

주요우울증에서 치료반응을 예측할 수 있는가?*

고 영 훈** · 김 용 구***†

Can We Predict Treatment Response in Major Depression?*

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ABSTRACT

Due to the high population prevalence of major depression and the strong emphasis on pharmacotherapy for this disorder, antidepressants are among the most frequently prescribed pharmacological agents. But the clinicians are still unable to predict accurately the response of their depressed patients to medication. This article reviews the biological predictors of treatment response including monoamine, neuroendocrine, pharmacogenetic, and psychophysiologic markers. The biological predictors of response, despite some interesting leads that may in the long term be of considerable importance, are not yet sufficiently established to be of routine clinical usefulness.

Many of the predictive factors explored in this article are examples of mediators and moderators that affect outcomes. Each one alone may not provide definitive answers for predicting response to treatment, but each must be taken into account at the outset of treatment. It is clear that treatments must be individualized for each patient.

It would be necessary to develop the algorithm in order to predict the responsiveness of antidepressant treatment with integration of the results from the previous studies.

KEY WORDS : Depression · Predictor · Monoamine · Neuroendocrine · Pharmacogenetics · Antidepressant.

서론 3.47% .²⁾ 가
가
3~4% 가
1) 3.31~

(0405 - NS01 - 0704 - 0001).

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1. 단가아민계의 치료반응 예측인자

가 (TCAs), (SSRIs), 가 , 가 (SNRIs) , 가 2 가 가 (MAOIs), 가 (RIMA) , , 2 , 3 (messenger) , trazodone, mianserine, mirtazapine . 가 3 - methoxy - 4 - hydroxyphenylglycol(MH- PG) . Sac- MHPG keim³⁾ 60% , . 7) MHPG 가 SSRI 가 4)5) TCA 7 - 10) . 11) MHPG 가 SSRI 가 , , 12- 15) nortriptyline¹⁴⁾ maprotiline¹⁵⁾ , amitriptyline SSRI . 12)16 - 18) MHPG , . 6) , 가 CSF . 가 , , 가 , dexamethasone suppression test (DST) , (hyperintensity) 가 , REM(Rapid Eye Move- 19 - 22) (ECT) . 가 20)23)24) John- ston²⁵⁾ 40 8 가

가
(5-HT)

가 5-HT

4)5) 가
26)27) , 5-HT 가
27) Karege

28) 5-HT

5-HT 가

paroxetine

29)30) fluvoxamine
Celada 31) 5-HT

가
가 5-HT

가

MHPG
5-hydroxyindoleacetic acid(5-HIAA)

32)
5-HIAA
33)34)

35)
5-HIAA

5-hydroxytryptophan
32) clomipramine³⁶⁾

5-HIAA amitriptyline,³⁷⁾

nortriptyline³⁸⁾

Homovanillic acid(HVA)

HVA 가

39)40)

가

가

tryptophan⁴¹⁾ amitriptyline⁴²⁾
nortrip-
tyline⁴²⁾ maprotiline⁴³⁾

가
가

(monoamine oxidase) 가 가
isocarboxid, nortriptyline, phenelzine

44)45)

가

A B

clomipramine, maprotiline

가

가 가⁴⁶⁾
catechol o- methyltransferase(CO-
가 imipramine
47)

2. 신경내분비계의 치료반응 예측인자

가

(dexamethasone suppression test : DST)
(non - suppression) ⁴⁸⁾ DST

가

DST 가 ⁵⁰⁾⁵¹⁾ DST

가

50)52)
DST 53) 54)

50)55 - 57)

DST

55)58)59)

DST 60) 61)

가 , DST
 combined dexamethasone/corticotrophin - releasing hormone test

6 가
 62)
 protirelin thy-
 rotropin clonidine
 thyrotropin
 가
 52)63)
 , 가 protirelin thyro-
 tropin thyrotropin 가가 sub-
 clinical hypothyroidism

64) Neurosteroid GABA_A
 가 dehydroepiandrosterone sulfate
 (DHEAS) 65)
 가 DHEAS
 66)

3. 약물유전학의 치료반응 예측인자 (pharmacogenetics)

가
 가
 가
 가
 transporter : 5 - HTT
 (serotonin

(serotonin reuptake inhibitors : SSRIs)

(serotonin and norepinephrine reuptake inhibitors : SNRIs)

5 - HTT 17
 SLC6A4
 , 35kb 14 exon . SLC6A4
 가 (polymorphism)
 가 (promotor)
 5 - HTT - linked polymor-
 phic region(5 - HTTLPR)
 . 44 - bp
 , long(l) short(s)
 가 long
 short 67)
 intron 2
 (variable number of tandem repeat, VNTR)
 STin2*9, Stin2*10,
 (allele)

Stin2*12
 , 5 - HTTLPR
 67)68) Intron 2 VNTR

5 - HTT
 Smeraldi 70)
 DSM -
 102
 6 fluvoxamine pindolol fluvoxamine
 placebo , 5 -
 HTTLPR genotype
 . // allele /s allele 가 ss
 allele 가 fluvoxamine
 . Fluvoxamine pindolol
 genotype
 . 5 - HT (raphe nuclei)
 (somatodendritic receptor)

5 - HT1A (ne-
 gative feedback)
 genotype
 pindolol 5 - HT1A

가
 , Smeraldi 70)

Zanardi ⁷¹⁾ 6 par-
 oxetine 5 - HTTLPR ss 가
 l allele genotype paroxetine .
 genotype ls , ls ss
 Serretti ⁷²⁾ 217 s allele
 fluvoxamine 300mg/d+placebo fluvoxamine+ l allele 가 36.5~45% 55~63.5%
 pindolol 2.5mg/d 5 - HTTLRP // genotype 80-82) 24%
 ls genotype ss genotype fluvoxamine 76% 83)
 , pindolol
 . Zanardi 5 - HTT-LPR
⁷³⁾ fluvoxamine 5 - HTTLPR (locus) 가 (linkage
 disequilibrium)
 Pollock ⁷⁴⁾ paroxetine nortriptyline Benedetti ⁸⁴⁾
 , paroxetine 5 - HTT- 5 - HTTLPR l
 LRP // genotype ls genotype ss genotype , Mundo ⁸⁵⁾
 , nortriptyline 5 -
 riptyline , nort- HTT gene
 intron 2 VNTR
 short 4~6 가 s allele 가
 12 , 5 - HTTLPR short
⁷⁵⁾ (1).
 Tryptophan hydroxylase(TPH) 5 - HT
 (rate - limiting enzyme) TPH gene
 , 5 - HTTLPR fluoxetine, paroxetine intronic A218C . TPH gene
⁷⁶⁾ 5 - HTTLPR Serretti ⁷²⁾
 short 5 -
 ss genotype // HTTLPR TPH*
 ls genotype A/A 가 fluvoxamine
 Yosida ⁷⁷⁾ 6 fluvoxamine short 5 - HTTLPR
 가 . Ser-
⁷⁸⁾ 1 , 8 , 16 retti ⁸⁶⁾ TPH paroxetine
 5 - HTTLRP genotype TPH* A/A TPH* A/C
 , pindolol
 1, 2, 3 // genotype ls , ls
 ss , Smeraldi ⁷⁹⁾ Cusin ⁸⁷⁾ 5 - HT2A
 (T102C, C - 1420T) MAO - A 30 -

Table 1. 5-HTTLPR variants and antidepressants treatment in affective disorders

Author	Sample	Duration	Treatment	Results
Smeradi et al. ⁷⁰⁾	30 BP, 69 MD	6 weeks	Fluvoxamine	l allele subjects were more likely to respond
Zanardi et al. ⁷³⁾	47 BP, 108 MD (replication sample)	6 weeks	Fluvoxamine	l allele subjects were more likely to respond
Serretti et al. ⁷²⁾	73 BP, 144 MD	6 weeks	Fluvoxamine	l allele subjects were more likely to respond
Zanardi et al. ⁷¹⁾	18 BP, 46 MD	6 weeks	Paroxetine	s allele associated with less favorable and slower response
Pollock et al. ⁷⁴⁾	95 late-life depression	12 weeks	Paroxetine	s allele associated with slower response
Benedetti et al. ⁸⁴⁾	68 BP	1 night	Sleep deprivation	l/l patients showed better mood amelioration
Mundo et al. ⁸⁵⁾	56 BP	-	SSRIs, TCAs	Patients with manic or hypomanic episodes induced by antidepressant treatment had an excess of s alleles
Kim et al. ⁷⁶⁾	120 Korean MD	6 weeks	Fluoxetine and paroxetine	s/s genotype showed better response
Yoshida et al. ⁷⁷⁾	66 Japanese MD	6 weeks	Fluvoxamine	s/s genotype showed better response
Arias et al. ⁷⁵⁾	102 MD	12 weeks	Citalopram	s/s genotype was significantly more frequent in no remission group
Lee et al. ⁷⁸⁾	175 Korean depression	3 years	TCAs, MAOIs, and SSRIs	l/l genotype showed better response

BP : Bipolar affective disorder, MD : Major depressive disorder

bp 48 - bp paroxetine fluvoxamine
 5 - HT - 2A T102C, MAOA 30 - bp Mi- D4 ,⁹²⁾ D3
 nov⁸⁸⁾ 5 - HT - 2A⁹³⁾
 His452Tyr C - allele , (ECT), (TMS)
 angiotensin - converting enzyme(ACE), dopamine D2, D4 G protein 3 subunit C825T
 TT 가 Serretti⁹⁵⁾
 protein 3 subunit Gbeta3 T/T
 Baghai⁸⁹⁾ , ECT, TMS 가 paroxetine fluvoxamine
 가⁹⁹⁾ 가 ,
 ACE I/D ACE⁹⁶⁾ 106 T allele가
 D allele , l - l
 가
 Hong⁹⁰⁾ ACE I/D ge-
 notype 4. 정신생리학의 치료반응 예측인자 EEG
 Serretti⁹¹⁾ REM
 D2 VNTR D4 ,

Table 2. Candidate Gene variants and antidepressants treatment in affective disorders

Author	Gene	Sample	Treatment	Results
Serretti et al. ⁷²⁾	TPH	73 BP, 144 MD	Fluvoxamine	A/A genotype was associated with slower response
Serretti et al. ⁸⁶⁾	TPH	34 BP, 87 MD	Paroxetine	A/A and A/C genotypes were associated with slower response
Cusin et al. ⁸⁷⁾	MAOA 5-HT2A	195 BP, 248 MD	Fluvoxamine, Paroxetine	No association
Minov et al. ⁸⁸⁾	5-HT2A	173 MD	SSRI, TCA, ECT, combinations	C containing variants associated with response
Baghai et al. ⁸⁹⁾	ACE	99 MD	Various antidepressants, ECT, TMS, combinations	D allele associated with more favorable and rapid response
Hong et al. ⁹⁰⁾	ACE	151 MD	Venlafaxine, Fluoxetine	No association
Serretti et al. ⁹¹⁾	DRD2, DRD4	167 BP, 197 MD	Fluvoxamine, Paroxetine	No association
Serretti et al. ⁹²⁾	DRD4	124 BP	Sleep deprivation	No association
Schumann et al. ⁹³⁾	DRD3	52 MD	Sleep deprivation	No association
Zill et al. ⁹⁴⁾	GNB3	10 BP, 78 MD	SSRI, TCA, ECT, combinations	TT homozygosity associated with response
Serretti et al. ⁹⁵⁾	GNB3	200 BP, 290 MD	Fluvoxamine, Paroxetine	Gbeta3 T/T variants showed better response to treatment
Lee et al. ⁹⁶⁾	GNB3	106 MD	Various antidepressants	T allele had a better response to antidepressant treatment

BP : Bipolar affective disorder, MD : Major depressive disorder

REM 가 (corrugator muscle), (zygomatic muscle) 가

97)98) 1~2 REM 가 (speech)

102) EEG (rostral anterior cingulate gyrus) Pizzagalli (Theta pause) 109)

PET 6 Mayberg 103) 결론 가

Wu 104) 가

105)106) imipramine clomipramine 107) 가 가

가 가

중심 단어 : 가

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