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Progranulin Mutations in Clinical and Neuropathological Alzheimer's Disease

Badri N. Vardarajan[a,b,c,*], **Dolly Reyes-Dumeyer**[a,b,c], **Angel L. Piriz**[a,b], **Rafael A. Lantigua**[a,e], **Martin Medrano**[i], **Diones Rivera**[n,o], **Ivonne Z. Jiménez-Velázquez**[h], **Eden Martin**[j], **Margaret A. Pericak-Vance**[j], **William Bush**[k], **Lindsay Farrer**[l], **Jonathan L. Haines**[k], **Li-San Wang**[m], **Yuk Yee Leung**[m], **Gerard Schellenberg**[m], **Walter Kukull**[g], **Philip De Jager**[a,c], **David A. Bennett**[d], **Julie A. Schneider**[d],

Alzheimer's Disease Sequencing Project,

Richard Mayeux[a,b,c,f,g]

[a.]Taub Institute for Research on Alzheimer's Disease and the Aging Brain, College of Physicians and Surgeons, Columbia University. 630 West 168th Street, New York, NY 10032.

[b.]The Gertrude H. Sergievsky Center, College of Physicians and Surgeons, Columbia University. 630 West 168th Street, New York, NY 10032.

[c.]Department of Neurology, College of Physicians and Surgeons, Columbia University and the New York Presbyterian Hospital. 710 West 168th Street, New York, NY 10032

[d.]Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL 60612

[e.]Department of Medicine, College of Physicians and Surgeons, Columbia University, and the New York Presbyterian Hospital. 630 West 168th Street, New York, NY 10032.

[f.]Department of Psychiatry, College of Physicians and Surgeons, Columbia University. 1051 Riverside Drive, New York, NY 10032.

[g.]Department of Epidemiology, School of Public Health, University of Washington, Seattle WA 98195

[h.]Department of Medicine, University of Puerto Rico School of Medicine, Medical Sciences Campus, San Juan, Puerto Rico, USA 00936

[i.]School of Medicine, Pontificia Universidad Catolica Madre y Maestra (PUCMM), Santiago, Dominican Republic

[j.]The John P. Hussman Institute for Human Genomics, and Dr. John T. Macdonald Foundation Department of Human Genetics, Miami, FL

[k.]Department of Biostatistics and Epidemiology, Case Western Reserve University, Cleveland, OH

[l.]Boston University School of Medicine, Boston, MA

[*]Address Correspondence to: Badri N. Vardarajan, PhD, Taub Institute, Columbia University, 620 West 168th Street, New York, NY 10032, Tel: 212-305-2391, Fax: 212-305-2518, bnv2103@cumc.columbia.edu.

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B.N.V is a cancer bioinformatics consultant for Kodikaz Therapeutics

[m.]School of Medicine, University of Pennsylvania, Philadelphia, PA

[n.]Department of Neurology, CEDIMAT, Plaza de la Salud, Santo Domingo, Dominican Republic

[o.]School of Medicine, Universidad Pedro Henriquez Urena (UNPHU)

Abstract

INTRODUCTION: Progranulin (*GRN*) mutations occur in Frontotemporal lobar degeneration (FTLD) and in Alzheimer's disease (AD), often with TDP-43 pathology.

METHODS: We determined the frequency of rs5848 and rare, pathogenic *GRN* mutations in two autopsy and one family cohort. We compared Braak stage, β-amyloid load, hyper-phosphorylated Tau (PHFtau) tangle density and TDP-43 pathology in *GRN* carriers and non-carriers.

RESULTS: Pathogenic *GRN* mutations were more frequent in all cohorts compared to the Genome Aggregation Database (GnomAD), but there was no evidence for association with AD. Pathogenic *GRN* carriers had significantly higher PHFtau tangle density adjusting for age, sex and *APOE*ε4 genotype. AD patients with rs5848 had higher frequency of hippocampal sclerosis and TDP-43 deposits. Twenty-two rare, pathogenic *GRN* variants were observed in the family cohort.

DISCUSSION: *GRN* mutations in clinical and neuropathological AD increase the burden of tau-related brain pathology but show no specific association with β-amyloid load or AD.

Keywords

progranulin; Alzheimer's disease; TDP43; neuropathology

Introduction

Alzheimer's Disease (AD) is the primary cause of dementia among older people with a strong genetic predisposition[1] (60–80% heritability), a prevalence of 30% at age 70 years and an annual incidence rate of 6–8% by age 85 years[2]. Extra-cellular accumulation and deposition of β-amyloid in brain is thought to be an early event. Although phosphorylated tau is thought to have a role in the cause of AD its role in pathogenesis is uncertain. Understanding biological mechanisms of AD could reveal insights about etiology, and aid in the development of novel treatments and pre-symptomatic diagnosis[3,4].

Progranulin (*GRN*), a microglial protein, is neurotrophic and anti-inflammatory, and there is increased expression by microglia in conditions of pathology[5]. *GRN* mutations are consistently associated with frontotemporal lobar degeneration (FTLD)[6] but recent genetic and epidemiological studies suggest that *GRN* variants may also be observed in AD. *GRN* depletion heightens Aβ and tau deposition in mice, and its expression rises in microglia surrounding plaques[7–9].

Progranulin levels are increased in the cerebrospinal fluid (CSF) of patients with both an autosomal-dominant early onset AD and sporadic late-onset AD[10]. *GRN* mutations in patients with clinical AD have been previously reported in large families in the National Institute on Aging family-based study[11], among large, multiply affected families of Caribbean Hispanic ancestry[12] and in patients from a large exome-sequencing study[13].

A family clinically diagnosed with AD and also carrying a *GRN* mutation (c.154delA) had FTLD with ubiquitin-positive, tau-negative, and lentiform neuronal intranuclear inclusions (-U NII) with neuronal loss and gliosis, affecting the frontal and temporal lobes, and TDP43 inclusions[14]. Only one of the six family members had mixed pathology meeting NIA-Reagan criteria[15] of high likelihood and coexisting FTLD-U N11 with TDP43 inclusions. *GRN* mutations were also observed in a patient with postmortem evidence of AD: NIA-Reagan criteria of high likelihood[15] and coexisting FTLD-U N11 with TDP43 inclusions[16].

Here we investigated the frequency of pathogenic *GRN* mutations in large unrelated AD cohorts and in families among patients with either clinical or postmortem AD. In clinical AD, we compared the frequency of behavioral and other symptoms (such as learning disabilities) consistent with a FTLD presentation. In autopsied-confirmed AD, we evaluated the presence of co-pathologies including tauopathies and TDP-43 presentation.

Methods

ROSMAP Cohort

Cohorts and Whole Genome Sequencing (WGS).—WGS data from 1,161 autopsied brain tissues were accessed from the ROSMAP cohort which is comprised of two prospective studies of aging-The Religious order Study (ROS) and the Memory and Aging Project (MAP). The detailed description of the study design and data collection scheme are described elsewhere[17–19]. All individuals have longitudinal clinical assessments of AD based on the NINCDS-ADRDA criteria[20,21] and neuropathological diagnosis based on the NIA-Reagan criteria[15]. We defined neuropathological diagnosis of AD as having a NIA-Reagan score of 1 or 2 (high or intermediate likelihood of disease). Both studies were approved by an Institutional Review Board, and all participants signed an informed consent, Anatomic Gift Act, and a repository consent to all their data to be shared. WGS was performed at the New York Genome Center using DNA extracted from brain tissue (n=806), whole blood (n=389) or lymphocytes transformed with EBV virus (n=5). Details of the sequencing technology and bioinformatics pipeline for data processing, read alignment and variant calling have been described[22].

Correlation of GRN mutations with neuropathological phenotypes: We first evaluated the frequency of rare putatively pathogenic *GRN* variants in the ROSMAP autopsy cohort. Pathogenicity was defined as coding mutations that have a Combined Annotation Dependent Depletion (CADD) greater than 20 or mutations that affect splicing. Joint frequency of *GRN* mutations was defined as the sum of minor allele frequencies (MAF) of pathogenic mutations. We then correlated the *GRN* mutation dosage (number of mutations carried by each individual) with neuropathological traits. Neuropathological traits included a) global pathology defined as global measure of pathology based on the scaled scores of five brain regions where the scaled variable is the original count divided by the standard deviation, b) Braak Stage[23], c) diffuse plaque burden, d) neuritic plaque burden, e) PHFtau tangle density across eight brain regions, f) area occupied by β-amyloid across eight brain regions, g) hippocampal sclerosis (present/absent), h) TPD-43 inclusions (present/absent), i) synaptic measure across three cortical (hippocampus, midfrontal cortex,

and inferior temporal) and j) presence of Lewy bodies. Three stages of TDP-43 pathology were measured (stage 1, localized to amygdala; stage 2, extension to hippocampus and/or entorhinal cortex; stage 3, extension to the neocortex), and the severity of the TDP-43 cytoplasmic inclusions in neurons and glia were rated on a 6-point scale[24].

Correlations were computed as follows: a) unadjusted, b) adjusted for age at death and sex, c) adjusted for age at death, sex and pathological AD diagnosis. Pathological AD was derived using the NIA-Reagan diagnosis of Alzheimer's disease[25].

The National Alzheimer's Coordinating Center (NACC)

Cohort and WGS: NACC coordinated collection of phenotype data from the 29 National Institute on Aging (NIA) Alzheimer's Disease Centers (ADCs), stored and shared all data, coordinated implementation of definitions of AD cases and controls, and coordinated collection of samples. For autopsy samples, clinical and neuropathologic information were recorded in either the minimal dataset (MDS) or the more extensive uniform data set (UDS) (after 2006), and neuropathologic information was recorded in the Neuropathology Data Set (NPDS). Details of the cohort have been reported [26,27]. Clinical diagnosis of AD was based on the NINCDS-ADRDA criteria[20,21] and neuropathological AD was defined as a score of 1 or 2 (high or intermediate likelihood) on the NIA-AA Alzheimer's disease neuropathologic change (ADNC) scale[15].

Whole exome sequencing (WES) data for the NACC autopsied individuals were generated as a part of the Alzheimer's Disease Sequencing Project and were accessed from The National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site (NIAGADS)[28]. The study design and details of the WES experiment and variant calling are described elsewhere[29,30].

Correlation of GRN mutations with neuropathological measures: *GRN* mutation dosage defined as the sum of non-reference alleles in pathogenic mutations was correlated with presence of FTLD with tau pathologies (FTLD-tau) such as argyrophilic grains, tau intracytoplasmic inclusions, TDP-43 inclusions, neurofibrillary tangles or pre tangles (see reference)[31] from the NACC MDS and UDS. The proportion of individuals with clinical AD and with FTLD-tau pathology were compared between *GRN* carriers and non-carriers.

Estudio Familiar de Influencia Genetica en Alzheimer (EFIGA)

Cohort and WGS: WGS data from 307 families in the cohort was accessed. Study design, adjudication, and clinical assessment of AD in this cohort was previously described[32]. Participants were followed-up every two years with a neuropsychological test battery[33], a structured medical and neurological examination and an assessment of depression[34,35]. The Clinical Dementia Rating Scale (CDR)[36,37] and functional status were done and the clinical diagnosis of AD was based on the NINCDS-ADRDA criteria[20,21]. Seventy-seven families in EFIGA underwent sequencing as a part of the ADSP discovery and extension phases[38].

WGS on 1886 individuals from 264 families was also performed at the New York Genome Center (NYGC) using one microgram of DNA, an Illumina PCR-free library protocol, and sequencing on the Illumina HiSeq platform.

We harmonized the WGS the EFIGA families (n=307), and jointly called variants to create a uniform, analysis set. Genomes were sequenced to a mean coverage of 30x. Sequence data analysis was performed using the NYGC automated analysis pipeline which matches the CCDG and TOPMed recommended best practices[39]. Briefly, sequencing reads were aligned to the human reference, hs38DH, using BWA-MEM v0.7.15. Variant calling was performed using the GATK best-practices. Variant filtration was performed using Variant Quality Score Recalibration (VQSR at tranche 99.6%) which identified annotation profiles of variants that were likely to be real and assigns a score (VQSLOD) to each variant.

Correlation of GRN variants with clinical assessment of FTLD-like symptoms: Behavioral traits associated with FTLD had been collected in a sub-group of the EFIGA cohort and was compared in those with clinical AD with and without pathogenic *GRN* mutations. Presence of FTLD like behavioral symptoms were assessed on a ten-point Middelheim Frontality Score[40].

Statistical analysis—Partial correlations adjusting for covariates were computed using the ppcor R package[41] and results were assessed for significance at $p \leq 0.05$.

Results

Frequency of GRN mutations:

We annotated mutations from the AD and FTD Mutation Database (https://uantwerpen.vib.be/) to assess the CADD scores of putatively deleterious variants in *GRN* (Supplementary Figure S1). Of the 171 mutations in the AD and FTD database, 78 (45%) were classified as “pathogenic” and 45 (26%) were considered “unclear”, with average CADD scores of 28.4 (±7.6) and 19.3 (±9.73) respectively. Thus, we used CADD≥20 to define pathogenic *GRN* loss of function, non-synonymous and splice variants mutations.

Table 1 shows the frequency of pathogenic *GRN* mutations in each dataset. Only summary level data were available from gnomAD and the total frequency of pathogenic variants was assessed as the sum of frequencies of individual variants (assuming that each variant was observed once in an individual). The population frequency of pathogenic *GRN* variants in gnomAD was 0.75%. In the EFIGA family cohort, a significant enrichment of pathogenic *GRN* mutations, although no significant differences were observed between clinical AD and unaffected family members. In the ROSMAP study, the frequency of *GRN* mutations in post-mortem AD cases was observed at 1.4% and 0.8% for controls cohort.

Association of GRN with neuropathological traits in ROSMAP:

We observed eight pathogenic *GRN* mutations at a MAF=1.4% in autopsy confirmed cases and 0.8% in controls. We assessed the correlation of *GRN* carrier status with neuropathological, behavioral and cognition-related traits (Table 2, Supplementary Figures S2–S3 and Supplementary Table S3). *GRN* mutations in both cases and controls was accompanied by an advanced Braak Stage (cor=0.06, p=0.04) and higher PHFtau tangle density (cor=0.08, p=0.008). Adjusting for age, sex and AD diagnosis, correlations with PHFtau tangle density was statistically significant (cor=0.065, p=0.02). The association

was significant after adjustment for *APOE* ε4 (cor=0.06, p=0.048). Upon further analysis of *GRN* and *APOE ε4* (Supplementary Figures S2–S3), we found higher tangle density in AD patients and healthy individuals who carried both a *GRN* mutation and *APOE* ε4 alleles. This observation was particularly strong in tangle density measured in the entorhinal cortex and the hippocampus. However, this pattern was observed in only had two unaffected individuals. There was no association of *GRN* variants with other neuropathological traits.

Of the 20 individuals in ROSMAP with a neuropathological diagnosis of AD and carrying a *GRN* mutation, 9(45%) showed TDP-43 inclusions that was either stage 2 (extension to hippocampus and/or entorhinal cortex) stage 3 (extension to the neocortex). Moderate to severe TDP-43 pathology was slightly higher in *GRN* mutation carriers with a confirmed neuropathological diagnosis of AD (45% vs. 39.5%). In addition, one patient with confirmed AD and a second individual without dementia but a carrier of a *GRN* variant had neuropathological characteristics of hippocampal sclerosis.

Common SNP, rs5848 in ROSMAP cohort:

SNP rs5848 (SNP) rs5848, located in the 3′-untranslated region of *GRN,* and predicted to be a binding site for the microRNA miR-659, is the most frequent *GRN* variant associated with frontotemporal dementia[42]. Several small independent and meta-analysis studies from several populations have reported association of the T allele of rs5848 with risk for clinical AD[43]. Recently, a large meta-analysis of genome-wide association studies (39,106 clinically diagnosed AD, 46,828 proxy-ADD cases and 401,577 controls) and replication in 25,392 independent AD cases and 276,086 controls implicated rs5848 as a genome-wide significant locus for AD[44].

We evaluated the association of rs5848 with neuropathological, behavioral and cognition traits (Table 3, Supplementary Table S4) using unadjusted and adjusted models for age, sex, AD diagnosis and *APOE ε4* dosage. rs5848 was modestly associated with presence of hippocampal sclerosis (cor=0.09, p=3.07e-03) and TDP-43 pathology (cor=0.082, p=0.01) adjusting for age, sex and AD diagnosis. The association was significant after adjusting for APOE ε4 status. Within homozygous rs5848 carriers with pathological AD, 17.4% had concomitant hippocampal sclerosis and 68% exhibited some TDP-43 pathology (9.7% and 58% respectively for hippocampal sclerosis and TDP-43 respectively amongst rs5848 non-carriers or heterozygotes) (Table 4, Supplementary Table S5).

GRN mutations in the autopsied cohort of NACC WES:

We used whole-exome sequencing data from the Alzheimer's Disease Sequencing Project[29] and neuropathological measures obtained from NACC to evaluate the frequency of *GRN* variants. Overall, we identified 30 putatively deleterious *GRN* variants in the NACC cohort. Among 3,252 individuals, for whom autopsy information was available, 31 (1%) individuals carried a *GRN* mutation (MAF=0.0047) which is lower compared to the ROSMAP cohort. The low frequency here may be partially explained by the intersection of capture regions of the various exome kits used in the ADSP[29], which could reduce the reliably of regions called within the gene. We evaluated the frequency of FTLD-tau using the variables specified in the NACC neuropathological dataset. Three out of fifteen individuals (20%) patients with

postmortem AD and carrying a *GRN* mutation showed criterion of FTLD (as described below). In patients with clinical AD who did not carry a *GRN* mutation, presence of FTLD neuropathological features was observed at 5.5% (p-value = 0.063).

Three patient examples reveal the variation in *GRN* related neurodegeneration. Patient A, with clinical AD, carried a *GRN* mutation and had the pathological hallmarks of AD including Braak Stage=5, Consortium to Establish a Registry for Alzheimer's Disease (CERAD) C score of 2 (moderate neuritic plaques) and NIA-AA Alzheimer's disease neuropathologic change (ADNC) of 3 (high and frequent diffuse plaques). The patient had little tau pathology (FTLD-tau) but TDP- 43 immunoreactive inclusions in the amygdala were observed. Patient B also had both clinical and pathological AD (Braak Stage=5, CERAD C score=3 and NIA-AA ADNC). Concomitantly, TDP-43 immunoreactive inclusions were widespread in the amygdala, hippocampus, inferior temporal cortex and neo-cortex. Interestingly both patients, carried the *GRN* p.Arg433Trp mutation. Patient C (p.Val8Met mutation), was diagnosed as clinical AD but did not have the pathological hallmarks of AD (Braak Stage=0, CERAD C score=0 (no neuritic plaques and no diffuse plaques) at autopsy. The patient had FTLD with parkinsonism, tau-positive or argyrophilic inclusions and tauopathy but without ubiquitin-positive (tau-negative) inclusions.

GRN mutations in families:

To investigate the clinical characteristics of AD in pathogenic *GRN* carriers, we compared the frequency of behavioral and other psychiatric manifestations in EFIGA families between carrier and non-carrier in living patients with AD. Presence of FTLD like behavioral symptoms were assessed on the ten-point Middelheim Frontality Score (MFS)[40]. Frequency of individuals with at least one behavioral symptom consistent with FTLD was compared between pathogenic GRN carriers and non-carriers. Medical record reviews were conducted in all *GRN* carriers and a similar number of randomly selected non-carriers to assess behavioral, mood and psychosis like symptoms.

In clinically diagnosed AD, there was no difference (Supplementary Table S1) in the presence of FTLD-like symptoms on the MFS scale between carriers and non-carriers of pathogenic *GRN* variants (9% in carriers vs 11% in non-carriers) or between carriers and non-carriers of the common rs5848 SNP (Supplementary Tables S1, S2). Interestingly, within unaffected family members, carriers of *GRN* variants and the common rs5848 were more likely to have behavioral symptoms, assessed using the MFS (5.4% in carriers vs 1.3% in non-carriers, p=0.03). We found that 3.7% of the individuals carrying a *GRN* mutation also displayed parkinsonism while it was absent in non-carriers. Four patients in one family with clinical AD (Supplementary Figure S4) and with a *GRN* splice variant (rs72824736) had learning disabilities and one patient carrying another splice variant (rs112873166) had progressive aphasia. These observations were not present among non-carriers.

Discussion

GRN mutations explain up to 20 percent of familial and 5 percent of sporadic FTLD but lead to a variety of clinical presentations, predominantly presenting as behavioral variant FTLD or progressive aphasia. Less frequently, variants in *GRN* are found in clinical AD

with or without parkinsonism. Among patients with clinical AD and not carrying mutations in *PSEN1, PSEN2 and APP,* 6.3% carried putatively pathogenic *GRN* mutations[45]. The authors recommended re-examination of clinical AD patients, particularly those who were diagnosed prior to identification of causal FTLD genes including *GRN*.

In this report, we systematically evaluated the frequency of putatively pathogenic *GRN* mutations in two large autopsy cohorts and one clinical cohort, and further examined the presence of concomitant tauopathy or other FTLD-like neuropathological or clinical presentations among patients with AD. In addition, we also examined the frequency of FTLD like symptoms in patients with AD carrying rs5848, the strongest variant linked to FTLD-TDP43 pathology.

We found higher than expected frequency of pathogenic *GRN* mutations among autopsied and clinically diagnosed AD compared to publicly available exome and genome datasets (GnomAD)[46]. In the ROSMAP cohort, we found an association between rs5848 and hippocampal sclerosis and TDP-43 pathology. It has been previously reported that up to 25–50% of patients with AD have been found to have TDP-43 pathology at autopsy[47], especially those with hippocampal sclerosis. However, in carriers of the rs5848 SNP, we found that 60% of pathologically confirmed AD patients exhibited TDP-43 pathology, and it increased to 67% if they were homozygous for the variant (Supplementary Table S5). Interestingly, 95% (41 out of 43) rs5848 positive, AD patients presenting with hippocampal sclerosis also had TDP-43 pathology. Among the collection of Hispanic families, we found learning disabilities and aphasia concomitant with clinical AD in *GRN* carriers, but this was absent in non-carriers. *GRN* variants are present in ~16% primary progressive aphasia (PPA), 7% of behavioral-FTLD and ~5% of AD with learning disabilities[48,49] suggesting that increased language and behavioral deficits in the presence of *GRN* variants in clinically diagnosed AD.

There are some limitations of this study including the diverse ascertainment and neuropathological characterizations across the autopsy cohorts. The in-silico pathogenic classification of *GRN* variants requires additional validation. Patients with mixed AD and FTLD presentations that carry *GRN* mutations with incomplete penetrance or mutations in other genes such as *MAPT* and *C9orf72* or would be missed in this analysis.

Progranulin levels in cerebrospinal fluid (CSF) is associated with the progression of early and late onset, clinically diagnosed AD[10]. In addition, progranulin levels are also associated with cortical thinning on brain MRI[50] and AD neuropathology[51]. Future studies should attempt to relate CSF progranulin levels, *GRN* variants, neurofibrillary tangle pathology and Braak stage.

Taken together, the data presented here indicate that both rare and common *GRN* variants are associated with specific neuropathological findings in AD that are also present in FTLD. Postmortem data reveal that among neuropathologically diagnosed AD with *GRN* mutations, Braak stage and tau pathology exceeds what is normally present in AD. Interestingly, *GRN* variants in AD were not accompanied by the typical behavioral manifestations occurring in FTLD. While *GRN* variants are strongly associated with FTLD,

this report validates the numerous studies indicating that they can also be present in AD, but are not causal. As suggested earlier, it is possible that progranulin impacts AD, FTLD and other neurodegenerative disease putatively by its effect on lysosomal storage in neurons and microglia[5]. Progranulins mutations may also explain concomitant tauopathies or other manifestations in AD neuropathology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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RESEARCH IN CONTEXT

SYSTEMATIC REVIEW:

Common variants and rare progranulin (*GRN*) mutations, typically associated with frontotemporal lobar degeneration, have been identified in genome wide arrays and genome wide sequencing of Alzheimer's disease (AD). We sought to determine whether *GRN* variants were specifically associated with AD and establish their impact on the disease phenotype.

INTERPRETATION:

We found the frequency of *GRN* mutations among patients with AD ranged from 0.5% in unrelated individuals to 5% in families, but there was no specific association with clinical or pathological AD. Between carriers and non-carriers there were no statistical difference in behavioral manifestations. Compared with non-carriers at autopsy, patients with AD and *GRN* mutations had advanced Braak stages, increased tangle density, TDP-43 pathology and evidence of other tauopathies.

FUTURE DIRECTIONS:

GRN mutations are not associated with an increased risk of AD, but when present in neuropathological AD alters the phenotype by increasing the burden of tau-related brain pathology.

Table 1:

Frequency of pathogenic GRN mutations with CADD score>=20 in the different cohorts

Dataset	Number of Variants	Frequency in Affected	Frequency in Unaffected
GnomAD exomes (all populations)	127	NA	0.0075
EFIGA families	22	0.0512	0.0473
ROSMAP	8	0.014	0.0082
NACC	30	0.0052	0.0052

Table 2:

GRN carrier status is correlated positively with tangle load and Braak stage

	Unadjusted model		Adjusted for age and sex		Adjusted for age, sex and AD status		Adjusted for age, sex and APOE ε4 dosage	
	correlation coefficient	P-value	correlation coefficient	P-value	correlation coefficient	P-value	correlation coefficient	P-value
global pathology *	0.04	1.79E-01	0.03	3.32E-01	0.01	6.93E-01	0.02	5.21E-01
Braak Stage	0.06	4.10E-02	0.05	9.04E-02	0.04	1.72E-01	0.04	1.36E-01
diffuse plaque burden	0.02	5.43E-01	0.02	5.64E-01	0.00	9.29E-01	0.01	7.41E-01
neuritic plaque burden	0.03	3.27E-01	0.02	5.85E-01	−0.01	8.63E-01	0.01	8.27E-01
square-root of tangle density across eight brain regions	0.08	8.83E-03	0.07	2.68E-02	0.06	4.93E-02	0.06	4.88E-02
square-root of the overall amyloid levels	0.03	3.61E-01	0.02	4.88E-01	0.00	9.86E-01	0.01	6.96E-01
hippocampal sclerosis (present/ absent)	−0.01	7.88E-01	−0.01	7.31E-01	−0.01	6.96E-01	−0.01	6.61E-01
TPD-43 pathology (present/absent)	0.03	4.27E-01	0.02	4.37E-01	0.02	4.93E-01	0.02	4.82E-01
presence of Lewy bodies	0.00	9.60E-01	0.00	9.78E-01	0.00	9.72E-01	0.00	9.98E-01
synaptic measure **	0.05	2.91E-01	0.06	2.20E-01	0.06	2.05E-01	0.05	2.47E-01

* global pathology defined as global measure of pathology based on the scaled scores of pathology in 5 brain regions, where the scaled variable is the original count divided by the standard deviation

** synaptic measure across three cortical (hippocampus, midfrontal cortex, and inferior temporal)

Table 3:

Correlation of pathological measures with rs5848 in the ROSMAP cohort

	Unadjusted model		Adjusted for age and sex		Adjusted for age, sex and AD status		Adjusted for age, sex and APOE ε4 dosage	
	correlation coefficient	P-value	correlation coefficient	P-value	correlation coefficient	P-value	correlation coefficient	P-value
global pathology *	−0.02	4.45E-01	−0.02	4.84E-01	−0.03	3.76E-01	−0.03	3.47E-01
Braak Stage	−0.03	3.40E-01	−0.02	4.91E-01	−0.02	4.14E-01	−0.02	4.86E-01
diffuse plaque burden	−0.01	6.26E-01	−0.01	6.73E-01	−0.01	6.56E-01	−0.02	5.54E-01
neuritic plaque burden	−0.01	6.86E-01	−0.01	7.06E-01	−0.01	6.57E-01	−0.02	5.57E-01
square-root of tangle density across eight brain regions	−0.02	5.22E-01	−0.01	6.64E-01	−0.02	5.87E-01	−0.02	5.34E-01
square-root of the overall amyloid levels	−0.02	5.78E-01	−0.01	7.51E-01	−0.01	6.76E-01	−0.02	5.51E-01
hippocampal sclerosis (present/ absent),	0.08	4.88E-03	0.09	3.08E-03	0.09	3.09E-03	0.08	4.55E-03
TPD-43 pathology (present/absent)	0.08	1.84E-02	0.08	1.00E-02	0.08	9.52E-03	0.08	1.65E-02
presence of Lewy bodies	0.00	8.82E-01	0.00	9.00E-01	0.00	9.08E-01	0.00	9.62E-01
synaptic measure **	0.00	9.68E-01	0.00	9.76E-01	0.00	9.37E-01	0.00	9.88E-01

*global pathology defined as global measure of pathology based on the scaled scores of pathology in 5 brain regions, where the scaled variable is the original count divided by the standard deviation

**synaptic measure across three cortical (hippocampus, midfrontal cortex, and inferior temporal)

Table 4:

Frequency of Hippocampal Sclerosis and TDP-43 pathology in GRN rs5848 carriers in ROSMAP

a) Hippocampal Sclerosis (% of individuals with rs5848 within each category (AD and HS absent, AD and HS present, Healthy and HS absent, healthy and HS present), p=0.016 in 6-df chi-square test. Raw numbers are shown in (Supplementary Table S5)

b) TDP-43 Pathology (% of individuals with rs5848 within each category (AD and TDP-43 pathology absent, AD and TDP-43 pathology present, Healthy and TDP-43 pathology absent, healthy and TDP-43 pathology present), p=0.16 in 6-df chi-square test. Number of individuals in each cell is given in Supplementary Table S5.

rs5848 T alleles	Healthy at Autopsy (No AD)		Neuropathologically Confirmed AD	
	HS Absent	HS Present	HS Absent	HS Present
0	0.50	0.27	0.48	0.43
1	0.41	0.46	0.44	0.42
2	0.09	0.27	0.08	0.14

rs5848 T alleles	Healthy at Autopsy (No AD)		Neuropathologically Confirmed AD	
	TDP-43 Absent	TDP-43 Present	TDP-43 Absent	TDP-43 Present
0	0.53	0.43	0.50	0.47
1	0.40	0.43	0.43	0.43
2	0.07	0.14	0.07	0.10