

**Table S1.** Single nucleotide polymorphisms in the *GABRD* coding region on chromosome 1.

SNP	Position	Location <sup>a</sup>	Function	HWP	MAF	Allele
rs3121819	2020388	5' UTR		0.199	0.22	G/A
rs28502222	2021166	5' UTR		0.199	0.22	C/T
rs28407473	2021171	5' UTR		0.199	0.22	C/T
rs3128318	2021343	5' UTR		0.199	0.22	A/C
rs3128321	2021813	5' UTR		0.199	0.22	C/T
rs3128322	2022997	5' UTR		0.199	0.22	A/G
rs3128323	2023641	5' UTR		0.199	0.22	A/G
rs2889475	2024545	<b>Exon1</b>	Missense / ACC ⇒ ATC, T [Thr] ⇒ I [Ile]	0.199	0.22	T/C
rs2376805	2024923	<b>Exon1</b>	Missense / CGG ⇒ CAG, R [Arg] ⇒ Q [Gln]	0.300	0.229	A/G
rs28574670	2027822	Intron4		0.250	0.217	G/A
rs28581504	2029487	Intron6		0.199	0.22	C/T

MAF = Minor allele frequency; HWP = *P*-value of Hardy-Weinberg equilibrium test.

<sup>a</sup> Localization: according to the isoform of *GABRD* SV1 mRNA (XM\_017000936.2) at NCBI database GRCh38.p14.

**Table S2.** Association analyses of all *GABRD* SNPs and amphetamine (+/-) in patients under MMT

SNP	Genotype		Allele	
	<i>P</i> -value	FDR	<i>P</i> -value	FDR
rs3121819	<b>0.005</b>	<b>0.007</b>	<b>0.002</b>	<b>0.002</b>
rs28502222	<b>0.005</b>	<b>0.007</b>	<b>0.002</b>	<b>0.002</b>
rs28407473	<b>0.005</b>	<b>0.007</b>	<b>0.002</b>	<b>0.002</b>
rs3128318	<b>0.005</b>	<b>0.007</b>	<b>0.002</b>	<b>0.002</b>
rs3128321	<b>0.005</b>	<b>0.007</b>	<b>0.002</b>	<b>0.002</b>
rs3128322	<b>0.005</b>	<b>0.007</b>	<b>0.002</b>	<b>0.002</b>
rs3128323	<b>0.005</b>	<b>0.007</b>	<b>0.002</b>	<b>0.002</b>
<b>rs2889475 (Exon1)</b>	<b>0.005</b>	<b>0.007</b>	<b>0.002</b>	<b>0.002</b>
<b>rs2376805 (Exon1)</b>	<b>0.012</b>	<b>0.012</b>	<b>0.004</b>	<b>0.004</b>
rs28574670	<b>0.005</b>	<b>0.007</b>	<b>0.001</b>	<b>0.002</b>
rs28581504	<b>0.006</b>	<b>0.007</b>	<b>0.002</b>	<b>0.002</b>

*P*-value, Logistic regression adjusted for urine morphine test (+/-).

FDR, False Discovery Rate.

**Table S3.** Association analyses of *GABRD* and amphetamine (+/-) in patients under MMT **with a positive urine morphine test**

SNP	Genotype	Amphetamine (-)		Amphetamine (+)		<i>P</i> -value	FDR	Allele	Amphetamine (-)		Amphetamine (+)		<i>P</i> -value	FDR
		N <sup>1</sup>	( % )	N <sup>1</sup>	( % )				N <sup>2</sup>	( % )	N <sup>2</sup>	( % )		
<b>rs2889475</b>	<b>TT</b>	89	( 87.25 % )	13	( 12.75 % )	<b>0.013</b>	<b>0.018</b>	<b>T</b>	221	( 83.08 % )	45	( 16.92 % )	<b>0.004</b>	<b>0.006</b>
	<b>CT</b>	43	( 69.35 % )	19	( 30.65 % )			<b>C</b>	53	( 67.95 % )	25	( 32.05 % )		
	<b>CC</b>	5	( 62.50 % )	3	( 37.50 % )			<b>C vs T</b>						
	<b>CC vs TT</b>		4.11 (0.88~19.26) <sup>odds</sup>		0.073					2.32 (1.31~4.11) <sup>odds</sup>		<b>0.004</b>		
	<b>CT vs TT</b>		3.03 (1.37~6.69) <sup>odds</sup>		<b>0.006</b>									
<b>rs2376805</b>	<b>AA</b>	87	( 87.00 % )	13	( 13.00 % )	<b>0.023</b>	<b>0.023</b>	<b>A</b>	217	( 82.82 % )	45	( 17.18 % )	<b>0.010</b>	<b>0.010</b>
	<b>AG</b>	43	( 69.35 % )	19	( 30.65 % )			<b>G</b>	57	( 69.51 % )	25	( 30.49 % )		
	<b>GG</b>	7	( 70.00 % )	3	( 30.00 % )			<b>G vs A</b>						
	<b>GG vs AA</b>		2.87 (0.66~12.51) <sup>odds</sup>		0.161					2.12 (1.20~3.74) <sup>odds</sup>		<b>0.010</b>		
	<b>AG vs AA</b>		2.96 (1.34~6.55) <sup>odds</sup>		<b>0.007</b>									

N<sup>1</sup>, subject number. N<sup>2</sup>, allelic number. <sup>odds</sup> Odds ratio (95% confidence interval)

*P*-value, Logistic regression. FDR, False Discovery Rate.

**Table S4.** *GABRD* gene dosage in the study population.

Gene Dose	N	Genotype		Number of mutation
		rs2889475	rs2376805	
0	12	CC	GG	Wild type
1	2	CT	GG	1 mutation
	125	CT	AG	2 mutation
2	4	TT	AG	3 mutation
	200	TT	AA	4 mutation

rs2889475, Missense / ACC  $\Rightarrow$  ATC, T [Thr]  $\Rightarrow$  I [Ile]

rs2376805, Missense / CGG  $\Rightarrow$  CAG, R [Arg]  $\Rightarrow$  Q [Gln]

**Table S5.** Mutation number of gene dose association between *GABRD* and amphetamine (+/-) in patients under MMT.

Gene dosage	Genotype	Amphetamine (-)		Amphetamine (+)		P-value
		N	( % )	N	( % )	
Gene Dose in all MMT	0	8	( 66.67 % )	4	( 33.33 % )	<b>0.005</b>
	1	99	( 78.57 % )	27	( 21.43 % )	
	2	182	( 90.10 % )	20	( 9.90 % )	
	0 vs 2	4.55 (1.26~16.46) <sup>odds</sup>				<b>0.021</b>
	1 vs 2	2.48 (1.33~4.65) <sup>odds</sup>				<b>0.005</b>
Gene Dose in urine morphine test positive patients	0	5	( 62.50 % )	3	( 37.50 % )	<b>0.013</b>
	1	43	( 69.35 % )	19	( 30.65 % )	
	2	89	( 87.25 % )	13	( 12.75 % )	
	0 vs 2	4.11 (0.88~19.26) <sup>odds</sup>				0.073
	1 vs 2	3.03 (1.37~6.69) <sup>odds</sup>				<b>0.006</b>

<sup>odds</sup> Odds ratio (95% confidence interval)

P-value, Logistic regression.

**Table S6.** Haplotype association analyses between *GABRD* and urine amphetamine test (+/-).

Block / Group	Haplotypes (Frequency)	Estimate	S.E.	Wald Chi-Square	<i>P</i> -value	Global <i>P</i> -value
<b>Block [rs2889475-rs2376805]</b>						
Overall patients	TA ( 0.77 )	-0.75	0.25	8.96	<b>0.003</b>	<b>0.013</b>
	CG ( 0.22 )	0.83	0.25	10.73	<b>0.001</b>	
Urine morphine test positive	TA ( 0.77 )	-0.76	0.30	6.42	<b>0.011</b>	<b>0.026</b>
	CG ( 0.22 )	0.89	0.31	8.16	<b>0.004</b>	

*P*-value calculated by generalized estimating equation (GEE) model for the logit link function based on the binomial distribution.

incorporating haplotypes frequency  $\geq 0.1$  only.

**Table S7.** Association analyses of *GABRD* genotype frequency between MMT patients and the age- gender matched controls.

SNP	Genotype	NC		MMT patients		UAN/MMT patients		UAP/MMT patients		<i>P</i> -value (FDR)		
		N	( % )	N	( % )	N	( % )	N	( % )	<i>MMT</i> vs. <i>NC</i>	<i>UAN</i> vs. <i>NC</i>	<i>UAP</i> vs. <i>NC</i>
<b>rs2889475</b>	<b>TT</b>	405	( 62.7 % )	192	( 59.6 % )	173	( 63.6 % )	17	( 36.2 % )	0.668 ( 0.767 )	0.504 ( 0.554 )	<b>0.002</b> ( <b>0.002</b> )
	<b>CT</b>	210	( 32.5 % )	119	( 37.0 % )	91	( 33.5 % )	27	( 57.4 % )			
	<b>CC</b>	31	( 4.8 % )	11	( 3.4 % )	8	( 2.9 % )	3	( 6.4 % )			
<b>rs2376805</b>										0.438	0.807	<b>0.002</b>
	<b>AA</b>	403	( 62.4 % )	188	( 58.4 % )	169	( 62.1 % )	17	( 36.2 % )	0.438 ( 0.767 )	0.807 ( 0.807 )	<b>0.002</b> ( <b>0.002</b> )
	<b>AG</b>	211	( 32.7 % )	121	( 37.6 % )	93	( 34.2 % )	27	( 57.4 % )			
	<b>GG</b>	32	( 5.0 % )	13	( 4.0 % )	10	( 3.7 % )	3	( 6.4 % )			

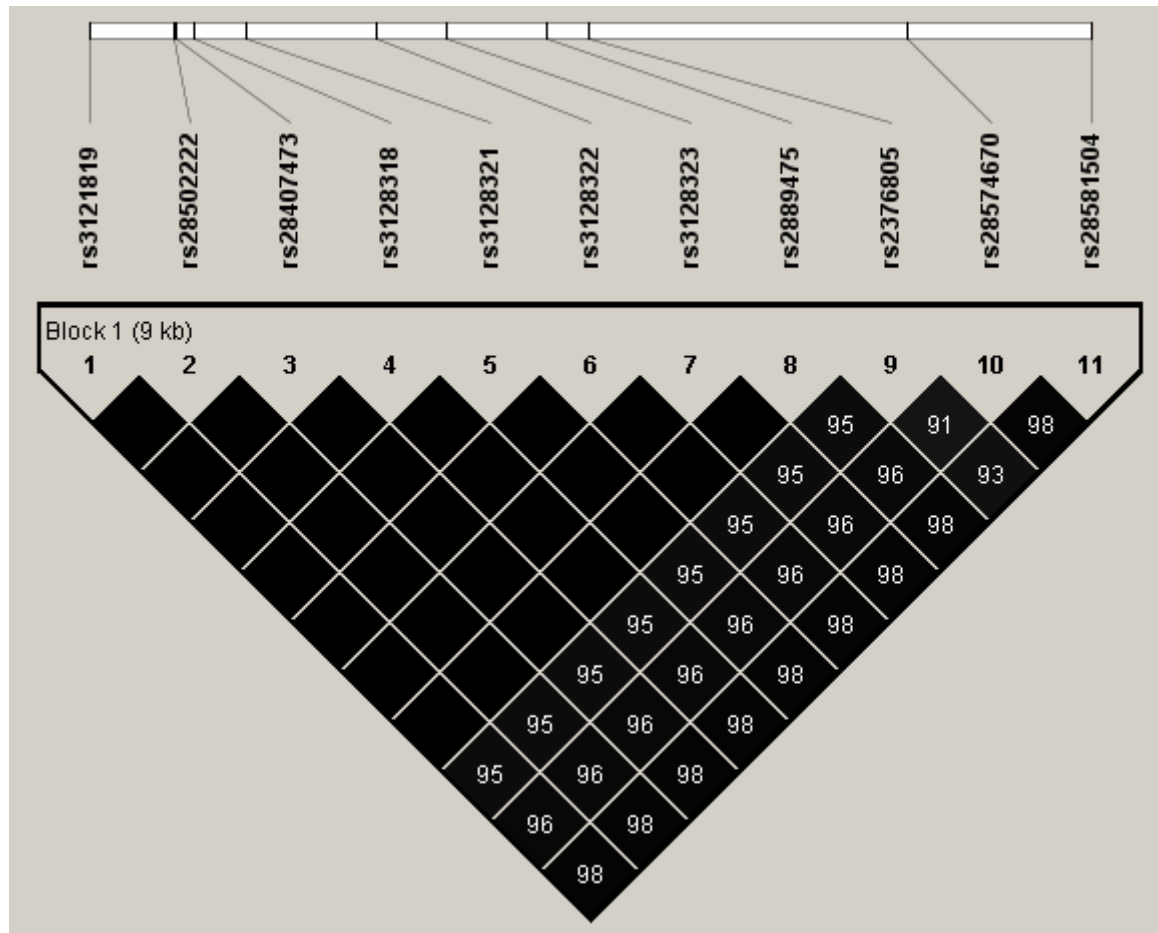
*P*-value, Logistic regression analysis. FDR, False Discovery Rate.

NC, Normal controls; MMT, Methadone maintenance treatment; UAN, Urine amphetamine negative; UAP, Urine amphetamine positive.

**Table S8.** The sequence of TaqMan probes and primers for GABRD expression assay.

Assay name	Accession number	Forward primer sequence	Reverse primer sequence	Probe sequence	Context sequence
<i>GABRD</i>	NM_000815.5	GCGCGCAGCAGCTC	GGTTGGAGCCCACGTAGTC	CCAGAGCGATGAATGAC	GCGCGCAGCAGCTCCGCGGCACCAG
<i>GABRD</i> SV1	XM_017000936.2	CTGCAAGGGCTCCCACAGT	GGTCAGACAGGCCAGGACTTAAT	CCCAGGTGCCCAGAA	NA
<i>GABRD</i> SV2	XM_011541194.4	GACCAATCCCCATCCTGTGT	CACGTAGTCGCCGATGTCAT	AGGAGGACAGAGCGAT	NA

**Figure S1.** The linkage disequilibrium ( $r^2$ ) of the *GABRD* gene by Haploview 4.2. The black color indicates  $r^2 \geq 0$ .



**Figure S2.** The expression of three GABRD isoforms in ten human brain regions. The GABRD SV1 protein contain the mutations of the two missense mutations of SNPs rs2889475 and rs2376805.

