

기분장애 및 기분관련장애에서 세로토닌 수용체 유전자 프로모터 다형성*

지 익 성**†

Serotonin(2A) Receptor Gene Promoter Polymorphism in Mood Disorder and Mood-Related Disorders*

Ik-Seung Chee, M.D.**†

ABSTRACT

Genes involved in the serotonin system are good candidates for the pathogenesis of mood disorder and mood-related disorders, such as eating disorder, obsessive-compulsive disorder, alcoholism, and suicide. Serotonin type 2A(5-HT2A) receptor gene promoter polymorphism(-1438A/G) has been reported. In this article, authors reviewed the literatures regarding association studies between -1438A/G and mood disorder and mood-related disorders. There are controversial results with limited data to date. Further researches on the -1438A/G in psychiatric disorders are required.

KEY WORDS : Mood disorders · 5-HT2A receptor gene promoter · Polymorphism · -1438A/G.

서 론

1)2) type 2(5-HT2) 가 5-HT2 가 5-HT2 가 3) 5-HT2 가 4)5) 5-HT2 가 6)7) 5-HT2

2002 가

Department of Psychiatry, College of Medicine, Chungnam National University, Daejeon, Korea

†교신저자 : 640 (042) 220 - 7291, (042) 220 - 7288 E - mail) ischee@cnu.ac.kr

가

8)9)

가

5-HT2

가

10-12)

5-HT

가

Warren¹³⁾

5-HT2A

102T/C

102 T/C

가

가

14-20)

5-HT2A

102T/C

5-HT2A

HT2A

가

Collier²¹⁾

5-HT2A

-1438G/A

Spurlock²²⁾

-1438A/G

5-HT2A

-1438A/G

기본장애

-1438A/G

Ohara²³⁾

(

)

BN

²⁸⁾ Nishiguchi²⁹⁾

AN BN

가

-1438A/G

가

AN

BN

가

BN

가

AN

가

가

가

가

Enoch²⁴⁾

가

가

가

가

가

-1438A/G가

가

sonality Score

(seasonality)

Hinney³⁰⁾

AN

가

Chee²⁵⁾

3

가

(stratification effects)

AN

-1438A/G가

transmission disequilibrium test

기본관련장애

1. 식이장애

Collier²¹⁾

-1438 G/A

(anorexia nervosa ; AN)

Enoch

(bulimia

²⁶⁾

AN

nervosa ; BN)

가

AN

BN

, AN

BN

가

Sorbi

²⁷⁾

AN

가

AN

(restricting type)

(purging

type)

가

AN

AN

BN

AN

가

, AN

(binge/pur-

ging type)

BN

²⁸⁾ Nishiguchi²⁹⁾

AN BN

AN

BN

BN

가

AN

가

Enoch²⁴⁾

가

가

가

가

가

-1438A/G가

가

sonality Score

(seasonality)

Hinney³⁰⁾

AN

가

Chee²⁵⁾

3

가

(stratification effects)

AN

-1438A/G가

transmission disequilibrium test

(TDT) 가 . Ca- 가
mpbell ³¹⁾ AN . 5 - HT2A G -
, Ando ³²⁾ AN , phospholipase C
가 , AN . ³⁸⁾ 5 - HT2A
(transcription)
가 - 1438A/G가 AN
. Ziegler ³³⁾ AN BN
가 , AN 가
5 - HT2A , , - 1441 +128
Zhu ³⁹⁾ - 1316
²¹⁾²⁶⁾²⁷⁾³⁰⁾³¹⁾ meta analysis - 577 0.74kbp Hae /Pvu
AN - 1438A/G . 가 , - 577
- 125 0.45kbp Pvu /Sma
2. 광박장애
Enoch ²⁶⁾ . Du ⁴⁰⁾ - 25 +1
가 가 (basal
가 , promoter unit) - 1314 - 75
가 가 (basal promoter activity)
가 가 , - 1438A/G
³⁴⁾ ,
3. 알코리즘
Preuss ³⁵⁾ 가 ²³⁾
Zhang ⁴¹⁾ 5 - HT2A 가 20
kbp , 5 - HT2A
- 1438A/G , 가 가
-1438
enhancers, repressors
gene activation, transcriptive initiation, posttran-
slational processing , 5 - HT2A
(up - regulation)
가
4. 자 살
Turekei ³⁶⁾ - 1438A/G
, Ono ³⁷⁾ -1438 , , , ,
A/G 가 5 - HT2A
- 1438A/G가 promoter - 1438A/G
가 , - 1438A/G
가
고 찰
- 1438A/G TDT Haplotype Re-
, lative Risk 가
가 , 5 - HT2A
, - 1438A/G

A G가 (basal activity)
 (promoter activity) 가
²²⁾ - 1438A/G가 5-HT2A
 5-HT2A

중심 단어 :

- 1438A/G.

참고문헌

1. Maes M, Meltzer HY(1995) : *The serotonin hypothesis of major depression. In Psychopharmacology : The Fourth Generation of Progress. Ed by Bloom FE and Kupfer DJ, New York, Raven Press, pp933-944*
2. Smith KA, Cowen PJ(1997) : *Serotonin and Depression. In : Depression : Neurobiological, Psychopathological and Therapeutic Advances. Ed by Honig A and van Praag HM, Chichester, John Wiley, pp129-146*
3. Charney DS, Delgado PL(1992) : *Current concept of the role of serotonin function in depression and anxiety. In : Serotonin Receptor Subtypes : Pharmacological Significance and Clinical Implication. Ed by Langer SZ, Brunello N, Racagni G, Mendelwicz J. Karger series, Basel, pp89-104*
4. Biegón A, Weizman A, Karp L, Ram A, Tiano S, Wolff M(1987) : *Serotonin 5-HT2 receptor binding on blood platelets-a peripheral marker for depression. Life Sci 41 : 2485-2492*
5. Arora RC, Meltzer HY(1989) : *Increased serotonin 2 (5-HT2) receptor binding as measured by ³H-lysergic acid diethylamide (3H-LSD) in the blood platelets of depressed patients. Life Sci 44 : 725-734*
6. Yates M, Leake A, Candy JM, Fairbairn AF, McKeith IG, Ferrier IN(1990) : *5-HT2 receptor changes in major depression. Bio Psychiatry 27 : 489-496*
7. Arango V, Underwood MD, Mann JJ(1992) : *Alterations in monoamine receptors in the brain of suicide victims. J Clin Psychopharmacol 12 : 8S-12S*
8. Staner L, Kempnaers C, Simonnet MP, Fransolet L, Mendelwicz J(1992) : *5-HT2 receptor antagonism and slow wave sleep in major depression. Acta Psychiatr Scand 86 : 133-137*
9. Sharpley AL, Gregory CA, Solomon RA, Cowen PJ (1990) : *Slow wave sleep and 5-HT2 receptor sensitivity during maintenance tricyclic antidepressant treatment. J Affect Disord 19 : 273-277*
10. Cowen PJ(1990) : *A role for 5-HT in the antidepressant drugs. Pharmacol Ther 46 : 43-51*
11. Leysen JE, Pauwels P(1990) : *5-HT2 receptors, role and regulation, the neuropharmacology of serotonin. Ann NY Acad Sci 600 : 183-193*
12. Leysen JE(1992) : *5-HT2 receptors : location, pharmacological, pathological and physiological role. In : Serotonin Receptor Subtypes : Pharmacological Significance and Clinical Implication. Ed by Langer SZ, Brunello N, Racagni G, Mendelwicz J, Karger series, Basel, pp31-43*
13. Warren JT Jr, Peacock ML, Rodríguez LC, Fink JK (1993) : *An Msp I polymorphism in the human serotonin receptor gene (HTR2) : detection by DGGE and RFLP analysis. Hum Mol Genet 3 : 338*
14. Gutierrez B, Arranz M, Fananas L, Valles V, Guillamat R, van Os J, et al(1995) : *5HT2A receptor gene and bipolar affective disorder. Lancet 346 : 969*
15. Gutierrez B, Bertranpetit J, Collier D, Arranz M, Valles V, Guillamat R, et al(1997) : *Genetic variation of the 5-HT2A receptor gene and bipolar affective disorder. Hum Genet 100 : 562-584*
16. Mahieu B, Souery D, Lipp O, Mendelbaum K, Verheyen G, De Maertelaer V, et al(1997) : *No association between bipolar affective disorder and serotonin receptor (5-HT2A) polymorphism. Psychiatry Res 5 : 65-69*
17. Arranz MJ, Erdmann J, Kirov G, Rietschel M, Sodhi M, Albus M, et al(1997) : *5-HT2A receptor and bipolar affective disorder : association studies in affected patients. Neurosci Lett 224 : 95-98*
18. Chee Ik-Seung, Shin Suk-Chul, Wang Sung-Keun, Lee Sun-Woo, Shin Young-Jae, Kim Choong-Su, et al(1999) : *Serotonin receptor (5-HT2A) gene polymorphism (102T/C) in bipolar mood disorder. J Korean Society of Biological Therapies in Psychiatry 5 : 122-126*
19. Bondy B, Kuznik J, Baghai T, Schule C, Zwanzger P, Minov C, et al(2000) : *Lack of association of serotonin-2A receptor gene polymorphism (T102C) with suicidal ideation and suicide. Am J Med Genet 96 : 831-835*
20. Du L, Bakish D, Lapierre YD, Ravindran AV, Hrdina PD(2000) : *Association of polymorphism of serotonin 2A receptor gene with suicidal ideation in major depressive disorder. Am J Med Genet 96 : 56-60*
21. Collier DA, Arranz MJ, Li T, Mupita D, Brown N, Treasure J(1997) : *Association between 5-HT2A gene promoter polymorphism and anorexia nervosa. Lancet 350 : 412*
22. Spurlock G, Heils A, Holmans P, Williams J, D'Souza UM, Cardno A, et al(1998) : *A family based association study of T102C polymorphism in 5HT2A and schizophrenia plus identification of new polymorphism in the promoter. Mol Psychiatry 3 : 42-49*
23. Ohara K, Nagai M, Tsukamoto T, Tani K, Suzuki Y, Ohara K(1998) : *5-HT2A receptor gene promoter polymorphism -1438G/A and mood disorders. Neuroreport 9 : 1139-1141*
24. Enoch MA, Goldman D, Barnett R, Sher L, Mazzanti CM, Rosenthal NE(1999) : *Association between seasonal affective disorder and the 5-HT2A promoter poly-*

- morphism, -1438G/A. *Mol Psychiatry* 4 : 89-92
25. Chee IS, Lee SW, Kim JL, Wang SK, Shin YO, Shin SC, et al(2001) : 5-HT_{2A} receptor gene promoter polymorphism -1438A/G and bipolar disorder. *Psychiatr Genet* 11 : 111-114
 26. Enoch MA, Kaye WH, Rotondo A, Greenberg BD, Murphy DL, Goldman D(1998) : 5-HT_{2A} promoter polymorphism -1438G/A, anorexia nervosa and obsessive-compulsive disorder. *Lancet* 351 : 1785-1786
 27. Sorbi S, Nacmias B, Tedde A, Ricca V, Mezzani B, Rotella CM(1998) : 5-HT_{2A} promoter polymorphism in anorexia nervosa. *Lancet* 351 : 1785
 28. Namiias B, Ricca V, Tedde A, Mezzani B, Rotella CM, Sorbi S(1999) : 5-HT_{2A} receptor gene polymorphism in anorexia nervosa and bulimia nervosa. *Neurosci Lett* 277 : 134-136
 29. Nishiguchi N, Matsushita S, Suzuchi K, Murayama M, Shirakawa O, Higuchi S(2001) : Association between 5HT_{2A} receptor gene promoter region polymorphism and eating disorders in Japanese patients. *Biol Psychiatry* 50 : 123-128
 30. Hinney A, Ziegler A, Nothen MM, Remschmidt H, Hebebrand J(1997) : 5-HT_{2A} receptor gene polymorphisms, anorexia nervosa, and obesity. *Lancet* 350 : 1324-1325
 31. Campbell DA, Sundaramuthy D, Markham AF, Pieri LF(1998) : Lack of association between 5-HT_{2A} gene promoter polymorphism and susceptibility to anorexia nervosa. *Lancet* 351 : 499
 32. Ando T, Komaki G, Karibe M, Kawamura N, Hara S, Takii M, et al(2001) : 5-HT_{2A} promoter polymorphism is not associated with anorexia nervosa in Japanese patients. *Psychiatr Genet* 11 : 157-160
 33. Ziegler A, Hebebrand J, Gorg T, Rosenkranz K, Fichter M, Herpertz-Dahlmann B, et al(1999) : Further lack of association between the 5-HT_{2A} gene promoter polymorphism and susceptibility to eating disorders and a meta-analysis pertaining to anorexia nervosa. *Mol Psychiatry* 4 : 410-412
 34. Enoch MA, Greenberg BD, Murphy DL, Goldman D (2001) : Sexually dimorphic relationship of a 5-HT_{2A} promoter polymorphism with obsessive-compulsive disorder. *Biol Psychiatry* 49 : 385-388
 35. Preuss UW, Koller G, Bondy B, Bahlmann M, Soyka M(2001) : Impulsive traits and 5-HT_{2A} receptor promoter polymorphism in alcohol dependents : possible association but no influence of personality disorders. *Neuropsychobiology* 43 : 186-191
 36. Turecki G, Briere R, Dewar K, Antonetti T, Lesage A, Seguin M, et al(1999) : Prediction of level of serotonin 2A receptor binding by serotonin receptor 2A genetic variation in postmortem brain samples from subjects who did or did not commit suicide. *Am J Psychiatry* 156 : 1456-1458
 37. Ono H, Shirakawa O, Nishiguchi N, Nishimura A, Nushida H, Ueno Y(2001) : Serotonin 2A receptor gene polymorphism in not associated with completed suicide. *J Psychiatric Research* 35 : 173-176
 38. Conn PJ, Sandler-Bush E, Hoffman BJ, Hartig PR (1986) : A unique serotonin receptor in choroid plexus is linked to phosphatidylinositol turnover. *Proc Nat Acad Sci USA* 83 : 4086-4088
 39. Zhu Q-S, Chen K, Shih JC(1996) : Characterization of the Human 5-HT_{2A} receptor gene promoter. *J Neurosci* 15 : 4885-4895
 40. Du Y-L, Wilcox ED, Jeffrey JJ(1995) : Regulation of rat 5-hydroxytryptamine type2 receptor gene activity : identification of cis elements that mediate basal and 5-hydroxytryptamine-dependent gene activation. *Mol Pharmacol* 47 : 915-922
 41. Zhang HY, Ishigaki T, Tani K, Chen K, Shih JC, Miyasato K, et al(1997) : Serotonin 2A receptor gene polymorphism in mood disorders. *Biol Psychiatry* 41 : 768-773