

정신의학에서의 cDNA Microarray*

양 병 환**† · 김 자 윤**

cDNA Microarray in Psychiatry*

Byung-Hwan Yang, M.D.,**† Ja-Yoon Kim, M.D.**

ABSTRACT

The development of inexpensive high throughput methods to identify individual DNA sequences is important to the future growth of medical genetics. This has become increasingly apparent as psychiatric geneticists focus more attention on the molecular basis of complex multifactorial diseases at which most of psychiatric disease is estimated.

Furthermore, candidate gene approaches used in identifying disease associated genes necessitate screening large sequence blocks for changes tracking with the disease state. Even after such genes are isolated, large scale mutational analysis will often be needed for risk assessment studies to define the likely medical consequences of carrying a mutated gene.

This review provide basic knowledge of up - to - date technology, cDNA microarray which enables above mentioned various research themes.

KEY WORDS : cDNA microarray · Psychiatric genetics · Pxparmacogenetics.

서 론

가

, Alzheimer , Parkinson

, AIDS,

가 가

가

의학에서의 유전학

가

가

가

(mode of transmission)

(genetic locus)

2000 10 24

This article was presented at the annual academic meeting of the Korean Neuropsychiatric Association, Oct. 24, 2000, Seoul, Korea.

Department of Neuropsychiatry, College of Medicine & The Mental Health Research Institute, Hanyang University, Seoul, Korea

† : , 133 - 792 17
) (02) 2290 - 9421,) (02) 2298 - 2055

Table 1. Heritability estimates for selected psychiatric disorders

Disorder	Heritability estimate (%)
Schizophrenia	80
Bipolar disorder	80
Major depression	40
Generalized anxiety disorder	30
Panic disorder	40
Phobia	35
Alcohol problem or dependence	60

Heritability is the proportion of liability to a disorder accounted for by genetic effects. The heritability estimates are based on twin studies which employed DSM-III-R research diagnoses. NB : the heritabilities should be regarded only as approximations. Table from Owen MJ, Cardno AG, O'Donovan MC (2000) : Psychiatric genetics : back to the future. Mol Psychiatry 5 : 22-31

genetics 가 forward genetics reverse genetics (Hyman 1999). Forward (functional gene cloning) 가

(candidate gene) , dopamine serotonin 가 (alleles)

가 reverse genetics (positional cloning) DNA (polymorphic DNA marker) (trait)

morphisms) 가 SNPs(single nucleotide poly - (linkage analysis) (association study)

정신의학에서의 유전학

(1), 가

가

Alzheimer amyloid precursor protein(APP), presenilin - 1(PS1), presenilin - 2(PS2)

(Hyman 1999).

Thapar McGuffin 1996)

(Owen 2000).

(genetic locus)가 가 (alleles)가

(multifactorial disorder)

(Kendler 1993 ;

(linkage analysis)
 (association study)
 (penetration)
 Huntington
 (positive linkage)
 (Risch Merikangas 1996 ; Suarez 1994).
 6 8 가
 (Suarez 1994).
 가
 (2).

(allelic association study)
 가 (pseudopositive) 가 Alzheimer
 apolipoprotein E(APOE) 4
 가 (Corder 1993).
 가 가 (3).

Table 2. Selected linkage findings for psychiatric disorders

Disorder	Chromosomal regions showing evidence of linkage	
	Suggestive	Significant
Schizophrenia	5q	13q
	6p	
	8p	
	18p	
	22q	
Bipolar disorder	6p	4p
	16p	12q
	18q	18p
	21q	
Autism	22q	
	Xq	
Alcohol dependence	6q	
	7q	
Late onset Alzheimer's disease	1, 9, 10, 19, 12	

Suggestive, statistical evidence greater than would be expected to occur once by chance in a genome scan : significant, statistical evidence greater than would be expected to occur 0.05 times by chance in a genome scan including adjustments for multiple testing. Table from Owen MJ, Cardno AG, O'Donovan MC(2000) : Psychiatric genetics : back to the future. Mol Psychiatry 5 : 22-31

genome genome -
 wide association study가 (Collins 1997 ;
 Owen 1992 ; Risch Merikangas 1996)(1).
 가 가
 가 (SNPs가
 가) 가
 가 genome linkage
 disequilibrium(LD) , , LD
 가 (Corder 1993 ; Lander 1996 ; Owen 2000).

가 가
 SNPs

Table 3. Selected allelic association findings for psychiatric disorders

Disorder	Evidence for allelic association	
	Suggestive	Strong
Late onset Alzheimer's disease	A2M, ACE	APOE
Schizophrenia	5HT2A, DRD3	
Bipolar disorder/depression/neuroticism	SERT	
Attention-deficit hyperactivity disorder	DAT, DRD4	

Suggestive, evidence for association in some studies but not consistently and/or further replications awaited : strong, consistent evidence for association. Gene symbols : A2M, alpha 2 macroglobulin, APOE, apolipoprotein E : ACE, angiotensin converting enzyme : 5HT2A, 5HT2A receptor : DRD3, dopamine D3 receptor : SERT, serotonin transporter : DAT, dopamine transporter : DRD4, dopamine D4 receptor. Table from Owen MJ, Cardno AG, O'Donovan MC(2000) : Psychiatric genetics : back to the future. Mol Psychiatry 5 : 22-31

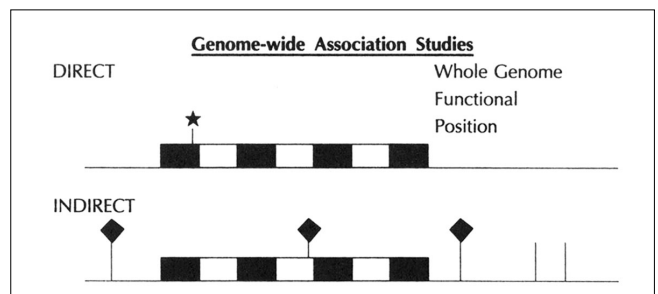


Fig. 1. The direct study detects particular polymorphisms(*) that alter structure, function or expression of the gene in affected individuals within the coding gene. In indirect study a dense map of markers is studied in the hope of detecting linkage disequilibrium with a susceptibility locus. Figure from Owen MJ, Cardno AG, O'Donovan MC(2000) : Psychiatric genetics : back to the future. Mol Psychiatry 5 : 22-31.

(Hacia Collins 1999 ; Kendler 1993 ; Owen 2000 ; Wang 1998). SNPs DNA 가 nucleotide DNA DNA coding region 20 SNPs가 (Owen 2000). SNPs DNA

2. cDNA microarray의 종류와 제작
Microarray 가 chip (synthesis technology) chip (delivery technology) photolithography Photomask DNA

가 SNPs DNA microarray가

slide DNA 가 (Chee 1996 ; Fordor 1997 ; Lipshutz 1999 ; Schena 1998 ; Wodicka 1997).

cDNA Microarray

1. cDNA microarray의 특징과 장점

Microarray mRNAs (Watson Akil 1999). 100 x 100

DNA groups 가 (Lipshutz 1999 ; Schena 1998). photomask가 mask mRNA mRNA cDNA (Guschin 1997 ; Schena 1995), ink jet pump(Blanchard 1996) chip

DNA mRNA complementary DNA microarray chip

가 가 microarray chip DNA cDNA microarray 8~25 nucleotide oligonucleotide microarray 100 nucleotide (Hacia Collins 1999).

가 (Schena 1998). 5~10% 가 가 BRCA1 BRCA2 가 가 , BRCA1 400 가 (Hacia Collins 1999), 가 가

3. cDNA microarray의 응용
Microarray chip cDNAs 가 가 microarray (2)(Collins 1999 ; Evans Relling 1999 ; Schena 1998). microarray

1999). microarray (Collins DNA 가

1) Universal combinatorial oligonucleotide array(Hacia와 Collins 1999) DNA 가

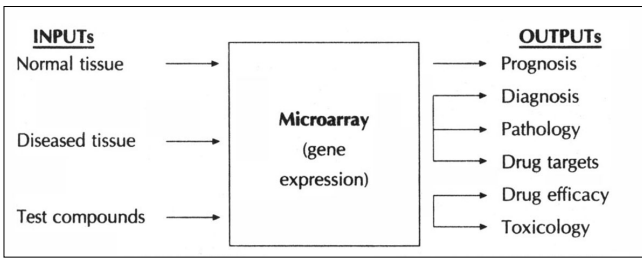


Fig. 2. Microarrays for gene-expression analysis provide an integrated platform for functional genomics. Changes in the physiological state of the cells and tissues used for microarray analysis lead to specific changes in gene-expression patterns. Figure from Schena M, Heller RA, Theriault TP, Konrad K, Lachenmeier E, Davis RW(1998) : Microarrays : biotechnology's discovery platform for junctional genomics. Trends Biotechnol 16 : 301-306

. Cystic fibrosis 95 nucleotide
 CFTR exon 11 coding SNPs 37
 (Cronin 1996), BRCA1
 (Hacia
 1996).
 microarray
 . HIV - 1 protease reverse transcriptase
 (Kozal 1996), Mycobacterium tu-
 berculosis rpoB rifampin
 (Gingeras 1998).

가 probe . 9 nucl -
 eotide probe 가 oligonucleotide
 262,144 가 (Gunderson 1998).
 가 PCR hybridize pat -
 tern
 500bp 99%

(Service 1998).
 microarray Affymetrix 20
 가 DNA array , HIV , P53
 tumor suppression
 array , cytochrome P450
 chip (Service 1998).

2) Customized oligonucleotide array(Hacia와 Collins 1999)

가
 chip DNA 가
 probe
 가
 (deletion) , (insertion)
 probe가

4. 정신의학에서의 cDNA microarray

1) 정신 유전학

microarray
 ,
 microarray
 , 가 SNPs

3) 의학에서의 연구성과 및 진행

가
 , 가
 ACE inhibitor
 (Nakano 1997 ; O 'Toole 1998)
 2 - adrenergic (Lipworth 1999 ; Martinez 1997),
 (Essen 1996), (Arranz 1995),
 tacrine(Poirier 1995)
 가

가
 가
 , 가
 ,
 가

2) 정신과 임상

Microarray 30 DNA 가

8 가
(Collins 1997 ; Hyman 1999).

4) 실험연구
microarray 가

model psychosis

가

5. cDNA microarray의 한계

Microarray gelbased sequencing
microarray

가

(triplet repeat based
mutations) (Brice 1998), (nucleic
acid), primer

가 가

microarray

가

dopa -
Collins 1999).

가 (Hacia

serotonin, dopamine
(tardive dyskinesia)

dopa -

mine

(Arranz 1995 ; Chen 1997 ; Steen 1997).

가

가

가

가

microarray

가

결 론

가

DNA

가

microarray

가

가

가

3) 신약개발

중심 단어 : cDNA microarray

가

참고문헌

가

microarray

가

Arranz M, Collier D, Sodhi M, Ball D, Roberts G, Price J, Sham P, Kerwin R(1995) : Association between clozapine response and allelic variation in 5-HT 2A receptor gene. *Lancet* 346 : 281-282

Blanchard AP, Kaise RJ, Hood LE(1996) : High-density oligonucleotide arrays. *Biosens Bioelectron* 11 : 687-690

- Brice A(1998)** : *Unstable mutations and neurodegenerative disorders. J Neurol* 245 : 505-510
- Chee M, Yang R, Hubbell E, Berno A, Huang XC, Stern D, Winkler J, Lockhart DJ, Morris MS, Fodor SP(1996)** : *Accessing genetic information with high-density DNA arrays. Science* 274 : 610-614
- Chen CH, Wei FC, Koong FJ, Hsiao KJ(1997)** : *Association of TaqI A polymorphism of dopamine D2 receptor gene and tardive dyskinesia in schizophrenia. Biol Psychiatry* 41 : 827-829
- Collins FS(1999)** : *Genetics : an explosion of knowledge is transforming clinical practice. Geriatrics* 54 : 41-47
- Collins FS, Guyer MS, Chakravarti A(1997)** : *Variations on a theme : cataloging human DNA sequence variation. Science* 278 : 1580-1581
- Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA (1993)** : *Gene dose of apolipoprotein E type-4 allele and the risk of Alzheimer's disease in late-onset families. Science* 261 : 921-923
- Cronin MT, Fucini RV, Kim SM, Masino RS, Wespi RM, Miyada CG(1996)** : *Cystic fibrosis mutation detection by hybridization to light-generated DNA probe arrays. Human Mutat* 7 : 244-255 Cited from Hacia JG, Collins FS(1999) : *Mutational analysis using oligonucleotide microarrays. J Med Genet* 36 : 730-736
- Essen GGV, Rensma PL, Zeeuw D, Sluiter WJ, Scheffer H, Apperloo AJ, Jong PED(1996)** : *Association between angiotensin-converting enzyme gene polymorphism and failure of renoprotective therapy. Lancet* 347 : 94-95
- Evans WE, Relling M(1999)** : *Pharmacogenomics : translating functional genomics into rational therapeutics. Science* 286 : 487-491
- Fodor SPA(1997)** : *Massively parallel genomics. Science* 277 : 393-395
- Gingeras TR, Ghandour G, Wang E, Berno A, Small PM, Drobniowski F, Alland D, Desmond E, Holodniy M, Drenkow J (1998)** : *Simultaneous genotyping and species identification using hybridization pattern recognition analysis of generic Mycobacterium DNA arrays. Genome Res* 8 : 435-448
- Gunderson KL, Huang XC, Morris MS, Lipshutz RJ, Lockhart DJ, Chee MS(1998)** : *Mutation detection by ligation to complete n-mer DNA arrays. Genome Res* 8 : 1142-1153 Cited from Hacia JG, Collins FS(1999) : *Mutational analysis using oligonucleotide microarrays. J Med Genet* 36 : 730-736
- Guschin D, Yershov G, Zaslavsky A(1997)** : *Manual manufacturing of oligonucleotide, DNA, and protein microchips. Anal Biochem* 250 : 203-211
- Hacia JG, Brody LC, Chee MS, Fodor SP, Collins FS(1996)** : *Detection of heterozygous mutations in BRCA1 using high density oligonucleotide arrays and two-colour fluorescence analysis. Nat Genet* 14 : 441-447
- Hacia JG, Collins FS(1999)** : *Mutational analysis using oligonucleotide microarrays. J Med Genet* 36 : 730-736
- Hyman SE(1999)** : *Introduction to the complex genetics of mental disorders. Biol Psychiatry* 45 : 518-521
- Kendler KS, Neale M, Kessler R, Heath A, Eaves L(1993)** : *A twin study of recent life events and difficulties. Arch Gen Psychiatry* 50 : 789-796
- Kozal MJ, Shah N, Shen N, Yang R, Fucini R, Merigan TC, Richman DD, Morris D, Hubbell E, Chee M, Gingeras TR (1996)** : *Extensive polymorphisms observed in HIV-a clade B protease gene using high-density oligonucleotide arrays. Nat Med* 2 : 753-759 Cited from Hacia JG, Collins FS(1999) : *Mutational analysis using oligonucleotide microarrays. J Med Genet* 36 : 730-736
- Lander ES(1996)** : *The new genomics : global views of biology. Science* 274 : 536-539
- Lipshutz RJ, Fodor SPA, Gingeras TR, Lockhart DJ(1999)** : *High density synthetic oligonucleotide arrays. Nat Genet Suppl* 21 : 20-24
- Lipworth BJ, Hall IP, Tan S, Aziz I, Crabbe JC(1999)** : *Effects of genetic polymorphism on ex vivo and in vivo function of beta 2-adrenoceptors in asthmatic patients. Chest* 115 : 324-328
- Martinez FD, Graves PE, Baldini M, Solomon S, Erickson R (1997)** : *Association between genetic polymorphisms of the beta2-adrenoceptor and response to albuterol in children with and without a history of wheezing. J Clin Invest* 100 : 3184-3188
- Nakano Y, Oshima T, Watanabe M, Matsuura H, Kajiyama G, Kambe M(1997)** : *Angiotensin I-converting enzyme gene polymorphism and acute response to captopril in essential hypertension. Am J Hypertens* 10 : 1064-1068
- O'Toole L, Stewart M, Padfield P, Channer K(1998)** : *Effect of the insertion/deletion polymorphism of the angiotensin-converting enzyme gene on response to angiotensin-converting enzyme inhibitors in patients with heart failure. J Cardiovasc Pharmacol* 32 : 988-994
- Owen MJ(1992)** : *Will schizophrenia become a graveyard for molecular geneticists? Psychol Med* 22 : 289-293 Cited from Owen MJ, Cardno AG, O'Donovan MC(2000) : *Psychiatric genetics : back to the future. Mol Psychiatry* 5 : 22-31
- Owen MJ, Cardno AG, O'Donovan MC(2000)** : *Psychiatric genetics : back to the future. Mol Psychiatry* 5 : 22-31
- Poirier J, Delisle MC, Quirion R, Aubert I, Farlow M, Lahiri D, Hui S, Bertrand P, Nalbantoglu J, Gilfix BM(1995)** : *Apolipoprotein E4 allele as a predictor of cholinergic deficits and treatment outcome in Alzheimer disease. Proc Natl Acad Sci USA*. 92 : 12260-12264
- Risch N, Merikangas K(1996)** : *The future of genetic studies of complex human disease. Science* 273 : 1516-1517
- Schena M, Heller RA, Theriault TP, Konrad K, Lachenmeier E, Davis RW(1998)** : *Microarrays : biotechnology's discovery platform for junctional genomics. Trends Biotechnol* 16 : 301-306
- Schena M, Shalon D, Davis RW, Brown PO(1995)** : *Quantitative monitoring of gene expression patterns with a complementary DNA microarray. Science* 270 : 467-470
- Service RF(1998)** : *Microchip arrays put DNA on the spot. Science* 282 : 396-399
- Steen VM, Movlie R, MacEwan T, McCreadie RG(1997)** : *Dopamine D3-receptor gene variant and susceptibility to tardive dyskinesia in schizophrenic patients. Mol Psychiatry* 2 : 139-145
- Suarez BK, Hampe CL, Van Eerdewegh P(1994)** : *Problems of replicating linkage claims in psychiatry. In : Genetic Approaches to Mental Disorders, Ed by Gershon ES, Cloninger CR, Washin-*

gton DC, American Psychiatric Press, pp23-46. Cited from Owen MJ, Cardno AG, O'Donovan MC(2000) : *Psychiatric genetics : back to the future. Mol Psychiatry* 5 : 22-31

Thapar A, McGuffin P(1996) : Genetic influences on life events in childhood. *Psychol Med* 26 : 813-820. Cited from Owen MJ, Cardno AG, O'Donovan MC(2000) : *Psychiatric genetics : back to the future. Mol Psychiatry* 5 : 22-31

Wang DG, Fan JB, Siao CJ, Berno A, Young P, Lander ES, Sapolsky R, Ghandour G, Perkins N, Winchester E, Spencer J, Kruglyak L, Stein L, Hsie L, Topaloglou T, Hubbell E, Robin-

son E, Mittmann M, Morris MS, Shen N, Kilburn D, Rioux J, Nusbaum C, Rosen S, Hudson TJ, Lipshutz R, Chee M, Lander ES(1998) : Largescale identification, mapping, and genotyping of singlenucleotide polymorphisms in the human genome. *Science* 280 : 1077-1082

Watson SJ, Akil H(1999) : Gene chips and arrays revealed : a primer on their power and their uses. *Biol Psychiatry* 45 : 533-543

Wodicka L, Dong H, Wittmann M, Ho MH, Lockhart DJ(1997) : Genome-wide expression monitoring in *Saccharomyces cerevisiae*. *Nat Biotechnol* 15 : 1359-1367