Chapter 6
Genetic Risk Factors for Neurodegenerative Diseases

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Abstract The contribution of a single gene to each neurodegenerative disease is diverse in its effect size, depth, and mode of action. In those relatively rare neurodegenerative diseases that show a Mendelian pattern of inheritance, mutations in a major causative gene are solely responsible for the disease phenotype and underlying pathogenesis; whereas, the occurrence of more common neurodegenerative diseases likely requires the combined effect of alterations in many genetic factors and independent environmental factors. The pathological process of neuronal degeneration stems from deficits in neuronal or non-neuronal genes. Therefore, understanding the genetic landscape of neurodegeneration requires delineation of the general or unique effect of individual disease-related genes on the neurodegeneration process. Additionally, the interaction among genes should be determined. This chapter overviews, from distinct aspects, representative examples of genetic factors that have a major impact on the pathophysiology of neurodegenerative diseases.

Keywords Mendelian inheritance • Susceptibility • Alzheimer's disease • Amyotrophic lateral sclerosis • Frontotemporal dementia • Leukodystrophy • Astrocyte • Oligodendrocyte • Microglia

6.1 Introduction

Recent advances in the technology underlying comprehensive genetic and genomic analyses have enabled rapid and high-throughput studies that delineate numerous causative and susceptibility genes for neurodegenerative disorders. It has become apparent, from the many examples reported during the last two decades or so, that genetic factors play a major role in the pathological development of many neurodegenerative diseases. Moreover, we know that the effect size and depth of each genetic factor may vary among different diseases and genes. In a simple model

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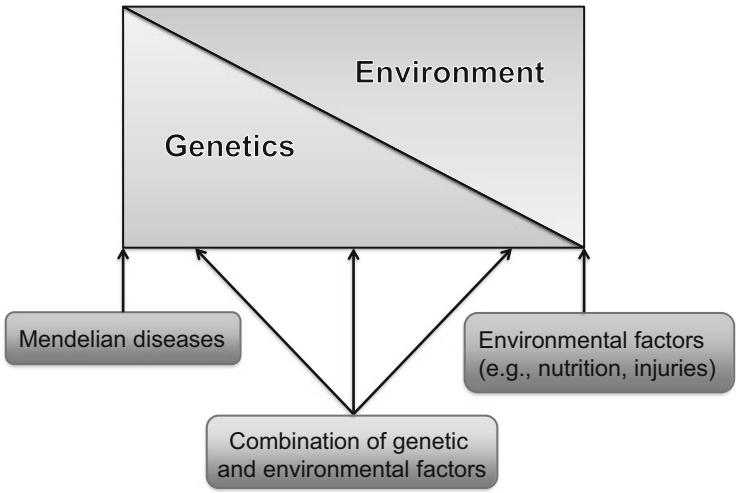

Fig. 6.1 The genetic and environmental factors that contribute to the occurrence of neurodegenerative diseases. (*Left*) Disease defined by a mutation in a single gene (as observed in monogenic Mendelian diseases). (*Right*) Some diseases are actually the result of environmental factors (such as injuries or nutrition). (*Middle*) The most common neurodegenerative diseases (in which multiple factors including susceptibility genes and environmental effects contribute to disease occurrence)

showing the contribution of genetic and environmental factors, Mendelian disorders are placed at the extreme end where an abnormality in a single gene is sufficient to cause a disease (Fig. 6.1). At the other end, some diseases are entirely dependent on environmental factors, such as infections and traumatic accidents. In reality, most neurodegenerative diseases are placed somewhere in the middle of these two extremes. Therefore, an understanding of both genetic and environmental factors is critical to delineating the pathogenesis of neurodegenerative diseases.

What is important yet difficult to understand is that genetic and environmental factors not only contribute to the pathogenesis independently, but also interact with each other to elicit their effect. Investigation and determination of such an interaction between genetic and environmental factors requires analysis of the disease as a systematic disorganization; techniques to uncover such dynamic interactions have not been well developed.

This chapter focuses on the genetic factors that primarily influence the pathology of neurodegenerative diseases at different levels and discusses the effect of environmental factors on the genetic basis of neurodegenerative diseases.

6.2 Neuronal Autonomous Genetic Factors

6.2.1 Genetic Factors That Directly Cause Neurodegenerative Disorders

Single genetic factors, mostly alterations in the coding exons of genes, can directly cause neurodegenerative diseases. In rare Mendelian disorders such single-gene defects are responsible for most of the disease mechanisms and phenotypes. This is the most simple and straightforward way of modeling the influence of genetic factors on neurodegeneration. A good example of such modeling is Huntington's disease (HD). HD is an autosomal-dominant neuropsychiatric disease characterized by progressive movement disorder, most commonly presenting as chorea, progressive cognitive decline leading to dementia, and various psychiatric symptoms that often precede diagnosis (Paulson and Albin 2011). The mutation causing HD is a CAG repeat expansion in the *HTT* gene (Group THsDCR 1993). This unique mutation is highly specific; no other type of mutation in *HTT* has been found to cause HD and all affected individuals with HD carry the CAG repeat expansion in *HTT*. It has been well recognized that the number of repeats is inversely correlated with age of onset (Andrew et al. 1993). Similarly, expanded CAG repeats commonly lead to a lengthy polyglutamine (polyQ) stretch in other autosomal-dominant neurodegenerative disorders including spinocerebellar ataxias, spinobulbar muscular atrophy, and dentatorubral–pallidoluysian atrophy (Zoghbi and Orr 2000). The strong correlation between the number of CAG repeats and age of onset has also been identified in these diseases, suggesting that the disease-associated polymorphic genotype also determines disease onset. Although the presence of a common pathology influencing the age of onset (and presumably disease progression) among these diseases has been expected, molecular mechanisms underlying these polyQ expansions appear to be quite complex, as reviewed elsewhere (La Spada et al. 2011). Nevertheless, CAG expansion involving multiple genes is a unique genetic factor that is specifically associated with neurodegeneration.

Sometimes, a single clinical phenotype can be caused by an alteration in many different genes. This condition is called "genetic heterogeneity." Charcot–Marie–Tooth (CMT) disease is one of the most common neurogenetic disorders, with a prevalence of 1 in 2500. CMT is characterized by bilateral distal wasting, weakness, and sensory loss that begins in the lower limbs and slowly progresses in a length-dependent manner. CMT is further divided into two forms, CMT1 (demyelinating neuropathy) and CMT2 (axonal neuropathy), based on electrophysiological findings. CMT can be dominant, recessive, or X-linked; more than 60 CMT-associated genes have been identified and the list is still growing (Timmerman et al. 2014). Mutations in each gene likely affect the diverse functions of Schwann cells (associated with CMT1) and neurons (associated with CMT2) in the peripheral nervous system. The most common CMT-causing mutation is the genomic duplication of 17p11.2 that harbors *PMP22*, which encodes a myelin membrane protein. Another myelin-associated gene, *MPZ*, is also commonly

mutated in patients with CMT1. Mutations in *GJB1,* encoding connexin32, affect the gap junctions of the myelin membrane. Genes involved in transcription and mRNA processing (*EGR2* and *CTDP1*), cytoskeletal structure (*PRX*, *IFN2*, *FGD4*, and *FBLN5*), endosomal sorting and cell signaling (*LITAF*, *SH3TC2*, *MTMR2*, *MTMR13*, *SBF1*, *FIG4*, *DNM2*, and *NDRG1*), and mitochondria (*GDAP1* and *HK1*) in Schwann cells can be affected in CMT1 (reviewed in Rossor et al. 2013). In CMT2, abnormalities that are even more diverse occur in the subcellular components of the neuronal axon and cell body, including defective nuclear envelope and mRNA processing, endoplasmic reticulum and Golgi apparatus, endosomal sorting and cell signaling, proteasome and protein aggregation, mitochondria, channels, axonal transport, and synaptic transmission (Rossor et al. 2013). These findings suggest that a single neurodegenerative phenotype can occur as a consequence of multi-layered pathological steps affecting tissues, cells, subcellular functional units, and genes, each of which can be responsible for the disease phenotype when mutated.

Single-gene alterations may only explain the common forms of neurodegenerative diseases in a small number of patients, while the vast majority of patients with the same disease may carry no such alterations. Dissecting the molecular pathology of such mutations not only explains the disease in rare cases, but also sheds light on the pathogenesis in most patients, because the rare genetic defect may affect the pathway followed by the common form of the disease. Alzheimer's disease serves as an example of such a case. Analyses of a small number of early-onset Alzheimer disease families showing an autosomal-dominant pattern of inheritance uncovered highly penetrant mutations in three genes: *APP*, *PSEN1*, and *PSEN2* (Goate et al. 1991; Sherrington et al. 1995; Rogaev et al. 1995; Levy-Lahad et al. 1995). *APP* encodes a single transmembrane protein from which amyloid β (Aβ) polypeptides are cleaved by β- and γ-secretases. Aβ polypeptides polymerize to form insoluble Aβ aggregates, the main component of senile plaque, which is the pathological hallmark in patients' brains. Most *APP* mutations are heterozygous missense alterations located in or near Aβ-coding exons (Goate et al. 1991). Rare whole-gene duplications (Rovelet-Lecrux et al. 2006) as well as small recessive deletions and missense alterations have also been reported (Di Fede et al. 2009). These *APP* mutations either change Aβ production, increase the $A\beta_{42}$ to $A\beta_{40}$ ratio (which differs in length according to cleavage sites; $A\beta_{42}$ is more toxic), or enhance fibril formation. Interestingly, one particular *APP* single-nucleotide polymorphism (SNP), which leads to a change in Ala673Thr, was reported to strongly protect carriers from Alzheimer's disease (1/OR = 5.29) (Jonsson et al. 2012). This SNP is located close to the cleavage site of BACE1 (β-site APP cleaving enzyme 1) and functionally inhibits BACE1 cleavage to produce Aβ. *PSEN1* and *PSEN2* are both critical components of γ-secretase, and mutations in either gene result in an increased ratio of $A\beta_{42}$ to $A\beta_{40}$ (De Strooper et al. 1998; Scheuner et al. 1996). Findings from these early-onset familial Alzheimer disease cases provided the solid genetic basis for the central role of Aβ in the pathogenesis of the common form of Alzheimer's disease.

6.2.2 *Genetic Factors That Affect Susceptibility to Neurodegenerative Disorders*

In most patients suffering from neurodegenerative diseases, genetic factors play a more complex role in the pathogenesis, onset, phenotype, and prognosis of the disease than in patients suffering from rare Mendelian forms of diseases (discussed in the previous section). Multiple genes appear to orchestrate together with environmental factors to formulate disease status. Recent advances in genome-wide association studies (GWAS) have been successfully delineating the susceptibility genes that contribute to each part of pathogenesis in the complex process of neurodegenerative diseases.

The best known example of such susceptibility genes with the largest effect size is the *APOE* gene in Alzheimer's disease (Corder et al. 1993). In fact, the Manhattan Plot (an overview of GWAS results encompassing the entire human genome) demonstrated a single incomparable high peak at the *APOE* locus, while other associated loci across the entire genome revealed only modest effects. The *APOE* gene harbors three polymorphic alleles, ε2, ε3, and ε4, of which the ε4 allele is a risk allele for Alzheimer's disease (Farrer et al. 1997). A meta-analysis in individuals of European descent showed that the risk of Alzheimer's disease is increased in people carrying one copy of the ε4 allele (ε2/ε4, odds ratio 2.6; ε3/ε4, odds ratio 3.2) or two copies (ε4/ε4, odds ratio 14.9), compared with those carrying an ε3/ε3 genotype (Farrer et al. 1997). This association is also observed in other populations with a weaker (African American ε4/ε4, odds ratio 5.7; Hispanic ε4/ε4, odds ratio 2.2) or a stronger (Japanese ε4/ε4, odds ratio 33.1) effect (Farrer et al. 1997). *APOE* genotypes strongly affect Aβ deposition as a result of haplotype-specific differences in metabolizing Aβ. Findings from multiple studies in humans and mice suggest that *APOE* ε4 increases the risk by initiating and accelerating the accumulation, aggregation, and deposition of Aβ in the brain (Liu et al. 2013). *APOE* ε4 is less efficient at clearing Aβ from the brain. *APOE* genotypes are also associated with mild cognitive impairment (MCI), which is now considered a pre–Alzheimer disease condition. Individuals with MCI who carry the ε4 genotype are at a higher risk of progression from MCI to Alzheimer-type dementia (Petersen et al. 1995) and suffer a faster cognitive decline than non-carriers (Cosentino et al. 2008). Thus, *APOE* serves as a major susceptibility gene for Alzheimer's disease with the ε4 allele increasing the risk by direct enhancement of Aβ pathogenesis.

By contrast, other susceptibility genes in at least nine loci (*CLU*, *CR1*, *PICALM*, *BIN1*, *EPHA1*, *ABCA7*, *MS4A* cluster, *CD33*, and *CD2AP*), identified and confirmed by multiple GWAS, have shown a much smaller effect size (reviewed in Bettens et al. 2013). Pathogenic mechanisms of variations in these nine susceptibility genes have not yet been established; however, these susceptibility genes may be related to specific functions including lipid processing (*CLU* and *ABCA7*), functioning of the complement system, inflammation, immune system (*CLU*, *CR1*, *ABCA7*, *CD33*, and *EPHA1*), and synaptic cell functions such as endocytosis (*PICALM*, *BIN1*, *CD33*, and *CD2AP*). However, the mechanisms by which these

gene variations affect the pathological process of Alzheimer's disease remains largely undetermined. Interestingly, common gene variants that have a predominant effect when mutated (i.e., *APP*, *PSEN1*, and *PSEN2*) are not risk factors for the complex forms of Alzheimer's disease (Harold et al. 2009; Lambert et al. 2009). This contrasts with the findings in Parkinson's disease, wherein common variants in the genes that are responsible for the Mendelian form of the disease (i.e., *MAPT*, *SNCA*, and *LRRK2*) also serve as risk alleles in the common form of the disease (Simon-Sanchez et al. 2009; Satake et al. 2009).

6.2.3 Genetics Factors That Contribute to Multiple Neurodegenerative Disorders

Genetic exploration and identification of the genes contributing to neurodegenerative disorders have begun to uncover the fact that clinically distinct neurodegenerative disorders share a common genetic basis to a significant degree. A single gene can contribute to the occurrence of different diseases. There are striking examples of this in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD).

ALS is a devastating degenerative disorder of motoneurons. It is characterized by the onset of focal weakness, typically in the limbs but sometimes in bulbar muscles. This progresses to paralysis of almost all skeletal muscles, leading to death from respiratory failure typically within 5 years (Sreedharan and Brown 2013). FTD is a distinct form of dementia characterized by progressive degeneration of the frontal or temporal lobe, or both (Loy et al. 2014). FTD is clinically characterized by deterioration in behavior and speech, but memory and visuospatial function are spared to a certain degree. ALS and FTD have been thought of as distinct clinical entities, although rare overlapping cases have been reported. The seminal molecular pathology discovery connecting ALS and FTD was the identification of TDP-43 as the major component of ubiquitinated neuronal cytoplasmic inclusions in both diseases (Neumann et al. 2006), which also led to the identification of mutations in the *TARDBP* gene (which encodes TDP-43) in autosomal-dominant ALS and FTD families (Sreedharan et al. 2008; Chio et al. 2010). More recently, a massive expansion of a hexanucleotide repeat in an intron of C9ORF72 linked to chromosome 9q21 was found to cause ALS and FTD (Renton et al. 2011; DeJesus-Hernandez et al. 2011). Subsequently, it became apparent that this locus was responsible for a major part of both familial ALS (~40 %) and FTD (~25 %) (Majounie et al. 2012). In addition, at least three other genes are known to link ALS and FTD. *FUS* encodes an RNA-binding protein that has functional homology with TDP-43. *FUS* mutations have been found in about 4 % of familial ALS cases without dementia (Kwiatkowski et al. 2009; Vance et al. 2009); however, in rare families, *FUS* mutations also cause FTD (Blair et al. 2010). Note that FTD exhibiting a *FUS*-positive histopathological subtype is commonly observed; however, most of these cases do not carry *FUS* mutations (Snowden et al. 2011).

Mutations in the *VCP* gene, which encodes valosin-containing protein, were initially found to cause inclusion body myopathy, an unusual clinical syndrome characterized by FTD, and Paget's disease of the bone (Watts et al. 2004); however, they were later found to be responsible for 1–2 % of familial ALS cases too (Johnson et al. 2010). Ubiquitin 2 regulates the proteasome degradation of ubiquitinated proteins. The gene encoding this protein, *UBQLN2,* is responsible for rare familial cases of ALS and ALS/FTD syndrome (Deng et al. 2011). Since *UBQLN2* pathology has been observed in patients with ALS who do not carry mutations in this gene, this protein may play an important role in the final common pathway associated with motor neuron degradation. These cumulative genetic findings have drastically changed our understanding of unexpectedly common molecular pathologies between ALS and FTD.

6.3 Non-neuronal Genetic Factors Affecting Neurons

In a number of neurodegenerative diseases, the disease genes primarily function in non-neuronal cells including astrocytes, oligodendrocytes, microglia, and vascular cells. Deficits in these non-neuronal genes also affect neurons by causing neurodegeneration. The following examples highlight the contribution of genetic factors affecting cells other than neurons.

6.3.1 Genetic Deficits in Astroglia That Cause Neurodegeneration

Astrocytes constitute the largest volume of cells in the central nervous system (CNS). Named for its star-like shape, astrocytes are distributed throughout the CNS in both the gray and white matter. Once considered little more than scaffolds for neurons, astrocytes play multiple roles by interacting with many types of cells and structural components in the CNS – including neurons, oligodendrocytes, other astrocytes, blood vessels, pial membranes, and the ependymal layer that lines ventricles – to maintain tissue homeostasis (Lanciotti et al. 2013).

In their interaction with neurons, astrocytes extend many fine processes to contact synapses and establish highly regulated bidirectional communication. By secreting trophic factors – such as brain-derived nerve growth factor (BDNF), glial cell–derived neurotrophic factor (GDNF), nerve growth factor (NGF), insulin-like growth factor (IGF), and thrombospondin – astrocytes contribute to the formation, maintenance, and remodeling of synapses. Astrocytes also modulate neuronal function by secreting cholesterol, apolipoprotein E, glutathione, and hydrogen sulfide. They express receptors to take up neurotransmitters – including glutamate, gamma-aminobutyric acid (GABA), norepinephrine, dopamine, serotonin,

acetylcholine, and glycine – to remove them from the synaptic cleft and maintain their low extracellular concentrations. The clearance of glutamate, mainly mediated by a high-affinity excitatory amino acid transporter 1 (EAAT1, also known as "GLT1"), is critical to protecting neurons from excitotoxicity (Rothstein et al. 1996). Dysfunction of EAAT1 and accumulation of excessive extracellular glutamate have been implicated in several neurodegenerative processes and associated diseases, such as epilepsy, stroke, ALS, HD, and Alzheimer's disease (Coulter and Eid 2012; Rothstein 2009; Faideau et al. 2010; Simpson et al. 2010). Astrocytes also supply neurons with energy substrates. Both glucose and lactate are transported to neurons to maintain the energy source for intense neuronal activity. Astrocytes also control the homeostasis of water and ion fluxes in the synaptic interstitial space through numerous ion channels and transporters.

Astrocytes also provide growth factors – such as platelet-derived growth factor alpha (PDGF-α), fibroblast growth factor 2 (FGF2), neurotrophin-3 (NT-3), IGF-1, and ciliary neurotrophic factor (CNTF) – which are necessary for the survival of oligodendrocytes (Lanciotti et al. 2013). Astrocytes are thought to regulate CNS myelination probably by secreting growth factors; elucidation of the underlying mechanism is important to understanding how astrocytes contribute to CNS repair and remyelination, which could be useful in the treatment of demyelinating diseases.

Astrocytes not only play essential roles to maintain healthy CNS homeostasis, they are also involved in many pathological processes. Specifically, genetic deficits in astrocyte-specific genes can cause neurodegenerative disorders, characterized as cystic leukodystrophies including Alexander disease (AxD), megalencephalic leukodystrophy with subcortical cysts (MLC), and vanishing white matter (VWM). These are all rare genetic diseases that commonly show the characteristic features of demyelinating leukodystrophy with progressive cystic or spongy (vacuolating) degeneration of myelin.

AxD is an autosomal-dominant disease caused by heterozygous mutations in the astrocyte-specific type III intermediate filament *GFAP* gene (Brenner et al. 2001). Clinical manifestations of AxD vary in severity and onset from more severe infantile and juvenile forms to milder adult onset forms (Messing et al. 2012). Patients with the infantile form show progressive features with seizures, bulbar dysfunction, psychomotor regression, and short lifespan. Pathologically, the brains of patients with severe AxD show loss of oligodendrocytes and myelin; cystic degeneration; neuronal loss most commonly in the hippocampus, striatum, and neocortex; and the presence of Rosenthal fibers in the cytoplasm of astrocytes (Messing et al. 2012). The exact mechanisms for neurodegeneration in AxD remain unknown, but both toxic gain-of-function and impairment of normal astrocyte supportive function have been implicated. Specifically, a marked downregulation of GLT-1 in astrocytes expressing mutant GFAP, and the vulnerability of hippocampal neurons to glutamate-induced cytotoxicity in co-cultures with astrocytes expressing mutant *GFAP* have been reported (Mignot et al. 2007). These findings may link *GFAP* mutations to glial glutamate transporter-1 (GLT-1) dysfunction and impairment of the neuron–astrocyte interaction, suggestive of a potential

mechanism underlying neuronal loss in AxD. Similarly, dysregulation of the homeostatic functions of astrocytes – including extracellular K^+ buffering by Kir4.1 and Na^+/K^+–ATPase activity – have been implicated in the demyelination of AxD (Hagemann et al. 2005).

6.3.2 *Genetic Deficits in Oligodendrocytes That Cause Neurodegeneration*

Mature oligodendrocytes extend cell processes that are modified into thin sheaths of plasma membrane wrapping around a portion of an axon in a spiral fashion (so-called "myelin"). Each oligodendrocyte interacts with as many as 50 different axons by extending multiple processes. Each axon is ensheathed by multiple continuous segments of myelin, separated by small areas of bare axons exposed to interstitial spaces called "nodes of Ranvier." Myelin functions as an insulator of electronic circuits in neuronal networks, where it enables rapid, efficient, and distant transmission without attenuation. In addition to these unique features of myelin as a structural component for highly efficient axonal conduction, oligodendrocytes communicate with axons through several signaling processes. Axonal signals that support myelin include neuregulins, neurotrophins, and the electrical activity of axons, while oligodendrocytes support axons through the function of some myelin membrane–bound proteins, such as *PLP1* and *CNP1*. Mice in which either *PLP1* or *CNP1* has been disrupted develop normal myelin, suggesting that these myelin proteins are dispensable for normal myelination. On the other hand, these mice develop broad axonal swelling, indicating that *PLP1* and *CNP1* support axons independent of myelin (Nave and Trapp 2008). Of these two myelin proteins only *PLP1* is directly associated with human disease.

Leukodystrophy comprises a group of rare genetic disorders that primarily target white matter in which myelinating oligodendrocytes and axons predominate. Pelizaeus–Merzbacher disease (PMD) is a hypomyelinating leukodystrophy characterized by deficit in CNS myelination (Inoue 2005). PMD is caused by mutations in *PLP1*, which encodes a major myelin membrane protein. PMD-causing *PLP1* mutations include point mutations that mostly result in amino acid substitutions, genomic duplications that lead to an additional copy of the gene, and null mutations caused by deletions or early-truncating mutations (Inoue 2005). In PMD the structure of the neuronal network is essentially intact. However, slowly progressive axonal degeneration may occur later in the disease probably because of the loss of axonal support by myelin and the resulting metabolic and electronic insufficiency in the axons. Activated microglia have also been found at the site of hypomyelinated axons; thus, microglia may additionally contribute to hypomyelination-associated axonopathy (Ip et al. 2006). In addition to these features (generally observed in all types of mutations), patients with null mutations show an apparent length-dependent progressive axonopathy

characterized by axonal swelling (Griffiths et al. 1998; Garbern et al. 2002). This is despite the fact that clinical severity and associated leukodystrophy observed by magnetic resonance imaging (MRI) in patients with null mutations are surprisingly milder than in patients with either point mutations or duplications. It is not completely understood why a milder condition with almost normal myelinating oligodendrocytes with no *PLP1* expression is more susceptible to axonal degeneration than severe conditions with bare axons and almost no mature oligodendrocytes caused by other types of mutations. Nevertheless, the expression of myelin-specific genes such as *PLP1* appears to play a role in preventing the degeneration of axons.

More than 30 leukodystrophies and their causative genes are known, and most, if not all, involve neurodegeneration (Kohlschutter and Eichler 2011), suggesting that a variety of genetic factors lead to this specific type of neurodegeneration. These diseases commonly show disruption of the myelin sheath in the CNS accompanied by axonal degeneration and inflammatory changes, together called "demyelination." The genetic bases of leukodystrophies are complex; genes involved in many different cells and functions have been implicated (Kohlschutter and Eichler 2011). X-linked adrenoleukodystrophy is caused by mutations in *ABCD1*, which encodes a member of the superfamily of ATP-binding cassette transporters (Steinberg et al. 1993). *ABCD1* is present on the peroxisomal membrane and is involved in the transport of very long chain fatty acids (VLCFA)–coenzyme A (CoA) synthetase. Defects in *ABCD1* result in accumulation of VLCFA, which is toxic to brain cells, especially microglia and oligodendrocytes, and thus leads to axonal degeneration. Mutations in a gene encoding the lysosomal enzyme, arylsulfatase A, cause metachromatic leukodystrophy, which is characterized by abnormal accumulation of cerebroside sulfate (the major component of myelin lipids), which leads to myelin breakdown and neuronal death. Further examples of neurodegenerative leukodystrophies are hypomyelination with atrophy of the basal ganglia and cerebellum (mutations in the β-tubulin4A gene), Canavan disease (mutations in the aspartoacylase gene), and Krabbe disease (mutations in the galactocerebrosidase gene).

6.3.3 *Genetic Deficits in Microglia That Cause Neurodegeneration*

Microglial activation and neuroinflammation are major components in neurodegeneration. Numerous genes and pathways are associated with the important role microglia play in neurodegeneration. However, the focus here is on a small number of microglia-specific genes, in which mutations primarily cause neurodegenerative disorders. Nasu–Hakola disease (NHD), also known as "polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy," is a rare autosomal-recessive neurodegenerative disease characterized by multifocal bone

cysts and progressive early-onset dementia. Two genes are known to be responsible for NHD – *TYROBP* and *TREM2* (Paloneva et al. 2000, 2002). Both these genes encode components of cell surface receptors that are expressed not only in blood immune system cells, but also in microglia in the CNS and bone osteoclasts. *TYROBP* and *TREM2* form a receptor-signaling complex that triggers the activation of immune responses in macrophages and dendritic cells (Lanier and Bakker 2000). Although the exact molecular pathogenesis is unknown, loss-of-function mutations in *TYROBP* and *TREM2* are predicted to cause dysfunction of microglia. The brains of patients with NHD show sudanophilic leukodystrophy characterized by loss of myelin and nerve fibers, and gliosis especially in the frontal and temporal lobes (Nasu et al. 1973). Note that these broad neurodegenerative changes involving oligodendrocytes, astrocytes, and neurons primarily result from the abnormal function of microglia. NHD is an extremely rare disease and the vast majority of patients are either Finnish or Japanese (Hakola 1972; Nasu et al. 1973). However, the NHD-associated microglial gene, *TREM2*, appears to have a broader impact on common neurodegenerative diseases. Heterozygous mutations in *TREM2* are associated with an increased risk of several neurodegenerative disorders including Alzheimer's disease, Parkinson's disease, ALS, and FTD (Guerreiro et al. 2013; Jonsson et al. 2013; Rayaprolu et al. 2013; Cady et al. 2014; Cuyvers et al. 2014; Borroni et al. 2014). Although the allele frequency of the variant *TREM2* is relatively low (~0.3 %), the effect size is remarkably high in Alzheimer's disease (odds ratio > 3, which is close to that of the *APOE4* allele). The exact mechanisms by which *TREM2* mutations increase susceptibility to different neurodegenerative diseases is still unknown, but a recent study suggested that reduced function of *TREM2* impairs phagocytosis, which may contribute to neurodegeneration (Kleinberger et al. 2014). These findings suggest that normal function of microglia is critical to preventing neurodegeneration in the brain.

6.4 Conclusions

This chapter overviewed the genetic factors that contribute to the development of neurodegenerative disorders from a wide variety of viewpoints. Neurodegenerative disorders can occur because of a mutation in a single gene or because of multiple contributions from alterations in some genes, or possibly many genes. In addition, environmental factors may also influence the development of neurodegenerative disorders through many different pathophysiological pathways. Such findings have of course been made possible by the rapid and dramatic technological advances in comprehensive genetic and genomic analyses, including genome-wide linkage analysis, GWAS, SNP array analysis, array comparative genomic hybridization (aCGH) analysis, whole-exome sequencing, and whole-genome sequencing. However, despite these advances, we have barely scratched the surface of the genetic contribution to pathogenesis of the most common neurodegenerative disorders. A prominent peak of the pathophysiological landscape of neurodegenerative disorders

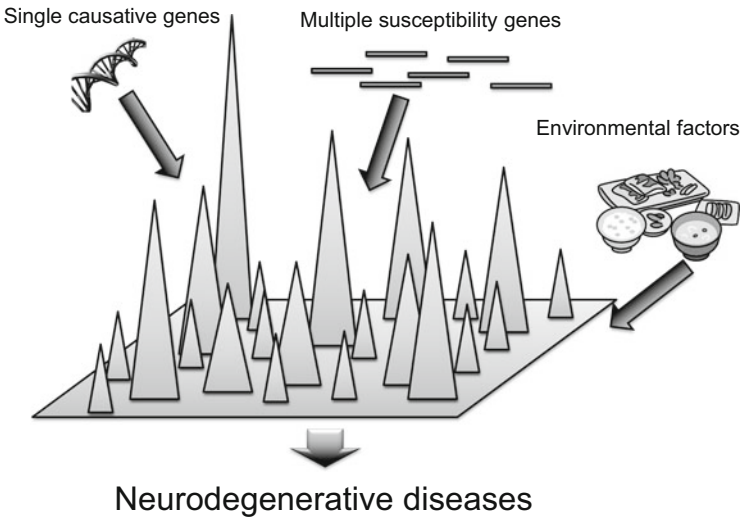

Fig. 6.2 The fundamental basis of genetic and environmental factors that contribute to the occurrence of neurodegenerative diseases

delineated by the discovery of underlying genetic and genomic bases can now be seen (Fig. 6.2). However, many small peaks representing genes with smaller effect size have yet to be identified. Furthermore, the risk factors stemming from interactions within these genetic factors or between genetic and environmental factors have not been fully elucidated. The fundamental basis of neurodegenerative disorders awaits clarification by future advances in high-throughput deep genomic exploration technology incorporating the multi-factorial interaction with environmental effects.

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