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Genetics of dementia

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This article reviews seven of the most prominent examples of dementing disorders for which genes have been identified. These disorders comprise the most common causes of dementia in the elderly; however, this list is not exhaustive. Interested readers should refer to the texts by Pulst [1] and Terry et al [2] for detailed descriptions regarding specific disorders.

Alzheimer's disease

Clinical features

Alzheimer's disease (AD) is the most common cause of dementia [2]. It is a slowly progressive disease that initially presents with short-term memory loss. Additional symptoms include executive dysfunction, confusion, aphasia, gait, and behavioral disturbances. The typical age of onset is older than 65 years. The average duration of illness ranges from 4 to 20 years. More women than men are affected even after adjustment for the greater longevity of women.

Pathologic features

Pathologically, AD is characterized by diffuse cerebral atrophy associated with β-amyloid (Aβ) neuritic plaques, neurofibrillary tangles, and amyloid

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angiopathy as first described by Alois Alzheimer in 1911 [3]. Senile plaques are complex structures consisting primarily of a core of abnormal aggregates of a small protein molecule known as Aβ. Neurofibrillary tangles are dense bundles of helically wound abnormal fibers composed of a modified form of a normally occurring neuronal protein, the microtubule-associated protein tau. The presence of either senile plaques or neurofibrillary tangles is not pathognomic of AD [4]. They are both known to occur in other neurodegenerative disorders as well as in normal aging. A higher density of these lesions in specific brain regions along with the presence of a clinical history of dementia consistent with AD confirms the diagnosis of AD.

Epidemiology

The risk for AD increases with advancing age. Approximately 10% of the white population over the age of 70 years have dementia, and more than half of these patients have AD [5]. In addition, approximately 20% to 40% of individuals older than 85 years have clinically significant dementia.

The next most important risk factor for AD is family history. Epidemiologic studies show that individuals who have an affected first-degree relative with AD have an approximately fourfold greater risk of developing AD and a total lifetime risk of 23% to 48% [6], although more recent European studies do not report such high estimates [7]. To date, reports on monozygotic and dizygotic twin pairs have suggested higher concordance rates in monozygotic twins than in dizygotic twins [8]. Although the sample sizes are small, they suggest that genetic components play an important role. The lack of complete concordance in monozygotic twins suggests that environmental components are also important in the etiology of AD.

The risk for AD is even higher if there are individuals in more than one generation with the disease, especially when the disease is of early onset (age <65 years). In some of these rare families, AD occurs as a single-gene autosomal dominant trait. Further proof for a genetic basis in AD is that all persons with trisomy 21 (Down syndrome) who survive beyond the age of 40 years invariably demonstrate the neuropathologic features of AD [9]. These observations led to the finding of mutations in the amyloid precursor protein (APP) gene on chromosome 21, the first documented genetic cause of AD [10]. Although there are fewer than 20 families worldwide with APP mutations, the discovery of these mutations confirmed that genetic factors are important in AD.

Familial Alzheimer's disease

Although there is no universally accepted definition of familial AD (FAD), a working definition is three or more affected first-degree relatives (with at least one individual's diagnosis confirmed at autopsy). The clinical features of FAD are typically indistinguishable from nonfamilial (or sporadic) AD [11]. Disease duration is usually 6 to 10 years but can range from

2 to 20 or more years. Familial AD is typically divided into early-onset (<65 years old) and late-onset (>65 years old) types. Thus far, three causative genes have been found in early-onset families. Although these genes account for less than 2% of all cases of AD, the discovery of these genetic mutations has been critical in designing studies to investigate the underlying pathophysiology in AD. A fourth gene, the apolipoprotein E (APOE) ε4 is a major genetic risk factor for both early- and late-onset AD. Other important genetic and environmental risk factors remain to be discovered.

Amyloid precursor protein

The APP gene maps to the long arm of chromosome 21. It encodes for a precursor protein that is proteolytically cleaved to form Aβ protein. Aβ is a 39 to 43 amino-acid peptide that is the major component of the neuritic plaque, one of the neuropathological hallmarks of AD. Two proteolytic pathways for APP processing have been shown to occur normally (Fig. 1). The first is cleavage within the Aβ sequence by a protease referred to as α-secretase [12]. Aβ is destroyed by this cleavage, meaning that this pathway does not contribute to Aβ formation. The second cleavage is on either side of the Aβ sequence. Enzymes called β- and γ-secretase cleave APP to form the N (amino) and C (carboxy) termini of Aβ peptide, respectively. β-secretase cleaves APP first, followed by γ-secretase cleavage, which can result in Aβ peptides of different lengths [13]. Two β-secretases have been identified and are referred to as BACE 1 and BACE 2 [14]. γ-secretase cleavages occur within the predicted transmembrane domain of APP, resulting in the Aβ40 and Aβ42 species. The predominant species, Aβ40, is formed by cleavage after the fortieth amino acid of Aβ. Conversely, Aβ42 only accounts for 10% of the totally secreted Aβ. It is hypothesized that Aβ42 is the pathogenic

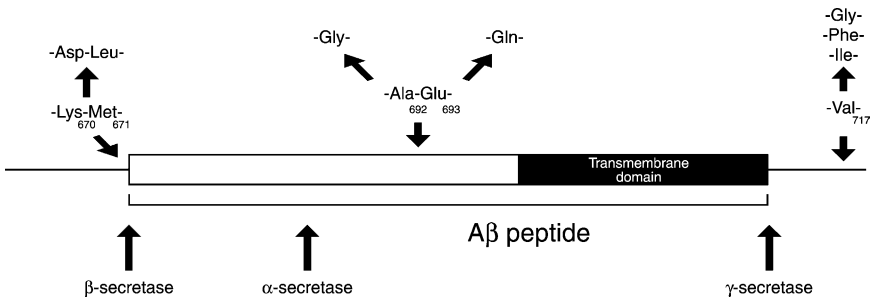

Fig. 1. Schematic representation of the amyloid β (Aβ) peptide portion of the amyloid precursor protein (APP) demonstrating mutation sites associated with familial Alzheimer's disease (positions 670-671 and 717) and hereditary cerebral hemorrhagic amyloidosis of the Dutch type (positions 692 and 693). The three normally occurring sites for processing this portion of the APP are also indicated by the α-, β-, and γ-secretases. Note that cleavage by the α-secretase interrupts the Aβ peptide, whereas cleavage by only the β- and γ-secretases allows the Aβ peptide to remain intact. (*From* Levy-Lahad E, Bird TD. Genetic factors in Alzheimer's disease. Ann Neurol 1996;40:829–40; with permission.)

species in FAD, because plasma exhibits a selective increase in Aβ42 and because Aβ42 is the major constituent of amyloid plaque deposits in the brain [13,15]. β- and γ-secretases are potential therapeutic targets, because inhibition of their activity would decrease Aβ production. There is evidence that presenilin-1 has γ-secretase activity and may be the major γ-secretase [16].

In 1990, a mutation in the APP gene was first discovered in the rare condition called cerebral hemorrhagic amyloidosis of the Dutch type [17]. Because cerebral amyloidosis is also a hallmark of AD, this led to the search for APP mutations in FAD. In 1991, it was discovered that a valine-to-isoleucine substitution existed at codon 717 (Val717Ile) in two families [10]. Subsequently, more than 20 different families have been identified with disease-causing APP mutations. APP mutations are a rare cause of early-onset FAD (which is itself uncommon). They account for probably less than 10% of early-onset FAD and certainly less than 1% of all AD. Clinically, APP mutations result in autosomal dominant early-onset AD, which is typically fully penetrant by the time an affected individual reaches his/her early sixties. In the Val717Ile mutation, age of onset ranges from 41 to 64 years (mean = 50 50 years). There is no evidence that APP mutations are responsible for late-onset FAD. There is no commercially available test for APP mutations.

Presenilin 1/chromosome 14 gene

In 1992, genetic linkage of FAD to a chromosome 14 locus was established and confirmed [18]. The gene, presenilin 1 (PS-1), was subsequently discovered in 1995 [19]. This gene is predicted to encode a 467–amino acid protein with 7 to 10 hydrophobic transmembrane domains (Fig. 2). More than 70 different mutations in PS-1 have been identified worldwide [20]. Most of the mutations are missense mutations (ie, a single base-pair change that results in a single amino acid substitution). However, very few of these mutations result in a truncated normal protein, however, suggesting that the mutations likely cause a change or gain in protein function rather than a loss of function. The function of PS-1 remains unknown, but it may have γ-secretase–like activity [16,21].

Of the three genes known to cause FAD, PS-1 mutations are associated with the earliest age of onset and cause the most rapidly progressive disease. Disease onset ranges from 35 to 55 years of age. Penetrance is nearly complete by the age of 65 years. Disease duration is usually short (5.8–6.8 years) [6]. PS-1 mutations are more common than APP mutations, representing approximately 30% to 60% of early-onset FAD and less than 5% of all AD [6]. A commercial test is available for PS-1 mutations. It is critical that genetic counseling take place before genetic testing in asymptomatic individuals, however [22].

The clinical picture associated with PS-1 mutations is typically characterized by severe dementia associated with language disturbance and myoclo-

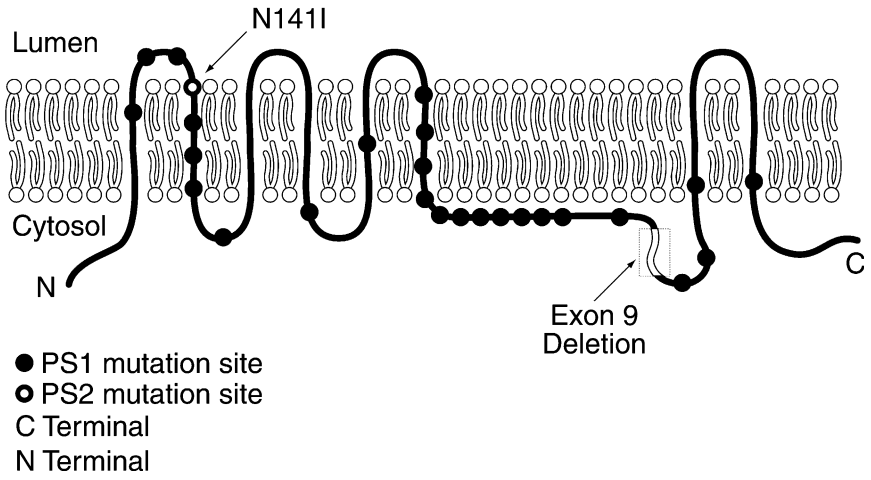

Fig. 2. Schematic representation of one possible form of the transmembrane proteins encoded by the presenilin-1 (PS-1) gene on chromosome 14 and presenilin-2 (PS-2) gene on chromosome 1. This diagram shows eight transmembrane domains, but other configurations remain possible. Several known mutations are indicated, including PS-1 (*filled circles*) and PS-2 (*open circles*). Not all mutations are shown. The arrow at the top left of the figure points to the Volga German PS-2 N141I mutation, the first PS-2 mutation discovered. The arrow at the bottom of the figure points to a PS-1 mutation (an exon 9 deletion) that is often associated with early spasticity.

nus, which appear relatively early in the course of the disease [23,24]. One mutation in the PS-1 gene (an exon 9 deletion) is often associated with early spasticity (see arrow in Fig. 2) [25].

Presenilin 2/chromosome 1 gene

The third AD gene was discovered shortly after the discovery of the PS-1 gene. It was found in FAD kindreds with Volga German (VG) ancestry [26]. These families are ethnic Germans who migrated to Russia but remained separated from the native Russian population. Many of these families subsequently immigrated to the United States, and eight of these families were found to have FAD presumably on the basis of a genetic founder effect (ie, a single common affected ancestor). The presenilin 2 (PS-2) gene was cloned through its homology with the PS-1 gene [27]. It was also called STM-2 (seven-transmembrane domains), although the exact number of transmembrane domains remains unknown. PS-2 is predicted to encode a 448–amino acid protein that is 67% identical to PS-1 (see Fig. 2). The highest degree of conservation is within the hydrophobic/transmembrane domains, suggesting that these regions are important in the normal functioning of the protein. Furthermore, the genomic similarity between PS-1 and PS-2 suggests that they arose by duplication. To date, only four or five mutations in PS-2 have been discovered, making this the least common known genetic cause of AD [20]. A single mutation (N141I) occurs in all the reported early-onset VG

pedigrees, which is consistent with the founder effect hypothesis. All PS-2 mutations are also missense mutations.

Clinical features associated with PS-2 mutations have been reported primarily in the VG families. The mean age of onset in these families is 54.9 ± 8.5 years, and mean disease duration is 7.6 ± 3.2 years. Within the VG families, there is high variability in age of onset, ranging from 40 to 75 years [26]. Ths PS-2 mutation is highly penetrant (>95%). The dementia in PS-2 AD is clinically and neuropathologically indistinguishable from that of sporadic AD.

Apolipoprotein E

The APOE gene was initially identified as a genetic risk factor in AD by genetic linkage analysis of late-onset FAD pedigrees [28]. Because APOE was known to be present in amyloid plaques and neurofibrillary tangles, these observations made APOE a plausible candidate gene. A strong allelic association between APOE ε4 and AD was established in 1993 [29,30] and was rapidly confirmed in autopsy-proven sporadic and familial late-onset AD cases. AD risk associated with APOE is dose dependent [29,31]. The presence of the ε4 allele seems to modify the age of onset of AD [32]. Compared with the most common APOE genotype (ε3/ε3), odds ratios range from 2.8 to 4.4 for AD subjects with one ε4 allele compared with normal controls; the odds ratio increases from 7.0 to 19.3 for subjects with two ε4 alleles [33,34]. These risk estimates are not as strongly observed in blacks or Hispanics (reviewed by Farrer et al [33]), although Hispanics with an ε4 allele and blacks who are ε4 homozygous remain at increased risk for developing AD [35]. Studies suggest a different ε4 allele effect in men than in women. In men, only ε4/ε4 homozygotes have a younger age of onset; whereas one ε4 allele is sufficient to reduce the age of onset in women [36]. The APOE ε4 risk seems to be more pronounced in women [32]. This study reported that women with the ε4/ε4 genotype (approximately 1% of the general population) have a 40% risk of developing AD by the age of 73 years. Not all studies support these findings, however. In addition, several studies suggest a reduced frequency of the APOE ε2 allele in AD patients [37,38].

Apolipoprotein E genetic testing in Alzheimer's disease

APOE genotyping is not recommended in asymptomatic persons without dementia, because the presence or absence of ε4 is not highly predictive of future AD. Individuals with an ε4 allele may not develop AD, whereas those without an ε4 allele sometimes develop AD. Some have advocated APOE testing as an adjunct in the diagnostic evaluation of demented persons [39]. A community-based study suggests that such testing only adds a small amount of certainty to diagnostic accuracy [40].

Late-onset Alzheimer's disease

More than 50 genes have been implicated in late-onset AD [41]. Linkage studies suggest that chromosome 12 contains such candidate genes, including the α-2 macroglobulin gene [42] and low-density lipoprotein receptors [43]. Neither has been clearly established as an AD gene, however [44,45]. Other studies requiring further evaluation have suggested the involvement of genes on chromosome 10 [46,47]. Numerous association studies have implicated other potential genetic factors in AD, but most have not been confirmed or replicated. These factors include interleukin-6, human leukocyte antigen, α_1-antichymotrypsin, and angiotensin converting enzyme [41].

Dementia with Lewy bodies

Dementia with Lewy bodies (DLB) [48] encompasses any case that exhibits clinical dementia and has Lewy bodies (LBs) on autopsy, thereby including (1) diffuse LB disease, (2) LB variant of AD, as well as (3) dementia associated with classic Parkinson's disease (PD). As anticipated, there is substantial clinical overlap between DLB and AD as well as PD. Clinically, DLB is characterized by progressive and fluctuating cognitive impairment, parkinsonism (either de novo or neuroleptically induced), and psychosis with prominent visual hallucinations. Over half of the patients with autopsy-proven DLB have hallucinations or systematized delusions during the course of their illness [49]. Behavioral disturbances (ie, systematized delusions or hallucinations) that require neuroleptic treatment, which can worsen parkinsonian signs and symptoms, present therapeutic challenges for clinicians.

Neuropathologically, DLB is characterized by the presence of LBs, which is also the hallmark of PD. Twenty to fifty percent of cases with neocortical LBs also have substantial AD pathologic findings, namely, Aβ deposition [49]. The boundaries of DLB are still far from being clearly defined because of its shared clinical and neuropathologic features with PD and AD.

Although most cases with DLB are considered sporadic, there are several reports in which LB disease seems to be familial [50,51]. To date, no genes have been identified that cause DLB, and additional genetic and neuropathologic studies are necessary to further investigate the role of genetic factors in DLB. Two genes have been shown to cause rare genetic types of PD: α-synuclein and parkin. Families with α-synuclein mutations have LB pathologic findings and may develop dementia [52,53]. Patients with parkin mutations do not necessarily have dementia or LB pathologic findings [54].

Vascular dementia

Clinical features

Binswanger (1894) and Alzheimer (1911) described behavioral disorders related to arteriosclerosis. Initially, these conditions were categorized as

subcortical arteritis; later, they were classified as Binswanger's disease. With newer neuroimaging techniques, small vessel ischemic disease is now commonly observed in geriatric patients. The contribution of small vessel atherosclerotic disease to clinical dementia remains controversial. Vascular dementia typically does not have a distinct genetic risk factor, although multiple cerebrovascular risk factors are heritable (eg, hyperlipidemia, hypertension). The genetics of vascular dementia is likely multifactorial. As a result, assessing the genetic contributions of each of the risk factors is extremely complicated. For the purposes of this article, we focus on a rare cerebrovascular disease associated with dementia for which a gene has been discovered.

An autosomal dominant syndrome of hereditary multi-infarct dementia has been described with subsequent gene identification [55]. This disorder is called cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Although this is a rare form of vascular dementia, it is the first genetic form of geriatric dementia and depression to be identified. As a result, this disorder should be considered in the differential diagnosis of geriatric patients presenting with these symptoms.

Clinically, patients with CADASIL can have dementia (80%), depression (30%–50%), and migraine with an aura (30%) during the course of their disease. The typical age of onset is in the 50s or 60s; the typical age at death is 64.5 years. Cognitive impairment in CADASIL is best characterized as frontal lobe disturbance, including inattention, perseveration, apathy, and pseudobulbar affect. On T2-weighted MRI, patients with CADASIL have areas of high signal in the periventricular and deep white matter as well as in the basal ganglia. These abnormalities may be observed while patients are in their 20s, asymptomatic, and are initially similar to patients with multiple sclerosis. Hyperintensities increase over the next two decades of life until confluent areas of high signal in the subcortical white matter are observed. Transient ischemic attacks begin to occur when patients are in their 40s and 50s, with some cases showing extensive lacunar infarcts. The patients are not hypertensive. Pathologically, there is a narrowing of small arteries throughout the brain caused by smooth muscle layer hypertrophy, with electron microscopy showing osmophilic densities in the arteriolar media. The diagnosis of CADASIL can sometimes be confirmed by skin biopsies showing the arteriolar pathologic changes. False-negative skin biopsies have been reported, however.

Notch3

Linkage analysis mapped the CADASIL gene to the short arm of chromosome 19. Mutations in the Notch3 gene were first reported in 1996. Subsequent studies reported that these mutations may be present in individuals without a positive family history [56]. The frequency of Notch3 mutations in sporadic and familial cases with vascular dementia remains unclear but seems to be rare. In addition, mutations in the APP and cystatin-β genes are rare causes of cerebral amyloid angiopathy and hemorrhagic strokes.

Regardless of their prevalence, the discovery of these mutations provides an opportunity to explore the genetics of cerebrovascular disease.

The interaction of the multitude of risk factors related to stroke remains unclear. Each of these risk factors is influenced by diverse pathogenetic mechanisms. In the future, additional knowledge regarding the genetic and environmental risk factors related to conditions such as atherosclerosis, diabetes mellitus, and hypertension should result in prevention of and intervention in dementia associated with cerebrovascular disease in the future.

Huntington's disease

Clinical features

The clinical triad in HD includes chorea, cognitive impairment, and behavioral disturbances. Chorea is the main motor sign in HD. These involuntary movements are present only during waking hours. Typically, they cannot be voluntarily suppressed and can increase with stress. Some patients may develop bradykinesia, rigidity, and dystonia. Aspiration secondary to dysphagia is the most common cause of mortality and morbidity. A typical pattern of cognitive decline includes slowness of thought and impaired ability to integrate new knowledge, particularly new motor skills, and a lack of awareness of one's own disability. Visuospatial memory is particularly affected, whereas verbal memory remains preserved until late in the course of the disease. Patients may be able to remember facts, stories, and words but have difficulty copying designs on the Mini-Mental State Examination. Orientation to time and place remains intact until late in the illness. Changes in mood and personality are common, ranging from irritability to prolonged periods of depression as well as psychosis [57]. Suicide is more common in patients with HD than in the general population. Psychiatric symptoms may precede motor signs and symptoms by many years and do not necessarily relate to the severity of chorea or dementia. Other symptoms commonly observed include apathy, aggressive behavior, sexual disinhibition, and alcohol abuse.

The diagnosis of HD is indicated by the presence of a positive family history of an autosomal dominant degenerative disorder consistent with HD; presence of progressive motor disability, including voluntary and involuntary movements; cognitive decline; and behavioral disturbances. Caudate atrophy on CT or MRI provides additional support for the diagnosis. Finally, DNA analysis confirms the diagnosis. The mean age of onset in HD is approximately 40 years [58], although the age of onset ranges from 2 to 80 years. The duration of HD is typically 15 years, with the age of death ranging from 51 to 63 years.

Pathologic features

The primary pathologic feature in HD is neuronal loss in the corpus striatum, occurring first in the caudate and later in the globus pallidus. Caudate

atrophy is evident on MRI, with characteristic concavity of the ventrolateral aspect of the lateral ventricles. A neuropathologic grading system rates the macroscopic and microscopic appearance of the striatum [59]. The neuronal loss seems to be selective, with the medium spiny neurons being preferentially lost. Neurons containing gamma-aminobutyric acid and enkephalin are the most severely affected, and the most consistent neurochemical findings suggest low levels of these two neurotransmitters. The discovery of intranuclear inclusions in HD brains that contain the protein encoded by the HD gene (huntingtin) [60] has resulted in new avenues of animal research. Whether these inclusions interfere with nuclear function or whether they are markers for neurodegeneration remains unknown.

Epidemiology

Many epidemiologic studies have been performed worldwide. There is general agreement that the prevalence of HD in Western European countries is between 3 and 10 cases per 100,000 persons. The rates are lower in Japan, China, and Finland as well as in African black populations. George Huntington, who first described the syndrome in 1872 [61], noted clear familial aggregation in HD.

Genetics

HD is inherited as an autosomal dominant trait. In 1983, HD became the first genetic disorder to be linked by restriction fragment length polymorphism markers to a locus on chromosome 4. [62] Ten years later, an international research consortium reported the successful cloning and sequencing of the HD gene [63]. A novel gene containing a trinucleotide repeat (CAG) that is repeated beyond the normal range is associated with HD. This highly polymorphic CAG repeat is located in the 5′ region of the HD gene (Fig. 3).

Individuals with symptomatic HD have more than 36 CAG repeats in the HD gene. Individuals with the greatest number of repeats (>60) are more likely to have juvenile-onset illness. Most adult-onset HD cases have 38 to 50 CAG repeats. A significant correlation between the number of CAG repeats and age of onset of HD has been demonstrated [64–67]. The association was the greatest in patients with higher CAG repeats (>60), who tended to have a lower age of onset. But the number of CAG repeats is not useful in predicting the age of onset or type of symptoms at presentation in individual patients, however. HD is the first of numerous neurodegenerative disorders associated with a trinucleotide repeat expansion. Several other neuropsychiatric disorders (eg, fragile X mental retardation, hereditary ataxias) that exhibit anticipation are also trinucleotide repeat disorders [68,69]. Genetic testing issues in HD are complex and require careful thought and counseling [70,71].

Interestingly, the discovery of dynamic repeat mutations helps to account for the long-observed clinical phenomenon of anticipation. Anticipation is

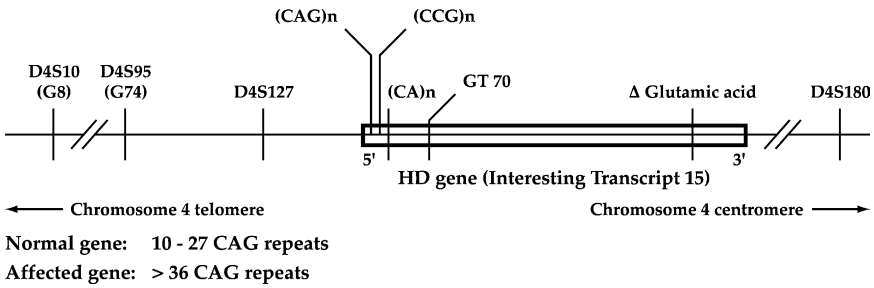

Fig. 3. The Huntington's disease (HD) gene on chromosome 4. Genetic markers are indicated at the top of the figure. D4S10 was the initial marker linked to HD. The bold lines indicate the HD gene, which was called Interesting Transcript-15. This novel gene contains highly polymorphic trinucleotide repeats, (CAG)n, at the 5′ end of the HD gene. Individuals with symptomatic HD have more than 36 CAG repeats at this locus. (Courtesy of Elisabeth Almqvist, PhD, Stockholm, Sweden).

the observation that a disease becomes more severe and appears earlier with each successive generation. As in other trinucleotide repeat disorders, this is a result of the unstable expansion of the CAG trinucleotide repeats when the disorder is passed from parent to offspring. In addition, paternal HD alleles are more likely to undergo significant expansion than maternal alleles, resulting in the observation that those individuals with larger repeat sizes are more likely to have affected fathers.

Frontotemporal dementia

Clinical features

Initially, Pick described a clinical syndrome with dementia, progressive aphasia, and frontal cortical atrophy [72]. Neuronal cytoplasmic inclusions (Pick bodies) were observed later in neuropathologic studies of some cases. Because most patients with dementia and prominent frontal lobe dysfunction do not have Pick bodies, confusion has reigned in the nosology of frontotemporal dementia (FTD). Terminology has included Pick's disease, Pick complex, non-AD dementia, disinhibition-dementia-parkinsonism-amyotrophy complex, and frontal lobe degeneration with spinal motor degeneration. In the 1970s, clinical and pathologic studies helped to solidify consensus diagnostic criteria for FTD [73–75]. Specifically, the discovery of genetic mutations in some FTD families with taupathies (eg, FTD, parkinsonism-linked to chromosome 17 [FTDP-17]) has resulted in new diagnostic categories (see below).

Typically, the clinical presentation of FTD includes personality or behavioral change (often disinhibition) with a relatively intact memory. Later in the course of disease, there may be marked confusion, mutism, and parkinsonian features. There are at least three subtypes of FTD, including progressive

aphasia, semantic dementia, and frontal lobe degeneration [76]. Patients with progressive aphasia have progressively nonfluent speech with agraphia, alexia, and acalculia with preservation of word meaning. Patients with semantic dementia have predominantly temporal lobe abnormalities with progressive loss of word meaning but a preserved ability to read and write regular words. Patients with frontal lobar degeneration have a marked loss of personal and social awareness with hyperorality, distractibility, and task impersistence. In general, patients with inferior-frontal lobe involvement tend to be more disinhibited, whereas patients with involvement of dorsolateral-frontal regions tend to be abulic.

Pathologic features

Pathologically, there is frontal or temporal lobar atrophy. Many cases have only gliosis and neuronal loss without distinctive features. Other cases have cytoplasmic inclusions that may be typical Pick bodies or other varieties of tau-positive material, sometimes resembling neurofibrillary tangles. Classic Pick's disease with Pick bodies is considered a subtype of FTD. Some cases also have anterior horn cell loss in the spinal cord.

Epidemiology

Incidence and prevalence estimates of FTD are not well established, partly due to the clinical heterogeneity of the disorder. The only available sample estimating disease incidence is based on clinician referrals. In this study [77], the prevalence rises from 1.2 to 28 cases per 1 million persons from the third decade to the sixth decade. But because this was not a population-based study, this is probably an underestimate. Among all patients with dementia, FTD is thought to comprise approximately 10% of cases (and probably more in younger age groups).

FTD is the most common syndrome with prominent frontal lobe degeneration. It is commonly misdiagnosed as AD, and less commonly as DLB or AD with vascular disease. Most FTD cases are misdiagnosed as AD. In the Consortium to Establish a Registry for Alzheimer's Disease neuropathologic studies, FTD-like pathologic findings were observed in 3% to 9% of patients with a clinical diagnosis of AD [78]. The frequency of FTD in autopsy case series with dementia varies from 0% to 15% [79].

Genetics

Familial aggregation was the first feature of FTD suggesting that there may be an underlying genetic cause. Several groups reported a positive family history in 10% to 60% of cases [77,80]. Segregation analyses have suggested that first-degree relatives of FTD patients are 3.5 times more likely to develop dementia than first-degree relatives of normal controls. It has also been suggested that age of onset in relatives of FTD patients is, on average,

11 years younger than in other dementia patients [77]. There are clearly a few large families with multiple affected individuals in which FTD seems to segregate in a highly penetrant and autosomal dominant fashion. The success of gene identification (see below) in families with atypical dementia not only confirmed the genetic basis of FTD but established it as a distinct clinical and pathologic entity.

Frontotemporal dementia and parkinsonism-linked to chromosome 17

The first systematic linkage study of FTD families mapped the causative gene to chromosome 17 [81]. Subsequently, many other families with FTD-like features also showed linkage to the same region. Interestingly, several other clinically distinct syndromes also mapped to 17q21-22, including parkinsonism [82] and schizophreniform features [83].

At the consensus meeting on chromosome 17-linked dementia in 1996, these syndromes were classified as FTD and FTDP-17 [84]. Even though many clinical differences exist, pathologic similarities between the various syndromes include tau protein aggregates in the absence of amyloid plaques. Some of these aggregates have similar morphology to the neurofibrillary tangles (NFTs) seen in AD. Because tau is a major component of NFTs and the tau gene is located in the critical region, it has been considered an important candidate gene for FTDP-17. After some failed attempts to identify mutations in this gene, the first tau mutation was identified in a family with familial presenile dementia with psychosis [85] and was confirmed in additional studies [86,87]. This mutation (V337M) is located in exon 12 of the tau gene (Fig. 4). Since then, more than 20 tau mutations have been identified in FTDP-17 families [88,89]. Other families not linked to chromosome 17 have been identified, however, and linkage to chromosome 3 has been reported in one such family [90]. The causative gene in this family is yet to be identified.

Tau gene

The modified product of the tau gene is a major component of NFTs seen in AD. The tau gene is large, with 100,000 base pairs of DNA and 15 exons. It also exhibits complex splicing (see Fig. 4). There are commonly six alternatively spliced isoforms of the tau gene involving exons 2, 3, and 10. All but one of the currently identified mutations affect microtubule binding domains. Most of these mutations are missense, appearing in the coding regions as well as in the noncoding regions (introns). Some mutations are believed to cause disease by producing functional changes that interfere with the normal binding of microtubules, whereas other mutations appear to change the ratio of tau isoforms in the brain (3 and 4 repeat tau). The discovery of tau mutations in families with FTDP-17 has confirmed the fact that genetics plays a role in a subgroup of FTD cases. More work needs to be done to determine the range of tau mutations in FTD and related disorders.

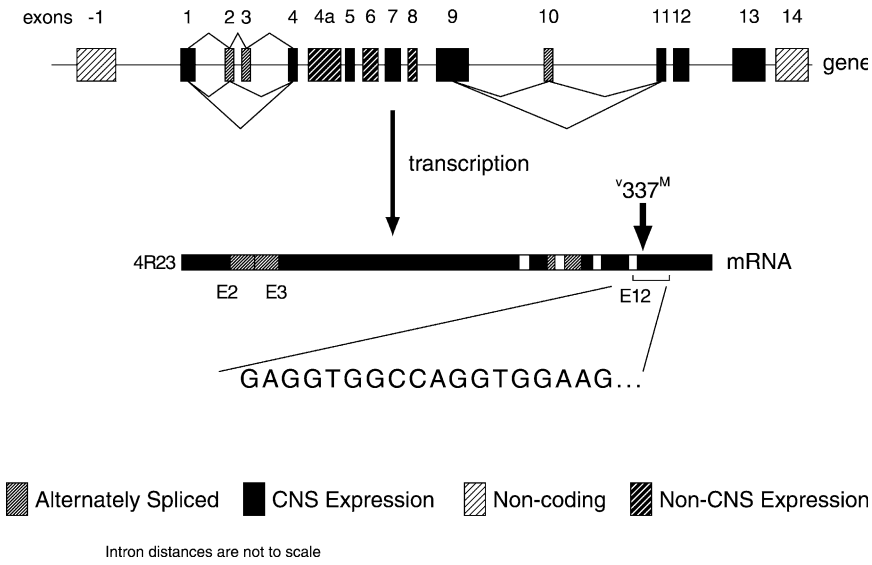

Fig. 4. The tau gene on chromosome 17 has a complex genomic structure with more than 15 exons spread over 100,000 base pairs of genomic DNA (top of figure). It undergoes complex differential splicing. Exons 2, 3, and 10 are alternatively spliced, making up six commonly alternatively spliced isoforms of the tau gene. The large bold arrow points to the first tau mutation (V337M) associated with frontotemporal dementia, which was discovered in exon 12. (Courtesy of Parvoneh Poorkaj, PhD, Seattle, WA).

Tau mutations have not been found in AD or sporadic cases of FTD. In conditions with tau aggregate pathologic findings, such as Guamanian-amyotrophic lateral sclerosis-parkinsonism-dementia complex and progressive supranuclear palsy, there are genetic association data that suggest that tau may play a role in the disease process [91–93]. Explanations for these various clinical, pathologic, and molecular findings are necessary to better understand the role of tau and the frontal lobes in behavior and cognition. Understanding the in vivo processing of the tau gene is likely to be important in the eventual development of therapeutic treatments. But most FTD cases are sporadic and are not associated with mutations in the tau gene [94,95]. If FTD is familial and affected individuals have tau-related neuropathologic findings, the frequency of tau mutations increases to as high as 30% to 40%.

Prion disease

Although prion diseases are relatively uncommon, they exemplify both transmissible and heritable forms of dementia. What we now know as prion diseases were first described in the 1800s, with reports of scrapie in sheep. Scrapie was shown to be experimentally transmissible in 1936 [96]. Human prion diseases were recognized in the 1920s by Creutzfeldt and Jakob and

were called spongiform encephalopathies [97,98]. In the 1960s, kuru (a deadly neurodegenerative disorder transmitted through ritualistic cannibalism) was recognized to be similarly transmissible. In the 1990s, the occurrence of bovine spongiform encephalopathy (mad cow disease) further increased the recognition of these disorders. The prevalence of Creutzfeldt-Jakob disease (CJD) is approximately 1 case per 1 million persons.

Prions are small proteinaceous particles that resist inactivation by conventional proteinases. The normal cellular prion protein (PrP^{C}) is a membrane protein primarily expressed in astrocytes [99–101]. The mechanisms by which PrP^{C} converts to the scrapie isoform (PrP^{Sc}) remain unclear, but the protein structure undergoes a three-dimensional configuration change.

Six human diseases associated with prions have been described, including kuru, CJD, Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal familial insomnia (FFI), atypical prion disease, and new variant CJD (Fig. 5).

The identification of the prion protein (PRNP) gene that encodes the prion protein (PrP) [102] has rapidly transformed neurobiologic and genetics research in this area. Although some families have mutations in the PRNP gene that are transmitted in an autosomal dominant fashion and other cases are caused by known exposure to contaminated tissue, most sporadic cases have no known cause. Interestingly, some prion diseases (eg, CJD, new variant CJD) can be both vertically (heritable) and horizontally

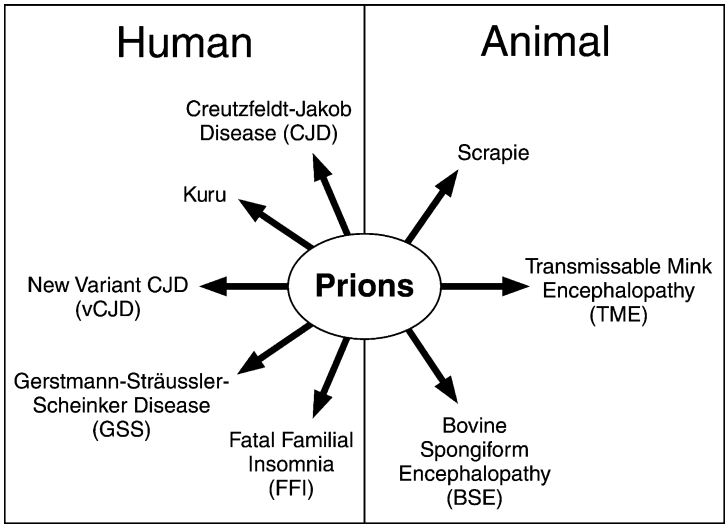

Fig. 5. The human prion diseases include Creutzfeldt-Jakob disease, kuru, Gerstmann-Sträussler-Scheinker disease, and fatal familial insomnia. The animal prion diseases include scrapie, transmissible mink encephalopathy, and bovine spongiform encephalopathy. Because these diseases all share the property of transmissibility and the characteristic pathologic finding of spongiform changes, they are often collectively referred to as transmissible spongiform encephalopathies.

(infectious) transmitted. In this section, we review the genetics of CJD, GSS, and FFI. Current nosology may be replaced in the future by specific DNA mutations, such as "familial prion disease with a P102L mutation and predominant ataxia."

Creutzfeldt-Jakob disease

Sporadic CJD most often affects patients in their 50s and 60s. The typical clinical presentation includes rapid progressive cognitive decline (<2 years to death) accompanied by a variety of neurologic signs (most commonly rigidity, ataxia, and myoclonus) and characteristic synchronous spikes on the electroencephalogram in an afebrile individual. The classic symptoms occur in less than 60% of cases, however. Other clinical features may include psychotic symptoms resembling schizophrenia as well as extrapyramidal and cerebellar dysfunction or akinetic mutism.

The diagnosis of CJD should be entertained in individuals with rapidly progressive neuropsychiatric disorders. Clinical diagnostic criteria have been established by a large CJD surveillance group in Europe [103], although definitive diagnosis can only be made on neuropathologic or biochemical examination of the brain. The neuropathologic hallmarks of CJD include spongiform degeneration, neuronal loss, and astrocytic gliosis. PrP^{Sc}-positive kuru plaques and other PrP-containing amyloid plaques are pathognomic of prion disease. They are almost exclusively found in familial CJD cases with PRNP mutations. A cerebrospinal fluid test for the 14-3-3 protein has been found to be diagnostically useful.

Prion protein mutations

The human PRNP gene is located on the short arm of chromosome 20. This gene is highly conserved throughout many species, suggesting that its function is critical. The cellular function of PrP^{C} remains unknown, however. In families with inherited prion diseases, more than 15 types of mutations have been described [104]. There are no systematic studies that provide frequency estimates of known mutations in different patient samples.

The most common PRNP mutation associated with familial prion disease is the E200K (glutamic acid [GAG] to lysine [AAG]) mutation. This mutation has been found in more than 50 families worldwide. Up to 50% of familial cases have this mutation. The largest known cluster is a group of Libyan Jews living in Israel, who have an incidence of CJD 100-fold greater than the population worldwide [105].

Another missense mutation (D178N) in the PRNP gene has been reported in a number of different families. Surprisingly, the phenotype depends heavily on the genotype present at an entirely different codon (codon position 129). In families with the D178N mutation and valine at position 129, the presentation is that of fairly typical CJD with memory loss,

ataxia, and myoclonus. The age of onset is in the 50s and 60s, with the disease duration ranging from 9 months to 4 years. The electroencephalogram shows generalized slowing rather than periodic triphasic waves. Neuropathologic findings include diffuse spongiform degeneration in the cerebral cortex and basal ganglia with relative sparing of the thalamus.

Alternatively, in families with the same D178N mutation but with methionine at position 129, the phenotype is that of FFI. These patients often present with insomnia and dysautonomia. They may later show signs of ataxia, dysarthria, myoclonus, and pyramidal tract dysfunction. In the later stages, patients exhibit complete insomnia, dementia, rigidity, dystonia, and mutism. The duration of illness is short (mean = 13 months).

Neuropathologically, FFI is characterized by neuronal loss and astrocytic gliosis preferentially affecting the thalamus. At least 21 families with FFI-D178N mutations have been reported [106]. It is unclear why the codon 129 genotype dramatically influences the phenotype associated with the D178N mutation, but it presumably affects the three-dimensional structure of PrP.

Another phenotype, the GSS syndrome, is caused by several different mutations in the PRNP gene [107]. Clinical symptoms include early ataxia, dementia, dysphagia, dysarthria, and hyporeflexia. Patients with GSS are more likely to exhibit ataxia than patients with CJD. Conversely, patients with CJD are more likely to have dementia and myoclonus. Clinical symptoms often overlap, however, and do not always ''breed true'' within families. As such, family members with the same PRNP mutation may have either phenotype. GSS is always considered to be solely genetic and often has a longer disease duration than CJD. Neuropathologically, GSS is distinct from CJD in that GSS is characterized by the presence of large multicentric PrP-containing amyloid plaques with variable spongiform changes.

The most common mutation associated with GSS is the P102L mutation. More than 30 affected families in the Northern Hemisphere have been described to date [108]. This was the first mutation to be formally linked to a human prion disease and is the causative mutation originally described by Gerstmann, Straüssler, and Scheinker [109].

The clinical and neuropathologic characteristics of these families are indistinguishable from those of sporadic CJD. Interestingly, when infected brain tissue from CJD E200K patients was injected into primates, the disease was transmitted in most trials, but transmission has not been demonstrated in other families with different mutations [110]. This finding is similar to the results observed in experiments using brain tissue from sporadic CJD cases.

Mitochondrial disorders

Mitochondrial disorders are clinically diverse and are defined by structural or functional abnormalities in the mitochondria or mitochondrial DNA

(mtDNA). Because mtDNA has a poorly developed repair system, mutations are rarely repaired. Although infrequent, an increasing number of mtDNA mutations have been described in several neurologic disorders. The characteristics of inherited mitochondrial disorders include maternal inheritance, heteroplasmy, mitotic segregation, and the threshold effect. Because mtDNA is almost exclusively maternally inherited, all mtDNA mutations are passed on by mothers. Because of the clinical heterogeneity associated with mitochondrial disorders, analysis of large families is often necessary to establish the pattern of maternal inheritance. Heteroplasmy refers to the mixture of both mutant and wild-type molecules within mitochondria. In normal cells, all mtDNA molecules are identical. As heteroplasmic cells undergo cell division, the proportions of mutant and normal mtDNA allocated to daughter cells shift. As a result, some clinical symptoms may improve as a child ages. Mitotic segregation explains the markedly different levels of mutant mtDNA in members of the same family as well as among different tissues in a single individual. The threshold effect is the observation that a certain level of mutant mtDNA must be achieved before a cell expresses a defect. Variability in onset and severity of clinical manifestations results from a changing balance between the energy supply and oxidative demands of different organ systems.

Mitochondrial disorders have been implicated in prevalent neurodegenerative disorders (eg, AD, PD) as well as in aging itself, but the evidence is controversial. Aging is associated with an increase in mtDNA mutations. These are not specifically germline mutations but accumulating mutations that may increase over time in any organ, including the brain. The precise effects of these mutations are not known. These mutations are not genetically transmitted to the next generation but may cause dysfunction of the organs in which they occur. It has been hypothesized that several different mutations may ultimately contribute to functional impairment. There is evidence that mtDNA mutations may be involved in neurodegenerative conditions such as AD. In AD, it is postulated that mtDNA mutations may lower the oxidative efficiency of critical neuronal populations early in life [111]. An increase in oxidative damage to mtDNA in AD brains has been reported. In addition, younger AD patients (<75 years old) are more likely to have an increased level of common mtDNA mutations than age-matched controls. Nevertheless, the data need to be confirmed. It remains unclear whether these observations are the consequences of the disease or whether they contribute to the pathophysiology. Screening for mtDNA mutations is not recommended for any neurodegenerative conditions until these frequency of these mutations is better established [112].

Summary

Many neurodegenerative diseases are exceedingly complex disorders (Fig. 6). In the past decade, we have made tremendous advances in our under-

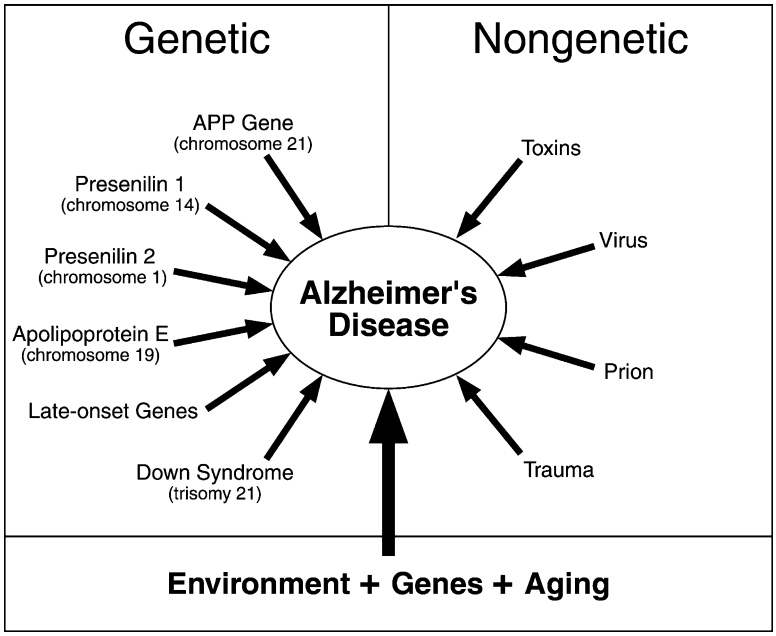

Fig. 6. This diagram demonstrates the concept that the Alzheimer's disease (AD) phenotype (as well as the other neurodegenerative conditions) is phenotypically heterogeneous. On the left are the four known genetic factors associated with AD. There are likely other early-onset as well as late-onset genes yet to be discovered. On the right are four potential nongenetic causes of AD that presently remain speculative. In summary, the bottom arrow shows that most cases of AD in the general population may be the result of a complex interplay between environment, genetic predisposition, and aging.

standing of the genetic basis of these disorders. One common characteristic of these disorders is the existence of rare families in which a given disease is inherited as a Mendelian trait. In this article, we have reviewed the genetics of several common neurodegenerative disorders that are associated with cognitive disturbances and for which causative genes have been identified. Further genetic analysis should clarify the roles of known genes in the pathogenesis of common sporadic forms of these various diseases. Investigation of the normal and aberrant functions of these genes should provide insight into the underlying mechanisms of these disorders. Such research should facilitate new strategies for therapeutic interventions.

Although molecular genetics has helped to clarify the etiology of these disorders, clinicians have played a critical role in the careful identification and classification of many families who were involved in the eventual mapping and cloning of causative mutations. The role of the clinician should not be underestimated. Future clinical and molecular genetics findings hold many clinical implications. It is likely that new diagnostic and therapeutic strategies for dementing disorders are just on the horizon.

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