

Supplementary Table 1 Characteristics and psychiatric comorbidity of cases and controls in NESARC-III EA.

Characteristic	Categories	AUD (4,487)	NUD (4,394)	CUD (954)	NMPOUD (346)	Any SUD (6,525)	Controls (3,959)
Sex	Men	54.5%	50.2%	61.2%	50.6%	51.2%	40.7%
	Women	45.5%	49.8%	38.8%	49.4%	48.8%	59.3%
Age	18-29	24.7%	19.2%	31.1%	26.0%	21.6%	14.9%
	30-44	30.5%	26.9%	34.1%	34.4%	27.8%	19.5%
	45-64	35.5%	38.9%	32.1%	34.4%	37.4%	31.2%
	65+	9.4%	15.1%	2.7%	5.2%	13.1%	34.5%
Marital status	Married/cohabitating	47.9%	46.2%	42.7%	40.5%	48.2%	57.5%
	Previously married	25.5%	32.6%	22.2%	30.9%	28.4%	26.9%
	Never married	26.7%	21.2%	35.1%	28.6%	23.4%	15.6%
Education	< high school	7.5%	13.2%	8.7%	18.8%	9.9%	7.6%
	High school	22.7%	29.2%	26.4%	27.5%	25.2%	23.8%
	Some college	69.8%	57.6%	64.9%	53.8%	64.9%	68.6%
Income	\$0-\$19,999	23.4%	29.5%	29.9%	41.9%	25.5%	19.0%
	\$20,000-\$34,999	19.5%	22.1%	20.7%	19.7%	20.5%	17.4%
	\$35,000-\$69,999	28.3%	27.8%	29.4%	23.4%	28.0%	28.8%
	\$70,000 or more	28.8%	20.6%	20.1%	15.0%	26.0%	34.8%
Urbanicity	Urban	78.0%	72.3%	80.0%	75.1%	75.7%	72.8%
	Rural	22.0%	27.7%	20.0%	24.9%	24.3%	27.3%
Any mood disorder	Yes	41.5%	39.7%	54.0%	58.7%	38.7%	NA
	No	58.6%	60.3%	46.0%	41.3%	61.3%	NA
Any anxiety disorder	Yes	29.3%	29.8%	36.0%	46.2%	27.9%	NA
	No	70.7%	70.3%	64.1%	53.8%	72.1%	NA
Posttraumatic stress disorder	Yes	11.8%	12.8%	16.5%	27.5%	11.1%	NA
	No	88.2%	87.2%	83.5%	72.5%	88.9%	NA
Personality disorder (Antisocial, Borderline, Schizotypal)	Yes	30.6%	30.4%	46.4%	58.4%	27.3%	NA
	No	69.4%	69.6%	53.6%	41.6%	72.7%	NA

Supplementary Table 2 Evidence for association in NESARC-III of previously robustly replicated genes for SUD (all substances) in EA (P<0.05).

Disorder	Gene	SNP	Function	Chr	Pos	REF	ALT	N	AF ^a	EFFECT ^b	SE	Pvalue
AUD	ADH1B	rs1229984	Nonsynonymous	4	100239319	T	C	8446	0.964	0.31	0.09	7.98E-04
AUD	OPRM1	rs34427887	Stop Gain	6	154567863	C	T	8446	0.068	0.21	0.07	1.83E-03
AUD	ALDH16A1	rs11558188	Synonymous	19	49967981	T	G	8446	0.348	0.09	0.03	7.39E-03
AUD	OPRM1	rs712242	Intron	6	154333172	T	C	8446	0.474	0.08	0.03	1.85E-02
AUD	OPRM1	rs1294092	Intron	6	154335673	A	G	8446	0.160	0.09	0.04	4.06E-02
AUD	OPRM1	rs2075572	Intron	6	154412004	G	C	8446	0.567	-0.07	0.03	4.76E-02
NUD	CHRNA3	rs578776	Utr3	15	78888400	G	A	8353	0.273	-0.11	0.04	3.04E-03
NUD	CHRNA5	rs569207	Intron	15	78873119	C	T	8353	0.221	-0.11	0.04	3.13E-03
NUD	CHRNA5	rs667282	Intron	15	78863472	T	C	8353	0.221	-0.11	0.04	3.33E-03
NUD	CHRNA3	rs6495308	Intron	15	78907656	T	C	8353	0.222	-0.11	0.04	4.00E-03
NUD	CHRNA3	rs938682	Intron	15	78896547	G	A	8353	0.776	0.11	0.04	4.24E-03
NUD	CHRNA3	rs11637630	Intron	15	78899719	G	A	8353	0.775	0.11	0.04	4.93E-03
NUD	CHRNA3	rs3825845	Intron	15	78910258	C	T	8353	0.217	-0.11	0.04	4.98E-03
NUD	CHRNA3	rs8042494	Intron	15	78908010	C	T	8353	0.223	-0.11	0.04	5.01E-03
NUD	CHRNA3	rs28669908	Intron	15	78910267	C	A	8353	0.203	-0.11	0.04	5.53E-03
NUD	CHRNA5	rs1700006	Intron	15	78875623	A	G	8353	0.208	-0.11	0.04	6.13E-03
NUD	CHRNA3	rs12910984	Intron	15	78891627	G	A	8353	0.776	0.10	0.04	6.29E-03
NUD	CHRNA5	rs684513	Intron	15	78858400	C	G	8353	0.203	-0.10	0.04	8.58E-03
NUD	CHRNA3	rs4887069	Intron	15	78909070	A	G	8353	0.229	-0.10	0.04	8.59E-03
NUD	CHRNA3	rs7177514	Intron	15	78907406	C	G	8353	0.225	-0.10	0.04	1.01E-02
NUD	OPRM1	rs34427887	Stop Gain	6	154567863	C	T	8353	0.067	0.17	0.07	1.02E-02
NUD	ALDH16A1	rs11558188	Synonymous	19	49967981	T	G	8353	0.344	0.07	0.03	3.45E-02
CUD	COMT	rs4646312	Intron	22	19948337	T	C	4913	0.398	-0.17	0.06	2.44E-03
CUD	COMT	rs740601	Intron	22	19950763	T	G	4913	0.402	-0.17	0.06	2.92E-03
CUD	OPRM1	rs9397688	Intron	6	154466607	C	G	4913	0.126	-0.21	0.08	1.28E-02
CUD	OPRM1	rs34427887	Stop Gain	6	154567863	C	T	4913	0.065	0.28	0.12	1.46E-02
CUD	ADH1B	rs4147536	Intron	4	100239112	A	C	4913	0.771	0.16	0.07	1.88E-02
NMPOUD	COMT	rs737864	Intron	22	19930159	C	T	4305	0.286	0.23	0.09	1.18E-02
NMPOUD	COMT	rs174697	Intron	22	19953832	A	G	4305	0.951	0.39	0.19	4.60E-02
Any SUD	OPRM1	rs34427887	Stop Gain	6	154567863	C	T	10484	0.069	0.19	0.06	1.58E-03
Any SUD	CHRNA3	rs578776	Utr3	15	78888400	G	A	10484	0.272	-0.09	0.03	5.18E-03
Any SUD	ALDH16A1	rs11558188	Synonymous	19	49967981	T	G	10484	0.348	0.08	0.03	6.59E-03
Any SUD	ADH1B	rs1229984	Nonsynonymous	4	100239319	T	C	10484	0.964	0.22	0.08	7.36E-03
Any SUD	CHRNA3	rs938682	Intron	15	78896547	G	A	10484	0.775	0.08	0.04	2.72E-02
Any SUD	CHRNA3	rs6495308	Intron	15	78907656	T	C	10484	0.223	-0.08	0.04	2.82E-02
Any SUD	CHRNA5	rs569207	Intron	15	78873119	C	T	10484	0.222	-0.08	0.04	2.85E-02
Any SUD	CHRNA5	rs667282	Intron	15	78863472	T	C	10484	0.222	-0.08	0.04	3.02E-02
Any SUD	CHRNA3	rs11637630	Intron	15	78899719	G	A	10484	0.774	0.08	0.04	3.05E-02
Any SUD	CHRNA3	rs660652	Utr3	15	78887832	A	G	10484	0.621	-0.07	0.03	3.26E-02

Any SUD	CHRNA3	rs2869546	Intron	15	78907345	C	T	10484	0.614	-0.06	0.03	3.34E-02
Any SUD	CHRNA3	rs8042494	Intron	15	78908010	C	T	10484	0.224	-0.08	0.04	3.39E-02
Any SUD	CHRNA3	rs12910984	Intron	15	78891627	G	A	10484	0.775	0.07	0.04	3.74E-02
Any SUD	CHRNA5	rs11637635	Intron	15	78877150	A	G	10484	0.619	-0.06	0.03	3.74E-02
Any SUD	CHRNA3	rs62010327	Intron	15	78892784	G	A	10484	0.380	0.06	0.03	4.14E-02
Any SUD	CHRNA5	rs1700006	Intron	15	78875623	A	G	10484	0.209	-0.07	0.04	4.28E-02
Any SUD	COMT	rs4646312	Intron	22	19948337	T	C	10484	0.397	-0.06	0.03	4.41E-02
Any SUD	CHRNA5	rs495090	Intron	15	78870003	A	G	10484	0.614	-0.06	0.03	4.46E-02
Any SUD	CHRNA3	rs3743074	Normal_Splice_Site	15	78909480	G	A	10484	0.620	-0.06	0.03	4.47E-02
Any SUD	CHRNA5	rs495956	Intron	15	78869930	C	T	10484	0.618	-0.06	0.03	4.69E-02

^a AF: Allele freq for ALT allele.

^b Positive value indicates ALT allele is the risk allele.

Supplementary table 3 Evidence for association of previously robustly replicated genes for AUD in NESARC-III EA (P<0.05).

Disorder	Gene	SNP	Function	Chr	Pos	REF	ALT	N	AF ^a	EFFECT ^b	SE	Pvalue
AUD	GRIK1	rs107034	Intron	21	31266406	C	T	8446	0.958	0.29	0.08	4.86E-04
AUD	GRIK1	rs466559	Intron	21	31258083	T	G	8446	0.958	0.28	0.08	7.37E-04
AUD	GRIK1	rs466612	Intron	21	31264389	T	G	8446	0.959	0.28	0.08	7.69E-04
AUD	ADH1B	rs1229984	Nonsynonymous	4	100239319	T	C	8446	0.964	0.31	0.09	7.98E-04
AUD	GRIN2B	rs2284404	Intron	12	13804359	A	G	8446	0.382	0.11	0.03	1.11E-03
AUD	GRIN2B	rs1805479	Intron	12	13753091	C	A	8446	0.368	0.11	0.03	1.19E-03
AUD	GRIN2B	rs1805485	Intron	12	13766887	C	A	8446	0.378	0.11	0.03	1.28E-03
AUD	GRIN2B	rs12582333	Intron	12	13767536	C	T	8446	0.378	0.11	0.03	1.46E-03
AUD	GRIN2B	rs4764023	Intron	12	13794318	A	G	8446	0.378	0.11	0.03	1.55E-03
AUD	GRIN2B	rs10845819	Intron	12	13805633	G	C	8446	0.377	0.11	0.03	1.63E-03
AUD	GRIN2B	rs10845811	Intron	12	13759721	A	G	8446	0.379	0.11	0.03	1.73E-03
AUD	OPRM1	rs34427887	Stop Gain	6	154567863	C	T	8446	0.068	0.21	0.07	1.83E-03
AUD	GRIN2B	rs2268097	Intron	12	13752832	A	G	8446	0.382	0.10	0.03	2.65E-03
AUD	GRIN2B	rs1805480	Intron	12	13753778	C	T	8446	0.372	0.10	0.03	2.69E-03
AUD	GRIK1	rs466093	Intron	21	31267040	A	C	8446	0.957	0.24	0.08	2.76E-03
AUD	GRIN2B	rs2284402	Intron	12	13775958	G	A	8446	0.616	-0.10	0.03	2.87E-03
AUD	GRIN2B	rs2268100	Intron	12	13792067	T	C	8446	0.389	0.10	0.03	3.89E-03
AUD	FAAH	rs2295633	Intron	1	46874383	A	G	8446	0.632	-0.10	0.03	4.67E-03
AUD	GRIN2B	rs1805481	Intron	12	13763455	A	C	8446	0.389	0.10	0.03	4.71E-03
AUD	GRIN2B	rs1805539	Intron	12	13770190	G	C	8446	0.388	0.10	0.03	4.79E-03
AUD	GABRA2	rs573400	Utr3	4	46252066	C	T	8446	0.572	0.09	0.03	4.92E-03
AUD	GABRA2	rs2350772	Intron	4	46293351	C	T	8446	0.437	-0.09	0.03	4.96E-03
AUD	GABRA2	rs541418	Intron	4	46253216	C	T	8446	0.572	0.09	0.03	5.07E-03
AUD	GABRA2	rs279862	Intron	4	46313309	T	G	8446	0.434	-0.09	0.03	5.42E-03
AUD	FAAH	rs3766246	Intron	1	46865671	A	G	8446	0.623	-0.09	0.03	5.44E-03
AUD	GSK3B	rs17810676	Intron	3	119780549	T	C	8446	0.384	0.09	0.03	5.67E-03
AUD	GABRA2	rs481311	Intron	4	46254382	A	T	8446	0.569	0.09	0.03	5.72E-03
AUD	GABRA2	rs3113346	Intron	4	46255176	T	G	8446	0.571	0.09	0.03	6.29E-03
AUD	FAAH	rs4141964	Intron	1	46865040	T	C	8446	0.625	-0.09	0.03	6.38E-03
AUD	GABRA2	rs12647055	Intron	4	46355479	T	C	8446	0.532	0.09	0.03	6.38E-03
AUD	GRIN2B	rs2300239	Intron	12	13815210	C	T	8446	0.422	-0.09	0.03	6.78E-03
AUD	GRIN2B	rs10845814	Intron	12	13772993	T	C	8446	0.430	0.09	0.03	6.78E-03
AUD	GABRA2	rs548260	Intron	4	46268484	G	A	8446	0.563	0.09	0.03	7.29E-03
AUD	GABRA2	rs28753386	Intron	4	46303800	C	A	8446	0.435	-0.09	0.03	7.30E-03
AUD	GSK3B	rs12630592	Intron	3	119768246	G	T	8446	0.385	0.09	0.03	7.47E-03
AUD	GABRA2	rs537787	Intron	4	46288543	T	C	8446	0.564	0.09	0.03	7.50E-03
AUD	GABRA2	rs1808851	Intron	4	46311447	T	C	8446	0.435	-0.09	0.03	7.58E-03
AUD	GABRA2	rs279872	Intron	4	46305194	G	A	8446	0.434	-0.09	0.03	7.78E-03
AUD	CHRNA4	rs4809541	Intron	20	61982881	C	T	8446	0.861	-0.13	0.05	8.06E-03

AUD	GABRA2	rs279873	Intron	4	46304367	A	G	8446	0.436	-0.09	0.03	8.09E-03
AUD	GRIK1	rs16984653	Intron	21	31020557	A	G	8446	0.122	-0.13	0.05	8.29E-03
AUD	GSK3B	rs6805251	Intron	3	119560606	T	C	8446	0.596	-0.09	0.03	8.73E-03
AUD	DDC	rs12718611	Intron	7	50593906	G	A	8446	0.858	0.12	0.05	8.75E-03
AUD	GABRA2	rs13119741	Intron	4	46289015	G	A	8446	0.554	0.09	0.03	8.90E-03
AUD	HTR1A	rs1799921	Nonsynonymous	5	63257465	T	C	8446	0.013	0.38	0.15	8.94E-03
AUD	GRIN2B	rs11055550	Intron	12	13776283	A	G	8446	0.426	-0.09	0.03	9.07E-03
AUD	GABRA2	rs490967	Intron	4	46265033	T	C	8446	0.547	0.09	0.03	9.15E-03
AUD	GRIK1	rs2832438	Intron	21	31137937	T	C	8446	0.124	-0.13	0.05	9.16E-03
AUD	GSK3B	rs7644234	Intron	3	119691611	G	T	8446	0.383	0.09	0.03	9.28E-03
AUD	GABRA2	rs279861	Intron	4	46313325	G	C	8446	0.433	-0.09	0.03	9.29E-03
AUD	GABRA2	rs35007802	Intron	4	46299716	A	C	8446	0.434	-0.09	0.03	9.46E-03
AUD	GABRA2	rs2350770	Intron	4	46293307	A	G	8446	0.435	-0.09	0.03	9.53E-03
AUD	GABRA2	rs2083423	Intron	4	46295082	A	G	8446	0.435	-0.09	0.03	9.71E-03
AUD	GABRA2	rs279821	Intron	4	46346270	T	G	8446	0.433	-0.09	0.03	9.72E-03
AUD	GABRA2	rs568144	Intron	4	46282926	C	G	8446	0.570	0.09	0.03	1.00E-02
AUD	GABRA2	rs558111	Intron	4	46284923	T	C	8446	0.567	0.09	0.03	1.01E-02
AUD	GSK3B	rs4687890	Intron	3	119759173	A	G	8446	0.379	0.09	0.03	1.02E-02
AUD	GABRA2	rs279826	Intron	4	46334209	A	G	8446	0.451	-0.09	0.03	1.02E-02
AUD	GRIK1	rs363528	Intron	21	31014359	A	G	8446	0.122	-0.13	0.05	1.04E-02
AUD	GABRA2	rs279837	Intron	4	46339323	A	G	8446	0.432	-0.09	0.03	1.04E-02
AUD	GABRA2	rs279842	Intron	4	46340956	T	C	8446	0.432	-0.09	0.03	1.05E-02
AUD	GABRA2	rs203656	Intron	4	46316361	A	T	8446	0.425	-0.09	0.03	1.05E-02
AUD	GABRA2	rs279845	Intron	4	46329723	T	A	8446	0.449	-0.09	0.03	1.05E-02
AUD	GSK3B	rs9873477	Intron	3	119645976	A	G	8446	0.396	0.09	0.03	1.05E-02
AUD	GABRA2	rs279863	Intron	4	46313022	C	A	8446	0.445	-0.09	0.03	1.08E-02
AUD	GSK3B	rs334563	Intron	3	119786887	C	A	8446	0.383	0.09	0.03	1.10E-02
AUD	GSK3B	rs334533	Intron	3	119792882	C	T	8446	0.379	0.09	0.03	1.11E-02
AUD	GABRA2	rs189957	Intron	4	46346679	A	G	8446	0.452	-0.08	0.03	1.11E-02
AUD	GABRA2	rs279827	Normal_Splice_Site	4	46334702	A	G	8446	0.450	-0.08	0.03	1.11E-02
AUD	GABRA2	rs279849	Intron	4	46320757	G	T	8446	0.434	-0.08	0.03	1.11E-02
AUD	GABRA2	rs279828	Intron	4	46334810	A	C	8446	0.451	-0.08	0.03	1.13E-02
AUD	GABRA2	rs530329	Intron	4	46281119	C	T	8446	0.569	0.08	0.03	1.14E-02
AUD	GABRA2	rs279856	Intron	4	46317923	C	A	8446	0.435	-0.08	0.03	1.15E-02
AUD	GABRA2	rs279854	Intron	4	46319264	A	G	8446	0.434	-0.08	0.03	1.15E-02
AUD	GSK3B	rs3732361	Utr3	3	119542297	A	G	8446	0.607	-0.09	0.03	1.17E-02
AUD	GABRA2	rs279867	Intron	4	46308303	A	C	8446	0.433	-0.08	0.03	1.19E-02
AUD	GABRA2	rs279852	Intron	4	46319761	G	T	8446	0.434	-0.08	0.03	1.20E-02
AUD	GABRA2	rs279841	Intron	4	46340763	G	A	8446	0.431	-0.08	0.03	1.21E-02
AUD	GRIN2B	rs1805478	Intron	12	13752145	T	C	8446	0.546	-0.08	0.03	1.23E-02
AUD	GABRA2	rs10805145	Intron	4	46358331	C	T	8446	0.547	0.08	0.03	1.23E-02
AUD	GABRA2	rs279838	Intron	4	46339501	A	G	8446	0.432	-0.08	0.03	1.23E-02
AUD	GABRA2	rs450571	Intron	4	46311346	A	G	8446	0.434	-0.08	0.03	1.25E-02

AUD	GABRA2	rs279839	Intron	4	46339538	G	A	8446	0.433	-0.08	0.03	1.26E-02
AUD	GABRA2	rs279857	Intron	4	46317759	G	A	8446	0.435	-0.08	0.03	1.26E-02
AUD	GABRA2	rs279848	Intron	4	46322945	C	G	8446	0.433	-0.08	0.03	1.26E-02
AUD	GRIN2B	rs971165	Intron	12	13848184	A	C	8446	0.509	0.08	0.03	1.29E-02
AUD	GABRA2	rs279869	Intron	4	46307995	G	T	8446	0.431	-0.08	0.03	1.30E-02
AUD	GABRA2	rs1440130	Intron	4	46333253	T	C	8446	0.446	-0.08	0.03	1.30E-02
AUD	GRIN2B	rs11055584	Intron	12	13843092	A	G	8446	0.415	-0.08	0.03	1.32E-02
AUD	GRIN2B	rs1012587	Intron	12	13854914	T	A	8446	0.239	0.09	0.04	1.32E-02
AUD	GSK3B	rs4261913	Intron	3	119546197	C	T	8446	0.607	-0.08	0.03	1.33E-02
AUD	GABRA2	rs28873227	Intron	4	46294578	A	G	8446	0.433	-0.08	0.03	1.35E-02
AUD	GABRA2	rs175931	Intron	4	46316323	A	T	8446	0.433	-0.08	0.03	1.37E-02
AUD	GABRA2	rs525630	Intron	4	46268570	G	A	8446	0.569	0.08	0.03	1.37E-02
AUD	GSK3B	rs6438553	Intron	3	119640029	A	T	8446	0.393	0.08	0.03	1.37E-02
AUD	GABRA2	rs279865	Intron	4	46309912	C	G	8446	0.435	-0.08	0.03	1.40E-02
AUD	GABRA2	rs175929	Intron	4	46338148	A	G	8446	0.432	-0.08	0.03	1.41E-02
AUD	GABRA2	rs537134	Intron	4	46271268	C	G	8446	0.569	0.08	0.03	1.44E-02
AUD	SLC6A3	rs28364999	Deletion	5	1400998	CG A	C	8446	0.018	-0.30	0.12	1.45E-02
AUD	GSK3B	rs1154595	Intron	3	119736594	C	T	8446	0.384	0.08	0.03	1.45E-02
AUD	GABRA2	rs279831	Intron	4	46335812	G	C	8446	0.449	-0.08	0.03	1.45E-02
AUD	GABRA2	rs517134	Intron	4	46279117	T	G	8446	0.565	0.08	0.03	1.46E-02
AUD	GABRA2	rs507788	Intron	4	46257458	C	T	8446	0.565	0.08	0.03	1.46E-02
AUD	GABRA2	rs554112	Intron	4	46262776	A	C	8446	0.570	0.08	0.03	1.47E-02
AUD	GABRA2	rs1440129	Intron	4	46333121	C	A	8446	0.448	-0.08	0.03	1.48E-02
AUD	GABRA2	rs183961	Intron	4	46331028	T	C	8446	0.449	-0.08	0.03	1.50E-02
AUD	GABRA2	rs279846	Intron	4	46329886	C	T	8446	0.448	-0.08	0.03	1.50E-02
AUD	GABRA2	rs279840	Intron	4	46340406	G	T	8446	0.429	-0.08	0.03	1.50E-02
AUD	GABRA2	rs519869	Intron	4	46285362	G	T	8446	0.569	0.08	0.03	1.50E-02
AUD	GABRA2	rs2439209	Intron	4	46274771	C	T	8446	0.570	0.08	0.03	1.51E-02
AUD	GABRA2	rs548583	Intron	4	46263344	A	G	8446	0.570	0.08	0.03	1.53E-02
AUD	GABRA2	rs1822016	Intron	4	46275776	G	A	8446	0.570	0.08	0.03	1.54E-02
AUD	GABRA2	rs532363	Intron	4	46282566	T	G	8446	0.568	0.08	0.03	1.54E-02
AUD	GRIN2B	rs2300233	Intron	12	13792620	T	C	8446	0.392	-0.08	0.03	1.55E-02
AUD	GABRA2	rs279830	Intron	4	46335681	G	A	8446	0.449	-0.08	0.03	1.58E-02
AUD	CRHR1	rs34186148	Intron	17	43854655	G	C	8446	0.372	-0.08	0.03	1.60E-02
AUD	GABRA2	rs490102	Intron	4	46273584	C	G	8446	0.570	0.08	0.03	1.61E-02
AUD	GABRA2	rs526805	Intron	4	46263391	C	A	8446	0.569	0.08	0.03	1.61E-02
AUD	GABRA2	rs279833	Intron	4	46338190	T	A	8446	0.433	-0.08	0.03	1.63E-02
AUD	GABRA2	rs279844	Intron	4	46329655	A	T	8446	0.449	-0.08	0.03	1.64E-02
AUD	GABRA2	rs552174	Intron	4	46269136	C	T	8446	0.569	0.08	0.03	1.67E-02
AUD	GABRA2	rs279834	Intron	4	46338299	G	C	8446	0.433	-0.08	0.03	1.70E-02
AUD	GABRA2	rs532780	Intron	4	46261366	C	T	8446	0.570	0.08	0.03	1.74E-02
AUD	GRIN2B	rs12308271	Intron	12	13853245	A	T	8446	0.338	-0.08	0.03	1.74E-02
AUD	GABRA2	rs1442059	Intron	4	46356952	C	T	8446	0.562	0.08	0.03	1.75E-02

AUD	GABRA2	rs279843	Intron	4	46325204	C	T	8446	0.435	-0.08	0.03	1.76E-02
AUD	GABRA2	rs10004122	Intron	4	46346657	A	G	8446	0.431	-0.08	0.03	1.79E-02
AUD	GABRA2	rs279868	Intron	4	46308110	A	T	8446	0.424	-0.08	0.03	1.81E-02
AUD	CHRNA4	rs1044393	Synonymous	20	61982124	A	G	8446	0.881	-0.12	0.05	1.82E-02
AUD	OPRM1	rs712242	Intron	6	154333172	T	C	8446	0.474	0.08	0.03	1.85E-02
AUD	GABRA2	rs543809	Intron	4	46274590	G	A	8446	0.569	0.08	0.03	1.86E-02
AUD	GSK3B	rs6800622	Intron	3	119580678	A	C	8446	0.594	-0.08	0.03	1.87E-02
AUD	GABRA2	rs279847	Intron	4	46324630	G	T	8446	0.433	-0.08	0.03	1.87E-02
AUD	GABRA2	rs505474	Intron	4	46260587	T	C	8446	0.569	0.08	0.03	1.88E-02
AUD	GRIN2A	rs3852745	Intron	16	10248860	G	T	8446	0.307	0.08	0.04	1.91E-02
AUD	GABRA2	rs534459	Intron	4	46256805	A	G	8446	0.563	0.08	0.03	1.91E-02
AUD	GSK3B	rs6795653	Intron	3	119610565	T	C	8446	0.396	0.08	0.03	1.91E-02
AUD	GRIN2B	rs11833339	Intron	12	14008727	A	G	8446	0.044	0.19	0.08	1.92E-02
AUD	GSK3B	rs2319398	Intron	3	119612942	C	A	8446	0.394	0.08	0.03	1.92E-02
AUD	GSK3B	rs6782799	Intron	3	119610793	C	T	8446	0.395	0.08	0.03	1.95E-02
AUD	GABRA2	rs279866	Intron	4	46309764	A	G	8446	0.436	-0.08	0.03	1.98E-02
AUD	GRIN2A	rs3852746	Intron	16	10249021	C	T	8446	0.307	0.08	0.04	2.07E-02
AUD	GABRB3	rs12915684	Intron	15	26816889	A	G	8446	0.278	-0.08	0.04	2.08E-02
AUD	GABRA2	rs693547	Intron	4	46256557	A	T	8446	0.565	0.08	0.03	2.12E-02
AUD	GSK3B	rs9813864	Intron	3	119590974	C	T	8446	0.604	-0.08	0.03	2.13E-02
AUD	GABRA2	rs577544	Intron	4	46278859	C	A	8446	0.560	0.08	0.03	2.14E-02
AUD	GABRA2	rs6833452	Intron	4	46354731	C	T	8446	0.568	0.08	0.03	2.22E-02
AUD	GRIN2B	rs2300236	Intron	12	13811372	G	A	8446	0.478	0.07	0.03	2.22E-02
AUD	GABRB2	rs7709316	Intron	5	160725600	C	T	8446	0.067	0.15	0.07	2.24E-02
AUD	GABRA2	rs6447508	Intron	4	46361545	G	C	8446	0.572	0.08	0.03	2.25E-02
AUD	FAAH	rs2295632	Downstream	1	46879562	T	G	8446	0.723	-0.08	0.04	2.25E-02
AUD	GSK3B	rs9878473	Intron	3	119650788	T	C	8446	0.395	0.08	0.03	2.28E-02
AUD	GABRA2	rs279822	Intron	4	46351162	C	A	8446	0.567	0.08	0.03	2.31E-02
AUD	CRHR1	rs242937	Intron	17	43898368	A	G	8446	0.561	0.08	0.03	2.31E-02
AUD	GRIK1	rs417979	Intron	21	31228214	T	G	8446	0.960	0.19	0.08	2.32E-02
AUD	GRIK1	rs3787671	Intron	21	31073100	T	G	8446	0.152	-0.11	0.05	2.39E-02
AUD	GABRA2	rs526608	Intron	4	46268681	A	T	8446	0.564	0.08	0.03	2.47E-02
AUD	GSK3B	rs16830567	Intron	3	119570175	T	C	8446	0.187	0.09	0.04	2.50E-02
AUD	DDC	rs6593011	Intron	7	50632796	C	A	8446	0.148	-0.10	0.05	2.50E-02
AUD	GRIK1	rs118730	Intron	21	31220217	T	C	8446	0.951	0.19	0.08	2.51E-02
AUD	GRIK1	rs363516	Intron	21	31042500	C	T	8446	0.033	-0.20	0.09	2.51E-02
AUD	GABRB3	rs4281679	Intron	15	26886442	C	T	8446	0.109	-0.12	0.05	2.52E-02
AUD	GRIN2B	rs12578850	Intron	12	13847424	C	T	8446	0.147	0.10	0.05	2.55E-02
AUD	GSK3B	rs12108149	Intron	3	119721171	T	C	8446	0.186	0.09	0.04	2.55E-02
AUD	GABRB3	rs2017247	Utr3	15	26789162	T	C	8446	0.738	0.08	0.04	2.56E-02
AUD	GRIN2B	rs2041889	Intron	12	13743245	T	G	8446	0.412	0.08	0.03	2.57E-02
AUD	GRIN2B	rs2268110	Intron	12	13853101	C	T	8446	0.149	0.10	0.05	2.59E-02
AUD	GRIN1	rs12238250	Intron	9	140046682	C	A	8446	0.939	-0.15	0.07	2.59E-02

AUD	HTR2A	rs12876614	Intron	13	47463990	C	T	8446	0.207	0.09	0.04	2.63E-02
AUD	GRIK1	rs469563	Intron	21	31228193	A	G	8446	0.959	0.19	0.08	2.67E-02
AUD	GRIN2B	rs2268112	Intron	12	13853503	G	A	8446	0.150	0.10	0.05	2.72E-02
AUD	GRIK1	rs2254136	Intron	21	31047208	G	C	8446	0.159	-0.10	0.04	2.72E-02
AUD	GRIK1	rs16984622	Intron	21	31017620	T	C	8446	0.104	-0.12	0.05	2.75E-02
AUD	CNR1	rs11756397	Intron	6	88873728	T	C	8446	0.217	0.09	0.04	2.80E-02
AUD	GSK3B	rs6792572	Intron	3	119636096	A	C	8446	0.396	0.07	0.03	2.80E-02
AUD	DDC	rs4490786	Normal_Splice_Site	7	50544314	C	T	8446	0.207	0.09	0.04	2.86E-02
AUD	GRIK1	rs363544	Intron	21	31050277	T	C	8446	0.162	-0.10	0.04	2.88E-02
AUD	GRIN2B	rs11055589	Intron	12	13848219	G	A	8446	0.147	0.10	0.05	2.88E-02
AUD	GRIN2A	rs11074613	Intron	16	10248694	G	A	8446	0.307	0.08	0.04	2.89E-02
AUD	GRIN2B	rs2216129	Intron	12	13853596	C	T	8446	0.492	0.07	0.03	2.90E-02
AUD	CRHR1	rs4074461	Intron	17	43855156	G	T	8446	0.535	-0.07	0.03	2.97E-02
AUD	FAAH	rs2145408	Intron	1	46861907	A	G	8446	0.736	-0.08	0.04	2.97E-02
AUD	GRIN2A	rs7501071	Intron	16	10248789	G	A	8446	0.307	0.08	0.04	2.98E-02
AUD	GSK3B	rs2873950	Intron	3	119547062	A	C	8446	0.187	0.09	0.04	3.01E-02
AUD	OPRK1	rs6473797	Intron	8	54152982	T	C	8446	0.246	-0.08	0.04	3.06E-02
AUD	HTR2A	rs34420017	Intron	13	47443889	A	G	8446	0.208	0.09	0.04	3.08E-02
AUD	GSK3B	rs12635018	Intron	3	119749770	C	T	8446	0.187	0.09	0.04	3.10E-02
AUD	GSK3B	rs12629015	Intron	3	119618053	A	G	8446	0.188	0.09	0.04	3.13E-02
AUD	GRIN2B	rs74067128	Intron	12	14004012	A	T	8446	0.037	0.19	0.09	3.16E-02
AUD	GRIN2B	rs11836523	Intron	12	13857884	T	C	8446	0.091	-0.12	0.06	3.18E-02
AUD	CRHR1	rs173365	Intron	17	43901074	A	G	8446	0.559	0.07	0.03	3.18E-02
AUD	DDC	rs3779084	Intron	7	50568735	A	G	8446	0.205	0.09	0.04	3.18E-02
AUD	HTR2A	rs6561335	Intron	13	47433497	G	A	8446	0.728	0.08	0.04	3.19E-02
AUD	FAAH	rs324418	Intron	1	46872698	A	G	8446	0.223	0.08	0.04	3.20E-02
AUD	GSK3B	rs10934500	Intron	3	119568123	T	C	8446	0.187	0.09	0.04	3.20E-02
AUD	GABRB3	rs7169596	Intron	15	26808859	T	C	8446	0.261	-0.08	0.04	3.22E-02
AUD	NTRK2	rs77438563	Intron	9	87579803	C	T	8446	0.078	-0.13	0.06	3.27E-02
AUD	GABRB3	rs2114485	Intron	15	26802824	G	A	8446	0.733	0.08	0.04	3.27E-02
AUD	GABRB3	rs12901061	Intron	15	26803412	C	G	8446	0.262	-0.08	0.04	3.34E-02
AUD	GABRB3	rs2052991	Intron	15	26803543	G	A	8446	0.260	-0.08	0.04	3.34E-02
AUD	GRIN2B	rs7297761	Intron	12	13853579	A	G	8446	0.380	-0.07	0.03	3.35E-02
AUD	GRIN2B	rs74067133	Intron	12	14006943	T	C	8446	0.038	0.18	0.09	3.36E-02
AUD	GSK3B	rs1574154	Intron	3	119627247	T	C	8446	0.188	0.09	0.04	3.36E-02
AUD	GSK3B	rs12054090	Intron	3	119668285	T	C	8446	0.187	0.09	0.04	3.36E-02
AUD	CRHR1	rs9303521	Intron	17	43805194	T	G	8446	0.531	0.07	0.03	3.37E-02
AUD	GSK3B	rs10433404	Intron	3	119693240	C	G	8446	0.186	0.09	0.04	3.38E-02
AUD	GSK3B	rs4340737	Intron	3	119622014	C	T	8446	0.187	0.09	0.04	3.38E-02
AUD	GSK3B	rs7639388	Intron	3	119609953	T	A	8446	0.187	0.09	0.04	3.39E-02
AUD	GRIN2B	rs2268099	Intron	12	13780726	G	A	8446	0.383	-0.07	0.03	3.40E-02
AUD	GABRA2	rs519270	Intron	4	46274451	T	C	8446	0.555	0.07	0.03	3.40E-02
AUD	GSK3B	rs62264739	Intron	3	119688402	A	G	8446	0.187	0.09	0.04	3.44E-02

AUD	GSK3B	rs6808874	Intron	3	119557851	A	T	8446	0.187	0.09	0.04	3.45E-02
AUD	DRD3	rs56087035	Intron	3	113852778	T	C	8446	0.017	0.26	0.12	3.47E-02
AUD	GABRB2	rs2964778	Intron	5	160900642	C	T	8446	0.032	0.20	0.09	3.48E-02
AUD	GRIN2A	rs79225924	Intron	16	10167872	C	T	8446	0.012	0.32	0.15	3.48E-02
AUD	GRIN2A	rs2008342	Intron	16	10003192	A	C	8446	0.261	0.08	0.04	3.51E-02
AUD	CRHR1	rs242924	Intron	17	43885367	G	T	8446	0.439	0.07	0.03	3.52E-02
AUD	GABRB3	rs8033560	Intron	15	26815561	G	A	8446	0.264	-0.08	0.04	3.53E-02
AUD	GSK3B	rs4688046	Intron	3	119663870	T	C	8446	0.186	0.09	0.04	3.55E-02
AUD	PTTG2	rs200376306	Frameshift	4	37962608	CAT	C	8446	0.011	0.33	0.16	3.57E-02
AUD	GSK3B	rs4688042	Intron	3	119590880	A	G	8446	0.188	0.09	0.04	3.58E-02
AUD	GSK3B	rs12638973	Intron	3	119684827	C	T	8446	0.187	0.09	0.04	3.62E-02
AUD	OPRK1	rs6473798	Intron	8	54153105	C	T	8446	0.246	-0.08	0.04	3.62E-02
AUD	HTR2A	rs594242	Intron	13	47458052	C	G	8446	0.785	-0.08	0.04	3.64E-02
AUD	GRIN2B	rs73047488	Intron	12	13758325	G	C	8446	0.349	-0.07	0.03	3.64E-02
AUD	GRIN2B	rs11055670	Intron	12	14051237	T	A	8446	0.090	-0.12	0.06	3.66E-02
AUD	GABRB3	rs2114217	Intron	15	26960029	T	A	8446	0.832	-0.09	0.04	3.67E-02
AUD	GSK3B	rs12634476	Intron	3	119678825	G	A	8446	0.186	0.09	0.04	3.67E-02
AUD	GSK3B	rs10934502	Intron	3	119669136	T	C	8446	0.186	0.09	0.04	3.69E-02
AUD	GABRA2	rs3822051	Intron	4	46256712	T	C	8446	0.255	-0.08	0.04	3.72E-02
AUD	GSK3B	rs4688047	Intron	3	119682761	C	T	8446	0.186	0.09	0.04	3.72E-02
AUD	GSK3B	rs62264749	Intron	3	119747919	T	C	8446	0.188	0.09	0.04	3.73E-02
AUD	GABRB3	rs4264366	Intron	15	26808989	C	T	8446	0.264	-0.08	0.04	3.76E-02
AUD	GRIK1	rs743321	Intron	21	31018770	G	T	8446	0.104	-0.11	0.05	3.78E-02
AUD	GRIN2B	rs59457485	Intron	12	14009694	T	C	8446	0.039	0.18	0.08	3.81E-02
AUD	GSK3B	rs12634889	Intron	3	119596514	A	G	8446	0.187	0.09	0.04	3.82E-02
AUD	HTR2A	rs1002513	Intron	13	47454440	G	A	8446	0.208	0.08	0.04	3.82E-02
AUD	CRHR1	rs110402	Intron	17	43880047	G	A	8446	0.437	0.07	0.03	3.82E-02
AUD	GRIN2B	rs4764027	Intron	12	13835534	A	C	8446	0.509	-0.07	0.03	3.83E-02
AUD	GRIN2B	rs10505778	Intron	12	14125564	A	G	8446	0.353	-0.07	0.03	3.84E-02
AUD	NTRK2	rs75887034	Intron	9	87553443	G	T	8446	0.042	-0.17	0.08	3.85E-02
AUD	GRIN2A	rs79479110	Intron	16	10168899	T	C	8446	0.012	0.31	0.15	3.85E-02
AUD	GSK3B	rs10934505	Intron	3	119767322	A	T	8446	0.190	0.09	0.04	3.89E-02
AUD	GRIK1	rs2832428	Intron	21	31074039	A	C	8446	0.117	-0.10	0.05	3.95E-02
AUD	GRIN2B	rs4764014	Intron	12	13763321	G	A	8446	0.338	-0.07	0.03	3.97E-02
AUD	CNR1	rs10944345	Intron	6	88871626	T	C	8446	0.236	0.08	0.04	3.97E-02
AUD	GSK3B	rs4688054	Intron	3	119733710	T	C	8446	0.188	0.09	0.04	4.03E-02
AUD	GRIK1	rs11908807	Intron	21	31019853	C	T	8446	0.105	-0.11	0.05	4.05E-02
AUD	OPRM1	rs1294092	Intron	6	154335673	A	G	8446	0.160	0.09	0.04	4.06E-02
AUD	GABRB3	rs3751582	Intron	15	26806064	T	C	8446	0.266	-0.08	0.04	4.08E-02
AUD	GABRA2	rs3775282	Intron	4	46321863	T	C	8446	0.179	-0.09	0.04	4.08E-02
AUD	DDC	rs7808025	Intron	7	50576903	G	A	8446	0.211	0.08	0.04	4.08E-02
AUD	GSK3B	rs4688059	Intron	3	119811568	G	A	8446	0.186	0.09	0.04	4.11E-02
AUD	HTR2A	rs582385	Intron	13	47445994	A	G	8446	0.192	0.08	0.04	4.14E-02

AUD	GSK3B	rs62264747	Intron	3	119741298	T	C	8446	0.186	0.09	0.04	4.20E-02
AUD	NTRK2	rs7019212	Intron	9	87575074	T	G	8446	0.086	-0.12	0.06	4.28E-02
AUD	GRIN2B	rs56317148	Intron	12	14018127	A	G	8446	0.040	0.17	0.08	4.30E-02
AUD	GRIK1	rs464144	Intron	21	31210998	C	T	8446	0.385	-0.07	0.03	4.30E-02
AUD	GRIN2B	rs11055557	Intron	12	13788827	G	A	8446	0.346	-0.07	0.03	4.32E-02
AUD	HTR2A	rs666693	Intron	13	47446916	C	T	8446	0.192	0.08	0.04	4.37E-02
AUD	GRIN2B	rs4763354	Intron	12	13734352	G	A	8446	0.567	-0.07	0.03	4.41E-02
AUD	GRIN2A	rs1868285	Intron	16	10122457	C	G	8446	0.967	0.19	0.09	4.43E-02
AUD	TPH2	rs1487278	Intron	12	72400851	T	C	8446	0.226	0.08	0.04	4.43E-02
AUD	GSK3B	rs58863896	Intron	3	119785527	C	A	8446	0.186	0.08	0.04	4.47E-02
AUD	CRHR1	rs12950522	Intron	17	43859106	A	C	8446	0.457	0.07	0.03	4.47E-02
AUD	GRIK1	rs743320	Intron	21	31018915	G	A	8446	0.105	-0.11	0.05	4.48E-02
AUD	GRIK1	rs2300315	Intron	21	31078003	T	C	8446	0.124	-0.10	0.05	4.52E-02
AUD	CRHR1	rs171440	Intron	17	43893487	G	A	8446	0.461	0.07	0.03	4.54E-02
AUD	NTRK2	rs10868238	Intron	9	87530935	T	C	8446	0.600	0.07	0.03	4.55E-02
AUD	GSK3B	rs62264706	Intron	3	119560856	G	T	8446	0.186	0.08	0.04	4.58E-02
AUD	GRIN2B	rs11832404	Intron	12	14006305	T	C	8446	0.038	0.17	0.09	4.59E-02
AUD	CNR1	rs806375	Utr5	6	88858521	A	T	8446	0.439	0.07	0.03	4.60E-02
AUD	GABRB2	rs3850733	Intron	5	160738317	C	A	8446	0.065	0.13	0.07	4.62E-02
AUD	OPRM1	rs2075572	Intron	6	154412004	G	C	8446	0.567	-0.07	0.03	4.76E-02
AUD	GRIN2B	rs11835020	Intron	12	14016610	A	C	8446	0.040	0.17	0.08	4.76E-02
AUD	SLC18A2	rs363230	Intron	10	119029515	C	T	8446	0.513	0.07	0.03	4.77E-02
AUD	GRIN2B	rs57382938	Intron	12	13858771	T	C	8446	0.105	-0.11	0.05	4.81E-02
AUD	CRHR1	rs7209436	Intron	17	43870142	C	T	8446	0.425	0.07	0.03	4.83E-02
AUD	GRIN2B	rs57055881	Intron	12	14007497	T	C	8446	0.039	0.17	0.08	4.87E-02
AUD	GABRB2	rs869647	Intron	5	160739626	A	G	8446	0.065	0.13	0.07	4.87E-02
AUD	DRD3	rs79626250	Intron	3	113894684	T	A	8446	0.027	-0.20	0.10	4.93E-02
AUD	GRIK1	rs16984636	Intron	21	31019785	T	G	8446	0.104	-0.10	0.05	4.93E-02
AUD	DDC	rs11575521	Intron	7	50535497	C	A	8446	0.110	0.10	0.05	4.94E-02

^a AF: Allele freq for ALT allele.

^b Positive value indicates ALT allele is the risk allele.

Supplementary table 4 Single-point SNP associations ($5 \times 10^{-5} < P < 10^{-4}$) to any of four SUDs in NESARC-III EA.

Disorder	Chr	Pos	SNP	Gene	Function	Ref	Alt	N	AF ^a	Effect ^b	SE	Pvalue
AUD	2	163697314	rs13031375	Intergenic	Intergenic	G	T	8446	0.142	-0.19	0.05	6.23E-05
AUD	2	144208523	rs35942385	ARHGAP15	Intron	G	T	8446	0.369	-0.13	0.03	7.14E-05
AUD	2	163706766	rs56900781	Intergenic	Intergenic	C	T	8446	0.603	0.14	0.03	7.88E-05
AUD	17	48456193	rs12450550	EME1	Nonsynonymous	T	C	8446	0.268	-0.15	0.04	7.94E-05
AUD	2	208994045	rs2242073	CRYGC	Intron	T	G	8446	0.168	-0.17	0.04	8.16E-05
AUD	7	98957880	rs740160	ARPC1A	Intron	C	T	8446	0.043	-0.32	0.08	8.41E-05
AUD	1	165370757	rs283690	RXRG	Intron	G	A	8446	0.507	0.13	0.03	8.78E-05
AUD	6	116325142	rs3756772	FRK	Nonsynonymous	C	T	8446	0.425	0.13	0.03	9.28E-05
AUD	2	144187516	rs12991555	ARHGAP15	Intron	A	T	8446	0.367	-0.13	0.03	9.39E-05
AUD	7	99118801	rs11761528	ZKSCAN5	Intron	C	T	8446	0.079	-0.24	0.06	9.62E-05
AUD	7	130568334	rs157913	LOC646329	Intron	A	C	8446	0.578	0.13	0.03	9.86E-05
NUD	15	36139024	rs2646782	LOC100507466	Intron	A	G	8353	0.548	0.13	0.03	5.38E-05
NUD	10	84088633	rs7912362	NRG3	Intron	G	T	8353	0.192	-0.16	0.04	5.49E-05
NUD	19	58861808	rs145144275	A1BG	Nonsynonymous	A	G	8353	0.010	-0.64	0.16	5.56E-05
NUD	10	84022385	rs72827304	NRG3	Intron	A	C	8353	0.135	-0.19	0.05	5.57E-05
NUD	10	84110196	rs6584663	NRG3	Intron	G	C	8353	0.191	-0.16	0.04	5.78E-05
NUD	10	84091078	rs3904726	NRG3	Intron	T	C	8353	0.130	-0.19	0.05	6.22E-05
NUD	10	84088903	rs7088954	NRG3	Intron	G	T	8353	0.191	-0.16	0.04	6.23E-05
NUD	2	136407479	rs1446585	R3HDM1	Intron	A	G	8353	0.326	-0.14	0.03	6.4E-05
NUD	10	84112020	rs7914005	NRG3	Intron	C	T	8353	0.175	-0.17	0.04	6.5E-05
NUD	6	116325142	rs3756772	FRK	Nonsynonymous	C	T	8353	0.425	0.13	0.03	7.3E-05
NUD	13	67694136	rs1028899	PCDH9	Intron	G	A	8353	0.936	-0.26	0.07	7.81E-05
NUD	10	84094052	rs7900818	NRG3	Intron	T	C	8353	0.216	-0.15	0.04	7.86E-05
NUD	10	84080228	rs10884538	NRG3	Intron	C	T	8353	0.215	-0.15	0.04	8.13E-05
NUD	2	120413984	rs116625089	PCDP1	Nonsynonymous	C	G	8353	0.018	-0.47	0.12	8.48E-05
NUD	10	84115932	rs1937965	NRG3	Intron	T	C	8353	0.191	-0.16	0.04	8.6E-05
NUD	13	67692751	rs17588668	PCDH9	Intron	A	G	8353	0.062	0.26	0.07	8.68E-05
NUD	10	84092199	rs11193778	NRG3	Intron	C	G	8353	0.130	-0.19	0.05	8.77E-05
NUD	11	100493240	rs1216526	Intergenic	Intergenic	G	C	8353	0.839	-0.17	0.04	8.82E-05
NUD	2	135837906	rs7570971	RAB3GAP1	Intron	C	A	8353	0.370	-0.13	0.03	9.08E-05
NUD	10	84093523	rs3862549	NRG3	Intron	G	C	8353	0.131	-0.19	0.05	9.47E-05
NUD	10	84012865	rs11193199	NRG3	Intron	A	G	8353	0.135	-0.18	0.05	9.5E-05
NUD	13	67694464	rs9529189	PCDH9	Intron	C	T	8353	0.935	-0.26	0.07	9.7E-05
NUD	13	67695402	rs9571714	PCDH9	Intron	C	T	8353	0.937	-0.26	0.07	9.71E-05
CUD	7	25687828	rs1859041	Intergenic	Intergenic	A	G	4913	0.583	0.22	0.06	6.57E-05
CUD	15	58852526	rs7179938	LIPC	Intron	A	C	4913	0.984	-0.88	0.22	7.16E-05
CUD	22	38715222	rs1997644	Intergenic	Intergenic	G	A	4913	0.531	0.22	0.05	8.23E-05
CUD	15	58851684	rs2414601	LIPC	Intron	C	T	4913	0.985	-0.87	0.22	8.28E-05
CUD	15	58854218	rs1839927	LIPC	Intron	G	A	4913	0.984	-0.87	0.22	8.69E-05

CUD	15	58852788	rs7180795	LIPC	Intron	G	A	4913	0.984	-0.87	0.22	8.78E-05
CUD	6	153296541	rs2073260	FBXO5	Nonsynonymous	G	C	4913	0.671	-0.23	0.06	8.81E-05
CUD	15	58851677	rs2414600	LIPC	Intron	C	A	4913	0.985	-0.86	0.22	9.31E-05
CUD	15	58853079	rs3829462	LIPC	Nonsynonymous	C	A	4913	0.980	-0.85	0.22	9.36E-05
CUD	15	58854587	rs7170227	LIPC	Intron	A	G	4913	0.985	-0.86	0.22	9.44E-05
CUD	15	58865388	rs74016912	Intergenic	Intergenic	C	A	4913	0.015	0.87	0.22	9.44E-05
CUD	15	58850734	rs2414593	LIPC	Intron	T	C	4913	0.984	-0.86	0.22	9.55E-05
CUD	15	58851169	rs2414597	LIPC	Intron	A	C	4913	0.984	-0.86	0.22	9.61E-05
CUD	15	58854506	rs10851636	LIPC	Intron	T	C	4913	0.984	-0.86	0.22	9.65E-05
CUD	15	58852669	rs7181592	LIPC	Intron	T	C	4913	0.985	-0.86	0.22	9.66E-05
CUD	15	58854439	rs8030903	LIPC	Intron	C	T	4913	0.985	-0.86	0.22	9.66E-05
CUD	15	58852639	rs7180130	LIPC	Intron	A	G	4913	0.985	-0.86	0.22	9.68E-05
CUD	15	58867080	rs74016918	Intergenic	Intergenic	T	C	4913	0.015	0.86	0.22	9.73E-05
CUD	15	58855368	rs11071390	LIPC	Intron	G	A	4913	0.985	-0.86	0.22	9.74E-05
CUD	15	58851369	rs2414598	LIPC	Intron	G	A	4913	0.985	-0.86	0.22	9.76E-05
CUD	15	58867207	rs74016919	Intergenic	Intergenic	G	T	4913	0.015	0.86	0.22	9.84E-05
CUD	15	58851619	rs2414599	LIPC	Intron	C	T	4913	0.984	-0.86	0.22	9.91E-05
NMPOUD	21	31661691	rs8127420	KRTAP25-1	Nonsynonymous	A	G	4305	0.293	-0.35	0.09	8.18E-05
Any SUD	7	115369270	rs78689621	Intergenic	Intergenic	C	G	10484	0.050	-0.28	0.07	5.21E-05
Any SUD	7	115372297	rs78329989	Intergenic	Intergenic	G	A	10484	0.051	-0.27	0.07	6.34E-05
Any SUD	2	208994045	rs2242073	CRYGC	Intron	T	G	10484	0.167	-0.15	0.04	7.12E-05
Any SUD	7	115379708	rs77794355	Intergenic	Intergenic	C	T	10484	0.050	-0.27	0.07	7.44E-05
Any SUD	7	115353131	rs78346484	Intergenic	Intergenic	T	G	10484	0.049	-0.27	0.07	7.47E-05
Any SUD	7	115370568	rs80312226	Intergenic	Intergenic	C	T	10484	0.050	-0.27	0.07	7.73E-05
Any SUD	7	115367094	rs114763305	Intergenic	Intergenic	C	T	10484	0.049	-0.27	0.07	7.85E-05
Any SUD	7	115369325	rs79679457	Intergenic	Intergenic	C	A	10484	0.050	-0.27	0.07	9.19E-05
Any SUD	16	22237118	rs9935059	EEF2K	Nonsynonymous	A	G	10484	0.074	-0.22	0.06	9.28E-05
Any SUD	2	144248718	rs35789697	ARHGAP15	Intron	G	A	10484	0.368	-0.12	0.03	9.55E-05
Any SUD	7	115348085	rs6975616	Intergenic	Intergenic	A	T	10484	0.048	-0.28	0.07	9.81E-05
Any SUD	7	115374498	rs6958606	Intergenic	Intergenic	C	T	10484	0.050	-0.26	0.07	9.87E-05

^a AF: Allele freq for ALT allele.

^b Positive value indicates ALT allele is the risk allele.

Supplementary table 5 Gene-based association ($10^{-4} < P < 5 \times 10^{-4}$) of uncommon variants to four SUDs in NESARC-III EA.

Disorder	Gene	Range	N	Num of Poly variants	Q	rho	Pvalue(EA)	Pvalue(AA)	Pvalue (Burden Meta)
AUD	TUFT1	1:151512780-151556059,1:151512780-151556059	8446	2	69679.9	0.2	1.42E-04	3.43E-01	6.80E-01
AUD	TACC1	8:38644721-38710546,8:38644721-38710546,8:38585703-38710546	8446	1	22137.2	0	1.75E-04	4.57E-01	4.30E-02
AUD	ZNF835	19:57174952-57184246	8446	1	115151.0	0	2.52E-04	NA	7.40E-01
AUD	B3GALT4	6_dbb_hap3:4526238-4527924,6_mcf_hap5:4718690-4720376,6_qbl_hap6:4477155-4478841,6:33244916-33246602,6_cox_hap2:4688726-4690412	8446	1	107638.0	0	3.63E-04	3.07E-01	6.28E-02
AUD	ARHGAP22	10:49654078-49813138	8446	2	120595.0	0	4.35E-04	1.00E+00	1.93E-02
AUD	A1BG	19:58858171-58864865	8446	1	89431.7	0	4.50E-04	8.35E-01	1.03E-02
NUD	TACC1	8:38644721-38710546,8:38644721-38710546,8:38585703-38710546	8353	1	25027.1	0	1.09E-04	8.27E-01	3.73E-01
NUD	B4GALT6	18:29202208-29264686	8353	2	106390.0	0	1.21E-04	5.75E-01	4.61E-02
NUD	SLC2A13	12:40148822-40499661	8353	3	137772.0	0	1.39E-04	1.30E-01	1.14E-03
NUD	PPIL3	2:201735678-201753849,2:201735678-201753849	8353	1	64952.3	0	1.42E-04	1.26E-01	4.44E-04
NUD	IGSF5	21:41117333-41174023	8353	8	230799.0	0	1.52E-04	1.70E-02	1.38E-01
NUD	LIPE	19:42905665-42931578	8353	6	109415.0	0	1.59E-04	1.00E+00	1.68E-01
NUD	ARHGAP22	10:49654078-49813138	8353	2	134052.0	0	2.41E-04	3.70E-01	8.69E-04
NUD	NOC2L	1:879582-894679	8353	1	46282.9	0	2.61E-04	1.00E+00	3.83E-01
NUD	ARL13B	3:93698982-93774522,3:93698982-93774522,3:93698982-93774522,3:93698982-93774522,3:93698982-93774522	8353	3	78593.0	0.2	2.71E-04	1.00E+00	1.69E-02
NUD	PCDP1	2:120302024-120414237	8353	3	152717.0	0	3.78E-04	6.79E-01	5.12E-01
NUD	TTLL6	17:46839592-46871686,17:46839592-46894469	8353	4	200737.0	0	4.13E-04	5.44E-02	5.33E-03
NUD	TAGLN	11:117070039-117075508,11:117070039-117075508	8353	1	64035.8	0	4.23E-04	7.77E-01	4.68E-01
NUD	IMPG1	6:76631061-76782335	8353	6	133953.0	0	4.68E-04	7.22E-01	2.10E-01
NUD	CARNS1	11:67183148-67193078,11:67183148-67193078	8353	1	43667.5	0	4.81E-04	NA	5.02E-01
CUD	OR10H3	19:15852202-15853153	4913	1	20173.2	0	1.12E-04	1.34E-01	8.52E-01
CUD	SPTAN1	9:131314836-131395944,9:131314836-131395944,9:131314836-131395944	4913	1	6923.1	0	1.28E-04	9.05E-01	3.16E-01
CUD	G6PC2	2:169757749-169766510,2:169757749-169766510	4913	3	67603.6	1	1.33E-04	4.67E-01	4.21E-03
CUD	SMG5	1:156219014-156252620	4913	4	133355.0	1	1.64E-04	7.79E-01	7.81E-03
CUD	MBLAC2	5:89754019-89770585	4913	1	7746.9	0	2.16E-04	7.20E-01	1.00E+00
CUD	BARHL2	1:91177578-91182794	4913	1	6563.9	0	2.73E-04	1.79E-02	3.92E-04
CUD	CALHM1	10:105213143-105218648	4913	1	39441.7	0	3.05E-04	4.05E-01	1.51E-03

CUD	CYB5R4	6:84569369-84670146	4913	2	15553.7	0.8	3.33E-04	7.71E-02	8.32E-02
CUD	PRDM8	4:81106423-81125482,4:81118656-81125482	4913	1	20623.4	0	3.61E-04	NA	2.03E-01
CUD	ARHGAP5	14:32546494-32628934,14:32546494-32628934	4913	2	34763.1	0.2	3.81E-04	3.28E-01	5.14E-04
CUD	AKAP1	17:55162552-55198710	4913	2	47829.6	1	4.05E-04	3.89E-01	2.06E-01
CUD	WDR27	6:169857302-170102159,6:169857302-170102159	4913	6	71406.7	0.2	4.54E-04	7.07E-01	2.86E-01
NMPOUD	MMP14	14:23305792-23316803	4305	2	24610.2	0.9	1.01E-04	2.62E-01	2.08E-04
NMPOUD	UROS	10:127477146-127511837	4305	1	10555.8	0	1.15E-04	5.65E-01	5.70E-03
NMPOUD	CCDC15	11:124824016-124911385	4305	1	3019.3	0	1.45E-04	2.53E-01	6.38E-03
NMPOUD	HSPB7	1:16340522-16345285	4305	1	1869.1	0	1.77E-04	6.23E-01	5.74E-01
NMPOUD	LIPK	10:90484300-90512513	4305	5	45557.2	0	1.86E-04	1.00E+00	4.40E-03
NMPOUD	TES	7:115863004-115898837,7:115850546-115898837	4305	1	7943.2	0	1.98E-04	6.45E-01	1.40E-03
NMPOUD	C19orf28	19:3538262-3557571,19:3544196-3557571,19:3538262-3557571	4305	4	27428.1	0.3	2.08E-04	8.32E-01	2.25E-01
NMPOUD	CENPP	9:95087740-95377437	4305	15	40684.9	0.1	2.48E-04	1.03E-01	3.39E-01
NMPOUD	AKAP7	6:131456825-131604675,6:131571298-131604675,6:131571298-131604675	4305	3	20094.0	0	3.19E-04	1.25E-01	2.65E-01
NMPOUD	HSPA1B	6:31795511-31798031,6_apd_hap1:3110275-3112789,6_cox_hap2:3305093-3307616,6_dbb_hap3:3081098-3083618,6_qbl_hap6:3089162-3091686	4305	1	15323.6	0	3.86E-04	7.05E-01	4.35E-04
NMPOUD	CDC42EP5	19:54976209-54984422	4305	1	12493.9	0	4.38E-04	1.61E-01	1.35E-04
NMPOUD	LOC729178	6:147162524-147525750	4305	2	19173.3	0	4.80E-04	8.07E-01	NA
NMPOUD	CCDC65	12:49297892-49315359	4305	2	17629.9	0.1	4.87E-04	7.34E-01	4.34E-02
Any SUD	SEMA3G	3:52467267-52479043	10484	2	102218.0	0.2	1.36E-04	7.35E-01	1.44E-02
Any SUD	TACC1	8:38644721-38710546,8:38644721-38710546,8:38585703-38710546	10484	1	30321.6	0	1.45E-04	8.58E-01	2.00E-01
Any SUD	ARHGAP22	10:49654078-49813138	10484	2	164483.0	0	1.60E-04	6.97E-01	2.30E-03
Any SUD	B3GALT4	6_dbb_hap3:4526238-4527924,6_mcf_hap5:4718690-4720376,6_qbl_hap6:4477155-4478841,6:33244916-33246602,6_cox_hap2:4688726-4690412	10484	1	142625.0	0	1.69E-04	1.69E-01	6.39E-02
Any SUD	LIPE	19:42905665-42931578	10484	7	118616.0	0	3.31E-04	5.97E-01	2.33E-01
Any SUD	RBM11	21:15588465-15600693	10484	3	149445.0	0	3.64E-04	2.35E-01	4.84E-01
Any SUD	LTBP2	14:74964885-75079034	10484	4	247146.0	1	4.93E-04	5.48E-01	1.70E-03

Supplementary table 6 Gene-based association ($P < 5 \times 10^{-4}$) of common variants ($MAF \geq 0.01$) to SUDs in NESARC-III EA.

Disorder	Gene	Chr	No.SNPs	Chisq	Pvalue(EA)	Pvalue(AA)	Chisq(Meta)	Pvalue(Meta)
AUD	OR1M1	19	4	31.9	2.07E-04	8.99E-01	17.2	1.78E-03
AUD	N4BP2L1	13	4	22.9	2.40E-04	1.14E-01	21.0	3.15E-04
AUD	EEF2K	16	4	25.7	2.52E-04	6.87E-01	17.3	1.67E-03
AUD	CRYGD	2	3	22.7	2.84E-04	7.97E-01	16.8	2.13E-03
AUD	ARPC1B	7	2	16.3	2.93E-04	9.75E-01	16.3	2.61E-03
AUD	SCIN	7	5	30.5	3.21E-04	7.83E-01	16.6	2.33E-03
AUD	SMIM17	19	2	17.0	3.25E-04	3.66E-02	22.7	1.47E-04
AUD	ZNF835	19	2	17.0	3.25E-04	3.66E-02	22.7	1.47E-04
AUD	LRRC59	17	5	28.9	3.83E-04	9.77E-01	15.8	3.33E-03
NUD	ULBP3	6	2	20.8	3.12E-05	2.32E-01	23.7	9.27E-05
NUD	ZMYM4	1	2	17.9	1.36E-04	5.28E-01	19.1	7.55E-04
NUD	CCDC150	2	2	17.2	1.88E-04	9.51E-02	21.9	2.13E-04
NUD	EEF2K	16	4	26.6	1.91E-04	7.99E-01	17.6	1.50E-03
NUD	RAB3GAP1	2	4	34.5	2.45E-04	8.33E-02	21.6	2.40E-04
NUD	CCNL1	3	4	33.2	2.50E-04	5.40E-01	17.8	1.34E-03
NUD	MIR575	4	16	63.0	3.62E-04	9.30E-01	16.0	3.03E-03
NUD	DPH6-AS1	15	6	26.0	4.87E-04	1.86E-01	18.6	9.32E-04
NUD	MXRA7	17	1	12.3	4.89E-04	9.32E-03	24.6	6.06E-05
CUD	CCDC150	2	2	18.0	1.30E-04	1.05E-01	22.4	1.66E-04
CUD	FRK	6	5	34.7	1.78E-04	5.45E-01	18.5	9.94E-04
CUD	EXOC2	6	7	34.8	2.43E-04	6.56E-03	26.7	2.29E-05
NMPOUD	SAMSN1	21	5	31.0	1.11E-04	6.45E-02	23.7	9.17E-05
NMPOUD	BRWD1	21	5	40.0	1.53E-04	3.69E-01	19.6	6.08E-04
NMPOUD	PSMG1	21	5	40.0	1.53E-04	3.10E-01	19.9	5.18E-04
NMPOUD	MARCH11	5	1	13.9	2.06E-04	6.35E-01	17.9	1.30E-03
NMPOUD	AKAP7	6	2	16.9	2.46E-04	2.39E-01	19.5	6.32E-04
NMPOUD	SPTLC1	9	2	22.0	2.67E-04	NA	NA	NA
NMPOUD	INTS4	11	2	16.4	4.46E-04	5.60E-01	16.6	2.32E-03
Any SUD	TAS2R19	12	2	26.0	6.69E-05	5.74E-01	20.3	4.29E-04
Any SUD	TAS2R31	12	2	26.0	6.69E-05	5.74E-01	20.3	4.29E-04
Any SUD	EEF2K	16	4	28.2	1.12E-04	5.67E-01	19.3	6.79E-04
Any SUD	CCNL1	3	4	34.2	1.98E-04	4.04E-01	18.9	8.33E-04
Any SUD	CRYGD	2	3	23.0	2.60E-04	8.03E-01	16.9	1.98E-03
Any SUD	TUBGCP5	15	4	27.1	2.76E-04	4.20E-01	18.1	1.16E-03
Any SUD	MXRA7	17	1	13.3	2.80E-04	1.93E-02	24.3	7.09E-05
Any SUD	PRH1	12	9	43.1	3.48E-04	1.76E-01	19.4	6.55E-04

Supplementary table 7 Genetic Pathway association analysis ($P < 10^{-3}$) in NESARC-III EA.

Disorder	Set	No.S NPs	Chisq (Obs)	Pvalue(E A)	Pvalue(A A)	Chisq (Meta)	Pvalue (Meta)
AUD	BIOCARTA EIF PATHWAY	15	40.5	4.20E-04	2.67E-01	18.2	1.13E-03
AUD	REACTOME_MRNA_DECAY_BY_3_TO_5_EXORIBONUCLEASE	12	37.8	5.72E-04	5.26E-01	16.2	2.74E-03
NUD	BIOCARTA_RANMS PATHWAY	14	43.8	1.28E-04	7.21E-01	18.6	9.51E-04
NUD	BIOCARTA EIF PATHWAY	15	41.9	2.55E-04	1.70E-01	20.1	4.79E-04
NUD	REACTOME_EGFR_DOWNREGULATION	31	63.7	8.84E-04	8.98E-01	14.3	6.47E-03
CUD	REACTOME_LIPID_DIGESTION_MOBILIZATION AND TRANSPORT	242	417.5	8.32E-05	5.57E-01	20.0	5.09E-04
CUD	REACTOME_LIPOPROTEIN_METABOLISM	209	368.7	1.68E-04	6.04E-01	18.4	1.03E-03
CUD	REACTOME_CHYLOMICRON_MEDIATED_LIPID_TRANSPORT	149	291.2	3.40E-04	4.91E-01	17.4	1.62E-03
Any SUD	BIOCARTA EIF PATHWAY	15	44.2	1.16E-04	9.57E-02	22.8	1.38E-04

Supplementary table 8 Genetic variants associated with SUDs (single-point Pvalue < 10⁻⁴) and implicated in gene expression (either eQTL or mQTL)(at least one Pvalue of SMR < 10⁻³) in NESARC-III EA.

Disorder	Chr	Pos	SNP	Gene	Function	REF	ALT	Samples	AF	Pvalue (EA)	Pvalue SMR mQTL_Brain	Pvalue SMR mQTL_LBC	Pvalue SMR eQTL_CAGE
AUD	2	208994045	rs2242073	CRYGC	Intron	T	G	8446	0.168	8.16E-05	3.78E-04	2.24E-04	NA
AUD	7	98957880	rs740160	ARPC1A	Intron	C	T	8446	0.043	8.41E-05	3.00E-04	NA	NA
AUD	6	116325142	rs3756772	FRK	Nonsynonymous	C	T	8446	0.425	9.28E-05	1.01E-04	4.41E-04	NA
AUD	7	99118801	rs11761528	ZKSCAN5	Intron	C	T	8446	0.079	9.62E-05	1.05E-04	NA	1.33E-03
NUD	16	22237273	rs17841292	EEF2K	Nonsynonymous	C	G	8353	0.073	3.96E-05	NA	4.48E-05	NA
NUD	6	116325142	rs3756772	FRK	Nonsynonymous	C	T	8353	0.425	7.30E-05	8.02E-05	3.76E-04	NA
CUD	6	116325142	rs3756772	FRK	Nonsynonymous	C	T	4913	0.420	1.41E-05	1.61E-05	1.33E-04	NA
CUD	6	32814942	rs1057149	TAP1	Nonsynonymous	C	T	4913	0.025	1.99E-05	1.23E-04	2.06E-05	NA
CUD	6	625673	rs2294669	EXOC2	Intron	C	G	4913	0.715	4.51E-05	1.29E-04	1.00E-04	NA
CUD	15	58862825	rs71478677	Intergenic	Intergenic	C	T	4913	0.015	4.66E-05	NA	2.20E-04	NA
CUD	7	25687828	rs1859041	Intergenic	Intergenic	A	G	4913	0.583	6.57E-05	NA	1.26E-04	NA
CUD	15	58865388	rs74016912	Intergenic	Intergenic	C	A	4913	0.015	9.44E-05	NA	1.50E-04	NA
CUD	15	58850734	rs2414593	LIPC	Intron	T	C	4913	0.984	9.55E-05	NA	5.11E-04	NA
NMPOUD	16	79682751	rs1424233	Intergenic	Intergenic	T	C	4305	0.515	1.89E-05	NA	2.21E-05	NA
NMPOUD	16	53769677	rs6499640	FTO	Intron	G	A	4305	0.608	2.58E-05	NA	NA	5.74E-04
NMPOUD	9	94821861	rs12237598	SPTLC1	Intron	A	G	4305	0.019	4.96E-05	4.05E-04	NA	NA
Any SUD	12	11183108	rs12318612	TAS2R31	Nonsynonymous	G	C	10484	0.269	8.78E-06	1.09E-04	NA	NA
Any SUD	15	22816713	rs8035524	Intergenic	Intergenic	A	C	10484	0.351	3.56E-05	4.89E-04	3.58E-05	NA
Any SUD	6	116325142	rs3756772	FRK	Nonsynonymous	C	T	10484	0.427	4.58E-05	5.09E-05	2.78E-04	NA
Any SUD	2	208994045	rs2242073	CRYGC	Intron	T	G	10484	0.167	7.12E-05	3.44E-04	2.01E-04	NA

Supplementary table 9 Colocalization analysis using the LocusFocus tool in NESARC-III EA (Simple Sum Pvalue < 10⁻³). Genetic variants associated with SUDs (single-point Pvalue < 5x10⁻⁵) and implicated in gene expression in GTEx.

Disorder	Gene	Tissue	Simple Sum Pvalue
AUD	ARHGAP15	Brain Substantia nigra	5.50E-05
AUD	KCNH7	Lung	7.59E-05
NUD	PCDH9	Brain Spinal cord cervical c-1	2.45E-09
NUD	PCDH9	Brain Caudate basal ganglia	2.51E-08
NUD	PCDH9	Skin Not Sun Exposed Suprapubic	5.37E-06
NUD	ZMYM4	Muscle Skeletal	4.27E-04
CUD	FRK	Brain Spinal cord cervical c-1	3.80E-04
CUD	FRK	Pancreas	3.98E-05
CUD	FRK	Colon Transverse	2.04E-04
CUD	FRK	Adipose Visceral Omentum	2.88E-05
CUD	FRK	Brain Hippocampus	8.51E-05
CUD	FRK	Small Intestine Terminal Ileum	7.76E-05
NMPOUD	FTO	Esophagus Gastroesophageal Junction	1.41E-04
NMPOUD	SPTLC1	Skin Sun Exposed Lower leg	3.31E-04
NMPOUD	SPTLC1	Cells Transformed fibroblasts	3.31E-04
NMPOUD	SPTLC1	Adipose Visceral Omentum	3.31E-04
NMPOUD	SPTLC1	Adipose Subcutaneous	3.31E-04
NMPOUD	SPTLC1	Esophagus Mucosa	3.31E-04
NMPOUD	SPTLC1	Skin Not Sun Exposed Suprapubic	3.31E-04
NMPOUD	SPTLC1	Nerve Tibial	3.31E-04
Any SUD	FRK	Brain Spinal cord cervical c-1	1.70E-04
Any SUD	FRK	Pancreas	1.74E-04
Any SUD	FRK	Colon Transverse	1.58E-04
Any SUD	FRK	Adipose Visceral Omentum	2.04E-04
Any SUD	FRK	Small Intestine Terminal Ileum	1.55E-04
Any SUD	FRK	Pituitary	3.09E-04

Supplementary table 10 Joint analysis of SNPs in four SUDs accounting for comorbidity in NESARC-III, via MTAG ($P < 5 \times 10^{-5}$), .

Disorder	SNP	Gene	Function	Chr	Pos	A1	A2	Z	N	Frq	mtag z	Pvalue (MTAG)
AUD	rs35789697	ARHGAP15	Intron	2	144248718	A	G	-4.15	8446	0.37	-4.33	1.50E-05
AUD	rs35942385	ARHGAP15	Intron	2	144208523	T	G	-3.97	8446	0.37	-4.13	3.63E-05
NUD	rs35789697	ARHGAP15	Intron	2	144248718	A	G	-3.50	8353	0.37	-4.29	1.79E-05
NUD	rs35942385	ARHGAP15	Intron	2	144208523	T	G	-3.43	8353	0.37	-4.10	4.20E-05
CUD	rs35789697	ARHGAP15	Intron	2	144248718	A	G	-2.05	4913	0.38	-4.30	1.70E-05
CUD	rs35942385	ARHGAP15	Intron	2	144208523	T	G	-1.98	4913	0.38	-4.10	4.05E-05
NMPOUD	rs35789697	ARHGAP15	Intron	2	144248718	A	G	-2.98	4305	0.38	-4.31	1.64E-05
NMPOUD	rs35942385	ARHGAP15	Intron	2	144208523	T	G	-2.70	4305	0.38	-4.11	3.94E-05

Supplementary table 11 Multivariate analysis of four SUDs via TATES ($P < 10^{-4}$) in NESARC-III.

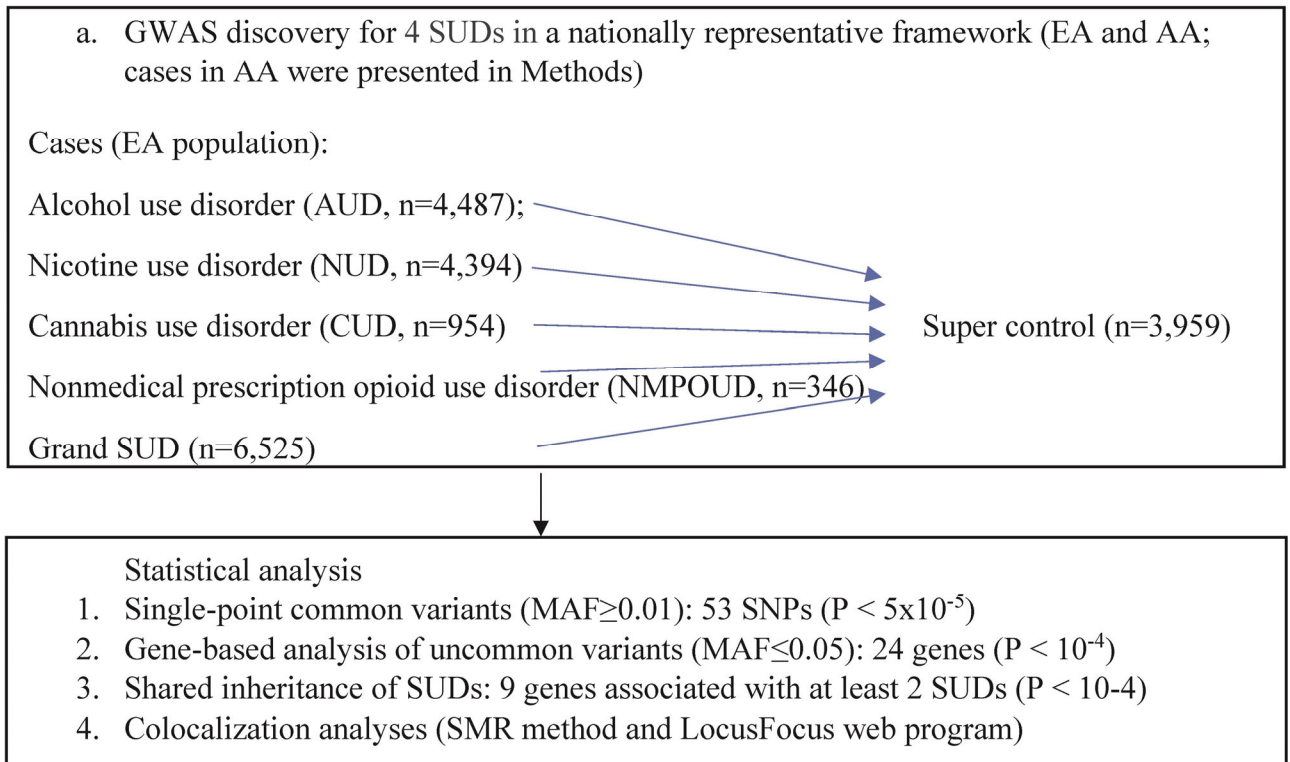
SNP	Gene	Function	n phen	Pvalue-AUD	Pvalue - NUD	Pvalue - CUD	Pvalue - NMPOUD	Pvalue-Multivariate
rs4574131	KCNH7	Intron	4	6.39E-06	1.98E-02	2.49E-01	1.54E-03	2.50E-05
rs10930073	KCNH7	Intron	4	8.83E-06	3.04E-02	3.02E-01	3.26E-03	3.45E-05
rs12476629	Intergenic	Intergenic	4	8.88E-06	2.13E-02	2.85E-01	2.85E-03	3.47E-05
rs12465289	KCNH7	Intron	4	1.05E-05	2.28E-02	2.67E-01	2.21E-03	4.11E-05
rs16847467	Intergenic	Intergenic	4	1.15E-05	2.53E-02	2.89E-01	2.60E-03	4.47E-05
rs4888599	Intergenic	Intergenic	4	3.45E-03	1.26E-05	2.01E-04	8.71E-04	4.90E-05
rs10180917	KCNH7	Intron	4	1.36E-05	3.30E-02	3.31E-01	2.79E-03	5.30E-05
rs3756772	FRK	Nonsynonymous	4	9.28E-05	7.30E-05	1.41E-05	5.76E-01	5.49E-05
rs10171918	KCNH7	Intron	4	1.56E-05	2.68E-02	3.28E-01	4.54E-03	6.09E-05
rs12476040	KCNH7	Intron	4	1.59E-05	3.15E-02	3.41E-01	3.09E-03	6.19E-05
rs10169170	KCNH7	Intron	4	1.64E-05	2.77E-02	3.38E-01	2.00E-03	6.41E-05
rs3912909	KCNH7	Intron	4	1.71E-05	3.51E-02	3.11E-01	2.65E-03	6.67E-05
rs1424233	Intergenic	Intergenic	4	3.65E-02	4.25E-02	3.10E-01	1.89E-05	7.36E-05
rs11898091	KCNH7	Intron	4	1.93E-05	3.46E-02	3.12E-01	3.12E-03	7.54E-05
rs1057149	TAP1	Nonsynonymous	4	2.30E-02	1.64E-01	1.99E-05	8.11E-02	7.79E-05
rs41550019	TAP1	Nonsynonymous	4	2.29E-02	1.66E-01	2.02E-05	8.19E-02	7.90E-05
rs4667768	KCNH7	Intron	4	2.12E-05	3.36E-02	3.66E-01	2.49E-03	8.27E-05
rs4933836	NRG3	Intron	4	5.49E-02	3.77E-03	2.14E-05	6.95E-01	8.37E-05
rs3912911	KCNH7	Intron	4	2.25E-05	3.12E-02	3.00E-01	3.16E-03	8.78E-05
rs12611890	KCNH7	Intron	4	2.34E-05	4.23E-02	3.55E-01	2.59E-03	9.14E-05
rs1389092	KCNH7	Intron	4	2.34E-05	4.21E-02	2.88E-01	4.66E-03	9.15E-05
rs3912910	KCNH7	Intron	4	2.36E-05	3.67E-02	3.35E-01	2.74E-03	9.21E-05
rs9646728	KCNH7	Intron	4	2.48E-05	5.00E-02	3.10E-01	4.20E-03	9.69E-05
rs4667759	KCNH7	Intron	4	2.51E-05	3.43E-02	3.58E-01	3.61E-03	9.81E-05
rs7330064	PCDH9	Intron	4	4.23E-03	2.55E-05	2.56E-02	2.29E-01	9.95E-05

Supplementary table 12 Replication signals for SNPs/genes reported in Table 1 for NESARC-III in other large GWAS for alcohol/nicotine/drug related phenotypes (P<0.05).

Disorder	Chr	Pos	SNP	Genea	Ref	Alt	Pvalue (NESARC-III)	Trait and Pvalue in large GWAS (same SNP or SNPs in the same gene)
AUD	2	163678535	rs4574131	KCNH7	T	G	6.39E-06	AUDIT; P=4.62E-02 (Sanchez-Roige, S. 2019)
AUD	2	163689483	rs10930073	KCNH7	C	T	8.83E-06	Drink per week; P=1.17E-04 (Liu, M. 2019)
AUD	2	163703739	rs12476629	Intergenic	T	G	8.88E-06	AUDIT; P=4.90E-02 (Sanchez-Roige, S. 2019)
AUD	2	163682494	rs12465289	KCNH7	G	T	1.05E-05	Drink per week; P=1.35E-04 (Liu, M. 2019)
AUD	2	163696863	rs16847467	Intergenic	A	G	1.15E-05	Drink per week; P=9.89E-05 (Liu, M. 2019)
AUD	2	163691715	rs10180917	KCNH7	T	A	1.36E-05	Drink per week; P=1.30E-04 (Liu, M. 2019)
AUD	2	163692689	rs10171918	KCNH7	G	A	1.56E-05	Drink per week; P=1.32E-04 (Liu, M. 2019)
AUD	2	163687672	rs12476040	KCNH7	T	C	1.59E-05	Drink per week; P=1.18E-04 (Liu, M. 2019)
AUD	2	163692347	rs10169170	KCNH7	G	A	1.64E-05	Drink per week; P=1.45E-04 (Liu, M. 2019)
AUD	2	163669642	rs3912909	KCNH7	G	T	1.71E-05	Drink per week; P=1.38E-04 (Liu, M. 2019)
AUD	2	163690219	rs11898091	KCNH7	C	T	1.93E-05	Drink per week; P=1.16E-04 (Liu, M. 2019)
AUD	2	163694878	rs4667768	KCNH7	C	G	2.12E-05	Drink per week; P=1.12E-04 (Liu, M. 2019)
AUD	2	163670203	rs3912911	KCNH7	C	T	2.25E-05	Drink per week; P=1.92E-04 (Liu, M. 2019)
AUD	2	163681163	rs12611890	KCNH7	G	A	2.34E-05	Drink per week; P=1.28E-04 (Liu, M. 2019)
AUD	2	163689167	rs1389092	KCNH7	G	T	2.34E-05	Drink per week; P=1.28E-04 (Liu, M. 2019)
AUD	2	163669750	rs3912910	KCNH7	G	A	2.36E-05	Drink per week; P=1.99E-04 (Liu, M. 2019)
AUD	2	163684757	rs9646728	KCNH7	A	G	2.48E-05	Drink per week; P=1.12E-04 (Liu, M. 2019)
AUD	2	163680351	rs4667759	KCNH7	C	T	2.51E-05	Drink per week; P=1.39E-04 (Liu, M. 2019)
AUD	2	144248718	rs35789697	ARHGAP15	G	A	3.25E-05	Alcohol Dependence; P=1.18E-02 (Walters, R.K 2018)
AUD	2	163666127	rs7601793	KCNH7	G	A	3.25E-05	Drink per week; P=1.30E-04 (Liu, M. 2019)
AUD	2	163694024	rs10221628	KCNH7	C	G	3.70E-05	Drink per week; P=1.15E-04 (Liu, M. 2019)
NUD	6	150390149	rs72501734	ULBP3	G	C	1.10E-05	rs150836130: Cigarettes Per Day; P=1.87E-02 (Liu, M. 2019)
NUD	16	77154226	rs4888599	Intergenic	C	G	1.26E-05	intergenic
NUD	13	67697374	rs7330064	PCDH9	C	G	2.55E-05	rs9571688: Cigarettes Per Day; P=1.42E-06 (Liu, M. 2019)
NUD	1	35847032	rs34924462	ZMYM4	G	A	2.59E-05	rs554746273: Cigarettes Per Day; P=5.98E-03 (Liu, M. 2019)
NUD	12	10383316	rs10772246	Intergenic	A	G	2.62E-05	intergenic
NUD	10	84098252	rs7918769	NRG3	T	A	3.34E-05	Cigarettes Per Day; P=3.46E-02 (Liu, M. 2019)
NUD	10	84098752	rs3897738	NRG3	C	T	3.58E-05	Cigarettes Per Day; P=3.11E-02 (Liu, M. 2019)
NUD	10	84094771	rs3862550	NRG3	T	C	3.66E-05	Cigarettes Per Day; P=3.03E-02 (Liu, M. 2019)
NUD	16	22237118	rs9935059	EEF2K	A	G	3.69E-05	rs528623954: Cigarettes Per Day; P=8.69E-03 (Liu, M. 2019)

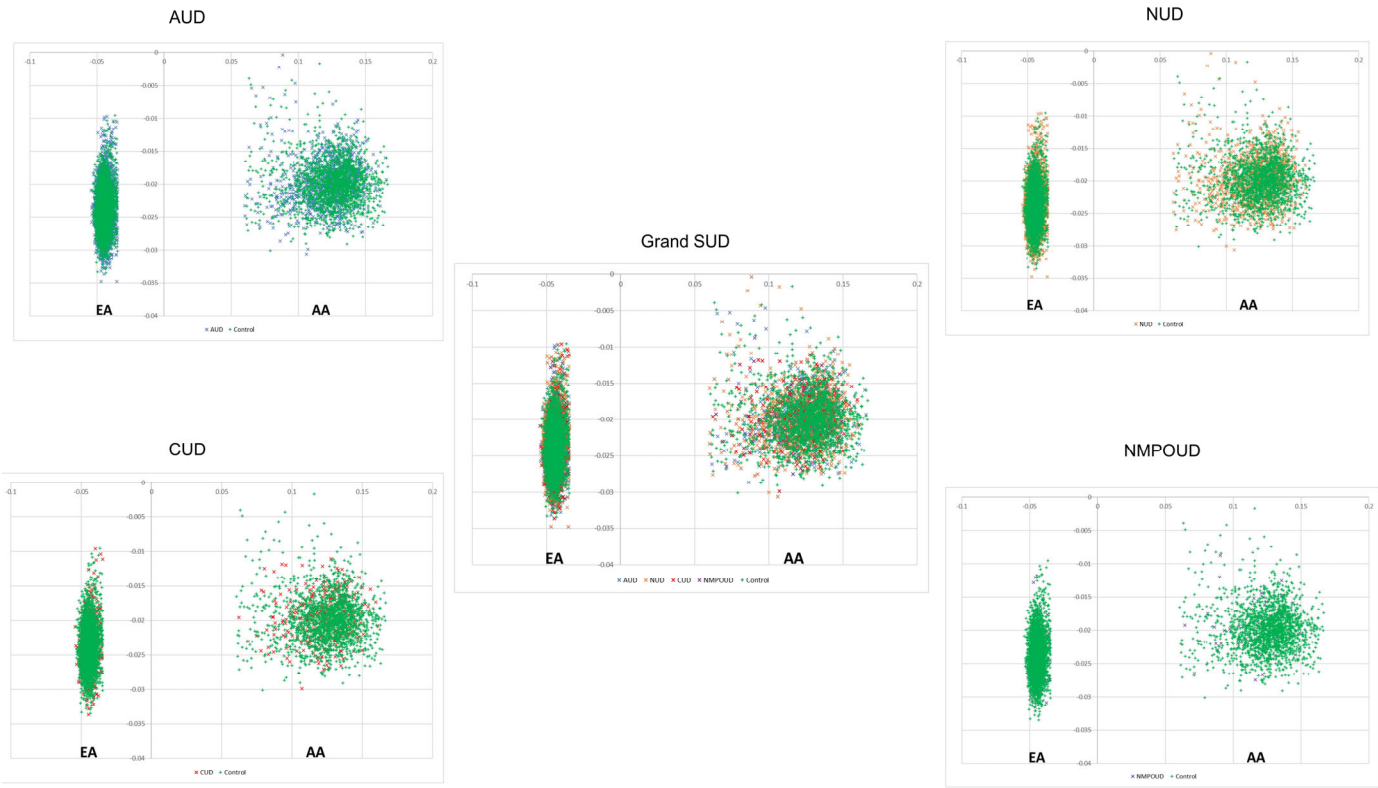
NUD	16	22237273	rs17841292	EEF2K	C	G	3.96E-05	rs528623954: Cigarettes Per Day; P=8.69E-03 (Liu, M. 2019)
NUD	10	84110564	rs7917348	NRG3	A	G	4.38E-05	Cigarettes Per Day; P=4.10E-02 (Liu, M. 2019)
NUD	10	84087761	rs7476649	NRG3	C	T	4.84E-05	rs79723357; Cigarettes Per Day; P=2.69E-05 (Liu, M. 2019)
NUD	10	84113099	rs11193893	NRG3	A	G	4.87E-05	Cigarettes Per Day; P=4.16E-02 (Liu, M. 2019)
NUD	10	84117730	rs12248513	NRG3	G	A	4.99E-05	Cigarettes Per Day; P=3.64E-02 (Liu, M. 2019)
CUD	6	116325142	rs3756772	FRK	C	T	1.41E-05	rs17077492: CUD; P=6.41E-03 (Demontis, D. 2019)
CUD	6	32814942	rs1057149	TAP1	C	T	1.99E-05	rs55874331: AUD; P=2.04E-02 (Kranzler, H.R 2019)
CUD	6	32816772	rs41550019	TAP1	C	A	2.02E-05	rs55874331: AUD; P=2.04E-02 (Kranzler, H.R 2019)
CUD	10	84137873	rs4933836	NRG3	C	T	2.14E-05	rs34940289: CUD; P=5.58E-03 (Demontis, D. 2019)
CUD	10	84168912	rs10787129	NRG3	T	A	2.93E-05	rs34940289: CUD; P=5.58E-03 (Demontis, D. 2019)
CUD	6	625673	rs2294669	EXOC2	C	G	4.51E-05	Smoking Initiation; P=3.61E-02 (Liu, M. 2019)
CUD	15	58862825	rs71478677	Intergenic	C	T	4.66E-05	intergenic
NMPOUD	16	79682751	rs1424233	Intergenic	T	C	1.89E-05	intergenic
NMPOUD	16	53769677	rs6499640	FTO	G	A	2.58E-05	AUD; P=3.20E-03 (Kranzler, H.R 2019)
NMPOUD	9	94821861	rs12237598	SPTLC1	A	G	4.96E-05	rs147565708: OUD; P=1.25E-02 (Zhou, H. 2020)
Any SUD	16	77154226	rs4888599	Intergenic	C	G	6.74E-06	intergenic
Any SUD	12	11183108	rs12318612	TAS2R31	G	C	8.78E-06	Cigarettes Per Day; P=3.20E-02 (Liu, M. 2019)
Any SUD	15	36139024	rs2646782	LOC100507466	A	G	1.19E-05	Cigarettes Per Day; P=3.76E-02 (Liu, M. 2019)
Any SUD	19	58861808	rs145144275	A1BG	A	G	2.86E-05	Smoking Cessation; P=2.97E-03 (Liu, M. 2019)
Any SUD	7	115335567	rs78431260	Intergenic	C	T	3.07E-05	Intergenic
Any SUD	15	22816713	rs8035524	Intergenic	A	C	3.56E-05	Intergenic
Any SUD	7	115336270	rs74960260	Intergenic	T	C	3.87E-05	Intergenic
Any SUD	6	116325142	rs3756772	FRK	C	T	4.58E-05	rs76882893: Alcohol dependence; P=2.11E-02 (Walters, R.K 2018)

Supplementary Fig. 1 Study design of NESARC-III SUD GWAS and analysis of cross-transmission of four SUDs.

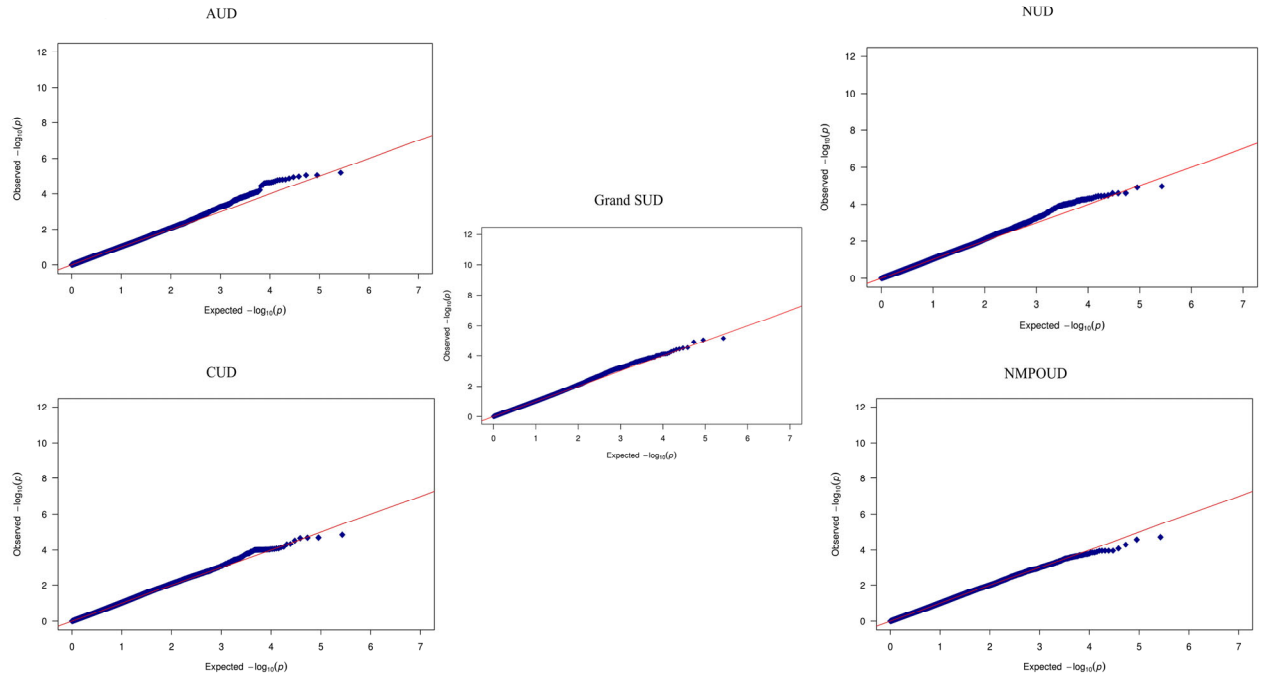


- b. Prediction of severe, moderate and mild SUD by 4 SUD polygenic scores (PGS)
- c. Phenotypic correlation and genetic correlation.

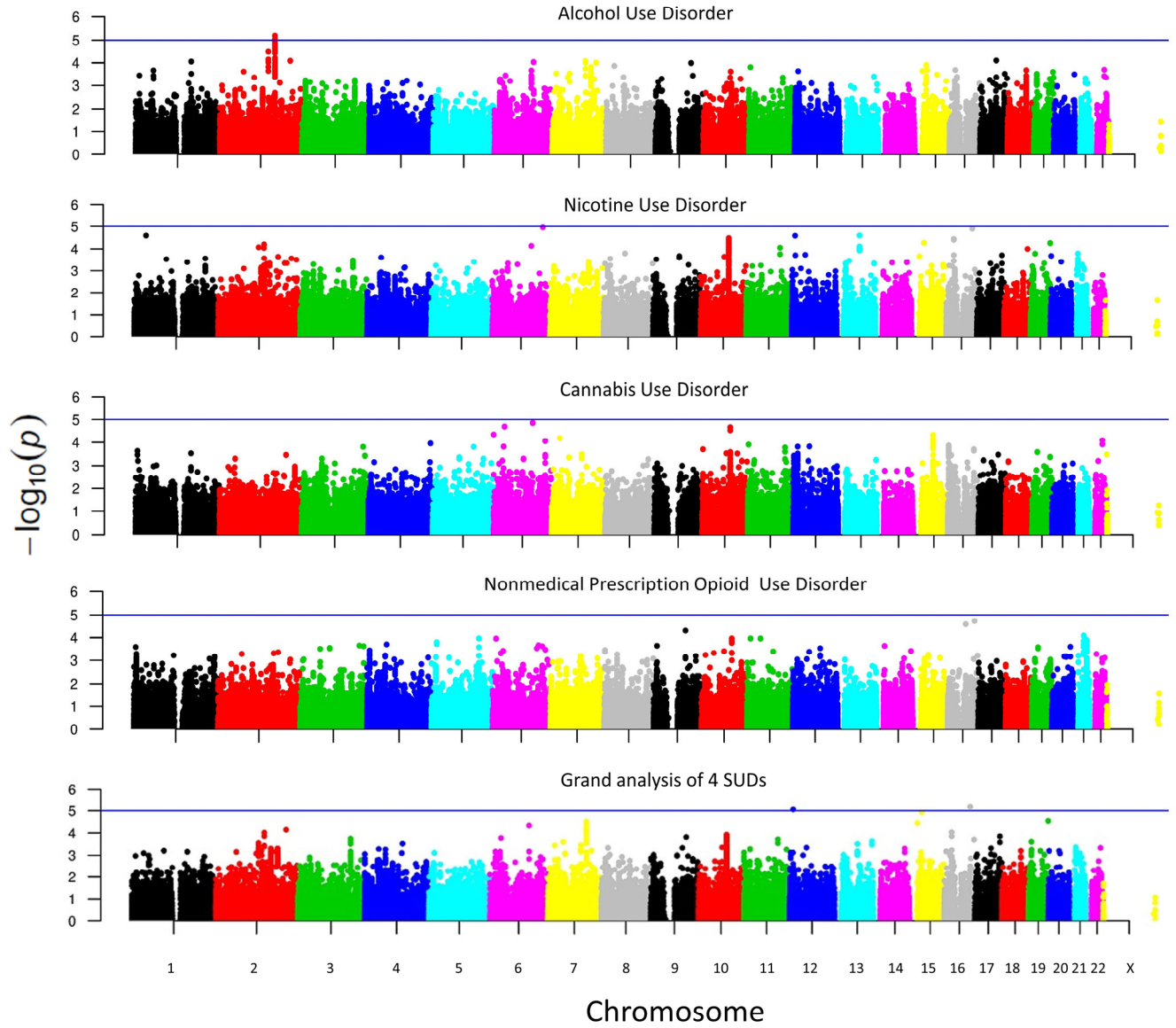
Supplementary Fig. 2 Multidimensional scaling (MDS) plots with the top two MDS scores for cases and controls in EA and AA from NESARC-III.



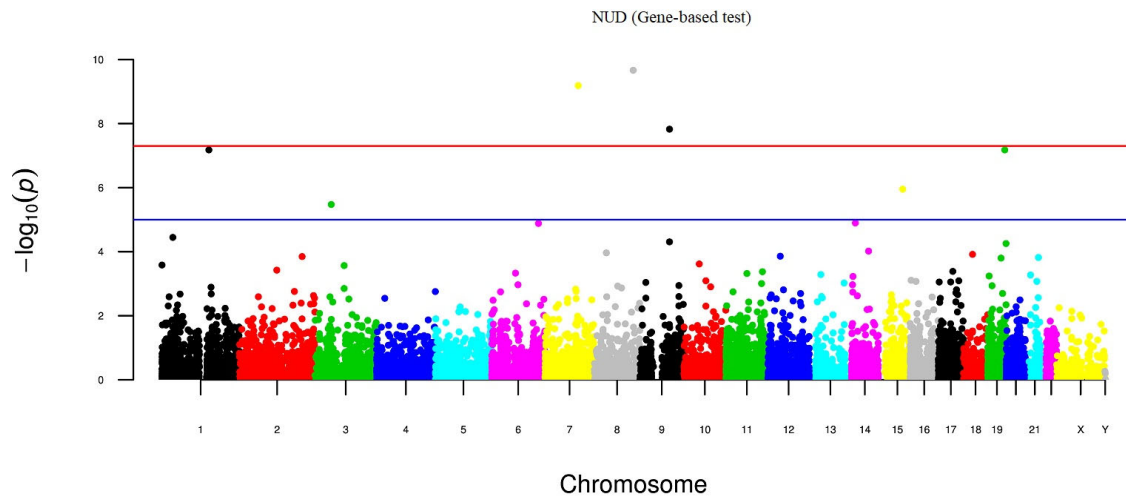
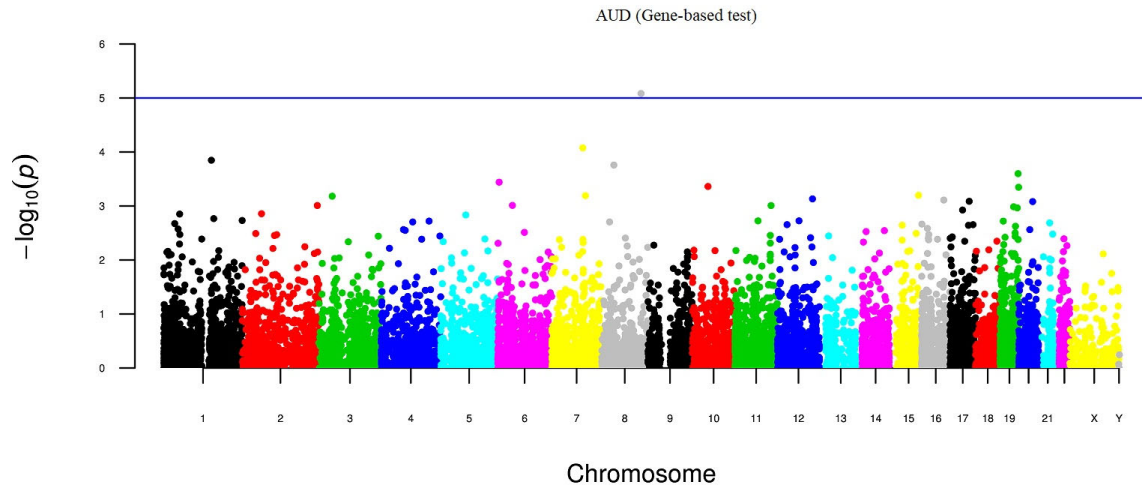
Supplementary Fig. 3 Quantile–quantile (QQ) plots for GWAS of four SUDs and Grand analysis of 4 SUDs GWAS in NESARC-III EA. Lambda values were AUD:1.02, NUD:1.03, CUD:1.03, NMPOUD:1.01, and any SUD:1.01.

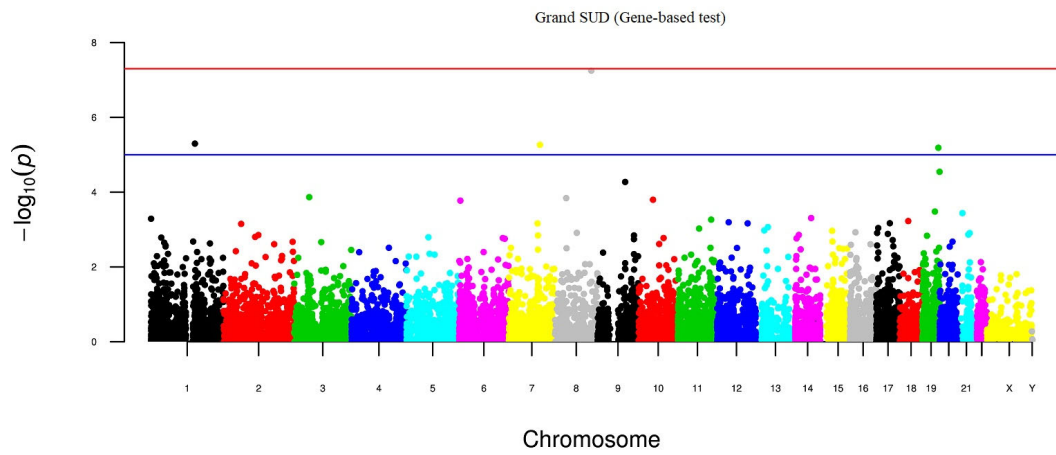
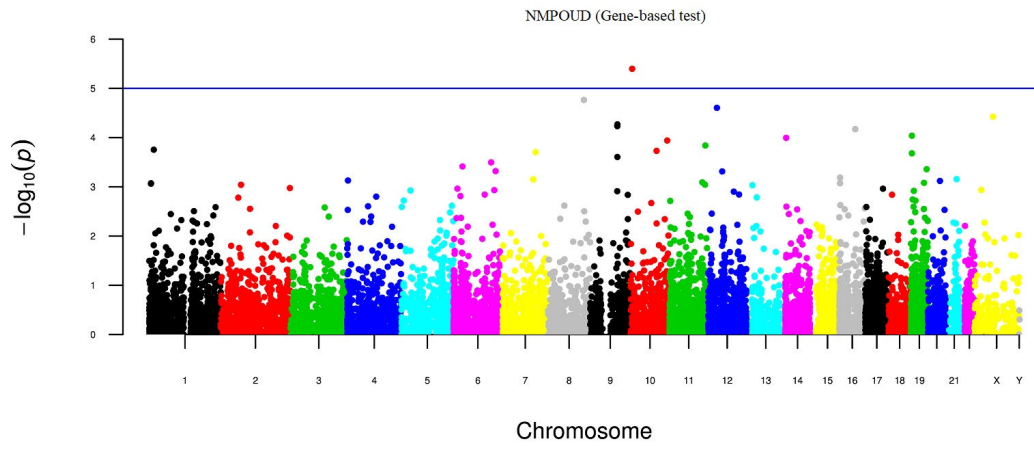
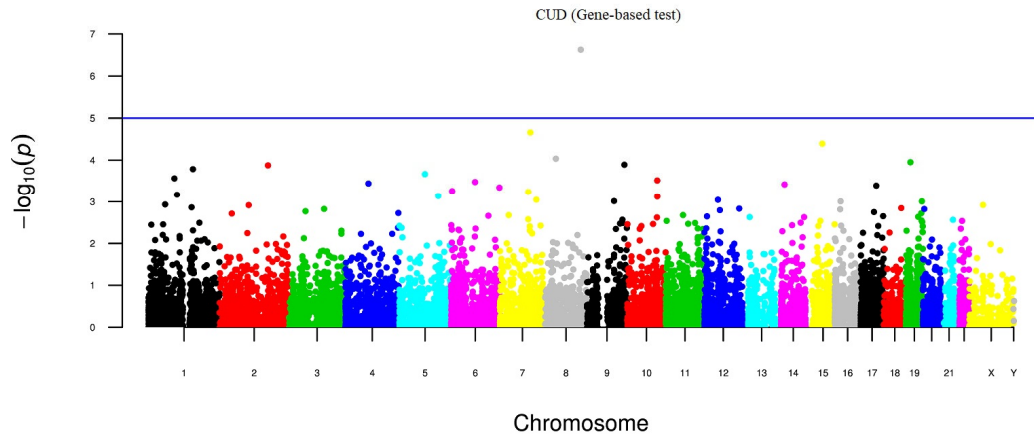


Supplementary Fig. 4 Manhattan plots of exome-wide association for four substance use disorders in EA in the NESARC-III sample. $-\log_{10}$ of the score test P value for 134,238 directly genotyped common variants ($MAF \geq 0.01$). The blue line is $P < 10^{-5}$.



Supplementary Fig. 5 Manhattan plot (Gene-based test for uncommon variants) of gene-based (exome-wide) association of four SUDs in NESARC-III EA. $-\log_{10}$ of the score test P value for gene-based test with uncommon variants ($MAF \leq 0.05$), with genome wide significant $P < 5 \times 10^{-8}$ highlighted in red and $P < 1 \times 10^{-5}$ in blue.





Supplementary Fig. 6 Genes pleiotropically affecting multiple SUDs in NESARC-III identified from single-point analysis ($P < 5 \times 10^{-5}$), and gene-based association of uncommon variants ($P < 10^{-4}$), Multi-trait analysis controlling for comorbidity via MTAG ($P < 5 \times 10^{-5}$), multivariate test on 4 SUD via TATES ($P < 10^{-4}$).

<i>NRG3</i>		■	■			■
<i>FRK</i>			■		■	■
<i>FER1L6</i>	■	■	■	■	■	
<i>OMD</i>		■		■	■	
<i>TUFT1</i>		■			■	
<i>KCNH7</i>						■
<i>PCDH9</i>						■
<i>TAP1</i>						■
<i>ARHGAP15</i>	■	■	■	■		

AUD NUD CUD NMPOUD Grand SUD 4SUD

■	single-point
■	Gene-based (uncommon variants)
■	Single-point; Multi-trait analysis (MTAG)
■	Multivariate test: 4SUD (TATES program)

Supplementary Fig. 7 Clinical (phenotypic) correlation vs. genetic correlation across pairs of SUDs in NESARC-III (n=12,505 EA samples). Genetic correlations were calculated as pairwise correlations between polygenic scores (PGS) of 2 SUDs, where PGS scores were formulated on the basis of external large GWAS (except for CUD for which we used NESARC-III CUD GWAS) summary statistics. Phenotypic correlations were derived as the phi correlation coefficient (r_ϕ) between a pair of SUDs.

