444e Biology of Neurologic Diseases

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The human nervous system is the organ of consciousness, cognition, ethics, and behavior; as such, it is the most intricate structure known to exist. More than one-third of the 23,000 genes encoded in the human genome are expressed in the nervous system. Each mature brain is composed of 100 billion neurons, several million miles of axons and dendrites, and $>10^{15}$ synapses. Neurons exist within a dense parenchyma of multifunctional glial cells that synthesize myelin, preserve homeostasis, and regulate immune responses. Measured against this background of complexity, the achievements of molecular neuroscience have been extraordinary. This chapter reviews selected themes in neuroscience that provide a context for understanding fundamental mechanisms underlying neurologic disorders.

NEUROGENETICS

The landscape of neurology has been transformed by modern molecular genetics. Several hundred neurologic and psychiatric disorders can now be diagnosed through genetic testing (*http://www.ncbi.nlm.nih.gov/sites/GeneTests/?db=GeneTests*). The vast majority of these represent highly penetrant mutations that cause rare neurologic disorders; alternatively, they represent rare monogenic causes of common phenotypes. Examples of the latter include mutations of the amyloid precursor protein in familial Alzheimer's disease, the microtubule-associated protein tau (MAPT) in frontotemporal dementia, and α-synuclein in Parkinson's disease. These discoveries have been profoundly important because the mutated gene in the familial disorder often encodes a protein that is also pathogenetically involved (although not mutated) in the typical, sporadic form. The common mechanism involves disordered processing and, ultimately, aggregation of the protein leading to cell death (see "Protein Aggregation and Neurodegeneration," below).

There is optimism that complex genetic disorders, caused by combinations of both genetic and environmental factors, have now become tractable problems. Genome-wide association studies (GWAS) have been carried out in many complex neurologic disorders, with many hundreds of variants identified, nearly all of which confer only a small increment in disease risk (1.15- to 1.5-fold). GWAS studies are rooted in the "common disease, common variant" hypothesis, as they examine potential risk alleles that are relatively frequent (e.g. >5%) in the general population. More than 1500 GWAS studies have been carried out, with notable successes such as the identification of 110 risk alleles for multiple sclerosis **(Chap. 458)**. Furthermore, using bioinformatics tools, risk variants can be aligned in functional biologic pathways to identify novel pathogenic mechanisms as well as to reveal heterogeneity (e.g., different pathways in different individuals). Despite these successes, many experienced geneticists question the real value of common disease-associated variants, particularly whether they are actually causative or merely mark the approximate locations of more important—truly causative—rare mutations.

This debate has set the stage for the next revolution in human genetics, made possible by the development of increasingly efficient and cost-effective high-throughput sequencing methodologies. It is already possible to sequence an entire human genome in approximately an hour, at a cost of only $1300 for the entire coding sequence ("whole-exome") or $3000 for the entire genome; it is certain that these costs will continue to decline. This makes it feasible to look for disease-causing sequence variations in individual patients with the possibility of identifying rare variants that cause disease. The utility of this approach was demonstrated by whole-genome sequencing in a patient with Charcot-Marie-Tooth neuropathy, in which compound heterozygous mutations were identified in the *SH3TC2* gene, which then were shown to co-segregate with the disease in other members of the family.

It is increasingly recognized that not all genetic diseases or predispositions are caused by simple changes in the linear nucleotide sequence of genes. Disease-causative mutations also occur commonly in noncoding sequences of DNA. For example, large intronic GGGGCC repeat expansions in a gene of unknown function *C9orf72* (chromosome 9 open reading frame 72) were recently identified as a common cause of both frontotemporal dementia and amyotrophic lateral sclerosis (ALS). This mutation is the most common cause of both familial and sporadic ALS identified thus far. It was shown to be associated with TDP-43 (tar DNA binding protein-43) inclusions in both hippocampal and cerebral neurons. Interestingly, despite the absence of a start codon, the three alternate dipeptide sequences consisting of two amino acids are translated and found in postmortem brain tissue of affected patients. Three potential pathogenic mechanisms have been proposed, including (1) haploinsufficiency, (2) repeat RNA-mediated toxicity, and (3) dipeptide protein toxicity. The possibility of RNA toxicity is supported by the finding of intranuclear RNA foci containing *C9orf72* hexanucleotide repeats and specific RNA-binding proteins. The *C9orf72* mRNA forms quadruplexes of DNA and RNA, which then can halt transcription and also bind transcription factors. Mutations in both *TARDP* (transactive region DNA binding protein) and *FUS* (fused in sarcoma) also encode DNA/RNA-processing polypeptides and are a cause of familial and sporadic ALS.

As the complex architecture of the human genome becomes better defined, many disorders that result from alterations in copy numbers of genes ("gene-dosage" effects) resulting from unequal crossing-over are also likely to be identified. As much as 5–10% of the human genome consists of nonhomologous duplications and deletions, and these appear to occur with a much higher mutational rate than is the case for single base pair mutations. The first copy-number disorders to be recognized were Charcot-Marie-Tooth disease type 1A (CMT1A), caused by a duplication in the gene encoding the myelin protein PMP22, and the reciprocal deletion of the gene causing hereditary liability to pressure palsies **(Chap. 459)**. Gene-dosage effects are causative in some cases of Parkinson's disease (α-synuclein), Alzheimer's disease (amyloid precursor protein), spinal muscular atrophy (survival motor neuron 2), the dysmyelinating disorder Pelizaeus-Merzbacher syndrome (proteolipid protein 1), late-onset leukodystrophy (lamin B1), and a variety of developmental neurologic disorders. It is likely that copy-number variations contribute substantially to normal human genomic variation for numerous genes involved in neurologic function, regulation of cell growth, and regulation of metabolism. It is also already clear that gene-dosage effects will influence many behavioral phenotypes, learning disorders, and autism spectrum disorders. Deletions at ch444eq and ch15q have been associated with schizophrenia, and deletions at 15q and 16p with autism. Interestingly, the 16p deletion is also associated with epilepsy. Duplications of the X-linked *MeCP2* gene cause autism in males and psychiatric disorders with anxiety in females, whereas point mutations in this gene produce the neurodevelopmental disorder Rett's syndrome. The understanding of the role of copy number variation in human disease is still in its infancy.

The role of splicing variation as a contributor to neurologic disease is another area of active investigation. *Alternative splicing* refers to the inclusion of different combinations of exons in mature mRNA, resulting in the potential for many different protein products encoded by a single gene. Alternative splicing represents a powerful mechanism for generation of complexity and variation, and this mechanism appears to be highly prevalent in the nervous system, affecting key processes such as neurotransmitter receptors and ion channels. Numerous diseases are already known to result from abnormalities in alternative splicing. Increased inclusion of exon 10–containing transcripts of *MAPT* can cause frontotemporal dementia. Aberrant splicing also contributes to the pathogenesis of Duchenne's, myotonic, and facioscapulohumeral muscular dystrophies; ataxia telangiectasia; neurofibromatosis; some inherited ataxias; and fragile X syndrome, among other disorders. It is also likely that subtle variations of splicing will influence many genetically complex disorders. A splicing variant of the interleukin 7 receptor α chain, resulting in production of more soluble and less membrane-bound receptor, is associated with susceptibility to multiple sclerosis (MS) in multiple different populations.

Epigenetics refers to the mechanisms by which levels of gene expression can be exquisitely modulated, not by variations in the primary