Supplements

Supplementary Tables

Supplementary Table 1 Demography of the combined studies

References	Studies	Years	Diagnosis Criteria	Ethnicities	No. Cases No. Families	No. Controls	Phenotypes of Cases	rs6313 (102T/C)	rs6311 (-1438A/G)
				Europeans					
(Fehr et al. 2001)	Fehr	2001	DSM-IV	German (male)	130	56	Alcohol dependence	+	
(Fehr et al. 2001)	Fehr	2001	DSM-IV	German (female)	46	19	Alcohol dependence	+	
(Parsian and Cloninger 2001)	Parsian	2001	DSM-III-R	Caucasian	133	88	Alcohol dependence		+
(Hill et al. 2002)	Hill	2002	DIS-III-R	Caucasian, Hispanic, African-American	HRR: 35 families		Type II alcoholism (antisocial)	+	
(Wrzosek et al. 2012)	Wrzosek	2012	DSM-IV & ICD-10	Caucasian Polish	150	80	Alcohol dependence	+	
				Hispanics					
(Saiz et al. 2008)	Saiz	2008	DSM-IV	Spanish	113	420	Heroin dependence		+
(Polina et al. 2009)	Polina	2009	DSM-IV	European Brazilian (male)	113	115	Alcohol dependence		+
				Asians					
(Nakamura et al. 1999)	Nakamura	1999	DSM-III-R	Japanese	507	361	Alcohol dependence		+
(Himei et al. 2000)	Himei	2000	DSM-111-R	Japanese	91	90	Alcohol dependence	+	
(Hwu and Chen 2000)	Hwu	2000	DSM-III	Chinese	85	70	Alcohol abuse	+	
(Hwu and Chen 2000)	Hwu	2000	DSM-III	Chinese	75		Alcohol dependence	+	
(Wang et al. 2001)	Wang	2001	CCMD-2-R	Chinese	72	109	Heroin dependence	+	
(Cao et al. 2002)	Cao	2002	DSM-IV & ICD-10	Chinese Han (male)	192	111	Heroin dependence		+
(Cao et al. 2002)	Cao	2002	DSM-IV & ICD-10	Chinese Han (female)	73	84	Heroin dependence		+
(Li et al. 2002)	Li	2002	DSM-IV	Chinese Han	121	194	Heroin abuse	+	+
(Terayama et al. 2003)	Terayama	2003	DSM-IV	Japanese	41	112	Alcohol dependence	+	+
(Shao et al. 2005)	Shao	2005	DSM-IV	Chinese Han	380	275	Heroin dependence		+
(Lee et al. 2009)	Lee	2009	DSM-IV	Korean male	97	76	Alcohol dependence	+	
(Tsunoka et al. 2010)	Tsunoka	2010	ICD-10-DCR	Japanese	196	802	Methamphetamine dependence (with induced psychosis)	+	+
(Yang et al. 2010)	Yang	2010	DSM-IV	Chinese (male)	588	194	Heroin dependence		+
(Gao et al. 2011)	Gao	2011	DSM-IV	Chinese Han	303	300	Heroin dependence	+	+

DSM = *Diagnostic and Statistical Manual of Mental Disorders*;

ICD = *International Statistical Classification of Diseases and Related Health Problems*;

CCMD = *Chinese Classification of Mental Disorders*.

Eight-six cases were diagnosed as type II alcoholism in the reference(Parsian and Cloninger 2001). The male and female subjects were analyzed as two independent studies for the two references(Cao et al. 2002; Fehr et al. 2001) and the studies of alcohol abuse and alcohol dependence were also analyzed as two independent studies in the reference(Hwu and Chen 2000). These studies included 3,506 cases and 3,556 controls, and 35 small nuclear families for the *HTR2A* rs6313 and rs6311 (or 3,820 cases and 3,776 controls including one study for *HTR2C*). The last three columns mark the studies included in the corresponding meta-analysis.

Supplementary Table 2 Results of the overall and sub-group analyses for the dominant and recessive models

SNPs / Groups	Studies[a]	Samples[b]	LnOR (95% CI)	OR (95% CI)	P(Z)	P(Q)	LnOR (95% CI)	OR (95% CI)	P(Z)	P(Q)
				Dominant model				Recessive model		
HTR2A **rs6313 (102T/C)**										
All the studies	12	1,407/1,908	-0.19 (-0.35,-0.04)	0.82 (0.71,0.96)	**0.0122**	0.5888	-0.23 (-0.5,0.03)	0.79 (0.61,1.03)	0.0836	0.0227
Europeans	3	326/155	-0.28 (-0.69,0.13)	0.76 (0.5,1.14)	0.1854	0.2523	-0.56 (-1.06,-0.07)	0.57 (0.35,0.94)	**0.026**	0.4194
Asians	9	1,081/1,753	-0.17 (-0.32,-0.02)	0.85 (0.73,0.98)	**0.0267**	0.5926	-0.17 (-0.46,0.13)	0.85 (0.63,1.14)	0.2661	0.0239
Alcohol dependence (abuse)	8	715/503	-0.29 (-0.5,-0.09)	0.75 (0.61,0.92)	**0.0056**	0.6728	-0.45 (-0.87,-0.02)	0.64 (0.42,0.98)	**0.0403**	0.0487
HTR2A **rs6311 (-1438A/G)**										
All the studies	12	2,760/3,056	-0.07 (-0.22,0.07)	0.93 (0.81,1.08)	0.3333	0.2035	0.12 (-0.07,0.31)	1.13 (0.93,1.36)	0.2207	0.0208
Europeans & Hispanic	3	359/623	0.44 (0.07,0.82)	1.56 (1.07,2.27)	**0.0205**	0.6965	0.63 (0.25,1.02)	1.89 (1.29,2.77)	**0.0012**	0.6047
Asians	9	2,401/2,433	-0.16 (-0.32,0)	0.85 (0.73,1)	**0.044**	0.7861	0.01 (-0.12,0.14)	1.01 (0.88,1.15)	0.9067	0.1709
Heroin dependence (abuse)	7	1,770/1,578	-0.02 (-0.22,0.17)	0.98 (0.81,1.18)	0.8067	0.236	0.14 (-0.03,0.3)	1.15 (0.97,1.36)	0.1079	0.7183
Alcohol dependence (abuse)	4	794/676	-0.18 (-0.44,0.09)	0.84 (0.64,1.1)	0.1969	0.1052	-0.26 (-0.55,0.02)	0.77 (0.58,1.02)	0.0707	0.1399

[a], the number of studies included are indicated.

[b], the number of cases/controls.

P(Z): Z test used to determine the significance of the overall OR. The *P* values < 0.05 are indicated in red boldfaces.

P(Q): Cochran's X2-based Q statistic test used to assess the heterogeneity.

P(T): T test used to estimate the significance of publication bias (not shown).

Supplementary Table 3 Results of sensitivity analysis

Polymorphisms/Studies	LnOR (95% CI)	OR (95% CI)	P value	df	P(Q)
rs6313 (102T/C): For all the combined studies					
Fehr 2001	-0.16 (-0.28,-0.05)	0.85 (0.76,0.95)	0.0039	11	0.1923
Fehr 2001	-0.15 (-0.26,-0.04)	0.86 (0.77,0.96)	0.0085	11	0.2398
Hill 2002	-0.14 (-0.25,-0.03)	0.87 (0.78,0.97)	0.0099	11	0.2791
Wrzosek 2012	-0.13 (-0.24,-0.02)	0.88 (0.78,0.98)	0.0221	11	0.3005
Himei 2000	-0.15 (-0.26,-0.04)	0.86 (0.77,0.96)	0.0093	11	0.1854
Hwu 2000	-0.16 (-0.27,-0.05)	0.86 (0.77,0.95)	0.005	11	0.1752
Hwu 2000	-0.16 (-0.27,-0.05)	0.85 (0.77,0.95)	0.0044	11	0.1818
Wang 2001	-0.17 (-0.28,-0.06)	0.84 (0.75,0.94)	0.0026	11	0.2373
Li 2002	-0.17 (-0.28,-0.05)	0.85 (0.75,0.95)	0.0038	11	0.1962
Terayama 2003	-0.16 (-0.27,-0.05)	0.86 (0.77,0.96)	0.0056	11	0.1752
Lee 2009	-0.12 (-0.23,-0.01)	0.89 (0.79,0.99)	0.0343	11	0.6456
Tsunoka 2010	-0.2 (-0.32,-0.07)	0.82 (0.73,0.93)	0.002	11	0.2618
Gao 2011	-0.17 (-0.3,-0.05)	0.84 (0.74,0.95)	0.0054	11	0.1937
rs6313 (102T/C): Alcohol dependence (abuse)					
Fehr 2001	-0.4 (-0.59,-0.21)	0.67 (0.55,0.81)	3.8E-05	7	0.6243
Fehr 2001	-0.33 (-0.51,-0.15)	0.72 (0.6,0.86)	3.6E-04	7	0.4085
Hill 2002	-0.32 (-0.51,-0.14)	0.72 (0.6,0.87)	4.8E-04	7	0.4467
Wrzosek 2012	-0.32 (-0.52,-0.12)	0.73 (0.6,0.89)	1.6E-03	7	0.3965
Himei 2000	-0.36 (-0.56,-0.17)	0.69 (0.57,0.84)	2.5E-04	7	0.3871
Hwu 2000	-0.35 (-0.53,-0.17)	0.7 (0.59,0.84)	1.2E-04	7	0.3863
Hwu 2000	-0.36 (-0.54,-0.18)	0.7 (0.58,0.84)	9.3E-05	7	0.4303
Terayama 2003	-0.37 (-0.56,-0.18)	0.69 (0.57,0.83)	1.1E-04	7	0.4363
Lee 2009	-0.28 (-0.47,-0.08)	0.76 (0.63,0.92)	5.1E-03	7	0.7209
rs6311 (-1438A/G): European populations					
Parsian 2001	0.4 (0.17,0.63)	1.5 (1.19,1.89)	0.0006	1	0.9141
Saiz 2008	0.42 (0.15,0.68)	1.52 (1.16,1.98)	0.0023	1	0.8269
Polina 2009	0.43 (0.19,0.66)	1.53 (1.21,1.94)	0.0004	1	0.892

Supplementary Table 4 Pair-wise LD measures (D' and r^2 values) of the HapMap European and Asian samples.

The results are shown in the Microsoft Excel file "Supplementary Table 4 LD.xlsx."

Supplementary Figures

Supplementary Figure 1 Forest plots of ln(OR) and overall ln(OR) with 95% CI of the allelic and genotypic analyses for rs6311.

Supplementary Figure 2 Egger's funnel plots of the combined studies of alcohol dependence (abuse) for rs6313.

Supplementary Figure 3 Retrospective analysis of all the combined studies for -rs6313.

Supplementary Figure 4 Retrospective analysis of the combined studies of alcohol dependence (abuse) for rs6313.

Supplementary Figure 5 Graphical representation of the LD structure of European ancestry. The LD structure, spanning 200 kp covering the *HTR2A* gene, was constructed using European genotype data of 273 SNPs. The current two polymorphisms are shown in red; other polymorphisms are shown in blue. The *HTR2A* gene, size 62, 662 bp, is indicated in red. Vertical tick marks above the name indicate the relative genomic position of each SNP. The LD structure represents the pairwise calculation of D' for each possible combination of SNPs. D' < 0.5 is shown in white, D' = 1.0 in dark red, with increasing shades of red representing increasing D' between the SNPs.

Supplementary Figure 6 Graphical representation of the LD structure of Asian ancestry. The LD structure, spanning 200 kp covering the *HTR2A* gene, was constructed using Asian genotype data of 249 SNPs.