

한국인에 있어서의 뚜렛 장애와 COMT유전자간의 상관 관계에 대한 연구

ASSOCIATION BETWEEN TOURETTE DISORDER AND CATECHOL-O-METHYL TRANSFERASE (COMT) GENE IN KOREAN SUBJECTS

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연구목적 : 가 COMT (,)
)
방 법 : 가
Kiddie - Schedule for Affective Disorders and Schizophrenia - Present and
Lifetime Version(K - SADS - PL)
YGTS
가
Symptom CheckList - 90(SCL - 90) Structured Clinical Interview for DSM -
(SCID -) 가 가 42 ,
84 , 86 catecholamine - O - methyl -
transferase(COMT) Val158Met
TDT
결 과 : L LL 가
TDT 가 가
결 론 : 가 TDT 가
COMT 가
중심 단어 : · COMT

가 , 0.05~0.1%
서 론

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1-3) 가
DSM - IV K - SADS - PL
4-6) 가 가 가 가 , test - retest
7) 가 가
100% 가 가 (segregation analysis) 22) 가 가 0.91
8-11) 가 가 (segregation analysis)
12) 가 (penetrance rate) 가
13) 가
14) 가 가 (Yale Global Tic Severity Scale : YGTSS)
15)16) 가 가
17) 가 가 K - WISC ADS
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1. 연구대상

2. 유전자형 연구(Genotyping)
Genomic DNA
standard phenol/chloroform method(Invitrogen Easy - DNATM Kit,Boehringer Mannheim, SanDiego, California, USA)
COMT Val158Met polymorphism oligonucleotide primer 5' - TCG TGG ACG CCG TGA TTC AGG - 3' 5' - AGG TCT GAC AAC GGG TCA GGC - 3' (Bioneer, Seoul, Korea)
217 - bp PCR PCR
Nla (New England Biolabs, Beverly, Mass.)

COMT

37 6 . 0.5% ethidium bromide (30.9%), (7.1%),
 2% Metaphor agarose gel 35 100V (7.1%), (4.7%) 가
 gel 28% IQ 107.4
 (restriction fragment) 114, 83, 20bp COMTH
 allele , 96, 83, 20, 18bp COMTL allele 가 (Table 1).
 Tiihonen
 31)

3. 통계 분석

SPSS v11.0(SPSS Inc., Chicago, IL)

1) - : ,
 chi - square

2) 가 : Transmission Disequilibrium Test
 (TDT) - ,
 가 transmission status 가 .(²=15.7, df=1, p<0.01)

3)
 t - test ANOVA

결 과

가 42 , 84
 , 86 가 . Table 1
 42 ,

Table 1. Demographic and clinical characteristics of the subjects with tourette's disorder

Age(years)	10.4(4.6)
Sex(number & frequency of male)	36 (85.7%)
Education(grade in primary school)	4.2(2.6)
Comorbidity	
OCD	3 (7.1%)
ADHD	13 (30.9%)
Anxiety disorder	3 (7.1%)
Others	2 (4.7%)
Family loading	
Tic	11 (28.5%)
OCD	3 (7.1%)
ADHD	6 (14.3%)
IQ score	107.4(12.1)

For continuous variables(Age, Education, IQ) mean and standard deviation are reported and, for categorical variables (Sex, Ethnicity, Comorbidity, Family loading), number and percent are reported

1. 대립유전자 분포(The allele frequencies for COMT in TD proband and controls : Table 2)

Hardy - Weinberg 가 .
 COMT H
 28(33.3%) 90(52.3%) , L
 56(66.7%) 82(47.7%) .

COMT L
 가 .(²=15.7, df=1, p<0.01)

2. 유전자형의 분포(The genotype frequencies for COMT in TD proband and control : Table 2)

HH, HL, LL 7
 (16.7%), 14(33.3%), 21(50%) ,
 16(18.7%), 58(67.4%), 12(13.9%) . COMT
 LL
 (²=16.6, df=2, p<0.01).

3. TDT결과(TDT result for COMT in TD families : Table 3)

(uninformative transmission)
 trios genotype HH, LL
 TDT .
 28 trio . TDT , COMT

Table 2. Alleles and genotypes frequencies of a COMT polymorphism in subjects with tourette's disorder and controls

Group	Alleles*		Genotypes**		
	H N %	L N %	HH N %	HL N %	LL N %
Subjects with TD(42)	28(33.3)	56(66.7)	7(16.7)	14(33.3)	21(50.0)
Control subjects(86)	90(52.3)	82(47.7)	16(18.7)	58(67.4)	12(13.9)

* : The frequency of the COMT allele(L) was significantly higher in the patients than in the comparison subjects (²=15.7, df=1, p<0.01).

** : The frequency of the L/L genotype was significantly higher in the patients than in the comparison subjects (²=16.6, df=2, p<0.01).

Table 3. Clinical characteristics, treatment response, and comt genotypes of 42 patients with tourette's disorder

Variables	Genotypes			Analysis		
	HH(n=7) Mean(SD)	HL(n=14) Mean(SD)	LL(n=21) Mean(SD)	F	df	p
Total IQ from WISC	108.3(19.2)	106.8(23.3)	108.1(13.4)	0.78	2,41	0.92
Global improvement scale	3.2(1.4)	3.3(1.5)	2.9(1.6)	0.93	2,41	0.91
Total IQ from WISC	108.3(19.2)	106.8(23.3)	108.1(13.4)	0.78	2,41	0.92
Global improvement scale	3.2(1.4)	3.3(1.5)	2.9(1.6)	0.93	2,41	0.91
	N	N	N	F	df	p
Familial loading for OCD,TIC,ADHD				3.52	2	0.17
Positive*	4	6	10			
Negative	3	8	11			
Comorbidity for psychiatric diagnosis				3.67	2	0.15
Positive	4	9	15			
Negative	3	5	6			

*Positive : positive rating if there is at least one family member who has Tic or OCD or ADHD among first degree relatives of probands with TD. OCD : Obsessive-compulsive disorder, TIC : Tic disorder, ADHD : Attention deficit hyperactivity disorder

Table 4. TDT analysis of COMT gene in the subjects with tourette's disorder

		Not transmitted	
		L	H
Transmitted	L	6	14
	H	10	18

$T_{MCC} : \chi^2 = 0.833 (p\text{-value} > 0.75)$

(TDT : $\chi^2 = 0.083, p > 0.75$).

4. 유전형과 임상변인(COMT genotype and clinical characteristics of TD subjects)(Table 4)

가 , 가 , 가 .
가
가
고 찰
COMT (Val158 Met)가 가
L 가 , COMT L TDT 가
COMT L 가 COMT 가

가
(population stratification)
²⁴⁾
가
²⁵⁾
가
TDT 가
DRD4 7
가 (TDT)
ADHD - DRD7
가 가
가
²⁶⁾ TDT
가 HH LL 가
가 가
가
COMT 가
COMT COMT
COMT COMT 3~4

COMT

COMT 158 methionine residue
valine
(L) (LL)

25%, 30%²⁷⁾

(LH) COMT

COMT

28-30)

COMT

63
COMT
²⁰⁾
linkage

linkage

가 COMT

가

COMT 가

가 , TDT
가

COMT

Val158Met L LL 가

COMT

COMT

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**ASSOCIATION BETWEEN TOURETTE DISORDER AND
CATECHOL-O-METHYL TRANSFERASE (COMT)
GENE IN KOREAN SUBJECTS**

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Objectives : This study was conducted to investigate the association of the COMT polymorphism with the TD in Korean sample of families with TD probands. The relationship between risk alleles and specific clinical features (tic severity, comorbidity, drug response) was also explored.

Method : Patients were recruited from the Tic Disorder clinic at the Child & Adolescent Psychiatric Division of Seoul National University Hospital and assessed through 2 stage evaluation. Firstly, all the patients and parents received semistructured interview using Korean version of K-SADS-PL. Secondly all the patients received clinical interview and tic severity assessment with Korean version of YGTSS. The subjects in control group were recruited from the health promotion center in our hospital and were evaluated by SCL-90 and SCID-IV. Through these process, total of 42 children and adolescents with TD, their 84 parents and 86 control subjects were finally recruited. Genotyping for The *Val158Met* polymorphism of the COMT gene was done by standardized method. After collection of genetic data of all the patients, parents and control subjects, case-control comparison and transmission disequilibrium test was executed by SPSS version 11.

Result : From the case-control comparison, the frequency of L-allele and LL genotype was significantly higher in TD group. However, no differences were found from the TDT. No significant differences were found in family history of tic, ADHD, OCD, drug response and comorbid conditions among the three different genotypes in patients with TD.

Conclusion : Though this study results should be interpreted cautiously due to small sample size and negative finding in TDT test, this study is the first report that there is positive association between the functional polymorphism of COMT gene and TD.

KEY WORDS : Tourette's disorder · COMT gene · Genetic polymorphism.