

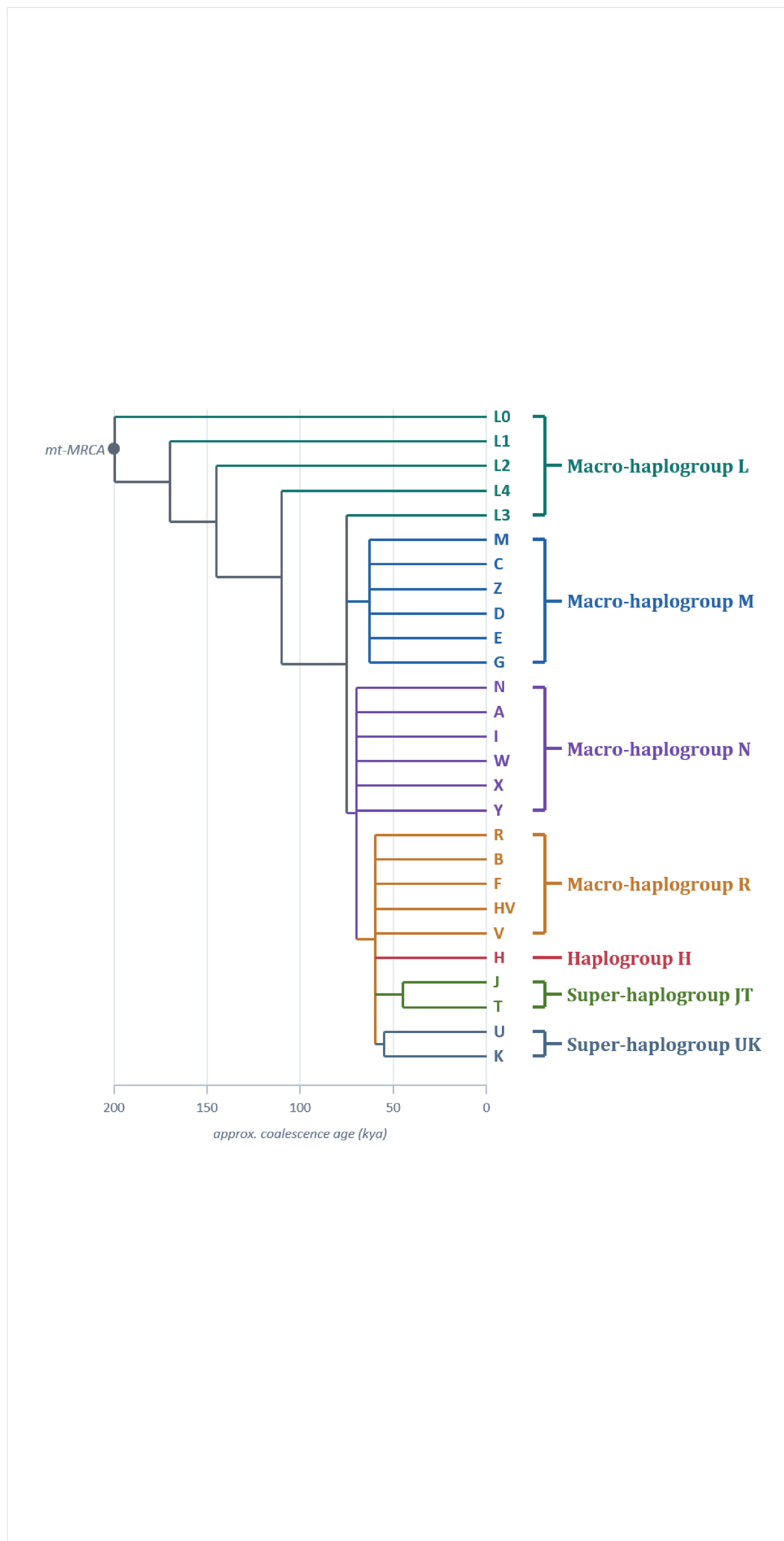
INTRODUCTION

Aging is the strongest risk factor for Alzheimer disease, and **mitochondrial dysfunction** is a hallmark of aging. Several AD GWAS signals implicate mitochondrial function, yet little is known about how variation in **mtDNA** relates to AD.

Because mtDNA is polyploid, variants are **homoplas mies** or **heteroplas mies**. Homoplas mies are germline and identical across all copies, whereas heteroplas mies are a largely somatic mixture of alleles. Haplogroups are phylogenetic branches defined by homoplasmic variants and have been inconsistently associated with AD.

We analyzed haplogroups, homoplasmic variants, and **heteroplasmy burden** in 34,631 multi-ancestry ADSP WGS samples.

MACRO- & SUPER-HAPLOGROUP REFERENCE TREE



MATERIALS & METHODS

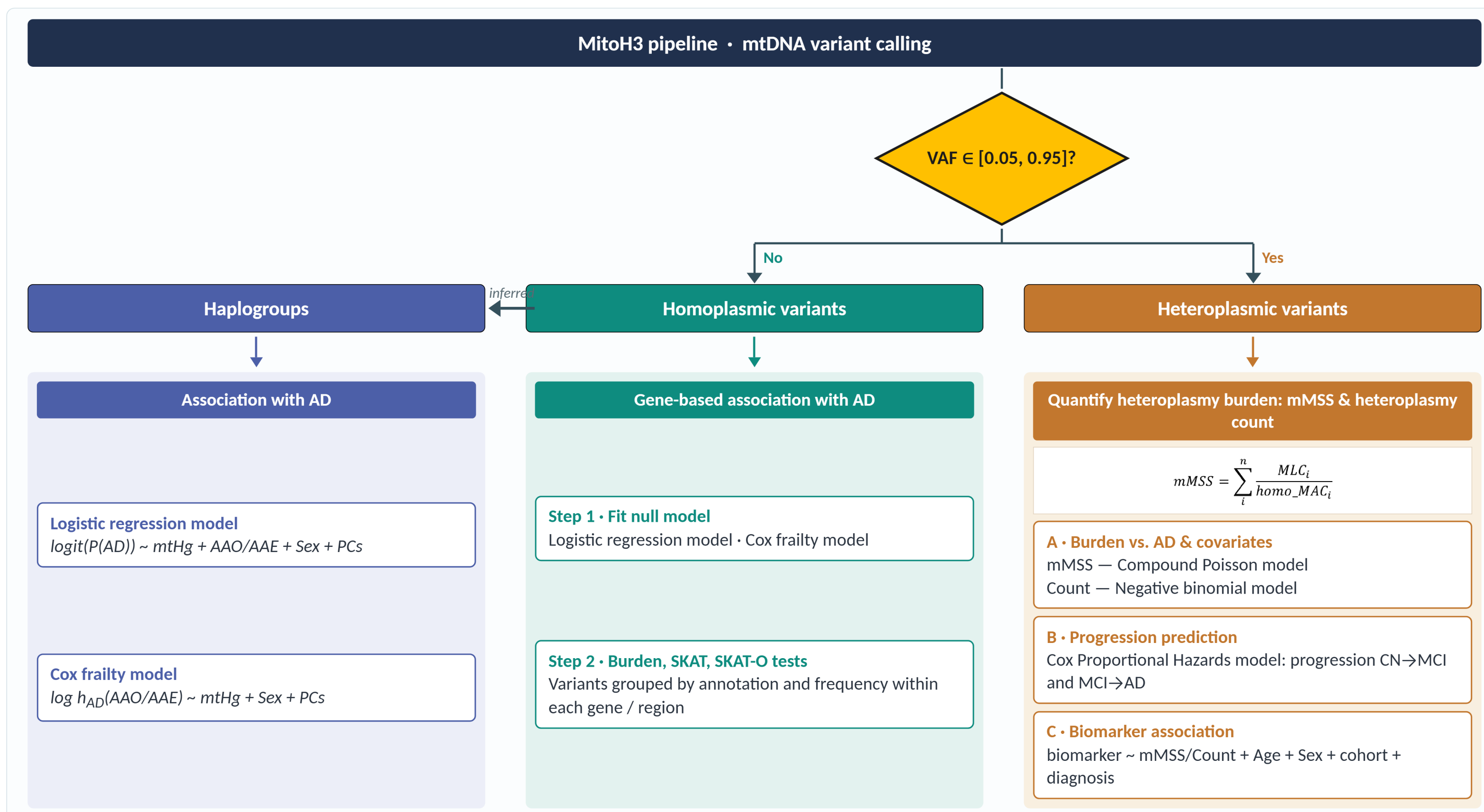
34,631

unique WGS samples (ADSP R4)

26,984

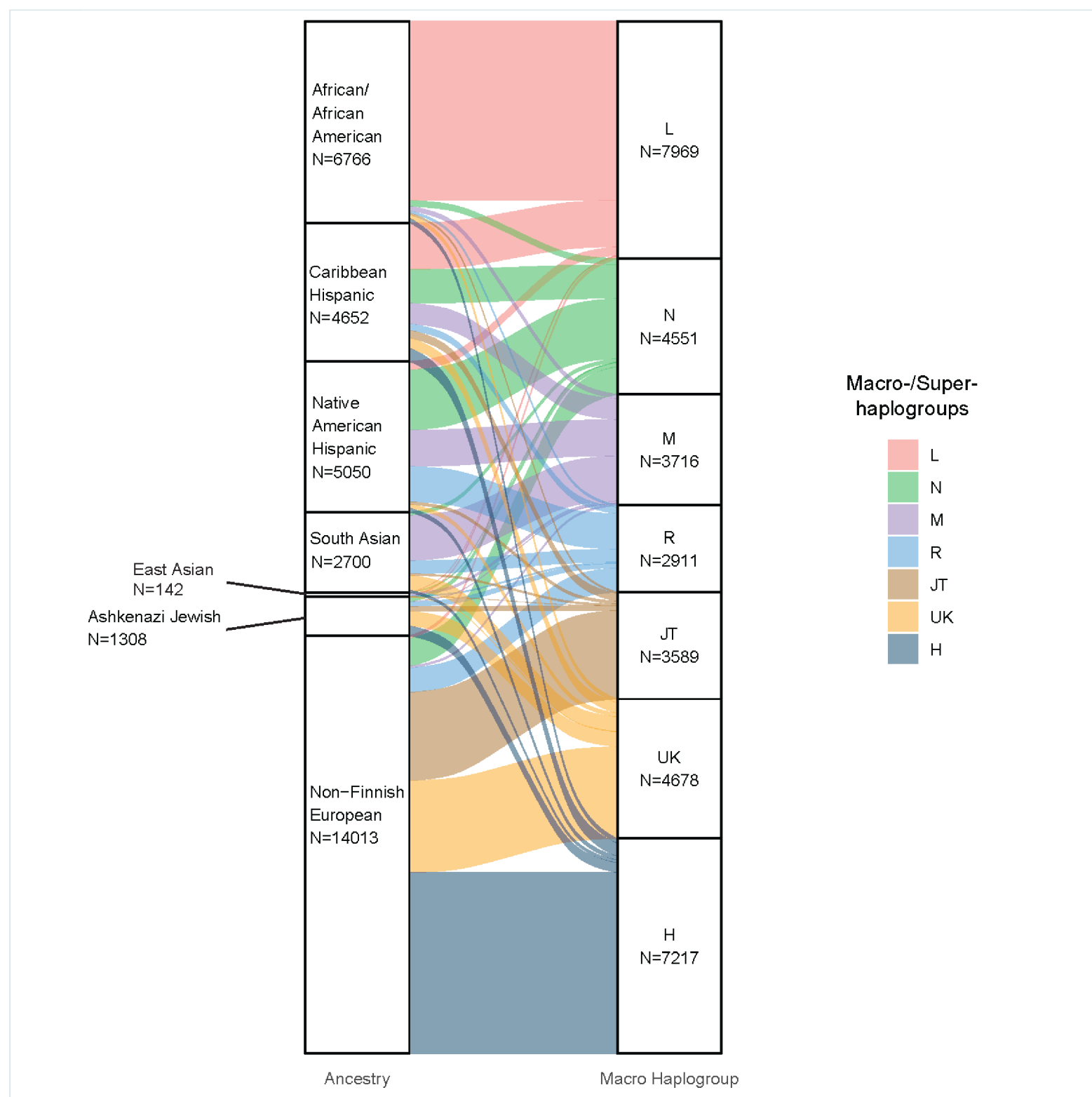
participants with AD diagnosis

STUDY DESIGN - MITOH3 VARIANT-CALLING WORKFLOW



RESULTS

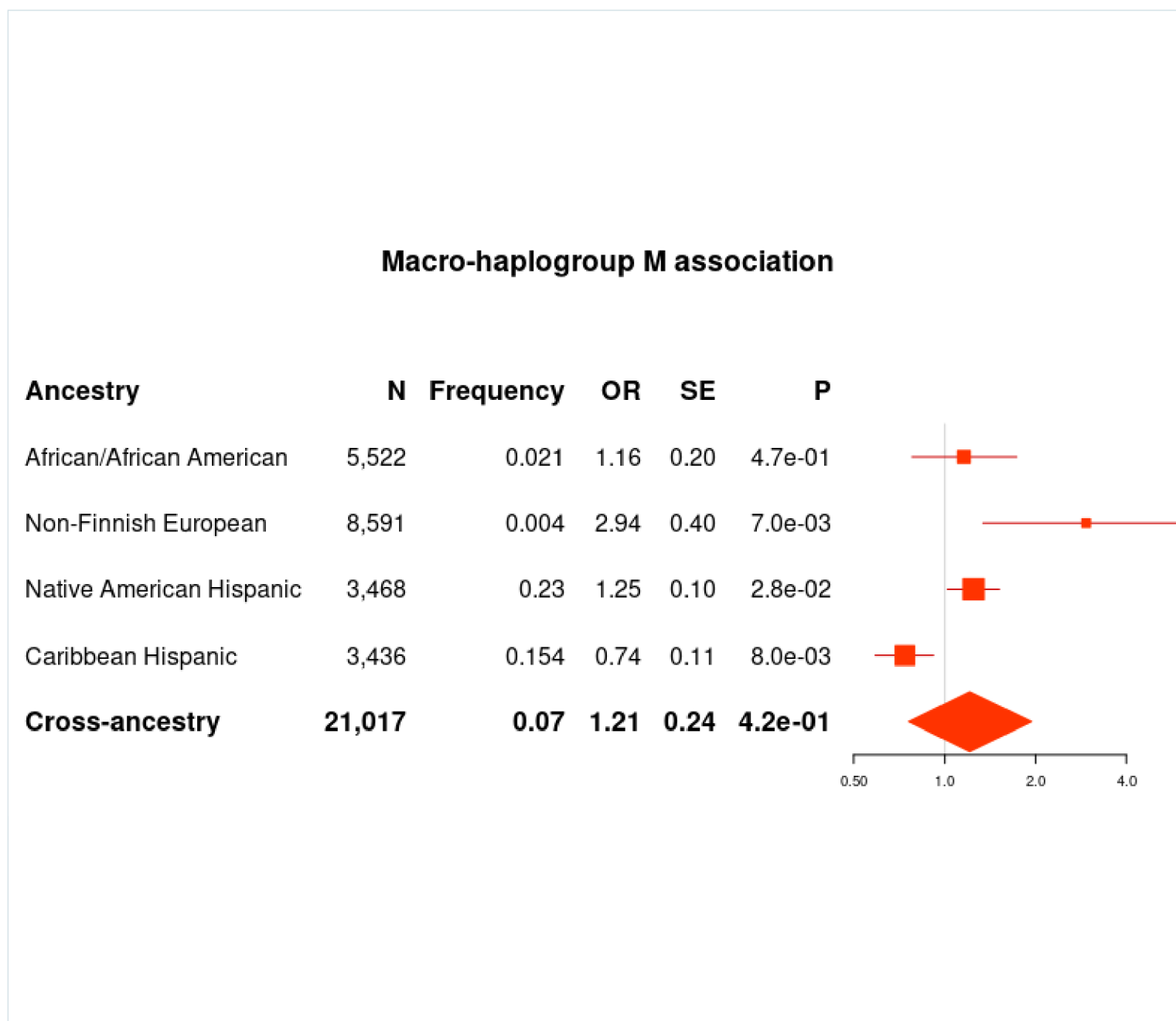
Macro-haplogroup distribution across ancestries



Macro-haplogroup M shows opposite effects by ancestry

Macro-haplogroup M associated with AD in Caribbean Hispanic (CH) and Native American Hispanic (NAH) groups in **opposite directions**. In NAH the signal is driven by **haplogroup C** (OR 1.36, $P = 0.006$; HR 1.32, $P = 0.003$), whereas C trends protective in CH.

FIG 1 • FOREST PLOT — MACRO-HAPLOGROUP M & AD



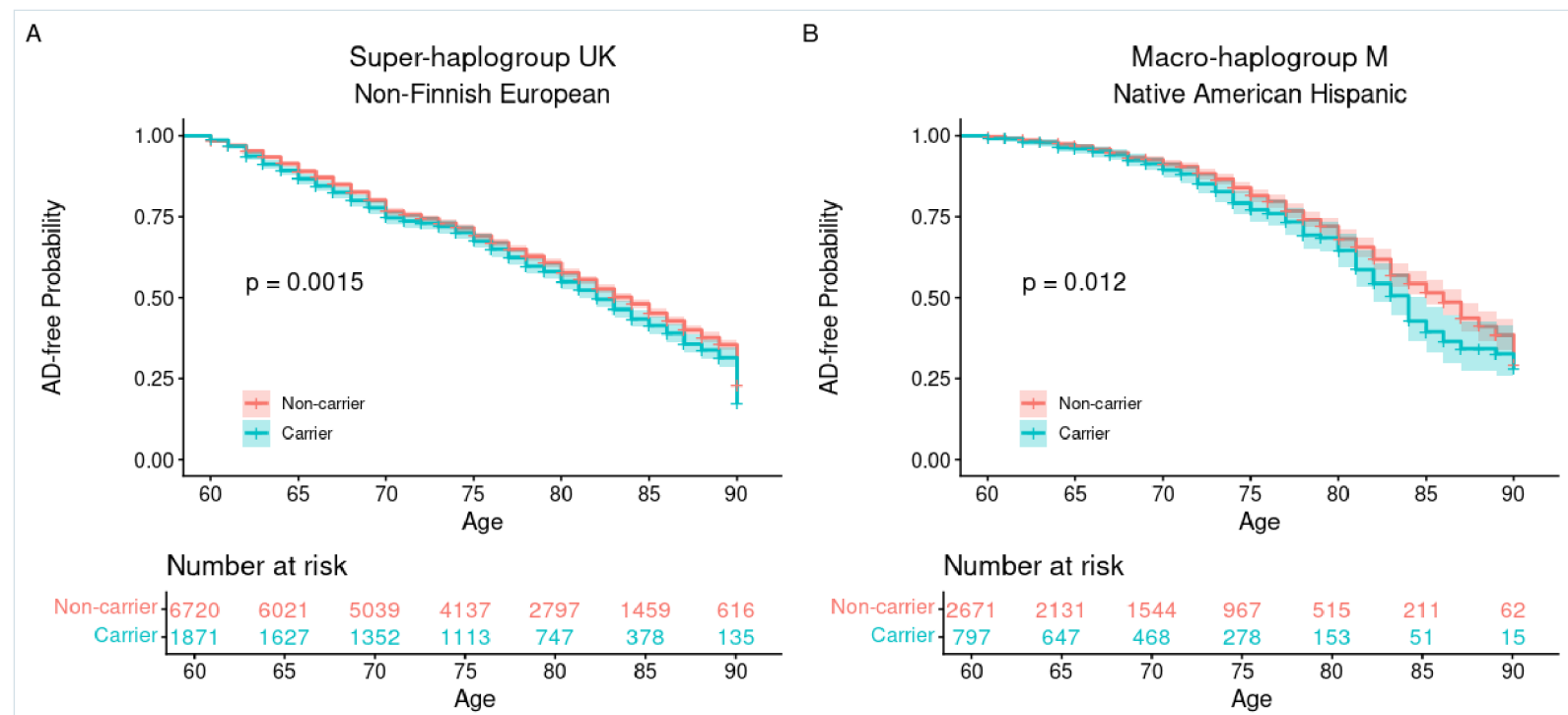
RESULTS (CONT.)

TABLE 1 • HAPLOGROUPS C & D — LOGISTIC & COX FRAILTY

Hg	Anc	N	Freq	Logistic		Cox frailty	
				OR	P	HR	P
C	CH	3436	0.137	0.78	0.042	0.90	0.277
	NAH	3468	0.161	1.36	0.006	1.32	0.003
D	CH	3436	0.016	0.54	0.055	0.78	0.319
	NAH	3468	0.068	0.91	0.589	0.93	0.629

CH = Caribbean Hispanic; NAH = Native American Hispanic. Significant P in red.

FIG 2 • KAPLAN-MEIER SURVIVAL BY HAPLOGROUP CARRIER STATUS



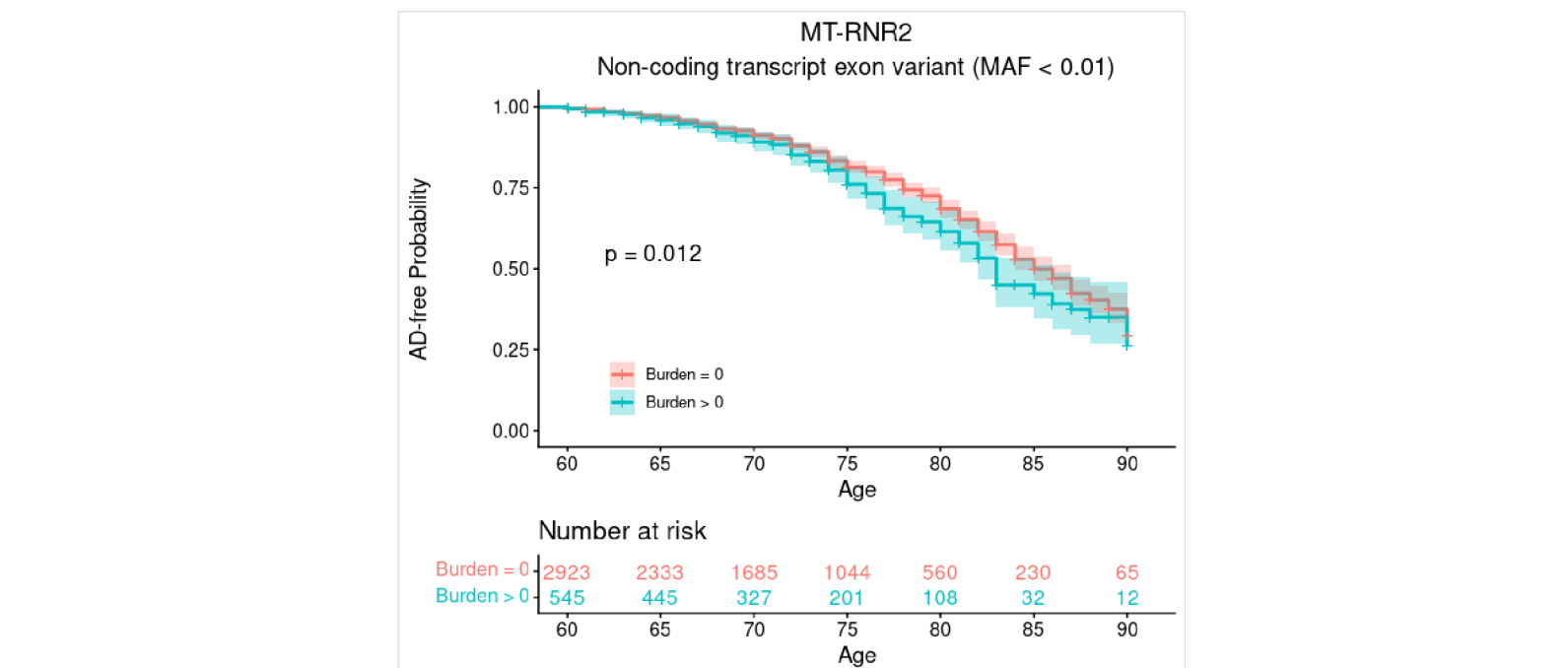
Rare variants in *MT-RNR2* are associated with AD in NAH

TABLE 2 • GENE-BASED ASSOCIATION OF *MT-RNR2* WITH AD (NAH)

Model	MAF @	#Rare	#Ultra Rare	P Burden	P SKAT	P SKAT-O
Logistic	<0.01	35	128	0.036	6.50×10 ⁻⁴	1.17×10 ⁻³
	<0.0001	0	116	0.026	0.026	0.026
Cox Frailty	<0.01	35	128	0.051	8.00×10 ⁻⁴	1.48×10 ⁻³
	<0.0001	0	116	0.011	0.011	0.011

Gene-based rare-variant tests in NAH at two MAF thresholds (0). #Rare / #Ultra Rare = variant counts; headline SKAT / SKAT-O P (0<0.01) in red.

FIG 3 • SURVIVAL BY *MT-RNR2* RARE-VARIANT BURDEN (NAH)



Blood heteroplasmy burden predicts early progression

Blood heteroplasmy burden was associated with **age**, but not sex or prevalent AD. mMSS predicted **progression $CN \rightarrow MCI$** (HR 3.55, $P = 0.033$) but not $MCI \rightarrow AD$; biomarkers were largely uncorrelated except CSF t-tau.

Outcome	Measure	Effect	P
$CN \rightarrow MCI$ progression	mMSS	HR 3.55	0.033
$MCI \rightarrow AD$ progression	mMSS	HR 0.63	0.164

ADNI cohort, N = 1,298.

CONCLUSIONS

Novel associations of **macro-haplogroup M** with AD in CH and NAH with **opposite effects**; in NAH driven by **haplogroup C**.

Rare variants in ***MT-RNR2*** are associated with AD in the NAH population.

Blood heteroplasmy burden (mMSS) predicts progression from **$CN \rightarrow MCI$** , but not prevalent AD.