the state of Missouri:
  - Washington University School of Medicine – expertise in biological psychiatry, genetic and epidemiologic aspects of alcoholism
  - Saint Louis University School of Public Health – expertise in public health, epidemiologic aspects of alcoholism research
  - University of Missouri–Columbia – expertise in psychosocial, psychobiological approaches to understanding alcoholism etiology and consequences
- Two other institutions collaborate in our research program:
  - Queensland Institute of Medical Research, Brisbane, Australia – provides access to a large number of families with adult twins (>10,000 families), permitting cross-cultural comparisons with a heavy drinking society
  - Palo Alto Veterans Administration, Palo Alto, California – provides additional expertise concerning psychosocial and family study approaches in alcoholism research

Center-Affiliated Research Projects, Science Cores, and Training Programs

- The Center's alcoholism research program is much broader than the scientific cores and three research projects directly funded through the NIAAA Center grant.
- Table 1 (later panel) summarizes (most of) the Center's relevant research and training portfolio that is supported through other research mechanisms. Eight research areas/approaches are represented:

Center-Affiliated Research Projects, Science Cores, and Training Programs (continued)

A. Genetic Methodology/Biometrics Projects
Methodological projects involving original theoretical work, computer simulation, and secondary data analysis, that are designed to develop improved methods of collecting and analyzing data on genetic influences on risk of alcoholism and related phenotypes, and their interactions with environmental risk factors.

B. Gene-Mapping Projects
The emphasis here is on projects using community-based rather than clinic-based sampling schemes, and using a Quantitative Trait Locus approach. One funded project is focused on smoking and nicotine dependence (4), but is included here because it is also assessing alcohol-related phenotypes, to take advantage of the overlap of genetic risk factors for alcohol and nicotine dependence. Two (13,15) are using both diagnostic and quantitative indices of alcohol dependence and consumption patterns. A fourth project is using a mutation screening approach to identify genes that contribute to risk of co-occurring alcohol and nicotine dependence. An additional project is pending resubmission (26th percentile).

C. Adult Twin Genetic Epidemiology Projects
Because of the relative maturity of the field of genetic epidemiologic research on alcoholism, these are primarily focused on comorbid phenotypes such as gambling (17,20) where mediators and modifiers of genetic influence are less well understood. Two additional projects, on personality disorder (19) and childhood physical/sexual abuse (18), are pending review.

Center-Affiliated Research Projects, Science Cores, and Training Programs (continued)

D. Prospective Studies of Children/Adolescents and Their Families

There are 8 projects focused on children, adolescents or young adults and their parents. These include (i) an African-American family study (21), focused on adolescent siblings and their parents,with oversampling of high-risk families where there is a paternal history of alcohol dependence and/or recurrent drunk-driving convictions; (ii) a twin-family study of childhood Attention Deficit Hyperactivity Disorder (ADHD) (26), a disorder of particular interest because it is observed much more commonly in the children with an alcoholic biologic parent; (iii) a prospective adolescent male twin study of adolescent smoking and nicotine dependence (25) which is coordinated with the MARC adolescent twin project; (iv) a mentored clinician scientist award focused on social phobia and alcohol dependence risk (26), and a second mentored clinician scientist award focused on parental alcoholism and adolescent suicidality (23); (v) a longitudinal study of drinking and high-risk sexual behavior which is following a panel of subjects first assessed as young adults (22). (vi) Finally, the sixth project, as noted previously, is an adolescent twin project focused on adolescent and young adult alcohol problems and dependence, with follow-up assessments at ages 17-25 of participants first assessed at ages 13-19 (24).

Center-Affiliated Research Projects, Science Cores, and Training Programs (continued)

E. Children of Alcoholic Twins Projects

Two projects (30,32) are focused on outcomes in the adolescent and young adult offspring of female alcoholic and control twins and their MZ and DZ cotwins. A third project is examining outcomes in the children of parents with both antisocial and alcohol dependence symptoms (31). A fourth project will collect data on the children of a comparison group of drug-dependent twins and their cotwins is pending resubmission (29). These projects will be especially powerful for detecting the environmental influences of parental alcoholism, including those whose effects may depend upon offspring genotype (genotype x environment interaction)

F. College Drinking and After

A 20-year project (33) has completed repeat assessments of student drinking and alcohol dependence, and comorbid problems, through the college years, with follow-up in adulthood. A new cohort is now being recruited, with assessment prior to entry to college, and planned follow-up through the same age range.

Center-Affiliated Research Projects, Science Cores, and Training Programs (continued)

G. Pharmacogenetic/Alcohol or Nicotine Challenge/Biomarker Projects

Four projects are using electrophysiological approaches, either in the absence of drug challenge – to identify potential baseline biomarkers of genetic risk of nicotine addiction (35,36), or using nicotine challenge (37,40) to define heritable dimensions of response to nicotine and/or alcohol, which may be associated with differences in alcohol dependence risk.

H. Follow-up Surveys of Adult Community Samples

Two long-term follow-up surveys of adult samples; one of Vietnam veterans, first assessed in 1972-74 (43,44) (with an oversample of veterans identified by urine sample as drug positive upon return from Vietnam; the other of participants in the St. Louis ECA study, first assessed in 1981, to determine the impact of a history of alcoholism on use and costs of health services) (44).

Table 1. Research projects and training programs (including grants pending funding or pending review) of MARC investigators

	PI	Grants Funding Agency	Mechanism	Title	Project Period	Annual Direct Costs[a]
A: Genetic Methodology/Biometrics Projects/Data Analysis Projects						
1.	R. Haber	NIH/NIAAA	R03	Behavioral Genetic Study of Religion and Alcoholism	6/01-5/03	$50,000
2.	A. Heath	NIH/NIAAA	R37	Genetic and Epidemiologic Models of Alcohol Abuse	7/89-6/03	$190,000
3.	K. Jackson	NIH/NIAAA	R21	Prospective Examination of Alcohol-Tobacco Comorbidity	8/99-7/02	NCE[c] -
4.	R. Neuman	NIH/NIAAA	R01	Classification Methods for Detecting Disease Loci	9/98-8/02	NCE $112,000
5.	R. Price	Longer Life Fndtn	Project Grant	Data-Mining Approaches to Suicide and Suicidal Behavior	8/01 - 7/04	$45,000
6.	A. Todorov	NIH/NIAAA	R01	Pharmacogenetic Analyses of Substance Dependence	4/99-3/02	$100,000
7.	H. Xian	NIH/NIDA	R03	Smoking Cessation: The Role of Withdrawal and Dependence	8/00-7/02	$50,000
8.	K. Bucholz	NIH/NIDA	R01	Symptom Based Transition in Addiction in Male Twins	9/01 - 8/04	$175,000
9.	R. Price	NIH/NIDA	R01	Computational Approaches to Substance Abuse Transitions	pending resubmission	-
10.	R Price	NIH/NIDA	R01	Substance Use and Abuse in AAPIs: A Model Minority?	pending review	-
11.	J. Romeis	NIH/NIA	K01	High-risk Health Behaviors, Health Services Use and Aging	12/01 - 11/04	$95,000
12.	N. Saccone					
					Total:	$817,000
B: Gene-Mapping Projects						
13.	A. Heath	NIH/NIAAA	R01	Molecular Epidemiology of Alcohol Dependence III. EDAC Sib Pairs	9/01 - 8/06	$789,224
14.	P. Madden	NIH/NIDA&NCI	R01	Genetics of Vulnerability to Nicotine Addiction	5/00-4/05	$1,059,273
15	N. Martin	NIH/NIAAA	R01	Molecular Epidemiology of Alcohol Dependence I. Candidate Genes	9/01 - 8/06	$433,050
16.	R. Todd	NIH/NIAAA	R01	Mutation Screening for Nicotine and Alcohol Dependence	4/02-3/07	-
					Total:	$2,281,547
C: Adult Twin Genetic Epidemiology Projects						
17.	S. Eisen	NIH/NIMH	R01	Pathological Gambling: Causes, Courses and Consequences	9/00-8/05	$439,986
18.	E. Nelson	NIH/NIMH/NICHD	R01	Childhood Trauma, Parental Alcoholism and Comorbidity	pending	-
19.	T. Trull	NIH/NIMH	R01	Genetic Analysis of Personality Disorder Symptoms	pending	-
20.	W. Slutske	NIH/NMH	R01		pending	
					Total:	$439,986
D: Prospective Child/Adolescent Studies, Including						
21.	K. Bucholz	NIH/NIAAA	R01	Alcoholism: Epidmiologic High Risk Family Study	9/01 - 5/06	$488,599
22.	L. Cooper	NIH/NIAAA	R01	Alcohol Use and Sexual Risk Taking among Adolescents	5/99-4/04	$650,048
23.	A. Glowinski	NARSAD	Project Grant	Mothers of Depressed Adolescent Female Twins	7-01-6/03	$30,000
24.	A. Heath	NIH/NIAAA	R01	Alcoholism: Genetic Epidemiologic Twin Study	3/94-2/05	$484,987
25.	P. Madden	NIH/NIDA	R01	Genetics of Adolescent Smoking and Nicotine Dependence	6/99-5/04	$439,246
26.	E. Nelson	NIH/NIAAA	K08	Genetic Epidemiology of Social Phobia and Alcoholism	8/99-7/04	$137,746
27.	R. Todd	NIH/NIMH	R01	Genetic Epidemiology of ADHD	5/02-4/06	NCE[c] -
28.	A. Glowinski	NIH/NIMH	K08	Familial Transmission of Youth Suicidal Behavior	pending review	-
					Total:	$2,230,626
E: Children of Alcoholic Twins/Pseudo-Adoption Projects						
29.	K. Bucholz	NIH/NIDA	R01	Gene-Environment in Outcomes of PSUD Twins' Offspring	7/01-6/06	$710,956
30.	T. Jacob	NIH/NIAAA	R01	Adult Offspring of Alcoholism Discordant Twins	2/98-1/02	$509,395
31.	W. Slutske	NIH/NIAAA	K01	Familial Transmission of Antisociality/Alcoholism	9/97-8/02	$114,701
32.	W. True	NIH/NIAAA	R01	Adolescent COAs: A Twin Family Design	4/98-3/03	$485,579
					Total:	$1,820,631

[a]First year annual direct costs.

[b]H:University of Helsinki, Finland; K: Karolinsk Instituet, Sweden; M:University of Missouri-Columbia; P:Palo Alto VA, California; Q: Queensland Institute of Medical Resesarch, Brisbane, Australia; S:Saint Louis University; W:Washington University. For each grant, the lead institution is listed first. Other institutions may be involved via subcontract, consulting, or co-mentoring relationships.

[c]NCE: No-cost extension

Table 1. Research projects and training programs (including grants pending funding or pending review) of MARC investigators

	PI	Grants Funding Agency	Mechanism	Title	Project Period	Annual Direct Costs[a]
F: College Sample (Including Follow-up) Projects						
33.	K. Sher	NIH/NIAAA	R37	A Prospective Study of Offspring of Alcoholics	6/97-5/07	$457,913
34.	T. Trull	NIH/NIMH	R01	Development of Borderline Personality Disorder Features	9/97-4/02	$140,000
					Total:	$597,913
G: Pharmacogenetic/Alcohol or Nicotine Challenge/Biomarker Projects						
35.	A. Anokhin	NIH/NIDA	K01	Biobehavioral Markers of Risk for Nicotine Addiction	7/01 - 6/06	$99,845
36.	A. Anokhin	American Cancer Society	Clinical Research Training	Electrophysiological Markers of Vulnerability to Tobacco Dependence	7/00-6/03	$120,583
37.	A. Heath	NIH/NCI	P01 Research Project	Behavioral Genetics of Nicotine Dependence	10/97-6/02	NCE[c] -
38.	J. Rohrbaugh	Alc. Beverage Medical Res. Fdn	Project Grant	Alcohol and Brain Function in Twins Discordant for Heavy Drinking	7/01-6/03	$40,000
39.	J. Rohrbaugh	Dept Defense Polygraph Inst	Research Grant	Noncontact Sensing of Emotion and Stress Using Laser Doppler Vibrometry	5/00-4/02	$150,000
40.	E. Sirevaag	NIH/NIDA	R01	Behavioral Genetics of Nicotine Dependence	7/01 - 6/06	$347,067
41.	E. Sirevaag	NIH/NIDA	P01 Research Project	Biometric and Measured Genetic Research on Smoking	pending review	-
					Total:	$757,495
H: Follow-up Surveys of Adult Community Samples, Cross-Cultural Comparisons						
42.	K. Bucholz	NIH/NIAAA	R01	Alcoholics' Long-Term Use and Costs of Health Services	12/96-11/01	NCE[c] -
43.	R. Price	NIH/NIDA	K02	Psychopathology and Enviroments in Drug Abuse	9/94-8/04	$60,179
44.	R. Price	NIH/NIDA	R01	Follow-up of Vietnam Veterans at Risk for Suicide	8/01 - 1/06	$438,212
					Total:	$498,391
I: Post-doctoral Training Programs						
45.	T. Cicero	NIH/NIDA	T32	Biomedical Training in Drug Abuse Research	9/91-6/06	$400,000
46.	A. Heath	NIH/NIAAA	T32	Biomedical Training in Alcoholism Research	7/00-6/05	$233,734
47.	K. Sher	NIH/NIAAA	T32	Psychology of Alcohol Use and Dependence Training	pending review	-
					Total:	$633,734
J: Missouri Alcoholism Research Center						
48.	A. Heath	NIH/NIAAA	P50	MARC: Alcoholism and Comorbidity in Adolescents and Youth	5/99-12/03	$1,100,000
					Total:	$1,100,000
				Overall Total Research Project Support (Excluding MARC)		**$9,443,589**
				Total Training, Other Support		**$633,734**
				MARC		**$1,100,000**
				MARC-Wide Total Direct Costs (Annual)		**$11,177,323**

[a]First year annual direct costs.

[b]H:University of Helsinki, Finland; K: Karolinsk Instituet, Sweden; M:University of Missouri-Columbia; P:Palo Alto VA, California; Q: Queensland Institute of Medical Resesarch, Brisbane, Australia; S:Saint Louis University; W:Washington University. For each grant, the lead institution is listed first. Other institutions may be involved via subcontract, consulting, or co-mentoring relationships.

[c]NCE: No-cost extension

MARC Organization: 1. Scientific Cores

- **Administrative Core** (PI Heath)
  - Responsible for coordinating the MARC research program, facilitating communications among the five participating sites, monitoring project productivity and human subjects protections, and arranging oversight by the External Scientific Advisory Board and Community Advisory Committee.
- **Ascertainment, Tracing and Tracking Core** (PI Madden)
  - Maintains resources for statewide ascertainment of families with adolescent and young adult children, including specialized family types (e.g., minority families, families with twins), and families with children born in Missouri who have since relocated to other parts of the U.S. Monitors productivity, tracking, completion of interview, questionnaire and other assessments of participating family members.

MARC Organization: 1. Scientific Cores (cont.)

- **Assessment Core** (PI Todd)
  - Coordinates adult and child assessments (including genotyping), provides interviewer training and maintains quality control for MARC projects, including reliability studies.
- **Data Management and Methodology Core** (PI Neuman)
  - Maintains locally-generated databases as well as national databases used by MARC and other investigators. Provides expertise in the latest methods in genetic statistics and other areas of quantitative methodology.
- **Pilot Project Core**
  - Provides pilot project support for junior investigators and others who are trying to develop new directions in alcoholism research.

Organization: 2. Center-Based Research Projects

1. **Male Adolescent Twin Study** (PI Heath)
   This is a prospective study of adolescent male like-sex twin pairs, assessed initially at ages 13,15, 17,19 and 21, and to be reassessed annually. Parents are also interviewed when a family is first recruited into the study. It is coordinated with two other RO1 projects – a parallel study of female adolescent like-sex twin pairs (PI Heath), now being assessed at ages 19-25; and a study of smoking and nicotine dependence in adolescent male twin pairs, assessed at ages 11-17 (PI Madden).

   - Powerful for testing hypotheses about mediators of genetic influences on adolescent alcohol problems;
   - Powerful for the identification of modifiers of such genetic influences (genotype x environment interaction effects);
   - Powerful for disentangling potentially reciprocal relationships between alcohol dependence and comorbid disorders (e.g., tobacco dependence, depression, suicidality).

Organization: 2. Center-Based Research Projects (continued)

2. **Nicotine and Alcohol Challenge Project** (PI Rohrbaugh)
   Using young adult smokers and non-smokers (including smoking-discordant twin pairs), this project is investigating the hypothesis that smokers have higher rates of alcohol problems because interactions between nicotine and alcohol (? cross-tolerance effects) are leading to reduced levels of intoxication after a standard dose of alcohol in smokers compared to non-smokers. It is further hypothesized, following the work of Schuckit, that lower levels of intoxication after a given dose of alcohol in turn predict increased risk of progressing to heavy drinking, and ultimately to alcohol dependence.

   Cross-tolerance effects between nicotine and alcohol have been documented in rodents, but have received little experimental investigation in humans. Three experiments are being conducted, outlined in detail on Poster 29.

Organization: 2. Center-Based Research Projects (continued)

3. **Offspring-of-Twins Project** (PIs True and Jacob)
   This project is studying the offspring of Australian women who are mothers and twins. It is comparing rates of alcohol problems and other behavioral and emotional outcomes in four groups of offspring:
   i. Mother is alcoholic (history of alcohol abuse or dependence) – children are at high genetic risk and high environmental risk;
   ii. Mother is not alcoholic, but mother's MZ twin sister is alcoholic – children are at high genetic risk but low environmental risk;
   iii. Mother is not alcoholic, but mother's DZ twin sister is alcoholic – children are at intermediate genetic risk but low environmental risk;
   iv. Mother is not alcoholic, and mother's DZ twin sister is also not alcoholic – children are at low genetic as well as low environmental risk.

   Of course, in these comparisons, it is also necessary to control for comorbid psychopathology in the mothers, as well as alcohol abuse/dependence and other psychopathology in the children's fathers.

   This is a prospective study, with initial assessments of children at ages 13-23. It is coordinated with two RO1 projects focused on U.S. national samples of alcoholic and control Vietnam-era veteran male twins and their cotwins, spouses, and offspring.

Investigators

- A multi-disciplinary team of faculty investigators is taking part in this research program, many with primary appointments in the Department of Psychiatry at Washington University, which has a long history of trans-disciplinary research on alcohol, tobacco, and other drug dependence; but with other investigators drawn from departments as diverse as Otolaryngology, Internal Medicine at Washington University, the Department of Psychological Sciences at University of Missouri–Columbia, and the Department of Community Health at St. Louis University School of Public Health. Five post-doctoral fellows also participate in this research program (Qiang Fu, MD, PhD – Health Psychology; Valerie Knopik, PhD – Psychology and Behavioral Genetics; Christina Lessov, PhD – Behavioral Neuroscience; Amelia Gallitano-Mendel, PhD, MD – Psychiatry; Michele Pergadia, PhD – Health Psychology). Seven faculty investigators are also former graduates from our training program.
- Because foreign populations may offer particular advantages for genetic research, foreign collaborators from Australia and Finland are included in our team of investigators, with other collaborations with investigators in Japan, China and the Netherlands under active development.

Table 2. Faculty Investigators

Investigator	Department/Division	Expertise	Research Projects/ Science Cores
A. Anokhin, PhD	Psychiatry	Psychology, genetics, psychophysiology	35,36
K. Bucholz, PhD	Psychiatry, SLU School of Public Health	Epidemiology, genetic epidemiology, adult assessment	8,21,29
L. Cooper, PhD	Psychological Sciences, University of Missouri-Columbia	Social psychology, adolescent risky sexual behavior	22
S. Eisen, MD	Internal Medicine	Psychiatric genetics	17,30,32
A. Goate, D Phil	Psychiatry, Genetics	Molecular genetics	13,14
J. Goebel, MD	Otolaryngology	Dynamic posturography	-
A. Heath, D Phil	Psychiatry, Psychology, Genetics	Behavioral genetics, genetic epidemiology	2,3,24,30,32,37,46
K. Jackson	Psychological Sciences, University of Missouri-Columbia	-	3
J. Kaprio, MD	Dept. of Public Health, University of Helsinki	Genetic epidemiology	14
D. Luke, PhD	Community Health, SLU	Biostatistics	21
P. Madden, PhD	Psychiatry	Psychology, genetic epidemiology	2,14,25
N. Martin, PhD	Population Health, QIMR, Brisbane, Australia	Genetics	2,13,14,15,18,19
E. Nelson, MD	Psychiatry	Psychiatric genetics	8,26
R. Neuman, PhD	Psychiatry	Mathematics, statistical genetics	4,16,27
R. Price, PhD	Psychiatry	Sociology, psychiatric epidemiology	5,9,10
W. Reich, PhD	Child Psychiatry	Anthropology, child assessment	24,30,32
J. Rice, PhD	Psychiatry, Biostatistics	Mathematics, statistical genetics	13,14
J. Rohrbaugh, PhD	Psychiatry, Psychology	Psychology, psychophysiology, alcohol and nicotine challenge	38,39
N. Saccone, PhD	Psychiatry	Mathematics, statistical genetics	14
K. Sher, PhD	Psychological Sciences, University of Missouri-Columbia	High-risk longitudinal research on alcoholism	19,26,31,33,34
E. Sirevaag, PhD	Psychiatry	Psychology, psychophysiology, alcohol and nicotine challenge studies	40,41
E. Spitznagel, PhD	Mathematics	Biostatistics	44
R. Todd, PhD, MD	Child Psychiatry, Genetics	Molecular neurobiology, psychiatric genetics	16,27
T. Trull, PhD	Psychological Sciences, University of Missouri-Columbia	Clinical psychology, personality disorder	19
A. Todorov, PhD	Psychiatry	Biostatistics, statistical genetics	6,8
W. True, PhD	Community Health, SLU	Anthropology, genetic epidemiology	29,30,32
H. Xian, PhD	Internal Medicine	Mathematics, statistical genetics	7
P. Wood, PhD	Psychological Sciences, University of Missouri-Columbia	Quantitative psychology	33
J. Whitfield	Clinical Biochemistry, RPAH Sydney, Australia	Clinical biochemistry	15