

REVIEW

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Clinic, neuropathology and molecular genetics of frontotemporal dementia: a mini-review

Xiao-dong Pan^{1,2,3} and Xiao-chun Chen^{1,2,3*}

Abstract

Frontotemporal lobar degeneration (FTLD) represents a group of clinically, neuropathologically and genetically heterogeneous disorders with plenty of overlaps between the neurodegenerative mechanism and the clinical phenotype. FTLD is pathologically characterized by the frontal and temporal lobar atrophy. Frontotemporal dementia (FTD) clinically presents with abnormalities of behavior and personality and language impairments variants. The clinical spectrum of FTD encompasses distinct canonical syndromes: behavioural variant of FTD (bvFTD) and primary progressive aphasia. The later includes nonfluent/agrammatic variant PPA (nfvPPA or PNFA), semantic variant PPA (svPPA or SD) and logopenic variant PPA (lvPPA). In addition, there is also overlap of FTD with motor neuron disease (FTD-MND or FTD-ALS), as well as the parkinsonian syndromes, progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS). The FTLD spectrum disorders are based upon the predominant neuropathological proteins (containing inclusions of hyperphosphorylated tau or ubiquitin protein, e.g transactive response (TAR) DNA-binding protein 43 kDa (TDP-43) and fused-in-sarcoma protein in neurons and glial cells) into three main categories: (1) microtubule-associated protein tau (FTLD-Tau); (2) TAR DNA-binding protein-43 (FTLD-TDP); and (3) fused in sarcoma protein (FTLD-FUS). There are five main genes mutations leading clinical and pathological variants in FTLD that identified by molecular genetic studies, which are chromosome 9 open reading frame 72 (*C9ORF72*) gene, granulin (*GRN*) gene, microtubule associated protein tau gene (*MAPT*), the gene encoding valosin-containing protein (*VCP*) and the charged multivesicular body protein 2B (*CHMP2B*). In this review, recent advances on the different clinic variants, neuroimaging, genetics, pathological subtypes and clinicopathological associations of FTD will be discussed.

Keywords: bvFTD, Nonfluent/agrammatic variant, Semantic variant, Logopenic variant, Molecular genetics, *MAPT*, *GRN*, *C9ORF72*

Introduction

Frontotemporal dementia (FTD) represents a group of clinically, neuropathologically and genetically heterogeneous disorders. It is a range of progressive dementia syndromes associated with focal atrophy of the orbitomesial frontal and anterior temporal lobes. And the term frontotemporal lobar degeneration (FTLD) to describe the pathological syndrome.

In 1892, Arnold Pick described a patient with progressive aphasia and lobar atrophy [1]. In 1911, Alois Alzheimer

described the histopathological status related to these patients, pointing the absence of senile plaques and neurofibrillary tangles, and the presence of argyrophilic neuronal inclusions (later called “Pick bodies”) and swollen cells (later called “Pick cells”) at neuropathological examination [2]. However, during the 20th century, these patients with frontotemporal lobar degeneration were generically referred to as patients with dementia, being often diagnosed with Alzheimer disease (AD) [2]. In 1994, two major research groups from Lund and Manchester proposed clinical and neuropathological criteria for the diagnosis of FTD [3]. In 1998, Neary et al [4] reported a consensus on clinical diagnostic criteria of frontotemporal lobar degeneration in the American Academy of Neurology (AAN).

FTD often begins when the patient is in the fifth to seventh decades. Epidemiological studies suggest that

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FTD is the second most common cause of dementia in individuals younger than 65 and is just less common than Alzheimer's disease (AD) within this age group [2,5]. Of over 65 years old dementia, the incidence of FTD ranks fourth, the top three is Alzheimer's disease, Lewy body dementia and vascular dementia [5-7]. There do not appear to be any clear gender differences in susceptibility [8-11]. Among the FTD clinical syndromes, sex distribution appears to vary from one subtype to the next. Several studies report a male predominance in bvFTD and SD, and a female predominance in PNFA [5,12]. There is a wide range in durations of illness (2-20 years) partly reflecting different underlying pathologies.

In the past few years, significant advances have been seen in the etiology, pathogenesis, and genetics, pathology and clinical phenotype of FTD, and many new terminology and classification of FTD have emerged. In this review, recent advances on the different clinical variant phenotypes, neuroimaging, hereditary forms, pathological subtypes and clinicopathological associations of FTD will be discussed.

FTLD clinical presentation: classification and characteristics

Frontotemporal lobar degeneration (FTLD) includes a group of progressive degenerative disorders characterised by progressive behavioural change, executive dysfunction and language difficulties [13]. Unlike AD, behavioral symptoms predominate in the early stages of FTLD. The clinical heterogeneity in familial and sporadic forms of FTD is remarkable, with patients demonstrating variable mixtures of disinhibition, dementia, PSP, CBD, and motor neuron disease [13,14]. Early symptoms are divided among cognitive, behavioral, and sometimes motor abnormalities, reflecting degeneration of the anterior frontal and temporal regions, basal ganglia, and motor neurons [13,14]. FTLD is a powerful model to study emotion, social cognition and language organization in the brain.

Behavioral variant frontotemporal dementia (bvFTD)

bvFTD has the highest prevalence amongst the FTD clinical syndromes, accounting for approximately 70% of all FTD cases [2,5]. The onset of bvFTD is typically before the age of 65 years, with an average onset age of 58 years [12,15]. Patients with this clinical variant present with marked changes in personality and behaviour and with relative preservation of the cognitive functions praxis, gnosis and memory [13,16]. Common behavioral deficits include apathy, disinhibition, weight gain, food fetishes, compulsions, euphoria, and an absence of insight into their condition. Poor business decisions and difficulty organizing work tasks are common. Cognitive testing typically reveals spared memory but impaired executive functions [3,13,17]. bvFTD has been associated with symmetrical ventromedial

frontal, orbital frontal, and insular atrophy and left anterior cingulate atrophy [18]. Behavioural assessment is at the core of assessment in patients with potential bvFTD and seems to be more sensitive in distinguishing bvFTD from AD than standard cognitive testing. The 'International Behavioral Variant FTD Criteria Consortium' developed international consensus criteria for bvFTD. Subclassifications were made in possible bvFTD defined by clinical criteria, probable bvFTD supported by neuroimaging data, and definite bvFTD confirmation by neuropathological evidence or a pathogenic mutation [17].

Primary progressive aphasia (PPA)

PPA is a language disorder that involves changes in the ability to speak, read, write and understand what others are saying. It is associated with early temporal lobe atrophy or brain lesions around the lateral fissure. PPA represents a spectrum of selective language disorders and the variant of PPA might provide clues to the underlying pathology [19]. Currently cerebrospinal fluid (CSF) biomarkers have limited ability to identify PPA reliably, which might be explained by the pathological heterogeneity. An indication of lower A β 1-40 levels or the lower T-tau to A β 1-42 ratio in FTD, might be useful to distinguish patients from subjects AD and control subjects [20,21]. In 2011, criteria were adopted for the classification of PPA into three clinical subtypes: nonfluent/agrammatic variant PPA (nfvPPA or PNFA), semantic variant PPA (svPPA or SD) and logopenic variant PPA (lvPPA) [22]. The proposal is an important step forward in establishing the consistency of terminology and classification of PPA. The diagnostic recommendations include two steps. First, the patient should meet the basic standard of PPA, which is an initial presentation of significant damage to language and accompanied by limited daily living skills and other cognitive impairment. Second, we need to assess the main language domains, including verbal generation, repeat, and understanding of words and syntax, naming, semantic knowledge and reading/spelling characteristics. Finally, clinical variants will be divided basing on specific speech and language features characteristic of each subtype. Classification can then be further specified as "imaging-supported" if the expected pattern of atrophy is found and "with definite pathology" if pathologic or genetic data are available. Therefore, the new proposal has a clear practical significance.

nfvPPA or PNFA is the second most prevalent presentation of FTLD, accounting for a large 25% [12]. The feature of nfvPPA includes grammatical error making agrammatism and/or laborious speech, but relatively preserved language comprehension. Apraxia of speech (AOS) or orofacial apraxia is frequently accompanying the aphasia [15]. Semantic variant PPA (svPPA) or SD presents in 20-25% of the FTLD patients [12]. svPPA

presents a significantly impaired naming ability and word comprehension, while speech production is spared [22,23]. LvPPA or logopenic progressive aphasia [24] is marked by impaired word finding and difficult repetition. lvPPA shows an impaired ability to repeat sentences or phrases, spontaneous speech and a single word extracting when naming. Unlike other FTD subtypes, lvPPA generally does not produce changes in behavior or personality until later stages of the disease. Most people with progressive aphasia maintain the ability to care for themselves, keep up outside interests and, in some instances, remain employed for a few years after onset of the disorder. LPA is mostly associated with a neuropathological diagnosis of AD [25]. Clinical distinction between bvFTD, nfvPPA and svPPA is often complicated for that overlap of the clinical syndromes between them can occur in advanced stages of disease.

FTLD overlaps with other clinical syndrome

The subcortical nuclei and motor systems are involved in FTLT variants. Motor neuron dysfunction (MND) has been described in 40% of the FTLT patients, referred to as FTLT-MND. The common comorbidity of Amyotrophic lateral sclerosis (ALS) with behavior abnormality, cognitive impairment or dementia has been noticed [26,27]. FTLT may precede, follow or coincide with the onset of motor symptoms [28]. Other disorders are closely related to FTLT, including progressive supranuclear palsy (PSP) syndromes, corticobasal syndrome (CBS), FTD with parkinsonism (FTDP) and argyrophilic grain disease (AGD). PSP and CBS are two common atypical parkinsonian syndromes demonstrating cognitive and behaviour disorders that overlap with FTD. Of them, behavioral and cognitive dysfunction promotes the development of dementia. And extrapyramidal system symptoms present as bradykinesia, abnormal posture, rigidity, but tremor uncommon. The co-occurrence of AGD in ALS is not uncommon, and comparable with that in a number of diseases belonging to the tauopathies or α -synucleinopathies [29]. Motion system damage presents as muscle atrophy. FTDP-17 showing genetic linkage to chromosome 17, presents with a clinical syndrome of autosomal dominant disinhibition, dementia, parkinsonism, and amyotrophy [30]. The clinical picture resembles bvFTD, while cognitive deficits include anterograde memory dysfunction in an early stage, later the deterioration of visuospatial function, orientation and global memory are gradually presented. Motor signs typically include the symmetrical bradykinesia without resting tremor, in combination with axial rigidity and postural instability. The early clinical presentation of AGD is similar to AD but it is less aggressive, with patients maintain mild cognitive impairment (MCI) for many years [31].

Neuroimaging in FTLT

Neuroimaging plays a critical role in diagnosis of FTD. Neuroimaging investigations can reliably differentiate FTLT subtypes from other dementias, and can help clinical diagnostics based on neuropsychiatric symptoms. Different clinical variants have different forms of brain atrophy, which can be used for some important clues for early clinical differential diagnosis. DTI can detect white matter damage, different subtypes of white matter injury also help clinical early differential diagnosis of clinical subtypes of FTLT [32]. Functional neuroimaging techniques, such as [99m Tc]-hexamethylpropyleneamine oxime single-photon emission computed tomography (SPECT) [33] or [18 F]-fluorodeoxyglucose (FDG)-PET are increasingly being used to help with the diagnosis of FTLT [34]. Arterial spin labeling imaging (ASL) like FDG-PET can be used for showing the hypometabolism in brain regions. Hypometabolism on FDG-PET is detected consistently and reliably in frontal brain regions in patients with bvFTD compared with those with AD, who show posterior cingulate hypometabolism early in the disease process [34]. However, in patients showing clear brain atrophy on structural MRI, little additional diagnostic benefit is gained by doing a PET scan, because focal atrophy is a positive predictive marker of FTD. The imaging presentation of nfvPPA indicates that predominant left posterior fronto-insular atrophy on MRI or predominant left posterior fronto-insular hypoperfusion or hypometabolism on SPECT or PET. Imaging-supported svPPA show predominant anterior temporal lobe atrophy and/or these brain regions hypoperfusion or hypometabolism on SPECT or PET. The imaging of lvPPA must show at least one of predominant left posterior perisylvian or parietal atrophy on MRI and/or hypoperfusion or hypometabolism on SPECT or PET [22,25,35-37].

Future in FTLT are very similar to imaging in AD—early detection, molecular diagnosis, monitor disease progression and validate and implement disease modifying therapies. Specific anatomic patterns in FTLT, and an amyloid-PET neuroimaging, which uses the amyloid- β -detecting [11 C]-Pittsburgh compound B, has shown promising results in discriminating or rule-out atypical AD and FTD cases [38,39] particularly those presenting with language deficits rather than behavioural changes. Micro PET with [18 F]-THK523 in Tau transgenic mice have been reported [40]. Tau specific imaging scanner that uses the [18 F]-THK523 may be a promising technique coming soon in future [40].

FTLT Neuropathology and cliniconeuropathological correlations

Neuropathology

The subtypes of underlying pathological changes in patients with FTD are classified on the basis of the

pattern of protein deposition, and are referred to collectively as frontotemporal lobar degeneration. Under a microscope, common pathologic changes of FTLT are atrophy brain region presenting neuronal loss, spongy change and gliosis in cortices of atrophied frontal and temporal lobes [41,42].

FTL have identified novel genetic defects and a chromosomal locus in hereditary forms of FTLT, as well as novel cliniconeuropathological associations. Immunohistochemistry allows subcategorization of these disorders into specific proteinopathies based on the major constituent of the inclusions.

- (1) FTLT-tau: One subtype is presented as neurons and glial cells containing inclusions of hyperphosphorylated tau protein, referred to as FTLT-tau [43]. Tau pathology was associated with FTLT with parkinsonism, PSP syndromes [44], CBS [45] and AGD [31].
- (2) FTLT-Ubiquitin or FTLT-U: Over 50% of the FTLT patients presented with tau-negative ubiquitin staining inclusions, referred to as FTLT-Ubiquitin or FTLT-U [46]. In 80–95% of this group, inclusions were found to be composed of transactive response (TAR) DNA-binding protein 43 kDa (TDP-43) [47–49], referred to as FTLT-TDP [50], or TDP-43-negative FTLT-U cases having inclusions of fusedin-sarcoma protein (FUS), referred to as FTLT-FUS [43,49,51,52]. However, in a small number of FTLT-U patients, the inclusion protein remains unclear. This group is referred to as FTLT-ubiquitin proteasome system (FTLT-UPS) [46,53].
- (3) Dementia lacking distinctive histopathology (DLDH) [54,55].
- (4) Other rare types: dementia with basophilic inclusion body, neuronal intermediate filament inclusion disease [52].

Association between pathology and clinical phenotype

Associations were noted between the clinical FTLT subtypes and underlying proteinopathies, but a strict one to one relationship is lacking. bvFTL is mostly associated with FTLT-TDP43, some cases are also correlated with FTLT-tau (PiD subtype). An FTLT-FUS proteinopathy is invariably associated with a clinical diagnosis of bvFTL, either with or without the signs of MND. Microscopic assessment of nfaPPA at autopsy often reveals FTLT associated with a tauopathy (FTLT-tau). nfaPPA is commonly associated with tau pathology, especially when AOS or orofacial apraxia is present. In most cases, the pathology underlying nfaPPA was mixed, including FTLT-tau and FTLT-TDP43, but with a predominance of FTLT-tau pathology. SvPPA is, in most cases, linked with TDP-43-immunoreactive pathology, although tau pathology is

sometimes observed. Some patients with predominantly right temporal lobe atrophy (RTLTA) are usually diagnosed clinically with either bvFTL or svPPA [56]. It has been suggested that patients with bvFTL and RTLTA have FTLT-tau pathology, whereas patients with svPPA and RTLTA have FTLT-TDP43 pathology [56]. svPPA patients who often present with acalculia is associated with FTLT-tau [57]. LvPA is predominantly associated with AD pathology. Many patients with lvPPA often have underlying AD pathology [58–60]. CSF tau:amyloid- β ratio [37] and PiB PET imaging [25] studies can be helpful in the identification of patients who are more likely to have lvPPA than nfaPPA. A recent study showed that 93% of patients with lvPPA on amyloid PET imaging was found PiB positive, but svPPA only 9%, nfaPPA is 13%, which suggests that there is some common pathological features between lvPPA and AD [59].

Tau pathology was also associated with FTLT with parkinsonism, PSP, CBD, AGD and Pick bodies (PiD) [30,44,61]. Similarly, TDP-43 and FUS proteinopathies are also commonly found in MND with or without FTLT [52]. Although these are relatively strong associations, they are not absolute, and it is currently not possible to predict with certainty the underlying pathology of specific FTLT syndromes.

Extrapyramidal system symptoms accompanied with apraxia indicates the presence of CBS, which mostly attributes to Tau disease. While dementia with FTLT-MND syndrome mostly attributes to TDP-43 pathology [15,45,57]. These suggest that it is contributing to therapeutic strategy for FTLT through elucidating the relationship between pathological and clinical presentation.

Molecular genetics

Approximately 40% of patients with FTLT have a family history [8]. bvFTL is the most prominent subtype with family history, especially when concomitant symptoms of MND are present (60%), while SvPPA appeared to be the least hereditary FTLT subtype (<20%) [62]. Molecular genetic studies have identified several common (*MAPT*, *GRN*) and rare (*VCP*, *CHMP2B*, *TARDBP*, *FUS*) genetic factors in hereditary FTLT over recent years. In 1998 microtubule associated protein tau (*MAPT*) gene was found, which located on chromosome 17q21.32, in which 13% of the cases is FTDP-17, those who have parkinson-like symptoms [63]. In 2004, the gene encoding valosin-containing protein (*VCP*) gene was found, located on chromosome 9p13.3, which is associated with the genes that cause FTLT in association with inclusion body myopathy and Paget's disease [64,65]. In 2005, the charged multivesicular body protein 2B (*CHMP2B*, also known as chromatin-modifying protein 2B) gene mutations, located on chromosome 3p11.2, was discovered in a large Danish cohort with familial FTLT [66,67]. In 2006, a mutated gene located on chromosome

Table 1 Clinical phenotypes, pathological and molecular genetic spectrum in FTLD [13,19,22,35,72,77,78]

| Core clinical feature | Praxiological obstacle | Logopathy | | | Extrapyramidal symptoms + praxiological obstacle | Dyskinesia + praxiological obstacle | |
|---|---|---|---|--|---|---|--|
| Clinical syndrome | Behavioral variant Frontotemporal dementia (bvFTD) | Primary progressive aphasia(PPA) | | | Corticobasal degeneration (CBD) | FTD-MND/ALS | |
| | | nonfluent/agrammatic variant PPA (nfvPPA) | Semantics variation (svPPA) | logopenic variant PPA (lvPPA) | progressive supranuclear palsy (PSP) | | |
| Brain morphologically affected parts | Prefrontal lobe and temporal lobe | Left posterior frontal lobe, insula | The front/ventral temporal lobe | left posterior superior temporal lobe and medial parietal lobe | Frontal and temporal lobe, Basal ganglia | Basal ganglia and brainstem | Cortex and motor neuron |
| Biochemistry and Neuropathology | FTLD-Tau (Pick type, 3R-tau) FTLT-TDP43 | FTLD-Tau more than FTLT-TDP43, AD like pathological visible | Most belongs to FTLT-TDP43; AD like pathological rare | AD-like pathological common; FTLT-TDP43 visible | FTLD-Tau (CBD type,4R-tau) common | FTLD-Tau (PSP type, 4R-tau) common | FTLD-TDP43, FTLT-FUS |
| Causative and Associated Genes | <i>C9ORF72</i> <i>PGRN</i> <i>MAPT</i> <i>VCP</i> <i>CHMP2B</i> | <i>PGRN</i> , <i>C9ORF72</i> <i>MAPT</i> <i>VCP</i> <i>CHMP2B</i> | <i>C9ORF72</i> <i>PGRN</i> <i>MAPT</i> <i>VCP</i> <i>CHMP2B</i> | <i>PGRN</i> | <i>PGRN</i> <i>MAPT</i> <i>C9ORF72</i> <i>VCP</i> <i>CHMP2B</i> | <i>MAPT</i> <i>PGRN</i> <i>C9ORF72</i> <i>VCP</i> <i>CHMP2B</i> | <i>C9ORF72</i> <i>FUS</i> <i>VCP</i> |

Note: 3R tau: three microtubulebinding repeats; 4R tau:four microtubule-binding repeats.

Table 2 The profile of main genes mutation and its possible disease mechanisms in FTLD

| Gene symbol | <i>MAPT</i> | <i>C9ORF72</i> | <i>PGRN</i> | <i>VCP</i> | <i>CHMP2B</i> |
|---|--|---|---|--|---|
| Full name | Microtubule-associated protein tau | Chromosome 9 open reading frame 72 | Progranulin | Valosin containing protein | Chromatin modifying protein 2B |
| Chromosomal localization | 17q21.32 | 9p21.2 | 17q21.32 | 9p13.3 | 3p11.2 |
| | <ul style="list-style-type: none"> • <i>MAPT</i> gives rise to six isoforms: three isoforms containing three amino-acid repeats (3R), and three isoforms with four repeats (4R) [79]. | <ul style="list-style-type: none"> • expressed as three major transcripts, the expanded G4C2 repeat is located in the proximal regulatory region of <i>C9ORF72</i> [70,73]. | <ul style="list-style-type: none"> • encodes progranulin, a ubiquitously expressed growth factor precursor consisting of 7.5 granulin peptides. | <ul style="list-style-type: none"> • Encodes a ubiquitously expressed member of a family of ATPases associated with a wide range of cellular functions [85]. | <ul style="list-style-type: none"> • Encodes a component of the heteromeric ESCRT-III complex with functions in the endosomal-lysosomal and the autophagic protein degradation pathway. |
| Functions and possible role in the disease mechanism | <ul style="list-style-type: none"> • Mutations result in a change in ratio of 3R to 4R tau isoforms. Mutations affect the normal function of the tau protein to stabilise microtubules, increase the tendency of tau to form neurotoxic aggregates and disturb neuronal plasticity and axonal transport [80]. | <ul style="list-style-type: none"> • Repeat expansion results in near complete loss of the major gene transcripts. And accumulation of transcripts harboring the expanded G4C2 repeat in nuclear RNA foci [70]. • G4C2 repeat leads to neuronal cytoplasmic inclusions throughout the entire cortical thickness [81]. • unidentified mechanisms exist. | <ul style="list-style-type: none"> • a wide range of biological processes such as inflammation and wound repair, or in pathological conditions including tumorigenesis [82]. • Neurotrophic function involved in neuronal survival and neurite outgrowth [83,84]. | <ul style="list-style-type: none"> • mutations reside at the interface between the D1 ATPase and the N-domain of the CDC48-like protein [85]. • mutations disturb ubiquitin-proteasome mediated protein degradation, autophagy, or both [86,87]. | <ul style="list-style-type: none"> • Expressed in neurons of all major brain regions. It is critical for development, sexual differentiation [88] and neuronal survival [89]. • Mutations affect the C-terminal end of the protein due to aberrant splicing [78]. |
| Estimated mutation frequency [69,72,79,81,90] | 0-50% | 14-48% | 3-26% | <1% | <1% |

17q21.31 are identified as the granule protein precursor (PGRN), only 1.7 M nucleotide away from the MAPT [68,69]. Approximately 10% of patients with FTLD is associated with this gene. In 2011, chromosome 9 open reading frame 72 (*C9ORF72*) gene was newly identified in FTLD [70,71].

Overall, patients with mutations in *GRN*, *MAPT* and *C9ORF72* together account for at least 17% of total FTD cases [53,72]. Summed *C9ORF72*, *GRN* and *MAPT* mutation frequencies were 32-40% [70,73]. Mutations in *VCP* and *CHMP2B* are rare, each explaining less than 1% of the familial FTLD.

The MAPT gene mutations often lead to FTLD-Tau pathological changes. The Both *PGRN* and *C9ORF72* mutations can cause FTLD-TDP-43. The symmetry frontal lobe atrophy in bvFTD patients is associated with *C9ORF72* and *MAPT* gene mutations, whereas the asymmetry of frontal lobe atrophy in bvFTD patients is associated with *PGRN* gene mutations [74]. The large hexanucleotide repeat expansion located within the non-coding portion of *C9ORF72* is the cause of chromosome 9-linked ALS and FTLD [70]. These suggest that specific gene mutations may affect the patterns of neuroanatomic injury in the development of frontal lobar atrophy.

C9ORF72 is expressed as three major transcripts and the expanded G4C2 repeat is located in the proximal regulatory region of *C9ORF72* [70,73], upstream of one

and in the first intron of the two other transcripts. Repeat expansion results in near complete loss of expression of the major gene transcripts. The pathogenic expansion was non-penetrant in individuals younger than 35 years, 50% penetrant by 58 years, and almost fully penetrant by 80 years. In normal population, the size of the G4C2 repeat ranges from 3 to 25 units, which is expanded to at least 60 units in FTLD patients [70,71,73].

The clinical phenotype of *C9ORF72* mutation often presents as bvFTD or ALS or FTD co-morbidities ALS. In patients with bvFTD, *C9ORF72* mutation is more common than *MAPT* or *PGRN*. Anxiety or agitation, and memory dysfunction (often episodic memory) is a common clinical feature. Those cases underlines that the hexanucleotide repeat expansion in chromosome 9 could be also associated with early onset psychiatric presentations [75]. Overexpressed p-62 inclusion body lesions in the cerebellum is one of pathological features [76]. Neuroimaging presents as the symmetrical frontal and/or temporal lobe atrophy, and parietal, occipital and cerebellar atrophy can also appear. Therefore, *C9ORF72* mutation is not only associated with cortical anatomic site but also with sub-cortical structures. However, it is unclear for the exact mechanism of action of this “repeat amplification *C9ORF72* gene”.

The clinical and pathological heterogeneity in FTLD causes a challenge for diagnosis of FTLD. A helpful

supplement for clinical evaluation using genetics and biological markers testing can significantly improve the forecast of potential histopathology *in vivo*. We summarize clinical phenotypes, molecular pathological and genetic spectrum in FTLD in Table 1. And the profile of main genes mutations and its possible disease mechanisms in FTLD is shown in Table 2.

Conclusion

In this review, we have systematically updated current understanding on clinical, genetic, neuropathological, and neuroimaging perspectives of FTD. This review aims to arouse awareness of FTD among clinicians, in particular when the overlapping clinical and neuroimaging characteristic features among dementia and different subtypes of FTD remain great challenges for clinicians. Identification of biomarkers for clinical diagnosis and differentiation FTD from other dementia is warranted for future studies. Gene diagnosis test should be considered for familial cases suspected with FTD in clinic practice. Longitudinal clinicopathological correlation studies will further elucidate the network functions of human brain in this complex disorder with behaviour, speech and motor abnormality. With further understanding of the genetics, clinical and neuropathological basis of FTD, we can visualise that FTD will be further clinically defined. And new consensus will be developed for better guidance in clinical practice.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

XdP collected the reference materials and drafted the manuscript. XcC revised the manuscript. All authors read and approved the final manuscript.

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References

1. Rossor MN: Pick's disease: a clinical overview. *Neurology* 2001, **56**:S3-S5.
2. Snowden JS, Neary D, Mann DM: Frontotemporal dementia. *Br J Psychiatry* 2002, **180**:140-143.
3. The Lund and Manchester Groups: Clinical and neuropathological criteria for frontotemporal dementia. *J Neurol Neurosurg Psychiatry* 1994, **57**:416-418.
4. Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, Freedman M, Kertesz A, Robert PH, Albert M, et al: Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* 1998, **51**:1546-1554.
5. Ratnavalli E, Brayne C, Dawson K, Hodges JR: The prevalence of frontotemporal dementia. *Neurology* 2002, **58**:1615-1621.
6. Arvanitakis Z: Update on frontotemporal dementia. *Neurologist* 2010, **16**:16-22.
7. Barker WW, Luis CA, Kashuba A, Luis M, Harwood DG, Loewenstein D, Waters C, Jimison P, Shepherd E, Sevush S, et al: Relative frequencies of Alzheimer disease, Lewy body, vascular and frontotemporal dementia, and hippocampal sclerosis in the State of Florida Brain Bank. *Alzheimer Dis Assoc Disord* 2002, **16**:203-212.
8. Rosso SM, Donker Kaat L, Baks T, Joosse M, de Koning I, Pijnenburg Y, de Jong D, Dooijes D, Kamphorst W, Ravid R, et al: Frontotemporal dementia in The Netherlands: patient characteristics and prevalence estimates from a population-based study. *Brain* 2003, **126**:2016-2022.
9. Mercy L, Hodges JR, Dawson K, Barker RA, Brayne C: Incidence of early-onset dementias in Cambridgeshire, United Kingdom. *Neurology* 2008, **71**:1496-1499.
10. Ikeda M, Ishikawa T, Tanabe H: Epidemiology of frontotemporal lobar degeneration. *Dement Geriatr Cogn Disord* 2004, **17**:265-268.
11. Hou CE, Yaffe K, Perez-Stable EJ, Miller BL: Frequency of dementia etiologies in four ethnic groups. *Dement Geriatr Cogn Disord* 2006, **22**:42-47.
12. Johnson JK, Diehl J, Mendez MF, Neuhaus J, Shapira JS, Forman M, Chute DJ, Roberson ED, Pace-Savitsky C, Neumann M, et al: Frontotemporal lobar degeneration: demographic characteristics of 353 patients. *Arch Neurol* 2005, **62**:925-930.
13. Piguet O, Hornberger M, Mioshi E, Hodges JR: Behavioural-variant frontotemporal dementia: diagnosis, clinical staging, and management. *Lancet Neurol* 2011, **10**:162-172.
14. Lillo P, Garcin B, Hornberger M, Bak TH, Hodges JR: Neurobehavioral features in frontotemporal dementia with amyotrophic lateral sclerosis. *Arch Neurol* 2010, **67**:826-830.
15. Josephs KA, Hodges JR, Snowden JS, Mackenzie IR, Neumann M, Mann DM, Dickson DW: Neuropathological background of phenotypical variability in frontotemporal dementia. *Acta Neuropathol* 2011, **122**:137-153.
16. Bathgate D, Snowden JS, Varma A, Blackshaw A, Neary D: Behaviour in frontotemporal dementia, Alzheimer's disease and vascular dementia. *Acta Neurol Scand* 2001, **103**:367-378.
17. Rascofsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, van Swieten JC, Seelaar H, Dopfer EG, Onyike CU, et al: Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* 2011, **134**:2456-2477.
18. Rohrer JD, Lashley T, Schott JM, Warren JE, Mead S, Isaacs AM, Beck J, Hardy J, de Silva R, Warrington E, et al: Clinical and neuroanatomical signatures of tissue pathology in frontotemporal lobar degeneration. *Brain* 2011, **134**:2565-2581.
19. Grossman M: Primary progressive aphasia: clinicopathological correlations. *Nat Rev Neurol* 2010, **6**:88-97.
20. Irwin DJ, McMillan CT, Toledo JB, Arnold SE, Shaw LM, Wang LS, Van Deerlin V, Lee VM, Trojanowski JQ, Grossman M: Comparison of cerebrospinal fluid levels of tau and Abeta 1-42 in Alzheimer disease and frontotemporal degeneration using 2 analytical platforms. *Arch Neurol* 2012, **69**:1018-1025.
21. Verwey NA, Kester MI, van der Flier WM, Veerhuis R, Berkhof H, Twaalfhoven H, Blankenstein MA, Scheltens AP, Pijnenburg YA: Additional value of CSF amyloid-beta 40 levels in the differentiation between FTLD and control subjects. *J Alzheimers Dis* 2010, **20**:445-452.
22. Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, Ogar JM, Rohrer JD, Black S, Boeve BF, et al: Classification of primary progressive aphasia and its variants. *Neurology* 2011, **76**:1006-1014.
23. Snowden JS, Thompson JC, Stopford CL, Richardson AM, Gerhard A, Neary D, Mann DM: The clinical diagnosis of early-onset dementias: diagnostic accuracy and clinicopathological relationships. *Brain* 2011, **134**:2478-2492.
24. Gorno-Tempini ML, Brambati SM, Ginex V, Ogar J, Dronkers NF, Marcione A, Perani D, Garibotto V, Cappa SF, Miller BL: The logopenic/phonological variant of primary progressive aphasia. *Neurology* 2008, **71**:1227-1234.
25. Rabinovici GD, Jagust WJ, Furst AJ, Ogar JM, Racine CA, Mormino EC, O'Neil JP, Lal RA, Dronkers NF, Miller BL, et al: Abeta amyloid and glucose metabolism in three variants of primary progressive aphasia. *Ann Neurol* 2008, **64**:388-401.
26. Phukan J, Pender NP, Hardiman O: Cognitive impairment in amyotrophic lateral sclerosis. *Lancet Neurol* 2007, **6**:994-1003.
27. Ringholz GM, Appel SH, Bradshaw M, Cooke NA, Mosnik DM, Schulz PE: Prevalence and patterns of cognitive impairment in sporadic ALS. *Neurology* 2005, **65**:586-590.

28. van Langenhove T, van der Zee J, van Broeckhoven C: **The molecular basis of the frontotemporal lobar degeneration-amyotrophic lateral sclerosis spectrum.** *Ann Med* 2012, **44**:817–828.
29. Soma K, Fu YJ, Wakabayashi K, Onodera O, Kakita A, Takahashi H: **Co-occurrence of argyrophilic grain disease in sporadic amyotrophic lateral sclerosis.** *Neuropathol Appl Neurobiol* 2012, **38**:54–60.
30. Spillantini MG, Bird TD, Ghetti B: **Frontotemporal dementia and Parkinsonism linked to chromosome 17: a new group of tauopathies.** *Brain Pathol* 1998, **8**:387–402.
31. Ferrer I, Santpere G, van Leeuwen FW: **Argyrophilic grain disease.** *Brain* 2008, **131**:1416–1432.
32. Zhang Y, Schuff N, Du AT, Rosen HJ, Kramer JH, Gorno-Tempini ML, Miller BL, Weiner MW: **White matter damage in frontotemporal dementia and Alzheimer's disease measured by diffusion MRI.** *Brain* 2009, **132**:2579–2592.
33. Varma AR, Adams W, Lloyd JJ, Carson KJ, Snowden JS, Testa HJ, Jackson A, Neary D: **Diagnostic patterns of regional atrophy on MRI and regional cerebral blood flow change on SPECT in young onset patients with Alzheimer's disease, frontotemporal dementia and vascular dementia.** *Acta Neurol Scand* 2002, **105**:261–269.
34. Kanda T, Ishii K, Uemura T, Miyamoto N, Yoshikawa T, Kono AK, Mori E: **Comparison of grey matter and metabolic reductions in frontotemporal dementia using FDG-PET and voxel-based morphometric MR studies.** *Eur J Nucl Med Mol Imaging* 2008, **35**:2227–2234.
35. Grossman M: **The non-fluent/agrammatic variant of primary progressive aphasia.** *Lancet Neurol* 2012, **11**:545–555.
36. Grossman M, Powers J, Ash S, McMillan C, Burkholder L, Irwin D, Trojanowski JQ: **Disruption of large-scale neural networks in non-fluent/agrammatic variant primary progressive aphasia associated with frontotemporal degeneration pathology.** *Brain Lang* 2012. In Press, doi: 10.1016/j.bandl.2012.10.005. [Epub ahead of print], PMID: 23218686.
37. Hu WT, McMillan C, Libon D, Leight S, Forman M, Lee VM, Trojanowski JQ, Grossman M: **Multimodal predictors for Alzheimer disease in nonfluent primary progressive aphasia.** *Neurology* 2010, **75**:595–602.
38. Engler H, Santillo AF, Wang SX, Lindau M, Savitcheva I, Nordberg A, Lannfelt L, Langstrom B, Kilander L: **In vivo amyloid imaging with PET in frontotemporal dementia.** *Eur J Nucl Med Mol Imaging* 2008, **35**:100–106.
39. Rowe CC, Ng S, Ackermann U, Gong SJ, Pike K, Savage G, Cowie TF, Dickinso KL, Maruff P, Darby D, et al: **Imaging beta-amyloid burden in aging and dementia.** *Neurology* 2007, **68**:1718–1725.
40. Fodero-Tavoletti MT, Okamura N, Furumoto S, Mulligan RS, Connor AR, McLean CA, Cao D, Rigopoulos A, Cartwright GA, O'Keefe G, et al: **18 F-THK523: a novel in vivo tau imaging ligand for Alzheimer's disease.** *Brain* 2011, **134**:1089–1100.
41. Broe M, Hodges JR, Schofield E, Shepherd CE, Kril JJ, Halliday GM: **Staging disease severity in pathologically confirmed cases of frontotemporal dementia.** *Neurology* 2003, **60**:1005–1011.
42. Kersaitis C, Halliday GM, Kril JJ: **Regional and cellular pathology in frontotemporal dementia: relationship to stage of disease in cases with and without Pick bodies.** *Acta Neuropathol* 2004, **108**:515–523.
43. Mackenzie IR, Rademakers R, Neumann M: **TDP-43 and FUS in amyotrophic lateral sclerosis and frontotemporal dementia.** *Lancet Neurol* 2010, **9**:995–1007.
44. Höglinger GU, Melhem NM, Dickson DW, Sleiman PM, Wang LS, Klei L, Rademakers R, de Silva R, Litvan I, Riley DE, et al: **Identification of common variants influencing risk of the tauopathy progressive supranuclear palsy.** *Nat Genet* 2011, **43**:699–705.
45. Boeve BF: **The multiple phenotypes of corticobasal syndrome and corticobasal degeneration: implications for further study.** *J Mol Neurosci* 2011, **45**:350–353.
46. Mackenzie IR, Neumann M, Bigio EH, Cairns NJ, Alafuzoff I, Kril J, Kovacs GG, Ghetti B, Halliday G, Holm IE, et al: **Nomenclature for neuropathologic subtypes of frontotemporal lobar degeneration: consensus recommendations.** *Acta Neuropathol* 2009, **117**:15–18.
47. Benajiba L, Le Ber I, Camuzat A, Lacoste M, Thomas-Anterion C, Couratier P, Legallic S, Salachas F, Hannequin D, Decousus M, et al: **TARDBP mutations in motoneuron disease with frontotemporal lobar degeneration.** *Ann Neurol* 2009, **65**:470–473.
48. Neumann M, Sampathu DM, Kwong LK, Truax AC, Micsenyi MC, Chou TT, Bruce J, Schuck T, Grossman M, Clark CM, et al: **Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis.** *Science* 2006, **314**:130–133.
49. Mackenzie IR, Foti D, Woulfe J, Hurwitz TA: **Atypical frontotemporal lobar degeneration with ubiquitin-positive, TDP-43-negative neuronal inclusions.** *Brain* 2008, **131**:1282–1293.
50. Grossman M, Wood EM, Moore P, Neumann M, Kwong L, Forman MS, Clark CM, McCluskey LF, Miller BL, Lee VM, et al: **TDP-43 pathologic lesions and clinical phenotype in frontotemporal lobar degeneration with ubiquitin-positive inclusions.** *Arch Neurol* 2007, **64**:1449–1454.
51. Mackenzie IR, Munoz DG, Kusaka H, Yokota O, Ishihara K, Roeber S, Kretschmar HA, Cairns NJ, Neumann M: **Distinct pathological subtypes of FTLD-FUS.** *Acta Neuropathol* 2011, **121**:207–218.
52. Roeber S, Mackenzie IR, Kretschmar HA, Neumann M: **TDP-43-negative FTLD-U is a significant new clinico-pathological subtype of FTLD.** *Acta Neuropathol* 2008, **116**:147–157.
53. Rohrer JD, Guerreiro R, Vandrovcova J, Uphill J, Reiman D, Beck J, Isaacs AM, Authier A, Ferrari R, Fox NC, et al: **The heritability and genetics of frontotemporal lobar degeneration.** *Neurology* 2009, **73**:1451–1456.
54. Giannakopoulos P, Hof PR, Bouras C: **Dementia lacking distinctive histopathology: clinicopathological evaluation of 32 cases.** *Acta Neuropathol* 1995, **89**:346–355.
55. Josephs KA, Jones AG, Dickson DW: **Hippocampal sclerosis and ubiquitin-positive inclusions in dementia lacking distinctive histopathology.** *Dement Geriatr Cogn Disord* 2004, **17**:342–345.
56. Gainotti G: **Different patterns of famous people recognition disorders in patients with right and left anterior temporal lesions: a systematic review.** *Neuropsychologia* 2007, **45**:1591–1607.
57. Rabinovici GD, Miller BL: **Frontotemporal lobar degeneration: epidemiology, pathophysiology, diagnosis and management.** *CNS Drugs* 2010, **24**:375–398.
58. Josephs KA, Whitwell JL, Duffy JR, Vanvoorst WA, Strand EA, Hu WT, Boeve BF, Graff-Radford NR, Parisi JE, Knopman DS, et al: **Progressive aphasia secondary to Alzheimer disease vs FTD pathology.** *Neurology* 2008, **70**:25–34.
59. Mesulam M, Wicklund A, Johnson N, Rogalski E, Leger GC, Rademaker A, Weintraub S, Bigio EH: **Alzheimer and frontotemporal pathology in subsets of primary progressive aphasia.** *Ann Neurol* 2008, **63**:709–719.
60. Rohrer JD, Rossor MN, Warren JD: **Alzheimer's pathology in primary progressive aphasia.** *Neurobiol Aging* 2012, **33**:744–752.
61. Neary D, Snowden J, Mann D: **Frontotemporal dementia.** *Lancet Neurol* 2005, **4**:771–780.
62. Goldman JS, Farmer JM, Wood EM, Johnson JK, Boxer A, Neuhaus J, Lomen-Hoerth C, Wilhelmsen KC, Lee VM, Grossman M, et al: **Comparison of family histories in FTLD subtypes and related tauopathies.** *Neurology* 2005, **65**:1817–1819.
63. Hutton M, Lendon CL, Rizzu P, Baker M, Froelich S, Houlden H, Pickering-Brown S, Chakraverty S, Isaacs A, Grover A, et al: **Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17.** *Nature* 1998, **393**:702–705.
64. Watts GD, Wymmer J, Kovach MJ, Mehta SG, Mumm S, Darvish D, Pestronk A, Whyte MP, Kimonis VE: **Inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia is caused by mutant valosin-containing protein.** *Nat Genet* 2004, **36**:377–381.
65. Dai RM, Li CC: **Valosin-containing protein is a multi-ubiquitin chain-targeting factor required in ubiquitin-proteasome degradation.** *Nat Cell Biol* 2001, **3**:740–744.
66. Holm IE, Isaacs AM, Mackenzie IR: **Absence of FUS-immunoreactive pathology in frontotemporal dementia linked to chromosome 3 (FTD-3) caused by mutation in the CHMP2B gene.** *Acta Neuropathol* 2009, **118**:719–720.
67. Skibinski G, Parkinson NJ, Brown JM, Chakrabarti L, Lloyd SL, Hummerich H, Nielsen JE, Hodges JR, Spillantini MG, Thusgaard T, et al: **Mutations in the endosomal ESCRTIII-complex subunit CHMP2B in frontotemporal dementia.** *Nat Genet* 2005, **37**:806–808.
68. Baker M, Mackenzie IR, Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, Snowden J, Adamson J, Sadovnick AD, Rollinson S, et al: **Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17.** *Nature* 2006, **442**:916–919.
69. Gass J, Cannon A, Mackenzie IR, Boeve B, Baker M, Adamson J, Crook R, Melquist S, Kuntz K, Petersen R, et al: **Mutations in progranulin are a major cause of ubiquitin-positive frontotemporal lobar degeneration.** *Hum Mol Genet* 2006, **15**:2988–3001.
70. DeJesus-Hernandez M, Mackenzie IR, Boeve BF, Boxer AL, Baker M, Rutherford NJ, Nicholson AM, Finch NA, Flynn H, Adamson J, et al: **Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes**

- chromosome 9p-linked FTD and ALS. *Neuron* 2011, **72**:245–256.
71. Renton AE, Majounie E, Waite A, Simon-Sanchez J, Rollinson S, Gibbs JR, Schymick JC, Laaksovirta H, van Swieten JC, Myllykangas L, et al: **A hexanucleotide repeat expansion in C9orf72 is the cause of chromosome 9p21-linked ALS-FTD.** *Neuron* 2011, **72**:257–268.
 72. Majounie E, Renton AE, Mok K, Dopper EG, Waite A, Rollinson S, Chio A, Restagno G, Nicolaou N, Simon-Sanchez J, et al: **Frequency of the C9orf72 hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study.** *Lancet Neurol* 2012, **11**:323–330.
 73. Gijssels I, Van Langenhove T, van der Zee J, Slegers K, Philtjens S, Kleinberger G, Janssens J, Bettens K, Van Cauwenbergh C, Pereson S, et al: **A C9orf72 promoter repeat expansion in a Flanders-Belgian cohort with disorders of the frontotemporal lobar degeneration-amyotrophic lateral sclerosis spectrum: a gene identification study.** *Lancet Neurol* 2012, **11**:54–65.
 74. Whitwell JL, Xu J, Mandrekar J, Boeve BF, Knopman DS, Parisi JE, Senjem ML, Dickson DW, Petersen RC, Rademakers R, et al: **Frontal asymmetry in behavioral variant frontotemporal dementia: clinicoimaging and pathogenetic correlates.** *Neurobiol Aging* 2012, **34**:636–639.
 75. Arighi A, Fumagalli GG, Jacini F, Fenoglio C, Ghezzi L, Pietroboni AM, De Riz M, Serpente M, Ridolfi E, Bonsi R, et al: **Early onset behavioral variant frontotemporal dementia due to the C9orf72 hexanucleotide repeat expansion: psychiatric clinical presentations.** *J Alzheimers Dis* 2012, **31**:447–452.
 76. Al-Sarraj S, King A, Troakes C, Smith B, Maekawa S, Bodi I, Rogelj B, Al-Chalabi A, Hortobagyi T, Shaw CE: **p62 positive, TDP-43 negative, neuronal cytoplasmic and intranuclear inclusions in the cerebellum and hippocampus define the pathology of C9orf72-linked FTL and MND/ALS.** *Acta Neuropathol* 2011, **122**:691–702.
 77. Boeve BF, Boylan KB, Graff-Radford NR, DeJesus-Hernandez M, Knopman DS, Pedraza O, Vemuri P, Jones D, Lowe V, Murray ME, et al: **Characterization of frontotemporal dementia and/or amyotrophic lateral sclerosis associated with the GGGGCC repeat expansion in C9orf72.** *Brain* 2012, **135**:765–783.
 78. Sieben A, Van Langenhove T, Engelborghs S, Martin JJ, Boon P, Cras P, De Deyn PP, Santens P, Van Broeckhoven C, Cruts M: **The genetics and neuropathology of frontotemporal lobar degeneration.** *Acta Neuropathol* 2012, **124**:353–372.
 79. Edwards TL, Scott WK, Almonte C, Burt A, Powell EH, Beecham GW, Wang L, Zuchner S, Konidari I, Wang G, et al: **Genome-wide association study confirms SNPs in SNCA and the MAPT region as common risk factors for Parkinson disease.** *Ann Hum Genet* 2010, **74**:97–109.
 80. Rademakers R, Cruts M, van Broeckhoven C: **The role of tau (MAPT) in frontotemporal dementia and related tauopathies.** *Hum Mutat* 2004, **24**:277–295.
 81. Mackenzie IR, Neumann M, Baborie A, Sampathu DM, Du Plessis D, Jaros E, Perry RH, Trojanowski JQ, Mann DM, Lee VM: **A harmonized classification system for FTL-TDP pathology.** *Acta Neuropathol* 2011, **122**:111–113.
 82. He Z, Bateman A: **Progranulin (granulin-epithelin precursor, PC-cell-derived growth factor, acrogranin) mediates tissue repair and tumorigenesis.** *J Mol Med (Berl)* 2003, **81**:600–612.
 83. Van Damme P, Van Hoecke A, Lambrechts D, Vanacker P, Bogaert E, van Swieten J, Carmeliet P, Van Den Bosch L, Robberecht W: **Progranulin functions as a neurotrophic factor to regulate neurite outgrowth and enhance neuronal survival.** *J Cell Biol* 2008, **181**:37–41.
 84. Yin F, Banerjee R, Thomas B, Zhou P, Qian L, Jia T, Ma X, Ma Y, Iadecola C, Beal MF, et al: **Exaggerated inflammation, impaired host defense, and neuropathology in progranulin-deficient mice.** *J Exp Med* 2010, **207**:117–128.
 85. Weihl CC, Pestronk A, Kimonis VE: **Valosin-containing protein disease: inclusion body myopathy with Paget's disease of the bone and frontotemporal dementia.** *Neuromuscul Disord* 2009, **19**:308–315.
 86. Ju JS, Weihl CC: **p97/VCP at the intersection of the autophagy and the ubiquitin proteasome system.** *Autophagy* 2010, **6**:283–285.
 87. Ju JS, Weihl CC: **Inclusion body myopathy, Paget's disease of the bone and fronto-temporal dementia: a disorder of autophagy.** *Hum Mol Genet* 2010, **19**:R38–R45.
 88. Suzuki M, Lee HC, Kayasuga Y, Chiba S, Nedachi T, Matsuwaki T, Yamanouchi K, Nishihara M: **Roles of progranulin in sexual differentiation of the developing brain and adult neurogenesis.** *J Reprod Dev* 2009, **55**:351–355.
 89. Ahmed Z, Sheng H, Xu YF, Lin WL, Innes AE, Gass J, Yu X, Wuertz CA, Hou H, Chiba S, et al: **Accelerated lipofuscinosis and ubiquitination in granulin knockout mice suggest a role for progranulin in successful aging.** *Am J Pathol* 2010, **177**:311–324.
 90. Gijssels I, Van Broeckhoven C, Cruts M: **Granulin mutations associated with frontotemporal lobar degeneration and related disorders: an update.** *Hum Mutat* 2008, **29**:1373–1386.

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