MIP CONFERENCE ON GENETICS AND BEHAVIOR

Conference Report

April 18 to 19 2014

HCEO

The conference on "Genetics and Behavior" was held in order to provide a beginning for genetics-related initiatives by the Human Capital and Economic Opportunity Global Working Group. The meeting brought together researchers from the fields of anthropology, psychology, neuroscience, sociology, and economics who have all been exploring the role of genetic differences in determining socioeconomic outcomes. The purpose of the conference was to provide a venue for a fruitful and collaborative discussion of different approaches taken to incorporate genes into social science models. Alternative perspectives were proposed for understanding the main mechanisms driving how genetic endowment and behavioral choices shape lifetime outcomes. The participants, who came from diverse backgrounds, presented various methodologies and frameworks and critically discussed and evaluated different theoretical models, empirical studies based on twins and adoptees, observed gene-environment interactions based on molecular genetics and neuroscience, Genome-Wide-Association-Studies, and epigenetic studies.

SHORT SUMMARY

Genes and Socioeconomic Aggregates

Gregory Cochran, University of Utah

Gregory Cochran began the conference by stressing the empirical validity of Turkheimer's laws—(1) everything is heritable, (2) additive genetics effects are stronger than shared family effects, (3) a lot of variability in human traits still remains unexplained, and (4) common genetic variants have small effects. However, he pointed out that these laws represent more of an empirical regularity in human studies, rather than iron laws of biology: studies of animal and particular sub-populations could behave differently. He stressed the importance of understanding that every society selects for something—a trait, a class, a status—usually unintentionally or not consciously. The speed of natural selection for such traits can vary widely based on heritability, genetic isolation, and selection differential, but even a small difference in means can lead to substantial differences in the extremes. As an example, he pointed out that it is not by chance that the same countries often rank highest in Olympic marathon: athletes are selected from the extremes of different distributions. He concluded by dismissing the importance of trans-generational epigenetic inheritance, a hot topic which sparked a lively debate about the need to keep an open mind to new inheritance mechanisms, while at the same time having a good understanding of the biological foundations and channels necessary to those mechanisms.

Henry Harpending, University of Utah

Henry Harpending continued the previous presentation by reinforcing the idea that each social system selects for something. He argued that the strength of genetic models in social sciences is that they improve our understanding by allowing us to make predictions using models and then use empirical correlations to test them. As an example, he considered a model of assortative mating: even if the trait is selectively neutral, strong assortative mating can lead to a quick and harsh truncation of the population into two subgroups. As an empirical counterpart to the model, he considered the case of the Amish: strong assortative mating among the Amish and a low rate of exit from the population (about 10%) lead to stark differences in personality traits, as estimated aggregating a PF16 personality test.

Aldo Rustichini, University of Minnesota

In order to investigate the relation between inequality and intergenerational mobility, Aldo Rustichini presented a model that integrated molecular genetic insights into the standard Becker-Tomes model of intergenerational income elasticity. In his model, income is a function of human capital, which in turn is determined by family investments and heritable skills. These skills are determined by the sum of the genetic variants present in the DNA of an individual. Considering perfect assortative mating on income, Rustichini analyzed the steady state distribution of skills (and therefore genotypes) and income under different scenarios, drawing conclusions about the level of inequality and intergenerational mobility in a society. With simulations from the model, he highlighted a tension between the effect of parental income and the effect of heritable skills on the income of the offspring. He showed how the extent of inequality, bimodal income distribution, and immobility across generations can vary widely, even when considering many genetic determinants of skills.

Enrico Spolaore, Tufts University

Enrico Spolaore delved into the relationship between the ancestral composition of current populations and their aggregate social and economic outcomes. Taking a long term historical perspective, he proposed a mechanism that could connect population ancestry to the spread of the industrial revolution and the decline in marital fertility: a mechanism of diffusion. He argued that a key to understanding differences in social and

economic outcome is to dig into the historical characteristics of a population's ancestors. He considered two main examples. First, a country's per capita income can be tied back to its share of European descendants, and particularly to its genetic distance from the English. Second, the spread of the fertility transition correlates strongly with the genetic distance from France. Arguing that linguistic and cultural ties could accelerate the spread of life-changing customs such as fertility choices or the industrial revolution, he proposed a model of "barrier effect" that could nest the effects of biological, cultural, and gene-cultural interaction. The English pushed forward the technological frontier, while the French pushed forward the cultural frontier.

Steven Durlauf, University of Wisconsin–Madison

Steven Durlauf concluded the session by bringing to the table two remarks on the issues of identification of underlying mechanisms and limitation in the use of observational data. He stressed the empirical difficulty of explaining cross-country and cross-population differences in behaviors due to uncertainty of the proper models and parameters to use as well as the issue of exchangeability, or the ability to validly compare empirical results across countries and cultures. He described how Bayesian model averaging may be used to reduce reliance of inferences on ad hoc modelling assumptions. Finally, he discussed the issue of identification of individual, social, and group level genetic effects. The true underlying parameters of a canonical model containing genetic group level effects (such as genomic data, ancestry, or ethnicity) can be identified only if the researcher has prior information on the structure of genetic, social, and economic outcomes at the population level. He argued that this is one of the reasons why some economists are skeptical of using heritability calculations to elucidate aggregate behaviors.

Population-Based Studies

Matthew McGue, University of Minnesota

Matthew McGue introduced population and twin-based studies by looking at the heritability of educational attainment. He argued that both cognitive (hard) and socio-emotional (soft) skills are fundamental to attaining social achievements such as college graduation, and that genetic and environmental transmission within families may play a major role, augmented by strong evidence of assortative mating on education. Looking at the Minnesota Twin Family Survey, he showed that educational attainment aggregates strongly in families, with about 1/3 of the variation ascribable to genetic similarities and a little more (39%) due to the common environment shared by the siblings. He then looked further into the determinants of intergenerational mobility and showed that both hard and soft skill differences between parents and their children were associated with upward movement in education. In order to understand whether such skills were fostered by the family environment or passed down the genetic line, he focused on adoptive parents and found much milder patterns of correlation between parental abilities and child's outcomes. However, he found a strong gradient of education on family income even within adoptive families. Such a finding spurred a lively conversation on whether policy-relevant questions (such as helping college graduation via increases in family income or alleviations of credit constraints) can be properly addressed using estimates of heritability, going back to Goldberger's 1979 criticism of twin-based studies but viewed through the lenses of current practices.

Peter Molenaar, The Pennsylvania State University

Peter Molenaar presented a method for testing Gene-Environment interaction (GxE) and evaluating the nonlinear effect of epigenetics. Based on an earlier paper published in 1990, he first suggested looking at fourth-order moments of genetic and environmental factor scores in order to test for the presence of GxE, since the normality and linearity assumptions usually invoked when estimating standard ACE models induce stark differences in kurtosis when GxE is present. He then introduced the concept of subject-specific heritability and the idea that differences in outcome can be driven mechanically by differences in the growth process rather than genetic or environmental influences. Building on foundational literature on epigenetic modifications and on reaction diffusion models, he argued that genetic factor models can and should be used to estimate the evolution of within-individual phenotypes by using a panel of repeated measurements on the same pair of twins. He developed the statistical underpinning of a Genetic Factor Model for Intra-Individual Variations (iFACE) that allows for all the parameters of the model to be individual-specific, and showed an application of this model using electroencephalography (EEG) data. He concluded by showing how individual heterogeneity over time can trump the effect of both genes and environment and called for a deeper understanding of the dynamic nature of behavior, going beyond a static variance decomposition.

Jenae Neiderhiser, The Pennsylvania State University

Jenae Neiderhiser focused on the importance of using rich twin and adoption designs to better understand the influence of parenting and environment on the child's development. After introducing the concepts of active, passive, and evocative

gene-environment correlation (rGE), she showed how parenting can be influenced by the parent's genes, the child's genes and other contextual environment factors. She then discussed in detail how rGE can be properly accounted for by cleverly using an extended children of twins design. Leveraging the genetic similarities between twin parents and their children and between twin children and their parents together in the same model, the different forms of rGE, as well as direct environmental effects of parents on children, can be estimated. In addition, the model can be further enriched by looking at the same families over time to better understand how these influences operate over time. In the empirical section, she showed how evocative rGE appears to be quite relevant in the case of child impulsivity and rearing mother hostility.

Sara Jaffee, University of Pennsylvania

Sara Jaffee discussed the current state and the potential future of the estimation of gene-environment interactions by using genotyped data and focusing on measured genes and measured environment. First she laid out the common criticisms of candidate gene-environment interactions (GxE): studies are often guided only by a weak hypothesis of the biological mechanism underlying the GxE; studies with small sample sizes risk being severely underpowered; and publication bias and multiple hypothesis testing might cripple the validity of many published studies. Taking stock of these drawbacks, she suggested some potential solutions. One option could be Genome Wide x Environment Interaction Studies (GWEIS), but they would require massive sample sizes and clear two-step analytic procedures, not to mention the need for consistently measured environments. Dalton Conley also pointed out that by pooling different samples, GWAS usually capture the genetic effects least affected by different environments. Jaffee then mentioned the possibility of using genetic risk scores instead of single genetic polymorphisms, and suggested that future endeavors should focus on understanding better how the effect of candidate genes vary across development and what pathways can account for the observed GxE effects.

Genome-Wide Association Studies (GWAS)

David Cesarini, New York University

Working alongside Daniel Benjamin and Philipp Koellinger, David Cesarini introduced the topic of Genome Wide Association Studies (GWAS) by juxtaposing them with the approach of candidate gene studies, which he argued have not worked so far in the social sciences. While GWAS is based on atheoretical and hypothesis-free testing of a large number of Single-Nucleotide-Polymorphisms (SNPs), allowing the creation of new knowledge, candidate gene studies require previous knowledge and are based on specifying ex-ante which genes and genetic loci might have an effect on a certain phenotype. Such an approach has worked only when the underlying genetic hypothesis was well-formed and grounded in molecular studies. However Cesarini argued that social science studies often lack such a strong basis for forming hypotheses, and therefore the results are often biased by population stratification, incorrect multiple hypothesis testing, and low power, and ultimately lead to a consistent failure to replicate previous findings.

Daniel Benjamin, Cornell University

Daniel Benjamin continued the previous discussion by stressing the need for appropriate power calculations when hunting for new genetic associations. He argued that studies based on less than 3,000 individuals rely on the assumption of finding SNPs that explain a sizeable portion of phenotypic variation (with an R2 between 0.3% and 8%). While such effects exist for certain phenotypes that are closer to the biological chain of causation, such as those researched in the medical literature, this is very unlikely to be true when assessing social science outcomes, given what is known about effect sizes for phenotypes such as smoking, height, and BMI. The issue of small effect sizes is further aggravated by the lack of proper and uniform measures of social outcomes in most datasets containing the whole genome. For example, accurate and reliable cognitive testing requires time and money and is often hard to perform on a large scale study. Combining low effect sizes with poor measures, Benjamin used various power calculation analyses to argue in favor of the need for very large sample sizes. In order to facilitate gene-discovery for social science outcomes, he concluded the talk by introducing the Social Science Genetic Association Consortium (SSGAC), which pools GWAS data from several large samples and allows meta-analyses of the results.

Philipp Koellinger, University of Amsterdam

Philipp Koellinger built upon the talks of Cesarini and Benjamin by showing how the findings from properly designed studies replicate consistently. As an example, he considered educational attainment: in a discovery stage, 3 SNPs were found to be associated to education. Even if the effect size was quite small (R2 around 0.02%, or roughly 2 months more of education), such relations were replicated in independent samples with stringent controls for population stratification. He then introduced the idea

of using appropriately weighted polygenic scores to increase the amount of variation explained and improve the out-of-sample predictability of genetic associations. The use of these polygenic risk scores sparked discussion among the audience regarding different ways of optimally and efficiently constructing such summary scores: LASSO and other dimension reduction techniques were proposed and considered for future research endeavors. Finally, Koellinger concluded the talk by showing evidence of how the association between these genotypes and educational attainment can be used to shed light on cognitive performance.

Jason Fletcher, University of Wisconsin–Madison

Jason Fletcher provided the perspective of a user, rather than a producer, of GWAS analysis. He asked three main questions: Should we trust GWAS results? Should we join forces and collaborate with the consortiums producing GWAS? And, finally, how can we best use these results? Regarding the issue of reliability, he suggested that GWAS can provide robust results, even if at first there seems to be limited degree of overlap with traditional social science methods of inquiry. On the matter of how to best allocate researchers' efforts and how to handle new genotyped datasets, he mentioned that the structure of the GWAS enterprise suggests a natural monopoly. Audience discussion determined that an efficient allocation of resources seems to be a concentration of all the data (old and new) into a handful of consortia that can allow researchers, when needed, to request results using only a sub-set of the data, in order to minimize the overlap between the discovery sample and the one used by individual researchers for their in depth analysis. Finally, Fletcher suggested that results from GWAS studies can be best utilized to improve our understanding of the interplay between genes and the environment (GxE); this is where social scientists hold a comparative advantage. However, he warned against a mindless use of polygenic risk scores in GxE studies: for example, he reported the finding of two nicotine receptor genes which, when interacted with state level tobacco taxations, induced similar effects but of opposing signs. Therefore, although each gene showed significant interaction with the environment, constructing a score that summed the two genotypes would lead to a GxE indistinguishable from zero.

Dalton Conley, New York University/NBER

Dalton Conley concluded the panel by discussing the importance of using family models even when dealing with genotyped data. First, he argued that the recent method of Genomic-Related-Matrix Restricted Maximum Likelihood (GREML) used to estimate heritability from genomic data rests on unproven assumptions. In particular, it assumes away common environmental factors. However, a GREML model predicts that urbanicity is 15% heritable, although the fact of living in a city should not be predicted by your genotype. He therefore argued that GREML might be biased when run across families, even when controlling for ancestry. A better approach would be to consider only within-family models, which can provide reliable methods of estimating heritability even when using genotyped data. Finally, he concluded by suggesting that future research should focus on genetic effects on the variance of a phenotype and alleles that are related to plasticity.

Neuroscience

Paul Glimcher, New York University

Paul Glimcher started the second day of the conference by arguing for the futility of imposing a sharp distinction between genetic influences and environmental ones. In order to support the argument that genes and environment together join forces to shape the final phenotype, he discussed the neuroscience behind the formation of the human eye and the ability to see. The visual cortex in the brain is an affine transformation of the topographic map of the retina. The visual cortex displays a very complex structure, but very similar across different individuals and different species, suggesting that such structure might be hardwired in the DNA code. However, only a handful of genes are responsible for the formation of this part of the brain. On the other side, various animal tests demonstrated that stark variations in the environment during the developmental phase of the brain – such as frogs raised in total darkness or in a stroboscopic environment – completely prevented the proper formation of the visual cortex. Therefore, he concluded that the question of whether genes or environment are more important is fundamentally ill-posed.

Jonathan King, National Institute on Aging

Jonathan King discussed the thorny issue of measurement. As an initial example, he considered self-regulation; this concept is multifaceted and composed of various sub-constructs that are not clearly mapped or distinct from one another, making it extremely hard to pin down what self-regulation really is and how it can be consistently measured. He then discussed the possibility of leveraging the psychometric information developed in previous studies in order to construct shorter scales that can still span the same amount of variation in underlying constructs. For example,

looking at the Health and Retirement Study, he discussed some short measures of cognitive ability, mental retirement, and episodic memory that combine previous scales using only a few questions. To conclude, he suggested that future research could focus on intermediate phenotypes, measuring them first by designing appropriate tasks and experiments, then replicating these results, and finally linking the new and more established measurements by using item-response theory.

Aldo Rustichini, University of Minnesota

Aldo Rustichini concluded the panel on neuroscience and laid the groundwork for the following panel by discussing the relationship between intelligence, choice, and reward processing. First, by using an experimental design where students were subjected to random wins or losses, he argued that intelligence modulates reward processing in the caudate region of the brain. He showed how Blood Oxygenation Level Dependent (BOLD) signals differed by the subjects' IQ. In particular, percentage BOLD change increased with IQ, especially in the loss condition, suggesting that higher IQ students could better formulate prediction error and were not trying to find a pattern in vain. Using a second experiment where payment of the reward was delayed, Rustichini showed how intelligence modulates choice responses in the caudate but not in the ventromedial prefrontal cortex. In particular, higher IQ was correlated with a lower BOLD response in the anterior caudate. Finally, drawing from three separate studies, he presented evidence of how intelligence relates to caudate volume, especially when looking at vocabulary IQ.

Intelligence

Stephen Hsu, Michigan State University

Stephen Hsu started the panel by discussing the genetic architecture of intelligence. First of all he argued that intelligence can be reliably and validly measured by applying statistical methods of dimension reduction to appropriate tests, and that this measure of cognitive ability represents the most interesting and important phenotype for genetic research. Small differences in DNA between chimps, Neanderthals, and humans lead to extremely complex brain structures and allowed a few outliers in cognitive ability to pave the way for scientific progress. He then introduced a general model for quantitative phenotype, which depends on the sum of linear and non-linear genetic effects, and argued that the linear part of such model could be reliably estimated with a sample size of roughly one-million individuals, which could be happen in the next decade if enough genotyped datasets also collect the relevant phenotypic information. He defended the validity of linear models in predicting important phenotypes in plant and animal breeding models, and suggested that a more relevant question rests in understanding the number of causal genetic loci connected to intelligence. Finally, he suggested that using compressed sensing and LASSO methods, most causal loci can be uncovered in the next decade.

Wendy Johnson, University of Edinburgh

Wendy Johnson discussed whether assortative mating for IQ could restrain upward social mobility. After describing how educational and other assortment in the marriage market leads to correlations in spousal IQ in the range of .3 to .4, she introduced novel results from the Minnesota Twin Family Study showing asymmetries in the mating distributions by gender and educational status. In particular, there was evidence of greater assortative mating in the lower part of the IQ distribution: The difference in partners' IQs was greater at higher IQ levels. Johnson speculated on potential reasons for such asymmetries: both low IQ and high IQ individuals are rare, but intelligent individuals are more valued in the marriage market, and likely to attract spouses from the center of the distribution. On the other hand, individuals with limited cognitive ability are not pursued by the average person; therefore they tend to intermarry or not to marry. The correlation between partners' IQ was less strong when the female was more intelligent, suggesting that high-IQ women were more willing to accept mates with lower IQs. Taken together, these results suggest increases in genetic variance and population stratification that would tend to limit upward social mobility. Replication is required before conclusions should be drawn, and is in process.

Rodrigo Pinto, The University of Chicago

Rodrigo Pinto concluded the panel by introducing a novel approach to identification of causal effects by craftily using twin models. Twin studies satisfy two useful properties: confounding dependence, or the fact that siblings share the same family environment and potential confounding variables, and independent genetic variation, since MZ and DZ twins naturally have different levels of genetic similarity. While the field of behavioral genetics has used these properties to identify an additive model of variance decomposition (ACE), the same assumptions can be leveraged to identify non-parametrically the causal effect of one variable X on another variable Y. In this regard, one parametric approach was suggested by Kohler and coauthors (ACE-β model). Pinto suggests further extending this model by focusing on the causal relation between X and Y (β): using the fact that twins have the same ex-ante distribution of the variables of

interest, the natural genetic differences between MZ and DZ twins can help shed light on the causal pathway connecting X to Y. Such an approach can allow the formulation of counterfactual statements and the use of twin studies for policy analysis.

Role of Genes in Understanding Socioeconomic Status

Steven Durlauf, University of Wisconsin–Madison

In close continuity with the previous presentation by Pinto, Steven Durlauf discussed how twin studies can be nested into a model of intergenerational transmission of genes and environment. Introducing an intergenerational ACE model in the form of a system of linear stochastic difference equations, he argued that economic theory and prior knowledge of twin models and kinship relationship can provide credible identifying assumptions by restricting some of the coefficients of interest and providing additional structure to unobserved shocks. He then mapped this intergenerational ACE model in the usual economic model of intergenerational income elasticity (IGE), and proved how the equivalence between the two is non-generic. Finally, he linked economic theory and ACE analysis via a family investment model which endogenizes shared family environment, building on the seminal model by Becker and Tomes.

Felix Elwert, University of Wisconsin–Madison

Felix Elwert discussed how to identify peer effects on obesity by using genes as instrumental variables. First he introduced the potential drawback of using genotypic data as instrumental variables, which has been dubbed "Mendelian randomization"; the exclusion restriction necessary for identification can be undermined by pleiotropic effects when a single genotype affects multiple outcomes. To resolve this problem, Elwert leverages inter-individual variation, examining the effect of an individual's genotype on a friend's outcome. He argued that such an approach still requires assumptions, but leads to a more defendable exclusion restriction, since genes are invisible to social others. Furthermore, it can overcome the problem of unobserved homophily (friends self-select based on common characteristics) and latent confounding. After carefully laying out potential identification issues and threats to the validity of the instrumental procedure, Elwert argued that using time-varying genetic expression as instrumental variable represented the most promising path.

James Lee, University of Minnesota

James Lee focused his presentation on the book "The Son Also Rises: Surnames and the History of Social Mobility" by Gregory Clark. Providing a critical perspective on the social and historical work of Clark, Lee highlighted some ambiguities in the book's analysis. In particular, Lee pointed out how the intergenerational mechanism of transmission of status and wealth proposed by Clark strongly resembles a standard model of genetic transmission. However, the book estimates an intergenerational coefficient of 0.75, which requires an implausibly high degree of assortative mating if it is to be ascribed entirely to genetic transmission. Lee concluded that the observed correlations between the fate of fathers and sons may require some environmental mechanism. Discussion in the audience focused on the importance of institutional features of society that could reinforce and strengthen the status of particular families, de facto limiting social mobility.

Gabriella Conti, University College London

Gabriella Conti concluded the conference by discussing the promises of epigenetic research. First, she laid out the definition and biological foundation of epigenetics, a field that aims at understanding the pathways and mechanisms involved in how molecular responses are affected by experiences. After providing examples of recent epigenetic research in the fields of health, disease, and smoking habits, she outlined three potential avenues for developing epigenetic research in the social sciences: the epigenome can be used as a biomarker of exposure and a predictor of health; it can inform public policy by highlighting interventions that enrich the environment; and it can shed light on the casual pathways connecting genes, the environment, and the final outcome of interest. She concluded the presentation by discussing three caveats. First, research must move away from correlational analysis into establishing causal pathways. In this regard, recent experiments in rats, monkeys, and humans—twins studies, famine studies, and randomized control trials such as the Nurse Family Partnership (NFP)—provide promising results. Second, the methods of measuring and analyzing epigenetic data need to account for small sample sizes, multiple hypothesis testing, measurement errors, and high dimensionality. As example of how to deal with such issues, she presented an experimental research design with rhesus monkeys where different patterns of gene expression arose as a consequence of early rearing environment. Finally, she argued that more research is needed to fully understand the qualitative importance and policy implication of epigenetic changes.