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Chapter 4

Evolving views of human genetic variation and its relationship to neurologic and psychiatric disease

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Abstract

Recent advances in exome and genome sequencing in populations are beginning to define the genetic architecture of neurologic and psychiatric disease. At the same time these findings are changing our perspective of genetic variant contributions to disease, implicating both rare and common genetic variation in common diseases. Most of what we know about genetic contributions to disease so far comes from analysis of mutations in protein-coding genes. Since most genetic variation lies in nonprotein-coding regions of the genome whose presumed function is entirely regulatory, understanding gene regulation in a cell type and developmental state-specific manner will be important to connect human genetic variation to disease mechanisms.

THE CONTRIBUTION OF COMMON VERSUS RARE GENETIC VARIATION

The modern era of neurogenetics was framed by the discovery of the triplet repeat disorders and of rare Mendelian forms of both rare and common disorders. The advent of genetic linkage permitted mapping (Huntington disease, spinal and bulbar muscular atrophy, Friedreich ataxia, spinocerebellar ataxia type 1: [Harding, 1981](#); [Brzustowicz et al., 1990](#); [Verkerk et al., 1991](#); [The Huntington's Disease Collaborative Research Group, 1993](#); [Orr et al., 1993](#); [Lefebvre et al., 1995](#); [Campuzano et al., 1996](#)), and eventually cloning rare, highly penetrant, Mendelian disease genes based on studying families. This was an exciting time for neurogenetics, because for the first time major causal genetic factors for many neurologic diseases, including Alzheimer disease (AD), Parkinson disease, amyotrophic lateral sclerosis, Huntington disease, as well as dozens of

hereditary ataxias and neurodevelopmental disorders, were identified ([Orr and Zoghbi, 2007](#)) over the course of the ensuing decade, a process greatly accelerated in part by the Human Genome Project ([Lander et al., 2001](#); [Venter et al., 2001](#)). Although finding major gene causes were seminal events in the history of neurology, the vast majority of these mutations were rare, and, with a few exceptions, explained only a limited fraction of the population risk for common diseases, sometimes only in a handful of families. However, these discoveries opened a new window through which to build an understanding of disease mechanisms (e.g., [Orr and Zoghbi, 2007](#); see also Chapter 9, this volume).

In common neurologic diseases, early successes, such as the identification of relatively large effect size, common variants within the apolipoprotein E (*APOE*) gene that increase risk four- to fivefold for AD ([Strittmatter et al., 1993](#); [Roses, 1996](#)), suggested that common genetic variants carrying risk for common disorders

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would have relatively high effect sizes. Had this been true, the causes of common diseases would likely be few in number and would have been identified with relatively small-scale association studies. This is because the sample size necessary to find genetic risk factors is based on several factors, including the effect size of the risk variant, its frequency, and the frequency of the disorder in the population. Early genomewide association studies, which look for common variants that predispose to disease using a case-control design, overestimated the effect sizes of contributing loci, and underestimated their heterogeneity, leading to several early failures to identify common loci due to low power. The *APOE4* allele in AD turned out to be an outlier, in that no common variants imparting greater than twofold relative risk for other common neurologic disorders have been identified. Rather, most common variants imparting risk for AD, as well as other common neurologic disorders, have a relative risk of < 1.5 , the majority below 1.2 (Welter et al., 2014; MacArthur et al., 2017). Appreciating these challenges has informed study design, leading to well-powered genomewide association studies that now have identified many new loci contributing to common neurologic and psychiatric diseases (Simon-Sanchez and Singleton, 2008).

Based largely on extrapolation from these experiences, the prevailing genetic model over the last two decades has been that rare disorders are caused by rare alleles of major effect size (monogenic), whereas genetic risk for common diseases is primarily borne by common genetic variation ($> 1\%$ in the population; polygenicity). However, genomewide analyses of common variation so far indicate that common variants, while contributing substantially, cannot alone account for all of the heritability of common diseases (Manolio et al., 2009; Geschwind and Flint, 2015). In parallel, advances in technology that have facilitated high-throughput analysis in large populations, such as microarrays and next-generation sequencing (Metzker, 2010), have further informed this issue in several major ways (McCarthy and MacArthur, 2017).

The first is the finding that rare variants ($< 1\%$ frequency in the population) comprise the majority of human genetic variation. Rare loss-of-function variants have been found in more than 90% of genes in the genome, with only a small fraction of the human population sequenced (Keinan and Clark, 2012; Tennessen et al., 2012; Dewey et al., 2016; Lek et al., 2016). Second, rare, very rare, and ultra-rare frequency variants ($< 1\%$, $< 0.1\%$ and $< 2.5 \times 10^{-6}$, respectively) contribute to common diseases, ranging from AD (Steinberg et al., 2015) and frontotemporal dementia (Coppola et al., 2012) to autism spectrum disorder (ASD: Sanders et al., 2012; Leppa et al., 2016). Some of these rare

variants have a very large estimated effect size, and are therefore considered causal, while others have small to intermediate effect sizes, thus acting as risk factors for, rather than causes of, disease, contributing to a continuum of risk. Even rare de novo (noninherited, typically germline) genetic variation is more common than previously thought, with each person on average harboring nearly one de novo protein-coding mutation (Samocha et al., 2014; Auton et al., 2015). The third observation is that, similarly to common variants, evidence is accumulating that rare variants are likely to contribute to normal variation in cognitive and behavioral phenotypes in the population (Stefansson et al., 2014; Ulfarsson et al., 2017), consistent with small to intermediate effects on disease risk for many.

This appreciation that rare genetic variation occurs more frequently and contributes more to common disease than was previously thought means that risk for most common neurologic diseases is likely imparted by all classes of variants, common and rare, inherited and de novo. A corollary of this is that the relative contribution of each class is likely to vary quite substantially by disorder (Geschwind and Flint, 2015); variants that cause disorders related to aging are likely under different evolutionary constraints than those that occur in childhood. Thus, whole-genome analysis at single base pair resolution will be necessary to fully understand genetic risk for common neurologic disorders, and since we need to have power to detect effects for very rare variants, large population-scale studies will be needed. Moreover, as noted above, since rare loss-of-function variants are not rare as a class when combined, caution is warranted when assigning pathogenicity to newly identified singleton protein-disrupting variants. Guidelines for interpretation of causality identified by sequencing have recently been published (MacArthur et al., 2014; see also Chapter 2, this volume) which will no doubt evolve and mature over the next decades as our databases of whole-genome sequence grow to encompass entire populations connected to medical records.

Why does the frequency of genetic variation matter?

Defining common or rare risk contributions to disease is not simply an esoteric issue. As outlined above, it clearly informs the design of studies attempting to discover genetic risk factors for neurologic disorders. But, it also has functional implications that impact treatment development (Gandal et al., 2016) and genetic testing (e.g., Chapter 2, this volume; Fogel and Geschwind, 2015). Allele frequency in the population is related to the population history and the degree of natural selection. Rare variants are new and mostly under purifying

selection, whereas common variants are old and either neutral or under positive selection. Because of this, different biologic pathways may be affected by different forms of variation. For example, in AD, rare Mendelian forms involve genes involved in amyloid processing or beta-amyloid itself, whereas common variants implicate largely neural-glial/immune genes such as *CRI*, or genes involved in trafficking, such as *CLU* (Harold et al., 2009), suggesting innate immune pathways that were not originally implicated by rare Mendelian acting variants. Similarly, rare and common variations appear to impact different pathways in certain neurodevelopmental disorders (Parikshak et al., 2013). An important experimental challenge is to understand where pathways implicated by common and rare variants defining common variant contributions to disease diverge or intersect; in some cases the intersection may be at the gene level itself, rather than broad pathways. Rare variants in genes also implicated by genomewide association studies (Guerreiro et al., 2013; Jonsson et al., 2013) may also act as risk factors. The contributions of rare genetic variants also highlight the need for broad population genetic screening, rather than relying only on patient cohorts, to fully understand how disease risk impacts human biology and have an unbiased estimate of the true relative risk that the variant imparts for the disorder.

Identification of rare structural variants or protein-disrupting single-nucleotide mutations in a number of disorders has also identified unexpected links between clinically and pathologically distinct neurologic and psychiatric disorders. Examples include the *MAPT* gene, which codes for the tau protein, and is implicated in neurodegenerative syndromes, ranging from AD, frontotemporal dementia, corticobasal degeneration, and progressive supranuclear palsy (Coppola et al., 2012; Ng et al., 2015; Lopez et al., 2017). Here, genetic findings link conditions that are clinically considered to be distinct and suggest the potential for a common molecular pathway. Similarly, schizophrenia and ASD, which are behaviorally defined disorders, share similar rare genetic risk factors, including copy number variants such as (del) 22q11 and Neurexin 1 deletions (Cantor and Geschwind, 2008; Doherty and Owen, 2014; Fromer et al., 2014; Iossifov et al., 2014; McCarthy et al., 2014).

Lastly, although common variants are expected to have quite small individual effects on disease risk, composite risk scores that take into account all variants potentially contributing to disease may provide power to predict disease risk. Such polygenic risk scores can be used to explore cross-disorder overlap and have shown a remarkable intersection between common risk factors for ASD and schizophrenia, similar to the rare variant overlap mentioned above (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013, St Pourcain

et al., 2017; Weiner et al., 2017). Polygenic risk scores also provide an avenue for identifying potential etiologic factors, such as intermediate brain structural, functional, or cognitive phenotypes (Lancaster et al., 2016; Reus et al., 2017). For example, common genetic risks for schizophrenia and bipolar disorder overlap with genetic factors promoting creativity (Power et al., 2015) and genetic risk for ASD coincides substantially with factors that underlie increased educational attainment (Weiner et al., 2017). Such relationships may also provide a framework for understanding the biologic factors that may have led to the persistence of these disease risk variants in the population (predicted by the presence of natural selection).

EVOLVING VIEWS OF GENOME FUNCTION

Along with the changing view of genetic variation in humans, our view of the genome itself and its potential contribution to disease are also evolving rapidly. Most of the major advances in this arena have occurred via exploration of the >95% of the genome that is nonprotein coding (ENCODE Project Consortium, 2012). These studies have identified multiple new classes of nonprotein-coding RNA, including multiple small RNA species, including pi, sno, and miRNAs, tens of thousands of long coding RNA, as well as, more recently, RNA transcribed from active enhancers (Deveson et al., 2017; Ko et al., 2017; Rothschild and Basu, 2017; Xue et al., 2017). These mRNA do not code for protein and hence are nonprotein-coding gene products. The primary role of these RNA species is thought to be regulatory; for example, miRNA act by repressing transcription or translation (Ivey and Srivastava, 2015; Xue et al., 2017). Some lncRNA are thought to act as antisense transcripts, repressing transcription of mRNA, while others act as presumed sponges for miRNA (Deveson et al., 2017). Currently, the functions of most miRNA and lncRNA are not known, but they play critical roles in gene regulation (Deveson et al., 2017; Xue et al., 2017). Enhancer RNA are transcribed in parallel with the transcription of the target gene mRNA, and they likely regulate structural changes that result in proximity between enhancers and promoters to regulate gene expression (Ko et al., 2017).

The importance of the contribution of the regulation of gene (mRNA) expression to disease is underscored by the observation that the vast majority of common genetic variation that contributes to disease risk in humans lies in noncoding regions of the genome and does not directly affect protein-coding exons (Zhang and Lupski, 2015). These regions are predicted to have regulatory functions, which are not limited to regulation of transcript expression, but may affect splicing as well

(Li et al., 2016). Analysis of rare variation in noncoding regions of the genome is in its very early stages and faces many challenges, so the extent of noncoding rare variation contributions to disease is not yet as well delineated as it is for common variation. Since regulatory regions comprise a significant fraction of the genome, we expect that they will play important roles in disease. This is supported by the discovery of multiple rare, Mendelian mutations that affect splicing and are known to cause neurodegenerative disorders, such as frontotemporal dementia (Pickering-Brown et al., 2002). In a broader sense, variation in splicing, including genes involved in RNA processing or metabolism, has been clearly linked to disease mechanisms in multiple neurologic and psychiatric conditions, ranging from ASD to amyotrophic lateral sclerosis and multiple other neuromuscular disorders (Belzil et al., 2013; Nussbacher et al., 2015; Van Alstyne and Pellizzoni, 2016; Wang et al., 2016a; Cookson, 2017; Liu et al., 2017).

One crucial mechanism for the regulation of gene expression and splicing is dynamic control of epigenetic modifications, which are changes to DNA that do not change its sequence, but still alter its function (see Chapter 5, this volume). Dozens of such modifications, ranging from DNA methylation and hydroxymethylation to histone methylation and acetylation, have been identified (see Chapter 5, this volume). These form a combinatorial code that is just beginning to be deciphered, but which when measured in a tissue or cell reveals the local states of regulatory elements, such as the activity of enhancers and promoters in that cell at that time. It is presumed that one mechanism via which disease-related DNA variation acts is by altering these regulatory relationships, which makes uncovering these relationships a priority. This priority is further emphasized by the observation that many neurodevelopmental and neurodegenerative disorders involve specific regional or cell vulnerabilities, highlighting the necessity of understanding the complexities of cell type and stage-specific gene regulation (Seeley, 2008; Miller et al., 2013; Parikshak et al., 2013; Wang et al., 2016b).

Further complicating matters when it comes to gene regulation is that, rather than being a simple linear arrangement of regulatory elements, such as an operon, mammalian chromatin (which consists of DNA and its protein complexes) exists in a complex three-dimensional (3D) structure. This 3D structure is modified by epigenetic changes and this structure plays a major role in gene regulation by creating boundaries, and bringing distant regions, such as noncontiguous enhancers and promoters, in contact to exert effects on gene transcription in a tissue-specific manner (Dekker and Mirny, 2016; Won et al., 2016). While the 3D genome is a relatively new concept, I expect that future

volumes will contain multiple examples of both proximal and distal (long-range) regulatory variation and its disease-relevant mechanisms.

Finally, since these complex gene-regulatory processes are what translate the DNA sequence into cellular function, understanding these regulatory relationships at a cellular level is going to be critical for understanding the mechanisms of most neurologic disorders. Behavior and cognition are related to specific circuits and regions, which consist of specific cell types, and thus the manifestations of neurologic disease, for example, cellular and regional vulnerability in neurodegenerative diseases, ultimately depend upon cell type-specific gene regulation. Placing disease-causing genetic variation that affects either gene product sequence or gene regulation into this cell type and circuit context remains a critical challenge for neurogenetics in the decade to come.

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