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Supplemental Data

**A Common Polymorphism in *HIBCH*
Influences Methylmalonic Acid Concentrations
in Blood Independently of Cobalamin**

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Figure S1. Q-Q Plot of association results of \log_{10} transformed MMA with age and sex adjustment, using 758,443 genotyped SNPs after QC; plot truncated at $-\log_{10}(p) = 10$ and excluding chromosomes 2 and 16.

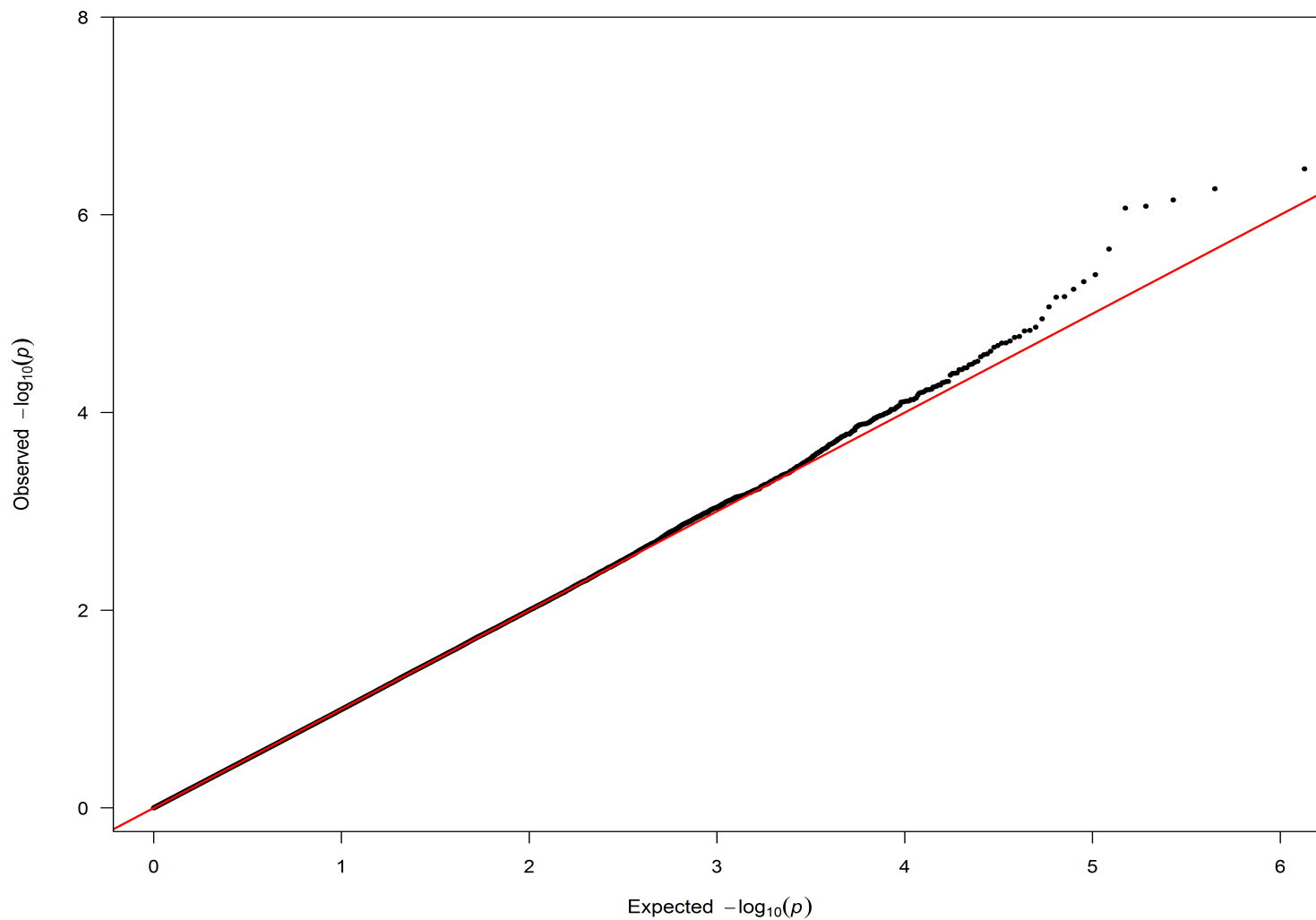


Figure S2. Manhattan Plot of association results of \log_{10} transformed MMA with age and sex adjustment, using 2,350,751 imputed genotypes (HapMapII panel) after QC (imputation quality $R^2 > 0.5$). Two horizontal lines in the plot represent: red: $-\log_{10}(p) = 5$ ($p = 1 \times 10^{-5}$) : Suggestive significance; and blue: $-\log_{10}(p) = 7.3$ ($p = 5 \times 10^{-8}$) : Genome-wide significance.

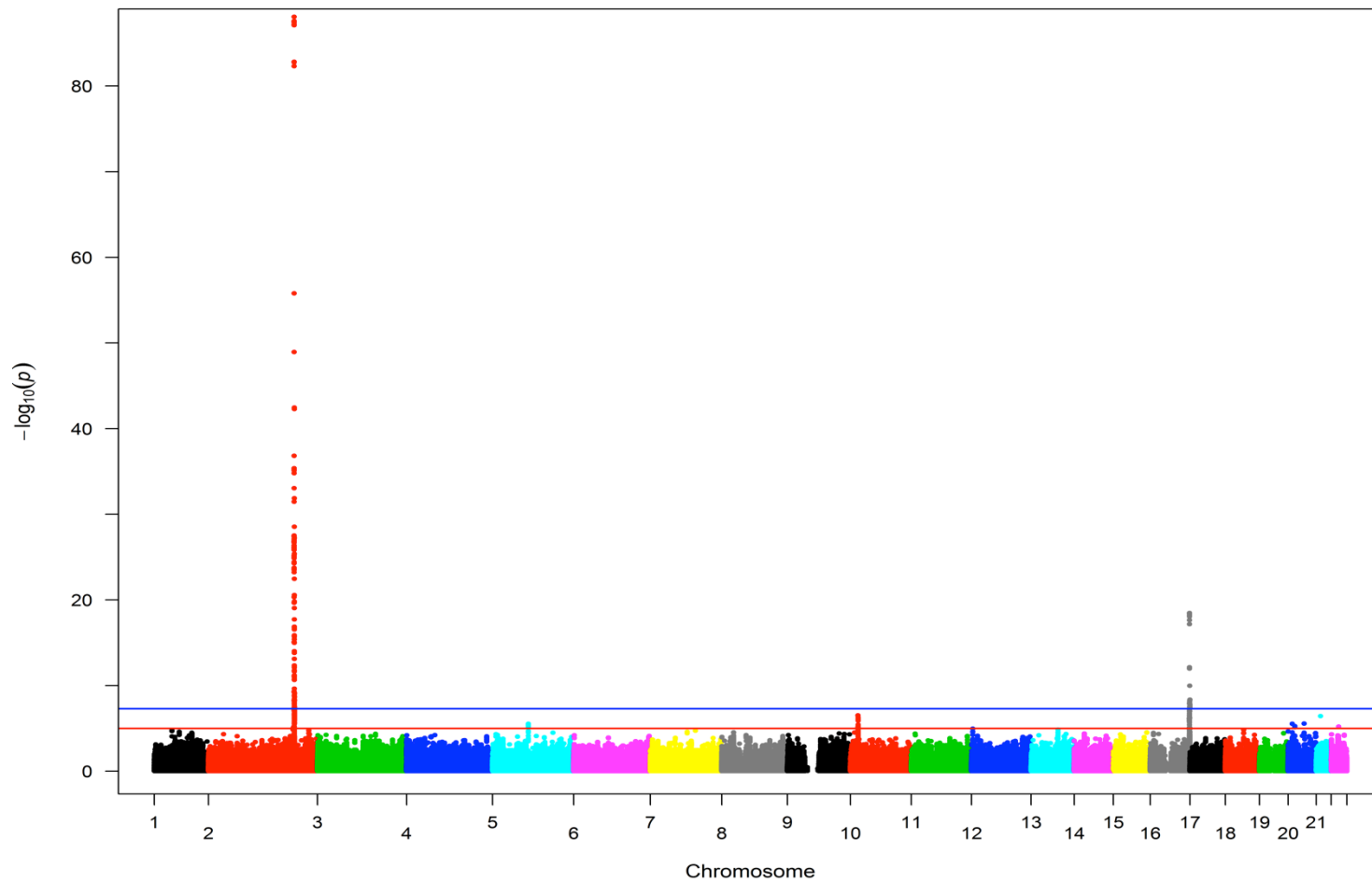
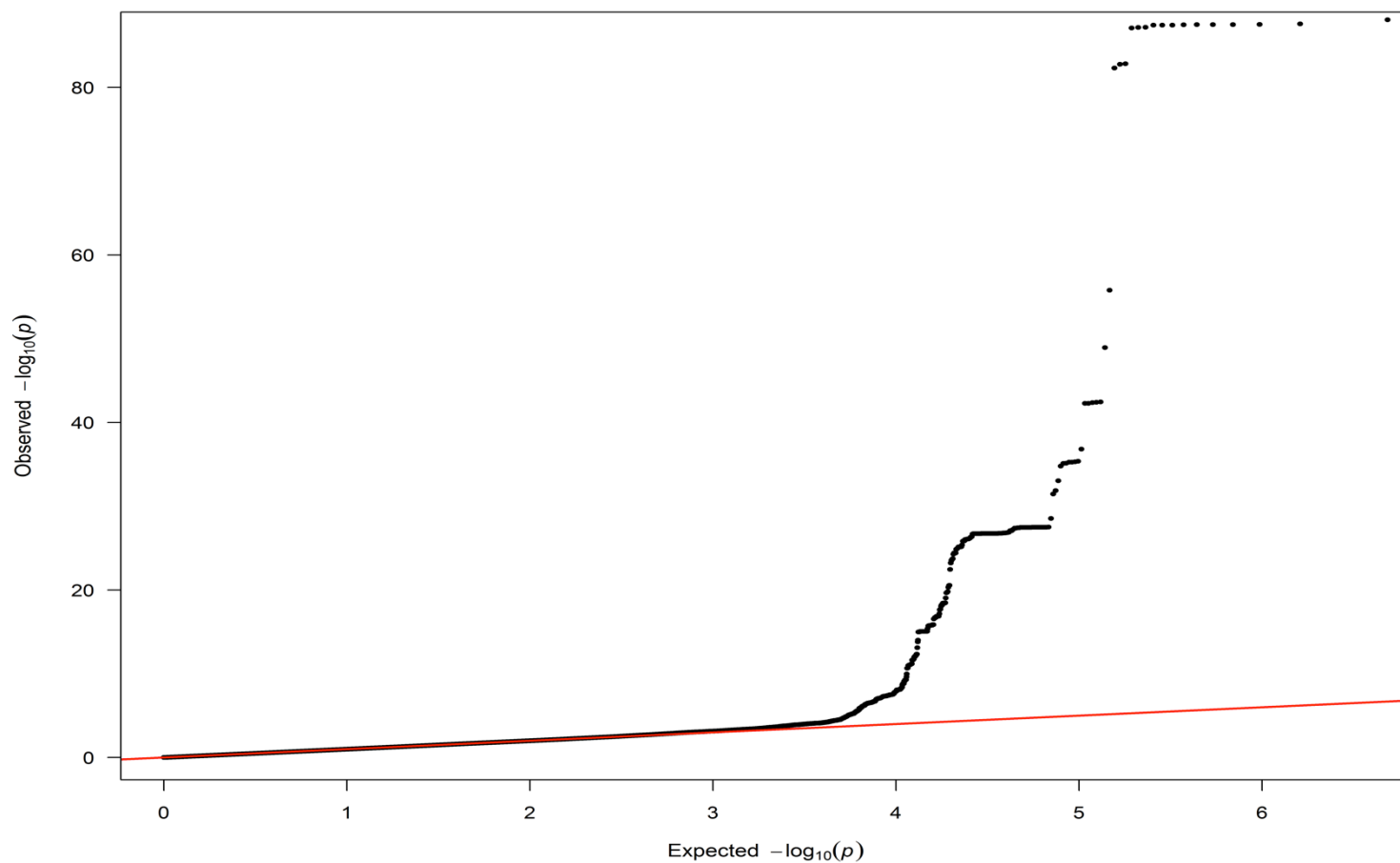
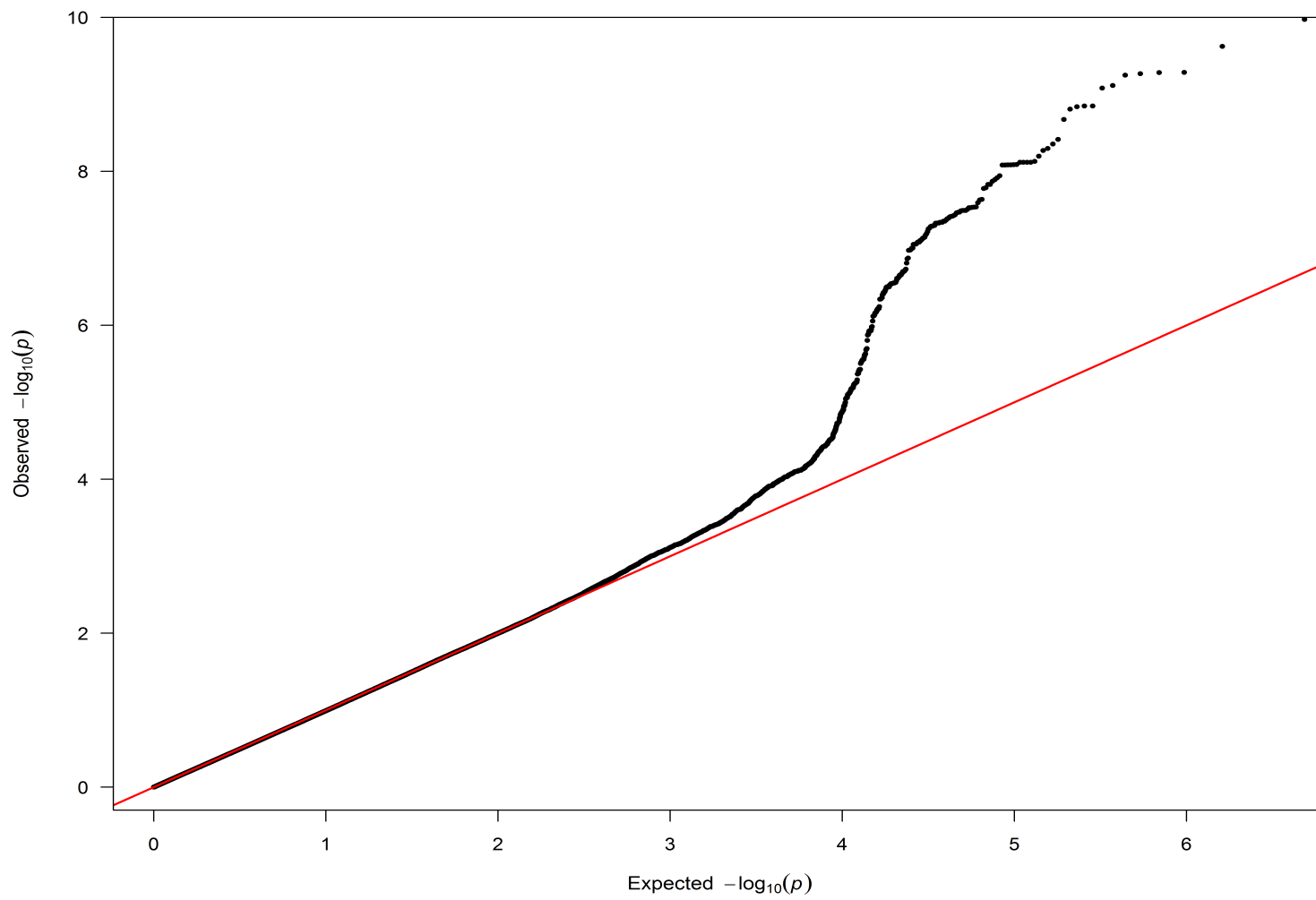


Figure S3. A) Q-Q Plot of association results of \log_{10} transformed MMA with age and sex adjustment, using 2,350,751 imputed genotypes (HapMapII panel) after QC (imputation quality $R^2 > 0.5$); B) Same plot truncated at $-\log_{10}(p) = 10$; C) Same plot excluding chromosomes 2 and 16.

A)



B)



c)

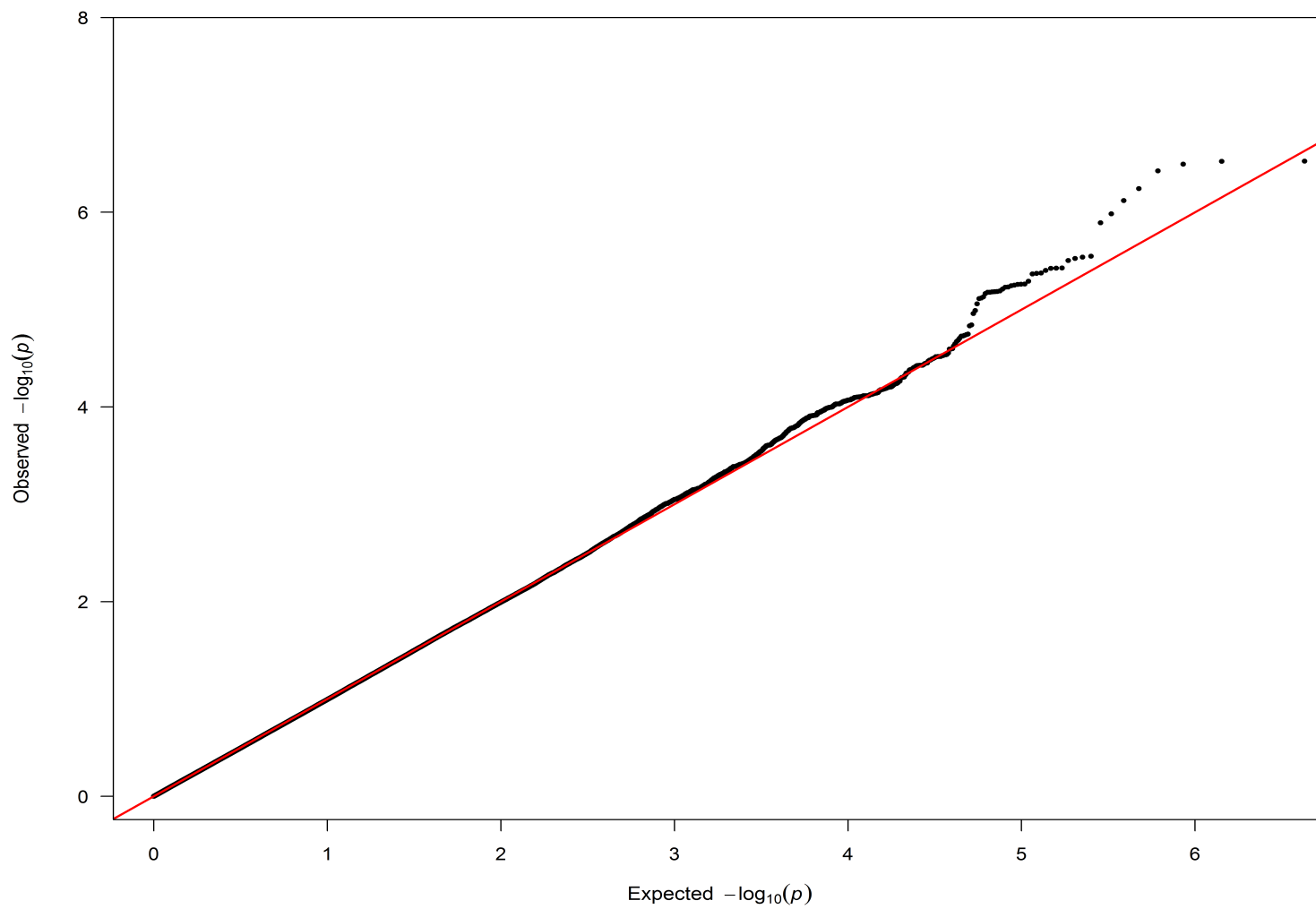


Figure S4. Western blotting of cellular fractions for HIBCH. Subcellular fractions of thirteen Coriell lymphoblastoid cell lines were collected using the Qproteome Cell compartment Kit (Qiagen). The cytoplasmic (C), membrane (including mitochondria, M) and nuclear (N) fractions are shown. Western blotting was performed with antibodies to heat shock protein A9 (HSPA9) or HIBCH, as shown. Fraction purity was assessed by blotting for HSPA9, which localizes to mitochondria.

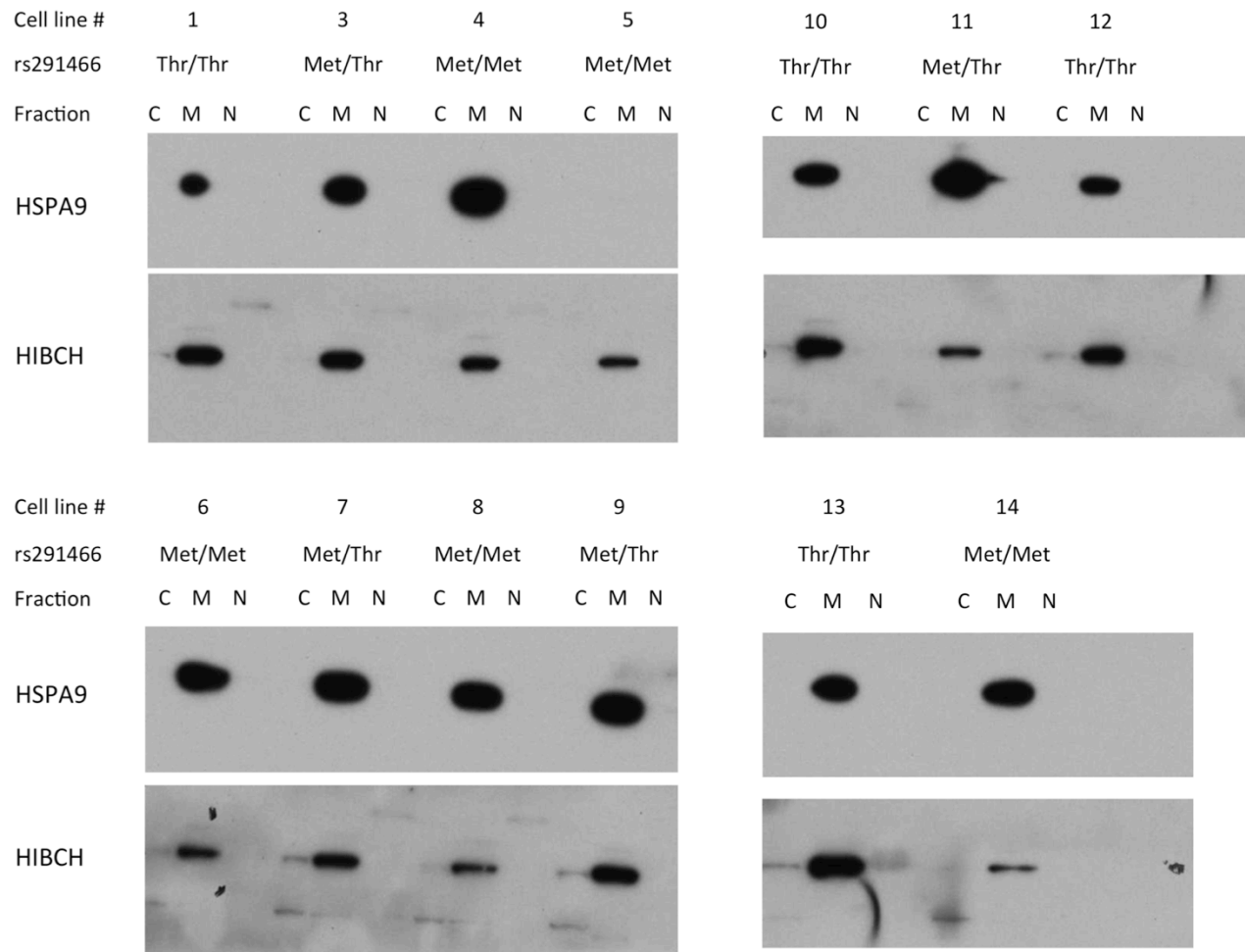


Figure S5. Association of *ACSF3* rs1054747 genotype with *ACSF3* mRNA. Left: Relative amounts of *ACSF3* rs1054747 mRNA isoforms expressed in heterozygous individuals. The fraction of RNA-seq reads for each *ACSF3* rs1054747 allele was calculated for 52 heterozygotes using genotype and expression data from the GEUVADIS RNA Sequencing Project, based on the 1000 Genomes EUR samples. Distributions for each allele are shown, and are not significantly different (t-test, $p=0.92$). Right: *ACSF3* mRNA expression by rs1054747 genotype. Distribution of *ACSF3* RPKM (reads per kilobase of transcript per million reads mapped) scores for each *ACSF3* rs1054747 genotype group (2 AA, 52 AG and 391 GG) based on 1000 Genomes EUR samples. The means are not significantly different by genotype group (ANOVA, $p=0.37$).

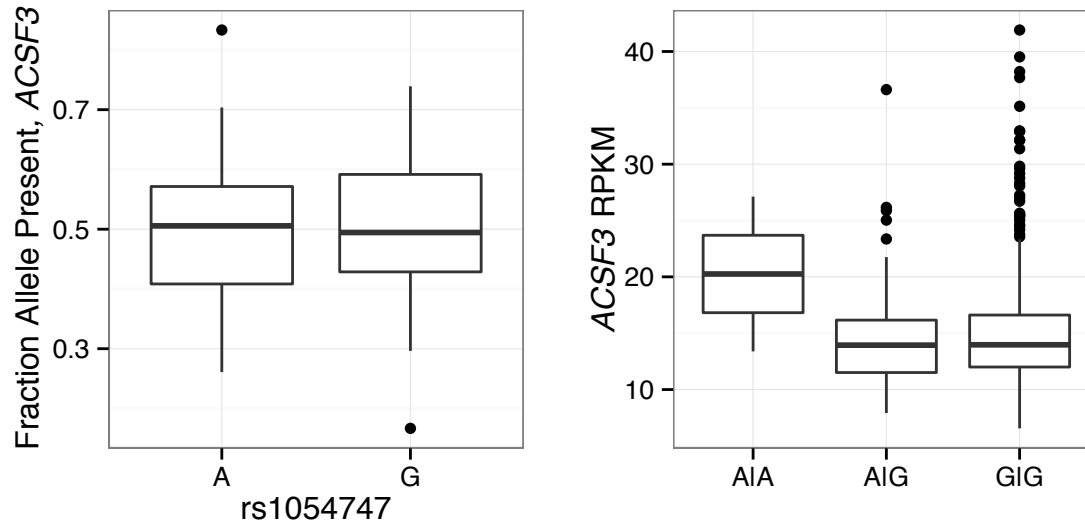


Table S1. Genomic control (λ) results for untransformed and \log_{10} transformed MMA GWAS of genotyped SNPs after adjustment for age and sex

PHENOTYPE	Median(of T^2)/0.456 *	# of markers with ($-\log P$value) > 7
MMA_raw_AS	0.991	46
MMA_log_AS	0.991	56

* Lambda ideal range is from approximately 0.95 to 1.1

Table S2. Seven SNP loci with missense or nonsense variants that show significant association with untransformed or log₁₀ transformed MMA adjusted for age and sex: association p-values < 5x10⁻⁰⁵

chromosome	SNP	Gene	Function	Genotyped (G) or Imputed (I)	Beta (raw MMA)	MMA_raw_A S P-value	Beta (log MMA)	MMA_log_A S P-value
chr2	rs291466	HIBCH	missense	G	-0.038	4.92E-52	-0.088	8.42E-89
chr2	rs1058180	HIBCH	missense	G	-0.026	3.94E-18	0.061	3.41E-28
chr2	rs6753459	C2or88	missense	I	-0.026	2.62E-17	-0.059	4.46E-27
chr16	rs2270416	CDH15	nonsense	G	-0.042	3.40E-12	-0.098	6.22E-19
chr16	rs455527	CPNE7	missense	G	-0.026	1.72 E-06	-0.063	1.07E-10
chr16	rs885479	MC1R	missense	G	-0.025	5.79E-06	-0.059	4.43E-09
chr16	rs7188200	ACSF3	missense	G	0.015	1.66E-06	0.032	1.22E-08