Influence of dopamine-related genes on craving, impulsivity, and aggressiveness in Korean males with alcohol use disorder

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Background

The development of alcohol use disorder(AUD) progresses from impulsive drinking to compulsive alcohol intake via repeated binge drinking, withdrawal, and craving. The dopamine system, which plays a crucial role in various cognitive and reward processes, as well as risk-taking and impulsive behaviors, is a promising target for understanding the underlying molecular mechanism and treatment of AUD.

Recent evidence has suggested that abnormality of dopaminergic neurotransmission is implicated in the pathophysiology of AUD. Several studies have shown associations between dopamine-related gene variants and alcohol-related severity and cravings in patients with AUD. The aim of the study was to examine the genetic influence of dopamine system on the problematic drinking, impulsivity and aggression in a Korean male population with alcohol use disorder (AUD).

Methods

Participants: 295 males with AUD (Korean)

Measurements: Alcohol Use Disorders Identification Test (AUDIT), Obsessive-Compulsive Drinking Scale (OCDS), UPPS-P Impulsive Behavior Scale (UPPS-P), Buss-Perry Aggression Questionnaire (BPAQ) and Beck Depression Inventory (BDI)

Genetic polymorphism selection and genotyping

- 6 polymorphisms of dopamine-related genes, 1) 5 SNPs - rs4532 in *DRD1*, rs2283265 in *DRD2*, rs6280 in *DRD3*, rs1800497 in *ANKK1* and rs4680 in *COMT* genes

2) VNTRs of the *DAT1* gene

The analyses were conducted with the R package SNPassoc, statistical significance was set at $p < 0.0083$ after Bonferroni correction.

Results

A significant association was detected between *DRD3* SNP rs6280 and OCDS score ($p = 0.0061$). With respect to impulsivity and aggression, rs4532 of *DRD1* was significantly related to UPPS-P score ($p = 0.0037$). Although it did not reach statistical significance after correction for multiple comparisons, rs4532 also showed nominally significant association ($p = 0.0261$) with BPAQ score.

Table 1. Socio-demographic and clinical characteristics of the study sample

	[a]AUD (n=295)
Age, years	48.40 ± 7.87
Education, years	13.62 ± 3.91
Duration of AUD, years	17.62 ± 10.46
AUDIT	26.70 ± 7.69
OCDS	19.07 ± 7.29
UPPS-P	140.47 ± 18.05
BPAQ	71.54 ± 18.11
BDI	18.98 ± 12.58

Table 2. Characteristics of dopamine-related gene variants in the study

Gene	rs number	Chr	Position[a]	Geno[b]	P_{HWE}[c]	MAF	D/d[d]	Function
DRD1	rs4532	5	174870150	99.3	0.3990	0.119	A/G	5 prime UTR variant
DRD2	rs2283265	11	113285536	99.0	0.9061	0.457	G/T	Intron variant
DRD3	rs6280	3	113890815	98.3	0.4604	0.272	A/G	Missense variant
ANKK1	rs1800497	11	113270828	98.3	0.7210	0.434	G/A	Missense variant
COMT	rs4680	22	19951271	99.7	0.5607	0.276	G/A	Missense variant
DAT1	VNTR	5	1393746 - 1393824	99.7	0.2687	0.06	10R≤/9R≥	3 prime UTR variant

Table 3. The effects of dopamine-related gene variants on the severity of AUD

			AUDIT					OCDS				
rs number	D/d[a]	DD/Dd/dd[b]	DD[c]	Dd[c]	dd[c]	Mean difference (95% CI)	p[d]	DD[c]	Dd[c]	dd[c]	Mean difference (95% CI)	p[d]
rs4532	A/G	225/66/2	27.20 ±0.50	25.06±0.97		-1.724 (-3.66,0.22)	0.0825	19.61 ±0.49	17.13±0.81		-2.128 (-3.82,-0.44)	0.0141
rs2283265	G/T	85/147/60	26.87 ±0.83	26.82 ±0.63	26.35 ±1.04	0.0309 (-1.14,1.20)	0.9589	19.52 ±0.84	19.35 ±0.61	17.78 ±0.85	-0.4543 (-1.48,0.57)	0.3874
rs6280	A/G	156/110/24	26.14 ±0.61	27.65 ±0.75	26.88 ±1.48	1.1839 (-0.10,2.46)	0.0710	18.53 ±0.56	19.29 ±0.70	21.67 ±1.74	1.5753 (0.46,2.69)	**0.0061**
rs1800497	G/A	91/146/53	26.86 ±0.81	26.64 ±0.62	26.30 ±1.16	0.0168 (-1.18,1.21)	0.9780	19.78 ±0.81	19.18 ±0.60	17.53 ±0.91	-0.6972 (-1.75,0.35)	0.1942
rs4680	G/A	152/122/20	26.74 ±0.63	26.99 ±0.69	24.55 ±1.69	-0.4360 (-1.76,0.88)	0.5180	19.24 ±0.57	18.80 ±0.68	19.30± 1.80	-0.1453 (-1.31,1.01)	0.8061
DAT1 VNTR	≥10R/≤9R	261/31/2	26.55 ±0.48	27.52±1.30		1.538 (-1.05,4.12)	0.2446	19.10 ±0.46	18.70±1.05		0.4090 (-1.88,2.70)	0.7264

Table 4. The effects of dopamine-related gene variants on impulsivity and aggression in AUD

			UPPS-P					BPAQ				
rs number	D/d[a]	DD/Dd/dd[b]	DD[c]	Dd[c]	dd[c]	Mean difference (95% CI)	p[d]	DD[c]	Dd[c]	dd[c]	Mean difference (95% CI)	p[d]
rs4532	A/G	225/66/2	142.0 ±1.15	134.6±2.32		-6.367 (-10.63,-2.11)	**0.0037**	72.92 ±1.19	66.99±2.26		-5.3038 (-9.95,-0.65)	0.0261
rs2283265	G/T	85/147/60	140.8 ±2.06	142.0 ±1.46	136.1 ±2.24	-1.242 (-3.86,1.38)	0.3537	69.59 ±2.03	72.93 ±1.54	70.62 ±2.09	1.3059 (-1.53,4.14)	0.3671
rs6280	A/G	156/110/24	139.7 ±1.42	141.8 ±1.79	139.4 ±3.81	1.7072 (-1.18,4.59)	0.2473	72.62 ±1.37	70.55 ±1.83	68.54 ±3.54	-1.4920 (-4.55,1.56)	0.3389
rs1800497	G/A	91/146/53	141.5 ±1.96	141.9 ±1.50	134.7 ±2.22	-2.0831 (-4.75,0.58)	0.1266	70.26 ±1.95	72.93 ±1.53	70.11 ±2.31	0.9170 (-1.96,3.80)	0.5331
rs4680	G/A	152/122/20	141.3 ±1.43	139.2 ±1.69	140.5 ±3.89	-1.2109 (-4.14,1.72)	0.4188	72.11 ±1.49	69.98 ±1.49	74.05 ±4.88	-0.4783 (-3.59,2.64)	0.7635
DAT1 VNTR	≥10R/≤9R	261/31/2	140.6 ±1.12	139.1±3.22		0.0316 (-5.79,5.86)	0.9915	71.96 ±1.13	67.73±2.93		-2.715 (-8.98,3.54)	0.3958

Conclusion

Our results support that genetic variations of dopamine system may contribute to alcohol cravings and impulsivity in patients with AUD.

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