The Association between the MTR Gene A2576G Polymorphism and Alzheimer’s Disease: a Meta Analysis Study

Yun Wang, Shunliang Xu* and Jianzhong Bi

Department of Neurology, 2nd Hospital of Shandong University, Jinan, Shandong, 250033, P.R. China

Abstract

Background: Alzheimer’s disease (AD) individuals are characterized with high homocysteine (HCY) and low folate blood levels. Polymorphisms of genes encoding critical enzymes in folate metabolism have been associated with hyperhomocysteinemia and AD risk. An adenine to guanine transition at position 2756 (rs185087) of the methionine synthase (MS or MTR) gene causes hyperhomocysteinemia. However, the association between MTR A2756G polymorphism and AD remains controversial. We performed a Meta analysis pooling data from all relevant studies including cases and controls to reexamine the association between the MTR gene A2756G polymorphism and AD.

Methods: We applied random-effects or fixed-effects model according to the degree of heterogeneity to combine odds ratio (OR) and 95% coincidence intervals (95% CI). And we used the Quanto 1.2.4 software to calculate genetic power. Egger’s test was carried out to evaluate the potential publication bias.

Results and discussion: Eight case-control studies enrolling 2,880 cases and 2,807 controls were included in this meta analysis. The overall ORs with 95% CIs showed no statistical association between the MTR gene A2756G polymorphism and the risk of AD in the allele contrast, the recessive model or dominant model for allele A (random-effects pooled OR 1.09, 95% CI 0.92-1.30; random-effects pooled OR 1.11, 95% CI 0.91-1.35; fixed-effects pooled OR 1.13, 95% CI 0.83-1.54, respectively). The genetic power was 11.6% in the recessive model and 43.7% in the dominant model. No association between MTR A2756G polymorphism and AD was observed, but the conclusion based on relatively small numbers of participants. Large heterogeneity was detected among combined populations in the contrast of AA vs. AG+GG (p = 0.019, I² = 56.3%) and A vs. G (p = 0.016, I² = 57.5%). One study was considered as the main cause of heterogeneity in both contrasts. The heterogeneity doesn’t reduce in the subgroup analyses stratified by racial descents. It can be presumed that the heterogeneity mainly results from the diagnosis of AD and genotyping methods. No publication bias was observed.

Conclusions: In conclusion, the present Meta analysis suggests that MTR A2756G polymorphism is not a genetic determinant of AD. But small sample size may be one reason and it could not be ruled out that a true association exists.

Keywords: Alzheimer’s disease; Single-nucleotide polymorphisms; Methionine synthase; Meta analysis

Background

Alzheimer’s disease (AD) is the leading cause of dementia in the elderly, and its etiology is still not fully understood. Disease-causing mutations in the amyloid precursor protein (APP), presenilin 1 (PS1), and presenilin 2 (PS2) genes cause familial AD [1]. However, sporadic AD lacking an obvious familial aggregation accounts for as much as 90% patients of AD. Epigenetic modifications, such as DNA methylation, may contribute to the risk of sporadic AD [2]. Folate metabolism, also known as one-carbon metabolism, is required for the production of S-adenosylmethionine (SAM), which is the major DNA methylating agent [3]. Folate is essential nutrient required for one-carbon biosynthetic and epigenetic processes. Several investigators have measured plasma values of homocysteine (HCY) and folate in AD subjects. Overall, the majority of the studies agreed that plasma HCY values increased in AD subjects [4-6]; there was also indication that folate values reduced in the plasma of AD individuals respect to controls [4-7].

Polymorphisms of genes encoding critical enzymes in folate metabolism have been associated with hyperhomocysteinemia. Methionine synthase (MS or MTR) is a key enzyme in the one-carbon metabolism catalyzing HCY to methionine. An adenine to guanine transition at position 2756 (rs185087) of the MTR gene results in a substitution of aspartic acid for glycine and decreases methionine synthase activity. This polymorphism causes hyperhomocysteinemia [8]. However, results are still conflicting. Increased HCY levels have been reported in the presence of the wild type (MTR 2756A) allele [9], whereas other studies observed increased HCY levels in the presence of the mutant (MTR 2756G) allele [10,11].

Confused data were reported on the association between the MTR A2756G polymorphism and AD [12-21]. Some studies reported association between the MTR 2756G genotype and AD [12,13,21]. But other studies revealed no association between the MTR A 2756G polymorphism and AD [14-20]. So we performed a Meta analysis of
existing studies that examined allele and genotype frequencies of the MTR gene in patients with AD.

Methods

Search strategies

We searched MEDLINE (1966 to January 2012), EMBASE (1966 to January 2012), and Cochrane Collaboration Registry for Randomized Controlled Trials (1966 to January 2012). As a search criterion, we used the following: methionine synthase (MS) or MTR gene or MTR polymorphism and AD or Alzheimer’s; or MS gene or MS polymorphism and AD or Alzheimer’s. No language restriction was applied.

Selection criteria

We limited our search to full text, published articles and human studies. Abstracts, case reports, editorials, and review articles were excluded. We also retrieved relevant references of included studies for our search. When a report overlapped with a more detailed publication, only the latter was used. All studies that investigate the association of the MTR A2756G polymorphism with AD using a case-control design were considered in the meta analysis.

Clinical diagnosis of probable AD were all established according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) [22], the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) working group criteria [23] and the Consortium to Establish a Registry for Alzheimer’s disease (CERAD) working group criteria [24]. Controls were defined as subjects not meeting the dementia criteria with intact cognitive functions. All populations were consistent with Hardy-Weinberg equilibrium. Genotyping methods for each data set were described in the original publications.

Data abstraction

Two reviewers (Y. Wang and SL. Xu) independently extracted the data and disagreements were resolved by discussion. Characteristics abstracted from the studies included the name of first author, publication date, country origin, ethnicity, characteristic criteria, genotyping methods, total number of cases and controls, and numbers of cases and controls with MTR alleles and genotypes, respectively. Different ethnicity descents were categorised as Caucasian or Asian.

Quantitative data synthesis

The primary analysis was conducted by comparing the AA homoygous genotype with G-carrying genotypes, and also A allele with G allele. This meta analysis examined the contrasts of AA vs AG+GG and AA+AG vs GG, corresponding to the recessive and dominant effects, respectively of the A allele. We also examined the association between A allele and AD risk compared with that for G allele (A vs G). We used StataSE 12.0 statistical software packages to analyze our data. The odds ratio (OR) with 95% coincidence interval (95% CI) was calculated to assess the association of the MTR A2756G polymorphisms with AD risk.

The summary OR for AA vs. AG+GG was 1.11 by random-effects model (OR 1.11; 95% CI 0.91 to 1.35, Figure 1a). And the summary OR for AA+AG vs. GG was 1.13 by fixed-effects model (OR 1.13; 95% CI 0.83 to 1.54, Figure 1b). The OR for A vs. G is shown in Figure 1c. The summary OR with its 95% CI was 1.09 (0.92 to 1.30) by random-effects model.

In the stratified analysis by racial descent, no significant risks were found among Caucasians. The detailed data were shown in Table 3.

MTR is a key enzyme in the metabolism of HCY, catalyzing the remethylation of HCY to methionine. When the MTR reaction is impaired, as observed in vitamin B12 deficiency, a substantial proportion of cellular folate is converted into a metabolically unavailable form, which results in a functional folate deficiency [33]. MTR A2756G polymorphism was reported as a candidate gene polymorphism for coronary heart disease [34], cancer [35], and...
Citation: Wang Y, Xu S, Bi J (2012) The Association between the MTR Gene A2576G Polymorphism and Alzheimer’s Disease: a Meta Analysis Study. Human Genet Embryol S2:003. doi:10.4172/2161-0436.S2-003

| Study          | Country | Criteria          | Genotyping methods | AD N (% Female) | Control N (% Female) | Mean age | Mean age |
|----------------|---------|-------------------|--------------------|-----------------|----------------------|----------|----------|
| Beyer [12]     | Spain   | DSM-IV; NINCDS-ADRDA | RFLP               | 172(62%)        | 166 (60%)            | 70.8     | 68.7     |
| Bosco [13]     | Italy   | CERAD             | RFLP               | 152 (54%)       | 136 (55%)            | 74.8     | 69.3     |
| Dorszewska [15]| Poland  | NINCDS-ADRDA      | RFLP               | 38(61%)         | 30 (68%)             | 66.3 ± 12.2 | 44.6 ± 16.2 |
| Giedraitis [18]| Sweden  | NINCDS-ADRDA; DSM-IV | high and ultra-high throughput genotyping | 86 (0%) | 80.2(AAO) | 404 (0%) | 81.8 |
| Li [17]        | Canada  | NINCDS-ADRDA      | GWAS               | 753 (56%)       | 736 (64%)            | 77.8 ±8.6 | 73.4 ± 7.9 |
| Linnebank [14] | Germany | DSM-IV            | RFLP               | 162 (68%)       | 169 (56%)            | 72 ±9    | 71 ± 7   |
| Reiman [16]    | USA, Netherlands | NM             | GWAS               | 861 (-)         | 550 (-)              | 74.9 ± 6.6 | 77.4 ± 7.3 |
| Zhao [19]      | China   | DSM-IV; NINCDS-ADRDA | RFLP               | 353 (52%)       | 346 (47%)            | 68.9 ± 9.2 (AAO) | 68.5 ± 9.1 |
| Coppede [20]   | Italy   | DSM-IV; NINCDS-ADRDA | RFLP               | 375(63%)        | 307(63%)             | 74.2±6.46 | 71.7±8.02 |

Note: ULSAM, Uppsala Longitudinal Study of Adult Men; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders IV; NINCDS-ADRDA, the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association; CERAD, the Consortium to Establish a Registry for Alzheimer’s Disease. NM, Not mentioned; RFLP, restriction fragment length polymorphism; GWAS, genome-wide association study; AAO, Age at onset

Table 1: Clinical characteristics of the populations included in the meta analysis.

### Table 2: Distribution of MTR allele and genotype among AD cases and controls in the included studies.

| Study          | AD G-Allele A-Allele GG (frequency) | AG (frequency) | AA (frequency) | Control G-Allele A-Allele GG(frequency) | AG(frequency) | AA(frequency) |
|----------------|-------------------------------------|---------------|---------------|----------------------------------------|---------------|---------------|
| Beyer [12]     | 0.08 0.92 1 (0.006)                 | 25 (0.145)    | 146 (0.849)   | 0.18 0.82 5 (0.030)                     | 49 (0.295)    | 112 (0.675)   |
| Bosco [13]     | 0.16 0.84 4 (0.026)                 | 42 (0.276)    | 106 (0.697)   | 0.19 0.81 5 (0.036)                     | 42 (0.307)    | 90 (0.657)    |
| Dorszewska [15]| 0.29 0.71 2 (0.053)                 | 18 (0.474)    | 18 (0.474)    | 0.18 0.82 0 (0.000)                     | 18 (0.360)    | 32 (0.640)    |
| Giedraitis [18]| 0.22 0.78 4 (0.047)                 | 30 (0.353)    | 51 (0.600)    | 0.20 0.80 19 (0.048)                    | 121 (0.303)   | 260 (0.650)   |
| Li [17]        | 0.18 0.82 20 (0.029)                | 205 (0.297)   | 466 (0.674)   | 0.18 0.82 29 (0.043)                    | 190 (0.279)   | 463 (0.679)   |
| Linnebank [14] | 0.22 0.78 7 (0.043)                 | 58 (0.358)    | 97 (0.599)    | 0.26 0.74 8 (0.047)                     | 71 (0.420)    | 90 (0.533)    |
| Reiman [16]    | 0.19 0.81 29 (0.034)                | 259 (0.304)   | 563 (0.662)   | 0.19 0.81 20 (0.036)                    | 167 (0.304)   | 363 (0.660)   |
| Zhao [19]      | 0.07 0.93 2 (0.006)                 | 47 (0.133)    | 305 (0.862)   | 0.08 0.92 2 (0.006)                     | 54 (0.156)    | 290 (0.838)   |
| Coppede [20]   | 0.14 0.86 12(0.032)                | 80(0.213)     | 283(0.746)    | 0.13 0.87 5(0.016)                      | 72(0.236)     | 230(0.749)    |

Note: D-L, the DerSimonian-Laird method; M-H, the Mantel-Haenszel method; p_H, p-value of Q-test for heterogeneity test; p_OR, p-value of Z-test for OR; p_E, p-value of t-test for Egger’s test.

Table 3: Main results of heterogeneity pooled ORs, stratification analysis and Egger’s test of the MTR gene functional polymorphisms on AD risk in the meta analysis.

inflammatory bowel disease [36], all of which were characterized by hyperhomocysteinemia caused by impaired one-carbon metabolism [37-39].

There is still a long way to go to fully understand the relationship between folate metabolism and AD. Updated meta analysis studies demonstrated that individuals with AD had higher HCY levels than controls; however, a causal relationship between hyperhomocysteinemia and risk of developing AD was not supported [40], and no benefit of folic acid in reducing cognitive decline was observed [41].

The primary analysis demonstrated that the MTR gene has been considered as a candidate gene for AD and MTR AA genotype was a risk factor of AD [12]. This meta analysis suggested that no association...
between MTR A2756G polymorphism and AD, but the conclusion reached in the present study was based on relatively small numbers of studies and participants.

**Genetic power calculator**

The overall allele A frequency was set as 0.83, determined by the included studies. With the overall OR 1.11 in the recessive model, the total genetic power was calculated as 11.6%. For the dominant model, the total genetic power was calculated as 43.7%, with the overall OR 1.13. Neither of the power has the potential to draw a conclusion whether this polymorphism is in association with AD or not (power<90%). So even though our meta analysis suggests that MTR A2756G polymorphism is not a genetic determinant of AD, small sample size may be one reason and it could not be ruled out that a true association exists. Whether the MTR A2756G polymorphism indeed associated with AD has to be confirmed in additional studies.

**Heterogeneity**

In the contrast of AA vs. AG+GG, large heterogeneity among combined populations (p = 0.019, I² = 56.3%) and Caucausian subgroup (p = 0.012, I² = 61.1%) study was observed. Large heterogeneity was detected among combined populations (p = 0.016, I² = 57.5%) and...
Caucasion subgroup (p = 0.010, I² = 62.3%) in the contrast of A vs. G. By contrast, no heterogeneity among studies was observed in the contrast of AA+AG vs. GG among combined populations (p = 0.531, I² = 0%) and Caucasion subgroup (p = 0.425, I² = 0.6%, Table 3).

The AA vs. AG+GG and A vs. G results showed large heterogeneity among combined populations and Caucasion subgroup studies in this meta analysis. Through stratified analyses, the heterogeneity of the subgroup didn’t reduce.

The study of Beyer and co-workers in 2003 [12] was considered as the main cause of heterogeneity in both contrasts as shown in the galbraith plot for heterogeneity (Figures 2a and 2b). After exclusion of this study, the heterogeneity no longer existed, but still reached a negative association (data not shown).

We explored potential sources of heterogeneity in following aspects: (1) Diagnosis of AD. The most frequently used diagnostic criteria for AD are NINCDS-ADRDA, DSM-IV and International Classification of disease-10 (ICD-10). In the included studies, AD was diagnosed by different criteria. These different criteria may result in an inconsistent diagnosis of AD. (2) Genotyping methods. Depending on the center, a broad range panel of technologies were used to genotype the rs1805087 polymorphism, such as restriction fragment length polymorphism (RFLP), genome-wide association study (GWAS), high and ultra-high throughput genotyping, et al. The heterogeneity may not be caused by ethnicity, because it can be found that the heterogeneity doesn’t reduce in the subgroup analyses stratified by racial descents.

In the study of Beyer and co-workers in 2003 [12], patients were sporadic AD with clinical diagnosis of probable AD according to the DSM-IV and NINCDS-ADRDA criteria and without a first-degree relative with either AD or progressive memory loss. And the method used for genotyping was RFLP, based on HaeIII-digested PCR. Therefore, it can be presumed that the heterogeneity mainly results from the diagnosis of AD and genotyping methods.

Bias diagnostics

Begg’s funnel plot and Egger’s test were performed to assess the publication bias of the literature. The shapes of the funnel plot for the contrast of the AA vs. AG+GG seemed approximately symmetrical (Figure 3), and Egger’s test did not show any evidence of publication bias (t = -0.54; p = 0.609; 95%CI -2.54 to 4.11). So did the contrast of the AA+AG vs. GG (t = 0.77; p = 0.464) and the contrast of A vs. G (t = 0.57; p = 0.587), as shown in Table 3.

The result for publication bias was not statistically significant. But publication bias may exist, because only published studies were included in this meta analysis.

Conclusion

In summary, this meta analysis can’t prove that the rs1805087 in MTR gene is associated with the risk of AD. But small sample size may be one reason and it could not be ruled out that a true association exists. More well-designed studies with larger sample size are warranted to validate these findings.

Acknowledgement

The study is supported by Independent Innovation Foundation of Shandong University, IIFSDU, Grant number: 2010JC016.

References

1. Bertram L, Tanzi RE (2004) The current status of Alzheimer’s disease genetics: What do we tell the patients? Pharmaco Res 50: 385-396.
2. Chouliaras L, Rutten BP, Kenis G, Peerbooms O, Visser PJ, et al. (2010) Epigenetic regulation in the pathophysiology of Alzheimer’s disease. Prog Neurobiol 90: 498-510.
3. Coppede F (2010) One-Carbon Metabolism and Alzheimer’s disease: focus on epigenetics. Curr Genomics 11: 246-260.
4. Koseoglu E, Karaman Y (2007) Relations between homocysteine, folate and vitamin B12 in vascular dementia and in Alzheimer disease. Clin Biochem 40: 859-863.
5. Cazzaniga E, Bulbarelli A, Lonati E, Re F, Galimberti G, et al. (2008) Enhanced folate binding of cultured fibroblasts from Alzheimer’s disease patients. Neurosci Lett 436: 317-320.
6. Bi XH, Zhao HL, Zhang ZX, Zhang JW (2009) Association of RFC1 A80G and MTHFR C677T polymorphisms with Alzheimer’s disease. Neurobiol Aging 30: 1601-1607.
7. Galimberti G, Conti E, Zini M, Piazza F, Fanaroli F, et al. (2008) Post-methionine load test: A more sensitive tool to reveal hyperhomocysteinemia in Alzheimer patients? Clin Biochem 41: 914-916.
8. Fredrikson A, Meyer K, Ueland PM, Vollset SE, Grotmol T, et al. (2007) Large-scale population-based metabolic phenotyping of thirteen genetic polymorphisms related to one-carbon metabolism. Hum Mutat 28: 856-865.
9. Fillon-Emery N, Chango A, Mircher C, Barbe F, Blehaut H, et al. (2004) Homocysteine concentrations in adults with trisomy 21: effect of B vitamins and genetic polymorphisms. Am J Clin Nutr 80: 1551-1557.
10. Feix A, Fritsche-Polanz R, Kletzmayr J, Vychytil A, Hörl H, et al. (2001) Increased prevalence of combined MTR and MTHFR genotypes among individuals with severely elevated total homocysteine plasma levels. Am J Kidney Dis 38: 956-964.
11. Laraqui A, Allami A, Carrie A, Coiffard AS, Benkouka F, et al. (2006) Influence of methionine synthase (A2756G) and methionine synthase reductase (A66G) polymorphisms on plasma homocysteine levels and relation to risk of coronary artery disease. Acta Cardiol 61: 51-61.
12. Beyer K, Lao Ji, Lalor P, Riuotb N, Matufe B, et al. (2003) Methionine synthase polymorphism is a risk factor for Alzheimer’s disease. Neuroreport 14: 1391-1394.
13. Bosco P, Gueant-Rodriguez RM, Anello G, Romano A, Namour B, et al. (2004) Association of IL-1 RN*2 allele and methionine synthase 2756 AA genotype with dementia severity of sporadic Alzheimer’s disease. J Neurol Neurosurg Psychiatry 75: 1036-1038.
14. Linnebank M, Linnebank A, Jeub M, Klockgether T, Wüllner U, et al. (2004) Lack of genetic dispositions to hyperhomocysteinemia in Alzheimer disease. Am J Med Genet 131: 101-102.

15. Dorszewska J, Florczak J, Rozycka A, Kempisty B, Jaroszewska-Kolecka J, et al. (2007) Oxidative DNA damage and level of thiols as related to polymorphisms of MTHFR, MTR, MTHFD1 in Alzheimer’s and Parkinson’s diseases. Acta Neurobiol Exp (Wars) 67: 113-129.

16. Reiman EM, Webster JA, Myers AJ, Hardy J, Dunckley T, et al. (2007) GAB2 alleles modify Alzheimer’s risk in APOE epsilon4 carriers. Neuron 54: 713-720.

17. Li H, Wetten S, Li L, St Jean PL, Uramanyu R, et al. (2008) Candidate single-nucleotide polymorphisms from a genomewide association study of Alzheimer disease. Arch Neurol 65: 45-53.

18. Giedraitis V, Kilander L, Degerman-Gunnarsson M, Sundelöf J, Axelsson T, et al. (2009) Genetic analysis of Alzheimer’s disease in the Uppsala Longitudinal Study of Adult Men. Dement Geriatr Cogn Disord 27: 59-68.

19. Zhao HL, Li XQ, Zhang ZX, Bi XH, Wang B, et al. (2008) Association analysis of methionine synthase gene 2756 A>G polymorphism and Alzheimer disease in a Chinese population. Brain Res 1204: 118-22.

20. Coppede F, Tannorella P, Pezzini I, Mighele F, Ricci G, et al. (2011) Folate, Homocysteine, Vitamin B12, and Polymorphisms of Genes Participating in One-Carbon Metabolism in Late-Onset Alzheimer’s Disease Patients and Healthy Controls. Antioxid Redox Signal [Epub ahead of print].

21. Beyer K, Lao J, Latore P, Ariza A (2005) Age at onset: an essential variable for the definition of genetic risk factors for sporadic Alzheimer’s disease. Ann N Y Acad Sci 1057: 260-278.

22. APA (1994) Diagnostic and Statistical Manual of Mental Disorders DSM. (4thedn), Washington DC: American Psychiatric Association 37-39.

23. McKearn H, Drachman D, Folstein M, Katzman R, Price D, et al. (1984) Clinical diagnosis of Alzheimer’s disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer’s Disease. Neurology 34: 939-944.

24. Mirra SS, Heyman A, McKeel D, Sumi SM, Crain BJ, et al. (1991) The Consortium to Establish a Registry for Alzheimer’s Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer’s disease. Neurology 41: 479-486.

25. Menashe I, Rosenberg PS, Chen BE (2008) PGA: power calculator for case-control genetic association analyses. BMC Genet 9: 36.

26. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, et al. (2005) Global prevalence of dementia: a Delphi consensus study. Lancet 366: 2112-2117.

27. Lau J, Ioannidis JP, Schmid CH (1997) Meta analysis, and meta-regression. Am J Geriatr Psychiatry 18: 370-378.

28. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327: 557-560.

29. Mantel N, Haenszel W (1959) Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 22: 719-748.

30. DerSimonian R, Laird N (1986) Meta analysis in clinical trials. Control Clin Trials 7: 177-188.

31. Galbraith RF (1988) A note on graphical presentation of estimated odds ratios from several clinical trials. Stat Med 7: 889-894.

32. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta analysis detected by a simple, graphical test. BMJ 315: 629-634.

33. Smolders YM, Smith DE, Kok RM, Teerlink T, Swinkels DW, et al. (2006) Cellular folate vitamer distribution during and after correction of vitamin B12 deficiency: a case for the methylfolate trap. Br J Haematol 132: 623-629.

34. Chen L, Liu L, Hong K, Hu J, Cheng X (2011) Three Genetic Polymorphisms of Homocysteine-Metabolizing Enzymes and Risk of Coronary Heart Disease: A Meta analysis Based on 23 Case-Control Studies. DNA Cell Biol 31: 238-249.

35. Yu K, Zhang J, Zhang J, Dou C, Gu S, et al. (2009) Methionine synthase A2756G polymorphism and Alzheimer’s disease: a meta analysis. Eur J Hum Genet 15: 370-376.

36. Zintzaras E (2010) Genetic variants of homocysteine/folate metabolism pathway and risk of inflammatory bowel disease: a synopsis and meta analysis of genetic association studies. Biomarkers 15: 69-79.

37. Veeranna V, Zalawadiya SK, Niraj A, Pradhan J, Ference B, et al. (2011) Homocysteine and reclassification of cardiovascular disease risk. J Am Coll Cardiol 58: 1025-1033.

38. Zacho J, Yazdanyar S, Bojesen SE, Tybjaerg-Hansen A, Nordestgaard BG (2011) Hyperhomocysteinemia, methylenetetrahydrofolate reductase c.677C>T polymorphism and risk of cancer: cross-sectional and prospective studies and meta-analyses of 75,000 cases and 93,000 controls. Int J Cancer 128: 644-652.

39. Oussalah A, Gueant JL, Peyrin-Biroulet L (2011) Meta analysis: hyperhomocysteinaemia in inflammatory bowel diseases. Aliment Pharmacol Ther 34: 1173-1184.

40. Ho RC, Cheung MW, Fu E, Win HH, Zaw MH, et al. (2011) Is high homocysteine level a risk factor for cognitive decline in elderly? A systematic review, meta analysis, and meta-regression. Am J Geriatr Psychiatry 19: 607-617.

41. Wald DS, Kasturiratne A, Simmonds M (2010) Effect of folic acid, with or without other B vitamins, on cognitive decline: meta analysis of randomized trials. Am J Med 123: 522-527.e2.

This article was originally published in a special issue, Epigenetics, stem cells and tumorigenicity handled by Editor(s): Dr. Yue Zhang, Harvard Medical School, USA; Yujing Li, Emory University School of Medicine, USA; Yonghong Ji, Xian Jiaotong University, China.