

한국인 우울 장애 환자에서 5-HTTLPR과 항우울제의 장기 치료 반응

이화영* · 함병주* · 이민수*[†]

5-HTTLPR and Long-term Effect of Antidepressant Treatment in Korean Depressive Patients

Hwa Young Lee, M.D.,* Byung-Joo Ham, M.D.,* Min Soo Lee, M.D., Ph.D.*[†]

ABSTRACT

Background : Since serotonin neurotransmission plays an important role in the pathophysiology of depression, the drug that acts on serotonin transporter can be an effective antidepressant. The aim of this study was to investigate the relationship between serotonin transporter polymorphisms(5-HTTLPR) and the long-term effect of the antidepressant treatment.

Method : The 175 depressive patients, who met DSM-IV criteria for major depressive disorder or dysthymic disorder were enrolled into three year study. The genotypes of the patients were investigated by polymerase chain reaction of genomic DNA with promoter regions of the serotonin transporter gene. The patients were assessed by the Clinical Global Impression Scale, at the 1st visit, 8th week, 16th week, 1st year, 2nd and 3rd year after the antidepressant treatment.

Result : The genotypes of 138 patients were investigated and 128 of them finished this 1st year study and 107 remained in the study after 2-year treatment, and, 97 completed this 3-year study. The therapeutic response of each subset was not different at 8th, 16th week, but the subset with homozygote(l/l) of long variant showed a better antidepressant therapeutic response than heterozygote(l/s). The heterozygote(l/s) showed a better response than the subset with homozygote(s/s) of short variant at 1st, 2nd and 3rd year after the antidepressant treatment in CGI - global improvement score.

Conclusion : This result shows that the serotonin transporter polymorphism may be related to the long-term effect of antidepressant treatment and there may be also ethnic difference.

KEY WORDS : Depression · Serotonin transporter · Polymorphisms · Long-term · Antidepressant.

Department of Psychiatry, College of Medicine, Korea University, Seoul, Korea

[†]교신저자 : , 136-075 574 126-1
) (02) 920-5354,) (02) 923-3507 E-mail) leeminso@korea.ac.kr

서 론

가

5 - HIAA 가 ' s ' 가
 (5 - hydroxyindoleacetic acid ; 5 - HIAA) 가 .¹⁰⁾
 가 가 , Smeraldi ¹¹⁾ 102
 가
 . SSRI(Selective Serotonin re-uptake inhibitor ; SSRI) (fluvoxamine) / 5-HT1A receptor antagonist (pindolol)
¹⁾ 6
 SSRI가 가
 TCA (' l ') (l/l) (l/s)
 , (' s ') (s/s)
²⁾ SSRI
 17q11 - 12
 가 . (paroxetine)
 (intron) ¹²⁾ ,
 VNTR(variable number of tandem repeats) l/l l/s s/s
 9/10/12 copy ³⁾ ¹³⁾ 6
 (5 - HTT linked polymorphic region ; 5 - HTTLPR) 44 , s/s ¹⁴⁾
 / (insertion/depletion ; ' l ' , ' s ') ⁴⁾⁵⁾ (Caucasian)
 VNTR ³⁾⁶⁻⁸⁾가
 , VNTR 3~5 가 1
 , 5 - HTTLPR ¹⁵⁻¹⁷⁾ 가가
⁶⁾⁸⁾
 (In vitro study) (long vari- ¹⁸⁾ , ,
 ant ; ' l ' allele) (short variant ; ' s ' allele) ¹⁹⁾
 3 , 가 .
 mRNA 가 가 가
 가 가 가 ²⁰⁾ , (proband)가
⁴⁾ SSRI 가 가 , (genetic
 가 가 가 loading) ²¹⁾²²⁾
 가 ⁹⁾ , 가
 가 가 가 ,
 ' s ' 가 가 ,

TCA, MAOI, SSRI

가
가

2. 연구 방법

1) 유전자형 분석

(1) DNA

1.5ml 13,000rpm 1 pellet ACE shocking solution(NH4Cl 8g, Na2EDTAH2O 1g, KH2PO4 0.1g 1) 500 µl

3 . 2

pellet 400 µl nucleic lysis Buffer[Tris(pH 8.0) 10mM, NaCl 400 mM, EDTA 2mM] pellet

10% SDS 27 µl proteinase K 10 µl 가 56 2 saturated NaCl 135 µl 15 . 13000rpm 1 2

DNA

(lymphocyte) DNA

70% µl . 100

(2) (Polymerase Chain Reaction : PCR)

7)(11)(12)(24)

l/l , l/s s/s

가

가

가

. 128 , 1 , 2 , 3 Global Impression ; CGI),

(Clinical

연구 대상 및 방법

1. 연구 대상

1) 20~65 , 2) DSM - (American Psychiatric Association 1994)

, 3) 가

5 - HTTLPR Forward : 5` - GGC GTT GCC GCT CTG AAT GCC - 3`

5 - HTTLPR Reverse : 5` - CAG GGG AGA TCC TGG GAG AGG T - 3`

25 µl 32

가 1) , 2)

Takara GC buffer 12.5 µl, Takara LA Taq 1.5U, 10pmol/25 µl , dNTP 2.5 mM 4 µl , Template DNA 200ng 25 µl .

, 3) DSM - 가

94 30, 54 30, 72 30
 32, 72 5
 1

(3) 44 /
 5% poly acrylamide
 ethidium bromide
 (ultraviolet transilluminator)
 (polaroid, film 667)
 (4) 265bp, 221bp 1

2) 임상증상의 평가
 baseline, 8, 16, 1
 CGI (CGI-S),
 CGI-GI)
 CGI-S가 4 3

3) 통계 분석
 (l/l, l/s, s/s) 1, 2,
 CGI-S, GI
 Repeated measure ANOVA
 가 Levene test
 (p=0.606).

(Kaplan - Meier estimate) SPSS/

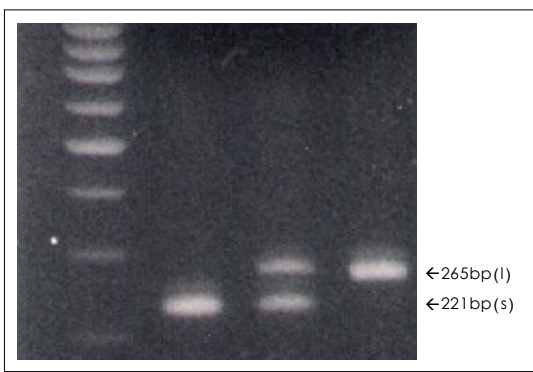


Fig. 1. The PCR products after gel electrophoresis.

PC+ version 10.0
 0.05

결 과

1. 인구사회학적 특성
 175,
 138 . 1
 128 (31, 97)
 2 107, 3 97
 l/l 8, l/s 20, s/s 100
 l/l 44.50 ± 14.16, l/s
 50.60 ± 13.58, s/s 47.77 ± 13.55,
 (1).
 , , 가
 , 가 1
 CGI-S l/l 4.37 ± 0.91, l/s 3.75
 ± 0.91, s/s 3.76 ± 0.76,
 (2).

2. 세로토닌 전달체 다형성에 따른 분포
 l/l 8 6.3%, l/s 20 15.6%,
 s/s 100 78.1%
 's' 21.9%, 93.7%

3. 세로토닌 전달체 다형성과 치료반응과의 관계
 CGI-S
 가 8, 16, 1, 2,

Table 1. Demographic data in depressive patients

	l/l	l/s	s/s
Sex			
Female	7	14	76
Male	1	6	24
Age (years)	44.50 ± 14.16	50.60 ± 13.58	47.77 ± 13.55
Age of onset (years)	38.00 ± 16.22	41.68 ± 14.01	40.64 ± 13.79
Education (years)	9.62 ± 3.29	10.77 ± 3.47	9.37 ± 4.50
Number of previous admission	0.13 ± 0.35	0.40 ± 0.68	0.25 ± 0.55
Percentile of patients with psychotic feature	25.0%	15.0%	8.0%
Percentile of patients with family history	12.5%	10.0%	6.0%

3 CGI repeated measure ANOVA
 VA *
 , CGI - GI
 가 (p=0.030). 1 ,
 2 , 3 I/I s/s
 가 . One - way
 ANOVA 가
 . 8 , 16 CGI - S, GI
 가 , 1 , 2 , 3 CGI - S
 , CGI - GI
 (3, 1 p=0.050, 2 0.041, 3
 0.034).

4. 세로토닌 전달체 다형성과 증상이 없는 재발까지의 기간과의 관계

CGI - S 4 가
 가 ,
 가 .
 가
 I/I 33.86 ± 1.98 , I/s
 34.35 ± 1.61 , s/s 31.83 ± 1.03 I/s
 > I/I > s/s ,

Table 2. The result of repeated measure ANOVA for time(1yr, 2yr, 3yr) and genotype

	df	F	p	Post Hoc Test
Genotype	2	5.002	0.009	I/I < s/s

Table 3. CGI-global improvement scores at 1st year, 2nd year and 3rd year after antidepressant treatment

Global Improvement	I/I	I/s	s/s	p
8wks	2.87 ± 0.64	2.85 ± 0.93	2.96 ± 0.86	0.117
16wks	2.75 ± 0.46	2.65 ± 0.74	2.89 ± 0.75	0.518
1 year	2.00 ± 0.92	2.35 ± 0.67	2.65 ± 0.84	0.050
2 year	2.00 ± 0.81	2.05 ± 0.42	2.44 ± 0.70	0.041
3 year	1.85 ± 0.69	2.07 ± 0.47	2.43 ± 0.71	0.034

Table 4. Symptom-free period until the recurrences and recurrence index

	I/I	I/s	s/s	p
Symptom-free time until the recurrence	33.86 ± 1.98	34.35 ± 1.61	31.83 ± 1.03	0.60
Recurrence index	0.03 ± 0.08	0.10 ± 0.17	0.13 ± 0.34	0.707

(4, p=0.60).

5. 세로토닌 전달체 다형성과 재발 지수(재발회수/유병기간)와의 관계

I/I 0.03 ± 0.08, I/s 0.10 ± 0.17, s/s 0.13 ± 0.34 . I/I 가
 , (4, p=0.707).

고찰

64 , 64
 128 CGI - S
 가 ,
 가 .
 가 , 's'
 (neurotic-
 ism : , , ,)
 ,⁵⁾
 .²⁵⁾
 가 가
 ,
 가 .

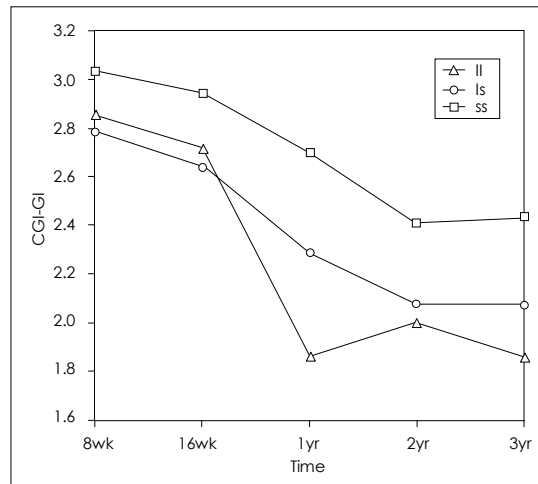


Fig. 2. CGI-GI change according to genotype for 3 years.

가 , , 8 , 16 , 1 , 2 , 3 CGI

가 . CGI Repeated mea- CGI 가 ,
 sure ANOVA , * I/I I/s, s/s .
 , CGI - GI ,
 가 가 ,
 (p=0.030). . Smeraldi ²⁸⁾

2 s/s s allele
 가 1 , 2 , 3 (transcriptional activity)
 I/I s/s 가 가 가
 . One - way ANOVA
 가 . , 8 , 16 ,
 가 , 1 , 2 , 3
 CGI - GI I/I, I/s, s/s 가 .
 I/I , I/s , s/s
 (3).

가 ' s '
 , I/I , I/s , s/s I/I ' I ' 36.5~
 가 , I/s 45% 55~63.5% ,⁴⁾⁽⁶⁾⁽²⁵⁾
 , I/I , s/s I/s 24% 76% ' I '
 s 가 ,³⁰⁾
 ' I ' allele ' s ' allele 가 가
¹¹⁾⁽¹²⁾⁽²⁴⁾⁽²⁶⁾ , I/I 가
 s/s 가
¹⁴⁾ , 가
 ' s ' allele ,²⁷⁾ 가 가
 ,
 Smeraldi ²⁸⁾ 가 ,
 , s/s 가
 가
 . Ho ²⁹⁾ 가
 , s/s 가 가
 I/s , I/I ' I ' .
 가 ¹⁹⁾ 중심 단어 : Serotonin .

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