Workshop on Social and Behavioral Epigenetics

July 29-30, 2014

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July 29-30, 2014

I. Background

The nature versus nurture debate has a new contender – nature and nurture intertwined. The emerging field of social and behavioral epigenetics is based on the premise that one's social and behavioral environment can modify which aspects of the genome are expressed and which are not. Furthermore, the effects of these molecular adjustments may then feedback to influence social and behavioral outcomes. Epigenetic changes are chemical modifications to the genome that do not alter the DNA sequence but do influence gene expression. Thus, epigenetic alterations may play a broad, and largely unexplored, role in translating social, psychological, behavioral, biological, and other environmental factors into changes in both gene expression and phenotype. From an evolutionary perspective, such a role for epigenetics makes sense in that an epigenetic mechanism may have evolved in higher order organisms to enable short-term responses to changes in the environment without changing the underlying DNA sequence. Much of the excitement in the field is driven by the hope that we may be able to address some of society's most vexing problems, such as chronic social stressors and multigenerational cycles of violence, abuse and poverty, with a better understanding of the role of environmentally induced changes in epigenetic modifications that alter gene expression.

The field of social and behavioral epigenetics is both emerging and exploding, providing a critical window in which to influence the development and direction of the field. A workshop on social and behavioral epigenetics was held July 29-30, 2014 in Potomac, MD. Forty scientists from the US, UK and Canada, drawn equally from the biological and social sciences, were in attendance. The National Science Foundation (NSF grant BCS-1448213), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, and UK Science & Innovation Network, Economic and Social Research Council (ESRC), Biotechnology and Biological Sciences Research Council (BBSRC) and Research Councils UK (RCUK) provided the funding and initial impetus for the workshop, a rare collaboration attesting to the strong interest and support for the field. Organization of the workshop was shared by academic faculty members (Appendix A) and representatives from the funding agencies (Appendix B).

The goal of the workshop was to identify gaps in knowledge or critically important questions that must be addressed in order for the field to mature and reach its full potential. Feedback on these questions and input on research priorities was solicited from study participants before, during and after the meeting and this information represents the data that are presented in this report and that were used to identify top research priorities in the field of social and behavioral epigenetics.

II. Workshop breakout sessions & related questions

Prior to the meeting, all workshop participants were asked to respond in writing (2 page maximum) to the following two questions:

- What do you see as a critically important research question or line of inquiry that would move the emerging field of social/behavioral epigenetics forward (in either the short or long term)?
- What do you see as the most salient obstacle to effectively addressing such a question or line of inquiry, or advancing the field of social/behavioral epigenetics, more generally?

Based on participants' responses to these two questions, ten broad topics of high research priority were identified and these topics were developed into breakout sessions for discussion at the workshop. Each breakout session topic, and accompanying questions, was addressed by two different groups of participants during the workshop. In addition to the general themes of what is known, what resources are available, research priorities and gaps, and new directions for research, participants were charged with addressing the following specific subjects in each of the breakout groups.

<u>Workshop breakout sessions & related questions:</u>

Animal models

- What has already been learned from animal models?
- What is already known from human studies?
- Integration of animal and human models
- How can animal models best be used (i.e., hypothesis development and/or testing)?

Biological mechanisms

- Biological mechanisms and pathways underlying the regulation of genetic activity by the social/behavioral environment
- How do certain exposures affect epigenetic marks and how is this translated into functional/behavior/phenotype outcomes?
- Epigenetic regulation of genes (including the role of imprinted genes and repeat elements in the brain on behavior)
- Modeling parallel, non-additive, and reciprocal influences of genes and social environment (e.g., differential susceptibility hypothesis)
- Genetic/epigenetic–environment interactions; what role does epigenetics play in gene–environment interactions?
- Genetic versus environmentally determined epigenetic changes

Evolution & Intervention

- Evolutionary basis of epigenetic changes
- Evolutionary advantage of epigenetics-related plasticity in a long-lived species
- Clinical usefulness of epigenetic changes (i.e., biomarkers or screening)
- Potential for epigenetic interventions

- Policy implications

Functional relevance

- Functional relevance (health/behavioral effects/cognitive effects/memory) of epigenetic changes
- Mechanisms or pathways by which these effects are achieved
- Do different experiences lead to different epigenetic changes?
- Which epigenetic changes matter most/have largest effect?

Longitudinal studies

- Longitudinal data collection and integration of epigenetics
- How can previously collected data/samples be enhanced with new epigenetic data?
- Epigenetic changes across generations
- Collection of social and biological data in same studies
- Need for populations/samples of different ancestries
- Tissue banks
- Development of optimal protocols for collection of samples, generation of data, analysis of data

Measurement & stability

- Measurement and temporal stability of epigenetic markers (also implications for tissue specificity and biological mechanisms)
- Under what conditions is epigenetic variation stable or changeable?
- Distribution and cumulative effect of different epigenetic changes across the genome (critical CpG sites for methylation or critical number of CpG sites to be methylated or critical level of methylation per site)
- Relationship between cross-sectional patterns and longitudinal epigenetic patterns
- What variation should be measured (DNA methylation, histone modifications, acetylation, chromatic remodeling, microRNAs) in what samples and under what conditions, and how do we integrate multiple layers of epigenetic information?

Methods

- What methodologies are currently available to measure epigenetic variations, which are best, what are the constraints, how does sample size affect choice of method?
- Best methods and cross-training for biological and social scientists; how to organize and fund
- Statistical/evidentiary requirements to reduce false discovery rate (FDR) in epigenetics
- How to combine bioinformatics approaches familiar to biologists with statistical approaches used in the social sciences
- New methods to link epigenetic changes to phenotype
- Need for theory-driven science
- What data should be collected or reported?
- What type of epigenetic variation should be measured?
- Functional relevance of small changes in methylation

- Analytical issues
- Identify reference epigenetic signatures (for cell types, for life course development, for differing experiences/behaviors)
- Optimal protocols for collection and storage of samples
- What can be done with previously collected samples?

Social & environmental effects

- Social and behavioral effects on epigenetic changes.
- Individual variations in social/behavioral-induced epigenetic changes.
- Do changes in social/behavior/perception/cognition change epigenetics?
- What are the downstream consequences from epigenetic changes that result from social or behavioral effects?
- What are the most promising approaches for finding epigenetic marks and processes that matter for social and behavioral outcomes?

Timing

- Lifespan trajectories of social and behavioral epigenetics
- Developmental origins of health and disease hypothesis/developmental plasticity
- Timing of social and behavioral epigenetics effects
- Critical and/or sensitive periods for social and behavioral epigenetics
- Stability of social and behavioral epigenetics changes
- Limits of social and behavioral epigenetics plasticity
- Reversibility of epigenetic changes and constraints on reversibility
- Are epigenetic changes the most important moderator of developmental changes in phenotype?
- Loss of information in epigenetic signals over a lifespan due to cell division

Tissue specificity

- Tissue specificity of social and behavioral epigenetics (mechanism implications)
- What is the relationship between epigenetic variations in central (e.g., brain) versus peripheral (e.g., blood, skin, saliva) tissues, and can a signal in the peripheral epigenome be used to predict changes in the central epigenome?
- Samples from all germ layers (i.e., ectoderm, endoderm, mesoderm)
- Are some tissues better biomarkers than others?
- Limitations and possible solutions of blood/saliva samples or cadaver samples to inform brain/behavior studies; are there endophenotypes that could connect blood/saliva samples to personality traits?
- Should human, population-based social and behavioral epigenetics research wait until basic questions about epigenetic variation are answered in experimental animal models?

III. Critical research topics identified by workshop participants

Identifying top research priorities was the main goal of the workshop and there were many sources of participant input in which to identify research priorities. The main sources of data include: 1) workshop participant responses to questions prior to the workshop (see Section II), 2) topics, discussions and summaries from the breakout sessions, 3) final discussion session attended by all workshop participants, and 4) workshop participant responses to an email query to identify the "top three research questions needed to push the field forward". Strong consensus emerged on multiple high-priority topics and questions. These topics, and representative questions, provide a blueprint for researchers across the disciplines to contribute to the future of social and behavioral epigenetics and create a foundation for establishing research priorities. The underlined questions are integrated into the top research priorities listed at the end of this report.

Critical research topics identified by workshop participants:

Animal models

- How generalizable are results from animal models to human populations and how can we create collaborative teams to address questions iteratively across animal and human models?
- Comments – A rat model was the first to demonstrate that nurturing behaviors of mothers could affect the methylation, gene expression and behavior of offspring and persist into adulthood. Animal models have great potential to demonstrate the long term persistence and intergenerational transmission as well as the underlying mechanisms of epigenetic changes more quickly than studies in humans. Ultimately, we are interested in the effect of the social and behavioral environment on methylation and gene expression in humans so it is also critical to understand how information gleaned from animal models relates to humans.

Biological mechanisms

- What are the biological mechanisms through which social and behavioral factors are translated into epigenetic marks and are there common pathways?
- How do different types of epigenetic change relate to each other and are there common pathways by which they may respond to social and behavioral stimuli?
- Comments – The vast majority of studies published on social and behavioral epigenetics are correlative studies in which social and behavioral stimuli are associated with epigenetic and outcome phenotype changes, but correlation or mediation is not proven. A better understanding of the underlying biological mechanisms and pathways will help strengthen the case for a causative relationship and will help develop hypotheses to test causative relationships.

Evolution

- Are social and behavioral induced epigenetic modifications heritable?
- Comments – One of the big questions is if social and behavioral induced epigenetic changes can be passed from one generation to the next. This idea has huge implications

for the multi-generation cycles of poverty and abuse in our society as well as for a neo-Darwinian view of evolution in which changes acquired during one's lifetime can be passed on to the next generation.

Functional relevance

- How do we distinguish between social and behavioral induced epigenetic modifications versus normal epigenetic variation across individuals and populations?
- Which, if any, epigenetic changes play a causative role in determining behavior or impacting psychological function?
- Comments – Most studies of epigenetic variation report very low levels of methylation and very small changes in methylation in association with a stressor/treatment/etc – the question is if these statistically significant changes are also biologically functional or if it is just normal variation in the epigenome. We don't yet know enough about how the epigenome changes throughout a lifetime to understand the range of normal epigenetic variation as opposed to changes that occur in response to a social or behavioral stimulus.

Intervention

- Is there a predictive epigenetic signature that can be used to detect early life adversity, cognitive decline, etc and also to evaluate the effectiveness of different interventions?
- Comments – See IV. A. Top research priority #3

Longitudinal studies

- Can samples and data from existing longitudinal studies be leveraged to determine the stability and temporal dynamics of epigenetic marks in association with social and behavioral stimuli?
- Comments – There was great support at the workshop for using existing data and samples (e.g. longitudinal epidemiological studies with a wealth of health data and biological samples) to investigate the long term persistence of epigenetic signals, particularly in association with social and behavioral stimuli such as early life adversity, abuse, etc.

Measurement & stability

- What are the functional consequences of small changes in methylation at different parts of the genome?
- Comments – There is great interest in the idea that epigenetic signatures might be used as a predictor of future behavior or vulnerability or that certain interventions might be developed that leverage the presumed impact that the environment has on gene expression.

Methods

- What new methods, e.g. bioinformatics, are needed to combine genetic, epigenetic, social, behavioral, and health data

- Comments – Datasets in social and behavior epigenetic often combine quantitative and qualitative data, thus new methods may be required to adequately analyze these datasets in a way that accurately reflects the social, behavioral, genetic, epigenetic and biological dimensions.

Social & environmental effects

- What social and behavioral environments produce long-lasting epigenetic signatures and is this effect timing and tissue dependent?
- To what extent are epigenetic processes mediators of the long term effects of early life events?
- Comments – This is the main focus and underlying premise of the field of social and behavior epigenetics, basically the idea that social and behavioral stimuli, such as stress, early-life adversity, poverty, etc, may have long-lasting effects on the genome through epigenetic changes that result in altered outcome phenotypes.

Timing

- What are the critical periods during the life course when the social and behavioral environment may induce epigenetic changes and to what extent are these changes stable or reversible?
- Comments - Are there critical periods in development in which changes in methylation are more likely to occur, more likely to elicit functional consequences, more likely to persist over time, etc?

Tissue specificity

- What can epigenetic analysis of peripheral tissues (e.g. white blood cells, buccal cells) tell us about the epigenetic status of other tissues/systems of interest, like the brain?
- Comments – It is important to know how epigenetic changes from easily available tissues, such as white blood cells and buccal cells, relate to epigenetic changes in less accessible tissues, such as the brain.

Training & resources

- Interdisciplinary training is needed at all levels (student to professor) across the biological and social sciences to train the next generation of scientists
- Online resources are critically important to span the disciplinary divides and provide information on methods, software, research findings, existing databases, funding opportunities, and career opportunities
- Comments – See IV. A. Top research priority #4 and IV. B. Top organizational recommendations #1, 2

IV. Research and organizational priorities

IV.A. Top research priorities:

The following research priorities were identified, based on discussions at the workshop and participants' comments during and after the workshop. These research priorities address the critical research topics that are underlined in the section above.

#1. Baseline variation in the epigenome – There is a critical need to determine the baseline variation in the epigenome in order to be more certain when variation exceeds the baseline and, therefore, may reflect social or behavioral stressors or actions. All epigenetic variation, i.e. DNA methylation, histone modification, etc, should be included in this investigation. Investigations might include the following: samples from different tissues or individuals of different ancestry/ethnicity or different organisms, samples from individuals of different ages or different development stages, etc. Existing databases or sample banks could be used as well as the collection of new samples and data. Relevant questions would include: Is there a functional consequence of small changes in methylation? How long do changes in methylation persist over time as opposed to normal stochastic changes in methylation over time? Are there critical periods in development in which changes in methylation are more likely to occur, more likely to elicit functional consequences, more likely to persist over time, etc? Are there stable changes in methylation between organisms that reflect evolutionary changes or speciation events? What evidence is there that environmentally induced epigenetic changes may be reversible?

#2. Integration of human and animal models – Research from human and animal models is optimal when research is iterative such that questions from one model are tested and used to develop hypotheses in the other model and vice versa, in an interactive and iterative manner. A research priority is collaborative projects in which PIs with expertise in human and animal models work together to create the synergy that comes from being able to move quickly to incorporate new (unpublished) results into ongoing studies between human and animal models and to develop and test new hypotheses relevant to social and behavioral epigenetics. It might be envisioned that human studies would identify relevant psychosocial stressors with downstream and possibly long-term effects and animal studies would reveal and test the underlying molecular or evolutionary mechanisms.

#3. Interventions based on epigenetic data or mechanisms – There is great interest in the idea that epigenetic signatures might be used as a predictor of future behavior or vulnerability or that certain interventions might be developed that leverage the presumed impact that the environment has on gene expression. These are two separate ideas and distinct applications of epigenetic data that both fall under the theme of applied science. In order to ensure that robust, hypothesis-driven science underlies these applications, a research priority should be to develop projects that test the potential of epigenetic data in interventions. An example might be to use methylation signals at particular genes to identify children with predicted vulnerability to future adversity/stress, or to identify children who have already experienced severe adversity/abuse and track those individuals into programs that provide necessary

social/counseling/etc support. Another example might be to test the effect of certain interventions or practices, e.g. breastfeeding, that mitigate the negative effects of prenatal stress/adversity based on reversal of an epigenetic signal relative to non-breastfed children. Existing databases and sample banks might be used as well as the collection of new samples and data to address this issue.

#4. Postdoctoral training – A key feature of the field of social and behavioral epigenetics is the transdisciplinary nature of the field, requiring all scholars (PIs, postdoctoral fellows, students, etc) to master multiple fields including the biological and social sciences as well as more quantitative areas such as statistical genetics and bioinformatics. A critical period in academic training is the postdoctoral stage when one can acquire new expertise that, combined with graduate training, can position a scholar for a career in a new field such as social and behavioral epigenetics. Postdoctoral support would require a candidate to branch into a new field relative to their graduate field and the relevant fields would be broadly divided into biological, social science, and quantitative disciplines.

IV.B. Top organizational recommendations:

The following suggestions were made by study participants as ways to move the field forward, and to allow more researchers to participate in the field by making studies, data, methods, and expertise more available to all interested researchers.

#1. Establish a professional organization – A professional organization dedicated to Social and Behavioral Epigenetics would provide a central forum for the collection and discussion of ideas and could use the 2014 workshop to grow into annual meetings. A professional organization would make it easier to make information on laboratory and statistical methods, software, research findings, existing databases, funding opportunities, career opportunities, etc widely available. In order to acknowledge the international scope of the field and the workshop, the following name is suggested – International Society for Social and Behavioral Epigenetics (ISSBE).

#2. Establish an epigenetics database – Currently, there are several different forums for depositing epigenetic data, e.g. NCBI GEO, Amazon Genomics, various public databases. The field would be best served by having a single public database in which all researchers deposit their data (publication of studies would be contingent on data being available through the database). The impact of funding dollars would be maximized if researchers could easily access existing data from multiple studies and incorporate such data in future studies.

#3. Workshop on statistical methods – A workshop on statistical genetic methods for the analysis of epigenetic data would greatly benefit the field. PIs, postdoctoral fellows and graduate students would be welcome to attend. The format would be similar to workshops held at the Summer Institute of Statistical Genetics at the University of Washington or Cold Spring Harbor Laboratory, NY, with participants bringing datasets to learn statistical methods on their own data.

Appendix A. Academic 0rganizing committee

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Appendix B. Interagency funding group

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