

ADAM10 Genotype Reveals Sex-Dependent Vulnerability to Depressive Symptoms in Aging

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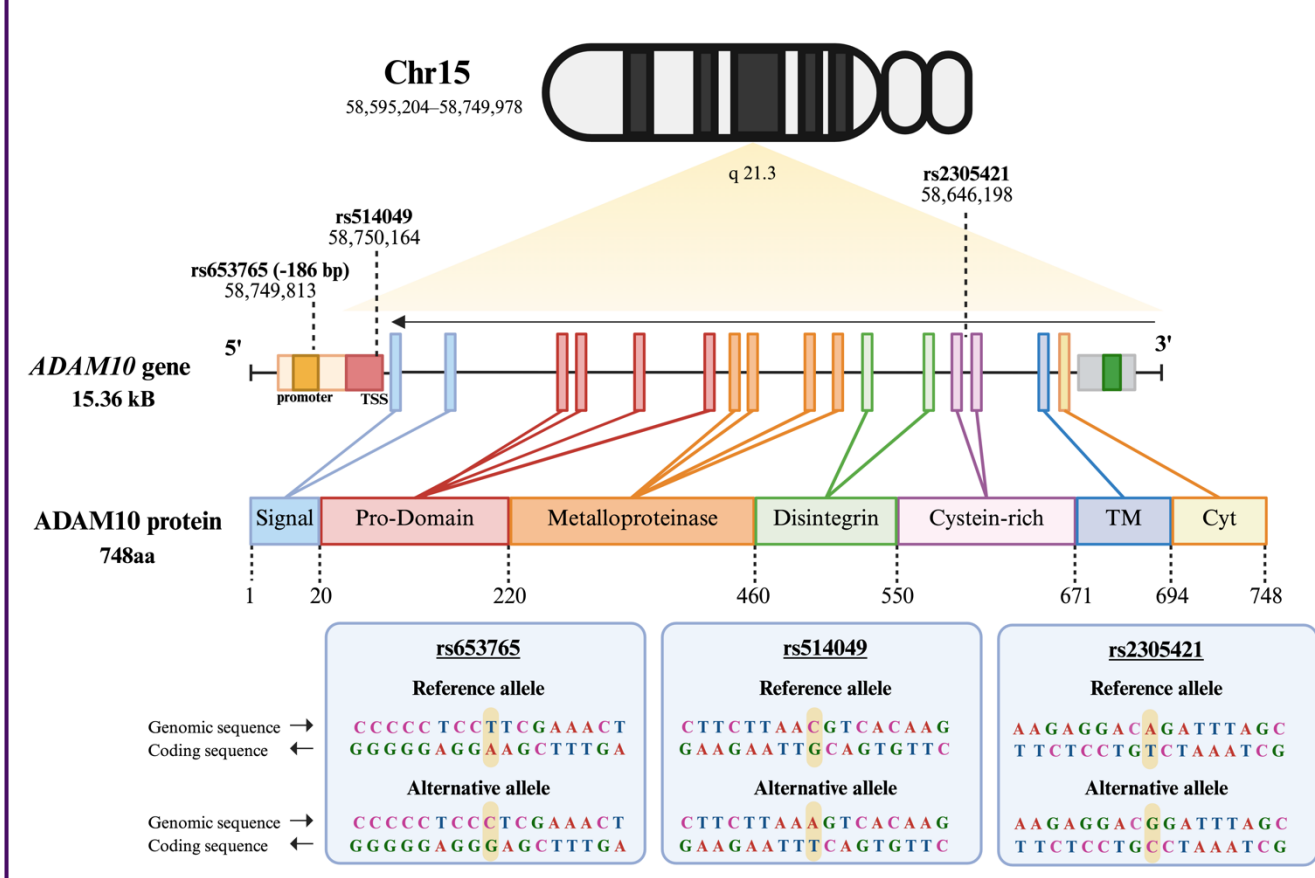
ADAM10 genetic variants are associated with depressive symptom severity in older adults, and sex modify these associations

INTRODUCTION

Depressive symptoms are highly prevalent and are associated with increased risk of cognitive decline and dementia [1]. Identifying biological and genetic factors that contribute to heterogeneity in depressive symptoms, particularly sex-specific mechanisms, is critical for improving risk stratification and informing precision psychiatry approaches in older adults.

Therefore, the objective of this work was to determine whether single-nucleotide polymorphisms (SNPs) in the ADAM10 gene (rs653765, rs514049, and rs2305421) (Figure 1) are associated with depressive symptom severity in older adults, and whether these associations are modified by sex or APOEε4 carrier status.

Figure 1. Schematic representation of the genomic organization of the human ADAM10 gene, location of selected SNPs, and correspondence with the ADAM10 protein domains.



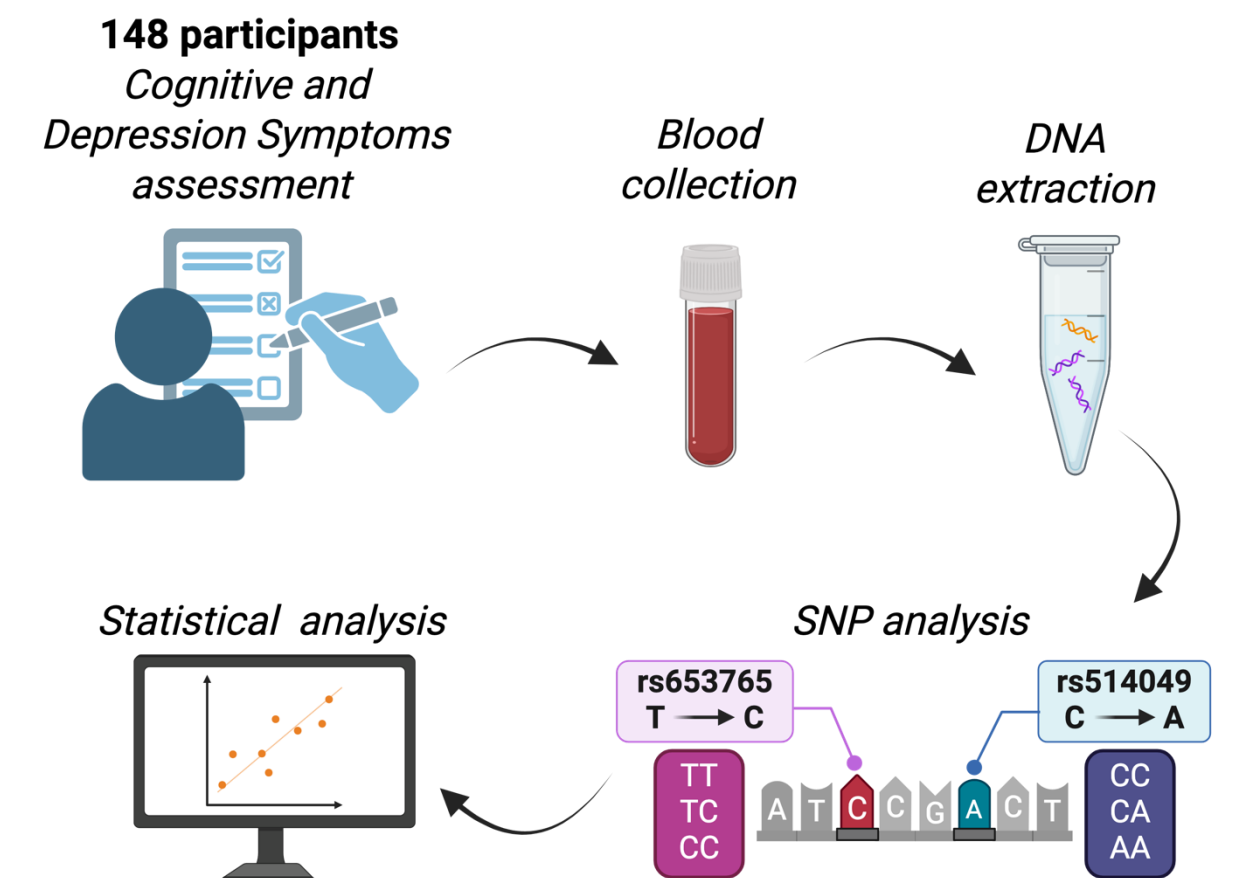
METHODS

A community-based study was conducted with a convenience sample of 148 cognitively healthy adults aged 55 years or older. Participants underwent standardized cognitive and functional assessments to confirm cognitive normality.

Genotyping of ADAM10 rs653765, rs514049 (promoter variants), and rs2305421 (intronic variant) using TaqMan SNP Genotyping Assays. APOEε4 status was also determined. Depressive symptom severity assessed using the 15-item Geriatric Depression Scale (GDS-15).

Associations between ADAM10 variants and GDS-15 scores were examined using multivariable negative binomial regression models adjusted for age, sex, education, antidepressant use, and APOEε4 status, with formal testing of sex-by-genotype and APOEε4-by-genotype interactions (Figure 2).

Figure 2. Schematic representation of the methods.



RESULTS

Table 1. Demographic, clinical, genetic and cognitive characteristics of the participants.

Characteristic	n = 148
Sex	
Female	86 (58.1%)
Male	62 (41.9%)
Race	
White	108 (73.0%)
Non-White	40 (27.0%)
Age in years	
Mean (SD)	68.5 (6.0)
Median (Q1, Q3)	68.0 (64.0, 73.0)
Education in years	
Mean (SD)	11.9 (5.8)
Median (Q1, Q3)	12.0 (7.0, 16.0)
Geriatric Depression Scale (GDS-15)	
Mean (SD)	2.8 (2.6)
Median (Q1, Q3)	2.0 (1.0, 4.0)
Use of antidepressants	
No	122 (82.4%)
Yes	26 (17.6%)
rs653765 ADAM10 polymorphism	
MAF	0.395
T/T	60 (40.5%)
C/T	59 (39.9%)
C/C	29 (19.6%)
rs514049 ADAM10 polymorphism	
MAF	0.470
C/C	44 (29.7%)
A/C	69 (46.6%)
A/A	35 (23.6%)
rs2305421 ADAM10 polymorphism	
MAF	0.140
A/A	112 (75.7%)
A/G	31 (20.9%)
G/G	5 (3.4%)
ε4 allele of the apolipoprotein E gene (APOEε4)	
No	110 (74.3%)
Yes	38 (25.7%)
Mini-Mental State Examination (MMSE)	
Mean (SD)	27.7 (1.9)
Median (Q1, Q3)	28.0 (27.0, 29.0)
Addenbrooke's Cognitive Examination (ACE-R)	
Mean (SD)	84.9 (9.0)
Median (Q1, Q3)	86.0 (79.5, 92.0)
Consortium to Establish a Registry for Alzheimer's Disease (CERAD)	
Mean (SD)	79.0 (13.2)
Median (Q1, Q3)	78.0 (69.0, 89.0)

CONCLUSIONS

Figure 3. Predicted GDS-15 scores from negative binomial regression models illustrating sex-by-genotype interactions. Values represent marginal means for each genotype-sex combination.

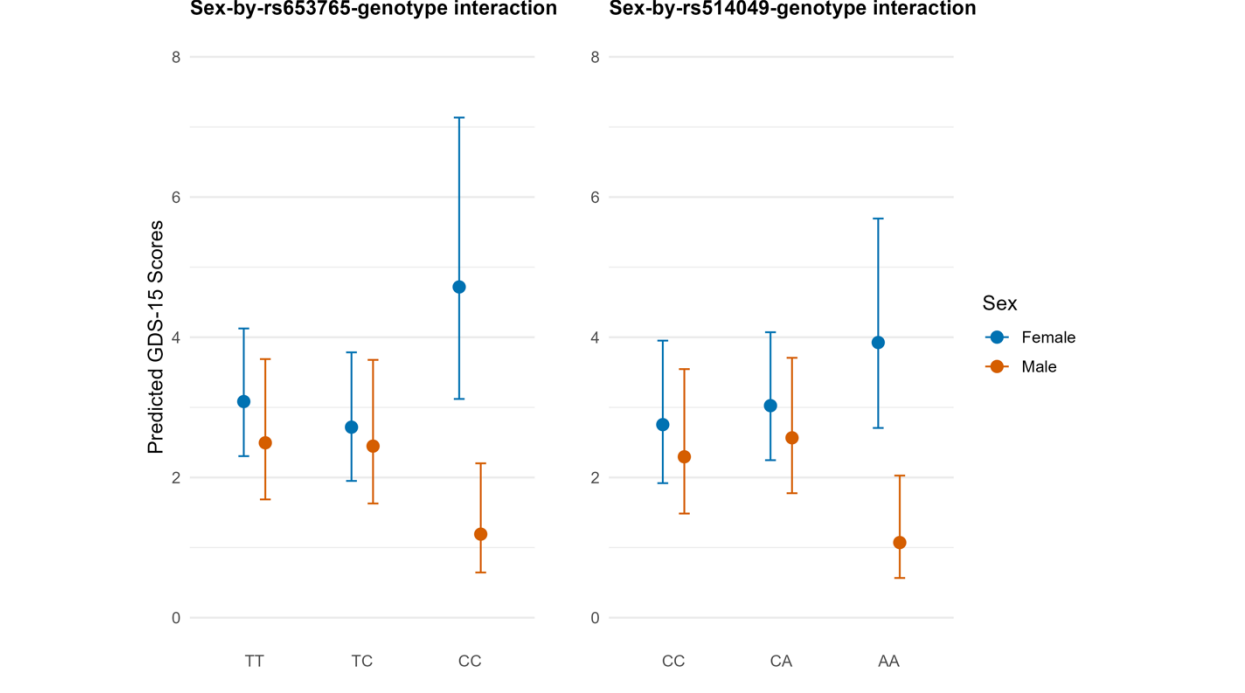
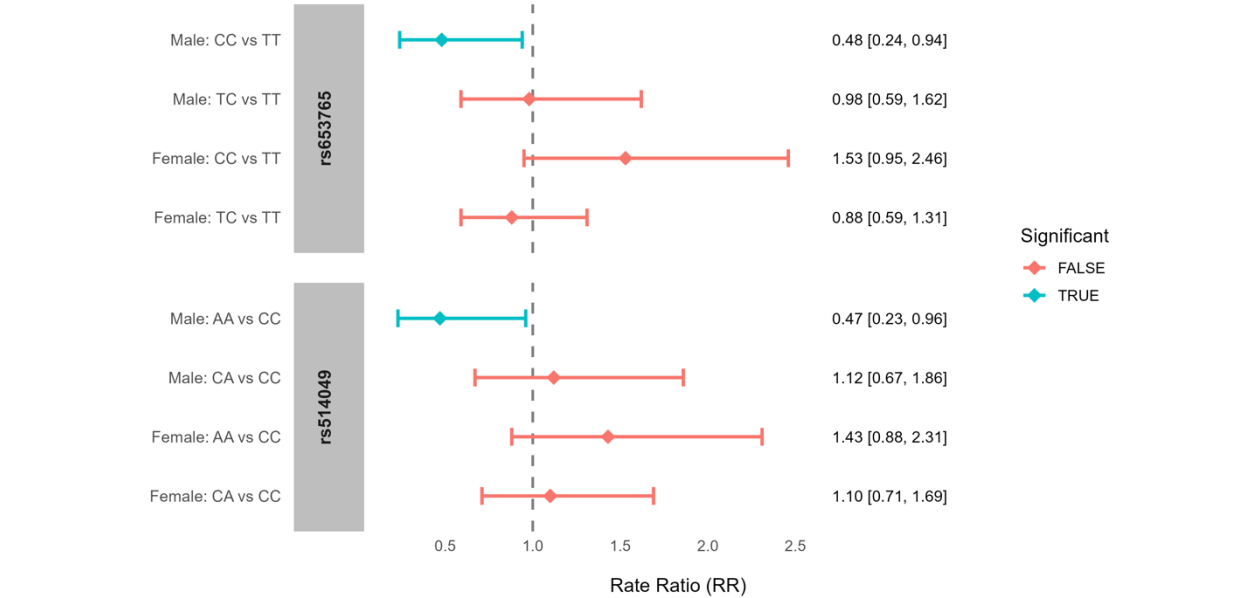


Figure 4. Effect sizes for the stratified analyses by sex for rs653765 and rs514049 SNPs.



ADAM10 polymorphisms are associated with depressive symptoms in a sex-dependent manner, which highlights the complex interplay between genetic factors and sex in shaping susceptibility to depressive symptoms, offering avenues for more personalized approaches to risk stratification and intervention.

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