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# Effects of Multiple Genetic Loci on Age at Onset in Frontotemporal Dementia

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**Abstract.**

In frontotemporal dementia (FTD), age at disease onset (AAO) is unpredictable in both early and late-onset cases; AAO variability is found even in autosomal dominant FTD. The present study was aimed at identifying genetic modifiers modulating AAO in a large cohort of Italian FTD patients. We conducted an association analysis on 411 FTD patients, belonging to 7 Italian Centers, and for whom AAO was available. Population structure was evaluated by principal component analysis to infer continuous axes of genetic variation, and single linear regression models were applied. A genetic score (GS) was calculated on the basis of suggestive single nucleotide polymorphisms (SNPs) found by association analyses. GS showed genome-wide significant slope decrease by  $-3.86$  (95%CI:  $-4.64$  to  $-3.07$ ,  $p < 2 \times 10^{-16}$ ) per standard deviation of the GS for 6 SNPs mapping to genes involved in neuronal development and signaling, axonal myelination, and neurotransmission. An increase of the GS was associated with a decrease of the AAO. Our data indicate that there is indeed a genetic component that underpins and modulates up to 14.5% of variability of AAO in Italian FTD. Future studies on genetic modifiers in FTD are warranted.

Keywords: Age at onset, frontotemporal dementia, GWAS, polymorphism

## INTRODUCTION

Frontotemporal dementia (FTD) is a neurodegenerative disorder characterized by behavioral abnormalities, impairment of executive functions, and language deficits [1]. Mutations in the Granulin (GRN), C9orf72, or Microtubule Associated Protein Tau (MAPT), and, recently, the TANK binding kinase 1 (TBK1) genes drive up to ~40% of Mendelian cases [2]; for the remaining cases, multiple loci and genes appear to influence FTD risk with rather small effect size [3, 4].

The clinical, pathological, and genetic profiles, as well as the age at onset (AAO), are highly heterogeneous in FTD. FTD is considered the most common neurodegenerative dementia in the young adulthood along with Alzheimer's disease with a mean onset age between late 50s and early 60s [5]; however, recent reports suggested an increased span in the range of disease onset up to >70 years of age [6, 7]. Similarly, variability of AAO is found in autosomal dominant FTD [8–11].

Genetic variants may influence and/or modulate specific features of a disorder, including disease onset and progression. Indeed, AAO, which is rather unpredictable in FTD, might associate with a genetic structure that contributes to an earlier or later disease development.

We recently carried out a genome-wide association study (GWAS) in FTD patients from Italy, and identified an extended number of genetic risk factors associated with disease in the Italian population [3].

In the present work, we sought to explore whether such risk factors might influence disease onset in the Italian FTD population by searching for genetic variants associated with age at disease onset, and computing a genetic risk score (GS) to stratify age of disease susceptibility.

## **METHODS**

### **Subjects**

Genotyping data of DNA samples diagnosed with FTD were available to us from the FTD-GWAS dataset [4]. Our association analysis was carried out on 411 FTD patients, belonging to 7 Italian Centers (see Supplementary Table 1), already included in our previous study [3] and for whom AAO was available.

Diagnosis of FTD, and FTD subtypes (i.e., behavioral variant FTD and primary progressive aphasia), was made according to current clinical criteria [12,13]. Estimated AAO was referred by the proxy caregiver by a semi-structured interview, and carefully recorded.

Informed consent and Ethic Committee approval were obtained at the individual sites and each center provided consent for their use for the purposes of this study. The cases were collected and genotyped at the University College London (UCL) by means of Illumina human 660K-Quad Beadchips assayed on the Illumina Infinium platform (Illumina, San Diego,CA, USA); 657231 single nucleotide polymorphisms (SNPs) were genotyped.

### ***Quality control***

Quality control (QC) was performed at both markers (per-marker) and samples (per-individual) level, as previously illustrated by Anderson et al. [14]. Specifically, per-marker QC of the data consisted of three different steps, namely 1) the identification and removal of SNPs with an excessive missing genotype ( $> 0.1$ ); 2) the identification and removal of SNPs with significant deviation from Hardy-Weinberg equilibrium (HWE) ( $p \leq 0.001$ ); and 3) the removal of all markers with a very low minor allele frequency (MAF) ( $MAF < 0.05$ ). Per-individual QC of the data consisted in identifying and removing of 1) the individuals with discordant sex information; 2) the individuals with outlying missing genotype (genotype failure rate  $\geq 0.03$ ); and 3) heterozygosity rate  $\geq 3$  standard deviations from the mean.

### ***Principal component analysis***

Population structure was evaluated by principal component analysis (PCA) to infer continuous axes of genetic variation. PCA was processed on the similarity matrix between any two individuals ( $i, j$ ), based on the genome-wide average proportion of alleles sharing identical by state (IBS) and using for the SNPs the additive coding (0, 1, 2 minor frequency alleles). We excluded outlier samples, defined as individuals exceeding a default number of standard deviations (6.0) from the whole sample. The 657,231 SNPs were reduced to 125,902 SNPs for IBS computation, by trimming the dataset so that no pair of SNPs (within a given number of base-pairs) had Linkage Disequilibrium (LD, measured by  $r^2$ ) greater than 0.2. PC axes were considered significant according to Tracy-Widom statistic [15].

### ***Linear regression model***

We used markers of highest quality to impute with Minimac [16] approximately 2.5 million SNPs, based on European-ancestry haplotype reference (HapMap II CEU population build 36, release 22). Imputed SNPs with a  $MAF < 0.01$ , and with low imputation quality ( $R_{sq} < 0.50$ ) were removed (for Minimac protocol details, see <http://genome.sph.umich.edu/wiki/Minimac> : 1000 Genomes Imputation Cookbook).

We then tested each available SNP (observed and imputed) to assess the association with AAO by using  $p$ -values (two-tailed) from a linear regression model (LRM), with an additive coding per SNP, and adjusting for sex and significant principal components. The fixed threshold for genome-wide significance was set at the consensus level of  $p < 5 \times 10^{-8}$ . We defined SNPs as suggestive if  $5 \times 10^{-5} > p > 5 \times 10^{-8}$ . We performed this analysis in presence and absence of apolipoprotein E (APOE)  $\epsilon_4$  homozygous carriers and also used APOE  $\epsilon_4$  as a covariate to assess and/or correct for any potential influence of this genetic marker on final results.

### ***Genetic score computation***

The suggestive SNPs obtained by association analysis were used to calculate a weighted genetic risk score (GS). Specifically, GS was defined as sum of the number of minor frequency alleles (0 (not present), 1 (heterozygous), 2 (homozygous)) per suggestive SNPs weighted by their log OR, i.e., the odds ratio (OR) estimate derived from our previous case-control study [4]. Thus, the weights were determined independently from the genetic-AAO association of this work, eluding over fitting biases. We defined three trimming rules for inclusion of SNPs in the GS: 1) SNPs with moderate to high case-control signal ( $\log ORs > \log(1.2)$ ), recoding all negative logOR into positive logOR on the basis of the risk allele; 2) SNPs observed or imputed with high quality ( $Rsq > 0.9$ ); and 3) SNPs in Linkage Equilibrium (LE). For SNPs in Linkage Disequilibrium, the SNP with the lowest AAO p -value was selected.

Then, GS was standardized as  $Z = (GS - \text{mean}(GS)) / \text{standard deviation}(GS)$ , and LRM of AAO on the standardized GS was performed adjusting for the following covariates: i) sex, ii) population structure (measured by geographical zone such as North, Center, South and/or by significant principal components), iii) type of FTD (5 subtypes: bvFTD, SD, PNFA, FTD-MND, and FTD spectrum), and iv) APOE (0 =  $\_23\_23$ , 1 =  $\_23\_4$ , 2 =  $\_4\_4$ ). QC analysis and statistical analyses were performed by free software PLINK [17] and R [18], respectively. Gene annotation on top-associated markers was performed by R package NCBI2R [19].

## **RESULTS**

AAO was available for 411 out of 532 FTD patients that underwent Italian GWAS [3]. The mean AAO was  $63.7 \pm 20.7$  (range, 36.0 – 82.0) with male/female ratio 187/224 (male 45.5%). Two hundred-fifty patients came from Northern Italy, 49 patients from the Center, and 112 from Southern Italy. Out of 411 FTD patients, 307 had bvFTD, 82 PPA, 20 FTD-MND, and 2 belonged to the FTD spectrum. A minority of cases, for which FTD genes had been screened, carried variants



in MAPT (n = 4), GRN (n = 38), and C9orf72 (n = 11). Two MAPT and one GRN variants are now reported to be pathogenic, whilst the remaining ones are common polymorphisms; considering that the mutations have very small frequency in the current sample set, thus they are negligible, and that, together with the C9orf72 positive cases they were kept in the previous studies [3, 4], we also kept and included them in our current analysis.

Population structure through PCA showed genetic pattern that correlated with geographical provenience (i.e., North, Center, and South), as displayed in the scatter plot of the first two PCs (Fig. 1). According to Tracy-Widom statistics, that tests additional population structure of the first 10 eigenvalues, only the first PC (TW1 = 5.03480,  $p < 0.001$ ) was deemed significant and used as covariate in AAO association analyses to correct for population stratification.

By single linear regression analysis, we identified suggestive evidence ( $p < 5 \times 10^{-5}$ ) of an association with AAO for 127 SNPs (using sex and first PC as covariates), while none achieved genome-wide significance (see Manhattan plot in Fig. 2).

As defined in the method section, log OR weighted GS was computed after three trimming rules identifying 6 SNPs mapping to the following loci: intergenic region on chromosome (chr) 1 encompassing the G protein-coupled receptor 137B (GPR137B) and the Endoplasmic Reticulum Oxidoreductase Beta (ERO1B) genes; chr 2, intronic to the Hypocalcinlike1 (HPCAL1) gene and LOC730100 (which is proximal to Neurexin 1 (NRXN1)); chr 9, intronic to the Protein Tyrosine Phosphatase, Receptor Type D (PTPRD) gene, and; chr 13, in LOC101926897, LOC105370219 and LOC105370220, and LOC105370290 and LINC00375 (Table 1).

Linear regression analysis of AAO based on the score effect of these 6 markers (GS), adjusted for covariates (see method), showed genome-wide significant slope decrease by  $-3.68$  (95%CI:  $-4.52$  to  $-2.84$ ,  $p < 2 \times 10^{-16}$ ) per standard deviation of the GS meaning that an increase of the GS was associated with a decrease of the AAO. When we excluded APOE  $\epsilon_4$  homozygous carriers from our analysis there still was a similar genome-wide significant slope decrease, and when using APOE  $\epsilon_4$  as a covariate results were again not affected indicating that effect on AAO is

independent from the APOE status.

Of note, considering all the predictors (GS + covariates) we found that total contribution ( $R^2$ ) to AAO variance was  $\sim 22\%$  where only gender and PC1 were the actual significant covariates contributing to AAO variance in addition to GS in the value of  $\sim 7\%$ .

Therefore and in summary, the AAO variance explained by GS only (excluding the covariates) reached  $\sim 14.5\%$ . The AAO-GS association is visualized and summarized in Fig. 3 and Table 2, respectively. For overfitting control, we also computed the prediction error (PE) by Leave-One-Out method ( $K = n$ ), and  $K= 10$ -fold Cross-Validation: the corresponding  $R^2$  were  $13.7\%$ , and  $14.2\%$ , respectively. Finally, backward stepwise analyses in the GS showed that  $7.8\%$  of this signal was driven by the AAO-associated SNPs in HPCAL1 and PTPRD .

## **DISCUSSION**

FTD is a complex disorder that encompasses heterogeneous phenotypes and variable AAO. Our current study supports the notion that individual genetic background modifies age at disease onset and modulates disease presentation.

We computed a genetic score (GS) able to weight the genetic contribution to the variability of AAO in FTD (the higher the GS, the lower the age at disease onset). Particularly, the GS of six SNPs indicated significant genetic contribution for up to  $14\%$  of variability of AAO in FTD. This is remarkable as it suggests that the genetic component underlying variability of AAO has a robust implication in FTD comparatively, for example, to Parkinson's disease for which a similar study approach revealed that their GS only contributed to  $0.6\%$  of variability of AAO [20]. Similar observations for Parkinson's disease were made in other studies [21]. Conversely, a recent study in Alzheimer's disease showed that either APOE or a combination of nine loci contributed to  $3.7\%$  and  $2.2\%$  of variability of AAO, respectively [22], whereas in our current study the contribution of the APOE status was basically negligible. Taken all this together, we gather that in FTD the genetic component appears to have a stronger influence on AAO prediction than in

Parkinson's disease and in Alzheimer's disease [20–22].

Considering the 6 loci that we identified influencing AAO in FTD, the literature suggests, particularly for NRXN, HPCAL1 , and PTPRD , a direct link with the biology of the brain through calcium-mediated neuronal signaling, development of neocortical regions as well as axonal myelination and glutamatergic/GABAergic synapses, respectively [23–26].

It is interesting to gather that variability in these genes, and their associated functions and processes, could underpin the modulation of disease onset in FTD. In addition, it is noteworthy that GPR137B was previously shown to associate with modulation of drug-response in schizophrenia, particularly mediating effect of antipsychotics on working memory [27].

NRXN1 has been implicated in neocortical development and aging [23], and NRXN1 genetic variations affect the risk of autism and schizophrenia [28, 29].

Of note, we reported the locus including NRXN1 already in our previous work highlighting novel suggestive loci for FTD in the Italian population [3]; here, we provide further support for this association and expand on its potential implication in driving AAO. All the more, in the previous [3] and the current work, the OR associated with SNPs at the NRXN1 locus were among the highest, 2.5 and 1.64, respectively, suggesting that variability at this locus might associate with disease as well as AAO with a moderate effect size. Moreover, a close relationship between NRXN1 and one of the main actors of FTD pathogenesis, namely TDP-43 protein, was recently shown: a novel miRNA (miR-NID1) processed from the intron 5 of NRXN1 is able to repress NRXN1 expression by binding to TDP-43, thus this complex (TDP-43 + miR-NID1) might hold relevance and be implicated in FTD-TDP pathology [30].

In the same view, HPCAL1 , a gene encoding the HPCAL1 protein that modulates calcium-mediated neuronal signaling [25], has been implicated in the risk of Alzheimer's disease and autism development [31, 32], thus supporting a general involvement in neurodegenerative disease,

including FTD, and PTPRD has been associated with obsessive-compulsive disorders [26]. Currently, there are no known relationships with conditions affecting the brain for ERO1B (involved in protein oxidative folding) [33], while the role of LOC101926897 , LOC105370219 and LOC105370220 , and LOC105370290 and LINC00375 appear to be more complicated to infer, given that the latter are non-coding RNAs, which belong to a different group of cellular functional elements, rather involved in transcription and/or translation regulation. Nevertheless, this piece of data raises the awareness that non-coding functional elements are important and deserve attention, fostering the implementation of study designs and analysis strategies that focus and shed light on such regulatory elements.

Our study overall suggests and supports the relevance of factors that modulate features of FTD; this goes along with other examples of common risk variants acting as genetic modifiers in Mendelian FTD such as TMEM106B . The latter has been reported as a genetic modifier affecting both AAO and circulating levels of progranulin in FTD patients carrying Granulin mutations [34, 35].

Another example of genetic modifiers of AAO is the one recently reported in PSEN1 -related Alzheimer's disease [36].

In summary, we herein describe an additive effect of 6 SNPs and their likely implication in modulating disease onset in Italian FTD patients, for which we further considered the genetic make-up of Italian regions (i.e., North, Center, and South) as possible confounder in the analyses, when a Mendelian trait was excluded a priori .

Our data indicate that there is a genetic component that underpins and modulates up to 14.5% of variability of AAO in Italian FTD.

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## **SUPPLEMENTARY MATERIAL**

The supplementary material is available in the electronic version of this article: <http://dx.doi.org/10.3233/JAD-160949>.

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