



Multimodal Clinical and Genomic Characterization of Trans Compound Heterozygosity for TREM2 Variants in Alzheimer's Disease



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Trans compound heterozygosity for TREM2 variants drives an atypical Alzheimer's phenotype characterized by early executive, social cognitive, and distributed structural impairment.

INTRODUCTION

Alzheimer's disease (AD) is a heterogeneous disorder where genetic factors drive clinical variability. Beyond **APOE ε4**, rare microglial variants in **TREM2** modify AD risk, but the clinical relevance of their haplotypic configuration (*cis* vs. *trans*) remains poorly understood. This study characterizes the clinical, cognitive, and neuroimaging phenotype of rare TREM2 variant combinations.

METHODS

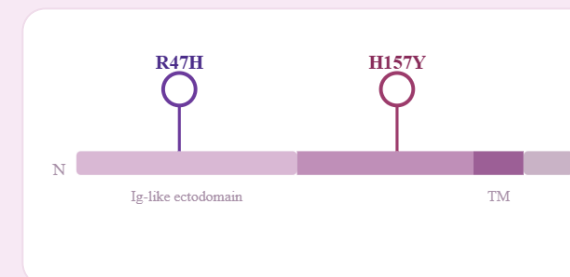
Three unrelated female carriers were characterized within the **ReDLat** consortium using standardized neuropsychological assessments. Whole-genome sequencing with **haplotype phasing** determined the allelic configuration of TREM2 H157Y and R47H. Structural MRIs evaluated regional volumes and an exploratory **composite brain integrity score** (PCA) integrating hippocampal, entorhinal, and ventricular measures.

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RESULTS

GENOMICS

Phasing analyses confirmed that TREM2 **H157Y** and **R47H** variants consistently segregated *in trans* across all individuals (trans compound heterozygosity).



CLINICAL PHENOTYPE

A convergent phenotype emerged, characterized by **early executive dysfunction** (attentional control, flexibility, working memory) and **social cognitive deficits**, followed by progressive episodic memory impairment.



Executive



Social cognition



Episodic memory

NEUROIMAGING

Ventricular enlargement correlated with global cognition (MMSE). The composite brain integrity score captured a distributed neurodegenerative pattern strongly associated with cognitive decline, overlapping with known cortical expression patterns of TREM2.

CONCLUSIONS

Trans compound heterozygosity for TREM2 variants is associated with a **distinctive AD phenotype**. Integrating haplotype-resolved genomics with clinical and neuroimaging phenotyping is key to understanding **AD heterogeneity**.

REFERENCES

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