Neuropsychiatric Disease and Treatment

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Association analysis of the *Cadherin13* gene with schizophrenia in the Japanese population

This article was published in the following Dove Press journal:
Neuropsychiatric Disease and Treatment
2 June 2015
Number of times this article has been viewed

Ikuo Otsuka[1]
Yuichiro Watanabe[2]
Akitoyo Hishimoto[1]
Shuken Boku[1]
Kentaro Mouri[1]
Kyoichi Shiroiwa[1]
Satoshi Okazaki[1]
Ayako Nunokawa[2]
Osamu Shirakawa[3]
Toshiyuki Someya[2]
Ichiro Sora[1]

[1]Department of Psychiatry, Graduate School of Medicine, Kobe University, Kobe, [2]Department of Psychiatry, Graduate School of Medical and Dental Sciences, Niigata University, Niigata, [3]Department of Neuropsychiatry, School of Medicine, Kinki University, Osaka, Japan

Background: *Cadherin13* (*CDH13*) is a glycosylphosphatidylinositol-anchored cell adhesion molecule that plays a crucial role in morphogenesis and the maintenance of neuronal circuitry. *CDH13* has been implicated in the susceptibility to a variety of psychiatric diseases. A recent genome-wide association study using Danish samples showed, for the first time, the involvement of a single nucleotide polymorphism (SNP) of *CDH13* (intronic SNP rs8057927) in schizophrenia. Here, we investigated the association between other SNPs of *CDH13* and schizophrenia and tried to replicate the association for the SNP of rs8057927, in the Japanese population.

Methods: Using TaqMan® SNP genotyping assays, five tag SNPs (rs12925602, rs7193788, rs736719, rs6565051, and rs7204454) in the promoter region of *CDH13* were examined for their association with schizophrenia in two independent samples. The first sample comprised 665 patients and 760 controls, and the second sample comprised 677 patients and 667 controls. One tag SNP for rs8057927 was also examined for the association with schizophrenia in the first sample set.

Results: A GACAG haplotype of the five SNPs in the promoter region of *CDH13* was significantly associated with schizophrenia in the first sample set (P=0.016 and corrected P=0.098). A combined analysis of the GACAG haplotype with the second sample set enhanced the significance (P=0.0026 and corrected P=0.021). We found no association between rs8057927 and schizophrenia in the first sample set.

Conclusion: Our results suggest that *CDH13* may contribute to the genetic risk of schizophrenia. Further replication on the association of *CDH13* with schizophrenia and functional studies are required to confirm the current findings.

Keywords: *CDH13*, promoter region, haplotype, SNP

Introduction

Schizophrenia is a severe mental disorder that ranks among the world's top ten causes of long-term disability, with a worldwide prevalence of approximately 1%. Although the causes of schizophrenia are still largely unknown, previous studies have suggested that the inheritability of schizophrenia is high and that there is a small but significant environmental effect associated with the susceptibility to schizophrenia.[1,2]

Recent genome-wide association study (GWASs) has shown that common variants of single nucleotide polymorphisms (SNPs) with relatively weak effects may be associated with schizophrenia.[3] Meanwhile, it is well established that macroscopic abnormalities, such as volume reductions of the prefrontal cortex, hippocampus, and generalized brain, are associated with schizophrenia.[4,5] In addition, significant alterations in neuron size, morphology, and synaptic connectivity have been reported.[6–8]

Correspondence: Akitoyo Hishimoto
Department of Psychiatry, Kobe University Graduate School of Medicine, 7-5-1, Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan
Tel +81 78 382 6065
Fax +81 78 382 6079
Email hishipon@med.kobe-u.ac.jp

These past studies suggest that neural development and mature brain function-related genes may also be schizophrenia-associated genes.

Cadherins (*CDH*s) belong to a superfamily of cell adhesion molecules that regulate morphogenesis by mediating cell adhesion. In the nervous system, *CDH*s play crucial roles in neural tube regionalization, neuronal migration, gray matter differentiation, neural circuit formation, spine morphology, and synapse formation and remodeling.[9,10] The finding that the gene locus of the *CDH* superfamily overlaps with potential regions underlying schizophrenia susceptibility implicate an association between *CDHs* and schizophrenia.[11,12] For example, protocadherin12 (*PCDH12*) and *CDH18* are candidate genes that have been indicated to confer an increased risk for schizophrenia.[7,12]

CDH13, also known as H-cadherin or T-cadherin, belongs to the *CDH* superfamily. In humans, *CDH13* is located on chromosome 16q23 and contains 1,169.8 kbp. Although the classical extracellular *CDH* structure is conserved, *CDH13* lacks transmembrane and cytoplasmic domains and is anchored to the cellular membrane through glycosylphosphatidylinositol.[13] *CDH13* has been implicated in the susceptibility to a variety of psychiatric diseases. A GWAS of attention deficit hyperactivity disorder (ADHD) identified *CDH13* as one of the genes that is most highly associated with ADHD,[14] and a meta-analysis of ADHD linkage scans indicated the only genome-wide significant region overlapped with *CDH13*.[15] GWASs have also indicated the involvement of *CDH13* in depression,[16] autism,[17,18] alcohol dependence,[19] nicotine dependence,[20] and methamphetamine dependence.[21] Recently, a GWAS of Danish samples indicated that rs8057927 in the intron of *CDH13* is associated with schizophrenia.[22] Although it was the first report to show an involvement of *CDH13* in schizophrenia, rs8057927 in the intron of *CDH13* is not a variant of coding region or promoter region. Therefore, the functional significance of rs8057927 in the intron of *CDH13* remains unclear. In addition, there is a possibility that other SNPs in the coding region and/or promoter region of *CDH13* are associated with schizophrenia.

Our present study was designed to investigate the association between coding or regulatory SNPs of *CDH13* and schizophrenia, and to replicate the association for the SNP rs8057927, in the Japanese population. Here, we focused on five tag SNPs from the linkage disequilibrium (LD) block in the promoter region of *CDH13* because we found neither cis-acting SNPs nor nonsynonymous SNPs after consulting the databases: mRNA by SNP Browser (http://www.sph.umich.edu/csg/liang/asthma/)[23] and Japanese SNP (JSNP) DATABASE (http://snp.ims.u-tokyo.ac.jp).[24]

Materials and methods

Subjects

The present study was approved by the Ethical Committee for Genetic Studies of Kobe University Graduate School of Medicine and the Ethics Committee of Genetics at Niigata University School of Medicine. Informed consent was obtained from all of the participants. All of the participants were of Japanese descent and were recruited in the Kobe city area (the first set) or the Niigata area (the second set) of Japan.

The first set of participants consisted of 665 unrelated schizophrenia patients, including 344 males (with mean age ± standard deviation [SD] of 53.3±14.0 years) and 321 females (53.5±15.2 years), and 760 unrelated healthy volunteers (359 males [53.1±18.9 years]; 401 females [54.9±18.3 years]). There were no significant differences in the sex (χ^2=1.277, P=0.258) and age (t=0.792, df=1381, P=0.429) distributions between the schizophrenia and the control groups. The second set consisted of 677 unrelated schizophrenia patients (363 males [39.5±13.3 years]; 314 females [39.7±14.3 years]) and 667 unrelated healthy volunteers (341 males [36.7±9.5 years]; 326 females [40.0±11.8 years]). There were no significant differences in the sex (χ^2=0.838, P=0.360) and age (t=1.897, df=1,336, P=0.058) distributions between the schizophrenia and the control groups.

The psychiatric assessment of each participant was conducted as previously described.[25,26] In brief, the patients were diagnosed by at least two psychiatrists according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* DSM-IV[27] criteria for schizophrenia, based on unstructured interviews and reviews of their medical records at each hospital. None of the patients had a history of substance abuse (excluding nicotine dependence) or organic mental disorders. All of the control subjects were interviewed and screened for psychiatric disorders, based on an unstructured interview by a psychiatrist. None of the control subjects had any present, past, or family (up to first-degree relatives) histories of psychiatric disorders or substance abuse (excluding nicotine dependence).

SNP selection and genotyping

We first identified one LD block in the promoter region of *CDH13* from the HapMap database (release#27, www.hapmap.org) (population: Japanese Tokyo, minor allele

frequencies [MAFs] of more than 0.05), using the Haploview software program version 4.2 (http://www.broad.mit.edu/mpg/haploview/).[28] We then selected five tagging SNPs (rs12925602, rs7193788, rs736719, rs6565051, and rs7204454) from the LD block, with the criterion of an r^2 threshold greater than 0.8 in "pair-wise tagging only" mode, using the "Tagger" program in the Haploview software, and we used these SNPs in the following association analysis.

For genotype determination, peripheral blood was drawn from all of the participants, and the leukocyte DNA was extracted. We used TaqMan® assays (Applied Biosystems®; Life Technologies Corp, Carlsbad, CA, USA) for genotyping all of the SNPs. We selected predesigned TaqMan SNP genotyping assays from the Life Technologies database for all five SNPs that were examined. The genotyping was performed according to the protocol recommended by the manufacturer.

Although we also tried to investigate the intronic SNP rs8057927 previously reported for its involvement in schizophrenia in the Danish population,[22] TaqMan assays for genotyping rs8057927 were not available. Therefore, we chose rs8049308 as the substitute for rs8057927 because rs8049308 is a tag SNP for rs8057927 (these two SNPs have strong LD to each other [D'=1.0, r^2=0.946]) (Figure S1).

Statistics

We used the Haploview software to determine the Hardy–Weinberg equilibrium (HWE), LD, allelic/haplotype frequencies, and genetic association, between the schizophrenia and control groups. The allele-based association was tested using the χ^2 test. If necessary, permutation tests based on 10,000 replications were performed to calculate the corrected P-values of the allelic or haplotypic analyses for multiple testing by the Haploview software. The genotype-based association was evaluated using the Cochran–Armitage trend test. The haplotype-based association was examined using the χ^2 test and the Fisher's exact test, using R version 2.15.0 (The R Foundation for Statistical Computing, Vienna, Austria). The power analysis was performed using the Power and Sample Size Calculations Version3.1.2 program with an α of 0.05.[29] Statistical significance was defined at $P<0.05$.

Results

rs12925602, rs7193788, rs736719, rs6565051, and rs7204454

The distributions of all of the SNPs did not deviate from the HWE in each set. Using the solid spine method, five selected SNPs (rs12925602, rs7193788, rs736719, rs6565051, and rs7204454) in LD with each other formed one haplotype block (D'=0.90–0.99) (Figure 1). The allelic frequencies of the tag SNPs in the promoter region of *CDH13* are shown in Table 1. Neither the genotype distribution nor the allelic frequency of these five SNPs was significantly associated with schizophrenia in either set. Even when the data of the first and second set were combined, no significant difference was found.

Detailed haplotype frequencies between the schizophrenia and control groups are shown in Table 2. Each haplotype analysis of the LD block revealed a nominal significant distribution of the GACAG haplotype between the schizophrenia and control groups in the first set (P=0.016). Although no significant difference was found in the second set, the distributions of each haplotype between the schizophrenia and control groups were similar to those in the first sample. When the data of the first and second set were combined, the significance was enhanced for the GACAG haplotype (P=0.0026). The GACAG haplotype was also significantly associated with schizophrenia even after correction for multiple testing (corrected P=0.021). The frequency of the GACAG haplotype in the schizophrenia group (0.006) was lower than that in the control group (0.014).

rs8049308 (as the substitute for rs8057927)

The allelic frequency of rs8049308 in the first set is shown in Table 1. The distributions of this SNP did not differ from the HWE in the first set. Neither the genotype distribution nor the allelic frequency of rs8049308 was significantly associated with schizophrenia.

Discussion

Here we showed that SNPs in the promoter region of *CDH13* are associated with schizophrenia in the Japanese population. Although *CDH13* has been implicated in the susceptibility to a variety of psychiatric diseases,[14–21] there has been no report regarding the association between *CDH13* and schizophrenia except for a recent GWAS of a Danish population sample.[22] In addition, this recent GWAS found the association between schizophrenia and an intron of *CDH13* but not the promoter region. Therefore, our present study was the first to investigate the association of the promoter region of *CDH13* with schizophrenia in the Japanese population.

In the human adult brain, *CDH13* expression is detected in the prefrontal cortex, hippocampus, hypothalamus, amygdala, and substantia nigra (http://www.gtexportal.org/),[30] which overlap with regions linked to a variety of psychiatric

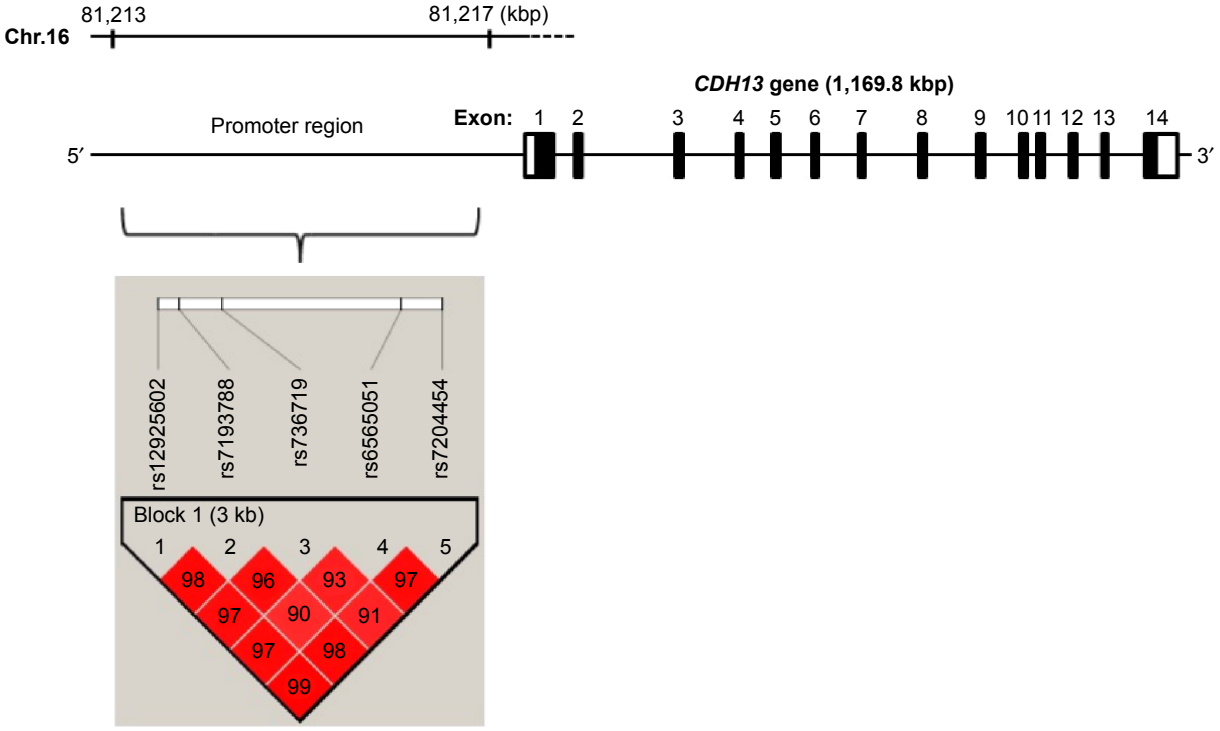

Figure 1 *Cadherin13* (*CDH13*) tag single nucleotide polymorphisms (SNPs) and the genetic structure of *CDH13*. The genetic structure of *CDH13* is shown at the top. The gene consists of fourteen exons spanning 1,169.8 kbp. Linkage disequilibrium (*D*' values) of five SNPs studied here are shown.

Table 1 Association between *CDH13* SNPs with schizophrenia

Sample	SNP ID position[a]	Phen	Genotype distribution			Minor allele		*P*-value			Power	OR (95% CI)
			MM	Mm	mm	MAF	Allele	HWE	Genotype[b]	Allele[c]		
rs12925602, rs7193788, rs736719, rs6565051, and rs7204454												
First set	rs12925602	SCZ	418	198	29	0.198	A	0.428	0.708	0.696	0.059	0.97 (0.80–1.16)
SCZ, n=665	81213402	CON	471	255	26	0.204		0.281		(0.991)		
CON, n=760	rs7193788	SCZ	203	304	139	0.449	G	0.269	0.327	0.369	0.099	1.08 (0.93–1.25)
	81213661	CON	234	384	132	0.432		0.241		(0.815)		
	rs736719	SCZ	515	121	5	0.102	T	0.643	0.130	0.138	0.188	0.83 (0.66–1.06)
	81214146	CON	575	161	9	0.12		0.698		(0.436)		
	rs6565051	SCZ	275	275	96	0.363	G	0.062	0.905	0.946	0.050	0.99 (0.85–1.16)
	81216229	CON	310	337	105	0.364		0.479		(1.000)		
	rs7204454	SCZ	268	284	93	0.364	C	0.271	0.473	0.454	0.085	1.06 (0.91–1.24)
	81216695	CON	315	342	92	0.350		0.982		(0.892)		
Second set	rs12925602	SCZ	433	215	27	0.199	A	1.000	0.3505	0.3476	0.100	1.10 (0.91–1.33)
SCZ, n=677	81213402	CON	444	196	25	0.185		0.629		(0.786)		
CON, n=667	rs7193788	SCZ	220	329	128	0.432	G	0.845	0.2825	0.6671	0.060	1.09 (0.94–1.27)
	81213661	CON	244	316	123	0.424		0.575		(0.985)		
	rs736719	SCZ	522	140	15	0.126	T	0.180	0.1495	0.1455	0.176	1.19 (0.94–1.51)
	81214146	CON	528	131	6	0.108		0.669		(0.445)		
	rs6565051	SCZ	265	308	101	0.378	G	0.497	0.3395	0.3389	0.104	0.93 (0.79–1.08)
	81216229	CON	237	324	100	0.396		0.600		(0.774)		
	rs7204454	SCZ	289	296	83	0.346	C	0.639	0.7327	0.7267	0.056	0.97 (0.83–1.14)
	81216695	CON	288	279	93	0.352		0.068		(0.993)		
Combined	rs12925602	SCZ	851	413	56	0.199	A	0.555	0.729	0.738	0.058	1.02 (0.90–1.17)
SCZ, n=1,342	81213402	CON	915	451	51	0.195		0.690		(0.994)		
CON, n=1,427	rs7193788	SCZ	423	633	267	0.440	G	0.334	0.161	0.366	0.098	1.08 (0.97–1.20)
	81213661	CON	478	700	255	0.428		0.670		(0.811)		

(*Continued*)

Table 1 (*Continued*)

Sample	SNP ID position[a]	Phen	Genotype distribution			Minor allele		*P*-value			Power	OR (95% CI)
			MM	Mm	mm	MAF	Allele	HWE	Genotype[b]	Allele[c]		
	rs736719	SCZ	1,037	261	20	0.114	T	0.511	0.999	0.992	0.050	1.00 (0.85–1.18)
	81214146	CON	1,103	292	15	0.114		0.462		(1.000)		
	rs6565051	SCZ	540	583	197	0.371	G	0.067	0.503	0.520	0.072	0.96 (0.86–1.07)
	81216229	CON	547	661	205	0.379		0.909		(0.931)		
	rs7204454	SCZ	557	580	176	0.355	C	0.243	0.806	0.788	0.056	1.01 (0.91–1.13)
	81216695	CON	603	621	185	0.351		0.245		(0.997)		
rs8049308 (as the substitute for rs8057927)												
First set	rs8049308	SCZ	309	267	69	0.314	C	0.357	0.634	0.630	0.066	1.04 (0.89–1.22)
SCZ, n=665	81252503	CON	363	313	72	0.305		0.753		(0.658)		
CON, n=760												

Notes: [a]SNP ID number and positions are available at http://hapmap.ncbi.nlm.nih.gov/. [b]Genotypic *P*-values were tested with the Cochran-Armitage test for trend. [c]Allelic *P*-values were tested with χ^2; corrections for multiple comparisons are in parentheses (for 10,000 permutations).
Abbreviations: *CDH13*, *cadherin13*; CI, confidence interval; CON, control; HWE, Hardy–Weinberg equilibrium; M, major allele; m, minor allele; MAF, minor allele frequency; OR, odds ratio; Phen, phenotype; SCZ, schizophrenia; SNP, single nucleotide polymorphism; SNP ID, single nucleotide polymorphism identification.

diseases including schizophrenia.[13,31] *CDH13* might have a role as an axonal pathfinder during neurodevelopment and play a role in the maintenance of inhibitory and excitatory synapses after maturation of neuronal circuits.[32] In addition, altered excitation/inhibition balance caused by the dysfunction or loss of inhibitory interneurons has been associated with the pathophysiology of schizophrenia.[33,34] These past studies suggest the involvement of *CDH13* in the pathophysiology of schizophrenia. Therefore, the attention to *CDH13* in this manuscript may be reasonable, and further studies are needed to confirm the role of *CDH13* in the pathophysiology of schizophrenia.

Our results showed significant differences in the distribution of the GACAG haplotype in the promoter region of *CDH13* between schizophrenia patients and healthy controls. Based on the frequency of the haplotype, the GACAG

Table 2 Association between haplotypes in the promoter region of *CDH13* and schizophrenia

Sample	Haplotype	Haplotype frequency		χ^2	*P*-value*	Global *P*-values	OR (95% CI)
		Schizophrenia	Control				
rs12925602–rs7204454							
First set	GACGG	0.343	0.336	0.162	0.688 (0.999)	χ^2=9.87, *df*=6	1.03 (0.88–1.21)
SCZ, n=665	GGCAC	0.261	0.232	3.072	0.080 (0.492)	*P*-value =0.130	1.17 (0.98–1.39)
CON, n=760	AACAG	0.191	0.201	0.441	0.507 (0.997)	(*P*-value =0.125 by	0.94 (0.78–1.13)
	GGTAC	0.097	0.107	0.863	0.353 (0.979)	Fisher's exact test)	0.89 (0.70–1.14)
	GGCAG	0.071	0.066	0.262	0.609 (0.999)		1.08 (0.81–1.45)
	GGCGG	0.011	0.011	0.019	0.890 (1.000)		0.95 (0.47–1.94)
	GACAG	0.009	0.020	5.842	0.016 (0.098)**		0.44 (0.21–0.87)**
Second set	GACGG	0.362	0.384	1.389	0.239 (0.881)	χ^2=7.26, *df*=6	0.91 (0.78–1.06)
SCZ, n=677	GGCAC	0.224	0.242	1.208	0.272 (0.917)	*P*-value =0.298	0.90 (0.76–1.08)
CON, n=667	AACAG	0.200	0.185	0.911	0.340 (0.967)	(*P*-value =0.303 by	1.10 (0.91–1.33)
	GGTAC	0.120	0.107	1.113	0.292 (0.938)	Fisher's exact test)	1.14 (0.90–1.44)
	GGCAG	0.070	0.061	0.773	0.380 (0.975)		1.15 (0.85–1.56)
	GGCGG	0.014	0.012	0.341	0.559 (0.996)		1.22 (0.62–2.40)
	GACAG	0.003	0.008	2.612	0.106 (0.575)		0.40 (0.13–1.26)
Combined	GACGG	0.352	0.359	0.229	0.632 (1.000)	χ^2=9.90, *df*=6	0.97 (0.87–1.09)
SCZ, n=1,342	GGCAC	0.242	0.237	0.176	0.675 (1.000)	*P*-value =0.129	1.03 (0.91–1.16)
CON, n=1,427	AACAG	0.196	0.194	0.033	0.855 (1.000)	(*P*-value =0.122 by	1.01 (0.89–1.16)
	GGTAC	0.109	0.107	0.033	0.8559 (1.000)	Fisher's exact test)	1.02 (0.86–1.21)
	GGCAG	0.071	0.064	0.953	0.3289 (0.995)		1.11 (0.90–1.37)
	GGCGG	0.012	0.012	0.040	0.8418 (1.000)		1.05 (0.65–1.71)
	GACAG	0.006	0.014	9.100	0.0026 (0.021)**		0.41 (0.23–0.75)**

Notes: *This column shows the nominal *P*-values and the corrected *P*-values for multiple testing (for 10,000 permutations). **Significant differences between the schizophrenia and control groups.
Abbreviations: *CDH13*, *cadherin13*; CI, confidence interval; CON, control; OR, odds ratio; SCZ, schizophrenia.

haplotype may have a protective role. None of the SNPs in the promoter region of *CDH13* evaluated in this study revealed a statistically significant association of the *CDH13* locus with schizophrenia. One reason is that the sample size was too small to detect an association of *CDH13* SNPs with schizophrenia. Based on the observed allele frequencies of rs12925602, rs7193788, rs736719, rs6565051, and rs7204454, the current combined samples provide powers of 0.058, 0.098, 0.050, 0.072, and 0.056, respectively, to detect nominally significant results. A recent mega analysis by the Psychiatric Genomics Consortium did not identify any association between *CDH13* SNPs and schizophrenia.[35] Although their analysis included 492 schizophrenia and 427 control Japanese samples, most of their samples were from European populations. Genetic association of *CDH13* SNPs with schizophrenia may be variable in different ethnic populations. Therefore, further studies with larger samples in the Japanese and other Asian populations are needed.

As shown in Table S1, the genotype and allele frequencies of the SNPs (rs12925602, rs7193788, rs736719, rs6565051, and rs7204454) are different among populations. The distributions of haplotypes of the five SNPs (rs12925602–rs7204454) are also different (Table S2). The frequency of the GACAG haplotype is rare among Asian and Caucasian populations, while the frequency of this haplotype in Africans is 0.024–0.126.[28] Therefore, replication studies, especially in other Asian populations and African populations, are required to confirm the findings of our present study.

Although we also conducted a case-control study for the intronic SNP rs8049308 as the substitute for rs8057927, which previously indicated an association with schizophrenia in the Danish samples,[22] neither the genotype distribution nor the allelic frequency of rs8049308 was significantly associated with schizophrenia in the first set. As shown in Table S1, the genotype and allele frequencies of rs8057927 and rs8049308 in the Caucasian populations are significantly lower compared with the Asian populations. These differences may explain why the result identified in the Danish samples was not replicated in our Japanese samples.

A limitation in the present study should be considered. The number of subjects in the association study was small and may not have been large enough to detect a significant difference because the genetic impact of *CDH13* on schizophrenia may be mild. Therefore, further investigations with larger sample sizes are needed to confirm the present results.

The results reported here raise the question: do nucleotide substitutions in the *CDH13* promoter actually affect the transcriptional activity of the *CDH13* promoter? Our computational analysis using the TFBIND (http://tfbind.hgc.jp/)[36] revealed that most of the SNPs we studied here were located in the putative transcription factor binding sites (Table S3). This suggests that nucleotide substitution in the *CDH13* promoter region may affect the transcriptional activity of this promoter region by affecting the ability of this promoter region to bind to transcription factors. To test this hypothesis, transcriptional assays, such as a luciferase assay, are required in future studies.

Conclusion

The present study suggests that haplotype variants in the promoter region of *CDH13* may affect the susceptibility to schizophrenia. To confirm this result, further replication studies using larger sample sizes and different populations and functional studies are required.

Acknowledgments

This work was supported in part by research grants from the Ministry of Education, Culture, Sports, Science, and Technology of Japan and the Smoking Research Foundation. We thank Y Nagashima and N Yamazaki for technical assistance.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. *Arch Gen Psychiatry*. 2003;60(12):1187–1192.
2. Mueser KT, McGurk SR. Schizophrenia. *Lancet*. 2004;363(9426):2063–2072.
3. Sullivan PF, Daly MJ, O'Donovan M. Genetic architectures of psychiatric disorders: the emerging picture and its implications. *Nat Rev Genet*. 2012;13(8):537–551.
4. McCarley RW, Wible CG, Frumin M, et al. MRI anatomy of schizophrenia. *Biol Psychiatry*. 1999;45(9):1099–1119.
5. Shenton ME, Dickey CC, Frumin M, McCarley RW. A review of MRI findings in schizophrenia. *Schizophr Res*. 2001;49(1–2):1–52.
6. Harrison PJ. The neuropathology of schizophrenia. A critical review of the data and their interpretation. *Brain*. 1999;122(Pt4):593–624.
7. Gregório SP, Sallet PC, Do KA, Lin E, Gattaz WF, Dias-Neto E. Polymorphisms in genes involved in neurodevelopment may be associated with altered brain morphology in schizophrenia: preliminary evidence. *Psychiatry Res*. 2009;165(1–2):1–9.
8. Stephan KE, Friston KJ, Frith CD. Dysconnection in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring. *Schizophr Bull*. 2009;35(3):509–527.
9. Takeichi M. The cadherin superfamily in neuronal connections and interactions. *Nat Rev Neurosci*. 2007;8(1):11–20.
10. Hirano S, Takeichi M. Cadherins in brain morphogenesis and wiring. *Physiol Rev*. 2012;92(2):597–634.
11. Pedrosa E, Stefanescu R, Margolis B, et al. Analysis of protocadherin alpha gene enhancer polymorphism in bipolar disorder and schizophrenia. *Schizophr Res*. 2008;102(1–3):210–219.

12. Redies C, Hertel N, Hübner CA. Cadherins and neuropsychiatric disorders. *Brain Res*. 2012;1470:130–144.
13. Rivero O, Sich S, Popp S, Schmitt A, Franke B, Lesch KP. Impact of the ADHD-susceptibility gene CDH13 on development and function of brain networks. *Eur Neuropsychopharmacol*. 2013;23(6):492–507.
14. Neale BM, Lasky-Su J, Anney R, et al. Genome-wide association scan of attention deficit hyperactivity disorder. *Am J Med Genet B Neuropsychiatr Genet*. 2008;147B(8):1337–1344.
15. Zhou K, Dempfle A, Arcos-Burgos M, et al. Meta-analysis of genome-wide linkage scans of attention deficit hyperactivity disorder. *Am J Med Genet B Neuropsychiatr Genet*. 2008;147B(8):1392–1398.
16. Terracciano A, Tanaka T, Sutin AR, et al. Genome-wide association scan of trait depression. *Biol Psychiatry*. 2010;68(9):811–817.
17. Wang K, Zhang H, Ma D, et al. Common genetic variants on 5p14.1 associate with autism spectrum disorders. *Nature*. 2009;459:528–533.
18. Sanders SJ, Ercan-Sencicek AG, Hus V, et al. Multiple recurrent de novo CNVs, including duplications of the 7q11.23 Williams syndrome region, are strongly associated with autism. *Neuron*. 2011;70(5):863–885.
19. Treutlein J, Cichon S, Ridinger M, et al. Genome-wide association study of alcohol dependence. *Arch Gen Psychiatry*. 2009;66(77):773–784.
20. Uhl GR, Drgon T, Johnson C, et al. Genome-wide association for smoking cessation success: participants in the Patch in Practice trial of nicotine replacement. *Pharmacogenomics*. 2010;11(3):357–367.
21. Uhl GR, Drgon T, Liu QR, et al. Genome-wide association for methamphetamine dependence: convergent results from 2 samples. *Arch Gen Psychiatry*. 2008;65(3):345–355.
22. Børglum AD, Demontis D, Grove J, et al; GROUP investigators 10. Genome-wide study of association and interaction with maternal cytomegalovirus infection suggests new schizophrenia loci. *Mol Psychiatry*. 2014;19(3):325–333.
23. Dixon AL, Liang L, Moffatt MF, et al. A genome-wide association study of global gene expression. *Nat Genet*. 2007;39:1202–1207.
24. Hirakawa M, Tanaka T, Hashimoto, et al. JSNP: a database of common gene variations in the Japanese population. *Nucleic Acids Res*. 2002;30:158–162.
25. Watanabe Y, Muratake T, Kaneko N, Nunokawa A, Someya T. No association between the brain-derived neurotrophic factor gene and schizophrenia in a Japanese population. *Schizophr Res*. 2006;84(1):29–35.
26. Okazaki S, Watanabe Y, Hishimoto A, et al. Association analysis of putative cis-acting polymorphisms of interleukin-19 gene with schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2014;50:151–156.
27. American Psychiatric Association. The *Diagnostic and Statistical Manual of Mental Disorders, Fourth edition*, text revision (DSM-IV TR). *American Psychiatric Association Press*. 2000.
28. Barrett JC, Fry B, Maller J, Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. *Bioinformatics*. 2005;21(2):263–265.
29. Dupont WD, Plummer WD. Power and sample size calculations for studies involving linear regression. *Control Clin Trials*. 1998;19(6):589–601.
30. GTEx Consortium. The Genotype-Tissue Expression (GTEx) project. *Nat Genet*. 2013;45(6):580–585.
31. Benes FM. Amygdalocortical circuitry in schizophrenia: from circuits to molecules. *Neuropsychopharmacology*. 2010;35(1):239–257.
32. Paradis S, Harrar DB, Lin Y, et al. An RNAi-based approach identifies molecules required for glutamatergic and GABAergic synapse development. *Neuron*. 2007;53(2):217–232.
33. Yizhar O, Fenno LE, Prigge M, et al. Neocortical excitation/inhibition balance in information processing and social dysfunction. *Nature*. 2011;477(7363):171–178.
34. Mao W, Watanabe T, Cho S, et al. Shank1 regulates excitatory synaptic transmission in mouse hippocampal parvalbumin-expressing inhibitory interneurons. *Eur J Neurosci*. 2015;41(8):1025–1035.
35. Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature*. 2014;511(7510):421–427.
36. Tsunoda T, Takagi T. Estimating transcription factor bindability on DNA. *Bioinformatics*. 1999;15(7–8):622–630.

Supplementary materials

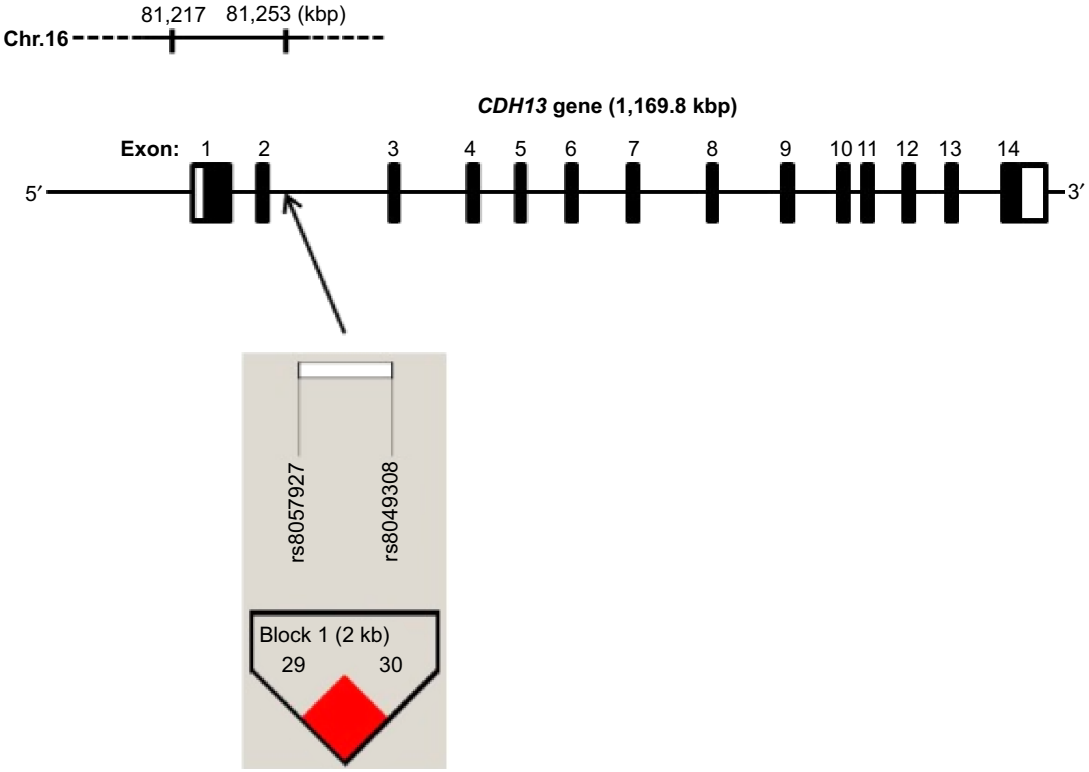

Figure S1 The intronic SNPs (rs8057927 and rs8049308) have strong LD to each other (*D'*=1.0, r^2=0.946). rs8049308 is a tag SNP for rs8057927 with the criteria of r^2 threshold greater than 0.8 in 'pair-wise tagging only' mode using the 'Tagger' program in the Haploview software.
Abbreviations: *CDH13*, *cadherin13*; SNPs, single nucleotide polymorphisms; LD, linkage disequilibrium.

Table S1 Genotype frequencies and allele frequencies of *CDH13* SNPs in different ethnic populations

SNP	Population	Genotype frequencies										Allele frequencies						
		Genotype	Freq	Count	Genotype	Freq	Count	Genotype	Freq	Count	Total	Allele	Freq	Count	Allele	Freq	Count	Total
rs12925602	JPT	G/G	0.708	80	A/G	0.265	30	A/A	0.027	3	113	G	0.841	190	A	0.159	36	226
	CHB	G/G	0.708	97	A/G	0.255	35	A/A	0.036	5	137	G	0.836	229	A	0.164	45	274
	CHD	G/G	0.642	70	A/G	0.339	37	A/A	0.018	2	109	G	0.812	177	A	0.188	41	218
	GIH	G/G	0.802	81	A/G	0.149	15	A/A	0.050	5	101	G	0.876	177	A	0.124	25	202
	CEU	G/G	0.850	96	A/G	0.142	16	A/A	0.009	1	113	G	0.920	208	A	0.080	18	226
	TSI	G/G	0.745	76	A/G	0.255	26	A/A	0.000	0	102	G	0.873	178	A	0.127	26	204
	ASW	G/G	0.750	42	A/G	0.250	14	A/A	0.000	0	56	G	0.875	98	A	0.125	14	112
	LWK	G/G	0.782	86	A/G	0.191	21	A/A	0.027	3	110	G	0.877	193	A	0.123	27	220
	MKK	G/G	0.833	130	A/G	0.160	25	A/A	0.006	1	156	G	0.913	285	A	0.087	27	312
	YRI	G/G	0.789	116	A/G	0.204	30	A/A	0.007	1	147	G	0.891	262	A	0.109	32	294
	MEX	G/G	0.741	43	A/G	0.224	13	A/A	0.034	2	58	G	0.853	99	A	0.147	17	116
rs7193788	JPT	A/A	0.265	30	A/G	0.504	57	G/G	0.230	26	113	A	0.518	117	G	0.482	109	226
	CHB	A/A	0.285	39	A/G	0.445	61	G/G	0.270	37	137	A	0.507	139	G	0.493	135	274
	CHD	A/A	0.275	30	A/G	0.560	61	G/G	0.165	18	109	A	0.555	121	G	0.445	97	218
	GIH	A/A	0.584	59	A/G	0.366	37	G/G	0.050	5	101	A	0.767	155	G	0.233	47	202
	CEU	A/A	0.690	78	A/G	0.274	31	G/G	0.035	4	113	A	0.827	187	G	0.173	39	226
	TSI	A/A	0.784	80	A/G	0.186	19	G/G	0.029	3	102	A	0.877	179	G	0.123	25	204
	ASW	A/A	0.719	41	A/G	0.246	14	G/G	0.035	2	57	A	0.842	96	G	0.158	18	114
	LWK	A/A	0.691	76	A/G	0.273	30	G/G	0.036	4	110	A	0.827	182	G	0.173	38	220
	MKK	A/A	0.679	106	A/G	0.282	44	G/G	0.038	6	156	A	0.821	256	G	0.179	56	312
	YRI	A/A	0.796	117	A/G	0.190	28	G/G	0.014	2	147	A	0.891	262	G	0.109	32	294
	MEX	A/A	0.741	43	A/G	0.241	14	G/G	0.017	1	58	A	0.862	100	G	0.138	16	116
rs736719	JPT	C/C	0.779	88	C/T	0.186	21	T/T	0.035	4	113	C	0.872	197	T	0.128	37	226
	CHB	C/C	0.679	93	C/T	0.277	38	T/T	0.044	6	133	C	0.818	224	T	0.182	50	274
	CHD	C/C	0.688	75	C/T	0.303	33	T/T	0.009	1	109	C	0.839	183	T	0.161	35	218
	GIH	C/C	0.762	77	C/T	0.228	23	T/T	0.010	1	101	C	0.876	177	T	0.124	25	202
	CEU	C/C	0.699	79	C/T	0.265	30	T/T	0.035	4	113	C	0.832	188	T	0.168	38	226
	TSI	C/C	0.784	80	C/T	0.186	19	T/T	0.029	3	102	C	0.877	179	T	0.123	25	204
	ASW	C/C	0.737	42	C/T	0.228	13	T/T	0.035	2	57	C	0.851	97	T	0.149	17	114
	LWK	C/C	0.700	77	C/T	0.264	29	T/T	0.036	4	110	C	0.832	183	T	0.168	37	220
	MKK	C/C	0.679	106	C/T	0.288	45	T/T	0.032	5	156	C	0.824	257	T	0.176	55	312
	YRI	C/C	0.796	117	C/T	0.190	28	T/T	0.014	2	147	C	0.891	262	T	0.109	32	294
	MEX	C/C	0.776	45	C/T	0.207	12	T/T	0.017	1	58	C	0.879	102	T	0.121	14	116
rs6565051	JPT	G/G	0.133	15	A/G	0.469	53	A/A	0.398	45	113	G	0.367	83	A	0.633	143	226
	CHB	G/G	0.146	20	A/G	0.416	57	A/A	0.438	60	137	G	0.354	97	A	0.646	177	274
	CHD	G/G	0.148	16	A/G	0.463	50	A/A	0.389	42	108	G	0.380	82	A	0.620	134	216
	GIH	G/G	0.079	8	A/G	0.356	36	A/A	0.564	57	101	G	0.257	83	A	0.743	150	202
	CEU	G/G	0.071	8	A/G	0.354	40	A/A	0.575	65	113	G	0.248	56	A	0.752	170	226
	TSI	G/G	0.108	11	A/G	0.461	47	A/A	0.431	44	102	G	0.338	69	A	0.662	135	204
	ASW	G/G	0.088	5	A/G	0.421	24	A/A	0.491	28	57	G	0.298	34	A	0.702	80	114
	LWK	G/G	0.073	8	A/G	0.355	39	A/A	0.573	63	110	G	0.250	55	A	0.750	165	220
	MKK	G/G	0.052	8	A/G	0.426	66	A/A	0.523	81	155	G	0.265	82	A	0.735	228	310
	YRI	G/G	0.095	14	A/G	0.442	65	A/A	0.463	68	147	G	0.316	93	A	0.684	201	294
	MEX	G/G	0.140	8	A/G	0.509	29	A/A	0.351	20	57	G	0.395	45	A	0.605	69	114

(*Continued*)

Table S1 (*Continued*)

SNP	Population	Genotype frequencies										Allele frequencies						
		Genotype	Freq	Count	Genotype	Freq	Count	Genotype	Freq	Count	Total	Allele	Freq	Count	Allele	Freq	Count	Total
rs7204454	JPT	G/G	0.319	36	C/G	0.540	61	C/C	0.142	16	113	G	0.588	133	C	0.412	93	226
	CHB	G/G	0.382	52	C/G	0.441	60	C/C	0.176	24	136	G	0.603	164	C	0.397	108	272
	CHD	G/G	0.394	43	C/G	0.486	53	C/C	0.119	13	109	G	0.638	139	C	0.362	79	218
	GIH	G/G	0.158	16	C/G	0.406	41	C/C	0.436	44	101	G	0.361	73	C	0.639	129	202
	CEU	G/G	0.100	11	C/G	0.436	48	C/C	0.464	51	110	G	0.318	70	C	0.682	150	220
	TSI	G/G	0.147	15	C/G	0.598	61	C/C	0.255	26	102	G	0.446	91	C	0.554	113	204
	ASW	G/G	0.263	15	C/G	0.439	25	C/C	0.298	17	57	G	0.482	55	C	0.518	59	114
	LWK	G/G	0.164	18	C/G	0.536	59	C/C	0.300	33	110	G	0.432	95	C	0.568	125	220
	MKK	G/G	0.141	22	C/G	0.449	70	C/C	0.410	64	156	G	0.365	114	C	0.635	198	312
	YRI	G/G	0.284	40	C/G	0.504	71	C/C	0.213	30	141	G	0.535	151	C	0.465	131	282
	MEX	G/G	0.310	18	C/G	0.500	29	C/C	0.190	11	58	G	0.560	65	C	0.440	51	116
rs8057927	JPT	T/T	0.478	54	C/T	0.425	48	C/C	0.097	11	113	T	0.690	156	C	0.310	70	226
	CHB	T/T	0.478	65	C/T	0.412	56	C/C	0.110	15	136	T	0.684	186	C	0.316	86	272
	CHD	T/T	0.514	56	C/T	0.394	43	C/C	0.092	10	109	T	0.711	155	C	0.289	63	218
	GIH	T/T	0.901	91	C/T	0.089	9	C/C	0.010	1	101	T	0.946	191	C	0.054	11	202
	CEU	T/T	0.876	99	C/T	0.124	14	C/C	0	0	113	T	0.938	212	C	0.062	14	226
	TSI	T/T	0.853	87	C/T	0.147	15	C/C	0	0	102	T	0.926	189	C	0.074	15	204
	ASW	T/T	0.632	36	C/T	0.351	20	C/C	0.018	1	57	T	0.807	92	C	0.193	22	114
	LWK	T/T	0.620	67	C/T	0.324	35	C/C	0.056	6	108	T	0.782	169	C	0.218	47	216
	MKK	T/T	0.692	108	C/T	0.250	39	C/C	0.058	9	156	T	0.817	255	C	0.183	57	312
	YRI	T/T	0.623	91	C/T	0.336	49	C/C	0.041	6	146	T	0.791	231	C	0.209	61	292
	MEX	T/T	0.807	46	C/T	0.175	10	C/C	0.018	1	57	T	0.895	102	C	0.105	12	114
rs8049308	JPT	T/T	0.455	20	C/T	0.500	22	C/C	0.045	2	44	T	0.705	62	C	0.295	26	88
	CHB	T/T	0.364	16	C/T	0.477	21	C/C	0.159	7	44	T	0.602	53	C	0.398	35	88
	CEU	T/T	0.650	39	C/T	0.333	20	C/C	0.017	1	60	T	0.817	98	C	0.183	22	120
	YRI	T/T	0.583	35	C/T	0.383	23	C/C	0.033	2	60	T	0.775	93	C	0.225	27	120

Note: Genotype frequencies and allele frequencies data were determined by the HapMap database (HapMap data release 28, Phase 2+3, August 10), on NCBI B36 assembly, dbSNP b126 (http://hapmap.ncbi.nlm.nih.gov/).

Abbreviations: ASW, African ancestry in southwest USA; *CDH13*, *cadherin13*; CEU, residents of UT, USA with Northern and Western European ancestry, from the Centre d'Etude du Polymorphisme Humain collection; CHB, Han Chinese in Beijing, People's Republic of China; CHD, Chinese in metropolitan Denver, CO, USA; freq, frequency; GIH, Gujarati Indians in Houston, TX, USA; JPT, Japanese in Tokyo, Japan; LWK, Luhya in Webuye, Kenya; MEX, Mexican ancestry in Los Angeles, CA, USA; MKK, Maasai in Kinyawa, Kenya; SNP, single nucleotide polymorphism; TSI, Tuscan in Italy; YRI, Yoruba in Ibadan, Nigeria.

Table S2 Haplotype frequencies of *CDH13* SNPs (rs12925602–rs7204454) in different ethnic populations[1]

	JPT	CHB	CHD	GIH	CEU	TSI	ASW	LWK	MKK	YRI	MEX
GACGG	0.355	0.351	0.347	0.233	0.244	0.335	0.286	0.289	0.231	0.287	0.394
CGCAC	0.285	0.220	0.206	0.085							
AACAG	0.151	0.161	0.194	0.119	0.081	0.114	0.127	0.106	0.091	0.130	0.154
GGTAC	0.128	0.179	0.135	0.142	0.162	0.114	0.103	0.167	0.154	0.087	0.106
GGCAG	0.070	0.077	0.076								
GGCGG	0.012	0.006	0.018	0.006							
GACAG			0.006				0.071	0.067	0.024	0.126	0.010
AACGG		0.006				0.017					
GGCGC			0.012								
AGCAG				0.006							
AACAC					0.004						
GACGC				0.017		0.006	0.008			0.004	
GGCAC					0.009		0.008		0.003		0.019
AGTAC							0.008				
GGTGG									0.014		
GGTGC								0.006	0.014	0.022	0.010
GACAC			0.006	0.392	0.500	0.415	0.389	0.367	0.469	0.343	0.308

Note: Haplotype frequencies data were determined by the Haploview software program (version 4.2; Broad Institute, Cambridge, MA, USA) (http://www.broad.mit.edu/mpg/haploview/).

Abbreviations: ASW, African ancestry in southwest USA; *CDH13*, *cadherin13*; CEU, residents of UT, USA with Northern and Western European ancestry, from the Centre d'Etude du Polymorphisme Humain collection; CHB, Han Chinese in Beijing, People's Republic of China; CHD, Chinese in metropolitan Denver, CO, USA; GIH, Gujarati Indians in Houston, TX, USA; JPT, Japanese in Tokyo, Japan; LWK, Luhya in Webuye, Kenya; MEX, Mexican ancestry in Los Angeles, CA, USA; MKK, Maasai in Kinyawa, Kenya; SNPs, single nucleotide polymorphisms; TSI, Tuscan in Italy; YRI, Yoruba in Ibadan, Nigeria.

Table S3 Putative transcription factor binding site in each SNP on the promoter region of *CDH13*

SNP ID	Allele	Sequence	Predicted TF	Binding site	Function
rs12925602	A	TCTGCCTACATC[A] AGGAAATTCAGA	c-Ets-	ATCAAGGAAATT	Regulates numerous genes and involved in stem cell development, cell senescence and death, and tumorigenesis
			GATA-1	CATCAAGGA	Regulates the switch of fetal hemoglobin to adult hemoglobin for erythroid development
			CdxA	CA TCAAG	A transcription factor that binds to DNA to regulate the expression of genes, in particular the *Hox* genes
	G	TCTGCCTACATC[G] AGGAAATTCAGA	c-Ets-	ATCGAGGAAATT	Regulates numerous genes and involved in stem cell development, cell senescence and death, and tumorigenesis
			GATA-1	CATCGAGGA	Regulates the switch of fetal hemoglobin to adult hemoglobin for erythroid development
rs7193788	A	GCACGCAGCAGT[A] AAAATACAGAAA	CdxA	TAAAAAT AAAAATA	A transcription factor that binds to DNA to regulate the expression of genes, in particular the *Hox* genes
			AhR/Ar	GAGCA CGCAGCAGTAA	A ligand-activated transcription factor involved in the regulation of biological responses to planar aromatic hydrocarbons
			Sox5	GTAAAAATAC	A transcription factor involved in the regulation of embryonic development and in the determination of cell fate
	G	GCACGCAGCAGT[G] AAAATACAGAAA	AhR/Ar	ACGCAGCAGTGAAAA	A ligand-activated transcription factor involved in the regulation of biological responses to planar aromatic hydrocarbons
rs736719	C	CAGGAAGAAACA[C] GAAGCAGTGTTT	SRY	AAACACG	A transcription factor and a member of the HMG-box family of DNA binding proteins, which may directly generate some male-specific properties of the brain
	T	CAGGAAGAAACA[T] GAAGCAGTGTTT	SRY	AAACATG	A transcription factor and a member of the HMG-box family of DNA binding proteins, which may directly generate some male specific properties of the brain
			HNF-3b	GAAGAAACA TGA	A transcription factor and a member of the forkhead class of DNA-binding proteins
rs6565051	A	ACCTTCCCTGGA[A] TGGAGAAAAGTC	C/EBPb	GAATG GAGAAAAGT	A transcription factor that can bind as a homodimer to certain DNA regulatory regions and can also form heterodimers with other C/EBP
	G	ACCTTCCCTGGA[G] TGGAGAAAAGTC	C/EBPb	GAGTG GAGAAAAGT	A transcription factor that can bind as a homodimer to certain DNA regulatory regions and can also form heterodimers with other C/EBP
			MZF1	AGTG GAGA	A member of the SCAN domain family transcription factors that form dimers through their highly conserved SCAN motifs
rs7204454	C	GTGAGTTCAGTA[C] AATTTGTGTTTT	CdxA	TACAATT	A transcription factor that binds to DNA to regulate the expression of genes, in particular the *Hox* genes
	G	GTGAGTTCAGTA[G] AATTTGTGTTTT	CdxA	TAGAATT	A transcription factor that binds to DNA to regulate the expression of genes, in particular the *Hox* genes

Abbreviations: *CDH13*, *cadherin13*; SNP, single nucleotide polymorphism; SNP ID, single nucleotide polymorphism identification; TF, transcription factor.

Reference

1. Barrett JC, Fry B, Maller J, Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. *Bioinformatics*. 2005;21:263–265.