

Genetics: Genetics of cognitive aging, other dementia, and endophenotypes

Whole genome sequence association analyses of brain volumes in the TOPMed program

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Abstract

Background: Genome-wide association studies (GWAS) of brain volumes have identified common genetic variants with modest effect sizes that lie mainly in non-coding regions. We sought to identify low frequency and rare variants influencing brain volumes by performing whole genome association analyses using sequence data from the Trans-Omics for Precision Medicine (TOPMed) Program.

Methods: We analyzed up to 3,975 participants (58% women; 78% Europeans, 22% African-Americans), mean age of 62.5 (13.9), from four TOPMed population- or family-based studies (FHS, GENESTAR, CHS, and GENOA). We excluded participants with dementia, stroke, presence of large brain infarcts, tumor or any other finding affecting the scan. We tested the association of hippocampal (HV), total brain (TBV), lateral ventricular (LVV) and intracranial (ICV) volumes with individual genetic variants using mixed-effect linear regression models adjusted for age, age², sex, study and principal components. Models including HV, TBV and LVV were adjusted for ICV. We accounted for relatedness using a kinship matrix and trait variance variability using a random effects model. We retained variants with a minor allele count greater than 40.

Results: We detected new genome-wide significant ($P < 5 \times 10^{-8}$) low frequency or rare variants in five regions associated with HV (5q31, $P = 10^{-9}$) and TBV (2p22, $P = 10^{-8}$; 17q25, $P = 4 \times 10^{-9}$; Xp11, $P = 2 \times 10^{-10}$; Xq21, $P = 4 \times 10^{-8}$). We also confirmed previously observed common variants in GWAS loci for HV (12q14 & 12q24), LVV (3q28, 12q23 & 16q24) and ICV (6q21, 6q22 & 17q21). The top 5q31 hit for HV (rs246587) lies at 19kb from the *PCDHAC2* gene, encoding neural cadherin-like cell adhesion proteins that most likely play a critical role in the establishment and maintenance of specific neuronal connections in the brain.

Conclusions: Our whole genome analysis revealed intriguing new loci associated with brain volumes. Future work will include ancestry-specific and conditional analyses, gene-based and burden tests as well as the inclusion of additional TOPMed cohorts. Supported by: U01s AG058589, AG052409, R01s AG054076, AG033040 AG049607, HL112064, NS062059, FHS contracts HHSN2682015000011 and 75N92019D00031, R01HL131136 (Analysis Commons).

TABLE 1**Table 1: Top associated genetic variants (P<5E-08) identified by the TOPMed whole genome sequence association analyses of brain volumes**

Chr	Build 38 Pos	N	AF	B	SE	P	Ref/Alt	rsid	Trait
5	141,031,799	3410	0.01	-0.75	0.12	1.1E-09	T/A	rs246587	HV
2	37,510,412	3970	0.01	-33.01	5.73	8.6E-09	T/C	rs78483912	TBV
17	83,027,987	3971	0.01	-32.42	5.52	4.2E-09	A/G	--	TBV
X	44,787,907	3935	0.005	-41.85	6.61	2.4E-10	T/C	rs144877887	TBV
X	97,073,888	3942	0.01	-26.54	4.82	3.6E-08	T/C	rs73632876	TBV
6	108,694,115	3974	0.47	-14.90	2.50	2.5E-09	G/GC	rs35947181	ICV
6	126,383,649	3974	0.41	14.01	2.38	3.9E-09	C/T	rs9388490	ICV

TABLE 2**Table 2: TOPMed whole genome sequence association analyses of brain volumes results for the genetic variants reported associated with brain volumes by GWAS**

Chr	Build 38 Pos	N	AF	B	SE	P	Ref/Alt	rsid	Trait
2	161,999,638	3410	0.54	-0.02	0.02	0.24	C/T	rs2268894	HV
5	66,788,432	3410	0.35	-0.04	0.02	0.01	G/T	rs2289881	HV
7	156,005,284	3410	0.32	0.03	0.02	0.11	C/G	rs11979341	HV
9	116,485,695	3410	0.34	0.03	0.02	0.04	G/C	rs7020341	HV
12	65,438,688	3408	0.13	-0.06	0.02	0.005	T/G	rs61921502	HV
12	116,885,562	3410	0.09	0.08	0.03	0.005	T/C	rs77956314	HV
3	190,953,113	3974	0.05	9.59	5.02	0.06	G/C	rs9811910	ICV
6	108,624,167	3974	0.59	10.70	2.47	1.5E-05	A/C	rs2022464	ICV
6	126,470,949	3974	0.21	10.81	2.85	1.5E-04	A/G	rs11759026	ICV
10	103,410,892	3973	0.28	5.86	2.63	0.03	G/T	rs11191683	ICV
12	65,980,467	3974	0.55	-5.09	2.32	0.03	A/G	rs138074335	ICV
12	102,529,208	3974	0.21	-5.58	2.82	0.05	G/C	rs2195243	ICV
17	46,770,468	3974	0.17	-12.54	3.13	6.2E-05	T/G	rs199525	ICV
3	190,902,357	3971	0.37	-0.05	0.01	6.2E-07	G/A	rs34113929	LVV
7	2,720,700	3971	0.01	0.04	0.04	0.32	C/CT	--	LVV
10	21,589,215	3971	0.27	-0.02	0.01	0.03	T/A	rs35587371	LVV
11	111,207,001	3971	0.34	-0.02	0.01	0.08	A/G	rs7936534	LVV
12	106,083,027	3971	0.07	0.09	0.02	1.1E-06	T/C	rs12146713	LVV
16	87,191,495	3971	0.57	0.04	0.01	3.2E-05	G/A	rs9937293	LVV
22	37,714,443	3971	0.55	-0.02	0.01	0.01	C/T	rs4820299	LVV