Long Non-Coding RNA Profile in Genetic Symptomatic and Presymptomatic Frontotemporal Dementia: A GENFI Study

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Abstract.

Background: Long non-coding RNAs (lncRNAs) play crucial roles in gene regulation and are implicated in neurodegenerative diseases, including frontotemporal dementia (FTD). However, their expression patterns and potential as biomarkers in genetic FTD involving Chromosome 9 Open Reading Frame (*C9ORF72*), Microtubule Associated Protein Tau (*MAPT*), and Progranulin (*GRN*) genes are not well understood.

Objective: This study aimed to profile the expression levels of lncRNAs in peripheral blood mononuclear cells collected within the GENetic Frontotemporal dementia Initiative (GENFI).

Methods: Fifty-three lncRNAs were analyzed with the OpenArray Custom panel, in 131 patients with mutations in *C9ORF72*, *MAPT*, and *GRN*, including 68 symptomatic mutation carriers (SMC) and 63 presymptomatic mutation carriers (PMC), compared with 40 non-carrier controls (NC).

Results: Thirty-eight lncRNAs were detectable; the relative expression of NEAT1 and NORAD was significantly higher in *C9ORF72* SMC as compared with NC. GAS5 expression was instead significantly lower in the *GRN* group versus NC. *MAPT* carriers showed no significant deregulations. No significant differences were observed in PMC. Disease duration did not correlate with lncRNA expression.

Conclusions: NEAT1 and NORAD are upregulated in *C9ORF72* SMC and *GAS5* levels are downregulated in *GRN* SMC, underlining lncRNAs' relevance in FTD and their potential for biomarker development. Further validation and mechanistic studies are crucial for clinical implications.

INTRODUCTION

Long non-coding RNAs (lncRNAs) are RNA molecules encompassing more than 200 nucleotides. They do not possess canonical open reading frames[1] and are not the product of alternative splicing of a coding gene.[2] LncRNA regulates gene expression in neurodegenerative diseases. The majority of studies have been carried out in Alzheimer's disease (AD). For example, it has been shown that the lncRNA amyloid-β cleaving enzyme-1 antisense, named *BACE1-AS*, is transcribed from the opposite strand of *BACE1* gene, and can form an RNA duplex. It binds to the BACE1 mRNA to improve its stability and translation, positively regulating the expression of BACE1 protein and promoting an increase in the cleavage of the amyloid-β protein precursor.[3] Moreover, the lncRNA Brain Cytoplasmic 200 (BC200) was found to be upregulated in brain tissues from patients with AD and it has been shown that it enhances the production of amyloid protein through the regulation of *BACE1* expression.[4] Few data on the role of lncRNAs in other neurodegenerative disorders, including frontotemporal dementia (FTD) are available, although it is known that they are involved in a number of common mechanisms, such as inflammation, oxidative damage and synaptic dysfunction (see[5] for review).

FTD encompasses several clinical syndromes. The most common is the behavioral variant (bv)FTD, characterized by the development of behavioral disturbances, aggressiveness, lack of empathy, and decline in social conduct, followed by non-fluent variant primary progressive aphasia (nfvPPA) and semantic variant (sv)PPA. About 50% of FTD cases display a family history for dementia, often with dominant traits.[6] At histopathology, all syndromes described are collectively classified as frontotemporal lobar degeneration (FTLD). According to the type of protein depositing, FTLD is classified into FTLD-Tau, FTLD-TAR DNA Binding protein (TDP)43, and FTLD fused in Sarcoma (FUS).[7] Three major causal genes responsible for autosomal dominant inherited FTD have been discovered so far, including microtubule associated protein tau (*MAPT*), characterized by the deposition of tau protein in the brain, progranulin (*GRN*) and chromosome 9 open reading frame 72 (*C9ORF72*), both characterized by deposition of TDP-43. *MAPT* carriers quite often develop bvFTD with parkinsonism, whereas *GRN* mutations are associated with phenotypic heterogeneity, including the classical syndromes but also atypical presentations such as corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP).[8] The *C9ORF72* expansion instead may present not only with FTD but also with amyotrophic lateral sclerosis (ALS), or both, and is often associated with late onset psychosis.[9]

In FTD and ALS the lncRNAs nuclear paraspeckle assembly transcript 2 (NEAT2) and Metastasis Associated Lung Adenocarcinoma Transcript 1 (MALAT1) co-localize at nuclear paraspeckles with TDP-43 and FUS proteins.[10] Moreover, the binding to TDP-43 is markedly higher in brains from demented patients.[10] The expression of 84 lncRNAs was analyzed in serum samples from genetic and sporadic FTD. Despite the statistical threshold was not reached due to limited sample size, the results showed a generalized deregulation of lncRNA expression levels in both genetic and sporadic FTD as compared with non-demented controls. In detail, a trend toward downregulation was observed in *GRN* and *C9ORF72* patients, whereas a trend toward upregulation was observed in *MAPT* mutation carriers. Notably, a few lncRNAs, including hepatocellular carcinoma upreg-

Table 1
Demographic and clinical characteristics of the study population

	Non carriers (NC)	Presymptomatic mutation carriers (PMC)	Symptomatic mutation carriers (SMC)
Subjects (*n*)	40	63	68
Age, mean years (SD)	53 (15)	42 (11)	65 (8)
Age at onset, mean years (SD)	–	–	61 (8)
Gender distribution, females:males	27 : 13	36 : 27	28 : 40
Mutated gene *n* (%)			
GRN		22 (35)	22 (32)
C9ORF72		21 (33)	24 (36)
MAPT		20 (32)	22 (32)
Age at onset, mean years (SD)			
GRN			64 (7)
C9ORF72			59 (9)
MAPT			54 (6)
NfLpg/ml (SEM)	8.53 (0.18)	16.21 (2.83)	56.05 (3.81)*
GFAP pg/ml (SEM)	103.15 (10.21)	107.42 (6.12)	175.44 (9.32)**

*$p = 0.002$; **$p < 0.001$.

ulated EZH2-associated (HEIH), Eosinophil Granule Ontogeny Transcript (EGOT), and NEAT1, were downregulated in all groups.[11] The origin of circulating lncRNAs is not known and no studies on lncRNA in circulating cells are available so far.

Here, we show results of profiling of lncRNAs in peripheral blood mononuclear cells (PBMC) from the very well characterized genetic GENFI cohort. To our knowledge, a large study of these molecules has not been carried out yet in genetic FTD, which represent the best model of the disease as the pathology can be predicted in life.

MATERIALS AND METHODS

Population

All demographic and clinical data, as well as samples included in the study, were collected within the Genetic frontotemporal dementia initiative (GENFI), a natural history study of genetic FTD involving several research centers across Europe and Canada (http://www.genfi.org.uk).[12] The GENFI study was performed in accordance with the Declaration of Helsinki, reviewed and approved by all countries' respective Ethics Committees and all participants signed an informed consent to take part in the research. This research study was performed in Italy, Ethics Committee Milano Area 2, parere 882_2022 del 13-9-22.

Variables included were: age at sampling, age at onset, Gender, mutation group (symptomatic mutation carriers, SMC; presymptomatic mutation carriers, PMC; non-carrier family members con-

sidered as controls, NC), mutated gene (*MAPT*, *GRN*, *C9ORF72*). One hundred and seventy-one PAX gene samples were collected, including 68 SMC (22 *MAPT*, 22 *GRN*, and 24 *C9ORF72*), 63 PMC (20 *MAPT*, 22 *GRN*, and 21 *C9ORF72*) and 40 NC. Carriers of other rare FTD causing mutations were not included. Demographics of the population are shown in Table 1.

Sample processing

PAX gene tubes were stored and frozen according to the manufacturer. RNA was extracted using the PAX Gene blood miRNA kit that enable the extraction of total RNA including small ncRNA, according to the protocol of the manufacturer (Qiagen).

The quality and quantity of the extracted RNA were assessed using a Bioanalyzer 2100. The RNA Integrity Number (RIN) was determined, with values ranging from 7.9 to 8.4 across the samples, indicating that the RNA is of sufficient quality for further analysis (Supplementary Figure 1). Extracted RNA was stored at –80°C until use.

Retrotranscription and real-time PCR

Total RNA was retrotranscribed with the Super-Script VILO cDNA Synthesis Kit. The OpenArray Custom panel, comprising a total of 56 lncRNA genes (53 target genes and three housekeeping genes: *B2M*, *ACTB* and *GAPDH*, Supplementary Table 1) was used following the manufacturer's instructions (Thermofisher, 2012). The reproducibility between real-time PCR experiments was assessed by including the same cDNA sample in each run.

Plasma neurofilament light chain and glial fibrillary acidic protein

Plasma neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP) levels were measured on the SIMOA HD-1 Analyzer as previously described.[13]

Statistical analysis

Data were analyzed using the statistical spreadsheets Jamovi v 2.5.6.0 (https://www.jamovi.org). LncRNA expression levels (expressed as replicate $2^{-\Delta Ct}$ values for each gene) and gender were considered continuous variables and expressed as mean ± standard deviation (SD). Conversely, gender, biological group (no mutations, *MAPT*, *C9ORF72*, and *GRN*, respectively) and genetic status (NC, PMC, and SMC, respectively) were all considered categorical variables. Significant statistical threshold was set at 0.05. Shapiro–Wilk's test of normality was performed for continuous variables, and intergroup comparisons were carried out using ANCOVA test (gender and age as covariates). Post hoc analyses for multiple comparisons were performed with Tukey's correction. The Pearson test was applied for correlations between deregulated lncRNAs and NFL and GFAP protein levels.

RESULTS

Thirty-eight lncRNAs out of 53 were detectable. Among those, the relative expression of two lncRNAs, NEAT 1 and NORAD, were upregulated in *C9ORF72* biological group.

In particular, the ANCOVA analysis of NEAT1 showed that the overall model yielded a significant result ($p = 0.003$), indicating that these variables collectively explain a significant portion of the variance in $2^{-\Delta Ct}$. Biological group showed a significant effect ($F(3,96) = 5.35$, $p = 0.003$, $\acute{\eta}^2\ p = 0.143$), suggesting differences in $2^{-\Delta Ct}$ levels among the groups. Specifically, the *C9ORF72* group differed significantly from others in post hoc comparisons (0.098 ± 0.01 versus 0.04 ± 0.05-fold regulation, $t(96) = -2.66$, $p = 0.043$) compared to NC. As expected, age also had a significant influence ($p = 0.046$), indicating that older age was associated with altered $2^{-\Delta}$Ct levels, but the interaction between biological group and age was not statistically significant ($p = 0.256$). Stratifying results according to genetic status, the comparison between *C9ORF72* SMC

and NC showed a statistically increased of NEAT1 $2^{-\Delta Ct}$ values (0.12 ± 0.01 versus 0.04 ± 0.01-fold regulation versus NC, $t(43) = -2.49$, $p = 0.043$, Fig. 1).

Concerning NORAD analysis, the overall model was significant ($P < 0.001$), indicating substantial variability explained by these variables. Biological group significantly impacted $2^{-\Delta Ct}$ levels ($F(3,99) = 5.61$, $p = 0.001$, $\acute{\eta}^2 p = 0.145$), highlighting variability across NC, *MAPT*, *C9ORF72*, and *GRN* groups. Post hoc tests revealed that NORAD was significantly more abundant in *C9ORF72* biological group as compared with NC (0.014 ± 0.01 versus 0.0038 ± 0.00391-fold regulation, $t(99) = -2.49$, $p = 0.041$), but stratifying according to genetic status, the comparison between NC and *C9ORF72* SMC showed a trend towards significance ($p = 0.065$), suggesting potentially meaningful differences (Fig. 3).

In *GRN* biological group, one lncRNA, namely Growth Arrest Specific (GAS)5 was significantly lower than NC. The overall model was significant, indicating that the predictors collectively explain a significant portion of the variance in the dependent variable ($p < 0.001$). Age had a significant effect ($p < 0.001$), as did the biological group ($F(3,105) = 3.65$, $p = 0.015$, $\acute{\eta}^2 p = 0.095$). However, nor did the interaction between biological group and age ($p = 0.142$). Post hoc comparisons using the Tukey test revealed that the *GRN* group significantly differed from NC ($9.20 \times 10^{-4} \pm 0.0011$ versus $0.037 \times 10^{-2} \pm 0.1 \times 10^{-3}$, fold regulation, $t(105) = 3.14$, $p = 0.025$). In *GRN* biological group GAS5 was significantly lower, also stratifying results according to genetic status and after post hoc analysis (SMC versus NC; 0.00164 ± 0.0019 versus 0.013 ± 0.024, fold regulation, $t(55) = 2.78$, $p = 0.020$, Fig. 3).

Conversely, no significant lncRNA deregulations were observed in *MAPT* carriers, both SMC and PMC, versus NC.

No correlations between disease duration in symptomatic individuals and lncRNA relative expression was found ($p > 0.05$).

Considering NfL and GFAP levels, as expected, significant increases were observed between SMC and NC: NfL mean levels ± SEM were $56.05 \pm 3,81$ versus 8.53 ± 0.18 pg/ml, $p = 0.002$ and GFAP were 175.44 ± 9.32 versus 103.15 ± 10.21 pg/ml, $p < 0.0001$, respectively (Table 1). These differences in mean values remained significant even when stratifying symptomatic patients by the mutated gene ($p < 0.001$).
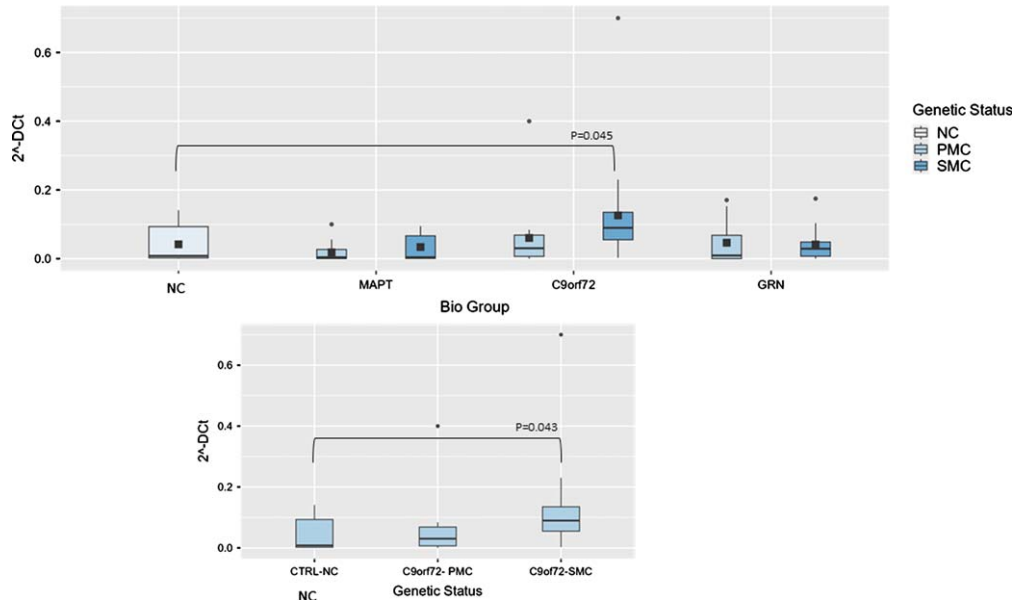
Fig. 1. Box plots of NEAT1 profiling in PBMC from SMC and PMC carrying mutations in *C9ORF72, GRN, MAPT* as compared with NC. Data are expressed as $2^{-\Delta Ct}$ fold regulation.
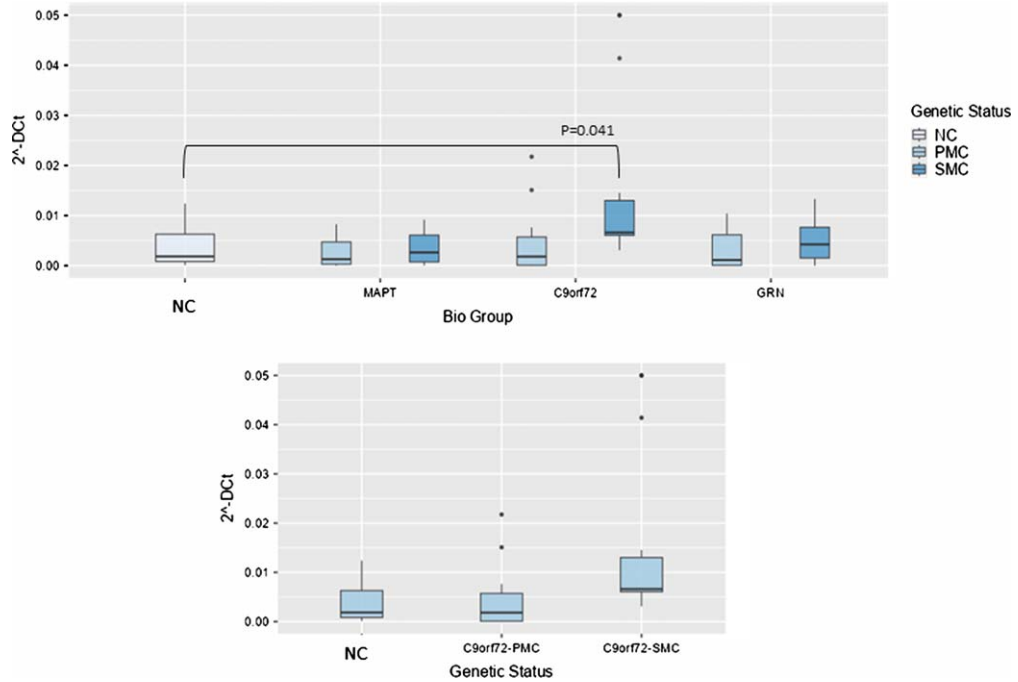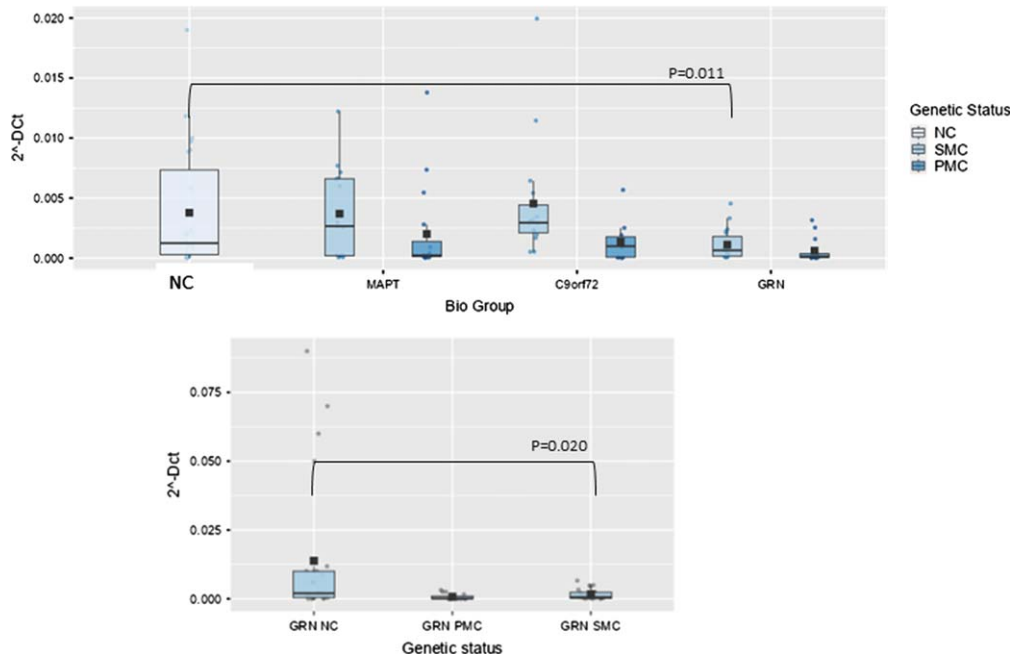

Fig. 2. Box plots of NORAD profiling in PBMC from SMC and PMC carrying mutations in *C9ORF72, GRN, MAPT* as compared with NC. Data are expressed as $2^{-\Delta Ct}$ fold regulation.

Fig. 3. Box plots of GAS5 profiling in PBMC from SMC and PMC carrying mutations in *C9ORF72, GRN, MAPT* as compared with NC. Data are expressed as $2^{-\Delta Ct}$ fold regulation.

Considering instead the levels of NfL or GFAP and the lncRNAs, no significant correlations emerged ($p > 0.05$).

DISCUSSION

Herein, we showed that the relative expression of NORAD and NEAT1 lncRNAs was higher in *C9ORF72* SMC, whereas relative levels of GAS5 were less abundant in *GRN* SMC. No significant differences were instead observed in PMC, although this group was very heterogenous as regards the age at sampling, and many subjects were still far from the mean age at disease onset in their families. Therefore, we cannot rule out whether the change observed in SMC occur in proximity of symptom manifestation.

LncRNA NORAD modulates the genome stability. It is expressed in cells after DNA damage and, when deleted, it expresses chromosomal instability and aneuploidy.[14] Notably, *C9ORF72* expansions are known to cause R-loops, in turn increasing genomic instability and DNA damage, and generate dipeptide repeat proteins, that lead to DNA damage and impairment of the DNA damage response.[15] Therefore, DNA damage may play a role in the pathogenesis of the disease in carriers of the hexanucleotide

expansion. Here, we considered only patients with FTD, therefore we cannot rule out whether the same modifications are present also in carriers developing ALS. It is interesting to note that dendritic cells isolated from C9ORF72–/– mice showed a marked early activation of the type I interferon response, and C9ORF72–/– myeloid cells were selectively hyperresponsive to activators of the stimulator of interferon genes (STING) protein, key regulator of the innate immune response.[16]

As regards lncRNA NEAT1, in samples from patients with AD, it was shown that NEAT1 expression is upregulated in different brain regions related to the disease.[17] Nevertheless, there are still controversial data on the role of this lncRNA (damaging versus protective) in AD and other neurodegenerative diseases. (see[18] for review)

LncRNA GAS5 has been shown to be downregulated in brain samples from patients with AD compared to age-matched healthy controls.[19] In line with this observation, a previous human transcriptomic analysis and microarray data of six brain regions from AD patients also showed that GAS5 is downregulated in AD.[20]

In a previous study, circulating levels of lncRNA were evaluated but, despite trends toward increased or decreased levels were observed, no significant data

were obtained.[11] It has to be considered however that the source of circulating lncRNA cannot be determined and that there are no study comparing PBMC and circulating lncRNA levels in the same individuals.

A strength of the study is represented by NC from the same families, reducing the genetic background variability. A weakness of the study is instead that we did not compare the same subjects from the asymptomatic to the symptomatic phase. As regards the longitudinal analysis of PMC, the follow up of participants in GENFI is ongoing and these findings could be confirmed longitudinally in the next future.

Lastly, it has to be acknowledged that, despite the extracted RNA being of good quality for subsequent expression analysis, several long non-coding RNAs were not detected. The lack of detection of long non-coding RNAs (lncRNAs) in blood can be attributed to several factors.

Firstly, the presence of ribonuclease enzymes in blood can lead to the rapid degradation of RNA molecules, including lncRNAs, making them difficult to detect.[21]

Additionally, many lncRNAs are expressed at intrinsically low levels, which may render them below the detection limit of standard real time PCR.[22] Another significant factor is the tissue-specific expression of many lncRNAs: if a lncRNA is predominantly expressed in specific tissues such as the brain or liver, it is unlikely to be detected in the blood.[23] RNA stability is another crucial element to consider, as some lncRNAs may be inherently unstable in blood, despite protective mechanisms such as encapsulation in exosomes or association with proteins, leading to their rapid degradation.[24] These combined factors can explain the difficulty in detecting lncRNAs in blood. Therefore, we cannot rule out whether these lncRNAs play a role in neurodegeneration, and the present results need to be validated in an independent cohort of patients, possibly also including sporadic cases.

Conclusions

Relative expression of NORAD and NEAT1 lncRNAs is more abundant in PBMC from *C9ORF72* SMC, whereas relative transcription of GAS5 is less abundant in PBMC from *GRN* SMC, whereas no significant changes have been observed in PMC. This study emphasizes the importance of lncRNAs in FTD and their potential for guiding genetic stratification and developing biomarkers. Further validation and mechanistic investigations are essential to facilitate clinical application.

CONFLICT OF INTEREST

Chiara Fenoglio, Barbara Borroni, and Daniela Galimberti are Editorial Board Members of this journal but were not involved in the peer-review process of this article nor had access to any information regarding its peer-review.

All other authors have no conflict of interest to report.

DATA AVAILABILITY

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-240557.

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