کارگاه‌های آموزشی مرکز اطلاعات علمی

مقاله نویسی علوم انسانی

اصول تنظیم قراردادها

آموزش مهارت‌های کاربردی در تدوین و چاپ مقاله
Additive effect of *MTHFR* and *GRIN1* genetic polymorphisms on the risk of schizophrenia

Ali Mohammad Foroughmand*, Hamid Galehdari, Atefeh Pooryasin, Tahereh Ajam, Seyed Reza Kazemi-Nezhad

Department of Genetics, College of Sciences, Shahid Chamran University, Ahvaz 61357-44337, Iran

ABSTRACT

Schizophrenia is a complex disorder with polygenic inheritance. The *MTHFR* gene (OMIM: 607093) plays an important role in the folate metabolism. It has been suggested that C677T (rs1801133) and A1298C (rs1801131) genetic polymorphisms in the *MTHFR* gene lead to the decreased activity of the methylenetetrahydrofolate reductase enzyme which may have significant effect on developing schizophrenia. We used a case-control study to establish the possible association between the C677T and the A1298C polymorphisms and susceptibility to schizophrenia in an Iranian population. The genotypes of the polymorphisms were determined using PCR-RFLP. The data were analyzed by logistic regression model. Data analysis revealed that the combination genotypes of 677CT/1298AA, 677CC/1298CC, 677TT/1298AA, 677CT/1298AC and 677CT/1298CC increase the risk of schizophrenia. In order to evaluate the effect of combined genotypes of the three mentioned polymorphic loci, the frequencies of the compound genotypes were compared between control and patient groups (Table 4). Based on the results, the existence of ≥4 risk factors showed about 32-fold increased risk for schizophrenia (OR=32.3, 95% CI: 5.52-188, P=<0.001).

Key words: Homocysteine; *GRIN1*; *MTHFR*; NMDA; Schizophrenia

INTRODUCTION

Schizophrenia is a complex psychotic disorder with a multiple gene inheritance, which affects approximately 1% of the general population worldwide [1]. In the past few years, several lines of evidence are suggesting that altered folate metabolism may increase vulnerability to schizophrenia [2].

*Address for correspondence: Department of Genetics, College of Sciences, Shahid Chamran University, Ahvaz 61357-44337, Iran  
Tel: +98 611 33338965  
Fax: +98 611 33338965  
E-mail: foroughmand.a@scu.ac.ir AND aliforough12@yahoo.com*
Folate is an important B vitamin that plays a pivotal role in remethylation of homocysteine to methionine, which is essential for DNA-synthesis, DNA-repair and DNA-imprinting processes [3]. Reduction of 5, 10-methylenetetrahydrofolate into 5-methyltetrahydrofolate, the predominant circulatory form of folate is catalyzed by the 5, 10-methylenetetrahydrofolate reductase (MTHFR), the regulating key enzyme for availability of active folate at the expense of elevated homocysteine levels [4]. The 5-methyltetrahydrofolate donates a methyl group to homocysteine in generation of S-adenosylmethionine (SAM), a major source of methyl groups in the brain [5].

The MTHFR (OMIM: 607093) gene is located at 1p36.3. Positive linkage of 1p36 with schizophrenia has been reported [6]. Two common polymorphisms in MTHFR gene, C677T (rs1801133) in exon 4 and an A1298C (rs1801131) in exon 7 are functional and result in diminished enzyme activity [7, 8]. Homozygote variants have 30 and 60 percent enzyme activity in comparison with homozygotes for the wild-types, for the C677T and A1298C polymorphisms, respectively [9, 10]. MTHFR deficiency has been associated with reduction in folate acid metabolism and hyperhomocysteinemia [11, 12]. The involvement of MTHFR in schizophrenia has been confirmed by the observation of clinical improvement in this psychiatric illness with folate [13]. Also, some authors have reported hyperhomocysteinemia in their schizophrenic patients [14-16]. Higher homocysteine concentrations were especially found in plasma of subjects with the MTHFR 677TT genotype with low plasma folate concentrations compared to subjects with the normal genotype [7, 17]. Several studies have been reported association between MTHFR polymorphisms and schizophrenia, but the results are not consistent [18-27].

The pathogenic mechanisms by which the hyperhomocysteinemia causes diseases are not fully understood, but there is an evidence that homocysteine disrupts the neurodevelopment by acting as an antagonist of the N-methyl-D-aspartate (NMDA) receptor glycine co-agonist site [28]. Furthermore, the NMDA receptor, a member of the family of ionotropic glutamate receptors, functions as a glutamate-gated cation channel [29]. These channels are implicated in both neural cell survival and neurotoxicity, and also have important role in development, synaptic plasticity and long term potentiation [30]. This receptor is a heterodimer consisting of the NR1 and NR2 (NR2A-D) subunits [31]. It has proposed that the hypofunction of NMDA receptors might be involved in the pathophysiology of schizophrenia [32]. The glutamate hypothesis of schizophrenia is based largely on the observation that NMDA receptor antagonists such as PCP, MK-801, and ketamine, produce both the positive and negative symptoms associated with this disorder. Furthermore, clinical trials have shown that treating patients with drugs that promote NMDA receptor function, such as D-serine, improves cognitive deficits associated with schizophrenia. In addition several lines of evidence have implicated that the N-methyl-D-aspartate 1 (GRIN1; OMIM: 138249) plays a fundamental role in many brain functions and its involvement in the pathogenesis of schizophrenia has been widely investigated [33]. Recently we found a positive association between G1001C polymorphism (rs11146020) in the promoter of GRIN1 and developing of schizophrenia [33].
In the present study, association between MTHFR polymorphisms and susceptibility to schizophrenia was investigated. According to possible effect of both MTHFR polymorphisms and the G1001C variant of GRIN1 on NMDA receptor activity, we also investigated combination of these polymorphisms as a potential risk factor for developing schizophrenia.

MATERIALS AND METHODS

Subjects: Two hundred (male 117, female 83) unrelated patients with a mean age of 43.3 (SD = 11.3) were recruited from hospitals in south and southwest Iran. The control group consisted of 200 healthy blood donors (male 117, female 83) with a mean age of 39.4 (SD = 11.1), which were matched for gender and ethnicity to the patient. Informed consent was obtained from all participants.

Genotyping assay: Genomic DNA was extracted from leucocytes using standard salting out method. The C677T and A1298C polymorphisms in MTHFR gene were determined by PCR-RFLP using HinfI and MboII restriction enzymes, respectively. To confirm the results, a random selection of 20% of all samples was retested. There were no discrepancies in replicating test. The evaluation of GRIN1 polymorphism has been explained in details and reported before [33].

Statistical analysis: Comparison of genotypes between gender groups was done by chi square-test. The association between genotypes and development of schizophrenia was examined using odds ratios (ORs) and 95% confidence intervals (CIs). Statistical significance was considered at P< 0.05.

RESULTS

The study of socio-demographic features of this case-control study identified that subjects in the case group were significantly lower than those in the control group in terms of marital status and educational level (Table 1).

Control and patient groups were initially classified according to their gender. Considering that there was no statistical difference between their genotypic frequencies (P>0.05), the samples were pooled. Detailed results of genotyping assay for C677T polymorphism are shown in Table 2. Genotype distributions were in Hardy-Weinberg equilibrium for both C677T and A1298C polymorphisms in patient and control groups.

In our samples, neither heterozygosity (OR=1.40, 95% CI: 0.92-2.14, P=0.115) nor homozygosity (OR=1.82, 95% CI: 0.86-3.83, P=0.116) of the T allele was associated with the increasing risk of schizophrenia (Table 2). There was significant linear trend in associated risk with zero, one, and two T alleles (P=0.044). For the A1298C polymorphism, a significant association between the CC genotype and schizophrenia risk was identified (OR=2.04, 95% CI: 1.14- 3.66, P=0.016). There was a significant linear trend in associated risk with zero, one, and two C alleles (P=0.039).
Table 1: The socio-demographic characteristics of the case and control samples

| Variables                        | Controls (n=200) | Patients (n=200) |
|----------------------------------|-----------------|-----------------|
| Age (mean±SD)                    | 39.4±11.1       | 43.3±11.3       |
| Age of onset (mean±SD)           | -               | 22.0±9.0        |
| **Educational level (%)**        |                 |                 |
| Illiteracy                       | 3 (1.5)         | 29 (14.72)      |
| Primary school                   | 13 (6.5)        | 119 (59.5)      |
| High school                      | 145 (72.5)      | 42 (22.1)       |
| College                          | 39 (19.5)       | 7 (3.68)        |
| **Marital status (%)**           |                 |                 |
| Single                           | 43 (21.5)       | 139 (69.5)      |
| Married                          | 156 (78)        | 35 (17.5)       |
| Divorced                         | 1 (0.5)         | 16 (8)          |
| Uncertain                        | -               | 10 (5)          |

Table 2: Association between C677T and A1298C polymorphisms of MTHFR and schizophrenia risk

| Genotypes                        | Controls | Patients | OR     | 95% CI     | P-Value |
|----------------------------------|----------|----------|--------|------------|---------|
| **C677T polymorphism**           |          |          |        |            |         |
| CC                               | 123      | 104      | 1.0    | -          | -       |
| CT                               | 64       | 76       | 1.40   | 0.92-2.14  | 0.115   |
| TT                               | 13       | 20       | 1.82   | 0.86-3.83  | 0.116   |
| **A1298A polymorphism**          |          |          |        |            |         |
| AA                               | 65       | 60       | 1.0    | -          | -       |
| AC                               | 108      | 89       | 0.89   | 0.57-1.39  | 0.621   |
| CC                               | 27       | 51       | 2.04   | 1.14-3.66  | 0.016   |

We next studied the joint effect of the two polymorphisms (Table 3). The combination genotypes of 677CT/1298AA, 677CC/1298CC, 677TT/1298AA, 677CT/1298AC and 677CT/1298CC increase the risk of schizophrenia.

Table 3: Comparison of the combination of C677T and A1298C genotypes of MTHFR within control and patient groups

| C677T   | A1298C | Controls | Patients | OR     | 95% CI     | P-Value |
|---------|--------|----------|----------|--------|------------|---------|
| CC      | AA     | 35       | 16       | 1.0    |            |         |
| CC      | AC     | 67       | 49       | 1.60   | 0.79-3.21  | 0.186   |
| CT      | AA     | 19       | 26       | 2.99   | 1.29-6.91  | 0.010   |
| CC      | CC     | 21       | 39       | 4.06   | 1.83-8.99  | 0.001   |
| TT      | AA     | 11       | 18       | 3.58   | 1.37-9.30  | 0.009   |
| CT      | AC     | 40       | 39       | 2.13   | 1.02-4.46  | 0.044   |
| CT      | CC     | 5        | 11       | 4.81   | 1.43-16.1  | 0.011   |
| TT      | AC     | 1        | 1        | 2.18   | 0.12-37.2  | 0.588   |
| TT      | CC     | 1        | 1        | 2.18   | 0.12-37.2  | 0.588   |

In order to evaluate the effect of combined genotypes of the three mentioned polymorphic loci, the frequencies of the compound genotypes were compared between control and patient groups (Table 4). Base on the results, the existence of ≥4 risk factors
showed about 32-fold increased risk for schizophrenia (OR = 32.3, 95% CI: 5.52-188, P < 0.001).

Table 4: Association between putative high risk alleles of MTHFR and GRIN1 polymorphisms and risk of schizophrenia

| Number of putative high risk alleles | Controls | Patients | OR   | 95% CI   | P-Value |
|-------------------------------------|----------|----------|------|----------|---------|
| 0                                   | 19       | 2        | 1.0  | -        | -       |
| 1                                   | 48       | 29       | 5.74 | 1.24-26.4| 0.025   |
| 2                                   | 81       | 80       | 9.38 | 2.11-41.6| 0.003   |
| 3                                   | 47       | 72       | 14.5 | 3.23-65.3| <0.001  |
| ≥4                                  | 5        | 17       | 32.3 | 5.52-188 | <0.001  |

**DISCUSSION**

In the present investigation, we did not find any significant association between the C677T polymorphism and schizophrenia. Our result is in accordance with some other investigations [19, 20, 22, 23, 34]. But, in contrast with our result, some case-control and family-based studies supported the relationship between T677T genotype and the rising of the schizophrenia risk [18, 21, 24, 25, 27].

The second polymorphism in the MTHFR gene, the A1298C, reduces enzyme activity for about 30-40% [10, 35] and the possible effect of this polymorphism in schizophrenia was examined in some investigations [24, 26]. In this study, we also found the 1298CC genotype as a risk factor in schizophrenia. In contrast, other researchers could not find this relationship [22, 23]. The A1298C polymorphism has been shown being associated with hyperhomocysteinemia [9, 35] while homocysteine has implicated as a risk factor in schizophrenia [14, 15, 36, 37].

Previous studies postulated a combined association between the A1298C polymorphism and the C677T variant with MTHFR activity and homocysteine levels [38]. Although we did not find any effect of the C667T polymorphism as a risk factor in schizophrenia. But significant association was revealed between schizophrenia and combinations of the A1298C and the C677T polymorphisms (Table 3). The recent meta-analysis reinforced the effect of the MTHFR on developing schizophrenia [39].

Low contents of the SAM in human tissues could result from deficiency in the de novo biosynthesis of the methyl group using folate-dependent one-carbon pathway [7, 40]. The MTHFR enzyme plays a central role in folate metabolism [5]. The C677T and A1298C polymorphisms have been associated with up to a 70% reduction in folate acid metabolism [11, 12]. On the other hand, schizophrenia is considered to be a neurodevelopmental disorder [41] which epigenetic mechanisms such as DNA methylation might be important in its etiology [42, 43]. DNA methylation is a critical epigenetic modifier of the genome that controls many biologic processes, including embryonic development, X-chromosome inactivation, imprinting, and gene expression. The link between folate, folate metabolism, and DNA methylation therefore provides a plausible biologic mechanism for the observed association between the MTHFR gene and schizophrenia [44]. Reduced MTHFR activity has been found in brain tissue of
schizophrenia patients [45]. In the brain, SAM is directly involved in the synthesis and metabolism of dopamine, epinephrine and serotonin, which as neurotransmitters play a crucial role in the pathogenesis of neurological disease [46].

Hyperhomocysteinemia can result from decreased MTHFR enzyme activity, owing to genetic polymorphisms [47]. Regland et al., demonstrated abnormally elevated homocysteine levels in 45% of schizophrenia patients [14]. It have been reported that homocysteine levels are elevated in both chronic and newly admitted schizophrenic patients [48, 49]. Hyperhomocysteinemia could lead to the mild cognitive impairments [50]. The homocysteine may contribute in developing schizophrenia by increasing oxidative stress processes [51, 52] and inducing DNA strand breakage and apoptosis [53-55]. Note worthily, the homocysteine was exerting an NMDA antagonist effect [56].

To our knowledge, the present study is the first to evaluate this combination effect. Interestingly, we found a significant association between the coexistence of these polymorphisms and increase the risk of schizophrenia.

Acknowledgements: We thank Research Deputy of Shahid Chamran University supporting this work and all of the participants have been making this research possible.

Conflict of Interest: The authors declare that they have no competing interest.

REFERENCES

1. O'Donovan MC, Williams NM, Owen MJ. Recent advances in the genetics of schizophrenia. Hum Mol Genet 2003;12:R125-R133.
2. Muntjewerff JW, Hoogendoorn ML, Kahn RS, Sinke RJ, Den Heijer M, Kluijtmans LA, Blom HJ. Hyperhomocysteinemia, methylenetetrahydrofolate reductase 677TT genotype, and the risk for schizophrenia: a Dutch population based case–control study. Am J Med Genet B Neuropsychiatr Genet 2005;135B:69-72.
3. Morgan HD, Santos F, Green K, Dean W, Reik W. Epigenetic reprogramming in mammals. Hum Mol Genet 2005;14:47-58.
4. Molloy AM, Daly S, Mills JL, Kirke PN, Whitehead AS, Ramsbottom D, Conley MR, Weir DG, Scott JM. Thermolabile variant of 5, 10-methylenetetrahydrofolate reductase associated with low red-cell folates; implications for folate intake recommendations. Lancet 1997;349:1591-1593.
5. Nishimura M, Yoshino K, Tomita Y, Takashima S, Tanaka J, Narisawa K, Kurobane I. Central and peripheral nervous system pathology of homocystinuria due to 5, 10-methylenetetrahydrofolate reductase deficiency. Pediatr Neurol 1985;6:375-378.
6. Kohn Y, Danilovich E, Filon D, Oppenheim A, Karni O, Kanyas K, Turetsky N, Korner M, Lerner B. Linkage disequilibrium in the DTNBP1 (dysbindin) gene region and on chromosome 1p36 among psychotic patients from a genetic isolate in Israel: findings from identity by descent haplotype sharing analysis. Am J Med Genet B Neuropsychiatr Genet 2004;128:65-70.

http://mbrc.shirazu.ac.ir

www.SID.ir
7. Frosst P, Blom HJ, Milos R, Goyette P, Sheppard CA, Matthews RG, Boers GJH, den Heijer M, Kluijtmans LAJ, van den Heuve LP, Rozen R. A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. Nat Genet 1995;10:111-113.

8. Weisberg I, Tran P, Christensen B, Sibani S, Rozen R. A second genetic polymorphism in methylenetetrahydrofolate reductase (MTHFR) associated with decreased enzyme activity. Mol Genet Metab 1999;4:511-512.

9. Rozen R. Molecular genetics of methylenetetrahydrofolate reductase deficiency. J Inherit Metab Dis 1996;19:589-594.

10. Lievers KJ, Boers GH, Verhoeof P, den Heijer M, Kluijtmans LA, van der Put NM, Trijbels F, Blom HJ. A second common variant in the methylenetetrahydrofolate reductase (MTHFR) gene and its relationship to MTHFR enzyme activity, homocysteine, and cardiovascular disease risk. J Mol Med 2001;79:522-528.

11. Klerk M, Verhoeof P, Clarke R, Blom HJ, Kok FJ, Schouten EG. MTHFR 677C>T polymorphism and risk of coronary heart disease: a meta-analysis. JAMA 2002; 288: 2023-2031.

12. Matthews RG. Methylenetetrahydrofolate reductase: a common human polymorphism and its biochemical implications. Chem Rec 2002;2:4-12.

13. Godfrey PS, Toone BK, Carney MW, Flynn TG, Bottiglieri T, Laundy M. Enhancement of recovery from psychiatric illness by methylfolate. Lancet 1990;336:392-395.

14. Regland B, Germgard CG, Gottfries CG, Grenfeldt B, Koch-Schmidt AC. Homozygous thermolabile methylenethetrahydrofolate reductase in schizophrenia-like psychosis. J Neural Transm 1997;104:931-941.

15. Susser E, Brown AS, Klonowski E, Allen RH, Lindenbaum J. Schizophrenia and impaired homocysteine metabolism: a possible association. Biol Psychiatry 1998;44:141-143.

16. Levine J, Sela BA, Osher Y, Belmaker RH. High homocysteine serum levels in young male schizophrenia and bipolar patients and in an animal model. Prog Neuropsychopharmacol Biol Psychiatry 2005;29:1181-1191.

17. Jacques PF, Selhub J, Bostom AG, Wilson PW, Rosenberg IH. The effect of folic acid fortification on plasma folate and total homocysteine concentrations. N Engl J Med 1995;334:1449-1454.

18. Arinami T, Yamada N, Yamakawa-Kobayashi K, Hamaguchi H, Toru M. Methylenetetrahydrofolate reductase variant and schizophrenia/depression. Am J Med Genet 1997;74:526-528.

19. Kunugi H, Fukuda R, Hattori M, Kato T, Tatsumi M, Sakai T, Hirose T, Nanko S. C677T polymorphism in methylenetetrahydrofolate reductase gene and psychoses. Mol Psychiatry 1998;3:435-437.

http://mbrc.shirazu.ac.ir
20. Virgos C, Martorell L, Simo JM, Valero J, Figuera L, Joven J, Labad A, Vilella E. Plasma homocysteine and the methylenetetrahydrofolate reductase C677T gene variant: lack of association with schizophrenia. Neuroreport 1999;10:2035-2038.
21. Joobér R, Benkelfat C, Lai S, Bloom D, Labelle A, Lalonde P, Turecki, G, Rozen R, Rouleau GA. Association between the methylenetetrahydrofolate reductase 677C–T missense mutation and schizophrenia. Mol Psychiatry 2000;5:323-326.
22. Yu L, Li T, Robertson Z, Dean J, Gu NF, Feng GY, Yates P, Sinclair M, Crombie C, Collier DA, Walker N, He L, St Clair D. No association between polymorphisms of methylenetetrahydrofolate reductase gene and schizophrenia in both Chinese and Scottish populations. Mol Psychiatry 2004;9:1063–1065.
23. Vilella E, Virgos C, Murphy M, Martorell L, Valero J, Simo JM, Joven J, Fernandez-Ballart J, Labad A. Further evidence that hyperhomocysteinemia and methylenetetrahydrofolate reductase C677T and A1289C polymorphisms are not risk factors for schizophrenia. Prog Neuropsychopharmacol Biol Psych 2005;29:1169-1174.
24. Sazci A, Ergul E, Kucukali I, Kara I, Kaya G. Association of the C677T and A1298C polymorphisms of methylenetetrahydrofolate reductase gene with schizophrenia: association is significant in men but not in women. Prog Neuropsychopharmacol Biol Psychiatry 2005;29:1113-1123.
25. Kempisty B, Mostowska A, Gorska I, Luczak M, Czerski P, Szczepankiewicz A, Joanna Hauser J, Jagodziński PP. Association of 677C>T polymorphism of methylenetetrahydrofolate reductase (MTHFR) gene with bipolar disorder and schizophrenia. Neurosci Lett 2006;400:267-271.
26. Kempisty B, Bober A, quczak M, Czerski P, Szczepankiewicz A, Hauser J, Jagodziński PP. Distribution of 1298A>C polymorphism of methylenetetrahydrofolate reductase gene in patients with bipolar disorder and schizophrenia. Eur Psychiat 2007;22:39-43.
27. Muntjewerff JW, Gellekink H, den Heijer M, Hoogendoorn MLC, René S, Kahn RS, Richard J, Sinke RJ, Henk J. Blom HJ. Polymorphisms in catechol-O-methyltransferase and methylenetetrahydrofolate reductase in relation to the risk of schizophrenia. Eur Neuropsychopharm 2008;18:99-106.
28. Rosenquist TH, Schneider AM, Monaghan DT. N-methyl-D-aspartate receptor agonists modulate homocysteine-induced developmental abnormalities. FASEB J 1999;13:1523-1531.
29. Hollmann M, Heinemann S. Cloned glutamate receptors. Annu Rev. Neurosci; 1994;17: 31-108.
30. Lipton SA, Kim WK, Choi YB, Kumar S, D'Emilia DM, Rayudu PV, Derrick R. Arnelle DR, Jonathan S, Stamler JS. Neurotoxicity associated with dual actions of homocysteine at the N-methyl-D-aspartate receptor. Proc Natl Acad Sci USA 1997; 94:5923-5928.
31. Monyer H, Sprengel R, Schoepfer R, Herb A, Higuchi M, Lomeli H, Nail Burnashev, Bert Sakmann, Peter HS. Heteromeric NMDA receptors: Molecular and functional distinction of subtypes. Science 1992;256:1217-1221.

http://mbrc.shirazu.ac.ir
32. Coyle JT, Tsai GC. NMDA receptor function, neuroplasticity, and the pathophysiology of schizophrenia. Disord Synaptic Plast Schizophr 2004;59:491-515.
33. Galehdari H, Pooryasin A, Foroughmand AM, Daneshmand S, Saadat M. Association between the G1001C polymorphism in the GRIN1 gene and Schizophrenia in the Iranian population. J Mol Neurosci 2009;38:178-181.
34. Kara I, Sazci A, Ergul E, Kaya G, Kilic G. Association of the C677T and A1298C polymorphisms in the 5, 10 methylenetetrahydrofolate reductase gene in patients with migraine risk. Mol Brain Res 2003;111:84-90.
35. Weisberg IS, Jacques PF, Selhub J, Bostom AG, Chen Z, Curtis Ellison R, Eckfeldt JH, Rozen R. The A1298C polymorphism in methylenetetrahydrofolate reductase (MTHFR): in vitro expression and association with homocysteine. Atherosclerosis 2001;156:409-415.
36. Muntjewerff JW, van der Put N, Eskes T, Ellenbroek B, Steegers E, Blom H, Zitman F. Homocysteine metabolism and B-vitamins in schizophrenic patients: low plasma folate as a possible independent risk factor for schizophrenia. Psychiatry Res 2003;121:1-9.
37. Muntjewerff JW, Kahn RS, Blom HJ, den Heijer M. Homocysteine, methylenetetrahydrofolate reductase and risk of schizophrenia: a meta-analysis. Mol Psychiatry 2006;11:143-149.
38. Van Der Put NM, Gabreels F, Stevens EMB, Smetsink JAM, Trijbels FJM, Eskes TKAB, van den Heuvel LP, Blom HJ. A second common mutation in the methylenetetrahydrofolate reductase gene: an additional risk factor for neural-tube defects? Am J Hum Genet 1998;62:1044-1051.
39. Shi J, Gershon ES, Liu C. Genetic associations with schizophrenia: Meta-analyses of 12 candidate genes. Schizophr Res 2008;104:96-107.
40. Matsushita S, Muramatsu T, Arai H, Matsui T, Higuchi S. The frequency of the methylenetetrahydrofolate reductase gene mutation varies with age in the normal population, Am J Hum Genet 1997;61:1459-1460.
41. Picker JD, Coyle JT. Do maternal folate and homocysteine levels play a role in neurodevelopmental processes that increase risk for schizophrenia? Harv Rev Psychiatry 2005;13:197-205.
42. Singh SM, Murphy B, O'Reilly RL. Involvement of gene-diet/drug interaction in DNA methylation and its contribution to complex diseases: from cancer to schizophrenia. Clin Genet 2003;64:451-460.
43. Singh SM, McDonald P, Murphy B. O'Reilly RL. Incidental neurodevelopmental episodes in the etiology of schizophrenia: an expanded model involving epigenetics and development. Clin Genet 2004;65:435-440.
44. Gilbody S, Lewis S, Lightfoot T. Methylenetetrahydrofolate reductase (MTHFR) genetic polymorphisms and psychiatric disorders: A HuGE review. Am J Epidemiol 2007;165:1-13.
45. Elliott GR, Sutherland K, Erdelyi E, Ciaranello RD, Barchas JD, Wyatt RJ. N-5, 10-methylenetetrahydrofolate reductase activity in autopsied brain parts of chronic schizophrenics and controls and in vitro tryptoline formation. Biol Psychiatry 1978;13:695-708.
46. Sherer MA, Cantoni MA, Golden RN, Rudorfer MV, Potter WZ. Effects of S-adenosylmethionine on plasma norepinephrine, blood pressure, and heart rate in healthy volunteers. Psychiatry Res 1986;2:111-118.
47. Selhub JL, Miller JW. The pathogenesis of homocysteinemia: interruption of the coordinate regulation by S-adenosylmethionine of the remethylation and transulfuration of homocysteine. Am J Clin Nutr 1991;55:131-138.
48. Applebaum J, Shimon H, Sela BA, Belmaker RH, Levine J. Homocysteine levels in newly admitted schizophrenic patients. J Psychiatr Res 2004;38:413-416.
49. Levine J, Stahl Z, Sela BA, Gavendo S, Ruderman V, Belmaker RH. Elevated homocysteine levels in young male patients with schizophrenia. Am J Psychiatry 2002;159:1790-1792.
50. Osher Y, Sela BA, Levine J, Belmaker RH. Elevated homocysteine levels in euthymic bipolar disorder patients showing functional deterioration. Bipolar Disord 2004;1:82-86.
51. Yao JK, Reddy RD, van Kammen DP. Oxidative damage and schizophrenia: an overview of the evidence and its therapeutic implications. CNS Drugs 2001;15:287-310.
52. Dimitrova KR, DeGroot KW, Suyderhoud JP, Pirovic EA, Munro TJ, Wieneke J, Myers AK, Kim YD. 17-B estradiol preserves endothelial cell viability in an in vitro model of homocysteine-induced oxidative stress. J Cardiovasc Pharm 2002;39:347-353.
53. Catts VS, Catts SV. Apoptosis and schizophrenia: Is the tumour suppressor gene, p53, a candidate susceptibility gene? Schizophr Res 2000;41:405-415.
54. Jarskog LF, Gilmore JH, Selinger ES, Lieberman JA. Cortical bcl-2 protein expression and apoptotic regulation in schizophrenia. Biol Psychiat 2000;48:641-650.
55. Mattson MP, Shea TB. Folate and homocysteine metabolism in neural plasticity and neurodegenerative disorders. Trends Neurosci 2003;26:137-146.
56. Kamudhamas A, Pang L, Smith SD, Sadovsky Y, Nelson DM. Homocysteine thiolactone induces apoptosis in cultured human trophoblasts: a mechanism for homocysteine-mediated placental dysfunction? Am J Obstet Gynecol 2004;191:563-571.
کارگاه‌های آموزشی مرکز اطلاعات علمی

مقاله نویسی علوم انسانی

ارسال تنظیم قراردادها

آموزش مهارت های کاربردی در تدوین و چاپ مقاله