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. ■

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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

random exogenous shocks to environments that are independent of the genetic composition of the populations exposed to them provides an opportunity to secure better estimates of genetic contributions. This same idea is echoed in Wagner et al. (p. S167–S173). In this way, social science ideas are suggested to help genetics.

Implicitly and explicitly, the design ideas proposed provide a way to think about the environment in novel ways. We certainly want to know if the population of genes around an individual, that is, gene–gene interactions at local scale (in peer groups, families, neighborhoods, and so on), make a difference for individual behavior and health. By analogy, driving drunk is never a good idea, but it becomes a really bad idea if everyone else is doing it at the same time—like on prom night. The design approach introduced here invites us to think in these terms and, hence, advances our understanding of the ways genes interact with environment—one key element of which are the genomes of others with whom we are in interaction.

But maybe these design ideas, put into place with genes in mind, can help social science and public health too. The advocates of the random shock approach remind us that one of the reasons it has been difficult to replicate findings from previous studies is that those findings may be artifacts of gene–environment correlation built into the study design. This is true. Random assignment solves some of those problems. The traditional worry about studies that rely on a crisp treatment to the environment is that we wonder how much we can infer from the results. Are students attending a prestigious university who are randomly assigned a roommate good to think with? Is 9/11 like other disruptive events in the lives of adolescents—as important as breaking up with your boy- or girlfriend, losing face among ones' peers, discovering that your best friend's best friend doesn't like you, experiencing a parental divorce—that may trigger depression? Right now we do not know. The hope is that if others take advantage of the experimental opportunities that abound, we will develop a better sense of the scope conditions for capturing genetic effects in the "wild." Because all wild human contexts are already experimental settings created by humans to advance some control project, our hope might be that the capture of genetic effects in such studies—should they be observed—will allow us to infer the nature of environments that matter. After all, because we built them, if we could understand which environments matter when, we might have some better ideas about how to modify them as well to advance one or another normative project we care about, perhaps even public health.

Boardman et al. (p. S64–S72) suggest, and rightly so, that actually thinking about the environment is a useful first step for those interested in understanding gene–environment interactions. Although we know little and want to know much more, we do know some things. First, the environments that matter change over the life course, a point strongly argued by Belsky et al. (p. S73–S83). Second, social relations constitute the environments that matter, and so we need to attend to the structure of the multiple networks in which individuals are embedded. Time and space matter. Most of the other articles in this collection argue for a version of this insight, either by focusing on large cohorts, intergenerational processes, or environments believed to be responsive to or repressive of gene expression. One of the environmental elephants in the room is identified by Short et al. (p. S93–S101): gender. Their review of the literature discovers that gender is almost universally invoked as a control variable. Their idea is to think about gender in a sociologically informed way, that is, to think about gender over the life course, to think about how social structures induce gendered behaviors in different ways, and then to integrate that theoretical work into a traditional gene–environment analysis framework. Another elephant in the room is the fact that diagnostic expansion of numerous disorders (the spectrum orientation of *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*[1]) will have the weird effect of increasing genetic heterogeneity. So if genes matter, they will matter more, and at the same time, less.[2]

Because there is agreement that thinking about the environments in which we would expect genetic influence is useful, maybe it is time to take the recommendation to do so seriously. The way to do this would be for distinguished journals like the *American Journal of Public Health* to reject studies that do not think deeply about the environment. High schools are important for adolescents, for instance, in ways they really should not be for adults. In one example, Boardman et al. show how gene expression on obesity is shaped by the high school weight context. We wouldn't imagine that such an environmental effect would be salient for genetic expression among adults, so we should not care if we do not observe any effects. The point is that having a theory makes it possible to deny observations as scientifically irrelevant. The implication here is that more sensitivity to selecting meaningful environments might suggest meaningful contributions of genes. This line of thinking has implications for those in search of the experimental discontinuity: the discontinuity has to be one that makes some sense for the inhabitants of the world(s) decoupled by the random treatment. Returning to Fletcher and Conley, if we can find a discontinuity that makes sense, it is powerful—think about tax policies designed to make smoking expensive—but if it does not make sense, we ignore the results.

For the most part, the articles collected here think about environments as settings in which genetic things can happen. They feel like little Petri dishes. It would be great to think about ways to make them come alive; that is, to identify mechanisms by which humans in interaction with one another constitute, through their interaction, genomic influence. Hacking, for example, proposes looping as one of these mechanisms.[3] Liu et al.[4] show how social influence processes amplify what may be very slight increases in autism incidence attributable to de novo mutations (among other drivers) to generate remarkable increases in prevalence, local clusters of increased risk, and—paradoxically—increased heritability over very short time frames.

To make environments come alive, new data structures able to embed large populations of individuals in interactive settings and to capture detailed observation of those settings over time (including interaction data), and that are linked to relevant administrative and genomic data are needed,

as proposed by El-Sayed et al. (p. S14–S18). The articles in this issue point in the right directions. Those interested in genes can learn a lot by taking seriously the suggestions made in this issue. Those interested in social structure may even learn more. ■

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