Story Landis is director at the National Institute of Neurological Disorders and Stroke, National Institutes of Health.

Thomas R. Insel is director at the National Institute of Mental Health, National Institutes of Health.

The "Neuro" in Neurogenetics

THIS ISSUE OF *SCIENCE* FEATURES A SPECIAL SECTION (SEE PAGE 891) THAT FOCUSES ON AN emerging area of neurogenetics—the effort to link genomics and behavior. We are all intrigued by the notion that genomics may yield "simple" explanations for complex behaviors, including our own. The power of genomics has already revealed new insights into human disease and development. So what lessons has this new field taught us so far about behavior, and what can we look forward to in the coming decade?

One area of neurogenetics seeks the molecular basis for complex behaviors that range from mate choice in flies and social status in fish, to fidelity in voles and humans. Our intuition tells us that it should be easier to identify the mechanism underlying a simple reflex behavior (escape from threat) than a complex one (mate selection). But recent findings suggest that apparently simple genetic mechanisms may underlie some ostensibly complex behaviors. The field is just beginning to identify mechanisms for adaptive behaviors that are both parsimonious and profound. Although most research has investigated the genetics of behaviors in model organisms such as mice and flies, the diversity of the natural world is waiting to be mined. Behaviors that are unique to a species may be experiments of nature that can yield important insights into how genomic variation (inherited DNA sequence differences) relates to behavioral adaptation.

But perhaps most important in this burgeoning field is pursuit of the "neuro" in behavioral neurogenetics. Genes code for proteins, not for behaviors. By identifying how genomic variation modifies circuits of neurons, we will better understand both how and where behavior is instantiated. Most of the recently discovered variations are differences in the regulatory regions of genes that control gene expression. One important lesson from neurogenetics is that genomic variations in regulatory regions can account not only for how much of a protein is made, or when it is expressed, but exactly where in the brain a protein is expressed. Because brain function is specified by precise regional circuits, even small differences in the location of the brain cells that produce a particular receptor or an enzyme can result in large differences in function. Importantly, the link between genomic sequence and behavior is the brain: We cannot hope to understand how genomic variation influences behavior without understanding how genomic variation influences neural circuitry.

An early mainstay of neurogenetics was the identification of mutations in mice with abnormal behaviors. Here, discrete brain changes could be tied to regional molecular mechanisms once the genes were cloned. For human neurological disorders like Huntington's and Parkinson's disease, such obvious structural and functional changes can indeed explain how gene defects give rise to certain behaviors. For psychiatric diseases, where the neurobiological lesions are not known, the challenge will be greater. But genomics now promises to be the key to unlock the neurobiology of these complex disorders: There is real hope that genomic variation will lead us to neural mechanisms that can begin to explain such complex syndromes as schizophrenia or autism.

Behavioral phenotypes are the result of a complex interaction between nature (DNA) and nurture (experience). The developing brain is the stage for this drama, but we still know little about the details of how genes and experience interact within the developing brain to create something as complex as the phenotype we call human nature. In the coming decades, epigenomics—changes in gene expression due to alterations in protein-DNA interactions rather than DNA sequence—will be critical for understanding how experience alters the genome, complementing the current focus on how genomic variation affects behaviors.

Already it is clear that, for the study of behavior, genomics is not destiny. Indeed, if genomic sequence "determines" anything behaviorally, it determines diversity. It is important that we be wary about extrapolating from model organisms to humans. We must also avoid using small statistical associations to make grand claims about human nature. Obviously, we have much to discover before understanding how genes influence behavior—a discovery process that will closely involve the brain.

–Story Landis and Thomas R. Insel

10.1126/science.1167707

CREDITS: (TOP LEFT); NINDS/NIH; (BOTTOM LEFT) BILL BRANSON; (RIGHT) JUPITER IMAGES