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GENOTYPE-PHENOTYPE CORRELATIONS IN FTLD-TDP

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Competing interest statement

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ABSTRACT

Frontotemporal lobar degeneration (FTLD) represents a group of neurodegenerative brain diseases that are highly heterogeneous at the level of the clinic, neuropathology and genetics. This high degree of heterogeneity is the result of different underlying molecular disease processes which make it unlikely that all FTLD patients will benefit from one and the same therapy. Since therapeutic strategies are currently being explored, there is an urgent need for tools to aid selection of those patients that will most likely benefit from a particular therapy. Defining the phenotypic characteristics of different FTLD subtypes in which patients share the same underlying disease process, would help to homogenize patient groups. One major subtype is FTLD characterized by TDP-43 pathology (FTLD-TDP). In this group, pathogenic mutations have been identified in four genes, *C9orf72, GRN*, *TBK1* and *VCP*. Here, we provide a comprehensive overview of the phenotypic characteristics of FTLD-TDP patients, highlighting shared features as well as differences between patient groups carrying a causal mutation in one of the four FTLD-TDP genes.

KEY POINTS

- Genotype-phenotype correlations will aid patient selection and stratification for targeted therapeutic strategies.
- The majority of the patients carrying a *C9orf72* repeat expansion, present with the behavioral variant of frontotemporal dementia (bvFTD) with frequent occurrence of psychotic symptoms and motor neuron disease (MND), and a symmetric, initial low-degree pattern of predominant frontotemporal brain impairment.
- FTD carriers of a *GRN* mutation are characterized by apathy-dominant behavior with frequent language output impairment, parietal lobe dysfunction and parkinsonism, associated with widespread, asymmetric impairment of frontotemporoparietal brain regions.
- FTD carriers of a *TBK1* mutation frequently have MND symptomatology as well as behavioral and language problems, though the predominant phenotypic features have yet to be distinguished. Brain impairment is mostly asymmetric.
- FTD carriers of a *VCP* mutation, present with or without myopathy or Paget disease of the bone. Characteristic features are apathy, anomia and psychotic signs, and a nonspecific pattern of brain impairment.

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INTRODUCTION

Frontotemporal lobar degeneration (FTLD) includes patients with neurodegenerative brain disorders with predominant degeneration of the frontal and/or the temporal lobes of the brain. In patients younger than 65 years, it is the second most common cause of neurodegenerative dementia after Alzheimer's disease (AD), accounting for 10.2%. In general, the prevalence of FTLD is 1 to 461 per 100000 individuals[1].

FTLD is remarkably heterogeneous in clinical presentation, neuropathological characteristics and underlying genetic causes. Clinically, frontotemporal dementia (FTD) is characterized by progressive deterioration in behavior, personality and/or language with initial relative preservation of memory function. A behavioral variant (bvFTD)[2] and a language variant, primary progressive aphasia (PPA), can be distinguished. The latter can be further divided in three subtypes: progressive non-fluent aphasia (PNFA) or non-fluent/agrammatic variant PPA (agPPA), semantic dementia (SD) or semantic variant PPA (svPPA), and logopenic variant PPA (LvPPA), although the latter is mostly characterized by underlying AD pathology[3]. Neuropathologically, FTLD is characterized by protein inclusions in degenerating neurons. Around 60% of FTLD patients have protein inclusions that stain positive for ubiquitin[4], and contain TAR-DNA binding protein (TDP-43)[5], as the major constituent. Four distinct FTLD-TDP pathology subtypes can be differentiated[5] (**TEXTBOX 1**). Ubiquitin-positive TDP-43 inclusions are also present in the central nerve system of patients with motor neuron disease (MND)[5,6] and 15% of all FTD patients develop amyotrophic lateral sclerosis (ALS), suggesting a disease continuum between FTLD and ALS.

In FTLD patients, genetics is a major contributor to disease with up to 43% of FTD patients having a positive family history (at least one affected first-degree family member with dementia, ALS, or Parkinson's disease (PD)) and between 10% and 27% of FTD patients having an autosomal dominant presentation of the disease[7–10]. Causal mutations have been identified in the genes coding for microtubule associated protein tau (*MAPT)*[11–13], progranulin (*GRN)*[14,15], chromosome 9 open reading frame 72 (*C9orf72)*[16–18], TANK binding kinase 1 *(TBK1)*[19–22], and more rarely in the valosin containing protein gene (*VCP)*[23] or charged multivesicular body protein 2B gene (*CHMP2B)*[24]. In *GRN*, *C9orf72*, *TBK1* and *VCP* mutation carriers, FTLD-TDP brain pathology has been documented. In FTD-ALS, mutations in *C9orf72* are most frequent[16], and in the remainder causal mutations were reported in *VCP* and *TBK1*[19–21,25].

These inherited forms of FTLD place a huge burden on families. Therefore, it is of major importance that the genetic cause in these families is uncovered as soon as possible. Genotype-phenotype correlations and the identification of phenotypic characteristics that are specific for a certain mutation or mutated gene, can guide the clinician in prioritizing the genes to be tested. In the future, genotype-phenotype correlations will also be valuable when new therapeutic strategies become available and patients need to be selected who will most likely benefit of a targeted therapy based on a common underlying disease mechanism. Further, specific phenotypic features on e.g. neuroimaging can lead to the development of biomarkers that enable to recognize mutation carriers early in the disease process and to monitor therapeutic effects. Therefore, reviewing genotype-phenotype correlations in FTLD is important and timely. Here, we provide an overview of the phenotypic characteristics of patients carrying a causal mutation in *C9orf72, GRN, TBK1* or *VCP*. We summarize the phenotypic characteristics of patient carriers per gene, including a first detailed report and analysis of the phenotypic features of all *TBK1* mutation carriers described so far. Further, we will discuss similarities and differences between carriers of a mutation in an FTLD-TDP gene and we will point out features that were suggested to be distinct for one of the four FTLD-TDP genes. Finally, we elaborate on the clinical and therapeutic opportunities and implications of FTLD-TDP genotype-phenotype correlations.

PHENOTYPIC CHARACTERISTICS OF MUTATION CARRIERS

C9orf72

In 2011, an expanded hexanucleotide, G_4C_2, repeat localized in the proximal regulatory region of *C9orf72*, was identified as a frequent genetic cause of FTD and ALS[16–18]. *C9orf72* is transcribed into three different transcripts encoding a largely uncharacterized protein that can be expressed as two isoforms. Healthy individuals mostly carry 2-24 copies of the repeat, whereas patients can carry expansions of over 1000 repeats. Controversy exists about the underlying pathomechanism with one haploinsufficiency hypothesis and two gain-of-function hypotheses. The latter two are characterized by toxic accumulation of dipeptide repeat proteins, translated from the G_4C_2 repeat through the unconventional repeat associated non-ATG translation (RAN translation), and by toxicity from the sense and antisense RNA foci generated from the expanded repeat[16,26–28].

Epidemiology

The pathological expansion of the *C9orf72* repeat is the most common genetic cause of FTLD and ALS, and explains disease in 4-29% of FTD[29–37], 11% of ALS[38] and 17-28% of FTD-ALS patients[29,33,35]. In patients with a positive family history of disease, the frequencies increased to 29% in FTD, 38% in ALS and up to 88% of FTD-ALS patients[39–41]. Also in seemingly sporadic patients, 6% of FTD and 8% of ALS patients carried a *C9orf72* expansion, which likely is due to incomplete penetrance[29,32,39,42].

Clinical

The clinical presentations of *C9orf72* carriers are remarkably heterogeneous, not only between but also within families[43,44]. Apart from FTD and ALS, the *C9orf72* repeat expansion has been identified in patients clinically diagnosed with AD, Parkinson's disease (PD), Huntington's disease phenocopy and several other diagnoses[44–50].

Among the FTD carriers, 65–100% exhibit the behavioral variant[16–18,29–34,36,37,40,41,51–53]. In some groups of *C9orf72* carriers, initial disinhibition was more frequently reported than apathy[30,41], while in other groups apathy was the predominant behavioral feature[32,33,36]. Sha et al investigated pure FTD and FTD-MND due to a *C9orf72* expansion separately: in the latter, disinhibition was more frequent than apathy (36% versus 18%), while in pure FTD none of the patients presented with disinhibition and 50% with apathy[31]. Some distinctive behavioral features have been suggested for *C9orf72* carriers: abnormal behaviors to some extent influenced by patients' delusional beliefs, typically complex repetitive behaviors with sometimes characteristics of an obsessive-compulsive disorder, absence of sweet food preference as dietary change, and remarkable irrational, frankly bizarre behavior[33,54].

An early manifestation of executive dysfunction is almost universal[30,31,33,36]. Although memory impairment is reported in up to 87% of the patients[30,32,34,55,56], it is hard to conclude if this is more frequent than in noncarriers. Different studies use other definitions and measurement methods, resulting in inconsistent results: impaired working memory or impairment in both learning and delayed recall at onset was more frequently observed in expansion carriers than in noncarriers[31,34], while comparable frequencies of impaired performance on episodic memory tasks and early relative-reported memory complaints were observed in carriers and noncarriers[36,57]. Although a comparable performance on episodic memory tasks, whole-brain voxel-based morphometric analysis revealed a distinct neuroanatomical signature of episodic memory dysfunction in *C9orf72* carriers, involving frontal, lateral and medial temporal, as well as lateral and medial parietal regions, lying

somewhat midway on a continuum between the more anterior network commonly reported in sporadic bvFTD and the more posteriorly-oriented substrates of AD[57].

A diagnosis of PPA, mostly PNFA, can be made in up to 30%[30,32,36,39,43,56], but in 84% of patients carrying the expansion speech and language difficulties occur[36], predominantly consistent with dynamic aphasia (reduced generation of propositional speech)[33].

Parietal lobe dysfunction such as apraxia and dyscalculia have been reported in 57% and 38% of *C9orf72* patients respectively[30,55].

An unusually high occurrence of psychiatric symptoms, including anxiety, psychosis, delusions and hallucinations, have been linked to neurodegeneration due to the *C9orf72* expansion[29–31,33–36,41,51]. These symptoms occur in 21-56% of the bvFTD patients with a *C9orf72* expansion in comparison to ≤ 18% of patients without[29–31,33–36,40,58]. Psychosis can be the first symptom in a *C9orf72* carrier, even years before other symptoms occur[36]. Nonetheless, the *C9orf72* expansion was rare or absent in patients with schizophrenia or a schizoaffective disorder[59,60].

Parkinsonism, mostly characterized by a relatively symmetric akinetic-rigid syndrome, was reported in 12% to 40% of FTD±MND patients[29,31,34,36,41,43,56], which was in most studies comparable to noncarriers (12-31%)[31,36,41], except for one study[35] in which parkinsonism was more frequent in *C9orf72* carriers. *C9orf72* expansions did not contribute to PD risk, and they are rarely identified in clinical PD patients and absent in autopsy-confirmed PD[61,62].

In ALS carriers of a *C9orf72* expansion, the frequency of bulbar symptoms at onset (20-89% [18,29,32,33,38,42,53,63]) inclined to be higher than in ALS patients without an expansion[33,39,42,51,64], although not observed in all studies[31,38,65].

Onset of disease in *C9orf72* expansion carriers occurred between the age of 27 and 83 years with an average onset age between 49.8 and 63.9 years depending on the cohort[16–18,29–34,36,38,41,52,64,66]. In most studies, average onset ages were not significantly different from noncarriers[33,34,36,38,42], except for three studies where *C9orf72* carriers (with FTD[41], FTD-MND[31] or ALS[65]) developed disease earlier than noncarriers. Disease duration ranged between 1 and 22 years, and average disease durations varied to a great extent between *C9orf72* cohorts, probably due to differences in the fraction of FTD versus ALS patients and the tendency of a shorter disease duration in ALS[16,29,30,32,33,38,41,66]. In *C9orf72* carriers with pure FTD, disease lasted on average 14 years[36] versus 2.5-3.6 years in pure ALS patients[16,38].

Progression of FTD±MND due to a *C9orf72* repeat expansion is often slow, although not slower than in FTD not caused by the expansion[31,35,36,40]. Conversely, in some cohorts progression in pure ALS due to a *C9orf72* repeat expansion was faster than in ALS cases

without an expansion[38,42]. In several *C9orf72* families an earlier onset age was observed in younger generations, suggesting a role of the *C9orf72* repeat in disease anticipation[29,37,43,51,53,64,66].

Neuroimaging and macroscopy

Patterns of atrophy or functional impairment are variable, but usually symmetric and diffuse with involvement of frontotemporal regions extending to parietal and even occipital lobes[29–32,34–36,57,67] (**FIG. 1**). Several studies observed remarkable atrophy of thalamus[30,31,55,68] and/or cerebellum[30,31,55,67] in *C9orf72*-positive FTD patients, more pronounced than in noncarriers. Some studies suggested that a greater precuneus atrophy can discriminate between FTD patients with the expansion and sporadic FTD[35,57,67]. Early in the disease course, brain atrophy might be of a relatively low degree[29,34,35], but in a neuropathological study comparing brains of *C9orf72*-positive FTLD±MND cases with *C9orf72*-negative FTLD±MND brains, the carriers had greater temporal, motor and hippocampal atrophy as well as greater motor cortex neuronal loss and gliosis[69]. In one study, *C9orf72* repeat expansions were independently associated with small volumes of the left sensorimotor cortex, the right occipital lobe and the left cerebellum, and a relatively large volume of the left inferior temporal region[67]. Longitudinally, a greater ventricular enlargement and volume loss of thalamus and cerebellum was reported in *C9orf72*-positive FTD±ALS patients than healthy controls, while rate of cortical thinning did not significantly differ with healthy controls[55,68].

Histopathology

Brains of clinical pure ALS patients with a *C9orf72* expansion were morphologically similar to typical sporadic ALS patients[56]. In comparison with any TDP-subtype without mutations, FTD (±MND) expansion carriers have more motor cortex atrophy, motor neuronal loss and gliosis, and this does not seem to correlate with the presence or absence of ALS[69]. TDP-43 pathology profiles closely parallels those of degeneration with less pathology in frontal and temporal cortex in pure MND groups than pure FTD groups and more abundant TDP-43 pathology in spinal cord in pure MND groups[26,43]. The majority of *C9orf72* patients with abundant cortical TDP-43, showed a pattern of neocortical pathology consistent with FTLD-TDP type B (**FIG. 2**)[26,40,43,56,69]. Nevertheless, a substantial number showed concomitant or pure FTLD-TDP type A pathology and occasionally FTLD-TDP type C[18,26,29,30,33,43,52,56,64,69]. Remarkably, even in the absence of clinical motor neuron dysfunction, some TDP-43-positive neuronal cytoplasmic inclusions (NCI) are usually present in LMN[43]. In pure ALS patients on the other hand, it was suggested that the finding of extra-motor p62-positive NCI

pathology, particularly in the CA4 subfield of the hippocampus, is a relatively reliable indicator of the presence of a *C9orf72* repeat expansion[38].

Characteristic for *C9orf72* expansions are ubiquitin- and p62-positive but TDP-43-negative inclusions, most abundant in cerebellar granule neurons, hippocampal neurons and all neocortex regions[29,30,32,33,36,43,56,69]. These inclusions, mostly NCI and neuronal intranuclear inclusions (NII), contain dipeptide repeat proteins (DPR) generated by non-ATG initiated translation from the expanded *C9orf72* repeat, GGGGCC, in all three reading frames[26,70,71] (**FIG. 2**). Another consistent pathological feature are the nuclear RNA foci, aggregates of sense and antisense repeat RNA, that are commonly present in frontal cortex, hippocampus and cerebellum[16,27,28]. Both the DPR pathology and the RNA foci poorly correlated with the presence of TDP-43 pathology[26,28].

If present, AD type pathology is minimal, and clinical AD patients with a *C9orf72* expansion were shown to have FTLD-TDP neuropathology[29,40,45,56], although AD patients with a *C9orf72* expansion and definite AD neuropathology have also been described[48]. In a study comparing AD pathology in 17 *C9orf72*-positive FTLD patients with 36 cases of sporadic FTLD, tau burden and distribution of amyloid plaques was similar between both[72].

GRN

In *GRN*, identified in FTD in 2006[14,15], over 70 pathogenic mutations have been identified to date. Most *GRN* mutations are loss-of-function (LOF) mutations that produce aberrant transcripts that are largely degraded (frameshift, nonsense or splice mutations) or prevent translation (e.g. mutation in the translation initiation codon), resulting in reduced expression of GRN up to 50% for the mutant allele, leading to FTD due to GRN haploinsufficiency[73–76]. Further, missense mutations have been identified that affect GRN structure and/or stability resulting in partial haploinsufficiency[77]. GRN is a secreted glycoprotein of 88 kDa, expressed in brain by neurons and microglia, increasingly with age[78]. It is composed of 7.5 cysteine-rich granulin domains that can be cleaved into 6 kDa units called granulins. Both GRN and granulins are involved in several biological processes including neuroinflammation, neurite outgrowth, stress response, lysosome biology, and synapse biology.

Epidemiology

Pathogenic mutations in *GRN* are the second major genetic cause of FTLD-TDP, and explain 1-12 % of FTD, 4-26% of familial FTD, 21-25% of autopsy-confirmed FTLD-TDP and 56% of familial FTLD-TDP patients[14,79–87].

Clinical

Neurodegenerative diseases caused by *GRN* LOF mutations are clinically heterogeneous, even among relatives carrying the same mutation[76,81,86,88–96]. Most *GRN* carriers are clinically diagnosed with FTD, and bvFTD is more frequent (50-75%[79–81,85,86,88,90,97,98]) than the language variant. Nonetheless, PPA, mainly consistent with PNFA, is reported to be more frequent in *GRN* carriers than in sporadic FTD[85,99]. Apart from FTD, clinical presentations resembling AD, PD, dementia with Lewy bodies (DLB), and remarkably frequently corticobasal syndrome (CBS) are observed[76,79,80,82,85,86,88–91,93,97,100–105]. Clinical diagnosis of PD, CBS or PSP were more frequent in *GRN*-positive FTLD-TDP than in *GRN*-negative FTLD-TDP cases (5.3% versus 1.3%)[101]. In case of a CBS diagnosis, there is an earlier onset and more cognitive dysfunction than in typical *GRN*-negative patients[76].

On neuropsychological testing, the majority of the *GRN* patient carriers exhibit executive dysfunction sooner or later in the disease course[79,90,91], and in the initial stage 9-33% have episodic memory deficits of the hippocampal type resembling AD or amnestic mild cognitive impairment (aMCI)[86,88–91,97,106]. Behavioral symptoms are an early feature in 75%[82,86,97,98,107], comparable to FTD patients without a *GRN* mutation. Apathy and social withdrawal are the main behavioral characteristics[79,83,85,86,90], while disinhibition is rarely a presenting feature[79].

In *GRN* carriers, language impairment is present at first evaluation in 21-91% and develops more frequent than in noncarriers (20-23%)[80,82,86,88,91,97,102,107]. In case of PPA, PNFA is most frequently diagnosed[76,79,85,90,99], but a distinct *GRN*-associated PPA subtype has been suggested with both elements of PNFA and LvPPA[108]. Aphasia in *GRN* carriers is typically non-fluent, characterized by impoverished propositional speech, severe anomia, prolonged word-finding pauses, impaired speech repetition most marked for sentences, and impaired verbal short-term memory[92,102,104,108–110]. Comprehension is variable with sometimes spared single-word comprehension but impaired comprehension of grammatically more complex sentences[92,102]. Rohrer et al described a case with a dissociated profile of semantic impairment: visual semantic processing was intact, while within the verbal domain, verbal comprehension was impaired and processing of nouns was intact on tasks requiring direct semantic processing but impaired on tasks requiring associative or inferential processing[108]. Phonemic and semantic paraphasias occur, as well as grammatical errors, although assessment of the latter can be difficult due to the scarcity of spontaneous speech[90,92,102,104,108,109,111]. Progressive apraxia of speech is extremely rare in *GRN*[111,112]. Some *GRN* cases can be diagnosed with LvPPA[113,114]. This PPA variant is mostly characterized by underlying AD pathology, but if β-amyloid deposition is lacking in an

LvPPA patient, chances are high they will carry a *GRN* mutation[114]. In *GRN*-positive FTD cases without diagnosis of PPA, language impairment is mainly characterized by mild anomia or decreased speech output consistent with dynamic aphasia[79,85,86,90,93].

Parietal lobe dysfunctions, including (limb) apraxia, dyscalculia, dysgraphia and visuospatial impairment, were observed in up to 82% of *GRN* patient carriers at initial neuropsychological assessment[79,86,90,115] and eventually significantly more frequent than in *GRN*-negative FTLD-U patients[79]. Hallucinations and delusions have been reported in up to 30%, more frequently than in noncarriers[81,86,106].

Parkinsonism is common (30-90%) and occurs more frequently in FTD due to a *GRN* mutation than in *GRN*-negative FTD[79,81,82,86,88,91,97,102,107,115]. On the contrary, pyramidal signs are less common, and concomitant MND is rare in *GRN* carriers[80,98,101,116]. So far, only *GRN* missense mutations with unknown pathogenicity have been reported in MND patients or FTD patients with family history of MND[115,117,118].

Onset ages and disease durations are highly variable amongst *GRN* carriers: even within the same family, variability can reach 30 years[83,92]. Onset ages range from 35 to 88 years[91,119] with averages of 53.3-64.5 years depending on the cohort[79–82,85,86,90,91,97,101,107,120]. Disease duration in *GRN* carriers is rather short with averages of 5-7 years[79,81,85,86,91,97,98,101,107,120], ranging from 1 to 22 years[119]. In most series mean/median onset ages[79,80,85,97,107] and disease durations[85,97,101,107] were comparable to noncarriers, although in a few series an earlier onset[101,121] or a shorter disease duration[79] was observed in *GRN* carriers than in noncarriers.

Neuroimaging and macroscopy

Brain atrophy and neuronal loss are more widespread and severe than in *GRN*-negative FTLD-TDP patients[97,107,116], and the whole-brain atrophy rate is faster[122]. The pattern of atrophy or functional impairment is remarkably asymmetric, more than in *GRN*-negative FTD patients[79], without a particular dominant hemisphere[67,79,86,122] (**FIG. 1**). Frontotemporal regions are predominantly affected[81,86,88,91,121], but early involvement of the parietal lobes is characteristic[79,86,88,90,97,103,123], and small volume of the right lateral parietal lobe was suggested to be predictive for *GRN* mutations[67]. Further, also longitudinal involvement of precuneus, posterior cingulate, thalamus, nucleus caudatus and long association white matter tracts is common[86,121–123], while occipital regions are mostly spared[79,81]. Another remarkable feature in *GRN* carriers is the presence of white matter hyperintensities in the atrophied regions[86,91,124–126]. In case a *GRN* carrier presents with LvPPA, strikingly asymmetric

neuroimaging findings with relatively preserved right hemisphere can distinct them from AD patients[127].

Histopathology

Severe neuronal loss often leads to status spongiosis, especially in layer II of the cortex[76,81,97,106,128]. Subcortical and deep cortical involvement is more pronounced in *GRN* carriers than in *GRN*-negative FTD, more frequently including the caudate nucleus and, to a lesser extent, the putamen[81,92,97,103,116,121,128].

The FTLD-TDP subtype A is typically found in *GRN* carriers, with a consistent pattern distinctive from *GRN*-negative FTLD characterized by severe involvement of the superficial neocortex and striatum, exclusively granular (rather than compact) nature of NCI in the hippocampus[85,97,128], absence of involvement of LMN and consistent presence of lentiform NII[80,97,120,128] (**FIG. 2**). Occasionally, neuronal loss is so severe that it is not possible to categorize the TDP-43 pathology into any of the established subtypes A-D[116].

In several patients, additional neuropathological features are present, such as AD pathology of neurofibrillary tangles and to a lesser extent amyloid plaques, as well as Lewy Body pathology, although not beyond what is expected in patients without *GRN* mutation[88,91,97,128,129].

TBK1

The *TBK1* gene was in 2015 initially identified in an extended ALS patient cohort and afterwards in FTD[20–22,130], based on LOF mutations leading to degradation of the mutant transcript and resulting in 50% reduction of TBK1. Our research group provided evidence for co-segregation in an extended FTD-ALS family of a small in-frame deletion leading to pathologic loss of TBK1[22,94]. TBK1 is an important serine/threonine kinase of the IκB kinase family involved in autophagy and neuroinflammation, phosphorylating a wide range of substrates, including optineurin and p62[131,132].

Epidemiology

TBK1 LOF mutations explain 0.4-3.4% of ALS patients, 0.2-1.3% of FTD patients and 3.3-4.5% of FTD-ALS patients[20,22,94,130,133,134]. In total, 54 index patients and 33 affected relatives were described with a LOF mutation in *TBK1* and available clinical information (**supplementary table 1**). Of note is that most of the mutations in *TBK1* are missense mutations with a yet unclear pathological and functional relevance[135]. Therefore, we limited the reviewing to LOF mutations and carriers.

Clinical

More than half of the *TBK1* LOF carriers were clinically diagnosed with pure MND, including mainly ALS, but rarely also progressive bulbar palsy, monoparesis and pure lower MND. About a quarter of the *TBK1* carriers were diagnosed with pure FTD or a few with unspecified dementia (D) (together abbreviated as (FT)D), and about a fifth with the combination of MND and (FT)D (**TABLE 1**)[20–22,63,94,99,133,136–144]. Some patients initially received a diagnosis of aMCI or AD, and two patients were diagnosed with progressive supranuclear palsy syndrome (PSPS) and progressive cerebellar ataxia (PCA), respectively. The relative overrepresentation of MND diagnoses is possibly a bias since so far, more ALS than FTD cohorts have been screened for *TBK1* mutations. Of the FTD patients with information on the clinical subtype, over 60% were diagnosed with the behavioral variant. Four patients were diagnosed with PNFA, of whom two clinically evolved to CBS, and three with SD[94,99,133,140].

To date, not many detailed phenotype descriptions were published, and whereas authors have observed remarkable similar characteristics amongst *TBK1* carriers in one patient cohort, these observations were rarely confirmed in other patient cohorts. Here, we will provide an overview of the published characteristics and remarkable features (**TABLE 1** and **supplementary table 2**), that though will need follow-up studies.

The majority of Belgian *TBK1* FTD carriers were diagnosed with the behavioral variant[99], while in a French-Portuguese patient cohort, all four *TBK1* FTD-ALS carriers had predominant language symptoms[133]. Apathy, as well as disinhibition and stereotyped behavior has been reported in *TBK1* carriers, but no remarkably predominant behavioral feature could be determined based on the available data (occurring in total in 75%, 60% and 55%, respectively). Concerning language and speech impairment, features of dynamic aphasia, as well as both semantic difficulties and non-fluent/agrammatic features were reported, but again none of these three subtypes was clearly predominant (occurring in 42%, 50% and 41%, respectively). Initial memory and/or orientation difficulties with potential misdiagnosis of AD were strikingly frequent in the Belgian cohort (in 8/9 FTD±ALS patients)[22,99], but in other cohorts this feature was not distinctly present (total frequency of early memory problems of 36%) and a recent study in 1253 patients with a clinical early onset AD diagnosis, could identify only one *TBK1* LOF carrier[145].

While a high frequency of psychiatric symptoms was observed in the Belgian *TBK1* carriers (57.1%), this was not confirmed in other cohorts (27% in total). The results in the Belgian patient cohort might have been flawed due to the overrepresentation of patients from one

single family, who might be sharing a yet unknown causal factor for this feature[99]. Overall, parkinsonism was reported in about one third, with an akinetic-rigid pattern in the majority of the *TBK1* carriers[21,99,133]. Mainly carriers of the p.Glu643del mutation seem to present with parkinsonism and this might be the reason why extrapyramidal symptoms were so frequent (57.1%) in the Belgian cohort. Of the MND patients with more detailed information on the region of onset, 25-32% had a bulbar onset[20,63,94,99,133,137–139,142]. In one cohort, the occurrence of bulbar symptoms was 87%[20]. In the combined dataset, bulbar symptoms were reported in 36% of pure dementia patients and 83% of spinal onset MND patients[20,63,94,99,133,136–141]. In cases with motor neuron symptoms, predominant UMN symptoms were twice as frequent as predominant LMN symptoms (28% versus 14%)[20,94,99,136,139]. More studies are needed in other neurodegenerative diseases apart from classical FTD and MND since most recently a patient with PSPS and one with PCA were identified with a *TBK1* variant[143].
Onset ages range from 35 to 78 years of age and disease durations from 1 to 16 years, with an average onset age of 60 years and an average disease duration of 4 years. Onset age tends to be lower (58 versus 66 years) and disease duration shorter (3 versus 7 years) in patients with MND compared to those with pure (FT)D (**TABLE 1**).

Neuroimaging and macroscopy

In the majority of *TBK1* carriers, cortical atrophy and functional impairment were predominantly located in the frontal and/or temporal lobes[21,94,99,133], and in medial temporal lobes or hippocampi in 25-30% of the patients[99,133] (**FIG. 1**). Only functional neuroimaging showed frequent parietal involvement, in 60%, while not many congruent symptoms were reported[99,140,141]. The pattern of atrophy and functional impairment was asymmetric in 69% and 89%[21,99,133,140,141]. Predominant involvement was mainly left-sided in PPA patients and right-sided in bvFTD patients. Most recently, mesencephalic and cerebellar atrophy was observed in *TBK1* carriers[143]. More research is warranted.

Histopathology

Neuropathology was reported for eight patients (2 ALS, 3 bvFTD, 1 PPA, 2 FTD-ALS) and in all TDP-43 inclusions were identified[20–22,94,99,140] (**FIG. 2**). One clinical PPA patient and one bvFTD patient were categorized as FTLD-TDP type A, while two bvFTD and the FTD-ALS patients were categorized as FTLD-TDP type B. Of note, in two patients an associated argyrophylic grain disease was reported[94,140].

VCP

In 2004, missense mutations were identified in *VCP* in autosomal dominant multisystem disorder inclusion body myopathy (IBM) associated with Paget disease of bone (PDB) and FTD (IBMPFD)[23]. To date, more than 30 missense mutations in *VCP* have been reported[146]. VCP is a member of the AAA-ATPase superfamily of proteins that utilize the energy gained from hydrolyzing ATP, to structurally remodel proteins. The protein regulates many cellular processes, including ubiquitin-dependent protein quality control, labeling proteins for recycling or degradation via the proteasome and coordinating the removal of aggregate prone proteins via multivesicular body formation[146,147].

Epidemiology

About 90% of *VCP* patients exhibit myopathy, 50% PDB and 30% FTD. In patients or families, one, two or three of these phenotypes may occur. In a cohort of 123 Belgian FTD patients, the frequency of *VCP* mutations was 1.6%[148], and no other studies on the frequency of *VCP* mutations in FTD have been reported. In 2010, *VCP* mutations were identified in 1-2% of familial ALS[25] expanding the FTD-ALS continuum. Among *VCP* carriers, about 8.9% were diagnosed with ALS and in 24% neurogenic changes like denervation or fibrillations were present on EMG[149,150]. Other reported comorbidities include liver abnormalities, cataract, cardiomyopathy as well as hearing impairment, although it is not known yet if all are part of the *VCP* disease spectrum[151–154].

Clinical

Apart from FTD, *VCP* patients have also been diagnosed with PD, AD, and rarely peripheral sensorimotor neuropathy, Charcot-Marie-Tooth type 2 and hereditary spastic paraplegia[149,155–158]. Few studies have carefully evaluated the clinical features of *VCP*-associated dementia in larger cohorts. Consequently, the phenotype characteristics described below are mainly extracted from case reports.

At neuropsychological testing, executive dysfunction was described in 26% of the *VCP* patients without overt dementia[148,152,159]. Rarely, early episodic memory problems were found[160]. Early behavioral changes, mainly apathy, emotional blunting and loss of initiative and spontaneity, have been frequently described in *VCP* patients[148,152,153,156,158]. Speech and language problems were described in several patients: both reduced speech eventually leading to mutism, and aphasia[154,158,161,162]. The most frequent reported language problem is anomia, and in a couple of patients comprehension deficits were described[148,152,158,161,163]. Both left- and right-lateralized SD have been reported[163], and pure slowly progressive dysarthria was described in a single patient[160].

In several *VCP* families, the appearance of early psychotic signs and schizophrenia with visual or auditory hallucinations is noteworthy[148,150,151,153,154,158,160,161].
Extrapyramidal symptoms such as bradykinesia and rigidity were reported in a few patients and some *VCP* carriers were diagnosed with PD or essential tremor[154,158,160].
In general, the onset of FTD in *VCP* carriers is later than the onset of IBM or PDB. Variable onset ages were described for FTD, ranging between 39 and 73 years, with an average of 55.3 years, and an average life span after onset of dementia of 6.5 years[149]. Average onset ages for IBM and PDB are 43.3 years and 40.7 years respectively[149].

Neuroimaging and macroscopy

Structural brain imaging displays rather nonspecific features ranging from normal over predominant frontal and temporal atrophy, to patterns of diffuse cortical and subcortical atrophy[148,153,154] (**FIG. 1**). Less frequently, hippocampal or parietal atrophy were reported[152,160,163]. Also on autopsy, the observed atrophy was variable, ranging from severe, diffuse atrophy, to mild, focal atrophy involving the frontal or medial temporal lobes and in some cases dorsolateral temporal or hippocampal regions[148,154,158,164]. On functional neuroimaging mainly frontotemporal impairment was described, but also involvement of parietal or cerebellar regions[148,160,162,163]. Asymmetry was rare[148,163]. In SD, impairment was suggested to be located more posteriorly compared to classic SD[163].

Histopathology

A first detailed neuropathology of eight *VCP*-associated IBMPFD patients including six clinically diagnosed FTD patients, described variable superficial spongiosis, neuron loss and gliosis in the neocortex and limbic structures with relative sparing of subcortical nuclei, brainstem and cerebellum[164]. Other reports, described severe neuronal loss at the level of the striatum, basal nuclei and thalamus, as well as the hippocampus and parahippocampal gyrus[148,158]. While initial neuropathological reports diagnosed patients with 'FTLD lacking distinctive histology'[151], the most striking feature were the abundant ubiquitin-positive inclusions – later demonstrated to be TDP-43-positive –, lentiform 'cat eye'-shaped or rod-shaped NII and dystrophic neurites (DN) that were present in a variety of brain regions, but most frequent in the neocortex, especially in the superior/middle temporal gyri[164,165] (**FIG. 2**). Cortical involvement and occipital lobe pathology was more extensive than in other FTLD-U patients, while the striatum tended to be less involved[164]. This pattern of TDP-43 pathology is specific for *VCP* mutations and was neuropathologically classified as FTLD-TDP type 4, later type D (**TEXTBOX 1**). Mostly, only low densities of senile plaques or tau-positive

cytoplasmic inclusions were observed, insufficient to meet neuropathological criteria for AD pathology or any of the defined tauopathies.

PHENOTYPIC SIMILARITIES AND DIFFERENCES BETWEEN CARRIERS

Direct comparative studies for clinical characteristics have been mainly performed between *MAPT*, *GRN* and *C9orf72* mutation carriers[29,30,32,41,54,67]. To date, only one comparative study has been performed between *TBK1*, *GRN* and *C9orf72* mutation carriers[99], and comparative studies with *VCP* mutation carriers are lacking. In this part, we will discuss similarities and differences between carriers of a mutation in a FTLD-TDP gene, based on the comparative studies concerned and the descriptions above, and we will point out features that were suggested to be distinct for one of the four FTLD-TDP genes.

Clinical

A common characteristic of all four genetic groups of FTLD-TDP is heterogeneity of the clinical and pathological presentation. In clinical diagnoses there are the behavioral and language variant of FTD, but also AD, PD and several other diagnoses. CBS, especially if familial, is suggestive for the presence of a *GRN* mutation[41,79].

Executive dysfunction, behavioral and language features, and memory complaints, are consistently present in all four FTLD-TDP carrier groups. In comparative studies, the neuropsychological profile, including the degree of executive dysfunctioning or memory impairment does not seem to remarkably differ between *GRN* or *C9orf72* carriers[29,54,67]. While apathy tends to be the major behavioral feature in *GRN* and *VCP* carriers[79,83,85,86,90,148,152,153,156,158], literature findings are inconsistent about apathy or disinhibition being more frequent in *C9orf72*[30,32,33,36,41]. Complex repetitive behaviors, and irrational, frankly bizarre behavior have been suggested to be distinctive for *C9orf72* carriers[33,54]. In the only comparative study including *TBK1* carriers, they exhibited significantly more frequent disinhibition and socially inappropriate behavior than *GRN* carriers[99], but this predominant disinhibition in *TBK1* carriers does not seem to hold true in other cohorts. Further, *C9orf72*- and *VCP*-associated disease are characterized by a strikingly frequent presence of psychosis and hallucinations[29–31,33–36,40,41,51,58,148,150,151,153,154,158,160,161], and psychotic features were reported to be more frequent in *C9orf72* carriers than *GRN* carriers[54]. Early unilateral apraxia is indicative for the presence of a *GRN* mutation[41,54,79]. While non-fluent language features or reduced speech output consistent with dynamic aphasia are common in *GRN* and *C9orf72* carriers[33,36,54,80,86,88,90,91], semantic impairment is

rather seldom and has been suggested to be, combined with behavioral FTD, a strong predictor for *MAPT* mutations[85]. PPA, mainly PNFA, and language impairment in general, is more frequently observed in *GRN* than *C9orf72* carriers[29,41,54,99]. Further, a distinct *GRN*-associated PPA subtype has been suggested characterized by impoverished propositional speech, severe anomia, prolonged word-finding pauses, impaired speech repetition most marked for sentences, impaired verbal short-term memory[92,102,104,108–110] and grammatical errors[108]. Language impairment consists most frequently of dynamic aphasia in *C9orf72* carriers[33] and of anomia in *VCP* carriers [148,152,158,161,163]. No clear predominant language feature has been distinguished for *TBK1* carriers. On the neuropathological level, PNFA has been linked to FTLD-TDP type A in both *GRN* and *C9orf72* carriers[54].

Parkinsonism in the FTLD-TDP carriers is most frequently characterized by an akinetic-rigid syndrome and its presence cannot discriminate between *C9orf72* and *GRN* carriers[29,41,54,67]. Belgian *TBK1* carriers exhibited more frequently extrapyramidal symptoms than *C9orf72* or *GRN* carriers[99], but larger international studies are necessary to see if this holds true. Parkinsonism seems to be especially associated with the *TBK1* p.Glu643del mutation, and in the meta-analysis above, parkinsonism was present in about one third of *TBK1* carriers, not more frequent than reported frequencies in *C9orf72* (12-40%) and *GRN* carriers (30-90%).

Associated MND has been described in all FTLD-TDP genetic subtypes except for *GRN* carriers. In FTLD-MND patients the *C9orf72* repeat expansion is the most frequent mutation, with the presence of MND doubling the chance of finding a *C9orf72* repeat expansion[33]. Patients or families with associated features of myopathy or PDB are indicative for the presence of a *VCP* mutation.

Wide ranges in onset age are described in all four FTLD-TDP genetic groups, varying at least over 30 years. Average onset ages are ranging between 50 and 64 years, which is higher than the average onset ages of 45 to 50 years in tauopathies[85,166,167]. In direct comparative studies between FTD patients with *GRN*, *C9orf72* or *MAPT* mutation, *MAPT* carriers often had an earlier onset than *GRN* and *C9orf72* carriers[29,54,67,81,85], and *GRN* carriers tended to be older at onset than *C9orf72* carriers[29,41,67]. In the only comparative study involving *TBK1* carriers, *TBK1* carriers had a significantly later mean onset than *C9orf72* carriers[99]. In the majority of comparative studies, no significant differences have been found for disease duration between *GRN* and *C9orf72* carriers[29,30,32]. Nevertheless, the data suggested that progression of FTD due to a *C9orf72* repeat expansion is rather slow[35], while the occurrence of ALS in *C9orf72* (or *TBK1*) carriers shortens survival[29,44,99]. Further, some studies have observed a shorter disease duration in *GRN*-positive FTD patients than *GRN*-negative FTD patients[79,101].

Neuroimaging and macroscopy

Predominant frontotemporal impairment is present in all four FTLD-TDP carrier groups. In most *GRN* and *TBK1* carriers an asymmetric pattern is present, while the pattern tends to be rather symmetric in *C9orf72* and *VCP* carriers[21,29,30,54,67,79,86,99,122,133,140,141]. In some studies predominant frontal instead of temporal atrophy tended to occur more often in *GRN* than *C9orf72* carriers[32,54]. One study suggested that predominant temporal atrophy occurs more often in *C9orf72* carriers than *GRN* carriers[32], although other studies showed a greater involvement of the left inferior temporal lobe in *GRN* carriers[30,67]. Further, a greater involvement of bilateral parietal lobes was observed in *GRN* compared to *C9orf72* carriers[67]. While parietal involvement in *GRN* carriers is consistent with clinical symptoms, parietal involvement in *TBK1* carriers seems to occur without clear congruent symptoms. The presence of white matter hyper-intensities correlated with disease progression seems to be characteristic for *GRN* mutations[168].

Histopathology

Neuropathologically, FTLD-TDP in *C9orf72* and *TBK1* carriers shows a pattern that is largely consistent with type B pathology and to a minor extent with type A. The FTLD-TDP pathology is consistently type A in *GRN* carriers and type D in *VCP* carriers, with the presence of NII. Specific for *C9orf72* carriers, is the presence of DPR pathology as well as RNA foci. Significantly more neurofibrillary tangles and a higher tau load were observed in FTLD patients carrying a *C9orf72* expansion than a *GRN* mutation, most markedly in limbic regions[72].

OPPORTUNITIES AND IMPLICATIONS OF FTLD-TDP GENOTYPE-PHENOTYPE CORRELATIONS

Understanding genotype-phenotype correlations in neurodegenerative diseases such as FTLD-TDP is important from several points of view. First of all in the clinic: the clinical phenotype is the first clue for a clinician to think about a certain disease, and the starting point for further investigations. Specific clinical characteristics can raise suspicion for the presence of a certain mutation and can guide the decision of a clinician to prioritize (a) particular gene(s) to be tested for the presence of mutations. Second, in the frame of counseling, genotype-phenotype correlations can aid to provide prognostic information to (pre)symptomatic carriers. For example, when a *C9orf72* expansion or *TBK1* mutation carrier

develops ALS, his expected lasting survival time is shortened to two-three years. *GRN* patient carriers might have a poorer survival prognosis than FTLD patients without a mutation in *GRN*, and in *C9orf72* families a decrease in onset age can be expected in next generations due to disease anticipation. However, in all four FTLD-TDP gene carrier groups, onset ages widely range over several decades, even within families, making it impossible to predict the timing of symptom onset in a newly diagnosed carrier. Also the lack of consistency of anticipation in *C9orf72* families[66] hampers robust predictions about onset age. Longitudinal studies of preclinical mutation carriers, such as the Genetic FTD Initiative (GENFI)[169], with extensive neurological examinations, including imaging and cerebrospinal fluid biomarkers, might help to develop integrated tools for the prediction of onset and prognosis of disease. Further, follow-up of phenotypic characteristics in patient carriers can lead to the identification of reliable biomarkers for disease progression, which will be of interest to follow effects of therapies yet to be developed. Presently, there are no disease modifying or curative therapies for FTLD patients and, taken the difference in disease pathology, it is unlikely that all patients will benefit from the same therapy. Neurologists and clinical researchers will need prediction tools that can differentiate the FTLD patients based on their underlying pathology. Genotype-phenotype correlations can aid in this future therapy stratification: the identification of phenotypic characteristics specific for patients with the same underlying disease mechanism or gene mutation will enable the selection of patients who will most likely benefit from a particular targeted therapy.

Not only phenotypic similarities between patients carrying the same mutations or mutations in the same gene, but also differences are of importance for prognostic predictions and development of disease modifying or delaying therapies. The phenotypic heterogeneity as discussed in this review can also be seen as an opportunity rather than as a constraint. The presence of highly variable onset ages within large families carrying the same mutation, e.g. the Belgian founder family carrying a *GRN* null mutation in the splice donor site of intron 1[89] or the Italian founder family carrying the *GRN* p.Thr272fs mutation[96,170], is a great opportunity to identify genetic modifying factors for onset age. Further, in a Belgian cohort of extended *C9orf72* families, analysis of the variable onset ages have led to evidence of the occurrence of disease anticipation[66] and of the association of onset age with repeat length[171]. Also the presence of both ALS and FTD in *C9orf72* as well as *TBK*1 families can be an opportunity to search for genetic factors that determine which of both phenotypic extremes of this disease spectrum develops. The identification of genetic modifiers will not only enable

prognostic predictions, but will also elucidate mechanisms and networks involved in the pathogenesis of disease and reveal novel therapeutic targets.

In an era of large NGS (next-generation sequencing) and GWAS (genomic wide association studies) projects, the importance of detailed phenotypic descriptions of patient carriers may be overlooked. For example, although the identification of *TBK1* as a causal gene for FTLD and ALS dates from three years ago, our review of the literature learned that in-depth phenotypic descriptions including detailed clinical and neuroimaging features are rather sparse. Considering the importance of genotype-phenotype correlations especially in the frame of therapy development and patient stratification for future clinical trials, phenotypic descriptions of mutation carriers remain valuable and necessary.

CONCLUSIONS/PERSPECTIVES

Here, we have reviewed the phenotypic presentations associated with the four major FTLD-TDP causing genes and highlighted characteristics that are indicative for a particular underlying gene, in order to guide genetic testing (**TEXTBOX 2**). Although no absolute associations can be identified, especially for *C9orf72*- and *GRN*-associated FTLD some distinctive characteristics have been suggested that can raise suspicion for the presence of a *C9orf72* repeat expansion or a *GRN* LOF mutation. The identification of distinctive clinical characteristics for *TBK1*- and *VCP*-associated FTLD is more difficult. This is partially due to the smaller size of the latter two groups of mutation carriers, since the mutation frequencies in *TBK1* and *VCP* are ten times lower compared to those of *C9orf72* and *GRN*. Also, there is a lack of extended studies aiming at evaluating the clinical features of *TBK1* and *VCP* carriers compared to those of *C9orf72* and *GRN* carriers.

In an era where the search for disease modifying or curative therapies for neurodegenerative diseases is rapidly evolving, large clinical studies are needed that follow-up patients from preclinical stages to disease onset and death, to identify specific clinical characteristics that allow discrimination between the different pathologic FTLD subtypes, including FTLD-TDP and FTLD-tau.

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TEXTBOXES

xxxxx - TEXTBOX 1: FTLD-TDP - xxxxx

The majority of FTLD patients without insoluble tau proteins in the form of intraneuronal neurofibrillary tangles or Pick bodies[172], contain ubiquitin-positive (U+) pathology in intraneuronal inclusions and/or neuritic changes in cerebral cortex and hippocampus, formerly referred to as FTLD-U, or FTLD-MND if clinical MND is also present[173]. In 2006, Mackenzie et al. and Sampathu et al., independently described the pathological heterogeneity in FTLD-U and recognized three distinct histological patterns.

Afterwards, a fourth type of FTLD-U was identified, which was specifically associated with the familial syndrome of inclusion body myopathy with Paget's disease of bone and frontotemporal dementia (IBMPFD) due to *VCP* mutations[164].

TDP-43 was identified as the hallmark protein in FTLD-U and FTLD-MND[5]. Pathologic TDP-43 was observed to be hyperphosphorylated, ubiquitinated, and cleaved to generate C-terminal fragments. Further, TDP-43 was detectable in the nuclei of unaffected neurons but absent in nuclei of neurons with ubiquitin-positive inclusions, suggesting that TDP-43 is redistributed from the nucleus to the cytoplasm in affected neurons[5].

It was confirmed that most FTLD-U patients, including FTLD-U type 4, had TDP-43 pathology[165,174,175], and consequently cases with TDP-43 pathology were referred to as FTLD-TDP while FTLD-U was no longer used[176].

To standardize the FTLD-TDP pathology classifications, the two existing classification systems were harmonized to four categories of FTLD-TDP from type A to D[177]. A fifth category was recently suggested by Lee et al[178].

FTLD-TDP classification	***Cortical pathology***	***Common phenotype***	***Associated genes***
Type A	-many intraneuronal cytoplasmic inclusions (NCI) -many short dystrophic neurites (DN)	*bvFTD* *PNFA*	*GRN* *TBK1* *(C9orf72)*

	-few neuronal intranuclear inclusions (NII) -in superficial cortical layers (predominantly layer II)		
Type B	-many NCI -few DN -no NII -in both superficial and deep cortical layers	*bvFTD* *FTD-MND*	*C9orf72* *TBK1*
Type C	-few NCI -many long DN -no NII -in superficial cortical layers (predominantly layer II)	*SD* *bvFTD*	
Type D	-few NCI -many short DN -many lentiform NII -most abundantly in neocortex	*Familial IBMPFD*	*VCP*

Adapted from Mackenzie et al. 2011[177]

xxxxx - end textbox 1 – xxxxx

xxxxx - TEXTBOX 2: Key phenotypic characteristics of FTLD-TDP genes - xxxxx

C9orf72

- Presence of MND in FTD patient or family
- BvFTD much more frequent than PPA
- Frequent complex repetitive behaviors and irrational, bizarre behavior
- Frequent occurrence of anxiety, psychosis, delusions, hallucinations
- Occurrence of anticipation in families
- Symmetric pattern of brain atrophy/functional impairment with frontotemporal predominance extending to parietal-occipital cortex and subcortical regions
- FTLD-TDP mostly type B, to a lesser extent type A, and rarely type C
- p62-positive but TDP-43-negative inclusions in cerebellar granule neurons and hippocampal neurons

GRN

- Apathy much more frequent than disinhibition
- Frequent language impairments
- PPA characterized by impoverished speech, anomia, impaired sentence repetition, impaired verbal short-term memory, aggramatism
- Frequent and early unilateral parietal lobe dysfunctions, sometimes CBS
- Absence of MND
- Asymmetric pattern of brain atrophy/functional impairment with early involvement of parietal lobes
- Common shrunken caudate nucleus
- FTLD-TDP type A

TBK1

- Presence of MND in FTD patient or family
- BvFTD more common than PPA
- No clear predominance of apathy or disinhibition
- No clear predominance of dynamic aphasia, PNFA or SD
- Frequent bulbar symptoms, also in pure FTD and spinal onset ALS
- Rather asymmetric pattern of brain atrophy/functional impairment with frontotemporal predominance extending to parietal without congruent symptoms
- FTLD-TDP mostly type B, but also type A

VCP

- Presence of IBM or PDB in FTD patient or family
- Less frequent cause of ALS
- Apathy more common than disinhibition
- Anomia is the most frequent language problem
- Frequent occurrence of early psychotic signs and schizophrenia with hallucinations
- Variable, nonspecific, mainly symmetric patterns of brain atrophy/functional impairment
- FTLD-TDP type D

xxxxx - end textbox 2 - xxxxx

FIGURE LEGENDS

FIGURE 1: Affected brain regions

This schematic image presents the main brain regions and the extent to which they are involved in neurodegeneration caused by the four FTLD-TDP genes (from left to right, top to bottom: *C9orf72, GRN, TBK1, VCP*). Color and intensity indicate severity and likelihood of degeneration: severity increases from yellow to orange to red, likelihood increases with increased intensity. For each gene, the following brain views were pictured left to right, top to bottom: left lateral, right lateral, superior, right medial, left medial, inferior. In *GRN*- and *TBK1*-associated FTLD, an asymmetric pattern is almost certainly. As an example, predominant left-side involvement was pictured, though for neither gene a predominant is known.

FIGURE 2: Neuropathology

1. *TDP-43 immunostaining* of a sample of the frontal cortex (**1a**) and the superior temporal gyrus (**1b**) of a *C9orf72* expansion carrier, showing both intraneuronal cytoplasmic inclusions (NCI) (black arrowhead) and dystrophic neurites (DN) (arrow) consistent with FTLD-TDP type B pathology. *Immunohistochemistry with poly-GA-specific antibodies* detects DPR-positive dot-like NCI in the granular cell layer of the cerebellum (**1c**) and the dentate gyrus of the hippocampus (**1d**) of a *C9orf72* repeat expansion carrier.

2. *TDP-43 immunostaining* of samples of the frontal cortex (**2a** and **2b**), superior temporal gyrus (**2c**) and parietal cortex (**2d**) of a *GRN* LOF mutation carrier shows a mild to moderate amount of NCI (black arrowhead), which are mainly present in the second cortical layer. Further, DN (arrow) are spread throughout the entire cortex and rare neuronal intranuclear inclusions (NII, white arrowhead) can be observed. This pattern is consistent with FTLD-TDP type A.

3. *TDP-43 immunostaining* of the frontal cortex (**3a**) and the spinal cord (**3b**) of a *TBK1* LOF mutation carrier reveals a moderate amount of NCI (black arrowhead) and short DN, but no NII, consistent with FTLD-TDP type B. These inclusions can also be observed after *p62 staining* (**3c**: frontal cortex, **3d**: hippocampus).

4. *TDP-43 immunostaining* of samples of the frontal cortex (**4a** and **4c**) and superior temporal gyrus (**4b** and **4d**) of *VCP* mutation carriers shows both NCI (black arrowhead), DN (arrow) as well as NII (white arrow head), which often have a characteristic cat-eye shape but can also present as more rounded, consistent with FTLD-TDP type D.

FIGURE 3: Phenotype-genotype correlations

The shade of blue indicates the likelihood that a certain phenotype characteristic (columns) occurs in frontotemporal lobar degeneration (FTLD) caused by a mutation in one of the four FTLD-TDP43 genes (rows): the darker the shade of blue, the higher the likelihood.
Abbreviations: MND: motor neuron disease, PDB: Paget disease of the bone

TABLES

TABLE 1: summarized phenotypic characteristics of TBK1 mutation carriers

			all patients[11] (n = 87)		**index patients only** (n = 54)	
Mean age at onset, year (SD, range)	**All diagnoses**		60 (11, 35 – 78)		60 (9, 35 - 78)	
	(FT)D only (inclusive PSPS)		66 (7, 48 – 78)		65 (8, 48 - 78)	
	MND ± FTD		58 (11, 35 – 77)		58 (9, 35 - 76)	
Mean disease duration till death, year (SD, range)	**All diagnoses**		4 (3, 1 – 16)		4 (3, 1 - 13)	
	(FT)D only		7 (5, 2 – 16)		5 (3, 2 - 9)	
	MND ± FTD		3 (2, 1 – 13)		4 (3, 1 - 13)	
diagnosis, n (%[1])	**(FT)D**		20 (23)		11 (22)	
	MND		49 (56)		31 (57)	
	(FT)D-ALS		16 (18)		10 (19)	
	PSPS		1 (1)		1 (2)	
	PCA		1 (1)		1 (2)	
subdiagnosis, n (%[1])	**FTD variant**	**bvFTD**	13(65)		11 (61)	
		PPA: nfv / sv	4 (20) / 3 (15)		4 (22) / 3 (17)	
	ALS onset	**bulbar**	15 (28)		13 (35)	
		spinal	39 (72)		24 (65)	
behavioral feature, n (%[1])	**apathy**		9+6* (45+30*)[2]	20 (69)	6+5* (43+36*)[2]	14 (70)
	disinhibition		8+4* (40+20*)[2]		6+3* (43+21*)[2]	
	stereotype / compulsive		8+3* (40+15*)[2]		7+3* (50+21*)[2]	
executive dysfunction, n (%[1])			5+2* (19+8*)		3+2* (16+11*)	
memory / orientation difficulties , n (%[1])			12+3* (36+9*)		7+3* (29+13*)	
language feature, n (%[1])	**economy of speech / mutism**		5 (42)[3]	12 (40)	4 (36)[3]	11 (52)
	semantic difficulties		4+2* (33+17*)[3]		4+2* (36+18)[3]	
	agrammatic / non fluent		4+1* (33 + 8*)[3]		4+1* (36+9*)[3]	
psychiatric symptoms, n (%[1])			7 (27)		2 (11)	
prosapognosia, n (%[1])			1+1* (4+4*)		1+1* (5+5*)	
apraxia, n (%[1])			3 (10)		1 (5)	
parkinsonism, n (%[1])	**akinetic-rigid**		9 (90)[4]	10 (34)	6 (86)[4]	7 (35)
	tremor-dominant		1 (10)[4]		1 (14)[4]	
bulbar symptoms, n (%)	**in pure (FT)D**		4 (36)[5]		2 (33)[5]	
	in spinal onset MND		25 (83)[6]		16 (84)[6]	
predominant UMN/LMN, n (%)			10 (28)[7] / 5 (14)[7]		6 (27)[7] / 4 (18)[7]	
atrophy on structural brain imaging, n (%)	**present**		17		12	
	predominant frontotemporal		11 (65)[8]		8 (67)[8]	
	medial temporal/ hippocampi		4 (24)[8]		3 (25)[8]	
	parietal involvement		1 (6)[8]		1 (8)[8]	
	aspecific global		1 (6)[8]		0	
	mesencephalic		2 (12)[8]		2 (17)[8]	
	cerebellar		1 (6)[8]		1 (8)[8]	
	asymmetric		9 (69)[9]		7 (78)[9]	

functional impairment, n (%)	**present**	10	9
	predominant frontotemporal	9 (90)[10]	8 (89)[10]
	medial temporal/ hippocampi	3 (30)[10]	3 (33)[10]
	subcortical involvement	2 (20)[10]	2 (22)[10]
	parietal involvement	6 (60)[10]	5 (56)[10]
	asymmetric	8 (89)[9]	7 (88)[9]

▭ no information available; ***** later in disease course; [1]percentage within informative group; [2]percentage within those with reported behavioral features; [3]percentage within those with reported language features; [4]percentage within those with reported parkinsonism; [5]percentage within pure (FT)D patients with available information on the development of bulbar symptoms; [6]percentage within spinal onset MND patients with available information on the development of bulbar symptoms; [7]percentage within patients who exhibit motor neuron signs and in whom information is available on the relative presence of UMN and LMN sign; [8]percentage within patients with reported atrophy; [9]percentage within patients of whom information about (a)symmetric pattern was reported; [10]percentage within patients with reported functional impairment; [11]all index + affected relatives carrying a *TBK1* LOF mutation with reported clinical information. ***Abbreviations:*** ALS: amyotrophic lateral sclerosis; D: unspecified dementia; FTD: frontotemporal dementia; (FT)D: frontotemporal dementia or unspecified dementia; MND: motor neuron disease; nfv: non fluent variant; PCA: progressive cerebellar ataxia; PPA: primary progressive aphasia; PSPS: progressive supranuclear palsy syndrome; sv: semantic variant