CHAPTER

41

Genetics of Neurodegenerative Diseases

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OUTLINE

GENETIC ASPECTS OF COMMON NEURODEGENERATIVE DISEASES

For most neurodegenerative conditions outlined in this chapter, familial aggregation had already been recognized as a salient feature decades before any of the underlying molecular genetic and biochemical properties were known (Bertram & Tanzi, 2005). As a matter of fact, it was often only the identification of specific, disease-segregating mutations in previously unknown genes that directed the attention of molecular biologists to certain proteins and pathways (Figure 41-1) that are now considered to be crucial to the development of the various diseases. These include the discovery of mutations in the β-amyloid precursor protein, causing Alzheimer's disease; mutations in α-synuclein, causing Parkinson's disease; and mutations in microtubule-associated protein tau, causing frontotemporal dementia with parkinsonism. Another feature observed in most common neurodegenerative diseases—as well as in other common conditions such as certain forms of cancer—is the prominent dichotomy of familial (rare, often following Mendelian inheritance) vs. seemingly non-familial (common, following non-Mendelian inheritance) forms. The latter are also frequently described as "sporadic" or "idiopathic" forms, although this terminology has proved oversimplistic since a large proportion of apparently "sporadic" cases are actually also significantly influenced by genetic factors.

Despite the previous successes and recent advances in molecular and analytic techniques, the identification of genuine risk factors for the diseases outlined in this chapter—genetic and non-genetic—is aggravated by several circumstances. First, while diagnostic criteria have been proposed for all syndromes, these are usually based on clinical and/or neuropathological observations, which are never 100% specific and may even be assessed differently from one research center to the next. Thus, a sample described to consist of probable (i.e., clinically diagnosed) late-onset Alzheimer's disease cases may actually be a conglomerate of predominantly Alzheimer's patients, but

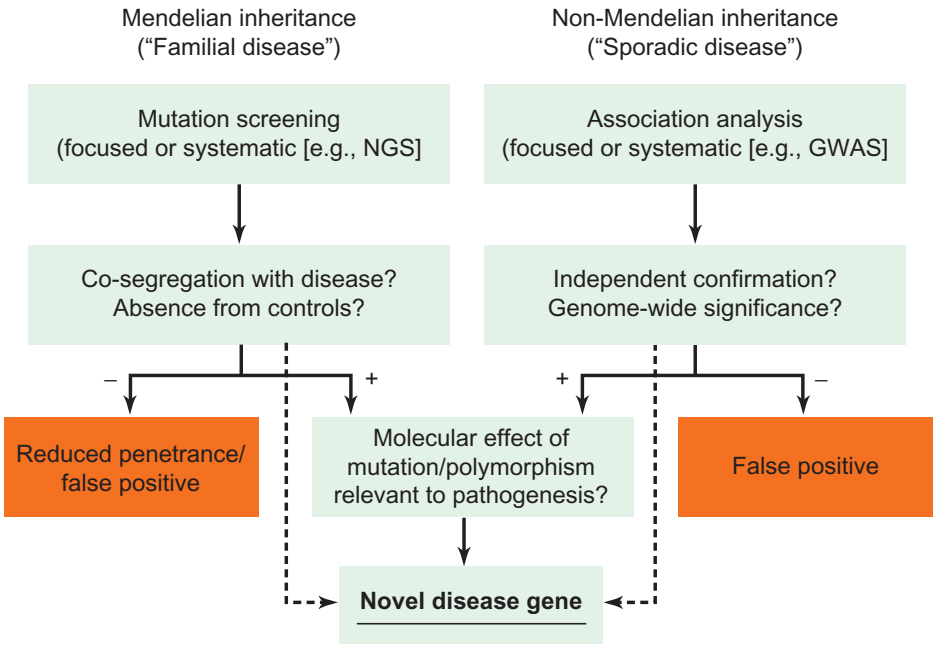

FIGURE 41-1 This schema outlines popular strategies to identify mutations and polymorphisms causing or predisposing to disease. Depending on the observed or suspected mode of inheritance, the search for disease-related sequence variants typically involves mutation screenings (Mendelian forms) or association analyses (non-Mendelian or sporadic forms). "Focused" in this context usually entails the study of certain gene(s) (usually considered "candidate genes" based on evidence from functional experiments or genetic linkage data), while "systematic" refers to large-scale approaches unbiased with respect to the nature of the underlying genes. The latter can be achieved by applying sequencing or genotyping technologies such as high-throughput next-generation sequencing (NGS, analyzing the entire exome or genome), or genome-wide association studies (GWAS). Initial findings are followed up depending on the original design, and are subsequently (or simultaneously) subjected to functional characterization. Broken lines indicate "short-cuts" allowing definition of novel disease genes based on the genetic evidence alone, which is the case for most of the currently known susceptibility genes in the neurodegenerative disease field. Note examples of genes/mutations with reduced penetrance (left-hand red box) that are considered *bona-fide* disease genes (e.g., certain mutations in *PSEN1* in Alzheimer's disease).

also patients with other forms of dementia, e.g., Lewy-body dementia and frontotemporal dementia. A second and related issue is that most neurodegenerative diseases manifest in old age, i.e., beyond 60 or 70 years. This makes the assessment of reliable familial histories—a prerequisite for genetic analyses—very difficult because a number of relatives may not have lived through the typical onset age, or may suffer from other conditions that can mask or mimic the phenotype of interest. Third, common diseases typically display a large degree of genetic and phenotypic heterogeneity. This means not only that the same phenotype can be caused or modified by a number of different genetic loci and alleles, but also that mutations or polymorphisms in the same gene may lead to clinically distinct syndromes. Further, certain combinations of genetic and nongenetic risk factors may significantly increase the odds of a disease in one ethnic group or geographic area, while another set of factors may be acting together elsewhere.

Collectively, these and other issues have led to the accumulation of a large number of proposed susceptibility genes and environmental risk factors in all of the diseases covered here. Until recently, however, these have traditionally only received inconsistent support from subsequent and independent studies, except for a few notable exceptions. This situation has changed to some degree since the advent of massively parallel genotyping (and, more recently, sequencing) techniques, which now allow us to interrogate the genomes of a large number of subjects at varying degrees of resolution. Currently the most popular approach is based on genome-wide association screening, whereby up to one million genetic markers are simultaneously genotyped and assessed for potential correlations with disease risk and other phenotypic variables (e.g., disease onset, progression, survival). Since 2005, the genetics community has seen a deluge of so-called genome-wide association studies (GWAS), including several dozen for the neurodegenerative disorders covered in this chapter. While the success rate still varies from study to study, a number of well-replicated neurodegenerative disease loci have already emerged from these projects, and more are likely to be discovered over the coming years. Despite its achievements, the GWAS approach is limited to studying only relatively common types of genetic variation ("polymorphisms"), i.e., those occurring with a frequency greater than 1% in the general population. It is likely, however, that much of the genetic liability underlying common polygenic disorders is actually conferred by rare sequence variants, i.e., those with <1% frequency in the general population. *De novo* identification of these rare variants requires actual resequencing in affected patients, which can now be achieved using novel high-throughput ("next-generation") massively parallel sequencing technologies. These can reliably measure any sequence change—common or rare—allowing, for the

first time in scientific history, the study of whole genomes at base-pair resolution. This approach has already led to a number of breakthrough discoveries in 2009 and 2010 (Manolio et al., 2009; McClellan & King, 2010), and can be expected to become the mainstay of human genetics research by the end of 2020.

Notwithstanding the current difficulties and limitations, genetic analyses have laid the foundation for us to understand a wide variety of pathomechanisms leading to neurodegeneration and associated symptoms. A detailed understanding of the genetic basis of neurodegeneration will be essential for the development of effective strategies aimed at early prediction, prevention, and treatment of these devastating diseases. In the following sections, we will outline both the peculiarities and the similarities of genetic findings across a number of neurodegenerative conditions. Note that more details on the molecular genetic consequences, as well as neuropathogenic mechanisms influenced by the various disease genes discussed here, can be found in other chapters of this book.

ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is the most common form of age-related dementia and one of the most serious health problems in the industrialized world (Chapter 46). AD is an insidious and progressive neurodegenerative disorder that accounts for the vast majority of dementia, and is characterized by global cognitive decline and the accumulation of β-amyloid deposits and neurofibrillary tangles in the brain. Family history is the second greatest risk factor for the disease after age, and the growing understanding of AD genetics has been central to the explosion in knowledge of AD biology from neuropathology to the molecular level. Genetically, AD is complex and heterogeneous and appears to follow an age-related dichotomy where rare and highly penetrant early onset familial AD (EOFAD) mutations are transmitted in an autosomal dominant fashion, while increased risk for late onset AD without Mendelian inheritance (LOAD) is mainly conferred by common polymorphisms with relatively low penetrance, but high prevalence (Tanzi, 1999). The complexity and heterogeneity of AD genetics, as well as the genetics of other neurodegenerative disorders, are ill defined, and thus it is difficult to model gene–gene and gene–environment interactions.

Early onset familial AD

(EOFAD) represents only a small fraction of all AD cases (≤5 %) and typically presents with onset ages prior to the completion of the sixth decade, showing Mendelian, autosomal dominant disease transmission within affected families. To date, more than 200 mutations in three genes have been reported to cause EOFAD (Table 41-1A). These include the β-amyloid precursor protein (*APP*) on chromosome 21 (Goate et al., 1991), presenilin 1 (*PSEN1*) on chromosome 14 (Sherrington et al., 1995) and presenilin 2 (*PSEN2*) on chromosome 1 (Rogaev et al., 1995; Levy-Lahad et al., 1995). The most frequently mutated gene, *PSEN1*, generally leads to AD with onset ages in the 40s, and accounts for the majority of AD cases with onset prior to age 50. (For an up-to-date summary consult the AD & FTD Mutation database at http://www.molgen.ua.ac.be/ADMutations/; Cruts & van Broeckhoven, 1998). While these AD-causing mutations occur in three different genes located on three different chromosomes, they all share a common biochemical pathway, i.e., the altered production of Aβ leading to a relative overabundance of the $A\beta_{42}$ species, which eventually results in neuronal cell death and dementia. Aβ is produced by the sequential cleavage of APP by two enzymatic events, β- and γ-secretase cleavage. In contrast, the alternative α-secretase cleavage results in the production of a non-amyloidogenic soluble APPα fragment. Interestingly, most currently known AD-causing mutations in the APP gene are actually located near the respective cleavage site (i.e., in exons 16 and 17), or increase the expression of APP by duplication of the *APP*-containing chromosomal interval (Rovelet-Lecrux et al., 2006). Furthermore, it has now been shown that the presenilins are the catalytic subunits of the enzymatic complex responsible for γ-secretase cleavage of APP (Wolfe et al., 1999; Ahn et al., 2010). These discoveries provided the essential connection between the occurrence of disease-causing mutations in *APP*, *PSEN1* and *PSEN2* and the increase in Aβ production observed in the brains of autopsied AD patients, and have provided further support for the "amyloid hypothesis" of AD (reviewed in Tanzi & Bertram, 2005).

Apolipoprotein E in late-onset AD

Late-onset AD (LOAD) is classically defined as AD with onset ≥65 years and represents the vast majority of all AD cases. While segregation and twin studies conclusively suggest a major role for genetic factors in this form of AD (Gatz et al., 2006), until the advent of genome-wide screening technologies (see above), only one such gene had been *established* for LOAD, i.e., the ε4 allele of the apolipoprotein E gene (*APOE*; Table 41-1B) (Strittmatter et al., 1993). In contrast to most other association-based findings from the pre-GWAS era in AD, the risk effect of *APOE*-ε4 had been consistently

TABLE 41-1A Genes Causing Mendelian Forms of Alzheimer's Disease

Gene	Protein	Location	Inheritance	Proposed molecular effects/pathogenic relevance
APP	β-amyloid precursor protein	21q21	dominant	increase in Aβ production or $A\beta_{42}/A\beta_{40}$-ratio
PSEN1	presenilin 1	14q24	dominant	increase in $A\beta_{42}/A\beta_{40}$-ratio
PSEN2	presenilin 2	1q31	dominant	increase in $A\beta_{42}/A\beta_{40}$-ratio

For an up-to-date overview of these and other potential Mendelian AD genes see the AD & FTD Mutation database at http://www.molgen.ua.ac.be/admutations/.

TABLE 41-1B Susceptibility Genes for Non-Mendelian Forms of Alzheimer's Disease

Gene	Protein	Location	% Risk change‡	Proposed molecular effects/pathogenic relevance*
APOE	apolipoprotein E	19q13	~400%	aggregation & clearance of Aβ; cholesterol metabolism
BIN1†	bridging integrator 1	2q14	~15%	production & clearance of Aβ
CD33†	CD33 molecule (siglec 3)	19q13.3	~10%	innate immune system response
CLU†	clusterin	8p21.1	~10%	aggregation & clearance of Aβ; inflammation
CR1†	complement component (3b/4b) receptor 1	1q32	~15%	clearance of Aβ; inflammation
PICALM†	phosphatidylinositol binding clathrin assembly protein	11q14	~15%	production & clearance of Aβ; synaptic transmission

Only genes/loci showing genome-wide significant ($P \leq 5 \times 10^{-8}$) risk effects and independent replication are included. For an up-to-date overview of these and other potential susceptibility genes see the AlzGene database at http://www.alzgene.org.
†Indicates genes/loci originally identified by GWAS.
‡Approximate change in disease risk (increase or decrease) per copy of minor allele as compared to non-carriers of minor allele.
*Selection of proposed effects; note that the functional evidence for these loci is often scarce (see text for more details).

replicated in a large number of studies across many ethnic groups with odds ratios between ~4 for heterozygous to ~15 for homozygous carriers of the ε4 allele (Farrer et al., 1997). The three major alleles of the *APOE* locus, ε2, ε3 and ε4, correspond to combinations of two amino acid changes at residues 112 and 158 (ε2: Cys_{112}/Cys_{158}; ε3: Cys_{112}/Arg_{158}; ε4: Arg_{112}/Arg_{158}). In addition to the increased risk exerted by the ϵ4-allele, several studies have also reported a weak, albeit significant, protective effect for the minor ε2-allele. Unlike the mutations in the known EOFAD genes, the *APOE*-ε4 allele is neither necessary nor sufficient to cause AD, but instead operates as a genetic risk modifier by decreasing the age of onset in a dose-dependent manner. Even after the completion of over a dozen GWAS in AD, *APOE*-ε4 (or genetic markers highly correlated with it) remains by a margin the single most important genetic risk factor for AD, both in terms of effect size and statistical significance (Table 41-1b).

Despite its long-known and well-established genetic association, the biochemical consequences of *APOE*-ε4 in AD pathogenesis are not yet fully understood. Current hypotheses are based on the observation that Aβ accumulation is clearly enhanced in the brains of carriers as well as in transgenic mice expressing the human ε4 allele and mutant APP (reviewed in Vance & Hayashi, 2010). Further, apolipoprotein E normally plays a role in cholesterol transport and lipid metabolism, and *APOE*-ε4 predisposes to vascular disease as a result of its association with increased plasma cholesterol levels. High plasma cholesterol, in turn, has been correlated with increased β-amyloid deposition in the brain. Interestingly, cholesterol has also been shown to both increase Aβ production and to stabilize the peptide in the brains of transgenic AD mice. Thus, it is possible that *APOE*-ε4 confers risk for AD via a mechanism that is shared with its effect on vascular disease by increasing a carrier's risk for hypercholesterolemia, as this would also elevate accumulation of Aβ.

Genome-wide screening in late-onset AD

As outlined above, GWAS have substantially reshaped the landscape of genetics research of common diseases, including AD, during the course of only a few years. At the time of writing (December 2010), the most promising GWAS findings in AD relate to the identification of variants in or near *BIN1*, *CD33*, *CLU*, *CR1*, and *PICALM* whose status as novel AD risk loci can now be considered established based on extensive independent replication data (Table 41-1B) (Lambert et al., 2009; Harold et al., 2009). Other potential AD susceptibility loci derived from GWAS, such as *ATXN1*, *EXOC3L2*, *GAB2*, *MTHFD1L* and *PCDH11X* should be considered more provisional until further replication data becomes available (reviewed in Bertram et al., 2010). While fine mapping and biochemical studies are still needed to identify the actual sequence variants underlying the observed genetic associations and to confirm and characterize their presumed molecular effects, nearly all of the newly reported GWAS loci have been proposed to be linked to Aβ metabolism in one or more ways (Table 41-1B). In particular, this relates to Aβ aggregation or clearance of Aβ from the brain either directly or indirectly, e.g., via effects on the immune response to Aβ-related toxicity. However, these potential, Aβ-centered functional connections are still preliminary in most instances, and further research is needed to clarify whether or not other pathways are affected by these loci. Furthermore, it can be expected that several additional AD susceptibility variants will be identified in future genome-wide efforts using higher-density microarrays in combination with substantially increased sample sizes. It remains to be seen whether these findings will reveal hitherto unrecognized, novel pathogenic mechanisms beyond those related to the metabolism of APP and Aβ. An up-to-date overview on the status of these and other potential AD candidate genes, including meta-analyses across published genetic association studies, can be found at the Alzheimer Research

TABLE 41-2A Genes Causing Mendelian Forms of Parkinson's Disease

Gene	Protein	Location	Inheritance	Proposed molecular effects/pathogenic relevance
LRRK2	leucine-rich repeat kinase 2	12q12	dominant	mishandling of α-synuclein
PARK2	parkin (E3 ubiquitin protein ligase)	6q25	recessive	proteasomal and lysosomal degradation; mitochondrial dysfunction
PARK7	DJ-1	1p36.23	recessive	oxidative stress; proteasomal degradation
PINK1	PTEN induced putative kinase 1	1p36	recessive	proteasomal and lysosomal degradation; mitochondrial dysfunction
SNCA	α-synuclein	4q21	dominant	aggregation of α-synuclein; neurotransmitter release and vesicle turnover

For an up-to-date overview of these and other potential Mendelian PD genes see the Parkinson's disease mutation database at http://www.molgen.ua.ac.be/pdmutations/. Note that mutations in other genes have also been proposed to cause familial forms of PD, albeit with inconclusive evidence (see text for more details).

Forum genetic database maintained by our group, "AlzGene" (URL: http://www.alzgene.org) (Bertram et al., 2007).

PARKINSON'S DISEASE

Parkinson's disease (PD) is the second most common neurodegenerative disease of adult onset and shows an increased prevalence with age (Chapter 47). Histopathologically, it is characterized by a severe loss of dopaminergic neurons in the substantia nigra and cytoplasmic inclusions in the remaining neurons, consisting of insoluble protein aggregates (Lewy bodies). Clinically, PD is characterized by a progressive movement disorder including the cardinal signs of resting tremor, bradykinesia, rigidity, and postural instability, with an initially good response to dopamine-replacement treatment. Although the heritability—and thus the contribution of genetic factors to the overall prevalence of PD—is likely smaller than that of AD, genetic research has played a major role in elucidating the potential causes of nigrostriatal neuronal loss in PD and other forms of parkinsonism. Similar to AD, there appears to be a dichotomy of rare monogenic forms versus common, genetically complex forms which are likely caused by an interplay of multiple environmental and genetic factors.

Autosomal-dominant forms of PD

As in AD, the first PD-causing mutations to be identified are located in the gene (*SNCA*; protein α-synuclein) that encodes the major constituent of one of the classic neuropathological hallmarks of PD (Polymeropoulos et al., 1997). α-synuclein is a small presynaptic protein that modulates neurotransmitter release and vesicle turnover (Abeliovich et al., 2000). Aggregated α-synuclein is at the core of Lewy bodies, round eosinophilic intraneuronal inclusion bodies that are typically found in affected brain regions of PD patients. *SNCA* point mutations result in a rare, early-onset form of PD often accompanied by cognitive dysfunction. To date, three autosomal-dominant missense mutations in *SNCA* (A53T, A30P, and E46K) have been described in a handful of families worldwide (Table 41-2A; for an up-to-date overview of these and other PD-causing mutations see the Parkinson Disease Mutation database at http://www.molgen.ua.ac.be/PDmutDB/) (Nuytemans et al., 2010). It has been hypothesized that these mutations increase the tendency of the protein to form oligomers, fibrils and eventually fibrillary aggregates, although the exact mechanisms underlying α-synuclein toxicity are currently only incompletely understood (Gasser, 2009). Interestingly, an overexpression of the wild-type protein due to duplications and triplications of the *SNCA*-containing chromosomal region also causes autosomal-dominant PD (Singleton et al., 2003), similar to *APP* locus duplications, which can cause early-onset Alzheimer's disease with cerebral amyloid angiopathy (see above). In addition to these findings in monogenic PD, there is unequivocal support for a role of *SNCA* variation in risk of the complex genetic form of PD from both candidate-gene studies and GWAS (see below).

Autosomal-dominant mutations in a second gene, *LRRK2* (a.k.a. *PARK8* on chromosome 12q12, encoding leucine-rich repeat kinase 2) (Paisán-Ruíz et al., 2004), are the most common cause of monogenic PD. To date, more than 40 different *LRRK2* mutations have been reported as a cause of PD. Only for a few, however, can pathogenicity be considered established based on consistent evidence for co-segregation and functional data (R1441H/C/G, Y1699C, G2019S, I2020T) (for review see Cookson, 2010). All of these mutations lie in the central region of the *LRRK2* protein, including the enzymatic GTPase and kinase domains. Some mutations have been reported to cause an increase in kinase activity (West et al., 2005). This may imply a crucial role for enzymatic activities of the LRRK2 protein in the pathogenic process affecting downstream intracellular signaling pathways rather than other functions, although much remains to be learned about its precise physiological and pathogenic role(s). Similar to *SNCA*, *LRRK2* has several common polymorphisms that exert highly significant risk effects for the complex genetic form of PD (see below).

Autosomal-recessive forms of PD

To date, mutations in three genes have been reported to cause an autosomal-recessive form of PD, clinically

resembling the 'typical' form of PD except for a much earlier disease onset (Table 41-2A). In contrast to the autosomal-dominant mutations outlined above, these recessively transmitted mutations probably result in a loss of function, possibly leading to a decreased protection of dopaminergic neurons against toxic events.

The most frequently mutated gene in autosomal-recessive PD is *PARK2* (protein: parkin; located on chromosome 6q25) (Kitada et al., 1998). Parkin is an ubiquitin ligase that is involved in the ubiquitination of proteins targeted for degradation by the proteasomal system. The spectrum of parkin variants ranges from amino-acid–changing single-point mutations to complex genomic rearrangements and exon deletions (PD Mutation database). It is noteworthy, that—unlike α-synuclein-related PD—Lewy bodies are not regularly found in brains of PD cases bearing homozygous *PARK2* mutations.

In addition to PARK2, autosomal-recessively transmitted mutations have been found in two other genes, *PINK1* (a.k.a. *PARK6*; protein: PTEN induced putative kinase 1) (Valente et al., 2004) and *PARK7* (a.k.a. *DJ1*; protein: Parkinson disease [autosomal recessive, early onset] 7) (Bonifati et al., 2003). However, mutations in these genes are much less common than those in *PARK2*. PTEN-induced putative kinase 1 on chromosome 1p36 is a mitochondrial serine/threonine protein that protects cells against oxidative stress. The majority of the mutations identified to date map into the kinase domain indicating that loss of this activity is responsible for PD pathogenesis (Deas et al., 2009). *PARK7* (*DJ1*) mutations are a rare cause of PD (<1% of early-onset cases (Alcalay et al., 2010). The protein encoded by PARK7 on chromosome 1p36 belongs to the peptidase C56 family, and it has been proposed that it may be involved in the cellular response to oxidative stress and proteasomal inhibition (Martinat et al., 2004), and may possibly act as a redox-sensitive chaperone preventing aggregation of α-synuclein (Shendelman et al., 2004).

In addition to the five established Mendelian PD loci outlined above, a number of other genes have been proposed to cause familial forms of PD (e.g., *UCHL1* [PARK5], *GIGYF2* [PARK11], *OMI/HTRA2* [PARK13]), although the evidence supporting this notion remains unclear at the time of this writing.

Candidate-gene studies and genome-wide screening in PD

Based on findings from early candidate-gene studies, which were later independently confirmed by GWAS, it can now be considered unequivocal that common genetic variants in the Mendelian PD genes *SNCA* and *LRRK2* also increase the risk for idiopathic, non-Mendelian PD (Table 41-2B) (Simón-Sánchez et al., 2009), presumably by similar mechanisms of action (see above). Another highly significant association signal originally described in a candidate-gene setting and subsequently confirmed by GWAS is elicited by polymorphisms in the *MAPT* (protein: microtubule-associated protein tau [τ]) region on chromosome 17q21 (Martin et al., 2001). The signal is located in a chromosomal interval characterized by the presence of a genetically balanced inversion that is common in the Caucasian population. This inversion, which occurred nearly 3 million years ago, results in a region of high intermarker correlation (so called 'linkage disequilibrium' or 'LD') across *MAPT*, producing two extended LD haplotypes, H1 and H2. Consistent evidence of genetic association has been shown in Caucasians for the H1 haplotype with both

TABLE 41-2B Susceptibility Genes for Non-Mendelian Forms of Parkinson's Disease

Gene	Protein	Location	% Risk change‡	Proposed molecular effects/pathogenic relevance¶
BST1†	bone marrow stromal cell antigen 1	4p15	~25%	disruption of calcium homeostasis in dopaminergic neurons
GAK/DGKQ†	unknown*	4p16	~30%	n.a.
GBA	β-glucosidase	1q21	~300	aggregation of α-synuclein
HLA†	major histocompatibility complex, class II	6p21.3	~15%	immune system response
LRRK2	leucine-rich repeat kinase 2	12q12	~200%	mishandling of α-synuclein
MAPT	microtubule-associated protein tau (τ-protein)	17q21.1	~30%	aggregation of α-synuclein (?)
PARK16†	unknown**	1q32	~40%	n.a.
SNCA	α-synuclein	4q21	~40%	aggregation of α-synuclein; neurotransmitter release and vesicle turnover

Only genes/loci showing genome-wide significant ($P \leq 5 \times 10^{-8}$) risk-effects and independent replication are included. For an up-to-date overview of these and other potential susceptibility genes see PDGene database at http://www.pdgene.org.
†Indicates genes/loci originally identified by GWAS.
‡Approximate change in disease risk (increase or decrease) per copy of minor allele as compared to non-carriers of minor allele.
*Selection of proposed effects; note that the functional evidence for these loci is often scarce (see text for more details).
**For these loci, the associated markers map to several genes (see text for details).

PD and related Parkinsonian disorders, such as progressive supranuclear palsy (PSP) or corticobasal degeneration (CBD). Interestingly, in Southeast Asian populations, virtually all individuals are homozygous for the H1 haplotype, which may be why no association between risk for PD and *MAPT* has been reported in these populations to date. Despite the unequivocal role in modifying susceptibility for late-onset PD, *MAPT* does not appear to be involved in causing Mendelian PD, although rare *MAPT* mutations can cause related forms of neurodegeneration, e.g., frontotemporal dementia with parkinsonism (FTDP-17, see below), and a syndrome similar to PSP (Poorkaj et al., 2002).

In addition to *SNCA*, *LRRK2* and *MAPT*, there are at least two other PD susceptibility loci showing compelling evidence of association across a number of studies at the time of writing (December 2010). The first relates to *GBA* (protein: glucocerebrosidase) on chromosome 1q22, which was originally tested as PD risk gene in a candidate gene setting. Recessively transmitted *GBA* mutations cause Gaucher's disease, a lysosomal storage disorder. While affected patients only rarely show parkinsonian symptoms, it was observed that relatives of patients with Gaucher's disease had an increased incidence of PD. Subsequent association studies comparing the prevalence of *GBA* variants in PD cases vs. controls found a number of relatively rare polymorphisms (e.g., L444P, N370S) that very significantly increase the risk for PD (Sidransky et al., 2009). Owing to their low frequency, these polymorphisms are not included in any of the current GWAS arrays and were, therefore, not assessed in any of the hitherto published GWAS in PD (emphasizing the importance of well-designed candidate gene studies even in the "microarray era"). The other novel PD susceptibility locus is located on the tip of the short arm of chromosome 4 (4p16) near the genes *GAK* (protein: cyclin G–associated kinase) and *DGKQ* (diacylglycerol kinase theta) and shows highly significant association with PD risk, predominantly in Caucasian populations (Pankratz et al., 2009), although the precise pathophysiological basis for this association remains to be determined. Additional putative novel PD loci that have emerged from recent GWAS reside on chromosome 1q32 (*PARK16*, encompassing the genes *NUCKS1*, *SLC45A3*, *SLC41A1*, *PM20D1* among others) (Satake et al., 2009), on chromosome 4p15 in *BST1* (encoding bone marrow stromal cell antigen 1) (Satake et al., 2009), and in the HLA-region on chromosome 6p (Hamza et al., 2010). However, more independent data are needed to assess whether these findings will stand the test of time and eventually prove to be genuine PD risk genes. For an up-to-date overview of these and other genetic association signals consult the PDGene database maintained by our group (http://www.pdgene.org).

DEMENTIA WITH LEWY BODIES

According to some authors, dementia with Lewy bodies (DLB) is the second most common type of degenerative dementia in the elderly, possibly accounting for up to 15% of all dementia cases in autopsy samples. Clinically, DLB is characterized by progressive cognitive impairment with fluctuating course, recurrent visual hallucinations and parkinsonism. Although formal clinical criteria have been proposed (McKeith, 2006), there is a pronounced overlap with AD as well as PD with dementia (PDD), both on clinical as well as neuropathological grounds. The predominant histological feature of DLB is the presence of cortical and subcortical Lewy bodies, but many patients with DLB also have AD pathology, i.e., cortical amyloid plaques and neurofibrillary tangles. Conversely, Lewy bodies are also frequently observed in cases of classic AD, including patients with mutations in *APP*, *PSEN1* and *PSEN2*. While a familial aggregation of DLB has been described, the identification of specific DLB genetic factors is aggravated by the still-uncertain phenotypic classification of DLB, in particular its distinction from AD and PDD.

The genetics of DLB shows similarities with both PD and AD

While DLB occurs sporadically in most cases, familial forms have also been reported, suggesting the existence of genetic determinants (Bonifati, 2008). The first gene reported to be involved in DLB was α-synuclein (*SNCA*), which is also a cause of autosomal-dominant PD (see above). *SNCA* point mutations and copy number variants have been repeatedly associated with a number of phenotypes ranging from PD to PD with dementia (PDD) and DLB (Zarranz et al., 2004). From the currently available studies it appears that *SNCA* duplications are mostly involved in typical PD, whereas triplications and higher-order multiplications have been more frequently observed in PDD and DLB. Other established PD genes repeatedly reported to be mutated in DLB include *LRRK2* (Ross et al., 2006) and *GBA* (Goker-Alpan et al., 2006). In contrast to the overlap with PD, evidence for an overlap between DLB and AD genetics is scarcer and currently restricted to two *PSEN1* mutations that manifest in atypical AD cases with concomitant abundant Lewy body pathology. Finally, a genome-wide linkage screen in a multigenerational DLB family from Belgium has revealed a putative DLB-specific locus on chromosome 2q35-q36, although substantial resequencing of the implied chromosomal interval has not yet identified any clearly pathogenic mutations (Bogaerts et al., 2007). Interestingly, this locus partially overlaps with a PD locus that maps slightly distal (*PARK11*), although it currently remains unclear whether these two findings point to the same underlying gene.

In terms of common genetic risk factors responsible for DLB, several lines of evidence point to members of the synuclein gene family, in particular α-, β- and γ-synuclein (*SNCA*, *SNCB*, *SNCG*, respectively) (Nishioka et al., 2010), although sample sizes are collectively too small to reach anything but nominal support for these findings. At the time of writing (December 2010) no GWAS were reported that specifically focused on DLB. Finally, and not surprisingly, a potential association of DLB with *APOE*-ε4 has been observed, but only inconsistently. However, a meta-analysis on case-control studies published between 2000 and 2004 suggested that *APOE*-ε4 does, indeed, lead to a significantly increased risk for DLB (Bang et al., 2003). This would be in agreement with neuropathological data linking *APOE*-ε4 to Lewy-body pathology in AD (Tsuang et al., 2005).

FRONTOTEMPORAL DEMENTIA

Frontotemporal dementia (FTD) is a heterogeneous group of syndromes defined clinically by a gradual and progressive change in behavior and personal conduct and/or by a gradual and progressive language dysfunction. The initial symptoms typically occur without affecting other cognitive domains and rarely present with an onset age beyond 75 years. In some cases, behavioral and language deficits are accompanied by parkinsonism or progressive motor neuron disease. The major neuropathological finding consists of frontotemporal lobar degeneration (FTLD), which is further subdivided based on histochemical staining patterns and, more recently, the predominance of certain molecular abnormalities (Mackenzie et al., 2010). Historically, FTLD subtypes were classified based on the presence of an abnormal accumulation of tau (FTLD-tau) compared with those with tau-negative, ubiquitin-positive inclusions (FTLD-U). However, since patients with amyotrophic lateral sclerosis (ALS, see below) often present with prominent frontal lobe features together with neuropathology resembling FTLD-U, it was proposed that ALS and FTD represent a clinicopathological spectrum of the same underlying disease processes (Mackenzie et al., 2010). This notion was recently supported by histopathological data implicating two proteins, TDP-43 and FUS, showing abnormalities across both diseases. These exciting molecular commonalities have led to substantial (and still ongoing) reclassifications of both syndromes based on neuropathological and histochemical grounds, which will only be touched upon here (See Table 41-3A).

Genetic determinants of tau-positive FTLD

The first causal mutations in any of the FTD syndromes were found in families suffering from FTD with parkinsonism linked to chromosome 17 (FTDP-17) (Hutton et al., 1998). The mutations causing this subtype are located in the *MAPT* gene (Table 41-3A), located in an FTDP-17 linkage region on chromosome 17q21 near *MAPT*. Currently, there are over 40 known *MAPT* mutations in more than 100 families worldwide, the majority of which are located between exons 9 and 13 (AD & FTD Mutation database; http://www.molgen.ua.ac.be/ADMutations/). Molecular genetic studies could show that the biochemical consequences of the various *MAPT* mutations on the protein level are quite diverse, including reducing or increasing the binding of τ-protein to microtubules, enhancing τ aggregation, and affecting the ratio of the specific τ-isoforms (i.e., towards an increased ratio of 4-repeat vs. 3-repeat isoforms) by affecting alternative splicing (reviewed in Ingelsson & Hyman, 2002). Interestingly, it appears that *MAPT* mutations almost exclusively lead to FTD with immunohistochemical evidence of both 3- and 4-repeat tau, while classic Pick's disease (PiD), one clinical manifestation of FTD that typically lacks the 4-repeat isoform, has not yet been conclusively linked to *MAPT* or any other genetic defect (Morris et al., 2002; Mackenzie et al., 2010). The correlation between 4-repeat tau and genetic variants in *MAPT* is further supported by genetic association studies showing almost unanimous support for a *MAPT* risk haplotype (H1) in samples with PSP or CBD, both characterized by the abundance of 4-repeat tau, but no evidence of association with PiD. Note, that this is the same haplotype that has also frequently been associated with PD (see above), possibly suggesting common and as yet uncharacterized τ-related pathogenic mechanisms between FTD and late-onset PD, and/or the presence of substantial heterogeneity within the commonly defined late-onset PD samples.

Genetic determinants of tau-negative FTLD

Recent molecular work has suggested that the predominant pathological protein in τ-negative FTLD (and SOD1-negative ALS, see below) is TDP-43 (a.k.a. TAR DNA binding protein; gene: *TARDBP*) (Neumann et al., 2006). TDP-43 is a highly conserved and widely expressed DNA/RNA binding protein that is involved in a number of regulatory cellular functions including regulation of gene transcription and splicing, micro-RNA processing and apoptosis, as well as neuronal plasticity and the maintenance of dendritic integrity. FTD with pathological TDP-43 inclusions represents the most prominent form of τ-negative FTLD, which has since been renamed to FTLD-TDP) (Neumann et al., 2009). Genetically, FTLD-TDP is caused by mutations in a number of different loci. The leading cause are mutations in granulin (gene: *GRN*, a.k.a. progranulin), which is located only ~1.5 Mb proximal of *MAPT* on chromosome 17q21 (Cruts et al., 2006; Baker et al., 2006). The normal function of granulin, a secreted

TABLE 41-3A Genes Causing Mendelian Forms of Frontotemporal Dementia

Gene	Protein	Location	Inheritance	Proposed molecular effects/pathogenic relevance
CHMP2B	chromatin modifying protein 2B	3p11.2	dominant	interference with endosome-lysosome fusion
GRN	granulin	17q21.32	dominant	impairment of neuronal survival; inflammation
MAPT	microtubule-associated protein tau (τ–protein)	17q21.1	dominant	impairment of microtubule assembly and axonoplasmic transport
VCP	valosin-containing protein	9p13.3	dominant	unknown

For an up-to-date overview of these and other potential Mendelian FTD genes see the AD & FTD Mutation database at http://www.molgen.ua.ac.be/admutations/. Note that mutations in other genes have also been proposed to cause familial forms of FTD, albeit with inconclusive evidence (see text for more details).

growth factor that exists in several isoforms, is complex. In the CNS, it is expressed by neurons and microglia leading to the hypothesis that reduced levels of granulin could affect both neuronal survival and CNS inflammatory processes. To date, nearly 70 mutations across over 200 families worldwide have been reported to harbor *GRN* mutations causing FTD (AD & FTD Mutation database). Although the predominant mode of inheritance is autosomal dominant, all *GRN* mutations cause FTD through a haploinsufficiency/loss-of-function mechanism. The majority of mutations are small out-of-frame insertions or deletions, splice-site mutations, or nonsense mutations that introduce a premature termination codon and result in the degradation of the mutant messenger RNA via nonsense-mediated decay. The mechanism by which a loss of progranulin leads to TDP-43 pathology is currently unknown.

Other, less common genetic causes of FTLD-TDP are linked to mutations in the valosin-containing protein gene (*VCP*), where FTD is often accompanied by inclusion body myopathy and Paget's disease (Watts et al., 2004). Currently, just over a dozen different VCP mutations have been identified in ~40 families worldwide, including some ALS (see below) families (AD & FTD Mutation database). Another FTLD-TDP–linked locus is located on chromosome 9p13.2-p21.3, predominantly in families in which FTD co-occurs with ALS (Morita et al., 2006). Interestingly, the telomeric portion of the implied interval overlaps with a region recently identified to harbor a common risk factor for sporadic ALS identified by GWAS (see below), although it remains to be determined whether or not these two signals point to the same underlying locus. More recently, genome-wide screening of ~500 mostly sporadic cases of FTLD-TDP revealed strong evidence for the presence of an FTD locus on chromosome 7p, near transmembrane protein 106B (gene: *TMEM106B*), when compared to ~2,500 unaffected control individuals (Van Deerlin et al., 2010) (Table 41-3B). Initial functional genetic evidence published in the original GWAS suggests that the associated alleles may increase expression of *TMEM106B* mRNA. Finally, it is interesting to note that mutations in the TDP-43 gene itself (*TARDPB*) only appear to only be a rare cause of FTLD-TDP, but in fact represent one of the most frequently mutated loci underlying familial ALS (see below).

Up to 20% of tau-negative FTLD cases present without TDP-43 pathology and are clinically characterized by an atypical behavioral variant of FTD with only little familial clustering, the majority of which belong to the FTLD-FUS type (Mackenzie et al., 2010). Neurohistochemically, FTLD-FUS cases are characterized by the presence of insoluble inclusions immunoreactive for FUS (fused in sarcoma; gene: *FUS*). The *FUS* gene encodes a multifunctional protein component that, like TDP-43, is involved in DNA/RNA binding, although its precise function remains only poorly understood. While mutations in *FUS* are a major cause of familial ALS (see below), it remains doubtful whether *FUS* mutations also cause FTLD-FUS without ALS. Finally, another rare form of tau-negative, TDP-43-negative FTLD, termed FTLD-UPS, is caused by mutations in chromatin modifying protein 2B (gene: *CHMP2B*), following initial linkage evidence to the gene-containing region on chromosome 3 in a large Danish pedigree (Skibinski et al., 2005). To date, only four *CHMP2B* mutations across four independent families are reported to confer a clear pathogenic role (AD & FTD Mutation database). *CHMP2B* encodes a component of the heteromeric endosomal-sorting complex required for transport III (ESCRT-III complex), which functions in the recycling or degradation of cell surface receptors. Recently, it was proposed that mutant *CHMP2B* may interfere with endosome–lysosome fusion, which is required for neuronal function (Urwin et al., 2010). As with FTLD-TDP and FTLD-FUS, there also appear to be forms of ALS that can be caused by mutations in *CHMP2B* (Cox et al., 2010).

TABLE 41-3B Susceptibility Genes for Non-Mendelian Forms of Frontotemporal Dementia

Gene	Protein	Location	% Risk change‡	Proposed molecular effects/ pathogenic relevance¶
TMEM106B†	transmembrane protein 106B	7p21.3	~60%	unknown

Only genes/loci showing genome-wide significant ($P \leq 5 \times 10^{-8}$) risk-effects and independent replication are included.
†Indicates genes/loci originally identified by GWAS.
‡Approximate change in disease risk (increase or decrease) per copy of minor allele as compared to non-carriers of minor allele.

AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS; also known as Lou Gehrig's disease) is characterized by a rapidly progressive degeneration of motor neurons in the brain and spinal cord that ultimately leads to paralysis and death usually within one to five years (Chapter 45). The prevalence of ALS overall is low (~5/100,000), but incidence increases with age, showing a peak between 55 and 75 years. Neuropathological features of ALS include loss of motor neurons, the presence of ubiquitin-positive inclusions in the remaining motor neurons, and deposition of pathological TDP-43 aggregates. As outlined above, TDP-43 is also a pathologic hallmark in certain forms of FTD, which has led to the conclusion that ALS and FTD belong to the same clinicopathological spectrum of diseases. Along these lines, cognitive impairment and dementia co-occur with ALS in at least 10% of the cases.

Familial ALS

Familial ALS (FALS) is observed in ~5–10% of all cases with a predominantly autosomal-dominant pattern of inheritance (Tables 41-4A, 4B). At least 10 different loci (ALS1–10) have been suggested to cause a 'pure' ALS phenotype by genetic linkage, and disease-causing mutations have been described for seven of these (*SOD1* [ALS1], *Alsin* [ALS2], *SETX* [ALS4], *FUS* [ALS6], *VAPB* [ALS8], *ANG* [ALS9] and *TARDBP* [ALS10]) (reviewed in Valdmanis et al., 2009). Furthermore, a recent report implicated mutations in *VCP* on chromosome 9p13 (encoding valosin-containing protein) as an autosomal-dominant cause for ALS (Johnson et al., 2010); although this finding awaits further validation. Mutations in

the zinc copper superoxide dismutase gene (*SOD1* on chromosome 21q22) account for approximately 15–20% of familial ALS cases (Rosen et al., 1993). The *SOD1* protein catalyzes the conversion of superoxide radicals into hydrogen peroxide. Most of the more than 100 known *SOD1* mutations distributed throughout the gene (for an up-to-date list see the Amyotrophic Lateral Sclerosis Online Genetics Database at http://alsod.iop.kcl.ac.uk/) are inherited in an autosomal-dominant fashion, although one mutation (D90A) can act both dominantly and recessively (Andersen et al., 1995). The latter mode of inheritance was mainly observed in Scandinavian countries, a geographic region generally showing increased ALS incidence rates. Interestingly, abnormal TDP-43 is not present in cases of ALS with *SOD1* mutations. Mutant *SOD1* appears to have toxic properties that act selectively on motor neurons without altering enzymatic properties. However, this selective vulnerability of motor neurons may be modulated by other cell types harboring mutant *SOD1* as well, such as astrocytes, microglia, and macrophages, contributing to disease progression (Julien, 2007). The exact mode of action of mutant *SOD1* remains unclear; multiple possibly interrelated mechanisms have been postulated including toxic intracellular aggregation of mutant *SOD1*, oxidative damage, mitochondrial dysfunction, RNA binding and destabilization, alterations in axonal transport, growth factor deficiency, and glutamate excitotoxicity (for review see Rothstein, 2009).

In addition to *SOD1*, dominant mutations have recently been identified in *TARDBP* (a.k.a. *ALS10*) (Kabashi et al., 2008; Sreedharan et al., 2008), which encodes for the TAR DNA binding protein which found as a component of cytoplasmic inclusion bodies in pathological studies of patients with ALS (Neumann et al., 2006) and FTD (see above). More than 30 mutations have been described to date, mostly causing a 'typical' ALS phenotype without cognitive deficits. The protein seems to be cleaved in a disease-specific manner. Most of the identified mutations in *TARDBP* are located at the C-terminal domain, the majority of which are predicted to increase phosphorylation of TDP-43 (Kabashi et al., 2008). Curiously, while wild-type TDP-43 is mainly localized in the nucleus, mutant TDP-43 is redistributed to the cytoplasm, partly forming the above-mentioned aggregates (Lagier-Tourenne et al., 2010).

Cytoplasmic redistribution has been described for another Mendelian ALS gene, *FUS* on chromosome 16p11 (Vance et al., 2009; Kwiatkowski et al., 2009). FUS also shows other

TABLE 41-4A Genes Causing Mendelian Forms of Amyotrophic Lateral Sclerosis

Gene	Protein	Location	Inheritance	Proposed molecular effects/pathogenic relevance
ALS2	amyotrophic lateral sclerosis 2	2q33.1	recessive	endosome/membrane trafficking
ANG	angiogenin	14q11.1	dominant	effect on rRNA transcription
FUS	fused in sarcoma	16p11.2	both	RNA processing; formation of inclusion bodies
SETX	senataxin	9q34.13	dominant	DNA and RNA processing
TARDBP	TAR DNA binding protein (TDP-43)	1p36.22	dominant	RNA processing; formation of inclusion bodies
SOD1	superoxide dismutase 1	21q22.11	both	toxic aggregation of SOD1; oxidative damage; mitochondrial dysfunction; RNA destabilization; impairment of axonal transport; glutamate excitotoxicity
VAPB	VAMP (vesicle-associated membrane protein)-associated protein B and C	20q13.33	dominant	vesicle trafficking

For an up-to-date overview of these and other potential Mendelian ALS genes see the ALSod database at http://alsod.iop.kcl.ac.uk. Note that mutations in other genes have also been proposed to cause familial forms of ALS, albeit with inconclusive evidence (see text for more details).

TABLE 41-4B Susceptibility Genes for Non-Mendelian Forms of Amyotrophic Lateral Sclerosis

Gene	Protein	Location	% Risk change‡	Proposed relevance to ALS pathogenesis¶
GWA_9p21.2†	unknown*	9p21.2	~25%	n.a.
UNC13A†	unc-13 homolog A (*C. elegans*)	19p13.11	~20%	synaptic vesicle priming

Only genes/loci showing genome-wide significant ($P \leq 5 \times 10^{-8}$) risk-effects and independent replication are included. For an up-to-date overview of these and other potential susceptibility genes see the ALSGene database at http://www.alsgene.org.
†Indicates genes/loci originally identified by GWAS.
‡Approximate change in disease risk (increase or decrease) per copy of minor allele as compared to non-carriers of minor allele.
*For this locus, the associated markers map to no known genes (see text for details).
¶Selection of proposed effects, note that the functional evidence for these loci is often scarce (see text for more details).

notable structural and functional similarities with TDP-43, and is also found in brains of FTD patients (see above). The encoded protein (fused in sarcoma) was initially reported to form a fusion protein caused by chromosomal translocations in human cancer. Similar to those in *TARDBP*, most of the 30 described mutations to date are located in the C-terminal part of the protein. A nuclear localization signal is likely to reside in this domain; however, whether the mutations disrupt this signal and thereby cause the observed redistribution to the cytoplasm remains to be elucidated. Interestingly, inclusion bodies in ALS caused by *FUS* mutations are immunoreactive for the FUS protein but not TDP-43, suggesting that the pathomechanism of ALS in these patients is independent from TDP-43 relocalization (Vance et al., 2009). Except for one mutation (H517Q) that causes autosomal-recessive ALS, all mutations show autosomal-dominant inheritance, some with only incomplete penetrance (Lagier-Tourenne et al., 2010). Both *TARDBP* and *FUS* protein structures are very similar to a family of heterogeneous ribonucleoproteins (hnRNPs) that affect multiple levels of RNA processing, such as transcription, splicing, transport and translation. The fact that both mutated proteins show nuclear clearance suggests that at least part of the underlying pathobiology may be attributed to loss of nuclear function.

Other dominantly acting ALS mutations have been identified in the following three genes: *SETX* (ALS4) on chromosome 9q34 encoding senataxin, which contains a C-terminal DNA/RNA helicase domain suggesting involvement in DNA and RNA processing (Chen et al., 2004); *VAPB* (ALS8) (Nishimura et al., 2004) on chromosome 20q13 encoding VAMP (vesicle-associated membrane protein)-associated protein B and C), a type IV membrane protein found in plasma and intracellular vesicle membranes that may be involved in vesicle trafficking; and *ANG* (Greenway et al., 2006) on chromosome 14q11 encoding angiogenin, a member of the pancreatic ribonuclease A superfamily that is involved in rRNA transcription and protein translation. Furthermore, autosomal-recessive mutations have been described in *ALS2* (a.k.a. alsin) (Hadano et al., 2001) on chromosome 2q33 encoding 'amyotrophic lateral sclerosis 2', a guanine nucleotide exchange factor that may affect endosome/membrane trafficking. Mutations in these genes are less common than mutations in *SOD1*, *TARDBP* and *FUS*. However, it is remarkable that all of the currently known ALS genes appear to be involved either in DNA and/or RNA processing (*SOD1*, *TARDBP*, *FUS*, *SETX* and *ANG*) or in vesicle trafficking (*VAPB*, *ALS2*).

Most ALS cases do not show clear family segregation and are believed to suffer from a genetically complex form of the disease, a situation similar to many other neurodegenerative diseases (e.g., AD, PD, FTD; see above). These forms are often referred to as "sporadic ALS" or "SALS." While association studies using a candidate gene design have not led to the identification of any established genetic risk factors for SALS, recent GWAS have shown compelling evidence for risk effects conferred by at least two loci. The first signal is located in a 'gene desert' on chromosome 9p21.2 (van Es et al., 2009; Laaksovirta et al., 2010; Shatunov et al., 2010), close to a region also implicated by linkage studies in multiplex FTD families (see above). The other signal maps within *UNC13A* on chromosome 19p13 (van Es et al., 2009; Chiò et al., 2009) and encodes a presynaptic protein with an essential role in synaptic vesicle priming (Rossner et al., 2004). Despite the potentially compelling functional implication of this protein in ALS pathogenesis, it should be noted that the additional studies are needed to exclude the possibility that the association signal originates from another locus nearby. For an up-to-date overview of these and other genetic association signals consult the ALSGene database maintained by our group (http://www.alsgene.org).

NEURODEGENERATIVE TRIPLET REPEAT DISORDERS

Triplet repeat disorders are characterized by three base-pair nucleotide repeats that lie in either coding or non-coding regions and give rise to a multitude of different phenotypes that are inherited in an autosomal-dominant, recessive or X-linked fashion (Chapter 48). The nucleotide triplets are inherently unstable and the number of repeats tends to increase ("expand") across consecutive generations, especially following paternal transmission. This can lead to a decrease in onset age of the particular disease, a phenomenon described as "anticipation." The molecular basis of repeat instability is not well understood, but the presence of pathogenic triplet repeats gives rise to a variety of neurological and developmental disorders, such as Huntington's disease, spinocerebellar ataxias and fragile X syndrome (Chapter 59). Neurodegenerative triplet-repeat disorders are all caused by coding poly-CAG expansions, which are translated into an elongated polyglutamine (polyQ) tract. Although most of these proteins do not share any homology aside from polyQ, several salient features are shared by the CAG repeat disorders. For instance, they generally strike in midlife and cause increasing neuronal dysfunction and eventual neuronal loss ~10 to 20 years after onset of symptoms. Furthermore, it is most likely that all polyQ repeats confer a gain of function when they are pathologically expanded, and probability for pathogenic effects increases with the length of uninterrupted repeats until it reaches full penetrance at a certain threshold that is different across the specific diseases. Finally, despite the widespread expression of all currently known genes throughout the brain and other tissues, only a certain subset of neurons is vulnerable to dysfunction in each of the various diseases. In the remainder of this section we will discuss the genetics underlying Huntington's disease as an example of a neurodegenerative triplet-repeat disorder leading to dementia.

Huntington's disease (HD)

HD is caused by neuronal dysfunction and degeneration of neurons in the basal ganglia followed by cortical regions, leading clinically to involuntary movements (chorea), psychiatric symptoms and dementia. Mean age of onset is 40 years, with death occurring 15–20 years from disease onset. Its prevalence is similar to that of ALS, but much less than that of most of the other dementing illnesses discussed above. Approximately 90% of HD cases are hereditary and transmitted in an autosomal-dominant fashion. The other 10% are considered "de novo," i.e., these cases originate from asymptomatic parents with normal repeat lengths that have expanded to symptomatic range

(see below). HD is caused by a CAG repeat in exon 1 of *HTT* (protein: huntingtin, located on chromosome 4q16) (Gusella et al., 1983). As is typical for CAG repeat disorders, HD becomes clinically manifest in the presence of 36 repeats or more, although lengths of 36 to 39 sometimes cause only incomplete penetrance. The mean repeat length in HD patients is 40 to 45, although the variability is quite wide, ranging from 35–120 repeats (Gusella & MacDonald, 1995). Physiologically, huntingtin is mainly localized in the cytoplasm, but it can also translocate into the nucleus, where it may regulate gene transcription. It has also been reported to have a role in vesicle transport and RNA trafficking. Toxic effects of mutant huntingtin may include inhibition of chaperones, proteasomes and autophagy, which may cause accumulation of abnormally folded proteins or interference with gene transcription. Mutant huntingtin has the tendency to undergo conformational changes, e.g., by forming abnormal β-sheet structures. Thus, cellular characteristics in HD postmortem brains consist of large aggregates of huntingtin in neurons, predominantly in the nucleus, but also in the cytoplasm, in dendrites and axon terminals. However, rather than representing the toxic events themselves, these aggregates more likely merely constitute a way for cells to dispose of the more toxic monomeric or oligomeric mutated protein (for a review on the functional implications of huntingtin in HD see Ross & Tabrizi, 2011).

It is well established that repeat length of the polyQ tract shows a strong inverse correlation with onset age. However, only ~50–70% of the inter-individual onset age variation can be explained by triplet number, suggesting the presence of other factors (genetic and nongenetic) that modify onset age. Association studies have proposed a number of genes with a putative role in onset age (e.g., *HAP1*, *GRIK2* and *TCERG1)*; however, none of these findings have been compellingly replicated to date.

CREUTZFELD-JAKOB DISEASE AND OTHER PRION DISEASES

Prion diseases include a rare and heterogeneous spectrum of clinical and histopathological phenotypes, which are unique in the group of neurodegenerative diseases in that they can be inherited (e.g., familial Creutzfeld-Jakob disease [fCJD], fatal familial insomnia [FFI], Gerstmann-Sträussler-Scheinker disease [GSS]); spontaneous (e.g., CJD, sporadic fatal insomnia [sFI]); or acquired by infection (e.g., kuru, iatrogenic CJD, variant CJD) (Chapter 50). Clinical neurodegenerative symptoms typically include progressive motor dysfunction, dementia, and cerebral ataxia. The underlying pathogenic event in prion disease is the conformational change of the cellular prion protein (PrP^{c}) to the pathogenic isoform (PrP^{sc}), followed by misfolding and subsequent aggregation in the central nervous system. In most forms of prion disease, the brain shows characteristic spongiform degeneration and astrogliosis. Transmission of prion diseases via infection does not seem to require nucleic acids, but only the misfolded protein itself that then transmits its altered folding to the wild-type host protein ("protein-only model"). The latter form has drawn considerable interest in recent years due to the increase of variant CJD in the UK, and indications that this form has been transmitted from animals ("bovine spongiform encephalopathies" [BSE]) to humans. Only a relatively small subset of cases with prion disease shows a familial aggregation; notwithstanding this, genetics has played a crucial role in elucidating the molecular mechanisms as well as facilitating the clinical classification of the various subtypes of diseases (Gambetti et al., 2003). In particular, mutations and polymorphisms in the gene encoding PrP (*PRNP*) on chromosome 20p13 are major determinants of disease onset and phenotypic variation of familial prion diseases (Hsiao et al., 1989), but they also appear to affect risk for the spontaneous forms.

PRNP mutations are causal and influence disease progression

The mechanisms by which *PRNP* influences disease outcome are two-fold. First, more than two dozen different amino acid–changing mutations in the coding region of the gene have been identified to cause familial prion diseases, transmitted in an autosomal-dominant fashion with nearly 100% penetrance. There is a remarkable heterogeneity in the sense that different mutations throughout the gene can give rise to a variety of different phenotypes associated with all three familial forms of prion diseases, i.e., fCJD, FFI and GSS (Gambetti et al., 2003). In addition to these point mutations, there are also rare cases of fCJD and GSS caused by variable numbers of octapeptide (i.e., 24-bp) repeats within the coding sequence of the *PRNP* gene. Second, clinical presentation and disease progression are further modified by a common polymorphism at codon 129, leading to a methionine (M) to valine (V) change. Most of the mutated *PRNP* missense alleles are on the same haplotype as the 129 M-allele, which includes virtually all forms of fCJD (Gambetti et al., 2003). In the rare cases where they co-occur with the 129 V-allele, they lead to a distinct clinical phenotype, and in the case of D178N-129M vs. D178N-129V, even to a different disease entity; while the latter haplotype leads to typical fCJD, the former (i.e., M-associated) haplotype represents the only currently known genetic cause of FFI, which presents with a quite distinct clinical picture.

In addition to its effects on familial forms of prion disease, the M129V polymorphism was also found to increase the risk for spontaneous forms of CJD (sCJD) (Palmer et al., 1991). In particular, it was found that the homozygous state for either allele (i.e., M/M or V/V) was disproportionally more frequent in sCJD than the M/V genotype (Palmer et al., 1991; Croes et al., 2004). Furthermore, homozygosity for either allele at this polymorphism leads to a faster disease progression than heterozygosity in nearly all genetic as well as spontaneous (including iatrogenic) forms of prion diseases, and in most instances, the M/M genotype was associated with the most aggressive course of disease (Pocchiari et al., 2004). Interestingly, all individuals thus far known to be affected by the newly described "variant" form of CJD (vCJD), which is characterized by a prion protein isotype resembling that found in BSE, are also exclusively carriers of the M/M genotype (Michalczyk & Ziman, 2007). Only a few other genetic risk factors for the nonfamilial forms of CJD have been investigated, and none of them has shown any noteworthy results to date.

CONCLUDING REMARKS

Although displaying a diverse array of clinical and histopathological characteristics, the neurodegenerative disorders discussed in this chapter share a variety of epidemiologic and genetic aspects. First, with the exception of Huntington's disease, they all feature an etiologic dichotomy with less frequent familial forms on the one hand, and more frequent multifactorial forms on the other. It is possible (and likely) that a substantial number of the hitherto non-familial—appearing cases of neurodegeneration will eventually turn out to originate from specific disease-causing mutations, and that the majority of the remaining seemingly "sporadic" cases will prove to be governed by a variety of different but *bona fide* genetic risk factors (such as *APOE* ε4 in AD). Second, the same genes have been linked to clinically and neuropathologically diverse disease entities. For instance, sequence variants in the τ-gene can cause FTD and significantly increase the risk for PD, and mutations in *VCP* and *TARDBP* have been found in both familial FTD and ALS cases. In addition, common polymorphisms in the *APOE* gene show association with risk for AD, PD and FTD, albeit not always with the same alleles. If confirmed, and not simply caused by imperfectly ascertained and actually heterogeneous disease samples, these findings point to one or several common genetic and mechanistic denominators for neuronal cell death in neurodegenerative diseases. Owing to recent advances in high-throughput genotyping and sequencing technologies, genetic research is likely going to uncover a large number of additional disease-causing and disease-modifying sequence variants over the coming years (e.g., see Box). These discoveries will reshape our understanding of the pathogenic forces driving neurodegeneration and many other human disease conditions. Hopefully, this knowledge will translate into the development of effective early prediction and early treatment strategies, with the prospect of largely decreasing the incidence of these devastating disorders in the not-too-distant future.

EPIGENETIC MODIFICATIONS AND NEUROLOGIC DISEASE

George J. Siegel

The study of *epigenetics* is opening new fields of biomedical research in neurologic function and disease. Epigenetics refers to "modifications [of the genome] that result in heritable changes in gene expression that are independent of changes in the genetic sequence " (Probst et al., 2009). In this process, cells with identical genomes acquire distinct phenotypes, as in normal and abnormal development, cell differentiation, susceptibility to or pathogenesis of disease, neoplasia (Narayan & Dragunow, 2010) and synaptic activity-dependent neuron tagging in long-term memory (Lesburgueres et al., 2011). Both endogenous cellular factors and exogenous environmental factors may induce normal or abnormal regulation of gene expression This essay will point out the central biochemical processes and a few examples with implications for neurologic disease.

Gene expression is dependent on relaxation of the dense chromatin structure or nucleosomes, which consist of a protein core of histone octamers (a tetramer of H3 and H4 and two dimers of H2A and H2B) about which a length of DNA (about 146 base pairs) is wound tightly in two turns "like a thread around a spool" (Alberts, 2007). Modifications of these chromatin, nucleosome and DNA structures through actions of cytoplasmic factors regulate the differential expression of genes. The totality of these cellular factors impacting on the gene has been labeled the 'epigenome' (Qureshi & Mehler, 2010a).

The three levels of reactions modifying gene expression are (1) DNA methylation, (2) modifications of the histone cores, and (3) RNA-based regulatory paths, including noncoding (nc)RNAs such as microinterfering (mi)RNAs. (See Chapter 27 for details of transcription.)

Transfer of methyl groups from S-adenosylmethionine

Transfer of methyl groups from S-adenosylmethionine (SAM) to cytosine in DNA, catalyzed by DNA n-methyltransferases (DNMTs), occurs on cytosine residues in CpG-rich regions of the genome. Cytosine methylation interferes with binding of transcription factors to DNA, which may lead to decreased expression. However, these methylated cytosines also recognize methylCpG-binding proteins (MeCP1 and 2), which may recruit coactivator and/or corepressor factors. Activation or repression of a given gene may thus affect negative or positive transcription factors with respect to other genes (Narayan & Dragunow, 2010; Qureshi & Mehler, 2010b). For example, elevated levels of DNA methylation found in ischemic rodent brain are thought to promote neural cell death.

DNA methylation regulates diverse cellular processes, including genome stability, genomic imprinting and X-chromosome inactivation in females, and these processes are particularly relevant to normal embryologic development and regenerative mechanisms (Qureshi & Mehler, 2010a). The role of methylation in the nervous system is pleiotropic. For example, B12 and folate are essential cofactors for regeneration of methionine, precursor to SAM, and both are essential for normal DNA methylation. Deficiencies of B12 and folate can be factors in depression and other behavioral disorders as well as in producing neural tube defects (see Spina Bifida, see Ch. 28). Dietary supplements of B6, B12 and folate to raise methionine levels and DNA methylation have dramatically reduced the incidence of spina bifida and may be useful in treatment of depression, while their use in treatment of AD gave mixed results (see Narayan & Dragunow, 2010).

Modification of histones within the nucleosome

Modification of histones within the nucleosome occurs at lysines in their N-terminal. Histone modifications on lysines may be acetylation, methylation, phosphorylation, ubiquitination, ADP ribosylation, carbonylation, SUMOylation, glycosylation or biotinylation. These reactions also may have net positive or negative

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effects on expression of a given gene depending on which class of histones is modified and the position of these modifications. There is, in essence, a complex histone code since there are four isoforms, and for the most studied H3 isoform, there are three alleles. For H3 alone, about 150 different modifications have been shown (Garcia et al., 2007).

Histone acetylation and phosphorylation generally facilitate activation of a gene by decreasing attraction between histone and DNA, thereby relaxing nucleosome structure and allowing freer access of transcription factors. Histone phosphorylation adds a negative charge to the molecule, which results in a repulsion between the histone and DNA. Phosphorylation of the histone is itself subject to complex regulation by various protein kinases and phosphatases that are ultimately responsive to extracellular signals.

Histone acetylation of a lysine residue neutralizes its otherwise positive charge, decreases its affinity for DNA and relaxes the nucleosome/chromatin structure. The balance between acetylation and deacetylation derives from the activities of histone acetyl transferase (HAT) and histone deacetylases (HDACs), of which 18 different isoforms are categorized into four classes in human (Mai, 2007). Some HAT and the HDACs act also on cytoplasmic substrates other than histones, such as tubulin (see Ch. 6). Histone acetylation is usually activating; when the gene activator CREB is phosphorylated, it recruits HAT to activate gene transcription, an activating effect that is antagonized by HDAC (see in Ch. 27).

Thus, considerable attention is focused on investigating HDAC inhibitors as potential pharmacologic tools in therapy (Fischer et al., 2010). Frequently used HDAC inhibitors are valproic acid (VPA), trichostatin A, sodium or phenyl butyrate and curcumin, with newer more selective inhibitors continually being introduced. While this research is still in its early stages, some encouraging results have been reported in brain ischemia and traumatic brain injury (see references in Gibson & Murphy, 2010), mouse models of spinocerebellar ataxia 3 (Chou et al., 2011) and Huntington's disease HD (Thomas et al., 2008). VPA has been used in exploratory clinical trials in humans with some positive effects in fragile X syndrome (Torrioli et al., 2010) and X-linked adrenoleukodystrophy (ALD) (Fourcade et al., 2010). In ongoing research, evidence for epigenetic factors at all three levels mentioned above has been found in Alzheimer's disease (Coppede & Migliore, 2010) and in a variety of developmental diseases involving epilepsy in humans, mental retardation, X-linked syndromes, particularly fragile X syndrome, and thalassemia (Qureshi & Mehler, 2010c). The variety of histone isotypes, the diverse array of chemical modifications and the numbers of enzymes involved indicate the complexity in finding specific drugs to target a specific desired effect (Narayan & Dragunow, 2010; Qureshi & Mehler, 2010a; Dietz & Casaccia, 2010).

Microinterfering RNAs

Microinterfering RNAs (miRNA) represent the third class of epigenetic modifiers in the epigenome. They are the best characterized of the ncRNAs. These single-stranded, noncoding RNA segments of 19–25 nucleotides in length are derived in the cytoplasmic processing of noncoding RNA translocated from the nucleus (see Ch. 27). In the cytoplasm, miRNAs interfere with the translation into proteins of many mRNA molecules. Evidence for miRNA-induced dysregulation of gene expression has been described in Tourette's syndrome, fragile X mental retardation, HD, AD and schizophrenia (see Narayan & Dragunow, 2010; Qureshi & Mehler, 2010c for comprehensive reviews). Mutations in mitochondrial ncRNAs are implicated in mitochondrial encephalopathies. Differentially expressed profiles of miRNAs found in ischemic brain correlate with their target mRNAs, suggesting that miRNAs regulate various processes in postischemic brain. For a discussion of the complex subject of RNA-based epigenetic pathways in stroke, see in Qureshi and Mehler (2010b).

Enzymatic aberrations related to polyQ-htt

In HD, a number of enzymatic aberrations related to polyQ-htt (huntingtin) may lead to dysregulation of gene expression (Ch. 48). The long expansions of glutamine residues in polyQ-htt have been reported to sequester and decrease CREB binding protein/HAT activity, thereby decreasing DNA acetylation and CREB activation This conclusion is supported by results of experiments with *Drosophila* (see in Pallos et al., 2008). There is also evidence for increases in transglutamination (TG2) activity induced by the long expansions of glutamine producing increased protein cross-linking transaminations on lysine residues that may interfere with transcriptional regulation (see box, Ch. 48). Buckley, et al. (Buckley et al., 2010) have adduced evidence that levels of BDNF mRNA in cells *in vitro* and in HD mouse model brains are positively responsive to wild type htt but not to polyQ-htt and that BDNF levels are reduced in postmortem HD brain.

The nascent understanding of epigenetic programming is leading to development of new pharmacologic tools for investigating normal and pathologic neurobiological processes as well as for therapy of neurologic disease, such as HD and other neurodegenerative and developmental diseases (Narayan & Dragunow, 2010; Fischer et al., 2010; Qureshi & Mehler, 2010c).

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