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Frontotemporal degeneration genetic risk loci and transcription regulation as a possible mechanistic link to disease risk

Russell P. Sawyer, MD[a,*], Hillarey K. Stone, DO[b,c], Hanan Salim[d], Xiaoming Lu, PhD[d], Matthew T. Weirauch, PhD[d,e,f,g], Leah Kottyan, PhD[c,f,g]

Abstract

The etiology of Frontotemporal Degeneration (FTD) is not well understood. Genetic studies have established common genetic variants (GVs) that are associated with increased FTD risk. We review previous genome wide association studies (GWAS) of FTD and nominate specific transcriptional regulators as potential key players in the etiology of this disease. A list of GVs associated with FTD was compiled from published GWAS. The regulatory element locus intersection (RELI) tool was used to calculate the enrichment of the overlap between disease risk GVs and the genomic coordinates of data from a collection of >10,000 chromatin immunoprecipitation (ChIP-seq) experiments. After linkage disequilibrium expansion of the previously reported tag associated GVs, we identified 914 GV at 47 independent risk loci. Using the RELI algorithm, we identified several transcriptional regulators with enriched binding at FTD risk loci ($0.05 <$ corrected P value $< 1.18 \times 10^{-27}$), including Tripartite motif-containing 28 (TRIM28) and Chromodomain-Helicase DNA-binding 1 (CHD1) which have previously observed roles in FTD. FTD is a complex disease, and immune dysregulation has been previously implicated as a potential underlying cause. This assessment of established FTD risk loci and analysis of possible function implicates transcriptional dysregulation, and specifically particular transcriptional regulators with known roles in the immune response as important in the genetic etiology of FTD.

Abbreviations: FTD = frontotemporal degeneration, GV = genetic variants, GWAS = genome wide association study, RELI = regulatory element locus intersection.

Keywords: frontotemporal degeneration, genetic risk, single nucleotide polymorphism

1. Introduction

Frontotemporal degeneration (FTD) is now recognized as the most common cause of early-onset dementia in people under the age of 60 years.[1] A heterogeneous neurodegenerative disorder presenting with distinct changes in behavior, language and motor function, the heritability and genetics of FTD are complex.[2] Heritability is observed in 12% to 48% of FTD subjects,[3] with most of the heritability attributed to autosomal dominant mutations in progranulin (*GRN*), microtubule-associated protein tau (*MAPT*) and chromosome 9 open reading frame 72 (*C9orf72*).[4,5] The majority of cases, however, do not have an identifiable monogenic cause. Genome wide association studies (GWAS) in FTD have sought to fill the missing heritability gap by identifying common genetic variants (GV) associated with disease risk.[6] While several genomic regions associated with increased FTD risk have been identified, the functional relevance of the GV within these loci remains elusive.[6]

Our goal is to better understand the functional relevance of previously described FTD genetic risk variants. To this end, we first curated the independent association signals identified by previously published GWAS. Then, we performed a linkage disequilibrium expansion step to identify all variants that were tagged by the associated variants reported with significant (or suggestive) p values. We next used our analytical tool regulatory element locus intersection (RELI) to identify critical cell types and transcriptional regulatory molecules based on enrichment of chromatin immunoprecipitation data at disease risk loci. This algorithm assesses the significance of intersections of genomic coordinates of disease risk loci and DNA occupied by

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are publicly available.

Raw data were generated at University of Cincinnati and Cincinnati Childrens Hospital Medical Center. Derived data supporting the findings of this study are available from the corresponding author RPS on request.

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[a] Department of Neurology and Rehabilitation Medicine, University of Cincinnati, Cincinnati, OH, USA, [b] Division of Nephrology and Hypertension, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA, [c] Division of Allergy and Immunology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA, [d] Center for Autoimmune Genomics and Etiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA, [e] Division of Biomedical Informatics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA, [f] Division of Developmental Biology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA, [g] Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA.

**Correspondence: Russell P. Sawyer, Department of Neurology and Rehabilitation Medicine, University of Cincinnati, Cincinnati, OH, 45219, USA (e-mail: sawyerrl@ucmail.uc.edu).*

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transcriptional regulators. The data generated by RELI identify specific regulatory proteins that may be involved in disease pathogenesis, which therefore are good candidates for further experimental investigation. This is an important first step in generating hypotheses to understand the functional relevance of the genetic risk loci identified by genome wide association studies. Collectively, our analyses reveal potential gene regulatory mechanisms underlying the complex etiology of FTD, providing avenues for future studies examining possible therapeutic strategies.

2. Methods

2.1. Identification of independent genetic risk loci

A literature search was performed using PubMed and the NHGRI-EBI GWAS catalog[7] to identify genome wide association studies reporting significant genetic association for FTD. These databases were searched using the terms "FTD", "frontotemporal dementia", "genome wide association", "genomics", and "single nucleotide polymorphisms" on September 28th, 2020. Studies were required to utilize a discovery and validation cohort. Six studies met our search criteria. GVs with "suggestive" p values (uncorrected P value $<5 \times 10^{-8}$) were included in our analysis.[8–13] Starting with the "tag" genetic variant of each reported FTD risk variant (P value $< 5 \times 10^{-8}$), independent risk loci were identified using the "Variant pruning" function of PLINKv1.90b.[14] R^2 is a measure of linkage disequilibrium between GV. We used an R^2 threshold of 0.2 to define independent loci. Only variants on the same chromosome were assessed for linkage disequilibrium because variants on different chromosomes segregate completely independently in meiosis.

2.2. Linkage disequilibrium (LD) expansion

Each independent "tag" genetic variant reported in association studies was used to identify all GV in LD with the "tag" variant with $R^2 > 0.8$ in the ancestry of reported association.

2.3. Pathway analysis of genes near FTD risk loci

Genes within 50 kB pairs of FTD risk loci (Supplementary Tables S7, http://links.lww.com/MD/H591 and S8, http://links.lww.com/MD/H592) were used to identify the biological pathways enriched in this gene set using ENRICHR.[15,16]

2.4. Collection and processing of chip-seq datasets

A collection of 11,071 publicly available ChIP-seq datasets were identified in the Gene Expression Omnibus (GEO) as of February 4th, 2021, and downloaded from the NCBI Sequence Read Archive (SRA). The corresponding experimental data were analyzed using an in-house automated pipeline (https://github.com/MarioPujato/NextGenAligner). Briefly, the pipeline first downloads the SRA files, converts them to fastq files, and runs QC on the files using FastQC (v0.11.2).[17] If FastQC detects adapter sequences, the pipeline runs the fastq files through Trim Galore (v0.4.2),[18] a wrapper script that runs cutadapt (v1.9.1)[19] to remove the detected adapter sequence from the reads. The quality controlled reads are then aligned to the reference human genome (hg19/GRCh37) using bowtie2 (v2.3.4.1).[20] The aligned reads (in.bam format) are then sorted using samtools (v1.8.0)[21] and duplicate reads are removed using picard (v1.89).[22] Finally, peaks are called using MACS2 (v2.1.0),[23] using four different parameter settings (MODE1: callpeak -g hs -q 0.01 -t bamfile, MODE2: callpeak -g hs -q 0.01 --broad -t bamfile, MODE3: callpeak -g hs -q 0.01 --broad --nomodel --extsize 500 -t bamfile, MODE4: callpeak -g hs -q 0.01 --broad --nomodel --extsize 1000 -t bamfile). ENCODE blacklist regions[24] were removed from the called peaks using the hg19-blacklist.v2.bed.gz file available at https://github.com/Boyle-Lab/Blacklist/tree/master/lists.

2.5. Identification of particular transcriptional regulators enriched at risk loci using RELI

We used our RELI algorithm to identify ChIP-seq datasets whose genomic coordinates significantly intersect FTD genetic risk variants.[25] As previously published,[25] all of the genetic polymorphisms in linkage disequilibrium with the "tag" variant at each of the 47 independent FTD risk loci were intersected with ChIP-seq peaks. RELI uses a permutation-based strategy to estimate the significance of the overlap between each LD block and a given ChIP-seq dataset, which we designate the *observed intersection count*. As described previously,[25] this value is compared to the expected intersection distribution. In this procedure, the most strongly associated variant in the LD block is chosen as the reference variant. A distance vector is then generated providing the distance (in bases) of each variant in the LD block from this reference variant. A random genomic variant with approximately matched allele frequencies to the reference variant is then selected from dbSNP, and genomic coordinates of artificial variants are created that are located at the same relative distances from this random variant using the distance vector. Members of this artificial LD block are then intersected with each ChIP-seq dataset, as was done for the observed intersections. This strategy accounts for the number of variants in the input LD block and their relative distances, while prohibiting "double counting" due to multiple variants in the block intersecting the same dataset. We repeat this procedure 2000 times, generating a null distribution. The expected intersection distributions are used to calculate Z-scores and p values for the observed intersection. For each ChIP-seq dataset, only the top-performing peak set of the four MACS2 "modes" is reported, where performance is gauged based on the RELI algorithm corrected P value. Only ChIP-seq datasets with 3 or more FTD risk locus overlaps are reported in Table 1, this threshold was selected given.

2.6. Ethics statement

This study was approved by the Cincinnati Children's Hospital Institutional Review Board.

3. Results

3.1. Literature review and curation of previous studies

There have been limited studies assessing the genetic basis of FTD. To identify all possible candidates, we used Pubmed and the GWAS catalog[7] to identify FTD risk variants from genome wide association studies that reported significant genetic association for FTD. A total of six studies met our search criteria and identified 47 loci with an uncorrected P value $<5 \times 10–8$.[8–13] An expanded table of all reported FTD risk variants without filtering for statistical significance is provided in Supplementary Table S1, http://links.lww.com/MD/H585.

3.2. Inclusion of all possible statistically associated FTD variants

Genetic association studies report "tag" GV representing the most significant association observed at a particular locus. GV are inherited as a haplotype of variants in linkage disequilibrium - independent loci contain variants that are not in strong linkage disequilibrium. Using a linkage disequilibrium cutoff of $r^2 = 0.2$ in the ancestry of identification, we identified 47 independent genetic loci (Supplementary Table S2, http://links.lww.com/MD/

Table 1

Intersection between FTD risk loci and top overlapping transcriptional regulators.

Cell type	Cell line	Molecule	Overlap	Total	Enrichment	Corrected *P* value
HEK293T/17	Adenovirus fetal kidney	ZNF525	3	47	52.68	1.18×10^{-27}
Caki-1	Clear cell carcinoma	KDM5C	3	47	11.64	.0007
AD	Lung adenocarcinoma	CHD1	3	47	10.54	.002
T-47D	Ductal carcinoma	PGR	4	47	7.90	.01
WA01	Embryonic stem cell	TRIM28	11	47	3.37	.04

For this analysis, all the genetic polymorphisms in linkage disequilibrium with the "tag" variant at each of the 47 independent FTD risk loci were intersected with transcriptional regulator ChIP-seq peaks from publicly deposited experimental data. For each ChIP-seq dataset, the cell line, cell type, and molecule are provided. The number of times that the ChIP dataset had a peak that overlapped a genetic variant at an FTD risk locus is indicated ("Overlap"). Only one overlap was counted for each independent risk locus, even when multiple risk variants at the same risk locus overlapped a ChIP-seq dataset (i.e., the maximum overlap is 47). Only the top 5 unique transcriptional regulator datasets with three or more overlaps with independent FTD risk loci are shown. A permutation strategy is used by RELI to identify the significance of the "Overlap". The *P* value is identified based on the permutations of RELI and is calculated from the Z-score. The "Corrected *P* value" gives the *P* value after accounting for multiple testing of the many ChIP-seq datasets.

H586). Next, we identified all common GV in linkage disequilibrium (LD) $r^2 > 0.8$ with the identified risk variants in the ancestry of discovery; this resulted in a total of 914 variants with an average of 19.4 variants per locus. (Supplementary Table S3, http://links.lww.com/MD/H587).

While there are likely only one or two causal variants per FTD risk locus, all the variants within the LD-expanded list are candidates because they are statistically associated with disease risk. Using the National Center for Biotechnology Information's (NCBI) dbSNP database,[26,27] annotations of the position of the LD-expanded FTD risk variants relative to gene coding regions were assessed (Supplementary Table S4, http://links.lww.com/MD/H588). Only 27 variants (0.03%) in 914 LD expanded GV located within coding regions. PolyPhen2[28] and SIFT[29] were used to predict the functional effects of the 15 synonymous variants, one peptide shift variants, and 11 non-synonymous variants. These analyses showed that only two are predicted to cause changes to the resulting protein function by PolyPhen (Supplementary Table S5, http://links.lww.com/MD/H589), while one is predicted to be deleterious by SIFT (Supplementary Table S6, http://links.lww.com/MD/H590). Variant rs2725405 on chromosome 17 was found to be deleterious in both the SIFT model and possibly damaging in the PolyPhen model. The remaining coding variants were not predicted by either algorithm to impact protein function. The remaining 867, which represent the vast majority identified GVs, are in non-coding regions. Overall, these results are consistent with a possible role for alteration of gene regulatory mechanisms at most of the 47 FTD genetic risk loci.

3.3. Identification of genes near risk loci

Gene regulatory regions can affect the expression of genes that are located a great distance away in linear genomic space due to chromatin looping interactions. To create a list of genes whose expression might be affected by FTD risk variants, we identified a total of 62 genes within 50 kb of the list of LD-expanded risk variants (Supplementary Tables S7, http://links.lww.com/MD/H591 and S8, http://links.lww.com/MD/H592). This included several genes previously associated with FTD such as *APOE, HLA-DQA2, HLA-DQB1, HLA-DQB2, HLA-DRA, HLA-DRB5,TMEM106B,* and *TMEM184C*.[30,31] These 62 genes were significantly enriched for immune-related biological pathways defined by Gene Ontology (GO) enrichment terms associated with antigen presentation, T cell receptor signaling, and interferon-gamma associated signaling (Supplementary Table S9, http://links.lww.com/MD/H593). In addition to the immune functions, there was significant enrichment in cholesterol and phospholipid handling: chylomicron remnant clearance, phospholipid efflux, positive regulation of steroid metabolic process, and phosphatidylcholine-sterol O-acyltransferase activator activity.

3.4. Identification of key transcriptional regulators at FTD risk loci

We next applied RELI to a large dataset of transcriptional regulator ChIP-seq datasets. This approach identified five unique transcriptional regulators that overlap at least three out of 47 FTD risk loci, with enrichment ranging from 3.4 to 52.7 times that expected by random chance and corrected *p* values between 0.04 and 1.18×10^{-27} (Table 1). Included in these enriched transcriptional regulators were Tripartite motif-containing 28 (TRIM28), and Chromodomain-Helicase DNA-binding 1 (CHD1), which have previously been implicated in FTD through orthogonal approaches.[32,33] The final list also narrowly excluded Signal Transducer and Activator of Transcription 4 (STAT4), a central mediator of inflammatory signaling. STAT4 overlapped three out of the forty-seven loci, with an enrichment of 8.12, although its corrected *P* value was 0.06. The full results from our RELI analysis with corrected *p* values $<1 \times 10^{-5}$ are provided in Supplementary Table S10, http://links.lww.com/MD/H594.

4. Discussion and conclusions

Although the pathogenesis of FTD remains unclear, current evidence suggests that immune dysregulation and genetic factors play important roles in the development of this complex disease. Genetic association studies have identified several FTD genetic risk variants in *HLA* regions and *RAB38/CTSC* loci in FTD to support these mechanisms.[10,11] While GWAS are valuable tools for understanding the genetic basis of complex traits, there are several limitations to consider. First, although GWAS can be used to identify a region of the genome associated with disease risk, due to linkage disequilibrium these loci almost always represent several potentially causal variants. This makes it difficult to identify specific variants with functional relevance. Furthermore, most risk variants identified by GWAS are in non-coding regions. Thus, it is often unclear how these variants directly contribute to disease pathogenesis. Further functional testing is therefore required in order to fully understand the contributions of risk loci in the etiology of a particular disease.[34]

Results from our analysis demonstrate significant enrichment for GO pathways related to immune function. Specifically, in the adaptive immune system involving antigen presentation, T cell receptor signaling, and interferon-gamma associated signaling. Altered antigen presentation in microglial and peripheral immune cells has been shown to create a pro-inflammatory environment that stimulates neurodegeneration.[35] Additionally, interferon-gamma associated signaling is critical for social behavior; mice deficient in adaptive immunity exhibit social deficits and hyper-connectivity of fronto-cortical brain regions.[36] These two factors are possible causes for the frequent immune dysfunction seen in FTD.[11,37] Another potential pathophysiologic

mechanism is tau hyperphosphorylation; interferon-gamma (which signals through STAT4) has been shown to induce tau hyperphosphorylation, a key pathologic event in FTD due to tauopathies, in two mouse models.[38,39]

In addition to enrichment in immune function, we also found that GO pathways related to lipid and cholesterol handling/metabolism were enriched. Recent evidence has found higher serum low-density lipoprotein in the behavioral variant of FTD compared to Alzheimer's disease as well as healthy aging.[40] Though it remains unclear whether this is part of the pathophysiology of FTD or a result of increased appetite, as the elevated LDL levels were positively correlated with increased appetite and eating score.[40] Recently it was shown that the total serum HDL concentration was decreased in autosomal dominant FTD carriers when compared to non-carriers and, decreased concentrations of HDL particles of different sizes and subclass were consistently observed.[41] Though the etiology for this remains unclear. Regarding lipid handling, total abundance of triglyceride was increased significantly in the behavioral variant of FTD, whereas phosphatidylserine and phosphatidylglycerol decreased significantly in the behavioral variant FTD.[40] Our findings may provide insights into the mechanisms for altered cholesterol and lipid handling in FTD, serving as a novel direction for FTD research.

Our analysis identified several unique transcriptional regulators with significant enrichment at FTD disease risk loci. *TRIM28*, *KDM5C*, *ZNF525*, and *CHD1* are highly expressed in the brain as well as the immune system, further supporting a possible role of transcriptional regulation in this disease.[42] These transcriptional regulators have all been previously linked to dementia or other neurologic disorders, and therefore it is plausible that they may be involved in the genetic etiology of FTD. Tripartite motif-containing 28 (*TRIM28)* has previously been shown to regulate tau levels, as well as stabilize and promote nuclear accumulation and toxicity of tau, with the reduction of *TRIM28* reducing toxicity in animal models of tau-mediated neurodegeneration.[43] *KDM5C* has previously been associated with X-linked intellectual disability with apathy and socially inappropriate behaviors.[44,45] Because FTD is also associated with apathy and socially inappropriate behaviors, albeit later in life, it is unsurprising that *KDM5C* is associated with both FTD and X-linked intellectual disability. TAR DNA-binding protein 43, the pathologic hallmark of the majority of FTD cases (along with hyperphosphorylated tau), has been found to impair the induction of multiple key stress genes required to protect from disease by reducing the recruitment of the chromatin remodeler Chromodomain helicase DNA binding protein 1 (*CHD1*) to chromatin in animal models of FTD and amyotrophic lateral sclerosis.[32] CHD1 depletion robustly enhances TDP-43-mediated neurodegeneration and promotes the formation of stress granules.[32] Upregulation of *CHD1* restores nucleosomal dynamics, promotes normal induction of protective stress genes, and rescues stress sensitivity of TDP-43-expressing animals.[32] Therefore, depending on the underlying FTD pathology (tau vs TDP-43) there may be different transcriptional regulators with altered activity: TRIM28 or CHD1.

This study has several limitations. First, interpretation of GWAS results is challenging because the resulting genetic loci are largely located in non-coding regions, and therefore it is difficult to predict and validate their mechanistic roles. Furthermore, genetic association studies do not identify single GVs, but rather nominate a set of variants that are in linkage disequilibrium with one or more causal variant(s). Studies using larger populations are therefore needed to identify more robust associations. In addition, many currently identified FTD genetic risk loci are in the highly complex HLA region, further hindering the task of understanding the genetic etiology of the disease. Furthermore, there is a lack of ChIP seq data in neuronal and microglial cells, which are the most likely effectors of disease in FTD, resulting in a substantial missing data problem.

Our results have identified several transcriptional regulators that may play a role in the etiology of FTD. This focused list of regulatory proteins can now be used in ChIP-seq experiments using cells from patients with FTD. This important first step supports the role of immune associated transcriptional regulators in the pathogenesis of this complex disease and will help guide further studies evaluating the functional relevance of genetic risk loci in FTD.

Author contributions

Study conception and design: HKS, LCK, MTW, RPS; literature review: RPS; bioinformatic design, development, and analysis: RPS, LCK, MTW; data analysis/interpretation: RPS, HKS, HS, XL, LCK, MTW; drafting of manuscript: HKS, RPS. Each author contributed important intellectual content during manuscript drafting or revision, accepts personal accountability for the author's own contributions, and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Conceptualization: Russell P. Sawyer, Matthew T. Weirauch, Leah Kottyan.
Data curation: Hanan Salim.
Formal analysis: Hillarey K. Stone, Hanan Salim, Xiaoming Lu, Matthew T. Weirauch, Leah Kottyan.
Methodology: Hillarey K. Stone, Matthew T. Weirauch.
Writing – original draft: Russell P. Sawyer.
Writing – review & editing: Russell P. Sawyer, Hillarey K. Stone, Hanan Salim, Xiaoming Lu, Matthew T. Weirauch, Leah Kottyan.

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