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Mendelian and sporadic FTD: disease risk and avenues from genetics to disease pathways through *in-silico* modelling

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ABSTRACT

Frontotemporal dementia (FTD) is regarded as the 2nd most-common form of young-onset dementia after Alzheimer's disease (AD).

FTD is a complex neurodegenerative condition characterised by heterogeneous clinical, pathological and genetic features. No efficient measures for early-diagnosis and therapy are available.

Familial (Mendelian) forms of disease have been studied over the past 20 years. Conversely, the genetics of sporadic forms of FTD (up to 70% of all cases) is understudied and still poorly understood. All this taken together suggests that more powerful and in-depth studies to tackle missing heritability and define the genetic architecture of sporadic FTD, with particular focus on the different subtypes (i.e. clinical and pathological diagnoses), are warranted.

In parallel, it will be critical to translate the genetic findings into functional understanding of disease, i.e. moving from the identification of risk-genes to the definition of risk-pathways. It will be necessary to implement a paradigm shift – from reductionist to holistic approaches – to better interpret genetics and assist functional studies aimed at modelling and validating such risk-pathways.

In this chapter we focus on the heterogeneous features of FTD touching upon its complex genetic landscape, and discuss how novel approaches (e.g. computationally driven systems biology) promise to revolutionise the translation of genetic information into functional understanding of disease pathogenesis.

INTRODUCTION

Complex disorders are by definition non-linear conditions where environmental and genetic factors play an intertwined role in contributing to disease pathogenesis and progression. Environmental factors are challenging in that it is difficult to identify and measure those that specifically impact disease [1]. Conversely, the dissection of genetic factors has benefitted from constant improvements in the technologies for generating high resolution data and analytical tools (Wetterstrand KA. 2019. https://www.genome.gov/about-genomics/fact-sheets/Sequencing-Human-Genome-cost).

We have come to appreciate that, on the basis of genetics, there are two broad categories of patients: i) a minority of so-called *familial cases* where pathogenic (Mendelian) mutations in single candidate genes (i.e. Mendelian genes) co-segregate with disease, and; ii) a majority of so-called *sporadic cases* where, in the absence of Mendelian mutations, multiple genetic variants with small effect size increase the risk for developing disease.

Mendelian genes have been classically isolated *via* linkage analysis and/or whole-exome/genome sequencing of trios, first-degree relatives, or well-phenotyped pedigrees [2]. Sporadic forms of disease are conveniently investigated through case/control association studies, e.g. genome-wide association studies (GWAS) [3]. The idea that genetic investigation of *familial cases* is straightforward is only apparent. It is, in fact, worth noting that there are uncharacterised *familial cases* where Mendelian mutations have not been isolated [4]. Also, functional investigation of Mendelian genotype-phenotype correlation has proven neither time- nor cost-effective, to date. Moreover, the genetic architecture of risk for *sporadic cases* is challenging to assess and even harder to model, especially considering that multiple variants with small effect size are to be taken into account, simultaneously.

In this chapter we focus on the heterogeneous features of frontotemporal dementia (FTD) touching upon its complex genetic landscape, and discuss how novel approaches (e.g. *in-silico* systems biology) promise to revolutionise the translation of genetic information into functional understanding of disease. These approaches represent a stepping-stone towards functional validation of risk-pathways and, possibly, drug targets identification. All this holds relevance as the field is accelerating towards effective clinical trials design and the development of measures for early diagnosis, disease prevention/monitoring and cure.

FTD AND DISEASE RISK

Environmental factors

The environmental exposure contributing to FTD pathogenesis is an understudied and complicated matter. It is widely accepted that complex neurodegenerative conditions, including FTD, are influenced by environmental risk factors acting in concert with the genetic risk-architecture within a process referred to as gene-environment interaction [5].

No single environmental factor clearly leading to FTD has ever been indicated. Only concepts such as ‘cognitive reserve’ [6, 7] or ‘aging’ [8] have been suggested to influence disease risk and modulate age at onset. Additionally, few epidemiological studies highlighted possible links between FTD, cardiovascular disease and diabetes risk factors [9-11].

The environment is believed to influence risk for complex neurodegenerative disorders *via*, at least, two mechanisms. On one hand, the environmental exposure (e.g. aging) may modulate methylation profiles in the genome or the activity of non-coding RNAs (ncRNAs) impacting gene expression and influencing disease onset and progression [12, 13]. On the other, the environmental exposure can represent the direct mechanistic insult triggering processes that lead to disease. For example, lessons learned from other complex neurodegenerations, such as Parkinson’s disease (PD), indicate that certain toxins and pesticides can cause a cascade of effects resulting in oxidative stress that ultimately influences disease pathogenesis [14]. Also, traumatic brain concussions have been implicated in certain forms of dementia (including Alzheimer’s disease [AD] and FTD) [15] and it was suggested that physical insults were linked to toxic stress resulting in mitochondria alteration, oxidative stress [16] or amyloid aggregation [17], globally impacting brain homeostasis and, subsequently, disease pathogenesis.

A better understanding of the environmental risk factors playing a role in complex neurodegenerations, such as FTD, would critically complement our dissection of disease biology (e.g. it would help highlighting impacted pathways and molecular mechanisms). A substantial caveat here is represented by the lack of efficient and reliable methods to investigate and measure the environmental exposure(s) that influence and/or contribute to the pathogenesis of complex neurodegenerations. Nevertheless, a promising approach that might aid in closing this critical gap is Mendelian Randomization (MR). MR is a statistical approach where common variants such as single nucleotide polymorphisms (SNPs) that are associated with a certain environmental exposure (e.g. SNPs that increase individual risk/chance of smoking, drinking, developing cardiovascular disease) are used as proxies to assess association with SNPs in the disease under investigation [5]. This approach is still to be explored in FTD, yet it promises to shed light on those environmental exposures that might be relevant to FTD pathogenesis: power issues associated with GWAS performed in FTD have hampered the possibility of performing effective MR studies, to date.

Genetics

In line with its heterogeneous clinical and pathological characteristics (that can be reviewed in [18-20]), FTD's genetic features mirror its complicated global phenotypic picture [21, 22]. A positive familial history is seen in ~10-30% of cases – *familial* (fFTD) or Mendelian [23-25] – whilst a remainder ~70% of cases – individuals with disease but no clear familial history and/or genetic aetiology – are categorised as *sporadic* (sFTD) [21, 22].

Mendelian FTD

The vast majority (≥25%) of fFTDs strongly associates with pathogenic mutations in *MAPT* [26], *GRN* [27] and *C9orf72* [28, 29], whilst a small minority (<5%) associates with (very) rare mutations in *CHMP2B* [30, 31], *VCP* [32], *TBK1* [33-35], as well as *IFT74* [36], *OPTN* [35], *SQSTM1* [37], *UBQLN2* [38], *CHCHD10* [39], and *TIA1* [40].

Mutations in *MAPT*, *GRN* and *CHMP2B* have almost exclusively been described in "pure" FTD cases [21]. In few occasions issues were raised on whether (all) Mendelian mutations are fully penetrant (e.g. *GRN* mutations have shown to be associated with variable age at onset or a spectrum of phenotypes within the same family [22]). Expansions in *C9orf72* have shown to be ubiquitous across neurodegenerative disease. Although they are most frequently found in cases diagnosed with FTD, amyotrophic lateral sclerosis (ALS), or within the FTD-ALS spectrum, they have also been reported in a range of phenotypes, including AD, Parkinsonian syndromes, Huntington's disease (HD), corticobasal syndrome/degeneration (CBS/D), as well as non-demented elderly individuals [29, 41-49]. Mutations in the remainder genes have been isolated in small numbers of (at times even single) families displaying substantial syndrome-heterogeneity: a complex phenotypic signature characterised by inclusion body myopathy (IBM), Paget's disease of the bone (PDB) and FTD (IBMPFD) for *VCP* [50]; ALS and/or the FTD-ALS spectrum for *SQSTM1*, *UBQLN2*, *IFT74*, *OPTN*, *CHCHD10*, *TBK1* and *TIA1* [21, 22]. Of note, *TARDBP* and *FUS* mutations have been mainly reported in ALS, whilst very rarely in FTD cases [51, 52]. It is thus still debated whether or to what extent *TARDBP* and *FUS* are to be considered "FTD genes" [52, 53] (despite the fact that TDP-43 and FUS are clear pathological hallmarks of FTD [54]).

Regardless of complexity and heterogeneity, a key point is that Mendelian (i.e., for the most, coding) mutations, provided their large effect size, appear to be sufficient to trigger disease. Therefore, although quite rare and exclusive to a (rather small) number of families or private cases, they are indeed informative candidate-genes/targets to model disease.

Sporadic FTD

Sporadic FTD cases (sFTDs) are generally screened for known candidate genes: pathogenic variants have been reported in *MAPT*, *GRN*, *C9orf72* or *TBK1* in ≤10% of cases [21, 22, 55, 56]. These might be due to *de-novo* mutations that can (very rarely) occur in the population, or (likely) to the fact that they might be cryptic Mendelian cases.

Genetics of sFTD is still poorly understood. Sporadic cases are investigated through GWAS where millions of SNPs are compared across thousands of cases and

controls [3]. A GWAS assesses allele frequencies of 'common' genetic markers (SNPs) (i.e. they are present in the general population) in the two sample sets. Those markers that associate with increased risk for disease display a significantly increased frequency in cases when compared to controls. Genetic risk markers identified through GWAS are generally non-coding variants, and they are characterised by small effect sizes, thus one single SNP is neither necessary nor sufficient to lead to disease [57]. Rather, multiple SNPs cumulatively contribute to disease pathogenesis and represent the so-called genetic architecture of disease (i.e. the genome-wide asset of genetic risk) [58].

To date, a handful of GWAS have been performed in sFTD [4]. GWAS require large cohorts of cases and controls (n=thousands) and this may sometimes represent a drawback (especially when a disease is rare or heterogeneous). In order to cope with samples collection and power issues for genetic studies of sFTD, multicentre initiatives such as the International Frontotemporal dementia Genomics Consortium (IFGC; https://ifgcsite.wordpress.com/) and the International FTLD-TDP whole-genome sequencing consortium [56] have been established. Networks of this kind allow to share expertise and collate large numbers of samples across research centres to increase the statistical power of sFTD genetic studies.

The first FTLD-GWAS was published in 2010 by Van Deerlin *et al* using a cohort of 604 cases with either pathologically confirmed frontotemporal lobar degeneration with TDP-43 pathology (FTLD-TDP) and/or cases carrying a *GRN* mutation (515 discovery-phase; 89 replication-phase). This study highlighted risk variants at a locus on chromosome 7p21 [59]. Subsequently, a larger GWAS was published in 2014 by Ferrari *et al* using a cohort of 3,526 clinically diagnosed sFTD cases (2,154 discovery-phase; 1,372 replication-phase) leading to the identification of a risk-locus on chromosomes 6p21.3 (for the entire cohort) and a suggestive risk-locus on chromosomes 11q14 (for behavioural variant FTD [bvFTD]) [60]. A smaller GWAS was then performed by Ferrari *et al* in a population-specific cohort of 530 Italian sFTDs: two suggestive signals were indicated by this study in loci mapping to chromosomes 2p16.3 and 17q25.3 [61].

Genome-wide approaches can clearly be applied in the context of multiple and different experimental designs. In FTD this was the case of a couple of studies that analysed common variants in cohorts characterised by a genetic signature carried in two FTD genes – *GRN* and *C9orf72* – to specifically look for disease modifiers (i.e. genetic factors that influence measurable variables such as age at onset or disease progression). Both studies were published in 2018: i) one by Pottier *et al* assessing a cohort of 592 patient (382 discovery-phase; 210 replication-phase) carrying Mendelian mutations in *GRN* (and some being pathologically defined as FTLD-TDPs without *GRN* mutations) that led to the replication of the above described locus on chromosome 7p21 and the identification of a new locus on chromosome 8p21.3 [62], and; ii) one by Zhang *et al* assessing a cohort of 331 (144 discovery-phase; 187 replication-phase) *C9orf72* expansion carriers that suggested a locus on chromosome 6 acting as a modifier for age at onset [63]. Of note, a previous study by Barbier *et al* conducted on a cohort of 504 patients belonging to 133 families with pathogenic mutations in both *GRN* and *C9orf72* indicated potential chromosome X-linked modifiers of age at onset (for *C9orf72* expansions carriers, but not for *GRN* mutation carriers) [64]. More recently, a GWAS on 636 FTLD-TDP pathologically confirmed cases (517 discovery-phase; 119 replication-phase) – and not carrying mutations in any of the known FTD genes – by Pottier *et al*, suggested 3 risk loci on

chromosomes 7q36, 19p13.11 and 6p21.32 [56]. Of note, provided there being different pathological subtypes within the FTLD-TDP spectrum (i.e. subtypes 'A', 'B', 'C', and 'D'; c.f. [65]), this study suggested that: i) although the 7q36 locus had been previously associated with idiopathic ALS, here the signal represented an independent association; ii) the association with the 19p13.11 locus appeared to be the same as previously indicated in ALS studies, and it was specific to the FTLD-TDP subtype 'B', and; iii) the rare T-allele of rs5848, located within *GRN*'s 3'-UTR, appeared to specifically (and exclusively) increase risk for cases belonging to the FTLD-TDP subtype 'A' [56].

GWAS results described in this section are summarised in **Table 1**.

Although one might gather from these sections that the FTD genetics arena is globally quite heterogeneous, there are reasons to suspect that homogeneous subpopulations of patients exist and can be better defined and predicted through tailored genetic (and bioinformatics) studies [21, 22].

Missing heritability

Despite heterogeneity, it might be argued that FTD is a disorder with a robust hereditary component. However, our genetic understanding of FTD is still considerably incomplete in sporadic as well as in familial FTD (e.g. there are families where Mendelian mutations have not been isolated) [4]. It follows that missing heritability is a critical unresolved issue in FTD [66].

Recently, a number of sequencing projects in FTLD-TDP, clinical FTD and FTD-ALS cases further characterised mutations in either already established Mendelian or what could be considered as "novel" FTD genes. For example, an excess of loss-of-function variants in FTLD-TDP cases was evident in a number of genes (i.e. *DHX58*, *IRF3*, *IRF7*, *IRF8*, *NOD2* and *TRIM21*) suggested to be in strong functional link with *TBK1* within inflammatory response pathways [56]. Further, mutations were described in: *SORT1*, in a Belgian FTD cohort and subsequently confirmed in Mediterranean FTD cases [67]; *CCNF* in FTD and ALS cases [68]; *TREM2*, *CSF1R* and *AARS2* in Asian FTD cases [69, 70], and; *TYROBP* in Italian FTD-ALS pedigrees [71]. Besides many of these mutations needing additional replication, the above studies further support the notion of population and syndrome heterogeneity characterising genetics of FTD.

Considering sFTD, the scenario is possibly even more complicated. A first issue is that GWAS in FTD have still been quite underpowered to date. This can, e.g., be appreciated by comparing numbers of cases studied across different neurodegenerative diseases such AD (n~90,000 [72]) and PD (n~40,000 [73]) vs. the largest FTD-GWAS so far (n~3,500 [60]). A second issue is represented by the fact that underpowered GWAS in FTD have hampered appreciating the global contribution of the multiple risk-markers with small effect size through, e.g. polygenic risk scoring (PRS). PRS would indeed serve the purpose of measuring how well the global genetic architecture of risk discriminates sFTD cases from controls (and/or other closely related neurodegenerations). PRS aggregates whole-genome genetic risk into a single score using a test sample to weight SNPs contribution to a trait and assesses such weights in an independent target sample [74]. Since PRS has never been done in FTD the actual genetic architecture that confers globally increased risk for developing sFTD remains elusive, even more so when considering the different

FTD subtypes: i) the clinical syndromes belonging to the core FTD-spectrum, i.e. the behavioural and language variants [18, 20], and; ii) the pathologically defined subtypes characterised by Tau and TDP-43 (FTLD-tau, FTLD-TDP) or p62 (FTLD-UPS [ubiquitin proteasome]) or FUS, EWS and TAF15 (collectively referred to as FTLD-FET) protein aggregates [54, 65].

Although a large GWAS meta-analysis for sFTD is currently (at the time this chapter is being written) ongoing within the IFGC program – including over 5,000 cases – it is clear that the genetic architecture underpinning sFTD (and its various subtypes) is still poorly defined and understood, thus more work in this area is warranted.

FROM GENETICS TO DISEASE BIOLOGY

Despite our poor understanding of environmental risk factor in FTD, and the work ahead in further characterising the genetic architecture of risk, there is an important issue we can start addressing now: translation of our current knowledge of FTD's genetics into functional understanding of disease. This is indeed among the major topics gaining momentum in the biomedical field focusing on complex neurodegenerative disorders (including FTD) [75].

Translating GWAS genetics into biological meaning

One of the biggest challenges in population genetics is the interpretation of the risk signals derived from GWAS. While GWAS are instrumental in discriminating genetic risk markers and loci that associate with a trait of interest, such signals are not directly informative on the impacted gene(s) or disease mechanism(s) [76]. SNPs highlighted by GWAS are for the very vast majority non-coding (intronic or intergenic) meaning that additional investigations are required to identify the actual gene(s) and pathway(s) targeted by the risk-variants within the risk locus [3, 77]. This is not a trivial issue since the understanding of impacted genes and pathways is of primary importance to untangle the functional role of the risk-variants and generate more accurate disease models.

Besides increasing the resolution in prioritising genes at GWAS loci, e.g. through *ad-hoc* gene-burden analyses [78], other strategies involving integration of genetic and other types of data – e.g. gene-expression, protein-protein interaction and pathways analyses – are being fine-tuned [76]. Indeed, a first point to clarify is whether any SNP highlighted by a GWAS exerts an effect on gene-expression: this is done by assessing expression Quantitative Trait Loci (eQTL) [79], a bioinformatics technique that evaluates expression levels (mRNA) of genes in *cis* with the risk-allele(s) of the associated SNPs within the locus of interest. When the risk-allele significantly associates with a change of expression of a *cis*-gene, the latter might be *bona fide* considered the biological target of the genetic variant. There are other types of QTL analyses, e.g. methylation (mQTL), splicing (sQTL) and protein (pQTL) [80], that focus on the identification of alterations in methylation profile, splicing or protein levels. Such quantitative traits might be used as proxies to prioritise genes and support the definition of molecular mechanisms modulated by GWAS SNPs. And, clearly, these will need to be further validated in functional assays to confirm they are truly associated with a possible disease mechanism.

The FTLD-TDP GWAS, showing association with SNPs at the locus on chromosome 7p21 [59], revealed the risk alleles to affect expression levels (increased) of the *cis*-gene *TMEM106B* [59]. Further analyses showed elevated basal levels of *TMEM106B* in FTLD brains affected by TDP-43 pathology [81]. Also, multiple follow-up studies confirmed *TMEM106B* to be functionally relevant for FTD hinting at an interplay with two known fFTD (Mendelian) genes, i.e. *GRN* and *CHMP2B*. Studies on TMEM106B protein suggested its involvement in the endolysosomal system together with CHMP2B [82]. Furthermore, over-expression of *TMEM106B* was shown to be associated with impairment of the endolysosomal system and an increase in the levels of GRN [81], whilst ablation/reduction of *TMEM106B* was able to rescue the endolysosomal phenotype observed in *Grn* deficient mice [83] or in

CHMP2B mutants [84]. The GWAS on *GRN* mutation carriers [62] supported the notion that *TMEM106B* is a modifier in *GRN* mutation carriers (in line with the original study [59]) and, additionally, suggested the risk-allele of the top SNP at the chromosome 8p21.3 locus being a *cis*-eQTL of the GDNF family receptor alpha 2 (*GFRA2*) gene. The GFRA2 protein was shown to co-precipitate with the GRN protein possibly inferring to a potential involvement of the GDNF signalling pathway (a pathway promoting survival of neurons) in *GRN* mutation carriers. The clinical FTD-GWAS [60] indicated that both a mQTL for *HLA-DRA* (6p21.3 locus) and an eQTL for *RAB38* (11q14 locus) appeared to explain how the biological effect at those loci was possibly mediated. mQTLs at the *HLA* locus were also suggested in Zhang *et al* where regulation of expression in brain cortex of pro-inflammatory elements seemed to influence age at onset in FTD patients [63]. Further support for the involvement of the immune system in FTLD-TDP pathogenesis was more recently provided by Pottier *et al* who showed: i) eQTLs driven by the risk-allele of the top SNP at the chromosome 6p21.32 locus leading to increased expression of *HLA-DQA2* and *-DQB2* in brain, and; ii) excess of genetic burden in a number of genes acting in epistasis with *TBK1* within innate immune signalling pathways [56].

The loci characterisation described in the above paragraph are summarised in **Figure 1**.

Clearly, several of the above studies strongly suggest that perturbation of multiple genes and pathways of the immune system might specifically underpin subpopulations of patients and contribute to FTD pathogenesis. This view appears to be further supported by a handful of earlier studies hinting at altered cytokines profiling in the cerebrospinal fluid (CSF) and/or serum of FTD patients [85, 86] and the identification of changes in the expression of FTD-immune pleiotropic genes (within the *HLA* region) in post-mortem brain tissue of FTD patients with an enriched microglia/macrophages signature [87].

Are Mendelian and sporadic FTD the same disorder?

A relevant point in FTD research is that Mendelian genes are instrumental for disease modelling, i.e. they can be studied in *in vitro/in vivo* model systems (e.g. transgenic cellular and animal models or patient-derived iPS cells) to gather insights into the molecular mechanisms of disease. This is fundamental to understand the cellular functions that are compromised during disease onset and progression and to identify potential targets for therapeutic intervention.

This approach is hardly applicable to sporadic disease. Sporadic cases are associated with multiple risk factors that are very difficult to model because they: i) feature small effect size; ii) act as a whole, thus the experimental system would need to model multiple risk factors at the same time, and; iii) are non-coding, thus it is for the most unclear which gene/protein they impact. On top, the contribution of environmental exposures is, to date, impossible to model [77].

Familial models of disease do not fully capture or reflect disease complexity. In fact, by almost exclusively focusing on fFTD, FTD models are currently limited (despite a number of studies on *TMEM106B* [22, 88]) to models focused on Mendelian genes (*MAPT*, *GRN*, *C9orf72*) or models of tau pathology, a feature that is seen in FTLD-tau and beyond (e.g. AD, but also progressive supranuclear palsy [PSP] or CBD). As a consequence, using the familial models as proxies for the entire disease spectrum

(only because models for the sporadic forms of disease are not available) might not be entirely successful. Such *modus operandi*, indirectly relies on the assumption that, since familial and sporadic FTD are clinically classified under the "same label", the molecular mechanisms and pathways altered in familial cases might be the same or similar to those in the sporadic ones. This is, however, still an open and unexplored question. One possible example of shared mechanisms comes from the *MAPT* locus. In FTLD-tau, *MAPT* mutations – i.e. coding variants in exons 1, 9–13 [89, 90] – or heterogeneous genetic variability – e.g. intronic variants affecting expression and/or splicing of exon 10 [91, 92], or structural variants [93, 94] – cause disease and lead to tau pathology. At the same time, when considering the ~900 kb H1/H2 haplotype inversion at the *MAPT* locus [95], a yet to be identified combination of markers on this stretch may increase disease risk in a subgroup of patients with parkinsonism or broad FTD-like dementia phenotypes [96]. Further studying the genetics at the basis of tau pathology might help shedding light on communal disease mechanisms across fFTDs and sFTDs, as well as FTD and other tauopathies.

Moreover, one must not forget about a number of critical issues associated with the study of familial and/or pathologically defined cohorts: i) they represent a minority of all FTD cases, ii) they might be underpowered; iii) they might provide little or inadequate information on disease mechanism(s) underpinning the various clinical syndromes, and; drugs and intervention measures, currently under pre-clinical and clinical investigation (trials), appear tailored to fFTD or FTLD-tau only [97].

There is therefore an urgent need to expand the focus to sporadic FTD, and assess disease-pathways that might be communal across fFTDs and sFTDs, knowledge that will be critical and instrumental to pave the way for developing clinical trials and means for therapeutic intervention addressing all FTD cases.

Risk-pathways *in-silico* modelling

Multiple genes and genetic risk variants associate with FTD. However, as in the case of other complex neurodegenerations such as PD and AD, it is difficult to portrait why and how so many different genetic elements lead to the "same disease".

It is well known that, functional research is still not well equipped to model multiple genetic players at the same time. The classical approach relies on studying single genes (and risk factors) in isolation, collating reductionist pieces of information to recreate a global picture of disease. However, while this approach has been successful – e.g. the Amyloid cascade hypothesis in AD based on functional work assessing mutations in *APP* and *PSEN*s [98] – it appears promising – e.g. ongoing studies focusing on tau pathology [99] and the biology of *GRN*, *C9orf72* and *TMEM106B* [21, 22] – only in a limited number of cases due to intense and costly mechanistic studies that impact the timely dissection of disease mechanisms [100].

Conversely, more recent bioinformatics and systems biology methods – incorporating notions from graph theory, network analysis and machine learning – have seen the light to model the genetic landscape associated with a complex trait and predict risk-pathways to assist hypothesis-driven functional validation in the wet-lab. This represents a holistic paradigm-shift where risk-pathway(s) are hypothesised, *in-silico*, *a priory*, in a time- and cost-effective fashion, and can be subsequently tested. Systems biology approaches based on network analysis have

started being applied to FTD to evaluate possible functional commonalities across FTD genes.

Weighted gene co-expression network analysis (WGCNA) – a bioinformatics method that applies mathematics, statistics and graph theory to expression (and possibly tissue-specific) level data [101] – was applied to evaluate impacted biological processes/pathways and connectivity of genes of interest within co-expression networks in knowingly impacted brain regions [102]. Specifically, FTD-relevant genes (called 'seeds' in this context) were mapped to modules representative of expression profiles in brain and mathematically assessed for their relevance within each module, prior functionally annotating each module. Such a pipeline allows to swiftly investigate the set of functions in which each single FTD genes might be expected to be involved. At the same time, it allows to evaluate possible functional overlap(s) across several different genes in a brain-regional specific manner. The FTD-WGCNA work [102] did reduce the impacted biological processes/pathways (for both familial and sporadic forms of disease) down to: i) gene expression, DNA protection (e.g. DNA damage repair) and protein metabolism (e.g. waste disposal) processes for a majority of FTD-Mendelian genes, and; ii) immune response and endolysosomal metabolism for sFTD risk factors. The intrinsic novelties of this approach can be summarised as follows: i) the annotated modules are critical in mapping specific impacted biological processes to specific brain regions relevant to disease, and; ii) the list of genes found to be co-expressed with the FTD-relevant genes might provide informative suggestions on novel potential genetic and/or functional candidates. For example, *TBK1* mapped to a co-expression module together with *C9orf72*, *VCP*, *UBQLN2* and *OPTN* [102]. The fact that mutations in *TBK1* were isolated in the FTD and FTD-ALS spectrum, reinforces the notion that members of modules including FTD-relevant genes might be (retrospectively) considered for prioritising sequencing and burden analyses aimed at the discovery of novel genes associated with disease.

Weighted protein-protein interaction network analysis (WPPINA) – another bioinformatics approach, this time taking into account protein-protein interactions (PPI) – was applied to extract physical interactors of the protein products of FTD-relevant genes [103]. This method first determined (two-layered) protein interactomes around each FTD-relevant gene (or 'seed') and then investigated communal nodes (interactors) across as many seeds as possible. Such interconnectome (made of so-called inter-interactome hubs [IIH]) was then used to perform functional annotation analysis (similarly to the case of the WGCNA modules). The FTD-WPPINA work [103] confirmed three major biological processes/pathways shared across FTD-relevant genes (previously also suggested by the FTD-WGCNA) such as: gene expression, DNA damage response and waste disposal. Similarly (although slightly differently) to the WGCNA approach described above, WPPINA was instrumental in indicating, in addition to the above highlighted impacted pathways, a list of potential genetic and/or functional candidates either directly or indirectly interacting with the protein products of FTD-relevant genes. This is all the more important in that it provides protein targets within impacted pathways to be taken forward for: i) designing *ad-hoc* functional assays to model disease, and; ii) lead to the identification of potential drug targets. Moreover, WPPINA proved promising in other contexts such as those of prioritising genes within GWAS loci and comparing/discriminating impacted biological processes across neurodegenerative diseases. Specifically, WPPINA was helpful in narrowing down potential functional

candidates at PD-GWAS loci and proved useful in computationally discriminating specific sub-cellular pathways while comparing FTD and PD [104]. WPPINA suggested that, for same (or similar) impacted biological processes (e.g. biology of “stress” and “waste disposal”), it was ‘endoplasmic reticulum (ER) stressors’ that correlated with FTD vs. ‘mitochondria stressors’ in PD, or, elements of the ‘unfolded protein response’ and ‘ubiquitin proteasome’ in FTD vs. ‘autophagy’ and ‘lysosomal’ biology in PD [104].

It is relevant to note that, in parallel to the WGCNA and WPPINA studies and in the context of bridging the biology of fFTDs and sFTDs, additional bioinformatics work showed association of risk variants in sporadic FTD-GWAS with the biology of immune-related disorders [87] or RNA metabolism and cell death pathways to be associated with FTD’s language variant syndrome [105], and cell cycle and immune signalling to be associated with tissue-specific expression changes in bvFTD [106].

It must be acknowledged that these are *in-silico* approaches and no practical steps have yet been undertaken to functionally prove the above highlighted risk-pathways. Nevertheless, discussions between field professionals (e.g. geneticists, bioinformaticians and functional biologists) on these topics have started and are ongoing, with a focus on FTD models as well. Functional studies will be the next critical step in comparing and understanding disease processes affected in fFTD and sFTD, and may subsequently support the development of interventional measures.

FUTURE DIRECTIONS

The study of FTD – from genetic dissection to disease modelling – will require a significant number of efforts in the years to come. Importantly, the research carried out this far provides us with a solid basis to optimistically look into the future with a clear understanding of the (still) open challenges that will need to be addressed.

FTD genetics will require more powerful and in-depth studies – based on GWAS, fine-mapping and sequencing techniques – to: i) dissect common (i.e. prioritise genes impacted by the genetic risk-markers isolated through GWAS), oligogenic and rare genetic factors underpinning disease; ii) tackle missing heritability; iii) define the genetic architecture of sFTD with particular focus on the different FTD subtypes (based on both clinical and pathological diagnoses), and; iv) foster meta- and pleiotropy-analyses with other closely related neurodegenerative conditions.

In parallel, it will be critical to translate the genetic findings into model systems and molecular mechanisms of disease. More specifically, it will be necessary to implement a paradigm shift from reductionist to holistic approaches to interpret genetics (**Figure 2**), and subsequently assist and drive functional studies. This means that precise experimental models (including cell-specificity studies) investigating and validating risk-pathways and biological processes that are impacted by genetic variability will (have to) become reality [107, 108].

All this taken together will be instrumental in improving our understanding of the aetiopathogenesis of disease, help stratifying patients for syndrome-specific clinical trials, highlight efficient endpoints for disease monitoring and therapeutic intervention, and deciphering whether and to what extent molecular mechanisms at the basis of fFTD and sFTD are overlapping, convergent or divergent.

Normalising these strategies will be extremely valuable in setting the ground for the development of effective disease management measures in FTD within the frame of precision medicine.

FIGURE LEGENDS

Figure 1. Translating (sporadic) genetics into functional meaning

The pipeline for translating GWAS genetic signals into biological functions is illustrated. A GWAS is conducted to isolate ‘DNA level information’ on risk-variants associated with FTD (**level 1**). The risk-variants at the risk-locus are assessed for effect(s) on gene transcription levels and/or methylation patterns (**level 2**). Validation at the protein level is pursued through functional models to characterise the impacted pathway(s) and the associated molecular mechanisms of disease (**level 3**).

The original FTLD-TDP GWAS signals are depicted in orange; the International FTLD-TDP GWAS signals are depicted in red; the GRN-GWAS signals are depicted in yellow; the methylation GWAS on *C9orf72* expansion carriers signals are depicted in green, and; the clinical FTD-GWAS signals are depicted in blue.

Figure 2. Reductionist and holistic approaches scheme

The ‘reductionist’ approach studies one gene/risk-marker at the time. The ‘holistic’ approach aims at defining communal functional features across the multiple gene(s)/risk-marker(s). Both approaches are important. They are not mutually exclusive, rather incremental and complementary.

Figure 1

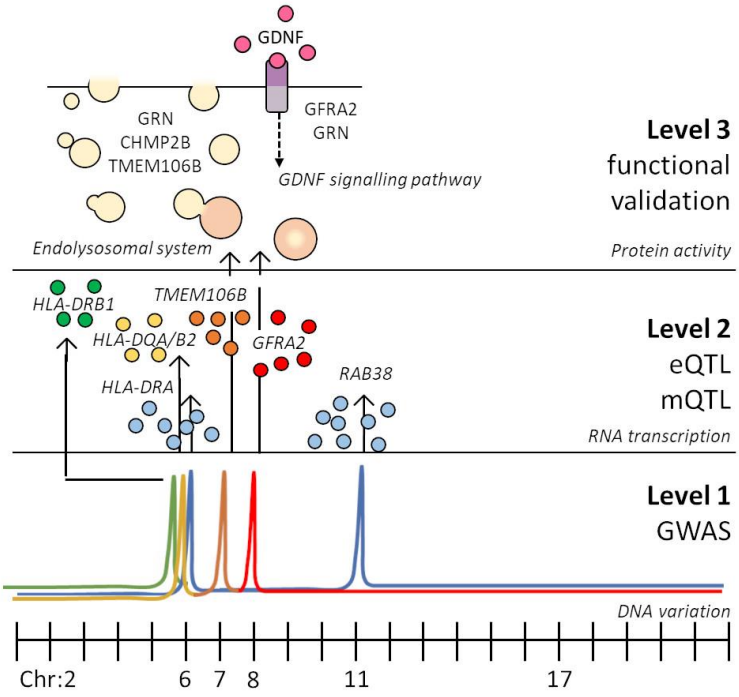
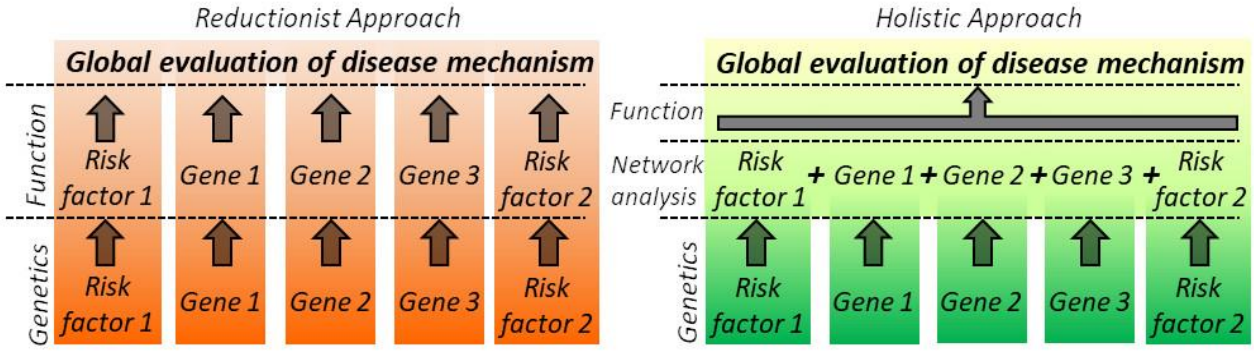


Figure 2



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