

REVIEW ARTICLE

MTHFR Gene Polymorphisms as Potential Risk Factors for Down Syndrome and Its Associated Phenotypes: A Review

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ABSTRACT

The present article sheds light on the methylenetetrahydrofolate reductase (MTHFR) gene polymorphisms as potential risk factors for Down syndrome, in the context of the existing literature. Ample evidence suggests that polymorphisms in the MTHFR gene significantly increase the risk of DS by interfering with the metabolism of folate. The MTHFR gene affects homocysteine levels and DNA methylation processes as it codes for an enzyme that is essential to the folate cycle. As mutations in the MTHFR gene are linked to incorrect chromosomal segregation during meiosis, trisomy 21 becomes more likely. This review outlines the currently available literature connecting MTHFR gene variants to Down syndrome, emphasising the potential effects of disturbances in folate metabolism on chromosomal integrity and developmental outcomes. The review also emphasises the potential for nutritional treatments, such as vitamin B12 and folate supplements, to reduce these risks by establishing the metabolic pathways impacted by MTHFR mutations. In conclusion, gaining insights into the MTHFR gene's genetic and metabolic roles could help prevent the risk factors associated with Down syndrome and Down syndrome-related clinical phenotypes.

Keywords: MTHFR polymorphism, Down syndrome, folate metabolism, Trisomy 21, chromosome segregation

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INTRODUCTION

The most prevalent genetic condition that impacts both cognitive and physical development is Down syndrome (DS). Chromosome 21 aneuploidy has been reported to be the major etiological factor of DS and is brought about by improper chromosomal segregation during meiosis. Although maternal age of >35 years is a known risk factor for chromosome 21 aneuploidy, ample evidence suggests that genetic alterations in the methylenetetrahydrofolate reductase (MTHFR) gene have a significant role in the pathophysiology of DS¹.

An enzyme necessary for the metabolism of homocysteine and folate is encoded by the MTHFR gene. The remethylation of homocysteine into methionine depends on this enzyme's ability to convert 5,10- MTHFR into 5-methyltetrahydrofolate, the active form of folate. DNA synthesis and methylation, which are essential for cell

division and embryonic development, depend on methionine. Variants in the MTHFR gene, especially the C677T polymorphism, result in lower enzyme activity, which elevates homocysteine levels and hinders folate metabolism². MTHFR C677T polymorphism is substantially linked to a higher risk of maternal nondisjunction, which occurs when chromosomal pairs do not correctly split during meiosis. DS may arise from an extra copy of chromosome 21 caused by this failure. Additionally, folate and vitamin B12, which are both necessary for preserving genomic integrity, are frequently seen in lower concentrations in women with this MTHFR variation. DNA hypomethylation, which can interfere with normal chromosomal segregation and raise the likelihood of

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aneuploidy, including trisomy 21, has been connected to folate deficiency in particular. Several studies have proposed that folate deficiency increases Hcy level and the incidence of hyperhomocystenemia³. Furthermore, folate supplementation has been found to contribute to reducing the toxicity of high concentrations of Hcy caused due to MTHFR genetic variants⁴. Studies have found that the joint effect of MTHFR C677T, MTHFR A1298C, MTR A2756G and MTRR A66G polymorphisms elevates the risk of folate deficiency⁵.

Apart from its function in folate metabolism, MTHFR polymorphisms have also been linked to congenital abnormalities seen in DS, including low birth weight, preterm birth and congenital heart defects, neural tube defects and orofacial clefts. These conditions are frequently more common in children whose mothers have the MTHFR gene mutation. Studies have demonstrated that maternal polymorphisms of genes involved in folate metabolism, when transmitted to a DS embryo, contribute to the onset of congenital heart defects⁶. Both MTHFR C677T polymorphisms and PR (PROGINS) mutations have been reported to be genetic risk factors associated with the susceptibility of preterm delivery, negative pregnancy outcome and low birth weight⁷. Knowing how MTHFR polymorphisms contribute to DS not only improves our understanding of its genetic etiology but also makes preventive measures like taking vitamin B12 and folate supplements before and throughout pregnancy possible.

METHODOLOGY

Literature searches were conducted in PubMed and Google Scholar using the keywords like folic acid deficiency and Down syndrome risk, Folate metabolism and Down syndrome phenotypes, homocysteine imbalance and Down syndrome, MTHFR gene variants and Down syndrome risk. Original research and review articles were included if they met the following criteria: (1) the study aimed to investigate the role of MTHFR in DS birth risk; (2) the research addressed the role of folate metabolism in the development of associated clinical features in DS; (3) showed the role of folate and Vitamin B12 supplementation in DS children.

Genetic spectrum of Down syndrome

Down syndrome, being the most prevalent chromosomal disorder, is characterized by an extra copy of chromosome 21. The distinctive phenotypes of the condition are caused

by the additional genetic material's effect on normal development. Clarifying the pathophysiology of DS and its possible connections with other genetic variables, such as those involving the MTHFR gene, requires an understanding of its genetic underpinnings.

DS primarily results from non-disjunction during meiosis that results in a zygote with three copies of chromosome 21, a condition known as Trisomy 21⁸. Approximately 95% of DS cases are attributed to this chromosomal anomaly. The remaining 5% of cases are due to other chromosomal variations that include translocations or mosaicism⁹.

Numerous pathways, including those involved in cellular signaling, metabolism and development, are impacted when the usual gene dosage balance is upset. For example, the pathophysiology of DS has been linked to impaired mitochondrial activity and elevated levels of oxidative stress¹⁰. Furthermore, an imbalance in protein expression levels caused by an extra copy of chromosome 21 might impact multiple physiological systems and contribute to the variety of clinical presentations of the condition.

There are other variables besides the extra chromosome 21 that can affect the phenotypic variability seen in people with DS. Variability in clinical presentation can result from interactions between the genetic predisposition imparted by Trisomy 21 and environmental factors, genetic background and epigenetic alterations¹⁰. This encompasses variations in physical characteristics, cognitive aptitude and vulnerability to related medical disorders.

Role of MTHFR

MTHFR is a crucial enzyme involved in the metabolism of folate and homocysteine. It facilitates the conversion of 5,10-methylenetetrahydrofolate into 5-methyltetrahydrofolate, which serves as a methyl donor for the remethylation of homocysteine into methionine. A reduction in MTHFR activity increases the demand for folic acid to sustain normal homocysteine remethylation. When folic acid levels are insufficient, homocysteine accumulates within cells, methionine synthesis decreases, and remethylation pathways are disrupted. Folate is vital for numerous cellular functions, including the synthesis of DNA and RNA, methylation and developmental processes such as embryogenesis and cardiovascular system formation¹¹.

The active form of folate, 5-methyltetrahydrofolate, is

produced when 5,10-methylenetetrahydrofolate is converted by the MTHFR enzyme. This pathway is essential for the remethylation of homocysteine to methionine, an amino acid required for subsequent methylation reactions in the body ¹¹. Entire cellular function, including DNA synthesis and repair, depends on this mechanism operating effectively. Figure 1 is an illustration of how nutritional deficiency of folates and other essential nutrients and MTHFR polymorphisms have a plausible role in chromosome non-disjunction.

The MTHFR gene has two frequent polymorphisms viz A1298C and C677T. A thermolabile form of the enzyme with decreased activity is produced when the C677T mutation causes thymine to be substituted for cytosine at position 677 ¹². People who are homozygous for this mutation usually have higher blood levels of homocysteine and decreased enzyme activity ¹³. Although it affects enzyme function less than C677T, the A1298C mutation, which contains a change at position 1298, also has an effect ¹⁴.

Elevated homocysteine levels, which have been linked to a higher risk of cardiovascular disorders, neural tube malformations, and other health problems, can be the result of these mutations. Since sufficient folate consumption can lessen some of the negative effects linked to these genetic polymorphisms, the relationship between MTHFR mutations and folate status is crucial ¹⁴.

Moreover, people with DS might have different metabolisms of folate, which might be caused by mutations in the MTHFR gene. Evidence suggests that MTHFR polymorphisms may influence homocysteine and folate levels in people with DS, thereby affecting their general development and health ¹⁵. Furthermore, the severity of the clinical characteristics of DS may also be influenced by the interaction of MTHFR mutations with other genetic or environmental factors; however, more studies are required to fully understand these relationships ¹⁶.

Understanding the role of the MTHFR gene in relation to DS birth risk and its associated phenotypes can have significant clinical implications. Gaining insights into how this gene functions may open the door to more personalized approaches to care. Genetic testing to identify mutations in the MTHFR gene can further provide valuable information about folate metabolism in individuals with DS and may

subsequently help in tailoring dietary interventions and treatment strategies to better address their specific needs, ultimately improving their health outcomes ¹⁷.

Association between MTHFR and Down Syndrome risk

As a key enzyme in the pathway that provides methyl groups for DNA methylation, MTHFR may play a significant role in DS by impacting the regulation of this process and the subsequent expression of genes. An earlier study found an association between the MTHFR C677T polymorphism and DS birth risk ¹⁸. The study suggested that mothers who carry the homozygous (TT) mutations for MTHFR have an increased likelihood of giving birth to a child with DS ¹³.

Researchers are actively investigating whether specific MTHFR gene variants play a role in the associated phenotypes of DS. This includes studying how these genetic variations might contribute to associated health challenges, such as cardiovascular issues, developmental delays, or metabolic differences. Understanding this connection could provide deeper insights into the interplay between genetic factors and health outcomes in DS, paving the way for more targeted interventions and personalized care strategies.

Numerous studies have investigated the possible connection between MTHFR gene polymorphisms and DS risk, though the findings have given mixed outcomes ¹⁹. Studies that looked into the occurrence MTHFR C677T polymorphism in people with DS discovered that this variant was more prevalent in the case group than controls ¹³. Besides, the C677T mutation has also been linked to changed folate levels, which may have an impact on how severe some DS symptoms are. Besides, numerous health problems, such as cardiovascular disorders and neural tube malformations, have been connected to elevated homocysteine levels, which are frequently linked to MTHFR mutations ¹⁶. Furthermore, normal metabolism of folate is essential for DNA synthesis and repair and MTHFR mutations, if present, may interact with the genetic background of Down syndrome, where development and cellular processes may already be impacted by extra chromosome material ²⁰.

Although certain studies propose a potential link between MTHFR gene variants and DS birth and its associated clinical phenotypes, the clinical significance of these findings remains a topic of debate. Further, the influence of

MTHFR polymorphisms on the management of DS, including the use of folate supplementation or other therapeutic strategies, has yet to be conclusively determined²¹.

There is conflicting evidence on the relationship between MTHFR polymorphisms and DS characteristics, with some studies reporting significant associations²². The contradictory findings in the literature can be attributed to differences in study design, sample sizes and population characteristics. This discrepancy emphasizes the necessity of large-scale, well-designed investigations to evaluate whether MTHFR gene polymorphisms influence the variability in DS phenotypes and whether they hold any practical significance for patient care. Exploring the interactions between MTHFR mutations and other genetic or environmental factors could offer deeper insights into their role in DS, paving the way for a more thorough understanding of these connections.

Clinical Implications

The role of MTHFR polymorphisms, particularly A1298C and C677T, in folate metabolism and homocysteine regulation may have important clinical implications for individuals with DS. Although DS results from trisomy 21, these MTHFR polymorphisms could potentially contribute to an increased risk of secondary health issues, especially those affecting neural development, cardiovascular health and metabolic processes²³.

Ample evidence suggests a crucial role of folate in the synthesis, repair and methylation of DNA, all of which are critical for proper chromosome segregation and in the development of associated health issues in DS children. Besides, the reduced enzyme activity caused by MTHFR mutations, especially C677T, results in increased homocysteine levels and poor folate metabolism and worsens cognitive impairments and neurodevelopmental delays in people with DS^{18,24}. This implies that in clinical settings, keeping an eye on the levels of homocysteine and folate in patients with DS may be essential for early intervention and averting additional neurological issues. Some physicians recommend folate supplementation for people with both DS and MTHFR polymorphisms, but further study is needed to determine the efficacy and long-term effects of this intervention²⁵.

Elevated homocysteine levels caused by reduced MTHFR function have been reported to be a well-known risk factor for cardiovascular disorders, such as atherosclerosis and thrombosis²⁶. Therefore, MTHFR mutations can raise the risk of cardiovascular issues for people with DS, who may already be more susceptible to congenital heart malformations and other cardiovascular abnormalities²⁷. Some clinical studies have investigated the potential benefits of folate and vitamin B12 supplementation in lowering homocysteine levels and reducing cardiovascular risk in individuals with MTHFR mutations. For people with DS, such interventions could offer dual benefits by not only lowering cardiovascular risks but also supporting neuro development through improved folate metabolism²⁸. However, excessive folate intake, especially in individuals without a marked deficiency, has been associated with adverse effects, such as masking vitamin B12 deficiency and potentially impairing immune function²⁹. As a result, any interventions aimed at addressing MTHFR polymorphisms in individuals with DS should be carefully tailored and closely monitored.

Studies suggest that identifying MTHFR polymorphisms in individuals with DS could facilitate more personalized treatment and management strategies. Genetic screening for MTHFR variants may enable clinicians to categorize patients based on their susceptibility to certain complications, such as cardiovascular disorders or neurodevelopmental challenges²². By customizing interventions such as folate or vitamin B12 supplementation according to an individual's genetic profile, healthcare providers could enhance outcomes and improve the overall quality of life for those with DS³⁰.

Despite the potential clinical advantages, the link between MTHFR polymorphisms and health outcomes in individuals with DS remains a topic of debate. Some studies have failed to identify significant associations between MTHFR variants and major health issues, prompting caution from experts against over-reliance on genetic screening for these polymorphisms³⁰. The variability in findings highlights the necessity for more comprehensive and longitudinal studies to clarify the clinical significance of MTHFR mutations in DS.

Besides, it is essential to conduct further research to understand the clinical relevance of MTHFR

polymorphisms in individuals with DS. Large-scale, controlled studies are necessary to determine the effectiveness of folate and vitamin B12 supplementation and to investigate alternative therapeutic options. Future research should aim to uncover how the interplay between MTHFR polymorphisms and other genetic or environmental factors has a role in the DS birth risk and the development of associated clinical phenotypes in individuals with DS.

CONCLUSION

The MTHFR gene and its polymorphisms, particularly C677T and A1298C, have been extensively studied for their roles in folate metabolism and the regulation of homocysteine levels. While DS arises from the presence of an extra chromosome 21, increasing evidence suggests that variations in the MTHFR gene may influence susceptibility to certain health complications in individuals with this condition. Research indicates that MTHFR polymorphisms may exacerbate disruptions in folate metabolism, potentially contributing to neurodevelopmental delays, cognitive deficits and a heightened risk of cardiovascular issues in people with DS. Although the relationship between the MTHFR gene and DS is not directly causal, it raises important questions about how genetic variations may affect the clinical characteristics of individuals with trisomy 21. In particular, the association between elevated homocysteine levels and cardiovascular health warrants further investigation, especially considering the higher prevalence of congenital heart defects in this population.

From a clinical standpoint, identifying MTHFR polymorphisms could facilitate personalized treatments, such as folate or vitamin B12 supplementation, to mitigate the effects of impaired folate metabolism. However, the inconsistent results reported in various studies underscore the need for larger, well-designed trials to confirm the therapeutic efficacy of these interventions. Furthermore, the interaction between genetic factors like MTHFR polymorphisms and environmental or epigenetic influences in individuals with DS represents a critical area for future research. Gaining a deeper understanding of these complex interactions could improve clinical care by enabling more targeted strategies to address the unique metabolic and developmental challenges faced by this group. Overall, while the MTHFR gene provides valuable insights into the

intricate pathophysiology of DS, continued research is essential to fully establish its clinical significance.

Author Contributions

Mahrukh Hameed Zargar and Jaffer Abbas Wani wrote the original draft. Tahir Mohiuddin Malla, Syed Asra Kirmani, Wasia Showkat reviewed and edited the article.

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Conflict of interest disclosure

The authors declare no conflict of interest.

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Patient consent statement

This article does not contain any studies with human or animal subjects performed by any of the authors.

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