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A REVIEW STUDY ON THE IMPACT OF MTHFR POLYMORPHISMS ON FOLATE RELATED DISEASES

Genetics

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ABSTRACT

Folate plays a crucial role in homocysteine metabolism, DNA and methionine synthesis, and other biochemical pathways. These are collectively known as one-carbon metabolism mediated by folates. Methylenetetrahydrofolate reductase (MTHFR) gene loci present on chromosome 1 encode an enzyme critical for folate metabolism, cellular metabolism, and methylation processes. MTHFR gene variations like A1298C and C677T, are responsible for hyperhomocysteinemia and folate deficiencies leading to various health-related adverse outcomes. The current review attempts to highlight the role of genomics in MTHFR expression and how gene-level variations impact MTHFR gene etiologies. Knowledge about such associations can help devise therapeutic approaches for folate-related conditions.

KEYWORDS

5,10-methylenetetrahydrofolate reductase, Disease risk, MTHFR gene, Polymorphism

INTRODUCTION

Folate is an essential micronutrient and cofactor in one-carbon metabolism. It is associated with the vitamin B group and regulates purine and pyrimidine synthesis, and amino acid metabolism[1]. Folates act as methyl donors for the conversion of homocysteine, a sulfhydryl-containing amino acid, to methionine[2]. Mammals are unable to synthesize folate and thereby rely on supplementation. Despite this, drug interactions and poor absorption are major reasons for folate deficiency[3].

Folate deficiency leads to neural tube defects, cardiovascular diseases, congenital heart defects, cancers, migraines, dementia, and depression, impaired embryonic development, birth defects, morbidity and mortality in children, preterm and low birth weight [4,5].

The enzyme methylenetetrahydrofolate reductase (encoded by the MTHFR gene) regulates homocysteine metabolism, folate pathways, synthesis of methionine, cysteine, etc. The MTHFR gene is present on chromosome 1 at the edge of the short arm (1p36.6)[6]. It is involved in DNA methylation and RNA synthesis by catalyzing the conversion of 5,10-methylenetetrahydrofolate (5,10-MTHF) to 5-methyltetrahydrofolate (5-MTHF) as observed in figure 1. This is the prime folate found in the blood which regulates the homocysteine to methionine conversion. Cells use this type to synthesize glutathione, taurine, S-adenosylmethionine (SAM), and creatine for the functioning of normal bodily processes.

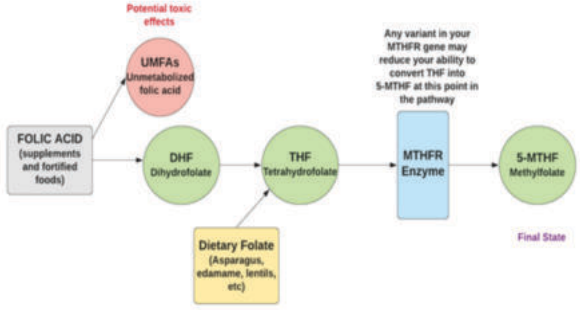

Figure 1: The folate pathway wherein supplemented folic acid is converted into 5-MTHF methyl folate via different intermediates

There are nearly 14 polymorphisms associating MTHFR with enzymatic deficiency[6]. Amongst all, C677T and A1298C are the most common ones, decreasing enzyme capacity to 70% and 40%, respectively. C677T (rs1801133) results in a valine-to-alanine conversion at codon 222, while A1298C (rs1801131) results in a transversion of adenosine to cytosine at nucleotide position 1298 resulting in glutamate-to-alanine substitution[7]. MTHFR variations affect folate and homocysteine levels, thereby disrupting associated pathways as observed in figure 2, leading to diseases.

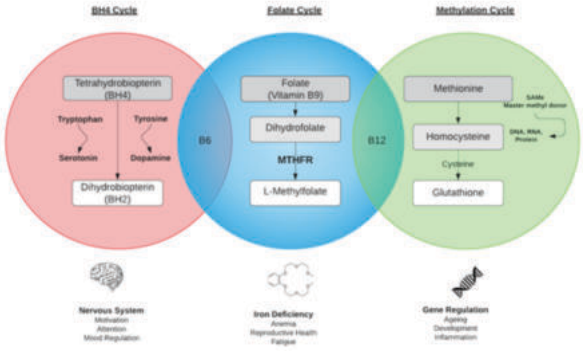

Figure 2: The MTHFR gene and its associated pathways

METHODOLOGY

A systematic literature review was conducted on MTHFR gene variations and associated conditions. Scientific databases such as PubMed, Google Scholar, and other resources were used to find the genotype-phenotype relationship between MTHFR gene and its clinical implications globally. These were obtained by using the following keywords: "MTHFR" or "methylenetetrahydrofolate reductase" or "polymorphism" or "variant", "C677T" or "A1298C" and "diseases".

Inclusion criteria:

- Well-defined meta-analysis, systematic review, case-control studies and review articles
- Publication year 2015 onwards

Exclusion criteria:

- Preclinical studies
- Articles in a different language than English
- Study with lower sample number

MTHFR gene variants and their role in fertility

Approximately 10%-15% of couples globally are affected by fertility complications, of which nearly half are attributed to males and about 20%-25% are ascribed to idiopathic male infertility[8]. Neural tube defects have an incidence of around 1 in 1,000[9]. Low folate and vitamin B12 levels are associated with infertility. MTHFR variants can cause homocysteine imbalance, thereby affecting DNA methylation and consequently affecting reproductive function. The C677T T allele expression is significantly higher in impaired spermatogenesis cases than in controls. Male infertility risk decreased following vitamin B9 and B12 intake, wherein a decreased total homocysteine level and development in semen parameters were observed[10].

The 677TT genotype remarkably decreased vitamin D levels and increased homocysteine than its counterpart genotypes (CC & CT) in recurrent pregnancy losses (RPL)[11]. A significant association was compared between MTHFR C677T and A1298C genetic variants and unexplained pregnancy loss (UPL) using samples of Korean origin[12]. An Eastern Indian study suggested that the rs1801133 polymorphism was associated with an increased risk of neural tube defects (NTD) in mothers with NTD-containing fetuses[13]. Studies have proved a significant correlation between MTHFR polymorphisms and neural tube defect development, fertility problems, and recurrent pregnancy loss[14]. Summarily, evidence shows that MTHFR variations may cause poor pregnancy-related outcomes, hence, genetic screening is important to understand the causal variants and undergo supplementation if required.

MTHFR gene variants and their role in neurological and psychiatric diseases

MTHFR activity reduction or folate deficiency is associated with depression, autism, schizophrenia, mood disorders, bipolar disorder, and ADHD[15,18]. Research suggests associations between C677T and Parkinson's disease, Alzheimer's disease, migraine, cerebral venous thrombosis and unipolar depressive disorder[6,16]. It is also associated with hyperactivity-impulsivity among East Indians, indicating that folate-homocysteine pathway variants affect ADHD pathogenesis[17]. The MTHFR enzyme reduces gray matter volume in the hippocampus, indicating susceptibility hyperhomocysteinemia correlation with epilepsy or spastic paraparesis[19], and antiepileptic-induced psychosis in a case with C677T polymorphism which may improve medical management for epileptic patients[20]. MTHFR may also be associated with suicide risk in schizophrenic patients[21]. It is important to understand variants underlying such conditions for better management and prevention.

MTHFR gene variants and their role in cancer

DNA destabilization, leading to reduction of cytosine methylation due to folate deficiency, may trigger pro-oncogene expression. Since MTHFR is involved in folate metabolism, its variants affect cancer susceptibility[6]. Several research studies state the association of A1298C polymorphism with an increased cervical cancer risk and cervical intraepithelial neoplasia (CIN) development in patients and a decreased risk for lung cancer[22, 23, 24]. Studies also demonstrated that C677T variant was significantly associated with lung cancer and adenocarcinoma among Chinese individuals, especially in females as well as decreased gastric cancer risk among elders[24, 25, 26]. A Taiwan-based study found that the T allele of this variant is a predictive marker for colorectal cancer given its lower risk-conferring property than the wild-type C allele[27]. Meta-analysis studies also showed that C677T increased breast and ovarian cancer risk, especially in Asians, and is associated with pancreatic cancer[28, 29]. It is considered a therapeutic target for breast cancer[30] but research among Northern Sardinians CT genotype exerted a protective effect on its development[31].

Various studies show associations between polymorphisms in folate-pathway genes, and pancreatic cancer development[32]. Hence it can be inferred that folate deficiency may increase but also be protective for various risks of cancer including thyroid, colorectal, ovarian, lung, prostate, cervical and breast[33,34,35,36,37,38,39,40]. Considering that MTHFR variants play a substantial role in cancer development, screening to prevent disease onset is essential for well-being.

MTHFR gene variants and their role in vascular health

In a meta-analysis, C677T showed association with abdominal aortic aneurysm (AAA) risk, especially in non-smoking and younger patients[41]. In another study, C677T was more prevalent in women with abnormal triglyceride levels, linking it to inflammatory, vascular and metabolic dysfunction[42]. Evidence indicates associations between C677T, hyperhomocysteinemia and severe coronary lesions in acute coronary syndrome patients[43].

Another study highlighted a significant association between C677T and deep venous thrombosis, intracerebral hemorrhage[44,45], ischemic stroke[46], coronary artery disease[47] premature coronary artery disease[48], congenital heart defects[49], atherosclerosis[50], coronary atherosclerotic lesions[51]. C677T also demonstrates a protective role by negatively impacting left ventricular hypertrophy, with increased resistance of intrarenal arterial and hyperparathyroidism[52]. While A1298C polymorphism is a factor in the development of congenital heart disease[53] and conotruncal heart disease[54].

MTHFR variants are highly prevalent in non-valvular atrial fibrillation (NVAF) cardioembolic stroke subjects causing a higher risk of developing cardiovascular-related comorbidities with an enhanced inflammatory state, dyslipidemia, lacunar stroke or stroke recurrences. The detection of risk-related MTHFR variants may serve a major role in reinforcing recommendations towards nutrient intake and personalized management.

MTHFR gene variants and their role in diabetes and related complications

A study indicates that C677T confers type 2 diabetes mellitus risk, especially among Asians[55]. Studies show its association with diabetic nephropathy[56], diabetic neuropathy[57,58], and diabetic retinopathy[57]. It may also be associated with higher total homocysteine levels in type 2 diabetes patients with dyslipidemia[58]. Additionally, C677T could impact folic acid supplementation efficacy in diabetic polyneuropathy[59].

The A1298C polymorphism significantly increased diabetic retinopathy, diabetic polyneuropathy[57], diabetic nephropathy[60], hypermethylation related to hyperglycemia, and dyslipidemia[61] susceptibilities.

Table I: Summary of the correlation between MTHFR gene polymorphisms and its clinical implications

Category	Disease	Variant	References (PMID)
Neurology and Psychiatric Diseases	Schizophrenia	MTHFR C677T A1298C	23318463 28822116
	Bipolar Disorder, Depression	MTHFR C677T A1298C	25744938, 28968218, 24751310
	Autism Spectrum Disorders	MTHFR C677T A1298C	31033224, 31920317
	Attention Deficit Hyperactivity Disorder	MTHFR C677T A1298C	29407547, 23227261 21618410
	Parkinson's Disease	MTHFR C677T A1298C	33574311, 29097250
	Alzheimer's disease	MTHFR C677T A1298C	21663380, 25359311, 26820674, 32804129
	Migraine	MTHFR C677T A1298C	31045246, 30451038, 19559392, 19925624,
	Epilepsy	MTHFR C677T A1298C	33096746, 31354331
	Cerebral Venous Thrombosis	MTHFR C677T A1298C	33375456, 26261166, 30466296
Vascular Diseases	Atherosclerosis	MTHFR C677T A1298C	32404177, 29087287
	Ischaemic Stroke	MTHFR C677T A1298C	31932513, 31456518, 32722170, 32098547
	Congenital Heart Defects	MTHFR C677T A1298C	33219830, 32418960, 30333252, 20664391
	Abdominal Aortic Aneurysm	MTHFR C677T	27603386, 24613192
	Coronary Artery Disease	MTHFR C677T A1298C	32682401, 30115070, 21567207, 29972410
	Acute Coronary Syndrome	MTHFR C677T	29245302, 27051002
	Dyslipidemia	MTHFR C677T A1298C	32795354, 28890888
	Embolism, Deep Vein Thrombosis	MTHFR C677T A1298C	33128086, 28500484, 26261166, 30466296

	Conotruncal Heart Defects	MTHFR C677T A1298C	22495907
Pregnancy and infertility	Male Fertility Problems/Infertility	MTHFR C677T A1298C	24265582, 33371103, 32912251, 30813130, 28081209, 27173242, 16888682
	Recurrent Implantation Failure	MTHFR C677T A1298C	27560137, 29073227
	Recurrent Pregnancy Loss	MTHFR C677T A1298C	29785531, 33751263
Developme nt Anomalies	Down's Syndrome Child Birth	MTHFR C677T A1298C	27659321, 24668664, 20680153, 15834031
	Neural Tube Defects	MTHFR C677T A1298C	29222906, 31238314, 24737468, 23056169
Diabetes	Type 2 Diabetes	MTHFR C677T	31663297, 24452036
	Hypermethylation Profile	MTHFR A1298C	30675189
	Diabetic Nephropathy	MTHFR C677T A1298C	32871871, 22554825, 29227003
	Diabetic Neuropathy	MTHFR C677T A1298C	24452036, 28231061, 31557408
	Diabetic Retinopathy	MTHFR C677T A1298C	32582807, 24452036
	Gestational Diabetes	MTHFR C677T	32440179
Cancer	Breast	MTHFR C677T A1298C	32192442, 22291746
	Cervical	MTHFR C677T A1298C	33406167, 29740106
	Ovarian	MTHFR C677T A1298C	32639550, 28487897, 22524826
	Hepatocellular	MTHFR C677T A1298C	26662389, 31694048, 23457501, 27803768
	Prostate	MTHFR C677T A1298C	22296369, 22938427, 26782572, 15298954
	Lung	MTHFR C677T A1298C	24648965, 30323671, 27173216
	Brain	MTHFR C677T A1298C	25809864, 30583664, 18483342
	Thyroid	MTHFR C677T	24805831, 25070812, 27173331
	Gastric	MTHFR C677T A1298C	33920562, 25170232, 30884202, 20237899
	Colorectal	MTHFR C677T A1298C	28983337, 31740010, 20078613

CONCLUSION

MTHFR regulates protein synthesis and the folate pathway. It is majorly involved in the conversion of homocysteine to methionine, which is important for DNA methylation and gene regulation. Variations are associated with MTHFR deficiency, homocystinuria and hyperhomocysteinemia. This enhances risk of conditions related to fertility, cardiovascular, diabetes, cancers, neurodevelopmental, and psychiatric disorders.

Hyperhomocysteinemia is rarely attributed to two variants alone. Patients should be evaluated for factors affecting homocysteine levels such as diet, age, thyroid disease, certain medications, hypercholesterolemia, or lifestyle-related factors. In the absence of such factors, identification of the genetic basis of high homocysteine levels is helpful.

Considering the clinical implications of polymorphisms, genetic counselors should focus on various queries on etiologies to understand the role of MTHFR in health. In this review, we documented a brief on the role of MTHFR in diseases as summarized in table I. Advancement in research and genomics is leading to a better understanding of folate, methylation, and epigenetics which can pave the way for advanced research in folate metabolism efficacy roles for therapeutic purposes.

REFERENCES

1. Lan, X., Field, M. S., & Stover, P. J. (2018). Cell cycle regulation of folate□mediated one□carbon metabolism. Wiley Interdisciplinary Reviews: Systems Biology and Medicine, 10(6), e1426.
2. Zheng, Y., & Cantley, L. C. (2019). Toward a better understanding of folate metabolism in health and disease. Journal of Experimental Medicine, 216(2), 253-266.
3. Scaglione, F., & Panzavolta, G. (2014). Folate, folic acid, and 5-methyltetrahydrofolate are not the same thing. Xenobiotica, 44(5), 480-488.
4. Hiraoka, M., & Kagawa, Y. (2017). Genetic polymorphisms and folate status. Congenital anomalies, 57(5), 142-149.
5. Geng, Y., Gao, R., Liu, X., Chen, X., Liu, S., Ding, Y., ... & He, J. (2018). Folate deficiency inhibits the PCP pathway and alters genomic methylation levels during embryonic development. Journal of cellular physiology, 233(9), 7333-7342.
6. Liew, S. C., & Gupta, E. D. (2015). Methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism: epidemiology, metabolism and the associated diseases. European journal of medical genetics, 58(1), 1-10.
7. Cięszczyk, P., Zarębska, A., Jastrzębski, Z., Sawczyn, M., Kozakiewicz-Drobnik, I., Leońska-Duniec, A., ... & Massidda, M. (2016). Does the MTHFR A1298C Polymorphism Modulate the Cardiorespiratory Response to Training?. Journal of Human Kinetics, 54(1), 43-53.
8. Liu, S. Y., Zhang, C. J., Peng, H. Y., Sun, H., Lin, K. Q., Huang, X. Q., ... & Yang, Z. Q. (2017). Strong association of SLC1A1 and DPF3 gene variants with idiopathic male infertility in Han Chinese. Asian journal of andrology, 19(4), 486.
9. Cai, C. Q., Fang, Y. L., Shu, J. B., Zhao, L. S., Zhang, R. P., Cao, L. R., ... & Liu, W. (2019). Association of neural tube defects with maternal alterations and genetic polymorphisms in one-carbon metabolic pathway. Italian journal of pediatrics, 45(1), 1-7.
10. Najafipour, R., Moghbelinejad, S., Aleyasin, A., & Jalilvand, A. (2017). Effect of B9 and B12 vitamin intake on semen parameters and fertility of men with MTHFR polymorphisms. Andrology, 5(4), 704-710.
11. Ota, K., Takahashi, T., Han, A., Damvaeba, S., Mizunuma, H., & Kwak-Kim, J. (2020). Effects of MTHFR C677T polymorphism on vitamin D, homocysteine and natural killer cell cytotoxicity in women with recurrent pregnancy losses. Human Reproduction, 35(6), 1276-1287.
12. Kim, J. Y., Kim, J. W., Sung, S. R., Park, J. E., Shim, S. H., & Cha, D. H. (2018). Impact of RFC1, MTHFR, and MTHFD1 polymorphism on unexplained pregnancy loss (UPL): comparative analysis of maternal and fetal components using mother–abortus paired samples. European Journal of Obstetrics & Gynecology and Reproductive Biology, 231, 152-157.
13. Paul, S., Sadhukhan, S., Munian, D., Bankura, B., & Das, M. (2018). Association of FOLH1, DHFR, and MTHFR gene polymorphisms with susceptibility of Neural Tube Defects: A case control study from Eastern India. Birth defects research, 110(14), 1129-1138.
14. Karaca, M. Z., Konac, E., Yurteri, B., Bozdag, G. Ü. R. K. A. N., Sogutdelen, E., & Bilen, C. Y. (2017). Association between methylenetetrahydrofolate reductase (MTHFR) gene promoter hypermethylation and the risk of idiopathic male infertility. Andrologia, 49(7), e12698.
15. Wan, L., Li, Y., Zhang, Z., Sun, Z., He, Y., & Li, R. (2018). Methylenetetrahydrofolate reductase and psychiatric diseases. Translational psychiatry, 8(1), 1-12.
16. Yadav, U., Kumar, P., Gupta, S., & Rai, V. (2016). Role of MTHFR C677T gene polymorphism in the susceptibility of schizophrenia: An updated meta-analysis. Asian journal of psychiatry, 20, 41-51.
17. Saha, T., Chatterjee, M., Sinha, S., Rajamma, U., & Mukhopadhyay, K. (2017). Components of the folate metabolic pathway and ADHD core traits: an exploration in eastern Indian probands. Journal of human genetics, 62(7), 687-695.
18. Sadeghiyeh, T., Dastgheib, S. A., Mirzaee-Khoramabadi, K., Morovati-Sharifabad, M., Akbarian-Bafghi, M. J., Poursharif, Z., ... & Neamatzadeh, H. (2019). Association of MTHFR 677C> T and 1298A> C polymorphisms with susceptibility to autism: A systematic review and meta-analysis. Asian journal of psychiatry, 46, 54-61.
19. Gales, A., Masingue, M., Millecamps, S., Giraudier, S., Grosliere, L., Adam, C., ... & Nadjar, Y. (2018). Adolescence/adult onset MTHFR deficiency may manifest as isolated and treatable distinct neuro-psychiatric syndromes. Orphanet journal of rare diseases, 13(1), 1-8.
20. Shimura, M., Yamada, H., Takahashi, H., Yamada, N., Go, S., Yamanaka, G., & Kawashima, H. (2019). Antiepileptic drug-induced psychosis associated with MTHFR C677T: a case report. Journal of medical case reports, 13(1), 1-5.
21. Liu, J. H., Zhu, C., Zheng, K., Tang, W., Gao, L. L., Trihn, T. H., ... & Zhang, X. Y. (2020). MTHFR Ala222Val polymorphism and clinical characteristics confer susceptibility to suicide attempt in chronic patients with schizophrenia. Scientific reports, 10(1), 1-9.
22. Gong, J. M., Shen, Y., Shan, W. W., & He, Y. X. (2018). The association between MTHFR polymorphism and cervical cancer. Scientific reports, 8(1), 1-7.
23. Yi, K., Yang, L., Lan, Z., & Xi, M. (2016). The association between MTHFR polymorphisms and cervical cancer risk: a systemic review and meta analysis. Archives of gynecology and obstetrics, 294(3), 579-588.
24. Zhong, R., Chen, Q., Zhang, X., Li, M., Zhang, X., & Lin, W. (2019). Association between methylenetetrahydrofolate reductase (MTHFR) polymorphisms and lung cancer risk in Chinese people: An updated meta-analysis. Medicine, 98(24).
25. Tong, W., Tong, G., Jin, D., & Lv, Q. (2018). MTHFR C677T and A1298C polymorphisms and lung cancer risk in a female Chinese population. Cancer management and research, 10, 4155.
26. Han, Z., Sheng, H., Gao, Q., Fan, Y., & Xie, X. (2021). Associations of the MTHFR rs1801133 polymorphism with gastric cancer risk in the Chinese Han population. Biomedical Reports, 14(1), 1-1.
27. Lin, K. M., Yang, M. D., Tsai, C. W., Chang, W. S., Hsiao, C. L., Jeng, L. B., ... & Bau, D.

T. (2018). The role of MTHFR genotype in colorectal cancer susceptibility in Taiwan. Anticancer research, 38(4), 2001-2006.
28. He, L., & Shen, Y. (2017). MTHFR C677T polymorphism and breast, ovarian cancer risk: a meta-analysis of 19,260 patients and 26,364 controls. OncoTargets and therapy, 10, 227.
29. Nie, F., Yu, M., Zhang, K., Yang, L., Zhang, Q., Liu, S., ... & Liu, W. (2020). Association of MTHFR gene polymorphisms with pancreatic cancer: meta-analysis of 17 case–control studies. International journal of clinical oncology, 25(2), 312-321.
30. Zhang, Y., Jia, H., Wang, S., & Jiang, D. (2016). Cumulative review and meta-analyses on the association between MTHFR rs1801133 polymorphism and breast cancer risk: a pooled analysis of 83 studies with 74,019 participants. Minerva medica, 108(1), 57-73.
31. Floris, M., Sanna, D., Castiglia, P., Putzu, C., Sanna, V., Pazzola, A., ... & Muroni, M. R. (2020). MTHFR, XRCC1 and OGG1 genetic polymorphisms in breast cancer: a case-control study in a population from North Sardinia. BMC cancer, 20(1), 1-15.
32. Chittiboyina, S., Chen, Z., Chiorean, E. G., Kamendulis, L. M., & Hocevar, B. A. (2018). The role of the folate pathway in pancreatic cancer risk. PloS one, 13(2), e0193298.
33. Zara-Lopes, T., Galbiatti-Dias, A. L. S., Castanhole-Nunes, M. M. U., Padovani-Júnior, J. A., Maniglia, J. V., Pavarino, E. C., & Goloni-Bertollo, E. M. (2019). Polymorphisms in MTHFR, MTR, RFC1 and CssS genes involved in folate metabolism and thyroid cancer: a case-control study. Archives of Medical Science, 15(2), 522-530.
34. Jalilvand, A., & Soltanpour, M. S. (2019). Investigating the methylation status of DACT2 gene and its association with MTHFR C677T polymorphism in patients with colorectal cancer. Molecular Biology Research Communications, 8(2), 53.
35. Chen, X. L., Wang, Y. M., Zhao, F., Chen, Z., Yang, X., Sun, C., ... & Liu, F. B. (2019). Methylenetetrahydrofolate reductase polymorphisms and colorectal cancer prognosis: A meta□analysis. The journal of gene medicine, 21(9), e3114.
36. Jara, L., Morales, S., Mayo, T. D., Gonzalez–Hormazabal, P., Carrasco, V., & Godoy, R. (2017). Mutations in BRCA1, BRCA2 and other breast and ovarian cancer susceptibility genes in Central and South American populations. Biological research, 50.
37. Chen, F., Wen, T., Lv, Q., & Liu, F. (2020). Associations between Folate Metabolism Enzyme Polymorphisms and Lung Cancer: A Meta-Analysis. Nutrition and cancer, 72(7), 1211-1218.
38. Chen, P. L., Li, W. T., Wang, J., Jiang, Y. D., Wu, P., Chen, T., & Zheng, S. B. (2015). Association between MTHFR gene polymorphisms (C677T, A1298C) and genetic susceptibility to prostate cancer: a meta-analysis. Genetics and molecular research: GMR, 14(4), 19191–19202.
39. Wu, J. L., Zhou, S. X., Zhao, R., Zhang, X., Chang, K., Gu, C. Y., ... & Ye, D. W. (2016). MTHFR c. 677C> T inhibits cell proliferation and decreases prostate cancer susceptibility in the Han Chinese population in Shanghai. Scientific reports, 6(1), 1-10.
40. Hajiesmaeil, M., Tafvizi, F., & Sarmadi, S. (2016). The effect of methylenetetrahydrofolate reductase polymorphisms on susceptibility to human papilloma virus infection and cervical cancer. Infection, Genetics and Evolution, 46, 1-6.
41. Liu, J., Jia, X., Li, H., Jia, S., Zhang, M., Xu, Y., ... & Guo, W. (2016). Association between MTHFR C677T polymorphism and abdominal aortic aneurysm risk: A comprehensive meta-analysis with 10,123 participants involved. Medicine, 95(36).
42. Chedraui, P., Pérez-López, F. R., Escobar, G. S., Espinoza-Caicedo, J. A., Montt-Guevara, M., Genazzani, A. R., & Simoncini, T. (2016). Polymorphisms of the FTO and MTHFR genes and vascular, inflammatory and metabolic marker levels in postmenopausal women. Journal of endocrinological investigation, 39(8), 885-890.
43. Li, M. N., Wang, H. J., Zhang, N. R., Xuan, L., Shi, X. J., Zhou, T., ... & Li, H. (2017). MTHFR C677T gene polymorphism and the severity of coronary lesions in acute coronary syndrome. Medicine, 96(49).
44. Xu, J., Li, K., & Zhou, W. (2019). Relationship between genetic polymorphism of MTHFR C677T and lower extremities deep venous thrombosis. Hematology, 24(1), 108-111.
45. Hu, X., Tao, C., Xie, Z., Li, Y., Zheng, J., Fang, Y., ... & You, C. (2016). The MTHFR C677T polymorphism and risk of intracerebral hemorrhage in a Chinese Han population. Medical science monitor: international medical journal of experimental and clinical research, 22, 127.
46. Li, A., Shi, Y., Xu, L., Zhang, Y., Zhao, H., Li, Q., ... & He, Y. (2017). A possible synergistic effect of MTHFR C677T polymorphism on homocysteine level variations increased risk for ischemic stroke. Medicine, 96(51).
47. Long, Y., Zhao, X. T., Liu, C., Sun, Y. Y., Ma, Y. T., Liu, X. Y., & Liu, J. X. (2019). A case-control study of the Association of the Polymorphisms of MTHFR and APOE with risk factors and the severity of coronary artery disease. Cardiology, 142(3), 149-157.
48. Zhang, S. Y., Xuan, C., Zhang, X. C., Zhu, J., Yue, K., Zhao, P., ... & Tian, Q. W. (2020). Association Between MTHFR Gene Common Variants, Serum Homocysteine, and Risk of Early-Onset Coronary Artery Disease: A Case–Control Study. Biochemical genetics, 58(2), 245-256.
49. Liu, P. F., Ding, B., Zhang, J. Y., Mei, X. F., Li, F., Wu, P., ... & Chen, T. (2020). Association Between MTHFR C677T Polymorphism and Congenital Heart Disease A PRISMA-Compliant Meta-Analysis. International heart journal, 19-389.
50. Lin, X., Zhang, W., Lu, Q., Lei, X., Wang, T., Han, X., & Ma, A. (2016). Effect of MTHFR Gene Polymorphism Impact on Atherosclerosis via Genome-Wide Methylation. Medical science monitor : international medical journal of experimental and clinical research, 22, 341–345.
51. Heidari, M. M., Khatami, M., Hadadzadeh, M., Kazemi, M., Mahamed, S., Malekzadeh, P., & Mirjalili, M. (2015). Polymorphisms in NOS3, MTHFR, APOB and TNF-α Genes and Risk of Coronary Atherosclerotic Lesions in Iranian Patients. Research in cardiovascular medicine, 5(1), e29134.
52. Trovato, F. M., Catalano, D., Ragusa, A., Martines, G. F., Pirri, C., Buccheri, M. A., ... & Trovato, G. M. (2015). Relationship of MTHFR gene polymorphisms with renal and cardiac disease. World journal of nephrology, 4(1), 127.
53. Kocakap, B. D. S., Sanli, C., Cabuk, F., Koc, M., & Kutsal, A. (2015). Association of MTHFR A1298C polymorphism with conotruncal heart disease. Cardiology in the Young, 25(7), 1326-1331.
54. Chita, D. S., Tudor, A., Christodorescu, R., Buleu, F. N., Sosdean, R., Deme, S. M., ... & Dragan, S. R. (2020). MTHFR gene polymorphisms prevalence and cardiovascular risk factors involved in cardioembolic stroke type and severity. Brain Sciences, 10(8), 476.
55. Meng, Y., Liu, X., Ma, K., Zhang, L., Lu, M., Zhao, M., ... & Qin, G. (2019). Association of MTHFR C677T polymorphism and type 2 diabetes mellitus (T2DM) susceptibility. Molecular Genetics & Genomic Medicine, 7(12), e1020.
56. Hamidi, A. K., Radfar, M., & Amoli, M. M. (2018). Association between MTHFR variant and diabetic neuropathy. Pharmacological Reports, 70(1), 1-5.
57. Settin, A., El-Baz, R., Ismaeel, A., Tolba, W., & Allah, W. A. (2015). Association of ACE and MTHFR genetic polymorphisms with type 2 diabetes mellitus: susceptibility and complications. Journal of the Renin-Angiotensin-Aldosterone System, 16(4), 838-843.
58. Raza, S. T., Abbas, S., Siddiqi, Z., & Mahdi, F. (2017). Association between ACE (rs4646994), FABP2 (rs1799883), MTHFR (rs1801133), FTO (rs9939609) genes polymorphism and type 2 diabetes with dyslipidemia. International journal of molecular and cellular medicine, 6(2), 121.
59. Mottaghi, T., Khorvash, F., Kheirollahi, M., Maracy, M., & Askari, G. (2019). The MTHFR C677T polymorphism influences the efficacy of folic acid supplementation on the nerve conduction studies in patients with diabetic polyneuropathy; A randomized, double blind, placebo-controlled study. Journal of Research in Medical Sciences: The Official Journal of Isfahan University of Medical Sciences, 24.
60. Zhou, T. B., Drummen, G. P., Jiang, Z. P., & Li, H. Y. (2015). Methylenetetrahydrofolate reductase (MTHFR) C677T gene polymorphism and diabetic nephropathy susceptibility in patients with type 2 diabetes mellitus. Renal failure, 37(8), 1247-1259.
61. Fekih-Mrissa, N., Mrad, M., Ibrahim, H., Akremi, I., Sayeh, A., Jaidane, A., Ouertani, H., Zidi, B., & Gritli, N. (2017). Methylenetetrahydrofolate Reductase (MTHFR) (C677T and A1298C) Polymorphisms and Vascular Complications in Patients with Type 2 Diabetes. Canadian journal of diabetes, 41(4), 366–371.