Nutrigenetic Impact of PEMT Gene Polymorphism Rs7946 On Choline Metabolism and Its Role in Personalised Nutrition

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Abstract: The PEMT (phosphatidylethanolamine N-methyltransferase) gene plays a critical role in the endogenous synthesis of phosphatidylcholine, an essential compound in lipid metabolism and liver health. The single nucleotide polymorphism (SNP) rs7946 (V175M) within the PEMT gene influences the enzymatic activity and structural stability, leading to altered choline metabolism. Individuals carrying Aallele exhibit reduced PEMT activity, predisposing themto non-alcoholic fatty liver disease (NAFLD), elevated homocysteine levels, and reproductive or cognitive risks under low choline diets. This impact is modulated by sex hormones, particularly oestrogen, rendering postmenopausal women more susceptible. This review summarises recent findings linking PEMT rs7946 variants with metabolic, hepatic, and psychological outcomes and explores gene diet interactions that informs genotype based nutritional recommendations. It also suggests tailored choline intake strategies based on genotype. We argue for the integration of PEMT screening in nutritional counselling, especially for vulnerable groups. Future nutrigenetics research is necessary to refine these guidelines and assess long-term impacts.

Keywords -PEMT gene, rs7946, polymorphism, SNP, phosphatidylcholine choline, nutrigenetics, NAFLD, one carbon metabolism.

I. Introduction

Nutrigenetics is transforming dietary guidelines by incorporating genetic variability to optimise health outcomes. One such gene of interest is phosphatidylethanolamine N-methyltransferase (PEMT), essential for synthesising phosphatidylcholine (PC) from phosphatidylethanolamine (PE), especially when dietary choline is insufficient. It also plays a vital role in lipid metabolism, liver function, and cardiovascular health. The rs7946 Single Nucleotide Polymorphisms (SNP) In PEMT involves a Guanine (G) to Adenine (A) substitution, which constitute amino acid change of valine to methionine in the position of 175 (V175M) and reduces the structural stability and activity of the enzyme (Wu et al., 2023). Thus, it causes a variability in nutrient metabolism and disease susceptibility.

Studies have shown that individuals with A allele (methionine variant) may have reduced choline biosynthesis and increased risk to non-alcoholic fatty liver disease (NAFLD), metabolic disorders and adverse pregnancy outcomes, especially under low choline diets (Zhu et al., 2020; Tan et al., 2016). This gene-diet interaction is modulated by hormonal factors such as oestrogen which upregulates PEMT making postmenopausal women or those with low oestrogen levels more vulnerable (Harrison et al., 2020).

Emerging data also suggest that rs7946 influences choline's effects on lipid metabolism, anxiety, cognitive function, and cancer risk (Myoidzk et al.,2021 ; He et al., 2024; Zhang et al., 2024). These findings highlight the need to incorporate PEMT genetic profiling into dietary recommendations, especially for populations at higher metabolic risk.

This paper reviews the structure, function, and health implications of PEMT rs7946 polymorphism and proposes genotype-guided choline intake recommendations based on findings from recent clinical and molecular studies to build a foundation for precision nutrition strategies.

II. Objectives of the Review

This review aims to:

Summarise the structure and biological function of the PEMT gene, with a specific focus on the rs7946 polymorphism.

Explore the genetic, hormonal and dietary factors influencing PEMT-related metabolic outcomes.

Evaluate evidence-linking rs7946 with choline metabolism, NAFLD, cardiovascular risk, cognitive function, and reproductive health.

Highlight genotype specific choline intake recommendations and implications for precision nutrition strategies.

Identify gaps in current knowledge and propose future research directions.

Functional Role of PEMT Gene

Gene Structure and Expression –The PEMT gene is located in chromosome 17, specifically at the p11.2 band and consists of multiple exons encoding the enzyme responsible for catalysing the conversion of phosphatidylethanolamine to

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phosphatidylcholine via methylation. This reaction occurs primarily in the liver and plays a compensatory role when dietary choline intake is low (Ganz et al., 2017). Expression of PEMT is modulated by various factors, including hormonal levels and methyl donor availability.

PEMT in phosphatidylcholine Biosynthesis- PEMT catalyses three methylation steps, using S-adenosylmethionine (SAM) as a methyl donor, to synthesise phosphatidylcholine (PC) from phosphatidylethanolamine (PE). This reaction is crucial in maintaining Very Low Density Lipoprotein (VLDL) assembly and liver lipid export.(Wu et al., 2023). In individuals with impaired PEMT activity, phospholipid homeostasis is disrupted, predisposing them to hepatic steatosis and elevated homocysteine levels (Zhu et al., 2020).

Hormonal Regulation of PEMT- Oestrogen is known to upregulate PEMT transcription by binding to oestrogen response elements on the gene's promoter region (Tan et al., 2016). This partially explains why premenopausal women are relatively protectedfrom choline deficiency disorders, while postmenopausal women and men with PEMT variants are more vulnerable (Harrison et al., 2020). Oestrogen deficient states also reduce endogenous choline synthesis, increasing dietary choline dependence.

rs7946 Polymorphism and Health Implications

The diagram below illustrates how the rs7946 mutation in the PEMT gene inhibits endogenous phosphatidylcholine synthesis, with impaired PEMT activity, reliance on dietary choline increases. The resulting choline deficiency may lead to conditions such as NAFLD, elevated homocysteine levels, and cognitive deficits.

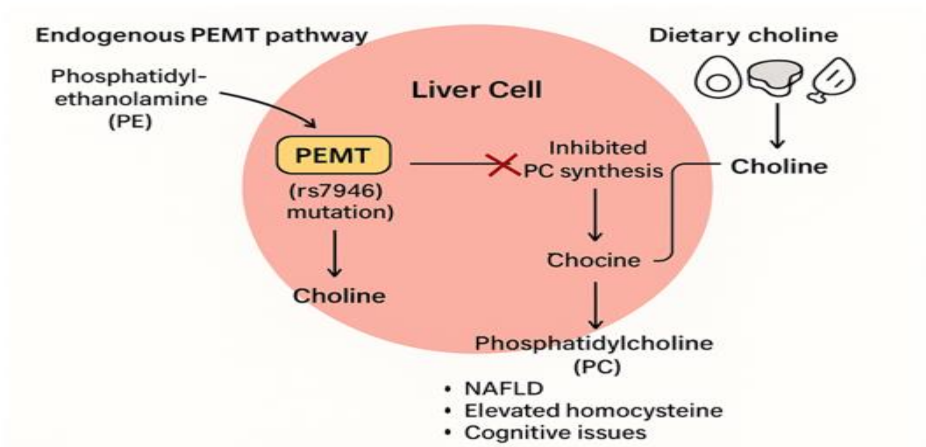

Figure 1: Disruption of PEMT pathways in liver cells due to the rs 7946 Mutation

Source: Illustration created by the author based on data from (Sharma 2019), (Wu 2023) and (Zhu 2020).

Choline Deficiency and One-Carbon Metabolism- The rs7946 polymorphism results in a valine tomethionine substitution, which impairs PEMT enzymatic activity. Individuals with the **A** allele variation of gene require higher dietary choline to maintain adequate methyl group availability, influencing one-carbon metabolism, particularly in the remethylation of homocysteine to methionine. Elevated plasma homocysteine, a risk factor for cardiovascular diseases, has been observed in PEMT deficient individuals with low choline intake (Sharma et al., 2019; Myodzik, et al., 2021).

Association with Non-Alcoholic Fatty Liver Disease – Numerous studies have linked the PEMT rs7946 polymorphism to NAFLD risk. A 2023 meta-analysis study showed that carriers of the **A** allele had significantly higher hepatic fat accumulation and liver enzyme levels than non-carriers, particularly when choline intake was inadequate (Wu et al., 2023). Oestrogen's protective role means that postmenopausal women with this genotype are disproportionately affected (Harrison et al., 2020).

Cardio metabolic and Cognitive Impacts – Altered PEMT function has been associated with increased cardio-metabolic risk markers such as LDL cholesterol and insulin resistance (Zhu et al., 2020). Moreover, reduced choline biosynthesis affects brain acetylcholine synthesis, influencing memory and cognitive flexibility. Another study Myoidzk et al. (2021) demonstrated higher anxiety scores in **A** allele carriers with low dietary choline, underlying a genetic basis for choline responsive neurological traits.

Reproductive Health and Cancer Risk- PEMT activity also influences reproductive outcomes. Women with the **A** allele have shown higher risk for pre-eclampsia, neural tube defects in offspring, and fertility when dietary choline is insufficient (Tan et al., 2016).Another recent study by Zhang et al., (2024) have suggested a correlation between rs7946 and colorectal cancer susceptibility,although mechanistic links require further investigation.

Nutrigenetics Insights and Implications for Precision Nutrition

The integration of nutrigenetics into dietary planning represents a significant advancement in both public health and clinical nutrition. Among the key examples of gene-nutrient interactions, the PEMT rs7946 polymorphism stands out due to its direct

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influence on endogenous phosphatidylcholine synthesis and methylation metabolism. This variant alters choline requirements, lipid metabolism and susceptibility to several non-communicable diseases.

Emerging research highlights the impact of the rs7946 **A** allele on the enzymatic activity of PEMT, often resulting in reduced capacity for de novo phosphatidylcholine synthesis. Individuals with the genotype, especially under conditions of low dietary choline or reduced oestrogen levels, may experience adverse effects such as hepatic steatosis, elevated homocysteine levels or cognitive changes .Nutrients gene interactions involving folate, betaine and methionine further modify these outcomes by influencing one carbon metabolism and methylation balance (Myodzik,etal.2021).

Recent population based studies demonstrate that the health impacts of the rs7946 variant are also influenced by sex and body composition. For example, women with **GG** genotype may benefit from higher choline intake, whereas men with the same genotype may exhibit increased risk for NAFLD at elevated intake level (Wu et al., 2023).Similarly, individuals with the **AA** genotype require greater choline intake, particularly during pregnancy or in postmenopausal life stages when hormonal support is diminished.

These findings emphasize the need for precision nutrition strategies that incorporate genetic screening, particularly in clinical nutrition and dietetic practice. Nutrigenetic profiling for PEMT variants can guide healthcare professionals in identifying individuals who require modified dietary choline levels or closer metabolic monitoring.

This approach supports the movement toward personalised health care, in which nutritional recommendations influenced by genotype, sex, age, lifestyle and physiological status. The implementation of PEMT focused dietary planning holds potential for reducing disease burden and improving outcomes in at risk populations.

Recent evidence indicate the influence of rs 7946 PEMT gene on individual dietary responses.Myoidzk et al.(2021) reported that rs7946 variant, along with rs12325817,affects lipid profiles and liver markers particularly in over weight individuals, while the effects of choline were dependent on genotype and weight status. These indicates the importance of tailored nutrition based on both genetics and anthropometry.

In Chinese adults, those with the **CC** genotype had a 31% higher risk of digestive cancers when choline to betaine ratios were low, this highlights choline's role in one-carbon metabolism(He.Q et al., 2024).Similarly , Da Costa et al, (2017) found that women with the **A** allele showed altered choline metabolism, even with sufficient intake particularly during pregnancy and lactation.

Another study reveals that women with the **GG** genotype seem to benefit from higher choline intake, while men with the same genotype may face increase NAFLD risk (Wu et al., 2023).Mechanistically, the variant reduces PEMT activity, disrupting PC synthesis and VLDL production, leading to liver fat build up (Li et al.,2022).It may also affect glucose metabolism and PUFA pathways, with early life implications(Loinard et al., 2022).

Similarly, Harrison et al. (2020) linked low choline intake and the risk allele to increased anxiety symptoms, suggesting a possible role in mental health. These findings collectively support the integration of genetic, hormonal and lifestyle factors in precision nutrition.

The recognition of PEMT rs7946 polymorphism in shaping individual responses to dietary choline marks a critical advancement in personalised nutrition. Carriers of the **A** allele have a reduced capacity for endogenous choline synthesis, necessitating higher dietary intake,particularly during life stages or conditions of increased demand such as pregnancy, menopause or chronic liver disease(Ganz et al., 2017 ; Tan et al., 2016).

Knowledge of an individual's PEMT genotype can inform dietary recommendations, particularly regarding choline intake. Current adequate intake levels for choline may be insufficient for individuals with impaired PEMT function. Dietary sources rich in Choline such as eggs, meat and soybeans can help mitigate deficiency in genetically predisposed populations (Niculescu ,2022).Table 1 summarises the relationship between PEMT rs7946 genotypes, their impact on enzymatic activity and the associated choline requirements and health risks.

Table 1: PEMT rs7946 Genotype Effects on Health Outcomes

Genotype	PEMT Activity	Choline Requirement	Associated Health Risks
GG (Wild type)	Normal	Standard	Low risk of NAFLD and choline deficiency
GA (Heterozygous)	Reduced	Elevated	Moderate risk of NAFLD, elevated homocysteine
AA (Homozygous mutant)	Significantly Reduced	High	High risk of NAFLD, liver dysfunction, metabolic syndrome

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Current Choline intake recommendations (550 mg/day for men and 425 mg/day for women) may be insufficient for individuals with PEMT variants, especially when estrogen levels are low. Emerging research proposes genotype-specific choline guidelines to mitigate risks of NAFLD, neurocognitive decline, and cardio metabolic disturbances (Wu et al ., 2023; Zhu et al ., 2020).

From a public health standpoint, nutrigenetic screening could identify at risk populations and inform early dietary interventions.Integrating PEMT genotyping in clinical settings may help dietitians and physicians develop evidence based, genotype guide dietary plans. This aligns with the boarder trend towards precision medicine and lifestyle based disease prevention.

Furthermore, Choline rich dietary sources should be emphasized in nutrition education programs, especially for women with low oestrogen status or those following vegetarian orvegan diets. Supplementation strategies should also consider bioavailability, metabolic demand, and concurrent B vitamin intake, which supports methylation pathways.

Future implementation of PEMT focused nutrition requires collaborative research, digital decision tools, and clinician education. The intersection of nutrigenetics, gender medicine, and public policy represents a promising frontier in chronic disease prevention.

Personalised Dietary Guidance for carriers of the PEMT rs7946 Variant

Tailored dietary strategies are essential for individuals carrying the PEMT rs7946 polymorphism, particularly those with reduced enzymatic activity due to the **A** allele. Given the gens' role in endogenous phosphatidylcholine synthesis, these individuals are more reliant on adequate dietary choline intake. Personalised recommendations based on sex, genotype, and physiological state (e.g. Pregnancy, menopause) are warranted to mitigate metabolic risks such as hepatic steatosis and homocysteine accumulation.

Optimising Choline Intake According to sex and Genotype

Dietary choline requirements vary depending on PEMT genotype and sex specific hormonal influences. Choline rich foods such as eggs, liver, salmon, poultry, soybeans and legumes are recommended to support methylation and lipid metabolism pathways. The effects of choline on hepatic steatosis (HS) appear genotype-dependent:

-Men with GG genotype are advised to moderate their choline intake, as daily consumption exceeding 424 mg has been associated with a 3.7-fold increased risk of hepatic steatosis (Wu et al., 2023).

-Women with theGG genotype may benefit from higher choline intake, with intakes above 448mg/day linked to a 79% reduction in HS risk.

Choline supplementation, such as phosphatidylcholine or choline bitartrate, may be considered for individuals following low-choline diets, as well as pregnant or post-menopausal women with reduced estrogen levels. However, supplementation should be administered under clinical supervision. Notably, inadequate choline intake in pregnant women with **AA** genotype has been associated with increased risk of preterm birth (Zhu et al., 2020).

Balancing One carbon Nutrients: Folate, Betaine, and Methionine

In individuals with PEMT rs7946 variants, the balance between choline and other carbon nutrients such as folate, betaine, and methionine is critical for maintaining methylation efficiency. An imbalance in the choline-to-betaine ratio may contribute to increased cancer risk, particularly within the digestive system (Zhang et al., 2024).

Recommended strategies include:

Regular assessment of plasma choline and beta in levels to evaluate choline to beta in ratios.

Enhanced dietary intakes of folate (green leafy vegetables), betaine (beets, quinoa) and methionine (eggs, dairy, meat) to support homocysteine remthylation and overall methylation processes linked to PEMT activity.

Periodic liver function tests to detect early signs of hepatic dysfunction in genetically predisposed individuals.

Moreover, adopting a nutritionally balanced diet, maintaining a healthy body weight, and limiting alcohol consumption are key lifestyle interventions to support liver health and reduce metabolic burden (Piras et al.,2022).

Future Scope

Advancing the integration of PEMT rs7946 genotyping into public health and clinical nutrition offers immense potential for preventing choline deficiency related conditions. Future studies should examine gene-diet interactions across diverse ethnic populations to validate risk associations. Additionally, longitudinal cohort studies and randomised controlled trials are needed to explore long-term outcomes of genotype tailored choline intake on liver health, cognitive function, and cardio metabolic parameters. The development of digital tools for Nutrigenetics counselling and health monitoring could empower both clinicians and patients, allowing for dynamic and personalised dietary strategies. Finally, policy-level support for including nutrigentics in national dietary guidelines may accelerate the translation of PEMT research into meaningful public health benefits.

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VI. Conclusion

The PEMT rs7946 polymorphism has emerged as a key genetic set of choline metabolism, with wide ranging implications for liver function, cognitive health, and cardio, metabolic risk. This review highlights the need to recognise genetic diversity in dietary choline requirements, particularly among **A**allele carriers and women with low estrogen levels. Personalised nutrition strategies, based on PEMT genotyping and nutrition education support, can mitigate disease risk and will improve health outcomes. Future transactional efforts must bridge the gap between genetic insights and practical clinical application, shaping a new era of precision nutrition grounded in molecular evidence.

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