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March 1, 2012

Pamela Herd
Associate Professor of Public Affairs and Sociology
Department of Sociology
University of Wisconsin – Madison
3454 Social Science Building
1180 Observatory Drive
Madison, WI 53706

Dear Pam,

I am writing this letter on behalf of myself and the other organizers of the Social Science Genetic Association Consortium (SSGAC), David Cesarini (New York University) and Phillip Koellinger (Erasmus University Rotterdam).

We are thrilled to support your proposal to GWAS the WLS sample. The work we have already been doing together with WLS investigators—such as attempting to replicate published associations genetic polymorphisms and psychological, economic, and political phenotypes measured in the WLS—will be pushed forward substantially once GWAS data become available.

Once GWAS data are available, it will become possible to include the WLS in Consortium-wide research efforts. As you know, we have more than 40 collaborating groups in the SSGAC, and we are currently pursuing GWAS projects on educational attainment and subjective well-being. The WLS could immediately become a major contributor to these efforts. Moreover, many the collaborating groups in the SSGAC are collecting harmonized data that will allow us to study the fundamental economic preferences of risk aversion and time preference. Since the WLS has already collected these data, the WLS would be a central player in these initiatives.

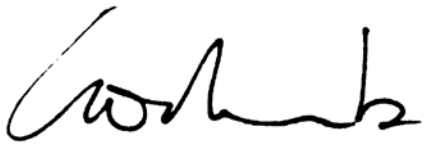
Once the WLS obtains GWAS data, we are also excited to conduct analyses that focus specifically on the WLS. In particular, newly developed statistical methods that exploit the greater signal-to-noise ratio from examining the effects of many genes considered jointly are well-powered in samples the size of WLS.

The WLS would be particularly valuable for Consortium participation and for stand-alone analysis using the GWAS data because of the age homogeneity in the graduate sample (with variation among siblings), the ethnic homogeneity (relative to national samples), and the sibling design of the WLS.

Having GWAS data will open so many possibilities!

Sincerely, the organizers of the Social Science Genetic Association Consortium,

Dan Benjamin



David Cesarini

Phil Koellinger

Rush Alzheimer's Disease Center

RUSH UNIVERSITY MEDICAL CENTER

RUSH UNIVERSITY
COLLEGE OF NURSING
RUSH MEDICAL COLLEGE
COLLEGE OF HEALTH SCIENCES
THE GRADUATE COLLEGE

March 9, 2010

Robert M. Hauser
Vilas Research Professor of Sociology
Director, Center for Demography of Health and Aging
University of Wisconsin-Madison
4430 Social Science Bldg.
1180 Observatory Drive
Madison, WI 53706

Dear Dr. Hauser,

I was excited to learn about your efforts to establish a GWAS consortium to study economic phenotypes as one component of your proposal with the Wisconsin Longitudinal Study being submitted to NIH. I am fully supportive and would be delighted to contribute data to such an effort. We have recently completed a GWAS that includes nearly 900 participants from the Rush Memory and Aging Project (R01AG17917), a cohort study of common chronic conditions of aging that includes more than 1350 participants. The GWAS was conducted by Dr. Philip De Jager and colleagues at the Broad Institute with an Affymetrix 6.0 genome scan (R01AG15819). The imputation is in process and we will soon have more than 6 million SNPs for analyses. Of particular interest to your proposal is that more than 425 of these persons also participated in a behavioral economic decision making survey (with more than 150 undergoing two waves of interviews) conducted in collaboration with Dr. David Laibson at Harvard (R21AG30765). Further, the behavioral economic decision making survey data will continue to be collected as part of a separately funded decision making study being led by Dr. Patricia Boyle from my group (R01AG33678). The new survey instrument, which includes many of the behavior economic measures used in the prior survey, has already been administered to more than 100 participants. We plan to complete the GWAS on the remaining Memory and Aging Project participants and also plan to collect behavioral economic decision making data on more than 800 participants. Thus, I think we will be in a position to make an important contribution to your proposed consortium.

Best of luck with your proposal.

Best Wishes,

David A. Bennett, M.D.
Director, Rush Alzheimer's Disease Center
Robert C. Borwell Professor of Neurological Sciences

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Laboratory
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Patient Research & Clinical Services
Rush Memory Clinic
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SCHOOL OF MEDICINE
VANDERBILT UNIVERSITY

Monday, March 05, 2012

Pamela Herd, PhD
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Jeremy Freese, PhD
Dept. of Sociology
Northwestern Uni.
1810 Chicago Ave
Evanston, IL 60208

M Geoffrey Hayes, PhD
Div. of Endocrinology, Metabolism
& Molecular Medicine
Northwestern University
303 E Chicago Ave
Chicago, IL 60611

Re: Developing Longitudinal Resource for Genetic Research in Behavioral & Health Sciences (R01).

Dear Pam, Jeremy, and Geoff:

Thank you for inviting me to participate in your planned R01 proposal to conduct genome-wide association studies in the Wisconsin Longitudinal Study.

For over a decade, I have led research and development efforts for assessing re-identification risk and formally anonymizing health information and genetic data. In doing so, I have engineered novel algorithms, implemented in publicly-available software, to support such endeavors. For the past five years, I have directed the data privacy research and consultation program for the coordination center of NIH-sponsored Electronic Medical Records and Genomics (EMERGE) consortium and have de-identified data shared to the NIH-managed Database of Genotypes and Phenotypes (dbGaP).

As I understand it, your study will focus on a 1/3 sample of all 1957 Wisconsin high school graduates and a sibling of these graduates. There is also considerable longitudinal data on participant's education, marital patterns and quality, children, cognition, health (chronic conditions, general health, symptoms, Health Utility Index), employment, pensions, job characteristics, health care access and use, income, assets, intertransfers (time and money), volunteering, alcohol and tobacco use, religion (beliefs and practice), internet use, psychological well-being, personality, depression, end of life preparations, voting, social and civic participation among others. Given these features and characteristics, the WLS study provides some unique challenges with respect to identifiability assessments and anonymization.

As a consultant to your project, I will contribute expert review and feedback on your data sharing plan, including the determination of which data to release to dbGaP, in order to protect WLS subjects confidentiality and reduce the risk of their re-identification.

I look forward to working with you in the future. I wish you the best of luck with this grant proposal on this exciting and important research program.

Sincerely,

Bradley A. Malin, Ph.D.
Associate Professor of Biomedical Informatics, School of Medicine
Associate Professor of Computer Science, School Engineering
Vanderbilt University
Nashville, TN 37203
Email: b.malin@vanderbilt.edu
Phone: +1 615 343 9096

HRS | HEALTH AND RETIREMENT STUDY

David R. Weir
Research Professor and
Director, Health and Retirement Study

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Professor Robert M. Hauser
Director, Wisconsin Longitudinal Study
Department of Sociology
University of Wisconsin

March 10, 2010

Dear Bob,
I'm delighted to hear that you are applying for funds for genotyping respondents in the WLS on the same platform as we have begun genotyping HRS respondents. We in the social and behavioral sciences are relative latecomers to the world of genetics, which brings the advantage of being able to learn from the example of others and to benefit from rapidly falling costs. One of the key lessons is the importance of statistical power and replication designs, both of which are facilitated by consortia arrangements. The collaborations already established between WLS and HRS on the measurement of key phenotypes such as cognition provide a solid foundation for building a consortium to address key behavioral questions. The many other studies here and around the world with significant harmonization to HRS and WLS offer the prospect of a truly substantial pool of linked genotype-phenotype samples. At the same time, the WLS has a number of unique strengths that will appeal to some research communities. These include the matched sibling sample design and the availability of measures from early life, notably intelligence testing in high school. Finally, your personal leadership through the National Academy of Sciences panel on the ethical issues of genetic research on subjects in ongoing longitudinal studies has been important for all of us in setting this course.

Best of luck with your proposal.

Sincerely,

David R. Weir

BRIGHAM AND
WOMEN'S HOSPITAL

HARVARD
MEDICAL SCHOOL

Program for Neuropsychiatric Genomics
BWH Neurosciences Institute

Brigham and Women's Hospital

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Lori B. Chibnik, Ph.D., MPH

Instructor in Neurology
Harvard Medical School

Research Associate
Broad Institute of Harvard and MIT

December 18, 2013

Dear Pam,

I am writing this letter to offer my support to your proposal to genotype, impute and analyze the Wisconsin Longitudinal Study (WLS) samples at the Center for Inherited Disease Research at Johns Hopkins University via the National Institutes for Health CIDR program.

We would like to include the WLS in our current project with the Alzheimer's Disease Genetics Consortium, which is "Genome-Wide Analysis of Cognitive Decline in Older Individuals." Once genome-wide genotyping data are available, it will become possible to include the WLS in Consortium-wide research efforts. The WLS could immediately become a major contributor to these efforts because of the inclusion of multiple measures of cognition collected in 1957, 1992, 2005, and 2011 for almost 9,400 respondents, which span the participants' lives from late adolescence until their early 70s.

Longitudinal data on cognition and aging is rare, we are excited to be able to work with you and the WLS on this project

Sincerely Yours,

Lori B Chibnik, PhD, MPH

Duke University Medical Center
Center for the Study of Aging and Human Development
2020 West Main Street, Suite 201
Box 104410
Durham, North Carolina 27708

Jeremy Freese
Ethel and John Lindrgen Professor of Sociology
Weinberg College of Arts and Sciences
Northwestern University
1810 Chicago Avenue
Evanston, IL 60208

December 18, 2013

Dear Jeremy,

I am delighted to join and support the new genetics initiative with the Wisconsin Longitudinal Study (WLS). Translating discoveries from the frontiers of genome science to improve public health depends on our ability to integrate new genetic discoveries with information about the developmental antecedents and social and environmental causes of health and disease. To achieve this advance, data are needed that capture the life histories of individuals and the social and environmental contexts they grow and develop in. Few data resources stand equal to the WLS in these respects. The WLS offers a well-defined sample, a unique sibling design, prospective data, well-characterized phenotypes and exposures, and measurements that are harmonized with other studies around the world. The WLS has been a leader in social science research, and a valuable resource to economists, sociologists, psychologists, and health researchers. It is sure to become a valuable resource for genetics research.

Personally, I see these data as a resource to investigate two key drivers of morbidity in the population: obesity and accelerated cognitive aging. Genome wide association studies have discovered many risk-associated loci for these health problems. Although individually of small effect, my own work and that of others shows that, in aggregate, discovered genetic risks represent a potent source of health risks that can be studied on cohorts like the WLS. I use genetic risk scores to summarize sets of risk-associated genetic loci in order to investigate how genetic risks manifest across development and what features of the social and physical environment may mitigate or amplify genetic risk. The WLS is an ideal setting to pursue such research.

With best wishes

Dan Belsky

Jason D. Boardman, Ph.D.
Department of Sociology
Institute of Behavioral Science
1440 15th Street, UCB 483
Boulder, Colorado 80309-0483

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boardman@colorado.edu

December 26, 2013

Pamela Herd, Principal Investigator
Wisconsin Longitudinal Study
Associate Professor of Public Affairs and Sociology
University of Wisconsin, Madison

Dear Professor Herd,

I am writing to express my enthusiasm about the genome-wide data linked to respondents of the Wisconsin Longitudinal Study (WLS). As one of the principal investigators of the genome-wide genotyping project of the sibling pair samples from the National Longitudinal Study of Adolescent Health, I am very excited to know that additional longitudinal studies will also contain genotypes of the respondents across the genome. The potential for new and collaborative research is enhanced dramatically by genotyping the WLS respondents and making these data available to the larger research community.

Specifically, the richness of the environmental and behavioral measures within the WLS and the long and successful history of collaborative projects and data sharing with the WLS make this a particularly exciting opportunity for social, behavioral, and biological scientists. I have published behavior genetic and candidate gene studies linking genetics to the school environment but we have not, thus far, done this work across the entire human genome. The study design of the WLS provides opportunities for genome-wide gene-environment interaction analyses that are not possible with other data sources.

I am specifically interested in using the WLS to expand upon my work with genetic relationship matrices. These additional samples in conjunction with detailed environmental measures will make important contributions to this new body of work.

Sincerely,

Jason D. Boardman, Ph.D.
University of Colorado

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Heart, Lung, and
Blood Institute
Center for Population Studies
Framingham Heart Study
73 Mt. Wayte Avenue, Suite 2
Framingham, MD 01702-5827

December 20, 2013

Dear Pam,

I am writing this letter on behalf of the CHARGe adiposity working group.

We are delighted to support your proposal to GWAS the Wisconsin Longitudinal Study (WLS) sample at the Center for Inherited Disease Research at Johns Hopkins University via the National Institutes for Health CIDR program. We have an ongoing suite of adiposity-related projects that involve cohorts with genome-wide association, exome chip and sequencing data, and would be delighted for your data to ultimately contribute. The WLS could immediately become a major contributor to these efforts because of the inclusion of multiple measures of adiposity collected in 1992, 2005, and 2011—including anthropomorphic measures collected in 2011 for almost 9,400 respondents. In particular, longitudinal data on weight change could potentially contribute to our weight change GWAS project.

I look forward to this potential collaboration and wish you best of luck with your application. Since I am a NHLBI Employee, I may not receive any monetary rewards from the proposed grant

Sincerely,

Caroline S. Fox, MD MPH
Director of Metabolic Research, the Framingham Heart Study
Associate Director, Center for Population Studies, National Heart, Lung, and Blood Institute

New York University
A private university in the public service

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December 10, 2013

To Whom It May Concern:

I am writing to enthusiastically support the efforts of the Wisconsin Longitudinal Survey to genotype participating subjects with a deeper, more extensive platform that will yield much richer genetic data on the sample that currently is available. The WLS will provide a very important resource for scholars if this genotyping gets done due to the combination of its sibling design, its long panel and its rich set of phenotypic measures.

Large consortiums have been formed to perform genome-wide association studies; but such studies are vulnerable to population stratification—the non-random distribution of genotypes across environments. But within-family studies—for example controlling for parental genotype or using sibling fixed effects (as would be possible with WLS)—breaks the environment-genotype covariance completely, allowing for true causal inference of genetic markers that are assigned (randomly) at conception. To date, there are only a handful of studies that I am aware of in the US that allow for this sort of analysis: Add Health, Framingham, and the Minnesota Twin Family Study. Adding the WLS to this group would be of enormous benefit to the scholarly community. Currently, only Framingham has a sample of genotyped older Americans within a family based design. And this 2nd generation of respondents is generally the parents of the 3rd generation respondents, where the rich sibling data reside. Thus having WLS siblings will provide a unique asset to modeling genetic effects on older adult outcomes with family controls (the Health and Retirement Study has the right age group but no siblings).

Second, siblings are useful to model variance. Namely, increasingly scholars are interested not just in discovering the genetic architecture of main (levels / mean) effects but also of looking for regulators of variation through what has become known as vGWAS. Measuring sibling divergence on phenotypes is a very fruitful way to pursue this aim because it allows for controls for mean effects, checks for dominance effects that may be causing apparent but artifactual effects on variation, and because it allows for other controls (unlike a typical GWAS approach that merely uses individual data and regresses the squared z-score in the entire population—(c.f. Yang, Loos, & Powell, 2012).[1]

[1] Yang, J., Loos, R., & Powell, J. (2012). FTO genotype is associated with phenotypic variability of body mass index. *Nature*. Retrieved from http://www.nature.com/nature/journal/v490/n7419/abs/nature11401.html

When you consider these important ways that sibling data allow us to answer fundamental questions about genetic influence and its interaction with social environment, and you add to this advantage the fact that the WLS dataset is so rich in phenotypes (consider even that H.S. yearbook photos have been rated for attractiveness) and so extensive over time (with one of the lowest attrition rates in survey studies) the possibilities for important research to emerge from its analysis are staggering. I personally intend to apply for the genome-wide data as soon as they are made available via dbGAP.

In closing, I recommend without hesitation that this worthy project be funded. Thanks for your consideration of this letter.

Sincerely,

Dalton Conley
University Professor &
Professor of Sociology, Medicine and Public Policy

Assoc. Prof. Dr. Martin Fieder

Department of Anthropology, University of Vienna,

Althanstraße 14, 1090 Vienna, AUSTRIA

Letter of Support for further genotyping of the „Wisconsin Longitudinal Study“.

Dear Pamela,

Thank you and the team of the Wisconsin Longitudinal Study at aiming to provide more genotype data for the “Wisconsin Sample” as the Wisconsin Longitudinal Study is one of the rare studies which really follow the life of a huge sample of individuals for meanwhile more than 50 years. Providing more genotype data will give a worldwide unique opportunity to investigate the association between the life course, behavior, health and potential genetic predispositions. Many of the studies that have been done by my colleagues and me (worldwide from the field of behavioral anthropology and demography to evolutionary psychology) would have not been possible without the wonderful and sophisticated basis of the “Wisconsin Longitudinal Study” that recently also included genetic data. I think with the integration of genetic data, Wisconsin Longitudinal opened completely new research perspectives and I am sure, with additional genetic data Wisconsin Longitudinal will be on the edge of very important discoveries.

With the help of the Wisconsin data set I plan to investigate on basis of a population genetic approach which genes and single nucleotide polymorphisms are associated with pro-social behavior. The first candidates will be the arginine vasopressin receptor gene 1a (avpr1a) and SNPs on the oxytocin receptor gene OXTR that are known to influence pro-social behavior in experimental settings (Epstein et al. 2010, Israel et al. 2009). The length of the Rs3 promoter region of the avpr1a gene as well as certain SNPs on the OXTR gene (Israel et al. 2009), for instance, influences allocation of funds in the dictator game (Knafo et al. 2008). To my knowledge, however, only little is known on the association between genetic variants and every day cooperative and pro-social behavior. Furthermore I know of no information on other gene x gene interactions and pro-social behavior in humans. I therefore plan in a GWA to investigate

the association between as many SNPs as possible and pro-social behavior using a “candidate gene approach”.

In detail, I plan with the help of Wisconsin Longitudinal and statistical tools from population genetics to investigate which SNP variants are associated with every day pro-social activities, such as: voluntary work, the kind of voluntary work, frequency of voluntary work, helping and giving behavior, kind and frequency of helping and giving behavior. Furthermore with the Wisconsin data set it is possible not only to investigate these factors and their potential genetic basis, but also to control for various confounding factors such as SES and to investigate the potential linkage between SNPs.

I hope that the additional genotyping on basis of the Wisconsin Sample will be possible and I really thank the team of the Wisconsin Longitudinal for their efforts and great work!

With best regards,

Martin Fieder

Robert M. La Follette
School of Public Affairs
UNIVERSITY OF WISCONSIN–MADISON

December 20, 2013

Dear Dr. Herd:
I enthusiastically support your proposal to GWAS the Wisconsin Longitudinal Study sample at the Center for Inherited Disease Research at Johns Hopkins University via the National Institutes for Health CIDR program. I look forward to working with the data on a variety of projects. My expertise investigating topics at the intersection of genetics and social science as well as my extensive experience using novel study designs for robust causal inference, make me particularly well suited to leverage these new data.

I have several projects in mind once the WLS GWAS file becomes available. One set of work will use the genome wide data to generate polygenetic risk scores for phenotypes of interest, including obesity, depression, and health habits. These risk scores will then serve as a summary measure of genetic liability and risk in broader examinations of gene-environment interactions in determining the phenotypes at single points-in-time as well as dynamically. As second set of work will be in exploring candidate gene approaches to specific gene-environmental interaction hypotheses, where the gene(s) of interest is currently not assessed in the WLS genetic files. This would allow a broadening of hypotheses that complement ongoing work that I am doing with the WLS. For example, I have examined whether three candidate genes (*COMT*, *BDNF*, and *APOE*) are related to potential heterogeneity in the impacts of low birth weight on adult outcomes. A larger set of candidate genes would allow further examination of these heterogeneous impacts.

In summary, I look forward to collaborating with you and your talented team of experts. The data source is innovative and will add considerable breadth to longitudinal phenotypes not currently available in the literature. I believe the data source will be widely used and will advance discovery in a variety of fields.

Sincerely,

Jason M. Fletcher, PhD
Associate Professor of Public Affairs
University of Wisconsin-Madison

THE UNIVERSITY OF MICHIGAN
SCHOOL OF PUBLIC HEALTH
DEPARTMENT OF BIOSTATISTICS

1420 WASHINGTON HEIGHTS
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734 764-5450 FAX: 734 763-2215

Pamela Herd, PhD
Principal Investigator, Wisconsin Longitudinal Study
Associate Professor of Public Affairs and Sociology
University of Wisconsin, Madison

Dear Pam,

I am writing this letter on behalf of the GWAS & Sequencing Consortium of Alcohol & Nicotine Use (GSCAN).

We are pleased to support your proposal to GWAS the Wisconsin Longitudinal Study (WLS) sample at the Center for Inherited Disease Research at Johns Hopkins University via the National Institutes for Health CIDR program. We would like to include the WLS in our consortium effort. GSCAN is a collaborative effort bringing together a wide array of diverse studies to investigate genetic associations with smoking and drinking behavior.

Once GWAS data are available in WLS, it will become possible to include the WLS in consortium-wide research efforts. The WLS could immediately become a major contributor to these efforts because of the inclusion of detailed nicotine and alcohol use among study participants collected in 1992, 2005, and 2011. The combination of the prospective and retrospective measures will be very valuable for our analyses.

Sincerely,

Scott Vrieze, PhD
Research Investigator
Department of Biostatistics
University of Michigan

THE UNIVERSITY OF
CHICAGO

DEPARTMENT OF ECONOMICS

1126 East 59th Street
Chicago, Illinois 60637

James J. Heckman
Henry Schultz Distinguished Service
Professor of Economics

Pamela Herd
Principal Investigator, Wisconsin Longitudinal Study
Associate Professor of Public Affairs and Sociology
University of Wisconsin, Madison

December 24, 2013

Dear Pam,

We are writing to enthusiastically support your proposal to genotype the Wisconsin Longitudinal Study (WLS) sample at the Center for Inherited Disease Research at Johns Hopkins University via the National Institutes for Health CIDR program. We would like to use the resulting GWAS data, combine with the extensive WLS phenotypic data, which would be made available from this endeavor.

In our research we explore the interplay between genetic endowment and lifestyle investment decisions in explaining obesity and health inequality. Currently we are focusing our analysis on a single genetic variant, but having access to the whole genomic data would allow us to construct a genetic risk profile for obesity, leveraging the full range of genetic variants that have been associated to fat-mass and obesity in large Genome-Wide Association Studies. This would dramatically increase the power of our study, and allow us to better identify the multiple genetic pathways that interact with lifestyle decisions and obesogenic environments in determining fat mass.

The WLS sample is a unique source of data and important for our analyses because it provides a life-cycle perspective of health and well-being. Following the respondent since late adolescence, it enables us to capture and evaluate the importance of cumulative differences in healthy lifestyles and investments in human capital.

Obesity is a complex and polygenic phenotype; its behavioral and genetic causes are multiple and dynamic in nature, and a thorough investigation of these causes is required in order to curtail the rise in obesity rates witnessed in the last decades. For these reasons we are looking forward to be able to use for our research a more extensive genotyping of the WLS.

Sincerely,

James J. Heckman

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RCGD RESEARCH CENTER FOR GROUP DYNAMICS

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December 6, 2013

To whom it may concern,

This letter is to express my strong support in the NIH providing further funding for more extensive genotyping of the Wisconsin Longitudinal Study sample. My research is on the association between social relationships and health, and I've recently begun to examine potential genetic moderators of such findings. The WLS is an important study in my research program because it includes a number of detailed questions on volunteering behavior, giving and receiving social support, and other variables related to social relationships. It also includes a number of variables related to psychological well-being and physical health, including objectively assessed mortality status.

I am specifically interested in whether oxytocin and vasopressin receptor genes moderate the association between social relationships and health, particularly with respect to volunteering and other forms of prosociality. The Wisconsin Longitudinal Study's initial inclusion of some genetic variables has been promising, but without more extensive genotyping, limited conclusions can be made. For example, there are a number of oxytocin receptor (OXTR) SNPs, but the WLS presently only includes one. Including other OXTR SNPs that have been implicated in prosociality and stress regulation would be helpful in better understanding if the health benefits of giving to others are stronger for some people (e.g. certain allele carriers) compared to others. Moreover, currently the WLS has not genotyped any vasopressin receptor genes, which I would also expect to moderate the association between prosociality and health.

Thank you for considering this request.

Sincerely,

Sara Konrath, PhD
Assistant Professor
Institute for Social Research & Social Psychology, University of Michigan
Member, BioSocial Methods Collaborative
Email: skonrath@umich.edu
Web: www.ipearlab.org; Phone: 734-945-3322

To Whom It May Concern,

It is my pleasure to write this letter to support the application to have the Wisconsin Longitudinal Study (WLS) data genotyped by the NIH Center for Inherited Disease Research. I am a graduate researcher at University of Southern California (advisor, John J. McArdle) and study gene-by-environment interaction effects on cognitive decline among older adults. In 2012, I was awarded a pilot grant to analyze the WLS data.

I plan to analyze the WLS GWAS data using an innovative data-mining technique called *structural equation model trees*, which combines the strengths of structural equation modeling and decision trees. Over the course of fifty years, the WLS has asked about various aspects of life experiences; therefore, adding GWAS data to my analysis will help me deepen the understanding of the gene-by-environment effect on cognitive decline. Furthermore, I plan to replicate the findings from the WLS GWAS data using the Health and Retirement Study's GWAS data, which were genotyped by the NIH Center for Inherited Disease Research.

In conclusion, I support the application to have the WLS data genotyped by the NIH Center for Inherited Disease Research. The WLS is the most unique and comprehensive longitudinal study of life course in social science. I am excited that more extensive genotyping will be done on the WLS data.

Sincerely,

Yusuke Kuroki, MA
Doctoral candidate
The United Studies of Cognition
University of Southern California

Boston University School of Medicine
The Framingham Heart Study

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December 20, 2013

Pamela Herd
Principal Investigator, Wisconsin Longitudinal Study
Associate Professor of Public Affairs and Sociology
University of Wisconsin, Madison

Dear Pam,

I am writing this letter on behalf of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium Aging and Longevity working group. We are a group of investigators from over fifteen studies in the United States and Europe conducting genetic association studies of human longevity and age-related phenotypes. I am delighted to support your proposal to GWAS the Wisconsin Longitudinal Study (WLS) sample at the Center for Inherited Disease Research at Johns Hopkins University via the National Institutes for Health CIDR program. Once GWAS data are available, it will become possible to include the WLS in our working group research efforts. The WLS could immediately become a major contributor to these efforts because of the breadth of longitudinal measures for almost 9,400 respondents. We are currently working on GWAS of performance measures including hand grip strength and gait speed and new measures of healthy aging for example the healthy aging index originally developed and validated in the Cardiovascular Health Study and Health ABC.

The CHARGE Aging and Longevity Working Group is looking forward to working with you.

Sincerely,

Joanne Murabito, MD ScM
Associate Professor of Medicine,
Boston University School of Medicine
Clinic Director & Investigator, Framingham Heart Study

Boston University School of Medicine
Department of Neurology

The Framingham
Heart Study

Sudha Seshadri, MD

Professor of Neurology, Boston University School of Medicine
Senior Investigator, The Framingham Study,
Co-ordinator, Neurology Working Group, CHARGE
72 East Concord Street, B-602, Boston, Massachusetts 02118-2526
T 617-414-1337 F 617-638-8086; suseshad@bu.edu

December 29, 2013

Dear Pam,

I am writing on behalf of myself and my colleagues within the neurology phenotype working group within the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium. As you know the CHARGE consortium was formed to conduct genetic analyses of various cardiovascular and aging related traits within community-based cohorts. The neurology phenotype working group (neuroCHARGE) focuses on genetic studies of 'normal' cognitive function, dementia including Alzheimer's disease, stroke and brain MRI measures.

We are delighted to support your proposal to GWAS the Wisconsin Longitudinal Study (WLS) sample at the Center for Inherited Disease Research at Johns Hopkins University via the National Institutes for Health CIDR program. We would like to include the WLS several of our ongoing GWAS projects which include GWAS of executive function, verbal memory-delayed recall, verbal memory-immediate recall, general cognitive function and visuospatial memory and function and a proposed GWAS of abstraction; we have currently included data from more than 20 cohorts of European ancestry with overall sample sizes varying from 20,000 to 45,000 depending on the test and cognitive domain being assessed.

I understand that the WLS has data on the following tests that could be utilized for the projects listed above, (i) the Henmon-Nelson IQ scores as a measure of general cognition, (ii) the Letter/Category Fluency test as a measure of executive function, (iii) the Digit Ordering test as a measure of immediate verbal memory, (iv) the Word Recall Test as a measure of delayed verbal memory and (v) the Similarities and Number Series Tasks as tests of abstraction ability. Once GWAS data are available, it will become possible to include the WLS in these Consortium-wide research efforts. The WLS could immediately become a major contributor to these efforts because of the inclusion of multiple measures of cognition collected in 1957, 1992, 2005, and 2011 for almost 9,400 respondents at approximate mean ages of 19, 53, 66, and 71 years. We are very excited about the proposed collaboration that we expect will lead to identification of novel genetic variation underlying cognitive function and age-related cognitive decline in community-based samples.

Yours sincerely

Sudha Seshadri

Sudha Seshadri, MD

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December 6, 2013

Pamela Herd, Ph.D.
Associate Professor of Public Affairs and Sociology
University of Wisconsin, Madison

Dear Dr. Herd:

I am writing in support of your application for funding for the Wisconsin Longitudinal Study (WLS) Genetic Data. The WLS Genetic data is an invaluable resource for my research with my Ph.D. student Hyunseung Kang. Hyunseung and I are developing new methods for Mendelian Randomization (MR) analysis and applying them to the WLS data. In MR, the goal is to estimate the causal effect of an exposure on an outcome by using genetic markers, specifically single nucleotide polymorphisms (SNPs) as instrumental variables. Hyunseung and I are using MR and the WLS genetic data to estimate the estimate the effect of health-related indicators, such as body mass index (BMI), mobility scores, and medical costs, on utility-based quality of life. Having accurate assessment of such effects drive design and implementation of health related policy decisions that attempt to modify such health-related indicators to maximize individual utility. A fundamental difficulty with these studies is controlling for possible confounders that affect the relationship between the indicator and the outcome. The outcome, utility-based quality of life, encompasses various factors about the individual, making it difficult to control for all possible confounders that may affect these measures. For example, in examining the relationship between BMI and a health-based utility measure, diet is a possible confounder. To make matters worse, there's no straightforward way to numerically quantify diet, making it difficult to control for this confounder, even if it were observed. In MR, the goal is to estimate the causal effect of an exposure on an outcome by using genetic markers, specifically single nucleotide polymorphisms (SNPs), as instruments. Traditional approaches to MR require that all candidate instruments be checked for validity. However, the method we developed allows for possibly invalid instruments amongst the candidate instruments. This feature is attractive since the biology of the genes is not always fully understood, especially when dealing with complex outcomes like utility-based quality of life and its biological association with the candidate genetic instruments.

To measure health related quality of life in the WLS, we use the Health Utility Index Mark 3 (HUI3). We have begun looking at the effect of obesity on the HUI3 using our method of MR analysis and plan to look at the effect of other exposures and outcomes.

The WLS Genetic Data is a super resource for our applying our methods. The WLS' rich record of sociological, economic and health outcome outcomes combined with the genetic data allows us to use MR analysis to investigate many interesting causal relationships such as the effect of health related indicators on utility based quality of life. I strongly support your application for additional funding to further develop the WLS genetic data.

Sincerely,

Dylan Small