Social and Behavioral Epigenetics Workshop

Osgood Building, Stained Glass Hall

Bolger Center, Potomac, MD

July 29–30, 2014

Sponsored by the National Science Foundation (Grant #BCS-1448213), the Research Councils United Kingdom, the U.K. Science and Innovation Network, and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

Introduction

Epigenetics is essentially the study of the biochemical and physicochemical regulation of chromatin structure, which gates transcription factor binding and genomic transcription. Social and behavioral genetics proposes that social stressors, behavior, memory, cognitive behavior, disease and disorders, and other aspects of the environment can affect epigenetic modifications. Those modifications can lead to changes in gene expression and, ultimately, changes in a phenotype. Epigenetics research and related technology have now reached the point where it is possible to reasonably discuss combining more qualitative measures of life, environment, and experiences with more quantitative measures of genetic variants, gene expression, and epigenetic variation. As its findings shed light on both typical and atypical development, social and behavioral epigenetics has the potential for broad and far-ranging social impact to secure humans' health and well-being. This workshop was designed to explore the idea that social and behavioral stressors and experiences can, through epigenetic changes, affect gene expression. The workshop brought together an international cast of leading scientists to think about where the field is, to consider the relationship between social environment and phenotype, and to outline where the field is going.

Workshop Description

The goal of the workshop was to harness the assembled expertise to inform a research agenda, focused on both long- and short-term goals, to guide joint efforts by international research funding agencies. The point of the workshop was to focus on social and behavioral data and how those data can better inform epigenetics research to facilitate interdisciplinary and international research in the emerging field of social and behavioral epigenetics. The workshop's questions were:

1. What are critically important research questions or lines of inquiry that would move the emerging field of social and behavioral epigenetics forward (in either the short or long term)?
2. What are the most salient obstacles to effectively addressing such questions or lines of inquiry or advancing the field of social and behavioral epigenetics more generally?

On Day 1, a keynote presented an overview of some epigenetics concepts, followed by three other presentations. Then participants divided into two breakout sessions, each considering a different set of topics, with a brief report to the entire group. The reports focused on what is currently known about the topics and on research gaps, proposed research questions, and directions for new research. Day 2 began with two consecutive breakout sessions discussing the same questions, again followed by a brief report. In the afternoon, the entire group discussed key questions.

Research Recommendations and Important Questions

Timing

- Establish a normal range of epigenetic variation using global populations and taking into account different countries, ethnicities, and ecologies. Use the normal range as a benchmark to identify when pathologies, stress exposures, and so on create methylation patterns that fall outside the norm.
- Design studies that are likely to show causality. For example, where it is known that modification of a trait causes a certain outcome, add epigenetics to see whether an epigenetic variation is causally involved.
- Use double randomization studies in animal models to pair stressor and intervention in both combinations to determine and quantify the magnitude of any epigenetic change.
- To answer the question of the extent to which reversibility is possible in an environmentally determined epigenetic change, design an intervention in a high-risk population, see who responds, and look for reversibility.
- To answer questions regarding which genes show methylation changes in response to the environment and how long the changes persist, use breeding and phenotypic data from agricultural scientists (large animals and plants) and zebrafish.
- Determine whether epigenetics can be used in a policy setting to identify children most at risk and most likely to benefit by interventions and whether such a biological basis for such predictions gives more robust predictions than those made without a biological basis (e.g., sociological or socioeconomic).
- The timing of epigenetic changes is little understood. For example, the effects of aging on the epigenome are inconsistent, and it is not known whether this is related to biologic or chronologic age. An important challenge is to identify the critical periods during development when the genome is most susceptible to exposures.
- One key research priority is large cohort collections, with white blood cells, complete blood counts, buccal cells, and other materials. Existing cohorts, especially longitudinal ones, do not include social and environmental variables, and it is crucial to collect those.
- The relationship of genetic heterogeneity and methylation needs to be better understood in terms of its effect on the genome and how methylation occurs in the context of environments and different time points across the lifespan.
- Autism spectrum disorders could be a promising area of research, but it might be too early to undertake such studies.

Measurement and stability

- Conduct time course longitudinal studies in humans and animals in order to observe changes at early and later points. Examples include circadian rhythms, various hormone exposures, and cortisol.
- Establish the direction of causality of the epigenetic and phenotypic outcomes.
- Develop an open-access resource with a large database that establishes the ground rules of the stability and temporal dynamics of environmentally induced epigenetic variation.
- Establish and adhere to standards of reporting so that research may be replicated.
- Design experimental studies to establish the factors that could induce dynamic changes in epigenetic variation that need to be considered in methodologies.
- Studies are needed to:
    - Determine the repeatability of epigenetic techniques and how much measurement error is present in these techniques and thus might interfere with stability.
    - Discover a methodology for dealing with outliers.
    - Find a strategy for identifying factors that might predict stability versus variability, such as genetics and epigenetic inheritance.
    - Account for the degree of environmental stability in assessing epigenetic stability and variability.
- In longitudinal samples, it is necessary to consider batch effects and changes in tissue extraction techniques that could alter measures of stability.
- Think about population stratification and how to address it in research.

Functional relevance

- Select areas of convergence from what is known about animal and human models.
- Identify and study in depth areas of psychology and brain chemistry (e.g., neurotransmitters).
- Focus on imprinted genes known to be important for behavior and brain development.
- Use germline studies.
- Inferences from blood might help to understand what is going on in the brain.
- Standardize research so that methodologies are consistent for cross-study comparability.
- Use more mechanistic insights from biologists.
- Use animal studies to manipulate data to determine functional relevance; for example, targeted DNA methylation information can be applied from animal to human studies.
- A better integrated dialogue is needed between social, biological, and animal studies.
- Funding for intervention studies will become available only when potential sponsors are convinced that there is benefit in knowing about epigenetic changes. They could be an important predictor of future outcomes.
- Socioeconomic status (SES) appears to have a greater influence in childhood than at other life stages, but large studies are needed to determine whether epigenetic changes are part of childhood changes due to SES.
- Rich phenotypic data and large samples are available in social sciences research. It is necessary to scale up and coordinate some of that work to sort out key questions, such as where epigenetics can play a role in social processes.
- The ultimate goal is to describe pathways up and down, starting with blood and other accessible tissue. Investigators should choose topics in which there is promise of a return, such as mental and brain-related issues. This research could have functional relevance to the offspring of the subjects being studied.
- In intervention studies, researchers need to look at the epigenome before and after the intervention to identify changes. Epigenetic changes are effective to determine whether interventional changes occur.

Methods

- Analyses are needed with cell types as covariates or using isolated cell types.
- Consider genome-wide data rather than candidate genes; the 450K array covers less than 3 percent of all CpG sites. It is enriched for promoters but sparse on enhancers.
- Research is needed on:
    - What regions will show variability in methylation
    - How big an array is necessary, and of what it should consist
    - Methylation as a consequence of gene expression rather than a cause
    - Gene expression levels and expression quantitative trait loci mapping
- Improve focus on the specific social stimulus or perceived social stimulus.
- Theoretically motivated investigations are needed, including measures of potential confounding variables, to disconfirm candidate dimensions of the environment rather than allowing confirmation biases to operate.
- Longitudinal studies are needed with repeated measures to examine stability, change, and cause; keep cells alive and cryopreserve them for future measurements.
- Perform studies that both maximize the environmental variance (extreme groups) and that focus on variance across the normal ranges to ask different but important questions while controlling for cellular heterogeneity, population structure, and family structure.
- Develop purified cell types in various model species to help in animal models of epigenetics across different types of genetic marks.
- Long-term studies are needed that look at open chromatin assays, histone marks (modifications), gene expression, cytokines, and inflammatory markers.
- Studies are needed that focus on variable sites on the genome rather than all possible sites.
- Create a chip or protocol to generate methylation data and histone marks across the genome.

- Design an epigenetic counterpart to the gene bank to provide standardization for the specification of data collection and conditions (e.g., cell lines, species, phenotypic characterization) and a public repository for epigenetic data comparable to the Gene Expression Omnibus (GEO), a public functional genomics data repository (geo.ncbi).
- Define distinctions among reproducibility, minimal replicability (cross-validation), and generalizability.
- Assess whether conditions are responsible for the failure to replicate.
- Describe the cumulative nature of the science. Procedures are needed that permit aggregation and meta-analysis of data sets. Include online materials in a table summarizing data or effect sizes for associations above and below the false discovery rate.

Longitudinal studies

- New efforts can be launched to pool and mine several new data sets coming online. The National Collaborative Perinatal Cohort analyzes samples at birth and could be a useful resource.
- Researchers should give careful consideration to what can be derived from existing data.
- Studies involving appropriate animal models could provide longitudinal data on epigenetic marks in a range of tissues.
- Collect and archive a range of biological samples, including blood, saliva/buccal cells, hair, sperm/semen, stool, and cord blood and placenta where these can be collected and archived.
- Standardize protocols and guidelines for collecting, processing, and storing biological samples to maximize utility of the material. This could include "novel" methods of collection and storage such as dried blood spots, which might offer economies in cost and space requirements. Routinely collected dried blood spots could offer a unique resource dating back to the 1980s.
- Analyse epigenetic data from cross-sectional studies that include participants across the lifespan.
- The increased plasticity in children compared with adults highlights the utility of longitudinal studies. Designs used in twin populations might be helpful.
- Risk prediction can be a baseline intervention, and epigenetics can show a risk prediction for obesity, for example, in contrast to genome-wide association studies (GWAS).
- Replicate interventions that were successful in specific population subgroups. Power the studies to detect heterogeneity.
- Pharmacoepigenetics might allow treating preconditions, but it could also allow those who are resistant to become susceptible.
- Longitudinal studies provide more insights than cross-sectional studies, but it can be difficult to design robust longitudinal studies. Another difficulty is stability. A portfolio that covers the lifespan is needed. Because of the rarity of intergenerational studies, existing longitudinal studies of migrants could be useful.
- Priorities for funding include the banking of data, with supplemental funding for special issues; stability or instability studies; and epigenetic studies in longstanding birth cohorts.

Biological mechanisms

- Studies are needed to determine whether epigenetic changes really drive changes in behavior.
- Studies are needed that look for the mechanisms of response to environmental influences across multiple levels of analysis (e.g., genetic, epigenetic, physiological, neurological, behavioral).
- Studies are needed to determine whether and how epigenetic marks are correlated by social space and actually mediated by social context. Questions include:
    - What are the corollary effects of the environment?
    - What are the downstream effects of methylation in controlled conditions where the social status is experimentally manipulated, such as in nonhuman primate studies?
- Another important related question is the relationship between the magnitude of methylation changes and the outcomes.
- Studies are needed to link the biochemical mechanism to the social environment and discover how the social environment is transferred to genetic changes. There is also a question of the importance of this linkage.

- Studies are needed to uncover the key stimuli in social contexts that lead to epigenetic changes. Social stimuli are much more complicated and less discrete than, for example, nutritional manipulation.
- Studies are needed to determine how epigenetic changes in blood relate to changes in other tissues and what the mechanism of that relationship is.
- Studies are needed that ask whether plasticity genes map onto the epigenome and whether genetic variants in these genes result in different epigenetic changes.
- Studies are needed to determine whether epigenetic changes are actually created in response to a stressor and what the biological mechanism is of that connection.
- Studies are needed to determine the role of individual differences in epigenetics changes in response to the environment and whether some individuals with genetic variants are more likely to respond to environmental stressors with epigenetic changes than other individuals.
- Studies are needed to determine whether variants in the epigenome moderate gene-environment interactions and whether these epigenetic variants can be considered moderators of a genotype-phenotype interaction.
- Studies are needed to determine whether epigenetic response is biased toward negative exposures compared with positive exposures or whether this is a research bias toward studying negative exposures more commonly than studying positive exposures.
- Studies are needed to better understand intergenerational transmission of epigenetic changes, how malleable that transmission is, and what mechanism might underlie this transmission.
- To study the underlying mechanism of epigenetic imprinting in early cell stages, collect pluripotent cells from individuals with different stress exposures and look at whether the epigenome signal is retained after the cell differentiates.
- Studies are needed with large numbers of samples (from 1,000 to as many as 10,000) with well-defined exposures.
- To determine what sample size is required, conduct a study of plasticity genes (for example) to see how many samples are needed to see an effect on epigenetic changes.
- Invest in existing brain banks to maximize the potential and collection of brain tissue for epigenetic studies, adding the collection of social and behavior phenotype data to make these banks even more useful.
- Use existing birth cohorts for epigenetic studies.
- Well-designed phenomenological experiments are necessary, even if they do not approach biological and molecular mechanisms, because they will inform and motivate future studies. Eventually such studies will be paired with mechanistic studies. Animal models are not fully valued, but each has its strengths and limitations.

Tissue specificity

- Consider what tissues can be collected for analyses (e.g., saliva, buccal, blood, hair, fecal boli, skin) and their relative strengths and weaknesses. Tissue must be interpreted appropriately to answer the intended question.
- Determine what is relevant for epigenetic analyses in the collection and storage of samples. For example, frequency of hair washing could influence hair samples, and recent dietary intake could influence buccal cells. Determine and use best practices.
- Conduct profiles of environmentally induced epigenetic variation across tissues (target and peripheral) in animal models, considering timing, genotype, strain, and sex of animals.
- Consider cell sorting and how to avoid the potential problems of multiple cell types, such as the relationship between determining cell type using bioinformatics and using flow cytometry. Critical information could be lost.
- Consider cultural and ethical constraints that could affect compliance with tissue collection and thus create self-selected groups and differential responses.
- Research is needed to determine whether a correlation between peripheral and brain epigenetic patterns is necessary. Peripheral samples could be predictive biomarkers of exposure and long-term outcomes

independent of the relation to the brain. Brain and tissue banks must collect more environmental life history information.
- Use of existing databases can help establish epigenetic–phenotype relationships that can be used in studies of environmentally induced changes.
- Databases are needed that document tissue type and epigenetic profiles to answer the question of what functional information can be obtained from tissues (e.g., immune function, cellular metabolism, and allergy information from blood). Consider alternative tissue sources such as teeth.

Social and environmental effects

- Research is needed to determine whether social factors are important in epigenetics because of their impact on or determination of environmental effects. Social exposures are likely near the top in a hierarchy of exposure importance.
- Research is needed on the extent to which important recognized effects, such as post-traumatic stress disorder, are epigenetically regulated. Ongoing military studies might be relevant.
- Research is needed on the mechanisms of social and environmental effects and whether the effects of exposure are encoded in epigenetics themselves or whether there is another cause for the effects.
- Research is needed on the half-life of epigenetic effects and how quickly they wash out. Observational studies can be used to determine peak measures.
- Stratify the population in studies because of the sex-specific nature of epigenetics.
- Because of the mechanics of methylation, timing of exposure plays a role. Further research is needed, particularly about key stages of life, such as adolescence, when important developmental changes occur.
- Studies of two different cell types, such as blood and buccal cells, are one approach to the problem of generalizability of results.
- Studies of the possibility of group sharing of epigenomes might be relevant to many research issues. Population feedbacks and the nature of interactions could be interesting.
- Public engagement is necessary, and the public and policymakers must be convinced of the need for this research. Social scientists and biologists must set aside their differences and learn to collaborate successfully.
- New informatics tools are needed to deal with different measurements, understanding of the measurements, and understanding of the analytics.

Animal models

- Studies are needed that integrate animal and human research and influence the nature of both types. Bring together human and animal researchers to cross-fertilize and make modeling more profitable.
- Differentiate between comparative and animal model research. Sequential motivation of research (human-animal) versus integration—the process of the research is codependent across human and animal models so that more dots are connected more quickly.
- Studies are needed of longitudinal and transgenerational effects.
- Studies are needed of experimental mechanisms.
- Studies are needed that seek to specify explicit environmental stimuli.
- Investigations of long-term effects of epigenetic modifications.
- Studies to elucidate the lifespan modulation of social influences on epigenetics.
- Explore neurobiological substrates by investigating effects of lesions on epigenetic effects of environmental exposures.
- Test whether experience-induced epigenetic modifications are genetically modulated (i.e., variations in susceptibility to social environmental influences on epigenetics).
- Test whether epigenetic changes are adaptive or simply a constraint.
- Direct targeting and manipulation can be done on epigenetic marks, clarifying causal effects on functional outcomes such as SES (enriched versus impoverished environments), executive functioning (parental support versus negligence and abuse), and differences in status hierarchies (discrimination, hostility, and exclusion).

- Base funding decisions on the integration and influence of the two literatures of the fields, with the goal of specifying underlying mechanisms (and stimulus specification) with implications for addressing human problems.
- Directly manipulate social factors so that the vector of the social environment can be identified.
- Opportunities in the field that can be more fully realized using animal models include:
    - Specification of the classes of social stimuli that act as causal signals and alter the epigenome. Given an epigenetic signature, what are its functional implications downstream?
    - Clarification of the essential aspects of the social signals.
- Funding instruments are needed that support integrated, iterative work among human and animal researchers to improve specification of the social regulators of key genomic variants and the biological pathways through which these pathways operate to produce important functional outcomes.
- This is a young area of research, with a new generation of investigators just beginning to work in the field. Social and behavioral epigenetics offers opportunities that can be taken advantage of now with long-term implications. Training programs (or summer programs) are needed to produce the next generation of more integrated human/animal researchers and emphasize integration.

Evolution and intervention

- Transgenerational studies might look at maternal smoking as a useful exposure to prioritize because of its functional consequences and because smoking "marks" the epigenome.
- Studies of twins might be useful.
- Design and test particularly interventions that attempt to reverse an earlier adverse influence that marks the epigenome. The challenges in this approach are long term because most agents and interventions have pleiotropic effects on the epigenome.
- Great opportunities are available for adding epigenetic measurements to conventional lifestyle or other interventions to (1) understand how the intervention might work (or not work) and (2) identify *a priori* those who would or would not benefit from the intervention. This could lead to a new style of interventions in which, based on epigenetic marks, participants are "pre-conditioned" before an intervention to enhance effectiveness.
- Opportunities should be pursued to develop epigenetics-based risk scores for multiple outcomes, possibly leading to screening programs and, subsequently, better targeted interventions.
- Better communication is needed with the public (and some peers) to avoid overhyping the social and behavioral epigenetics story. The role of epigenetics in the human body should be conveyed in a realistic manner.
- Consider research opportunities that use an evolutionary life history approach within social and behavioral epigenetics.
- Consider and research the possibility that some developmental strategies might play out differently in males and females. For example, influences may be more important in early life for females, and males are more regulated in middle childhood and subject to peer influences.
- Important questions include:
    - Which environmental social and behavioral cues are recognized, received, and recorded by the epigenome and through what signal transduction processes?
    - Are all environmental cues equal? Cues unique to modern society might not be recognized as efficiently by the epigenome machinery because the appropriate mechanism has not had an opportunity to evolve.
    - Are epigenetic mechanisms preserved across species?

Key questions: Discussion

1. In terms of social and behavioral epigenetics, what do biologists feel they can get out of social and behavior data?
2. What do social scientists think they can learn about epigenetics from biologists?
3. How can new data be integrated into existing research projects to strengthen the research?

- Behavioral and biological scientists need to be brought together, and they need common terminology and common approaches. It will be an integrative process in which behavior goes into biology and biology goes back into behavior.
- Funding mechanisms need to make collaboration enticing.
- Statisticians must collaborate with molecular biologists from the beginning, not after the data have been collected.
- The group agreed widely on the value of intervention studies, but they need pre- and post-testing. It might be 5 or 20 years before it becomes clear what works and what does not. Recent work on African-American families and parenting interventions and genetic moderation are examples of intervention studies pertinent to epigenetics. Perhaps some sort of epigenetics consortium could review work of potential relevance and explore findings of value not already included in publications.
- Editors friendly to interdisciplinary work and with understanding of its value are needed to get such research published. A possible solution is to develop special sections for journals and to solicit papers. Individual papers can be submitted with an explanation of the value of interdisciplinary work and the unique role the paper fills in reporting and translating across diverse fields. Senior people who serve on editorial boards can also solicit papers, talk to their junior colleagues, and facilitate interdisciplinary research by selecting appropriate reviewers.
- Special issues of journals can emphasize linkages between fields. The more general a journal is, the more likely it is to buy into large-scale interdisciplinary work. Several journals are currently soliciting or planning special issues.
- Postdoctoral training could be useful in establishing trust across disciplines, which is essential in a field moving so quickly.
- This is a very new field in the context of the social and behavioral sciences, so it is important not to oversell its promise. Be realistic, and focus on problems that are soluble. For example, confront problems such as stability realistically. Have a clear way forward, set achievable goals, put off pie-in-the-sky objectives with a clear message that they are down the road, and don't say "causation" when you mean "correlation." Expectations can be managed and over interpretation prevented by establishing guidelines for how investigators interpret results.
- Biology may not appear to be important in explaining big questions in social science, but epigenetics has the potential to be the vehicle for crossover between the fields.
- Critiques of the 450K chip will likely result in a wave of funding for new technologies, with the potential for promising results across a range of studies.
- Awareness of the Human Epigenome Consortium needs to be raised.
- A professional society that addresses the topics and questions raised at this workshop is needed to give prestige to young faculty members and to signal that this is a field that will have professional rewards.
- Sharing of 450K data would be useful, allowing many others to interrogate the data. Currently, about 15,000 arrays are available with a variety of tissues divided by age and sex.
- A compilation of basic information would be helpful for users of methylation data. It could include measures of measurement error with correlation across methylation sites, linkage disequilibrium structure of the epigenome, and predictions using 450K data. This could be comparable to HapMap for genetics. It is more difficult to identify epigenetic variability than variability in genetic sites. For epigenetics, it is necessary to capture geography, ethnicity, and types of tissue. Linkage disequilibrium could be used for leverage to find out where the informative sites and associations are. This might be useful to go across the entire epigenome, without being tissue specific.
- A database is needed that includes the normal range of variation across populations, sexes, and races. Financial support for the creation of such a database would be a huge resource. A potential source might be the NIH National Center for Biotechnology Information.
- Perhaps the easiest way to get such a database started would be for investigators to submit their data to sources such as GEO and for journals to require this separate database. It would need to have search options and develop options for sharing data and analytical methods.

- Different methods, including principal component analysis, independent component analysis, cluster techniques, and vector space, could be used to compare methylation data using existing data sets to provide a better understanding of what each data set represents. Comparing data would not require the creation of additional data, but it might result in different answers about which method is most robust. Different fields might use different analytical methods and interrogate the data differently.
- A standard set now could make a huge difference 10 years from now. Meta-analyses might identify much smaller signatures not seen otherwise.
- Workshops could be used to add modules on biostatistics, but finding someone to teach a module on social and behavioral epigenetics could be challenging. Several free 450K workshops held in London included talks from scientists who use the data; these were widely attended.
- A funding mechanism for postdoc exchanges would be very useful. One possibility is the National Science Foundation Office of International and Integrative Activities, which funds interdisciplinary behavioral and social science research that integrates multiple disciplines in the same lab or with multiple mentors.
- Training on how to collect and store samples would be useful, although guidelines are cheaper. Perhaps a nuts-and-bolts workshop on collecting samples could be held and protocols deposited online. A series of videos already exists on collecting dried blood spots, and the *Journal of Visualized Experiments* publishes videos and shows experiments.
- Existing databases might be useful for moving toward the goal of improving social outcomes with better designed epigenetic policies and interventions, although different research questions may require different analytic methods. Places to start include NIH's collection of dried blood spots from various sponsored research projects, the English Longitudinal Study of Ageing, Whitehall II, the Cohort and Longitudinal Studies Enhancement Resources program, the 1958 National Child Development Study, the Southampton Women's Survey, the Hertfordshire Cohort Studies, and the EarlyBird study. Privacy issues can be a problem with accessing existing databases, and it is not always easy.
- Longer-term investment and commitment can lead to integration of all types of data. The need is for projects, research questions, and knowledge gaps that can drive the field forward to integrate different types of genetic data, methylation data, GWAS, metaregressions, and genome transcription. Computational biologists, bioinformatics specialists, and statisticians should be brought into the community.
- Good animal studies will be the key to understanding long-term outcomes. The effects of long-term studies can take months in a rat, but they can take years in a human. Multiple organisms should be used for research, and new and longer-term models should be developed to look for effects that are expected to take a long time to manifest. It might not be possible to study the effects of aging in humans. Causal mechanisms might also be best studied using animal models.
- International studies might not have the mechanisms to do animal studies, but international studies are important because they bring together different types of expertise.
- Multiple levels of analysis require thoughtfulness because the layers can be complex. Researchers might be interested in DNA, RNA, and histone modification, but much of interest is in between. Making connections must be done thoughtfully. There are also controversies about hypothesis-driven research versus hypothesis-generating research and the difficulty of bridging the gaps.
- Experimental lab studies offer better manipulation and control of variables and can determine the mechanisms of mediated pathways and look at each step of the pathway.
- Imaging studies are an important way to study behavior and the brain because it is impossible to actually get to the brain.
- Looking at the most extreme stressors can be a place to start. For example, if there is interest in the effect of social isolation, is methylation or some other epigenetic effect a mediator? Is the interest only in methylation? The effects can overlap, but the interests can differ. The extreme is needed initially to move forward to more subtle phenotypes with more nuanced effects. This is analogous to GWAS studies that looked for a small number of genes that could have huge effects on a common disease. It has not really worked out that way, but it is still a good place to start without a more definitive starting point. What is found from the most extreme phenotypes might not hold up, but it might provide some insight.

- What phenotypes lend themselves to being well-defined and clean? In the early days of GWAS studies, researchers broke complicated diseases like breast cancer into early and late onset, which helped define the disease. In the Puerto Rico blood pressure study, when skin color was added to SES, a genetic association emerged. Investigators need to learn to clean up and classify phenotypes in a more defined way but still answer questions of interest.
- Parenting, maternal depression, social position, and early life experiences are strong, well-defined phenotypes and leave strong legacies of early and later childhood effects. Social position is known to play a huge role. Researchers should look at whether the known strong signals relate to outcomes and what their influence is. That is interesting and potentially hugely important. Do those genetic signals play a role in mediating behavior through life?
- Social scientists need to keep up with technical developments or risk being 5 years behind. For example, there are better ways to analyze data than 450K microarrays. The field has moved beyond next-generation sequencing. The group expressed a consensus on overreliance on 450K and the need for unbiased ways to assay epigenetic sites. Right now, the focus has been on methylation sites, which may be more important to biology. Specimen collection is different when looking for histones. Methods for histone modification are not as robust or universal as looking for methylation, but biologists are rapidly approaching this problem, and it is important for social scientists to be aware of this work.