Genetics of neurological disorders

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Neurological diseases are defined as an inappropriate function of the peripheral or central nervous system due to impaired electrical impulses throughout the brain and/or nervous system that may present with heterogeneous symptoms according to the parts of the system involved in these pathologic processes. Growing evidence on genetic components of neurological disease have been collected during recent years. Genetic studies have opened the way for understanding the underlying pathology of many neurological disorders. The outcome of current intense research into the genetics of neurological disorders will hopefully be the introduction of new diagnostic tools and the discovery of potential targets for new and more effective medications and preventive measures.

In this review, information on genetic components of major neurological disorders will be collated to provide an update on current thinking and progress in our understanding of such diseases. Some important and more abundant neurological disorders are reviewed in greater detail. Genes implicated in Alzheimer’s disease (AD), frontotemporal dementia (FTD), Pick’s disease, normal pressure hydrocephalus (NPH), Parkinson’s disease (PD), amyotrophic lateral sclerosis (ALS) and Kennedy’s syndrome are also discussed in more detail. Examples of different categories of other neurological disorders with few or no novel gene discoveries are listed in TABLE 1. Some rare neurological diseases with a known genetic factor or with no novel gene discoveries are not mentioned in this article.

The polygenic properties of most neurological diseases have been discussed in detail and pharmacogenomic approaches for the treatment of these diseases are proposed based on recent work.

A neurological disease is defined as a pathologic condition that affects and impairs normal electrical impulses throughout the brain and/or nervous system. General symptoms that may occur during the course of the disease include malfunction of the motor system, voluntary and involuntary movement, sensory network, cognitive function, memory and abstract thinking. Due to their comparably high prevalence, generally unknown mechanisms and significant impact on affected individuals, their family and society, understanding neurological disease etiology and pathophysiology is one of the most important challenges facing medical and biological sciences today.

The role of genetic components in neurological diseases varies widely from direct predisposition, such as in Huntington’s disease and spinocerebellar atrophy, to more complex roles, such as in AD, PD and prion disorders. Although genetic risk factors have a great impact on these chronic illnesses, most neuronal diseases are multifactorial in nature; that is, they are influenced by an interplay of genes and environment. Some diseases can be caused by single gene defects, while others are more complex. Molecular genetic studies and genetic epidemiology approaches introduce two main groups of genes related to disease: causative genes and susceptibility genes. Case-control studies are used in an attempt to identify the genes and the extent to which they contribute to the disease state, as well as their interaction with other genes. Furthermore, cellular and animal model studies are used to identify the role of mutations in causative genes, or polymorphisms in susceptibility genes. The identification of genes causing or...
associated with each of the neuronal disorders and the use of transgenic approaches have helped us to understand the underlying molecular mechanisms and have opened the way to discovering potential therapeutic targets.

The majority of currently available drugs for neuronal diseases are based on symptomatic treatment. However, recent research has helped to define the cellular mechanisms, thus paving the way toward finding new targets for therapy.

This review focuses on the roles of genetic factors in some neurological diseases in which the underlying genetic factors are better understood and, based on current successes, suggests a direction for future investigations.

**Alzheimer’s disease**

AD is the most common cause of senile dementia and is the sixth leading cause of death in Western countries. The clinical symptoms of AD can be described as an initial onset of memory loss followed by cognitive dysfunction and slow progressive dementia over the course of several years. Microscopically there are two pathognomic lesions in the brain of affected patients: senile plaques, which are extracellular neurotic plaques containing Β-amyloid, and silver staining neurofibrillary tangles (NFTs) in neuronal cytoplasm. Some patients also have an accumulation of Β-amyloid in the arterial wall of cerebral blood vessels. The NFTs, which were first noted by Alzheimer, are twisted neurofilaments in neuronal cytoplasm that are composed of abnormally phosphorylated Tau protein. They appear as paired helical filaments by electron microscopy. Tau is a microtubule-associated protein that is involved in assembly and stabilization of microtubules in neurons. Phosphorylation decreases the microtubule-binding ability of the Tau protein.

**Genetics of familial & sporadic forms**

Although the major risk factor for AD is old age, many studies have shown a strong genetic component for both senile and presenile forms of the disease. Genetic cases are more frequent in presenile AD. More than ten genes or loci have a reported association with AD to date, and four of these are widely accepted to be involved in AD. TABLE 2 lists the genes implicated in AD. Early-onset disease, defined as the illness occurring before the age of 60–65 years, is rare. In one study in France, the prevalence of early-onset disease was 41 per 100,000, comprising around 6–7% of all cases of AD [1]. Approximately 7% of early-onset AD cases are familial, mostly with an autosomal dominant pattern of inheritance, however, their importance extends far beyond their frequency because these inherited forms are the main source for studying critical pathologic pathways of more common sporadic cases [2]. Mutations in the presenilin (PSEN1 and PSEN2) and amyloid precursor protein (APP) genes cause autosomal dominant early-onset AD. The apolipoprotein E (APOE) gene is the fourth gene implicated in AD. Most of the early-onset AD cases are due to mutations in the PSEN1 gene, while mutations in the APP and PSEN2 genes are rare. Carriers of the ε4 variant of APOE have an increased risk of both senile and presenile AD. The primary effect of the APOE ε4 allele is to shift the age of onset an average of 5–10 years earlier in the presence of one allele, and 10–20 years earlier in the presence of two alleles in persons with an underlying susceptibility to AD [3]. APOE appears to play the most important role in the general population. Mutations in APP and the presenilin genes account for less than 1% of the prevalence of the disease in the general population, compared with 10–17% for the APOE variation [4].

**Pathophysiology of normal & abnormal gene products**

**APP**

APP on chromosome 21 (21q 21.1) encodes the APP protein, which is a large membrane-spanning protein that has been implicated in early-onset AD. More than 20 pathological mutations have been reported for the APP gene. Point mutations have been observed in a few families with familial-type AD. Although very rare, these families were the first cases of single-gene autosomal dominant transmission of AD. The most frequent of these APP mutations is a substitution of valine for isoleucine at position 717 [5]. Release of Β-amyloid from the APP requires cleavages by β- and γ-secretases. Mis-sense mutations in the APP gene causing familial AD are clustered around the β-, α- and particularly the γ-secretase cleavage sites [6]. APP has been shown to have neuroprotective activity and proteolytic processing of APP plays a key role in the development of AD. The cleavage activity of the β- and γ-secretase enzymes liberate the Β-40 form, which is a 42-kDa protein of 39–42 amino acids [7]. The γ-secretase, in particular, appears to be responsible for generating Β-42, which has pathogenic importance because it is shown to form deposits in the central cores of senile plaques [8]. Β-amyloid may be a physiological metabolite in the brain and the increased production of Β-42, which is probably the primary neurotoxic involved in the pathogenesis of the disease, leads to neuronal cell death [9,10]. This is the basis for the amyloid hypothesis of AD, which explains neuronal cell death due to production of Β-42 and interactions between APP and PSENs [11]. Neprilysin is the major Β-42 catalytic enzyme. Neprilysin deficiency results in defects in the metabolism of endogenous Β-40 and Β-42 in a gene dose-dependent manner. Even partial downregulation of neprilysin activity, which could be caused naturally by aging, can contribute AD development by promoting Β-amyloid accumulation; thus, neprilysin downregulation has a role in sporadic AD pathogenesis [12]. Neuritic plaques made by damaged brain cells and amyloid family proteins were found in the brains of patients with Down’s syndrome (trisomy of chromosome 21). Down’s syndrome patients have one extra copy of the APP gene and after the fourth decade of life display some of the neuropathological features of AD. In these cases, the symptoms of AD may superimpose existing mental dysfunction of patients [13]. Increased plasma levels of Β-amyloid peptide may be a risk factor for developing AD in the general population, and novel APP mutations have been reported in patients with late-onset AD [14].
### Table 1. Neurological disorders.

<table>
<thead>
<tr>
<th>Disease category</th>
<th>Disease name</th>
<th>Phenotype</th>
<th>Known genetic loci</th>
<th>Pattern of inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia</td>
<td>Prion disease</td>
<td>Spongiform encephalopathy</td>
<td>Prion protein gene Chr. 20</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Movement disorders</td>
<td>Huntington’s disease</td>
<td>Chorea, dementia</td>
<td>CAG repeat in huntingtin gene</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Neuromuscular disorders</td>
<td>Spinal muscular atrophy</td>
<td>Spinal motor neuron death and muscular atrophy</td>
<td>SMN1 and SMN2 genes Chr. 5</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td></td>
<td>Myotonic dystrophy</td>
<td>Mental retardation and muscle weakness</td>
<td>Trinucleotide repeats in DM gene Chr. 19</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td></td>
<td>Duchene muscular dystrophy</td>
<td>Early-onset male muscle degeneration</td>
<td>Dystrophin gene Chr. X</td>
<td>X linked recessive</td>
</tr>
<tr>
<td>Metabolic disorders</td>
<td>Wilson disease</td>
<td>Copper accumulation in the liver and brain</td>
<td>ATP7B Chr. 13</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td></td>
<td>Menkes syndrome</td>
<td>Cerebral degeneration due to impaired copper transport</td>
<td>ATP7A and ATP7B</td>
<td>X-linked recessive</td>
</tr>
<tr>
<td></td>
<td>Tay-Sach disease</td>
<td>Neurodegeneration due to accumulation of metabolic wastes</td>
<td>HEXA Chr. 15</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td></td>
<td>Neimann-Pick’s disease type-c</td>
<td>Brain and nervous system impairment</td>
<td>NP-c locus Chr. 18</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td></td>
<td>Phenylketonuria</td>
<td>Mental retardation</td>
<td>PAH Chr. 12</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Tumor lesions</td>
<td>Tuberous sclerosis</td>
<td>Benign tumor-like nodule of the brain</td>
<td>TSC1 Chr. 9 TSC2 Chr. 16</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td></td>
<td>Neurofibromatosis type 2</td>
<td>Acoustic neuromas and malignant CNS tumors</td>
<td>NF2 gene Chr. 22</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Neurodevelopmental disorders</td>
<td>Rett syndrome</td>
<td>Female mental retardation</td>
<td>MeCP2 Chr. X</td>
<td>X linked</td>
</tr>
<tr>
<td></td>
<td>Fragile X syndrome</td>
<td>Mental retardation</td>
<td>CGG repeats of FMR1 gene</td>
<td>X linked</td>
</tr>
<tr>
<td>Ataxic disorders</td>
<td>Spinocerebellar ataxia type 1</td>
<td>Degeneration of cerebellum and spinal cord</td>
<td>CAG repeats in SCA1 gene Chr. 6</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td></td>
<td>Friedreich's ataxia</td>
<td>Progressive loss of muscular coordination</td>
<td>GAA repeats in Frataxin gene Chr. 9</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td></td>
<td>Ataxia telangiectasia</td>
<td>Progressive degenerative disease with immunodeficiency</td>
<td>ATM gene Chr. 11</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Lafora disease</td>
<td>Progressive myoclonic epilepsy leading to dementia</td>
<td>EPM2A gene mutation Chr. 6</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td></td>
<td>Nocturnal frontal lobe epilepsy</td>
<td>Seizure occurring at night</td>
<td>CHRNA4 gene mutation</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Charcot-Marie-Tooth syndrome</td>
<td>Peripheral neuropathy and muscle atrophy</td>
<td>PMF22 protein Chr. 17</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Neurovascular disorders</td>
<td>Familial cerebral angiopathy</td>
<td>Cerebral hemorrhage</td>
<td>APP gene mutation Chr. 21</td>
<td>Autosomal dominant</td>
</tr>
</tbody>
</table>

Pattern of inheritance indicates the known mode of transmission. Recessive and dominant modes transmitted autosomally or via X chromosome are indicated. Diseases in this table, although classified as neurological disorders, are not discussed in this review due to lack of recent, novel gene discoveries related to them.

APP: Amyloid precursor protein; ATM: Ataxia telangiectasia mutated; ATPTA: ATPTase Cu^{2+} transporting α polypeptide; ATPTB: ATPTase Cu^{2+} transporting β polypeptide; CHRNA4: Cholinergic receptor, nicotinic, α polypeptide 4; Chr: Chromosome; DM: Dystrophy myotonica; EPM: Epilepsy, progressive myoclonus; FMR: Fragile X mental retardation; HEXA: Hexosaminidase A (α polypeptide); MeCP: Methyl CpG binding protein; SMN: Survival motor neuron gene; NF: Neurofibromatosis gene; NP: Neimann-Pick; PAH: Phenylalanine hydroxylase; PMP: Peripheral myelin protein; SCA: Spinocerebellar ataxia; TSC: Tuberous sclerosis.
The PSEN1 gene is located on chromosome 14 (14q24.3) and encodes a protein named S182. Mutations in this gene produce an early-onset AD that is transmitted as an autosomal dominant disease. More than 80 different mutations of this gene are known, which together account for 50% of early-onset familial AD. Different mutations have specific phenotypic properties; for instance, Tyr256Ser shows the highest expression of Aβ40 and Aβ42 compared with other PSEN1 mutations and thus contributes to the severity of disease pathology [15]. PSEN1 may in fact be the γ-secretase itself or a necessary cofactor in its activity, and the toxic Aβ42 peptide is increased in the serum of patients with various APP, PSEN1 and PSEN2 mutations [16,17]. PD features have also been reported in some families with PSEN1 mutations that show clinical and pathological diversity in PSEN1-mutated AD [18]. There are also reports of association of genetic variability in the regulatory region of PSEN1 with a risk for AD [19]. Mutations in PSEN1 usually produce AD with an earlier age of onset (mean 45 years) and more progressive course than the diseases caused by PSEN2 mutations (onset 53 years).

Association between late-onset sporadic AD and some polymorphic variants of PSEN1 have been identified, but the extent of contribution is unclear due to lack of replication [20,21].

The PSEN2 gene is located on chromosome 1 (1q42.1) and encodes a protein named STM2. Different mutations in PSEN2 have been reported in patients with early- and even late-onset AD. One spliced isoform of the PSEN2 gene transcript, skipping exon 5, has been reported as a possible diagnostic feature of sporadic AD and has been proposed as a novel mechanism of sporadic AD that involves aberrant splicing of PSEN2 pre-messenger RNA (mRNA) in the absence of any mutations [22]. Elevated levels of Aβ-amyloid among patients with a mutation in the two presenilin genes suggests a possible common pathway between PSEN1 and PSEN2 (i.e., increased production or decreased clearance of Aβ42-amyloid and formation of protein aggregate, the amyloid plaque, implicates the amyloid pathway in the pathogenesis of AD [23]).

<table>
<thead>
<tr>
<th>Table 2. Genes and loci implicated in Alzheimer’s disease.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Category</strong></td>
</tr>
<tr>
<td>Genes under investigation</td>
</tr>
<tr>
<td>Genes under investigation</td>
</tr>
<tr>
<td>Aβ-amyloid precursor protein</td>
</tr>
<tr>
<td>Apolipoprotein E</td>
</tr>
<tr>
<td>Genes implicated</td>
</tr>
<tr>
<td>Macroglobulin</td>
</tr>
<tr>
<td>Cystatin C</td>
</tr>
<tr>
<td>Oxidized LDL-receptor 1</td>
</tr>
<tr>
<td>Estrogen receptor</td>
</tr>
<tr>
<td>Nicotinic acetylcholine</td>
</tr>
<tr>
<td>Neurotrophic factor</td>
</tr>
<tr>
<td>Insulin-degrading enzyme</td>
</tr>
<tr>
<td>Homocysteine</td>
</tr>
<tr>
<td>α-Synuclein</td>
</tr>
<tr>
<td>Interleukin-6</td>
</tr>
<tr>
<td>Mitochondrial transfer RNA</td>
</tr>
</tbody>
</table>

AD: Alzheimer’s disease; APOE: Apolipoprotein E; APP: Amyloid precursor protein; Chr: Chromosome; CST3: Cystatin C; EOF: Early-onset familial; ER: Estrogen receptor; IDE: Insulin-degrading enzyme; IL: Interleukin; LDL: Low-density lipoprotein; LO: Late-onset; LOF: Late-onset familial; OLR1: Oxidizing low-density lipoprotein receptor 1; PSEN: Presenilin; SAD: Sporadic Alzheimer’s disease.
APOE

APOE is located on chromosome 19 and has three different alleles, ε2, ε3 and ε4; it has been demonstrated that the latter is strongly correlated with late-onset familial and sporadic AD. Different population studies agree with this correlation and approximately 40–65% of patients with AD have at least one ε4 allele, compared with only 24–30% of the control population. Although the ε4 allele is neither necessary nor sufficient for AD, it is, especially in homozygote carriers, a strong risk factor for AD. Carrying one APOE ε4 allele nearly doubles the lifetime risk of AD (from 15 to 29%), whereas not carrying it reduces the risk by 40% [24,25]. The APOE gene has been implicated in cholesterol transport although its mode of action in AD is not well understood. APOE is produced predominantly in astrocytes and is carried by the low-density lipoprotein receptor into neurons, where it binds to NFTs [26,27]. The variants of APOE vary in their affinity for β-amyloid. The ε4 variant increases the deposition of fibrillar β-amyloid, so cholesterol and APOE are involved in fibrillar plaque formation. Some studies have noted presence of APOE in senile plaques and formation of NFTs [28].

Other implicated genes

In addition to these four well-studied genes, linkage studies suggest the existence of other susceptibility genes for late-onset AD. It is worth noting that reporting a genetic association means taking a risk of nonreplication or even complete refutation by follow-up studies. Association studies should have large sample size, small p-values and report association accounting for biological function and alleles that affect the gene product in a physiologically meaningful manner. Although the standards of new association studies have improved over the years by using adequate statistical methods, the majority are never replicated and while that does not necessarily render the original result false, repeated nonreplication is nonetheless a good reason to dismiss the association [29]. Recent findings suggest the existence of novel AD genes on chromosomes 9, 10, 11, 12 and 20. The α2 macroglobulin gene, which is located on chromosome

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Phenotype</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>P301L*</td>
<td>Classic and Pick’s type B with corticobasal degeneration</td>
<td>[140]</td>
</tr>
<tr>
<td>G272V, R406W, E10+16, E10+13, E10+14</td>
<td>Classic and Parkinsonian features</td>
<td>[140]</td>
</tr>
<tr>
<td>N279K, Δ280k, S305N, E10+3, E10+29, L284L</td>
<td>Parkinsonian and supranuclear palsy</td>
<td>[141]</td>
</tr>
<tr>
<td>R5L</td>
<td>Supranuclear palsy</td>
<td>[142]</td>
</tr>
<tr>
<td>V337M</td>
<td>Classic frontotemporal dementia</td>
<td>[143]</td>
</tr>
<tr>
<td>G389R,</td>
<td>Pick’s disease</td>
<td>[144]</td>
</tr>
<tr>
<td>L259T, L266V</td>
<td>Pick’s disease</td>
<td>[145]</td>
</tr>
<tr>
<td>S320F</td>
<td>Pick’s disease</td>
<td>[146]</td>
</tr>
<tr>
<td>K369I</td>
<td>Pick’s disease</td>
<td>[147]</td>
</tr>
<tr>
<td>N296N</td>
<td>Pick’s type B with corticobasal degeneration</td>
<td>[148]</td>
</tr>
<tr>
<td>P301S</td>
<td>Epileptic seizure</td>
<td>[149]</td>
</tr>
<tr>
<td>S305A</td>
<td>Personality change</td>
<td>[150]</td>
</tr>
<tr>
<td>E10+11</td>
<td>Very early onset</td>
<td>[151]</td>
</tr>
<tr>
<td>A5H</td>
<td>Late-onset frontotemporal dementia</td>
<td>[152]</td>
</tr>
<tr>
<td>Intron 10+11-splice site (T to C)</td>
<td>Mental retardation, early-onset frontotemporal dementia</td>
<td>[153]</td>
</tr>
<tr>
<td>G342V</td>
<td>Classic frontotemporal dementia</td>
<td>[154]</td>
</tr>
<tr>
<td>E10+12</td>
<td>Classic frontotemporal dementia</td>
<td>[155]</td>
</tr>
<tr>
<td>S305S</td>
<td>Progressive supranuclear palsy</td>
<td>[156]</td>
</tr>
<tr>
<td>L315R</td>
<td>Pick’s disease</td>
<td>[157]</td>
</tr>
<tr>
<td>N296H</td>
<td>Classic frontotemporal dementia, negative characteristic pathological features</td>
<td>[158]</td>
</tr>
</tbody>
</table>

List of disease-associated mutations and single nucleotide polymorphisms (SNPs) reported in recent years. The list of references for each SNP is not included in the review but is available from the authors on request. E10 + number indicates mean site of mutation after exon 10. \*Most common mutation.
12, the cystatin C and its coding gene CST3 on chromosome 20 and the oxidized low-density lipoprotein receptor (OLR-1) have been reported as candidate genes for AD, however, further studies have produced equivocal results [30,31]. Implication of CST3 in the amyloidogetic pathway suggests the need for more intensive investigation [32]. Increased plasma levels of homocysteine [33], polymorphism of the estrogen receptor-α [34], brain-derived neurotrophic factor (BDNF) [35] and neuronal nicotinic acetylcholine receptor genes have also been implicated in AD [36]; however, further studies are needed to prove or exclude the role of these genes or loci in AD pathogenesis [37]. The insulin-degrading enzyme (IDE) gene located on chromosome 10 is a strong candidate gene because of its biological function of degrading β-amyloid protein and its effects in some cases are as large as that of the ε4 allele of APOE. Animal studies also reveal accumulation of amyloid in the brain of null mice for IDE [38].

There are possible links between AD and PD pathogenesis. Conflicting reports exist on the association of the α-synuclein gene polymorphism with AD. The α-synuclein gene is implicated in PD pathogenesis and a Japanese research group reported association between this gene and sporadic AD in women independent of APOE status [39]. Another possible link between AD and PD pathogenesis is the mutation in the mitochondrial transfer RNA (tRNA) genes that have been described in a variety of neurological disorders. For instance, the A to G transition at nucleotide position 4336 of the mitochondrial tRNA (Gln) gene appears to be associated with both AD and PD [40].

Neuroinflammatory signaling pathways and genes implicated in the inflammatory response are novel areas of investigation of AD pathogenesis. This approach tries to explain how nonsteroidal anti-inflammatory drugs reduce the risk of AD [41]. Several studies have demonstrated that interleukin (IL)-6 is involved in the pathogenesis of AD. However, it is not clear whether the IL-6 gene or its promoter polymorphism are directly implicated in AD pathogenesis or interactions of other genes with IL-6 affect the development and progression of AD [42].

Clinical relevance of diagnostic genetic testing

Mutations in the genes related to late-onset AD are relatively rare; therefore, screening for these mutations has a limited clinical prognostic value. This type of test should only be restricted to research purposes where there is an elevated probability of having such mutations; for example, patients with early-onset familial AD. Relatives of patients with documented mutations may also request testing for family, financial and personal planning reasons. Experts in the field of AD do not recommend testing of presymptomatic individuals and it should be undertaken with extreme care and only after extensive pretest counseling so that the patient is aware of the potential psychological complication of testing positive for an incurable, devastating illness [2]. APOE ε4 allele testing also has a limited value for the diagnosis and prediction of disease course and might be used as an adjunct to clinical diagnosis in a symptomatic demented patient [11]. APOE testing should be avoided in an asymptomatic person because of very poor predictive value and even in the demented patient as its negative predictive value is very limited [24,43].

Future areas of research

Identification of mutations in the genes implicated in early-onset AD or susceptibility genes for late-onset sporadic AD are providing sources for future research into the exact pathogenesis of AD and possible therapeutic targets. Animal models will assist in evaluating new drugs and studying effects of different known mutations in sporadic AD [44,45]. Studying uses of nonsteroidal anti-inflammatory drugs, secretase inhibitors and inhibitors of β-amyloid peptide production in transgenic mouse models have started and are aimed at finding more effective drugs and preventive measures [24,43]. Confirmation studies of many genes and polymorphisms proposed as possible susceptibility genes for AD, studies on their functional role, investigation into immunization therapy and the manner in which the genetic profile of the patient alters the therapeutic response will form the future area of research in this field [46,50].

Frontotemporal dementia & Pick’s disease

FTD is the cause of 10% of all dementia cases and an even greater proportion of presenile (<65 years) cases. The disease is characterized by behavioral, social, cognitive and motor disturbances. Behavioral changes such as irritability and loss of inhibition are the initial symptoms. Early-stage patients are unaware of these changes then memory loss and mental dysfunction occur and progress with rigidity and mutism. Atrophy of frontal and temporal lobes are marked and reported from imaging studies and confirmed by autopsy post mortem. Approximately 25–40% of FTD cases have a positive family history and 10–30% of patients with a positive family history have mutations in the Tau gene.

Pick’s disease, usually categorized as a subcategory of FTD, is a slowly progressive dementia and is difficult to differentiate clinically from AD. Silver staining of cytoplasmic inclusion bodies known as Pick’s bodies are the main pathologic finding of Pick’s disease. The Pick’s body and NFTs of AD have some shared antigenic components. Tau inclusion is another shared pathologic lesion in the brain of patients with Pick’s disease, FTD and AD.

The different phenotypical variants of FTD range from dementia associated with motor neurone disease to Parkinsonian features. The autosomal dominant form of FTD has been linked to DNA markers on chromosome 17 [51]. This is an important subgroup of FTD referred to as FTD with Parkinsonism linked to chromosome 17 (FTDP-17). Many FTDP-17 families are reported to have missense mutations in the Tau gene, which disturbs the microtubule binding function of the Tau protein. The Tau protein is encoded by a single gene but due to differential alternative RNA splicing is expressed in six isoforms in adult human brain. The Tau protein regulates the dynamic stability of the neuronal cytoskeleton and plays an
important role in neuronal differentiation and axonal development. Mutations are located in both coding and noncoding sequences of the gene. Intronic mutations are all located in intron 11. Table 3 lists some of the mutations related to FTD. There are two other genetically distinct forms of FTD: FTD linked to chromosome 9 and FTD linked to chromosome 3. The gene responsible for FTD on chromosomes 9 and 3 remains undiscovered. Ubiquitin inclusions have been found in FTD with motor neurone disease linked to chromosome 9 (9q13.3-p12). FTD with ALS has been reported to be linked to chromosome 9 (9q21-q22). In FTD linked with chromosome 3, clinical presentations are the same as the other forms of FTD and the presence of Tau inclusion without β-amyloid deposition has been reported from the brain autopsy of affected patients. Although this disease has not been defined as a tauopathy, the presence of Tau deposit in the brains of patients favors a possible link between the responsible gene and the Tau gene [52].

Normal pressure hydrocephalus
NPH is a neurological syndrome characterized by dementia, gait disturbance and urinary incontinence. Enlarged lateral ventricle (hydrocephalus) with little or no cortical atrophy is the main radiological finding in an affected patient. This enlarged ventricle is due to a communicating hydrocephalus with a patent duct and normal cerebrospinal fluid protein glucose, cell content and pressure. Familial X-linked NPH has been reported in a Japanese family. The symptoms initiate with epileptic attacks proceeded with urinary incontinence, mental and psychiatric deterioration. An enlarged ventricle has been observed by computerized tomography scanning. The pathologic gene is transferred via asymptomatic daughter to the grandson, which is suggestive of possible X-linked recessive mode of inheritance [53]. APOE ε4, which is associated with the presence and severity of dementia in AD patients, has been shown to be involved in the pathogenesis of NPH [54,55].

Parkinson’s disease
PD is a chronic progressive disorder with a prevalence of 0.2% in the general population and 2% among individuals over 65 years of age. The term Parkinsonism defines clinical syndromes including tremors, balance difficulties, bradykinesia, muscular stiffness and characteristic disturbances of gait and posture. The most common cause of Parkinsonism is PD. The age of onset in most cases is over 50 years, however, it can also occur in younger patients. A classic pathology of PD is exemplified by the loss of dopaminergic neurons, particularly at the substantia nigra, and presence of an eosiophilic intraneural inclusion body, called a Lewy body, in many regions of the brain, including basal ganglia, brainstem, spinal cord and sympathetic ganglia.

Genetics of familial & sporadic forms
PD was not regarded as a genetic disease until as late as 7 years ago, and growing evidence of genetic predisposition and correlation has accumulated since. Approximately 5% of PD patients have a familial form of the disorder [56]. The majority of familial early-onset PD cases have genetic factors, in contrast with late-onset sporadic disease [57]. During the past 7 years, nine chromosomal regions and five genes have been introduced that are related to PD. Table 4 summarizes the chromosomal loci and related genes. Identification of the α-synuclein gene is regarded as causal for familial PD and the presence of this protein in Lewy bodies in all forms of Parkinsonism disorders emphasizes the biological importance of genetics in the pathogenesis of PD [58,59].

Pathophysiology of normal & abnormal gene products

α-synuclein
PARK 1, located on chromosome 4 (q21-23), is the first locus reported to contain the α-synuclein gene. Two different mutations of the α-synuclein gene with an autosomal dominant form of inheritance are related to PD. These are A30P and A53T [60–62]. α-Synuclein is a protein with an uncertain function and is abundant in neurons, especially at synaptic terminals and in Lewy bodies. The synucleinopathies refer to disorders in which staining with α-synuclein is seen in the affected region, implicating synuclein dysfunction in their pathogenesis [63]. Fragments of this protein are a known constituent of AD plaques. This protein is implicated in neurodegenerative diseases, thus providing evidence that there may be a shared pathologic mechanism between AD and PD. Subclinical dopaminergic loss has been noted in otherwise asymptomatic carriers of the α-synuclein mutation. Genetic association of the α-synuclein gene have been shown to be more common in sporadic forms of PD and there is evidence for linkage between promoter variants of α-synuclein and a lifetime risk of sporadic PD [64]. There is a direct relationship between increasing α-synuclein gene expression and the risk of PD. Dementia is the additional clinical feature of affected patients with α-synuclein-related PD. A recent report indicates that gene triplication in the region containing α-synuclein causes early-onset autosomal dominant PD in a large family [65]. The triplicated region is between 1.61 and 2.04 Mb in size and in addition to α-synuclein contains 16 annotated or putative genes. Increased dosage of α-synuclein is the cause of PD in this family and the disease process may resemble the etiology of AD in Down’s syndrome, where overexpression of the APP gene due to chromosome 21 trisomy is the key pathologic event [65].

Transgenic mouse models for α-synuclein and parkin mutations have been created that facilitate study of gene function. Although some groups report clear α-synuclein pathology, others have observed no changes [66–68]. Parkin-deficient mice exhibit nigrostriatal deficits but not loss of dopaminergic neurons [66]. Transgenic Drosophila with α-synuclein have intracellular inclusions resembling Lewy body in dopaminergic neurons and mitochondrial pathology, and apoptotic muscle degeneration is observed in Drosophila transgenic with parkin mutants [69,70]. Dopaminergic neuronal loss and motor deficits have also been reported for Caenorhabditis elegans overexpressing human α-synuclein [71]. Studies based on these models suggest that protein folding and degradation pathways play an important role in PD [72].
endogenous chaperone activity accelerates protein refolding and/or degradation \[73\]. Recent research supports a role for chaperone proteins, including torsinA HSPs, in cellular responses to neurodegenerative inclusion \[74\]. HSP70 is a potent suppressor of both PD and polyglutamine disease in *Drosophila*. These studies provide the promise of treatment for human neurodegeneration through the upregulation of stress and chaperone pathways \[75\]. The expression of the molecular chaperone HSP70 prevents dopaminergic neuronal loss associated with α-synuclein in *Drosophila* and the interference with endogenous chaperone activity accelerates α-synuclein toxicity. Furthermore, Lewy bodies in human post mortem tissue immunostained for molecular chaperones also suggests that chaperones may play a role in PD progression \[76\].

**Parkin**

**Table 4. Mode of transmission of different linked loci.**

<table>
<thead>
<tr>
<th>Loci</th>
<th>Chromosome region</th>
<th>Gene</th>
<th>Pathology</th>
<th>Pattern of inheritance</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARK 1</td>
<td>Chr.4 (q21-23)</td>
<td>α-Synuclein</td>
<td>A30P, A53T mutations</td>
<td>Autosomal dominant</td>
<td>[66]</td>
</tr>
<tr>
<td>PARK 2</td>
<td>Chr.6 (6q25-q27)</td>
<td>Parkin</td>
<td>Deletion of locus and promoter variability</td>
<td>Autosomal recessive</td>
<td>[83]</td>
</tr>
<tr>
<td>PARK 3</td>
<td>Chr.2 (2p-13)</td>
<td>Unknown</td>
<td></td>
<td>Autosomal recessive</td>
<td>[100,159]</td>
</tr>
<tr>
<td>PARK 4</td>
<td>Chr.4 (p14-16.3)</td>
<td>Unknown</td>
<td></td>
<td>Autosomal recessive</td>
<td>[160]</td>
</tr>
<tr>
<td>PARK 5</td>
<td>Chr.4 (4p14)</td>
<td>UHCL1</td>
<td>I93M mutation</td>
<td>Autosomal dominant</td>
<td>[160]</td>
</tr>
<tr>
<td>PARK 6</td>
<td>Chr.1p (35-36)</td>
<td>Unknown</td>
<td></td>
<td>Autosomal recessive</td>
<td>[99]</td>
</tr>
<tr>
<td>PARK 7</td>
<td>Chr.1 (p36)</td>
<td>DJ-1</td>
<td>Deletion mutation</td>
<td>Autosomal recessive</td>
<td>[95,96]</td>
</tr>
<tr>
<td>PARK 8</td>
<td>Chr.12 (12p11.2-q13.1)</td>
<td>Unknown</td>
<td></td>
<td>Autosomal dominant</td>
<td>[102,161]</td>
</tr>
<tr>
<td>PARK 10</td>
<td>Chr.1 (p32)</td>
<td>Unknown</td>
<td></td>
<td>Autosomal recessive</td>
<td>[104]</td>
</tr>
<tr>
<td>NurR1</td>
<td>Chr.2 (q22-q23)</td>
<td>NR4A2</td>
<td>Point mutation, deletion</td>
<td>Autosomal recessive</td>
<td>[104]</td>
</tr>
</tbody>
</table>

Pattern of inheritance indicates the known mode of transmission. Recessive and dominant modes of transmission indicated.

Chr: Chromosome; NR4A2: Nuclear receptor subfamily 4 group A member 2; UHCL1: Ubiquitin carboxy-terminal hydrolase L1.

**Heat shock proteins**

Molecular chaperones and their functions in protein folding have been implicated in several neurodegenerative diseases, including PD and Huntington’s disease, which are characterized by accumulation of protein aggregates (e.g., α-synuclein and huntingtin, respectively). Heat shock proteins (HSPs) are a family of chaperones that are both constitutively expressed and induced by stressors and that serve essential functions for protein refolding and/or degradation \[73\]. Recent research supports a role for chaperone proteins, including torsinA HSPs, in cellular responses to neurodegenerative inclusion \[74\]. HSP70 is a potent suppressor of both PD and polyglutamine disease in *Drosophila*. These studies provide the promise of treatment for human neurodegeneration through the upregulation of stress and chaperone pathways \[75\]. The expression of the molecular chaperone HSP70 prevents dopaminergic neuronal loss associated with α-synuclein in *Drosophila* and the interference with endogenous chaperone activity accelerates α-synuclein toxicity. Furthermore, Lewy bodies in human post mortem tissue immunostained for molecular chaperones also suggests that chaperones may play a role in PD progression \[76\].

**Parkin**

**Table 4. Mode of transmission of different linked loci.**

**PARK 2** is a large (>1 Mb) locus on chromosome 6 (6q25-q27) and contains the parkin gene \[77,78\]. Several parkin gene mutations have been reported, including a deletion of locus and promoter variability, which causes a form of autosomal recessive juvenile PD. Parkin is a protein expressed in the substantia nigra and in contrast with the α-synuclein gene, lower transcriptional activity of the parkin gene is related to increased risk of PD \[79\]. The age of onset in this form of familial PD is usually below 40 years, but may be between 20 and 65 years \[77\]. Association between parkin mutations and Lewy bodies imply a connection between α-synuclein and parkin \[80\]. Parkin is one member of a family of proteins known as E3 ubiquitin ligases, which attach short ubiquitin peptide chains to the proteins, a process termed ubiquination, thereby tagging them for degradation through the proteosomal degradation pathway. Although the substrates of parkin are not known there are several candidates, some of which induce neuronal damage if overexpressed \[81\]. Recent publications suggest that α-synuclein is a substrate for parkin and this evidence is the clue for ubiquitin pathway involvement in PD pathogenesis \[82,83\].

**Ubiquitin carboxy-terminal hydrolase**

The PARK 5 locus is located on chromosome 4 (4p14) and contains ubiquitin carboxy-terminal hydrolase L1 (UCHL1), which is arguably accepted as a gene responsible for PD \[82\]. A single mutation of this gene (I93M) has been reported in a small German family with PD. Heterozygous missense mutation of the gene has also been identified in another family with PD. Two polymorphic variants of UCHL1 with substitution of serine by tyrosine at position 18 have been reported in which the Y18 variant has a protective role against PD \[82,84,85\]. UCHL1 is found throughout the brain and is seen in Lewy bodies. Furthermore, it is involved in the ubiquitin-dependent pathway of proteolysis. Mutation of this gene could cause abnormal aggregation of the α-synuclein protein and thus PD pathogenesis \[86,87\]. Further supporting this theory, parkin is an ubiquitin protein ligase \[88\]. Thus, mutations in UCHL1 further support ubiquitin as a central PD pathogenesis pathway. These mutations are hypothesized to lead to aberration in the proteolytic pathway and to aggregation of proteins such as Lewy bodies.

**DJ-1**

The PARK 7 locus is on chromosome 1 (1p36) and its related gene, DJ-1, were cloned independently by three groups \[89\]. The penetrance is assumed to be 100% by the age of 40 years and the disease is characterized by slow progression. Mutations in this region lead to loss of function of the DJ-1 protein. The DJ-1 gene has seven exons and encodes a 189-amino acid protein \[90\].
Other PARK loci

PARK 3 and 4 loci on chromosomes 2 and 4, respectively, have been reported in large families where no specific gene has been implicated. As the penetrance of both loci is low, there is weak evidence to show the extent of the relationship between these loci and PD. The age of onset is variable and dementia is the additional clinical feature of affected patients, as seen in \( \alpha \)-synuclein mutations [91,92].

PARK 6 and 10 loci are located on the small arm of chromosome 1, although the regions are clearly separated from each other. PARK 6 was reported in an Italian family with early-onset autosomal recessive PD and has been confirmed in other families [93,94]. PARK 10 linkage has been reported in an Icelandic family with PD and it could be of particular interest as it may represent a locus for sporadic PD [95]. PARK 8 has been reported in a Japanese family with adult-onset autosomal dominant PD [96]. This finding has also been confirmed in a German family with autosomal dominant PD [97].

Nuclear receptor subfamily

The nuclear receptor subfamily 4 group A, member 2 (NR4A2) gene, located on chromosome 2 (2q22-q23), has recently been reported as a susceptibility gene for PD. This gene is essential for differentiation of nigral dopaminergic neurons and has been implicated in schizophrenia pathogenesis. Two point mutations in the first exon of the NR4A2 gene are related to PD. These mutations can cause dopaminergic dysfunction associated with PD [98].

\( \alpha \)-synuclein

The role of \( \alpha \)-synuclein in synaptic vesicle transport and plasticity has been suggested [99] and pathologic mutations may interfere with these functions. Mutant proteins are more prone to oligomerization and fibrillogenesis, which may be the key feature leading to Lewy body formation [100]. The process leading to PD may include a synuclein–ubiquitin pathway to cell death [101]; however, the synuclein pathway is one of several pathways leading to cell death and other possible mechanisms may be involved [65]. Tauopathies and amyloidopathies can lead to cell death or loss of function in substantia nigra pars compacta.

Proteasome

Reduced proteasome function as a key pathway of PD, in which neurotoxic effects of mutant proteins leads to improper ubiquitination and impairment of proteasome function, is proposed by some researchers. This impairment eventually causes decreased protein hydrolysis activity and damage to neurons by neurotoxic effects of unhydrolysed proteins. Both parkin and UCHL1 are involved in ubiquitination so there may be a similar pathway of action between these two genes. Parkin-mediated ubiquitination of \( \alpha \)-synuclein suggests that dysregulation of \( \alpha \)-synuclein has damaging effects on neuronal cells. The form of \( \alpha \)-synuclein that appears to be recognized by parkin is glycosylated and it is possible that mutations may affect glycosylation and subsequently detection of \( \alpha \)-synuclein by parkin [102]. UCHL1 may exhibit a ligase activity toward \( \alpha \)-synuclein and its ubiquitination. There is another way in which \( \alpha \)-synuclein might affect proteosome function independently of other genes. Direct binding of a mutant such as A30p \( \alpha \)-synuclein to the proteasome is one way in which this mutation can exert its effect [103]. Indirect effects of \( \alpha \)-synuclein gene mutations on mitochondria and eventually inhibition of ATP production leading to impairment of highly energy-consuming ubiquitination processes is the other possible way for defining the role of this gene [104]. There is evidence indicating a plausible relationship between DJ-1 function, parkin and \( \alpha \)-synuclein. DJ-1 also affects mRNA expression via protein–protein interactions. It is possible that DJ-1 participates in oxidative stress response and there is evidence that shows the role of free radicals and oxidative events in pathogenesis of PD.

Signaling pathway

Another hypothesis proposed the role of signaling pathways in the pathogenesis of PD and suggests that DJ-1 and parkin are possibly part of the signaling pathways that control synaptic events. Mutant proteins may exert their effects via signaling pathways at the synapse [105]. Another proposed model explains all these three different pathways in a cascade form. The inhibition of the proteasome may be a result of signaling pathway impairment and is followed by the accumulation of oxidatively damaged proteins as a tertiary event. Full understanding of these pathways will introduce new therapeutic targets and new diagnostic tools for presymptomatic diagnosis of PD.

Interaction between genetic & environmental factors

PD can be considered as the final outcome of a sequence of cellular events. At each stage the process is likely to be modified at the cellular level due to genetic or environmental factors [106]. The discovery of methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced Parkinsonism in intravenous drug abusers led to numerous epidemiological studies evaluating potential environmental causes, although no specific agent has yet been identified [29,107]. He interest in interactions between genetic and environmental factors has spurred a great number of association studies on polymorphisms of different genes. The hypothesis is that differences in the ability of certain individuals to metabolize environmental toxins may increase their risk of developing PD. Most association studies produce results of low significance or cannot be reproduced in subsequent studies. Researchers should follow well designed studies with sound molecular methods, carefully selected patients and controls, appropriate statistical analysis and presentation of complete results for association studies [108,109]. The roles of lifestyle, diet, cigarette smoking, alcohol consumption and pesticide exposure have been studied extensively during recent years and some controversial results have been found. In one study, precursors of PD included constipation, adiposity, years worked on a sugar or pineapple plantation, years of exposure to pesticides and...
exposure to sugarcane processing. Factors showing an inverse association with PD included coffee intake and cigarette smoking. Among dietary factors, carbohydrates increased the risk of PD, while the intake of polyunsaturated fats appeared protective [110]. Other research revealed that pesticide exposure was positively associated with PD [111,112]. The risk of PD was similar in individuals who usually consume moderate amounts of alcohol and in abstainers [113].

**Clinical relevance of diagnostic genetic testing**

The α-synuclein mutations are extremely rare and genetic testing should be performed only on a research basis when there is a strong family history of autosomal dominant PD. Parkin homozygous mutations are not rare in childhood or adolescent PD cases, however, they have only been observed in 5% of young adults with PD and there is little evidence supporting a role for mutations in typical late-onset PD. Neither α-synuclein nor parkin gene testing is recommended or available as a routine clinical service [114,115].

**Future areas of research**

PD is presently treated with dopamine replacement therapy, however, with progress in the pathophysiology and molecular biology of PD it is likely that therapy will be targeted at the pathogenic processes upstream of cell loss [106]. Presymptomatic detection and neuroprotective treatment for people at risk are among the areas researched by many scientists in this field. Additional genetic factors and modifying environmental factors must be identified and the underlying biology understood. With public availability of the human genome sequence, the possibility of finding causative genes within genomic regions of linked loci has increased tremendously, thus the role of these genes in the proposed pathological pathways may be elucidated. In the light of known pathological pathways, target-specific drugs will be innovated.

**Amyotrophic lateral sclerosis**

ALS is the most common form of progressive motor neurone disease and affects both upper and lower motor neurons and causes loss of function of both categories. The disease is selective for motor and sensory neurons and the regulatory mechanism of coordination and cognitive function remains intact. ALS is a progressive disease and leads to death due to respiratory failure within 3–5 years. Clinically, the disease manifests as a progressive weakness of muscles and virtually all motor neurons are affected as the disease progresses. Of ALS cases, 5–10% are inherited as an autosomal dominant trait known as familial ALS. **Table 5** summarizes chromosomal loci implicated in ALS [116]. A mutation in the gene encoding CU/ZN superoxide dismutase (SOD1) was reported 10 years ago as the cause of one form of familial ALS. Since then, mutations in SOD1 account for 20% of familial ALS incidences. Over 100 mutations have been reported in the SOD1 gene and among them, A4V missense mutations are the most prevalent and account for more than 40% of SOD1 gene mutations. Mutations in this gene are also found in sporadic forms of ALS. Different loci have been identified in association with ALS, which indicates that there is heterogeneity in the genetic cause of ALS. The underlying mechanism of pathogenesis of these mutations is still obscure. There is support for the role of glutamate as an excitotoxic neurotransmitter. Diminished uptake of glutamate by its transporter excitatory amino acid transporters (EAAT2) can cause neuronal cell death. SOD1 mutations might lead to impaired protection of the neuronal cells against free radicals of the superoxide anion and against toxicity from glutamatergic transmission. Kennedy’s syndrome, which has some aspects of ALS, is a familial adult-onset X-linked motor neurone disease mainly affecting males. Trinucleotide repeats (CAG) in the first exon of the androgen receptor gene on the X chromosome is the molecular basis of the disorder. There is inverse correlation between the number of repeats and age of onset [117].

---

**Table 5. Chromosomal loci implicated in amyotrophic lateral sclerosis.**

<table>
<thead>
<tr>
<th>Category</th>
<th>Phenotype</th>
<th>Chromosome region</th>
<th>Gene</th>
<th>Pathology</th>
<th>Pattern of inheritance</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS1</td>
<td>FALS</td>
<td>21q-21.1</td>
<td>SOD1</td>
<td>Over 100 mutations</td>
<td>Autosomal dominant</td>
<td>[162]</td>
</tr>
<tr>
<td>ALS2</td>
<td>Juvenile slowly progressive ALS</td>
<td>2q33</td>
<td>ALS</td>
<td>Deletion</td>
<td>Autosomal recessive</td>
<td>[163]</td>
</tr>
<tr>
<td>ALS3, ALS4</td>
<td>Juvenile ALS</td>
<td>16, 20 and 9q34</td>
<td>Unknown</td>
<td></td>
<td>Autosomal dominant</td>
<td>[164]</td>
</tr>
<tr>
<td>ALS6</td>
<td>Familial adult-onset ALS</td>
<td>18q21</td>
<td>Unknown</td>
<td></td>
<td>Autosomal dominant</td>
<td>[165]</td>
</tr>
<tr>
<td>ALS-FTD</td>
<td>ALS related with FTD</td>
<td>9q21-22</td>
<td>Unkown</td>
<td></td>
<td>Autosomal recessive</td>
<td>[166]</td>
</tr>
<tr>
<td>ALS-FTDP</td>
<td>ALS related with FTD and Parkinson</td>
<td>17q</td>
<td>Tau protein</td>
<td>Mutation</td>
<td>Autosomal dominant</td>
<td>[167]</td>
</tr>
<tr>
<td>ALS5</td>
<td>Juvenile ALS</td>
<td>15q15-q22</td>
<td>Unknown</td>
<td></td>
<td>Autosomal recessive</td>
<td>[168]</td>
</tr>
<tr>
<td>Kennedy’s syndrome</td>
<td>Spinobulbar muscular atrophy</td>
<td>X</td>
<td>Androgen receptor</td>
<td>Trinucleotide repeats (CAG)</td>
<td>X-linked recessive</td>
<td>[169]</td>
</tr>
</tbody>
</table>

Pattern of inheritance indicates the known mode of transmission. Recessive and dominant modes transmitted autosomally or via X chromosome are indicated.

ALS: Amyotrophic lateral sclerosis; FALS: Familial amyotrophic lateral sclerosis; FTD: Frontotemporal dementia; FTDP: Frontotemporal dementia with Parkinsonian features.

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For a recent review refer to [123].

**Table 5.** Chromosomal loci implicated in amyotrophic lateral sclerosis.
Genetic studies of neurological diseases have discovered many susceptibility and causative genes in recent years. Some of these genes have been implicated in two or more distinct neurological disorders and, conversely, each neurological disorder has many genetic causes. The implication of amyloid protein in AD and neurovascular disorders, Tau protein in AD as well as in FTD and Pick's disease, and α-synuclein protein in AD and PD are examples of common pathways in different neurological disorders. In addition, α-synuclein, PSEN1, NR4A2, neprilysin and APOE-ε4 have been reported in more than one neurological disorder and may share certain pathological pathways.

Treatment plans for neurological diseases need to shift towards a more appropriate pharmacogenomics approach. Genetic background as a predisposition or causative agent has only been reported for a small proportion of the neuronal diseases and a few genetic neurological disorders have significant penetrance. Due to the polygenic properties of the most complex neuronal diseases, having a single genetic marker is usually neither necessary nor sufficient for disease manifestation and the interplay between different related genes and environmental factors contributes to the disease phenotype. However, there is at least one reported gene or locus for most disorders, whose dysfunction has been associated with the neurological disease and almost always multiple loci for one disease are distributed on all human chromosomes. Any specific disease treatment could be based on a collective knowledge of each patient’s genetic profile, including all the mutations related to neurological disease and differential drug response. By using a pharmacogenomics approach, every patient could receive his or her own tailored and more effective therapy, instead of the currently practiced symptomatic treatment. Although pharmacogenomic (investigation of large number of genes and their expression) and pharmacogenetic (investigation of a limited number of genes) strategies for treatment of diseases are in their infancy, they hold a strong incentive for the use of an alternative treatment policy.

Interindividual variability in antidepressant drug response and polygenic properties of AD have been reported by many researchers as evidence of the need for a genome-wide view prior to treatment of the patient suffering from a neurological disorder. It appears that AD patients show about three- to five-times higher genetic variation than the control population. Pharmacogenomic studies also indicate that the therapeutic response in AD is genotype-specific and that approximately 15% of the cases with efficacy and/or safety problems are associated with a defective CYP2D6 gene [118,119]. Polymorphic variants of AD-related genes and genes associated with drug metabolism, disposition and elimination, as well as neurotransmitter receptors, have been shown to affect sensitivity of patients treated with different AD drugs, such as cholinesterase inhibitors, noncholinergic compounds and antidepressant drugs [120–122]. Adverse drug reactions are likely to be influenced by genetic polymorphisms, thus pharmacogenetics holds promise for improving patient compliance to mood-affecting drugs. Preliminary studies have also shown that pharmacogenetic information can be used for the pretreatment prediction of treatment response [123]. Pharmacogenomic studies of antipsychotic response have focused on polymorphisms of genes for dopamine and serotonin receptors, with most positive results reported for polymorphisms of genes of the 5HT2a and 5HT2c serotonin receptor subtypes [124]. The D2 dopamine receptor gene has been one of the most extensively investigated in neuropsychiatric disorders and opens the potential of a targeted pharmacogenomic approach to the treatment of these disorders [125–127]. Other reports indicate effects of polymorphisms in major drug metabolizing genes in patients with multidrug-resistant epilepsy [128].

Innovation of highly technological methods for evaluation and study of individual genomic sequences, availability of whole human genome databases, single nucleotide polymorphism databases and high-throughput genome scan methods provide opportunities to better understand these diseases, their pathophysiology, diagnostic methods and target-specific therapeutic possibilities. Intensive research has continued to elucidate the metabolic or signaling pathway influenced by disease genes. These technological advances will increase the rate at which genes responsible for neurological disorders are discovered, leading to the discovery of major pathological processes behind each disease and the introduction of new diagnostic and therapeutic tools.

Expert opinion
Studying the genetics of neurological disease provides a powerful tool for understanding the pathology behind these disorders and helps us to identify new targets for treatment. By availability of the human genome and introduction of high-technology gene detection methods, the rate of discovery of novel genes directly influencing or changing the risk of neurological diseases has increased over the past few years. The aim of all researchers in this field is to find a way of preventing processes that lead to irreversible neuronal cell loss. However, the genetic component of complex neurological disorders is low and only a small part of each disease category has known causative or even susceptibility genes. By detection of each responsible gene and discovery of its function, a part of big puzzle is formed which will finally provide the whole picture of disease pathophysiology and teach us how to combat it.

Five-year view
It is anticipated that over the next 5 years, more family-based linkage studies will add further evidence to currently reported susceptibility loci and discovery of new genes and environmental factors for each neurological disorder will help us to understand the complex nature of these disorders. Hopefully, a method for presymptomatic detection of these devastating neurological diseases will be developed. Animal models for many neurological diseases have now been introduced and by use of
these, new drugs targeted towards the upper pathophysiological pathway prior to cell damage may be developed in the foreseeable future, at least for trials in animal models. How the genetic profile of individuals and environmental factors interact and affect susceptibility to neurological disease, its age of onset and response to available therapies are some of the very important areas of research in this field and results are eagerly awaited. Progress in stem cell research has been hopeful and the rate of survival of transplanted neuronal cells in various stages of differentiation has improved tremendously. Perhaps stem cell research will help in recovery and treatment procedures.

### Key issues

- A neurological disorder is a chronic debilitating condition that has a high impact on the patient, their family and society as a whole.
- Finding genetic components of neurological disorders is the aim of worldwide scientific investigations and growth of evidence for genetic predisposition indicates definite progress.
- Genetic studies have paved the way for discovery of underlying pathologic processes and helped us to understand disease manifestation.
- Development of diagnostic tools for presymptomatic detection and the prevention of neuronal cell death is the direction of future studies.
- Pharmacogenomic studies have been proposed by leaders in the field because of the complex nature of neurological diseases and the marked interindividual differences in the pathologic process, response to environmental biohazards and therapeutic interventions.
- The outcome of genetic studies in this field will hopefully be the replacement of existing palliative therapy for the majority of neurological diseases with target-specific drugs.

### References

Papers of special note have been highlighted as:
- of interest
- of considerable interest

3. Describes the molecular pathways, gene mutations and pathology of Parkinson's (PD) and Alzheimer's diseases (AD).
4. Faghihi, Mottagui-Tabar & Wahlestedt

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• Extensive and complete review on AD.


• Describes various mutations within genes and corresponding proteins and the implication of these changes in the pathogenesis of AD.


- Explains the penetrance and epidemiology of genetic forms of PD.


- Observations and descriptions of pathogenesis and molecular mechanism leading to PD.


- Describes animal models for the study of complex neurodegenerative diseases.


- Involvement of specific proteins in neurodegeneration, which occurs during progressive PD.


Contains a very good explanation about the roles of different reported mutations and their influence in PD pathogenesis.


Importance of environmental risk factors involved in etiology and pathology of complex diseases, with particular reference to PD.


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