

Long Runs Of Homozygosity Association With Alzheimer’s Disease

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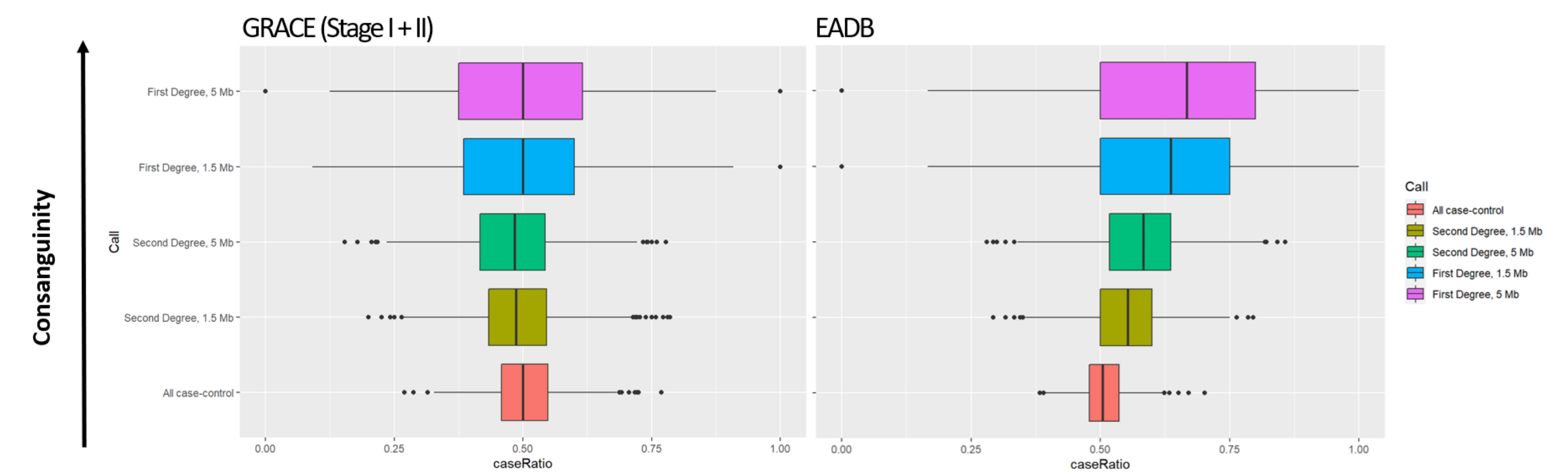
INTRODUCTION

Long runs of homozygosity (ROH) are contiguous genomic regions inherited identical-by-descent from a common ancestor and serve as markers of autozygosity. In our previous work [1], we demonstrated increased ROH burden in outbred individuals of European ancestry with Alzheimer’s disease (AD), supporting a role for consanguinity and recessive genetic inheritance in AD risk. The present study aims to further investigate and strengthen the evidence for a recessive genetic component underlying AD susceptibility.

Table 1. Association of ROH parameters with AD

	PCs1-4 + age + sex			
	EADB		Meta-analysis	
	OR [CI95%]	P value	OR [CI95%]	P value
FROH	1.03 [1.00-1.05]	0.017	1.02 [1.00-1.04]	0.01
AVROH	1.03 [1.01-1.05]	0.012	1.02 [1.00-1.04]	0.03
NROH	1.02 [1.00-1.05]	0.042	1.02 [1.00-1.04]	0.04

Fig 1. Case ratio distribution shifts toward cases when increasing consanguinity in EADB.



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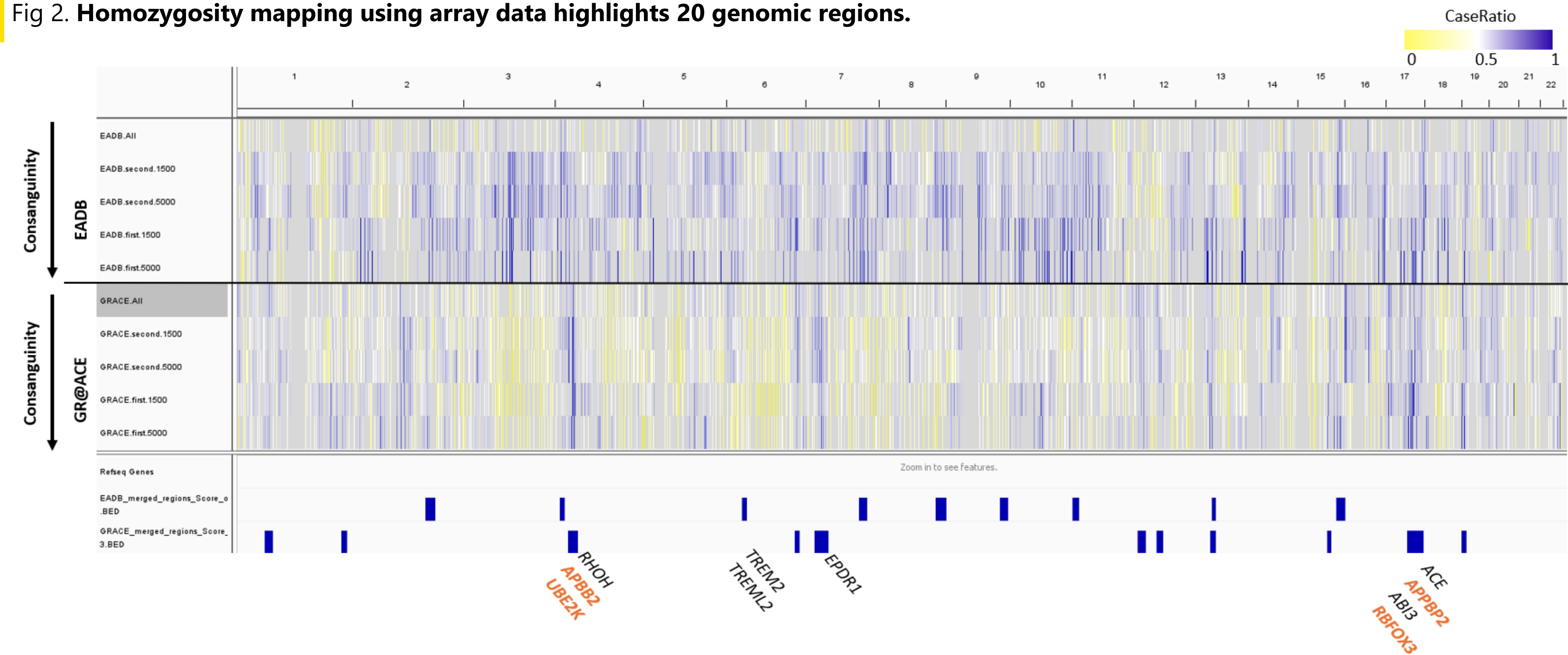
METHODS

Homozygosity patterns (inbreeding coefficient FROH; average ROH length AVROH; number of ROH segments NROH) were analyzed in the EADB dataset which comprises 41,755 outbred individuals across 15 European countries, as an independent replication of previous results [1]. Following replication, we conducted the largest meta-analysis to date incorporating data from 72,017 individuals across three independent cohorts of European ancestry: GR@ACE1 [1], GR@ACE2 and EADB. We used Plink software for ROH identification and R for meta-analysis. Homozygosity mapping was conducted to prioritize genomic regions enriched in inbred AD cases.

RESULTS

We found increased homozygosity in AD cases compared to controls (Table 1). These findings were reinforced in the meta-analysis (Table 1). Additionally, AD cases were overrepresented in the identified ROH segments in both the EADB and GR@ACE2 cohorts (Fig. 1). We identified 20 genomic regions consistently enriched in AD cases with high levels of consanguinity by homozygosity mapping; six of them: *RHOH*, *TREM2*, *TREML2*, *EPDR1*, *ACE*, and *AB13*, have been previously associated with AD (in black; Fig. 2) whereas four of them: *APBB2*, *UBE2K*, *APPBP2*, and *RBFOX3*, are related to amyloid-beta precursor protein or nervous system development (in orange; Fig. 2).

Fig 2. Homozygosity mapping using array data highlights 20 genomic regions.



REFERENCES

1. Moreno-Grau et al. (2021). Translational psychiatry, 11(1), 142.