# Towards Unveiling the Genetics of Neurodegenerative Diseases

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## ABSTRACT

In addition to sharing several clinical, pathologic, and molecular characteristics, many neurodegenerative disorders show extensive familial histories suggesting a substantial contribution of genetic factors to disease causation and progression. In this review, the authors provide overviews of the status of current genetics research in Alzheimer's disease, Parkinson's disease, frontotemporal dementia, and amyotrophic lateral sclerosis. Across these four disorders alone, nearly 60 different loci can now be considered as established to be involved in pathogenesis for both Mendelian and non-Mendelian disease forms. In addition to reviewing the most compelling of these loci based on current data from genome-wide association studies and next-generation sequencing projects, genes that have been linked to more than one disease entity are emphasized. Such overlapping findings could point to one or several common genetic and mechanistic denominators for neuronal death in neurodegeneration. Unveiling the identity of these and other genetic factors will not only improve our understanding of the underlying pathophysiology, but may also lead to new avenues for preventing and treating these devastating diseases.

**KEYWORDS:** Neurodegeneration, neurodegenerative disease, genetics, mutation, polymorphism, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, frontotemporal dementia, AlzGene, PDGene, ALSGene, genome-wide association study, GWAS, meta-analysis

## GENETIC ASPECTS OF COMMON NEURODEGENERATIVE DISEASES

Many neurodegenerative diseases share several clinical, pathologic, and molecular characteristics.[1] Clinically, these disorders are often represented by an insidious onset during adulthood, after which they progress at varying rates, ultimately leading to severe physical disability or death. Clinical symptoms are often common to more than one disease: dementia is not only a characteristic of Alzheimer's disease (AD) or frontotemporal dementia (FTD), but can also accompany Parkinson's disease (PD) or amyotrophic lateral sclerosis (ALS). Pathologically, neurodegeneration is initially limited to specific types of cells or tissues in the central nervous system (CNS), for example, dopaminergic neurons in the substantia nigra in PD or hippocampal neurons in AD. In later stages, it often extends to other regions of the CNS, frequently leading to substantial macroscopic atrophy. In addition to these alterations, neuronal cell death is often accompanied by widespread inflammation and immune activation. Histopathologically, many neurodegenerative diseases are characterized by deposits of

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misfolded and aggregated proteins.[2] Although some characteristics are considered pathognomonic for the respective clinical phenotypes (e.g., β-amyloid plaques and neurofibrillary tangles for AD), it has been recognized that seemingly identical clinical entities may show a considerable degree of histopathologic heterogeneity (e.g., FTD, see below). On the other hand, a considerable number of histopathologic characteristics are shared across different clinical entities (e.g., the aggregation of hyperphosphorylated tau [τ] protein in AD and FTD, or the accumulation of transactivating responsive sequence DNA binding protein [TDP-43] in FTD and ALS).

In addition to these features, many neurodegenerative disorders show an extensive family history suggesting a substantial contribution of genetic factors to disease causation and progression. Furthermore, the neurodegenerative diseases discussed in this review—AD, PD, FTD and ALS—show rare and familial (following Mendelian inheritance) versus more common and seemingly nonfamilial (not following Mendelian inheritance) disease forms.[1] The latter are also frequently described as "sporadic"," although this terminology is oversimplistic because a large proportion of these cases are likely also substantially controlled by genetic factors. Based on the clinical and pathologic commonalities observed across apparently distinct neurodegenerative clinical syndromes, the question arises whether or not certain neurodegenerative diseases also share some of their underlying genetic defects. In this review, we provide overviews of the status of current genetics research in AD, PD, FTD, and ALS, and place particular emphasis on genes that have been linked to more than one disease entity.

## CURRENT TECHNOLOGIES TO STUDY THE GENETICS OF NEURODEGENERATION

During recent years, genetics research has seen some spectacular advances due to the advent of massively parallel genotyping and sequencing techniques. These techniques now allow researchers to interrogate the genomes of increasingly large numbers of subjects at varying degrees of resolution. These advances come after three decades of small-scale, low-resolution, so-called candidate gene association studies which have yielded only few results that continue to hold.[3] Since 2005, the genetics community has seen a deluge of genome-wide association studies (GWAS), including several dozen for the neurodegenerative disorders covered in this review. Although the success rate still varies from study to study, several 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)—those occurring with a frequency greater than ~1% in the general population. It is likely, however, that some of the genetic liability underlying common polygenic disorders is actually conferred by rare sequence variants—those <<1% frequency in the general population.[4] De novo identification of these rare variants requires actual resequencing in affected patients, which can now be achieved using novel, massively parallel (next-generation) sequencing technologies. These can reliably measure both common and rare sequence changes, allowing for the first time in the history of genetics research the study of whole genomes at base-pair resolution. This approach has already led to several breakthrough discoveries recently,[5–7] and can be expected to become the mainstay of human genetics research over the next decade.

## GENETICS OF ALZHEIMER'S DISEASE

Alzheimer's disease is the most common form of age-related dementia and one of the most serious health problems in the industrialized world. Histopathologically, it is characterized by the accumulation of extracellular β-amyloid (Aβ) deposits and intraneuronal neurofibrillary tangles containing hyperphosphorylated τ-protein 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.

Mendelian forms of AD represent only a small fraction of all AD cases (≤5%), and often present with onset ages prior to the completion of the sixth decade (early-onset familial AD [EOFAD]). To date, more than 200 disease-causing mutations in three genes (*APP*, *PSEN1*, and *PSEN2*) have been described that show autosomal dominant transmission within affected families (Table 1; for an up-to-date summary of AD mutations consult the AD & FTD Mutation database, http://www.molgen.ua.ac.be/ADMutations).[8]

**Table 1 Established Mendelian Genes for Alzheimer's Disease**

| Gene | Protein | Location | Inheritance | Proposed Molecular Effects/Pathogenic Relevance |
|---|---|---|---|---|
| *APP* | β-amyloid precursor protein | 21q21.3 | dominant | Increase in Aβ production or $A\beta_{42}/A\beta_{40}$ ratio |
| *PSEN1* | presenilin 1 | 14q24.2 | dominant | Increase in $A\beta_{42}/A\beta_{40}$ ratio |
| *PSEN2* | presenilin 2 | 1q42.13 | dominant | Increase in $A\beta_{42}/A\beta_{40}$ ratio |

Note. For an up-to-date overview of these genes, see the AD & FTD mutation database (http://www.molgen.ua.ac.be/admutations).[8]

Although these AD-causing mutations occur in three genes located on three different chromosomes, they all share a common biochemical pathway. 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 the transmembrane protein APP by two enzymatic events, β-and γ-secretase cleavage. The discovery that the presenilins, encoded by *PSEN1* and *PSEN2*, represent the catalytic subunits of the enzymatic complex responsible for γ-secretase cleavage of APP provided the essential connection between the occurrence of disease-causing mutations in these genes and the increase in Aβ production observed in the brains of autopsied AD patients.[9]

Non-Mendelian forms of AD represent the vast majority of all cases (>95%), typically presenting with an onset age ≥65 years (late-onset AD [LOAD]). Although segregation and twin-studies conclusively suggest a major role of genetic factors in this form of AD,[10] until the advent and application of genome-wide screening technologies, only one such non-Mendelian AD gene had been *established*, the ε4 allele in *APOE* (Table 2). The risk effect of *APOE*-ε4 had been consistently 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.[11] Even after the completion of over a dozen GWAS in AD, *APOE*-ε4 (or genetic markers highly correlated with it) remains the single most-important genetic risk factor for AD, both in terms of effect size and statistical significance. However, despite its long known and well-established genetic association, its biochemical mechanisms in AD pathogenesis are not yet fully understood.

As outlined above, GWAS have substantially reshaped the landscape of genetics research during the course of only a few years. In AD, more than three dozen GWAS and other large-scale association studies have highlighted nearly 50 putative novel risk genes besides *APOE*.[12] To date, polymorphisms in or near the following loci can be considered as *established* non-Mendelian AD risk factors: *ABCA7*, *BIN1*, *CD2AP*, *CD33*, *CLU*, *CR1*, *MS4A4E*, *MS4A6A*, and *PICALM* (Table 2). They can be considered *established* because they contain at least one polymorphism displaying genome-wide significant association at $P$ values $\leq 5 \times 10^{-8}$ in meta-analyses across all currently available data, and show consistent replication across datasets not included in the original GWAS in regard to effect size direction (see the AlzGene database for more details, http://www.alzgene.org).[13] Although 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, many of the newly established GWAS loci have been proposed to be linked to Aβ metabolism in one or more ways (e.g., *APOE*, *BIN1*, *CR1*, *PICALM*), lipid metabolism (*ABCA7*, *APOE*), or inflammation (*CD33*, *CLU*, *CR1*). 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 AlzGene database.[13]

## GENETICS OF PARKINSON'S DISEASE

Parkinson's disease is the second most common neurodegenerative disease of adult onset and shows an increased prevalence with age. 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).

**Table 2 Established Susceptibility Loci for Alzheimer's Disease**

| Gene/Locus | Protein | Location | Polymorphism | # Subjects | OR (95% CI) |
|---|---|---|---|---|---|
| *ABCA7* | ATP-binding cassette, subfamily A, member 7 | 19p13.3 | rs3764650 | 60,569 | 1.23 (1.18–1.28) |
| *APOE* | Apolipoprotein E | 19q13.32 | rs429358 (ε4) | 7,304 | 3.81 (3.37–4.30) |
| *BIN1* | Bridging integrator 1 | 2q14.3 | rs744373 | 49,650 | 1.17 (1.13–1.20) |
| *CD2AP* | CD2-associated protein | 6p12.3 | rs9349407 | 35,840 | 1.12 (1.08–1.16) |
| *CD33* | CD33 molecule (siglec 3) | 19q13.41 | rs3865444 | 37,767 | 1.12 (1.08–1.16) |
| *CLU* | Clusterin | 8p21.1 | rs11136000 | 72,432 | 1.14 (1.11–1.17) |
| *CR1* | Complement component (3b/4b) receptor 1 | 1q32.2 | rs3818361 | 47,052 | 1.17 (1.14–1.21) |
| *MS4A4E* | Membrane-spanning 4-domains, subfamily A, member 4E | 11q12.2 | rs670139 | 64,577 | 1.08 (1.05–1.11) |
| *MS4A6A* | Membrane-spanning 4-domains, subfamily A, member 6A | 11q12.2 | rs610932 | 63,026 | 1.11 (1.07–1.14) |
| *PICALM* | Phosphatidylinositol binding clathrin assembly protein | 11q14.2 | rs3851179 | 65,711 | 1.14 (1.11–1.17) |

CI, confidence interval; OR, allelic summary risk odds ratio (i.e., the increase of the odds of getting the disease per additional risk allele after combining all available data).
Note. Only genetic loci showing genome-wide significant ($P \leq 5 \times 10–8$) risk-effect estimates upon random-effects meta-analysis on the AlzGene database (http://www.alzgene.org)[13] are listed. Note that results details are for Caucasian populations only.

**Table 3 Established Mendelian Genes for Parkinson's Disease**

| Gene | Protein | Location | Inheritance | Proposed Molecular Effects/Pathogenic Relevance |
|---|---|---|---|---|
| *EIF4G1* | eukaryotic translation initiation factor 4 gamma, 1 | 3q27.1 | Dominant | Impaired mRNA translation initiation, altered oxidative stress response by mitochondrial dysfunction |
| *LRRK2* | Leucine-rich repeat kinase 2 | 12q12 | Dominant | Mishandling of α-synuclein, reduction of neurite outgrowth, alteration of endosomal trafficking |
| *PARK2* | Parkinson protein 2 (parkin, E3 ubiquitin protein ligase) | 6q26 | Recessive | Impaired proteasomal and lysosomal degradation; mitochondrial dysfunction |
| *PARK7* | Parkinson protein 7 (DJ1) | 1p36.23 | Recessive | Oxidative stress; impaired proteasomal degradation |
| *PINK1* | PTEN-induced putative kinase 1 | 1p36.12 | Recessive | Impaired proteasomal and lysosomal degradation; mitochondrial dysfunction |
| *SNCA* | α-synuclein | 4q22.1 | Dominant | Aggregation of α-synuclein; altered neurotransmitter release and vesicle turnover |
| *VPS35* | Vacuolar protein sorting 35 homolog | 16q12 | Dominant | Altered endosomal trafficking and recycling of transmembrane proteins |

Note. For an up-to-date overview of these genes see the Parkinson's disease mutation database (http://www.molgen.ua.ac.be/pdmutations).[14] Note that mutations in additional genes have been proposed to cause Mendelian forms of PD, albeit with hitherto inconclusive evidence.

Mendelian forms of PD show both autosomal dominant and recessive patterns of inheritance (for an overview of the below discussed genes see the PD mutation database, http://www.molgen.ua.ac.be/PDmutDB).[14] The first PD-causing mutations were identified in the gene that encodes the major constituent of Lewy bodies, α-synuclein (gene: *SNCA*; Table 3), a presynaptic protein modulating neurotransmitter release and vesicle turnover. In addition to rare mutations directly causing PD in a small number of families, there is also unequivocal evidence for a role of common *SNCA* DNA variation, i.e. polymorphisms, on risk for non-Mendelian PD (see Table 4 and below). In addition to *SNCA*, autosomal-dominant PD-causing mutations have been found in *LRRK2*, and more recently in *VPS35* and *EIF4G1*. The latter two PD genes were identified following exome sequencing using next-generation technologies in PD multiplex kindreds.[7,15,16] Similar to *SNCA*, there are several common polymorphisms in *LRRK2* that exert highly significant risk effects for non-Mendelian PD (see below).

In contrast to the autosomal-dominant Mendelian PD genes outlined above, 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* (a.k.a. *PRKN*),[17] a ubiquitin ligase that is involved in the ubiquitination of proteins targeted for degradation by the proteasomal system. In addition to *PARK2*, autosomal recessively transmitted, but much less common, mutations have been found in two other genes, *PINK1* and *PARK7* (a.k.a. *DJ-1*). Finally, mutations in several genes have been reported to cause atypical forms of parkinsonism.[18,19]

Non-Mendelian forms of PD show the lowest heritability of all neurodegenerative diseases discussed in this review. Ironically, however, the number of (currently) established susceptibility loci for PD is greater than for all other three disorders combined (Table 4). All but the top four of these (*SNCA*, *MAPT*, *LRRK2*, *GBA*) were identified only recently by GWAS and meta-analysis of various GWAS datasets[20–22]. Of note, many of the PD susceptibility loci recently described by GWAS still contain more than one potential PD candidate gene, so that additional data are needed to assess which of the underlying genes is functionally active. Although also still subject to fine-mapping, the strong association between common variants in the *HLA* locus and PD risk implies a role of the immune system in the disease etiology, similar to what was recently described for AD (see above). For more details and an up-to-date overview of these and other genetic association signals, consult the PDGene database (www.pdgene.org).[23]

Two of the top-ranked non-Mendelian PD susceptibility genes deserve further discussion. The *MAPT* signal is located in an interval on chromosome 17 that in Caucasian populations is characterized by an inversion giving rise to two extended haplotypes, H1 and H2.[24] Of these, H1 is associated with an increased risk for PD, and at least two other related parkinsonian diseases (progressive supranuclear palsy and corticobasal degeneration).[25] Interestingly, virtually all individuals are homozygous for the H1 haplotype in East Asian populations, which may be why no association between risk for PD and variants in *MAPT* has been reported in these populations to date.[26] Despite its strong risk effects in Caucasians, *MAPT* does not appear to be involved in causing Mendelian forms of PD, but have been estab-

**Table 4 Established Susceptibility Loci for Parkinson's Disease**

| Gene/Locus | Protein | Location | Polymorphism | # Subjects | OR (95% CI) |
|---|---|---|---|---|---|
| *ACMSD/TMEM163** | Unknown | 2q21.3 | rs6710823 | 12,815 | 1.40 (1.20–1.63) |
| *BST1* | Bone marrow stromal cell antigen 1 | 4p15.32 | rs11724635 | 32,909 | 1.16 (1.10–1.22) |
| *CCDC62/HIP1R** | Unknown | 12q24.31 | rs12817488 | 16,372 | 1.17 (1.09–1.25) |
| *FAM47E/STBD1** | Unknown | 4q21.1 | rs6812193 | 65,527 | 1.12 (1.08–1.17)* |
| *GAK/DGKQ* | Unknown | 4p16.3 | rs1564282 | 24,708 | 1.29 (1.20–1.38) |
| *GBA* | Glucosidase, β, acid | 1q22 | N370S | 44,851 | 3.51 (2.55–4.83) |
| *GPNMB* | Glycoprotein (transmembrane) NMB | 7p15.3 | rs156429 | 32,028 | 1.12 (1.08–1.16) |
| *GWA_8p22/FGF20* | Unknown | 8p22 | rs591323 | 32,483 | 1.12 (1.08–1.17) |
| *HLA-II** | Major histocompatibility complex, class II | 6p21.32 | chr6:32588205 | 10,756 | 1.33 (1.19–1.48) |
| *LRRK2* | Leucine-rich repeat kinase 2 | 12q12 | rs1491942 | 34,123 | 1.17 (1.13–1.22) |
| *MAPT* | Microtubule-associated protein tau | 17q21.31 | H1/H2 | 48,162 | 1.29 (1.25–1.33) |
| *MCCC1/LAMP3* | Unknown | 3q27.1 | rs11711441 | 33,788 | 1.18 (1.13–1.24)* |
| PARK16 | Unknown | 1q32.1 | rs11012 | 22,213 | 1.26 (1.18–1.34) |
| *SETD1A/STX1B* | Unknown | 16p11.2 | rs4889603 | 31,163 | 1.14 (1.09–1.19) |
| *SNCA* | α-Synuclein | 4q22.1 | rs356220 | 52,974 | 1.30 (1.26–1.35) |
| *SREBF1/RAI1*† | Unknown | 17p11.2 | rs11868035 | See ref.[20] | 1.18 (1.11–1.25)* |
| *STK39* | Serine threonine kinase 39 | 2q24.3 | rs2102808 | 16,839 | 1.28 (1.19–1.38) |
| *SYT11/RAB25* | Unknown | 1q22 | chr1:154105678 | 14,993 | 1.67 (1.41–1.98) |

CI, confidence interval; OR, allelic summary risk odds ratio (i.e., the increase of the odds of getting the disease per additional risk allele after combining all available data).
Note. Only genetic loci showing genome-wide significant ($P \leq 5 \times 10–8$) risk-effect estimates upon random-effects meta-analyses (except where denoted with (*), which are based on fixed-effects analyses) on the PDGene database (http://www.pdgene.org)[22] are listed. Note that results details are for Caucasian populations only.
†Result was extracted from ref. [20], as insufficient data were available on PDGene to perform meta-analyses at the time of writing.

lished as a cause of frontotemporal dementia with parkinsonism (FTDP-17, see below and Table 5). The other noteworthy association relates to *GBA*, which was originally tested in a candidate gene setting (Table 4). Recessively transmitted *GBA* mutations cause Gaucher's disease, a lysosomal storage disorder. Relatives of Gaucher's patients show an increased incidence of PD. Subsequent association studies on the role of *GBA* in PD found several relatively rare polymorphisms (L444P, N370S) that very significantly increase the risk for PD.[27] These polymorphisms are not included on the current GWAS arrays and were thus—unless genotyped separately—not featured in any of the hitherto available PD GWAS.

## FRONTOTEMPORAL DEMENTIA

Frontotemporal dementia is a heterogeneous group of syndromes. The major neuropathologic 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. Historically, FTLD subtypes were classified based on the presence of an abnormal accumulation of tau (FTLD-tau) versus those with tau-negative, ubiquitin-positive inclusions (FTLD-U). However, because patients with 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 clinicopathologic spectrum of the same underlying disease processes.[28] This notion was recently supported by histopathologic data implicating two proteins, TDP-43 and FUS, showing abnormalities across both diseases. These exciting molecular commonalities have led to (still ongoing) reclassifications of both syndromes based on neuropathologic and histochemical grounds, which will only be touched upon here.

### Genetic Determinants of Tau-Positive Frontotemporal Dementia

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). The mutations causing this subtype are located in the *MAPT* gene (Table 5). 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 (for details, see the AD & FTD mutation database, http://www.molgen.ua.ac.be/ADMutations/).[8] Molecular genetic studies show that the biochemical

**Table 5 Established Mendelian Genes for Frontotemporal Dementia**

| Gene | Protein | Location | Inheritance | Proposed Molecular Effects/Pathogenic Relevance |
|---|---|---|---|---|
| *C9ORF72* | Chromosome 9 open reading frame 72 (uncharacterized protein) | 9p21.2 | Dominant | Loss of alternatively spliced C9ORF72 RNA, formation of nuclear RNA foci |
| *CHMP2B* | Chromatin modifying protein 2B | 3p11.2 | Dominant | Interference with endosome—lysosome fusion |
| *GRN* | Granulin | 17q21.31 | Dominant | Impaired neuronal survival; inflammation |
| *MAPT* | Microtubule-associated protein tau (τ-protein) | 17q21.31 | Dominant | Impaired microtubule assembly and axoplasmic transport |
| *VCP* | Valosin-containing protein | 9p13.3 | Dominant | Impaired proteasomal degradation, altered membrane sorting at endosomes/degradation in lysosomes, impaired ER-induced stress response, aggregation of huntingtin |

ER, endoplasmic reticulum.
Note. For an up-to-date overview of these genes, see AD & FTD mutation database (http://www.molgen.ua.ac.be/admutations).[8] Note that mutations in additional genes (such as *FUS* and *TARDBP*) have been proposed to cause Mendelian forms of frontotemporal dementia (FTD), albeit with hitherto less conclusive evidence (see text for more details). *VCP* mutations cause an FTD syndrome associated with inclusion body myopathy and Paget's disease of the bone (see text).

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., toward an increased ratio of 4-repeat vs 3-repeat isoforms) by affecting alternative splicing (reviewed in[29]).

## Genetic determinants tau-negative FTLD

Recent molecular work has suggested that the predominant pathologic protein in τ-negative FTLD (and *SOD1*-negative ALS, see below) is TDP-43.[30] TDP-43 is a highly conserved and widely expressed DNA/RNA binding protein that is involved in several 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. Frontotemporal dementia with pathologic TDP-43 inclusions represents the most prominent form of τ-negative FTLD, which has since been renamed FTLD-TDP. Genetically, FTLD-TDP is caused by mutations in several different loci. The leading cause is an only recently identified hexanucleotid repeat expansion in *C9ORF72*, an open reading frame coding for a still uncharacterized protein on chromosome 9p21 (Table 5).[31,32] The affected region shows more than ~30 repeats in patients as compared to healthy controls. Within affected families, the hexanucleotide repeat is transmitted in an autosomal-dominant fashion. *C9ORF72* repeat expansions have been found in >10% familial FTLD patients and in an even larger fraction of familial ALS patients (20-50%).[31,32] There is also a considerable number of families harboring this mutation and showing a combined FTLD and ALS phenotype, which supports the notion that FTLD and ALS belong to the same continuous disease spectrum. In addition, this new work has shown that a considerable fraction of seemingly "sporadic" FTLD and ALS patients also carry repeat expansions in *C9ORF72*, in line with earlier work implying this region by GWAS in both FTLD[33] and ALS.[34,35] The repeat region is located in a non-coding region of *C9ORF72*, and has been reported to lead to a loss of an alternatively spliced transcript of *C9ORF72*. Furthermore, the expansion leads to a nuclear aggregation of *C9ORF72* mRNA.[30] The second most common form of monogenic FTLD-TDP is caused by mutations in *GRN*, a secreted growth factor located only ~1.5 Mb proximal of *MAPT* on chromosome 17q21. Although their predominant mode of inheritance is autosomal dominant, all currently known *GRN* mutations cause FTLD through a haploinsufficiency/loss-of-function mechanism.[36] A less common genetic cause of FTLD-TDP has been attributed to mutations in *VCP (*Table 5), leading to a syndrome of FTLD associated with inclusion body myopathy and Paget's disease of the bone.[37] Interestingly, a recent study applying whole-exome sequencing also described mutations in *VCP* in ALS kindreds without FTLD symptoms.[6] Another potential FTLD-TDP susceptibility locus was identified in a recent GWAS implying a region on chromosome 7p, near *TMEM106B*[33] (Table 6). Finally, it is interesting to note that mutations in the TDP-43 gene itself (*TARDPB*) appear to be sparse for FTLD-TDP, while they represent a frequent cause of familial ALS (see below).

**Table 6 Proposed Susceptibility Loci for Frontotemporal Dementia**

| Gene/Locus | Protein | Location | Polymorphism | # Subjects | OR (95% CI) |
|---|---|---|---|---|---|
| *TMEM106B* | transmembrane protein 106B | 7p21.3 | rs1990622 | See ref.[32] | 1.64 (1.41–1.89) |

Note. Allelic odds ratio (OR) and 95% confidence intervals (CI) were extracted from ref.[32] Listed is the single locus to show genome-wide significant ($P \leq 5 \times 10^{-8}$) risk-effect estimates in the only frontotemporal dementia genome-wide association studies published to date.[32]

### Genetic Determinants of Other Frontotemporal Dementia Forms

Up to 20% of tau-negative FTLD 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.[38] 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. Although mutations in *FUS* are a major cause of familial ALS (see below), they are rare among FTLD-FUS without ALS. Finally, another rare form of tau-negative, TDP-43-negative FTLD, termed FTLD-UPS, can be caused by mutations in *CHMP2B* (AD & FTD mutation database).[8]

## AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis is characterized by a rapidly progressive degeneration of motor neurons in the brain and spinal cord, which ultimately leads to paralysis and death usually within 1 to 5 years. The prevalence of ALS overall is low (~5/100,000), but incidence increases with age showing a peak between 55 and 75 years. Neuropathologic features of ALS include loss of motor neurons, the presence of ubiquitin-positive inclusions in the remaining motor neurons, and deposition of pathologic 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 clinicopathologic spectrum of diseases.

### Mendelian Forms of Amyotrophic Lateral Sclerosis

Mendelian forms of ALS (familial ALS [FALS]) make up ~5 to 10% of all ALS cases and show predominantly autosomal dominant inheritance. At least 10 different loci (ALS1–10) have been suggested to cause a pure ALS phenotype by genetic linkage, but for many of these, evidence for mutations segregating with the disease has been sparse. Genes with compelling evidence for causing Mendelian ALS include *ALS2*, *ANG*, *C9ORF72*, *FIG4*, *FUS*, *OPTN*, *TARDBP*, *SETX*, *SOD1*, *SPG11*, *UBQLN2*, *VAPB*, and *VCP* (for an overview, see Table 7, and the ALSoD database, http://alsod.iop.kcl.ac.uk/).[39] Twenty to fifty percent of familial ALS cases can now be explained by autosomal-dominant mutations in *C9ORF72* (see above), whereas mutations in the zinc copper superoxide dismutase gene (*SOD1*) only account for ~15 to 20% of Mendelian ALS cases. 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 are inherited in an autosomal-dominant fashion, although one mutation (D90A) can act both dominantly and recessively. 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.

In addition to *SOD1*, dominant mutations have recently been identified in *TARDBP*, which encodes for the TAR DNA binding protein (TDP-43) that was found as a component of cytoplasmic inclusion bodies in pathologic studies of patients with ALS and FTD (see above). More than 30 mutations have been described to date mostly causing a typical ALS phenotype without cognitive deficits (see ALSoD database).[39] 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.[40] Another Mendelian ALS gene, *FUS* on chromosome 16p11, shows several structural and functional similarities with TDP-43, and is also found in brains of FTD patients (see above). The encoded protein, FUS, was initially reported to form a fusion protein caused by chromosomal translocations in human cancer. Similar to *TARDBP*, most of the 30 described mutations to date are located in the C-terminal part of the protein. Except for one mutation (H517Q) that causes autosomal-recessive ALS, all currently known *FUS* mutations show autosomal-dominant inheritance, some with only incomplete penetrance.[41] 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. Very recently, mutations in a

**Table 7 Established Mendelian Genes for Amyotrophic Lateral Sclerosis**

| Gene | Protein | Location | Inheritance | Proposed Molecular Effects/Pathogenic Relevance |
|---|---|---|---|---|
| *ANG* | Angiogenin | 14q11.2 | Dominant | Effect on rRNA transcription |
| *ALS2* | Amyotrophic lateral sclerosis 2 (alsin) | 2q33.1 | Recessive | Altered endosome/membrane trafficking |
| *C9ORF72* | Chromosome 9 open reading frame 72 (uncharacterized protein) | 9p21.2 | Dominant | Loss of alternatively spliced C9ORF72 RNA, formation of nuclear RNA foci |
| *FIG4* | FIG4 homolog (SAC1 lipid phosphatase domain containing) | 6q21 | Recessive | Effect on endosome trafficking |
| *FUS* | Fused in sarcoma | 16p11.2 | Both | Altered RNA processing; formation of inclusion bodies |
| *OPTN* | Optineurin | 10p13 | Both | Impaired inhibition of NF-kBkb-mediated transcription, impaired maintenance of the Golgi apparatus, altered membrane trafficking and exocytosis, formation of inclusion bodies |
| *SETX* | Senataxin | 9q34.13 | Dominant | Effect on DNA and RNA processing |
| *SOD1* | Superoxide dismutase 1 | 21q22.11 | Both | Toxic aggregation of SOD1, oxidative damage, mitochondrial dysfunction, RNA destabilization, impaired axonal transport, glutamate excitotoxicity |
| *SPG11* | Spastic paraplegia 11 (spatacsin) | 15q21.1 | Recessive | Impaired axonal transport |
| *TARDBP* | TAR DNA binding protein (TDP-43) | 1p36.22 | Dominant | Effect on RNA processing; formation of inclusion bodies |
| *UBQLN2* | Ubiquilin 2 | Xp11.21 | X-linked dominant | Formation of inclusion bodies, impaired proteasomal protein degradation |
| *VAPB* | VAMP (vesicle-associated membrane protein)- associated protein B and C | 20q13.32 | Dominant | Effect on vesicle trafficking |
| *VCP* | Valosin-containing protein | 9p13.3 | Dominant | Impaired proteasomal degradation, altered membrane sorting at endosomes/degradation in lysosomes, impaired ER-induced stress response, aggregation of huntingtin |

Note. For an up-to-date overview of these and other potential Mendelian ALS genes see the ALSoD database (http://alsod.iop.kcl.ac.uk).[36] Note that mutations in additional genes have been proposed to cause Mendelian forms of amyotrophic lateral sclerosis, albeit with hitherto inconclusive evidence.



proline-repeat motif in *UBQLN2* (ubiquilin 2) have been implicated to cause autosomal-dominantly inherited ALS and ALS/FTLD-type dementia complex.[42] Currently known *UBQLN2* mutations have been shown to impair the proteasomal degradation of proteins. Interestingly, ubiquilin 2 colocalizes with the C terminal fragment of TDP-43 in cytoplasmic inclusion bodies.[42] However, this was only observed in an overexpression system, necessitating further experiments to clarify the role of *UBQLN2* in ALS.

Other genes suggested to cause a Mendelian form of ALS include *DAO* (encoding D-amino-acid oxidase), *NEFH* (neurofilament, heavy polypeptide), *SIGMAR1* (sigma nonopioid intracellular receptor 1), *PRPH* (peripherin), *DCTN1* (dynactin 1), and *TAF15* (TATA box binding protein-associated factor), although data are currently insufficient to draw any firm conclusions about these loci (see the ALSoD database for details).[39]

## Non-Mendelian Forms of Amyotrophic Lateral Sclerosis Recent

Although association studies using candidate gene approaches have not led to the identification of any established genetic risk factors for non-Mendelian ALS (sporadic ALS [SALS]), recent GWAS have shown evidence for a risk effect conferred by polymorphisms in two loci. One signal maps within *UNC13A* on chromosome 19p13(Table 8)[34,43] (see Table 6). *UNC13A* encodes a presynaptic protein with an essential role in synaptic vesicle priming. Despite the potentially compelling functional implication of this protein in ALS

**Table 8 Established Susceptibility Loci for Amyotrophic Lateral Sclerosis**

| Gene/locus | Protein | Location | Polymorphism | # Subjects | OR (95% CI) |
|---|---|---|---|---|---|
| *GWA_9p21.2** | Unknown | 9p21.2 | rs2814707 | 25,435 | 1.25 (1.19–1.32) |
| *UNC13A* | unc-13 homolog A (C. elegans) | 19p13.11 | rs12608932 | 28,835 | 1.18 (1.13–1.24) |
| *ATXN2* | Ataxin 2 | 12q24.12 | PolyQ | 9,277 | n.a. |

OR, allelic summary risk odds ratio (i.e., the increase of the odds of getting the disease per additional risk allele after combining all available data); CI, confidence interval.
*Note that the locus on chromosome 9p21.2, which shows genome-wide significant evidence for association with ALS, is likely linked to C9ORF72, which was recently shown to contain a hexanucleotide repeat extension causing dominant ALS (see Table 7).
Note. Only genetic loci showing genome-wide significant ($P \leq 5 \times 10–8$) risk-effect estimates upon random-effects meta-analyses on the ALSGene database (http://www.alsgene.org)[36] are listed. Note that results details are for Caucasian populations only. The polyQ-variant in *ATXN2* has been added to this table based on the observation that all currently published independent studies have confirmed the initial report.[40]

pathogenesis, it should be noted that additional studies are still needed to exclude the possibility that the association signal originates from another locus nearby. The second genome-wide significant SALS GWAS signal is located close to the above mentionened hexanucleotid expansion in *C9ORF72* on chromosome 9p21.2,[34,43] providing yet another example on how dominantely acting structural genetic aberations leading to Mendelian ALS also appear to correlate with sporadic disease forms. In addition, a polyglutamine (polyQ) repeat in *ATXN2* (ataxin 2) has recently been associated with ALS using a candidate-gene approach.[44] *ATXN2* is the causative gene in spinocerebellar ataxia type II. The association of an extended polyQ repeat has thus far been consistently replicated in independent samples and has also been reported to show association with progressive supranuclear palsy.[45] For an up-to-date overview of these and other genetic association signals, consult the ALSGene database (http://www.alsgene.org).[39]

## CONCLUSIONS AND OUTLOOK

The neurodegenerative diseases discussed in this review share several epidemiologic and genetic aspects. First, they may present either as rare Mendelian forms or as common non-Mendelian (and likely multifactorial) forms. It appears likely that several of the hitherto "sporadic"-" appearing cases will eventually turn out to originate from specific disease-causing mutations, just as current GWAS signals may in fact be elicited by Mendelian mutations. One of the first examples in the neurodegenerative diseases described in this chapter is *C90RF72* as a disease-causing Mendelian gene in ALS that also seems to underly the association signal on chromosome 9p21. Second, although the majority of disease-causing or susceptibility genes do not overlap across disorders, some genes have been linked to diverse-appearing clinical entities. For instance, sequence variants in the τ-gene can cause FTD and significantly increase the risk for PD, whereas mutations in *VCP* and causal repeat expansions in *C90RF72* have been described for both ALS and FTD. Moreover, *TARDBP* and *FUS*, both harboring ALS-causing mutations, also appear to be a rare cause of FTD. Uncertainty also still exists for *SPG11,* which has been connected to a parkinsonian phenotype[19] as well as to ALS. 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 death in neurodegenerative diseases. Due 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. There is virtually no doubt that these discoveries will substantially reshape our understanding of the pathogenic forces driving neurodegeneration and many other human diseases, and will lay the foundation for developing better and more reliable diagnostic and treatment approaches.

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