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Review

Genetics and molecular mechanisms of frontotemporal lobar degeneration: an update and future avenues

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ABSTRACT

Frontotemporal lobar degeneration (FTLD) is the second most common form of dementia after Alzheimer's disease. The study and the dissection of FTLD is complex due to its clinical, pathological, and genetic heterogeneity. In this review, we survey the state-of-the-art genetics of familial FTLD and recapitulate our current understanding of the genetic architecture of sporadic FTLD by summarizing results of genome-wide association studies performed in FTLD to date. We then discuss the challenges of translating these heterogeneous genetic features into the understanding of the molecular underpinnings of FTLD pathogenesis. We particularly highlight a number of susceptibility processes that appear to be conserved across familial and sporadic cases (e.g., and the cellular waste disposal pathways, and immune system signaling) and finally describe cutting-edge approaches, based on mathematical prediction tools, highlighting novel intriguing risk pathways such as DNA damage response as an emerging theme in FTLD.

1. Introduction

Frontotemporal dementia (FTD)—with onset age that can vary from ≥45 to ≤70 years of age—is the second most common early-onset form of dementia after Alzheimer's disease (AD) affecting about 3–15/100,000 individuals, based on North American and European epidemiological studies (Rabinovici and Miller, 2010).

FTD is clinically heterogeneous and comprises behavioral FTD (Rascovsky et al., 2011) and language (primary progressive aphasia [PPA]) impairments. The behavioral FTD syndrome is characterized by cognitive decline and behavioral dysfunctions, while the PPA syndrome is further subdivided into semantic dementia (SD or semantic variant PPA) and progressive nonfluent aphasia (PNFA or nonfluent/agrammatic variant PPA) (Gorno-Tempini et al., 2011; Neary et al., 1998). Atypical forms of FTD present an overlap with motoneuron disease (FTD-MND), mainly summarized by the FTD–amyotrophic lateral sclerosis (ALS) condition or with parkinsonian features (FTDP-17) (Rohrer and Warren, 2011).

Macropathological assessments have indicated that the major brain areas affected in patients with FTD are the frontal and temporal lobes. On these bases, FTD is also referred to as frontotemporal lobar degeneration (FTLD) (Mackenzie and Neumann, 2016). More generally, FTLD is used as an umbrella term to define clinically and pathologically diagnosed cases (Rabinovici and Miller, 2010). We will use the abbreviation FTLD throughout the rest of this review article.

Micropathological studies suggest glia hyperproliferation and aberrant protein inclusions in the cytoplasm and nucleus of neurons as the major pathological hallmarks of FTLD (Mackenzie and Neumann, 2016). Tau, the protein product of the *MAPT* gene, and TDP-43, the protein product of the *TARDBP* gene, are the most frequent protein aggregates (~45% of FTLD-tau, ≤50% FTLD-TDP) identified in FTLD brains (Halliday et al., 2012). Rarely (~10%), other proteins are found in the inclusion bodies: these comprise *p*62 (the protein product of the *SQSTM1* gene) that define the FTLD–ubiquitin proteasome category, and fused in sarcoma (the protein product of the *FUS* gene), Ewing's sarcoma (the protein product of the *EWS* gene), and TATA-binding protein associated factor 15 (the protein product of the *TAF15* gene) that are collectively referred to as FTLD-FET (Halliday et al., 2012; Deleon and Miller, 2018; Mackenzie and Neumann, 2016).

FTLD's complex clinical and pathological landscape is mirrored by heterogeneous genetic features. Despite enormous advances in FTLD genetics over the past 20 years, clearly, the substantial lack of understanding of how genetics, phenotypic, and pathological

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features are wired by underlying molecular mechanisms represents to date the major gap to the dissection of FTLD pathogenesis.

In this review, we will survey the state of the art of FTLD genetics and discuss their biological implications (i.e., FTLD risk pathways) and touch on next steps to be taken in the field to increase our genetic and functional understanding of FTLD pathogenesis. Clearly, these 2 subjects will need to jointly advance to accelerate and support the implementation of programs to identify biomarkers and drug targets, design clinical trials, and develop strategies for early diagnosis, disease prevention/monitoring, and cure.

2. FTLD genetics

Neurodegenerative disorders are characterized by complex genetic features, and, generally, a minority of familial cases are outnumbered by a large population of sporadic cases.

Mendelian genes have been classically isolated in familial studies through linkage analysis and, more recently, whole-exome sequencing studies of trios, first-degree relatives, or large (well phenotyped) pedigrees (Hardy and Singleton, 2009).

Sporadic forms of disease are investigated through case/control association studies: for example, genome-wide association studies (GWASs) allow to assess whether allele frequencies of common genetic markers significantly differ across large cohorts of patients and population-matched controls and thus isolate disease-associated genetic risk factors (Manolio et al., 2009).

2.1. Familial FTLD—mendelian genetics

Familial forms of FTLD account for up to 30%–40% of all cases and are associated with mutations in a handful of genes that are usually referred to as Mendelian FTLD genes (Seelaar et al., 2011; Snowden et al., 2002; Turner et al., 2017).

The microtubule (MT)-associated protein tau [MAPT, ≥44 pathogenic mutations (Ghetti et al., 2015)] and progranulin (GRN, ≥70 pathogenic mutations (Gijselinck et al., 2008)) are classical familial FTLD genes (Table 1). Truncation mutations in the charged multivesicular body protein 2B (*CHMP2B*) gene have been linked to a large Danish family with FTLD and a Belgian patient with FTLD (Skibinski et al., 2005; van der Zee et al., 2008); this genetic form of FTLD is extremely rare and nomenclated as FTLD-3 (i.e., FTLD linked to chromosome 3) (Brown et al., 1995; van der Zee et al., 2008) (Table 1). An abnormal GGGGCC expansion in the chromosome 9 open reading frame 72 gene (C9orf72) has also been suggested as a frequent genetic cause of familial FTLD (DeJesus-Hernandez et al., 2011; van der Zee et al., 2013). The expansion has however been reported with variable prevalence across multiple neurodegenerative conditions: with higher prevalence in ALS and FTLD-ALS cases (Hardy and Rogaeva, 2014; Nguyen et al., 2018) as well as, although with lower prevalence, in AD, Parkinsonian, corticobasal (CBS) and ataxia cases (Al-Chalabi et al., 2017; Cooper-Knock et al., 2014; Ferrari et al., 2012; Ferrari and Momeni, 2013; Galimberti et al., 2014; Hensman Moss et al., 2014; Lindquist et al., 2013; Majounie et al., 2012; Simon-Sanchez et al., 2012; Smith et al., 2013; van der Zee et al., 2013) (Table 1). Interestingly, the expansion has also been reported in neurologically normal elderly individuals (Galimberti et al., 2014).

Very rare mutations in other genes such as sequestosome 1 (*SQSTM1*) (Le Ber et al., 2013), ubiquilin 2 (*UBQLN2*) (Synofzik et al., 2012), optineurin (*OPTN*) (Pottier et al., 2015), coiled-coil-helix-coiled-coil-helix domain containing 10 (*CHCHD10*) (Bannwarth et al., 2014), TANK binding kinase 1 (*TBK1*) (Gijselinck et al., 2015; Pottier et al., 2015), dynactin-1 (*DCTN1*) (Munch et al., 2005), and cyclin-F (*CCNF*) (Williams et al., 2016) have been associated with FTLD-ALS (Table 1); interestingly, kindred of individuals carrying mutations in these genes comprise variable FTLD and/or ALS features within the same pedigree (Hardy and Rogaeva, 2014; Van Mossevelde et al., 2018). Mutations in the valosin-containing protein (*VCP*) have been identified in few cases carrying a combination of conditions such as inclusion body myopathy (IBM) with Paget disease of the bone (PDB) and FTD (IBMPFD) (Watts et al., 2004), and in FTLD-ALS cases (Koppers et al., 2012), while mutations in *SQSTM1* have recently also been described in families whose affected members presented various phenotypes including gait abnormalities, ataxia, dysarthria, dystonia, vertical gaze palsy, and cognitive decline (Haack et al., 2016). The TIA1 cytotoxic granule–associated RNA-binding protein gene (*TIA1*), originally identified in an FTLD-ALS kindred (Mackenzie et al., 2017), was not replicated in a subsequent follow-up study (Baradaran-Heravi et al., 2018) (Table 1). Finally, it is noteworthy to consider that pathogenic genetic variability in *TARDBP* and *FUS*, whose protein products clearly represent FTLD pathological hallmarks (Mackenzie and Neumann, 2016), has been reported to be extremely rare (*TARDBP*) (Benajiba et al., 2009; Borroni et al., 2009, 2010; Caroppo et al., 2016; Huey et al., 2012), or, in some cases, equivocal (*TARDBP* and *FUS*) (Cannas et al., 2013; Hardy and Rogaeva, 2014; Pottier et al., 2016; Quadri et al., 2011).

In summary, one might categorize the Mendelian FTLD genes on the basis of their disease specificity: *MAPT*, *GRN,* and *CHMP2B* have mainly or exclusively been identified in FTLD cases; thus, we suggest to label them as "major-FTLD genes." *C9orf72*, *VCP*, *TARDBP*, *FUS*, *SQSTM1*, *UBQLN2*, *IFT74*, *OPTN*, *CHCHD10*, *TBK1,* and *TIA1* appear to encompass ALS and/or some heterogeneous array of disorders; thus, we suggest to label these as "spectrum-FTLD genes" (Ferrari and Momeni, 2018). Fig. 1 summarizes the global Mendelian genetics landscape of FTLD.

2.2. Sporadic FTLD

Sporadic forms of FTLD account for 60%–70% of all cases (Ferrari and Momeni, 2018; Turner et al., 2017).

The genetics of sporadic FTLD is poorly understood. Besides the reports of a few *MAPT*, *GRN,* and *C9orf72* mutations (Cruts et al., 2015; Takada, 2015; Pottier et al., 2016; Rademakers et al., 2012) (Table 1), the genetic architecture of idiopathic FTLD primarily refers to genetic risk markers with small effect size likely modulated by multiple modifying factors that span from genetic to environmental (Manolio et al., 2009).

To date, the most informative studies exploring genetic risk and/or modifying factors with small effect size in FTLD have been a number of GWASs. These studies were designed to address actual sporadic cohorts [i.e., the International clinical FTLD-GWAS (Ferrari et al., 2014) and the Italian clinical FTLD-GWAS (Ferrari et al., 2015)] or more selective cohorts either characterized by TDP-43 pathology [i.e., FTLD-TDP GWAS (Van Deerlin et al., 2010)] or including *GRN* mutations carriers [i.e., FTLD-GRN GWASs (Pottier et al., 2018)].

2.2.1. What is a GWAS?

A GWAS is designed as a large-scale case/control study to identify common genetic variants (i.e., variants with minor allele frequencies > 1%) associating with a trait of interest. A GWAS is hypothesis free; it interrogates the genome in an unbiased manner by means of millions of evenly distributed (genotyped and imputed) single-nucleotide polymorphisms (SNPs) and assesses differences in their allelic frequencies between the 2 study groups (cases and controls). Such analysis allows for the identification of loci (not genes) that increase susceptibility for a particular trait (i.e., genetic markers within genetic regions that increase risk of developing a particular trait with small to moderate effect size). A GWAS generally consists of a discovery phase (or phase I) where

Table 1
FTLD Mendelian genetics

Major phenotype	Gene	Familial cases	Sporadic cases	Clinical Presentation(s)	Brain pathology	Reference
FTD	*CHMP2B*	<1%	NA	FTD	ubiquitin/*p*62	(Ferrari et al., 2011; Isaacs et al., 2011; Pottier et al., 2016)
	GRN	5%–20%	1%–5%		TDP43	(Chen-Plotkin et al., 2010; Pottier et al., 2016; Rohrer and Warren, 2011; Takada, 2015)
	MAPT (tau)	5%–20%	0%–3%		tau	(Pottier et al., 2016; Rohrer and Warren, 2011; Takada, 2015)
FTD-ALS	*CHCHD10*	<1%	NA	ALS, FTD, myopathy	NA	(Bannwarth et al., 2014)
	C9orf72	30%	~5%	ALS	TDP43/*p*62/repeat-dipeptides/ubiquitin	(Pottier et al., 2016; van der Zee et al., 2013)
		~25%	~5%	FTD, FTD-ALS		
		~1%	NA	AD, PD, CBS, A		
	CCNF	<1%	NA	ALS, FTD	Not reported	(Williams et al., 2016)
	DCTN1	<1%	NA	ALS, HMN7B, Perry syndrome, FTD	TDP43	(Munch et al., 2005)
	OPTN	<1%	NA	ALS, FTD	TDP43/OPTN/ubiquitin	(Pottier et al., 2015)
	SQSTM1 (*p*62)	<1%	NA	ALS, FTD, IBM, Paget's disease	TDP43/*p*62	(Gang et al., 2016; Kovacs et al., 2016; Le Ber et al., 2013)
	TBK1	1%–3%	NA	ALS, FTD	TDP43/*p*62	(Pottier et al., 2016; Van Mossevelde et al., 2016)
	UBQLN2	<1%	NA	ALS, FTD	TDP43/*p*62/UBQLN2/FUS/OPTN	(Deng et al., 2011; Synofzik et al., 2012)
	VCP	~1%	NA	ALS, FTD, IBM, Paget's disease	TDP43/*p*62	(Ferrari et al., 2011; Gang et al., 2016)
ALS	*KIF5A*	<1%	NA	SP, ALS	TDP43	(Brenner et al., 2018)
	FUS	~4%	NA	ALS, FTD	FUS/ubiquitin/EWS/TAF15	(Mackenzie and Neumann, 2016; Nguyen et al., 2018; Urwin et al., 2010)
	MATR3	<1%	NA	ALS, myopathy	MATR3	(Johnson et al., 2014)
	SOD1	~20%	NA	ALS	SOD1/ubiquitin	(Ferrari et al., 2011; Saberi et al., 2015)
	TARDBP (TDP43)	~3%–4%	NA	ALS, FTD	TDP43	(Ferrari et al., 2011; Nguyen et al., 2018)
	TIA1[a]	<1%	NA	ALS, myopathy, FTD	TDP43	(Baradaran-Heravi et al., 2018; Mackenzie et al., 2017)

Key: A, ataxia; AD, alzheimer's disease; ALS, amyotrophic lateral sclerosis; CBS, corticobasal syndrome; FTLD, frontotemporal lobar degeneration; HMN7B, hereditary motor neuropathy, type 7B; IBM, inclusion body myopathy; MS, multiple sclerosis; PD, Parkinson's disease; SP, spastic paraplegia.
[a] Not replicated.

one or more genetic loci associated with the trait under study are "discovered" and a replication phase (or phase II), performed in an independent cohort, that assesses the statistically significant (and suggestive [i.e., SNPs that are close to but below statistical significance]) loci of phase I for validation. Most reported associations in GWAS are intronic or intergenic, most probably affecting DNA structure and gene expression rather than protein sequence (Manolio et al., 2009). Although GWASs identify risk loci, defined by SNPs that might be the actual reason of the signal or just in linkage disequilibrium with it, the associated variants might be informative implying to causal regulation of gene expression (e.g., expression quantitative trait loci [eQTLs]) or susceptibility functional pathways (Pearson and Manolio, 2008). The exponential growth in the number of GWASs in the past decade has led to the discovery of thousands of associations for a range of traits (over 25,000 unique SNP-trait associations from over 2500 studies [http://www.ebi.ac.uk/gwas]). More extensive information on the concept, study design, good practices, and results interpretation for GWASs can be found in the study by Ferrari and Momeni (2018), Hardy and Singleton (2009) and Manolio et al. (2009).

Major findings of the FTLD-GWASs are discussed in the next paragraphs and summarized in Tables 2 and 3.

2.3. FTLD-TDP GWAS

This study was published in 2010 by van Deerlin et al. (Van Deerlin et al., 2010).

It included FTLD-TDP cases diagnosed either by pathological (FTLD-TDP) or genetic (i.e., presence of pathogenic *GRN* mutations) assessments. As classical case-control studies, it was performed on 515 FTLD-TDP cases and 2509 controls (discovery phase) and 89 independent FTLD-TDP cases and 553 controls (replication phase). Discovery phase analyses indicated 3 significant lead SNPs (rs6966915, rs1020004, and rs1990622), encompassing the transmembrane protein 106B (*TMEM106B*) gene (7*p*21.3). Replication analysis confirmed the association and same direction of effect for 2 lead SNPs (rs1020004 and rs1990622), yet such associations could not be replicated in additional 192 individuals with unspecified

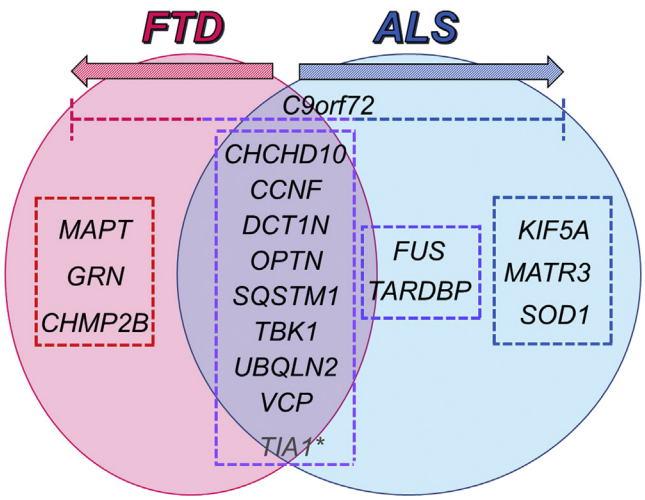

Fig. 1. Summary of Mendelian genetics associated with FTLD and the FTLD-ALS spectrum. Genes circled in red are "major-FTLD genes"; genes circled in violet are "spectrum-FTLD genes," that is, they belong to the FTLD-ALS spectrum. Genes circled in dark violet and blue are edge/borderline between FTLD and ALS and pure ALS genes, respectively. * =not replicated. Abbreviations: FTLD, frontotemporal lobar degeneration; ALS, amyotrophic lateral sclerosis.

FTLD (Van Deerlin et al., 2010). Authors also characterized the effects on *TMEM106B* expression levels in FTLD-TDP postmortem versus neurologically normal control brains (frontal cortex) for rs1020004 and rs1990622, indicating that risk allele carriers had 2.5-fold higher *TMEM106B* expression levels than controls (Van Deerlin et al., 2010). Of note, *GRN* mutation carriers showed highest increase of *TMEM106B* expression compared with non-carriers and controls (Van Deerlin et al., 2010).

Altogether, this study indicated SNPs encompassing the *TMEM106B* gene as risk factors for the FTLD-TDP subtype and that their risk alleles appeared to be particularly enriched in *GRN* mutation carriers, thus suggesting *TMEM106B* as a *GRN* modifier. In addition, not only it is relevant to note that *TMEM106B* association with FTLD has been confirmed in subsequent studies (Cruchaga et al., 2011; Finch et al., 2011; Van Deerlin et al., 2010; Vass et al., 2011) but also that TMEM106B is involved in endolysosomal pathways and modulates PGRN protein levels (Lattante et al., 2014).

2.3.1. International clinical FTLD-GWAS

This study was published in 2014 by Ferrari et al., 2014.

It included cases belonging to 4 clinical subgroups: behavioral frontotemporal lobar degeneration (bvFTLD), PPAs (SD and PNFA), and FTLD-MND. The discovery cohort (FTLD-GWAS phase I) consisted of 2154 cases and 4308 controls, while the replication cohort (FTLD-GWAS phase II) comprised 1372 cases and 5092 (for a total of 3526 FTLD samples and 9400 controls). Following the classical case-control strategy, analyses were performed after excluding Mendelian genes (*MAPT* and *GRN*) mutation carriers. The association analyses for the discovery phase were performed for each subtype before meta-analyzing the entire cohort: for the bvFTLD subtype (consisting of 1377 cases and 2754 controls), 2 suggestive lead SNPs—rs302652 and rs74977128—were identified, respectively, mapping to Ras-related protein Rab-38 and cathepsin C (*RAB38* and *RAB38–CTSC*) (11q14). Association analyses on the other subtypes—308 SD cases (vs. 616 controls), 269 PNFA cases (vs. 538 controls), and 200 FTLD-MND cases (vs. 400 controls)—did not indicate genetic markers reaching genome-wide significance (because of insufficient power). Conversely, the meta-analysis for all 4 subtypes indicated significant SNPs encompassing butyrophilin-like 2 (*BTNL2*; rs1980493) and major histocompatibility complex, class II, DRs (*HLA-DRA–HLA-DRB5*; rs9268877 and rs9268856) at 6*p*21.3. Replication (for 690 bvFTLD cases vs. 5094 controls), and joint analyses, indicated rs302668 as significant for the bvFTLD subtype (11q14; *RAB38*). Replication for the entire cohort and joint analyses confirmed strong association for 3 lead SNPs rs9268877, rs9268856, and rs1980493 at 6*p*21.3. From a functional perspective, although no eQTLs in brain were evident, the top SNP for *RAB38–CTSC* (rs302652) was associated with decreased levels of RAB38 mRNA in blood, while a significant *cis*–methylation quantitative trait loci for rs1980493 was evident for *HLA-DRA* in the frontal cortex (Ferrari et al., 2014).

Altogether, this study revealed two novel susceptibility loci for clinical FTLD: one suggestive involving lysosome-phagosome pathways (*RAB38–CTSC* locus) for the bvFTLD subtype, and one affecting immune system processes (*BTNL2* and *HLA-DRA–DRB5* locus) in global FTLD.

2.3.2. Italian clinical FTLD-GWAS

This study was published in 2015 by Ferrari et al., 2015.

It was performed on a multicenter Italian FTLD cohort of 530 samples (bvFTLD [n = 418], SD [n = 27], PNFA [n = 61], and FTLD-MND [(n = 24]) and 926 population-matched controls. The inclusion criteria were in line with those of the clinical FTLD-GWAS (see Ferrari et al., 2014). The work used a standard cases versus controls association strategy for the discovery phase followed by replication analyses based on the implementation of 3 different tests (also called "SNPs-to-genes" analyses)—GATES, supervised PCA, and the sequential kernel machine association test—to score and prioritize genes (Ferrari et al., 2015). Discovery analyses identified 2 suggestive loci (i.e., close to significance, yet not genome-wide significant): 1 defined by 7 SNPs encompassing LOC730100 (centromeric to neurexin 1 [*NRXN1*]) at 2*p*16.3 and the other also defined by 7 suggestive SNPs encompassing centrosomal protein 131 (*CEP131*), *C17orf89*, and ENTH domain containing 2 (*ENTHD2*) at 17q25.3. Interestingly, the risk alleles at 17q25.3 defined a suggestive risk haplotype causing decreased expression of the *cis*-genes RFNG O-fucosylpeptide 3-beta-N-acetylglucosaminyltransferase (*RFNG*), apoptosis-associated tyrosine kinase (*AATK*), and microRNA 1250 (*MIR1250*), suggesting this as the biological mechanism underlying the association. During replication, *CEP131* and *ENTHD2* were consistently identified as the most significant genes across the 3 analysis methods (GATES, supervised PCA, or sequential kernel machine association test).

Altogether, this study indicated two novel potential loci for FTLD and that, from a functional perspective, an effect on expression of genes involved in neuronal development, differentiation, and maturation processes might drive FTLD pathogenesis in the Italian population.

2.4. FTLD-GRN GWAS

This study was published in 2018 by Pottier et al., 2018.

Table 2
Summary of association results for FTLD-TDP, the International clinical FTLD-GWAS and the FTLD GRN GWAS

Phenotype	Chr	BP	Marker	Alleles	Risk allele	*p*-value Discovery	OR	*p*-value Replication	OR	*p*-value Joint	OR	Reference
FTLD-TDP	7	12,283,787	rs1990622	C/T	T	1.08×10^{-11}	1.64	0.0002[a]	1.75	NA	NA	(Van Deerlin et al., 2010)
		12,255,778	rs1020004	A/G	A	5.00×10^{-11}	1.67	0.004[a]	1.89	NA	NA	
		12,265,988	rs6966915	A/C/T	C	1.63×10^{-11}	1.64	NA	NA	NA	NA	
International clinical bvFTD	11	87,894,831	rs302652	T/A	T	2.02×10^{-08}	1.37	NA	NA	NA	NA	(Ferrari et al., 2014)
		87,876,911	rs302668′	T/C	T	NA	NA	0.041	1.14	2.44×10^{-07}	1.23	
		87,936,874	rs74977128	T/C	C	3.06×10^{-08}	1.81	NA	NA	NA	NA	
		87,934,068	rs16913634[b,c]	G/A	A	NA	NA	0.71	1.04	8.15×10^{-04}	1.25	
Meta International clinical FTLD	6	32,363,215	rs1980493	T/C	T	4.94×10^{-08}	1.39	0.02	1.17	1.57×10^{-08}	1.30	
		32,431,147	rs9268877	A/G	A	1.65×10^{-10}	1.33	0.104	1.08	1.05×10^{-08}	1.20	
		32,429,719	rs9268856	A/C	C	1.30×10^{-08}	1.33	0.014	1.14	5.51×10^{-09}	1.24	
GRN GWAS	7	12,283,787	rs1990622	C/T	T	1.61×10^{-10}	1.88	4.09×10^{-7}	1.81	3.54×10^{-16}	1.85	(Pottier et al., 2018)
	8	21,621,247	rs36196656	A/C/G/T	A	9.44×10^{-6}	1.51	4.4×10^{-4}	1.46	1.58×10^{-8}	1.49	

[a] Replication tested in 89 FTLD-TDP cases.
[b] surrogate/proxy SNPs for the bvFTD subtype.
[c] denotes heterogeneity *p*-value < 0.01 in the meta-analysis of the discovery and replication phases combined.

Table 3
Summary of association results for FTLD Italian clinical GWAS

Phenotype	Chr	BP	Marker	Alleles	Risk Allele	*p*-value	OR	Method	Gene	FDR	Study
						Discovery		Replication			
Italian clinical FTD	2	52,600,067	rs17042852	C/T	C	2.01×10^{-7}	2.82	NA			(Ferrari et al., 2015)
		52,635,727	rs1526678	G/A	G	2.19×10^{-7}	2.83				
		52,571,393	rs17042770	C/G	C	2.22×10^{-7}	2.83				
		52,509,876	rs12621157	T/G	T	3.73×10^{-7}	2.75				
		52,546,301	rs12622570	C/G	C	3.99×10^{-7}	2.76				
		52,532,874	rs12619513	A/G	A	6.39×10^{-7}	2.53				
		52,521,716	rs12614311	T/C	T	8.83×10^{-7}	2.55				
	17	79,173,462	rs906175	T/C	T	1.22×10^{-7}	1.58	GATES	*CEP131*	0.001469	
		79,192,430	rs2725391	T/C	T	2.50×10^{-7}	1.52		*ENTHD2*	0.004264	
		79,195,814	rs969413	A/T	A	4.26×10^{-7}	1.52		*C17orf89*	0.004264	
		79,177,974	rs2659030	A/G	A	4.42×10^{-7}	1.56	sPCA	*CEP131*	0.000650	
		79,213,562	rs2255166	C/T	C	6.19×10^{-7}	1.55		*ENTHD2*	0.001007	
		79,192,446	rs9319617	C/T	T	6.62×10^{-7}	1.51	SKAT	*CEP131*	0.000014	
		79,202,329	rs1048775	G/C	C	8.04×10^{-7}	1.51		*ENTHD2*	0.000651	
									C17orf89	0.000651	

Key: FTLD, Frontotemporal lobar degeneration; GWAS, genome-wide association study; SNP, single-nucleotide polymorphism.

It was performed on FTLD samples selected for the specific feature of carrying loss of function *GRN* mutations (n = 120 distinct mutations) (Pottier et al., 2018). The discovery phase was done using 382 patients and 1146 controls, while the replication phase included 210 patients (67 patients with *GRN* mutations and 143 confirmed FTLD-TDP type A cases). A standard case-control association study was performed to identify modifiers for *GRN* mutation carriers and/or FTLD-TDP in general. The discovery phase analyses did not reveal modifiers affecting age at onset (neither after conditioning on rs5848); yet a genome-wide significant lead SNP downstream to *TMEM106B* was evident (rs7791726; 7*p*21.3). Of note, rs7791726 appears to be in almost complete linkage disequilibrium with the previously indicated GWAS hits at this locus (rs1990622, rs3173615, and rs1990620); thus, it might be argued that this result further replicates the original findings by Van Deerlin et al., 2010. A total of 44 suggestive markers were carried forward for replication and, after meta-analyzing the discovery and replication phases, 2 markers resulted outstanding: rs3173615 (*TMEM106B*) and rs36196656 (*GFRA2* [GDNF family receptor alpha 2]). It was established that the effect allele for rs36196656 was a *cis*-eQTL to *GFRA2*, where homozygous carriers showed a reduced expression of GFRA2 in cerebellar tissue and it was shown that PGRN and GFRA2 coprecipitated in HEK293T cells, suggesting that both might be part of the GDNF signaling pathway that promotes neuronal survival.

Altogether, this study revealed *GFRA2* as a novel potential modifier in *GRN* mutation carriers. However, authors suggested that not only this genetic association needs to be replicated in follow-up studies but also that GFRA2's biological implication as a PGRN modifier needs to be further assessed in ad hoc functional studies and models.

Besides the typical GWASs, recently, epigenetic findings combined with GWAS data indicated that markers sitting in the *HLA* locus (i.e., rs9357140) might contribute to the regulation of proinflammatory players' expression in the brain cortex, impacting FTLD patients' age of onset (Zhang et al., 2018). This is interesting in that it further supports that multiple risk factors and/or modifiers (i.e., genetic markers with small effect size) might in fact significantly contribute to disease endophenotypes or disease-specific features.

The associations reported in the different FTLD-GWASs hardly replicated across each other. The only hit that appears to be seen in at least 2 independent GWAS (the FTLD-TDP and the FTLD-GRN GWAS) is the *TMEM106B* locus. Both studies targeted a category of cases presenting overlapping features: on 1 hand, the presence of genetic variability in the *GRN* gene, on the other, the underlying pathology (i.e., TDP-43 pathology). Considering that the *TMEM106B* locus was by far not a hit in the International and the Italian clinical GWASs, one might argue *TMEM106B* being an exclusive modifier of *GRN* mutation carriers and cases featuring TDP-43 pathology. The International and the Italian clinical GWASs indicated different loci and were not cross-supportive: here, the lack of replication in a bidirectional manner may underlie the fact that differences in populations might indeed play an important role in determining genetic association, even more than sample size and statistical power.

All this taken together warrants that future study designs take into account a number of points: from a statistical perspective, it is and will be fundamental to increase samples sizes to improve the power of associations. From a study design perspective, it will be fundamental to study the different FTLD subtypes (based on both clinical and pathological diagnoses) to better define their genetic architecture. This will be extremely valuable to genetically classify groups of patients both for later ad hoc inclusion in clinical trials and for the development, in the long run, of syndrome-specific prevention and treatment options.

2.4.1. Ongoing and future efforts to tackle sporadic FTLD

In comparison to other neurodegenerative disorders such as AD and Parkinson's disease (PD), FTLD is a rather rare condition with an insidious clinical presentation that embraces a spectrum of syndromes. As indicated in the previous paragraph, gathering large and phenotypically well-characterized cohorts of the various syndromes contributing to FTLD is a critical element to allow powered genetic studies of sporadic FTLD, and issues of this kind can only be overcome by large international collaborations involving multiple research centers, worldwide.

The International Frontotemporal Dementia Genomics Consortium (IFGC; https://ifgcsite.wordpress.com/) is among the largest consortia for the study of sporadic FTLD. The IFGC conducted the clinical FTLD-GWAS (see Ferrari et al., 2014) and is expanding its data set through the current *FTLD-GWAS phase-III* project. Through these efforts, the IFGC has been and is generating genetic data—through a mix of whole-genome array, exome chip, and NGS techniques—for about 6000 independent sporadic FTLD cases that encompass the various and major subtypes such as bvFTLD, SD, PNFA, and FTLD-MND.

The IFGC comprises research groups form Europe, North America, and Australia who share an interest in the genetics and understanding of sporadic FTLD. The IFGC's vision entails the use of genetics to expand on genes and genetic markers that cause or increase risk of developing FTLD and bioinformatics to interpret genetic data and predict risk pathways, *in silico*.

Clearly, this altogether represents a unique resource for the wider scientific community with an interest in FTLD and neurodegeneration as it helps increasing statistical power for genetic analyses and a range of cross-disciplinary studies and projects. Particularly, this resource allows well-powered studies aiming at dissecting syndrome-specific genetic fingerprints, disease-risk prediction through polygenic risk scores, genotype-phenotype correlation, defining parameters for the identification of cohorts qualifying for tailored clinical trials, as well as fostering large-scale meta-analysis and/or pleiotropy analysis with other closely related neurodegenerative conditions.

3. Molecular mechanisms of FTLD pathogenesis

The translation from genetic knowledge to functional understanding of impacted biological processes and molecular mechanisms at the basis of disease is currently among the major and most debated topics in biomedical research in the context of complex disorders (Karczewski and Snyder, 2018), including FTLD.

Genetics of FTLD clearly has and is contributing to drive research efforts aimed at better understanding its molecular mechanisms and underpinnings. Mendelian FTLD candidate genes are particularly informative to functional biologists to design experiments around their protein products and further their characterization in in vitro and in vivo models. Although it might be argued that Mendelian genes "just" account for a minority of cases (all together ~30%–40% of all FTLD), an intriguing hypothesis is that, if familial genes indicate functions and processes whose alteration is necessary and sufficient to trigger FTLD pathogenesis, they might be baits for defining the global pathogenic mechanisms leading to FTLD and thus being informative also for the vast majority, that is, the sporadic (~60%–70% of all FTLD), of cases. In the latter scenario, in fact, not only their genetic features are still understudied but also a specific link to genes is less clear than in Mendelian cases because of the nature of GWASs.

The study of protein products of Mendelian (and sporadic [or GWAS]) candidate genes and their functional characterization is thus, in the first instance, informative on the potential impacted processes. Nevertheless, this approach tends to take into consideration "one gene at a time" and might be reductionist in the long run. In addition, proteins encoded by the candidate genes are involved in multiple subcellular processes/pathways; thus, it is critical to highlight those that are truly involved in disease pathogenesis.

Innovative methods to aid in this respect rely on data integration and bioinformatics analyses. These are emerging alternatives to the classical studies in that they allow to evaluate altogether the genetic players contributing to the phenotype, to simulate different pathogenic scenarios and to isolate the most likely risk pathways to be validated and tested in the functional setting. For instance, network analyses based on gene co-expression and protein-protein interactions (PPIs) are becoming suitable methods to serve these purposes. Weighted gene co-expression network analysis (WGCNA) is a bioinformatics pipeline developed in 2008 by Langefelder (Langfelder and Horvath, 2008) that allows the generation of a network whose nodes are genes connected on the basis of their co-expression profile. This type of analysis relies on the assumption that genes that are temporospatially expressed together are likely to be involved in similar functions within the cells expanding on the functional environment of candidate genes. PPI networks are composed by proteins connected on the basis of proof of physical interaction (*as per* peer reviewed functional literature). The hypothesis, behind this second type of networks (work adopting PPI network analyses [WPPINAs]), is that proteins that interact with each other likely share the same function within a conserved pathway due to biochemical reasons (Ferrari et al., 2017). Network analyses have been recently supported by high-throughput approaches that have the advantage of being unbiased and can take into consideration multiple genes at a time. Comparative mass spectrometry has been used to compare FTD, ALS, and controls to define common and specific molecular players and cellular pathways possibly involved in disease onset and progression (Umoh et al., 2018).

The study of the physiology of Mendelian genes has to date indicated a number of susceptibility processes that appear to be conserved across familial and sporadic cases, suggesting these processes being commonly impacted biological processes underpinning FTLD pathogenesis. This appears to be the case for cellular waste disposal pathways and immune signaling. In addition, there seem to be a number of novel intriguing processes emerging from the more holistic (network based) approaches, including DNA damage response (DDR) (Fig. 2).

3.1. *Cellular waste disposal pathways (*CHMP2B, C9orf72, GRN, VCP, UBQLN2, OPTN, SQSTM1, TBK1, CCNF, TMEM106, RAB38*)*

The cellular waste disposal pathways involve an intertwined subcellular continuum of processes that comprise: (1) the endolysosomal pathway that delivers endocytic cargoes engulfed from the extracellular environments to the lysosomes for degradation; (2) the macroautophagy and chaperone-mediated autophagy pathways that target damaged organelles and misfolded proteins for lysosomal degradation; (3) the mitophagy pathway for mitochondrial removal via autophagy, and; (4) the unfolded protein response and the ubiquitin proteasome systems pathways that are responsible for degradation of ubiquitinated proteins. Different alterations of the waste disposal process have been associated with various neurodegenerative disorders including PD, AD, prion disease and Huntington's disease (Menzies et al., 2017). There is still no unequivocal agreement on the detailed mechanisms; however, it is accepted that an alteration of the waste disposal capacity can lead to an accrual of toxic molecules within the subcellular environment that, through time, accounts for progressive neuronal damage and accumulation of misfolded and aggregated proteins. Drugs to potentiate the cell waste disposal machinery have therefore been proposed at least as coadjutant therapies in neurodegenerative conditions (Sarkar et al., 2008).

Among the "major-FTLD genes," *GRN* encodes for a long glycoprotein product (PGRN) that is secreted in the extracellular space. Extracellular PGRN can be uptaken and subsequently cleaved into 7 units of granulins (GRNs) within the endolysosomal pathway (Holler et al., 2017). The function of PGRN and GRNs are still not completely clear, and it has been linked to grow factor like activities and modulation of the inflammatory response (Tang et al., 2011; Van Damme et al., 2008). However, it is interesting to note that homozygous mutations in *GRN* are causative of neuronal ceroid lipofuscinosis, a lysosomal storage disorder, whereas heterozygous mutations in *GRN* are associated with FTD (Almeida et al., 2016). These mutations appear to be loss of function (Cruts and Van Broeckhoven, 2008), and PGRN deficiency has been linked to defective autophagy (Chang et al., 2017) and alteration of lysosomal homeostasis (Evers et al., 2017).

CHMP2B encodes a component of the endosomal sorting complex required for transport III involved in the endosomal trafficking, concentration of ubiquitinated cargoes, and proteins/enzymes involved in the endocytic pathway as well as molding lipid bilayers (Bodon et al., 2011; Morita et al., 2010). Among the "spectrum-FTLD genes," *SQSTM1*, that encodes the *p*62 protein, is responsible for recognizing polyubiquitinated cargoes and for delivering them to the autophagy machinery for degradation (Katsuragi et al., 2015); also, it has been suggested that a dysfunctional *p*62 might impact

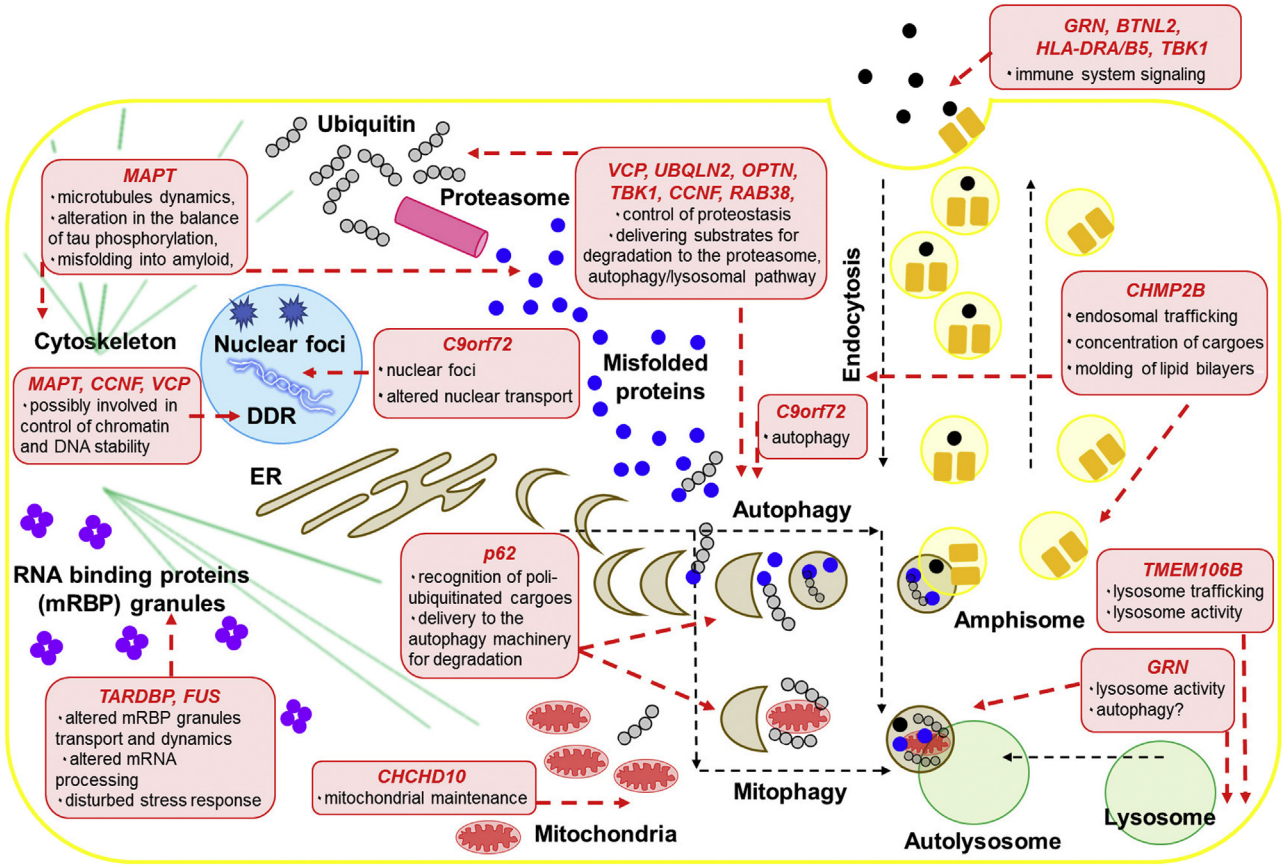

Fig. 2. Summary of all putative impacted molecular processes contributing to FTLD pathogenesis on the basis of the current global genetic characterization of FTLD including "major," "spectrum," and "GWAS" FTLD genes. Abbreviations: DDR, DNA damage response; ER, endoplasmic reticulum; GWAS, genome-wide association studies; FTLD, Frontotemporal lobar degeneration.

mitochondria depolarization and lead to a reduced autophagosome formation (Haack et al., 2016). *VCP* is well known for its relevant roles within the ubiquitin-mediated proteostasis (Meyer and Weihl, 2014). *UBQLN2* codes for a protein involved in the control of proteostasis by delivering substrates tagged for degradation to the proteasome (Hjerpe et al., 2016). *OPTN* has been reported to recognize protein aggregates in a ubiquitin-independent fashion and in association with the kinase *TBK1* before directing them to the autophagy/lysosomal pathway for degradation (Korac et al., 2013). *CCNF* holds a function in the E3 ubiquitin-protein ligase complex to mediate proteasomal targeting of ubiquitinated CP110 during G2 phase (Nguyen et al., 2018).

Peculiar is the case of *C9orf72*: although its physiological role is still not known, many studies have been carried out to evaluate the effect of the pathogenic hexanucleotide expansion, indicating that *C9orf72* expansions might reduce mRNA expression or generate toxic nuclear foci (Pottier et al., 2016) with a possible alteration of the nuclear transport. Nevertheless, more recently, *C9orf72* has been linked to autophagy and proteostasis (Pottier et al., 2016).

"GWAS" candidate genes also appear to play major roles within the endolysosomal trafficking and the waste disposal processes: such is the case of *TMEM106B* that is associated with maintenance of endolysosomal trafficking (Busch et al., 2016; Jun et al., 2015), while *RAB38* is responsible for vesicle trafficking, fusion, and autophagosome maturation (Wasmeier et al., 2006).

Altogether, this suggests that a number of "major," many of the "spectrum" and some of the "GWAS" genes point toward different yet convergent components of the more broad waste disposal pathway, indicating that both dominant mutations (high penetrance) as well as common markers with small effect size (low penetrance) support a common process involved in disease pathogenesis. Clearly, more studies will need to be performed to further characterize how genetic variability in the candidate genes affects these pathways and contributes to disease mechanisms to be able to recognize potential biomarkers and/or druggable targets within the waste disposal matrix.

CHCHD10 does not seem to fit in the waste disposal picture: *CHCHD10* codes for a mitochondrial protein that might play a role in maintaining mitochondrial physiological activity, yet further ad hoc investigations will be needed to verify whether CHCHD10 might exert a relevant role in mitochondria quality control and mitophagy.

3.2. *Immune system signaling (*GRN, TBK1, BTNL2, HLA-DRA*)*

Immune-related processes are extremely complex and heterogeneous. A few "major," "spectrum," and "GWAS" genes appear to support signaling pathways involved in immune responses.

PGRN has been shown to be upregulated in activated microglial cells (Baker et al., 2006) and, among multiple processes, to be involved in wound healing and inflammation (van Swieten and Heutink, 2008). Interestingly, PGRN appears to act as an anti-inflammatory agent, while GRNs, the products of PGRN cleavage, have been shown to promote proinflammatory activities (He and Bateman, 2003). All the more, it was also suggested that PGRN is involved in inflammatory processes acting as antagonist of the tumor necrosis factor α in binding the TNF receptor (Tang et al., 2011) or by regulating innate immunity gene expression and complement production thus, in turn, controlling synaptic pruning by microglia

(Lui et al., 2016). Interestingly, TBK1, although implicated in the proteostasis processes (see "Cellular waste disposal pathways" section) is, primarily known for mechanisms that relate to the innate immune response (Xiao et al., 2017), suggesting a potentially ubiquitous role in FTLD pathogenesis that warrants additional focused studies. The clinical FTLD-GWAS also clearly supported the involvement of the immune system signaling and inflammatory response: BTNL2 encodes a membrane protein that is ubiquitously expressed across different tissues, including the brain, and is involved in repressing T-cells proliferation (Valentonyte et al., 2005), while HLA-DRA encodes a monomorphic class II HLA-DR transmembrane receptor that is expressed on the surface of microglia. Interestingly, increased expression of HLA-DR molecules on microglia may reflect pathological activity, as previously indicated in AD and PD (McGeer et al., 1988), suggesting that aberrant HLA-DRA levels might in fact impact modulation and regulation of immune responses in the brain. The relevance of elements of the immune system mapping to the HLA locus was further supported by a recent study, assessing genetic pleiotropy across autoimmune disorders and FTLD (Broce et al., 2018).

Clearly, these avenues need to be further explored, yet it is relevant to note that rare and common genetic variability might imply that constitutive functional alteration of innate and adaptive immune responses may contribute to disease pathogenesis.

3.3. Gene expression regulation pathways

Despite the extremely rare genetic variability of *TARDBP* and *FUS* in FTLD, yet considering TDP-43 and FUS being pathological hallmarks of FTLD, a brief note about their contribution to disease pathogenesis is warranted: TDP-43 and FUS are functionally involved in processes that control gene expression and RNA metabolism (more details can be found in Ratti and Buratti, 2016). Particularly, it is widely accepted that defective and mislocalized RNA-binding protein granules (i.e., stress granules that have been directly associated with the activity of TDP-43 and FUS) cause neuronal dysfunctions, abnormal stress response, and ultimately neurodegeneration (Bowden and Dormann, 2016).

3.4. Other (minor) processes/pathways: protein aggregation (MAPT) and neuronal development and homeostasis (GRN, RFNG, AATK, GFRA2)

Interesting is the case of *MAPT* that encodes the tau protein. Our current knowledge about tau's functions and physiology points to binding and stabilization of MTs. The consequences exerted by mutations in *MAPT* have been associated with both alterations in splicing events leading to an imbalanced ratio of tau isoforms and with impairment in binding (and stabilizing) MTs (due to mutations affecting the MT-binding domain), all this leading to increased free cytosolic population of tau that favors its aggregative properties (Ferrari et al., 2011). Tau is target of multiple post-translational modifications such as phosphorylation and acetylation (Min et al., 2010), and balance in tau phosphorylation has shown to be essential for supporting tau physiological functions: hyperphosphorylation does occur in the disorder setting and increases tau's aggregative capacity (Bodea et al., 2016). It follows that, as mentioned previously, besides the occurrence of abnormal protein aggregation, it is not fully clear what pathways and cascades become disrupted in *MAPT*-driven Mendelian cases.

Other processes that might be impacted on the basis of genetic variability affecting both "major" and "GWAS" genes are neuronal development and homeostasis. Among the (many) functions associated with PGRN and GRNs, in fact, PGRN by activating several kinase-dependant signaling cascades, stimulates the induction of vascular endothelial growth factor (Tangkeangsirisin and Serrero, 2004), promotes endothelial cell migration during wound healing (He et al., 2003), and appears to play a role in brain development (Mackenzie and Rademakers, 2007) and neurite outgrowth (Van Damme et al., 2008). Similarly, PRGN has been shown to bind to EphA2 (a tyrosine kinase receptor) with consequent activation of mitogen-activated protein kinases and AKT, thus promoting vessel growth with capillary morphogenesis (Neill et al., 2016). Furthermore, recent GWAS (Ferrari et al., 2015; Pottier et al., 2018) indicated a number of loci including genes that, if confirmed as the real biological reason for association (provided that *RFNG* and *AATK* result from suggestive loci, i.e., close to but below genome-wide significance), support to some good extent additional processes related to neuronal development and protection (*RFNG*, *AATK*, and *GFRA2*).

3.5. Emerging pathways: DNA damage response (MAPT, VCP, CCNF)

Gene co-expression and protein interaction networks are state-of-the-art bioinformatics tools supporting fast *in silico* characterization of shared functions across groups of candidate genes/proteins. In this respect, results from extended bioinformatics work focusing on gene co-expression analyses (WGCNA) of "major," "spectrum," and "GWAS" genes confirmed susceptibility pathways belonging to the waste disposal processes such as autophagy, ubiquitin proteasome system, and immune response pathways (Ferrari et al., 2016). Other WPPINA further supported the waste disposal process driven by endoplasmic reticulum stress particularly referring to the ubiquitin/proteasome and unfolded protein response (Ferrari et al., 2017).

Most interestingly, these bioinformatics works jointly supported DDR as a novel potential mechanism underpinning FTLD (Ferrari et al., 2016, 2017). In the WGCNA work, it was evident that *MAPT* was a hub in modules indicating DNA protection among the most significant biological processes in frontal and temporal cortices (Ferrari et al., 2016). The WPPINA work replicated quite in detail the DDR results described previously (Ferrari et al., 2017).

This bioinformatics work globally raised the importance of DDR in FTLD. Recently, a number of studies showed indeed that alterations in the DDR are among the functional consequences of mutations in *MAPT*, suggesting that alterations of the cellular cycle, chromatin damage, and aberration of the normal DNA repairing process may be functionally linked to brain cells' death and neurodegeneration observed in FTLD (Rossi et al., 2008, 2013). More functional characterization of this process in FTLD models is currently under way.

Interestingly, *CCNF* plays a role in the E3 ubiquitin-protein ligase complex and mediates proteasomal targeting of ubiquitinated CP110 during G2 phase, thereby not only acting in the cell waste disposal (see section 3.1) but also in the control of the cell cycle check points that control genome stability through ubiquitin-mediated proteolysis (Nguyen et al., 2018). As well, *VCP* has been shown to be part of a complex of proteins recruited to the DNA double-strand breaks (Acs et al., 2011; Meerang et al., 2011).

The DDR is the general functional term indicating the process through which a cell keeps control of alterations/mutation in the genetic code through mechanisms of damage recognition, repair, tolerance, in addition to cell-cycle checkpoint pathways and signaling events (Giglia-Mari et al., 2011). Alterations of the DDR have been associated with different severe disorders such as Xeroderma Pigmentosum, a syndrome characterized by photosensitivity, increased risk of cancer (particularly skin cancer) often presenting with neurological symptoms (Garcia-Moreno et al., 2018). In addition, it is indeed remarkable that congenital and age-related neurodegeneration has been associated with accumulation of DNA lesions (Madabhushi et al., 2014).

4. Final remarks

Genetics and cell biology work over the past two decades have tremendously contributed shedding light on genetic causes and molecular mechanisms involved in FTLD.

However, there is much more to be learned on these matters as our current understanding of FTLD pathogenesis is clearly in its infant stages and not sufficient to achieve effective preventive and therapeutic measures.

From a genetics perspective, we are at a moment in time where the available and emerging technologies (e.g., genome-wide, exome-chip arrays and NGS techniques) are becoming more cost-effective, enabling a better characterization of common and rare genetic variability contributing to disease. Much of this work will need to be aimed at fine-mapping classical GWAS loci, exploring more in depth the (likely) oligogenic nature of disease and identifying novel causative genes. This will clearly impact the way and pace at which we will fill the gap of missing heritability in FTLD, a key step in deciphering and defining the genetic risk architecture of FTLD. Of course, these approaches will be best applied to large and well-defined patients' cohorts, the gathering of which is made possible by international disease-focused working groups and/or Consortia. Applying these techniques to large cohorts representative of the different FTLD subtypes (i.e., clinical bvFTLD, SD, and PNFA cases as well as pathologically defined cohorts [e.g., FTLD-tau or FTLD-TDP]) will aid improving genotype-phenotype correlation defining syndrome- and/or subtype-specific genetic fingerprinting (important, e.g., to identify cohorts qualifying for tailored clinical trials).

The gap from genes to mRNA and proteomics shall be reduced through better study designs, where multi-omics approaches are applied to the same sample source and disease-relevant tissue(s) to avoid inter-sample variability issues and correlate data by grounds of sample and tissue specificity (Manzoni et al., 2016). From a functional perspective, we need a more time-effective way to coherently translate genetic into functional knowledge. These goals will be achieved by the use of more holistic approaches to interpret the genetic knowledge and guide functional studies investigating risk pathways. For example, *in silico* methods involving assessments of genetic variability's effect on gene-expression regulation (e.g., eQTLs, methylation quantitative trait loci, allele-specific expression, transcriptome-wide association study) (Gusev et al., 2016; Manzoni et al., 2016) and molecular interactions and functional annotation analyses of gene co-expression and PPI networks will allow to better put into perspective the biological processes and pathways that are impacted by genetic variability (Furlong, 2013). In turn, this will provide solid ground for the development of testable hypotheses and aid functional biologists designing more precise experimental models, including cell-specificity studies (Skene et al., 2018), for validating risk pathways.

Normalizing all such strategies will require some time, yet this is the paradigm shift to improve basic and translational research and pave the way for advancements in preventive, monitoring, and therapeutic measures.

Disclosure

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