

강박장애와 도파민 D4 수용체 유전자형과의 연관성

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ABSTRACT

Association between Obsessive-Compulsive Disorder and
Dopamine Receptor D4 GeneSe Joo Kim, MD,¹ Sang Woo Yoo, MD,² Yoon Young Nam, MD,¹
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Objective : The definite causes of obsessive-compulsive disorder (OCD) are still unknown. Evidences from familial, twin and segregation studies support the role of a genetic component in the etiology of OCD. There are growing evidences that OCD has specific neurochemical and neuroanatomical basis. It has been shown that serotonergic neurons play the predominant pathophysiological role in OCD. Recently, it has also been proposed that neurotransmitters other than serotonin play a role in the pathophysiology of OCD, and a series of studies have provided evidence that dopamine is involved in some OCD patients. Therefore, the aims of this study were to investigate the association between dopamine receptor D4 (DRD4) and OCD. **Methods** : One hundred and fifteen OCD patients and 160 normal controls participated in this study. Genomic DNA was extracted from their blood. The genotypes and allele frequencies of the DRD4 polymorphism between OCD group and control group were compared. OCD patients were classified into early onset group (age of onset <17) and late onset group (age of onset ≥ 17) according to their onset age and the genotype and allele frequency were compared between two groups. Using principal component analysis, we had already derived 4 factors from 13 main contents of YBOCS checklist in the previous study and in this study, we investigated the association between these three factors and DRD4 genotypes. **Results** : In this case-control study, we could find that the L-genotype frequencies of DRD4 were significantly higher in OCD than in normal control groups (χ^2 test, $p=0.04$). There were no difference in genotype frequencies between early onset OCD group and late onset OCD group. In OCD group, patients with L-genotype had higher scores for the religious/somatic factor than the other groups (t test, $p=0.009$). **Conclusions** : The L-genotype of DRD4 may have negative effects on the development of OCD and religious/somatic factor of the obsessive-compulsive symptoms. (Korean J Psychopharmacol 2005;16(6):513-520)

KEY WORDS : Dopamine receptor D4 · Dopamine transporter · Genotype · OCD.

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D4

서론

10-12)

(obsessions)

가

가

(homogenous

illness)

(compulsions)

1)

(multidi-

mensional),

(heterogeneous)

13,14)

2)

가

(segregation study)

가

(subtype)

(symptom dimension)

3)

가

(candidate gene)

15)

가

가

16)

가

2)

(serotonin reuptake inhibitors, SRIs)가

가

가

가

17)

18)

4)

가

(30%)

5)

2)

DRD4

DRD4

가

가

가

가

가

DRD4

D4

가

6)

clo-

방법

zapine

7)

1. 연구 대상

8,9)

1) 강박장애군

D4

(DRD4)

115 Clinical Global Impression(CGI)²⁴⁾
가 Hamilton Depression Ra-
ting Scale(HDRS)²⁵⁾ Global
. Structured Assessment of Functioning(GAF)²⁶⁾ .
Clinical Interview for Diagnosis(SCID)²⁰⁾ YBOCS checklist²⁷⁾ .
. chorea가 (1)
. 가 , , , ,
, , , , , (2)
가 , 6 , , , , (3)
가 , , , , , (4)
. 115 52 4)
. 45
, 70 (factor loading)
6
. (factor score)

2) 정상 대조군

Beck Depression Inven-
tory(BDI) Beck Anxiety Inventory(BAI)
BDI 21 , BAI 22
. 195
(stratification)
(s stratified random
sampling) 160

2. 임상 양상의 평가

가²¹⁾
가 Yale - Brown Obsessive -
Compulsive Scale(YBOCS)²²⁾ YBOCS checklist²³⁾

3. 연구방법

1) 혈액의 채취 및 DNA 분리

EDTA ,
- 70
, 3 mL (cell lysis so-
lution) 9 mL 15 mL 10
3,500 rpm 10
(nuclei lysis solution) 3 mL 가 37(C 1
.
(protein pre-
cipitation solution) 1 mL 가 3,500 rpm
10 genomic DNA가
15 mL isopropanol 3 mL
가 3,500 rpm 5
70%
. 250 μL DNA rehy-
dration solution 가 4 24
DNA - 70

2) 유전자 형별(Genotyping)

(1) (PCR)

genomic DNA PCR
 . DRD4 exon III 48
 가
 , 5'-AGG TGG CAC GTC GCG CCA
 AGC TGC A-3' 5'-TCT GCG GTG GAG TCT
 GGG GTG GGA G-3' .²⁸⁾
 DNA 100 ng, 10 pmol, 1X pfu PCR
 buffer(,), 400 μM dATP, dTTP & dCTP,
 200 μM dGTP(,), 200 μM 7-Deaza-
 dGTP (Boehringer Mannheim, Germany), 5% DMSO
 2U pfu Taq 20 ul PTC-
 100 thermal cycler(MJ research, MN, U.S.A.)
 98 5 98 45 , 55 45 ,
 72 1 35 72 5
 . DNA 20 ul 10 ul 2% agarose gel
 100 volt 1 ethidium bro-
 mide 20
 . DNA molecular 100 bp marker
 DRD4 - exon III 2~10
 (1 - 48 bp) .

3) 통계분석

DRD4

2

² test

YBOCS checklist 4가
 YBOCS , CGI, HDRS, GAF

t test . SPSS
 11.0(window version, Chicago, U.S.A.) .

결 과

1. 강박장애군과 정상 대조군의 나이 및 성별 비교

115 79
 (68.7%), 36 (31.3%)

160 가 100 (62.5%), 가 60 (37.5%)
 (p=0.31).

31.81 ± 10.71 ,

32.51 ± 6.70

(p=0.51).

YBOCS

27.3 ± 5.7 .

2. 강박장애군과 정상 대조군의 DRD4 유전자형 빈도 비교

DRD4

Hardy - Weinberg Equilibrium

2/4

4/4

가

DRD4

2

1 가 (2/2, 2/4, 2/5
 , short genotype, S) 가

(4/4, 4/5, 4/6, 4/7 , long genotype,

L)

S 16 (13.9%), L 99 (86.
 1%), S 38 (23.8%),

L 122 (76.2%) L

가

S

(p=0.04)(1).

Table 1. Genotype frequency of DRD4 gene polymorphism in obsessive-compulsive disorder patients and controls

Genotype	OCD patients (N=115)	Controls (N=160)
S-genotype		
2/2	2 (1.7%)	0 (0.0%)
2/4	13 (11.3%)	37 (23.1%)
2/5	1 (0.9%)	1 (0.6%)
L-genotype		
4/4	95 (82.6%)	115 (71.9%)
4/5	2 (1.7%)	4 (2.5%)
4/6	1 (0.9%)	1 (0.6%)
4/7	1 (0.9%)	2 (1.3%)
S-genotype*	16 (13.9%)	38 (23.8%)
L-genotype*	99 (86.1%)	122 (76.2%)

* : p=0.04 by ² test (²=4.10, df=1). S-genotype : ge-
 notypes containing at least one copy of 2 repeats, L-
 genotype : genotypes containing no 2 repeats

3. 조기 발병군과 후기 발병군의 DRD4 유전자형 빈도 비교

DRD4	17	17
DRD4	115	115
S	56 (48.7%),	59 (51.3%)
L	13 (23.2%),	43 (76.8%),
L	24 (40.7%)	35 (59.3%),
(p=0.07).		13.91 ±
2.80		27.75 ±
8.66	DRD4	56
S	7 (12.5%), L	49
(87.5%)		59 S
9 (15.3%), L		50 (84.7%)
가	(p=0.67).	

4. DRD4 유전자형에 따른 강박요인들의 심각도 비교

DRD4	S	L
1,	2	3
가	S	가
(2).		

5. DRD4 유전자형에 따른 YBOCS 점수 및 우울증상, 전반적 기능의 비교

DRD4	S	L
	YBOCS, CGI, HDRS,	
GAF		
(3).		

고찰

DRD4
DRD4
1 가 S L
L
DRD4 2~10 (im-

Table 2. Comparisons of factor scores between obsessive-compulsive disorder patients with S- and L-genotype of DRD4 polymorphism

Factor score	S-genotype (N=16)	L-genotype (N=99)	p-value
Factor 1	0.23 ± 1.05	-0.29 ± 1.01	0.06
Factor 2	-0.23 ± 1.09	0.02 ± 0.94	0.34
Factor 3	-0.34 ± 0.63	0.03 ± 1.04	0.17
Factor 4	-0.63 ± 0.59	0.04 ± 0.98	<0.01

S-genotype : genotypes containing at least one copy of 2 repeat, L-genotype : genotypes containing no 2 repeats

Table 3. Comparisons of obsessive-compulsive, depressive symptom and global function between obsessive-compulsive disorder patients with S- and L- genotype of DRD4 gene

Clinical variables	S-genotype (N=16)	L-genotype (N=99)	p-value
Total YBOCS	26.44 ± 6.69	27.42 ± 5.62	0.53
CGI	5.30 ± 0.95	5.38 ± 1.21	0.80
HDRS	17.00 ± 12.79	13.46 ± 8.75	0.16
GAF	55.13 ± 8.95	53.68 ± 9.35	0.56

S-genotype : genotypes containing at least one copy of 2 repeats, L-genotype : genotypes containing no 2 repeats

perfect) tandem 48 bp (repeat, VNTR) 3
exon (coding) 가

²⁹⁾ DRD4
Cruz DRD4
7
¹¹⁾ , Frisch DRD4
³⁰⁾ Billett 118

2~4
(multiple testing)
³¹⁾ Millet
49 63
TDT(transmission disequilibrium test) 2 trio

2

D4

2 가 ¹²⁾ Millet 가

2 가 1 S DRD4 ³⁸⁾ . Sobin

가 4 (87.5%) 가 가

2 (10.2%) 5, 6, 7

3 (phenotypic)

DRD4 가 ³⁸⁾

4/4 가 59.0%, 4 ^{39,40)}

가 75.0% ¹²⁾ 76.

4% 87.5% DRD4 가

DRD4 가 (sample)

가 1 가 (S) 가

가 (L)

DRD4 DRD4

(cut-off value) S L / 가

DRD4 48 bp (receptor protein) 3 cytoplasmic loop 가

loop G-

cytoplasmic loop (confor- 가 SSRI

mation) ³²⁾ , loop 가 ^{14,41)} SSRI

Gi- 가 ⁶⁾ 가

cAMP 가 ³³⁾ 가

5, 6, 7 S L ⁴²⁾

³⁴⁻³⁶⁾ loop

가 Gi- DRD4 S

³⁷⁾

2 가

DRD4 G- 2

(2nd messenger)

DRD4 S 가 L
 가
 가
 가 가
 , DRD4
 S L
 가 , DRD4
 L /
 가
 , 가 , DRD4
 가
 중심 단어 : D4

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