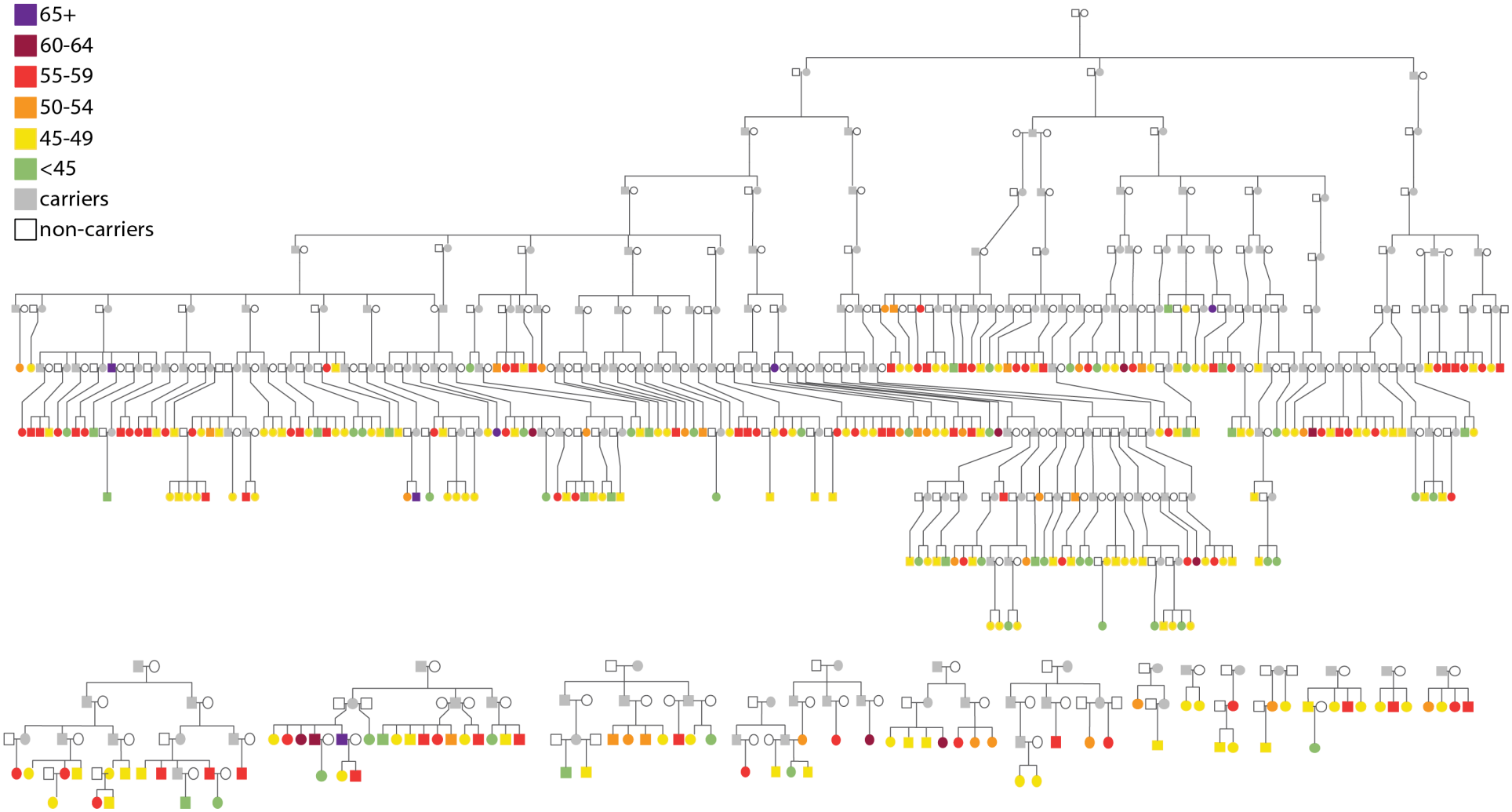
Supplemental Table 1: Summary statistics for all variants. Available at: https://www.ebi.ac.uk/gwas/studies/GCST90244571.

Supplemental Table 2: Annotated summary statistics including replication information from described cohorts for variants with $p<1x10^{-5}$, coding variants with $p<0.05$, *APOE* coding variants, and variants that are index variants for previous GWAS. (see supplemental Excel file)

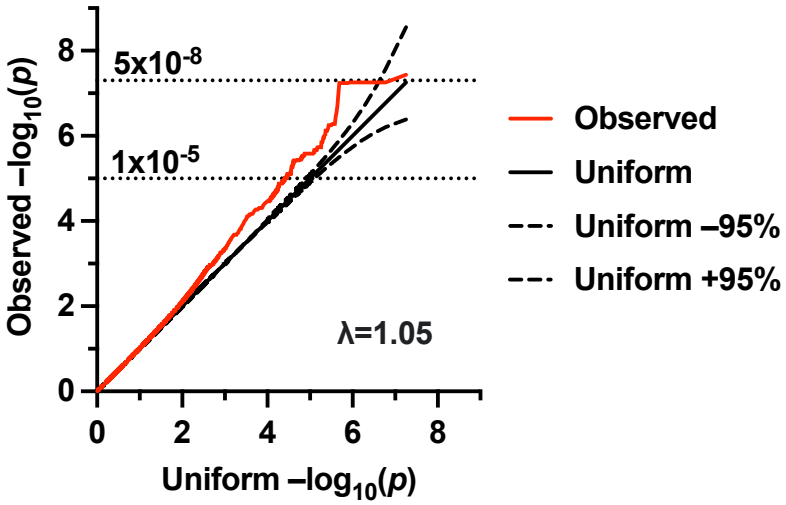
Supplemental Table 3: Single nucleus multiomics regions from a recent study [1] that overlap GWAS variants with $p<1x10^{-5}$. (see supplemental Excel file)

Supplemental Table 4: Full list of GWAS hits from previous studies evaluated. (see supplemental Excel file)

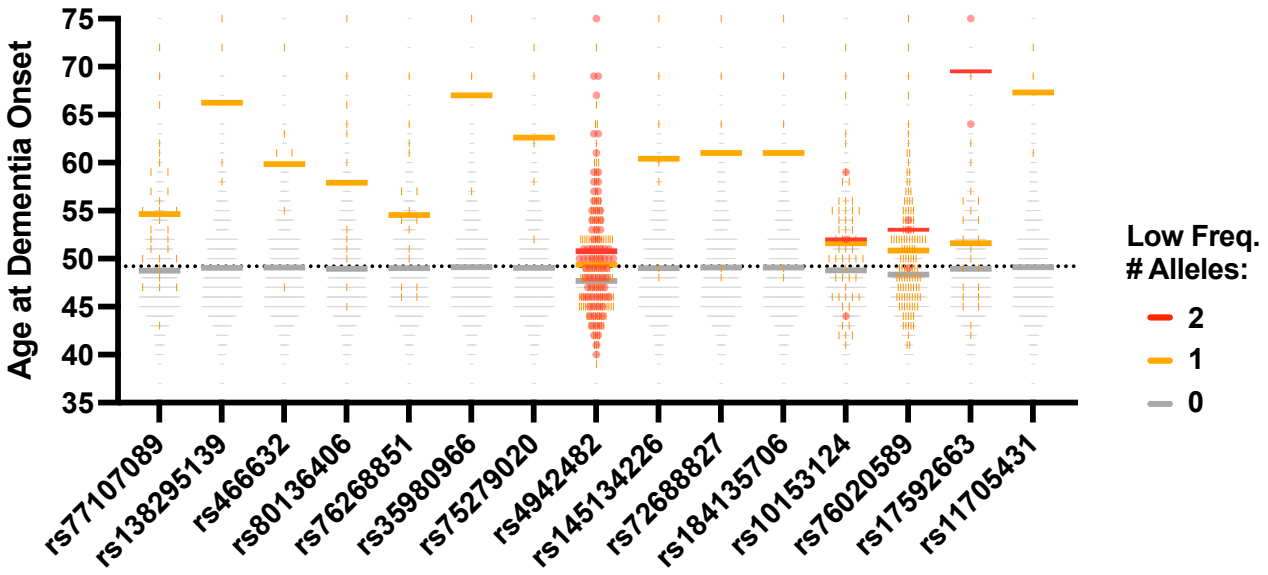
Supplemental File 1: LocusZoom plots of all regions with $p<1x10^{-5}$. (see supplemental LocusZoom file)



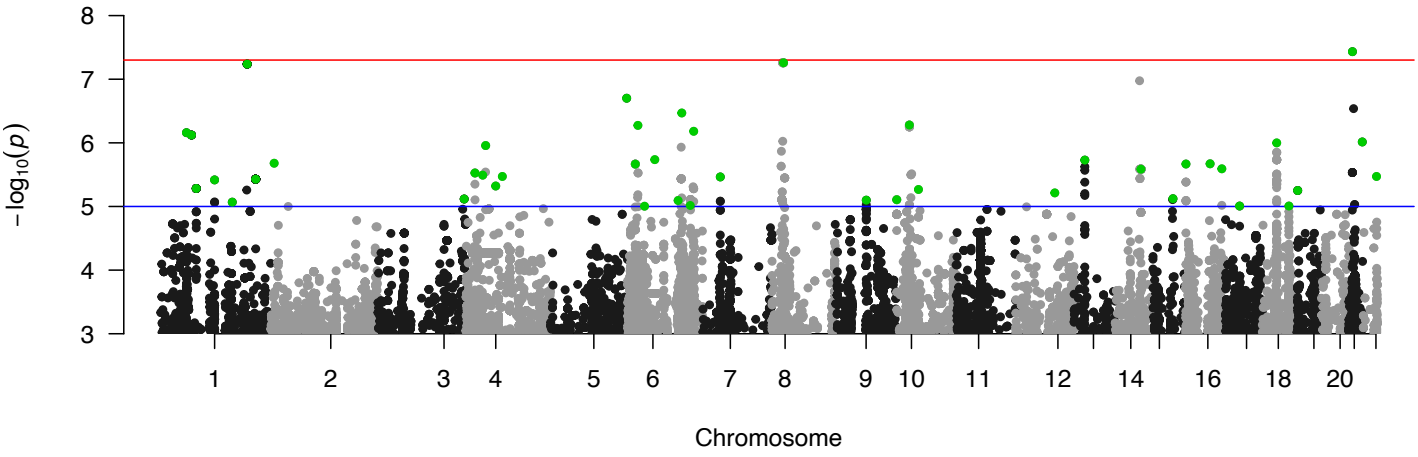
Supplemental Figure 1: Pedigrees of included patients colored according to age at dementia onset. The E280A mutation carriers (known and presumptive) that were not included in the present study are colored in gray. The large pedigree includes 252 of the sequenced participants, and their relatedness until the most recent common ancestors (which were born in 1743–1750). The small pedigrees in the lower row represent 87 additional participants. Healthy siblings and descendants of the participants were excluded for simplicity of the pedigree.



Supplemental Figure 2: QQ plot. Observed (actual age of dementia onset) $-\log_{10}(p)$ values are plotted vs. the uniform distribution of $-\log_{10}(p)$ values. The genomic inflation factor (λ) is modest at 1.05.



Supplemental Figure 3: Age distribution of variants displayed in Table 1.



Supplemental Figure 4: Manhattan plot. Variants selected for display in Table 1 with a discovery $p<1x10^{-5}$ are highlighted in green. Blue line indicates $p<1x10^{-5}$, red line indicates $p<5x10^{-8}$.

Supplemental Methods

IGAP replication study details

International Genomics of Alzheimer's Project (IGAP) is a large three-stage study based upon genome-wide association studies (GWAS) on individuals of European ancestry and served as one source of replication data. In stage 1, IGAP used genotyped and imputed data on 11,480,632 single nucleotide polymorphisms (SNPs) to meta-analyse GWAS datasets consisting of 21,982 Alzheimer's disease cases and 41,944 cognitively normal controls from four consortia: The Alzheimer Disease Genetics Consortium (ADGC); The European Alzheimer's disease Initiative (EADI); The Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium (CHARGE); and The Genetic and Environmental Risk in AD Consortium Genetic and Environmental Risk in AD/Defining Genetic, Polygenic and Environmental Risk for Alzheimer's Disease Consortium (GERAD/PERADES). In stage 2, 11,632 SNPs were genotyped and tested for association in an independent set of 8,362 Alzheimer's disease cases and 10,483 controls. Meta-analysis of variants selected for analysis in stage 3A (n = 11,666) or stage 3B (n = 30,511) samples brought the final sample to 35,274 clinical and autopsy-documented Alzheimer's disease cases and 59,163 controls.

Genome Sequencing and Annotation

Genome sequencing was conducted for a subset (80) of the individuals in the cohort and was used in this study for quality control only. Genome sequencing at HudsonAlpha was conducted using the Illumina NovaSeq platform. Sequencing libraries at HudsonAlpha were prepared by Covaris shearing, end repair, adapter ligation, and PCR using standard protocols. Library concentrations were normalized using KAPA qPCR prior to sequencing. Sequencing reads were aligned to the hg19 reference genome with bwa-0.7.12 [2]. BAMs were sorted and duplicates were marked with Sambamba 0.5.4 [3]. Indels were realigned, bases were recalibrated, and gVCFs were generated with GATK 3.3 [4]. Variants were called across all samples in a single batch with GATK 3.8 using the -newQual flag to minimize false negative singleton calls. Additional genomes were sequenced previously with CompleteGenomics technology and also aligned to the hg19 reference [5]. In order to facilitate annotation, multi-allelic sites were split using Vt [6]. SnpEff 4.3s [7] was used to annotate with the gene definitions from human genome build Ensembl GRCh37.75. All variants were annotated with CADD

v1.3 [8], including all indels. Population database frequency annotations included 1000 genomes phase 3, TOPMed Bravo [9] (lifted over from hg38 to hg19 using CrossMap 0.2.7 [10]), and several population database sets annotated using WGSA 0.7 [11] including ExAC [12], gnomAD [13], ESP, and UK10K. Variants were also annotated with dbSNP release 153 [14]. For intersection of array data, which was annotated with hg38, we lifted over genome sequencing data using CrossMap 0.3.4 [10].

Variant Measurement, Imputation, and Quality Control

Pre-imputation scripts (version 4.3.0 from William Rayner at the University of Oxford) [15] were run using default settings, which filtered out palindromic single nucleotide variants (SNVs) with minor allele frequency (MAF) > 0.4 or variants with > 0.2 MAF difference from the TOPMed reference panel. For samples with both array and genome sequencing data, imputed genotypes were checked for concordance with genome sequencing data using SnpEff 4.3s.

373 arrays were measured over two batches (299 in batch one and 74 in batch two) representing 368 presumed unique individuals. The five duplicated individuals were from the following: four individuals from batch one with high missingness were re-run, and a new aliquot of one sample from batch one that was identified as a duplicate of another sample was re-run. Of the 373 array measurements, three were excluded because they were identified as mislabeled duplicates of other samples, and 33 were excluded because they had a missingness rate of greater than 5%, heterozygosity >3 standard deviations from the mean, were <95% concordant with genome sequencing data, or lacked age at dementia onset data. 340 unique individuals with high quality array data remained for analysis.

26 genomes were sequenced at HudsonAlpha including seven out of eight of the oldest age at onset individuals along with their affected family members with more typical ages of onset. 55 genomes from additional E280A carriers were sequenced previously with CompleteGenomics technology [5].

We used both array and genome information to generate a high-quality variant set for use in imputation. Array data were further selected (beyond the already mentioned cutoff of a maximum 5% missingness for any sample) to a maximum missingness of 1% for any genotype. A Hardy-Weinberg equilibrium cutoff of $1x10^{-6}$ was used. Variants were quality checked against TOPMed Freeze 5 PASS filter variants using pre-imputation scripts as described above. The pre-imputation quality control pipeline is available at

https://github.com/HudsonAlpha/Pre-Imputation-QC-Pipeline and post-imputation at https://github.com/HudsonAlpha/Post-Imputation-Pipeline. Variants with Mendelian inconsistencies were excluded, resulting in 844,970 array-measured variants after QC. For genome sequencing data, we selected PASS filter variants in the HudsonAlpha-sequenced set that also had a 99% call rate across both HudsonAlpha and CompleteGenomics genomes. The intersection of variants from genome sequencing and array measurements was then used to assess concordance between samples with both types of measurements, and one sample was excluded for <95% concordance between measurement types (median concordance for the remaining 80 samples was 99.94%, indicating the high quality of this intersected variant set). 340 total unique individuals with high quality data remained for imputation, and 540,753 variants met all filtering criteria for both arrays and genome sequencing.

The set of 540,753 high quality variants for 340 unique E280A carriers was used as input for imputation using the TOPMed imputation server (version 1.3.3), with an output of 20,707,761 variants passing an r^2 cutoff of 0.3. Because of the importance of the *APOE* locus, we inspected the imputation results for rs429358 and rs7412, which together define *APOE* ε alleles. All genotypes matched between imputed and separately genotyped values for rs7412, and all but one genotype matched between imputed and separately genotyped values for rs429358. For the discordant genotype, the directly measured genotype was used. In addition, although it was not imputed because of rarity, we manually inserted directly measured genotypes for rs121918393 because of its implicated role in a previous study [16]. As an additional quality control measure, we filtered this imputation set to variants called in HudsonAlpha-sequenced genomes with a VQSLOD score > -3 and again filtered any variants with Mendelian inconsistencies, resulting in a final set of 9,430,010 high quality variants. We considered all variants as a part of the relatedness matrix to obtain the best adjustment for relatedness possible, but only considered variants with an allele count of at least 3 for association testing, yielding 9,012,264 variants.

Single Nucleus Multiomics

Single nucleus multiomics data were accessed from [1]. Implicated cell types from multiomics are listed for each multiomics association in **Supplemental Table 3**.

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DIAN

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DIAN study group

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ADDS

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ADGC (from ADGC website, https://www.adgenetics.org/)

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