



Genetic risk loci for limbic-predominant age-related TDP-43 encephalopathy neuropathologic change in the population-based Vantaa 85+ cohort

Elizaveta Mikhailenko^{1,2}, Sara Savola^{1,2}, Mia Kero^{1,2}, Pentti J. Tienari^{3,4}, Liisa Myllykangas^{1,2}, Karri Kaivola^{3,4}

1. Department of Pathology, University of Helsinki, 00014 Helsinki, Finland
2. Department of Pathology, HUS Diagnostic Center, Helsinki University Hospital, 00029 Helsinki, Finland
3. Translational Immunology, Research Programs Unit, University of Helsinki, Helsinki, 00014 Finland
4. Department of Neurology, University of Helsinki and Helsinki University Hospital, 00014 Helsinki, Finland

INTRODUCTION

Limbic-predominant age-related TDP-43 encephalopathy neuropathologic change (LATE-NC) is defined by TDP-43 accumulation spreading through the amygdala, hippocampus, and frontal cortex.¹ It affects more than 30% of people aged ≥85 and is independently associated with cognitive decline.^{2–4} Despite this high prevalence, its genetic etiology remains largely unknown.

Only one GWAS has targeted a LATE-NC phenotype, identifying *TMEM106B* and *APOE* as genome-wide significant (*GRN*, *API5* and *LHX1* suggestive).⁵ Several further candidate loci – including *GRN*, *KAZN*, *ARHGEF28*, *UNC13C*, *WWOX*, and *TPCN1* – have been reported but seldom replicated.^{6–10} Whether overall Alzheimer's disease genetic risk influences LATE-NC beyond APOE also remains unresolved. In the population-based Vantaa 85+ cohort of the oldest old, we asked:

- Do previously reported LATE-NC loci replicate in a single, uniformly assessed neuropathological cohort with a distinct (Finnish) genetic background?
- Is AD genetic risk associated with LATE-NC, or is the link primarily APOE-driven?

METHODS

Cohort: Vantaa 85+ includes all residents of Vantaa, Finland aged ≥85 in 1991 (n = 601); 304 neuropathologically assessed, **262** were **genotyped and analysed** (86% female, mean age 92.6 y).

LATE-NC staging : C-terminal anti-TDP-43 immunohistochemistry; regrouped into **4 ordinal levels** (Stage 0 → Stage 3; Stage 1c excluded, Stages 1a and 1b combined).

Genotyping: Illumina arrays, SISu v3 imputation (INFO ≥ 0.7, MAF ≥ 0.01); **9 previously reported LATE-NC variants** extracted.

AD polygenic risk: validated European AD PRS **excluding APOE** (PGS000898; 35/39 variants), z-scored across the cohort (n = 504).

Statistics: Fisher's exact test (2×6) → **ordinal logistic regression** (adjusted for age, sex; AD-PRS model also for APOE ε4 dose + AD pathology defined by NIA-AA ABC criteria); Benjamini–Hochberg correction for FDR.

TMEM106B Alu: Manta on whole-genome sequencing to test LD between rs13237518 and the AluYb8 element.

CONCLUSION

Our findings refine current knowledge on the genetics of LATE-NC and elucidate the interplay of Alzheimer's disease genetic risk and TDP-43 accumulation. These results contribute to the growing evidence that a polygenic and multifactorial architecture shapes LATE-NC.

RESULTS

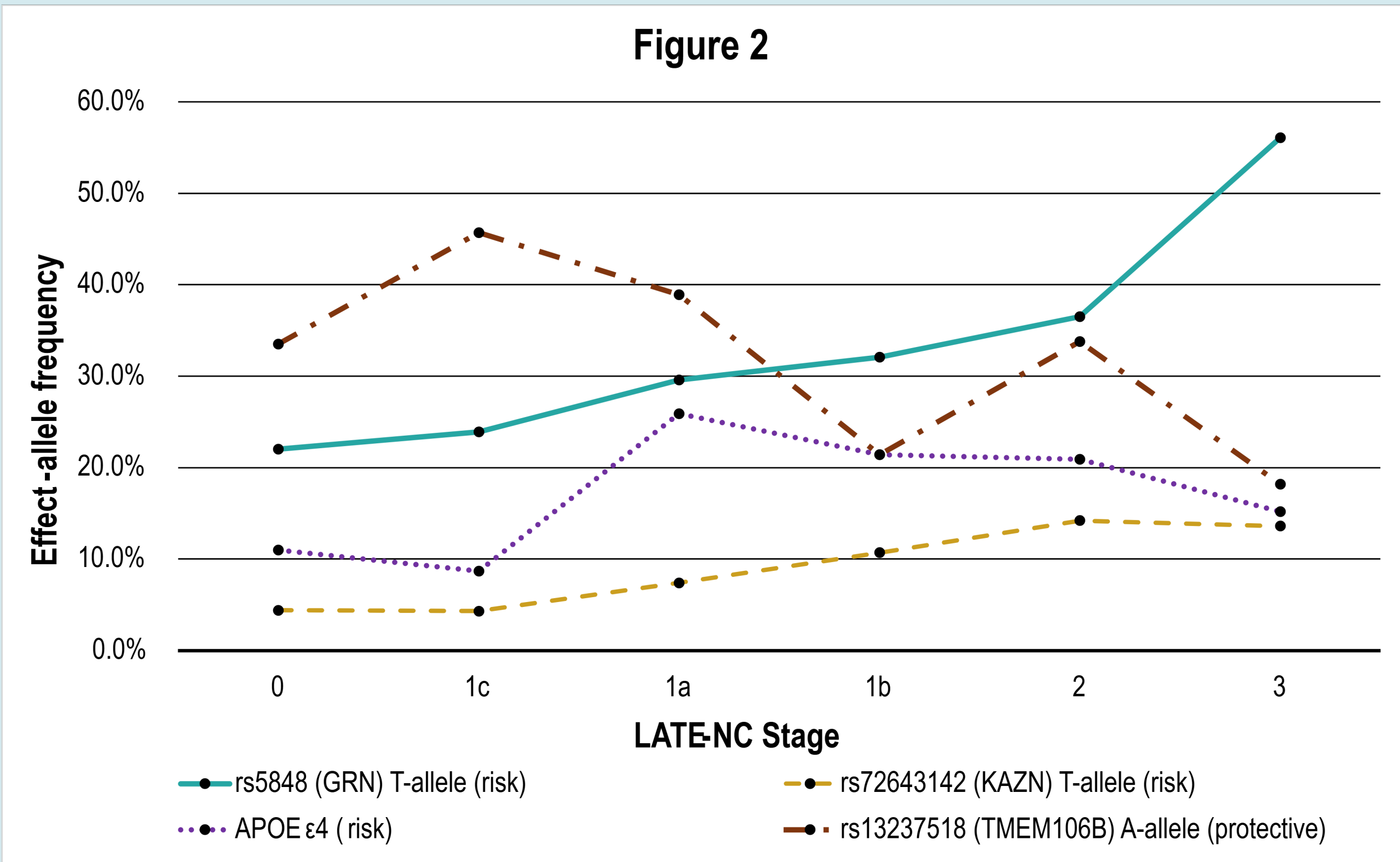


Figure 2. Effect-allele frequency across LATE-NC stages. Frequency of the disease-associated allele at each histological stage for the four variants whose distribution differed across stages by Fisher's exact test ($p < 0.05$) among 262 Vantaa 85+ participants: *GRN* rs5848 (T, risk), *KAZN* rs72643142 (T, risk), and *TMEM106B* rs13237518 (A, protective); *APOE* is plotted as the proportion of ε4 carriers (≥ 1 ε4 allele). Stages 0–3 follow the histological staging scheme; stage 1c was retained for this descriptive analysis but excluded from the ordinal regression. Full per-stage allele counts are available in the **online version of this poster**.

	Effect allele	Other allele	OR (95 % CI)	<i>P</i> -value	Adjusted <i>p</i> -value
<i>rs5848 (GRN)</i>	T	C	2.45 (2.09–2.82)	1.15×10^{−6}	5.75×10^{−6}
<i>rs72643142 (KAZN)</i>	T	C	2.38 (1.83–2.93)	0.0019	0.0048
AD PRS without <i>APOE</i>	NA	NA	1.36 (1.11–1.61)	0.016	0.027
<i>APOE</i>	ε4	ε3/ ε2	1.73 (1.25–2.21)	0.024	0.030
<i>rs13237518 (TMEM106B)</i>	A	C	0.72 (0.34–1.10)	0.091	0.091

Table 1. OR: odds ratio, CI 95%: 95 % confidence interval; *P*-value: raw *p*-value from ordinal logistic regression run on a four-level LATE-NC stage variable: stage 0 – stage 1a+stage 1b – stage 2 – stage 3; Adjusted *p*-value: Benjamin-Hochberg adjusted *p*-value; AD PRS: Alzheimer's disease polygenic risk score; NA: not applicable. Ordinal logistic regression models were adjusted for sex and age of death. The model with AD PRS without *APOE* was also adjusted with *APOE* ε4 dose and Alzheimer's disease pathology. N = 239 (23 individuals with LATE-NC stage 1c excluded).

Of nine candidate variants tested in 262 participants, four differed across LATE-NC stages and entered ordinal regression (Table 1); twelve hippocampal-sclerosis loci were non-significantly associated.

GRN is the strongest locus. *GRN* rs5848 showed the strongest association with higher stage (OR 2.45, adj p = 5.75×10^{−6}), its risk allele climbing from 22% to 56% across levels 0 → 3. Unusually, this effect was ~1.5× larger than *TMEM106B*s, reversing the hierarchy seen in most cohorts, likely reflecting population, ascertainment, or susceptibility differences.

TMEM106B is protective, but mainly at Stage 3. The protective effect was a trend only (OR 0.72, adj p = 0.091), confined to the most severe stage. Our estimate nearly matches the LATE-NC GWAS (OR 0.70), so the non-significance is probably power-limited, or alternatively the effect is genuinely stage-3-specific, and stage 3 is rarer in a population cohort. The *AluYb8* deletion tracked the rs13237518 risk haplotype (96.7% concordance), confirming it in Finnish ancestry but leaving the causal variant unresolvable under high LD.

KAZN replicates but in the opposite direction. *KAZN* rs72643142 was the only previously unreplicated locus to reach significance (OR 2.38, adj *p* = 0.0048), but with inverse effect direction. Its biology is plausible (neuronal cell adhesion, cytoskeletal organisation), though Finnish haplotype structure or chance cannot be excluded.

AD genetic risk acts beyond APOE. *APOE* ε4 dose associated with LATE-NC (OR 1.73), and novel here – so did an AD polygenic risk score excluding *APOE* (OR 1.36, adj *p* = 0.027), independent of age, sex, *APOE* ε4 dose, and AD pathology. This points to shared biology between LATE-NC and AD, though AD-pathology-mediated effects remain possible.

Strengths & limitations. A population-based cohort of the oldest old captures the full severity spectrum in an underrepresented, genetically distinct group; limitations include modest n, Finnish-only ancestry, and incomplete co-pathology data.

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