Published in final edited form as:

Curr Genet Med Rep. 2019 March ; 7(1): 41–52. doi:10.1007/s40142-019-0160-6.

Recent advances in the genetics of frontotemporal dementia

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Abstract

Purpose of review: In this review we highlight recent advances in the human genetics of frontotemporal dementia (FTD). In addition to providing a broad survey of genes implicated in FTD in the last several years, we also discuss variation in genes implicated in both hereditary leukodystrophies and risk for FTD (e.g., *TREM2*, *TMEM106B*, *CSF1R*, *AARS2*, *NOTCH3*).

Recent findings: Over the past five years, genetic variation in approximately 50 genes has been confirmed or suggested to cause or influence risk for FTD and FTD-spectrum disorders. We first give background and discuss recent findings related to *C9ORF72*, *GRN* and *MAPT*, the genes most commonly implicated in FTD. We then provide a broad overview of other FTD-associated genes and go on to discuss new findings in FTD genetics in East Asian populations, including pathogenic variation in *CHCHD10*, which may represent a frequent cause of disease in Chinese populations. Finally, we consider recent insights gleaned from genome-wide association and genetic pleiotropy studies.

Summary: Recent genetic discoveries highlight cellular pathways involving autophagy, the endolysosomal system and neuroinflammation, and reveal an intriguing overlap between genes that confer risk for leukodystrophy and FTD.

Keywords

frontotemporal lobar degeneration; leukodystrophy; genetics; autophagy; lysosomes; inflammation

Introduction

Frontotemporal dementia (FTD), one of the most common forms of dementia after Alzheimer's disease (AD) in people younger than 65, encompasses a broad, clinically

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Conflict of Interest

Daniel W. Sirkis, Ethan G. Geier, Luke W. Bonham, Celeste M. Karch and Jennifer S. Yokoyama each declare no potential conflicts of interest.

Human and Animal Rights

This article does not contain any studies with human or animal subjects performed by any of the authors.

heterogeneous group of disorders involving pathological changes in personality, behavior and/or language due to underlying neurodegeneration of the frontal and temporal lobes of the cerebral cortex (i.e., frontotemporal lobar degeneration [FTLD]). When the primary clinical manifestations include behavioral disinhibition, apathy, loss of empathy, hyperorality, and/or compulsive behaviors, patients are likely to meet clinical criteria for diagnosis of behavioral variant FTD (bvFTD). Conversely, patients that present with difficulty understanding the meaning of words or naming people or objects are most often diagnosed with semantic variant primary progressive aphasia (svPPA); difficulties with motoric aspects of speech (e.g., word generation, pronunciation) are associated with a diagnosis of nonfluent variant PPA (nfvPPA). Individuals diagnosed with FTD-spectrum disorders often have a family history of dementia or other neurodegenerative disease (~40% of cases [1,2]), and it has been estimated that ~10–30% of FTD is inherited in an autosomal-dominant manner [1–3], a much higher proportion than that which has been found for AD (<1% [4]), highlighting the importance of genetics in the etiology of FTD.

FTLD underlying clinical diagnoses within the FTD spectrum can be characterized neuropathologically by the abnormal accumulation of the proteins TDP-43 (FTLD-TDP; ~50–60% of cases; [5,6]), tau (FTLD-tau; ~40–45% of cases [5,7]) or FET (FUS, EWS, TAF15; FTLD-FET; ~5–10% of cases [5,7]). In rare cases, clinical FTD is associated with white matter degeneration rather than pathological protein accumulation (see leukodystrophy section below). It is important to note that clinical diagnosis of a particular FTD subtype (e.g., bvFTD) may be caused by a variety of distinct neuropathologies, while a particular subtype of FTLD (e.g., FTLD-TDP) may, in different individuals, lead to distinct diagnoses within the FTD spectrum. In addition, it is important to keep in mind that perhaps 20% or more of clinically diagnosed FTD cases may arise from underlying AD or other non-FTLD pathology [5]. These issues highlight how cohort selection (e.g., clinically vs. pathologically defined) will have a marked influence on the outcome of genetic studies.

A combination of clinical observation, genetic discovery and overlapping pathology described over the last 20 years has led to the current view that FTD and the motor neuron disease, amyotrophic lateral sclerosis (ALS), have a shared etiology and can be thought to exist within a disease continuum. In this review, we (i) highlight the most important genetic contributions to disorders within the FTD and FTD-ALS spectrum, emphasizing in particular those discoveries made in the last five years; (ii) place a special emphasis on genes involved in both leukodystrophy and FTD; and (iii) discuss genes implicated as disease risk factors in East Asian populations.

MAPT, GRN and C9ORF72

Pathogenic variation in *MAPT*, encoding the microtubule-binding protein tau, was first linked to an autosomal-dominant form of FTD with parkinsonism over 20 years ago [8–11] and has since been estimated to account for 5–20% of familial FTD cases (see Table 1 for a summary of the major genes implicated in familial FTD; [5,7,12,13]). The large range in estimated prevalence of pathogenic variation in *MAPT* (and other genes) in familial FTD reflects both the malleability of the term ‘familial’ and the nature and ethnicity of the cohorts being studied. To date, over 50 pathogenic mutations in *MAPT* have been identified

[13], but only rarely (0–2% of cases) do these mutations account for sporadic (non-familial) FTD (e.g., see [14]). Although *MAPT* mutations are generally thought to display complete penetrance, a recent report of the well-established p.V337M mutation (rs63750570) has described very slow disease progression in one carrier and apparent absence of disease in her 67-year-old son [15]. Relatedly, the p.G389R mutation (rs63750512) in some cases results in aggressive FTD, but it can also be found in unaffected individuals [16]. Cases such as these illustrate that even for well-characterized genes, presumed "causal" mutations may not be completely penetrant, possibly due to the modifying effects of other genetic or environmental factors. In addition, although the vast majority of pathogenic *MAPT* mutations are associated with bvFTD and FTD-spectrum disorders, the p.R406W mutation (rs63750424) is instead associated primarily with clinically diagnosed AD [17,18]. Curiously, however, in two independent families, patients that are homozygous for the p.R406W mutation present with bvFTD [19,20], suggesting that the dosage of this mutation can influence disease outcome.

After the discovery of pathogenic *MAPT* mutations linked to familial FTD with parkinsonism in 1998, several families remained who possessed neither *MAPT* mutations nor tau pathology but who displayed autosomal-dominant FTD linked to the same chromosomal region (17q21). In 2006, two groups independently identified null mutations in *GRN*, located <2 Mb centromeric of *MAPT* and encoding the secreted glycoprotein progranulin, as the cause of disease in these families [21,22]. Since this discovery, over 70 pathogenic mutations in *GRN* have been described, most of which are thought to result in loss of function via interference with *GRN* transcription or translation resulting in protein haploinsufficiency; missense mutations have also been described [6]. Pathogenic variation in *GRN* is currently estimated to account for 5–25% of familial FTD [6,13] and perhaps as much as 10% of all FTD cases [23]. *TMEM106B* is an important modifier of FTD risk and age at disease onset in individuals with *GRN* mutations [24] and will be discussed in more detail below. While the initial identification of pathogenic *GRN* mutations suggested an important role for microglia in FTD pathogenesis [22,25], the 2012 discovery of a homozygous, loss-of-function *GRN* mutation as a cause of neuronal ceroid lipofuscinosis (NCL) [26], a lysosomal storage disorder (LSD), provided additional insight into progranulin biology, and suggested that lysosomal homeostasis might represent a cellular pathway relevant to FTD pathogenesis. Moreover, the recent identification of potentially pathogenic mutations in the *CTSF* gene—encoding the lysosomal hydrolase, cathepsin F, mutations in which also cause NCL—in patients with FTD and early-onset AD indicates that additional NCL genes may contribute risk for FTD and related dementias [27,28]. In support of this idea, recent evidence from our laboratory suggests that rare variant enrichment in *MFSD8* (*CLN7*) may contribute to FTLD risk [29].

Additional rare causes of FTD, ALS-FTD and complex clinical syndromes that sometimes include FTD were reported in the years following the discoveries of pathogenic variation in *MAPT* (including mutations in *VCP* [30] and *CHMP2B* [31]) and *GRN* (including mutations in *TARDBP* [32], *FUS* [33] and *UBQLN2* [34]). However, as these mutations collectively account for only a small fraction (<5%) of familial FTD [7,13], it was clear by 2011 that there must be additional pathogenic mutations accounting for a larger proportion of familial FTD. Thus, the discovery that a hexanucleotide G_4C_2 repeat expansion intronic to

C9ORF72 was a common cause of familial and sporadic forms of FTD, ALS and ALS-FTD [14,35], reported independently by two groups, was met with great excitement. It is currently estimated that pathogenic repeat expansion in *C9ORF72* accounts for 20–30% of familial and 6% of sporadic FTD in cohorts of European descent [6,7,13], although the expansion appears to be much less common in East Asian patients with FTD (see below). *C9ORF72* repeat expansions have also been reported in a small proportion of familial, late-onset AD cases [36]. Models for the pathogenicity of *C9ORF72* expansion remain hotly debated and include haploinsufficiency; toxicity from the transcribed, expanded-repeat-containing RNA; and toxic dipeptide repeat proteins generated through non-canonical expanded-repeat translation. A detailed discussion of such mechanisms is beyond the scope of this article, but other recent reviews provide excellent descriptions (e.g., see [37]).

Additional FTD genes

SQSTM1, OPTN and TBK1

Mutations in *SQSTM1*, which encodes a multifunctional autophagy adaptor protein, p62, were first discovered in FTD patients in 2012 [38], and rare variants in this gene were subsequently found to increase risk for disease in a large cohort of European FTD patients [39]. Interestingly, the recent identification of compound heterozygous loss-of-function mutations in *SQSTM1* as a cause of childhood-onset neurodegenerative disease [40] suggests that heterozygous mutations implicated in FTD may confer risk via haploinsufficiency. Although mutations in *OPTN*, encoding another autophagy adaptor protein, optineurin, have generally been associated with ALS rather than FTD, several reports have identified heterozygous mutations in ALS cases that also presented with aspects of FTD [41,42]. In addition, compound heterozygous mutations in *OPTN* have more recently been identified in FTLD-TDP by whole-genome sequencing [43]. Functional studies suggest that disease-associated mutations in both *SQSTM1* and *OPTN* result in impaired macroautophagy (reviewed in [37]), strongly implicating this cellular pathway in FTD and ALS pathogenesis.

Heterozygous, loss-of-function mutations in *TBK1* (encoding TANK-binding kinase 1) were recently implicated in FTD and ALS as well as pathologically confirmed cases of FTLD-TDP [43,44]. Interestingly, some pathogenic *TBK1* mutations appear to impair the ability of TBK1 to bind optineurin, thus implicating these mutations in dysfunctional autophagy, similar to pathogenic *SQSTM1* and *OPTN* mutations [44]. Findings from European FTD cohorts indicate that pathogenic *TBK1* mutations may be a relatively common genetic cause of disease (accounting for 1–5% of FTD and FTD-ALS), perhaps second only to pathogenic variation in *C9ORF72* and *GRN* [45]. TBK1 was very recently suggested to be a key regulator of inflammation in the brain by acting as a negative regulator of RIPK1 kinase activity [46], thus placing TBK1 at the crossroads of autophagy and inflammation. Analogously, *PRKN*, encoding the key mitophagy regulator parkin, was recently shown to regulate inflammation by preventing the accumulation of damaged mitochondria [47]. Although a well-established familial Parkinson's disease (PD) gene, pathogenic mutations in *PRKN* may also be a rare cause of bvFTD in the absence of parkinsonism [48]. These

findings illustrate the interconnectedness of autophagy and neuroinflammation, and indicate both may represent key pathways in multiple forms of neurodegeneration.

TIA1 and CCNF

A missense mutation in the low-complexity domain (LCD) of *TIA1*, encoding T-cell-restricted intracellular antigen-1, was recently identified as the potentially causal mutation in a family with ALS-FTD [49]. Further analysis by the same investigators suggested an increased burden of rare variants specifically within the LCD of *TIA1* in ALS and ALS-FTD patients relative to controls. As an LCD-containing, RNA-binding protein, TIA1 shares characteristics with other well known FTD-associated proteins such as TDP-43 and FUS. However, it remains unclear whether rare variants in *TIA1* indeed impart risk for ALS or ALS-FTD, as several groups have more recently failed to replicate the aforementioned findings [50,51].

Intriguingly, in *Tia1* knockout mice, the phenotype of which was reported prior to the identification of rare variation in *TIA1* associated with ALS-FTD, cyclin F (*Ccnf*) is significantly up-regulated in the central nervous system [52], and a pathogenic mutation in human *CCNF* was recently linked to disease in a large ALS-FTD family [53]. Follow-up analyses identified additional rare variants enriched in sporadic FTD and ALS cohorts, as well as in familial ALS and FTD-ALS cohorts [53]. Cyclin F is a component of an SCF-type E3 ubiquitin ligase, and the variants associated with FTD/ALS have been suggested to impair protein degradation via the ubiquitin-proteasome system, indicating that cyclin F, like many other FTD-associated proteins, may regulate cellular proteostasis.

Genes implicated in hereditary leukodystrophies and FTD

Hereditary leukodystrophies (also referred to as leukoencephalopathies) represent a diverse array of inherited disorders of myelin formation and maintenance. Below we describe seven genes implicated in various classes of leukodystrophy that are also associated with FTD risk. In some cases, patients harboring pathogenic mutations in these genes present clinically with aspects of FTD occurring as part of a constellation of symptoms characteristic of the underlying white matter loss (e.g., *CSF1R*). In another scenario, one class of variant in a given gene may modify the onset of FTD, while a distinct, pathogenic mutation in the same gene (*TMEM106B*) may cause a childhood-onset leukodystrophy. The genes highlighted below have diverse expression patterns among human brain cell types, including predominant expression in microglia (*TREM2*, *TYROBP*, *CSF1R*); neurons, astrocytes and oligodendrocytes (*TMEM106B*); and, potentially, endothelial cells (*NOTCH3*) ([54]; brainrnaseq.org). Intriguingly, using publicly available data, we find that most genes implicated in both leukodystrophy and FTD risk show differential expression in FTLD postmortem brain (Figure 1; [55]). Using gene interaction network analysis, we found that leukodystrophy/FTD-associated genes are interconnected with genes regulating immunological function and lysosomal homeostasis, including some that are implicated in Mendelian neurodegenerative LSDs (Figure 2; [56]). Below we describe in more detail genes implicated in both leukodystrophy and FTD.

TREM2 and TYROBP

TREM2 and *TYROBP* (encoding DAP12), which together encode a receptor signaling complex expressed in myeloid cells, were first linked to autosomal-recessive Nasu-Hakola disease (NHD; also known as polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy) more than 15 years ago [57,58]. Although NHD classically involves early-onset dementia and recurrent bone fractures, a number of patients with FTD-like syndromes lacking a bone phenotype (often with early-onset symptoms) have also been identified who harbor homozygous or compound heterozygous mutations in *TREM2* [59–65]. Moreover, a recent meta-analysis of rare TREM2 variants found that variants p.R47H (rs75932628) and p.T96K (rs2234253) confer an ~2–3-fold increase in risk for FTD in European populations [66]; p.R47H is also a well known AD risk factor [67] and a possible risk factor for PD [68].

CSF1R

The *CSF1R* gene, expressed in microglia and encoding the colony stimulating factor 1 receptor, was originally linked to autosomal-dominant inheritance of adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) in 2011 [69]. More recently, heterozygous variants (including missense, splice-site, and in-frame deletion variants) in *CSF1R* have been identified in ALSP patients who presented clinically with aspects of bvFTD [70–72]. The clinicopathologic similarities between NHD and ALSP along with the shared microglial expression pattern of *CSF1R*, *TREM2* and *TYROBP* highlight the importance of microglial function in white matter homeostasis.

TMEM106B and PSAP

Variants in *TMEM106B* were first linked to FTLD in 2010 [73]. Though originally identified as a risk modifier in FTLD-TDP due to *GRN* mutations [24,73,74] and significantly associated with circulating progranulin levels [24,74], *TMEM106B* was subsequently found to modify FTLD risk due to *C9ORF72* expansion [75]. Interestingly, a recurrent *de novo* mutation in *TMEM106B* was recently identified in several unrelated patients of both European and Chinese descent with a form of hypomyelinating leukodystrophy [76,77].

Prosaposin, encoded by *PSAP*, regulates the sortilin-independent delivery of progranulin to the lysosome [78]. In addition, the *PSAP* locus has been shown to be an important regulator of circulating progranulin levels in humans [79]. Intriguingly, *PSAP* has also been implicated in hereditary sphingolipidoses including metachromatic leukodystrophy [80]. Thus, *PSAP* and *TMEM106B* collectively regulate circulating progranulin levels and can cause distinct forms of leukodystrophy. Given that *TMEM106B* is an established FTD risk modifier, it will be interesting to determine in the future if variants in *PSAP* also confer risk for FTD or act as disease modifiers.

In contrast to *TMEM106B* and *PSAP*, *SORT1* (encoding sortilin) has not, to our knowledge, been implicated in leukodystrophy, but like *TMEM106B* and *PSAP*, the *SORT1* locus is associated with plasma progranulin levels [81]; sortilin also affects the intracellular

trafficking of progranulin [82]. Intriguingly, rare variants in *SORT1* were recently reported to be enriched in FTD in multiple large, independent case–control cohorts [83].

AARS2

Compound heterozygous mutations in *AARS2*, which encodes mitochondrial alanyl-tRNA synthetase 2, have been identified in a leukodystrophy syndrome that includes features of cognitive decline, frontal lobe dysfunction and, in women, ovarian failure [84]. Pathogenic mutations in *AARS2* appear to be a common cause of disease in patients with symptoms characteristic of ALSP but who do not harbor *CSF1R* mutations (see above) [85]. Recent case reports implicate pathogenic mutations in *AARS2* in leukodystrophy in both Asian [86,87] and European populations [88], as well as bvFTD in Asian populations [72].

NOTCH3

NOTCH3 was originally linked to cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) in 1996 [89]. More recent findings suggest that pathogenic *NOTCH3* mutations may, in rare cases, be identified in patients that present primarily with aspects of bvFTD [90], ALS-FTD [91] or AD [92].

FTD genetics in East Asian populations

C9ORF72

As mentioned above, recent genetic analyses have indicated that hexanucleotide expansion intronic to *C9ORF72* is rare in Chinese FTD patients. For example, in a cohort of 82 sporadic FTD patients in which putatively pathogenic mutations were identified in *MAPT* and *CHCHD10*, no *C9ORF72* expansions were identified [93]. In another recent study, a small number of FTD-associated genes were sequenced in 38 FTD patients of Han Chinese ethnicity and, although presumptively pathogenic mutations were identified in *MAPT*, *GRN* and *VCP*, no *C9ORF72* expansions were identified [94]. Similarly, analysis of 52 Han Chinese FTD patients found mutations in *MAPT* and *GRN* but no *C9ORF72* expansions [95]. On the other hand, a cohort of 128 Chinese patients with ALS and/or FTD identified a single FTD patient with a *C9ORF72* expansion [96], while separate studies detected the hexanucleotide expansion at frequencies of <1% in large cohorts of Han Chinese ALS patients [97,98]. Importantly, the rare Chinese ALS patients that do harbor *C9ORF72* expansions also possess *C9ORF72* risk haplotypes similar to the 20-SNP haplotype identified in European expansion carriers, providing support for the idea that *C9ORF72* expansion may be derived from a single European founder [96,98,99].

CHCHD10

CHCHD10 encodes a mitochondrial protein reported to localize to cristae junctions, and represents the first reported link between FTD and a mitochondria-localized protein [100]. In contrast to the relative scarcity of *C9ORF72* hexanucleotide expansions in the Chinese FTD population, pathogenic mutations in *CHCHD10* may be quite common, accounting for ~8% of FTD cases in the first-reported Chinese cohort [101]. On the other hand, in a cohort of 82 sporadic FTD cases from the Shanghai area, only a single missense variant was identified [93]. Beyond Chinese patients, putatively pathogenic *CHCHD10* mutations have

been estimated to account for ~1–3% of cases in European populations [13], suggesting that variation in this gene may account for a greater proportion of FTD cases in East Asian populations relative to European populations. However, more studies are needed for a reliable estimate of pathogenic *CHCHD10* mutation prevalence in Chinese and other East Asian FTD populations.

TBK1

Although pathogenic mutations in *TBK1* appear to be relatively common in European FTD cohorts (see above), they appear to be rare in the limited studies available on East Asian populations. To date only a single sporadic ALS-FTD patient of Han Chinese descent has been reported to harbor a putatively pathogenic *TBK1* mutation; in this study the reported frequency of *TBK1* mutations in a cohort of 207 ALS and ALS-FTD patients was 0.5% [102].

ANXA11

ANXA11, encoding the calcium- and membrane-binding protein annexin A11, was first linked to ALS in 2017 [103]. Rare variants in *ANXA11* have recently been implicated in a relatively high proportion of Chinese cases of familial (~6%) and sporadic (~2%) ALS, and were detected in 1 of 12 patients with ALS-FTD in the same study [104]. Because of its recent association with ALS-FTD, it is unclear how prevalent pathogenic variation in *ANXA11* is in FTD-spectrum disorders in either European or East Asian populations.

Genome-wide association studies and genetic modifiers

Although FTD is a clinically and neuropathologically heterogeneous disease, genome-wide association studies (GWAS) have implicated common variants in or near multiple genes as risk factors in FTD patients of European ancestry. The largest GWAS to date included over 3,500 patients clinically diagnosed with an FTD-spectrum disorder, and identified three SNPs in the *HLA* locus associated with increased risk of FTD [105]. This region includes three genes with important immune system functions: *BTNL2*, *HLA-DRA* and *HLA-DRB5*. A sub-analysis in this study also identified two SNPs near *RAB38* and *CTSC*, both of which have roles in lysosomal biology, suggestive of an association with risk specifically for bvFTD. Subsequently, a separate study utilizing summary statistics from the 2014 Ferrari et al. GWAS found gene-wide aggregate common variation associated with different clinical subtypes of FTD. This study identified AD-associated genes *TOMM40* and *APOE* as risk factors for bvFTD, while *ARHGAP35* and *SERPINA1* were associated with nfvPPA risk [106]. Although findings from these studies require replication in independent cohorts, the identified novel genetic risk factors are consistent with results from rare variant studies implicating immune and lysosomal dysfunction in the pathobiology of FTD.

Other recent GWAS have focused on identifying risk factors for progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), both of which are tauopathies that fall within the FTLD spectrum. The first study included over 2,000 clinically and/or pathologically diagnosed PSP patients of European ancestry, and found SNPs associated with disease risk in *STX6*, *EIF2AK3* and *MOBP* [107]. This study also identified an

expression quantitative trait locus (eQTL) SNP in *MAPT* associated with PSP risk that influences brain expression of *MAPT*, and confirmed previously observed associations between the H1 allele of the H1/H2 *MAPT* haplotype and increased PSP risk. Two subsequent independent studies identified additional genetic risk factors for PSP by jointly analyzing the original PSP case–control cohort with additional PSP cases and controls. These studies confirmed the original findings and identified SNPs near *RUNX2* [108], *DUSP10* [109] and *SLCO1A2* [108,109] as PSP risk factors. Finally, a small GWAS confirmed the H1 *MAPT* haplotype as a CBD risk factor [110]. In addition, in this study the *MOBP* SNP previously associated with PSP also showed suggestive association with CBD risk. These findings suggest that beyond their clinical and neuropathological similarities, PSP and CBD may share genetic risk factors in addition to the H1 *MAPT* haplotype.

Beyond identifying novel genetic risk factors, GWAS have also identified several modifiers of risk and clinical characteristics such as age at onset for FTD-spectrum disorders. For example, a study confirming the association between SNPs in *TMEM106B* and FTLD-TDP risk in both *GRN* mutation carrier and non-carrier sporadic cases also identified *GFRA2* as a modifier of disease risk [111]. Similarly, genetic modifiers of disease course have been identified in FTLD caused by *C9ORF72* repeat expansion. A recent study analyzing variants in CpG islands that affect DNA methylation status found an association between a SNP near non-coding RNA gene *LOC101929163* and *C6ORF10* and later disease onset in *C9ORF72* repeat expansion carriers as well as non-carrier patients with FTD and/or ALS [112]. In addition, this SNP was shown to be an eQTL for both the above non-coding RNA and *HLA-DRB1* in the brain [112]. Taken together, these findings highlight the importance of genetic modifiers even in the context of mutations that cause autosomal-dominant FTLD.

Genetic pleiotropy studies

Pleiotropy studies leverage how a single gene may influence multiple distinct traits, making it possible to identify shared genetic risk across multiple biologically related diseases. Using this approach to jointly analyze summary statistics from FTD, AD and PD GWAS, SNPs nominally associated with AD and PD were up to 140- and 120-fold enriched, respectively, in FTD-associated SNPs; SNPs near *HLA-DRA, HLA-DRB5*, *MAPT* (tagging the H1 haplotype), *SCARB2* and *SLC2A13* (near *LRRK2*) were identified as risk factors for FTD and PD [113]. This study also provided further evidence that variation in the *APOE* region confers risk for FTD and AD, consistent with the recent finding that ApoE4 exacerbates tau-mediated neurodegeneration [114]. In line with previous findings, another recent study identified novel overlapping genetic risk factors shared between PSP and CBD, including SNPs in or near *CXCR4*, *EGFR* and *GLDC*, and confirmed *MAPT* and *MOBP* as risk factors for both disorders [115]. Interestingly, *CXCR4* was also identified as a shared risk factor for PSP and PD in a separate study [116]. The widely perceived shared etiology between FTD and ALS was further supported by a recent study of ALS and several FTD-spectrum disorders that identified 29 shared risk loci, 22 of which are novel risk loci for ALS [117]. This study found that SNPs nominally associated with FTLD-TDP were up to 300-fold enriched in ALS-associated SNPs. In addition, a SNP tagging the *MAPT* H1 haplotype was identified as a risk factor for ALS; this study also provided evidence that *BNIP1*, which encodes a pro-apoptotic protein with an important role in mitophagy,

represents an ALS risk gene. Beyond novel genetic risk factors shared between neurodegenerative disorders, pleiotropy has also been used to characterize the overlapping genetic architecture of FTD-spectrum and immune-mediated disorders. This approach identified up to 270-fold enrichment in FTD-associated SNPs for SNPs nominally associated with rheumatoid arthritis. Specifically, variants in or near *AGPAT1*, *BTNL2*, *GPSM3*, *HLA-DQA2*, *HLA-DQB1*, *HLA-DRA*, *PAQR8*, *TRIM15* and *TRIM26* in the *HLA* region; as well as those in or near the *MAPT* H1 haplotype, *TNS3*, *TWISTNB*, *CR590356*, *SLC2A13* and *DCC* were associated with risk for FTD and several immune system disorders [118]. Although limited to patient populations of European ancestry, these studies suggest that FTD and other neurodegenerative disorders share considerable genetic risk with disorders mediated by immune dysfunction.

Summary and conclusions

Recent research into the human genetics of FTD has highlighted the central roles of genes involved in autophagy and endolysosomal homeostasis. Beyond this, work in mouse models suggests that cellular regulators of autophagy such as TBK1 and parkin are also crucial regulators of the inflammatory response *in vivo*. These results dovetail nicely with other recent findings in FTD genetics indicating that a substantial amount of genetic risk for FTD derives from genes encoding regulators of the immune response.

In this review we highlighted accumulating evidence that several genes implicated in inherited leukodystrophies may also confer risk for FTD. Our gene expression analyses (Figure 1) indicate that many of these joint leukodystrophy/FTD genes show dysregulated expression in the brain in *GRN*+ FTD, and possibly in FTD more generally. In addition, our gene interaction network (Figure 2) suggests that joint leukodystrophy/FTD genes exist in a network of genes regulating immune processes and endolysosomal homeostasis. Importantly, some genes in the latter class are established causes of Mendelian neurodegenerative LSDs. Collectively, the findings from the last five years of human genetics point to the intersection between intracellular protein clearance (autophagy and lysosomal degradation) and neuroinflammation, as well as shared genetic risk not only between FTD and immune-mediated disorders but also between FTD and inherited leukodystrophies.

Finally, we have emphasized recent genetic studies of Chinese patients with FTD and/or ALS, which have indicated that pathogenic *C9ORF72* expansion appears to be less common in this population, while potentially pathogenic variation in *CHCHD10* may be more common than in European populations. These findings highlight the limitations of most FTD genetics studies conducted to date, which have primarily focused on populations of European ancestry. It will therefore be crucial for future studies to focus on non-European FTD cohorts to increase our understanding of the genetic architecture of FTD in diverse populations. In addition, it will be essential to clarify the link between intracellular degradation and the inflammatory response, to understand why these pathways confer risk for FTD and other forms of neurodegeneration, and to identify novel targets and pathways for therapeutic intervention.

Acknowledgements

We thank Lin Yuan (UCSF) for her helpful reading of the manuscript. Primary research support in the Yokoyama lab is provided by the Rainwater Charitable Foundation, the Bluefield Project to Cure FTD, the Association for Frontotemporal Degeneration Susan Marcus Memorial Fund Clinical Research Grant, the Larry L. Hillblom Foundation (2016-A-005-SUP), the National Institute on Aging (K01 AG049152), and the John Douglas French Alzheimer's Foundation. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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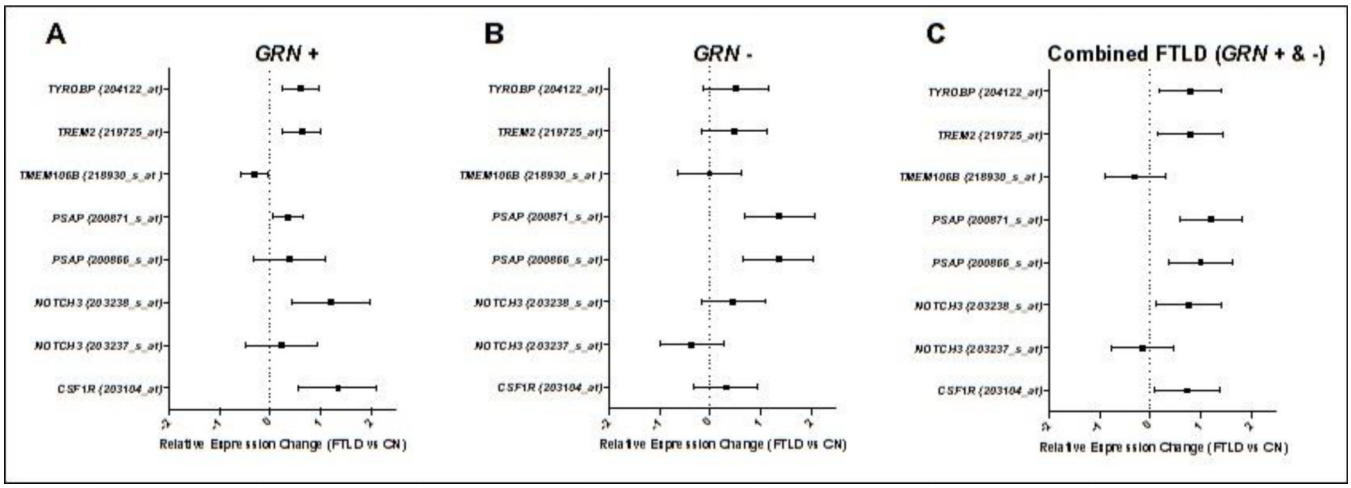

Figure 1. Leukodystrophy genes are dysregulated in pathologically proven FTLD.

Forest plots depict results from differential expression analyses in pathologically proven frontotemporal lobar degeneration (FTLD) due to progranulin mutations (*GRN*+; n=7) and sporadic FTLD (*GRN*−; n=10) compared to controls (n=11). (A) In *GRN*+ cases, all tested leukodystrophy genes (6/6) demonstrated dysregulated expression for at least one microarray probe ($p_{raw}<0.05$). (B) In contrast, the only dysregulated gene in *GRN*− cases was *PSAP* ($p_{raw}<0.05$). (C) In a combined analysis, all genes but *TMEM106B* demonstrated significant dysregulation for at least one microarray probe ($p_{raw}<0.05$). All analyses utilized linear regression. The main effect of diagnosis on relative expression for each gene is plotted with 95% confidence intervals. For details on the samples and gene expression measurement, see Chen-Plotkin et al., 2008 [55] and data available through GEO (GSE13162). Gene expression was estimated using an Affymetrix Human Genome U133A microarray. The forest plots depict all available microarray probes mapping to the query genes (*AARS2* was not available for analysis). Probe identifiers are provided alongside each gene's name in parentheses.

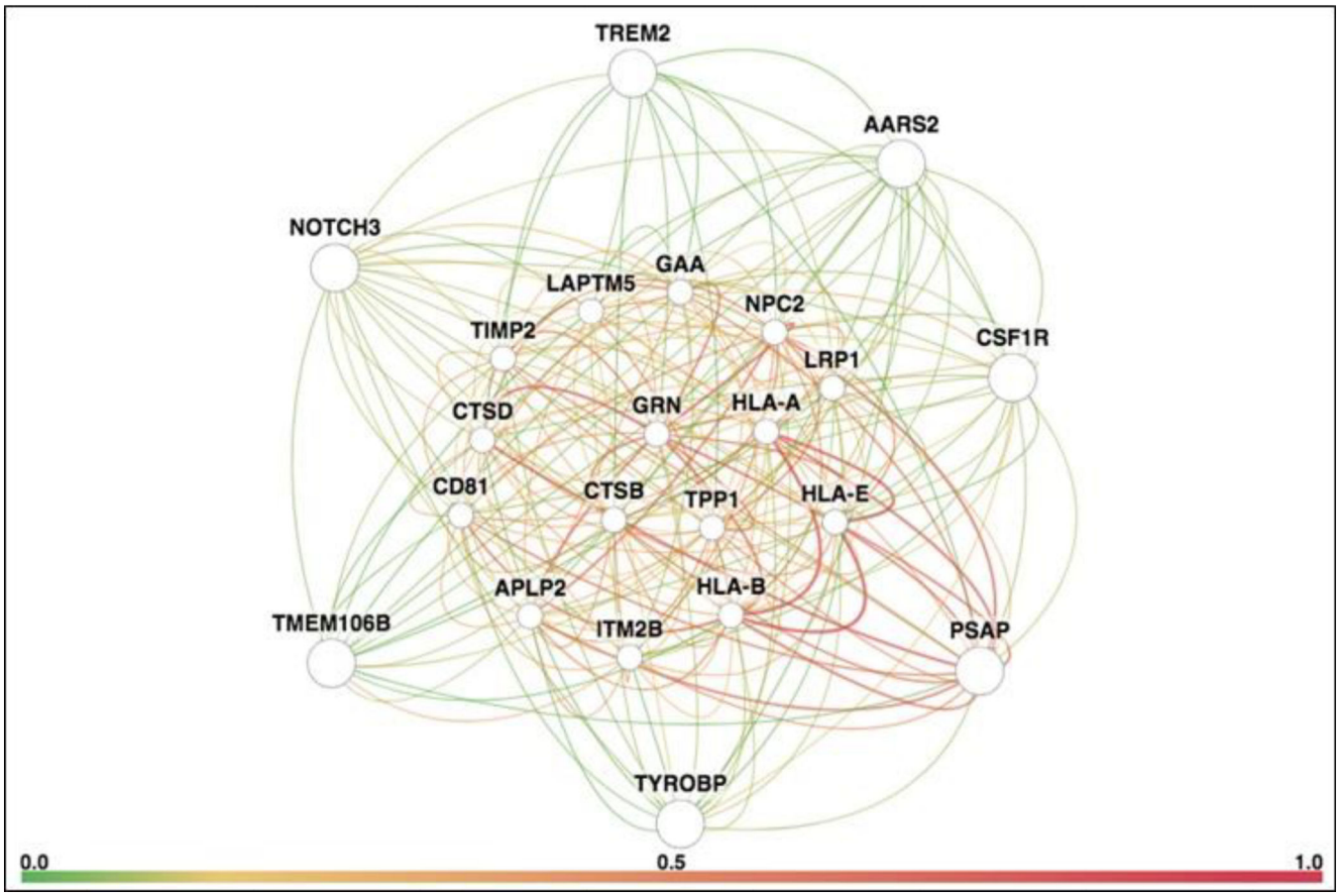

Figure 2. Gene interaction network for leukodystrophy genes (*PSAP, TYROBP, TMEM106B, NOTCH3, TREM2, AARS2* and *CSF1R*).

The network is remarkable for extensive interactions with progranulin (*GRN*, center of network), genes implicated in immunological function (*CD81*, *HLA-A*, *HLA-B* and *HLA-E*), lysosomal genes (*CTSB*, *CTSD*, *GAA*, *LAPTM5*, *LRP1*, *NPC2* and *TPP1*), genes implicated in neurodegenerative lysosomal storage disorders (*CTSD*, *GRN*, *NPC2* and *TPP1*), and a gene implicated in familial dementia (*ITM2B*). The network diagram was generated using HumanBase, a publicly available online database and analytical pipeline hosted by the Flatiron Institute (http://www.simonsfoundation.org/flatiron/). We limited our search to high-quality, brain-specific relationships connected to the query genes through co-expression, protein interaction, or shared transcription factor binding. Query genes are located on the periphery of the network to facilitate visualization of their connections with interacting network genes. The thickness of a connection represents edge weight, or strength of ties. Connection color represents 'evidence' for an edge, defined as the posterior probability of a functional relationship given the brain-tissue specific connectivity dataset, minus the prior probability. Detailed descriptions of the techniques used are provided in Greene et al., 2015 [56] and at https://humanbase.readthedocs.io/en/latest/functional-networks.html.

Table 1.

Major genes implicated in autosomal-dominant forms of FTD.

Genes implicated in ≥1% of familial FTD cases are listed in descending order of mutation frequency in cohorts of European ancestry. Estimated mutation frequency data are derived from sources indicated within the main text. Estimated numbers of pathogenic (including presumptive pathogenic) mutations are from the Alzheimer Disease & Frontotemporal Dementia Mutation Database (http://www.molgen.ua.ac.be/ADmutations/default.cfm?MT=1&ML=6&Page=StatPerGene) and [12,13,39].

Gene	Chr.	Protein	Protein function	Mutation freq. in familial FTD	Mutation freq. in sporadic FTD	# Pathogenic mutations[a]
C9ORF72	9p21.2	C9ORF72	Lysosomal homeostasis	20–30%	6%	*b*
GRN	17q21.31	Progranulin	Lysosomal homeostasis; inflammation	5–25%	5%	79
MAPT	17q21.31	Microtubule-associated protein tau	Microtubule stabilization and assembly	5–20%	0–2%	>50
TBK1	12q14.2	Serine/threonine-protein kinase TBK1	Regulator of autophagy and inflammation	3%	2–4%	28
SQSTM1	5q35.3	p62 (Sequestosome-1)	Selective autophagy receptor	1–3%	1–3%	~20
TARDBP	1p36.22	TAR DNA-binding protein 43 (TDP-43)	RNA processing and metabolism	1%	1%	33

[a] A subset of these mutations are implicated in ALS or ALS-FTD (e.g., *TARDBP* mutations). Pathogenicity is not established for all mutations.

[b] Indicates variable-length hexanucleotide repeat expansions in *C9ORF72*.