

National Institute on Aging

Using Genome-Wide Association Studies (GWAS) to Explore Fundamental Questions About Aging in the Health and Retirement Study (HRS) Sample

Summary of an Expert Meeting*

Committee on Population
National Academy of Sciences
Washington, D.C.

September 23-24, 2010

Revised November 30, 2010

Introduction

The Health and Retirement Study (HRS) is a nationally representative longitudinal project that studies labor-force participation and health transitions that individuals undergo toward the end of their work lives and in the years that follow. Every two years, a cohort currently containing more than 22,000 individuals aged 50 years and older are surveyed on such subjects as income, work, assets, pension plans, health insurance, disability, physical health and functioning, cognitive functioning, and health care expenditures. As a large-scale study with publicly accessible data and a leader in the field of behavioral/social research, the direction taken by the HRS serves as a role model for other behavioral/social cohort studies, for example, by introducing biomarkers in an economic context. The HRS has taken such a multidisciplinary approach—integrating behavioral, social, and life sciences—since its inception in 1992. This multidisciplinary aspect was recently expanded using funding obtained through the American Recovery and Reinvestment Act (ARRA) to perform a genome-wide scan on DNA samples from 20,000 cohort members in the HRS.

The National Institute on Aging (NIA) commissioned the National Research Council Committee on Population to convene a two-day expert meeting to consider what data to collect on which traits and endophenotypes to optimize the HRS GWAS information as well as to explore ways in which the HRS can be harmonized with other types of large-scale studies to help uncover complex phenotypes attributable to genetics. Toward this end, more than 30 leaders in the fields of gerontology, economics, sociology, demography, genetics, population genetics, epidemiology, and psychology from throughout the United States and Europe convened in Washington, D.C., on September 23-24, 2010. (See appendix 1 for list of meeting participants.)

* This meeting summary was prepared by Andrea Kelly and Rose Maria Li, Rose Li and Associates, Inc., under contract to the Division of Behavioral and Social Research, National Institute on Aging, National Institutes of Health (HHSN271201000424P). The statements, conclusions, and recommendations contained in this document reflect opinions of the meeting participants and are not intended to represent the official position of the National Institute on Aging, the National Institutes of Health, or the U.S. Department of Health and Human Services. We gratefully acknowledge comments provided on earlier drafts of this report by Yoav Ben-Shlomo, Daniel Benjamin, Jason Boardman, Steve Cole, Gabriella Conti, Eileen Crimmins, George Davey Smith, John Hobcraft, Alayee Hooman, Michael Hurd, Sharon Kardia, Jonathan King, Robert Krueger, David Reiss, Chandra A. Reynolds, Neil Risch, Brent Roberts, Erica Spotts, Barbara Torrey, George Uhl, and Maxine Weinstein.

The overarching goals of the meeting were to explore ways in which genotyping on the HRS cohort can be used to expand behavioral and social research perspectives, to identify areas of behavioral and social science research for re-examination with the addition of genetic information, to identify new and innovative questions to be asked using the newly available genetic information in the HRS, to facilitate collaboration and encourage synergy between the social-science and genetics-research communities, and to inform the development of a separate panel that might be convened to further explore these issues.

The remainder of this report summarizes the main presentations and discussions at the meeting.

Session 1—Setting the Stage

HRS Updates and Plans

David Weir, University of Michigan

The HRS is based on a nationally representative sample of the U.S. population aged 50 years and older (plus spouses), with an oversample of African and Hispanic Americans. This longitudinal study is multidisciplinary in content and designed for public use, and its organizers are experienced with the handling of restricted-access data. Although data collection began in 1992, it was only in 2004 that discussions began about including genetics data. The 2005 renewal application (requesting funding for the 2006-2011 period) proposed the collection of biomarkers, including DNA collection extracted from saliva samples, of current health as part of the in-home interview, but no funds were requested for genotyping or analysis at that time. The biomarkers collection began on the first half of the sample in 2006, and followed on the other half in 2008. Meanwhile, there was ongoing discussion with NIA staff, the NIA HRS Data Monitoring Committee, and co-investigators about what studies to perform on the collected DNA. The HRS preferred the genome-wide scan approach over the model used by the English Longitudinal Study on Ageing (ELSA) that allows researchers to access DNA to do their own genotyping. Given that the HRS saliva samples provide a very limited amount of DNA, the GWAS approach seemed to be the most effective way to maximize use of the genetics information by researchers.

With funds from the ARRA, the HRS was awarded grants to genotype using Illumina million-SNP (single nucleotide polymorphism) chip on 13,000 samples in repository from the 2006 to 2008 waves, and to genotype an additional 7,000 samples collected in 2010 and 2012, including the large new oversample of minorities. The HRS has since upgraded the genotyping platform to the Illumina 2.5-million SNP chip (now costing approximately \$500 each), which covers all SNPs with a minor allele frequency (MAF) of at least 5 percent, and also accords much better coverage of genetic variation in African-origin populations. In principle, the HRS seeks the most advanced chip for the same price without affecting comparability to other platforms.

The 2006 samples are now at the Center for Inherited Disease Research (CIDR) and have undergone “pretesting,” while DNA is being extracted from the 2008 samples. Statistical cleaning will be done at the University of Michigan by Sharon Kardia and Michael Boehnke. The first set of data to the database of Genotypes and Phenotypes (dbGaP) will probably occur by mid-2011. The 2010 samples will be delivered to CIDR probably in mid-2011, and the 2012 samples in early 2013.

The HRS encourages use of its genetic data while protecting the confidentiality of participants. The dissemination model proposed by the HRS is to use dbGaP as the primary point of distribution of the genotype data, with very limited phenotype data. The HRS holds the key to linking dbGaP identification (ID) numbers to the HRS public ID numbers, and users would require a restricted data agreement (RDA) to obtain the key to link to the public data, just as an RDA is needed to link to Centers for Medicare & Medicaid Services (CMS) or Social Security Administration (SSA) records.

Weir discussed the risks associated with data dissemination. Although dbGaP has restricted access, it is outside the HRS' control. Genotype information is potentially matchable to other sources of genotype information; this is rare now but perhaps will not be in the future. Phenotype information is potentially linkable to public data, so it must be limited and carefully selected before being placed in a public database.

The first batch of 13,055 HRS DNA samples came primarily from respondents aged 55 to 75 years. White respondents contributed 78 percent of the samples; 13 percent and 9 percent came from black and Hispanic respondents, respectively. (The next 7,000 samples will roughly double the number of DNA samples from black and Hispanic respondents.) There is excellent correspondence between DNA samples and the collection of almost all physical measures (blood pressure, body-mass index, waist circumference, grip strength, and peak flow lung function); only about 56 percent of the DNA samples came from individuals who also participated in the timed walk test. The correspondence between DNA samples and availability of blood assay results varied by the assay: glycosylated hemoglobin (HbA1c; 92 percent), total cholesterol (88 percent), and high-density lipoproteins (HDL; 74 percent). Among respondents interviewed in the home, Weir reported about 80 percent cooperation with biomarker collection and expected that this number would rise over time.

The HRS is a large and influential study in the world of social science. Because of its emphasis on public use, many thousands of people have used the data, more than a thousand have written papers, and numerous other studies harmonize with the HRS. What the HRS does, and how it does it, will help shape the early stages of the integration of genetic data and theory into social science. The HRS has facilitated the cross-education of social scientists and geneticists. Future needs include financial and statistical support for analysis, better theories for identifying which genes are pertinent, better statistical models, and consortia with other studies.

Discussion immediately following Weir's presentation focused on family distribution and data access. Some feel that siblings are more informative than spouses. Weir clarified that the HRS is not a family study; it has not collected data on siblings or children. This is a potential area to consider but would require a major investment of funds.

Regarding data access and the RDA process, Weir clarified that the HRS process typically does not demand much specificity about the research because generally the HRS is not vetting the quality of the research but is more interested in the data-security plan and demonstration of careful data handling. The HRS requires investigators to provide evidence of a federally funded grant to qualify for data access. Some principal investigators have an RDA that permits students and other collaborators to participate when they might not qualify on their own. Richard Suzman suggested that it might be worth exploring whether investigators with a comparable research grant from foreign sponsors might also qualify for an RDA.

Robert Hauser was concerned that restricting eligibility only to principal investigators with a current grant, whether from the United States or elsewhere, precludes people who need to generate preliminary results in order to develop a convincing grant application. He called for alternative ways to establish the credentials of potential investigators to permit some type of limited access. Suzman explained that the requirement of a current grant is in place in part to satisfy the U.S. Treasury, the SSA, and CMS as an added precaution in making linked data available. Other options might be using data enclaves, working with synthetic data pools, or establishing a central statistical laboratory to perform the analysis so outsiders would not need to access the data—all have clear limitations and would need new funding.

Human Genetics Research: Past, Present, and Future
Hooman Allayee, University of Southern California

The human genetics research landscape has changed considerably over the past 10 to 15 years, with GWAS now a household name and perhaps even passé. Allayee listed the difficulties in studying complex traits including biological phenotypes such as cholesterol level, diabetes, heart disease, Alzheimer's disease (AD), and behavioral phenotypes. There is often no identifiable inheritance pattern, unlike Mendelian disease, which makes complex phenotypes much more difficult to study. They frequently exhibit late onset, environmental factors can affect susceptibility, and the effect of any one gene is relatively small. Limited penetrance and genetic heterogeneity also have been issues. Traditionally two competing hypotheses attempt to explain the genetics of complex disease, both of which may be correct: 1) common disease/common variants and 2) common disease/rare variants.

The conventional way to study complex diseases (e.g., diabetes, heart disease, lipid levels) has been to try to apply the same linkage methods that were very successful for studying Mendelian-type diseases in families to identify regions of the genome that might be responsible and to correlate those with phenotype in families. In this approach, linkage peaks are identified but there is not necessarily the resolution to identify the actual gene or variant. Another approach is to use genetic associations involving unrelated subjects. In the mid-1990s, this was limited to a candidate-gene approach, which did not work well unless the researchers were familiar with the underlying biological process and which gene or variants to target. The idea of identifying Mendelian forms of complex diseases and then testing variants of those genes for association did not work well because most complex diseases do not conform to Mendelian inheritance patterns.

Allayee used examples mostly from the literature on lipids (high levels of which are a risk factor for atherosclerosis) because this has been his area of research. He illustrated the importance of sample size to reveal previously unknown associations.¹ The Wellcome Trust Case Control Consortium published a GWAS study of 14,000 cases of seven common diseases and 3,000 shared controls and demonstrated the power of GWAS in identifying genes involved in common human diseases.² A little more than three years later, research based on 100,000+ individuals of European ancestry found 95 significantly associated loci ($p < 5 \times 10^{-8}$) for blood lipids, with 59

¹ Cohen JC, Boerwinkle E, Mosley TH, and Hobbs HH. 2006. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Eng J Med* 354: 12.

² The Wellcome Trust Case Control Consortium. 2007. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* 447 (June 7): 661-78.

showing genome-wide significant association with lipid traits for the first time.³ This demonstrates that the unbiased GWAS approach clearly works and holds promise for generating new therapeutic targets.⁴

GWAS was not feasible until recently because of technology—SNP chips had to be developed, and cost and sample size issues had to be overcome. Only recently have costs become more affordable and large numbers of samples become possible. A number of lessons learned from GWAS to date include:

- New genetic information does not appear to have any additional prognostic value for predicting future risk; detailed family history is just as good as genotyping 10 or 20 SNPs.
- There is still a lot to be learned about biological processes. Large numbers of genes do not play an obvious role in what is known of biological mechanisms.
- Identified genes only explain a small fraction of the phenotypic variance. As an example, those 95 loci for blood lipids only explain about 20 percent maximum of the phenotypic variance and 30 percent of the genetic variance. It is possible that interactions between gene and environment explain the rest of the variance.
- It is hard to know to what social and behavioral phenotypes or traits this approach can be applied until tried.

Future challenges and directions include the following:

- Identification of causal variants and genes and what to do about them
- Resequencing efforts to identify rare variants
- Full sequencing of genes' exons to satisfy interests in functional variance, complementing whole transcriptome shotgun sequencing and the promising area of the epigenome
- Functionality of the associated variants and genes (which requires biochemistry to understand how the variants are having an influence)
- Gene-gene interactions
- Gene-environment (GxE) interactions.

George Davey Smith commented that behavioral follow-up can be pursued, and intensive measures only require small numbers. As an example, he pointed to the first common variant related to fat mass, the fat mass and obesity associated (FTO) variant. He divided his subjects into fat homozygotes and thin-variant homozygotes in a recall study and used a mandometer to record the speed with which they moved food to mouth to illustrate the importance accorded to construct or behavioral studies. He added that epidemiologist Paul Burton has been developing two approaches, DataSHIELD and DataSHaPER, to permit analyses and extracts of the data

³ Teslovich TM, Musunuru K, Smith AV, et al. 2010. Biological, clinical and population relevance of 95 loci for blood lipids. *Nature* 466 (August 5): 707-13.

⁴ The National Human Genome Research Institute (NHGRI) website publishes a catalog of GWAS publications attempting to assay at least 100,000 SNPs in the initial stage (see <http://www.genome.gov/gwastudies/>).

without needing to directly access the data.⁵ Davey Smith is using this approach to share access to his data on 21,000 people for GWAS.

Other than taking particular genes and putting them in rodents to see if and where they are expressed, there are approaches outside of animal models that can be tried, depending on the phenotype. For example, one might consider adipose biopsies, or gene expression from whole blood, or cell culture. The focus on SNPs is in part because it is lower cost. It also was noted that common variants may be more relevant for diseases associated with aging. Schizophrenia, on the other hand, is very complicated with possible common variants as well as environmental interactions. For conditions like schizophrenia and autism, copy number variants (CNVs) seem to play a role, unlike for cardiovascular disease where CNVs (inferred from SNP chips) do not seem to be an important factor.

One line of thought suggests that anything having a strong effect on reproductive fitness will shift the balance toward rare variants as responsible for a substantial portion of complex human disease.⁶ Allayee considered rare variants important but noted that it is unclear how much of the variance they explain. It is possible that some genes have common and rare variants, while other genes contribute only rare variants. Rare variants would predominate for traits that impair reproductive fitness; common variants may actually be more prevalent for traits associated with aging that do not necessarily affect reproduction.

Suzman reiterated the importance of getting data out rapidly and cautioned that a leak in this area would be detrimental, especially given the linked administrative data to earnings records. DataSHaPER may be worth considering, or a secure data portal that would permit remote access to the data without needing to take possession of the data. According to John Hobcroft, the United Kingdom has set up a secure data service that permits remote access to data. NIA also will consider rapid ways to marshal modest funds for quick pilot studies.

Genetic Thinking in the Study of Social Processes: Some Entry Points *David Reiss, Yale School of Medicine*

Reiss traced the sequence of research foci, from genome to proteome, cellular system-signaling pathway, neural system, cognitive phenotype, symptom, and syndrome. Interactions between levels are clearly iterative and work to redefine both phenotypes and genes to target. Reiss focused in particular on genetic analyses related to three social variables—marriage and marital status (for which the HRS already has produced more than 100 publications), social integration and social participation (for which the HRS has fewer publications), and sibling relationships (for which the HRS has no publications despite including some sibling data).

⁵ Fortier I, Burton PR, Robson PJ, et al. 2010. Quality, quantity and harmony: the DataSHaPER approach to integrating data across bioclinical studies. *Int J Epidemiol*: 1-11. Advance Access published September 2. Available at: <http://ije.oxfordjournals.org/content/early/2010/09/02/ije.dyq139.full>.

Wolfson M, Wallace SE, Masca N, et al. 2010. DataSHIELD: resolving a conflict in contemporary bioscience—performing a pooled analysis of individual-level data without sharing the data. *Int J Epidemiol*. First published online: July 14, 2010. Available at: <http://ije.oxfordjournals.org/content/early/2010/07/14/ije.dyq111.full?sid=9369c3ad-a273-4ceb-94c9-03bbc48c2d7d>.

⁶ McClellan J and King M-C. 2010. Genetic heterogeneity in human disease. *Cell* 141 (2): 210-7.

Drawing on a very substantial body of literature, Reiss began with the classic 1983 paper by David Rowe on genetic influences on adolescents' perception of family environment.⁷ This was perhaps the first time that a behavioral phenotype was studied that was not strictly a descriptor of the individual being genotyped, and the findings suggest that perceived environment depends as much on the child's inherited traits as on the actual environment.

Reiss then reviewed how genetic work has impacted scientific thinking about interpersonal relationships. He noted that the most pivotal concept in the past 40 years is the notion that a relationship itself can be a phenotype. If we were to genotype one individual in a relationship, we can detect genetic information about this first individual by observing the response of another individual to the first individual.

A second principle that derives from this very substantial literature is the notion that genes, through mechanisms that are only beginning to be explored, confer varying genetic sensitivity to environmental risk. An adverse environment can lead to an adverse outcome in the presence of a high-risk allele but not in the presence of a low-risk allele.

A third principle—one that is less discussed but nevertheless plays a critical role—is that genes not only influence sensitivity to the environment but also influence how people act and therefore change the environment, that is, on agentic processes. Thus, a high-risk allele that might be expressed in a fussy infant has an impact on the environment, and if the environment (e.g. parents) reacts adversely, there can be an adverse outcome, but the expression of that same high-risk allele in a non-reactive (laid-back) environment would be less likely to produce an adverse outcome.

A fourth principle is the genetic influence on covariance, where genes can play a huge role in reformulating social theory. Often social scientists pride themselves on robust correlations between social variables and various individual capabilities. As it turns out, not only can genetic factors influence social and individual factors, but also it is possible that the same genetic factors can account for the associations between social factors and individual capabilities. Once this common genetic influence is taken into account, the parents' social effect can disappear. In the case of siblings, if common genetic influences are taken into account, it is possible to identify social variables that have influence on capabilities independent of genotype. And these social variables then loom large because they have to some extent been identified through genetic techniques.

This field has been heavily influenced by several key studies, including those by meeting participants Nancy Pedersen and Chandra Reynolds. Studies of twins reared apart and together, along with studies of unrelated siblings (e.g., children adopted from different families into the same adopting family) have yielded a great deal of information about the environment. Environmental influences that make identical twins different must be by definition non-shared environment (and error measurement). Anything that makes genetically unrelated siblings the same is referred to as shared environment. These become tools for exploring, testing, refuting, and magnifying certain social theories. For many outcomes, shared environment seems to play a very small role.

⁷ Rowe DC. 1983. A biometrical analysis of perceptions of family environment: a study of twin and singleton sibling kinships. *Child Dev* 54: 416-23.

Efforts have been made to study genetic influences on social phenotypes. Using a sample of 752 Swedish twin women and their spouses, Erica Spotts and colleagues examined genetic and environmental influences on marital quality. Genetic influences were found on wives' reports of marital quality, which was not surprising given that the genetic information came from the twin women. What was more surprising were the findings that the husbands of monozygotic (MZ) twins were more likely to give similar answers about marital satisfaction than the husbands of dizygotic (DZ) twins—indicating that genetic characteristics of the wives were influencing husbands' reports of how they viewed their marriages. This finding provides evidence that genetic attributes of the wives extend to phenotypes exhibited by their partners. Further study suggests that wives' personality characteristics (e.g., aggression and optimism) act as a mediator between wives' genetic influences and husbands' reports of marital quality.

Animal models can enrich our understanding of genes and behavior in humans. For example monogamous prairie voles and promiscuous mountain voles can be distinguished by a very particular area in a promoter region of a gene regulating vasopressin (arginine vasopressin receptor gene or *avPR*).⁸ The long allele in prairie voles is associated with rich distribution of vasopressin receptors in the olfactory septum, which are areas connected to social recognition.⁹ In an effort to extend this animal work to humans, researchers used a measure of “partner bonding” (e.g., involved in common interests with partner, don't like people to come close, frequently kiss partner) in a human sample. Findings indicated that pair bonding in men, but not women, was significantly associated with the RS3 alleles of the vasopressin receptor gene. Additionally, pair bonding varied by the allele the men were carrying with bonding being lower for men carrying the 334 allele. This allele had a dose-dependent effect depending on how many copies the man was carrying. Men carrying the 334 allele were more likely to have experienced a marital crisis or threat of divorce in the past year and were more likely to be in a cohabiting relationship without being married than carriers of other alleles. There was also a dyadic effect in that the wives of male carriers of the 334 allele were less satisfied in their marriages than wives of non-carriers.

Reiss cautioned that these findings have not been replicated, and *d* (a measure of effect size) is small for true social phenotypes (equal or less than .20). He added two very important caveats. First, rodent data suggest that the short (promiscuous) *avPR* form evolved recently; the long form is more ancient and is widespread in many rodent species that are not monogamous.¹⁰ Therefore even though these genes may have an effect, clearly they are embedded in a network of genes, which might be identified through GWAS. Second, genetic effects on some marital variables are far from constant across the lifespan. If we take being currently married as a phenotype, the genetic influence on marriage is low in early adulthood, rises in middle adulthood, and is absent in late adulthood, and seems to have a great deal to do with both economic conditions and legislative changes about marriage and divorce. Thus there can be major cohort and/or developmental effects longitudinally on the expression of genetic influence on complex behavioral phenotypes.

⁸ Fink S, Excoffier L, and Heckel G. 2007. High variability and non-neutral evolution of the mammalian *avpr1a* gene. *BMC Evol Bio* 7 (September 27): 176.

⁹ Nair HP and Young LJ. 2006. Vasopressin and pair-bond formation: genes to brain to behavior. *Physiology* 21: 146-52.

¹⁰ Fink (2007).

If there is a genetic influence on a social phenotype, how might that allow us to reorganize or rethink classic associations? Reiss referred to a chart showing levels and trajectories along four dimensions of competence in aging (strength, depression, cognition, social activity) for the Longitudinal Study of Aging Danish Twins. Between ages 70 and 100, all dimensions show decline except for depression. Matt McGue and Kaare Christensen have shown that the levels and to a lesser extent the trajectories of these dimensions show genetic influence.¹¹ So too does social activity—a phenotype with genetic influence. Putting the two together in a third analysis suggested that the covariation between social activity and these various levels and slopes are due to common genes.

Reiss next described analyses by Jenae Neiderhiser on family process, peer-group delinquency, and illegal drug use initiation 11 years later. This study identified a common genetic factor that evoked marital conflict, that sibling conflict in the adolescent period also influenced illegal drug use 11 years later; and that a second genetic factor was common to parental monitoring, peer group delinquency, and illegal drug use 11 years later. Genetic analyses helped elucidate that for adolescents parental monitoring is not a capability of the parent as much as it is of the child. Variation among parents reflects how much the child discloses, not how much the parent discovers. It is not surprising that the same set of genes influences whether the child gets involved in peer-group delinquency and also leads 11 years later to illegal drug use. However, the relationship between sibling conflict and illegal drug use is entirely due to the shared environment. Sibling conflict predicts (not necessarily causes) illegal drug use 11 years later, independent of the child's genotype. Reiss drew two tentative conclusions from this genetic study: 1) Marital conflict, parental monitoring, and peer-group delinquency could be mediating processes through which genes influence adverse outcomes. As a consequence, there might be opportunities for interventions that are not pharmacogenetic but may be social. 2) Use of genetic data can bring to the fore the importance of sibling relationships, which have been little explored in the study of family processes, and can draw attention to their potential role as environmental variables.

Reiss concluded that the use of powerful genetic techniques in a study like the HRS, which has been focused on social processes, does not necessarily mean only the medicalization and geneticization of social science. It can also elevate, focus, and strengthen understanding of social processes and perhaps lead to interventions that may be social and not biological.

Discussion

Reiss agreed with Sharon Kardia that there is a very large gap between the 2.5 million SNPs and their associations with phenotypes on the one hand, and the biometrical approach of being able to partition variability and covariability on the other. Biometric quantitative genetic models help raise appreciation for variables thought to be very different biologically, such as peer-group involvement, sibling relationships, or marital relationships, and outcomes such as depression, and may have many common genes. Just as in the Wellcome studies, in which genes for very different illnesses turned out to overlap significantly, biometric analyses should push us to reassess our understanding of common pathways.

¹¹ McGue M and Christensen K. 2007. Social activity and healthy aging: a study of aging Danish twins. *Twin Res Hum Genet* 10(20): 255-65 (April).

Reiss considered it worthwhile to radically rethink the meaning of environment. Genetic data, even biometric models, help us recognize that we have to be absolutely certain when we are considering the environment-moderating genetic effects (whether inferred from quantitative studies or discovered from GWAS) that we are indeed talking about the environment and not an environmental variable that reaches its particular level because genes have selected individuals into such environments (i.e., individuals genetically prone to high stress level choosing calm jobs and vice versa), or genes have led to behavior that have changed that environment. In those two senses, biometric models are very useful guides in gene hunting, and having these genetic data can help encourage a new level of sophistication in analyses.

Robert Krueger considered the heritability of environment as an easy concept to misunderstand, despite it being an incredibly important contribution of behavioral genetics and the social sciences. An individual's perception about his or her environment (e.g., in response to a question about the family in which he or she was raised) can show some heritability. Environments are created by people and are therefore not completely exogenous, and some portion of the environment stems in part from the individual and his or her interpretation of it.

The advantage of twin and adoption studies is their ability to help disentangle genetic and environmental factors. One concern, however, is the assumed heterogeneity in environment between adopted and biological children. If their environments are actually not too different but partly matched, then this would overestimate the genetic heritability contribution. Some empirical studies have begun to tease this out. Hauser once estimated the correlation between socioeconomic status (SES) of the families of twins reared apart to be approximately 0.8.

Session 2—The Population Genetics Perspective: What Do SNPs Give Us When We Have a Population Representative Random Sample?

What Can Genes Tell Us About Modifiable Causes of Disease?

George Davey Smith, Bristol

Many biases may be inadvertently introduced into studies of the interaction of environmental and genetic factors on health outcomes. For example, studies of the influence of alcohol consumption on disease risk can be confounded by lifestyle and socioeconomic factors related to drinking, and biased by self-reporting inaccuracies or modification of drinking behavior due to the early stages of disease. Observational and randomized trials are likewise difficult to conduct on this topic. Studies of genotypes are not susceptible to such confounding or biases.

When alcohol is consumed, it is converted to acetaldehyde by alcohol dehydrogenase and then to acetic acid by aldehyde dehydrogenase (ALDH). Several recent studies have focused on ALDH genotypes and alcohol consumption in Japanese men—Japanese women tend not to drink alcohol, thus little correlation was seen between women's genotypes and their levels of alcohol consumption. Men with one copy of the null variant of ALDH on average drink less than half the amount of alcohol per day as men with two copies of the wildtype gene, whereas men with two copies of the null variant tend to drink very little or not at all.^{12,13} No correlations were seen

¹² Takagi S, Iwai N, Yamauchi R, et al. 2002. Aldehyde dehydrogenase 2 gene is a risk factor for myocardial infarction in Japanese men. *Hypertens Res* 25 (5): 677-81.

between ALDH genotype and age, smoking status, body-mass index (BMI), or blood cholesterol levels.¹⁴ A meta-analysis of pertinent studies shows a correlation between ALDH genotype and blood pressure and between blood pressure and alcohol consumption in Japanese men as well, and again no correlation of either in women.¹⁵ Combining and comparing such data from a variety of studies enables researchers to estimate the cause and effect of alcohol consumption on blood pressure.

Intermediate phenotypes, such as cholesterol levels in coronary heart disease or interleukin-6 levels in cardiometabolic diseases, can be investigated through Mendelian randomization studies. Whether such indices are causal or markers of disease may be teased out with careful experimental design. For example, BMI might be a cause, reverse cause (i.e., effect), or confounder in studies of health outcomes. The fat mass and obesity-associated (FTO) genotype is correlated with BMI. Metabolic traits, such as fasting insulin levels, have been demonstrated to vary with FTO genotype as expected if BMI is a causal factor.¹⁶ Mendelian randomization studies can demonstrate when pleiotropy is unlikely to have biased findings.¹⁷

A participant pointed out that public policy will be influenced by information pertaining to environmental effects, such as dietary choices that contribute to increased BMI, rather than genetic effects, such as FTO genotype. Davey Smith indicated that the Mendelian randomization approach is based on the fact that whether increased adiposity is of genetic origin or is due to overeating it will have the same effects on downstream health outcomes that are generated by adiposity. Mendelian randomization studies can parse out whether intermediate phenotypes such as BMI, or behaviors such as smoking and drinking alcohol, are causal for problems such as coronary heart disease (CHD) or lung cancer, and are therefore targets for intervention.

GWAS will allow the types of approaches described to be applied in the HRS to strengthen the understanding of causal associations, for example, the nature of the correlation between cholesterol levels and cognitive decline. However, genetic variants tend to account for only small percentages (approximately 3 percent) of variance in a population, which is why large numbers of subjects are required.

A Resource for Genetic Epidemiology Research in Adult Health and Aging *Neil Risch, University of California at San Francisco*

In collaboration with Kaiser Permanente and the laboratory of Elizabeth Blackburn, the University of California at San Francisco Institute for Human Genetics is conducting an RC2 Grand Opportunity project to create a resource for research into the genetic and environmental basis for common age-related diseases and their treatment, and factors influencing healthy aging and longevity.¹⁸ The project links electronic medical record and survey and environmental

¹³ Chen L, Davey Smith G, Harbord RM, Lewis SJ. 2008. Alcohol intake and blood pressure: a systematic review implementing a Mendelian randomization approach. *PLoS Med* 5 (3): e52.

¹⁴ See Takagi et al. (2002).

¹⁵ See Chen et al. (2008).

¹⁶ Freathy RM, Timpson NJ, Lawlor DA, et al. 2008. Common variation in the FTO gene alters diabetes-related metabolic traits to the extent expected given its effect on BMI. *Diabetes* 57 (5): 1419-26.

¹⁷ Davey Smith G. 2010. Use of genetic markers and gene-diet interactions for interrogating population-level causal influences of diet on health. *Genes and Nutrition* DOI 10.1007/s12263-010-0181-y.

¹⁸ Funded by the National Institute on Aging, the National Institute of Mental Health, and the National Institutes of Health Director's Office.

exposure data with genetic data from biospecimens from 100,000 adults. The study population self-selected from 1.9 million Kaiser Permanente members. The cohort is approximately two-thirds female and ranges in age from 18 to 90 years old with an average age of 65; approximately three-quarters of the cohort is white.

The project will analyze telomere length and perform GWAS using custom ethnicity-specific SNP array chips for 675,000 SNPs. GWAS, genetic, biomarker, and telomere data will be merged with the clinical (outpatient, inpatient, laboratory, pharmacy, imaging, pathology), patient survey and interview, and environmental (air, water, pesticide, and social) exposure data in a research database to create an infrastructure tailored to research datasets and to enable collaboration for prospective researchers. Unique advantages of the study include the consistency provided by 100,000 participants' biospecimens analyzed on the same platform in the same laboratory, facilitating comparisons between groups within the cohort, and the wealth of information on each cohort member from the clinical, demographic, and administrative databases.

The cohort includes thousands of patients representing many common diseases, including cancer, arthritis, depression, asthma, angina pectoris/myocardial infarction, and post-traumatic stress disorder. Common laboratory results, such as metabolic measures, BMI, and blood pressure, are available for all or nearly all members of the cohort, and brain imaging scans are available for tens of thousands. Because more than 70 percent of cohort members have been involved with Kaiser for 10 years or more, longitudinal data are available for many of these tests. Extensive co-morbidity information is also available through the electronic medical records. It has not yet been decided which of the numerous variables collected will be made publicly available in dbGaP.

Approximately 600 DNA extractions are performed daily on four automated systems; approximately 400 of these samples are analyzed daily on the custom SNP chips. A 128-processor Linux cluster provides the computing infrastructure necessary to facilitate quality control and data analysis for the project. A panel of advisors is addressing how privacy information and concerns will be managed and tracked with the data.

The SNP chips being designed for the project incorporate the unique set of rare variants and linkage disequilibrium patterns for Caucasian, Asian, African-American, and Latino ethnic groups. To optimize the chips, also included were known SNPs chosen for their demonstrated importance in published GWAS and candidate gene studies and SNPs recently identified in the *1000 Genomes Project*. Low-frequency variants were overrepresented for improved coverage.

To date, more than one-third of the cohort has been genotyped. The SNP call rate and reproducibility are greater than 99 percent, and the sample success rate has been approximately 95 percent for saliva samples and greater for blood samples. Results from some preliminary analyses should be available within a year.

Discussion

The SNPs on the custom Affymetrix chips are likely to significantly overlap with the SNPs on the Illumina chips in use for the HRS, allowing for the possibility of combined GWAS analyses

between the projects. It is possible that the excess DNA from each sample may be made available for additional genotyping as needed.

Telomere length evaluation has begun in a pilot project on saliva and blood samples from 40 patients. The results have proven highly reproducible, and samples from the different tissues from the same patient show approximately 60 percent correlation. The DNA from saliva samples appears to derive from leukocytes rather than buccal cells, as was previously believed, but it is not yet clear which tissue will prove to be optimal for the telomere-length study.

In response to a question concerning whether any socioeconomic characteristics were collected on participants in the Kaiser cohort, Risch explained that this project includes cross-sectional but not longitudinal data on social questions, and it does not include behavioral indices such as personality traits. Sociodemographics information is partially based on self-reporting and partially based on inferences from the cohort participants' neighborhood contexts.

Session 3—Can GWAS Be Used to Special Advantage in Longitudinal Data?

An Epidemiological Perspective on Longitudinal Data *Yoav Ben-Shlomo, University of Bristol*

From the perspective of a life-course epidemiologist, Ben-Shlomo covered issues related to diseases, traits, and trajectories, including longitudinal data for better phenotypic classification; better measurement of environmental factors for interactions; triangulation of outcomes and intermediaries; the study of variability as well as means; and the role of natural and real experiments and the potential for conducting sub-studies in the HRS to provide a better handle on causality.

The Wellcome Trust Case Control Consortium¹⁹ is a wonderful example of a case control study. Measures of phenotypes in such a study might capture severity (e.g., degree of heart failure), etiological origin (e.g., AD versus vascular dementia), age at onset, and type of onset (e.g., sudden versus gradual). However, only longitudinal data can provide evidence on pre-clinical features and rate of decline, which can be especially relevant for traits that may vary gradually or more rapidly (e.g., cognitive changes prior to the onset of dementia).

To illustrate the importance of temporal ordering of exposure variables, Ben-Shlomo pointed to a schematic representation of the life course of respiratory function for three groups:²⁰

- Group A—normative decline—respiratory function increases with developmental change, plateaus in midlife, and then declines with aging, which may or may not have any functional relevance in terms of activities of daily living (ADLs)

¹⁹ See, for example, <http://www.sanger.ac.uk/about/press/2008/081207-2.html>.

²⁰ Ben-Shlomo Y and Kuh D. 2002. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. *Int J Epidemiol* 31 (2): 285-93 (April).

- Group B—suboptimal developments—assumed to have the same genetic potential, these people have not developed as expected but by midlife their decline in respiratory function seems to follow the same normative pattern
- Group C—respiratory function develops normally but then experiences a more rapid decline.

In his example, Groups B and C end up at a lower level of clinical lung function relative to Group A, but genetics might play a larger role in particular pathways. One could argue that Group B experienced a sensitive period effect, whereas Group C might be influenced more by environmental contributions such as smoking.

Ben-Shlomo discussed other examples in which the availability of longitudinal data has generated new insights into the empirical literature (e.g., related to the probability of wheezing in childhood, depression and anxiety, quitting alcohol during pregnancy, and osteoporosis),²¹ including identifying instances of multiple pathways that generate different outcome measures and measuring environments for interactions (as illustrated by examples related to osteoporosis and obesity).²² These typologies are often generated purely from a statistical basis, but can relate to a variety of outcome measures and clinical diagnoses, and with genetic markers, which suggests some validity to this approach. The presence of GxE interaction suggests that single or even repeat measures may underestimate effects unless data on patterns and timing of trigger events are available to help sort out whether effects are being driven by sensitive periods of exposure or simply the accumulation of effects operating with genotypes.

Ben-Shlomo turned next to the importance of variability, instability, and episodic nature of measurements, using blood pressure as an example.²³ Rothwell (2010) has found that the variability in systolic blood pressure (SBP) is a stronger predictor of stroke risk than mean SBP and is independent of the mean. Thus, variability can be more than just measurement error and may capture important physiological parameters, and variability can only be measured with longitudinal data.

Ben-Shlomo called for the use of longitudinal data to study within- and between-subject variability to uncorrelated natural experiments stratified by genotype. For example, one can compare within-subject changes in phenotype (e.g., mood, cortisol, BP) before and after life events (e.g., unemployment due to factory closure) among subgroups with and without predisposing genotypes. Multiple repeat measurement points are needed because exposure is unpredictable and the short- and long-term effects should be captured.

²¹ Henderson J, Granel R, Heron J, et al. 2008. Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. *Thorax* 63: 974-80.

Colman I, Ploubidis GB, Wadsworth MEJ, et al. 2007. A longitudinal typology of symptoms of depression and anxiety over the life course. *Biol Psychiatry* 62: 1265-71.

Zuccolo L, Fitz-Simon N, Gray R, et al. 2009. A non-synonymous variant in ADH1B is strongly associated with prenatal alcohol use in a European sample of pregnant women. *Hum Mol Genet* 18 (22): 4457-66 (November 15).

²² Ralston SH and Uitterlinden AG. 2010. Genetics of osteoporosis. *Endocr Rev* (April 29) [Epub ahead of print].

Hardy R, Wills AK, Wong A, et al. 2010. Life course variations in the associations between FTO and MC4R gene variants and body size. *Hum Mol Genet* 19 (3): 545-52.

²³ Rothwell P. 2010. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. *Lancet* 375: 938-48.

He also considered the possibility of undertaking a randomized control trial (RCT) paradigm among subgroups sampled by genotype and longitudinal data on exposure (e.g., social support). One might then compare within- and between-subject changes in cognitive performance before and after a social stress test, stratified on longitudinal history of good, poor, and fluctuating social support. However, such studies are expensive and only evaluate subgroups, not the whole cohort.

Ben-Shlomo concluded with the following points for discussion, adding that harmonization and costs are challenges that need to be considered:

- Help tease out phenotypic heterogeneity using data on disease/trait trajectories; better characterize environmental exposure and study variability
- Develop inexpensive methods for repeat assessment (e.g., Web-based or telemedicine methods) or access routine data to provide contextual information about where people live and their experiences (e.g., crime rate, access to green space)
- Develop validated questions on retrospective data or record linkage to existing past data (e.g., school anthropometry data archive in Denmark)
- Develop methods to facilitate data harmonization for cross-cohort synthesis
- Consider whether the HRS can be used for nested sub-studies, sampling by genotype or phenotype.

Discussion

Risch noted that Kaiser Permanente historically has conducted health surveys and multiphasic examinations, and for approximately 20,000 individuals in Kaiser's cohort of 100,000 there are laboratory test results and self-administered questionnaires going back 40 years.²⁴ A real challenge is the impact of medication on phenotypes and subsequent outcomes. The virtue of the Kaiser cohort is the ability to reconstruct data (e.g., prescriptions filled) that make it possible to study pharmacogenetics, track complicated drug interactions, and look at other outcomes of interest. Ben-Shlomo agreed that these data could be very interesting, and that medication effects are going to be a challenge. In the case of BP, he noted that modeling the effect of a drug on BP helped smooth transitions with age. Medication use also can be differentially influenced by socioeconomic status and ethnicity.

Reiss commented on the various trajectories that are influenced by time-specific events, which raise significant cohort effects. Specifically considering the HRS, one must think about how to bootstrap harmonization or to look within the HRS sample to check if profiles are general development ones or highly specific historical profiles (e.g., before WWII). To Ben-Shlomo, it would be a very useful exercise, more for hypothesis generation, to plot the between-cohort variability (e.g., in age-related changes in the trajectory of a phenotype) to see whether it is a fundamental biological developmental trajectory that is altered.

²⁴ Rachel Whitmer has made good use of this information to show that midlife risk factors like BMI and lipidemia are 30 years later predictors of dementia. See: Whitmer RA, Gustafson DR, Barrett-Connor E, Haan MN, Gunderson EP, and Yaffe K. 2008. Central obesity and increased risk of dementia more than three decades later. *Neurology* 71 (14): 1057-64 (September).

In Kardia's experience, using longitudinal data to either estimate a parameter that represents the entire trajectory or the average of the variables increases the power to detect genetic effects. Longitudinal data therefore add value in that regression to the mean helps with measurement error. Looking at phenotypic variability as the actual outcome is directly related to GxE interaction because differences in variability are going to reflect the wider range that certain genotypes have in their phenotypic expression for the distribution of environments in a population. There is literature on variability differences as the outcome in biology where these differences are related to genetics or are actually reflections of other lines of interactions within the environment.

Maxine Weinstein sounded the theme that more is more, for example in terms of replication as a way of identifying false positives, increasing power, and resolving generalizability, which covers a multitude of issues such as representativeness of the sample. She observed that most social scientists do not see biological parameters as culturally dependent, even though they may be. Without a perfect dataset, how does one take the 20,000 cases in the HRS and merge them with the 100,000 cases in the Kaiser file, and stitch them together into a coherent data resource?

According to Kardia, the accepted practice for GWAS has been not to question the quality of others' data. There is a huge amount of collaborative trust. Participants trust that groups of people are capable of generating and executing plans, and that the organizational resources exist to pull the pieces together. At this stage, we are pooling data imperfectly and missing many of the details at the general level, but doing the best we can with what we have. In the next generation of studies, we would expect to pick up the next level of detail.

Risch was more optimistic given the fairly robust associations found in the Wellcome Trust lipids study despite the odds. One of the virtues of the Kaiser data is that the population includes people from all different SES backgrounds, making it possible to look across sociodemographic groups, ethnicity, personal behaviors, and interactions with genetic risk factors. Genes are operating in a context-dependent environment.

It seemed to Daniel Benjamin that the overall approach will have to be sequential. In terms of identifying associations between specific genetic variations and a given phenotype, we will need large samples to see results. Richard McCombie observed that population sizes of 100,000 or more will by design pick up associations with minor impact on phenotypes. Some of the metabolic research to date has used much smaller sample sizes to correlate genotypes, that is, using fewer people with richer information. Once identified in a large sample, smaller datasets (10,000 or 20,000 in size) can be used to look for interaction effects. Krueger underscored the importance of the phenotype and the ability of the model to characterize phenotypic variation.

Kardia observed that two decades of genetic association work have been plagued by lack of replication. Gene expression work is just as labile as surveys, with a great deal of variability. Researchers must be willing to demand accountability in that findings must demonstrate significance, must be sequential, and must have functional relevance. Davey Smith echoed this point, commenting that despite the enthusiasm among social scientists for GxE interactions, the literature is filled with utterly spurious interactions, and serious attempts at replication have failed. The few replicated GxE interactions typically have the name of the environmental exposure in the name of the gene (e.g., alcohol, lactase). The interactions that can be informative are the ones with genuinely no effect in one group, or an effect that reverses directions. The ones

involving evolutionarily novel exposures can produce a large interaction effect, the most prominent of which are in the area of pharmacogenetics.

Studying GxE interactions requires that there be sufficient variability in the environment, like there is in the HRS. Jason Boardman stated that we need to agree on what constitutes environmental moderators, which can go a long way toward replication when properly weighted. John Hobcraft considered it worth reinforcing that a fundamental question is why some findings do not replicate, although this can be partially explained by how the study is designed. For many purposes, it is appropriate to use relatively homogeneous populations. For other purposes, it is important to have accurate samples from an array of specific-origin peoples. In some ways, having larger samples of minority groups within a similar environment is necessary.

Risch added that the systems biology approach is critical. GWAS has produced by and large weak effects but also has identified pathways. This is where biological headway can be made to understand the SNP data. Having the risk variance identified for a large cohort is a good way to assimilate all available information. Population structure may be more of an issue than people recognize. There is relatively high assortive mating depending on ancestry. What surprised Risch was the high correlation (approximately 60 percent) of ancestry between spouses in the Framingham study. There is significant stratification even within major race/ethnicity groups. The impact of this on genetics is still unknown.

To Risch, it seemed most important to establish a relationship between known and clearly replicated gene findings, and known and clearly replicated environmental factors. Historically, people value interactions because they reveal something about biology or systems biology. But we are now in the realm of modest effects. In looking at multiple SNPs and many environmental factors, there is a significant risk of generating many false positives, with poor chances of replication. Risch therefore proposed starting with significant main effects to see what can be established in terms of relationships between known genetic and environmental risk factors.

For publication purposes, it is widely required now for a GWAS to have a replication sample. Risch suggested that attention should shift to other types of replication rather than using the same type of study. Publication in a high-visibility journal is less about having a replicable finding than it is about functional significance, which is much more challenging now with minor effects. However, that may be where the field is now; it is difficult to replicate in another cohort of 100,000 based on a different study design.

Weinstein added that replication is complicated by the fact that we are not actually looking at functional elements in GWAS. We are looking at genome-wide SNP identification rather than genes, and it would be a mistake to assume that SNPs are identical to the functional unit.

Session 4—Social Regulation of Gene Expression and Gene-Environment Interactions

Social Signal Transduction and Gene-Environment Interaction: Borrowing Power *in Silico* *Steve Cole, University of California at Los Angeles*

When conducting investigations to identify GxE interactions that influence health, blind searching is highly inefficient because of the billions of potential interactions generated. The process can be significantly accelerated by identifying likely genetic targets for investigation prior to the investigation. Candidate genes that seem likely to be influenced by the environmental factors in question might be identified from literature searches; however, this approach has the drawback of limiting discovery to information that is already known or suspected. A more general approach is to use unbiased, genome-wide bioinformatics to model GxE interactions *in silico* and to identify candidate gene sets, and then to confirm these theoretical results *in vivo*.

The dynamics of how social factors can interact with genes to regulate phenotype can be modeled to varying degrees of complexity. An example of such a “social signal transduction” interaction is the effect of stress on gene expression. Environmental or social stress will lead to changes in neuroendocrine function; stress-related hormones will bind to their specialized receptors to activate intracellular signal transduction cascades, which in turn bind to DNA, altering RNA transcription and leading to changes in protein levels that affect patient health.

One mechanism by which social signal transduction regulates gene expression is via binding of specific transcription factors to the promoter region of the gene. Even one polymorphism in the promoter region of a gene might influence the ability of the promoter to bind, leading to differential effects of environmental stimuli on that gene in different individuals via that single polymorphism. This offers a prediction opportunity to model GxE interactions at the molecular level: postulating which environmental stimuli interact with which intracellular transcription factors will identify promoter regions most likely to exhibit polymorphisms responsible for differential gene expression reactions to those stimuli; these, then, are the regions in which to search for polymorphisms using GWAS.

Another method that can narrow the search prior to performing GWAS is to perform gene expression analyses in response to the environmental stimulus of interest. This will enable researchers to evaluate empirically which genes’ expression levels are altered differently in different individuals by the environmental factor, and then evaluate GWAS results for polymorphisms in those genes. For example, this approach may be taken to evaluate GxE interactions in people confronting adversity. Chronically stressed individuals show an increase in the expression of genes with NF- κ B binding sites in the promoter and a decrease in the expression of genes with glucocorticoid receptor binding sites (likely due to a functional desensitization of the glucocorticoid receptor in chronic stress). To understand the genetics that modulate these responses, we must identify and evaluate SNPs in promoters that contain NF- κ B binding sites and glucocorticoid receptor binding sites to associate specific polymorphisms with differential responses.

An example in which power from *in silico* was used to inform GWAS may be seen in the case of inflammatory gene expression in response to socioenvironmental adversity leading to inflammatory promotion of cardiovascular and neurodegenerative diseases. Recognizing that adverse social conditions might be altering transcription activity via by activating transcription factors, investigations were performed on the promoter sequences of genes found to be up-regulated in people confronting chronic stress and in animal models of experimentally imposed social stress. GATA1 was identified as one socioenvironmentally responsive transcription factor, and *in silico* analyses then searched the human genome for polymorphisms in gene promoters that might affect GATA1 binding and thus socioenvironmental regulation of gene expression. One candidate polymorphism was identified in the IL-6 promoter, and test tube biochemical studies showed that this genetic variant blocked the ability of catecholamines to induce IL-6 gene expression. In a follow-up genetic epidemiology study, individuals experiencing subjective life adversity were identified by depressive symptoms, and those bearing the stress/GATA-sensitive version of the IL-6 gene promoter showed an increased rate of death due to inflammation-related diseases (cardiovascular, cancer, neurodegenerative). Individuals carrying the GATA1-insensitive variant of this polymorphism were protected from stress-associated increases in mortality, likely because social adversity could not increase IL-6-mediated inflammation via the GATA site in the gene's promoter.

Bioinformatic identification of GxE candidates offers the advantages of concentrating candidate causal GxE interactions while excluding functionally implausible or uninterpretable candidates. Investigating orders of magnitude fewer candidates considerably increases statistical power over blind-search studies. As computational models improve, this concept might be extended to other interactions. The approach has some drawbacks, however, such as the numerous candidates that require investigation even after constraining the search, and the possibility of overlooking influences that have not been previously modeled, such as unknown transcription factors or modifiers of transcription factor activity.

Specific opportunities offered by this approach include forming unbiased hypotheses *in silico* concerning first-order molecular genetics such as modeling the biology of the environment in the vicinity of pertinent genes. It also enables formation of second-order statistical hypotheses, such as those relating to environmental variance relating to the non-linear dynamics of gene expression over time. For example, recursive influences are abundant in gene expression, in which expression of the gene interacts with the subsequent environment to lead to other GxE effects that in turn are influenced by additional environmental factors.²⁵ The longitudinal nature of the HRS might facilitate studies into these sorts of recursive influences.

During the discussion immediately following Cole's presentation, it was noted that a limitation of this approach involves the inability to sample human brain tissue to evaluate intracellular transcription pathways and gene expression. However, model systems in non-human animals that, for example, elucidate transcription signal transduction, can do so and thus can inform GxE studies in humans.

The described approach will shift the focus to causal variants for some GxE investigations. Because of the wealth of genome-wide data currently available for analysis, the drawback of

²⁵ Cole SW. 2009. Social regulation of human gene expression. *Curr Dir Psychol Sci* 18 (3): 132-7.

potentially missing influences that are not currently adequately characterized will not be problematic until the logically plausible correlations have been identified.

Unlike blind searches, application of the *in silico* approach or Mendelian randomization can make researchers fairly confident that the GxE interactions they identify are causal and not due to random chance or reverse causation. However, it is true that all potential confounders can never be fully anticipated. The environment in which humans currently exist is vastly different from that in which they evolved, and this must be considered when attempting to reason through mechanisms of GxE interactions and correlations.

The Social Component of Gene-Environment Interplay: Potential Contributions from the HRS
Jason Boardman, University of Colorado at Boulder

The formal definition of social epidemiology is “the branch of epidemiology that studies the social distribution and social determinants of states of health.”²⁶ This paradigm emphasizes norms—that is, characteristics shared uniquely by people in discrete social environments—as well as mechanisms that enforce norms, environmental opportunities to engage in behaviors and why people are rewarded or punished for those behaviors, and exposure to ambient and chronic stressors. The embodiment theory of social epidemiology examines how humans biologically incorporate the material and social environment into their physical beings, that is, a biological expression of social relations. Thus, modern social epidemiology emphasizes the *pathways* of embodiment. For example, the social, economic, physical, and institutional environments act through the pathways of the individual’s psychology, physiology, and health-related behaviors to affect that individual’s morbidities, such as obesity, cancer, diabetes, or hypertension. Studying such pathways can be challenging because few data sources on morbidities include social, physical, institutional, and economic information.

The embodiment theory encourages consideration of both immediate and distant risk factors. A learned health-related behavior such as smoking, for example, occurs within a social context with numerous influences, such as whether cigarettes are inexpensive or expensive, cigarette use is limited or unlimited, and smoking is positively or negatively sanctioned. As such, it is difficult to parse out genetic associations without situating those associations within the proper social context.

Boardman’s research involved conceptual models of molecular-level operations as a function of social forces. In the example of smoking behavior, any latent tendency to use nicotine requires a social trigger that must be crossed before the genetic factors will come into play. Strong social regulation on smoking will decrease the influence of genetic factors on smoking behavior. The genetic differences between individuals will be most apparent when the social environment is most predictable and controlled.

The social component of the environment in GxE studies should be characterized as multilevel. This characterization includes social relationships such as friendships and families and physical and social places such as homes, schools, and workplaces; multidimensional, incorporating contexts such as culture, norms, attitudes, beliefs, institutions, and built environments as well as

²⁶ Berkman LF and Kawachi I. 2000. *Social Epidemiology*. Oxford: Oxford University Press.

sociodemographic and socioeconomic composition; and longitudinal, incorporating intra-individual growth and change along with changes in social settings over time.

It is possible that a failure to consider GxE interactions explains why the data published correlating number of stressful life events and risk of depression with a polymorphism in the serotonin transporter gene²⁷ have had a fairly weak replication record.²⁸ GWAS interpretation requires social context; it is unlikely that one polymorphism will correlate to one measured environment; one must consider multiple levels of the environment.

Boardman took advantage of the National Longitudinal Study of Adolescent Health (AddHealth) to study GxE interactions on smoking behavior in twins and siblings living in different states. Smoking onset and daily smoking were both shown to be genetically influenced. Because people are unlikely to choose a state in which to live based on the smoking rate in that state, exogenous factors in the state's environment, such as access restrictions and cigarette taxes, are likely to suppress or enhance genetic tendencies to smoke. Genetic influences on smoking onset were consistent across states, while the heritability of daily smoking varied, being lower in states with higher cigarette taxes and greater control on access and advertising.²⁹ This is an example of social control influencing the extent to which genes may predict a complex behavior like smoking.

In another study, Boardman evaluated school atmospheres and the heritability of smoking rates. Popularity, as measured by the number of other students listing an individual as a friend, age of smoking onset, and daily smoking were evaluated. The heritability of smoking onset was consistent across all schools measured, whereas daily smoking was higher in schools in which popular students smoke; the fact that popular students were smokers acted as a social trigger for others to do so.³⁰

The influence of social distinction can be seen in a study of the genetic influence on twins and siblings becoming smokers; strong genetic influences were seen for individuals born in the 1920s, 30s, and 50s, but not the 40s and 60s. The timing of the first Surgeon General's report warning of the harm from smoking coincided with increased genetic influence on becoming a regular smoker, but subsequent legislation restricting where individuals may smoke (social control) reduced the genetic influence. This demonstrates a potential pitfall of single-time-point GxE studies and the utility of longitudinal studies in estimating the genetic influence on health behaviors while accounting for the modulating effects of social factors.

This framework can be extended to GWAS with software packages that offer genome-wide GxE modeling. However, there is no consensus on the best method by which to incorporate the additional parameter of social context into GxE studies. Current genome-wide GxE efforts do not consider the "main" effects of the genes and the environment. The way that GWAS are currently conducted involves running millions of regressions on data that are inherently inductive to seek

²⁷ Caspi A, Sugden K, Moffitt TE, et al. 2003. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* 301 (5631): 386-9.

²⁸ Risch N, Herrell R, Lehner T, et al. Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis. 2009. *JAMA* 301 (23): 2462-71.

²⁹ Boardman JD. State-level moderation of genetic tendencies to smoke. 2009. *Am J Pub Health* 99 (3): 480-6.

³⁰ Boardman JD, Saint Onge JM, Haberstick BC. 2008. Do schools moderate the genetic determinants of smoking? *Behav Genet* 38 (3): 234-46.

interactions; because there are few counterfactuals, it is difficult to know which associations are meaningful. Consideration of the social context in which the interactions are taking place can help draw meaning from GWAS results.

The HRS is uniquely poised to conduct GWAS that account for social factors: It captures longitudinal data on important genetic moderators from a nationally representative sample; it includes sibling and family information that allows for expanded genetic analyses; and it involves rich environmental variables on economic and social resources, social stressors, and social control. There are many ways to characterize complex social environments in the HRS; combining HRS with geographic environmental indicators opens exciting possibilities. Genome-wide data can be used for a great deal more than GWAS—it can be used to identify cumulative risk score as genetic vulnerability, or to adjust for population differences that are otherwise difficult to identify.

Session 5—Using GWAS for Exploring Promising Links Among Constructs

(1) Longevity and Late Life Function

Longevity, Genetics, Evolutionary

Ken Wachter, University of California at Berkeley

Although biologists and specifically geneticists evaluate commonalities between species of age-specific traits of demographic schedules, Wachter's work focuses on the mathematics of the evolution of senescence in the context of mutation accumulation theory. This theory attempts to explain why patterns of demographics persist across species with different body plans and in different environments, and depends on unverified hypotheses about the nature of genetic variation. The theory postulates that large numbers of alleles have small age-specific effects on determinants of fitness and that there is a great deal of variety in the age of major onset of these effects. If these postulates are true, mathematical theories can account for the empirical findings of commonalities of survival across species that couple Gompertzian exponentially increasing hazards at moderate older ages with plateaus or tapering at extreme ages, such as are seen in species of worms and humans. This theory accounts for the irregularities of change and predicts that any allele whose major effects are evident at late ages might have smaller effects at early ages; it would be inconsistent to conjecture that the allele would have no effects at all throughout most of the lifespan and then have large effects at late ages.

An evaluation in German centenarians of the associations of longevity-associated FOXO3A-gene SNPs³¹ did not show statistical significance by age for either the proportional or additive model of hazard rate. In simulations, the proportional-hazard model is accurate approximately 90 percent of the time, but despite having nearly 1,745 subjects in the study, it does not reach significance, thus leading to the conclusion that one SNP does not offer clear answers about age specificity—regularities in age-specific schedules are likely the outcome of the statistical mechanics of numerous small genetic effects. However, it is encouraging that plausible

³¹ Flachsbart F, Caliebe A, Kleindorp R, et al. Association of *FOXO3A* variation with human longevity confirmed in German centenarians. 2009. *PNAS* 106 (8): 2700-5.

evolutionary explanations are being developed for the presence of genes that influence longevity, such as FOXO3A.

Is it reasonable to expect evolutionary explanations for social characteristics to be associated with SNPs identified with GWAS? The modern environment with which the human genome copes is vastly different from the environments in which the human genome evolved, thus social-genetic associations might be accidental. Many GWAS results concern biomedical associations; understanding complex biomedical pathways might enable medicine to identify new interventions. However, complex social-behavioral pathways rarely have effective interventions, and better understanding of these pathways is unlikely to lead to actionable interventions. An outcome of GWAS might simply be to provide individuals with excuses for their vices, rationalizations that drinking too much or being overweight is inevitable because it is in their genes, whether or not they have been sequenced to identify any such tendencies. So a question for those considering GWAS is how the uncovered information will be applied.

Demographers interested in evaluating the genetics of social characteristics will need a significant investment to learn how to interpret GWAS data; therefore, another question to be addressed is whether that would be a wise investment. Alternatively, many irregularities associated with age-related changes are not adequately explained by the pathways identified by biomedical science, and GWAS data might shed light on the statistical mechanics of many influences combining to have a large effect on longevity, leading to deeper theoretical insight.

During the discussion immediately following Wachter's remarks, a participant noted that although many believe that evolution does not play into senescence because it has little to do with reproductive fitness, at least two recent models offer explanations of evolutionary benefits of old age: the grandmother hypothesis that older women improve the fitness of their offspring and their offspring's offspring, and the Tuljapurkar theory that fertility in elderly males produces evolutionary pressure for longevity.³² Wachter clarified that he did not mean to imply that there was nothing evolutionarily significant about the HRS-aged population, only that the discussion had not as yet included much evolutionary perspective. He contended that a more plausible explanation than either the grandmother or Tuljapurkar hypotheses provide is that the genetics influencing older ages leaves its signature on younger individuals and are shaped by natural selection at younger ages.

Another participant commented that evolutionary leaps results from recombinations of genes already present, and the impact of evolution on senescence might be accounted for by the organization of the genome into systems that have evolved to be robust and adaptive rather than by a particular gene or SNP or any specific variation. In response to a question about whether GWAS data would enable identification of genes under evolutionary pressure, possibly through linkage analyses, another participant explained that the best way to estimate genetic selection is to estimate substitution rates within a gene and to look at functional elements, neither of which is possible with GWAS data.

³² Tuljapurkar SD, Puleston CO, Gurven MD. 2007. Why men matter: mating patterns drive evolution of human lifespan. *PLoS ONE* 2 (8): e785.

Genetics and Late-life Functioning: The Danish Experience

Matt McGue, University of Minnesota

Biometry may be used in combination with GWAS to address several issues, including whether late-life phenotypes are heritable, the utility of longitudinal or multivariate phenotypes, and the implications of GxE interplay. Such opportunities are offered by the Longitudinal Study of Aging Danish Twins (LSDAT), a 1995 to 2005 cohort-sequential study of Danish twins aged 75 years or older that biennially collected data on functional and cognitive abilities, health, and emotional functioning. The cohort includes almost 5,000 individuals, approximately 1,150 of which are twin pairs, the rest singleton twins.

One of the main findings to date from the LSDAT is that late-life characteristics and functioning are moderately heritable, approximately 25 to 50 percent for lifespan,³³ depression,³⁴ cognitive ability,³⁵ grip strength,³⁶ and functional ability³⁷ according to initial cross-sectional reports. This should not be surprising, because across most species lifespan exhibits only modest heritability³⁸ and is approximately 25 percent in humans.³⁹ Because these are cross-sectional reports, they do not account for underlying longitudinal variations.

Follow-up longitudinal studies are currently underway on an extension of the LSDAT cohort to include 3,000 twin pairs between 46 and 90-plus years old. These enable researchers to address the question of whether heritability changes as a function of age. One model suggests heritability might decrease over time with the accumulation of environmental effects, while the accumulation model postulates increased heritability with age. Correlations between monozygotic twins in composite cognitive measures, grip strength, and depression symptoms do not show a great deal of variance as a function of age aside from a moderate increase in depression, and the heritability associated with these traits is moderate through middle-late and late adulthood, measured through age 80. When the twin registries of Sweden, Denmark, and Norway were combined for a total of more than 20,000 twin pairs, the longevity phenotype showed overall 25 percent heritability; when age is factored in, however, there was little correlation between twins younger than age 60, but lifespan was highly correlated between twins greater than 80 years old, suggesting that exceptional longevity might be exceptionally heritable.⁴⁰

³³ Herskind AM, McGue M, Holm NV, et al. 1996. The heritability of human longevity: a population-based study of 2872 Danish twin pairs born 1870-1900. *Hum Genet* 97 (3): 319-23.

³⁴ McGue M, Christensen K. 1997. Genetic and environmental contributions to depression symptomatology: evidence from Danish twins 75 years of age and older. *J Abnorm Psychol* 106 (3): 439-48.

³⁵ McGue M, and Christensen K. 2001. The heritability of cognitive functioning in very old adults: evidence from Danish twins aged 75 years and older. *Psychol Aging* 16 (2): 272-80.

³⁶ Frederiksen H, Gaist D, Petersen HC, Hjelmberg J, McGue M, Vaupel JW, and Christensen K. 2002. Hand grip strength: a phenotype suitable for identifying genetic variants affecting mid- and late-life physical functioning. *Genet Epidemiol* 23 (2): 110-22.

³⁷ Christensen K, McGue M, Yashin A, et al. 2000. Genetic and environmental influences on functional abilities in Danish twins aged 75 years and older. *J Gerontol A Biol Sci Med Sci* 55 (8): M446-52.

³⁸ Finch CE and Tanzi RE. 1997. Genetics of aging. *Science* 278 (5337): 407-11.

³⁹ See Herskind et al. (1996) and Finch and Tanzi (1997).

⁴⁰ vB Hjelmberg J, Iachine I, Skytthe A, et al. 2006. Genetic influence on human lifespan and longevity. *Hum Genet* 119 (3): 312-21.

When twins are observed at a single data point in a cross-sectional analysis, many explanations might account for differences. The individuals might have begun at different points or changed at different rates due to aging, or both. Of three longitudinal studies that evaluated the growth curve of cognitive aging in the elderly,⁴¹ only one reported substantial heritability on the rate of change to age 74.⁴² It is possible that the others did not detect significant heritability due to limited follow-up intervals, or perhaps change in cognitive function is inherently unreliable, or possibly biological aging is not an adequate marker of neurological aging against which to measure change.

Biometry is useful for determining the extent to which genetic factors underlying serial observations are correlated. In the LSDAT, biennial measurements of functional and cognitive abilities and depression exhibit steady genetic effects over time with relatively unchanged heritability estimates. Therefore an average of the sequential heritability measurements may be taken to increase the signal-to-noise ratio. Heritability estimates for depression symptomatology are approximately 33 percent in any one wave, but when measurements are aggregated across four waves, they exhibit 69 percent heritability.⁴³

The computational power now available to perform multi-varied quantitative genetic analyses on several phenotypes enables complex models, involving pleiotropy, for example, to be evaluated. LSDAT data from four intercorrelated cognitive functions—fluency, digit span, memory, and speed—have been aggregated to filter out measurement error and demonstrate that cognitive ability has an underlying factor that tends to be highly heritable.

In conclusion, late-life phenotypes appear to be moderately and stably heritable. Longitudinal analyses indicate minimal genetic contribution to change, that serial assessments are highly genetically correlated, and that aggregation over multiple waves of data collection might increase the signal. Multivariate approaches based on pleiotropy may provide more optimal methods of aggregation, but they come at the expense of tests for specific genetic effects.

Discussion

Nancy Pedersen noted data that suggest that heritabilities are lower for characteristics with linear rates of change and higher for those with non-linear rates of change. McGue has tested non-linear models and found that change exhibits limited variance and that the reliability of some values is quite low.

⁴¹ Reynolds CA, Finkel D, McArdle JJ, et al. 2005. Quantitative genetic analysis of latent growth curve models of cognitive abilities in adulthood. *Dev Psychol* 41 (1): 3-16.

Lyons MJ, York TP, Franz CE, Grant MD, Eaves LJ, Jacobson KC, Schaie KW, Panizzon MS, Boake C, Xian H, Toomey R, Eisen SA, and Kremen WS. 2009. Genes determine stability and the environment determines change in cognitive ability during 35 years of adulthood. *Psychol Sci* 20 (9): 1146-52.

McArdle JJ and Plassman BL. 2009. A biometric latent curve analysis of memory decline in older men of the NAS-NRC twin registry. *Behav Genet* 39 (5): 472-95.

⁴² McArdle JJ and Plassman BL. 2009. A biometric latent curve analysis of memory decline in older men of the NAS-NRC twin registry. *Behav Genet* 39 (5): 472-95

⁴³ McGue M and Christensen K. 2003. The heritability of depression symptoms in elderly Danish twins: occasion-specific versus general effects. *Behav Genet* 33 (2): 83-93.

Gabriella Conti observed that these models assume additive genetic and environmental variance, and she asked whether models incorporating gene-environment interactions have been estimated. McGue replied that when GxE is taken into account (following Purcell [2002]⁴⁴) the genetic variance is reduced, especially for phenotypes like disability.

A participant commented that one theory of aging is that cells cannot repair as well in the elderly as in the young, rendering the elderly more susceptible to a variety of insults, and asked how the multitude of small genetic effects described by Wachter could account for this. Numerous possibilities might come into play, including various genes, polymorphisms, and epigenetic changes influencing such attributes as inflammatory responses or DNA repair.

Factors responsible for the greater evidence of genetic effects on lifespan at extreme ages might be elaborated through investigations of causes of death, which will change over a lifetime and for populations over time. Such an investigation is under way in Denmark. As Boardman elucidated, the influence of genetics on outcome changes rapidly with changing environments. Heritability of longevity in Denmark might be higher than in the United States because of greater environmental homogeneity. It will also be worthwhile to evaluate the amount of variance in heritability, which will differ for different phenotypes.

Commentaries

John Hobcraft, University of York

Hobcraft raised two key questions: 1) what will social science gain from the introduction of genomics in the broadest sense? and 2) what does social science have to offer genomics? He believed the answers will be positive. He observed that health inequalities indicate that the environment plays an important part in determining health and that genetics will not provide all the answers. In looking back 10 years he noted how quickly things have changed in all the -omics fields, making it difficult to keep up and underscoring the need to work outside disciplinary silos.

There has been a long-held view that attention needs to be paid to intermediate phenotypes, endophenotypes, pathways, and mechanisms that include biological pathways. When looking at individual behaviors, there are the -omics on one end and social structure, the environment, and the behavior of the individual on the other end. In terms of behavior, greater attention needs to focus on what happens in the brain. Psychologists are ahead in this area but need to integrate brain function more fully into links between genes and behavior. Aside from the tissue-specific problems of dealing with the brain, more is happening there because concerns with genetics have been better funded in the health domains. For example, support has been forthcoming to study pathways through the immune system, cardiovascular system, and other biological systems, and their implications for outcomes. Other key questions worth addressing include the following:

- The meaning of heritability in sibling/adoption studies, of GxE interplays, and issues associated with selection mechanisms

⁴⁴ Purcell, S. 2002. Variance components models for gene-environment interaction in twin analysis. *Twin Res* 5(6): 554-71.

- Issues of epigenetics and the ways in which the environment actually gets under the skin and alters transcription and the way that genes are expressed, which have lasting effects in those areas likely to be of considerable importance
- Gene networks and the ways in which whole systems are controlled.

Although Hobcraft considered this beginning to be truly exciting, he recognized that there is a long way to go, with still a great deal to learn. In the next five years, he expects the field still to be struggling to find the answers but considers it important to continue to strive toward a greater understanding so as to not get left behind.

Joseph Terwilliger, Columbia University Medical Center

As a geneticist, Terwilliger searches for natural experiments and works closely with social scientists including specialists such as cultural anthropologists, historians, and demographers to help build pedigrees, identify population structures, and evaluate cultural factors that are likely to contribute to health. In Terwilliger's view, GWAS and the International HapMap Project have failed at their original mission because so far there have been no findings that would affect the average person's health. If 100,000 samples are needed to find a significant effect, the effect is likely too tiny to be relevant for medicine. He also pointed to many examples in the popular press that demonstrate pervasive misunderstanding about what genetics and heritability mean. The promise of remarkable advances in molecular biology so far have not led to permanent cures for genetic disease as expected nearly 40 years ago.⁴⁵

In the early 1990s, it was thought that for multifactorial traits, sibling pairs are less informative than large families; however, they are much easier to collect, and their greater heterogeneity and the resultant loss of statistical power could be countered by increasing sample sizes. As Weeks and Lathrop (1995) state, "Genotyping a panel of affected sib pairs throughout the genome has proven to be a very powerful and efficient method for mapping disease susceptibility loci involved in complex disease."⁴⁶ But after hundreds of affected sib pair studies (between 1990 and 2000), only a handful of complex disease genes were identified. Terwilliger attributed this failure to the ill-advised strategy of going from what works in genetics (following a closed population) to looking at a large number of small populations. He noted that less of the variance of common traits was explained through all GWAS put together than in simple family studies.

As another example, Terwilliger reported the observation made by others that mutations in breast cancer (BRCA) genes BRCA1 or BRCA2 explain only a small percentage of the variance in breast cancer (although the mutation confers a meaningful genetic risk). It would be of greater interest to find common variants that explain most breast cancer in normal people. But 30,000 to 60,000 genotyped individuals later, numerous other genes have been found that together explain less than a tenth as much of the variance explained by BRCA1 and 2.

Although it also once was believed that "[d]espite the small effects of such genes, the magnitude of their attributable risk (the proportion of people affected due to them) may be large because

⁴⁵ Buchanan AV, Weiss KM, and Fullerton SM. 2006. On stones, wands, and promises. *Int J Epidemiol* 35 (3): 593-6 (June).

⁴⁶ Weeks DE and Lathrop GM. 1995. Polygenic disease: methods for mapping complex disease traits. *Trends Genet* 11 (12): 513-9 (December).

they are quite frequent in the population, making them of public health significance,”⁴⁷ it is now clear that individual genes generally do not have attributable fractions anywhere near 20 or 30 percent.

The bottom line is that family studies generate higher power because they permit association studies with linkage using pedigree material and involve more individuals with less genetic variation. The use of epidemiological study designs (with unrelated individuals) seems to stem primarily from the fact that samples are already in freezers and current technology can be applied immediately to analysis without the need for additional data collection. Citing numerous examples of where GWAS did not identify significant association, Terwilliger reported that more experts are now pulling away from performing GWAS for common disease because the method is not ideal.

Geneticists with blood samples tend to keep looking until they find something significant and then justify the finding *ex post*; they try to sample non-randomly to detect loci that might increase risk. In contrast, epidemiologists and sociologists generally begin with a hypothesis, and careful population sampling and description make the HRS a perfect study in which to take findings from biological studies and work out what they do and to estimate effect sizes and parameters of models. Terwilliger also conjectured that mapping does not work well on wildtype humans because of the enormous heterogeneity. Study of gene knockouts often involves work on autosomal recessive diseases.

Terwilliger expects full genome sequences to be available for everyone in perhaps 15 years. He has evaluated populations with a great deal of inbreeding (e.g., in some areas of Finland). However these populations work terribly for association studies because there is too much population structure. Terwilliger also ran GWAS in the 1990s, and genome scans of 40,000 Finns identified almost nothing at all. GWAS works when the model works; that is, when people sampled share the phenotype because they share the same variant of the same gene, identical from a common ancestor. So GWAS are essentially family studies where one assumes there is a family and can identify associations very quickly.

Inbred organisms used to be of most interest in rare disease studies, but they are just as useful for common diseases because they have a bigger population without adding variation. More is better for GWAS or GxE studies but only if more variation is not introduced. Increasing variation in genetics can lead to the ironic situation whereby increasing the sample size decreases statistical power because one must increase the sampling frame and therefore add more variants. The more variants added, the more causes of disease added, because every nucleotide in the genome that can cause disease is buried in somebody somewhere at some point. Every small town in America where people have been living for 300 to 400 years will have experienced inbreeding.

Terwilliger is working on a project with large pedigrees in Venezuela in which the population under study is highly inbred and each family generally has 12 to 15 children; half of the community lives on the water and half on the land. The former treats the water as their toilet, swims in the same water, and is more exposed to heavy metals and infectious diseases compared to its land-based counterpart. Members of this population tend to live until their 90s with very

⁴⁷ Risch N and Merikanga K. 1996. The future of genetic studies of complex human diseases. *Science* 272 (September 13): 1516-7.

low rates of infectious disease, no dementia, and little cardiovascular disease. Investigators are studying variations in blood pressure over a 24-hour period in this population; this variability appears to be heritable and is also the biggest risk factor for heart attack and stroke.

Terwilliger also is working with other social scientists to look at the relative contribution to complex outcomes of nature versus nurture. He discussed his study that compares a group of biological but not cultural Koreans to a group of biological and cultural Koreans. There are many such groups:

- Korean immigrants in Russia who were deported to Kazakhstan, stripped of all Korean culture, and steeped in the Russian culture
- Koreans in China, who are comparable to Koreans 30 years ago in South Korea
- Adopted Koreans in the United States. This is among the fastest-growing minority group in the United States.

By building a pedigree, Terwilliger and his colleagues are trying to quantify lifestyle and to evaluate how heritability changes when the culture and the environment change radically. He followed up with a similar story about the Kozak, the ethnic group whose culture was stripped by Stalin.

Discussion

When asked directly about the use of GWAS in the HRS, Terwilliger saw a role for a study like the HRS to estimate effect sizes and to identify risk factors. He concurred with the notion that the HRS was not designed, and is not necessarily suited, to look for new unknown effects and gene hunting.

Terwilliger was not arguing that GWAS cannot be used to identify new genes; his point was that even if these genes identified from GWAS are included in a predictive model, they typically only explain a very small part of the variance. He expected that more biological phenotypes will find more genes correlated with them, just as there are numerous genes correlated with gene expression because gene expression is a more clearly genetic phenotype than is an outcome such as Alzheimer's disease. Pathobiology is almost always more complicated than biology. It therefore makes sense to look at normal variation in real biological phenotypes, and in doing so not be restricted to cross-sectional data because it is possible to collect data on families and look at more statistically powerful variations found within families.

Suzman clarified that the idea for this workshop was to think several moves ahead, not get into the weeds of gene finding for which it is clear that the HRS is not optimal. Assuming genes are found by other sources, how will use of genetic information in social and behavioral studies change models and conclusions? How will it change science? What will it destroy, and what will it rebuild? Terwilliger allowed that it will be possible to use the HRS to confirm findings or debunk spurious findings from smaller samples.

Davey Smith cautioned against getting too concerned about the small effect size of genes. If interest is in environmentally modifiable mechanisms, then it is not the gene effect size but the

effect size of the modifiable environmental factors on which the use of genetic variants as instruments provide causal evidence that is important.

Terwilliger added that only a tiny percentage of gene variants has been found, and the ones not yet found would be expected to have smaller relative risks, are rarer, or both. If there is no selection, one gets mostly rare variants; if there is selection, one gets almost exclusively rare variants. It is not impossible to find common variants if there is no selection; one might be lucky to find a common enough variant with a big enough effect to be detectable. A lot of the genes of interest will have only rare variants because 99.99 percent are rare.

One participant observed that the reason earlier family studies have yielded less information than expected on complex disease is lack of resolution, which is no longer thought to be a problem. Psychiatric family studies previously were cost-prohibitive, but they are now increasingly doable, with technology improving and prices dropping—the going price of \$6,000 to \$8,000 for a full genome scan of an individual is expected to be halved next year.

One can genotype highly dense and highly affected families for rare variants, usually to perform linkage and complete genome sequencing. The process would be to look at every nucleotide that segregates with the phenotype in the family and in the linkage region and to look for causal variants (i.e., things that disrupt proteins and promoters). Within a family, one obtains a relatively more diagnostically and genetically homogeneous population and can exclude every chromosomal location where genes are not shared.

At this point it is not clear how much family studies will help. The argument favoring families is that if the same number of individuals is genotyped and more are related in families, then there is more power in every genetic model. If there is money to genotype 100,000 people, then there will be more power if the 100,000 come from 1,000 large families rather than a group of random people, assuming larger absolute effects can be found with study findings. Everything is ultimately a question of cost, efficiency, and what works best. It also is a question of relative power—if one doubles the sample size to 200,000 people, one might find more genes (e.g., lipid genes), but how much more variation is accounted for (probably not much) and is the variance causal? Implicating a gene is very different from implicating a variant.

Discussion turned next to GWAS findings related to height, specifically that:

Highly significant and well-replicated SNPs identified to date explain only ~5% of the phenotypic variance for height. Our results show that common SNPs in total explain another ~40% of phenotypic variance. Hence, 88% (40/45) of the variation due to SNPs has been undetected in published GWASs because the effects of the SNPs are too small to be statistically significant. Our results also suggest that the discrepancy between 80% heritability and 45% accounted for by all SNPs is due to incomplete [linkage disequilibrium] LD between causal variants and the SNPs, possibly because the causal variants have a lower [minor allele frequency] MAF on average than the SNPs typed on the array.⁴⁸

⁴⁸ Yang J, Benyamin B, McEvoy BP, et al. 2010. Common SNPs explain a large proportion of the heritability for human height. *Nat Genet* 42 (7): 565-9 (July). Citing Visscher PM. 2008. Sizing up human height variation. *Nat Genet* 40: 489-90.

The researchers estimated relatedness based on the SNPs, that is, the genetic architecture for height based on data and several assumptions. They evaluated putatively unrelated people who would be related in some previous generation, estimated the degree of relationship from the SNP data, and then estimated the heritability from the differential degrees of relationship among the people in their sample. These relationships will all be very low level (e.g., on the order of 0.01 or 0.005). The variance in the degree of relationship is correlated with the variance in the degree of height.

Terwilliger does most of his work with quantitative traits in big families. The advantage of working with big families is the ability to work with joint linkage and associations. Individuals within a family are correlated due to linkage components, but the founders in the family are all random in the population, which yields the association signal. A proper joint linkage association analysis will permit us to extract all information. If using quantitative traits, then it is possible to have random sampling, which would be estimating the model jointly with all data together but using linkage and association components at the same time, that is, getting more participants for less money.

In terms of human resources, who will analyze these data in reasonable ways? And how will NIA encourage this work structurally to promote collaborations that will encourage appropriate analyses of these data? Suzman responded that there is a lot to be discouraged.

Reiss commented that this meeting has illustrated the vast community of scientific strategies that feed into the HRS. He considered it important to try to identify the feeder studies that provide technical and intellectual material for HRS studies to use, the role of the HRS in metabolizing those feeder studies, and how that will alter the way we think in the social sciences. Many potential feeder studies may provide clues. Participants seemed to have reached a consensus that to use the GWAS information in the HRS as a gene-finding tool is a very inefficient idea. Among the feeder studies, the family studies contribute orientation, ideas, and hypotheses; they also may find in the HRS a comfortable arena for replication. Animal studies were mentioned briefly, which are a useful complement to natural experiments.

Mendelian randomization is a form of experimental study. There has so far been little discussion about imaging genetics, which speaks to Hobcroft's point about the importance of putting the brain in the sequence. This has been a very productive area, one that has produced genetic main effects. People seem to forget that the serotonin transporter links to the limbic systems, and these are notable main effects published prior to Caspi interaction studies. Imaging studies were a crucial stepping stone to the Caspi studies. Boardman spoke to what the HRS might substantively add to the mix—the notion of rich longitudinal characterization of the environmental context in which genes are expressed, which is a critical issue.

Reiss continued that little has been said about biometric studies. The formal gap between biometric analysis and molecular studies of any design is large but of enormous importance to biometric studies, not as specific data for inclusion in the design of HRS studies but as a model system for how genetic investigation has radically changed how social theories are constructed and tested. One way genetic investigation has changed substantially is in a radical rethinking of what the environment is. Biometric studies have paid great attention to selection mechanisms. Instead of dispensing with them, they can be used to focus in detail on how children, adolescents, and adults find themselves in the environment. Biometrics play a role not as feeder but as a first

attempt to bring genetics and social science together. It may be helpful to map more specifically the role of the HRS in the nexus of feeder model systems and its own specific characteristics.

Cole amplified Reiss' remarks and observed that the HRS is distinctive relative to the feeder studies in the breadth of its assessments. Other studies have a great deal of breadth and little depth in terms of sample size. The HRS has a robust sample size and at least fairly good if brief measures in a diverse array of social-environmental contexts. To illustrate the reason why this is important, Cole noted that the serotonin transporter concept seems to work well in experiments but not in free-range epidemiology. The explanation may be that people erase that phenotype: if your variant of the transporter gene is making you more irritable, then you will adjust your environment. A mouse, however, cannot make that adjustment, so the phenotype shows through. In most studies, if humans adjust their environment, then we will not be able to assess and account for that. That is one of the greatest and most unappreciated features of the HRS—a great sample size combined with a fairly good dimension-spanning set of assessments that will allow users to catch leakage out of the gene-environment situation, the GxE interaction, and the intergene correlations and selections.

Suzman looked forward to a new paradigm and generation of researchers who are fluent in multiple disciplines, and an increase in the number of MD/PhDs and PhD/PhDs. Perhaps a three-month course, such as an expanded version of RAND MiniMed, would help make people more fluent in multiple disciplines. There may need to be changes in the graduate notion of what demography or biodemography means. He also urged participants to review Burton Singer's paper, which argues that other surveys such as the National Survey of Midlife Development in the United States (MIDUS) might be better positioned for finding a gene(s) because it is more embedded to the endophenotype in terms of biological pathways. The HRS can add new variables, refine variables, and subtract variables. One can get, for example, venous blood, MRI or CAT scans, which are unlikely in the current budget system, and autopsy data, which are even less likely.

Session 6—Strategies for Analyzing Genetic Associations with Biomarker Data in Social Surveys

More Is Better: Genetic Associations in the GWAS Era *Sharon Kardia, University of Michigan*

GWAS can be intimidating to public-health population geneticists because they raise the possibility of unintended consequences, not least of which is misappropriation of the data for ethically abhorrent purposes. GWAS bear little resemblance to previous research and are only a step toward a goal and not the end goal in and of themselves. GWAS also represent a move to big science, with a different set of “rules” for sample sizes, analyses, and replication than ever before and in which more is better: the drive is toward more mutations on bigger SNP chips, more participants, more stringency, more replication, more kinds of validation, bigger sample sizes, more computing power and time, more collaborations, and evaluation of ever more interactions. Examples of this can be seen in the multiplicity of authors on GWAS papers; sample sizes of 1 million participants in the discovery plus replication groups, and evaluation of 2.5 million or 5 million SNPs; CNVs, or rare mutations; imputation to 17 million SNPs; exomic sequencing; and complete genome sequencing. P-values in GWAS are routinely at the level of 5

$\times 10^{-8}$, and hundreds of computers are dedicated for weeks to months to analyze GWAS data. GWAS opportunities seem to be ever increasing as well, in which relatively small cohorts get absorbed into larger studies and consortia to obtain the sample sizes needed to assess ever more numerous interactions that were never considered when the small cohort studies began.

To make sense of this bewildering expansion of human genetic research, it can be helpful to look at the state-of-the-science in animal and plant genetics, which tends to be approximately 10 years ahead. Currently, these fields are evaluating the biological implications of epistatic pleiotropy (i.e., gene-gene interactions)⁴⁹ and systems genetics.⁵⁰ Systems genetics work on *Drosophila* longevity has revealed that one-third of the 1,332 homozygous P-element insertion lines assessed had quantitative effects on lifespan, and mutations reducing lifespan were twice as common as mutations increasing lifespan. Mutations in the same gene were associated with both increased and decreased lifespan, depending on the location and orientation of the insertion and genetic background. The effects of the mutations increasing lifespan were highly sex-specific, as was epistasis among a sample of 10 mutations associated with increased lifespan. All mutations increasing lifespan had at least one deleterious pleiotropic effect on stress resistance or general health, with different patterns of pleiotropy for males and females. This suggests that

- longevity has a large mutational target size
- genes affecting lifespan have variable allelic effects
- alleles affecting lifespan exhibit antagonistic pleiotropy and form epistatic networks
- sex-specific mutational effects are ubiquitous.

In addition, transcript profiles of long-lived mutations revealed a transcriptional signature of the increased lifespan phenotype.

With its rich datasets, the HRS has an enormous capacity to contribute greatly to this field. However, the field is expanding to encompass more than just the genome and the outcome or disease process; it might be worthwhile for the HRS to consider evaluation of other -omes by banking the appropriate biospecimens, including the epigenome (peripheral blood), transcriptome (tissue), proteome (blood), and metabolome (urine).

Kardia recommended that the HRS should concentrate on:

- Confirming/estimating effects of previously demonstrated GWAS hits
- Setting up working groups
- Tapping other cohorts to join the HRS
- Leaving the biometrical for enough time to actually delve into the messiness of the genome
- Developing new theories in the hybrid zone
- Establishing new checks and balances on potential hazards that could result from misappropriation of the publicly available data.

⁴⁹ Wolf JB, Leamy LJ, Routman EJ, and Cheverud JM. 2005. Epistatic pleiotropy and the genetic architecture of covariation within early and late-developing skull trait complexes in mice. *Genetics* 171: 683-94.

⁵⁰ Jumbo-Lucioni P, Ayroles JF, Chambers MM, Jordan KW, Leips J, Mackay TF, and De Luca M. 2010. Systems genetics analysis of body weight and energy metabolism traits in *Drosophila melanogaster*. *BMC Genomics* 11: 297.

During the discussion following the presentation, Kardia was asked for clarification on what was meant by the “hybrid zone” and explained that it is easy for social or behavioral scientists to oversimplify and make assumptions in order to project social or behavioral theories onto genetic information. To avoid this pitfall requires a broader view encompassing, for example, plant, animal, and human genetics and the role of the brain in filtering environmental stimuli into physical responses.

A participant commented that little is known about the genetic loci that have already been associated with various biological outcomes; without knowing the incremental value of these loci it might be difficult to justify conducting more studies to identify more loci. Kardia responded that the number of loci to be identified is perhaps limited by the amount of funding available to conduct such experiments. However, each discovery uncovers more information that will eventually enable mapping of the underlying biological processes; hence, GWAS studies are not the end result but a step along the way to fuller understanding.

Another participant noted that a fundamental question for the HRS is what level resources should be invested in GWAS to the exclusion of other endeavors, such as evaluation of family members or phenotypic extremes. Kardia replied that GWAS are useful at the very least to acclimate researchers to dealing with huge quantities of data, which will be necessary when exome or whole-genome studies become the norm. Although tail studies of phenotypic extremes can be valuable, they ignore a great deal of phenotypic variation between the extremes. On the other hand, family studies are a key method for understanding biology and signaling pathways, and adding offspring genetic information to the HRS might be extremely useful; if it is easier to obtain specimens from siblings, that would also be beneficial. The extensive shared biology between family members enables the evaluation of genomic regions for causal modeling. Even adding phenotype without genotype information from family members can add power to GxE analyses.

Another participant commented that one reason for including GWAS in the HRS was not to be at the forefront of gene discovery but to integrate social scientists into genetic studies to participate in the social science being done by biologists. However, the numbers of authors frequently seen on GWAS papers is alarming; such large collaborations are unheard of in social science. Kardia agreed but noted that because the effect of any one SNP is small, sometimes large collaborations are needed to identify replicable effects. Another participant suggested limiting huge author lists by adopting a system in which individuals who contributed data have the right to their names only on the first five papers in which those data are used.

Collecting and Analyzing DNA in the Wisconsin Longitudinal Study *Robert Hauser, University of Wisconsin-Madison*

Hauser provided a brief introduction to the Wisconsin Longitudinal Study (WLS), genetic data, and GWAS possibilities. He saw the WLS as complementing the HRS and possibly contributing to a consortium in the making. The WLS is characterized by a high response rate and a more homogeneous population (all high school graduates and almost all whites, which is akin to two-thirds of Americans in the United States and to the white non-Hispanic high school graduates in the HRS). It covers participants from adolescence onward (ages 18 to 70+), has reasonably good DNA on 8,000+ cases, and has longitudinal sibling pair data with DNA.

The baseline sample is 10,317 high school graduates from the class of 1957. The relational structure of the data in the WLS is centered on these graduates, with reporting by the graduate about parents, siblings, spouse, children, and high-school friends. All of these relations except children provide information about the graduate, with many of those relations reporting on others in the network. There is therefore extensive data from and about siblings, from spouses, and about but not from offspring at this stage of the project (although Hauser has made various attempts to get support to bring offspring into the study). Subsequent data collection occurred in 1964, 1975, 1977, 1992-1994, 2004-2006, and 2010-2011.⁵¹

According to Hauser, the WLS data are especially strong in the following domains:

- Social/family background
- Educational history
- Marital history
- Children
- Physical/mental health
- Cognitive performance
- Employment history and job characteristics
- Income and wealth
- Retirement and pensions
- Leisure time activities
- Stressful life events

The WLS has a number of notable methodological features, including interviews by random replicates; bracketed amounts with random anchors; supplemental interview and survey with selected children; cognitive measurement; use of health vignettes (from the World Health Surveys); and recording of interviews. In addition to DNA for graduates and siblings (N=7,000+; about 65 percent compliance rate), the WLS includes anthropometric measures (height, weight, waist and hip circumference, and facial and full-body color photographs) and several measures of BMI over the life course; coding of facial characteristics from high school yearbooks (attractiveness, smiles, and facial mass); performance tests in the 2010 to 2011 home interviews (grip strength, timed walk test, chair rise, peak flow measure vision cognitive tests); and questions about experience with Medicare Part D. A considerable amount of non-survey data also was introduced this round, including high school standardized test scores, high school class rank, which has turned out to be much more of a predictive factor than had been imagined, tax records, college and employer characteristics, links to the National Death Index, geocodes of addresses, elementary and high school resources from state archives, high school yearbooks (for approximately 83 percent of all graduates), and soon Social Security earnings and benefit histories for survivors (although this requires written permission from the graduate). The leave behind Self-Administered Questionnaire (SAQ) is now 72 pages long, repeating a lot of previous measures, but also adding content related to economic literacy and economic games, elder abuse, and medication inventory.

Of the 7,000+ DNA samples, about 4,500 are from graduates and about 2,500 are from siblings; the WLS expects to add about 1,100 samples in the coming year. The WLS has not done a

⁵¹ See <http://www.ssc.wisc.edu/wlsresearch/> for more information about the WLS.

genome-wide scan but has information on 95 SNPs that are all candidate genes for such traits as AD, breast cancer, cognition, depression, diabetes, impulsivity, fertility, longevity, and obesity. The investigators also are working with an anesthesiologist to examine effects on cognitive function, and they are hoping someone will use the WLS data to evaluate the effect of playing high school football on later life cognitive function. Collecting biomarkers from spouses and expanding to include interviews with children of the graduates may be future considerations.

In the limited time that the WLS has had access to the genetic material, it has added to cases of non-replication for candidate genes (Taq1 by Jeremy Freese et al. and IQ by Christopher Chabris et al.). It also is pursuing inquiry about genetic markers for reproductive capacity and longevity, building on the idea that age at menopause is related to evolution and longevity. With support from the Centers for Disease Control and Prevention (CDC), the WLS has a separate set of assays under way to look at fragile X mental retardation 1 repeats and fragile-X syndrome.

The WLS is committed to making its data available for research, and it has many tools on the Internet to facilitate access. It is aware of the particular challenges for maintaining confidentiality given the wealth of information available, and it continues to be vigilant about developing a strong system for secure data analysis. Hauser welcomed collaborators and noted that he and David Weir have a joint paper forthcoming in *Demography* about recent developments in the HRS and the WLS. The WLS also has a small grants program to orient people to working with the data,⁵² a private website for users that contains proposals, instruments, and manuscripts, and a user-friendly website for study participants.⁵³

Although participants appreciated the promise in forming a consortium of studies, questions arose about combining GWAS data on multiple samples with comparable phenotypes, such as from the HRS, the WLS, and Add Health, as well as the inferences possible by combining studies with such different sample designs. Kardia responded that the model is for every group to do its own analyses in the way that best corresponds to its study sample, with the exception that collaborators agree on the covariates used to adjust. The least number of covariates (e.g., age and sex) as an adjustment is usually preferred in order to not penalize those resources that did not measure a particular covariate. Parameter estimates and the p-values are pooled, as well as the information about the quality of the genotyping or imputation. Essentially, every group puts a very small set of data into a central location for meta-analyses. The idea is to permit researchers to work with all the data simultaneously for added power.

Hauser clarified that the WLS, like the HRS and Add Health, was not designed for gene hunting. Investigators of these studies are mainly interested in GxE interactions, given the rich data collected about life histories, and whether or not there are points of likely intervention. Others added that it is intrinsically of interest to know the role of specific genes in people's behavior, and one can design experiments involving people with and without specific SNPs, for example to predict educational attainment, that might explain why some groups respond better to particular interventions. The question remains whether it is possible to use genetic information to improve the precision of behavioral models or disaggregate people into subgroups where specific models might better apply. It also may be possible to measure genetic distance between people as a way to summarize across the genome.

⁵² Available at: <http://www.ssc.wisc.edu/wlsresearch/pilot>.

⁵³ Available at: <http://wisls.org>.

Session 7—Using GWAS for Exploring Promising Links Among Constructs

(2) The State of GWAS Research on Personality

Personality Traits Are Key Organizing Constructs for Genetically Informed Research *Brent W. Roberts, University of Illinois, Urbana-Champaign*

Roberts focused on explaining personality traits in an evolutionary framework. He began with his definition of personality traits— “the relatively enduring patterns of thoughts, feeling, and behaviors that reflect the tendency to respond in certain ways under certain circumstances.”⁵⁴ An accepted and useful taxonomy of personality has five factors: extraversion, agreeableness, conscientiousness, emotional stability (neuroticism), and openness to experience.⁵⁵

Roberts contended that personality traits are key organizing constructs for genetically informed research because they are evolutionarily relevant. Analogues of human personality are conserved across species. There is a burgeoning field in animal personality looking at sheep, squid, fish, mice, and other species. There appears to be consistent variation over time, and the roles of animals within their social systems might explain individual differences. Personality traits also have been found to be heritable; temperamental dimensions are in place early and propagate throughout life; and personality traits solve adaptive problems.

Roberts used conscientiousness (the propensity to be organized, controlled, industrious, responsible, and conventional)⁵⁶ as an example to support his contention. This variable has a normal distribution and does not differ much by sex. It also has been demonstrated in other species. For example, a study of impulse control shows that a delay discounting task in mice is linked to serotonergic and dopaminergic systems and medial prefrontal and orbitofrontal cortices.⁵⁷

Conscientiousness also has been linked to temperamental dimensions in three basic systems: positive incentive motivation, fear, and non-affective impulse control as a child.⁵⁸ The latter can dampen or elevate the first two dimensions. Childhood temperament is influential in determining how personality proceeds in life course.⁵⁹

⁵⁴ Roberts BW. 2009. Back to the future: Personality and assessment and personality development. *J Res Pers* 43: 137-145.

⁵⁵ Goldberg LR. 1993. The structure of phenotypic personality traits. *Am Psychol* 48: 26-34.

⁵⁶ Roberts BW, Jackson JJ, Fayard JV, Edmonds G, and Meints J. 2009. Conscientiousness (Chapter 25, pp. 369-381). In M Leary and R Hoyle, eds. *Handbook of Individual Differences in Social Behavior*. New York, NY: Guilford Press.

⁵⁷ Winstanley CA, Theobald DEH, Daley JW, Cardinal RN, and Robbins TW. 2005. Double dissociation between serotonergic and dopaminergic modulation of medial prefrontal and orbitofrontal cortex during a test of impulsive choice. *Cereb Cortex* 16: 106-114.

⁵⁸ Depue R and Lenzenweger MF. 2005. Personality disorders as emergent phenotypes from multiple interaction neurobehavioral systems. In JF Clarkin and MF Lenzenweger, eds. *Handbook of Personality Disorders*, 2nd Ed. NY: Guilford Press.

⁵⁹ Deal JE, Halverson CF, Havill V, and Martin R. 2005. Temperament factors as longitudinal predictors of young adult personality. *Merrill-Palmer Q* 51 (3): 315-34.

Conscientiousness is linked to survival, reproduction, and thriving. Childhood self-control (from an amalgamation of teacher, parent, and clinician reports) up to age 10 predicts better physical and mental health in adulthood, fewer substance abuse problems in adulthood, and greater wealth accumulation (with decent effect sizes).

In terms of marriage domain, studies show marriage and getting married is heritable, primarily due to heritability of personality traits. Individuals who are more traditional and less neurotic are more likely to be married.⁶⁰ Personality plays a larger role in marital stability and whether a couple remains married than socioeconomic status or intelligence quotient (IQ).

For both men and women in the HRS, conscientiousness of the spouse is positively correlated with subjective physical health of the respondents.⁶¹ Longitudinal studies of personalities and other indices show conscientiousness to be the best predictor of longevity in comparison to the other personality components, SES, and IQ. Similar findings were seen with the HRS data, even after controlling for health, sex, age, and SES. Furthermore, conscientiousness measured in the HRS in 1996 predicted better cognitive functioning and lower mortality through 2006.⁶²

Roberts also presented a map showing the distribution of conscientiousness and neuroticism across the United States. Based on nearly 5 million responses to a Web-based personality component survey sorted by state and ZIP code, the maps show conscientiousness generally higher in the middle of the country and southeast, and neuroticism highest in the Midwest through northeast and in southern states east of Texas.⁶³ There may be selection effects at the state level because people choose where to live.

However, personality traits can change over the life course. For example, conscientiousness appears to increase through age 70, with the greatest change occurring in the 22 to 30, 30 to 40, and 60 to 70 age ranges.⁶⁴ Ongoing longitudinal data show that people who become healthier also tend to become more conscientiousness, and vice versa. Changes in conscientiousness might be important evolutionarily; people who increase neuroticism tend not to live as long. Personality change has been found to be partially heritable as well.⁶⁵

Theoretically one reason for this is that genetic factors constrain personality development. Roberts would like to investigate whether this is true and how plastic personality is across life course. This could potentially help narrow the search for associated physiological systems of interest. He posed several genetically informed questions that could be addressed in terms of personality measures, including the following:

⁶⁰ Johnson W, McGue M, Krueger RF, and Bouchard Jr. TJ. 2004. Marriage and personality: a genetic analysis. *J Pers Soc Psychol* 86 (2): 285-94 (February).

⁶¹ Roberts BW, Smith J, Jackson JJ, and Edmonds G. 2009. Compensatory conscientiousness and health in older couples. *Psychol Sci* 20: 553-9.

⁶² Hill PL, Edmonds GE, Roberts BW, and Mroczek D. 2010. Cognitive functioning and physical health do not mediate the relation between conscientiousness and mortality. Unpublished manuscript.

⁶³ Rentfrow PJ, Gosling SD, and Potter J. 2008. A theory of the emergence, persistence, and expression of geographic variation in psychological characteristics. *Perspect Psychol Sci* 3: 339-69.

⁶⁴ Roberts BW, Walton K, and Viechtbauer W. 2006. Personality changes in adulthood. Reply to Costa and McCrae (2006). *Psychol Bull* 132: 29-32.

⁶⁵ Takahashi Y, Edmonds GE, Jackson JJ, and Roberts BW. 2010. Longitudinal changes in conscientiousness, preventative health behaviors, and physical health. Unpublished manuscript.

- Do personality traits mediate the relation between genes and family structure, wealth, health, and mortality?
- Are the genes linked to health issues also implicated in personality?
- Can we link the epigenome to individual differences in personality?
- Can we discover gene-by-environment antecedents to personality and do they moderate continuity and change in personality?

Questions following Roberts' presentation centered on the evolutionary system in which traits like conscientiousness persevere. Roberts pointed to some provocative data on parent-daughter relationships, and their relationship to subsequent development, that show early menarche related significantly to a number of health issues. For example, girls who reach puberty earlier show greater impulsivity, drug use, and births. The better the relationship between the father and daughter at age 3, the later the time to puberty. This might be an example of evolution being expressed in child development. If a child is born into a hostile environment, it makes sense to try to introduce ones' genes into the gene pool quickly. Thus what is seen as a public health problem also might be viewed as a logical extension of an evolutionary system. This would suggest that people with less conscientiousness have more sex and more children as a manifestation of ensuring reproductive success.

Hauser noted that there is an industry in cognitive epidemiology that focuses on the correlation between early IQ and longevity. Data from the WLS show that the effect on longevity of high school rank is three times larger than the effect of IQ, and high school rank completely accounts for the association between IQ and longevity. Alberto Palloni and Hauser are working on the time-varying covariates. According to Roberts, there is substantial literature showing conscientiousness to be the best predictor of grade point average in high school and college. Conti added that, in her joint work with Heckman, not controlling for the effect of personality leads to a substantial overestimation of the effect of cognition on health.⁶⁶

Roberts reported very respectable internal consistency in test-retest. Combining information is the most defensible approach. One interesting approach is to get complementary variance, that is, by asking the subject to self-report and also by asking someone else to report on the subject, but combine the information to maximize prediction.

Conscientiousness is not necessarily something to glorify. Suzman called for adding something in the motivational sphere (drive, push to maximize or minimize in terms of energy). Roberts acknowledged that conscientiousness is negatively related to creativity.

Psychopathology, Personality, and Genetics **Bob Krueger, University of Minnesota**

Psychopathology is typically thought of in terms of 297 putatively discrete and separate categories that are polythetic, that is, multiple combinations of criteria can lead to the same diagnosis. The categories tend to be siloed in that each is typically studied by different people publishing in different journals attending different scientific meetings funded by different

⁶⁶ Conti, G and Heckman JJ. 2010. Understanding the early origins of the education-health gradient: a framework that can also be applied to analyze gene-environment interactions. *Perspect Psychol Sci* 5(5): 585-605.

institutions. Genetics can be useful in determining whether this is an accurate model of psychopathological variation and the best way to address the problem.

A dimensional-spectrum model divides common forms of psychopathology into internalizing and externalizing categories of broad interrelated disorders. Internalizing psychopathologies include distress disorders such as depression, dysthymia, and anxiety, and fear disorders such as phobias and panic disorder. Externalizing psychopathologies include substance abuse, conduct disorder, and antisocial behavior. Latent spectrum variables are continuous, not discrete as was previously believed, and phenotype correlations among indicators are primarily genetically mediated. The latent variables appear more heritable than the indicator diagnoses, more so for externalizing than internalizing disorders, although residual genetic effects on the indicators are small, but demonstrable.

This model indicates that research should focus on the spectrum while recognizing the different factors that contribute to it. Personality appears to be at the core of the spectrums, with dispositions functioning like diagnoses as indicators and being genetically correlated with diagnoses. Personality dispositions are key variables in behavioral public health, with negative emotionality at the core of internalizing disorders and disinhibition at the core of externalizing disorders. Because the social costs of psychopathologies such as depression and alcoholism are undeniable, understanding the etiology of these dispositions is important.

Although disposition has a genetic component, the degree of heritability is not necessarily constant across a population. There are usually GxE interactions and the moderating variables can have genetic components. For example, negative emotionality in children shows an estimated heritability of approximately 50 percent in twin studies; however, the genetic component is suppressed in children from families with a high degree of parental conflict. One interpretation of this is that environmental effects on personality are more evident in relevant environmental circumstances. This sort of evaluation can be performed without knowing which genetic polymorphisms are involved.

Meta-analytic GWAS of personality including more than 17,000 unrelated individuals of European ancestry were performed using imputation to render the genotyping platforms commensurate. Each participant had 2.5 million SNP data points and was rated on the phenotype of openness, conscientiousness, extraversion, agreeableness, and neuroticism. A SNP on chromosome 5 was found to be associated with openness and a SNP on chromosome 18 for conscientiousness; however, each was estimated to account for less than 1 percent of the effect. Furthermore, the openness SNP is 135 kilobases from any known gene; the conscientiousness SNP is in the intron of a gene known to be expressed in the brain, but a majority of genes are expressed in the brain. The vast majority of the genetic influences on disposition remain to be determined. It is possible that a larger sample size would offer more genetic insights.

Personality is an important element in behavioral epidemiology, but it is not clear what steps to take next in understanding the genetics of personality: imaging genomics, rare variants, epigenetics, or GxE interactions. It might be worthwhile to evaluate a constrained set of common variants, such as the genetics of the dopamine system in cocaine dependence, for association. Twin research continues to offer valuable insights into heritability, although not necessarily the identity of the responsible polymorphisms.

A participant commented that altered cognition is believed to be a major component in schizophrenia—studies are being conducted to evaluate whether candidate schizophrenia genes correlate with cognitive ability in IQ tests—and asked whether cognition had been similarly evaluated with psychopathologies. Krueger replied that cognition is not a compelling endophenotype for psychopathology disorders, although other indicators such as event-related potentials might be worth assessing.

Another participant asked, if personality traits are more heritable than personality disorders, then does that indicate that psychopathologies are more a result of environment than genetics? Krueger responded that this is not necessarily the case and the disparity between the heritability of latent variables compared to indicators might be an effect of psychometrics.

In clinical disorders, numerous maladies present with similar symptoms, such as paleness and tiredness. A participant asked whether this might not be the case in psychology as well. Krueger replied that differences between disorders can be evaluated with endophenotypes; common variances might also be assessed, for example with twin studies.

In response to a question about whether the relationship had been studied between personality type and cause of death as opposed to simply age at death, Krueger noted that few studies in his field have evaluated the specifics of mortality, and no pattern between cause of death and personality traits has been established to date.

Terwilliger commented that when performing studies in which a questionnaire must be translated into a different language, the translation is normalized so that the responses fall into the same distribution as those to the questionnaire in the original language. He asked whether similar normalization in psychology would mask gene, environment, or GxE effects. Krueger responded that this is an important consideration that can be made tractable through psychometric methods.

Suzman observed that the HRS data presented used a relatively crude measure of conscientiousness, and specific facets of each disposition would need to be evaluated to be able to uncover and evaluate endophenotypes. Although there will be a cost to adding evaluation of disposition facets to the HRS, in comparison to the investment in HRS GWAS, the addition might be worth making if it improved the likelihood of obtaining greater insight from the GWAS data.

Yang et al. (2010) applies an identity by descent (IBD) strategy to see how similar unrelated people's genomes are genome-wide to then determine similarity of phenotype. This approach is different from using GWAS to cross-predict (as Krueger does); Yang et al. (2010) look in one sample without cross-prediction, and they try to use knowledge about overall genetic similarity to predict similarity in height. But their approach does not identify what the relevant potentially causal variants might be. It was noted that the European samples studied are highly homogenous. Still, Krueger thinks their approach is intriguing if one believes that either common variants are in gross aggregate relevant or that they tag rare variants. Information on the SNP chips is what is needed to break phenotypic variation. It is not clear how to translate from the IBD strategy to something clinically useful, but the Yang et al. (2010) paper suggests that the information is in the SNPs. Kardina believes that common variants are tagging rare variants. She noted that the chip used in the HRS has the 40,000 amino acid substitutions that are in the relatively common range, which is probably the best one can expect in terms of functional polymorphisms on that chip.

Session 8—Using GWAS for Exploring Promising Links Among Constructs

(3) Genetics and Economics

Discovering Links Between Genetics and Economics

Daniel Benjamin, Cornell University

Benjamin traced interest in the field of “genoeconomics” to economist Paul Taubman’s work in the 1970s with twin studies documenting the highly heritable nature of schooling and income, even though that heritability work never really caught on in economics. However, in the past several years, some very interesting work has entered the literature on twin studies looking at basic economic preferences. Heritability on these types of traits is in the small- to medium-size range.

Benjamin saw a number of pay-offs from the integration of molecular genetics research in genoeconomics:

1. Genes as instrumental variables—Examples where genes as instrumental variables have already been used include studies of health on education, and obesity on labor market outcomes. Work so far has not been fully convincing, but new methods under development promise to make a contribution to economics in the long run.
2. Understanding market and behavioral mediation of genetic effects—Economics is fundamentally about GxE interactions. Genes are measures of (until now latent) parameters. Economic models provide basic parameters about the abilities and preferences of agents, how they react to environments, and how they select into environments. Economic analyses focus on when effects are dampened or amplified, for example, depending on whether a higher genetically predisposed ability increases or decreases the marginal return to investing in it.
3. Biological mechanisms for social behavior—Having molecular genetic data can help us better understand social behavior and can be useful for decomposing crude concepts like “risk aversion” (unwillingness to take risks) and “patience” (willingness to delay gratification). Some work along these lines already is occurring in economics, much of it with very small samples of a few hundred people in laboratory games, and more recently in samples of several thousands.

Benjamin further commented on the policy implications of genetic information, including the effects of public release of information on market prices and health insurance coverage. Do the benefits of public release (anticipatory behaviors, reduced uncertainty) outweigh the costs? Classic economic analyses are not specifically about genetic information. However, more tailored economic analyses could be conducted.

Also, one could think about targeting social science interventions, for example, children susceptible to dyslexia could be taught to read differently from an early age. This does not actually require causal knowledge about genes and outcomes; merely predicting sufficiently well would be adequate for targeting.

The pay-offs from genoconomics are long-term and unlikely to be realized in economics within the next 10 years (if at all) because of a number of challenges:

- Challenge #1: Phenotype selection (biological mechanisms). The phenotypes that should be studied need to be measured consistently across different datasets and with high reliability (e.g., height, general cognitive functioning, years of education) and are proximate as much as possible with effect. If the pathway is too distal, the effect will likely be small and therefore have low statistical power. If there are different pathways in different local environments, few datasets will be available for replication. A proximate pathway is more likely for phenotypes shared with animal models; some candidates might be risk averse or impulsive. The challenge is that there are still many pathways, and they may not be well measured across datasets. It also might be that the qualities about which economists are most interested (e.g., income and education) may not have consistent, proximate pathways.
- Challenge #2: Causal inference (biological mechanisms). Ethnicity, gene-environment correlation, and gene-gene correlation can confound causal inferences. Convergent evidence is needed from large family samples, modeling and estimation of environmental effects, knock-out experiments with animal models, and biological evidence on protein products of genes. This may take a long time to accumulate.
- Challenge #3: Statistical power (targeting/biological mechanisms/genes as instrumental variables). Low power is due to small effect sizes and is exacerbated by multiple hypothesis testing and publication bias, inconsistent or low-reliability phenotypes, and the search for GxE interaction. The literature is showing that many of the associations are not reproducible. The social science literature is not sufficiently attentive to issues of statistical power. It is important to narrow the range of plausible hypothesis so as to reduce the multiple hypothesis testing problem.

Benjamin then described his own experience with an ambitious gene-hunting exercise in economics.⁶⁷ Using Icelandic data from the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study, a large, ethnically homogeneous, well-characterized longitudinal dataset, Benjamin and his colleagues conducted association analysis with 415 SNPs and 8 “economic” phenotypes (discounting, happiness, self-reported health, housing wealth, human capital, income, labor supply, and social capital) and found that discounting, human capital, and social capital were statistically significantly associated with particular SNPs in the initial round of testing, and after adjustments. The team was able to replicate in a non-overlapping sample from the same dataset an association between one SNP and human capital (composed of years of schooling and number of languages learned). However, attempts to replicate this association in three other (unrelated) samples failed.

The sobering conclusion is that genoconomics is a high-risk enterprise that may end up contributing little to economics. Even if everything is done correctly (e.g., whole-genome

⁶⁷ Benjamin DJ, Chabris CF, Glaeser EL, Gudnason V, Harris TB, Laibson DI, Launer LJ, and Purcell S. 2008. *Genoconomics*. In M Weinstein, JW Vaupel, and KW Wachter, eds. *Biosocial Surveys*. Division of Behavioral and Social Sciences and Education. Washington, DC: National Academies Press.

sequencing), it may be the case that economic phenotypes are too distal from biology for associations to have measurable effects.

Nonetheless, the attraction to geno-economics lies in its potential for major pay-offs to economics, the data are available, and the potential for success cannot be realized unless tried. As genotyping costs plummet, genetic variables are expected to proliferate in many major economic datasets. It is important to set high standards for the field in terms of appropriate sample sizes (or a consortium) for adequate power and harmonized phenotypes and GWAS platforms. A workshop scheduled for February 2011 will explore the feasibility of a consortium with more than 100,000 subjects for “social science phenotypes.” The organizational structure piggybacks on the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium, which already has more than 40,000 individuals. The consortium hopes to add the WLS and HRS data.

Terwilliger described HRS researchers as typically dealing with one basic outcome phenotype and 2.5 million risk factors. So the question of interest is not whether a gene predicts a particular phenotype but whether the trait or phenotype predicts the gene, which is how GWAS or gene mapping works. This is the fundamental difference between gene identification and effect size estimation. Thus the focus in the HRS should be on identifying the variables that predict the same genes, not in measuring the variables in the same way. For example, conscientiousness may be measured in the same way in a German and a Sardinian but may not be predicting the same genes. Terwilliger illustrated with another example: breast cancer (BC)—most BC patients are women (a clear genetic effect), but not all women have breast cancer. He noted that BRCA1 has high predictive value for BC. However, a GWAS involving 30,000 cases of breast cancer did not register any signal in BRCA1 because there are approximately 500 possible BRCA1 mutations. Thus the genotype of BRCA1 is not predicted by the phenotype of breast cancer, but the variants of BRCA1 are very predictive of BC. It is therefore important to think about the difference between predicted value of outcome (what we care about) and what can be detected with a random GWAS approach. In other words, what are the most important factors that correlate with the outcome in the population? In breast cancer it is being a woman, not BRCA1. A common mistake in genetics is to try to refine clinical phenotypes based on treatments or what is salient to doctors, which is not necessarily what is salient to biology. In terms of finding the genes with the desired characteristics, Terwilliger advised that the guiding question should always be whether a trait is believed to likely predict genotypes at one locus in the selected sample. The next step would be to take a subset of the data and ascertain maybe in some non-random way a sample that is believed to have a different genotype from another group.

Conti posited that economists should not be doing GWAS. Economists can incorporate genetic data in model development and can study GxE correlations and selection into certain environments and how the effects of certain environmental factors vary by genotype, in order to design more personalized policies by targeting individuals with certain genetic endowments.⁶⁸ She agreed with Benjamin’s points that genes can be used as instruments—but using methods recently developed in econometrics that account for weak instruments, local effects, and heterogeneous responses.

⁶⁸ Conti G and Heckman JJ. 2010. Understanding the early origins of the education-health gradient: a framework that can also be applied to analyze gene-environment interactions. *Perspect Psychol Sci* 5(5): 585-605.

As a non-professional sociologist, Cole was puzzled by the notion that there are universal truths at the polymorphism level. He did not find it at all surprising that Benjamin was able to replicate results in a non-overlapping sample from the same dataset, and that the results could not be replicated in other datasets because there may be contextual differences. This raises the possibility of using such discontinuities or lack of replication as opportunities to learn about how environments contribute. He believed that social scientists can contribute most to genetic research because of exactly this preoccupation with phenotype and well-specified analytic models.

Boardman considered a genome-wide principal components-based approach in thinking about factors that can be used to actually predict the genes: that is, rotating eight or nine variables at each locus to maximize detection of heritability at each locus for each SNP in the model, and then unpacking those rotations at each of those loci to see what it is about certain characteristics of the gene that makes it more susceptible.

Jonathan King cautioned against selecting phenotypes that are time- and area-variable and may be negatively correlated to the extent that they occur in the same time and place. For example, he considered BMI plus number of cigarettes smoked (the phenotypes used in the Age, Gene/Environment Susceptibility Study) and remarked that the heritability of smoking in the United States varies depending on a number of factors and from state to state as Jason Boardman has noted; BMI also has been escalating nationally. King pointed out that one reason people smoke is to stay thin. It is therefore important to know clearly the latent variable that is really being measured. Although it may be unfortunate that a particular trait of interest varies with time and place, it also could be very fortunate precisely because knowledge about the right environment might actually lead to uncovering actual associations or causes.

The discussion highlighted for Benjamin the importance of involving social scientists in GWAS analyses. In addition to creating the sum score (of smoking and BMI), Benjamin and his colleagues also created a principal component on the theory that economics suggest that everything should be related to a patient parameter, and also looked individually at the constituency of the index once an effect was found, which is a key part of any analyses to create the index as a way to get higher power initially and then see what's driving it and interpret the pieces.

Davey Smith cautioned against researchers who say they're doing GWAS on a particular phenotype because it may not actually be the particular phenotype the investigators think they are studying, but an associated phenotype, that produces the association with a particular genetic variant. For example, an early GWAS of diabetes identified FTO as a risk variant for diabetes, but it turned out that primary effect of FTO was on body-mass index, and this high body-mass index increases diabetes risk. The CHARGE consortium did not detect the signal because it matched cases on BMI in the study. With a large enough sample, and BMI being causally related to so many outcomes, FTO would be detected as being a gene "for" high blood pressure, lipid abnormalities, joint pain, and all other things for which risk is increased by obesity. Another example relates to a variant related to autism, which has been replicated in many different populations. It is important to look at a whole host of phenotypes related to each variant, including social communication and behavioral issues. It is not a gene for autism but a variant

with a host of complex effects that may lead to greater likelihood of autism diagnoses.⁶⁹ According to Davey Smith, some traits (e.g., intelligence) are unlikely to be context-specific.

Session 9—Using GWAS for Exploring Promising Links Among Constructs

(4) Health Behavior and Addiction

GWAS for Addiction and Ability to Quit Smoking *George Uhl, NIH IRP (NIDA); Johns Hopkins University*

Because few studies have identified single SNPs statistically correlated with complex traits with P values of 10^{-8} , Uhl's group has instead focused on locating genes or gene clusters with more modest P values that are identified with addiction and abuse cessation in replicated studies. This is an important topic for study because the use of non-medical drugs is on the rise, even for populations aged 65 years and older; tobacco and alcohol, in particular, contribute to significant morbidity and mortality. Analyses of the genetics of substance abuse indicated that the risk of substance dependence has a genetic component⁷⁰ and is enhanced smoothly with closer relatedness to a substance-dependent proband, in ways that are consistent with additive polygenic effects rather than a common Mendelian/single-gene pattern of transmission.⁷¹

A large body of literature covering family, adoption, and twin studies suggests approximately 50 percent heritability for both the vulnerability for cigarette addiction and the ability to quit. There appears to be some degree of overlap in the genetics of vulnerability and cessation, but not 100 percent overlap⁷²; therefore some cessation variants are likely to differ from addiction variants. Like addiction in general, additive models from individually small effects of common allelic variants are consistent with classical smoking genetic data; however, it is also possible that rare variants play a role.

GWAS of smoking, alcohol, and illegal drug addiction phenotypes have identified many nominally significant loci over several chromosomes, but no single locus provided reproducible, robust influences on any of these addiction vulnerability phenotypes.⁷³ GWAS data have also

⁶⁹ St Pourcain B, Wang K, Glessner JT, Golding J, Steer C, Ring SM, Skuse D, Grant SFA, Hakonarson H, Davey Smith G. 2010. Association between a high-risk autism locus on 5p14 and social-communication-spectrum phenotypes in the general population. *Am J Psychiatry* 167: 1364-72

⁷⁰ Kendler KS, Jacobson KC, Prescott CA, Neale MC. 2003. Specificity of genetic and environmental risk factors for use and abuse/dependence of cannabis, cocaine, hallucinogens, sedatives, stimulants, and opiates in male twins. *Am J Psychiatry* 160 (4): 687-95.

⁷¹ Tyrfinngsson T, Thorgeirsson TE, Geller F, et al. 2010. Addictions and their familiarity in Iceland. *Ann N Y Acad Sci* 1187: 208-17.

⁷² Broman U, Madden PA, Heath AC, et al. 2007. The Nicotine Dependence Syndrome Scale in Finnish smokers. *Drug Alcohol Depend* 89(1): 42-51.

⁷³ Uhl GR, Drgon T, Johnson C, et al. 2008. Molecular genetics of addiction and related heritable phenotypes: genome-wide association approaches identify "connectivity constellation" and drug target genes with pleiotropic effects. *Ann N Y Acad Sci* 1141: 318-81.

Treutlein J, Cichon S, Ridinger M, et al. 2009. Genome-wide association study of alcohol dependence. *Arch Gen Psychiatry* 66(7): 773-84.

Bierut LJ, Agrawal A, Bucholz KK, et al. 2010. A genome-wide association study of alcohol dependence. *Proc Natl Acad Sci U S A* 107 (11): 5082-7 (March 16).

failed to identify major gene or oligogenic effects on cessation comparing current and former smokers⁷⁴ or successful and unsuccessful quitters.⁷⁵

Uhl and colleagues adopted the strategy of analyzing GWAS data to seek small genomic regions that contain clustered SNPs with nominally significant individual p values ($< 10^{-2}$) in each of several replicated samples, identifying clusters of SNPs that are different between cases and controls in numerous independent samples and that are unlikely to be so by chance. This approach allows more robustness for phenotypes with smaller effects of multiple variants within each gene and is more appropriate for phenotypes with complex genetic architectures: more loci, more variants per locus, and different repertoires of variants in individuals from differing genetic backgrounds. It also has the technical advantage of enabling easy combination of GWAS data from different genotyping platforms. Such an approach would be useful, for example, in identification of the gene for cystic fibrosis, which has more than 1,900 variants listed in databases.

By assessing overlapping regions of moderate power between several separate studies, this strategy provides evidence for the influence of variants in sets of genes as well as for variants in individual genes related to addiction and smoking cessation success. Many of these variants, such as cadherin-13, are expressed in brain and are likely to influence brain structure (i.e., wiring) and function (i.e., biochemistry). Participants' polygenic scores on more than 12,000 SNPs identified to correlate with quit success were shown in subsequent trials to help predict successful smoking cessation. This is the first experimental paradigm in which polygenic variants were reproducibly used to predict behavior. Importantly, however, this success might be due in part to the fact that the subsequent studies were performed on analogous populations to those in the earlier studies: participants in all had been recruited in the same way from the same location.

In the discussion following Uhl's presentation, a participant commented that Uhl's data reinforce the need to consider phenotypes clearly. In a study of participants with lung cancer, smoking self-reports were not reliable means of quantifying smoking due to reporting errors and differences in nicotine content, inhalation, and extraction. However, when cotinine is used as a biomarker for tobacco smoke exposure, it fully accounted for the association between polymorphisms in the nicotinic receptor gene on chromosome 15q and development of lung cancer. Uhl replied that his future studies include measurements of cotinine.

⁷⁴ Drgon T, Montoya I, Johnson C, et al. 2009. Genome-wide association for nicotine dependence and smoking cessation success in NIH research volunteers. *Mol Med* 15 (1-2): 21-7.

Caporaso N, Gu F, Chatterjee N, et al. 2009. Genome-wide and candidate gene association study of cigarette smoking behaviors. *PLoS One* 4 (2): e4653.

Tobacco and Genetics Consortium. 2010. Genome-wide meta-analyses identify multiple loci associated with smoking behavior. *Nat Genet* 42 (5): 441-7.

⁷⁵ Uhl GR, Liu QR, Drgon T, et al. 2008. Molecular genetics of successful smoking cessation: convergent genome-wide association study results. *Arch Gen Psychiatry* 65 (6): 683-93.

Uhl GR, Liu QR, Drgon T, et al. 2007. Molecular genetics of nicotine dependence and abstinence: whole genome association using 520,000 SNPs. *BMC Genet* 8:10.

Uhl GR, Drgon T, Johnson C, and Rose JE. 2009. Nicotine abstinence genotyping: assessing the impact on smoking cessation clinical trials. *Pharmacogenomics* 9 (2): 111-5. Epub 2008 Sep 9.

Rose JE, Behm FM, Drgon T, et al. 2010. Personalized smoking cessation: interactions between nicotine dose, dependence and quit-success genotype score. *Mol Med* 16 (7-8): 247-53.

In response to a question about how the cadherin-13 gene was identified from the association data, Uhl explained that hand curation was applied to information from gene databases.

Another participant asked whether family studies had identified any of the genes that Uhl's data associated with cessation of smoking. Uhl responded that prior to performing GWAS, other groups had performed linkage studies for smoking phenotypes.

When asked how this information could be used by the HRS, Uhl commented that he had the general suggestion that if the HRS were to capture allele frequency classes and haplotypes, it would be possible to evaluate variations on different subsets of populations.

Roberts noted that conscientiousness is known to influence the duration of the quitting period and recommended incorporating that measurement into the variables that Uhl studies and investigating SNPs identified to be related to conscientiousness or other disposition characteristics.

Session 10—Using GWAS for Exploring Promising Links Among Constructs

(5) Individual Variations in Cognitive Preservation and Decline

Contemporary Modeling of Gene x Environment Effects in Randomized Multivariate Longitudinal Studies

Jack McArdle, University of Southern California

The Aging, Demographics, and Memory Study (ADAMS) is a portion of the HRS that assesses the factors that influence memory and dementia with aging that can offer some insight into investigating GxE interactions with a longitudinal research design. The idea that intellectual ability could be partially under the influence of genetics became apparent when researchers discovered the ability, within a few generations, to breed rats that were good or poor at running mazes.⁷⁶ That the genetic influence on intellectual ability was modifiable by environmental factors was postulated when maze-bright rats were shown to be even better at running mazes when they had been raised in an enriched environment. The suggestion raised by the Caspi study⁷⁷ that the environmental influence on an outcome might depend on polymorphisms in a single gene leads to controversy in the area of intellectual functioning, particularly when considering GxE as a latent variable interaction. Latent variables are difficult to estimate correctly or accurately, thus analyses without measured variables should be used carefully or they will be misleading. On the other hand, latent variables for the improved measurement of change have proven to be very reasonable.

ADAMS includes episodic memory tasks in its longitudinal array of measured traits; any one participant in ADAMS might have been given a memory task up to nine times. Normal individuals are expected to perform at a certain level on this task and then show a gradual, linear

⁷⁶ Tryon RC. The genetics of learning ability in rats. 1929. *University of California Publications in Psychology* 4: 71-89.

⁷⁷ Caspi A, Sugden K, Moffitt TE, et al. 2003. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* 301 (5631): 386-9.

decrease in performance with additional biennial measurements. Individuals with cognitive impairment are expected to begin at a lower performance level and decrease at a greater but linear rate over time. Individuals with dementia might begin at a level somewhere between the other two groups and decrease over time at a more rapid and perhaps accelerating rate. A study evaluating a single time point evaluation of episodic memory, educational attainment, and Apolipoprotein $\epsilon 4$ (APOE $\epsilon 4$), which has been implicated in beta amyloid accumulation in the brain) allele status showed a significant negative impact of age on memory and a positive impact of education on memory, but no significant genotype or GxE interaction on memory. Neither multiple group regression nor the use of latent class regression altered these results.

However, when the same comparison was performed longitudinally on an average of seven points per participant, a linear latent curve model added significant individual differences in latent intercepts at age 70, which accounted for half the variance, were positively associated with education, and had a significant negative APOE $\epsilon 4$ -by-education impact. The latent slopes were negative over time, had negative education effects, and positive APOE $\epsilon 4$ -by-education effects. Race differences (as predictors) did not alter these results. The use of multiple group latent curves showed that no group differences in latent curves were attributable to genotypes. The use of multiple class latent curves showed that some potential class differences in latent curves could be attributed to genotypes. McArdle displayed a model illustrating how these factors might be interaction on episodic memory over time.⁷⁸

When performing GxE studies in the HRS, it is worthwhile to keep in mind that any research plan is a trade-off between Type I and II errors. When testing for the effects of specific genes on the HRS outcomes we need to consider that examination of multiple genes and multiple outcomes can lead to an unusually high probability of false positive results, that is, Type I errors. Type II errors, resulting from the possibility of a low frequency of specific sub-populations in the sample, or a failure to measure the key outcomes adequately, can lead to a high probability of false-negative results. Although the rich, multiple measurements of the HRS can and should be researched, McArdle reminded attendees that “what genes really determine are the reaction ranges exhibited by individuals with more or less similar genes over the gamut of environments,”⁷⁹ and expressed the hope that GxE models could be modified to reflect this.

In the discussion that ensued, a participant commented, and McArdle agreed, that the model used might not have been the most appropriate because it showed evidence of an interaction that prompted the evaluation of Apo $\epsilon 4$ for interactions that would not have been sought had the interaction not been initially modeled. Another participant asked whether the model could predict effects at an age-specific point. McArdle explained that is possible, and it is also possible that the model predicts more accurately at one age than another; it was included as an illustration of the research possibilities offered by the HRS.

⁷⁸ McArdle JJ and Prescott CA. Contemporary modeling of gene x environment effects in randomized multivariate longitudinal studies. *Perspect Psychol Sci*. In press.

⁷⁹ Dobzhansky T. 1973. Is genetic diversity compatible with human equality? *Soc Biol* 20 (3): 280-8.

Considerations and Caveats in Analyses of Cognitive Endpoints

Nancy Pedersen, Karolinska Institute

Although a great number of GxE studies focus on cross-sectional results, longitudinal studies offer the benefit of understanding changes in the variance of heritability over time. For example, cognitive abilities, including general abilities, crystallized, fluid, perceptual speed, and memory, show heritability in two different studies at average ages of 60⁸⁰ and 85⁸¹ years, but the percent heritability is not the same at these ages for general abilities, fluid, or memory. A comparison of the overlapping data points by age shows little difference between cohorts, suggesting that these were not simply cohort differences.⁸²

It is important to consider the variance because genetic effects might appear stable in absolute terms, but increases or decreases in the variance means a decrease or increase of genetic effects in relative terms. This can be seen when considering crystallized cognitive abilities: the genetic variance is generally stable between 50 and 80 years of age, while the environmental variance increases. The net effect is a slight decrease in heritability in late life, not because the genetic variance has changed but because environmental variance has increased.⁸³ This illustrates the need to focus on raw variances rather than on proportions of variance in longitudinal analyses. Unlike crystallized cognition, fluid and speed measures show a different pattern, with genetic variance decreasing more than environmental variance increases.⁸⁴ The increase in environmental variance might be accounted for by additive effects over time or long-term effect of chronic stress and the accompanying inflammatory processes. Decreases in genetic variance could be due to genes turning off or down-regulating, epigenetic effects, or selective loss of detrimental genetic variants.

The other factor identified to interact with cognition was occupational complexity before and after retirement.⁸⁵ Complexity involving other people was associated with differences in cognitive performance and cognitive rate of change, facilitating some abilities before retirement that then show a greater rate of decline after retirement, perhaps due to a protective effect.

Genes might play a role in the trajectories of components of cognition with age. Pedersen's current work is looking at candidate genes and pathways biologically associated with neurotransmission and neuropathology, performing association analyses with the latent growth curve model to evaluate changes in genetic and environmental variance. For example, longitudinal trajectories of working memory in individuals with zero, one, or two copies of the Apoε4 allele predict that homozygous carriers will begin at a lower level than heterozygotes or

⁸⁰ Pedersen NL, Plomin R, Nesselroade JR, and McClearn GE. 1992. A quantitative analysis of cognitive abilities during the second half of the lifespan. *Psychol Sci* 3: 346-53.

⁸¹ McClearn GE, Johansson B, Berg S, et al. 1997. Substantial genetic influence on cognitive abilities in twins 80 or more years old. *Science* 276 (5318): 1560-3.

⁸² Finkel D, Reynolds CA, McArdle JJ, and Pedersen NL. 2007. Cohort differences in trajectories of cognitive aging. *J Gerontol B Psychol Sci Soc Sci* 62(5): P286-94.

⁸³ Reynolds CA, Finkel D, McArdle JJ, et al. 2005. Quantitative genetic analysis of latent growth curve models of cognitive abilities in adulthood. *Dev Psychol* 41 (1): 3-16.

⁸⁴ See Reynolds et al. (2005)

⁸⁵ Finkel D, Andel R, Gatz M, and Pedersen NL. 2009. The role of occupational complexity in trajectories of cognitive aging before and after retirement. *Psychol Aging* 24(3): 563-73.

homozygous wildtypes but decrease at the same steady rate over time.⁸⁶ The association with another gene in the amyloid cascade process, alpha-2-macroglobulin, is quite different, with working memory beginning at the same level but showing a more dramatic decline over time for individuals homozygous for the deletion allele.⁸⁷ Associations may vary with factors other than age, such as gender: men homozygous for the rare variant of the SORL1 rs2070045 SNP demonstrated significantly steeper rates of memory declines after age 75 compared to carriers or those homozygous for the common variant, whereas women homozygous for the rare variant demonstrated worse memory performance, particularly before age 65, compared to carriers or those homozygous for the common variant.⁸⁸ Had these traits been examined at just one time point rather than longitudinally, vastly different conclusions would have been reached.

Not only may genetic associations differ as a function of age and sex, but also there may be interactions. Twin designs are useful to help identify GxE interactions even when the genes or the environments are unknown.⁸⁹ For example, the link between depression and stressful life events was indicated by twin data before the Caspi⁹⁰ paper added the putative genetic component. Associations suggested by twin studies help indicate in which direction to focus subsequent research.

Several considerations should be kept in mind for the HRS:

- Age- and survival-related effects may be considerable in elderly populations, even for genetic association, with possible “survival bias.”
- If longitudinal information is available, it should be used to give a more accurate picture than cross-sectional data.
- Genetic studies need to consider pleiotropy and the likelihood of gene-gene and GxE interactions.
- GWAS provide only limited new information, particularly for Alzheimer’s disease and cognitive aging, being limited by availability of appropriate samples; GWAS might be proving the polygenetic nature of complex phenotypes.
- Studies of genetics must not fail to account for the environment.

In the discussion that followed, a participant noted that in some cases, evaluating extremes in the distribution might be more informative than evaluating an entire sample. This approach worked well in studies of breast and colon cancer. In some cases, more extreme phenotypes are more heritable. Pedersen replied that key issues in cognition are the age-related declines and differentiating normal aging from dementia; data she has evaluated with and without individuals who are beginning to show signs of dementia did not reveal differences. However, there are different kinds of dementia and different associations might be affiliated with each, for example, cardiovascular disease and vascular dementia are associated regardless of the individual’s Apoe status, whereas cardiovascular disease is only associated with Alzheimer’s disease in individuals

⁸⁶ Reynolds CA, Prince JA, Feuk L, et al. 2006. Longitudinal memory performance during normal aging: twin association models of APOE and other Alzheimer candidate genes. *Behav Genet* 36 (2): 185-94

⁸⁷ Reynolds CA, Prince JA, Feuk L, et al. (2006).

⁸⁸ Reynolds CA et al. (in preparation).

⁸⁹ Reynolds CA, Gatz M, Berg S, and Pedersen NL. 2007. Genotype-environment interactions: cognitive aging and social factors. *Twin Res Hum Genet* 10 (2): 241-54.

⁹⁰ See Caspi et al. (2003).

who are ApoE4-positive. Another participant added that applying the extreme-phenotype approach to cognition would be quite different from applying it to cancer, which might reflect a failure in a tumor suppressor gene allowing the malignancy to grow; no patterns of cognitive decline show patterns remotely similar to that. Reynolds replied that multi-level models of longitudinal cognitive traits work best, followed by criterion-based models.

Another participant asked whether the polymorphism studies had been replicated. McGue replied that APOEε4 showed a small main effect for cognition, and Pedersen added that the linear design appears in other examples.

A Pathway Approach to Understanding Variation in Cognitive Decline and Dementia

Chandra Reynolds, University of California, Riverside

In GWAS, depth of phenotyping is as important as breadth of genotyping for understanding associations. To that end, longitudinal data can be extremely valuable in revealing pathways that are affected by genes interacting with the environment. Cognition shows clear declines with age, having a steeper decline after age 65, at which point genetic variance begins to decrease while environmental variance begins to increase.

The cholesterol metabolism pathway may be important to cognitive change and dementia outcomes. Reynolds investigated whether intermediate traits such as serum lipids predict cognitive change and dementia in the SATSA sample⁹¹ and considered potential moderators such as sex and age. More significant relationships were uncovered between lipids and cognition in women than men: higher HDL levels and lower levels of ApoB and triglycerides in particular, were associated with better longitudinal performance on cognitive tasks in women, whereas *higher* apolipoprotein B (ApoB) and total cholesterol were associated with better performance in men. In general, effects of serum lipids on cognitive trajectories were particularly notable prior to age 65. Because this study focused on individuals 50 and older, it is possible that the differential effects in men and women were related to differences in the life course timing of lipid profile shifts, which occur earlier in men than in women. Additionally, in dementia-discordant pairs, higher baseline ApoB and total cholesterol were seen in the twin that was subsequently diagnosed with dementia, six years later on average.

A subsequent study looked at cholesterol gene candidates, intermediate biomarkers – cerebrospinal (CSF) beta-amyloid (Aβ), and the risk for dementia/Alzheimer's disease (AD) in several combined Swedish twin samples and non-twin case-control sample.⁹² A systematic review of the literature between 2003 and 2008 led to a focus on 25 candidate genes associated with cardiovascular disease, dementia, or lipid metabolism. Of the nearly 450 markers ultimately examined, 5 markers showed significant differences in full dementia versus controls when accounting for multiple testing, including APOE as the most strongly associated, two already established ABCA1 markers and two markers near the SREBF1 region. Apart from APOE and ABCA1, associations of candidate SNPs with CSF Aβ in a subset of AD individuals were negligible with no signal from the SREBF1 markers. Bioinformatics tools were used to highlight

⁹¹ Reynolds CA, Gatz M, Prince JA, Berg S, and Pedersen NL. 2010. Serum lipid levels and cognitive change in late life. *J Am Geriatr Soc* 58 (3): 501-9.

⁹² Reynolds CA, Hong MG, Eriksson UK, et al. 2010. Analysis of lipid pathway genes indicates association of sequence variation near SREBF1/TOM1L2/ATPAF2 with dementia risk. *Hum Mol Genet* 19: 2068-78.

specific genes in associated regions around SRBEF1 by virtue of their gene-network similarities to known dementia genes. Combined with additional imputation and other GWAS samples, a follow-up meta-analysis revealed evidence of association of sequence variation near the SREBF1/TOM1L2/ATPAF2 region and dementia. The lack of abundant signals from the cholesterol candidates and that the SREBF1/TOM1L2/ATPAF2 region includes signals from candidate genes belonging to distinct pathways suggests that dementia is not particularly associated with the cholesterol metabolism pathway compared to other pathways. The cholesterol candidate analyses are ongoing now with eight cognitive outcome measures in a subset of the twin samples.

In similar work, six markers in the SORL1 gene were examined for association with CSF A β and tau biomarkers and the risk for dementia/AD.⁹³ The large-scale meta-analysis of published studies together with the data in the combined Swedish samples led to weak but significant evidence of association. In-progress analyses of cognitive outcomes in the Swedish twin samples suggest relationships with three SORL1 SNPs that might be moderated by gender, including the rare variant of the SORL1 rs2070045 SNP mentioned by Pedersen.⁹⁴ Men homozygous with this allele show a greater rate of decline compared to men of other genotypes and to women.

Given prior evidence of increasing variation in non-shared environments with age across cognitive traits,⁹⁵ a GxE study was conducted using monozygotic twins.⁹⁶ Within-pair differences in memory change showed greater variability in pairs who did not carry the APOE ϵ 4 allele. Similar results were seen for the ESR1a gene, the serotonin 2A receptor gene, and the serotonin transporter gene, that is, the non-carriers for rare variants were more variable than the carriers. Further analyses considered within-pair differences in memory change to within-pair differences in “environmental” or social factors, such as social support, perceived support, life events, uncontrollable life events, as well as depressive symptoms. Findings indicated that environmental factors impacting depressive symptoms and semantic memory change may be moderated by APOE and ESR1 genotypes.

The longitudinal and biomarker data in the HRS will be valuable for GWAS due to the multiple levels of analysis available with intermediate traits and endpoints. However, caution should be taken when assessing average effects versus variability (i.e., one should consider the potential presence of both). It is important to keep in mind that even for highly heritable traits, SNPs might be far from causal variants and might be difficult to detect. Follow-up sequencing will be needed to capture additional causal variants.

⁹³ Reynolds CA, Hong MG, Eriksson UK, et al. 2010. Sequence variation in SORL1 and dementia risk in Swedes. *Neurogenetics* 11(1):139-42.

⁹⁴ Reynolds CA et al. (in preparation).

⁹⁵ Reynolds CA, Finkel D, McArdle JJ, et al. 2005. Quantitative genetic analysis of latent growth curve models of cognitive abilities in adulthood. *Dev Psychol* 41 (1): 3-16.

⁹⁶ Reynolds CA, Gatz M, Berg S, and Pedersen NL. 2007. Genotype-environment interactions: cognitive aging and social factors. *Twin Res Hum Genet* 10 (2): 241-54.

Concluding General Discussions and Next Steps

The purpose of this expert meeting was to raise the level of discussion, not necessarily to reach consensus. The presentations and discussions served to inform NIA staff on the transformation of science, and the HRS principals on future directions.

Suzman expressed confidence that GWAS in the HRS will be useful and important. There is clearly more work to be done on phenotypes, for example to get facets of conscientiousness, and more importantly to capture some of the critical motivational aspects. It may be that some of the first advances come from cognition measures in the HRS. He considered it absolutely necessary to progress to some form of consortia-forming and perhaps consortia-joining activities. Which consortia to join will be a key consideration with a sample of only 20,000. If Project Talent moves forward, it would represent a potential cohort of 350,000 individuals.

Weinstein summarized a number of the questions that arose throughout the two-day meeting:

- What do we mean by heritability and environment, and what are the pay-offs from disentangling the genetic components?
- What are the underlying theories? In the absence of reasonable pre-existing hypotheses or theory, it is not clear how to interpret disparate GWAS results. The world of genetics necessarily draws social scientists into the world of evolutionary biology.
- Where will the inputs come from? There seemed to be general agreement that social scientists are not primarily interested in gene discovery, and other fields (such as biology) will need to provide the inputs. There did not seem to be many possibilities other than animal studies for identifying candidate genes.
- A new generation of multidisciplinary investigators is needed to pursue this line of inquiry—researchers conversant in diverse fields as sociology, pharmacology, demography, economics, genetics, evolutionary biology, molecular biology. How do researchers train for this, and where will they reside in academic structures, get funding, and get tenure?

She contended that publication bias causes the loss of a great deal of information. As such, it would be helpful to publish findings of non-reproducibility to try to determine if results are indeed irreproducible or are merely context-dependent.

Weinstein also summarized the many sources of error with which researchers must contend. There is selectivity even in population representative samples that are unbiased. There are measurement errors in phenotypes and outcomes, environment, genes, and SNPs, and from not measuring actual functional units. There are left-censoring (starting studies at 50+ or 85+) and frame-of-reference questions. When the observations are made will affect the conclusions drawn.

With respect to discovery, Hobcraft indicated that geneticists may not be motivated to look for the candidate genes that influence outcomes of interest to social scientists (e.g., economic variables, choice behaviors). He cautioned that one needs to disentangle the many different pathways that can lead to broad outcomes of interest (e.g., smoking behavior) in order to have a better chance of identifying the relevant genes. Researchers must sharpen their thinking in looking at economic domains (risk taking, time-discounting) that seem to be promising, but they

need to consider the issues more rigorously and not be satisfied with broad associations and averaging across pathways. As well, working with p-values in the range of 10^{-8} , which is common in genetics research, can be challenging for many social scientists. Maybe when all the rare variants are discovered, it will be easier to discern which pathways have discernable effect sizes. It may be that the epigenetic changes, or the interplay between the environment and the biology, are what really matter. At some stage, perhaps a few years from now, biologists will make more sense of the genome and how the bits fit together into constructs that social scientists can use. Uhl added that researchers need to state *a priori* what gene they are looking for as a matter of rigor rather than massaging the data *ex post* to justify the search.

Even though the HRS is not optimal for gene hunting, Terwilliger considered it wasteful not to do GWAS because the data are already collected and because a sample size of 20,000 is enormous and is therefore likely to reveal large effects for some traits.

McCombie saw the issue of phenotype as critical. He illustrated with his effort to come up with a linguistic phenotype that one can dissect genetically. Although somewhat contentious at the time, there appeared to be some linguistic traits that are heritable (e.g., word placement under unusual circumstances). In McCombie's view, some social and behavioral variables seem too broad to be useful for genetic dissection (e.g., income and wealth). To apply genetic dissection to traits in a serious way, one needs to know the underlying phenotypes rather than rely on crude measures of behavior.

From Reiss' viewpoint, this meeting has been extraordinary in its controversy and its clarification, which he considered a perfect state of affairs given the state of the field. He hoped others would cherish the controversies, allow different strategies to work themselves out in the data, and learn from this process. He organized these controversies into three categories:

1. Boundaries— There is controversy about whether the HRS is a study in its own right, whether it should be considered one in a sequence of studies, or whether it should be part of a larger consortium. These are all different strategies that are worth labeling and following to see what happens when one is pursued over another.
2. Phenotypic strategies—There are many different approaches to defining phenotypes. In addition to animal studies and brain scans, developmental data are sources for defining phenotypes. There are also different strategies for structuring data (e.g., longitudinal versus latent-variable data), and it is important to label these strategies in order to see what works best.
3. Social theories—Absent knowledge about specific theories, we can consider categories of theories that are likely to look different as a consequence of this research (e.g., causal modeling, instrumental variables, differential sensitivity issues, selection processes, environmental moderation, and the possible development of behavioral interventions). It is important to label these categories in order to track their progress.

As a trained psychoanalyst, Reiss considers the field of genetics to be a history of trauma. The field has been traumatized and has survived public humiliations, which can lead to strategies that are too conservative on the one hand, or too risky on the other, and also can lead to amnesia about what has been successful. He encouraged participants not to let repeated public failures

unduly influence or dampen their efforts, but to proceed with confidence that conflicts can energize the field.

The HRS has had to weigh the trade-offs between competing approaches, including a preference for breadth of samples and traits rather than for focusing on SNPs related to a particular domain (e.g., cognition). Much of what the HRS has done over the years is to lay the groundwork of data for the next generation of interdisciplinary minds. Weir saw merit in continuing to build the HRS DNA database until there is a sufficiently large sample for robust analyses. Because some might consider GWAS to be passé, Weir saw the WLS as perhaps well positioned to pursue more clever approaches for incorporating genetic data into social and behavioral analyses.

Looking ahead for the HRS, Weir noted a great deal of discussion about phenotypes and their heritability and lack of heritability. He saw nothing new in arguments about measurement in genetics, which are similar to long-standing arguments about measurement in economics, psychology, and sociology. He was optimistic that future research can help structure information going forward with discoveries about which phenotypes are closer to biology. The questions the HRS asks will evolve in response to what is done with the data over time. He imagined that the HRS will be pressed in the future to consider in a more directed fashion the complementary “-omes” that contribute to the disease process, for example, epigenome, transcriptome, proteome, and metabolome.

Thinking about the families in which HRS respondents are embedded, Weir noted that the HRS has a great deal of data on relationships with others in the family, but its researchers so far have not interviewed many of these relations and have not collected DNA from them. Other studies (e.g., Panel Study of Income Dynamics, the WLS) may be better candidates for collecting data and DNA on relatives, rather than doubling the size of the HRS by beginning to incorporate family members.

NIA staff encouraged researchers who have not before used the HRS data to do so, and to contact program officers with their ideas. Spotts saw parallels between social science and behavioral researchers grappling with analyses of genetic data and meteorologists dealing with huge quantities of data and making generally accurate predictions about the weather. Because data reduction to facilitate analysis is a major challenge, perhaps it would be helpful to look further afield to discover better ways to deal with this issue. King discussed the need to decide what minimal set of knowledge is needed to work productively in this area. He welcomed suggestions for multidisciplinary meetings, with, for example, social scientists and statistical geneticists, to continue to bridge the knowledge gaps. Another avenue is to invite faculty for summer courses outside their fields. John Haaga considered that lessons might be learned from the genetic marketing field to understand heritability of preferences. Suzman encouraged small demonstration models to better assess the costs and benefits of different approaches. He noted that this work is funded for the most part through grants and not contracts, therefore investigators ultimately must be convinced of the data’s value and that it is in their interests to undertake this work.

Appendix 1: List of Participants

Hooman Allayee, University of Southern California
Yoav Ben-Shlomo, University of Bristol
Daniel Benjamin, Cornell University
Partha Bhattacharya, National Institute on Aging
Jason Boardman, University of Colorado at Boulder
Nicholas Christakis, Harvard University
Steve Cole, University of California at Los Angeles
Gabriella Conti, University of Chicago
Eileen Crimmins, University of Southern California
George Davey Smith, University of Bristol
Rebecca J. Ferrell, National Institute on Aging
John Haaga, National Institute on Aging
Elizabeth Hamilton, National Institute on Aging
John Hobcraft, University of York
Michael Hurd, RAND
Sharon Kardia, University of Michigan
Andrea Kelly, Rose Li and Associates, Inc.
Jonathan King, National Institute on Aging
Robert Krueger, University of Minnesota
Alfonso Latoni, National Institute on Aging
Rose Maria Li, Rose Li and Associates, Inc.
Jack McArdle, University of Southern California
W. Richard McCombie, Cold Spring Harbor Laboratory
Matthew McGue, University of Minnesota
Marilyn Miller, National Institute on Aging
Lisbeth Nielsen, National Institute on Aging
Georgeanne Patmios, National Institute on Aging
Nancy Pedersen, Karolinska Institute
David Reiss, Yale University
Chandra A. Reynolds, University of California at Riverside
Neil Risch, University of California at San Francisco (by telephone)
Brent Roberts, University of Illinois, Urbana Champaign
Winifred Rossi, National Institute on Aging
James P. Smith, RAND
Erica Spotts, National Institute on Aging
Richard Suzman, National Institute on Aging
Joseph Terwilliger, Columbia University
Barbara Torrey, National Institute on Aging
George Uhl, Johns Hopkins University
Kenneth Wachter, University of California at Berkeley
Robert Wallace, University of Iowa
Maxine Weinstein, Georgetown University
David Weir, University of Michigan

National Research Council Staff

Barney Cohen, Director, Committee on Population

Robert Hauser, Interim Executive Director, Division of Behavioral and Social Sciences and
Education

Keiko Ono, Senior Program Associate, Committee on Population

Jacqui Sovde, Program Associate, Committee on Population