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Gene regulation and the architecture of complex human traits in the genomics era

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Virtually all human psychological and behavioral traits are at least partially heritable. For nearly a century, classical genetic studies have sought to understand how genetic variation contributes to human variation in these traits. More recently, genome-wide association studies have identified large numbers of specific genetic variants linked with complex traits. Many of these variants fall outside of protein-coding genes, in putative gene regulatory elements. This suggests that some fraction of causal human genetic variation acts through gene regulation. New developments in the field of regulatory genomics offer resources and methods to understand how genetic variants that alter gene expression contribute to human psychology and risk for psychiatric disease.

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Introduction

For close to a century, the tools of quantitative genetics have been used to study the sources of phenotypic variation in human populations [1]. This research largely comprises classical twin studies and adoption designs, capable of decomposing trait variance into that which is attributable to genetic variation from that which is attributable to environmental variation [2,3]. Twin studies still comprise a key research tool for scientists studying human behavior, since they act as quasi-experimental designs capable of holding constant shared genetic and family influences on a given phenotype [2,4]. However, behavioral scientists are also employing new genomic methods when studying the origins of human variation—in particular genome-wide association studies (GWAS), and the constituent tools that build off of their findings (e.g. polygenic risk scores; see the contributions by Anderson *et al.* in this special issue).

Along with an increased use of GWAS, social scientists are showing increasing interest in genomic studies of gene regulation, and in particular, epigenetic influences on gene expression [4]. Like quantitative genetics mentioned above, this area is not new, as geneticists have long recognized the importance of understanding the role of gene expression in disease and human complex traits [5,6]. However, recent developments in genomics have spurred a renewed interest in the role of gene regulation in psychological traits [7]. The repeated finding from GWAS that many trait-linked genetic variants occur within regulatory DNA [8–10], along with a wealth of new genome-scale data on gene regulation [11–14] highlight the need for a basic understanding of the contributions of epigenetics and gene regulation to complex human traits.

Two points of caution are worth mentioning before moving any further, however. First, despite advances in genomics, our understanding of the role of gene regulation in human cognitive and behavioral traits is based primarily on observational research (i.e. correlational findings), with only a few exceptions (see the contribution by Adams, as well as Quinn *et al.* in this special issue). Second, while gene regulation research appears essential to formulating a full understanding of the origins and progression of human disease and psychopathology, epigenetic and gene regulatory changes may not always be direct causes of outcomes (e.g. behavior). These changes in some cases may act as mediators of causal factors, or even spurious correlates [4]. That said, there are recent significant advances in the science of gene regulation as it relates to health and psychology. We briefly catalogue that research here, in the form of a 'user guide' to recent concepts that bear on the genomics of social science.

Association of gene regulation with human complex traits

GWAS analyses have become an important tool used by behavioral scientists to dissect the genetic architecture of human psychological traits [3]. One of the robust findings to emerge from GWAS is that many trait-linked genetic

variation falls outside of protein-coding genes, in the 'non-coding' regions of the genome [8,9,10,15,16]. These non-coding regions are estimated to contain hundreds of thousands of DNA regulatory elements [17]. This suggests that the genetic architecture of human complex traits consists of a substantial fraction of variants that act by altering the expression of genes, rather than altering the functional properties of genes themselves. Candidate genetic variants that affect gene expression have been associated with a range of behavioral traits and psychiatric diseases, including bipolar disorder, schizophrenia, autism, and neuroticism [3,18–20,21••,22–25].

Because of the likely significance of non-coding variants in human traits, researchers have begun systematically cataloging genetic variants that are directly linked with inter-individual differences in gene expression in a wide range of tissues. These variants, called expression quantitative trait loci (eQTL), are associated with extensive variation in gene expression in every human tissue that has been studied, including the brain. Among the largest eQTL studies are those produced by the Genotype-Tissue Expression (GTEx) project, which to date has collected gene expression profiles across 44 tissues, including 10 brain subregions, in 449 human donors. GTEx identified over 150 000 eQTL, which together affected more than 80% of human genes [26,27]. These studies found that genetic variation affecting gene expression is pervasive, and that extreme inter-individual differences in gene expression are common. While it remains unclear what fraction of eQTL will have a meaningful effect on human phenotypic variation, integrating eQTL data with GWAS associations has proven useful for prioritizing individual variants, genes, and pathways that for further study [27].

The current model of gene regulation

The current model of gene regulation has emerged from genomic and single gene studies conducted over the past several decades. Gene expression is controlled via two classes of DNA regulatory elements: promoters, which lie directly adjacent to genes, and enhancers, which are often located at a significant genomic distance from their target genes [28]. Genes are typically regulated by a single promoter and multiple distal enhancers, which are the primary regulators of tissue-specific expression [29]. Promoters and enhancers function by serving as binding sites for regulatory proteins that modify the epigenetic state of the local chromatin and recruit the molecular machinery to activate or repress the expression of the target gene. Some regulatory proteins respond specifically to developmental or environmental cues, and thus mediating changes in gene expression in response to those cues [30,31]. Given this basic model of gene expression, the field of regulatory genomics has focused on several key questions: Which DNA sequences in the human genome serve as regulatory elements, what genes to they regulate, and in which cell types? Which regulatory proteins control the epigenetic state of specific enhancers and promoters? And how do genetic variants alter the regulatory capacity of enhancers and promoters, as well as their response to external signals? To answer these questions, researchers have developed a set of methodological and data resources that are broadly applicable to studies of human complex traits, including cognitive and behavioral traits.

Regulatory genomics resources

A major goal of recent work in genomics more broadly is to discover and functionally characterize all regulatory DNA in the human genome [7,11–13]. As a result, there are now a large number of genomic technologies and datasets available that can help bridge the gap between molecular mechanisms and human phenotypes [9,14]. These new genomic datasets present both opportunities and challenges for social scientists, who, in meaningful collaborations with molecular genomic researchers, might have an opportunity to usefully merge basic psychometric and social science data with genomic data.

Several of the genomic data types used to study gene regulation (Box 1) are of potential interest to social scientists, because they offer a means to a) identify high-priority, disease-linked non-coding genetic variants that might causally contribute to the genetic architecture of complex traits or prove to be effective genomic biomarkers [9,15,16,19,32,33••,34,35]; and b) identify genes and biological pathways that are involved in development, pathology, and response to the environment

Box 1 Summary of functional genomics data types

Gene expression: Sequencing to quantify RNA levels (RNA-seq) is used as a measure of all genes expressed in a tissue. RNA-seq is widely used in a variety of genomic analyses, including identifying genes and pathways active in particular tissues [24,33••] and linking regulatory genetic variants with target genes [27].

Accessible chromatin: DNase I-seq [44] and ATAC-seq [45] identify regions of accessible chromatin using DNA-digesting enzyme DNAsel or transposase insertion, followed by sequencing. Tissue-specific maps of accessible chromatin are used to identify candidate sites of regulatory DNA [37•].

Epigenetic state: Chromatin immunoprecipitation followed by sequencing (ChIP-seq) is used to measure genomic sites bound by regulatory proteins [46], as well as chemical modification of histones that indicate repressed or active chromatin [12]. These measures of epigenetic state often change in response to environment [34].

3D genome: Sequencing-based technologies such as Hi-C [47] are used to map long-range interactions between distal genomic elements, such as enhancers, and their target genes. 3D genomic data can be used to map non-coding SNPs with candidate target genes [32] and to prioritize GWAS SNPs for follow-up [34].

Functional assays: Massively parallel reporter assays (MPRAs) [48] use DNA sequencing to test the regulatory capacity of thousands of DNA sequences in parallel. MPRAs are often used to identify non-coding variants that alter the regulatory capacity of DNA [21••].

(including social environment) [18,24,25,36•]. Importantly, there is a growing number of human brain-specific datasets that are potentially valuable resources for post-GWAS, functional analysis [21••,33••,37•,38•]. Cross-comparisons between GWAS findings and functional genomics data can identify high-priority SNPs, and be used to develop hypotheses about specific neural mechanisms that contribute to human cognitive traits

Regulatory genomics and social science

While more limited, several interesting themes have emerged in recent studies that apply regulatory genomics to human behavioral and cognitive traits. One is that SNPs linked to human cognitive traits and mental health may affect DNA regulatory elements that control the expression of genes that are active during brain development, especially prenatal development. DNA regulatory elements active in the human fetal cortex are enriched in genetic variants associated with intracranial volume, schizophrenia, attention deficit hyperactivity disorder, depression, neuroticism, and educational attainment [33••]. Rare non-coding SNPs present in Autism Spectrum Disorder (ASD) cases have been found in regulatory elements that might influence ASD-risk factor genes, as well as genes active in fetal brains [24]. These findings suggest that genetic variants linked with a range of cognitive traits may sometimes act by affecting expression of specific genes during early brain development [23]. A related theme is that cognitive-trait linked regulatory SNPs occur in human-specific brain enhancers human specific that often show signals of positive selection [20,21••,25,33••,39,40]. These findings suggest that mutations in evolutionarily recent regulatory DNA make a significant contribution to the genetic architecture of some neuropathologies [21••].

Another emerging theme is that genetic variation in regulatory DNA modulates the effect of environment on cognitive traits. Using functional genomic data, researchers have identified candidate enhancers and promoters linked with a variety of psychological traits, including alcohol dependence [41], memory [42], and drug response [31,33••,34,43],

Finally, the combination of GWAS and functional genomic data has proven useful for identifying neural cell types that underlie cognitive and psychiatric traits [21••,37•]. For example, de la Torre-Ubieta *et al.* found that schizophrenia-linked non-coding variants [33••] affected gene regulation in four neural cell types, suggesting specific hypotheses about how genetic variants contribute to the mechanism of disease.

Conclusion

As a whole, what the brief discussion above illustrates is the shifting nature of modern social and psychological scientific research. To be sure, social scientists looking to expand the scope of their work on topics such as the origins of various psychopathologies and other deleterious conditions and outcomes are only likely to benefit from a close alliance with geneticists working in the area of gene expression. A more concrete example of how these alliances could look was recently provided by Moffitt and Beckley [4] who argued for the use of discordant twins to better understand a host of negative psychosocial outcomes by gaining insight about possible divergences in gene expression. Research collaborations such as these require layers of social science insight (to measure and assess key constructs with precision), coupled with behavioral genetic insight (to maximally utilize twin and sibling samples), and insights from geneticists and bench scientists to perform the requisite genomic analyses. Indeed, these networks of interdisciplinary teams are, in some cases, already assembled and publishing major scientific contributions (see Lee *et al.* [3]). Getting beyond correlation, moreover, by combining functional data with GWAS, will only continue to improve study designs, and as Freese and Baer-Bositis [this special issue] noted, the use of genetic data not only facilitates a better understanding of genetics, but it also clarifies contributions of environmental effects by controlling for genetic influences.

What should not be lost in all of this, however, is that a shift of this nature does not necessitate a loss of 'identity' for social scientists. Nor does it require a qualitative change in research topics that are of interest to individual scholars. Rather, a shift of this variety represents an opportunity to further expand the current insight regarding how, and by what mechanisms, the environments of human beings exert impacts on the behavioral, psychological, and physiological outcomes that sociologists, anthropologists, and psychologists have long been interested in. The benefits, in fact, are reciprocal in every direction as the boundaries between to the 'social' and 'natural' sciences continue to blur.

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Conflict of interest statement

Nothing declared.

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