

약물유전체학과 정신분열병*

이 규 영** · 정 인 원**†

Pharmacogenomics and Schizophrenia*

Kyu Young Lee, M.D.,** In Won Chung, M.D., Ph.D.**†

ABSTRACT

The pharmacotherapy of schizophrenia exhibits wide inter-individual variabilities in clinical efficacy and adverse effects. Recently, human genetic diversity has been known as one of the essential factors to the variation in human drug response. This suggests that drug therapy should be tailored to the genetic characteristics of the individual. Pharmacogenetics is the field of investigation that attempts to elucidate genetic basis of an individual's responses to pharmacotherapy, considering drug effects divided into two categories as pharmacokinetics and pharmacodynamics. The emerging field of pharmacogenomics, which focuses on genetic determinants of drug response at the level of the entire human genome, is important for development and prescription of safer and more effective individually tailored drugs and will aid in understanding how genetics influence drug response.

In schizophrenia, pharmacogenetic studies have shown the role of genetic variants of the cytochrome P450 enzymes such as CYP2D6, CYP2C19, and CYP2A1 in the metabolism of antipsychotic drugs. At the level of drug targets, variants of the dopamine D₂, D₃ and D₄, and 5-HT_{2A} and 5-HT_{2C} receptors have been examined. The pharmacogenetic studies in schizophrenia presently shows controversial findings which may be related to the multiple involvement of genes with relatively small effects and to the lack of standardized phenotypes. For further development in the pharmacogenomics of schizophrenia, there would be required the extensive outcome measures and definitions, and the powerful new tools of genomics, proteomics and so on.

KEY WORDS : Pharmacogenomics · Schizophrenia · Cytochrome P450 enzymes · Dopamine receptor · Serotonin receptor · Phenotype.

서 론

가 . 가 .

2001 6
 " Postgenomic Era in Biological Psychiatry " (Human Genome Project)
 .. 1990

Department of Psychiatry, Chungbuk National University Hospital, Cheong-ju, Korea 2001 2 11 ,

†교신저자 : , 361 - 711 62
) (043) 269 - 6364,) (043) 267 - 7951 2001 6 17 ,
 E - mail) iwchung@med.chungbuk.ac.kr 가

(target)

가 가

(Pharma- 가

cogenomics)

가
가

1. 약물유전체학(Pharmacogenomics)

1) 약물유전체학의 역사와 현재

510 , Pythagoras fava

bean

(Nebert 1999).

glucose -

6 - phosphate dehydrogenase deficiency

가 1994

200

가

10

4~ 가

6

(Lazarou 1998).

(Mager 1965). Snyder(1932) phenylthiourea non -
taster phenotype , 가

(Sagar 2000).

(Wieczorek Tsongalis 2001). aldehyde dehydroge-
nase deficiencies ,

?

(Inoue 1984). , N - acetyl transferase

, 가

가 slowest acetylator가

(Weber 1999).

(Propping Nothen 1995).

1950

(metabolism) (distribution)

, Vogel(1959)

(:)

(pharmacogenetics) '

(Evans Relling

DNA , 가

1999).

가

, 가

(

(per-

sonalized tailored pharmacotherapy) '

(Vogel 1959 ; Nebert 1997).

(mutation)

(heterogen-

가 ,

eity)

(dis-

tribution)

(encoding)

(pharmacogenomics) 가
 (genetic variant) (target) (Propping) (Evans
 Nothen 1995). Relling 1999 ; Nebert 1999 ; Cichon 2000).
 ' snip ' single
 nucleotide polymorphism(SNPs) (Isaksson 2000 ; (Peet Bey 2001).
 McCarthy Hilfiker 2000). nucleotide , 가
 DNA 가
 DNA (Brookes (Cichon 2000).
 1999). DNA
 DNA 가
 1000 (Brookes 1999). , 가 , 가
 30 nucleotide 가 ,
 3 coding region 20 가
 SNPs가 (Owen 2000). ,
 SNPs screening 가 .

(Evans Relling 1999 ; Nebert 1999). 가
 가 (Wieczorek Tsongalis 2001 ; Roses 2000).
 SNPs - ,
 20 DNA microarray 가
 , mRNA 10%
 (Watson 2000). chip 7 가 (Jablensky 1995).
 cDNAs 가 (Kaplan Sadock
 1998), (risperi-
 done, olanzapine, clozapine, quetiapine)

2) 약물유전체학의 정의 및 의의

(pharmacogenetics) ' 가
 , , , (pharmacokine- 가
 tics) , (target) (Kaplan Sadock 1998 ; Worrel 2000).
 (pharmacodynamics) 가
 (heridity) (Cichon 2000 ; Roses 2000). 가

, 가

CYP2C19, CYP1A2, CYP3A4, CYP2D6
CYP
, extensive metabolizer(EM) poor
가 metabolizer(PM) . PM phenotype ho-
(phenotype) . mozygous compound heterozygous PM
가 , EM phenotype homozygous wild type
heterozygous wild type/PM
(Coutts Urichuk 1999 ; Cichon 2000).
CYP2D6 PM
(CYP2D6 *3,*4,*9,*10) , CYP2D6
(complexed disorder) (genetic lo-
cus)가 (Daly 1996 ; Ohmori 1998).
(allele)가 (probe drug) debriso-
(vulnerability) quine/sparteine . Dahl Bertilsson
(multifactorial disorder) thioridazine (1993) debrisoquine PM EM perphenazine
, PM , ,
SNPs (Spina 1992a,b ; Vandel 1999).
CYP2D6
(Arthur 1995 ;
Andreassen 1997 ; Kapitany 1998 ; Ohmori 1998),
(Cichon 2000 ; Masellis 2000). (Ohmori 1999).
(psycho- CYP2D6
pharmacogenetics) 가 Marez (1997) 5~10%,
(psychopharmacogenomics) ' 2%, 7~8%가 debrisoq-
(Kawanishi 2000). uine/spartein PMs
CYP2D6 EM debriso-
quine haloperidol (Johansson
1994).
1) 약물 대사 효소의 유전자 변이 haloperidol
가 (Frackiewicz 1997 ; Mihara 1999).
CYP2D6
, PM
가 (biotrans-
formation) clozapine (bioavailability)
Aitchison (2000) clozapine CYP1A2(-/-) mice
clozapine , 가 가
cytochrome P450(CYP) CYP1A2
(Nebert, 1997), CYP2C9, , CYP1A2 colzapine

가 . pine (Ohara 1998 ; Arranz 1998a).

clozapine missense , rispeidone, olanzapine, .

quetiapine Cravchik (1996, 1999) Val96Ala mutation dopamine, (Prior 1999 ; Scordo chlorpromazine, clozapine , cAMP 1999). 가 , Pro310Ser, Ser311Cys muta- tion cAMP . D₂

2) 약물 대상(Target)의 유전자 변이 가 , Schafer (2001) D₂ taq haloperidol)

가 D₃ missense variant(Ser9Gly) (Crocq 1992). Shaikh (1996) clozapine Ser9 homozygote 가 , Malhotra (1998) clozapine Ser9 homozy- gote Ser9 homozygote heterozygote가 wild type D₃ GR99841 가 (Lundstrom Turpin, 1996). Krebs (1998) (association study)가 , nucleotide (SNPs) 5'-leader , SNPs , Ser9Gly mutation (linkage disequilibrium) (Si- vagnanasundaram 2000). clozapine 가 , 5-HT 가 가 D₄ clozapine 가 exon 3 16 (1) (Dopamine receptor) 가 . (amino acid repeats) 가 , Van Tol (1991) clozapine . clozapine binding so- dium chloride cAMP (Asghari 1994, 1995). D₂ chlorpromazine, haloperidol D₂ pro- D₄ 16 moter region (- 141 Ins/Del)(Arinami clozapine 1997) coding region missense (Val96 가 (Shaikh 1993 ; Rao Ala, Pro310Ser, Ser311Cys)가 (Gejman 1994 ; 1994 ; Rietschel 1996). 16 Itokawa 1993). Arinami (1997) - 141 Ins/Del 4 (48 - base pair VNTR)가 promoter D₂ , cloza- ,

Table 1. Summary of dopamine system gene studies and drug response

Receptor	Variant	Position	Gene frequency(%)	Funcional consequence and association with drug response
D ₁	- 2218T/C	Promoter	2	
	- 2102C/A	Promoter	4	
	- 2030T/C	Promoter	3	
	- 1992G/A	Promoter	<1	
	- 1251G/C	Promoter	13	
	- 800T/C	Promoter	61	
	- 94G/A	5UTR	11	
	- 48G/A	5UTR of exon 2	45	
	90A/G	5UTR		
	Leu66Leu	TMD2	13	
Ser421Ser	N-term.	2.8		
1403T/C	3UTR	34		
D ₂	- 141C Ins/Del	Promoter	11	mRNA Expression
	Val96Ala	TMD2	<1	Dopamine, chlorpromazine and clozapine binding , inhibition of cAMP synthesis
	Pro310Ser	ICL3	<1	Inhibition of cAMP synthesis
	Ser311Cys	ICL3	3	Inhibition of cAMP synthesis
D ₃	- 707C/G	5'-leader	30	
	- 343A/G	5'-leader	30	
	- 204A/G(Lys9Glu)	5'leader(uORF)	30	
	Ser9Gly	N-term.	28	Dopamine and GR 99841 binding : clozapine, typical neuroleptics
D ₄	- 521C/T	Promoter	59	mRNA Expression
	Gly11Arg	N-term.	1	
	4 aa repeat	N-term.	4(1 repeat)96 (two repeats) <1 (three repeats)	Influence on clozapine and quinpirole binding
	7 aa deletion		<1	
	13 bp deletion	N-term.	2	Loss of function
	Vall94Gly	TMD2	12.5	Dopamine, clozapine and olanzapine binding , insensitivity to guanine nucleotide suggests non-functional receptor
	16aa repeat	ICL3	Highly polymorphic	Influence on sodium chloride sensitivity of clozapine binding and inhibition of cAMP synthesis clozapine, typical neuroleptics
D ₅	Leu88Phe	TMD2	<1	Dopamine binding , SCH-23390 and risperidone binding
	Ala269Val	ICL3	<1	No effect on binding affinities
	Pro330Gln	ECL3	10	No effect on binding affinities
	Cys355Stop	ECL3	<1	Loss of function
	Asn351Asp	TMD7	<1	Dopamine and R(+)-SKF-38393 binding
	Ser453Cys	N-term.	<1	No effect on binding affinities

(Hwu 1998). Cohen (1999) D₄ 가
clozapine (Nothen 1994). Liu (1996) Gly194 homozy-
gote wild type dopamine, olanzapine, clo-
zapine ,
D₄ (2) (5-HT receptor)
. Zenner
(1998) 4 (aa) clozapine quinpirole 가 , 5-
, 13 - base pair deletion HT 가 (Kaplan Sadock 1998 ;

Moore 1999 ; Worrel 2000).
 2 , 5 - HT
 . 5 - HT_{2A}, 5 - HT_{2C}, 5 - HT_{5A}, 5 - HT₆ (Ozaki 1997).
 5 - HT_{2A}
 . 5 - HT_{2A} 102T/C sil-
 ent polymorphism clozapine
 (Sodhi 1995 ; Masellis 1998), 5 - HT_{2C} Cys23Ser clozapine
 (Ma- 가 (Sodhi 1995).
 sellis 1995 ; Malhotra 1996a). 가
 5 - HT_{2A} 102T/C silent poly-
 morphism clozapine (Malhotra 1996b ; Rietschel
 (Arranz 1998c). promoter region 1997 ; Masellis 1998). 5 - HT
 - 1438G/A polymorphism 102T/C polymor- , 5 -
 phism 가 cloza- HT_{3A}, 5 - HT₅, 5 - HT₆ . 5 - HT_{1A} Gly22Ser
 pine (Arranz 1998b). 5 - HT_{1B} Phe124Cys cAMP
 102T/C polymorphism - 1438G/A polymorphism ligand binding
 (Jooper 1999). 가 (Bruss 1999 ;
 5 - HT_{2A} , His452Tyr clozapine Rotondo 1997).
 (Arranz 1996 ; 1998b,c). 5 - 가 . 5 - HT_{3A}
 HT_{2A} His452Tyr calcium mobilization silent polymorphism

Table 2. Summary of serotonin system gene studies and drug response

Receptor	Variant	Position	Gene frequency(%)	Functional consequence and association with drug response
5-HT _{1A}	- 1018C/G	Promoter	50	
	- 581C/A	Promoter	<1	
	- 480delA	Promoter	<1	
	- 321G/C	Promoter	<1	
	- 152C/G	Promoter	<1	
	- 51T/C	Promoter	<1	
	Pro16Leu	N-term.	4	
	Gly22Ser	N-term.	1	Agonist-medical receptor down-regulation Inhibition of cAMP synthesis
	Ile28Val	N-term.	1	No effect on agonist and antagonist binding and cAMP synthesis
	294G/A		5	
	549C/T		4	
	Arg219Leu	ICL3	<1	
	Gly272Asp	ICL3	3	
	Asn417Lys	C-term.	1	
5-HT _{2A}	- 1438A/G	Promoter	58	No effect on basal activity : clozapine
	Thr25Asn	N-term	2	
	102T/C		58	clozapine, typical neuroleptics
	516C/T		2	
5-HT _{2C}	His452Tyr	C-term.	8	Blunting of the shape of the Ca ²⁺ mobilization peak : clozapine
	- 330GT/ - 244CT	?		Clozapine
	Cys23Ser	N-term	13	Serotonin and MCPP binding : clozapine
	2831T/G		10	

(Arranz 2000). sive metabolizer CYP2D6*10B wild type

, 5-HT₅, 5-HT₆

polymorphism clozapine 5-HT₅ 12A/T silent (Birkett 2000). 5-HT₆ silent 267T/C clozapine (Yu 1999).

, 5-HT_{5A} 5-HT₆

3. 향후 전망과 제언

3) 국내의 연구동향

가

(3).

(1999) cytochrome P450 2D6

poor metabolizer poor

metabolizer 가

(1998) poor

metabolizer가

(2000) CYP2D6*4 CYP2D6*10 가

가

Yoon (2000) extensive (specificity), (reliability), (validity) 가 가

metabolizer metoprolol metabolic ratio(MR) 가 가

CYP2D6 paroxetine 가 가

CYP2D6*10B exten-

Table 3. Recent genetic studies with schizophrenia in Korea

Researchers	Gene polymorphism and studies	Results
1999	Dopamine D5 receptor gene between patients and normal controls	Significant difference of A2 allele (138 base pairs repeats)
1999	HUMTH01-VNTR polymorphism of tyrosine hydroxylase gene between patients and normal controls	No significant difference
1999	Tryptophan hydroxylase gene(218A/A, 218A/C, 218C/C) between patients and normal controls	No significant difference
1999	CYP2D6 polymorphism in Korean schizophrenic population(N=194)	wild type(n) : 193 heterozygote(n) : 1 homozygote mutant(n) : 0
2000	Tyrosine hydroxylase(VNTR polymorphism in intron 1) and tryptophan hydroxylase(RFLP[A218C])	No significant differences
2000	HLA-DQA1, HLA-DQB1, HLA-DRB1 gene between patients and normal controls	Significant difference of HLA-DQB1*04, HLA-DRB1*14
2000	CYP2D6*4, CYP2D6*10 polymorphism and tardive dyskinesia	No significant association
2000	Dopamine D5 receptor gene polymorphism(T978C) and treatment response	No significant association
2001	TNFB(RFLP polymorphism) gene between patients and normal controls	No significant difference
2001	5-HT _{2A} receptor gene promoter polymorphism(-1438A/G) between patients and normal controls	No significant difference

dopamine serotonin
가 가

가 가

중심 단어 : Cytochrome P450
· Dopamine · Serotonin

참고문헌

DNA bank, tissue bank
가

가

강성민·이민수·이충순(2000) : 정신분열병 환자의 도파민 D5 수용체 유전자형과 치료반응과의 연관. 생물정신의학 7 : 159-163

도규영·방승규·백인호(2000) : Tyrosine Hydroxylase 및 Tryptophan Hydroxylase와 정신분열병의 관련연구. 신경정신의학 39 : 638-646

박유진·전태연·배치운·이정태·유태열(2001) : 정신분열병에서 종양괴사인자 베타 유전자의 제한효소 절편길이 다형성. 신경정신의학 40 : 341-346

신규성·이민수·김영리·김영태·조윤정(2000) : 한국인 정신분열병 환자의 HLA-DQA1, HLA-DQB1, HLA-DRB1 대립유전자 빈도. 신경정신의학 39 : 747-753

우성일·강동우·서한길·김봉조·이인상·정근화·박소영·정치영·이환철·정경천·손진욱(2000) : 한국인 정신분열병 환자의 지연성 운동장애와 CYP2D5*4 및 CYP2D5*10 다형성들의 연합에 대한 고찰. 생물정신의학 7 : 140-146

이민수·남종원(1999) : 정신분열병 환자에서 Cytochrome P450 2D6 유형에 따른 부작용에 대한 연구. 생물정신의학 6 : 189-192

전진호·이창희·엄상화·손병철·박준한·정귀옥·손창학·윤혜경·손춘희·김형인·정진숙(1998) : 한국인 폐암환자와 대조군의 CYP2D6의 유전적 다형성에 관한 연구. 예방의학회지 31 : 1-14

전태연·권용실(1999) : 정신분열병과 Tyrosine Hydroxylase 유전자 HUMTHO1-VNTR 다형성 좌위의 연합연구. 신경정신의학 38 : 843-851

조주연·김준모·이민수·박두병(1999) : 한국인 정신분열병과 도파민 D5 수용체 유전자 연합연구. 신경정신의학 38 : 389-397

조현·지익성·손정우·이영호(2001) : 한국인 정신분열병과 5-HT_{2A} Receptor Gene Promoter 다형성(-1438A/G)과의 관련 연구. 신경정신의학 40 : 334-339

조희수·이성필·도규영·백인호(1999) : Tryptophan Hydroxylase 유전자 다형성과 정신분열병 및 임상변인과의 관련연구. 신경정신의학 38 : 1130-1136

Aitchison KJ, Jann MW, Zhao JH, Sakai T, Zaher H, Wolff K, Collier DA, Kerwin RW, Gonzalez FJ(2000) : Clozapine pharmacokinetics and pharmacodynamics studied with Cyp1A2-null mice. J Psychopharmacol 14 : 353-359

Andreassen OA, MacEwan T, Gulbrandsen AK, McCreadie RG, Steen VM(1997) : Non-functional CYP2D6 alleles and risk for neuroleptic-induced movement disorders in schizophrenic patients. Psy-

결론

가

가

가

가

cytochrome P450

- chopharmacology (Berl)* 131 : 174-179
- Arinami T, Gao M, Hamaguchi H, Toru M(1997) : A functional polymorphism in the promoter region of the dopamine D2 receptor gene is associated with schizophrenia. *Hum Mol Genet* 6 : 577-582
- Arranz MJ, Collier DA, Munro J, Sham P, Kirov G, Sodhi M, Roberts G, Price J, Kerwin RW(1996) : Analysis of a structural polymorphism in the 5-HT_{2A} receptor and clinical response to clozapine. *Neurosci Lett* 217 : 177-178
- Arranz MJ, Li T, Munro J, Liu X, Murray R, Collier DA, Kerwin RW (1998a) : Lack of association between a polymorphism in the promoter region of the dopamine-2 receptor gene and clozapine response. *Pharmacogenetics* 8 : 481-484
- Arranz MJ, Munro J, Owen MJ, Spurlock G, Sham PC, Zhao J, Kirov G, Collier DA, Kerwin RW(1998b) : Evidence for association between polymorphisms in the promoter and coding regions of the 5-HT_{2A} receptor gene and response to clozapine. *Mol Psychiatry* 3 : 61-66
- Arranz MJ, Munro J, Sham P, Kirov G, Murray RM, Collier DA, Kerwin RW(1998c) : Meta-analysis of studies on genetic variation in 5-HT_{2A} receptors and clozapine response. *Schizophr Res* 32 : 93-99
- Arranz MJ, Munro J, Birkett J, Bolonna A, Mancama D, Sodhi M, Lesch KP, Meyer JF, Sham P, Collier DA, Murray RM, Kerwin RW(2000) : Pharmacogenetic prediction of clozapine response. *Lancet* 6 : 1615-1616
- Arthur H, Dahl ML, Siwers B, Sjoqvist F(1995) : Polymorphic drug metabolism in schizophrenic patients with tardive dyskinesia. *J Clin Psychopharmacol* 15 : 211-216
- Asghari V, Schoots O, van Kats S, Ohara K, Jovanovic V, Guan HC, Bunzow JR, Petronis A, Van Tol HH(1994) : Dopamine D4 receptor repeat : analysis of different native and mutant forms of the human and rat genes. *Mol Pharmacol* 46 : 364-373
- Asghari V, Sanyal S, Buchwaldt S, Paterson A, Jovanovic V, Van Tol HH(1995) : Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants. *J Neurochem* 65 : 1157-1165
- Birkett JT, Arranz MJ, Munro J, Osbourn S, Kerwin RW, Collier DA (2000) : Association analysis of the 5-HT_{3A} gene in depression, psychosis and antipsychotic response. *Neuroreport* 11 : 2017-2020
- Brookes AJ(1999) : The essence of SNPs. *Gene* 234 : 177-186
- Bruss M, Bonisch H, Buhlen M, Nothen MM, Propping P, Gothert M (1999) : Modified ligand binding to the naturally occurring Cys-124 variant of the human serotonin 5-HT_{1B} receptor. *Pharmacogenetics* 9 : 95-102
- Cichon S, Nothen MM, Rietschel M, Propping P(2000) : Pharmacogenetics of schizophrenia. *Am J Med Genet* 97 : 98-106
- Cohen BM, Ennulat DJ, Centorrino F, Matthyse S, Konieczna H, Chu HM, Cherkerzian S(1999) : Polymorphisms of the dopamine D4 receptor and response to antipsychotic drugs. *Psychopharmacology (Berl)* 141 : 6-10
- Coutts RT, Urichuk LJ(1999) : Polymorphic cytochromes P450 and drugs used in psychiatry. *Cell Mol Neurobiol* 19 : 325-354
- Cravchik A, Sibley DR, Gejman PV(1996) : Functional analysis of the human D2 dopamine receptor missense variants. *J Biol Chem* 271 : 26013-26017
- Cravchik A, Sibley DR, Gejman PV(1999) : Analysis of neuroleptic binding affinities and potencies for the different human D2 dopamine receptor missense variants. *Pharmacogenetics* 9 : 17-23
- Crocq MA, Mant R, Asherson P, Williams J, Hode Y, Mayerova A, Collier D, Lannfelt L, Sokoloff P, Schwartz JC(1992) : Association between schizophrenia and homozygosity at the dopamine D3 receptor gene. *J Med Genet* 29 : 858-860
- Dahl ML, Bertilsson L(1993) : Genetically variable metabolism of antidepressants and neuroleptic drugs in man. *Pharmacogenetics* 3 : 61-70
- Daly AK, Brockmoller J, Broly F, Eichelbaum M, Evans WE, Gonzalez FJ, Huang JD, Idle JR, Ingelman-Sundberg M, Ishizaki T, Jacqz-Aigrain E, Meyer UA, Nebert DW, Steen VM, Wolf CR, Zanger UM(1996) : Nomenclature for human CYP2D6 alleles. *Pharmacogenetics* 6 : 193-201
- Evans WE, Relling MV(1999) : Pharmacogenomics : translating functional genomics into rational therapeutics. *Science* 286 : 487-491
- Frackiewicz EJ, Sramek JJ, Herrera JM, Kurtz NM, Cutler NR(1997) : Ethnicity and antipsychotic response. *Ann Pharmacother* 31 : 1360-1369
- Gejman PV, Ram A, Gelernter J, Friedman E, Cao Q, Pickar D, Blum K, Noble EP, Kranzler HR, O'Malley S, Hamer DH, Rao P, Virkkunen M, Linnoila M, Golidman D, Gershon ES(1994) : No structural mutation in the dopamine D2 receptor gene in alcoholism or schizophrenia. Analysis using denaturing gradient gel electrophoresis. *JAMA* 271 : 204-8
- Hwu HG, Hong CJ, Lee YL, Lee PC, Lee SF(1998) : Dopamine D4 receptor gene polymorphisms and neuroleptic response in schizophrenia. *Biol Psychiatry* 44 : 483-487
- Inoue K, Fukunaga M, Kiriya T, Komura S(1984) : Accumulation of acetaldehyde in alcohol-sensitive Japanese : relation to ethanol and acetaldehyde oxidizing capacity. *Alcohol Clin Exp Res* 8 : 319-322
- Isaksson A, Landegren U, Syvanen AC, Bork P, Stein C, Ortigao F, Brookes AJ(2000) : Discovery, scoring and utilization of human single nucleotide polymorphisms : A multidisciplinary problem. *Eur J Hum Genet* 8 : 154-156
- Itokawa M, Arinami T, Futamura N, Hamaguchi H, Toru M(1993) : A structural polymorphism of human dopamine D2 receptor, D2 (Ser311->Cys). *Biochem Biophys Res Commun* 196 : 1369-1375
- Jablensky A(1995) : Schizophrenia : the epidemiological horizon. In *Schizophrenia (Hirsch, S.R. and Weinberger, D.R., eds)*. Blackwell Science, pp211-215
- Johansson I, Oscarson M, Yue QY, Bertilsson L, Sjoqvist F, Ingelman-Sundberg M(1994) : Genetic analysis of the Chinese cytochrome P4502D locus : characterization of variant CYP2D6 genes present in subjects with diminished capacity for debrisoquine hydroxylation. *Mol Pharmacol* 46 : 452-459
- Joober R, Benkelfat C, Brisebois K, Toulouse A, Turecki G, Lal S, Bloom D, Labelle A, Lalonde P, Fortin D, Alda M, Palmour R, Rouleau GA(1999) : T102C polymorphism in the 5HT_{2A} gene and schizophrenia : relation to phenotype and drug response variability. *J Psychiatry Neurosci* 24 : 141-146
- Kapitany T, Meszaros K, Lenzinger E, Schindler SD, Barnas C, Fuchs K, Sieghart W, Aeschauer HN, Kasper S(1998) : Genetic polymorphisms for drug metabolism (CYP2D6) and tardive dyskinesia in schizophrenia. *Schizophr Res* 32 : 101-106

- Kaplan HI, Sadock BJ(1998) : *Kaplan and Sadock's synopsis of psychiatry : behavioral sciences, clinical psychiatry. 8th edn. Williams & Wilkins, Maryland, pp456-491*
- Kawanishi Y, Tachikawa H, Suzuki T(2000) : *Pharmacogenomics and schizophrenia. Eur J Pharmacol 410 : 227-241*
- Krebs MO, Sautel F, Bourdel MC, Sokoloff P, Schwartz JC, Olie JP, Loo H, Poirier MF(1998) : *Dopamine D3 receptor gene variants and substance abuse in schizophrenia. Mol Psychiatry 3 : 337-341*
- Lazarou J, Pomeranz BH, Corey PN(1998) : *Incidence of adverse drug reactions in hospitalized patients : A meta-analysis of prospective studies. JAMA 279 : 1200-1205*
- Liu IS, Seeman P, Sanyal S, Ulpian C, Rodgers-Johnson PE, Sergeant GR, Van Tol HH(1996) : *Dopamine D4 receptor variant in Africans, D4valine194glycine, is insensitive to dopamine and clozapine : report of a homozygous individual. Am J Med Genet 61 : 277-282*
- Lundstrom K, Turpin MP(1996) : *Proposed schizophrenia-related gene polymorphism : expression of the Ser9Gly mutant human dopamine D3 receptor with the Semliki Forest virus system. Biochem Biophys Res Commun 225 : 1068-1072*
- Mager J, Glaser G, Razin A, Izak G, Bien S, Noam M(1965) : *Metabolic effects of pyrimidines derived from fava bean glycosides on human erythrocytes deficient in glucose-6-phosphate dehydrogenase. Biochem Biophys Res Commun 20 : 235-240*
- Malhotra AK, Goldman D, Ozaki N, Breier A, Buchanan R, Pickar D(1996a) : *Lack of association between polymorphisms in the 5-HT_{2A} receptor gene and the antipsychotic response to clozapine. Am J Psychiatry 153 : 1092-1094*
- Malhotra AK, Goldman D, Ozaki N, Rooney W, Clifton A, Buchanan RW, Breier A, Pickar D(1996b) : *Clozapine response and the 5HT_{2C} Cys23Ser polymorphism. Neuroreport 7 : 2100-2102*
- Malhotra AK, Goldman D, Buchanan RW, Rooney W, Clifton A, Kosmidis MH, Breier A, Pickar D(1998) : *The dopamine D3 receptor (DRD3) Ser9Gly polymorphism and schizophrenia : A haplotype relative risk study and association with clozapine response. Mol Psychiatry 3 : 72-75*
- Masellis M, Paterson AD, Badri F, Lieberman JA, Meltzer HY, Cavazzoni P, Kennedy JL(1995) : *Genetic variation of 5-HT_{2A} receptor and response to clozapine. Lancet 346 : 1108*
- Marez D, Légrand M, Sabbagh N, Guidice JM, Spire C, Lafitte JJ, Meyer UA, Broly F(1997) : *Polymorphism of the cytochrome P450 CYP2D6 gene in a European population : characterization of 48 mutations and 53 alleles, their frequencies and evolution. Pharmacogenetics 7 : 193-202*
- Masellis M, Basile V, Meltzer HY, Lieberman JA, Sey S, Macciardi FM, Cola P, Howard A, Badri F, Nothen MM, Kalow W, Kennedy JL(1998) : *Serotonin subtype 2 receptor genes and clinical response to clozapine in schizophrenia patients. Neuropsychopharmacology 19 : 123-32*
- Masellis M, Basile VS, Ozdemir V, Meltzer HY, Macciardi FM, Kennedy JL(2000) : *Pharmacogenetics of antipsychotic treatment : lessons learned from clozapine. Biol Psychiatry 47 : 252-266*
- McCarthy JJ, Hilfiker R(2000) : *The use of single-nucleotide polymorphism maps in pharmacogenomics. Nat Biotechnol 18 : 505-508*
- Mihara K, Suzuki A, Kondo T, Yasui N, Furukori H, Nagashima U, Otani K, Kaneko S, Inoue Y(1999) : *Effects of the CYP2D6*10 allele on the steady-state plasma concentrations of haloperidol and reduced haloperidol in Japanese patients with schizophrenia. Clin Pharmacol Ther 65 : 291-4*
- Moore NA(1999) : *Behavioural pharmacology of the new generation of antipsychotic agents. Br J Psychiatry Suppl 38 : 5-11*
- Nebert DW(1997) : *Polymorphisms in drug-metabolizing enzymes : what is their clinical relevance and why do they exist? Am J Hum Genet 60 : 265-271*
- Nebert DW(1999) : *Pharmacogenetics and pharmacogenomics : why is this relevant to the clinical geneticist? Clin Genet 56 : 247-258*
- Nothen MM, Cichon S, Hemmer S, Hebebrand J, Remschmidt H, Lehmkuhl G, Poustka F, Schmidt M, Catalano M, Fimmers R, et al(1994) : *Human dopamine D4 receptor gene : frequent occurrence of a null allele and observation of homozygosity. Hum Mol Genet 3 : 2207-2212*
- Ohara K, Nagai M, Tani K, Nakamura Y, Ino A, Ohara K(1998) : *Functional polymorphism of -141C Ins/Del in the dopamine D2 receptor gene promoter and schizophrenia. Psychiatry Res 81 : 117-123*
- Ohmori O, Suzuki T, Kojima H, Shinkai T, Terao T, Mita T, Abe K(1998) : *Tardive dyskinesia and debrisoquine 4-hydroxylase (CYP2D6) genotype in Japanese schizophrenics. Schizophr Res 32 : 107-113*
- Ohmori O, Kojima H, Shinkai T, Terao T, Suzuki T, Abe K(1999) : *Genetic association analysis between CYP2D6*2 allele and tardive dyskinesia in schizophrenic patients. Psychiatry Res 87 : 239-244*
- Owen MJ, Cardno AG, O'Donovan MC(2000) : *Psychiatric genetics : back to the future. Mol Psychiatry 5 : 22-31*
- Ozaki N, Manji H, Lubierman V, Lu SJ, Lappalainen J, Rosenthal NE, Goldman D(1997) : *A naturally occurring amino acid substitution of the human serotonin 5-HT_{2A} receptor influences amplitude and timing of intracellular calcium mobilization. J Neurochem 68 : 2186-2193*
- Peet NP, Bey P(2001) : *Pharmacogenomics : challenges and opportunities. Drug Discov Today 6 : 495-498*
- Prior TI, Chue PS, Tibbo P, Baker GB(1999) : *Drug metabolism and atypical antipsychotics. Eur Neuropsychopharmacol 9 : 301-309*
- Propping P, Nothen MM(1995) : *Genetic variation of CNS receptors--a new perspective for pharmacogenetics. Pharmacogenetics 5 : 318-325*
- Rao PA, Pickar D, Gejman PV, Ram A, Gershon ES, Gelernter J(1994) : *Allelic variation in the D4 dopamine receptor(DRD4) gene does not predict response to clozapine. Arch Gen Psychiatry 51 : 912-917*
- Rietschel M, Naber D, Oberlander H, Holzbach R, Fimmers R, Eggemann K, Moller HJ, Propping P, Nothen MM(1996) : *Efficacy and side-effects of clozapine : testing for association with allelic variation in the dopamine D4 receptor gene. Neuropsychopharmacology 15 : 491-496*
- Rietschel M, Naber D, Fimmers R, Moller HJ, Propping P, Nothen MM(1997) : *Efficacy and side-effects of clozapine not associated with variation in the 5-HT_{2C} receptor. Neuroreport 8 : 1999-2003*
- Roses AD(2000) : *Pharmacogenetics and the practice of medicine. Nature 405 : 857-865*
- Rotondo A, Nielsen DA, Nakhai B, Hulihan-Giblin B, Bolos A, Goldman D(1997) : *Agonist-promoted down-regulation and functional desensitization in two naturally occurring variants of the human*

- serotonin1A receptor. *Neuropsychopharmacology* 17 : 18-26
- Sagar M, Tybring G, Dahl ML, Bertilsson L, Seensalu R(2000) : Effects of omeprazole on intragastric pH and plasma gastrin are dependent on the CYP2C19 polymorphism. *Gastroenterology* 119 : 670-676
- Schafer M, Rujescu D, Giegling I, Guntermann A, Erfurth A, Bondy B, Moller HJ(2001) : Association of short-term response to haloperidol treatment with a polymorphism in the dopamine D(2) receptor gene. *Am J Psychiatry* 158 : 802-804
- Scordo MG, Spina E, Facciola G, Avenoso A, Johansson I, Dahl ML (1999) : Cytochrome P450 2D6 genotype and steady state plasma levels of risperidone and 9-hydroxyrisperidone. *Psychopharmacology (Berl)* 147 : 300-305
- Shaikh S, Collier D, Kerwin RW, Pilowsky LS, Gill M, Xu WM, Thornton A(1993) : Dopamine D4 receptor subtypes and response to clozapine. *Lancet* 341 : 116
- Shaikh S, Collier DA, Sham PC, Ball D, Aitchison K, Vallada H, Smith I, Gill M, Kerwin RW(1996) : Allelic association between a Ser-9-Gly polymorphism in the dopamine D3 receptor gene and schizophrenia. *Hum Genet* 97 : 714-719
- Sivagnanasundaram S, Morris AG, Gaitonde EJ, McKenna PJ, Mollon JD, Hunt DM(2000) : A cluster of single nucleotide polymorphisms in the 5'-leader of the human dopamine D3 receptor gene (DRD3) and its relationship to schizophrenia. *Neurosci Lett* 279 : 13-16
- Snyder LH(1932) : Studies in human inheritance : IX. The inheritance of taste deficiency in man. *Ohio J Sci* 32 : 436-468
- Sodhi MS, Arranz MJ, Curtis D, Ball DM, Sham P, Roberts GW, Price J, Collier DA, Kerwin RW(1995) : Association between clozapine response and allelic variation in the 5-HT2C receptor gene. *Neuroreport* 7 : 169-172
- Spina E, Ancione M, Di Rosa AE, Meduri M, Caputi AP(1992a) : Polymorphic debrisoquine oxidation and acute neuroleptic-induced adverse effects. *Eur J Clin Pharmacol* 42 : 347-348
- Spina E, Sturiale V, Valvo S, Ancione M, Di Rosa AE, Meduri M, Caputi AP(1992b) : Debrisoquine oxidation phenotype and neuroleptic-induced dystonic reactions. *Acta Psychiatr Scand* 86 : 364-366
- Vandel P, Haffen E, Vandel S, Bonin B, Nezelof S, Sechter D, Broly F, Bizouard P, Dalery J(1999) : Drug extrapyramidal side effects. CYP2D6 genotypes and phenotypes. *Eur J Clin Pharmacol* 55 : 659-665
- Van Tol HH, Bunzow JR, Guan HC, Sunahara RK, Seeman P, Niznik HB, Civelli O(1991) : Cloning of the gene for a human dopamine D4 receptor with high affinity for the antipsychotic clozapine. *Nature* 350 : 610-614
- Vogel F(1959) : Modern probleme der Humangenetik. *Ergeb Inn Med Kinderheilkd* 12 : 125
- Watson SJ, Meng F, Thompson RC, Akil H(2000) : The "chip" as a specific genetic tool. *Biol Psychiatry* 48 : 1147-1156
- Weber WW(1999) : Populations and genetic polymorphisms. *Mol Diagn* 4 : 299-307
- Wieczorek SJ, Tsongalis GJ(2001) : Pharmacogenomics : will it change the field of medicine? *Clin Chim Acta* 308 : 1-8
- Worrel JA, Marken PA, Beckman SE, Ruechter VL(2000) : Atypical antipsychotic agents: a critical review. *Am J Health Syst Pharm* 57 : 238-255
- Yoon YR, Cha JJ, Shon JH, Kim KA, Cha YN, Jang JJ, Park CW, Shin SG, Flockhart DA, Shin JG(2000) : Relationship of paroxetine disposition to metoprolol metabolic ratio and CYP2D6*10 genotype of Korean subjects. *Clin Pharmacol Ther* 67 : 567-576
- Yu YW, Tsai SJ, Lin CH, Hsu CP, Yang KH, Hong CJ(1999) : Serotonin-6 receptor variant (C267T) and clinical response to clozapine. *Neuroreport* 10 : 1231-1233
- Zenner MT, Nobile M, Henningsen R, Smeraldi E, Civelli O, Hartman DS, Catalano M(1998) : Expression and characterization of a dopamine D4R variant associated with delusional disorder. *FEBS Lett* 422 : 146-150