Integrating genetic data into behavioral and social research:
A follow-up to the NAS meeting on the HRS and GWAS

The goal of this teleconference was to take several key themes that arose from the NAS workshop, *Using Genome-Wide Association Studies (GWAS) to Explore Fundamental Questions About Aging in the Health and Retirement Study (HRS) Sample,* held September 23-24, 2010 (the report from which can be found here: http://www.nia.nih.gov/NR/rdonlyres/C0B30519-359D-4D84-AA87-6855E95CB58F/0/HRSGWASfinal.pdf) and expand upon them.

Participants

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Purpose of call and background of the HRS

The goal of the conference call was to discuss gaps and themes that emerged at the NAS meeting held in September 2010, paying particular attention to how adding genetics to social surveys might be used to revise behavioral and social theory. Discussion topics that were considered of high importance were(1) leveraging longitudinal data via the HRS, (2) using neural and molecular pathways to inform the work that will be conducted on the HRS; and (3) understanding how smaller studies supported by NIA and other institutions can be leveraged to better understand broader survey data such as that of the HRS.

The HRS model has spread across the world with 30-40 national longitudinal studies that have emulated parts or most of HRS. Only a few of these studies have collected DNA data but many studies have plans to do so in the future and some studies are planning on moving on to sequencing.

A recent NIH Common Fund proposal includes developing a synthetic cohort where large number of longitudinal cohort studies and medical registries would be harmonized to provide the large samples that people need for GWA, gene finding and other approaches requiring large sample sizes; this proposal is under consideration.

The HRS sample is a population based, longitudinal sample with many panels of data. The collection of biomarkers will allow for the examination of intermediate phenotypes of biomarkers that would allow examining intermediate steps. This teleconference included experts who are already heavily involved in integrating genetic techniques into social behavioral models.

HRS Logistics data issues and information available on the HRS website

The HRS website has varying degrees of information on what phenotypes have been measured and are available. Genetic data from the HRS will be available through dbGaP. HRS and dbGaP are working together to streamline the application process to make data access as easy as possible. Specific phenotype data on age, sex, race, and top-coded episodic memory will be available through dbGaP; the remaining phenotype data will be available through HRS.

HRS also contains spousal phenotype and genotype data, but does not include information on participants' children unless the informant shared that information. One participant mentioned that currently the HRS website does not have clear information on the distribution of the specific types of dyads, household information and the biological relationship between individuals interviewed. This type of summary information would be useful to provide on the website for researchers interested in using the HRS data. NIA will ensure that this data is clearly available on the HRS website.

Participants suggested that it would be useful to have a workshop on the HRS data and how to use for geneticists and related experts. Most people use the RAND file, which is much easier to use but most family data is quite difficult to use (though work is being done to rectify this problem). It was suggested we have a HRS workshop on data utilization at appropriate genetics meeting.

Longitudinal Data and Leveraging

Chandra Reynolds: Defining trajectory: A major step towards leveraging smaller studies for use with the HRS data is by defining trajectories. HRS has multiple waves of data therefore it is important to define the trajectories. Depending on how the trajectories are defined, the variance of change might become an issue. Reynolds proposed that although polynomial models may be useful for multiple measurements or variance, there may be other approaches rather than polynomial models that may be more effective, such as multiple piece wise models. There may be an infinite variance concern with linear models when there are multiple waves of measurement. There needs to be careful simulation work to identify exactly what the problems are, as yet. Thus, there may be potential problems in terms of identifying whether genetic factors impact change, for example; one needs to be very careful in defining the trajectory first.

This modeling needs to be started with phenotypic data. Phenotypes of change and latent phenotypes must be carefully tested. These need to be described before any predictors are put in place. Once it is established that defining a phenotype of change is possible, then genetic and environmental predictors can be put into place.

Even before defining a trajectory one needs to ensure that the trait being measured is invariant across time. Make sure that the construct you're measuring within a time point is the same construct across

time points that you're going to identify the trajectory of. Measurement invariance versus the lack of measurement invariance typifies another kind of potentially interesting examination of 'change', but if one is going to identify trajectories of change for a construct, then measurement invariance is key. Developing the phenotypes first is very important.

Danielle Dick raised a concern with such complex models. Using more complex and intricate models necessarily restricts the number of datasets in which there is appropriate data for the use and replication of these models, both in terms of phenotype definition and sample size. The inability to accurately replicate makes it problematic to separate out genetic effects across samples, false positives, false negatives and analysis of how robust the findings are across samples. Dick suggested that as we fit more complex latent trajectory models and latent growth models, taking full advantage of the data that's in any one full dataset, the possibilities of other datasets that available for replication are narrowed. Therefore, the group needs to think about how to deal with and/or conduct analysis on a single large sample to help deal with potential problems like false positives.

Richard Suzman reminded meeting participants that NIA has begun a series of harmonization efforts across many studies. These efforts are both post hoc and looking for ways that studies could collect additional information to increase comparability as the studies move forward. He urged PIs to add additional measures to studies that would allow such harmonization efforts.

Research to Clinical practice

Terrie Moffitt : The ultimate goal of all the research is to inform clinical practice and intervention. Replication across samples and translation back to practice are two important issues, once the big psychometric of change issue is sorted out.

Danielle Dick: It's easier to make clinical diagnosis because clinical conditions can be found across a lot of samples. Although many feel that making diagnoses results in losing rich information from longitudinal data that has a depth of phenotypic information, it is important to work across samples when we're working with complex phenotypes like we have with the harmonized phenotypes and PhenX initiatives. A lot of phenotypic data needs to be translatable and findings need to be replicated. One should take into account the depth of phenotypic information and longitudinal assessments and figure out how to ensure data replication.

Chandra Reynolds: Identifying the phenotype is a start. We can ask: what is this phenotype about? Is it useful to the larger community and not just to the particular study or sample?

David Reiss: There seems to be two aspects of longitudinal data: First is the longitudinal data that comes from clinical practice. The difference between mean level and stability across time is an important model to examine clinically. The second is disruption and recovery as a longitudinal process. This type of data enables us to shine a light on genetic processes that are involved in recovery and disruption that is quite different from when we're modeling genetic contributions to trajectories.

Gene-environment correlation

Jason Boardman stated that clarifying the phenotype is critical, but he also stressed that environmental influences and rich measures of the environment, especially changes over time, are crucial. He stated that the discussion points for the teleconference: (1) genetic influences on environmental variables, (2) common pathways to diverse outcomes, and (3) improved estimates of environmental effects, need to be considered by social demographers and demographers that we normally see as exogenous factors. There has been an obvious focus in sociology and demography on social isolation in terms of the health of the community but the role of genes has not been considered in this process. Finally, in reference to the third point: divergent outcomes in social mechanisms, such as depression, stress, or alcoholism, may have different outcomes based on gender; social mechanisms that give the same exact fundamental structure can give very different outcomes.

Steve Cole suggested that there might be interesting opportunities to develop vector-based outcomes. He expressed concern that things that may appear as gene-environment interaction in an experimental context may actually become gene-environment correlation in real life setting. If environment is fixed, endophenotypes such as anxiety or social affinity will emerge. But in real life people don't like to be anxious, and will select environments that fit with their personalities. Therefore, gene-environment interaction often converts to gene-environment correlation. A particular concern is that when experimental models are converted to general association studies, only one of a number of possible phenotypes may be considered, and a lot of information will be missed. The HRS provides researchers with a rich opportunity to consider many phenotypes as the study covers multiple domains of an individual's life. The HRS data is useful since it surveys older adults who have already adopted certain lifestyles (occupation, social network characteristics, community and religious participation, etc.). It will be important to look for gene environment correlation under those circumstances, e.g. what kind of occupation you select yourself into, what kind of social environments are defined by social network characteristics. Community and religious participation may well be the resulting proclivity towards certain kind of neuro-biological endo-phenotype early in life; this is considered a gene-niche correlation. One of the bigger statistical results emerging from studies early in the life course is that if you can find any genetic predictors of outcome at all, they often seem to have a certain environmental feel; for example disruption is an exogenous variable that certain people seem to show genetic proclivity towards and in turn find their way towards disruptive circumstances. The broad range of phenotypes in the HRS provides researchers with a very distinctive opportunity for reasonable representation of various phenotypes. Suzman reminded the group to keep in mind the variations in class and race as they affect the ability to move around and the occupation one chooses.
Researchers need to determine ways to decipher individuals' propensity of selecting a certain environment compared to other age cohorts. Understanding this will provide a better measure of how environments affect different people. Suzman added that retirement migration is an important issue that should be looked at more closely, the HRS and its ally surveys provide that opportunity. Others (e.g. Terrie Moffitt) agreed, adding that simply the age of retirement is a niche-picking process. Individual characteristics, such as work place success, cognitive ability, and other variables that predict success, partially determine the timing of retirement.

Jon King mentioned that those who have been granted access to SSA administrative records can find out where people lived before and after retirement, as well as the whole work history. Although currently that data isn't available for all HRS participants, subject numbers will increase so this can become a longitudinal dataset.

Chandra Reynolds: to build on this from an analytical perspective there are very nice survival growth models, where timing of environmental events, e.g., such as the timing of 'disruptions', may impact growth processes. (Or, in turn, growth processes may predict an event). From an analytic perspective, there is some quantitative work that could help address some of these questions.

Partner Data

Suzman observed that the most important niche selection is the partner one chooses in life; everyone on the call agreed. Spotts mentioned that a similar theme had emerged on a teleconference with population geneticists, wherein the participants expressed particular interest in mate selection and looking at ancestry-based markers. The MHC complex genotyping which was used in the HRS, will provide the opportunity to look at selection effects. Burt indicated her interest in a proposal in relation to mate selection. Suzman and Spotts decided it would be beneficial to gather information on the rates of divorces, separations, widowhood and remarriages in the partner data for the researchers to use.

David Reiss summarized the discussion by saying that there was a potential synthesis between the initial discussion of techniques used to define trajectories and in thinking about that as a psychometric problem. Per Boardman's appeal, it will be important to keep the environment's role in these mechanisms in clear view. In the discussion renamed gene-niche correlation, Reiss wondered whether the group was collectively recommending that we think about the longitudinal data in the HRS that might give us a rich opportunity to characterize niches and people's entry and departure from them. Also attending to Suzman's point, it will be important to look at the differences among populations in the ability to choose various niches and of people's ability to enter and leave their niches. If that isn't a good, graphic, and clear way of using longitudinal data, then perhaps there are better techniques that aren't as complicated for clinicians but bear a great deal on understanding pathogenesis, etiology, and individual difference in the development of the aging sample.

Data in the HRS:

Suzman questioned which social and behavioral sciences could be moved forward with the new approaches and data available in the HRS. Reiss mentioned Boardman's recommendation of clear identification of social isolation.

Avshalom Caspi: Since genetic and phenotypic data is available on both members of the couple, many long standing question can be studied now, such as genetic similarity, human altruism in couples, inheritance, etc. Although these factors have been studied phenotypically using personality profiles, genetic similarity has never been incorporated into these models.

Richard Suzman inquired about what additional information would be needed to study partners' genetic similarity and phenotypic characteristics. He acknowledged that the HRS does not have much information on the emotional atmosphere within a family. He recommended making a list of additional data that would be desirable to researchers. HRS allows for experimental modules that are given to 2500, 5000, or 10000 people. Although the experimental module is quite full at the moment in terms of content, he encouraged researchers to submit requests for additional information.

Avshalom Caspi: Suggested that practically any psychological/behavioral phenotype would do, from personality to health behaviors to attitudes. Reiss suggested that this type of data analysis would be an additional argument for having straight forward marital data such as marriage, divorce, and separation rates. Spotts mentioned that the marital data is being gathered currently and will check on that. Reiss recommended that it would be great if investigators get access to that data to start an application.

Other Issues needing collaboration and discussion

Socially embedded vs. isolated individuals.

Boardman: It would be helpful to characterize what it means to be socially embedded and socially isolated at different points of a life course. How these measures change across representative samples of older adults is important. Some work like that has been done with the HRS but it's necessary to determine what constitutes a social resource or social risk and get that well established first. This is fundamental to broad based sociological questions and critical to social epidemiology. It was not clear if the HRS has a well-established metric that can show change over time or a meaningful metric on social resources. Suzman responded that it does have metrics for cognition but was unsure whether other variables, such as alcohol dependence, were observed in the surveys. Suzman suggested that a webpage be constructed showing how many phenotypes have trajectories and in how many waves.

Steve Cole: mentioned that if Boardman or others are interested in social isolation, there was a study by John Cacioppo that included measures of objective social network and subjective "loneliness." Although this has not been done on entire sample, one can look at the HRS study roster or contact John Cacioppo if they want more information on that study.

David Reiss: mentioned that social embededness, phenotypically a beneficial state, can be studied using HRS data at the genetic level to provide greater insight and asked for guidance on how we may proceed in this area.

Cole responded that polymorphisms related to inflammation seemed to be a common risk factor for various forms of morbidity and mortality for this cohort. Biological theory- based and brain- and behavior-based issues in this domain can be relatively easily addressed. Additionally, the genomic risk score can be very important, adding information on an individual's genetic makeup that can directly translate to into health outcomes.

Terrie Moffitt: inquired if it would be possible to have a webpage that lists what phenotypes have been measured repeatedly and what might have already been studied as trajectories and growth models and

how many repeated measures there are per phenotype. She suggested that this could be useful in getting researchers to submit proposals. Although research shows that cumulative history of a phenotype shows stronger effects of correlates (for ex. recurrent depression is more predictive than one time depression history, with the same pattern observed for alcoholism, unemployment, money matters), much of GWAS has been done on cross sectional and concurrent data. HRS can have larger effect size if we can leverage longitudinal data set to look at the longitudinal history of a phenotype. This will answer many important questions such as how big are the genetic effects, are they important to clinically, etc. Erica agreed and planned to post a table of measures with repeated assessments on the HRS website, as Moffitt suggested.

Leveraging Data

Erica Spotts: An important issue for consideration is how can we use the smaller studies funded by NIA and other institutes, many of which are very well characterized and many of which have genetic data, in conjunction with large survey studies. How can the smaller studies be leveraged against the larger surveys? She inquired about Freimer's phenotypic work and his views on the topic; do we need modules across studies to understand the cross talk or are there other ways that we can get to the smaller well characterized studies?

Nelson Freimer: An increasingly urgent question is how to take associations which are validated but with a small effect and find out if they have larger effect on traits that have not been measured in the validating study. It is also crucial to be able to take different types of measures, for example different phenotypes, from studies on heritability. Although these studies may not be easily harmonized with the HRS, there are measures potentially obtainable within the HRS that have been examined at in family and twin studies; it would be an efficient way of prioritizing. Jon King mentioned that Peter Visscher's lab has attempted to devise genome wide SNP-based methods for ascertaining heritability from estimating the correlation between individuals rather than looking at family or twin studies; King asked if that approach showed promise. Freimer was unsure how well this approach would work. He proposed that the best indication is having more data on heritability and behavioral measures. Therefore, it is not advisable to rely on just one approach as neither approach is very precise.

David Reiss: is there a way small scale studies can give us an idea of intermediate steps? For example, Steve Cole's study on gene expression profiles shows a substantial role of inflammatory processes as a potential intermediate step between genes and health outcome; are there ways of leveraging small scale studies to draw attention that inflammatory process as an important mediating phenotype?

Steve Cole: There is terrific opportunity to bring attention to important aspects between genetic and complex behavior by doing small scale studies. For example, the work Boardman and Dick are involved in, that defines behavioral risk syndrome in young people that have some identifiable neurobiological correlates, is a terrific opportunity. Right now we're sparse on theory about which particular genes are involved, and a big advance could come from more endophenotypic definitions of particular neurocircuits, and then going to animal and correlated human literature. The next step would be to go to databases and determine polymorphisms that might affect the activity of behaviorally relevant

neurobiological elements and then going to a place like HRS. Instead of going through millions of genomes and polymorphisms, one can narrow down to 10-100 polymorphisms to the particular pathway that are related to the specific phenotype of interest.

Freimer had a counterview. Although we maybe more sophisticated in our ability to do that than we were 10-15 year ago, the reason we continue to invest in genotyping one million and two million SNPs in 20,000 people is the recognition that our theory is not as powerful as the methods are at initial discovery. He suggested that having gene expression measures in relationship to genome wide genotypes accompanied by a rich behavioral environmental database would be much more powerful. If you could identify the polymorphisms that give you the association with gene expression measures in that kind of sample in relationship to some behavioral measure, that's going to be much more powerful. Steve Cole agreed with Freimer's views but stated that the method he suggested is an alternative as it can be done with what is available right now.

David Reiss posed multiple questions to the conference call participants. Is there an advantage to using HRS data to define behavioral risk syndromes? There may be intermediate phenotypes of interest that lead longitudinally to many negative outcomes or behavioral protection syndromes. Do we gain anything in the analysis of the HRS data that will be available by trying to map, let's say Danielle's study, much earlier in development and using that strategy in approaching HRS data? That is, we could define a cluster of behaviors that has multiple outcomes and that may be conceptually somewhat closer to genotype?

Terrie Moffitt: We can do that [define behavioral risk syndromes] using psychological traits measured in the HRS, but wouldn't advocate asking HRS participants to recall 80 years back if they had conduct disorder early life. We could infer if they're high on negative emotionality, low on constraint and conscientiousness, which could be associated with the high risk lifestyle history. Reiss stressed that personality is measured but not as well and it may be something that deserves more attention.

Danielle Dick: Proposed the idea of taking genes identified as influencing risk for psychiatric outcomes to large samples that have more phenotype data, with the goal of seeing how risk unfolds over the life course. Thinking of how that might affect phenotypes later in life using the HRS sample would be fascinating. In terms of previous discussion on what genotype should we be focusing on, it comes down to a finite amount of money, since genotyping and phenotyping on a large scale is expensive. We have a lot of smaller samples with deep phenotyping but no genotyping; or, alternately, large samples with genotyping but not the depth of longitudinal phenotypes. It will be necessary to integrate these two types of studies. We can move forward by creating polygene scores using GWAS data and thinking about ways that we can incorporate knowledge of biological pathways and networks. We can do focused genotyping in samples with deep phenotyping-- genes involved in a particular biological network for example.

Erica Spotts inquired if anyone knows example for where more focused genotyping has been done.

Nelson Freimer: Is aware of this work being done outside of behavior. Using metabolic measures and metabolic risk phenotypes, many individuals have now been genotyped with GWAS and exome

sequencing and researchers are now able to get very large numbers for the simplest crude measures of metabolic risk, like lipid levels. From GWAS, there are now probably somewhere near 200-300 clearly implicated genes with complete validation but not clear at the variant level. We obviously need a much more sophisticated measure for metabolism or we might want to look at smaller samples you want to look at over time. Once you have the initial validation of the simpler measure, there probably isn't much point in looking at all the measures in every study in association with 2 million SNPs. There are products that are cheaper and will give you a lot of information, such as the new exome chip (costing $70), which can be easily done. In general, genotyping is the least expensive of the whole proposition at this point.

S. Alexandra Burt: another approach might be to do something akin to standardizing across the smaller measures. Everyone has different measures and different instruments, so taking away investigator freedom in designing their study is not being advocated. Would it be possible for NIA to incentivize the collection of additional measures that would be similar across studies; smaller budget cuts was offered as a possible incentive. Suzman responded that he will not tell a PI to put a measure in or take it out of a study. The bottom line is what variables will be most productive. NIA has considered a few options and is open to hearing more. Spotts also relayed other post hoc efforts to harmonization, such as P3G, and the RAND Mega Data files that are geared towards larger surveys. Suzman described the RAND Mega Data file, as containing at least ten of NIA's studies, including the HRS. Burt recommended a centralized database where researchers can find information on what samples they can use, which Suzman confirmed is under development. John Phillips explained that the RAND Survey Meta Data Repository website includes data on what the questions are, the content, in what year measurement was taken, etc. Burt further proposed that it would be helpful if there was a way researchers can combine samples in terms of phenotype definition. Suzman called for candidate phenotypes that people would like to see in multiple waves and surveys; for example, conscientiousness, cognition, subject well-being, personality, etc.

Future Teleconference Topics

Erica Spotts: future teleconference could involve more discussion on environment. Terrie Moffitt agreed and added discussion points of measures of environmental and mental health constructs in the HRS. Additionally, future discussions should reactions to the thoughts that were brought up today while involving new people.