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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 comon 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 prevaling 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-throughtput 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 corrollary of this is that the relative contribution of each class is likely to vary quite subtantially 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 *CR1*, 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 promotors 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 promotors 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 promotors, 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 muliple 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.

References

Auton A, Brooks LD, Durbin RM et al. (2015). A global reference for human genetic variation. Nature 526: 68–74.

Belzil VV, Gendron TF, Petrucelli L (2013). RNA-mediated toxicity in neurodegenerative disease. Mol Cell Neurosci 56: 406–419.

Brzustowicz LM, Lehner T, Castilla LH et al. (1990). Genetic mapping of chronic childhood-onset spinal muscular atrophy to chromosome 5q11.2-13.3. Nature 344: 540–541.

Campuzano V, Montermini L, Molto MD et al. (1996). Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion. Science 271: 1423–1427.

Cantor RM, Geschwind DH (2008). Schizophrenia: genome, interrupted. Neuron 58: 165–167.

Cookson MR (2017). RNA-binding proteins implicated in neurodegenerative diseases. Wiley Interdiscip Rev RNA 8 (1).

Coppola G, Chinnathambi S, Lee JJ et al. (2012). Evidence for a role of the rare p.A152T variant in MAPT in increasing the risk for FTD-spectrum and Alzheimer's diseases. Hum Mol Genet 21: 3500–3512.

Cross-Disorder Group of the Psychiatric Genomics Consortium (2013). Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. Lancet 381: 1371–1379.

Dekker J, Mirny L (2016). The 3D genome as moderator of chromosomal communication. Cell 164 (6): 1110–1121.

Deveson IW, Hardwick SA, Mercer TR et al. (2017). The dimensions, dynamics, and relevance of the mammalian noncoding transcriptome. Trends Genet 33: 464–478.

Dewey FE, Murray MF, Overton JD et al. (2016). Distribution and clinical impact of functional variants in 50,726 whole-exome sequences from the DiscovEHR study. Science 354 (6319).

Doherty JL, Owen MJ (2014). Genomic insights into the overlap between psychiatric disorders: implications for research and clinical practice. Genome Med 6: 29.

Project Consortium ENCODE (2012). An integrated encyclopedia of DNA elements in the human genome. Nature 489: 57–74.

Fogel BF, Geschwind DH (2015). Clinical neurogenetics. In: R Daroff, G Fenichel, J Jankovic et al. (Eds.), Neurology in clinical practice, 7th ed. Elsevier, Philadelphia, PA.

Fromer M, Pocklington AJ, Kavanagh DH et al. (2014). De novo mutations in schizophrenia implicate synaptic networks. Nature 506: 179–184.

Gandal MJ, Leppa V, Won H et al. (2016). The road to precision psychiatry: translating genetics into disease mechanisms. Nat Neurosci 19: 1397–1407.

Geschwind DH, Flint J (2015). Genetics and genomics of psychiatric disease. Science 349: 1489–1494.

Guerreiro R, Wojtas A, Bras J et al. (2013). TREM2 variants in Alzheimer's disease. N Engl J Med 368: 117–127.

Harding AE (1981). Friedreich's ataxia: a clinical and genetic study of 90 families with an analysis of early diagnostic criteria and intrafamilial clustering of clinical features. Brain 104: 589–620.

Harold D, Abraham R, Hollingworth P et al. (2009). Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. Nat Genet 41: 1088–1093.

Iossifov I, O'Roak BJ, Sanders SJ et al. (2014). The contribution of de novo coding mutations to autism spectrum disorder. Nature 515: 216–221.

Ivey KN, Srivastava D (2015). microRNAs as developmental regulators. Cold Spring Harb Perspect Biol 7: a008144.

Jonsson T, Stefansson H, Steinberg S et al. (2013). Variant of TREM2 associated with the risk of Alzheimer's disease. N Engl J Med 368: 107–116.

Keinan A, Clark AG (2012). Recent explosive human population growth has resulted in an excess of rare genetic variants. Science 336: 740–743.

Ko JY, Oh S, Yoo KH (2017). Functional enhancers as master regulators of tissue-specific gene regulation and cancer development. Mol Cells 40: 169–177.

Lancaster TM, Linden DE, Tansey KE et al. (2016). Polygenic risk of psychosis and ventral striatal activation during reward processing in healthy adolescents. JAMA Psychiatry 73: 852–861.

Lander ES, Linton LM, Birren B et al. (2001). Initial sequencing and analysis of the human genome. Nature 409: 860–921.

Lefebvre S, Burglen L, Reboullet S et al. (1995). Identification and characterization of a spinal muscular atrophy-determining gene. Cell 80: 155–165.

Lek M, Karczewski KJ, Minikel EV et al. (2016). Analysis of protein-coding genetic variation in 60,706 humans. Nature 536: 285–291.

Leppa VM, Kravitz SN, Martin CL et al. (2016). Rare inherited and de novo CNVs reveal complex contributions to ASD risk in multiplex families. Am J Hum Genet 99: 540–554.

Li YI, van de Geijn B, Raj A et al. (2016). RNA splicing is a primary link between genetic variation and disease. Science 352: 600–604.

Liu EY, Cali CP, Lee EB (2017). RNA metabolism in neurodegenerative disease. Dis Model Mech 10: 509–518.

Lopez A, Lee SE, Wojta K et al. (2017). A152T tau allele causes neurodegeneration that can be ameliorated in a zebrafish model by autophagy induction. Brain 140: 1128–1146.

MacArthur DG, Manolio TA, Dimmock DP et al. (2014). Guidelines for investigating causality of sequence variants in human disease. Nature 508: 469–476.

MacArthur J, Bowler E, Cerezo M et al. (2017). The new NHGRI-EBI catalog of published genome-wide association studies (GWAS catalog). Nucleic Acids Res 45: D896–D901.

Manolio TA, Collins FS, Cox NJ et al. (2009). Finding the missing heritability of complex diseases. Nature 461: 747–753.

McCarthy MI, MacArthur DG (2017). Human disease genomics: from variants to biology. Genome Biol 18: 20.

McCarthy SE, Gillis J, Kramer M et al. (2014). De novo mutations in schizophrenia implicate chromatin remodeling and support a genetic overlap with autism and intellectual disability. Mol Psychiatry 19: 652–658.

Metzker ML (2010). Sequencing technologies – the next generation. Nat Rev Genet 11: 31–46.

Miller JA, Woltjer RL, Goodenbour JM et al. (2013). Genes and pathways underlying regional and cell type changes in Alzheimer's disease. Genome Med 5: 48.

Ng AS, Rademakers R, Miller BL (2015). Frontotemporal dementia: a bridge between dementia and neuromuscular disease. Ann N Y Acad Sci 1338: 71–93.

Nussbacher JK, Batra R, Lagier-Tourenne C et al. (2015). RNA-binding proteins in neurodegeneration: seq and you shall receive. Trends Neurosci 38: 226–236.

Orr HT, Zoghbi HY (2007). Trinucleotide repeat disorders. Annu Rev Neurosci 30: 575–621.

Orr HT, Chung MY, Banfi S et al. (1993). Expansion of an unstable trinucleotide CAG repeat in spinocerebellar ataxia type 1. Nat Genet 4: 221–226.

Parikshak NN, Luo R, Zhang A et al. (2013). Integrative functional genomic analyses implicate specific molecular pathways and circuits in autism. Cell 155: 1008–1021.

Pickering-Brown SM, Richardson AM, Snowden JS et al. (2002). Inherited frontotemporal dementia in nine British families associated with intronic mutations in the tau gene. Brain 125: 732–751.

Power RA, Steinberg S, Bjornsdottir G et al. (2015). Polygenic risk scores for schizophrenia and bipolar disorder predict creativity. Nat Neurosci 18: 953–955.

Reus LM, Shen X, Gibson J et al. (2017). Association of polygenic risk for major psychiatric illness with subcortical volumes and white matter integrity in UK Biobank. Sci Rep 7. 42140.

Roses AD (1996). Apolipoprotein E alleles as risk factors in Alzheimer's disease. Annu Rev Med 47: 387–400.

Rothschild G, Basu U (2017). Lingering questions about enhancer RNA and enhancer transcription-coupled genomic instability. Trends Genet 33: 143–154.

St Pourcain B, Robinson EB, Anttila V et al. (2017). ASD and schizophrenia show distinct developmental profiles in common genetic overlap with population-based social communication difficulties. In: Mol Psychiatry doi: 10.1038/mp.2016.198.

Samocha KE, Robinson EB, Sanders SJ et al. (2014). A framework for the interpretation of de novo mutation in human disease. Nat Genet 46: 944–950.

Sanders SJ, Murtha MT, Gupta AR et al. (2012). De novo mutations revealed by whole-exome sequencing are strongly associated with autism. Nature 485: 237–241.

Seeley WW (2008). Selective functional, regional, and neuronal vulnerability in frontotemporal dementia. Curr Opin Neurol 21: 701–707.

Simon-Sanchez J, Singleton A (2008). Genome-wide association studies in neurological disorders. Lancet Neurol 7: 1067–1072.

Stefansson H, Meyer-Lindenberg A, Steinberg S et al. (2014). CNVs conferring risk of autism or schizophrenia affect cognition in controls. Nature 505: 361–366.

Steinberg S, Stefansson H, Jonsson T et al. (2015). Loss-of-function variants in ABCA7 confer risk of Alzheimer's disease. Nat Genet 47: 445–447.

Strittmatter WJ, Saunders AM, Schmechel D et al. (1993). Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proc Natl Acad Sci U S A 90: 1977–1981.

Tennessen JA, Bigham AW, O'Connor TD et al. (2012). Evolution and functional impact of rare coding variation from deep sequencing of human exomes. Science 337: 64–69.

The Huntington's Disease Collaborative Research Group (1993). A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell 72: 971–983.

Ulfarsson MO, Walters GB, Gustafsson O et al. (2017). 15q11.2 CNV affects cognitive, structural and functional correlates of dyslexia and dyscalculia. Transl Psychiatry 7. e1109.

Van Alstyne M, Pellizzoni L (2016). Advances in modeling and treating spinal muscular atrophy. Curr Opin Neurol 29: 549–556.

Venter JC, Adams MD, Myers EW et al. (2001). The sequence of the human genome. Science 291: 1304–1351.

Verkerk AJ, Pieretti M, Sutcliffe JS et al. (1991). Identification of a gene (FMR-1) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome. Cell 65: 905–914.

Wang ET, Taliaferro JM, Lee JA et al. (2016a). Dysregulation of mRNA localization and translation in genetic disease. J Neurosci 36: 11418–11426.

Wang M, Roussos P, McKenzie A et al. (2016b). Integrative network analysis of nineteen brain regions identifies molecular signatures and networks underlying selective regional vulnerability to Alzheimer's disease. Genome Med 8: 104.

Weiner DJ, Wigdor EM, Ripke S et al. (2017). Polygenic transmission disequilibrium confirms that common and rare variation act additively to create risk for autism spectrum disorders. Nat Genet 49: 978–985.

Welter D, MacArthur J, Morales J et al. (2014). The NHGRI GWAS catalog, a curated resource of SNP-trait associations. Nucleic Acids Res 42: D1001–D1006.

Won H, de la Torre-Ubieta L, Stein JL et al. (2016). Chromosome conformation elucidates regulatory relationships in developing human brain. Nature 538: 523–527.

Xue M, Zhuo Y, Shan B (2017). MicroRNAs, long noncoding RNAs, and their functions in human disease. Methods Mol Biol 1617: 1–25.

Zhang F, Lupski JR (2015). Non-coding genetic variants in human disease. Hum Mol Genet 24: R102–R110.