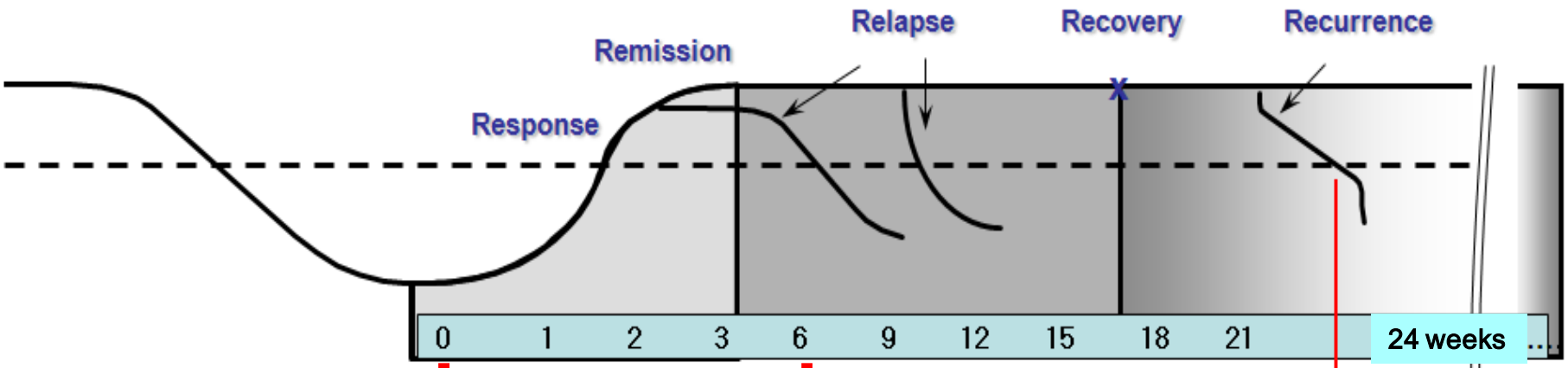
노년기 우울증의 약물유전학적 지표

성균관의대 정신과학교실
삼성서울병원 정신과
국가지정우울증치료연구실
김 도 관

Patent Cohort with DEPRESSION



Diagnosis	SCID
Severity DEP symptom	17-HAMD
	CGI-S
	CGI-I
	Suicidality
Function	GAF
Treatment related	Choice of Drug
	S/E
Confounding variables	Physical Illness
	Personality Trait
	Demographic
Blood specimen	LAB W/U
	Plasma concentration
	Genotype
	Endophenotype

Depression (mood):

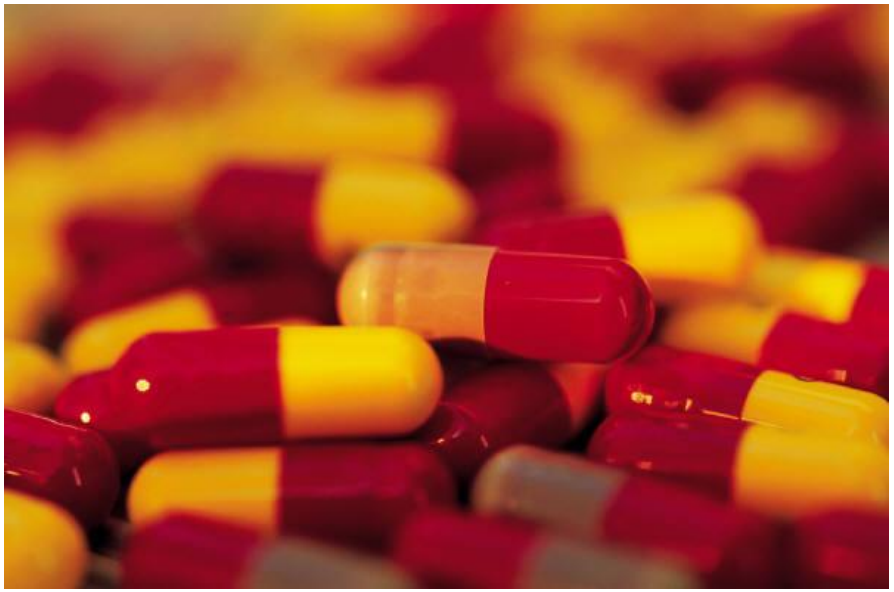
a state of low mood and aversion to activity

Experiencing feeling of sadness, helplessness and hopelessness


WPI
839
R149
WPI
839

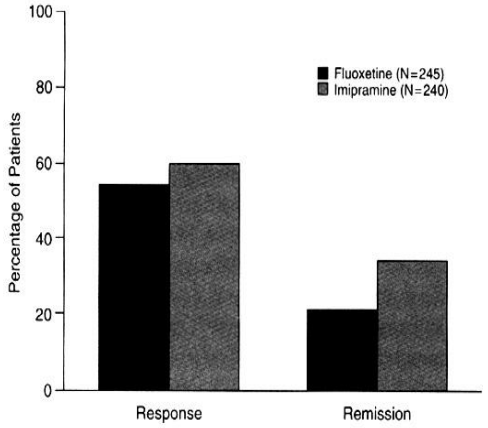
Which medication for which patients?

- Anticipated adverse events and tolerability
- History of prior response
- Comorbidity
- Patient profile
- Patient preferences
- Cost



현재 우울증 치료의 문제점

Figure 2. Response (≥ 50% decrease HAM-D-21 total score) and Remission (HAM-D-21 total score ≤ 7) in Inpatients With Major Depression[a]

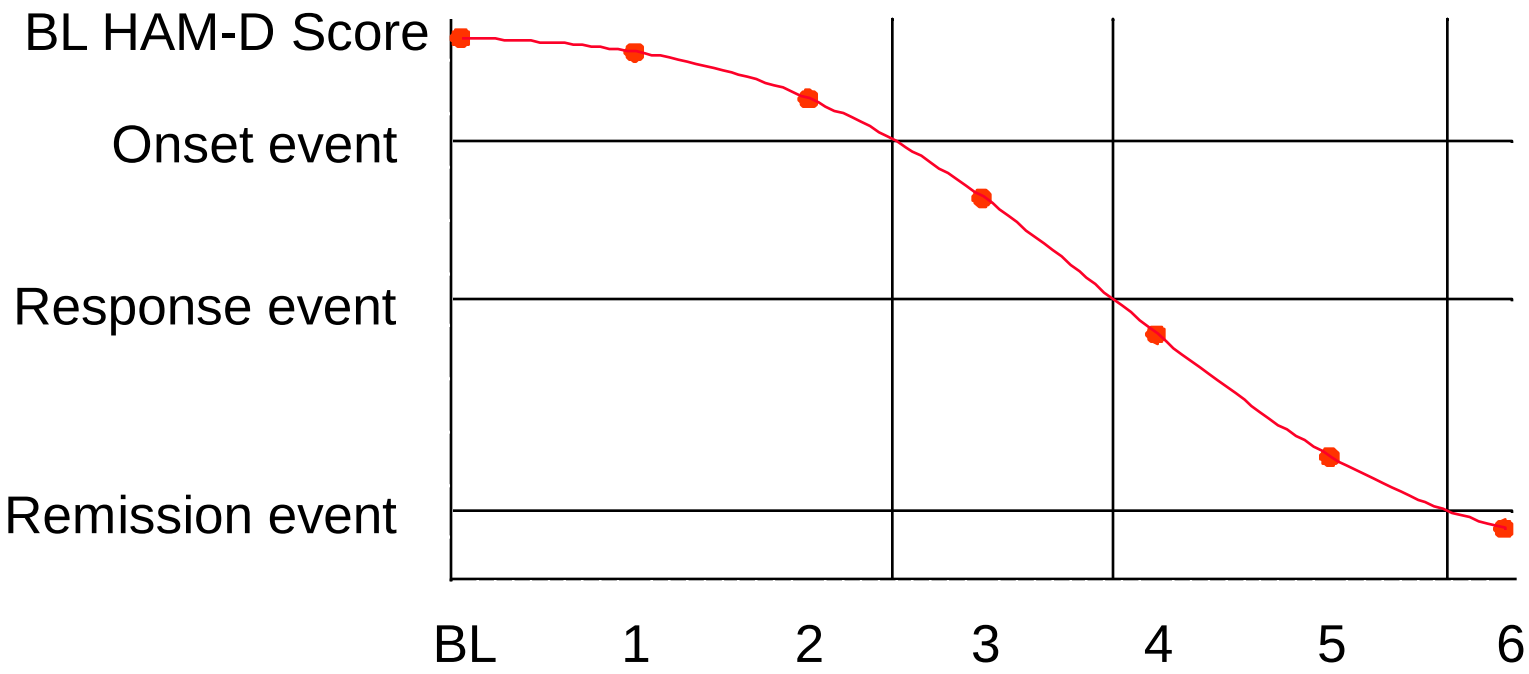


[a]Data from reference 14. Abbreviation: HAM-D-21 = 21-item Hamilton Rating Scale for Depression.

< 60%

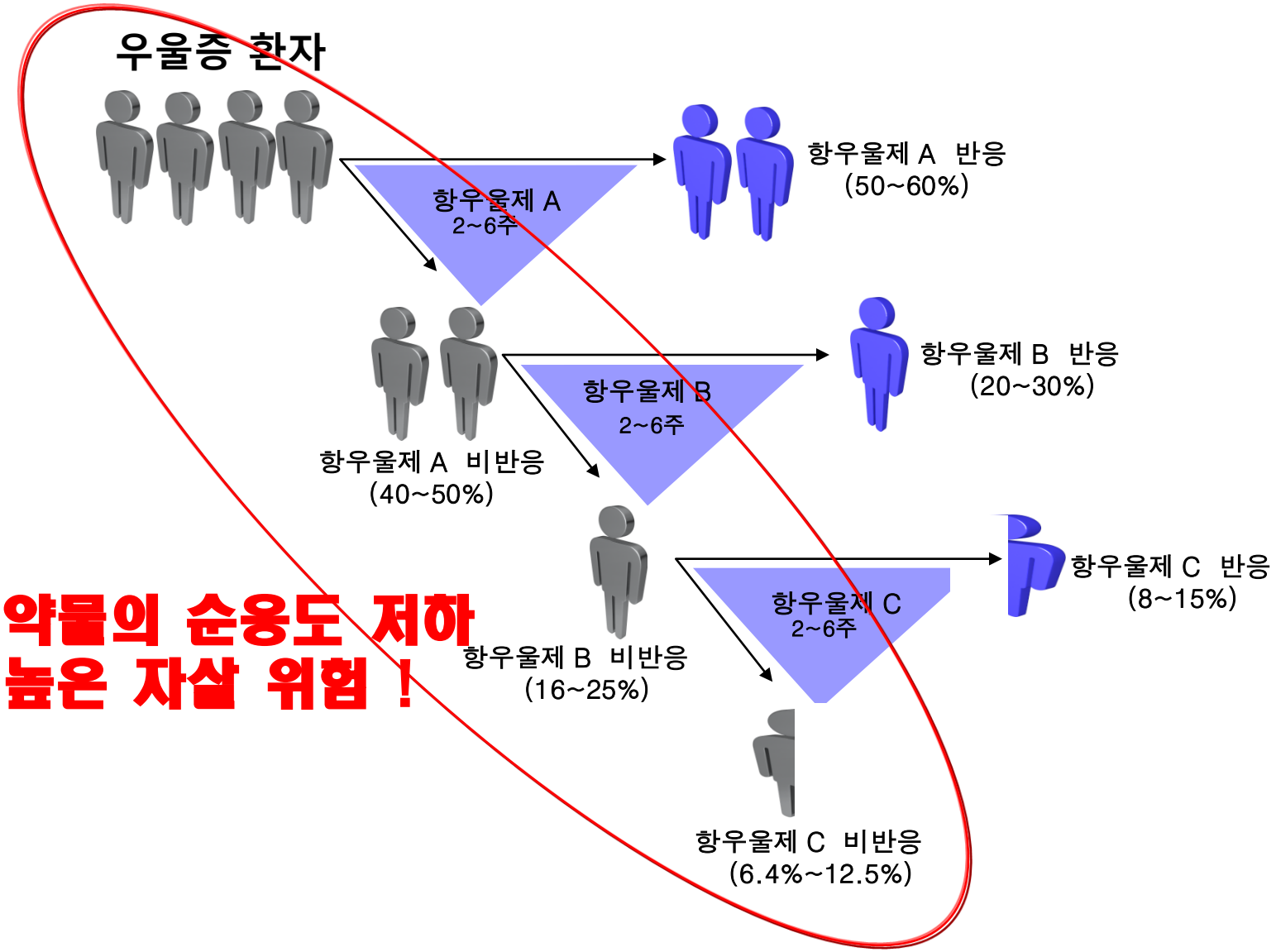
Time Lag

Onset of Antidepressant Action



항우울제의 치료 반응여부를 판단하기 위해서는 6주 이상 기다려야 합니다 !

우울증 환자 치료의 문제점

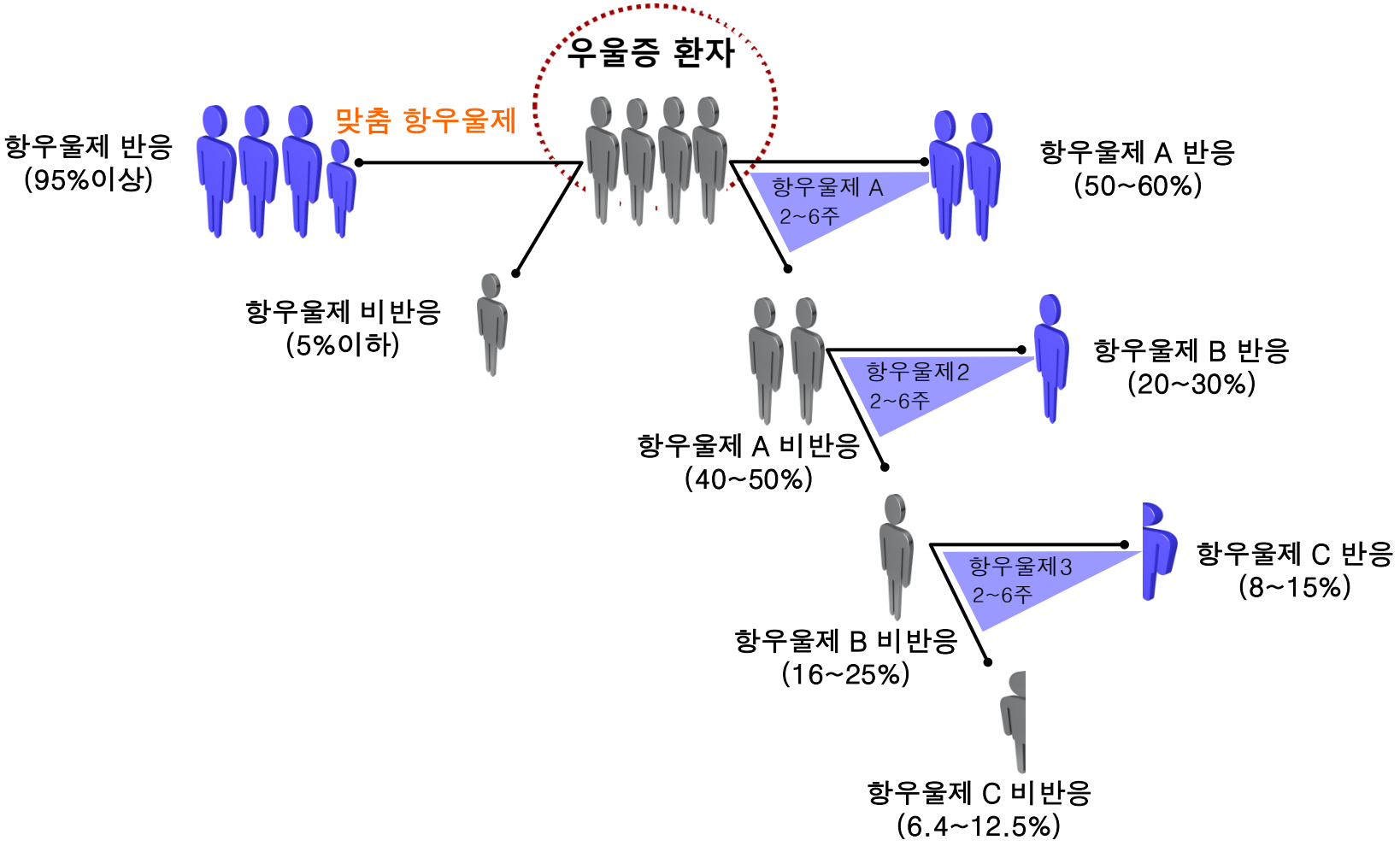


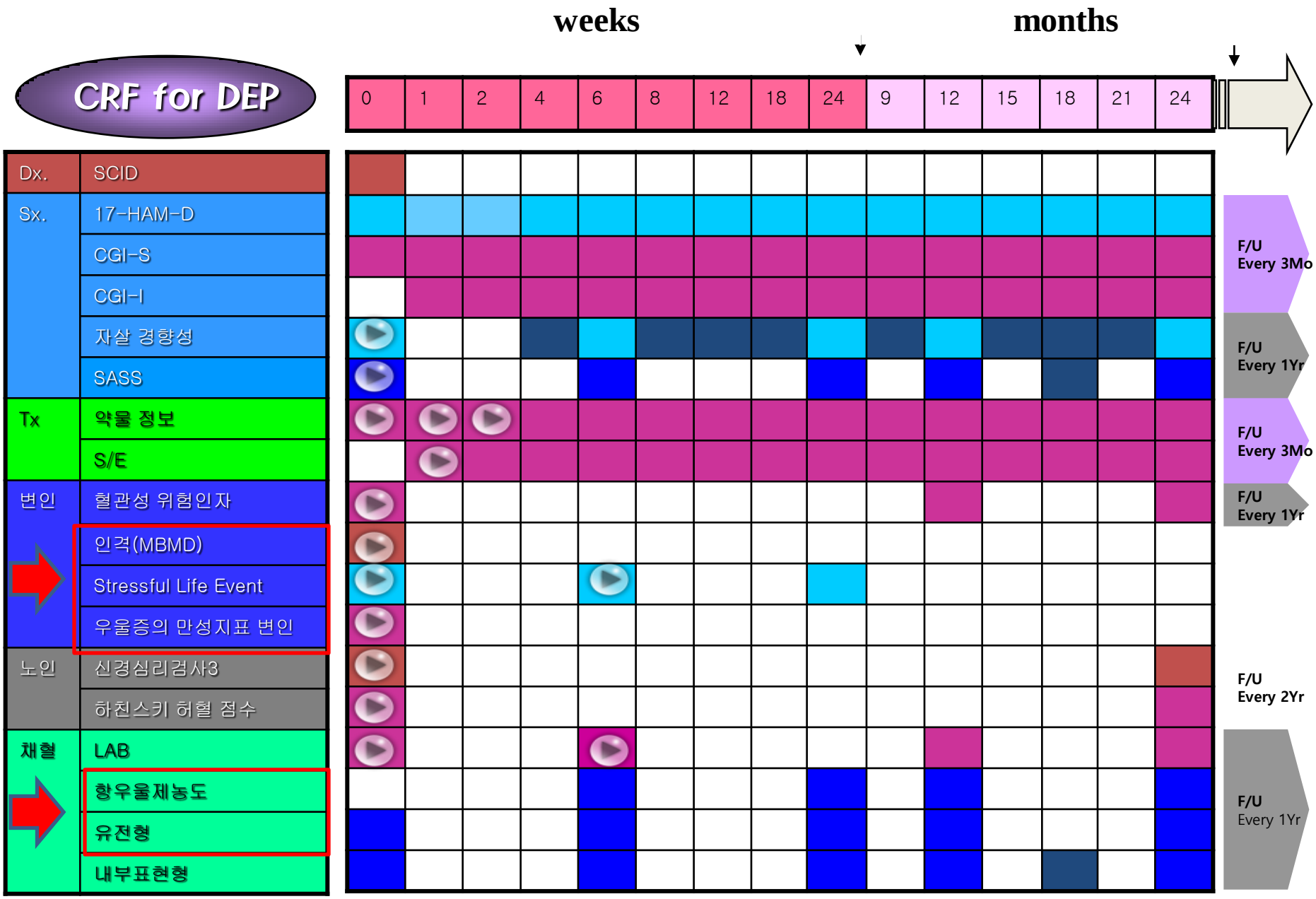
- **약물의 순응도 저하**
- **높은 자살 위험 !**

맞춤치료기술을 개발한다면 …

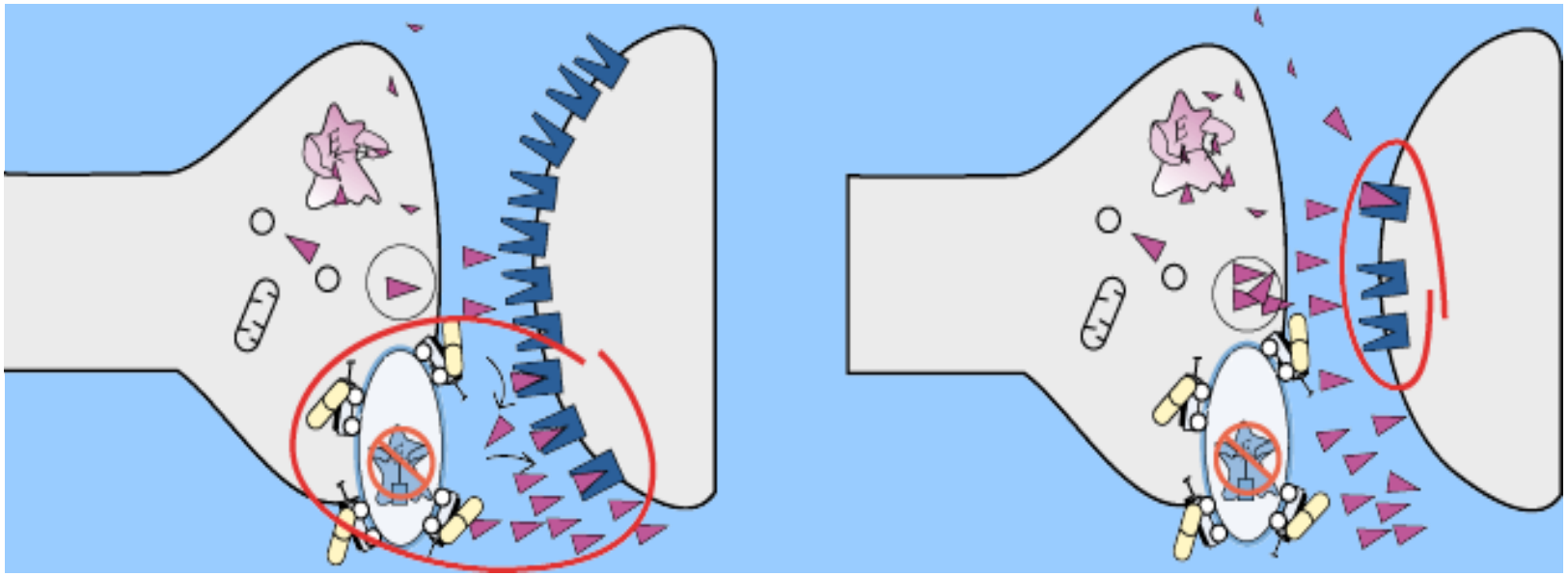
맞춤 치료 기술을 이용한 우울증 환자 의 치료

현재의 우울증 환자의 치료




weeks
months
CRF for DEP
0
1
2
4
6
8
12
18
24
9
12
15
18
21
24
Dx.
SCID
Sx.
17-HAM-D
CGI-S
CGI-I
자살 경향성
SASS
Tx
약물 정보
S/E
변인
혈관성 위험인자
인격(MBMD)
Stressful Life Event
우울증의 만성지표 변인
노인
신경심리검사3
하친스키 허혈 점수
채혈
LAB
항우울제농도
유전형
내부표현형
F/U
Every 3Mo
F/U
Every 1Yr
F/U
Every 3Mo
F/U
Every 1Yr
F/U
Every 2Yr
F/U
Every 1Yr

Which candidate genes or SNPs for the pharmacogenetic study?



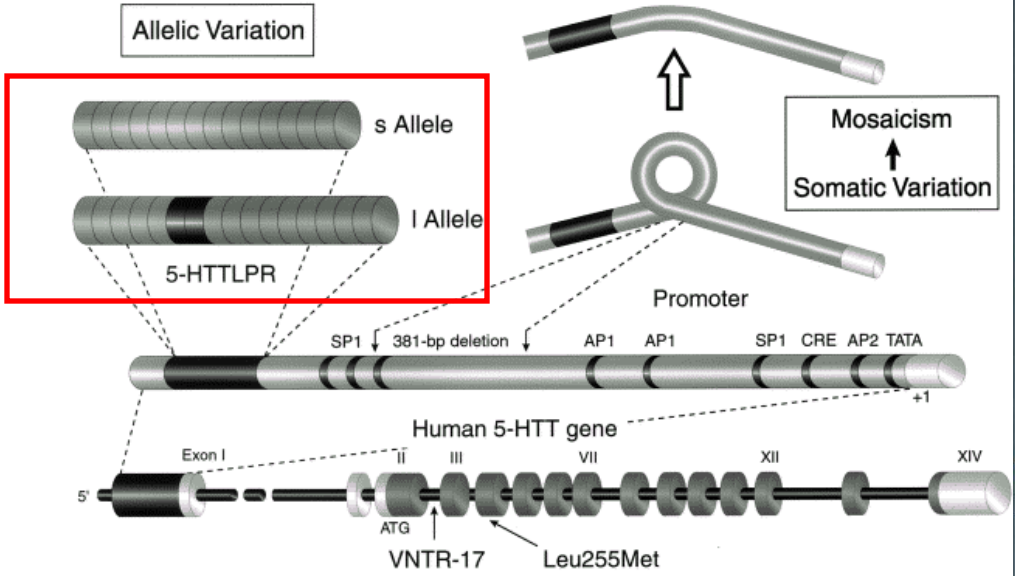
Antidepressant blocks the reuptake pump(eg. SERT), causing more NT(serotonin) to be in the synapse.

Increase in NT(serotonin) causes post-synaptic receptors to down-regulate.

항우울제 치료반응과 단일유전자형 연합연구

Question #1

- Do the allelic polymorphisms of SERT gene influence on the antidepressant response to 6 weeks' treatment with the SSRI drugs, fluoxetine or paroxetine ?



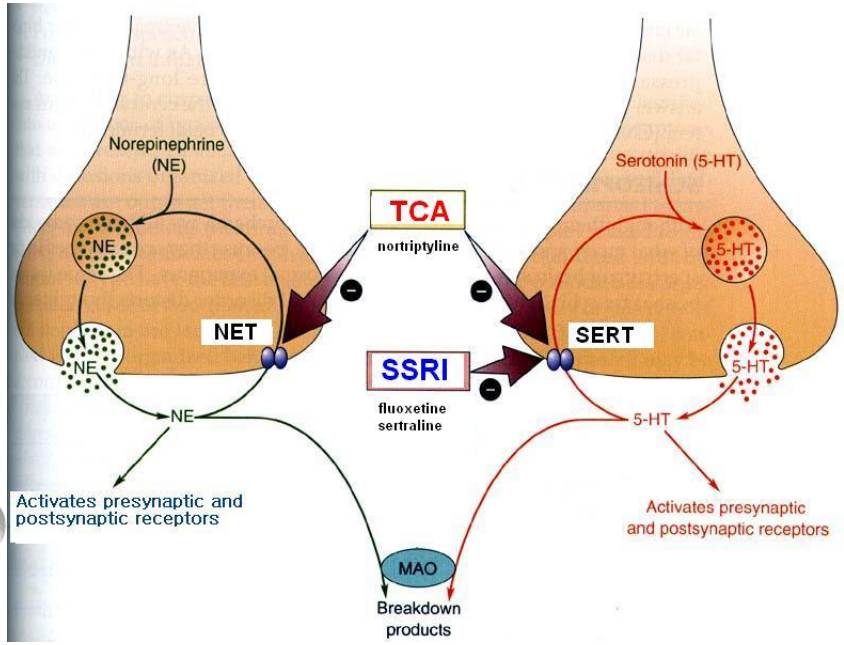
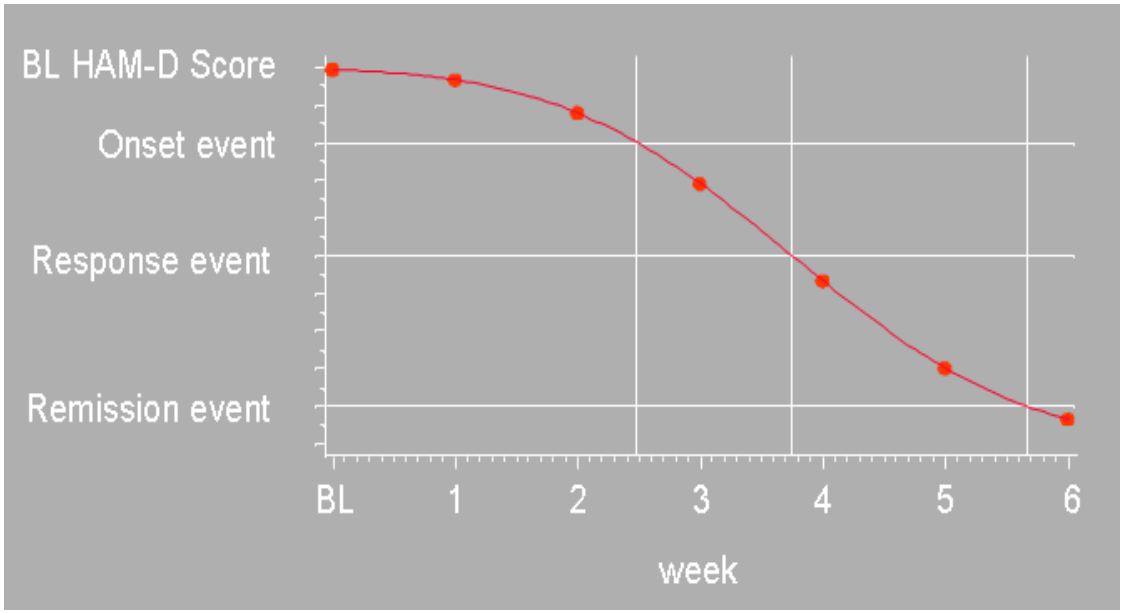


Table 1. Demographic characteristics of subject groups

Group	Number	F/M	Age, year	HAM-D baseline
Normal Volunteers	252	156/96	46.1±12.6	
Major Depression	207	129/78	53.9±15.1	22.3 ± 4.6
Drug Responsive	150	94/56	53.0±15.4	23.1 ± 4.7
Drug Non-responsive	57	35/22	56.2±14.1	22.8 ± 4.3

HAM-D-17-baseline: 17-item Hamilton Rating Scale for Depression score before antidepressant medication

Definition of Responsive Group in DEP



- ≥ 50% decrease in baseline HAM-D score at 6 weeks after SSRI treatment

Table 2. Genotype distribution of *5-HTTLRL* gene polymorphism in promoter region

Group	Number	Polymorphism in promoter		
		s/s	*s/l*	*l/l*
Normal Controls	252 (100%)	137 (54.4%)	103 (40.9%)	12 (4.8%)
Major Depression	207 (100%)	121 (58.5%)	69 (33.3%)	17 (8.2%)

s: short variant of polymorphism in promoter region

l: long variant of polymorphism in promoter region

Table 3. Genotype distribution of *5-HTTLPR* gene polymorphism in promoter region

Group	Number	Polymorphism in promoter		
		s/s	*s/l*	*l/l*
Major Depression	207 (100%)	121 (58.5%)	69 (33.3%)	17 (8.2%)
Drug responsive	150 (100%)	100 (66.7%)	41 (27.3%)	9 (6.0%)
Drug non-responsive	57 (100%)	21 (36.8%)	28 (49.1%)	8 (14.0%)

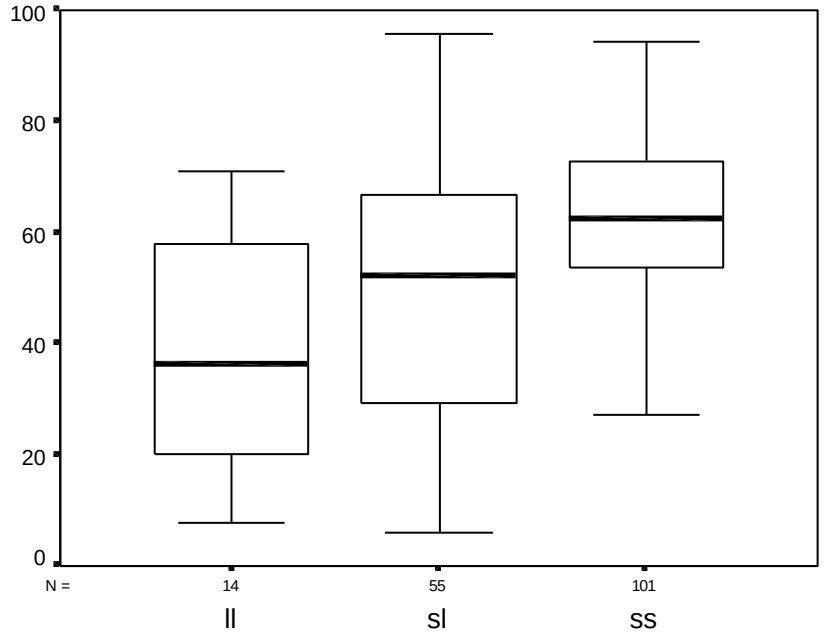
s: short variant of polymorphism in promoter region

l: long variant of polymorphism in promoter region

$P < 0.01$, χ^2 test

% decrease of HAM-D score after antidepressant treatment during 6 weeks according to promoter polymorphism on *5-HTT* gene

40.1±11.6 % **50.0±13.0 %** **59.8±10.3 %**

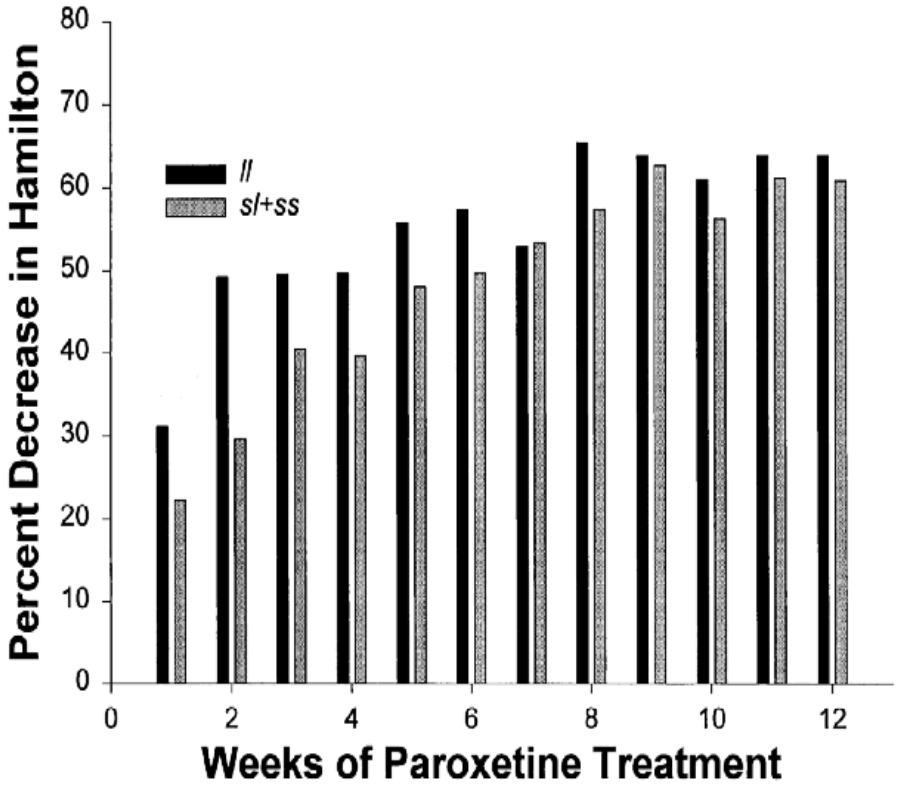


Each box displays the median, 75th percentile and 25th percentile values. Horizontal bars indicate the highest and lowest observed values.

Finding #1

- Response to SSRI is related to the allelic variation of SERT gene polymorphism in promoter region in Korean depressed patients (Kim et al. 2000).

Paroxetine Treatment Response and Promoter Polymorphism of 5-HTT Gene



During acute treatment with paroxetine, mean reductions from baseline in HAM-D were significanlty more rapid for patients with the *l/l* genotype than those possessing an *s* allele, despite equivalent paroxetine concentrations.

(Pollock et al. 2000)

Opposite Result #1

Asian Population

- The *s* allele of the *5-HTTLPR* rather than *l* allele is the favorable variant for response to SSRIs (Kim et al. 2000, Yoshida et al. 2002).

Caucasian Population

- The *l* allele of the *5-HTTLPR* is the favorable allele for responses to SSRIs (Pollack et al. 2000, Zanardi et al. 2000).

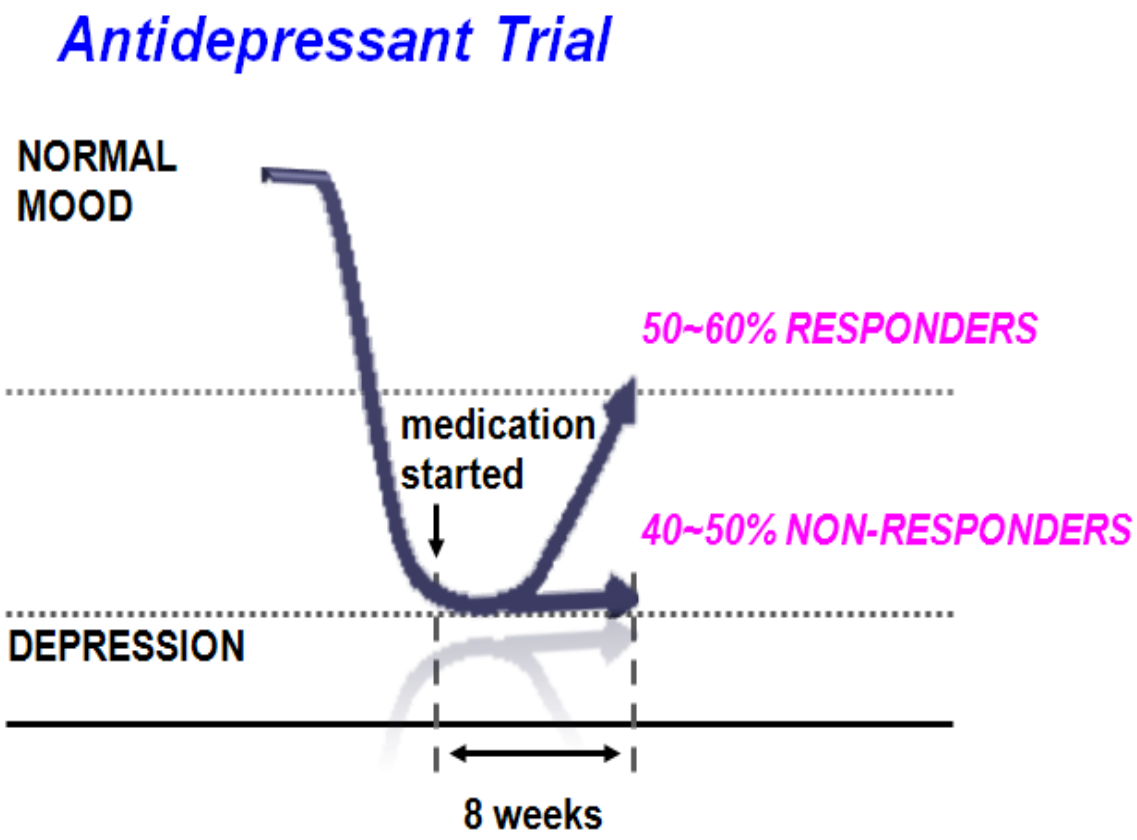
Comparison among the different ethnic groups on the allele frequencies for the promoter polymorphism

Population	2n	*s*	*l*
African American	102	25.4%	74.6%
Caucasian	208	40.4%	59.6%
Japanese	96	80.2%	19.8%
Korean	504	74.8%	25.2%

s: short variant of polymorphism in promoter region

l: long variant of polymorphism in promoter region

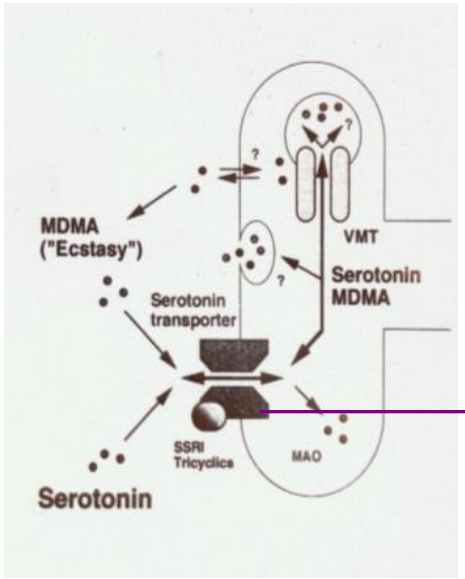
Antidepressant Response Rate in the Patients with Depression

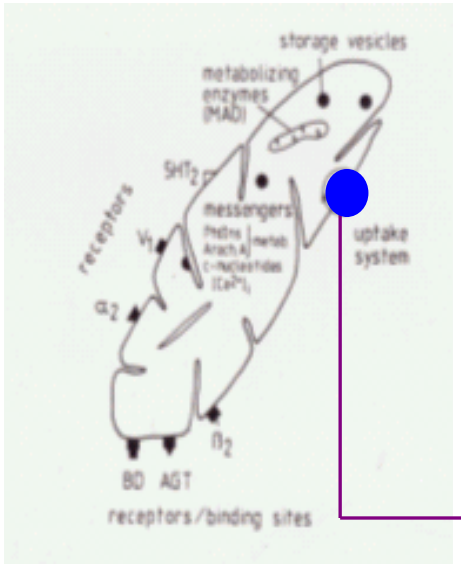


Question #2

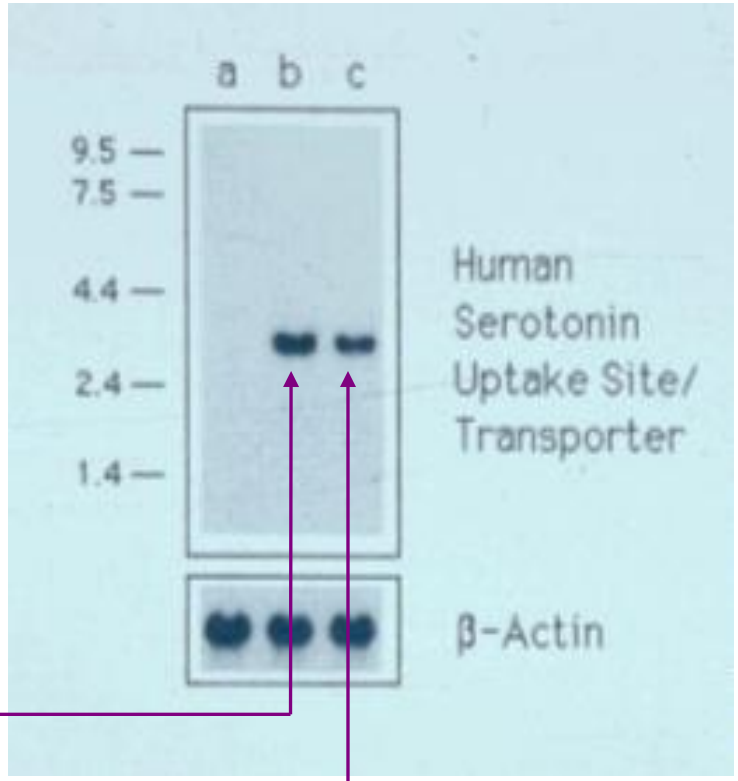
- Are there any different characteristics on the endophenotype of promoter polymorphism of SERT gene among the ethnic groups ?

Autoradiogram of 5-HT Transporter

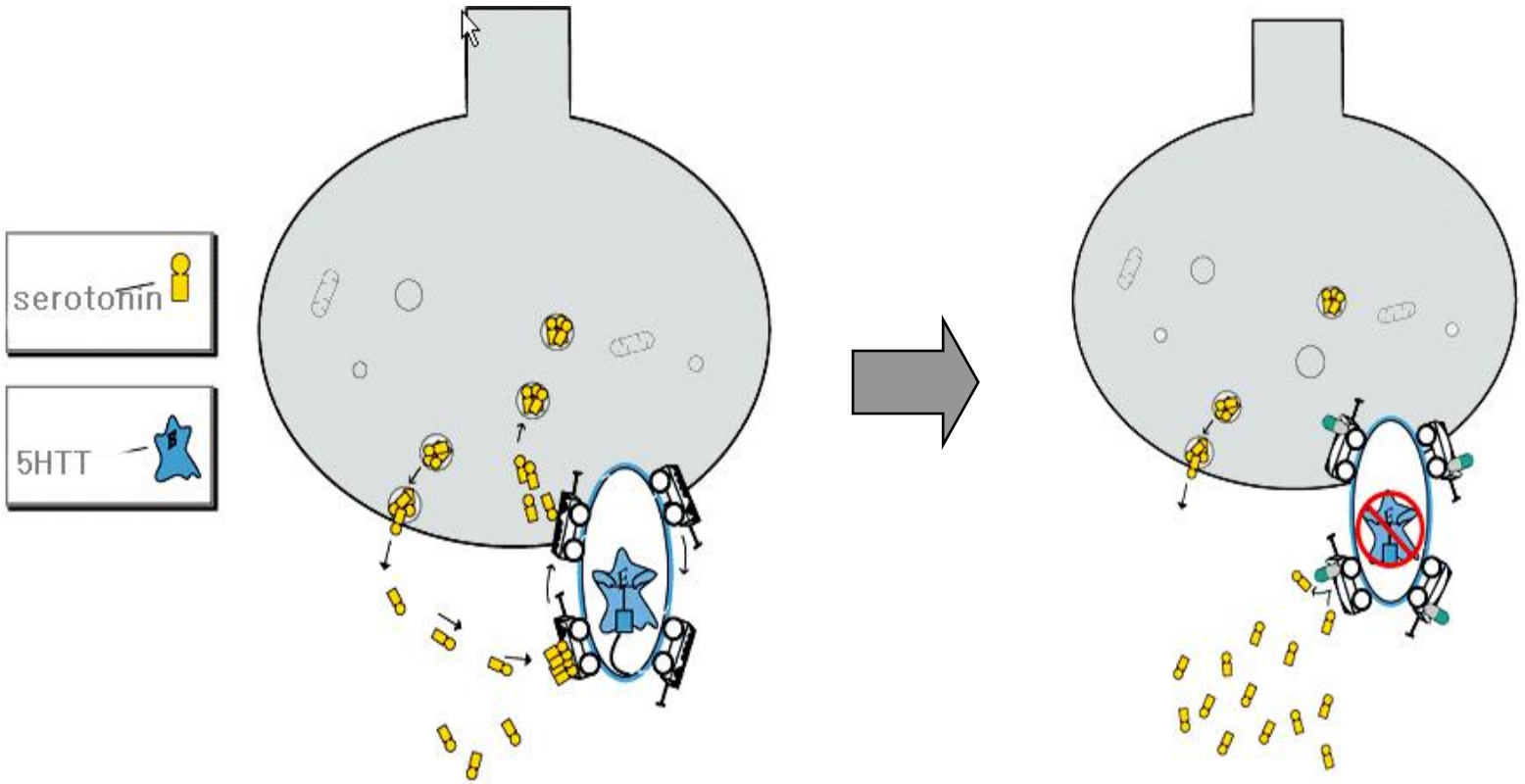




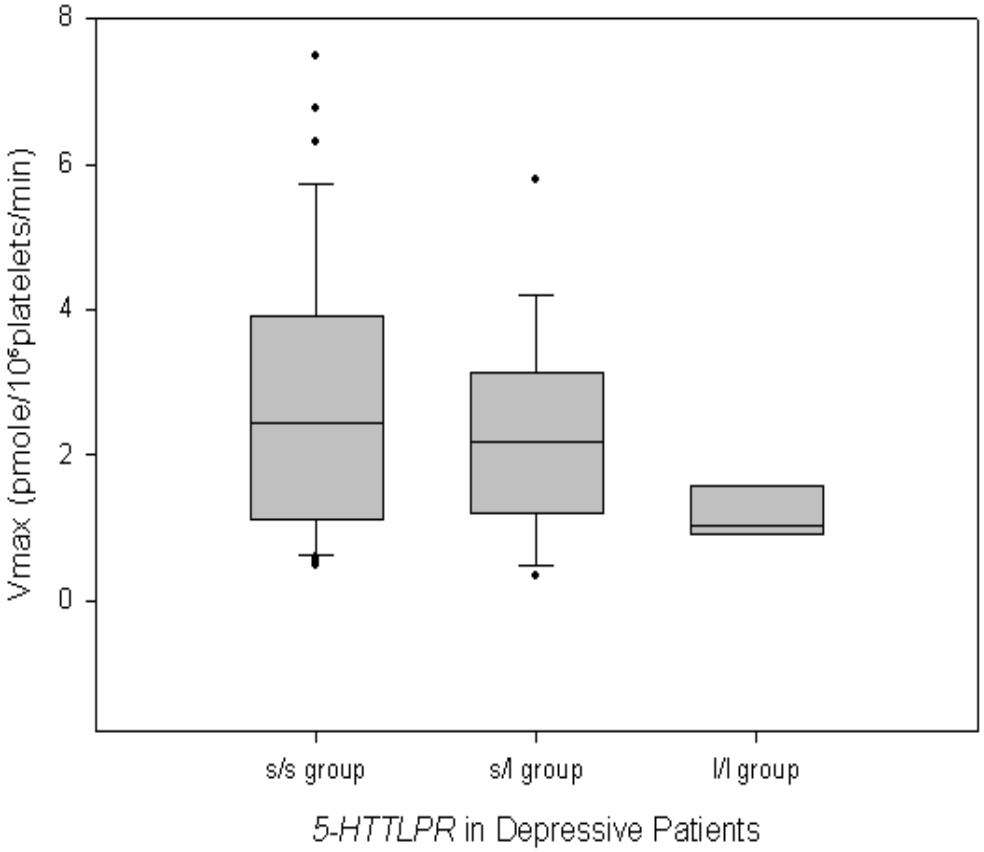
Brain Platelet



[^{3}H]-Serotonin Uptake Study in the Peripheral Platelet



Comparison of 5-HT uptake rates among the different variants of *5-HTTLPR*



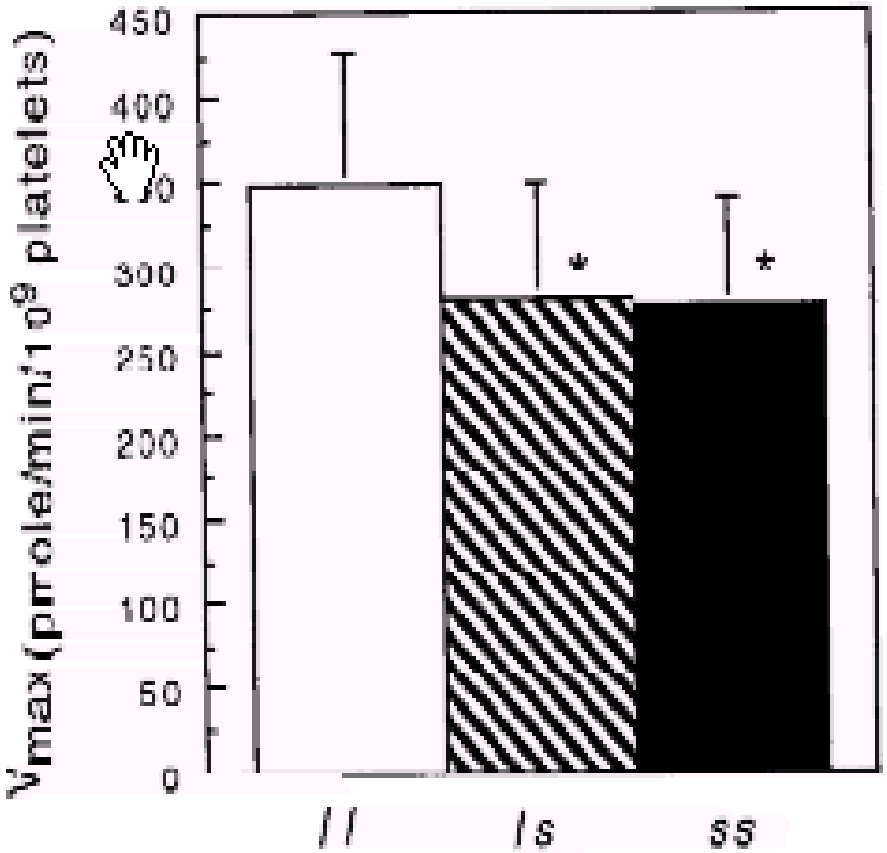
As the number of 's' alleles in *5-HTTLPR* increased, Vmax value in platelets increased in depressed patients.

(Kim et al., Arch Gen Psychiatry in Press)

P < 0.05 (Jonckheere-Terpstra test; Vmax of *ll* < Vmax of *ls* < Vmax of *ss*)

Endophenotype of Promoter Polymorphism of SERT Gene

Vmax value of 5-HT uptake in platelets from 41 normal Caucasians



The *l/l* genotype of *5-HTTLPR* was associated with significantly greater Vmax value than either the *l/s* or *s/s* promoter variants.

(Greenberg et al. 1999)

Finding #2

Korean Population

- The *s/s* genotype of *5-HTTLPR* was associated with greater Vmax value than either the *l/s* or *l/l* promoter variants (Kim et al., Arch Gen Psychiatry in Press).

Opposite Result #2

Caucasian Population

- The *l/l* genotype of *5-HTTLPR* was associated with greater Vmax value than either the *l/s* or *s/s* promoter variants. (Greenberg et al. 1999).

Korean Population

- The *s/s* genotype of *5-HTTLPR* was associated with greater Vmax value than either the *l/s* or *l/l* promoter variants (Kim et al. in Press).

Times Cited: 243

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Serotonin transporter gene polymorphism and antidepressant response

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Author(s): Kim DK, Lim SW, Lee S, Sohn SE, Kim S, Hahn CG, Carroll BJ

Source: NEUROREPORT **Volume:** 11 **Issue:** 1 **Pages:** 215-219 **Published:** JAN 17 2000

Times Cited: 213 **References:** 25 Citation Map

Abstract: We examined allelic polymorphisms of the serotonin transporter (5-HTT) gene and antidepressant response to 6 weeks' treatment with the selective serotonin reuptake inhibitor (SSRI) drugs fluoxetine or paroxetine. We genotyped 120 patients and 252 normal controls, using polymerase chain reaction of genomic DNA with primers flanking the second intron and promoter regions of the 5-HTT gene. Diagnosis of depression was not associated with 5-HTT polymorphisms. Patients homozygous 1/1 in intron2 or homozygous sis in the promoter region showed better responses than all others ($p<0.0001$, $p=0.0074$, respectively). Lack of the 1/1 allele form in intron 2 most powerfully predicted non-response (83.3%). Response to SSRI drugs is related to allelic variation in the 5-HTT gene in depressed Korean patients. NeuroReport 11:215-219 (C) 2000 Lippincott Williams & Wilkins.

Document Type: Article

Language: English

Question #3

- May genetic effects on antidepressant response be different by choice of drug (mode of mechanism) ?

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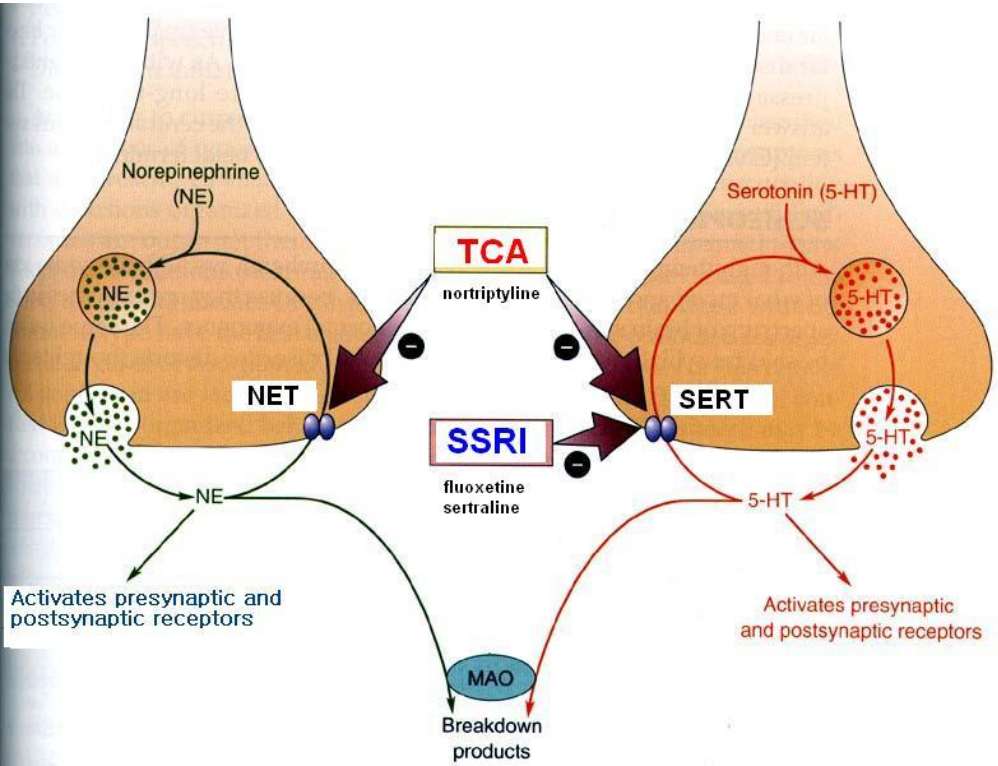
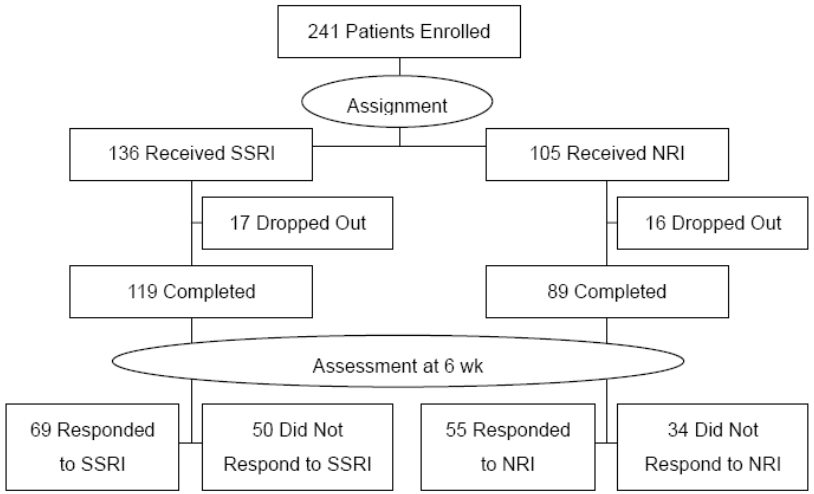
Question #3

- May genetic effects on antidepressant response be different by choice of drug (mode of mechanism) ?





Abbreviations: SSRI, selective serotonin reuptake inhibitor; NRI, noradrenergic reuptake inhibitor.

Searching Monoamine Transporter Gene Family

Gene		Polymorphism	Detection methods
Serotonin Transporter	(SERT, 5-HTT)		
Promoter		5-HTTLPR	3% agarose
Intron 2		VNTR	3% agarose
Dopamine Transporter (DAT)			
3'-untranslated region	VNTR		3% agarose
Noradrenergic Transporter (NET)			
Exon 2 (NET-1)		Thr99Ile	*BsiHKA*I / 8% PAGE
Exon 9 (NET-8)		1287G/A	*Sau96*I / 12% PAGE
Exon 10		Gly478Ser	*BsiHKAI* /12% PAGE

Table 2. Genotype and allele distribution of monoamine transporter gene polymorphisms to norepinephrine reupatke inhibitor (NRI)

		Response Rate (%)	Responder (%)	Non-responder (%)	*P**	OR 95% CI†	*P*†
NET G1287A in exon9	GG	35/42 (83.3)	35(63.6)	7(20.6)	‡.01	7.54 2.53-22.49	<.001
	GA	16/41(39.0)	16(29.1)	25(73.5)			
	AA	4/6 (66.7)	4(7.3)	2(5.9)			
	G		.782	.574	.012	3.48 1.67-7.30	.001
	A		.218	.426			
5HTT VNTR in Promoter	*ss*	38/50 (76.0)	38(69.1)	12(35.3)	§.006	3.73 1.32-10.53	.01
	sl	14/29 (48.3)	14(25.5)	15(44.1)			
	ll	3/10 (30.0)	3(5.4)	7(20.6)			
	S		.818	.574	.003	4.85 2.29-10.27	<.001
	L		.182	.426			
5HTT VNTR in Intron2	*ll*	51/77 (66.2)	51(92.7)	26(76.5)	¶.15	3.34 0.7-15.91	.13
	ls	4/12 (33.3)	4(7.3)	8(23.5)			
	ss	0	0(0)	0(0)			
	l		.964	.882	.18	3.49 0.92-13.24	.07
	s		.036	.118			

* Fisher's exact test with Bonferroni's correction due to multiple testing

† Multiple logistic regression

‡ Statistical analysis was performed between 'GG' and 'GA + AA'.

§ Statistical analysis was performed between '*ss*' and '*sl* + *ll*'.

¶ Statistical analysis was performed between *'ll'* and *'ls* + *ss'*.

Table 3. Genotype and allele distribution of monoamine transporter gene polymorphisms to selective serotonin reupatke inhibitor (SSRI)

		Response Rate (%)	Responder (%)	Non-responder (%)	*P**	OR 95% CI†	*P*†
NET G1287A in exon9	GG	44/75 (58.7)	44(63.8)	31(62)	‡1.00	.84 0.34-2.09	.71
	GA	21/37 (56.8)	21(30.4)	16(32)			
	AA	4/7 (57.1)	4(5.8)	3(6)			
	G		.790	.780	1.00	1.54 0.74-3.20	.25
	A		.210	.220			
5HTT VNTR in Promoter	*ss*	50/70 (71.4)	50(72.5)	20(40)	§.003	3.34 1.41-7.91	.006
	sl	17/42 (40.5)	17(24.6)	25(50)			
	ll	2/7 (28.6)	2(2.9)	5(10)			
	S		.848	.650	.003	2.28 1.17-4.47	.02
	L		.152	.350			
5HTT VNTR in Intron2	*ll*	67/97 (69.1)	67(97.1)	30(60)	¶.01	20.11 4.27-94.74	<.001
	ls	2/21 (9.5)	2(2.9)	19(38)			
	ss	0/1 (0)	0(0)	1(2)			
	l		.986	.790	.01	15.87 3.47-71.43	<.001
	s		.014	.210			

* Fisher's exact test with Bonferroni's correction due to multiple testing

† Multiple logistic regression

‡ Statistical analysis was performed between 'GG' and 'GA + AA'.

§ Statistical analysis was performed between '*ss*' and '*sl* + *ll*'.

¶ Statistical analysis was performed between '*ll*' and '*ls* + *ss*'.

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NET polymorphism(1287 GA)

Response Rate to	NRI class	SSRI class
• DEP with GG	35/42 (83.3%)	44/75 (58.7%)
• DEP with A allele	20/47 (42.6%)	25/44 (56.8%)

56% of Koreans (45% of whites) have the GG genotype

(Kim et al. JAMA, 2006)

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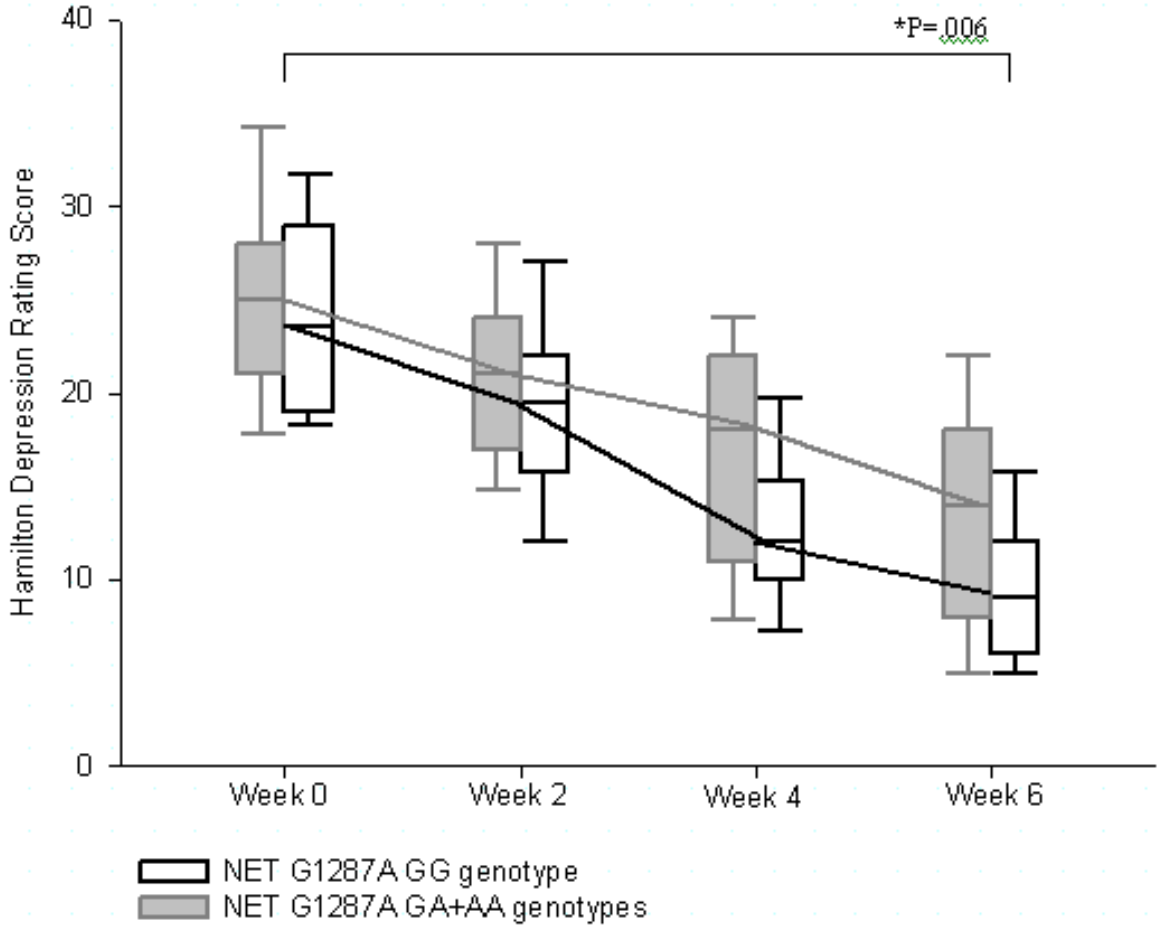

(Kim et al. JAMA, 2006)

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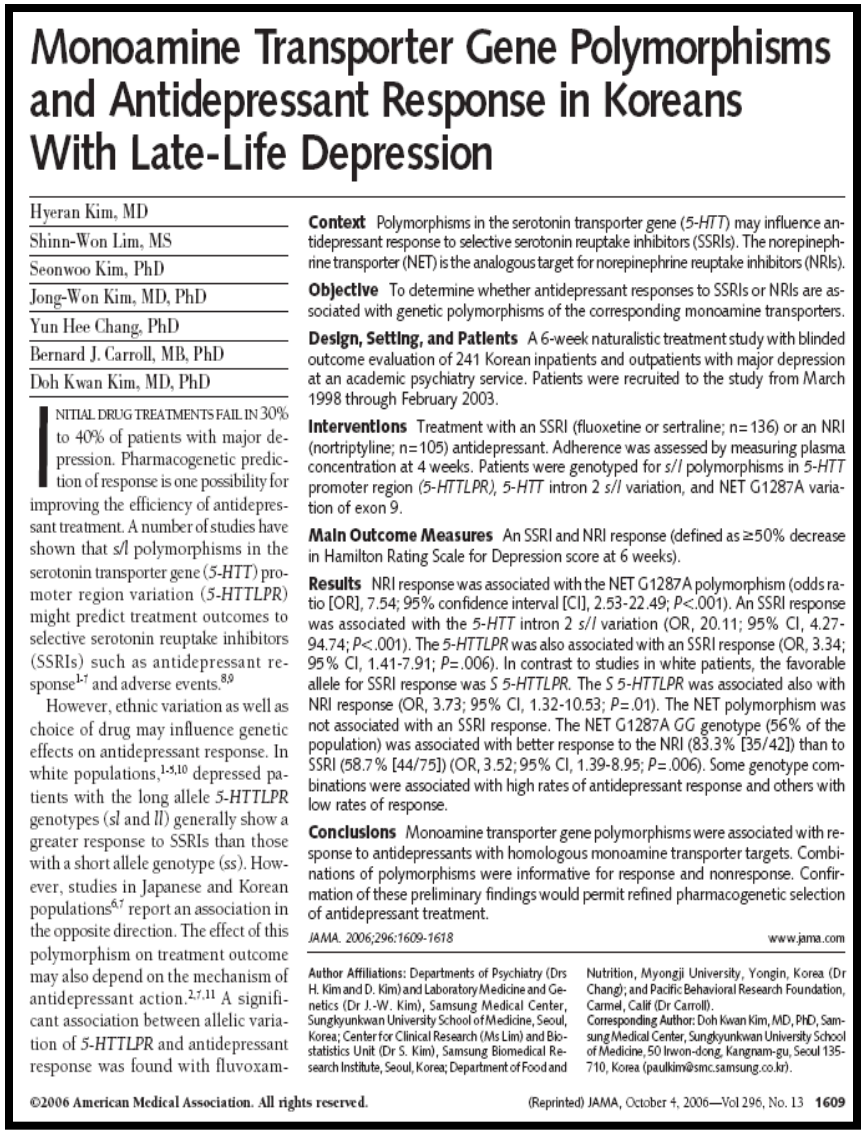
Table 4. Response Rates With Combinations of Monoamine Transporter Polymorphisms

NET G1287A	*5-HTT* Promoter	*5-HTT* Intron 2	Response Rate, No./Total (%)	*P* Value*
		Norepinephrine Reuptake Inhibitor		
GG	ss	Any genotype	23/26 (88.5)	<.001
GG	l Carrier	Any genotype	12/16 (75.0)	.008
A carrier	ss	Any genotype	15/24 (62.5)	.02
A carrier	l Carrier	Any genotype	5/23 (21.7)	Comparator

Abbreviations: *5-HTT*, serotonin transporter; NET, norepinephrine transporter.
*Fisher exact test.

(Kim et al. JAMA, 2006)

유전자형 조합을 이용한 항우울제 치료반응 연합연구와 임상적 약물선별법 개발



Monoamine Transporter Gene Polymorphisms and Antidepressant Response in Koreans With Late-Life Depression

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Context Polymorphisms in the serotonin transporter gene (*5-HTT*) may influence antidepressant response to selective serotonin reuptake inhibitors (SSRIs). The norepinephrine transporter (NET) is the analogous target for norepinephrine reuptake inhibitors (NRIs).

Objective To determine whether antidepressant responses to SSRIs or NRIs are associated with genetic polymorphisms of the corresponding monoamine transporters.

Design, Setting, and Patients A 6-week naturalistic treatment study with blinded outcome evaluation of 241 Korean inpatients and outpatients with major depression at an academic psychiatry service. Patients were recruited to the study from March 1998 through February 2003.

Interventions Treatment with an SSRI (fluoxetine or sertraline; n=136) or an NRI (nortriptyline; n=105) antidepressant. Adherence was assessed by measuring plasma concentration at 4 weeks. Patients were genotyped for *s/l* polymorphisms in *5-HTT* promoter region (*5-HTTLPR*), *5-HTT* intron 2 *s/l* variation, and NET G1287A variation of exon 9.

Main Outcome Measures An SSRI and NRI response (defined as ≥50% decrease in Hamilton Rating Scale for Depression score at 6 weeks).

Results NRI response was associated with the NET G1287A polymorphism (odds ratio [OR], 7.54; 95% confidence interval [CI], 2.53-22.49; *P*<.001). An SSRI response was associated with the *5-HTT* intron 2 *s/l* variation (OR, 20.11; 95% CI, 4.27-94.74; *P*<.001). The *5-HTTLPR* was also associated with an SSRI response (OR, 3.34; 95% CI, 1.41-7.91; *P*=.006). In contrast to studies in white patients, the favorable allele for SSRI response was *S 5-HTTLPR*. The *S 5-HTTLPR* was associated also with NRI response (OR, 3.73; 95% CI, 1.32-10.53; *P*=.01). The NET polymorphism was not associated with an SSRI response. The NET G1287A *GG* genotype (56% of the population) was associated with better response to the NRI (83.3% [35/42]) than to SSRI (58.7% [44/75]) (OR, 3.52; 95% CI, 1.39-8.95; *P*=.006). Some genotype combinations were associated with high rates of antidepressant response and others with low rates of response.

Conclusions Monoamine transporter gene polymorphisms were associated with response to antidepressants with homologous monoamine transporter targets. Combinations of polymorphisms were informative for response and nonresponse. Confirmation of these preliminary findings would permit refined pharmacogenetic selection of antidepressant treatment.

JAMA. 2006;296:1609-1618 www.jama.com

INITIAL DRUG TREATMENTS FAIL IN 30% to 40% of patients with major depression. Pharmacogenetic prediction of response is one possibility for improving the efficiency of antidepressant treatment. A number of studies have shown that *s/l* polymorphisms in the serotonin transporter gene (*5-HTT*) promoter region variation (*5-HTTLPR*) might predict treatment outcomes to selective serotonin reuptake inhibitors (SSRIs) such as antidepressant response[1-7] and adverse events.[8,9]

However, ethnic variation as well as choice of drug may influence genetic effects on antidepressant response. In white populations,[1-5,10] depressed patients with the long allele *5-HTTLPR* genotypes (*sl* and *ll*) generally show a greater response to SSRIs than those with a short allele genotype (*ss*). However, studies in Japanese and Korean populations[6,7] report an association in the opposite direction. The effect of this polymorphism on treatment outcome may also depend on the mechanism of antidepressant action.[2,7,11] A significant association between allelic variation of *5-HTTLPR* and antidepressant response was found with fluvoxam-

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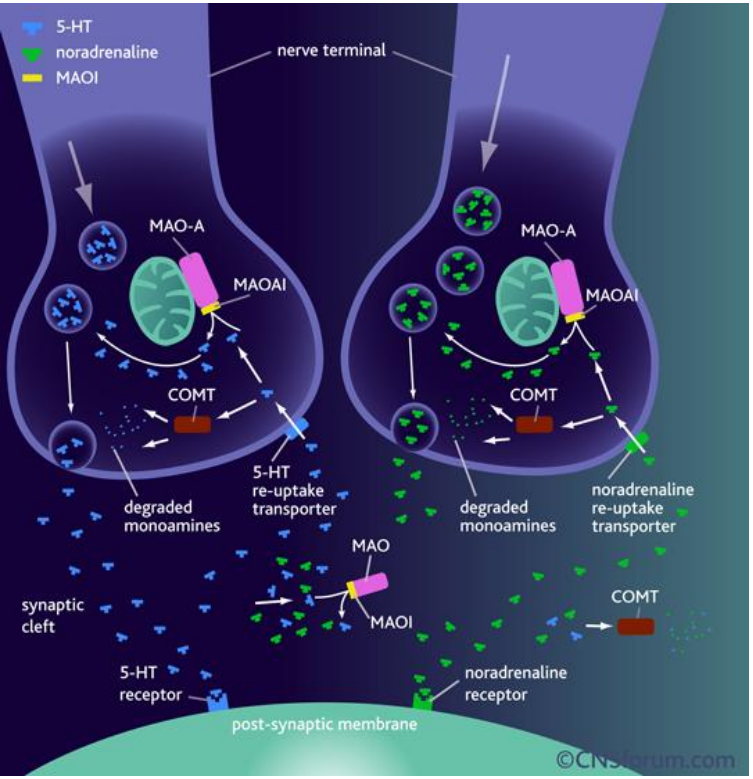
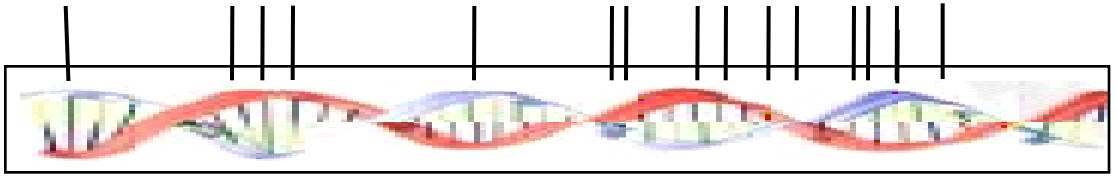
1. **유전형 조합을 통한 맞춤치료기술의 증거를 제시 : 항우울제의 치료반응을 85% 수준으로 예측**
2. **우울증 환자의 맞춤치료기술개발에 대한 1개의 국내특허등록 (2009.5.7) 과 1개의 해외특허 (2007.10.4) 와 2개의 특허를 국내 출원 (2007.4.4)**
3. **International SSRI Pharmacogenomic Consortium 과 일본 약물유전체 연구회 등과 국제공동연구 진행**

후보유전자형 연합연구





83 Candidate Genes !

1502 SNPs

- Transporters
- Receptors
- Synthetic and metabolic enzymes

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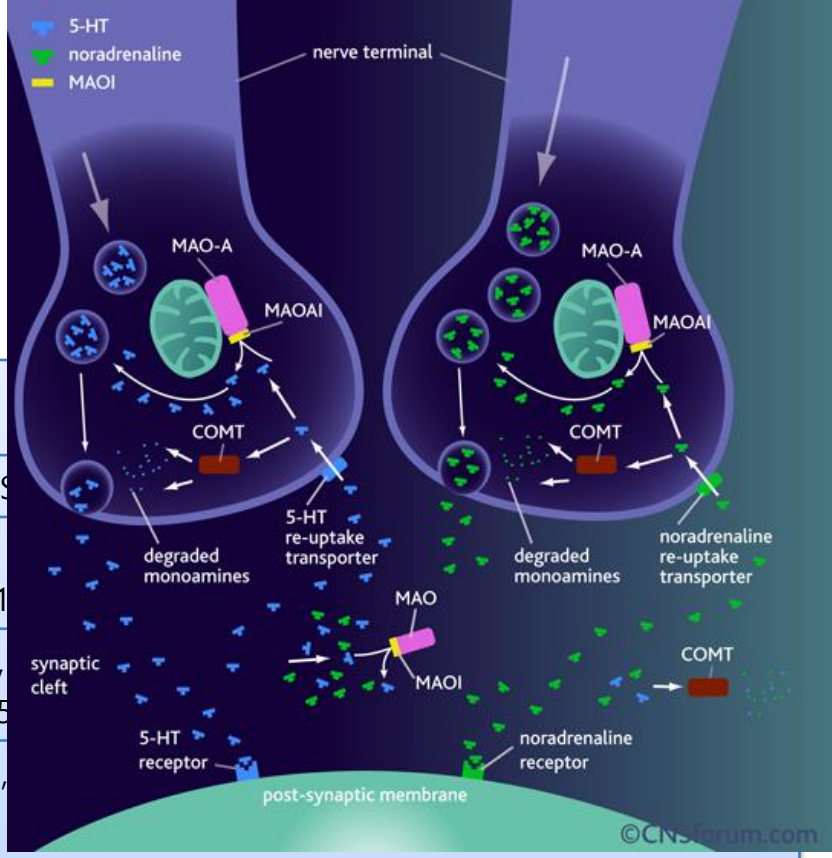
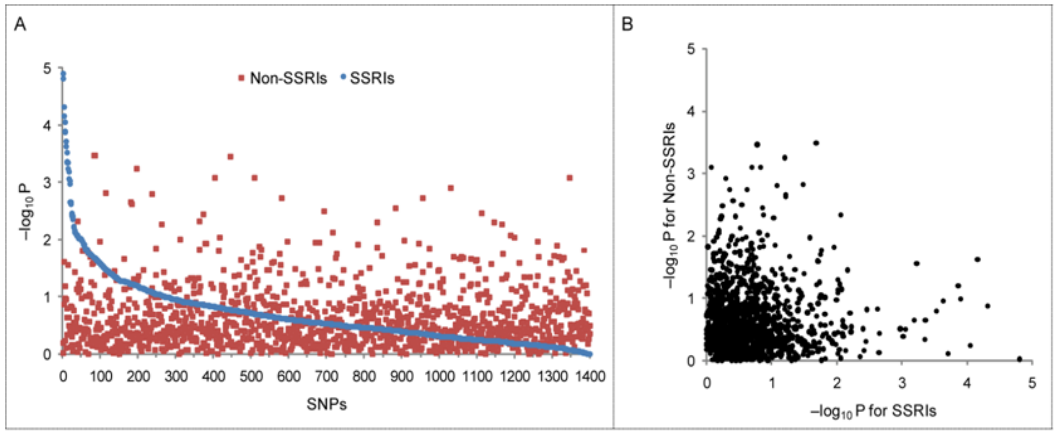


Class	No. of genes	Genes (No. of selected SNPs)	
Transporter	5	ABCB1 (23), SLC1A1 (36), SLC6A2 (26), SLC6A3 (7), S	
Metabolic enzyme	16	TPH1 (13), TPH2 (32), TH (7), MAOA (3), MAOB (4), PNMT (3), GAD1 (11), CPOX (8), DAO (3), DAOA (11	
Receptor	58	Indoleamine	Serotonergic System: HTR1A (3), (28), HTR2C (8), HTR3B (8), HTR5
		Catecholamine	Dopaminergic System: DRD1 (3), Noradernergic System: ADRA1A ADRB3 (1)
		Acetylcholine	CHRM1 (3), CHRM2 (22)
		Glutamate	Ionotropic N-methyl-D-aspartic Acid (NMDA): GRIN2A (61), GRIN2D(6), GRIN3A (47) Non-NMDA: GRIA1 (32), GRIA2 (7), GRIA3(54), GRIA4 (30), GRIK1 (69), GRIK2(83) Metabotropic NMDA: GRM1 (37), GRM3 (18), GRM4(37), GRM5 (72), GRM7 (221), GR M8(47)
		GABA, Glycine	GABBR1 (8), GABRA1 (7), GABRG2 (16), GLRB (5)
		Neuropeptide	CCK (6), CCKAR (7), TAC1 (6), TACR1 (51), NPY (8), OPRD1 (8), OPRM1 (11), OPRS1 (1) , CNR1 (4), AVPR2 (4)
		Channel	KCNA1 (2), KCNH2 (6), KCNJ3 (41), KCNK2 (16), KCNN1 (10), KCNN2 (9)

항우울제의 계열에 따라서 치료반응에 연관이 있는 유전형은 다르다!

SSRI 치료군과 Non-SSRI 치료군에서 항우울제 치료반응과의 연합연구 결과



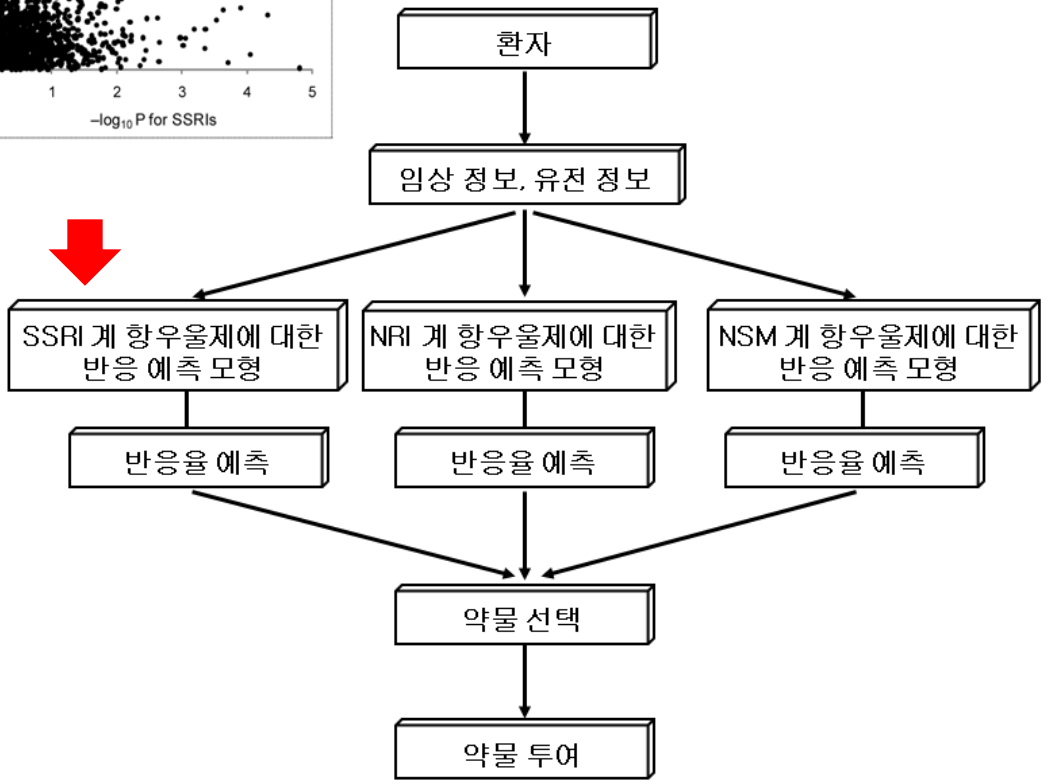


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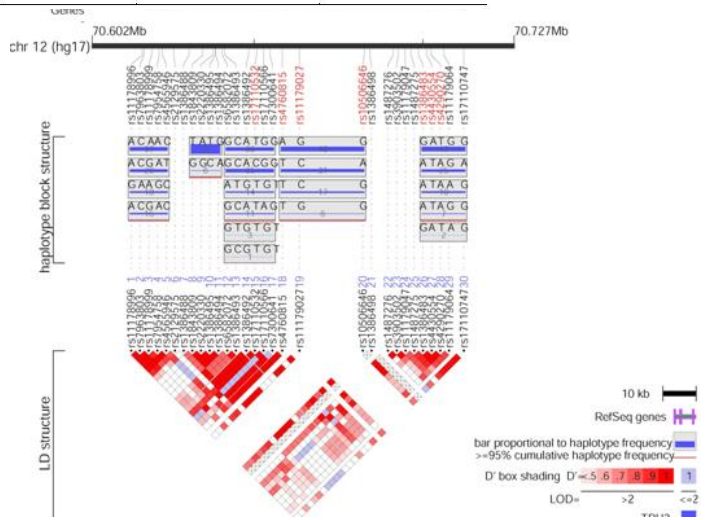
Table 2. The SNPs most strongly associated with SSRI response ($P < 0.05$ after FDR correction) and the strongly associated polymorphisms in *SLC6A4* from our previous study (5).

Gene	Chromosome	Position[a]	SNP	Responsive Allele	RAF in Responders	RAF in Nonresponders	P Value[b]	P Value by Bonferroni's Correction	P Value by Controlling FDR	Genetic Mode	Heterozygote Odds Ratio (95% CI)	Homozygote Odds Ratio (95% CI)
TPH2	12	70658496	rs4760815	T	0.60	0.41	1.26×10^{-5}	0.02	0.02	Dominant	3.77 (3.55–4.00)	4.39 (2.08–9.29)
TPH2	12	70663579	rs11179027	C	0.55	0.34	1.57×10^{-5}	0.02	0.02	Allele	2.69 (1.45–4.99)	4.77 (2.17–10.49)
GRIK2	6	102158042	rs543196	C	0.65	0.46	4.84×10^{-5}	0.07	0.02	Additive	1.69 (0.83–3.45)	5.02 (2.18–11.53)
GAD1	2	171390986	rs3828275	G	0.72	0.64	6.89×10^{-5}	0.10	0.02	Genotype	0.31 (0.17–0.55)	1.24 (0.43–3.62)
TPH2	12	70650935	rs17110532	C	0.42	0.24	8.86×10^{-5}	0.12	0.02	Allele	2.02 (1.14–3.59)	5.36 (1.93–14.87)
SLC6A4	17	25575791	rs2066713	C	0.96	0.86	1.26×10^{-4}	0.18	0.03	Recessive	0.48 (0.03–8.42)	2.27 (0.14–36.87)
GRIK2	6	102157181	rs572487	G	0.59	0.41	1.36×10^{-4}	0.19	0.03	Additive	1.65 (1.54–1.77)	4.76 (2.09–10.86)
TPH2	12	70712221	rs17110747	A	0.31	0.16	1.94×10^{-4}	0.27	0.03	Allele	2.53 (1.37–4.69)	3.88 (1.25–11.99)
GAD1	2	171379072	rs12185692	C	0.71	0.65	2.33×10^{-4}	0.33	0.04	Genotype	0.35 (0.20–0.62)	1.57 (0.49–5.03)
SLC6A4	17	25571040	rs2020942	G	0.95	0.85	2.96×10^{-4}	0.42	0.04	Additive	1.27 (1.21–1.34)	4.56 (0.41–51.22)

유의한 10개의 SNP
+ 5개 Haplotype block

약물반응예측모형의 기반



Genotypic Combinations for Prediction Modeling

	Haplotype model					
	TPH2 (H3)*	*SLC6A4* (H1)†	rs543196	rs3828275	*5-HTTLPR*	
Predicted Responders	H3-B	H1-A	CC	AA	*ss*	>80% (n=90)
	H3-B	H1-A	CC	GG	*ss*	
	H3-B	H1-A	CC	AA	*s/+l*	
	H3-B	H1-A	TC	AA	*ss*	
	H3-B	H1-A	CC	GG	*s/+l*	
	H3-B	H1-A	TC	GG	*ss*	
	H3-B	H1-A	CC	AG	*ss*	
	H3-B	H1-A	TC	AA	*s/+l*	
Predicted Nonresponders	H3-B	H1-B	TT	GG	*ss*	<30% (n=39)
	H3-B	H1-B	TC	AG	*ss*	
	H3-A	H1-A	TT	AA	*ss*	
	H3-A	H1-B	CC	AA	*ss*	
	H3-A	H1-A	TC	GG	*s/+l*	
	H3-A	H1-A	CC	AG	*s/+l*	
	H3-B	H1-B	TT	AA	*s/+l*	
	H3-A	H1-A	TT	GG	*ss*	
	H3-A	H1-A	TC	AG	*ss*	
	H3-A	H1-B	CC	GG	*ss*	
	H3-B	H1-B	TT	GG	*s/+l*	
	H3-B	H1-B	TC	AG	*s/+l*	
	H3-A	H1-A	TT	AA	*s/+l*	
	H3-B	H1-B	TT	AG	*ss*	
	H3-A	H1-B	CC	AA	*s/+l*	
	H3-A	H1-B	TC	AA	*ss*	
	H3-A	H1-A	TT	GG	*s/+l*	
	H3-A	H1-A	TC	AG	*s/+l*	
	H3-A	H1-B	CC	GG	*s/+l*	
	H3-A	H1-A	TT	AG	*ss*	
	H3-A	H1-B	TC	GG	*ss*	
	H3-A	H1-B	CC	AG	*ss*	
	H3-B	H1-B	TT	AG	*s/+l*	
	H3-A	H1-B	TC	AA	*s/+l*	
	H3-A	H1-B	TT	AA	*ss*	
	H3-A	H1-A	TT	AG	*s/+l*	
	H3-A	H1-B	TC	AA	*s/+l*	
	H3-A	H1-B	CC	AG	*s/+l*	
	H3-A	H1-B	TT	GG	*ss*	
	H3-A	H1-B	TC	AG	*ss*	
	H3-A	H1-B	TT	AA	*s/+l*	
	H3-A	H1-B	TT	GG	*s/+l*	
	H3-A	H1-B	TC	AG	*s/+l*	
	H3-A	H1-B	TT	AG	*ss*	
	H3-A	H1-B	TT	AG	*s/+l*	

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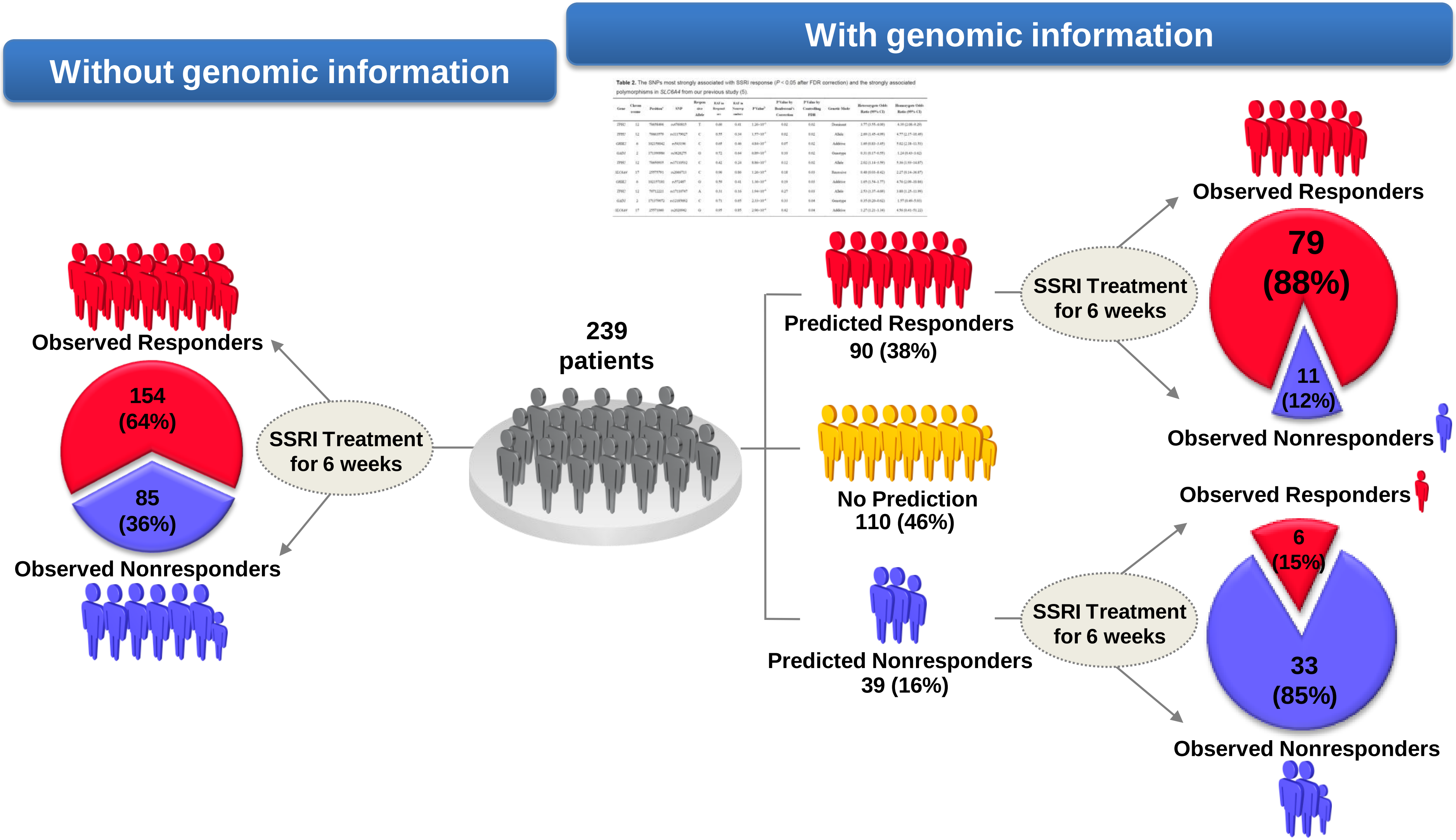
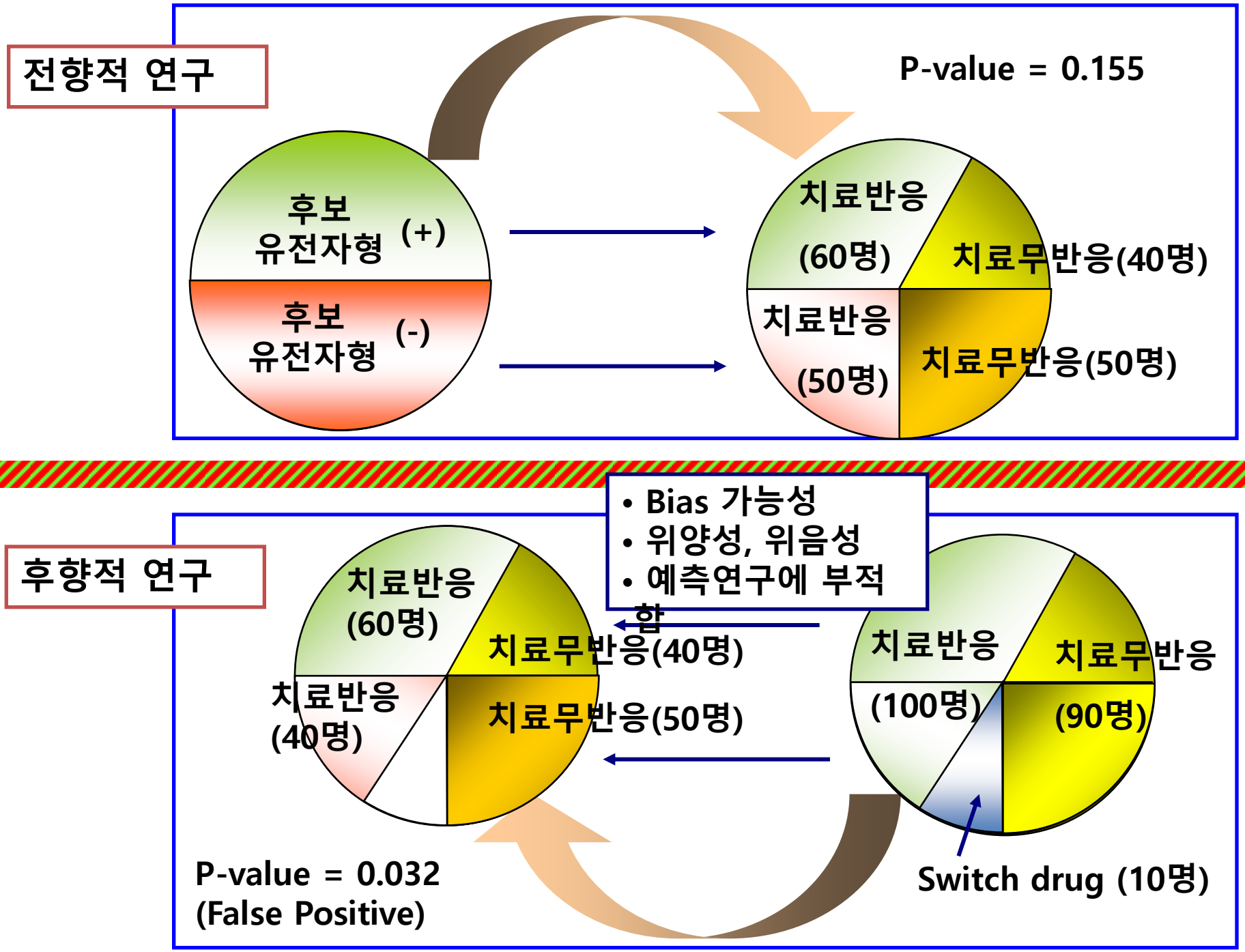
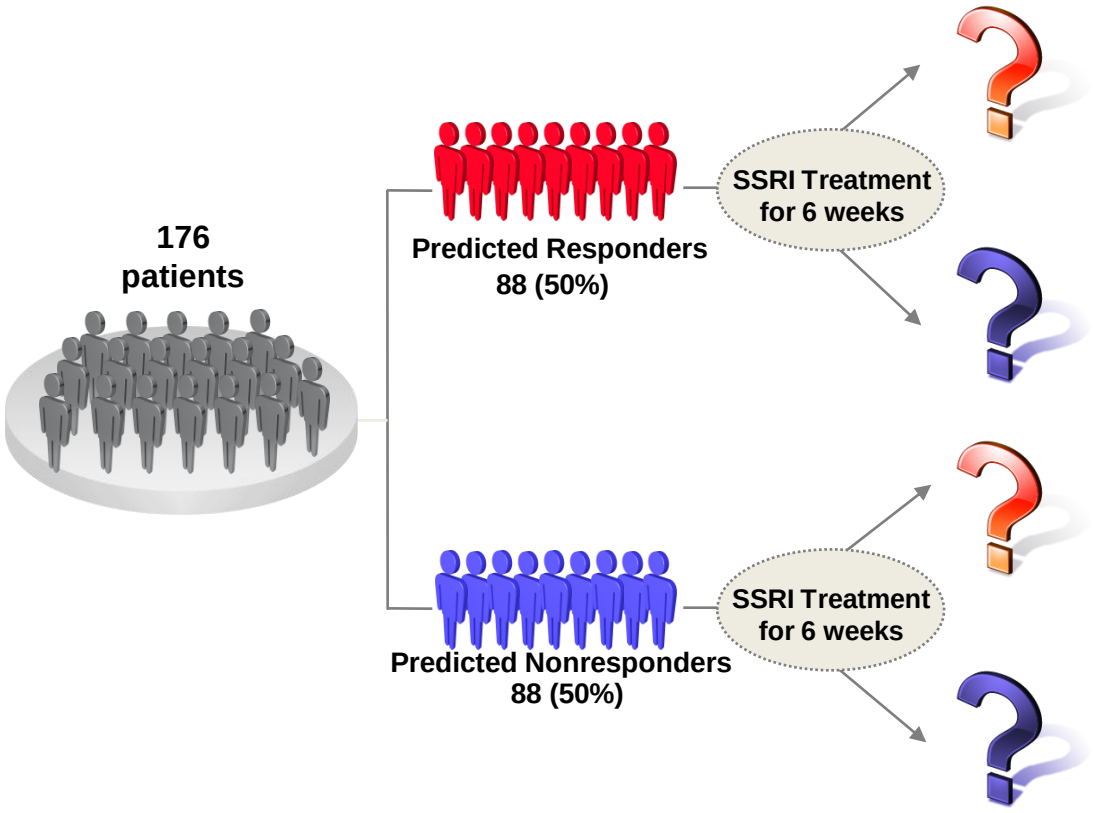
A 239 Patients in model development set



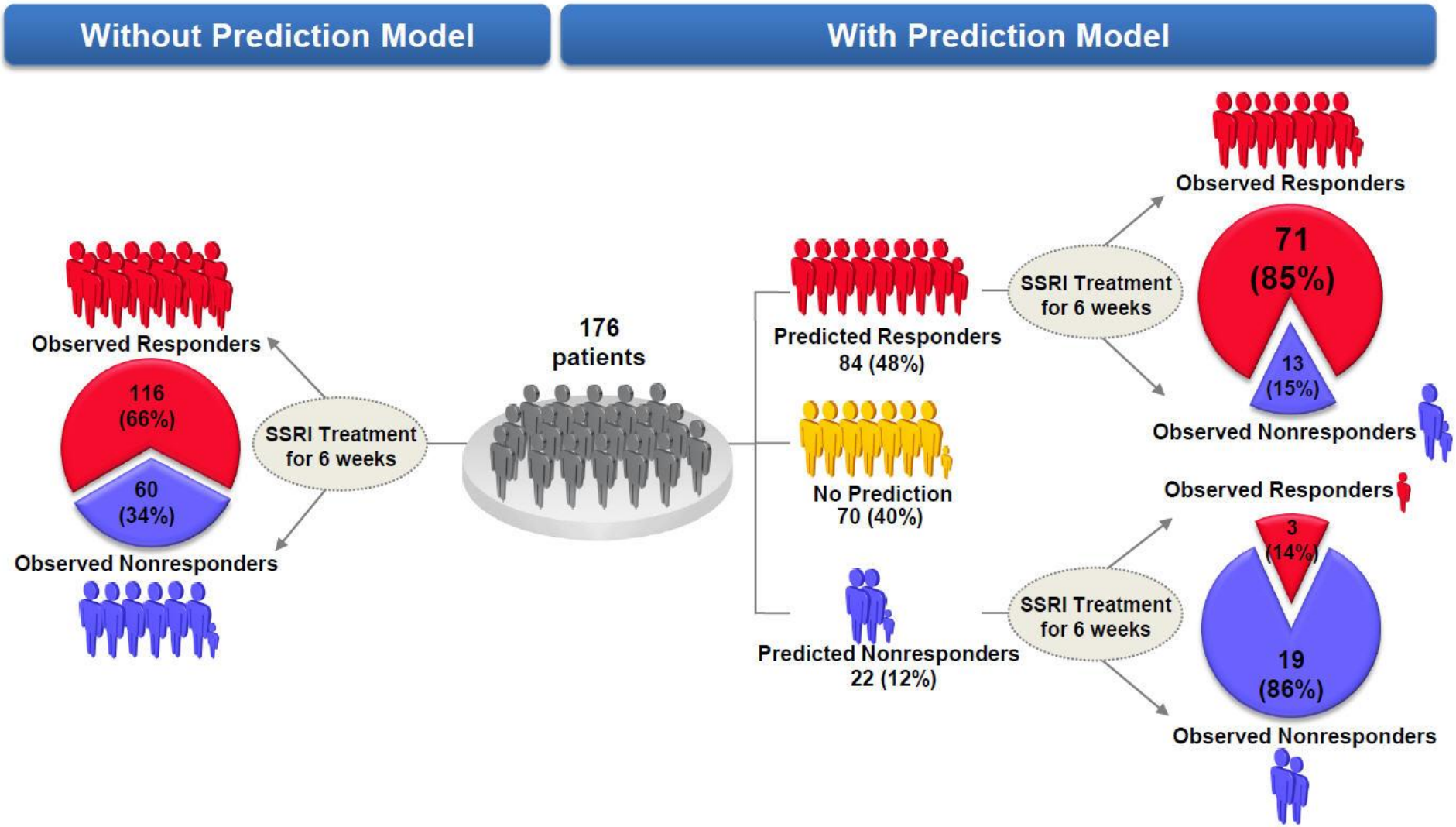

전향적 연구
P-value = 0.155
후보 유전자형 (+)
후보 유전자형 (-)
치료반응 (60명)
치료무반응(40명)
치료반응 (50명)
치료무반응(50명)
• Bias 가능성
• 위양성, 위음성
• 예측연구에 부적합
후향적 연구
치료반응 (60명)
치료무반응(40명)
치료반응 (40명)
치료무반응(50명)
치료반응 (100명)
치료무반응 (90명)
Switch drug (10명)
P-value = 0.032
(False Positive)

176 Patients in model validation set

With Prediction Model



(B) 176 Patients in Model Validation Set



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Cross-Validation of Prediction Modeling

Table 1. GOODNESS OF FIT TESTING
FOR 61 CASES PREDICTED TO BE SSRI RESPONDERS

	RESPONSE	NON-RESPONSE
Expected Outcome (base rate)	55 (90%)	6
Observed Outcome to **non-SSRI**	43 (70%)	18

PPV of 0.91 (from the developmentset and the SSRI validation set)
Goodness of Fit Chi square = 24.44, $p < 0.0001$
Odds Ratio of Response = 2.88 when model predicts response in these 84 cases.

Table 2. GOODNESS OF FIT TESTING
FOR 23 CASES PREDICTED TO BE SSRI NON-RESPONDERS

	RESPONSE	NON-RESPONSE
Expected Outcome (base rate)	3 (13%)	20
Observed Outcome to **non-SSRI**	12 (52%)	11

NPV of 0.87 (from the developmentset and the SSRI validation set)
Goodness of Fit Chi square = 27.69, $p < 0.0001$
Odds Ratio of Nonresponse = 13.6 when model predicts nonresponse in these 22 cases.

SSRI 예측모형에서 "predicted non-responder" 유전형을 가지는 환자들에게는 non-SSRI 계열의 항우울제를 투여함으로써 치료성공률을 유의한 수준으로 향상시킬 수 있다.

Derivation Sample

298 Received **SSRI** antidepressant
(129 Fluoxetine, 70 Paroxetine, 99 Sertraline)

59 Noncompleters
12 Low plasma drug concentrations
5 Extensive drug metabolism
7 Nonadherence
17 Did not follow scheduled clinic visits
30 Dropped out
21 Intolerable adverse events
(8 Fluoxetine, 5 Paroxetine, 8 Sertraline)
9 Consent withdrawal

239 Completed 6-week assessment and were included in analyses
(104 Fluoxetine, 56 Paroxetine, 79 Sertraline)

154/239 Responders (64%) | 90/239 Remitters (37%)

Validation Sample

219 Received **SSRI** antidepressant
(105 Fluoxetine, 68 Paroxetine, 46 Sertraline)

43 Noncompleters
8 Low plasma drug concentrations
3 Extensive drug metabolism
5 Nonadherence
11 Did not follow scheduled clinic visits
24 Dropped out
19 Intolerable adverse events
(8 Fluoxetine, 7 Paroxetine, 4 Sertraline)
5 Consent withdrawal

176 Completed 6-week assessment and were included in analyses
(86 Fluoxetine, 54 Paroxetine, 36 Sertraline)

116/176 Responders (66%) | 73/176 Remitters (41%)

Cross-Validation Sample

234 Received **non-SSRI** antidepressant
(35 Milnacipran, 41 Venlafaxine, 85 Nortriptyline, 73 Mirtazapine)

45 Noncompleters
10 Low plasma drug concentrations
3 Extensive drug metabolism
7 Nonadherence
9 Did not follow scheduled clinic visits
26 Dropped out
21 Intolerable adverse events
(4 Milnacipran, 4 Venlafaxine, 8 Nortriptyline, 5 Mirtazapine)
5 Consent withdrawal

189 Completed 6-week assessment and were included in analyses
(28 Milnacipran, 33 Venlafaxine, 68 Nortriptyline, 60 Mirtazapine)

114/189 Responders (60%) | 62/189 Remitters (33%)

Sent for external review
1 | view

Sent for external review

Manuscript 43119

Our reference: **43119-RG-1** | Submission details | Invoice
Submitted: March 25, 2010 | **Under consideration**

IF 16.6, 2010

Summary of submission details

Manuscript type

Regular

Title

Genomic Markers of Antidepressant Response to Selective Serotonin Reuptake Inhibitors

< 이전 | 목록 | 다음 >

답장 | 전달 | 전체답장 | 삭제 | 내용보기 | 원문보기 | 원문저장 | 인쇄

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제 목: JCI - Decision on manuscript 43119-RG-1

May 28, 2010

Prof. Doh Kwan Kim
Samsung Medical Center, Sungkyunkwan University School of Medicine
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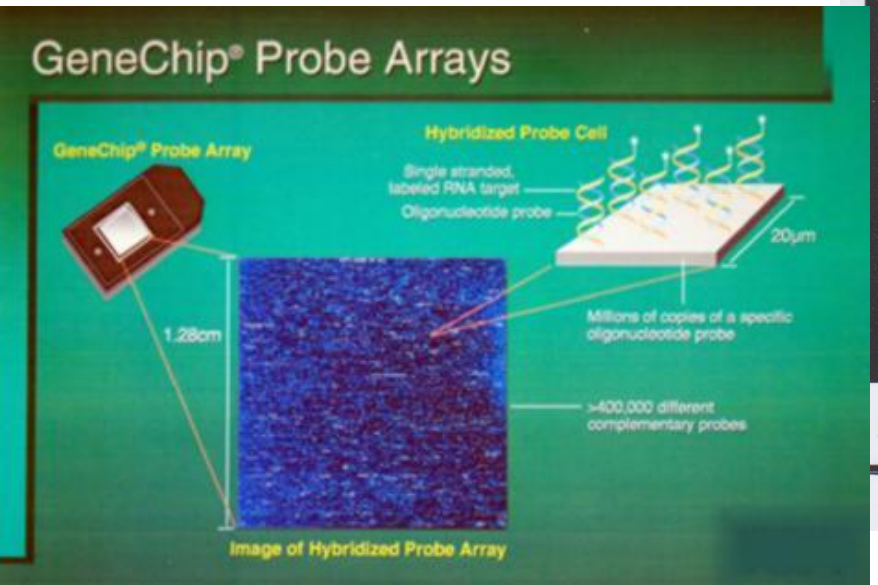
RE: Genomic Markers of Antidepressant Response to Selective Serotonin Reuptake Inhibitors (our reference 43119-RG-1)

Dear Prof. Kim,

Thank you again for the improvements in your manuscript. We are definitely interested in the paper but need what we hope will be a final revision to deal with the remaining points detailed below in order to make our final decision regarding publication. I hope we can receive your revision as soon as possible.

해외특허출원 –미국
(11/867,400) 2007.10.4



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October 16, 2007

VIA E-MAIL
nampat@nampat.co.kr

Nam & Nam
World Patent and Law Firm
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Re: New U.S. Provisional Patent Application Serial No. 11/867,400
Title: GENETIC SCREENING FOR PREDICTING ANTIDEPRESSANT DRUG RESPONSE BASED ON THE MONOAMINE TRANSPORTER GENE POLYMORPHISM COMBINATION
Our Ref: P08208US00 Your Ref: IPN-0034492.00/US

Dear Sir or Madam:

We have received notification from the Patent Office that the above application has been given Serial No. 11/867,400 under the filing date of October 4, 2007. Also enclosed please find the Information Disclosure Statement that was also filed with the U.S. Patent Office.

It will be sometime before further word is heard from Washington, but in the meantime your client may continue to exploit the invention under the term "Patent Pending". When an action from Washington is received, we will be in touch.

We have filed the application claiming "small entity status" which means that your client is entitled to the benefit of the lower filing fees required by the Patent Office. However, should this status change at any time during the pending application, it will be necessary for us to notify the Patent Office. For example, if your client were to license the patent, sell it, or enter into any agreement with a company which has more than 500 employees, it would be necessary to notify the Patent Office. Failure to do so could affect the validity of the patent. Therefore, if any such change occurs, please let us know immediately.

If you are aware of any patents or publications which are relevant to this application, please bring them to our attention immediately. We need to provide copies of these references to the Patent Office. Failure to do so could affect the validity of your patent.

Very truly yours,

WENDY K. MARSH

WKM/jc
Enclosure

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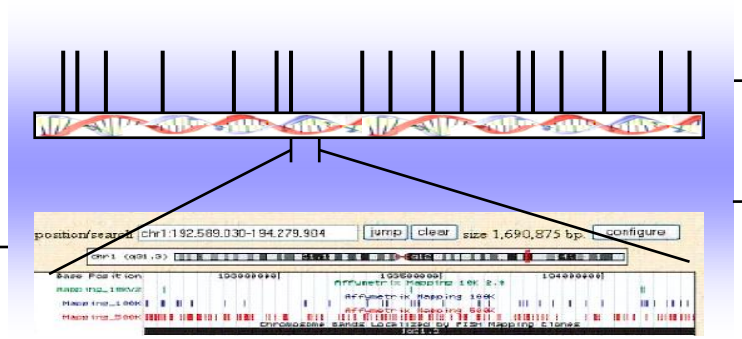
항우울제 반응예측 유전자형의 선별



gDNA

1502개 SNP

백만개 SNPs

백만개 CNVs

전체 게놈 연합연구

후보유전자형 연합연구

Copy Number Variation

최종 후보유전자형 선별

Replication 연합연구

유전자형 조합, haplotype 분석

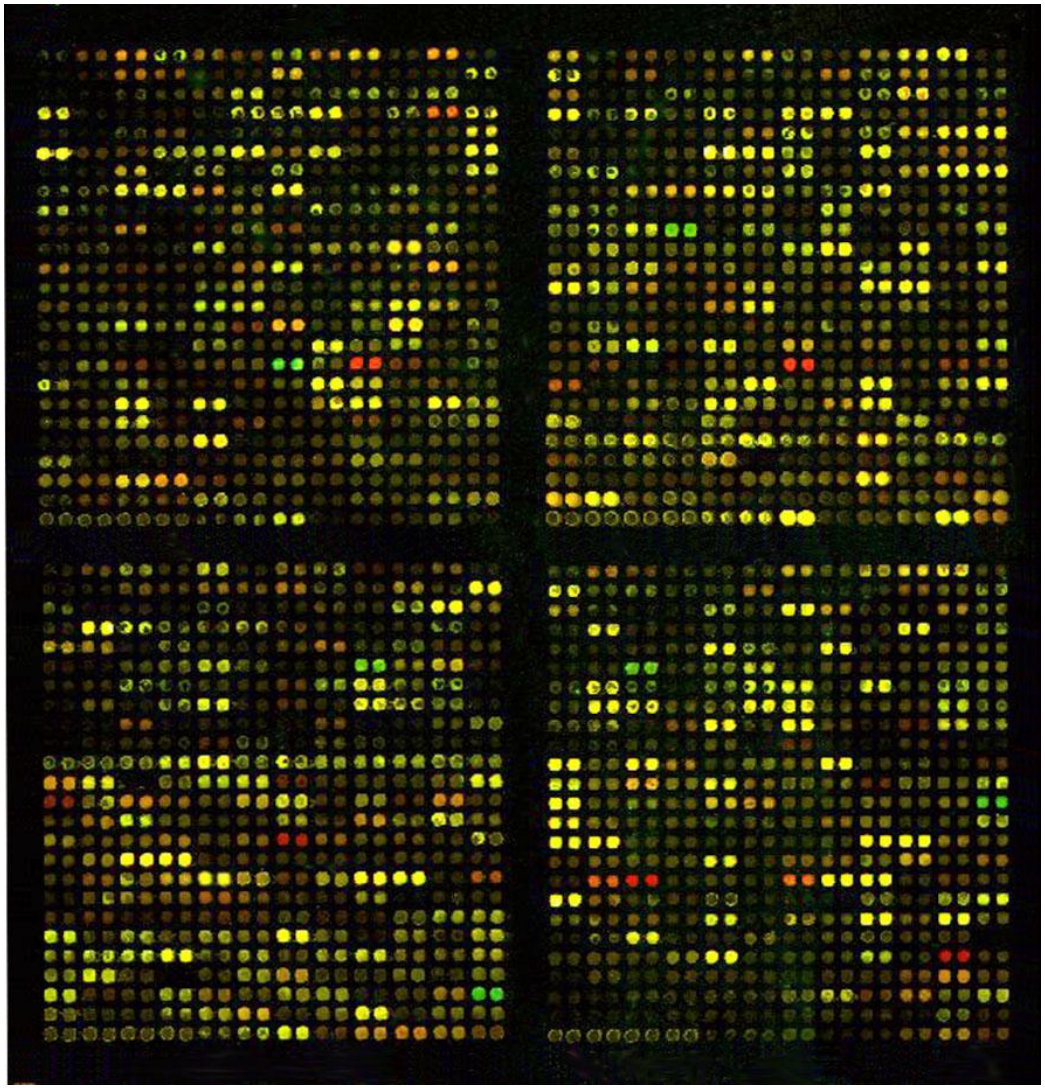
선별

선별

항우울제 치료 반응 예측 도구 개발

Model Development Set: GWAS

- Affymetrix 6.0 Genome-Wide SNP Array 6.0
- Platform to detect 1,852,600 markers (SNPs)

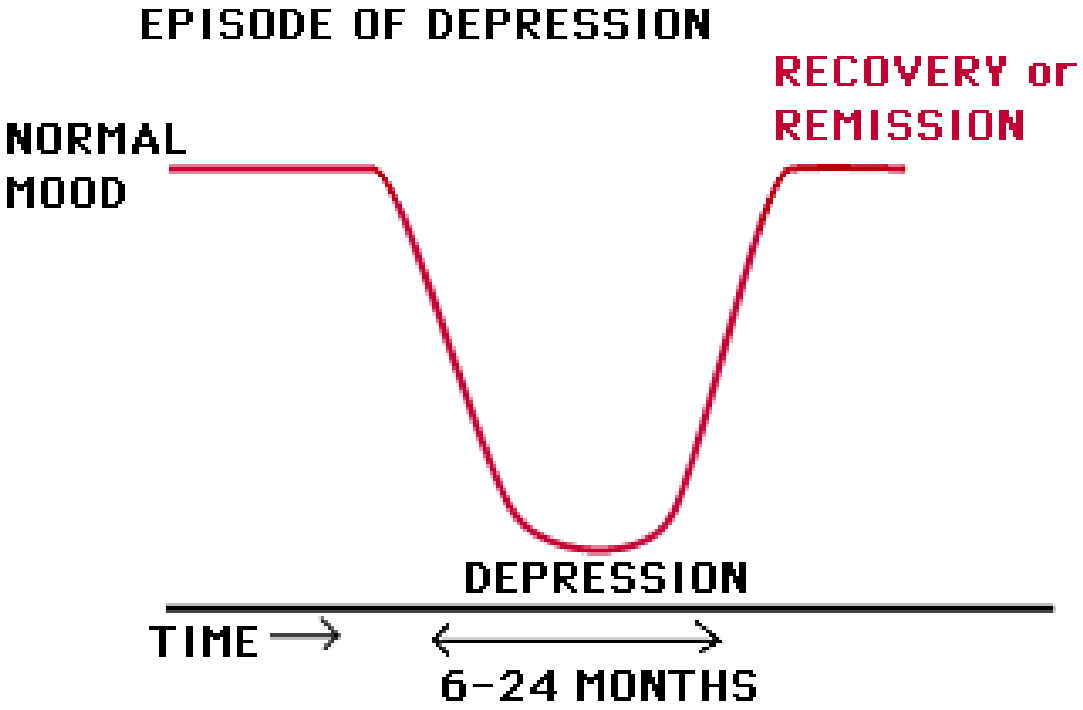


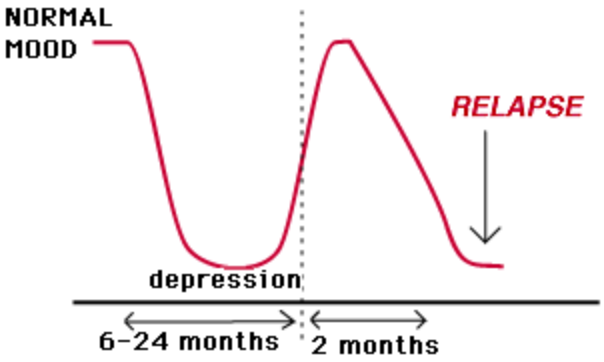
Human has

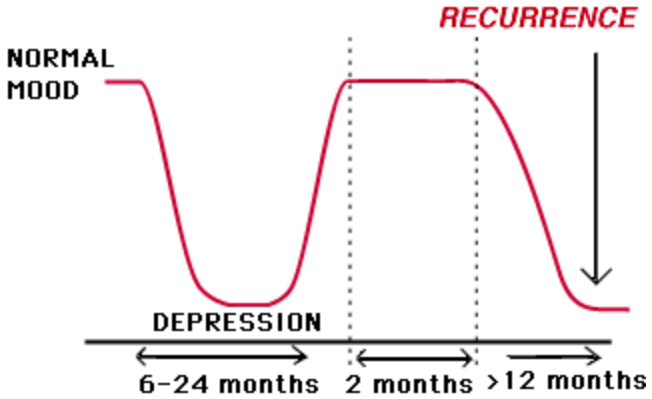
- 23 pairs of chromosome
- 20,000 ~ 35,000 genes
- 100,000 proteins
- 3,000,000,000 bp
- 10,000,000 ~ 30,000,000 potential SNPs (SNPs every 100~300 bases)

우울증 환자 치료의 문제점

우울증은 자꾸 재발하는 병입니다 !

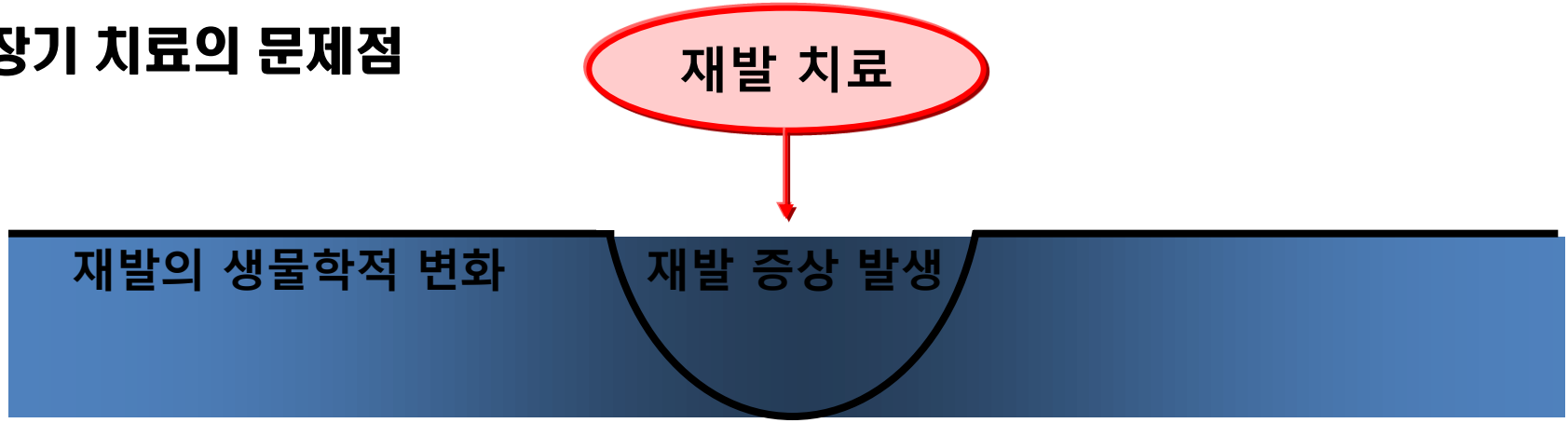




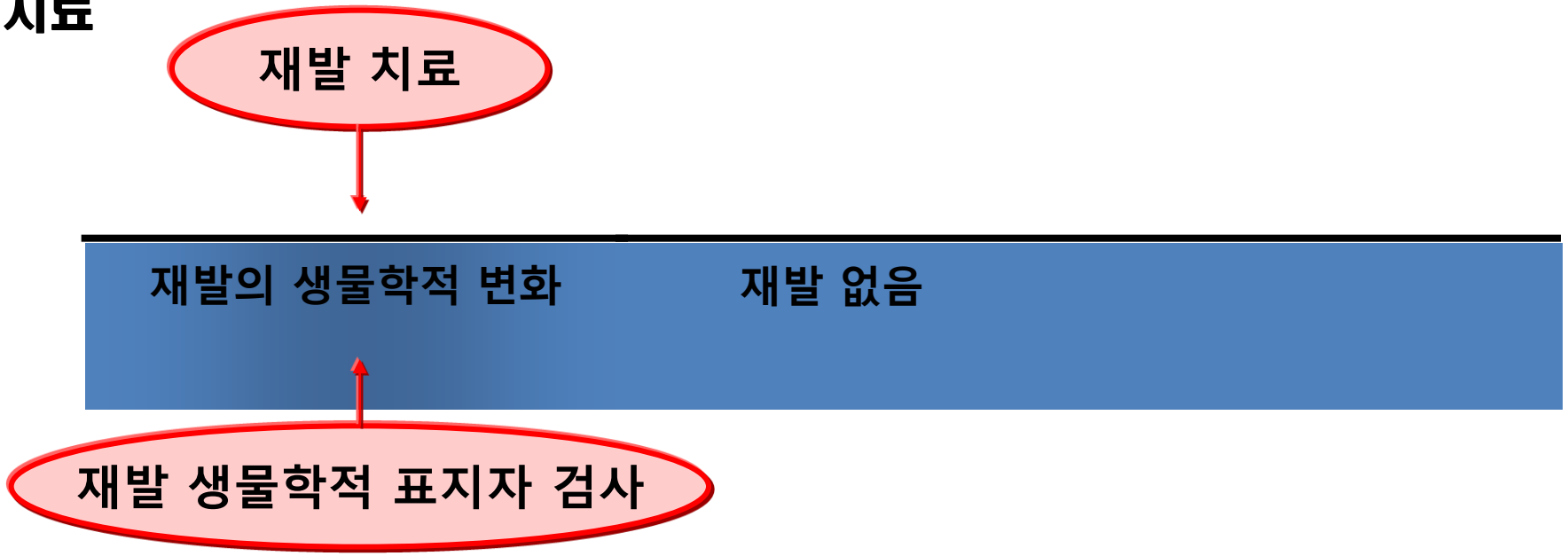


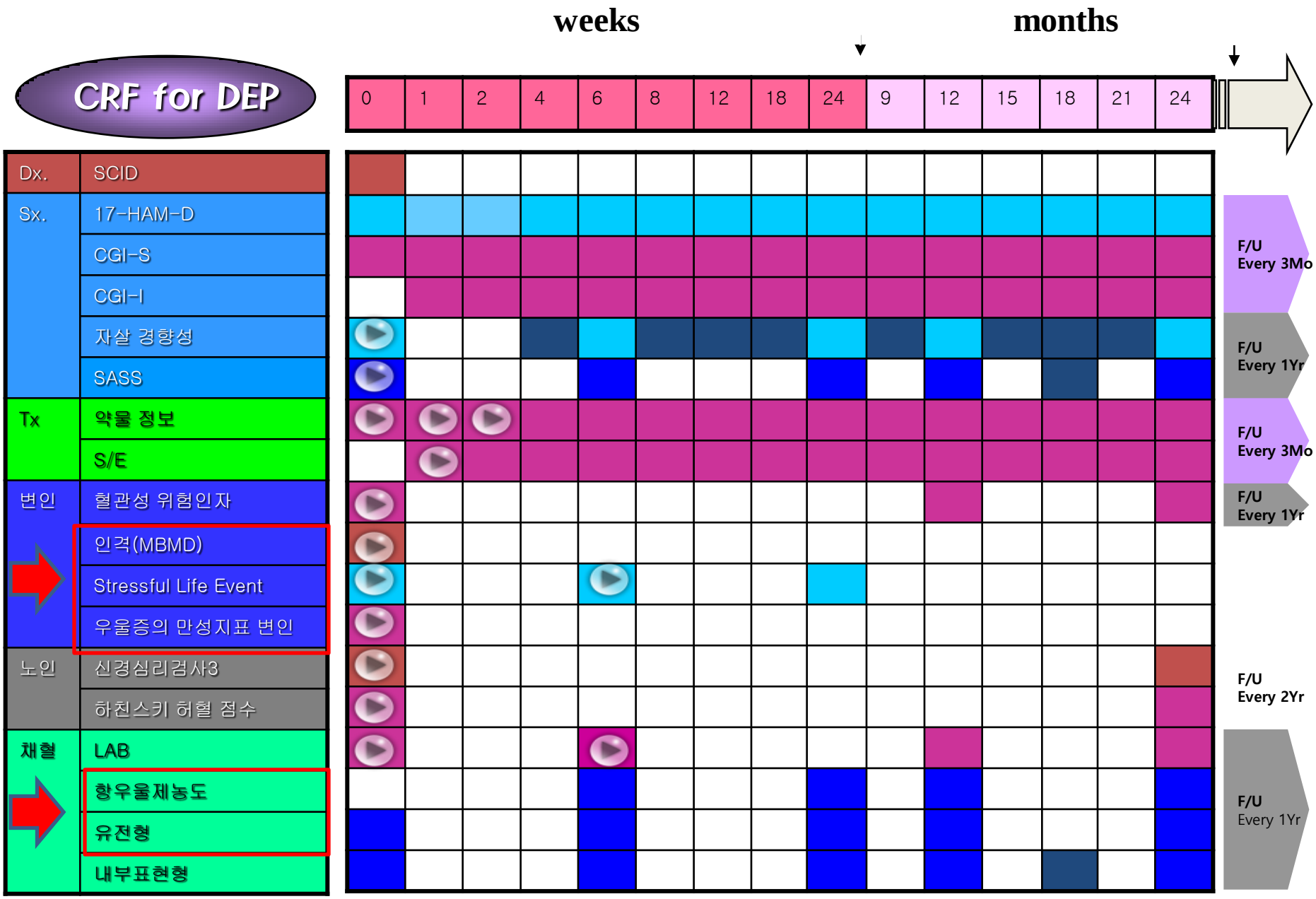
우울증 환자 중장기 치료의 문제점과 맞춤치료

현재 중장기 치료의 문제점



맞춤치료




weeks
months
CRF for DEP
0
1
2
4
6
8
12
18
24
9
12
15
18
21
24
Dx.
SCID
Sx.
17-HAM-D
CGI-S
CGI-I
자살 경향성
SASS
Tx
약물 정보
S/E
변인
혈관성 위험인자
인격(MBMD)
Stressful Life Event
우울증의 만성지표 변인
노인
신경심리검사3
하친스키 허혈 점수
채혈
LAB
항우울제농도
유전형
내부표현형
F/U
Every 3Mo
F/U
Every 1Yr
F/U
Every 3Mo
F/U
Every 1Yr
F/U
Every 2Yr
F/U
Every 1Yr

생물학적 표지자 개발 전략

항우울제 약물치료개시

Weeks

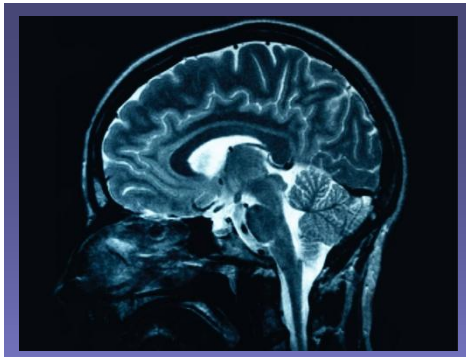
Month

0 1 2 4 6 12 HAM-D, CGI scoring 24 9 12 약물중단 18 재발 36

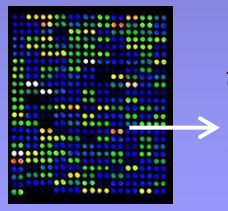
약물반응예측

치료경과확인

재발예측

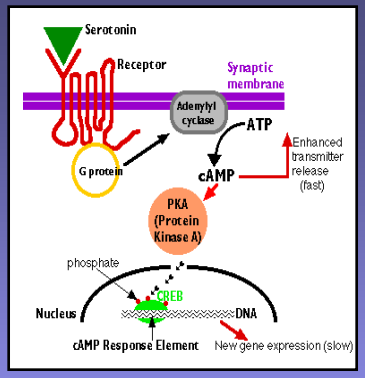


약물유전체학 결과



해당 내부표현형 연구

신호전달계



cAMP 계

Ca2+ 계

MAPK 계

신경발생계

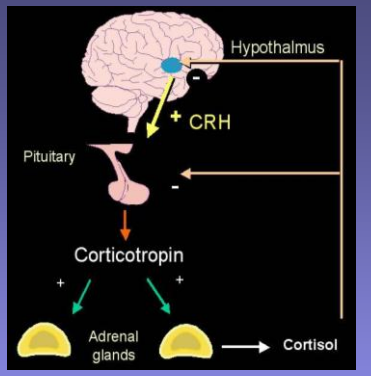
신경친화성인자

시냅스가소성 관련

프로제니터 세포증식

세포생존 관련

글루코코티코이드계



림프구 민감도

글루코코티코이드 수용체 활성화 (핵내 translocation)

신호전달계 표지자

CREB of T Lymphocyte

TABLE 2. Baseline Level of Transcription Factor, CREB.

Variables#	Normal (N=34)	Depressed patients (N=69)	p§	Responder (N=36)	Nonresponder (N=33)	p§
tCREB	69.9(61.7–89.9)	60.5(53.0–74.2)	0.0145*	56.7(50.6–66.5)	68.0(58.7–77.6)	0.0010*
pCREB	122.0(113.9–127.8)	98.6(86.6–112.3)	<0.0001*	93.8(85.3–110.3)	101.5(90.1–114.4)	0.3044
CRE-DNA binding	66.8(60.7–80.8)	72.6(60.3–81.8)	0.5676	64.4(58.2–77.3)	75.9(66.6–85.4)	0.0129*

Expressed as optical density (arbitrary units, Median (25% interquatial range–75% interquatial range)); tCREB represents the immunoreactivity level of total CREB proteins, comprising both activated and non-activated forms; pCREB denotes active phosphorylated CREB; CRE-DNA binding denotes the binding level of the radioisotope-labeled cre-consensus DNA sequence to pCREB.
* Significant differences between two groups (p<0.05)
§ Mann-Whitney test

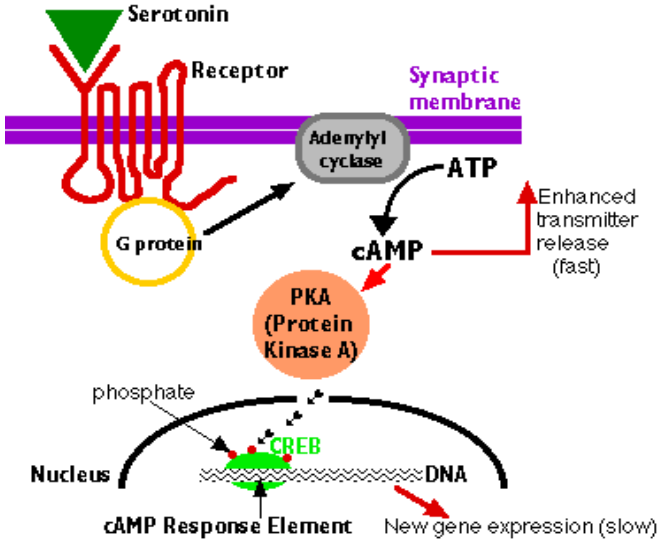
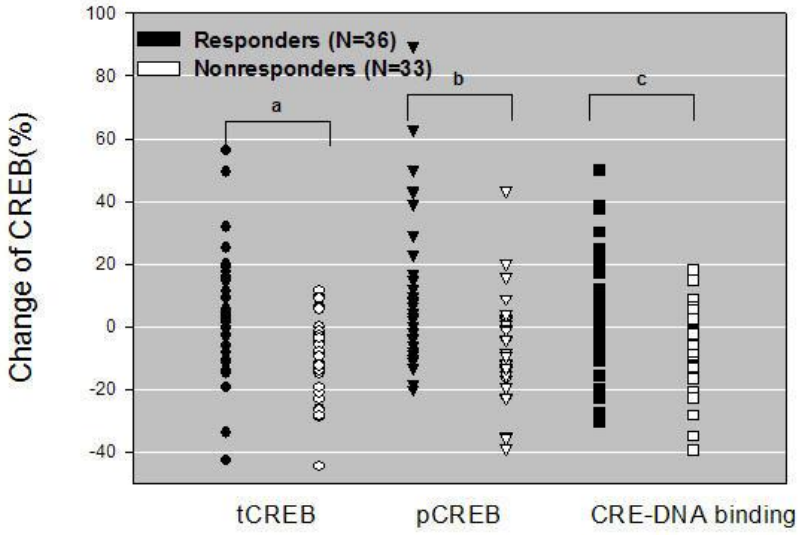


FIGURE 1. CREB Change in Responders and Nonresponders During 6 Week after Selective Serotonin Reuptake Inhibitor Treatment

(A) Different Changes of CREB between Responders and Nonresponders

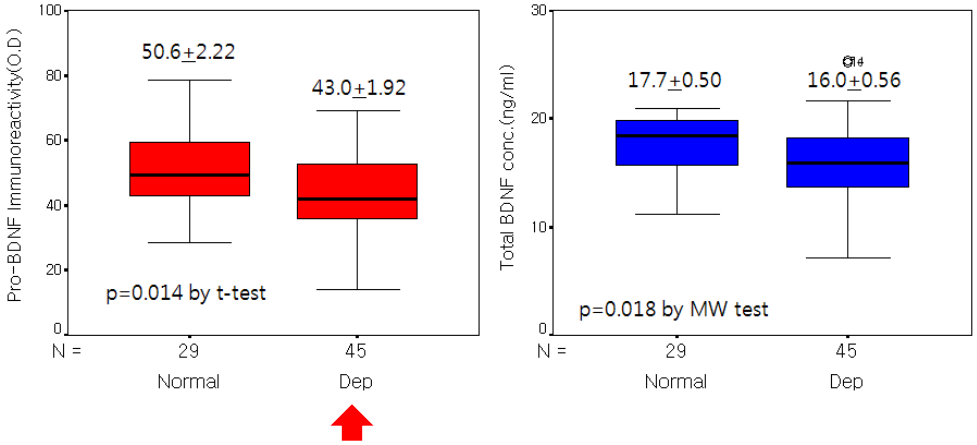


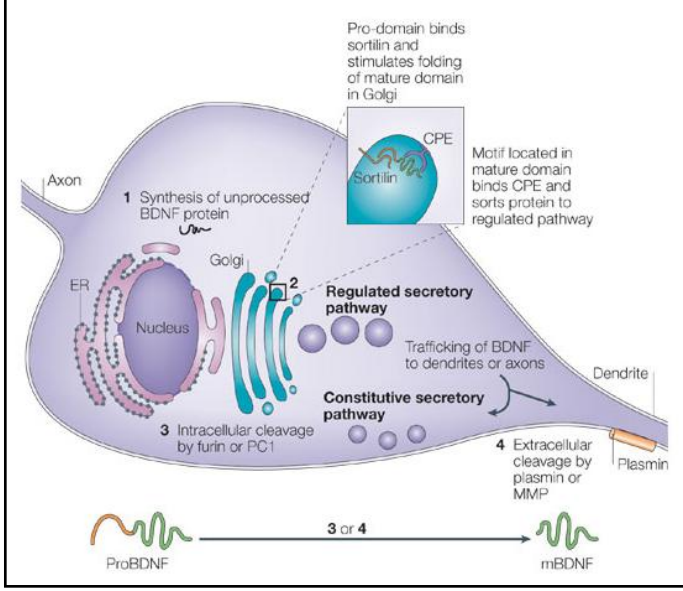
(Lim et al. in Press)

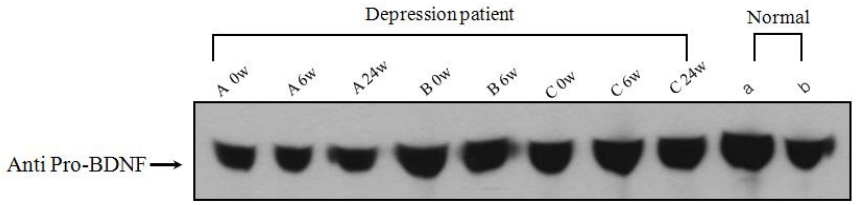
신경발생계 표지자

BDNF in Serum

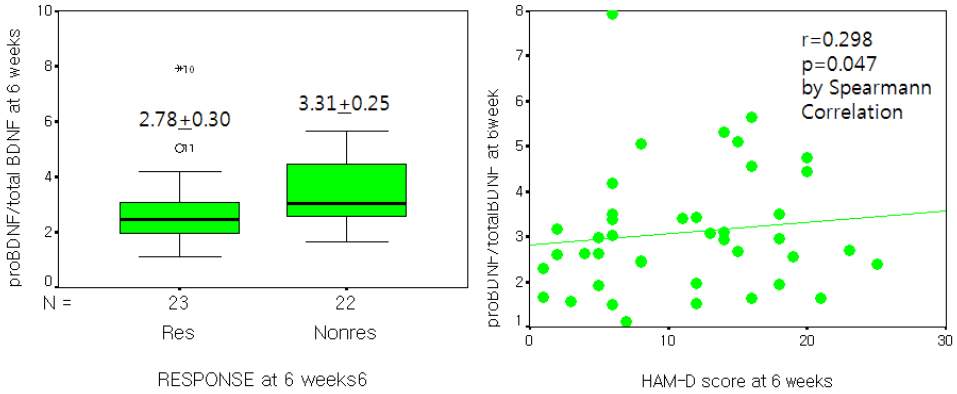
우울증 취약성 생물학적 표지자 가능성







약물 치료반응 예측능력



(Kim et al. 2008)

S100B in Serum

ORIGINAL ARTICLE
Psychiatry Investig 2008:5:193-198
Print ISSN 1738-3684 / On-line ISSN 1976-3026

Serum S100B Levels and Major Depressive Disorder: Its Characteristics and Role in Antidepressant Response

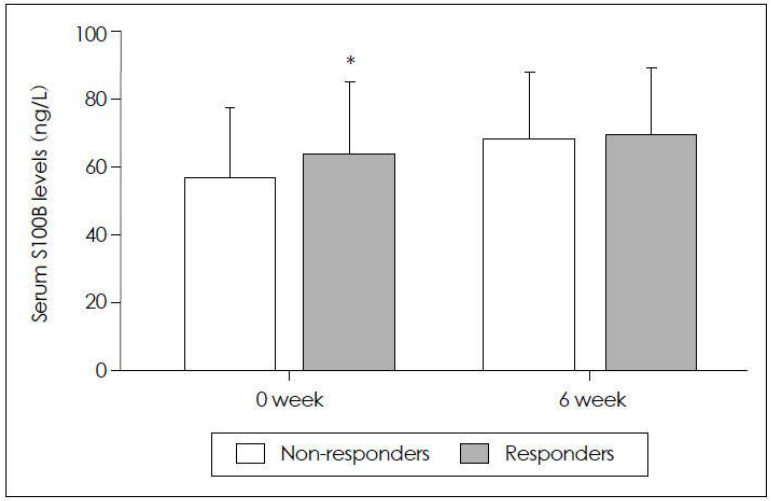


FIGURE 1. Comparison of serum S100B levels between antidepressant responders and nonresponders at baseline and after 6 week antidepressant treatment. Boxes represent means and error bars represent standard deviations. Serum S100B level was significantly higher in responders than in nonresponders at baseline. *p<0.05.

(Chang et al. 2008)

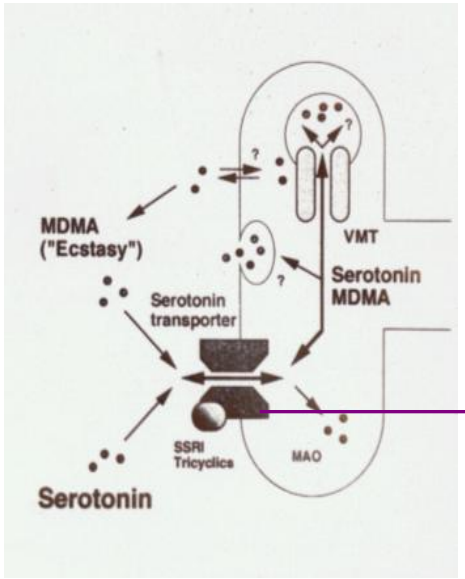
선별된 유전자에서의 표지자 개발

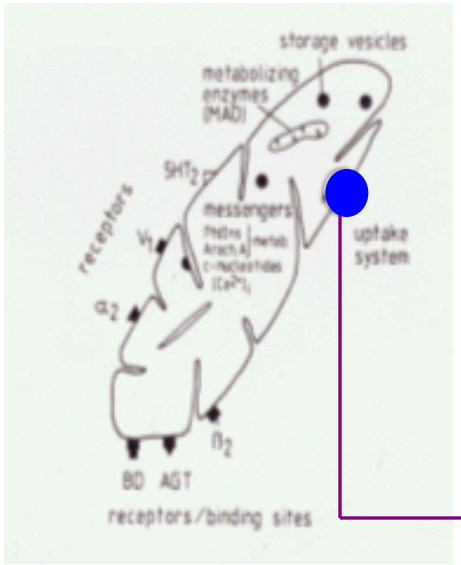
후보유전자형 연합연구결과에 기초

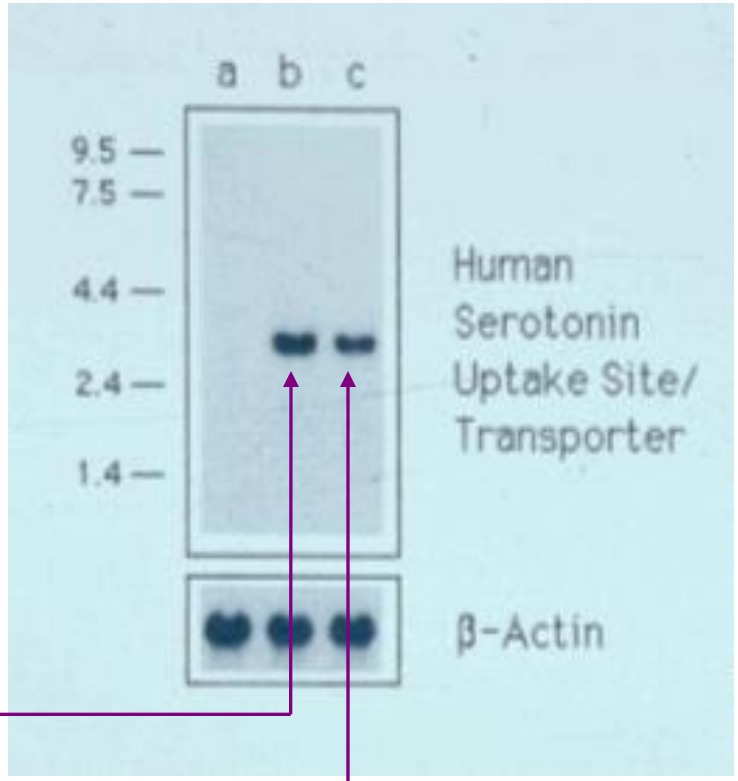
Table 2. The SNPs most strongly associated with SSRI response ($P < 0.05$ after FDR correction) and the strongly associated polymorphisms in *SLC6A4* from our previous study (5).

Gene	Chromosome	Position[a]	SNP	Responsive Allele	RAF in Responders	RAF in Nonresponders	P Value[b]	P Value by Bonferroni's Correction	P Value by Controlling FDR	Genetic Mode	Heterozygote Odds Ratio (95% CI)	Homozygote Odds Ratio (95% CI)
TPH2	12	70658496	rs4760815	T	0.60	0.41	1.26×10^{-5}	0.02	0.02	Dominant	3.77 (3.55–4.00)	4.39 (2.08–9.29)
TPH2	12	70663579	rs11179027	C	0.55	0.34	1.57×10^{-5}	0.02	0.02	Allele	2.69 (1.45–4.99)	4.77 (2.17–10.49)
GRIK2	6	102158042	rs543196	C	0.65	0.46	4.84×10^{-5}	0.07	0.02	Additive	1.69 (0.83–3.45)	5.02 (2.18–11.53)
GAD1	2	171390986	rs3828275	G	0.72	0.64	6.89×10^{-5}	0.10	0.02	Genotype	0.31 (0.17–0.55)	1.24 (0.43–3.62)
TPH2	12	70650935	rs17110532	C	0.42	0.24	8.86×10^{-5}	0.12	0.02	Allele	2.02 (1.14–3.59)	5.36 (1.93–14.87)
SLC6A4	17	25575791	rs2066713	C	0.96	0.86	1.26×10^{-4}	0.18	0.03	Recessive	0.48 (0.03–8.42)	2.27 (0.14–36.87)
GRIK2	6	102157181	rs572487	G	0.59	0.41	1.36×10^{-4}	0.19	0.03	Additive	1.65 (1.54–1.77)	4.76 (2.09–10.86)
TPH2	12	70712221	rs17110747	A	0.31	0.16	1.94×10^{-4}	0.27	0.03	Allele	2.53 (1.37–4.69)	3.88 (1.25–11.99)
GAD1	2	171379072	rs12185692	C	0.71	0.65	2.33×10^{-4}	0.33	0.04	Genotype	0.35 (0.20–0.62)	1.57 (0.49–5.03)
SLC6A4	17	25571040	rs2020942	G	0.95	0.85	2.96×10^{-4}	0.42	0.04	Additive	1.27 (1.21–1.34)	4.56 (0.41–51.22)

Autoradiogram of 5-HT Transporter







후보유전자형 연합연구결과에 기초

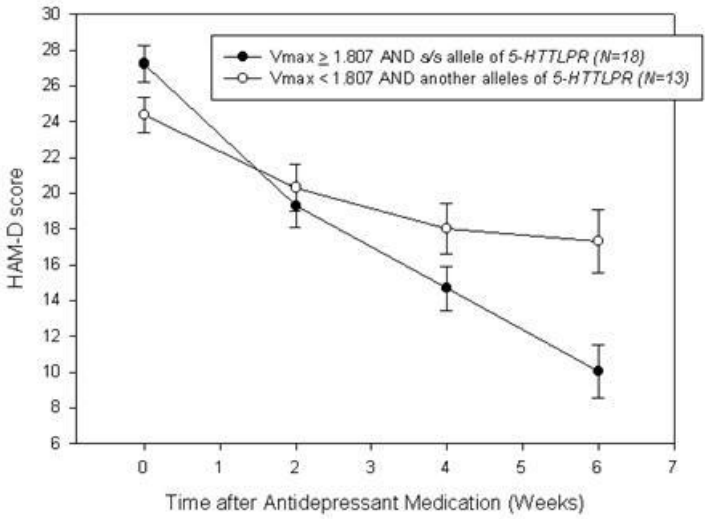
Table 5. Comparison of 5HTT Kinetic Characteristics between Depressive Patients and Normal Controls*

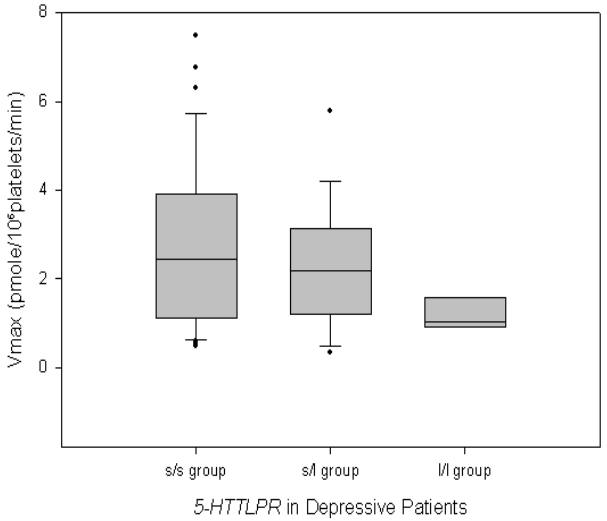
	Control Subjects (n=41)	Depressive Patients (n=87)	
5HTT Vmax Characteristics		Drug Responsive (n=54)	Drug Non-responsive (n=33)
Vmax (pmole/10^6platelets/min)	1.99 (1.35, 3.69)	1.78 (1.04, 3.58)	
		3.11† (1.68, 3.96)	0.93 (0.61, 1.44)
Km (10^{-7}moles)	3.11 (1.70, 5.42)	2.96 (1.54, 5.48)	
		4.07‡ (1.87, 6.47)	2.20 (0.95, 3.28)

*Data are given as median and interquartile range.

†$P<0.001$ vs drug non-responsive patient median (Mann-Whitney test).

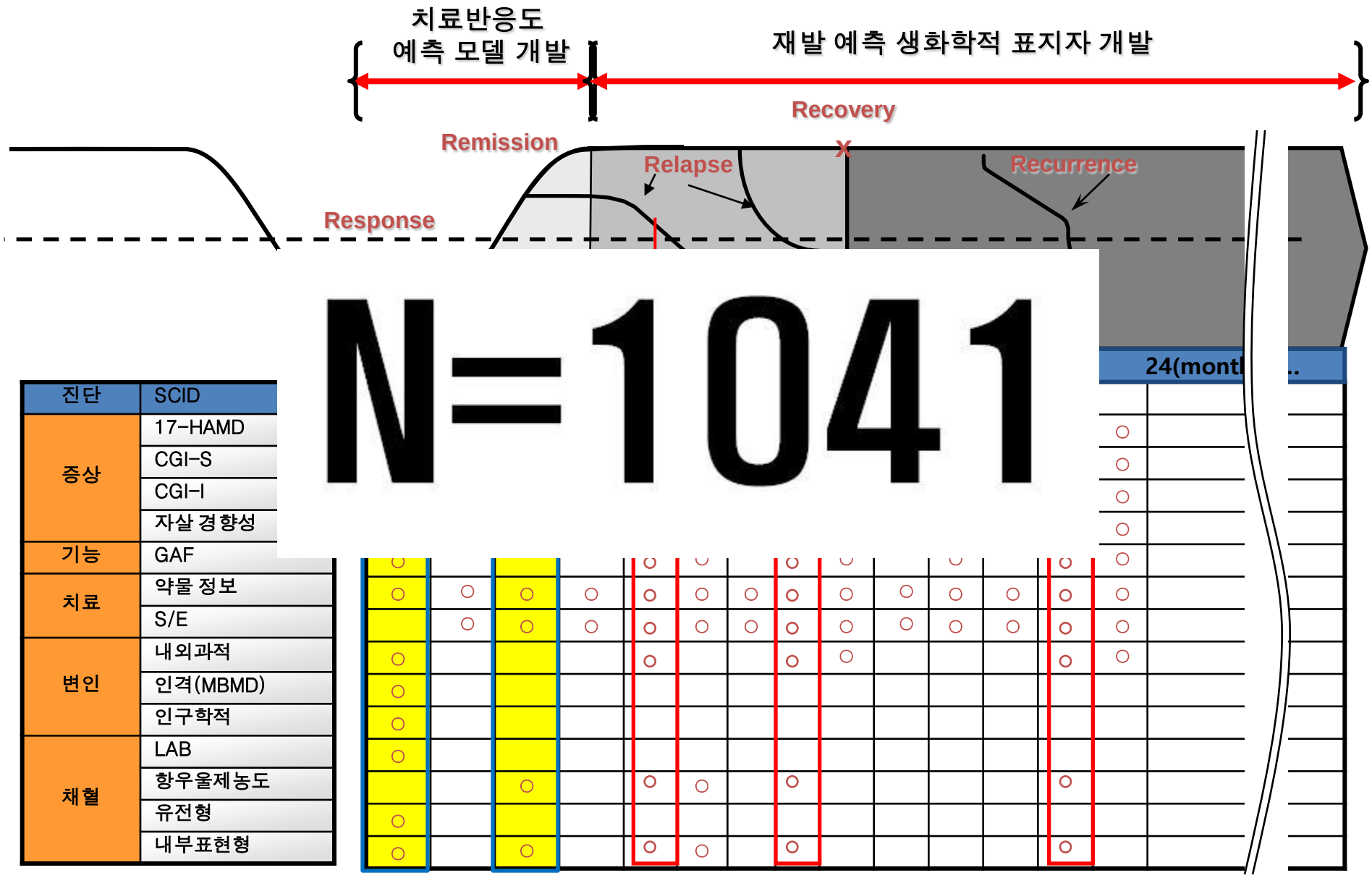
‡$P=0.006$ vs drug non-responsive patient median (Mann-Whitney test).





(Myung et al. Arch Gen Psychiatry, in Press)

우울증 질병경과와 재발을 예측하는 표지자 개발



N=1041

진단	SCID
증상	17-HAMD
	CGI-S
	CGI-I
	자살 경향성
기능	GAF
치료	약물 정보
	S/E
변인	내외과적
	인격(MBMD)
	인구학적
채혈	LAB
	항우울제농도
	유전형
	내부표현형

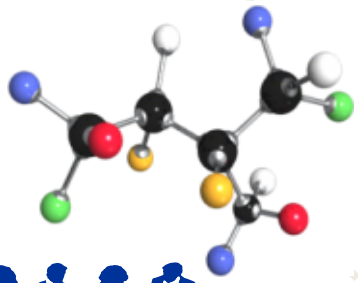
가. 우울증 환자 임상 코호트 운영

표현형

내부표현형

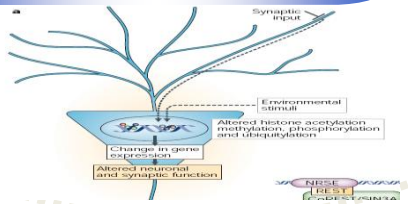
다. 치료반응/재발 예측 표지자 개발

유전형

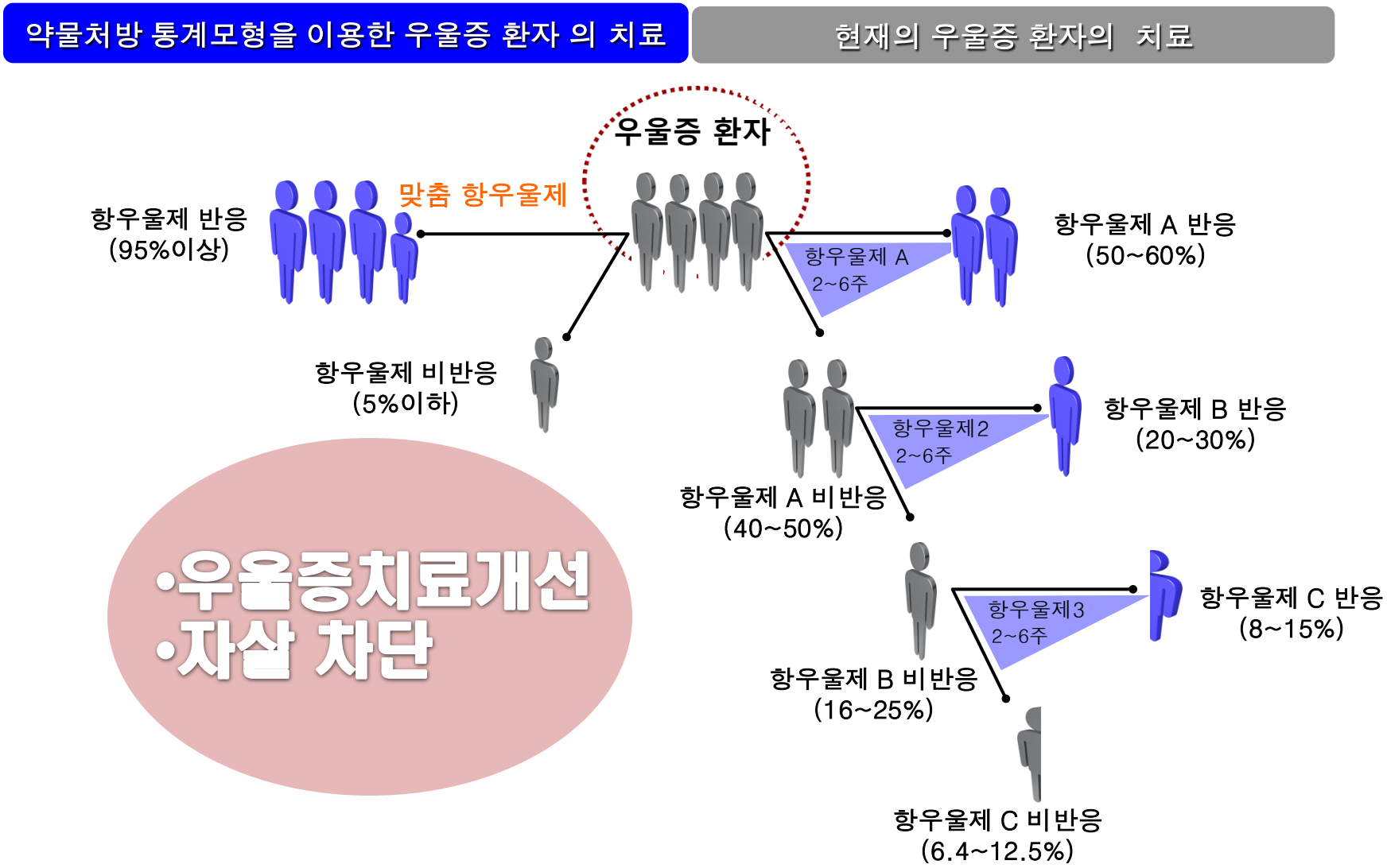


나. 유전자형선별 및 유전자 칩 개발

라. 유전형-내부표현형-표현형 기전 탐색

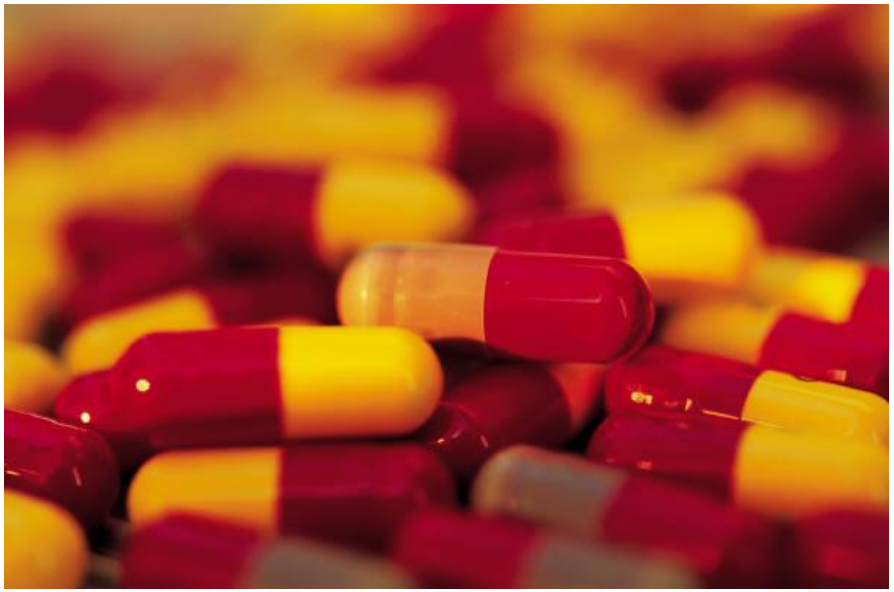


우울증 약물처방의 맞춤치료기술을 개발한다면…



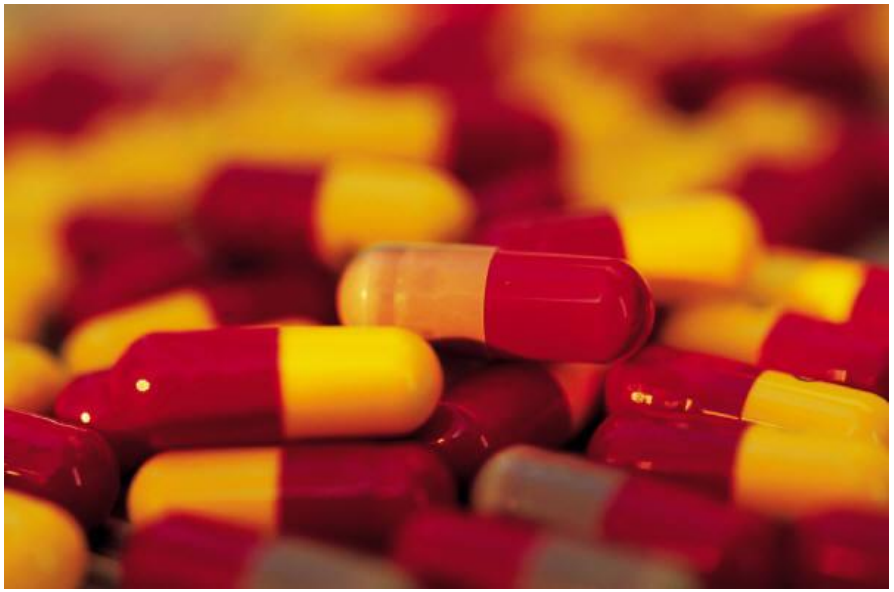
우울증 환자에 대한 항우울제 선택의 진료지침

- Anticipated adverse events and tolerability
- History of prior response
- Comorbidity
- Patient profile
- Patient preferences
- Cost

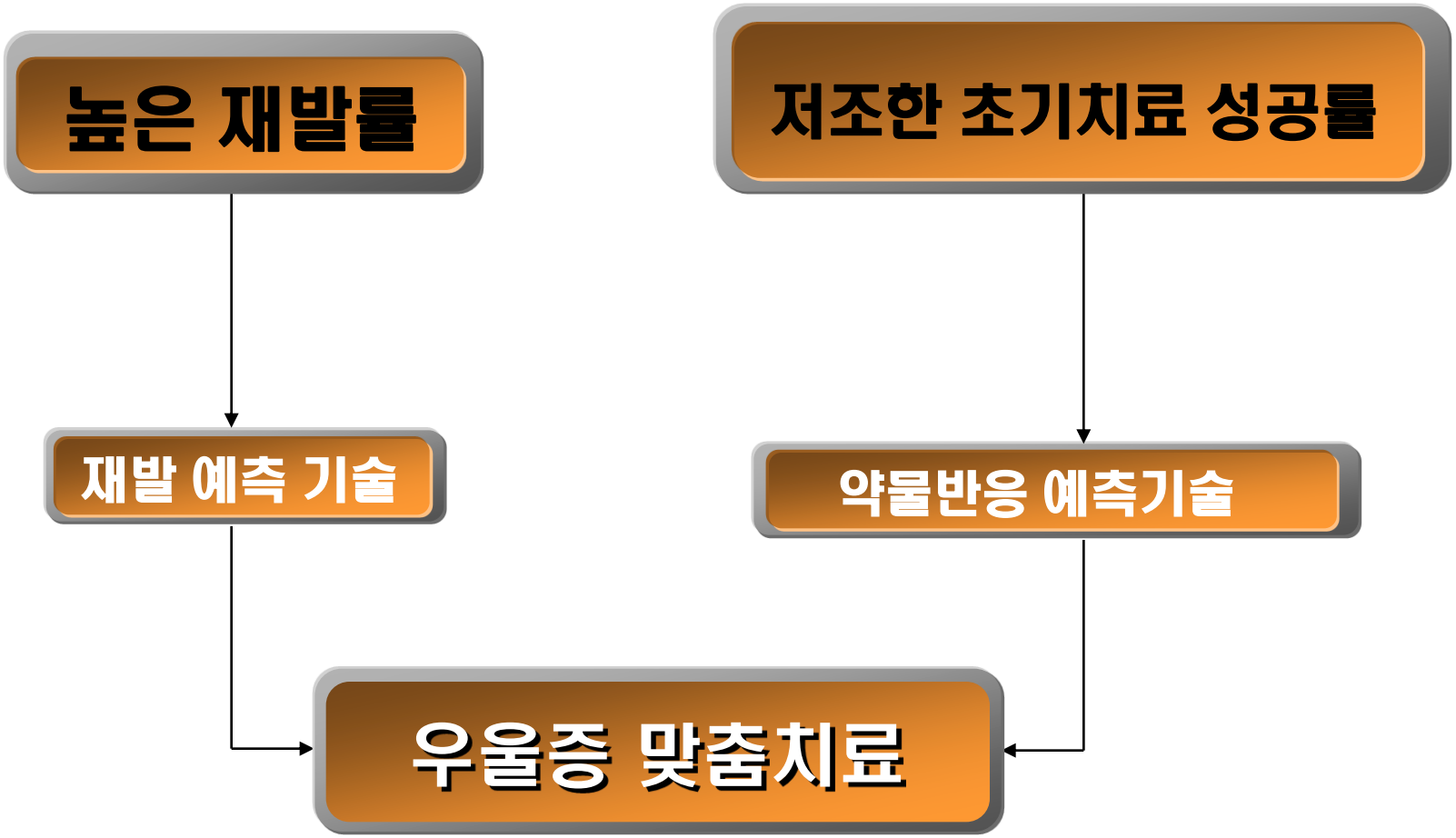


우울증 환자에 대한 항우울제 선택의 진료지침

- Favorable genomic markers for response
- Anticipated adverse events and tolerability
- History of prior response
- Comorbidity
- Patient profile
- Patient preferences
- Cost



우울증 맞춤치료기술



감사합니다!