

Review

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Novel insight into genetic impacts on neurodegenerative dementia

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Abstract

Dementia can be broadly categorized into neurodegenerative dementias and non-neurodegenerative forms. Neurodegenerative dementias include Alzheimer's disease (AD), frontotemporal lobar degeneration (FTLD), neuronal intranuclear inclusion disease (NIID), dementia with Lewy bodies (DLB), Huntington's disease (HD), and prion diseases. Genetic factors play a central role in the etiology of neurodegenerative dementias. In AD, heritability estimates range from 58%-79% for late-onset AD (LOAD) and over 90% for early-onset AD, with causal genes including *APP*, *PSEN1*, and *PSEN2*. LOAD is a complex polygenic disease. Genome-wide association studies have identified more than 70 susceptibility loci, among which *APOE* $\epsilon 4$ is the most established genetic risk factor; carriers of the *APOE* $\epsilon 4/\epsilon 4$ genotype are now considered genetically predisposed to AD. However, the known heritability of AD remains incomplete, with rare variants in dozens of genes contributing substantially to disease risk. FTLD often presents with behavioral and language impairments, with *MAPT*, *C9orf72*, and *GRN* being the most commonly implicated causal genes. DLB, which overlaps clinically with Parkinson's disease dementia,



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shares genetic risk factors with both AD and PD, including *APOE*, *BIN1*, *SNCA*, and *GBA*. NIID is caused by abnormal *NOTCH2NLC* GGC repeat expansions, which correlate with disease phenotype and age of onset. HD results from abnormal CAG repeat expansions in the *HTT* gene. Prion diseases arise from variants in the *PRNP* gene, with M129V being a notable risk factor. These findings underscore the pivotal role of genetic factors in the pathogenesis of neurodegenerative dementias.

Keywords: Neurodegenerative dementia, Alzheimer's disease, frontotemporal lobar degeneration, neuronal intranuclear inclusion disease, Huntington's disease, dementia with Lewy bodies, prion diseases, genetics

INTRODUCTION

Dementia is a syndrome characterized by progressive cognitive impairments in multiple cognitive domains. With the aging of the global population, the number of dementia patients is projected to increase from 57.4 million in 2019 to 152.8 million by 2050, posing a substantial burden on society and families^[1]. Clinically, dementia arises from various causes and is commonly classified into neurodegenerative and non-neurodegenerative types. Neurodegenerative dementia (NDD) includes Alzheimer's disease (AD), dementia with Lewy bodies (DLB), frontotemporal lobar degeneration (FTLD), neuronal intranuclear inclusion disease (NIID), Huntington's disease (HD), and prion diseases. Multiple risk factors contribute to the pathogenesis of NDD and can be broadly categorized as modifiable and non-modifiable^[2]. Among the non-modifiable factors, genetic components are well established. Advances in sequencing techniques and bioinformatic analyses greatly expanded our understanding of the genetics underlying NDD^[3]. In this review, we summarize recent genetic findings related to NDD.

AD

AD is the most common form of dementia in the elderly, accounting for approximately 60%-80% of all dementia cases. Based on the age of onset, AD is classified into early-onset AD (EOAD; onset < 65 years) and late-onset AD (LOAD; onset ≥ 65 years)^[4]. Genetics play a significant role in AD, with heritability estimates of 58%-79% for LOAD and over 90% for EOAD^[5]. The major causal genes include *APP*, *PSEN1*, and *PSEN2*. To date, 364 *PSEN1* variants, 115 *APP* variants, and 90 *PSEN2* variants have been identified (<https://www.alzforum.org/mutations>). Among these, 89% of *PSEN1* variants are pathogenic, compared with 47% of *APP* variants and 21% of *PSEN2* variants^[6]. In the Caucasian population, approximately 1.35% of EOAD patients carry pathogenic variants in *APP*, *PSEN1*, and *PSEN2*^[7]. Similarly, in the Han Chinese population, about 1.65% of EOAD patients carry pathogenic variants in these genes^[8].

Compared to EOAD, LOAD is much more common and is considered a complex disease with a polygenic background. Dozens of risk genes contribute to its development, with *APOE* being the first identified. The *APOE* gene, located on chromosome 19q13.2, has three major alleles: $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$ ^[9]. Among them, *APOE* $\epsilon 4$ is a well-established genetic risk factor for AD across various populations, with risk levels decreasing in the order: East Asian, White, Black, and Hispanic populations^[10]. Compared with heterozygotes or non-carriers, individuals with the *APOE* $\epsilon 4/\epsilon 4$ genotype are now considered to have a genetically determined form of AD, characterized by near-full penetrance, predictable symptom onset, and biomarker changes^[11]. Interestingly, loss-of-function (LoF) variants of *APOE* have been identified in two *APOE* $\epsilon 3/\epsilon 4$ carriers who remained cognitively healthy with normal amyloid levels at ages 76 and 90, suggesting that *APOE* $\epsilon 4$ knockdown may reduce the risk of AD^[12].

Beyond *APOE*, genome-wide association studies (GWAS) have identified over 70 common low-risk susceptibility loci for AD [Supplementary Table 1]. Since 2009, more than 10 large-scale GWAS have been

conducted. In 2009, two large GWAS identified *PICALM*, *CLU*, and *CR1* AD risk loci^[13,14]. In 2011, five additional AD loci were found using GWAS meta-analyses (*ABCA7*, *MS4A6A/MS4A4E*, *EPHA1*, *CD33*, and *CD2AP*)^[15,16]. In 2013, the International Genomic Alzheimer's Project (IGAP) confirmed nearly all previously reported loci - except *CD33* - and identified 11 new susceptibility loci^[17]. In 2019, a genome-wide association by proxy (GWAX) approach revealed several novel loci associated with AD risk^[18]. That same year, Kunkle BW *et al.* reported five new genome-wide loci (*IQCK*, *ACE*, *ADAM10*, *ADAMTS1*, and *WVVOX*), with *ACE* and *WVVOX* specifically linked to increased AD risk^[19]. In 2021, a large GWAX study replicated 31 LOAD-associated loci and identified seven novel loci in a cohort of 1,126,563 individuals^[20]. In 2022, another large GWAS revealed 75 LOAD loci - including 42 novel ones - based on 111,326 AD cases and 677,663 controls^[21]. The AD-associated loci are involved in amyloid plaque formation, neurofibrillary tangle development, cholesterol metabolism, endocytosis/phagocytosis, and immune responses^[22]. However, many of these common loci have not been fully verified in the Chinese population^[23]. Only a few GWAS conducted in China have identified novel susceptibility loci. In 2018, Zhou *et al.* revealed that *GCH1* and *KCNJ15* increased AD risk in eastern China^[24]. In 2020, Jia *et al.* identified four novel loci (*GLRX*, *CTC-278L1.1*, *CTD-2506J14.1*, and *CHODL*) associated with AD risk in the Chinese population^[25]. In 2024, Ge *et al.* discovered that *KIAA2013*, *SLC52A3*, *TCN2*, and *EGFR* contributed to AD risk in Southeast and Southwest China^[26]. Chinese GWAS have also replicated associations within the *APOE* region, though replication of many other loci has been unsuccessful. Differences between Hispanic white and Chinese populations may elucidate the complex etiology of AD across ancestries. While Chinese-specific genetic architecture reveals potential therapeutic targets, functional annotation remains limited compared to European-centric databases. Cross-ancestry functional genomics is therefore urgently needed to unlock diagnostic and therapeutic paradigms.

Although GWAS have revealed dozens of loci implicated in AD, the heritability estimated from GWAS summary statistics is only 3.1%-7.1%^[20]. The discrepancy between heritability estimates from twin studies and GWAS is referred to as “missing heritability”, which may be attributed to several factors, such as underexplored rare variants and the limited sample sizes of non-European populations^[22]. To address this missing heritability, several strategies can be explored, such as analyzing rare and complex variants, establishing large-scale cohorts across diverse ancestries, and incorporating gene-environment interactions. With the development of next-generation sequencing (NGS) technologies, including whole-exome sequencing (WES) and whole-genome sequencing (WGS), an increasing number of rare risk variants for AD have been identified. Unlike common variants detected through GWAS, rare variants identified by NGS are low-frequent in populations but have strong effect sizes. In European populations, genes such as *TREM2*^[27], *PLD3*^[28], *ABCA7*^[29], *UNC5C*^[30], *SORL1*^[31], *PLCG2*, *ABI3*^[32], *ATP8B4*, and *ABCA1*^[33] have been implicated in AD risk. In the Chinese population, rare variants in *PDE11A*^[34], *C7*^[35], *ACAA1*^[36], *ECE2*^[37], *GSN*^[38], *LMTK2*, and *CRB1*^[39] have been associated with AD risk [Figure 1]. These rare variants influence A β or tau metabolism and contribute to AD pathogenesis.

In addition to single nucleotide variants (SNVs) and insertions/deletions (indels), copy number variants (CNVs) have also been implicated in AD. CNVs are the most common type of structural variant, ranging in size from 50 bp to several Mb, and include duplications, deletions, insertions, inversions, and translocations^[40]. It is estimated that 4.8%-9.5% of the human genome is affected by CNVs, which are associated with AD^[41]. For example, 25 *APP* gene duplications have been shown to co-segregate with AD in autosomal dominant families^[42]. In a study of 755 AD cases and 811 controls from non-Hispanic white, AD cases exhibited more duplications and larger deletions compared to controls^[43]. Based on WGS data from 1,411 individuals, Chen Ming *et al.* identified 3,012 rare AD-specific CNVs enriched in biological processes such as cellular glucuronidation and neuronal projection. Integration of multi-omics data further revealed a

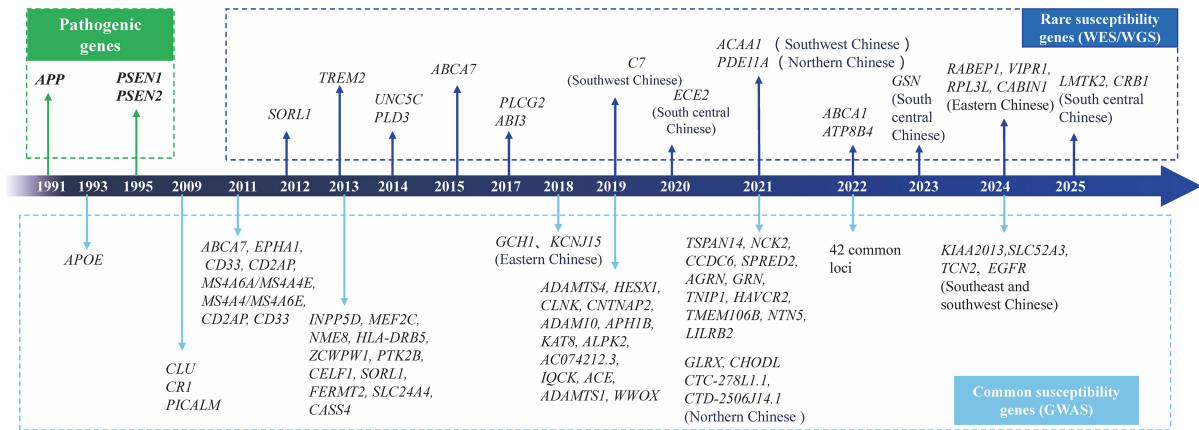


Figure 1. Pathogenic, common risk, and rare susceptibility genes associated with AD. Genes annotated with specific Chinese populations (e.g., Northern Chinese) represent novel associations first identified in our Chinese cohort. Genes without population annotations represent established risk genes originally discovered in European/American populations. AD: Alzheimer's disease; WES: whole-exome sequencing; WGS: whole-genome sequencing.

key CNV potentially involved in immune response^[44]. Tandem repeats represent another important type of genetic variation, consisting of DNA sequences repeated multiple times. Short tandem repeats (STRs) and variable number tandem repeats (VNTRs) are two major forms of repetitive sequences in eukaryotic genomes, with repeat units of 2-6 base pairs and 10-60 base pairs, respectively^[45]. In Caucasian populations, Arne *et al.* found a strong correlation between VNTR length in *ABCA7* and a GWAS signal. Expanded VNTRs were significantly enriched in AD patients, and VNTR length was negatively correlated with cerebrospinal fluid A β 42 levels and *ABCA7* expression^[46]. In mainland China, *NOTCH2NLC* repeat expansions were identified in three clinically diagnosed AD patients^[47]. Moreover, intermediate-length *NOTCH2NLC* CGG repeat expansions were also detected in a pathologically confirmed AD case^[48]. These findings suggest that *NOTCH2NLC* CGG repeat expansions may be associated with AD. Beyond nuclear genes, mitochondrial variants also contribute to AD risk. In a cohort of 18,031 AD patients, the rare *MT-ND4L* variant rs28709356 was associated with AD onset. Furthermore, SKAT-O analysis implicated *MT-ND4L* and mitochondrial-related nuclear genes such as *TAMM41* in AD pathogenesis^[49].

FTLD

FTLD is one of the most common types of early-onset dementia, typically presenting between the ages of 45 and 65, and is characterized by progressive behavioral and/or language impairments. FTLD clinical syndromes include behavioral variant frontotemporal dementia (bvFTD), progressive non-fluent aphasia (PNFA), and semantic dementia (SD)^[50]. PNFA and SD are classified as primary progressive aphasia (PPA). Among these, bvFTD shows the highest heritability, followed by FTD-ALS, PPA, and atypical Parkinson's syndrome. The etiology and pathogenesis of FTLD are not fully understood, although genetic factors play a significant role. Around 20%-25% of FTLD cases carry a mutation associated with FTLD pathology, with autosomal dominant inheritance. To date, more than 10 pathogenic FTLD genes have been identified, with *MAPT*, *C9orf72*, and *GRN* being the most frequently implicated^[51]. Over 50 pathogenic mutations in *MAPT* and more than 70 in *GRN* have been identified, accounting for 5%-20% and 5%-25% of hereditary FTLD cases, respectively^[52,53]. *C9orf72* variants account for 20%-30% of hereditary FTLD, with a pathogenic hexanucleotide repeat expansion (> 30 repeats) contributing to 25% of familial cases and 5% of sporadic cases in Caucasian populations^[50,54].

MAPT, the first gene identified in FTD, is located on chromosome 17 and encodes the microtubule-binding tau protein^[55]. Pathogenic *MAPT* variants can lead to predominantly 3R, 4R, or mixed 3R/4R tau. Missense variants usually disrupt tau's ability to bind microtubules, while splicing variants alter the 4R-to-3R tau ratio^[56]. *C9orf72*, located on chromosome 9, encodes a protein involved in endosomal transport and autophagy. In Asian populations, *C9orf72* variants are extremely rare (0-4.8%)^[57,58], but a recent large Chinese cohort study found that *C9orf72* expansion is the most common one in FTLT, accounting for 8.2% of hereditary cases^[59]. *GRN*, also located on chromosome 17, encodes progranulin (PGRN). Most pathogenic *GRN* variants are frameshift, splicing, or nonsense mutations that cause loss of function or haploinsufficiency^[60]. Other less common FTLT genes include *TBK1*, *VCP*, *CHMP2B*, *FUS*, *SQSTM1*, *TARDBP*, *CHCHD10*, *TIA1*, *CCNF*, and *CYLD* [Figure 2], which contribute to FTLT through multiple pathways, such as autophagy and inflammation^[50]. For example, *CHCHD10* mutations occur in up to 7.7% of Chinese FTD patients, a frequency much higher than that in European populations (0.7%-2.6%)^[61].

In 2010, the first GWAS revealed that rs1990622 in *TMEM106B* was associated with reduced FTLT risk in 515 patients and 2,509 controls of Caucasian ancestry^[62]. In 2014, a GWAS including 3,526 FTD patients and 9,402 controls showed a genome-wide significant association at the *HLA* locus and a suggestive association near *RAB38/CTSC*^[63]. In 2019, a novel genome-wide significant risk locus (*DPP6* rs118113626) was discovered using WGS data from 517 FTLT-TDP patients and 838 controls^[64]. Rare variants also contribute to FTD risk. In a cohort of 2,139 FTD patients and 9,047 controls, a rare missense variant in *MAPT* (p.A152T) was associated with FTD risk^[65]. Two rare variants near *C9orf72* were strongly associated with FTD in 354 FTD patients and 4,209 controls^[66]. Additionally, in European populations, GWAS have identified common CNVs in *C9orf72* and *MAPT* associated with FTD-ALS. Rare structural variants, including *LRKK2* duplication, *CHCHD10* deletion, and *FIG4* deletion, have been reported in patients with PPA, FTD-ALS, and FTD, respectively^[67].

DLB AND PARKINSON'S DISEASE DEMENTIA

Lewy body dementias (LBD) include DLB and Parkinson's disease dementia (PDD), which share substantial overlap in clinical features, genetics, and neuropathology^[68]. DLB is the second most common NDD after AD, accounting for approximately 10%-20% of all dementia cases^[69]. Genetic factors are estimated to contribute about 36% to the development of DLB. A GWAS including 1,743 DLB patients and 4,454 controls indicated that *APOE*, *SNCA*, and *GBA* loci were associated with DLB risk^[70]. A larger GWAS confirmed these associations and additionally revealed *BIN1* and *TMEM175* as novel risk loci in 2,591 DLB patients and 4,027 controls^[71]. The *APOE* ϵ 4 allele is associated with faster disease progression and worsened survival in DLB^[72]. *APOE* and *BIN1* were linked to AD, while *SNCA*, *GBA*, and *TMEM175* were associated with PD, highlighting the genetic overlap among DLB, AD, and PD. CNV also plays a role in DLB; in a European cohort, a common deletion in *TPCN1* was identified as a novel risk locus^[67]. Clinically, the "1-year rule" is often used to distinguish DLB from PDD: when dementia occurs more than one year after the onset of parkinsonian symptoms, the condition is more likely PDD; if cognitive symptoms precede or appear within one year of parkinsonism, DLB is more likely. Different variants in the *SNCA* gene are implicated in PDD, including missense variants and locus multiplications. In a cohort of patients with PD, PDD, and DLB, distinct associations were observed at the 3' and 5' regions of the *SNCA* gene, indicating that PD, PDD, and DLB may have partly distinct genetic etiologies^[73]. Among 740 PD patients, carriers of *GBA* variants exhibited more rapid progression of cognitive decline during follow-up^[74]. In another study of 37 PD patients and 40 controls, common variants in *MAPT* were associated with dementia in PD and with neural circuitry underlying cognition in controls^[75]. Furthermore, a genome-wide survival analysis of 3,923 clinically diagnosed PD patients identified *APOE* ϵ 4 and the APP receptor *LRP1B* as genetic risk factors for progression from PD to PDD^[76].

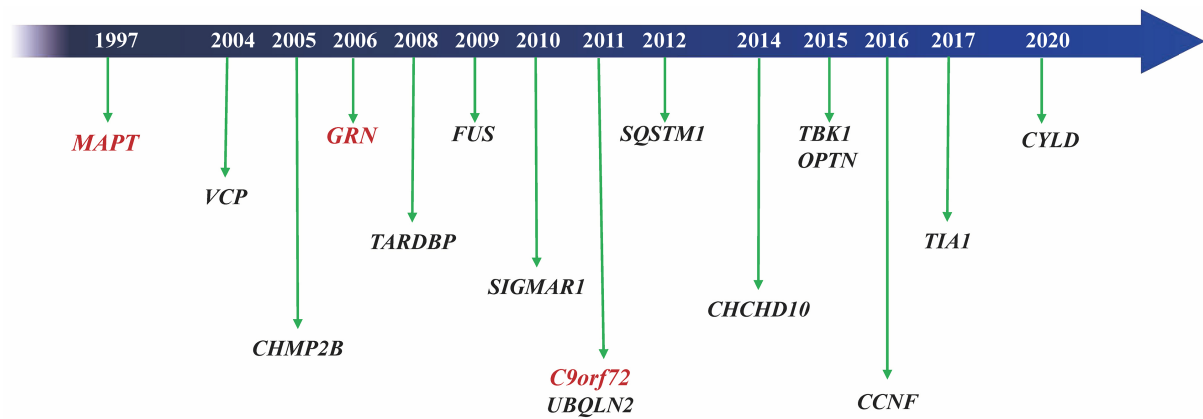


Figure 2. Pathogenic genes associated with FTD. FTD: Frontotemporal dementia.

NIID

NIID is a rare degenerative disease characterized by highly variable clinical symptoms and multisystem involvement. Based on predominant clinical features, NIID can be classified into four subtypes: dementia-dominant, movement disorder-dominant, muscle weakness-dominant, and paroxysmal symptom-dominant. Among these, the dementia-dominant subtype is the most common, present in 38.1% of patients and accounting for symptoms in 49.4% of cases^[77]. Typically, patients with the dementia-dominant subtype exhibit subcortical dementia symptoms, such as early executive dysfunction and memory impairment^[78]. In 2019, researchers in China and Japan identified abnormal GGC repeat expansions in the 5' region of the human-specific *NOTCH2NLC* gene as the genetic cause of NIID. Pathogenic GGC expansions are defined by repeat sizes ranging from 66 to 517. A repeat size greater than 65 establishes a diagnosis of *NOTCH2NLC*-associated NIID^[79,80]. Such pathogenic *NOTCH2NLC* GGC expansions are relatively common in Chinese NIID patients. However, they are rare among patients of European descent, indicating that additional genetic factors may contribute to NIID onset in these populations^[81]. The size of the *NOTCH2NLC* GGC expansion is associated with specific clinical phenotypes. Larger expansions (200-517 repeats) are frequently observed in muscle weakness-dominant cases and are often characterized by a higher frequency of GGA interruptions and fewer AGC interruptions. Intermediate repeat sizes (100-200 repeats) are typically carried by patients with the dementia-dominant subtype. In contrast, smaller expansions (< 100 repeats), with fewer GGA interruptions and more AGC interruptions, are commonly seen in the movement disorder-dominant subtype^[82,83]. Furthermore, repeat size has been shown to correlate negatively with age of onset in a cohort of 635 NIID patients^[84].

HD

HD is an autosomal dominant neurodegenerative disease, classified according to age of onset into juvenile (≤ 20 years), adult (21~59 years), and late-onset (≥ 60 years). Typical symptoms include chorea, cognitive decline, and psychiatric disturbances. In the early stages, some patients present with subtle or atypical chorea-like symptoms, which may instead manifest as dystonia, parkinsonian, or ataxia. In certain cases, cognitive impairment precedes movement symptoms, primarily affecting executive function and attention^[85].

HD is caused by an abnormal expansion of CAG trinucleotide repeats in exon 1 of the *HTT* gene on chromosome 4^[86]. In unaffected individuals, the number of CAG repeats is ≤ 26 . Carriers with 27-35 repeats do not develop HD, but the repeat length may expand when transmitted to offspring, increasing their risk of disease. Repeat lengths of 36~39 are associated with reduced penetrance, while ≥ 40 repeats confer full

penetrance, and all carriers eventually develop HD^[87]. It is important to distinguish HD from HD-like (HDL) diseases when *HTT* repeat lengths fall within the normal range. For example, HDL1, caused by *PRNP* mutations, and HDL2, resulting from abnormal *JPH3* CTG repeat expansions, can exhibit clinical phenotypes that closely resemble HD^[88,89].

PRION DISEASE

Prion diseases are a group of fatal, rapidly progressive neurodegenerative disorders caused by misfolded prion proteins. The primary pathological features include spongiform changes and gliosis in the central nervous system^[90,91]. Human prion diseases primarily include Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal familial insomnia (FFI), and Kuru disease. CJD is the most common prion disease, characterized clinically by rapidly progressive dementia, myoclonus, and ataxia^[92]. GSS typically presents with cerebellar ataxia and cognitive impairment, while FFI is primarily associated with progressive sleep disturbances and autonomic dysfunction. Prion diseases occur in sporadic, genetic, and acquired forms^[93].

Genetic forms account for approximately 10%-15% of human prion diseases^[94]. To date, more than 60 *PRNP* variants have been identified^[95]. The *PRNP* gene, located on chromosome 2, encodes the 253 amino acid PRNP protein. Reported PRNP variants include missense mutations, octapeptide repeats insertions (OPRIs), octapeptide repeats deletions (OPRDs), and premature termination variants^[96]. The frequency of specific variants varies significantly across populations. The E200K and V210I variants are the most common in Europe and the USA, with E200K particularly prevalent in Slovakia, Israel, Italy, and Chile^[97,98]. Different *PRNP* variants are associated with distinct symptoms, age of onset, and disease duration. Some variants, such as OPRI, A117V, and G114V, are fully penetrant and typically manifest in early adulthood^[99].

Approximately 85% of human prion disease cases are sporadic CJD (sCJD). The cause of sCJD remains largely unknown, aside from aging and certain genetic risk factors^[100]. Among these, the *PRNP* M129V polymorphism is the strongest known genetic risk factor^[101]. Specifically, in codon 129 of PRNP, about 70% of sCJD patients carry the MM genotype, 16% the VV genotype, and 13% the MV genotype^[102]. GWASs have identified several additional genetic variants that influence sCJD risk, including *PRNP* rs1799990 (M129V)^[103], *PRNP* rs6107516, and *GRM8* rs6951643^[104]. A recent large GWAS also revealed that *STX6* rs3747957 and *GAL3ST1* rs2267161 are associated with sCJD in a cohort of 5,208 cases^[105]. Furthermore, gene-based analysis of 3,767 sCJD cases demonstrated a significant association between *HS6ST3* and age at disease onset^[106]. In contrast, sequencing of 205 sCJD cases and 170 controls found no pathogenic somatic *PRNP* mutations, suggesting that somatic mutations may not play a major role in sCJD^[107].

CONCLUSION

In summary, genetic factors play a crucial role in neurodegenerative dementias, including both phenotypic expression and disease onset. In AD, more than 70 common loci have been implicated, alongside dozens of rare variants that contribute significantly to disease risk. In FTLD, variants in causal genes such as *MAPT*, *C9orf72*, and *GRN* are major contributors. DLB exhibits genetic overlap with both AD and PD. NIID is primarily associated with repeat expansions in the *NOTCH2NLC* gene, particularly within the Chinese population. HD results from abnormal CAG repeat expansions in the *HTT* gene. Although rare, prion diseases demonstrate strong genetic determinants, with *PRNP* variants influencing disease presentation. Collectively, these findings highlight the pivotal role of genetic mechanisms in neurodegenerative dementias and emphasize the need for further studies to elucidate their genetic basis.

DECLARATIONS

Authors' contributions

Literature search, writing, and original draft preparation: Xiao X, Luo S, Li J

Conceptualization, review, revision, and editing: Shen L, Jiao B

Availability of data and materials

Not applicable.

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Conflicts of interest

Lu Shen is an Editorial Board member of the journal *Ageing and Neurodegenerative Diseases*. She was not involved in any steps of editorial processing, notably including reviewer selection, manuscript handling, or decision making. The other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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