Development of a quantitative disordered gambling trait

Using the entire sample of 4,764 respondents, a single factor was extracted from the four indexes of non-disordered gambling involvement, the 10 items from the DSM-IV symptom set and the 20 items from the SOGS using Mplus (Muthén and Muthén, 1998-2004). Mplus is especially well-suited for this purpose because it allows for the proper factor analysis of dichotomous data (by using tetrachoric and biserial correlations). The factor score derived from this analysis was used as the quantitative DG phenotype used in the genetic analyses. The results of the confirmatory factor analysis are presented in Supporting Information Table S5.

The factor loadings (shown in Supporting Information Table S5) represent the strength of the association between the item and the latent disordered gambling factor. In order to fit a confirmatory factor analysis model, the factor loading for one item must be set to unity against which the remaining items are scaled. In this analysis, this was done for the 1st DSM-IV pathological gambling symptom. The factor loadings for all 10 of the DSM-IV symptoms were uniformly high ($\lambda = 0.972$ to 1.060). The factor loadings for the 20 SOGS items were also high ($\lambda = 0.709$ to 1.079). The factor loadings for the four gambling involvement items were less uniformly high ($\lambda = 0.591$ to 1.154), but it is noteworthy that the gambling versatility item appeared to be the single best indicator of the latent quantitative disordered gambling trait. The results of such a confirmatory factor analysis are equivalent to an IRT analysis. The factor loadings can be interpreted in the same way as item discriminations are interpreted in an IRT analysis -- items with higher factor loadings are better able to separate

people who are higher or lower on the underlying latent disordered gambling trait. Another important point to bear in mind is that the estimated factor score that was used in the GWAS was weighted by the factor loadings so that better items contributed more to the factor score than did the weaker items. By inspecting the relative factor loadings one can be reassured that the factor score represents an index of a continuum of disordered gambling – the five highest loading items came from the DSM-IV symptom set (3 items), the SOGS item set (1 item) and the gambling versatility item (which at least two experts have demonstrated is a good indicator of disordered gambling).

The item thresholds (also shown in Supporting Information Table S5) are required whenever categorical items are factor analyzed. The item thresholds can be interpreted in the same way as item difficulties are interpreted in an IRT analysis. The metric of the item thresholds are in z-score units from the z (standard normal) distribution. Higher thresholds indicate that the item is more "difficult" and lower thresholds indicate that the item is less "difficult." The thresholds for all 10 of the DSM-IV symptoms were uniformly high ($\tau =$ 1.549 to 2.779). The factor loadings for the 20 SOGS items were more variable ($\tau = 0.330$ to 3.225). The factor loadings for the three categorical gambling involvement items varied considerably ($\tau = -0.024$ to 1.762). For the development of a quantitative trait, it is desirable to have items that represent a broad range of difficulties because this will provide better measurement of the trait across the full continuum and will also lead to a latent trait that more closely approximates a normal distribution. By supplementing the symptoms from the DSM-IV with items from the SOGS and with indexes of gambling involvement we were able to improve the psychometric properties of our latent quantitative disordered gambling trait above what could have been achieved using the DSM-IV symptoms alone.

Supporting Information Table S1. Secondary case-control analyses of the top SNPs for the quantitative disordered gambling trait (DG).

Rank	Chr	SNP	Gene	Instrument(s)	Case Diagnosis/Phenotype	CA:CO	A1	OR	L95	U95	P-value	Pemp
1	16q13	rs8064100	MT1X	DSM-IV	Pathological Gambler	31:863	G	1.340	0.802	2.237	0.26370	0.7318
2	9p24	rs12237653	FLJ35024	DSM-IV	Pathological Gambler	31:863	C	0.181	0.044	0.752	0.01863	0.0662
3	12q24	rs11060736		DSM-IV	Pathological Gambler	31:863	C	2.532	1.254	5.114	0.00957	0.0360
4	9p24	rs10812227	FLJ35024	DSM-IV	Pathological Gambler	31:863	T	0.179	0.043	0.745	0.01803	0.0647
5	6p23	rs9383153	ATXN1	DSM-IV	Pathological Gambler	31:863	G	1.5E-08	0	infinite	0.99410	1.0000
6	12q24	rs12305135		DSM-IV	Pathological Gambler	31:863	C	2.579	1.298	5.124	0.00682	0.0269
1	16q13	rs8064100	MT1X	SOGS	Probable Pathological Gambler	44:850	G	1.530	0.993	2.359	0.05384	0.1712
2	9p24	rs12237653	FLJ35024	SOGS	Probable Pathological Gambler	44:850	C	0.271	0.097	0.758	0.01290	0.0463
3	12q24	rs11060736		SOGS	Probable Pathological Gambler	44:850	C	2.334	1.274	4.275	0.00605	0.0219
4	9p24	rs10812227	FLJ35024	SOGS	Probable Pathological Gambler	44:850	T	0.269	0.096	0.755	0.01260	0.0451
5	6p23	rs9383153	ATXN1	SOGS	Probable Pathological Gambler	44:850	G	1.1E-08	0	infinite	0.99410	1.0000
6	12q24	rs12305135		SOGS	Probable Pathological Gambler	44:850	C	2.272	1.253	4.118	0.00686	0.0243
1	16q13	rs8064100	MT1X	SOGS	Problem Gambler or Probable Pathological Gambler	101:793	G	1.397	1.039	1.877	0.02684	0.1023
2	9p24	rs12237653	FLJ35024	SOGS	Problem Gambler or Probable Pathological Gambler	101:793	C	0.496	0.288	0.854	0.01148	0.0450
3	12q24	rs11060736		SOGS	Problem Gambler or Probable Pathological Gambler	101:793	C	2.274	1.437	3.597	0.00045	0.0013
4	9p24	rs10812227	FLJ35024	SOGS	Problem Gambler or Probable Pathological Gambler	101:793	T	0.495	0.287	0.853	0.01132	0.0445
5	6p23	rs9383153	ATXN1	SOGS	Problem Gambler or Probable Pathological Gambler	101:793	G	0.400	0.158	1.014	0.05345	0.1989
6	12q24	rs12305135		SOGS	Problem Gambler or Probable Pathological Gambler	101:793	C	2.160	1.383	3.376	0.00072	0.0025
1	16q13	rs8064100	MT1X	DSM-IV & SOGS	Scored ≥1 symptom (out of 30)	425:469	G	1.339	1.107	1.618	0.00258	0.0109
2	9p24	rs12237653	FLJ35024	DSM-IV & SOGS	Scored ≥1 symptom (out of 30)	425:469	C	0.697	0.520	0.935	0.01616	0.0743
3	12q24	rs11060736		DSM-IV & SOGS	Scored ≥1 symptom (out of 30)	425:469	C	1.612	1.103	2.355	0.01366	0.0623
4	9p24	rs10812227	FLJ35024	DSM-IV & SOGS	Scored ≥1 symptom (out of 30)	425:469	T	0.707	0.527	0.949	0.02090	0.0945
5	6p23	rs9383153	ATXN1	DSM-IV & SOGS	Scored ≥1 symptom (out of 30)	425:469	G	0.422	0.264	0.674	0.00031	0.0007
6	12q24	rs12305135		DSM-IV & SOGS	Scored ≥1 symptom (out of 30)	425:469	C	1.610	1.125	2.304	0.00922	0.0401

Note: Case-control analyses were performed in PLINK (Purcell et al., 2007) controlling for sex, age and the first ten eigenvectors (PC1-PC10) from European-only principal components analysis of ancestry. Unrelated twins were included in the analysis (N = 894). *Rank,* SNP rank for association with the quantitative DG score, *Instrument* is the National Opinion Research Center DSM-IV Screen for Gambling Problems (DSM-IV; Gerstein et al., 1999) or South Oaks Gambling Screen (SOGS; Lesieur and Blume, 1987), *CA:CO* is the ratio of cases to controls, *A1* is the reference allele, *OR* is the estimated odds ratio for the reference allele,

L95 is the lower bound of 95% confidence interval for odds ratio, *U95* is the upper bound of 95% confidence interval for odds ratio, *P-value* is the asymptotic P-value, *Pemp* is the corrected empirical P-value following 10,000 permutations.

Supporting Information Table S2. The 50 genes most strongly associated with the quantitative disordered gambling factor score.

	Test statistics for the genes most strongly associated with Disordered Gambling					Test statistics for the SNP most strongly associated within each gene						
Rank	Position	Gene	#Simulations	#SNPs	P-value	SNP	P-value	Allele	Beta	SE	Imputed	Group
1	14q24.3	*PNMA1*	1.00E+06	77	0.000282	rs2075025	0.000371	T	-0.115	0.032	Genotyped	1
2	14q24.3	*DNAL1*	1.00E+06	104	0.000430	rs2075025	0.000371	T	-0.115	0.032	Genotyped	1
3	9q33.3	*CDK5RAP2*	1.00E+06	164	0.000456	rs10984956	0.000028	T	0.510	0.122	Imputed	
4	14q24.1	*C14orf43*	1.00E+06	118	0.000506	rs2075025	0.000371	T	-0.115	0.032	Genotyped	1
5	16q22	*ACD*	1.00E+06	12	0.000684	rs16957489	0.001006	G	0.153	0.047	Imputed	2
6	16q22.1	*C16orf48*	1.00E+06	12	0.000687	rs16957489	0.001006	G	0.153	0.047	Imputed	2
7	16q22.1	*RLTPR*	1.00E+06	12	0.000698	rs16957489	0.001006	G	0.153	0.047	Imputed	2
8	16q22.1	*C16orf86*	1.00E+06	12	0.000715	rs16957489	0.001006	G	0.153	0.047	Imputed	2
9	16q22.1	*PARD6A*	1.00E+06	12	0.000774	rs16957489	0.001006	G	0.153	0.047	Imputed	2
10	15q21.1	*USP50*	1.00E+06	118	0.000891	rs10519278	0.001402	A	-0.133	0.042	Imputed	3
11	16q22.1	*GFOD2*	1.00E+06	18	0.000958	rs7200950	0.001010	C	0.238	0.072	Imputed	
12	20q12	*JPH2*	1.00E+06	228	0.000983	rs4812785	0.000445	T	-0.114	0.032	Imputed	
13	16q22.1	*FAM65A*	1.00E+06	13	0.000989	rs13334205	0.001006	A	0.153	0.047	Imputed	4
14	16q21	*CTCF*	1.00E+06	17	0.001005	rs13334205	0.001006	A	0.153	0.047	Imputed	4
15	2q31.1	*SSB*	1.00E+06	83	0.001073	rs2114646	0.000065	C	0.149	0.037	Imputed	5
16	14q24.3	*ACOT6*	1.00E+05	47	0.001120	rs4635279	0.001225	G	0.111	0.034	Imputed	
17	15q21.1	*USP8*	1.00E+05	104	0.001150	rs10519278	0.001402	A	-0.133	0.042	Imputed	3
18	2q31.1	*METTL5*	1.00E+05	77	0.001200	rs2114646	0.000065	C	0.149	0.037	Imputed	5
19	15q13.3	*TRPM1*	1.00E+06	208	0.001218	rs11070765	0.000622	A	-0.110	0.032	Imputed	
20	19q13.42	*DPRX*	1.00E+06	35	0.001320	rs11672183	0.001348	C	0.465	0.145	Imputed	
21	1q42	*GPR137B*	1.00E+05	148	0.001560	rs12081734	0.000094	A	-0.189	0.048	Imputed	
22	17p11.2	*MED9*	1.00E+05	86	0.001560	rs1269402	0.000339	C	-0.127	0.036	Genotyped	6
23	16q22	*RANBP10*	1.00E+05	24	0.001620	rs9929423	0.001236	T	0.246	0.076	Imputed	
24	12q13.12	*TUBA1B*	1.00E+05	32	0.001670	rs10783307	0.000943	A	0.109	0.033	Imputed	7
25	1p33	*SLC6A9*	1.00E+05	101	0.001780	rs17413167	0.000021	T	0.146	0.034	Imputed	

26	14q24.1	*ACOT4*	1.00E+06	38	0.001786	rs11625042	0.001856	C	0.107	0.034	Imputed	
27	12q13.1	*DHH*	1.00E+06	32	0.001791	rs10783307	0.000943	A	0.109	0.033	Imputed	7
28	12q13.12	*TUBA1A*	1.00E+05	25	0.001900	rs10747563	0.000894	A	0.114	0.034	Imputed	
29	16q22.1	*LCAT*	1.00E+06	24	0.001962	rs1107767	0.001262	G	0.246	0.076	Imputed	8
30	16q22.1	*PSMB10*	1.00E+06	24	0.001971	rs1107767	0.001262	G	0.246	0.076	Imputed	8
31	16q22	*AGRP*	1.00E+05	20	0.002030	rs3892816	0.001492	T	0.249	0.078	Imputed	9
32	12q13.12	*LMBR1L*	1.00E+05	33	0.002090	rs10783307	0.000943	A	0.109	0.033	Imputed	7
33	1p36.12	*PLA2G2C*	1.00E+05	75	0.002110	rs6426617	0.001116	C	-0.124	0.038	Imputed	
34	11p15	*ST5*	1.00E+05	253	0.002120	rs3794153	0.000144	C	-0.119	0.031	Imputed	
35	12q13.12	*RHEBL1*	1.00E+06	32	0.002163	rs11614738	0.001134	G	0.107	0.033	Imputed	
36	16q22.2	*TSNAXIP1*	1.00E+06	24	0.002163	rs10775302	0.001255	C	0.247	0.077	Imputed	
37	16q22	*ATP6V0D1*	1.00E+06	35	0.002221	rs3892816	0.001492	T	0.249	0.078	Imputed	9
38	12q21.31	*CCDC59*	1.00E+05	75	0.002260	rs17009470	0.001021	A	-0.255	0.078	Imputed	10
39	16q22.1	*CTRL*	1.00E+06	23	0.002322	rs11574514	0.001262	C	0.246	0.076	Imputed	
40	15q21	*TRPM7*	1.00E+05	164	0.002340	rs2899463	0.000344	C	0.112	0.031	Imputed	
41	17p11.2	*RASD1*	1.00E+05	80	0.002420	rs1269402	0.000339	C	-0.127	0.036	Genotyped	6
42	12q21.31	*C12orf26*	1.00E+05	144	0.002450	rs17009470	0.001021	A	-0.255	0.078	Imputed	10
43	1p22-p21	*F3*	1.00E+05	54	0.002470	rs17365315	0.000383	G	0.195	0.055	Genotyped	
44	16q22.1	*ZDHHC1*	1.00E+05	52	0.002500	rs3892816	0.001492	T	0.249	0.078	Imputed	9
45	16q22	*HSD11B2*	1.00E+05	37	0.002570	rs3892816	0.001492	T	0.249	0.078	Imputed	9
46	16q22.1	*TPPP3*	1.00E+05	45	0.002590	rs9936306	0.001678	C	0.246	0.078	Imputed	
47	2p25.1	*CYS1*	1.00E+05	49	0.002660	rs7632	0.000064	C	-0.125	0.031	Genotyped	
48	14q13.2	*GARNL1*	1.00E+05	134	0.002710	rs17103397	0.000574	T	0.160	0.047	Imputed	11
49	14q13.1	*INSM2*	1.00E+05	33	0.002730	rs17103397	0.000574	T	0.160	0.047	Imputed	11
50	13q12.3	*RXFP2*	1.00E+05	186	0.002800	rs1324011	0.000073	G	-0.170	0.043	Imputed	

#SNPs is the number of SNPs in each gene (± 50 Kb), *Imputed* is whether the SNP was genotyped or imputed, *Group* indicates that the most strongly associated SNP was within 50 Kb of more than one of the top 50 genes listed.

Supporting Information Table S3. Gene overlap between the enriched Ingenuity canonical pathways for disordered gambling

Canonical Pathway	Rank	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	64	164
Neuropathic Pain Signaling In Dorsal Horn Neurons	1	17																
Synaptic Long Term Potentiation	2	16	17															
Synaptic Long Term Depression	3	11	11	17														
CREB Signaling in Neurons	4	15	16	11	21													
Breast Cancer Regulation by Stathmin1	5	11	12	9	14	20												
GNRH Signaling	6	10	12	8	13	13	16											
α-Adrenergic Signaling	7	9	9	7	12	12	10	12										
Hepatic Cholestasis	8	7	7	4	8	8	9	8	9									
Axonal Guidance Signaling	9	8	8	6	10	13	8	9	7	16								
Glutamate Receptor Signaling	10	5	5	4	8	1	0	1	0	1	8							
Melatonin Signaling	11	9	9	6	10	10	10	9	7	9	0	10						
Role of NFAT in Cardiac Hypertrophy	12	11	11	8	14	15	14	12	8	10	1	10	19					
G Beta Gamma Signaling	13	7	7	9	10	10	9	10	8	9	1	8	10	11				
Protein Kinase A Signaling	14	11	12	9	14	14	14	13	8	10	1	10	15	10	23			
Calcium Signaling	15	7	7	5	9	6	6	5	3	3	1	4	6	3	10	15		
Dopamine Receptor Signaling	64	3	4	0	3	5	3	4	4	3	0	3	4	4	6	3	7	
Parkinson's Signaling	164	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1

Below the diagonal are the numbers of genes present in each pairwise comparison of Ingenuity canonical pathways. Shaded numbers indicate the number of canonical pathway genes present in the uploaded GWAS dataset.

Supporting Information Table S4. Enrichment of KEGG pathways for disordered gambling.

KEGG ID	Genes	R	P-value	KEGG Pathway
05412	15	10.41	1.40E-09	Arrhythmogenic right ventricular cardiomyopathy (ARVC)
04540	14	8.2	6.16E-08	Gap junction
04020	19	5.63	6.16E-08	Calcium signaling pathway
04730	12	9.04	1.45E-07	Long-term depression
04720	12	9.04	1.45E-07	Long-term potentiation
05410	13	8.06	1.45E-07	Hypertrophic cardiomyopathy (HCM)
04520	12	8.22	3.76E-07	Adherens junction
05200	24	3.83	3.82E-07	Pathways in cancer
04360	14	5.72	2.01E-06	Axon guidance
05414	12	6.88	2.01E-06	Dilated cardiomyopathy

Enrichment analysis was performed in WebGestalt using the top 10,000 SNPs from the GWAS. The 10 most enriched KEGG pathways are listed. *Genes* is the number of genes in the GWAS dataset present in each KEGG pathway, *R* is the ratio of enrichment (the number of genes in the GWAS dataset divided by the expected number of genes in the pathway), *P-value* is the P-value of enrichment adjusted for multiple testing.

Supporting Information Table S5. Derivation of the quantitative disordered gambling trait based on extraction of a single factor from a confirmatory factor analysis of data obtained from 4,764 Australian adults.

| Item	Factor loadings	Thresholds
DSM1 (preoccupied with gambling)	1.000	1.565
DSM2 (needs to increase amounts of money gambled)	1.013	2.030
DSM3 (unsuccessful efforts to control)	1.060	2.156
DSM4 (restless or irritable when attempting to control)	1.056	1.979
DSM5 (gambles to escape from problems or mood)	0.972	1.549
DSM6 (chasing losses)	1.013	1.558
DSM7 (lies to conceal extent of involvement)	1.044	1.803
DSM8 (has committed illegal acts)	1.047	2.779
DSM9 (relationships or career suffered)	1.054	2.252
DSM10 (relied on others for money)	1.069	2.238
SOGS4 (chasing losses)	1.009	2.201
SOGS5 (lying about winning)	0.874	1.560
SOGS6 (felt had a problem)	1.079	1.808
SOGS7 (gambled more than intended)	0.769	0.330
SOGS8 (others criticized gambling)	1.011	1.759
SOGS9 (felt guilty about gambling)	1.015	1.404
SOGS10 (didn't think could stop)	1.031	1.982
SOGS11 (hid signs of gambling)	0.953	1.845
SOGS13 (gambling-related money arguments)	1.034	2.046
SOGS14 (failed to repay loans)	1.058	2.711
SOGS15 (gambling-related school or work absences)	0.940	2.400
SOGS16a (borrowed from household money)	0.942	1.899
SOGS16b (borrowed from spouse)	0.709	1.777
SOGS16c (borrowed from other relatives)	0.947	2.021
SOGS16d (borrowed from banks, finance companies…)	1.026	2.755
SOGS16e (obtained credit card loans)	0.869	1.953
SOGS16f (borrowed from loan sharks)	0.829	3.225
SOGS16g (cashed in shares, bonds…)	0.882	3.021
SOGS16h (sold personal or family property)	1.006	2.588
SOGS16i (written a bad check)	0.964	3.021
Gambling versatility (0-11)	1.154	---
Ever monthly gambling	0.591	-0.024
Ever weekly gambling	0.592	0.359
Ever daily gambling	0.763	1.762

Note: *Item* is the DSM and SOGS item numbers correspond to the diagnostic criterion numbers or scale item numbers provided in the original publications. *Thresholds* are only applicable to categorical items; all but one item (gambling versatility) are categorical. The mean gambling versatility score was 5.162 (SE 0.03).

Supporting Information Figure S1. Distribution of the disordered gambling factor score (DG) in 1,312 Australian twins: (a) DG by sex; (b) DG by lifetime DSM-IV Disordered Gambling status and sex.
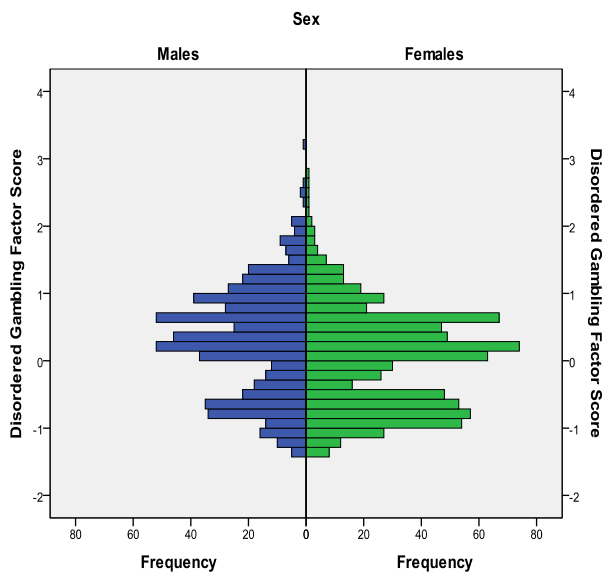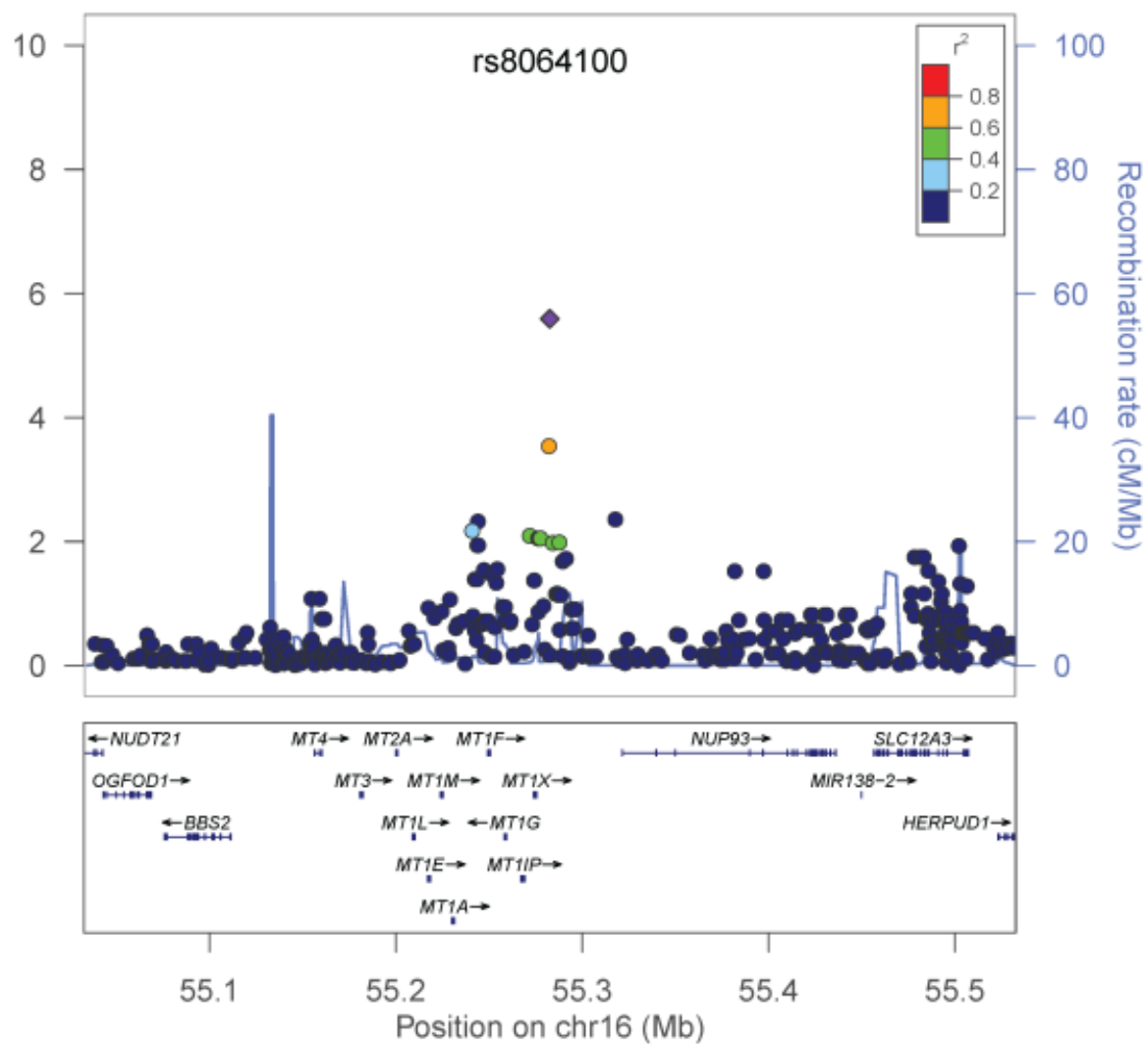
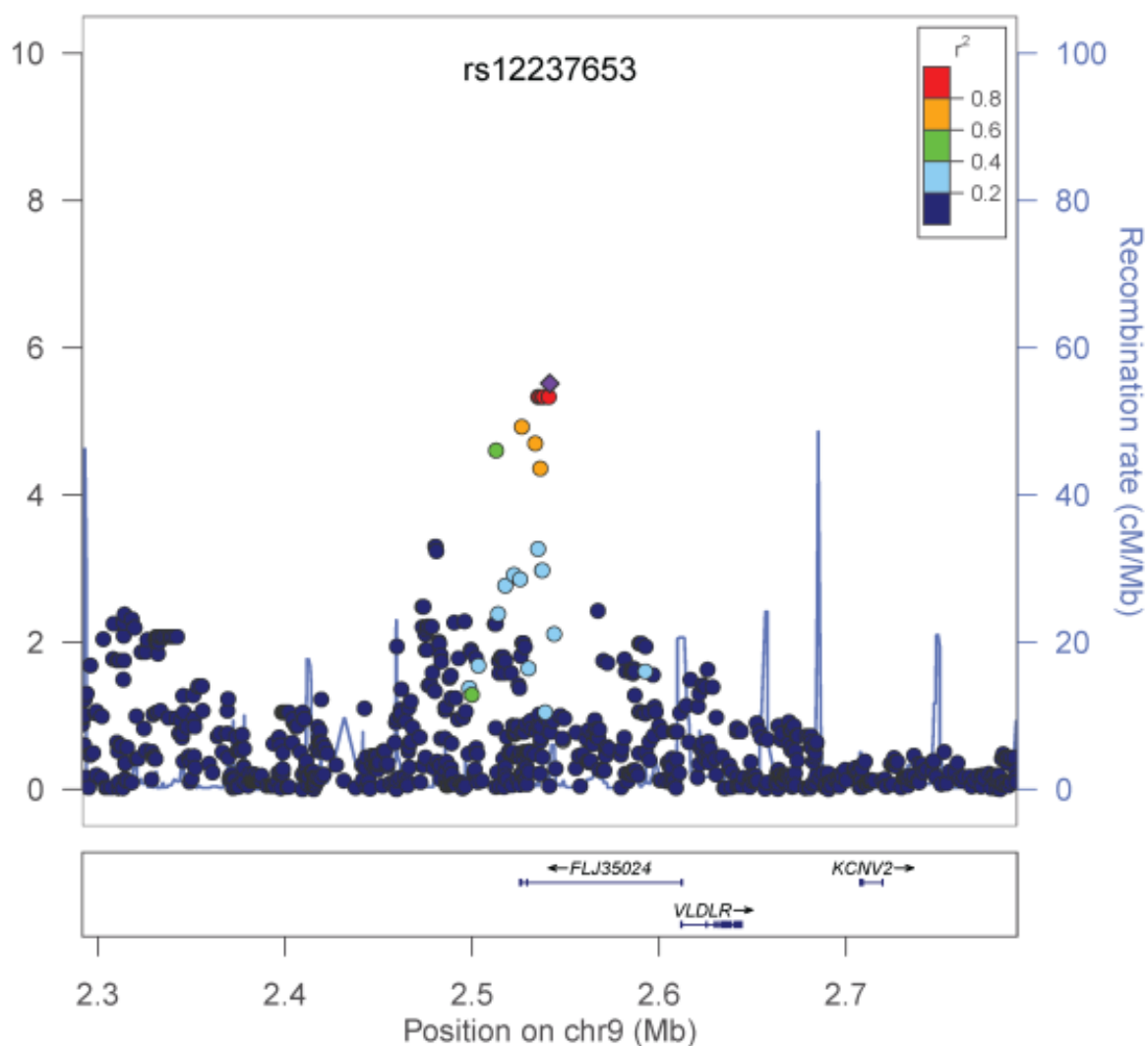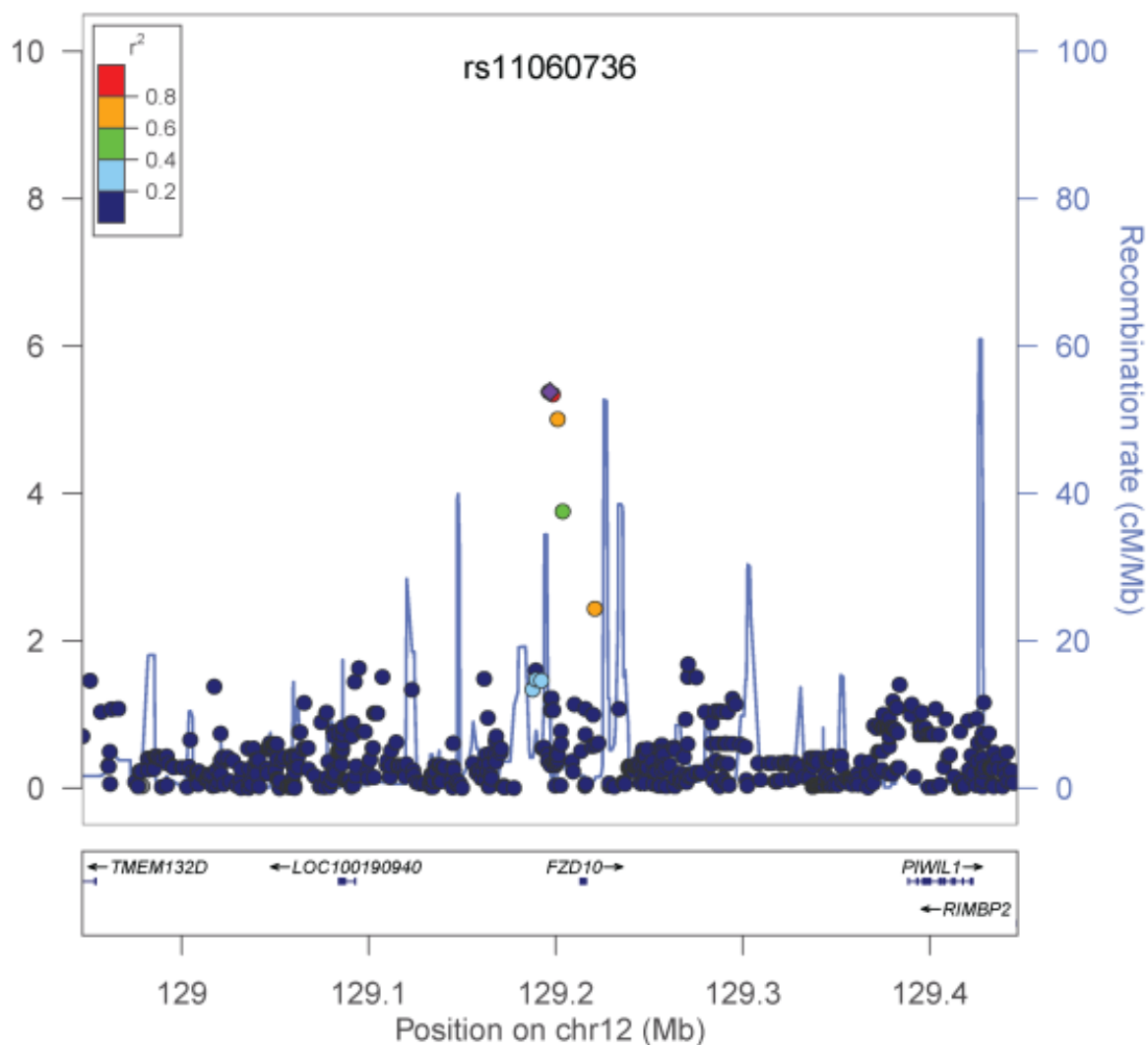**(a)**   **(b)**
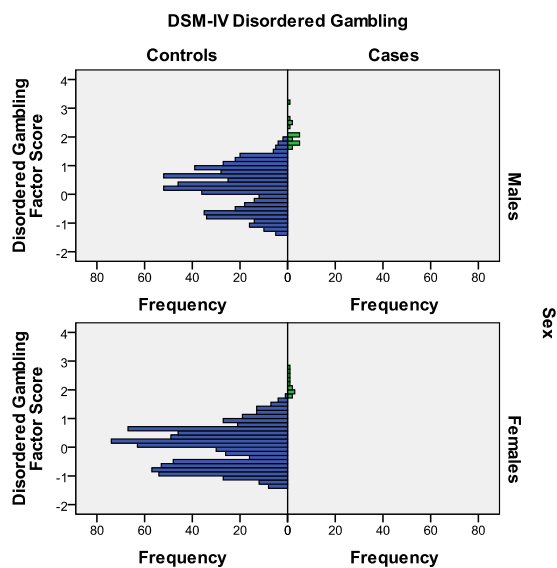
Supporting Information Figure S2. Regional association plot for chromosome 16 (rs8064100). The vertical axis shows the -log$_{10}$ of the association P-values and the horizontal axis shows the position in mega bases. Each dot represents a SNP with the purple dot representing the top SNP (rs8064100) in the region while other colours represent the extent of linkage disequilibrium of other SNPs with top SNP. Genes in the region are shown below the horizontal axis.
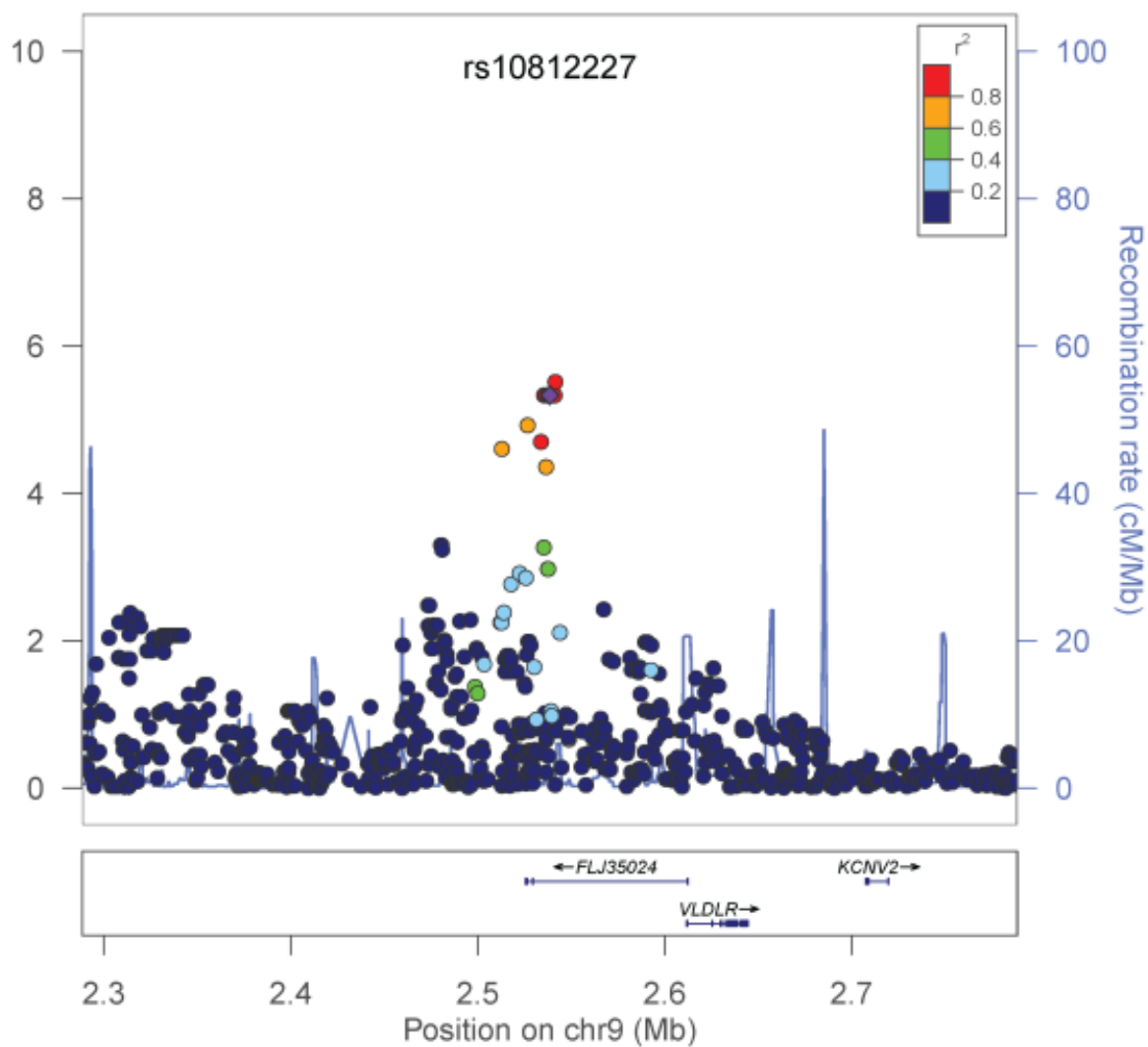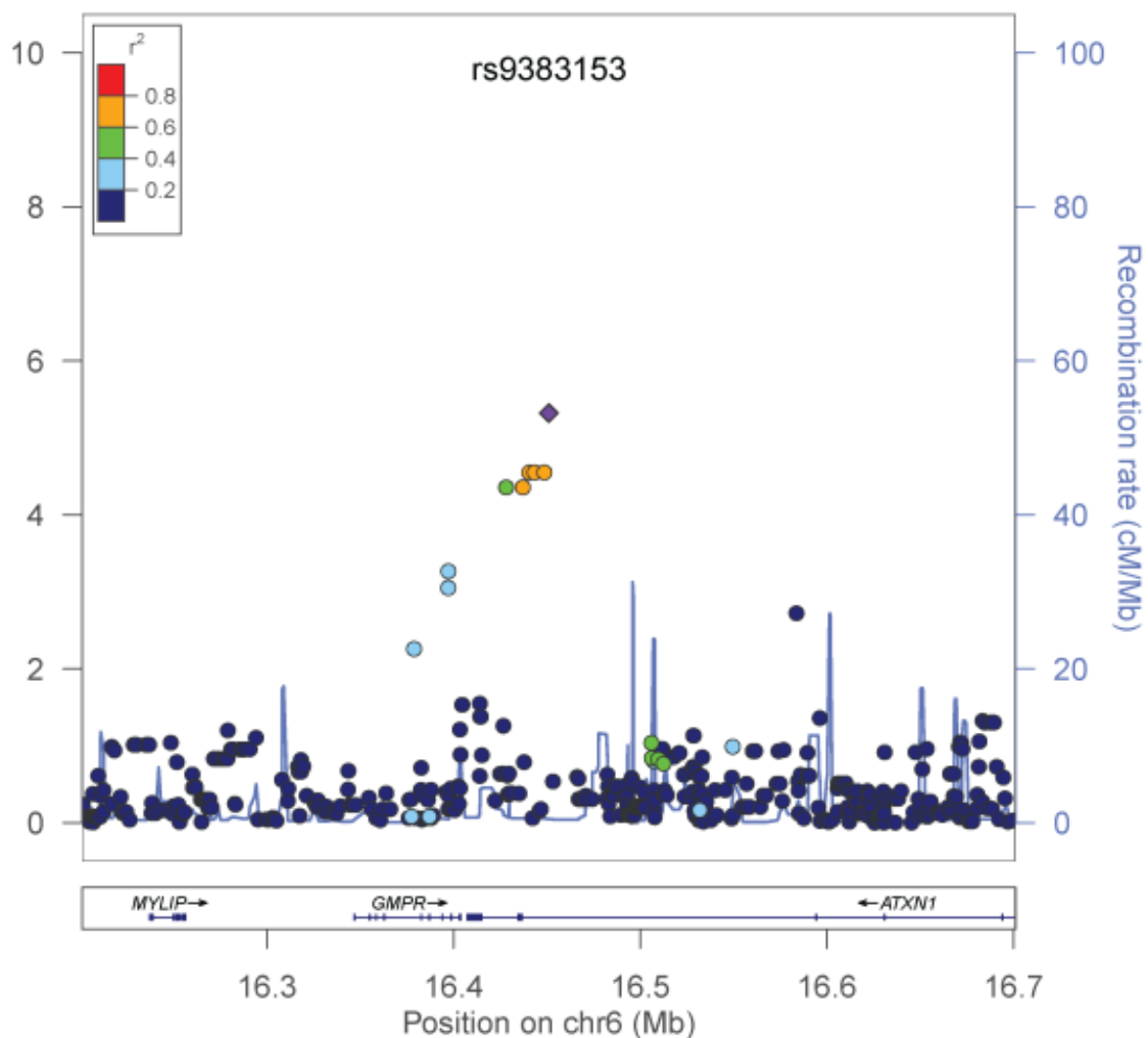
Supporting Information Figure S3. Regional association plot for chromosome 9 (rs12237653). The vertical axis shows the -$\log_{10}$ of the association P-values and the horizontal axis shows the position in mega bases. Each dot represents a SNP with the purple dot representing the top SNP (rs12237653) in the region while other colours represent the extent of linkage disequilibrium of other SNPs with top SNP. Genes in the region are shown below the horizontal axis.

Supporting Information Figure S4. Regional association plot for chromosome 12 (rs11060736). The vertical axis shows the -log$_{10}$ of the association P-values and the horizontal axis shows the position in mega bases. Each dot represents a SNP with the purple dot representing the top SNP (rs11060736) in the region while other colours represent the extent of linkage disequilibrium of other SNPs with top SNP. Genes in the region are shown below the horizontal axis.

Supporting Information Figure S5. Regional association plot for chromosome 9 (rs1081227). The vertical axis shows the -log$_{10}$ of the association P-values and the horizontal axis shows the position in mega bases. Each dot represents a SNP with the purple dot represents rs1081227 while other colours represent the extent of linkage disequilibrium of other SNPs with rs1081227. Genes in the region are shown below the horizontal axis.
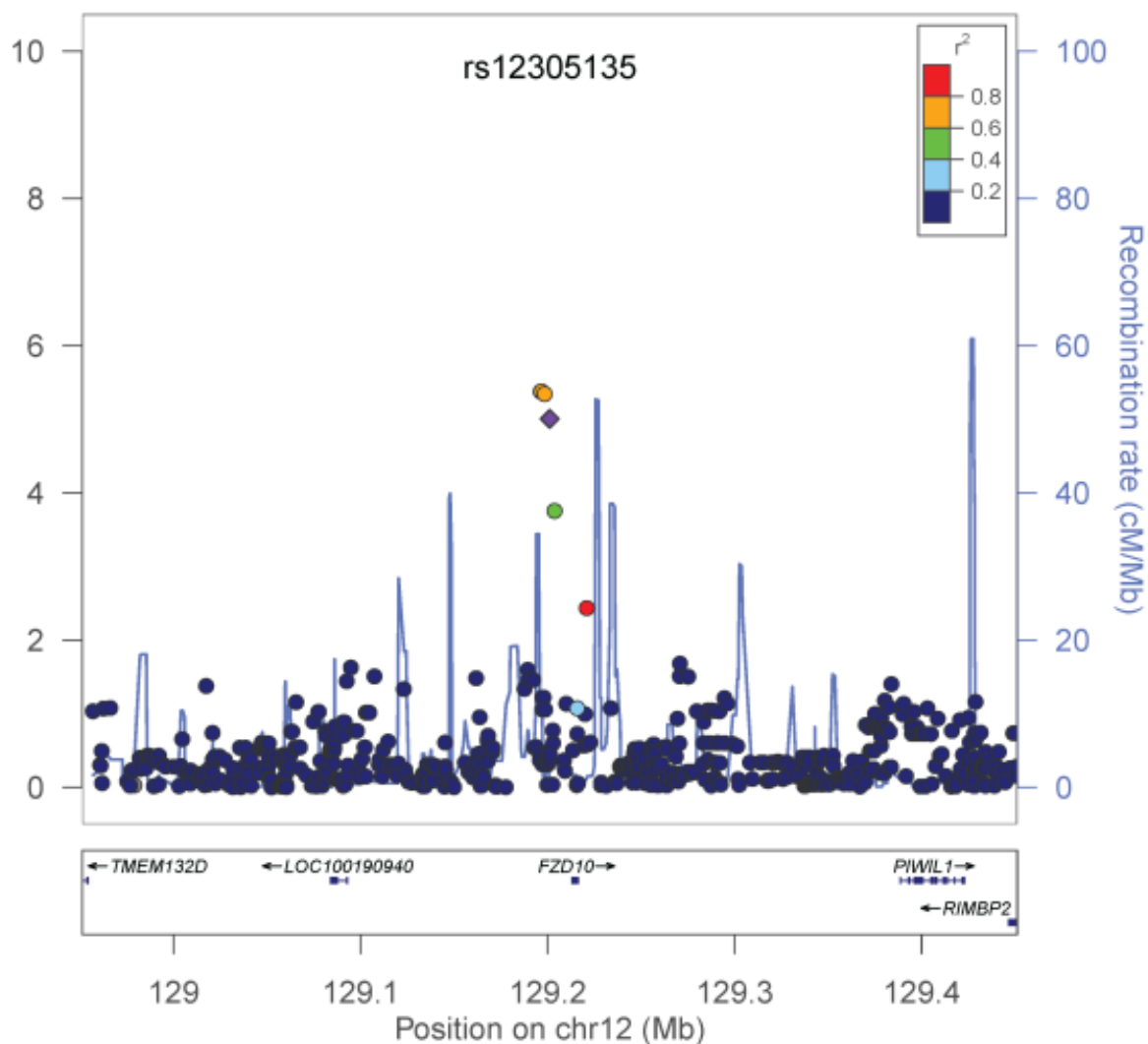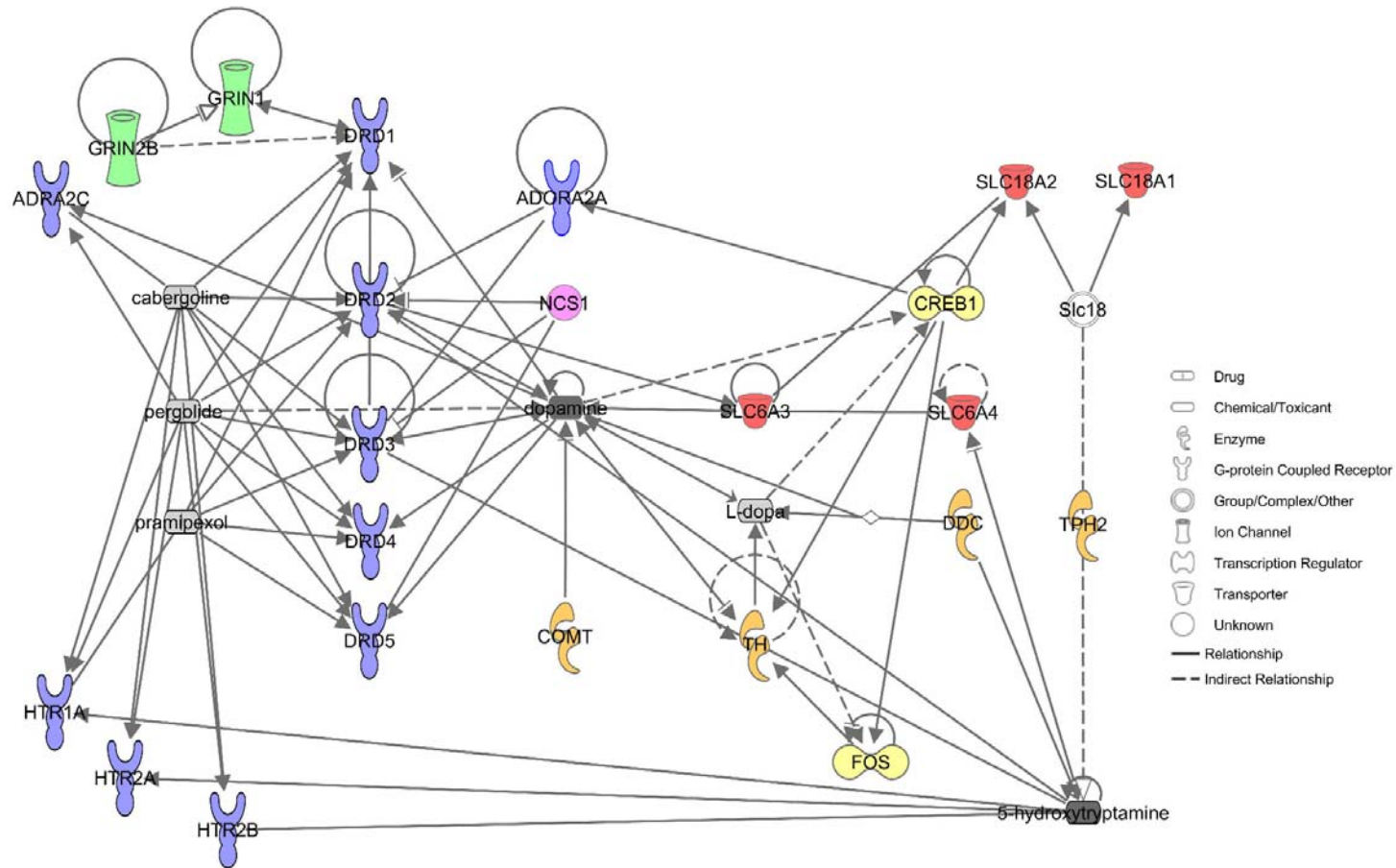
Supporting Information Figure S6. Regional association plot for chromosome 6 (rs9383153). The vertical axis shows the -log$_{10}$ of the association P-values and the horizontal axis shows the position in mega bases. Each dot represents a SNP with the purple dot representing the top SNP (rs9383153) in the region while other colours represent the extent of linkage disequilibrium of other SNPs with top SNP. Genes in the region are shown below the horizontal axis.

Supporting Information Figure S7. Regional association plot for chromosome 12 (rs12305135). The vertical axis shows the -log$_{10}$ of the association P-values and the horizontal axis shows the position in mega bases. Each dot represents a SNP with the purple dot represents rs1081227 while other colours represent the extent of linkage disequilibrium of other SNPs with rs12305135. Genes in the region are shown below the horizontal axis.

Supporting Information Figure S8. Connectivity diagram illustrating the interactions between proteins encoded by 24 candidate genes for disordered gambling and dopamine agonist (cabergoline, pergolide, pramipexole, levodopa [L-dopa]) induced disordered gambling. Note: Figure was generated through the use of Ingenuity Pathways Analysis (Ingenuity® Systems, www.ingenuity.com).

Supporting Information Figure S9. Quantile-Quantile (Q-Q) plot for 2,159 SNPs located within 24 candidate genes for disordered gambling (genomic inflation $\lambda = 1.503$). The horizontal axis shows the -$\log_{10}$ of expected P-values of association from a 1 d.f. chi-square distribution and the vertical axis shows the -$\log_{10}$ of P-values from the observed chi-square distribution. The shaded region represents the 95% confidence interval of the expected chi-square statistics under the null hypothesis of no association.
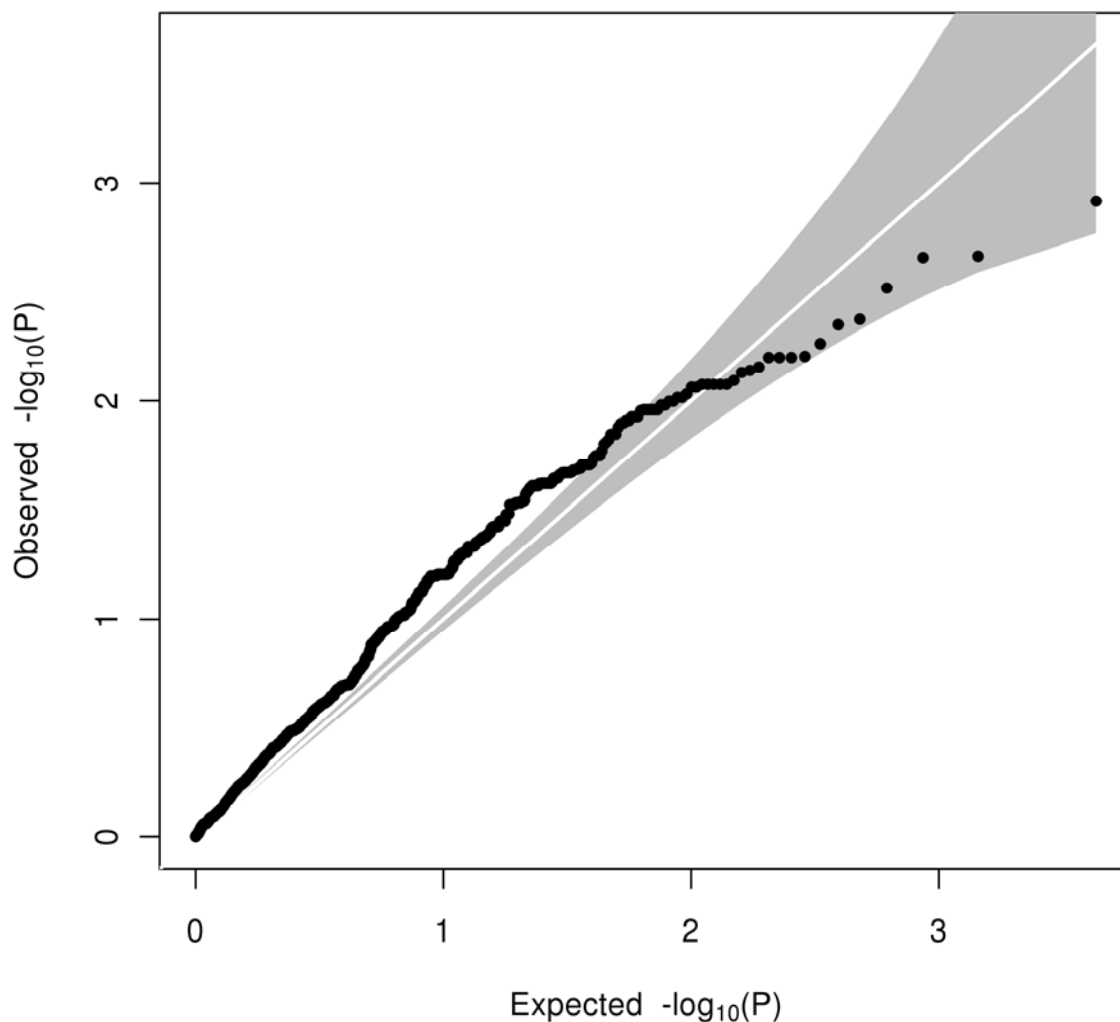
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