collaborative efforts with widespread sharing of data acquired using standardized assessment protocols. Even though there are legitimate concerns about the tradeoffs inherent to big-science approaches that must be considered, there is considerable potential payoff in terms of better prevention approaches within the social and behavioral domains. ■

Matt McGue, PhD

About the Author

The author is with the Department of Psychology, University of Minnesota, Minneapolis, and with the Institute of Public Health, University of Southern Denmark, Odense, Denmark.

Correspondence should be sent to Matt McGue, Department of Psychology/Elliott Hall, University of Minnesota, Minneapolis, MN 55455 (e-mail: mcgue001@umn.edu). Reprints can be ordered by clicking the "Reprints" link.

This editorial was accepted June 18, 2013.

doi:10.2105/AJPH.2013.301527

Acknowledgments

This research was supported in part by a US Public Health Service grant (U01-DA024417) from the National Institute on Drug Abuse.

References

1. Collins FS. Shattuck lecture - Medical and societal consequences of the human genome project. *N Engl J Med.* 1999;341(1):28–37.
2. Ioannidis JPA. Why most published research findings are false. *PLoS Med.* 2005;2(8):e124.
3. Visscher PM, Brown MA, McCarthy MI, Yang J. Five Years of GWAS Discovery. *Am J Hum Genet.* 2012;90(1):7–24.
4. Eichler EE, Flint J, Gibson G, et al. Missing heritability and strategies for finding the underlying causes of complex disease. *Nat Rev Genet.* 2010;11(6):446–450.
5. Yang J, Lee SH, Goddard ME, Visscher PM. GCTA: a tool for genome-wide complex trait analysis. *Am J Hum Genet.* 2011;88(1):76–82.
6. Huang W, Richards S, Carbone MA, et al. Epistasis dominates the genetic architecture of Drosophila quantitative traits. *Proc Natl Acad Sci USA.* 2012;109(39):15553–15559.
7. Hamilton CM, Strader LC, Pratt JG, et al. The PhenX toolkit: get the most from your measures. *Am J Epidemiol.* 2011;174(3):253–260.
8. Keyes M, Legrand LN, Iacono WG, McGue M. Parental smoking and adolescent problem behavior: An adoption study of general and specific effects. *Am J Psychiatry.* 2008;165(10):1338–1344.
9. Roberts NJ, Vogelstein JT, Parmigiani G, Kinzler KW, Vogelstein B, Velculescu VE. The predictive capacity of personal genome sequencing. *Sci Transl Med.* 2012;4(133).
10. Ma Q, Lu AYH. Pharmacogenetics, pharmacogenomics, and individualized medicine. *Pharmacol Rev.* 2011;63(2):437–459.
11. Duncan LE, Keller MC. A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. *Am J Psychiatry.* 2011;168(10):1041–1049.

The Dialogue Between Social Environments and the Genome

The relationship between innate, inborn inherited properties and the environment, particularly the social environment, has been one of the most contentious topics in human intellectual discourse for many generations. This discussion touches upon foundational moral and philosophical questions that define who we are, and is therefore highly emotionally loaded. This agelong discussion has been reinvigorated in recent times by leapfrog progress in genetic research and the emerging dominant dogma in biology that genotypes determine physical as well as behavioral phenotypes. The sequencing of the human genome and the increasing feasibility of whole genome sequencing raised hopes that the vast majority of human disorders and interindividual variation in health and behavior will be explained by interindividual variations in DNA sequence. Genetic determinism has been pervasively dominant in biological sciences for the last century and beyond. Strong evidence for heritability of behavioral traits has paved a path for these concepts into social and behavioral sciences as well.

GENOTYPE DEFINES PHENOTYPE: A PLACE FOR ENVIRONMENT?

Is there room for external environments in shaping the phenotype, and particularly is there any place for the ephemeral social environment in defining what are believed to be hardwired biological processes? If indeed differences in gene sequence define differences in behavior, then social environments themselves emerging in ethnic or familial clusters are genetically predetermined. Genetic dogmatism could at least formally argue that poverty and other stressful familial environments are genetically predetermined. A compromise between genetic determinism and social-environmental theory has been struck by introduction of the concept of gene–environment (G×E) interaction, which was supported by epidemiological evidence from the pioneering work of Caspi et al.[1] The age-old conflict of nurture versus nature was reformulated in the new emerging concept of gene–environment interaction. The integration of genetic data in social epidemiological research is the focus of this issue of the *American Journal of Public Health.* The articles included in this issue discuss both the promise and challenge of integrating genetic data with social-epidemiological data and its possible implications on prevention and intervention (Belsky et al. p. S73–S83).

The concept of G×E interaction is somewhat a misnomer because the current form of analysis does not delineate how environments act on genes. All humans have the same genes with very minor variations for most cases. Gene–environment interactions are understood in the literature to date as a measure of how a certain environment modulates the probability that a certain genetic variation will result or be associated with a particular variation in trait. A clear example in behavioral science is the

demonstration by Caspi et al. of the effect of early adverse environments on depression later in life in individuals who carry a risk allele of the serotonin transporter gene.[1]

GENETICS IN SOCIAL SCIENCES: PROMISE AND CHALLENGES

Why should investigators conducting social and public health studies consider incorporating information on genetic variants? It is a consensus in the articles presented in the current issue that integration of gene variant information in social sciences is still lacking but nevertheless valuable. There are conceptual and practical reasons for incorporating gene variant information that are discussed in detail and depth in this issue (Belsky et al.). Conceptually, the articles reverberate with the echoes of a titanic battle between genetic determinism and environmentalism, between the idea that social mental and physical health disparities are driven by social inequalities and the suggestion that these are genetically predetermined. Practically, for those interested in prevention and intervention, informative genetic variants might guide identifying individuals who would most benefit from an intervention. This is important in situations where there is evidence that risk allele (gene variant) bearers could benefit and flourish in certain environments that have no benefit for those bearing the low risk or beneficial allele.

However, as discussed in several of the reviews presented in this issue the evidence for G×E interaction might be methodologically deficient and underpowered. One of the main challenges in this field is the low effect size of even gene variants with highly significant genome wide associations (Chabris et al., p. S152–S166). Therefore, most studies that incorporated gene variant analysis were severely underpowered. This might be remedied by larger multiwave, multilevel-cohort population studies (El-Sayed et al., p. S14–S18; Harris et al., p. S25–S32; and Boardman et al., p. S64–S72). On the other hand, there is the fundamental question of whether the environmental measures are also genetically predetermined (gene–environment correlation [rGE]); therefore G×E interactions might be truly gene–gene interactions. This is especially pertinent for studies measuring the impact of early life familial environments on later phenotypes or ethnically associated social inequality that is not disentangled from genetic stratification. It is therefore formally possible that several reported G×E effects are truly gene–gene effects between gene variants that affect familial or ethnic social inequalities and gene variants that affect other behavioral traits. Several methodological approaches to disentangle rGE from GE interactions are proposed in this issue. For example, intervention studies could measure the interaction between gene variants and an external environment that is not a derivative of the genetic matrix of the group (Brody et al., p. S19–S24, and Roetker et al. p. S136–S144). Similarly, measuring impacts of policy changes through natural experiments as well as family-based quasi-experimental design could potentially delineate true G×E interactions (D'Onofrio et al., p. S46–S55, and Mezuk et al., p. S145–S151). It is also extremely critical to have a more defined measure of environmental factors at different time points during the life course to establish causal inferences and define causal intermediate pathways between environmental exposures and behavioral outcomes (Belsky et al., and Boardman et al.).

There are critical issues raised regarding the practical utilization of gene variant associations in prevention and intervention. First, the small effect size of most if not all variant alleles on behavior raises serious doubt whether they would be practically useful. If indeed large population studies are required to identify such associations, their effect size must be small, and they could not be highly practically informative. Even if this could be corrected by using a combination of gene variants, serious ethical issues of stigmatization and the large probability of false negatives that will be denied a beneficial intervention are paramount (Brody et al.).

THE ROLE OF EPIGENETICS

Gene function could be modulated not only by genetic variation but also by epigenetic variation, which includes chemical modification of the DNA by methylation[2] and hydroxymethylation, variations in the manner by which DNA is packaged in chromatin and modification of histones (the proteins that are the building blocks of chromatin).[3] Thus, variations in epigenetic marks might explain some of the variance in behavioral traits. The inclusion of epigenetic measurements in epidemiological and social studies is discussed in several articles in this issue and is increasingly visible in the field (Jackson et al., p. S33–S42, and Theall et al., p. S133–S135). Epigenetic variants might emerge stochastically and possibly be enhanced in response to environmental exposures. However, epigenetic variation might be also be driven by genetic variation as well, keeping in line with genetic determinism. Thus, proper designs are required to disentangle genetic versus environmentally driven epigenetic variations. However, epigenetic variation is still understood in the field as conceptually similar to genetic variation, as a random event whose probability might be enhanced under intense adverse environments and could explain a certain fraction of the phenotypic variance. However, I suggest that epigenetics could possibly lead to a paradigm shift in the way we examine and understand G×E interactions.

A NEW PARADIGM FOR GENE–ENVIRONMENT INTERACTION

Notwithstanding the discussion surrounding the question of what fraction of interindividual behavioral variation is determined by genetic variation or environment, there is no reasonable doubt to my knowledge that gene function defines behavior at multiple levels. Therefore, the question that should be posed is whether and how do social environments interact with genes to program their function? (Cole, p. S84–S92). To date, this interaction has been a statistical construct with no real attempt to unravel the underlying mechanisms. However, without delineating a physiological conduit that leads from perception of the social environment by individuals to translation of this perception into persistent

alterations in gene function, this elusive interaction remains almost a magical concept. It is formally possible but highly improbable that environmental stressors just increase the stochastic noise generated by genetic variation.

An alternative plausible hypothesis is that these mysterious G×E interactions reflect evolutionary conserved and broadly represented physiological processes that translate environmental information at different stages in life and at different time scales to persistent programs of gene function. These environmentally programmed genome functions adapt and define behavioral and physical phenotypes. These processes act on genes, not just variant gene alleles, although they might be modulated by gene variation. The small effect sizes of common gene variants suggest that genetic variation might be restricted by evolutionary selection (Chabris et al.). Delineating gene variants that modulate the response of genes to environments would identify important players in the matrix of genes that are programmed by the environment in all individuals. However, our main challenge remains to understand how the common human genetic landscape is shaped by the environment.

THE CHALLENGE FOR PUBLIC HEALTH AND SOCIAL SCIENCES

Social sciences and public health studies must face this challenge and grab the opportunity to integrate biological and chemical mechanisms in public health studies as well as investigate mechanisms linking social processes to genome function and those linking genome functions to social outcomes in several dimensions. Facing this challenge will require a combination of skills in both dissecting social processes as well as physiological and gene function analysis at multiple levels, which could be achieved by open-minded interdisciplinary collaboration (Fletcher and Conley, p. S42–S45). However, most importantly this challenge calls for devising new approaches for training a new generation of social scientists that could naturally integrate two seemingly disparate spheres of knowledge and a multitude of research platforms into their work. ■

Moshe Szyf, PhD

About the Author

Moshe Szyf is with the Department of Pharmacology and Therapeutics, McGill University, Montreal, Quebec.

Correspondence should be sent to Professor Moshe Szyf, McGill University, Phamacology & Therapeutics, 3655 Sir William Osler Promenade, room1309, Montreal, QC H4W1C7, Canada (e-mail: moshe.szyf@mcgill.ca). Reprints can be ordered at http://www.ajph.org by clicking the "Reprints" link.

This editorial was accepted June 20, 2013.

doi:10.2105/AJPH.2013.301533

References

1. Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science.* 2003;301(5631):386–389.

2. Razin A, Riggs AD. DNA methylation and gene function. *Science.* 1980;210(4470):604–610.

3. Razin A. CpG methylation, chromatin structure and gene silencing—a three-way connection. *EMBO J.* 1998;17(17):4905–4908.

Genes Can Point to Environments That Matter to Advance Public Health

As the call for contributions indicated,

> The NIH and the *AJPH* combined efforts to generate this remarkable special issue of the *AJPH* with the goal of advancing research that integrates knowledge about genetics and social science to better understand human health and development.

It has become almost routine—as one discovers in reading these articles—to bemoan the fact that despite an enormous investment of research energy, the promise of sequencing the human genome for understanding human health and behavior has not been fully realized. There are many reasons for this. One simple idea is that this may be a story of looking for the keys we dropped on the street only underneath the streetlight—people have been looking for answers in the wrong place, that is, at the genome. What if the sequencing promise is to be found not in the genome but instead in a better understanding of the social and cultural factors that shape health?

In the interest of fairness we should also bemoan the fact that despite a lot of work we have only a modest understanding of the sociocultural factors that shape human behavior, development, and health. It is quite remarkable how little we really know. One idea is that integrating knowledge about genetics may help clarify why this is the case, not because this information will trump sociocultural factors—as many social and cultural scholars, but not those in this issue, fear—but because genetic information may point toward better identification of which kinds of social and cultural factors matter, why they matter, and when they matter for public health.

The articles in this issue consider a large range of substantive health and behavior outcomes with quite different goals in mind. The main goal—different than that suggested above—is to get a handle on genes that matter and our strategy for estimating how much they matter. Fletcher and Conley (p. S42–S45) consider how social science design developments for identification of causal mechanisms—specifically exploiting natural experiments that treat the environment in crisp and temporally bounded ways—may enable researchers to identify with confidence genetic factors that matter for outcomes as diverse as smoking and depression. Because one of the difficulties in thinking about gene–environment interaction is that genes may lead to selection of environments, it follows that exploitation of