

Polymorphisms in SLC44A1 are Associated with Cognitive Improvement in Children Diagnosed with Fetal Alcohol Spectrum Disorder: An Exploratory Study of Oral Choline Supplementation.

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On-line Supplementary Materials

List of Supplementary Figures and Tables

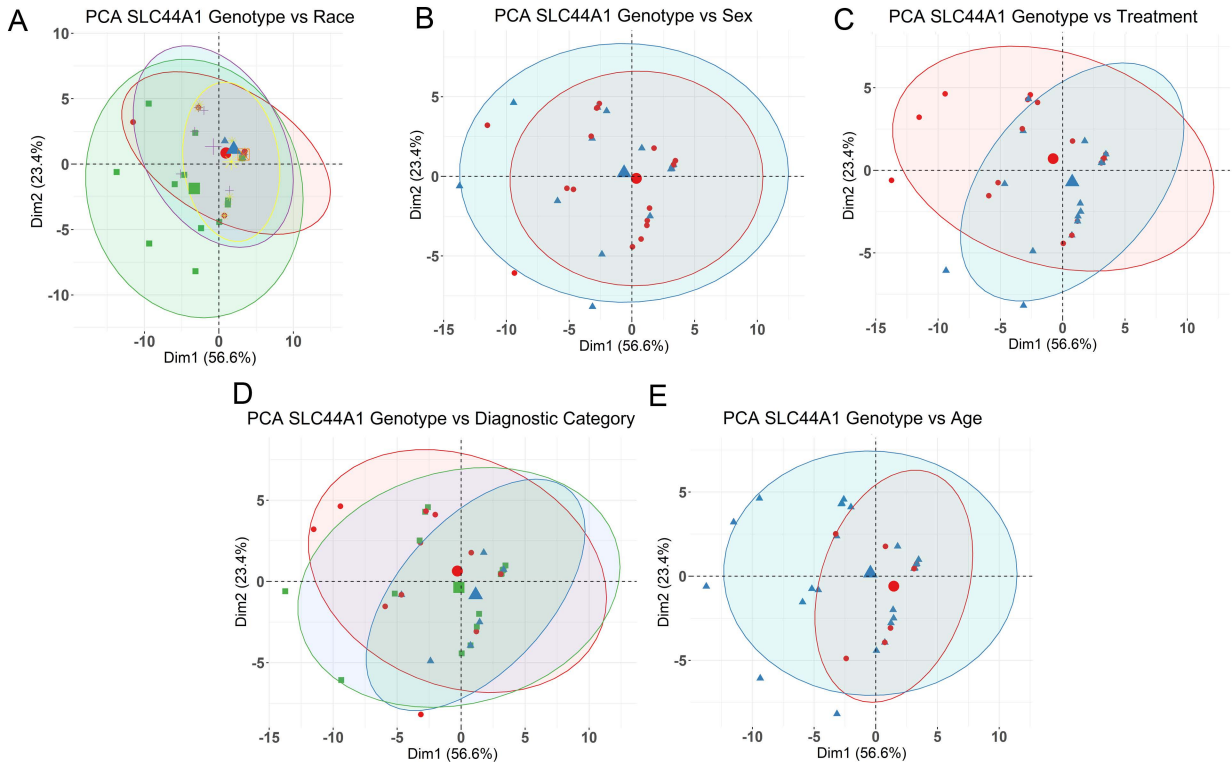
Supplementary Figure 1. Principal Component Analysis of SLC44A1 Genotype and Population Characteristics. Principal Component Analysis (PCA; FactoMineR, v2.3) was used to examine the genomic separation of the 52 participants based on race, sex, treatment, diagnostic category, or age. No significant associations between the 26 SNPs in SLC44A1 from Table 3 and any of these population characteristics were observed in any of the analyses. (A) Self-identified race vs genotype. Red circle, Native American (N=10); Blue triangle, Asian (N=2); Green square, black or African-American (N=13); Purple cross, multiracial (N=7); Yellow crossed square, white or Caucasian (N=19); Orange crossed square, unknown (N=1). (B) Sex vs genotype. Red circle, female (N=33); blue triangle, male (N=19). (C) Treatment vs. genotype. Red circle, choline-treated (N=26); blue triangle, placebo-treated (N=26). (D) Diagnostic category vs genotype. Red circle, alcohol-related neurodevelopmental disorder (ARND, N=23); blue triangle, fetal alcohol syndrome (FAS; N=9); green square, partial FAS (N=20). (E) Age vs genotype. Red circle, 3yrs or younger (N=12); blue triangle, older than 3yrs (N=40). The largest symbol for each population characteristic represents the group mean for that characteristic, and the ellipse represents the 95% confidence interval surrounding that group mean.

Supplementary Table 1. List of 243 Choline-Related Human Single-Nucleotide Polymorphisms (SNPs) that Were Evaluated.

Supplementary Table 2. Significance Values for Three Genetic Models Testing the Association between Cognitive Performance and Single Nucleotide Polymorphism (SNP) within the SLC44A1 Gene.

Supplementary Table 3. Single Nucleotide Polymorphism (SNP) Associations within All Participants and within Placebo-Treated Participants.

Supplementary Figure 1



Supplementary Table 1
List of 243 Choline-Related Human Single-Nucleotide Polymorphisms (SNPs) that Were Evaluated

rs10120572	rs17037390	rs3071	rs492842	rs7849463
rs10123494	rs17037396	rs31653	rs498793	rs7865985
rs10131416	rs17156442	rs31658	rs522951	rs786935
rs1017054	rs1736557	rs31662	rs526126	rs7873937
rs1025689	rs1736560	rs31666	rs538316	rs7904497
rs1045075	rs17367504	rs31671	rs542852	rs7946
rs1054411	rs17421511	rs31672	rs558133	rs8003379
rs1076991	rs174568	rs3199966	rs55931354	rs8003567
rs10820801	rs174570	rs327947	rs567754	rs8011839
rs10991611	rs174575	rs327956	rs569910	rs8016556
rs10991618	rs174589	rs327959	rs574122	rs8072971
rs10991639	rs174602	rs328006	rs5770917	rs8187799
rs1108579	rs174605	rs34750132	rs585800	rs822393
rs1109859	rs174618	rs35603631	rs5899654	rs838133
rs11481	rs17597141	rs3747806	rs6010024	rs868014
rs11557927	rs1801131	rs3753584	rs608622	rs877483
rs11627387	rs1801133	rs3754491	rs610745	rs877484
rs11656215	rs1801282	rs3761612	rs61588443	rs881883
rs11849530	rs1805087	rs3763945	rs631305	rs893363
rs1202283	rs1920149	rs3774616	rs6445606	rs909530
rs1207651	rs193008	rs3783726	rs6445607	rs909531
rs12121543	rs1950902	rs3783731	rs6479311	rs930367
rs12247426	rs1956545	rs3797546	rs6479313	rs936108
rs12335779	rs1979277	rs3818239	rs6591331	rs939883
rs12339823	rs2064074	rs3819255	rs6659176	rs9644967
rs12344346	rs2066471	rs3978768	rs6667720	rs9651118
rs12404218	rs2066534	rs41272270	rs6766480	rs968567
rs1242490	rs2071645	rs4148809	rs6793451	rs9840079
rs12539936	rs2072114	rs4148811	rs6798958	rs9846156
rs1256143	rs2088666	rs4148812	rs6875201	rs988448
rs1256146	rs2167444	rs4148822	rs6893970	rs9891119
rs12567062	rs2184226	rs4148824	rs6946119	rs9910747
rs12630070	rs2234970	rs4148828	rs7024985	rs99780
rs12632013	rs2236224	rs4244599	rs7029443	rs998671
rs12632779	rs2236225	rs440290	rs7088953	rs999515
rs12637288	rs2238834	rs443094	rs711352	
rs12676	rs2241766	rs4479310	rs7151163	
rs1275103	rs2241807	rs4545327	rs7214988	
rs12846498	rs2241808	rs4549843	rs7215833	
rs13342397	rs2266780	rs4563403	rs7224725	
rs1393491	rs2266782	rs4646340	rs7238	
rs140514	rs2281135	rs4646341	rs735877	
rs1476413	rs2289205	rs4646342	rs738409	
rs1526090	rs2289207	rs4646383	rs745686	
rs1531100	rs2289209	rs4646394	rs748196	
rs1535	rs234706	rs4687591	rs7539542	
rs1557503	rs2417614	rs4687747	rs7626693	
rs1580820	rs2417615	rs482548	rs7627178	
rs16876512	rs2511439	rs4846048	rs7634578	
rs16876528	rs2516557	rs4846049	rs7700970	
rs16924529	rs2771040	rs4846052	rs7789645	
rs16961834	rs2983733	rs4899135	rs7849	

Supplementary Table 2
Significance Values for Three Genetic Models Testing the Association between Cognitive Performance
and SNPs within the SLC44A1 Gene

SNP	<i>P</i>-values for delta_pairs_imm¹			<i>P</i>-values for delta_adjpairs_imm¹		
	Additive	Dominant	Recessive	Additive	Dominant	Recessive
rs10123494	0.005672	0.2693	0.1455	0.0005061	0.04397	0.06602
rs10820801	0.005141	0.08847	0.2693	0.0014686	0.1014	0.04397
rs10991639	0.005141	0.2693	0.08847	0.0014686	0.04397	0.1014
rs2417615	0.005141	0.2693	0.08847	0.0014686	0.04397	0.1014
rs2771040	0.005141	0.08847	0.2693	0.0014686	0.1014	0.04397
rs3199966	0.049691	1.0000	0.08847	0.001284	0.1191	0.1014
rs34750132	0.005672	0.1455	0.2693	0.0005061	0.06602	0.04397
rs35603631	0.005672	0.2693	0.1455	0.0005061	0.04397	0.06602
rs4549843	0.005141	0.2693	0.08847	0.001468	0.04397	0.1014
rs6479311	0.005141	0.2693	0.08847	0.001468	0.04397	0.1014
rs6479313	0.005672	0.1455	0.2693	0.0005061	0.06602	0.04397
rs7024985	0.005141	0.08847	0.2693	0.001468	0.1014	0.04397
rs7029443	0.005672	0.2693	0.1455	0.0005061	0.04397	0.06602
rs7865985	0.005672	0.2693	0.1455	0.0005061	0.04397	0.06602
rs12339823	1.00000	1.0000	1.0000	0.004567	0.1451	0.1191
rs16924529	0.8095	1.0000	1.0000	0.02303	0.6422	0.2861

¹ Associations between SNPs and outcomes were tested under an Additive, Dominant, or Recessive genetic model using the SNPAssoc package in R (v.1.9-2). *P*-values are adjusted for multiple correction testing using the Bonferroni correction. Delta_pairs_imm is the change in Elicited Imitation immediate memory task performance (pairs) between baseline (0 months) and 9 months; delta_adjpairs_imm is the change in Elicited Imitation immediate memory task performance (adjacent pairs of items) between baseline (0 months) and 9 months. SNP, single nucleotide polymorphism.

Supplementary Table 3
Single Nucleotide Polymorphism (SNP) Associations within All Participants
and within Placebo-Treated Participants

Gene	SNP	P-Value ¹	Reg. Coeff. ²	Outcome	Effect Allele (Major > Minor allele within this cohort ³)	# w/Effect Allele ⁴
All Participants						
<i>BHMT</i>	rs558133	0.00803	-1.1874	iib_tscore13	Increased with G (T > G)	12/31
	rs558133	0.00446	-1.2150	iib_tscore20	Increased with G (T > G)	12/31
	rs567754	0.04457	0.6522	weight_z_physical.1	Increased with C (C > T)	27/52
	rs567754	0.01134	0.7021	weight_pile_physical.1	Increased with C (C > T)	27/52
<i>C1orf167</i> ⁵	rs4846048	0.01013	0.7578	t_score3.1	Increased with T (T > C)	32/52
	rs6667720	0.01013	0.7578	t_score3.1	Increased with A (A > G)	32/52
<i>FADS2</i>	rs2072114	0.03062	1.0230	height_physical.11	Increased with A (A > G)	15/43
	rs17156442	0.03616	-1.2654	imt_adjpairs_imm_med.11	Increased with T (C > T)	10/45
<i>FMO3</i>	rs2064074	0.04245	0.7471	weight_pile_physical.3	Increased with A (A > G)	33/45
	rs2266782	0.04386	0.9812	stanfbi_wm	Increased with G (G > A)	19/30
<i>MTHFR</i>	rs4846048	0.01013	0.7578	t_score3.1	Increased with A (A > G)	32/52
	rs4846049	0.04725	0.6371	t_score8.11	Increased with G (G > T)	31/47
<i>SHMT1</i>	rs1979277	0.00565	0.8561	t_score8.11	Increased with G (G > A)	26/47
	rs1979277	0.03168	0.7864	t_score13.11	Increased with G (G > A)	26/47
<i>SLC44A1</i>	rs10991611	0.05041	-0.8590	weight_pile_physical.1	Increased with T (C > T)	19/52
	rs193008	0.04009	-0.8186	weight_pile_physical.1	Increased with C (T > C)	19/52
	rs328006	0.04009	-0.8186	weight_pile_physical.1	Increased with C (G > C)	19/52
Placebo-Treated Participants						
<i>ADIPOQ</i>	rs1501299	0.03572	1.4149	heart_rate.11	Increased with C (C > A)	14/23
<i>CHDH</i>	rs6445607	0.03454	1.0166	ilb_avg_imt_pairs	Increased with T (T > G)	8/16
<i>FADS2</i>	rs174570	0.0.0107	1.1459	height_z_physical.11	Increased with C (C > T)	10/20
	rs1535	0.02252	0.9336	height_pile_physical.11	Increased with A (A > G)	12/20
	rs174568	0.02495	0.9842	height_pile_physical.11	Increased with C (C > T)	12/20
	rs174570	0.00311	1.1913	height_pile_physical.11	Increased with C (C > T)	10/20
<i>FMO3</i>	rs1736557	0.02311	-2.0903	t_score_2.11	Increased with A (G > A)	3/23
<i>MDR3</i>	rs17149601	0.04610	-1.3515	height_z_physical.1	Increased with T (C > T)	4/26
	rs3747806	0.00040	-2.1382	weight_z_physical.11	Increased with C (T > C)	4/26
	rs988448	0.00040	-2.1382	weight_z_physical.11	Increased with C (T > C)	4/26
	rs3747806	0.00064	-2.0963	weight_z_physical.3	Increased with C (T > C)	4/24
	rs988448	0.00064	-2.0963	weight_z_physical.3	Increased with C (T > C)	4/24

	rs3747806	0.01805	-2.1050	weight_z_physical.8	Increased with C (T > C)	3/22
	rs988448	0.01805	-2.1050	weight_z_physical.8	Increased with C (T > C)	3/22
	rs3747806	0.03521	-1.8293	weight_pile_physical.1	Increased with C (T > C)	4/26
	rs988448	0.03521	-1.8293	weight_pile_physical.1	Increased with C (T > C)	4/26
	rs17149601	0.03633	1.4797	delta_imt_v1_v13_adjpairs	Increased with C (C > T)	2/16
<i>MTHFD1</i>	rs2236224	0.02142	1.1274	iib_tscore13	Increased with C (T > C)	7/16
	rs2236225	0.02142	1.1274	iib_tscore13	Increased with C (T > C)	7/16
<i>MTHFR</i>	rs17421511	0.04028	1.3885	stanfbi_viq	Increased with G (G > A)	3/16
	rs17421511	0.03304	1.3989	stanfbi_fsiq	Increased with G (G > A)	3/16
	rs17421511	0.02254	1.4180	stanfbi_wm	Increased with G (G > A)	3/16
<i>MTR</i>	rs1805087	0.01743	1.1302	memfaces_delcontrastsc	Increased with A (A > G)	5/13
<i>PCYT1A</i>	rs2088666	0.03441	-1.0092	blood_pressure_diastolic.1	Increased with A (G > A)	15/25
<i>SCD</i>	rs2167444	0.00679	2.6052	imt_comp_sd_avemh.11	Increased with T (T > A)	2/22
<i>SLC44A1</i>	rs10991618	0.00736	-1.7901	weightheight_z_physical.1	Increased with A (G > A)	5/26

¹ Associations between SNPs and outcomes were tested under an Additive genetic model using the SNPAssoc package in R (v.1.9-2). *P*-values are adjusted for multiple correction testing using the Bonferroni correction.

² Regression Coefficient

³ Measured on top strand, 5' → 3'. Effect allele; (Major > Minor allele in this cohort). All are Single Nucleotide Variants (SNVs).

⁴ Number of individuals carrying at least one copy of the effect allele; some outcomes were missing for some children, and these were excluded from that analysis.

⁵ Likely maps within MTHFR.