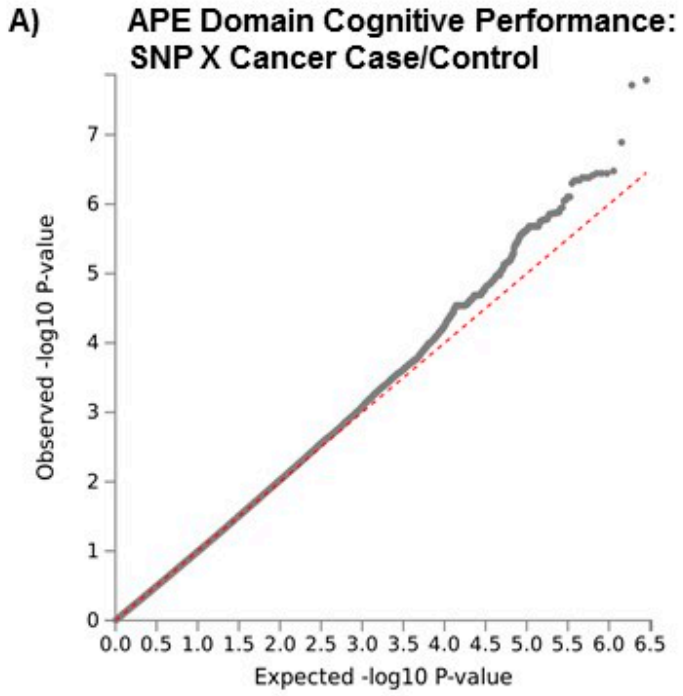
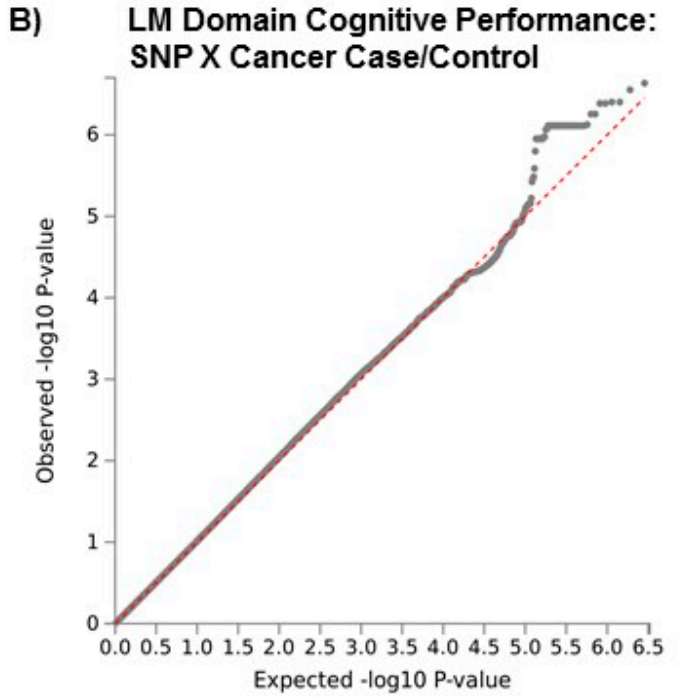
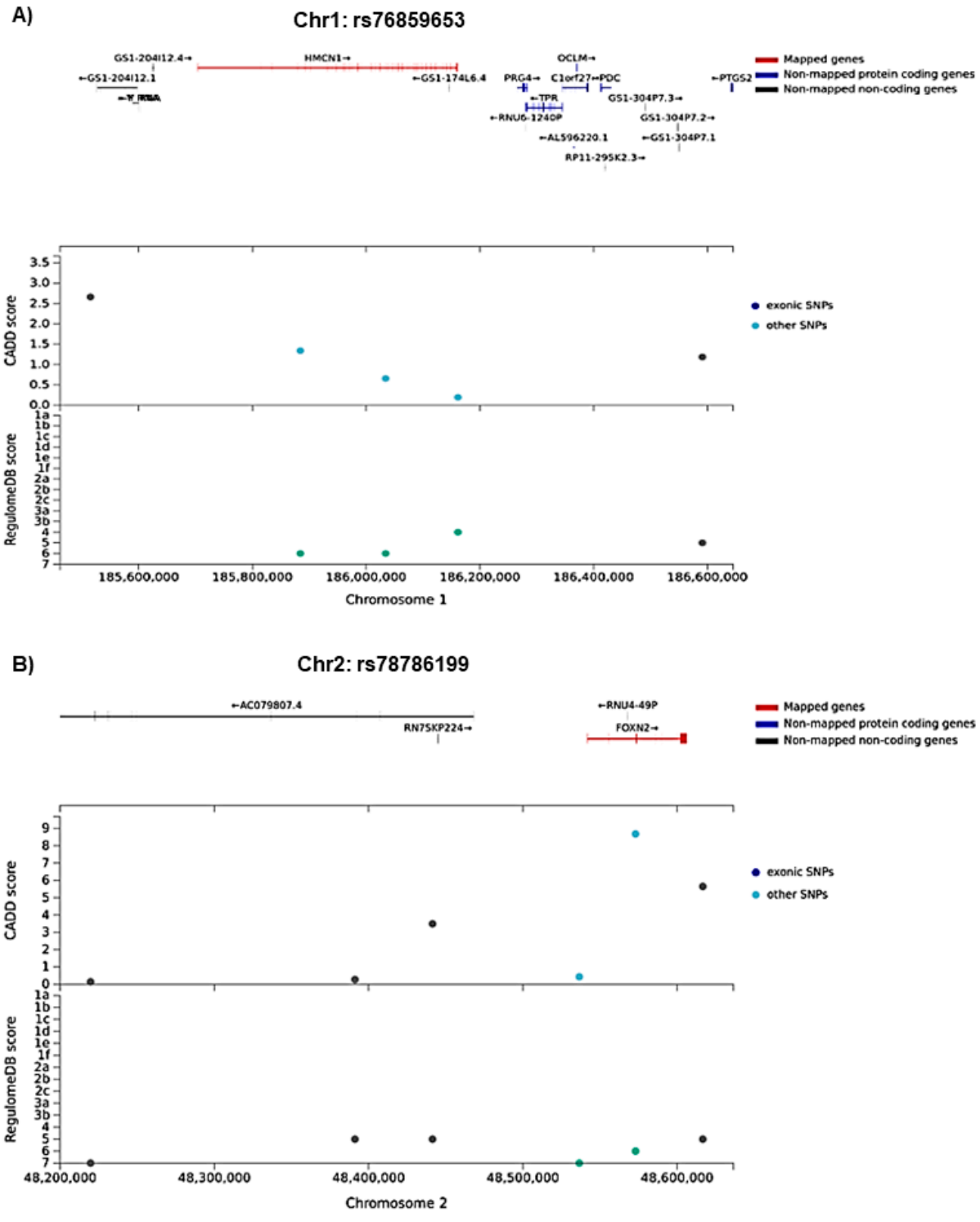
SUPPLEMENTARY FIGURES



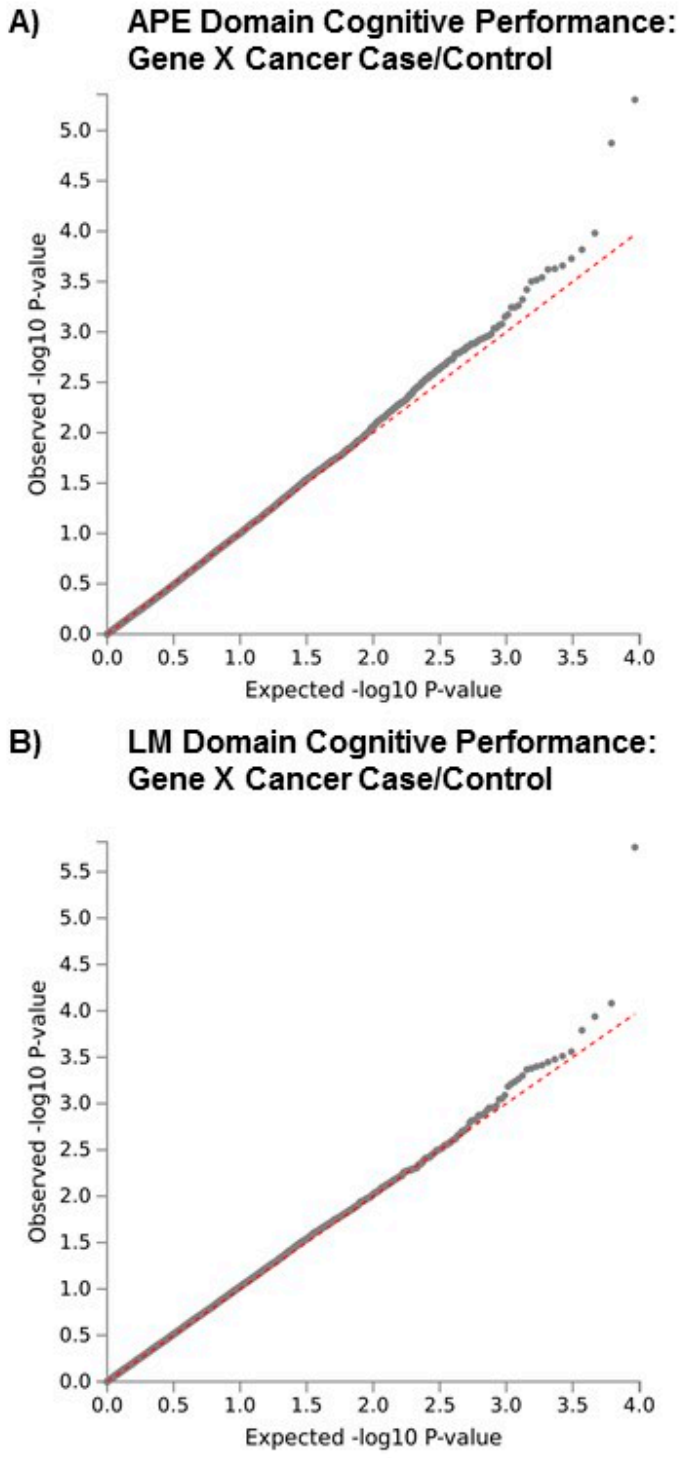


Supplementary Figure S1. GWAS QQ Plots. A) Attention, Processing speed, and Executive function (APE) QQ plot of –log10 p-values for GWAS analysis (APE domain one-year follow-up (1Y) visit ~ SNP*Cancer case/control). B) Learning and Memory (LM) QQ plot of –log10 p-values for GWAS analysis (LM domain 1-year follow-up (1Y) visit ~ SNP*cancer case/control). Dotted red lines depict 1:1 correlation of observed:expected p-values.



Supplementary Figure S2. Regional Plots for Lead SNPs from APE GWAS Analysis. Each panel shows exonic SNPs (dark blue) and other SNPs (light blue),

graphed for CADD score (SNP deleteriousness) and RegulomeDB score (evidence for transcription factor function) within the region of the lead SNP identified in the GWAS analysis; increasing values for both CADD and RegulomeDB indicate increasing likelihood of function. Location on the chromosome in base pairs is shown on the X-axis. A) Regional SNP Plot for rs76859653 on chromosome 1, a lead SNP significantly differently associated with APE cognitive domain performance at one-year follow-up (1Y) visit by group, covarying for age, baseline WRAT4 score, site, and baseline APE performance. B) Regional SNP Plot for rs78786199 on chromosome 2, a lead SNP significantly differentially associated with APE cognitive domain performance at 1Y visit by group, covarying for age, baseline WRAT4 score, site, and baseline APE performance.



Supplementary Figure S3. Gene QQ Plots. A) Attention, Processing speed, and Executive function (APE) QQ plot of –log10 p-values for gene-level analysis (APE

domain one-year follow-up (1Y) visit ~ Gene*Cancer case/control). B) Learning and Memory (LM) QQ plot of –log10 p-values for gene analysis (LM domain 1Y follow-up (1Y) visit ~ Gene*cancer case/control). Dotted red lines depict 1:1 correlation of observed:expected p-values.

SUPPLEMENTARY METHODS

Data Collection

Neuropsychological Testing

The APE domain score includes the Digits Forward and Backward subtests from the Neuropsychological Assessment Battery (NAB), Trail Making Tests A and B, the Controlled Oral Word Association Test, and the Digit Symbol subtest from the Wechsler Adult Intelligence Scale-III [1-5]. The LM domain includes the Logical Memory I and II subtests from the Weschler Memory Scale-III and the Immediate Recall, Short Delayed Recall, and the Long Delayed Recall scores from the NAB List Learning Test [1, 4, 5].

Genetics

GWAS quality control included genetic sex check (all female), removal of subjects with >10% SNP failure rate, removal of SNPs with >5% failure rate, removal of duplicate SNPs and those with minor allele frequencies <1%, and removal of SNPs with Hardy-Weinberg equilibrium (HWE) $p<1x10^{-6}$. SNPs that violate the assumptions of Hardy-Weinberg equilibrium were removed, as if SNPs have significantly different numbers of homozygous and heterozygous carriers based on the SNP population allele frequency, it could indicate genotyping errors. Identity-by-descent, which evaluates the

percentage of regions of identical DNA shared between two individuals to determine relatedness, was used to check for relationships among participants.

Each batch of genetic data was then merged with HapMap3 genotype data representing distinct genetic ancestral reference populations, and analyzed with multidimensional scaling (MDS) in PLINK [6]. Multidimensional scaling is used to evaluate the clustering of genetic data for TLC cases and controls with the reference population genetic data, to identify the genetic ancestry of each participant. Principal components were calculated for genetic ancestry using the clustering algorithm, and participants of white non-Hispanic ancestry were selected for imputation.

Imputed data was further filtered to remove SNPs with HWE $p<1x10^{-6}$, as well as SNPs with minor allele frequencies <1%.

Statistical Methods and Analyses

The Functional Mapping and Annotation of Genome-wide Association Studies (FUMA GWAS) program [7] v1.3.6a. was used to create Manhattan and Q-Q plots and identify significant SNPs. Manhattan plots visualize GWAS results across the genome (x-axis), showing each SNP result as a separate point by location and $-\log_{10}$ p-value (y-axis). Q-Q plots visualize the observed vs. expected $-\log_{10}$ p-value for SNPs to detect whether there is any unaccounted-for population structural bias (significant deviation from a linear trend line, also indicated by genome inflation calculation). The genomic inflation factor for observed vs. expected test statistics was calculated separately in R v3.6 [8].

References

[1] Stern R, White T. Neuropsychological Assessment Battery: Administration, Scoring, and Interpretation. Lutz, FL: Psychological Assessment Resources, Inc.; 2003.

[2] Reitan R. Validity of the Trail Making Test as an indicator of organic brain damage. Perceptual and motor skills. 1958;8:271-6.

[3] Patterson J. Controlled Oral Word Association Test. In: Kreutzer J, DeLuca J, Caplan B, editors. Encylopedia of Clinical Neuropsychology. New York, NY: Springer New York; 2011. p. 703-6.

[4] Wechsler D. WAIS-III, Wechsler Adult Intelligence Scale: Administration and Scoring Manual. San Antonio, TX: Psychological Corporation; 1997.

[5] Wechsler D. Manual for the Wechsler Memory Scale-Revised. San Antonio, TX: Psychological Corporation; 1987.

[6] Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet. 2007;81:559-75.

[7] Watanabe K, Taskesen E, van Bochoven A, Posthuma D. Functional mapping and annotation of genetic associations with FUMA. Nat Commun. 2017;8:1826.

[8] R Development Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2019.