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Association of fatty acid desaturase 2 gene polymorphism (rs28456) with susceptibility to bipolar disorder in the Turkish population: a case-control study

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Abstract: The *FADS2* gene encodes a key, rate-limiting enzyme involved in polyunsaturated fatty acid (PUFA) metabolism. Recent studies suggest that changes in plasma PUFA levels can lead to disruptions in the neurotransmission system and increase the risk of mood disorders. *FADS2* variations may contribute to the individual risk of developing bipolar disorder (BD). We investigated the association of regulatory *FADS2* rs28456 with BD in the Turkish population. We performed TaqMan genotyping on 100 patients with BD and 91 healthy controls. Our results did not show significantly different genotype or allele frequencies of rs28456 in the BD cases compared to controls. However, we stratified the cases based on family history, which revealed that minor rs28456-G was observed more frequently (P=0.056) in cases without a family history of psychiatric illness compared to those with a family history of psychiatric illness. A marginally significant difference in the distribution of the "G" allele (P=0.053) between male patients and healthy males without a family history was observed. Our findings did not provide strong evidence supporting the reported association between rs28456 and BD, yet they point to its potential gender-specific effect, which requires further investigation. Future studies are necessary to explore the impact of *FADS2* variations on BD risk in larger study groups, considering their potential interaction with non-inherited risk factors.

Keywords: fatty acid desaturase 2 (FADS2); bipolar disorder; rs28456; polyunsaturated fatty acids, PUFA

INTRODUCTION

Bipolar disorder (BD) is a chronic and complex mental health condition characterized by manic depression, affecting >1% of the world population [1-3]. It significantly impacts the mood, energy, and cognitive functions of those affected, leading to a substantial public health and economic burden [2-5]. In recent years, considerable efforts have been devoted to unraveling the molecular mechanisms and genetic factors that contribute to BD pathogenesis [1,6-9]. The findings from genetic studies estimate BD heritability to be about 0.7-0.8, highlighting the substantial role of genetic components in BD risk [1,10-13]. Despite advancements in healthcare technology and a deeper understanding of BD pathophysiology, appropriate risk assessment and preventive strategies for managing bipolar disorder remain lacking. [2]. Promising results were obtained from candidate gene and genome-wide association studies (GWAS), and multiple single nucleotide variants (SNVs) were shown to be associated with BD-related pathologies, influencing susceptibility to BD [1,7-11,13-17].

The human fatty acid desaturase (*FADS*) gene locus located on chromosome 11 consists of *FADS1*, *FADS2*, and *FADS3*, which encode rate-limiting desaturase enzymes that play vital roles in the synthesis and regulation of polyunsaturated fatty acids (PUFAs) [18-19]. Genetic variants in these genes are reported to be associated with the PUFA synthesis capacity of tissues and variations in plasma lipid levels [19-21].

Long-chain PUFAs (LC-PUFA) are known to be key to growth and development. They are also bioactive cellular components of membrane phospholipids and serve as substrates for signaling molecules [22,23]. Dysregulation of PUFA synthesis and fluctuations in LC-PUFA levels were reported to be associated with complex human diseases, including BD [24-28]. The *FADS* genotype was associated with altered PUFA levels and increased proinflammatory cytokines in BD patients [21]. Furthermore, FADS1 and FADS2 haplotypes were significantly linked to insulin resistance in patients with schizophrenia and bipolar disorder who are on antipsychotic medications. [29]. Moreover, high levels of *FADS2* expression were also detected in the prefrontal cortex of individuals with BD, suggesting the contribution of *FADS2* to BD pathophysiology [30]. Supporting this finding, a genome-wide association study identified the intronic *FADS2* rs28456 as an expression quantitative trait locus (eQTL) and proposed it as a novel risk locus for BD, having reached genome-wide significance in the Japanese population [11].

Due to the limited studies in this area, the possible association of *FADS2* rs28456 with BD in distinct populations remains elusive. We investigated the association of *FADS2* rs28456 with BD in the Turkish population.

MATERIALS AND METHODS

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki. The research protocol was approved (2011-KAEK-25 2022/06-14) by the local ethical committee of the Bursa Yuksek Ihtisas Training and Research Hospital, and informed consent was obtained from all volunteers participating in the study.

Study participants

The patient sample included 100 individuals (51 females, 49 males), aged 18-65, who sought care at the Mental Health and Diseases Clinic of Health Sciences University Bursa Yüksek Ihtisas Training and Research Hospital. All were diagnosed with bipolar disorder (BD) following a psychiatric evaluation based on the DSM-5 criteria [31], and none had any psychiatric comorbidity other than BD. The Hamilton Depression Rating Scale and Young Mania Rating Scale were completed by clinicians to assess the symptoms of BD in all patients. We recruited 91 healthy individuals (49 females, 42 males) aged 18-65 with no psychiatric disorder diagnosis. Individuals with mental or physical illnesses that prevented the understanding and completion of the clinical interview, acute or chronic central nervous system diseases, and those with a history of severe head trauma were excluded.

DNA isolation

DNA isolation was performed using peripheral blood samples collected in EDTA tubes using a genomic DNA isolation kit following the manufacturer's protocol (Invitrogen PureLink Genomic DNA Mini kit, Thermo Fisher Scientific, Darmstadt, Germany). Samples were stored at -20°C until DNA isolation. The concentration and purity of the DNA samples were evaluated with a Nanodrop 2000 spectrophotometer (Thermo Fisher Scientific, Darmstadt, Germany).

Genotyping

FADS2 rs28456 SNV was genotyped using TaqMan SNP Genotyping Assay Mix and TaqMan Universal Master Mix (Thermo Fisher Scientific, Darmstadt, Germany). A final reaction (10 µL) was prepared, which contained 4.75 µL of 10 ng/µL genomic DNA, 5 µL of 2X TaqMan™ Genotyping Master Mix, 0.25 µL of 40X Assay with VIC/FAM-labeled pre-designed probes. After an initial step at 95°C for 10 min, PCR amplification was performed using 40 cycles of denaturation (95°C, 15 s) and annealing (60°C, 1 min). Amplification and probe fluorescence detection were performed in the Quantgene 9600 Real-Time PCR system (Bioer Technology, Hangzhou, China).

Statistical analysis

Haploview software (Version 4.2) was used to determine the Hardy-Weinberg equilibrium (HWE) and allele frequencies. The chi-square or Fisher's exact test was used to analyze the distribution of allele and genotype frequencies. We also used the LDlink online tool to assess the genotype distributions of the variant

in populations worldwide (https://ldlink.nih.gov/?tab=home) (accessed 5 August 2023) [32]. Data on the regulatory effect of SNV and eQTL features were extracted from RegulomeDB and Genotype-Tissue Expression (GTEx) databases [33-34]. Logistic regression was used to analyze the associations of the *FADS2* genotype with BD. All statistical analyses were performed using SPSS software (version 20), and the statistical significance level was defined as P<0.05.

Table 1. Characteristics of patients with bipolar disorder and healthy controls

Characteristics		Case (n=100)	Control (n=91)	P
		Mean± SD; % (n)	*Mean± SD; % (n)*	
Gender	**Male**	49 (49%)	42 (46.2%)	0.694
	Female	51 (51%)	49 (53.8%)	
Age (year)		41.25±12.26	43.54±13.02	0.218
BMI (kg/m²)		27.15±5.97	29.91±26.97	0.502
Smoking		55 (55%)	30 (33%)	<0.05
Hypothyroidism (n, %)		5 (5%)	2 (2.2%)	0.303
Hypertension (n, %)		9 (9%)	6 (6.6%)	0.537
Hypercholesterolemia (n, %)		3 (3%)	-	0.096
Heart Diseases (n, %)		2 (2%)	11(12.1%)	<0.05
Diabetes Mellitus (n, %)		12 (12%)	6 (6.6%)	0.201
Psychiatric family history (n, %)		41 (41%)	-	<0.05

RESULTS

Study participants

The mean age for cases and controls was 41.25±12.26, and 43.54±13.02 years, respectively. The male-to-female ratio for cases was 49:51 for cases and 42:49 for controls. The number of smokers is higher in cases (n=55) than in controls (n=30). However, the number of individuals with heart disease was lower in cases (n=2) than in controls (n=11). The clinical characteristics of cases and controls are provided in Table 1.

Allelic distributions and their association with BD

We genotyped all samples successfully (genotyping call rate=100%) and found the minor allele frequency (MAF) of the rs28456 "G" to be 0.228 in the total sample (Table 2). However, the allele frequency for rs28456 "G" was determined as 0.240 for cases and 0.214 for controls (χ2=0.358, P=0.550) (Table 3). We also stratified the patients based on their family history of psychiatric illness and then compared the MAF distributions with controls (Table 4). Our analyses revealed a marginally significant MAF difference (P=0.053) in male patients without a family history of psychiatric illness (MAF=0.344) compared to healthy males (MAF=0.202). Additionally, the minor "G" allele occurred more frequently (P=0.056) in patients without a family history of psychiatric illness (MAF=0.288) than in patients with a family history (MAF=0.171)

Table 3. Genotype and allele distributions of rs28456 in individuals with bipolar disorder and healthy controls

		Cases	Controls	χ^2	P
Total (n=191)	AA	60 (60%)	55 (60.4%)	2.086	0.352
	AG	32 (32%)	33 (36.3%)		
	GG	8 (8%)	3 (3.3%)		
	A	152 (76%)	143 (78.6%)	0.358	0.550
	G	48 (24%)	39 (21.4%)		
Male (n=91)	AA	26 (53.1%)	26 (61.9%)	2.254	0.330*
	AG	18 (36.7%)	15 (35.7%)		
	GG	5 (10.2%)	1 (2.7%)		
	A	70 (71.4%)	67 (79.8%)	1.688	0.194
	G	28 (28.6%)	17 (20.2%)		
Female (n=100)	AA	34 (66.7%)	29 (59.2%)	1.122	0.610*
	AG	14 (27.4%)	18 (36.7%)		
	GG	3 (5.9%)	2 (4.1%)		
	A	82 (80.4%)	76 (77.6%)	0.243	0.622
	G	20 (19.6%)	22 (22.4%)		

*Fisher's exact test used

Table 2. Allele and genotype frequencies of rs28456 in the entire sample (n=191)

Ref SNP ID	Chr loc.[a]	Location	HW-P	Genotype (n, %)	Minor Allele Frequency	1000G[b]	TOPMed[c]
rs28456	61822009	Intron 1	0.764	AA (n=115, 60.21%) AG (n=65, 34.03%) GG (n=11, 5.76%)	G: 0.228	0.31 (n=5008)	0.29 (n=264690)

[a]Chromosomal location on chromosome 11 (GRCh38.p14); [b]minor allele frequency (MAF) in the 1000 Genomes Project; [c]MAF in the Trans-Omics for Precision Medicine Project; HW-P – Hardy-Weinberg P value

Table 4. Allele frequency distributions of rs28456 in individuals stratified according to family history of psychiatric illness

	Cases with family history of psychiatric illness	Cases without family history of psychiatric illness		
	MAF	MAF	χ^2	P
Total	0.171 (n=41)	0.288 (n=59)	3.656	0.056
Male	0.174 (n=17)	0.344 (n=32)	3.044	0.081
Female	0.167 (n=24)	0.222 (n=27)	0.498	0.481
	Cases without family history of psychiatric illness	**Controls**		
	MAF	**MAF**	χ^2	**P**
Total	0.284 (n=59)	0.214 (n=91)	1.905	0.168
Male	0.344 (n=32)	0.202 (n=42)	3.741	0.053
Female	0.222 (n=27)	0.224 (n=49)	0.001	0.974
	Cases with family history of psychiatric illness	**Controls**		
	MAF	**MAF**	χ^2	**P**
Total	0.179 (n=41)	0.214 (n=91)	0.453	0.501
Male	0.176 (n=17)	0.202 (n=42)	0.104	0.748
Female	0.167 (n=24)	0.224 (n=49)	0.660	0.417

(Table 4). We also retrieved the allele frequency distribution of rs28456 in other populations using the LDlink website and determined the allele frequency range as 4.55%-80% in populations including the 1000 Genome Project (Supplementary Table S1 and Supplementary Fig. S1).

Distribution of genotypes and their association with BD

The distribution of genotypes was found to follow the Hardy-Weinberg equilibrium (HWE P=0.764) (Table 2). The genotype distributions of rs28456 were not statistically different in cases and controls (Table 3).

Logistic regression analysis

Logistic regression analysis revealed no statistically significant difference in genotype frequencies between cases and controls under different genetic models (Table 5). Gender-stratified analyses including age as a covariate in males were performed, however, no statistically significant results were obtained (Table 5).

Functional annotations of the *FADS2* rs28456

RegulomeDB and GTEx databases were used to evaluate the functional impact of the SNV [33-34]. The RegulomeDB score of the SNV was 1f, indicating that it is located in a region that may affect transcription factor binding and has eQTL properties (Supplementary Table S2). Based on data from the GTEx database, the SNV can potentially affect the expression of multiple genes in different tissues (Supplementary Table S2). We found that rs28456 affects the expression of *FADS2* and other genes in the *FADS* gene family in 39 tissues such as the spleen, whole blood, small intestine, esophagus, thyroid, heart, etc.

DISCUSSION

We conducted a case-control study to examine the population-specific allele frequency and association of rs28456 with BD in Turkish samples. Our genotyping results showed that rs28456-G has a common minor allele frequency (MAF=0.228) in the total sample, yielding similar allele frequencies in cases (MAF=0.240) and controls (MAF=0.214). However, a marginally significant difference in MAF distributions was observed when stratifying patients based on family history of

Table 5. Logistic regression analysis for the association of rs28456 genotypes with bipolar disorder

		Total (n=191)		Male (n=91)		Female (n=100)	
		OR (Cl 95%)	P	OR (Cl 95%)	P	OR (Cl 95%)	P
Gender[a]		1.12 (0.64-1.98)	0.694	-	-	-	-
Age (years)		0.99 (0.96-1.01)	0.212	0.96 (0.92-0.99)	0.011	1.01 (0.98-1.05)	0.404
Dominant Model	AA vs. AG+GG	1.02 (0.57-1.82)	0.951	1.82 (0.74-4.46)	0.192[b]	0.73 (0.32-1.64)	0.439
Recessive Model	AA+AG vs. GG	2.55 (0.66-9.93)	0.177	6.26 (0.66-59.01)	0.109[b]	1.47 (0.24-9.19)	0.681
Additive Model	-	1.15 (0.72-1.85)	0.556	1.94 (0.92-4.08)	0.082[b]	0.85 (0.43-1.66)	0.628
Co-Dominant Model	AA vs. AG	0.89 (0.48-1.63)	0.704	1.49 (0.59-3.78)	0.405[b]	0.66 (0.28-1.56)	0.348
	AA vs. GG	2.44 (0.62-9.68)	0.203	7.45 (0.76-73.29)	0.085[b]	1.28 (0.20-8.19)	0.795
Over-Dominant Model	AA+GG vs. AG	0.83 (0.45-1.51)	0.535	1.21 (0.49-2.98)	0.673[b]	0.65 (0.28-1.52)	0.321

[a]Female was taken as a reference for gender; [b]adjusted by age; OR – odds ratio; CI – confidence interval; n – number of individuals

psychiatric illness. The rs28456-G variant appeared slightly more frequently (P=0.053) in male patients without a family history of psychiatric illness compared to healthy males. This finding indicates a potential impact of gender and environmental risk factors on its effect, contributing significantly to BD risk.

Research has shown that fatty acids play a crucial role in the pathophysiology of mental diseases such as depression, schizophrenia, and attention deficit and hyperactivity disorder [35-40]. Thus, uncovering the genetic factors contributing to the alterations in fatty acid levels is imperative. The *FADS2* encodes delta 6 desaturase, one of the key enzymes in fatty acid metabolism, involved in the linoleic acid and alpha-linolenic acid pathways [41]. Although little is known about the effects of FADS2 genetic variations on BD, several studies have reported associations between FADS2 variants, fatty acid levels, and metabolic diseases [28-29,42-44]. However, it was shown that *FADS2* variants regulate fatty acid metabolism by altering *FADS2* expression in brain tissue and may affect cognitive function [45]. Also, population-specific differences in the allele frequency of the sequence variants in *FADS2* are attributable to changes in the different dietary habits across populations [46]. Nevertheless, future research involving diverse population-based samples is needed to clarify the functionality and translational utility of *FADS2* variants for risk assessments of mental and metabolic disorders. rs28456, a functionally important *FADS2* sequence variant, was reported to be associated with BD in the Japanese cohort [11].

Public data retrieved from the 1000 Genome Project revealed the prevalence of the rs28456 alleles is highly variable among geographically distinct populations. Populations from Esan in Nigeria (ESN), Gujarati Indian from Houston, Texas (GIH), Indian Telugu from the UK (ITU), and Mende in Sierra Leone (MSL), have the lowest allele frequency (<10%) of rs28456-G among all populations in the 1000 Genome Project. In contrast, populations such as Peruvians from Lima, Peru (PEL), Kinh in Ho Chi Minh City, Vietnam (KHV), Chinese Dai in Xishuangbanna, China (CDX), Mexican ancestry from Los Angeles, USA (MXL), admixed American (AMR), Southern Han Chinese (CHS), East Asian (EAS) exhibit the highest allele frequency (>50%). The frequency of the rs28456-G allele in the Italian population (rs28456 (G: 0.22)) was similar to that observed in our study.

RegulomeDB and GTEx databases were used to assess the functional impact of the SNV. GTEx analysis also revealed that rs28456 has a functional role in regulating multiple genes including *FADS1* and *FADS2,* which have implications in infectious disease pathologies. Our preliminary data imply that the rs28456-G allele may not be a risk factor for developing BD in the Turkish population, but further studies are needed to verify this finding. In a previous genome-wide association study involving the Japanese population, the rs28456-G allele achieved genome-wide significance and was associated with an increased risk of BD [11]. However, the results were not supported by the Japanese case-control study conducted with 83 patients with BD and 127 healthy controls [21]. In this study, three SNVs in the *FADS2* (rs28456, rs174547, rs174576) were genotyped in 200 individuals, and perfect linkage disequilibrium (LD) was observed between rs174547 and rs28456. No statistically significant association was found between rs28456 and BD, with minor allele frequencies of 0.377 for cases and 0.444 for controls, respectively [21]. In agreement with our results, a GWA study consisting of European samples did not detect an association between rs28456 and BD [8]. The significant genome-wide association observed in the Japanese study may be population-specific, and the effect of rs28456 could be minimal or contingent upon a low-frequency functional variant that can be identified in larger cohorts.

Our study is the first to examine the population frequency and distribution of the rs28456 allele in the Turkish population. The results of this pilot study underscore the importance of validating genetic association findings in distinct populations with varying allele distributions. The findings of the present study do not reveal any hidden associations; rather, they suggest evidence of the potential regulatory role of rs28456 in the risk of bipolar disorder (BD) in conjunction with non-inherited risk factors. Analysis of the SNV distribution in a larger sample from our population, or sequencing the entire *FADS2* gene, may provide more representative data regarding the potential contributions of *FADS2* to the genetic basis of BD.

In conclusion, this study presents the frequency distribution of the *FADS2* polymorphism in Turkish samples and offers preliminary data on the proposed associations between genotypes and BD in our population. Identifying the associations between *FADS2* variants

and the susceptibility and severity of psychological disorders through comprehensive studies involving diverse genetic backgrounds offers potential for the development of translational medicine applications for these conditions.

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Data availability: Data underlying the reported findings have been provided as a raw dataset available here: https://www.serbiosoc.org.rs/NewUploads/Uploads/Pirim%20et%20al_Dataset.pdf

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SUPPLEMENTARY MATERIAL

Supplementary Table S1. Allele frequency distributions of rs28456 in worldwide populations (retrieved from https://ldlink.nih.gov)

Population	Abbreviation	N	rs28456 Allele Frequency
All Populations	ALL	2504	A: 69.23%, G: 30.77%
African	AFR	661	A: 88.58%, G: 11.42%
Yoruba in Ibadan, Nigeria	YRI	108	A: 87.96%, G: 12.04%
Luhya in Webuye, Kenya	LWK	99	A: 88.89%, G: 11.11%
Gambian in Western Divisions in the Gambia	GWD	113	A: 85.84%, G: 14.16%
Mende in Sierra Leone	MSL	85	A: 90.59%, G: 9.41%
Esan in Nigeria	ESN	99	A: 95.45%, G: 4.55%
Americans of African Ancestry in SW USA	ASW	61	A: 85.25%, G: 14.75%
African Caribbeans in Barbados	ACB	96	A: 85.42%, G: 14.58%
Ad Mixed American	AMR	347	A: 42.22%, G: 57.78%
Mexican Ancestry from Los Angeles USA	MXL	64	A: 31.25%, G: 68.75%
Puerto Ricans from Puerto Rico	PUR	104	A: 53.37%, G: 46.63%
Colombians from Medellin, Colombia	CLM	94	A: 57.45%, G: 42.55%
Peruvians from Lima, Peru	PEL	85	A: 20.0%, G: 80.0%
East Asian	EAS	504	A: 45.34%, G: 54.66%
Han Chinese in Beijing, China	CHB	103	A: 65.53%, G: 34.47%
Japanese in Tokyo, Japan	JPT	104	A: 67.31%, G: 32.69%
Southern Han Chinese	CHS	105	A: 43.81%, G: 56.19%
Chinese Dai in Xishuangbanna, China	CDX	93	A: 24.73%, G: 75.27%
Kinh in Ho Chi Minh City, Vietnam	KHV	99	A: 22.22%, G: 77.78%
European	EUR	503	A: 68.99%, G: 31.01%
Utah Residents (CEPH) with Northern and Western European Ancestry	CEU	99	A: 69.7%, G: 30.3%
Toscani in Italia	TSI	107	A: 77.57%, G: 22.43%
Finnish in Finland	FIN	99	A: 55.05%, G: 44.95%
British in England and Scotland	GBR	91	A: 67.03%, G: 32.97%
Iberian Population in Spain	IBS	107	A: 74.3%, G: 25.7%
South Asian	SAS	489	A: 87.12%, G: 12.88%
Gujarati Indian from Houston, Texas	GIH	103	A: 90.78%, G: 9.22%
Punjabi from Lahore, Pakistan	PJL	96	A: 84.9%, G: 15.1%
Bengali from Bangladesh	BEB	86	A: 81.4%, G: 18.6%
Sri Lankan Tamil from the UK	STU	102	A: 86.76%, G: 13.24%
Indian Telugu from the UK	ITU	102	A: 90.69%, G: 9.31%

Supplementary Table S2. Functional annotation of rs28456 (retrieved from RegulomeDB and GTEx databases)

RefSNP ID	RegulomeDB	eQTL	P	NES*	Tissue
rs28456	1f	*DAGLA*	8.9e-7	-0.14	Esophagus - Mucosa
		FADS1	5.2e-39	-0.75	Pancreas
			6.2e-36	-0.46	Esophagus - Mucosa
			1.3e-27	-0.78	Brain - Cerebellum
			1.2e-21	-0.36	Nerve - Tibial
			3.8e-20	-0.68	Brain - Cerebellar Hemisphere
			1.5e-16	-0.26	Thyroid
			6.3e-15	-0.22	Muscle - Skeletal
			2.9e-12	-0.32	Brain - Cortex
			7.8e-12	-0.31	Testis
			4.1e-11	-0.33	Stomach
			9.7e-10	-0.28	Colon - Sigmoid
			1.3e-9	-0.33	Brain - Hippocampus
			7.6e-9	-0.19	Artery - Tibial
			6.0e-8	-0.21	Esophagus - Muscularis
			6.7e-8	-0.18	Heart - Left Ventricle
			5.3e-7	-0.24	Brain - Frontal Cortex (BA9)
			0.0000010	-0.42	Liver
			0.0000012	-0.32	Brain - Hypothalamus
			0.0000013	-0.29	Brain - Putamen (basal ganglia)
			0.0000013	-0.21	Adipose - Subcutaneous
			0.0000054	-0.24	Brain - Caudate (basal ganglia)
			0.0000081	0.18	Whole Blood
			0.0000084	-0.21	Esophagus - Gastroesophageal Junction
			0.000014	-0.27	Prostate
			0.000016	-0.23	Brain - Anterior cingulate cortex (BA24)
			0.000016	-0.19	Adipose - Visceral (Omentum)
			0.000023	-0.41	Brain - Spinal cord (cervical c-1)
			0.000027	-0.13	Lung
			0.00015	-0.078	Cells - Cultured fibroblasts
		FADS2	2.1e-60	0.76	Whole Blood
			6.1e-26	0.49	Esophagus - Muscularis
			8.7e-25	0.30	Cells - Cultured fibroblasts
			2.2e-22	0.38	Thyroid
			1.2e-20	0.38	Heart - Left Ventricle
			1.2e-18	0.82	Spleen
			6.0e-18	0.31	Colon - Transverse
			1.1e-16	0.49	Esophagus - Gastroesophageal Junction
			4.0e-15	0.37	Heart - Atrial Appendage
			3.4e-14	0.27	Lung
			2.6e-13	0.25	Muscle - Skeletal
			2.7e-13	0.24	Artery - Tibial
			3.8e-13	0.65	Small Intestine - Terminal Ileum
			1.0e-12	0.31	Nerve - Tibial
			9.3e-12	0.34	Breast - Mammary Tissue
			1.4e-11	0.27	Artery - Aorta
			6.9e-10	0.32	Colon - Sigmoid
			2.3e-8	0.34	Testis
			1.0e-7	0.20	Adipose - Subcutaneous
			1.6e-7	0.20	Skin - Sun Exposed (Lower leg)

		FADS3	0.0000014	0.26	Stomach
			0.000019	0.29	Ovary
			0.000042	0.18	Adipose - Visceral (Omentum)
			0.000072	0.13	Skin - Not Sun Exposed (Suprapubic)
			0.000088	0.19	Esophagus - Mucosa
			4.6e-11	-0.37	Brain - Cerebellum
			5.2e-10	-0.34	Brain - Cerebellar Hemisphere
			6.5e-8	-0.41	Liver
		MYRF	0.0000088	-0.19	Esophagus - Mucosa
			0.00014	0.14	Adipose - Subcutaneous
		TMEM258	1.7e-9	0.13	Whole Blood
			6.5e-9	0.14	Cells - Cultured fibroblasts
			6.7e-8	0.12	Nerve - Tibial
			7.1e-8	0.13	Adipose - Subcutaneous
			8.2e-8	0.11	Artery - Tibial
			2.6e-7	0.12	Skin - Sun Exposed (Lower leg)
			0.0000015	0.18	Colon - Sigmoid
			0.0000020	0.13	Esophagus - Muscularis
			0.0000031	0.12	Breast - Mammary Tissue
			0.0000032	0.11	Muscle - Skeletal
			0.000035	0.11	Adipose - Visceral (Omentum)
			0.000055	0.11	Artery - Aorta
			0.000067	0.092	Thyroid

*Normalized Effect Size, 1f: eQTL/caQTL + TF binding / chromatin accessibility peak.

Supplementary Fig. S1. Minor allele frequencies of rs28456 in populations across the globe.