

Supplementary Material

Branched-chain amino acids and Alzheimer's disease: a Mendelian randomization analysis

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Table S1. Associations of the BCAA-associated single nucleotide polymorphisms with other phenotypes at $p < 0.05$ in published genome-wide association studies

BCAA	SNP	Nearest gene	Phenotype	p value	PMID
Isoleucine	rs7678928	PPM1K	Serum urate	2.4×10^{-4}	23263486
			Irritable bowel syndrome	0.002	18587394
			Geographic atrophy	0.005	23455636
			Bipolar disorder	0.007	22182935
			Age-related macular degeneration	0.013	23455636
			Crohn's disease	0.016	23128233
			Obesity class 1	0.022	23563607
			2 hour glucose	0.044	20081857
Isoleucine	rs1260326*	GCKR	Triglycerides	2.0×10^{-239}	24097068
			Serum urate	1.3×10^{-44}	23263486
			C-reactive protein	3.8×10^{-43}	23263486
			Fasting glucose	2.2×10^{-41}	22885924
			HDL cholesterol	6.3×10^{-36}	19936222
			Coagulation factor VII	1.7×10^{-28}	21676895
			Total cholesterol	7.0×10^{-27}	20686565
			Fasting insulin	2.7×10^{-22}	22885924
			Chronic kidney disease	3.0×10^{-14}	20383146
			Gout	2.0×10^{-12}	25646370
			Serum creatinine	3.4×10^{-12}	20383146
			Apolipoprotein C	8.7×10^{-12}	19060906
			Height	1.4×10^{-11}	25282103
			Type 2 diabetes	3.7×10^{-9}	26551672
			Age at menopause	1.0×10^{-9}	26414677
			Plasma palmitoleic acid	3.8×10^{-9}	23362303
			Alcohol consumption	2.3×10^{-8}	28485404
			Coffee consumption	7.0×10^{-8}	25288136
			Leptin	3.6×10^{-7}	26833098
			HOMA insulin resistance	9.2×10^{-7}	20081858
			Apolipoprotein A	9.9×10^{-7}	19802338
			Apolipoprotein B	1.6×10^{-6}	19802338
			Crohn's disease	2.3×10^{-6}	18587394
			Body mass index	4.6×10^{-5}	25673413
			LDL cholesterol	2.3×10^{-4}	20686565
Isoleucine	rs75950518	DDX19A	Lumber spine bone mineral density	0.019	26367794
			Femoral neck mineral density	0.021	26367794
Isoleucine	rs58101275	TRMT61A	Schizophrenia	0.004	25056061
			Femoral neck mineral density	0.004	26367794
			Crohn's disease	0.015	26192919
			Neuroticism	0.026	27089181
Isoleucine	rs1420601	CBLN1	Major depression disorder	0.003	26176920
			Schizophrenia	0.007	25056061
			Myocardial infarction	0.037	26343387
Leucine/valine	rs1440581	PPM1K	Metabolite levels	1.0×10^{-16}	24816252
			Serum Fischers ratio	2.0×10^{-16}	22286219
			Serum alanine/valine and valine	3.8×10^{-15}	22286219

*Only the major phenotypes are listed because of the large number of pleiotropic associations. This SNP was excluded from the analysis. BCAA: branched-chain amino acid; SNP: single nucleotide polymorphism.

Table S2. Characteristics of the BCAA-associated single nucleotide polymorphisms and their associations with Alzheimer's disease

BCAA	SNP	Chr	Nearest gene	EA/NEA	EAF	Beta (SE) of BCAA levels per EA	<i>p</i> value for BCAA	OR (95% CI) of AD per allele	<i>p</i> value for AD
Isoleucine	rs7678928	4	<i>PPM1K</i>	T/C	46%	0.090 (0.0125)	5.6×10^{-19}	1.010 (0.978–1.042)	0.56
Isoleucine	rs75950518	16	<i>DDX19A</i>	C/T	89%	0.107 (0.0190)	2.1×10^{-08}	1.050 (1.002–1.101)	0.04
Isoleucine	rs58101275	14	<i>TRMT61A</i>	G/A	79%	0.085 (0.0153)	2.8×10^{-08}	1.042 (1.003–1.084)	0.04
Isoleucine	rs1420601	16	<i>CBLN1</i>	C/T	40%	0.069 (0.0125)	3.7×10^{-08}	1.017 (0.974–1.062)	0.44
Leucine	rs1440581	4	<i>PPM1K</i>	C/T	53%	0.081 (0.0132)	3.9×10^{-25}	1.012 (0.980–1.045)	0.46
Valine	rs1440581	4	<i>PPM1K</i>	C/T	53%	0.098 (0.0133)	4.4×10^{-24}	1.012 (0.980–1.045)	0.46

AD: Alzheimer's disease; BCAA: branched-chain amino acid; Chr: chromosome; CI: confidence interval; EA: effect allele; EAF: effect allele frequency; NEA: non-effect allele; OR: odds ratio; SE: standard error; SNP: single-nucleotide polymorphism.