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MAT1A variants modulate the effect of dietary fatty acids on plasma homocysteine concentrations

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KEYWORDS
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Abstract *Background and Aim:* Dietary n-3 polyunsaturated fatty acids (PUFAs) are associated with decreased plasma homocysteine (Hcy), an important biomarker for cardiovascular disease. The S-adenosylmethionine synthetase type-1 (MAT1A), an essential enzyme in the conversion of methionine to S-adenosylmethionine, plays a key role in homocysteine metabolism. This study investigated the interaction between dietary fatty acids and *MAT1A* genotypes on plasma Hcy concentrations among Boston Puerto Ricans.
Methods and Results: Plasma Hcy and *MAT1A* genotypes were determined in 994 subjects of the Boston Puerto Rican Health Study. Dietary fatty acid intakes were assessed by interviews using a questionnaire adapted from the NCI/Block food frequency form.
Result: In the cross-sectional analysis, genetic variant *MAT1A* 3U1510 displayed a significant interaction with dietary n-3:n-6 PUFA ratio in determining plasma Hcy (p-value for interaction = 0.025). 3U1510G homozygotes had significantly lower plasma Hcy concentration than major allele homozygotes and heterozygotes (AA + AG) (p-value for trend = 0.019) when the n-3:n-6 ratio was >0.09. Two other *MAT1A* variants, d18777 and i15752, also showed significant interactions with different constituents of dietary fat influencing Hcy concentrations. Furthermore, haplotypes consisting of three variants displayed a strong interaction with n3:n6 ratio influencing Hcy concentrations.
Conclusions: Our results suggest that *MAT1A* genotypes appear to modulate effects of dietary fat on plasma Hcy.
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Introduction

Elevated plasma homocysteine (Hcy), a thiol-containing amino acid byproduct of methionine metabolism [1], has been demonstrated to be an independent risk factor for cardiovascular disease (CVD) [1]. In addition to pathophysiological conditions, including menopause, renal disease, and hypothyroidism [2], the etiology of hyperhomocysteinemia (HHcy) is known to be multifactorial, including genetic and environmental factors, such as diet and lifestyle [2,3]. The genetic causes of elevated plasma Hcy include rare inborn errors of Hcy metabolism, such as cystathionine beta-synthase (CBS) and methylenetetrahydrofolate reductase (*MTHFR*) [4]. Recently, studies of polymorphisms from the critical genes involved in Hcy metabolic pathways demonstrated that *MTHFR* 677C > T [5], *MTHFR* 1298A > C [6], 5-methyltetrahydrofolate-homocysteine methyltransferase (*MTRR*) 66A > G [7] and 5-methyltetrahydrofolate-homocysteine methyltransferase reductase (*MTR*) 2756A > G [8] were associated with elevated plasma Hcy concentration. For environmental factors, lifestyle and diet play an important role in Hcy metabolism. Two-thirds of HHcy subjects in an elderly US population were associated with low plasma/serum concentrations of one or more of B group vitamins [9]. Smoking, drinking alcohol and physical activity have also been associated with elevated plasma Hcy [10].

Importantly, n-3 polyunsaturated fatty acids (n-3 PUFA), which have a protective effect on the cardiovascular system [11], were shown to improve Hcy metabolism [12]. Previously, we reported that plasma Hcy was significantly negatively correlated with the plasma/platelet phospholipids (PL) n-3 PUFA and n-3:n-6 PUFA ratio [12,13]. Subsequent intervention studies have demonstrated that n-3 PUFA supplementation decreases plasma Hcy [14]. However, the results from studies evaluating the relationship between fatty acids and plasma Hcy are inconclusive [15]. Whether genetic variation may account for such inconsistent results is unknown. The relationship between n-3 PUFA and plasma Hcy is not yet fully understood. Methionine adenosyltransferase (MAT), an essential enzyme in methionine metabolism, catalyzes the conversion of methionine to S-adenosylmethionine (SAM). SAM is subsequently converted to S-adenosyl homocysteine and then Hcy in separate reactions [16]. We previously demonstrated that *MAT1A* variants were associated with stroke and hypertension [16]. Therefore, we hypothesize that *MAT1A* variants, single nucleotide polymorphisms (SNPs), modulate the effect of dietary fatty acids on plasma Hcy.

In the present study, we conducted a population-based evaluation to investigate the combined contributions of *MAT1A* genotype and dietary fatty acids to HHcy in the Boston Puerto Rican population. This population has experienced severe health disparity, including high rates of hypertension, diabetes, obesity, and CVD (16, 17). We examined the effects of *MAT1A* variants and dietary fatty acids on plasma Hcy concentration and assessed their potential interactions in modifying plasma Hcy.

Methods

Study design and subjects

This study was conducted within the ongoing Boston Puerto Rican Health Study (BPRHS) as described previously [17]. The analysis included 994 subjects who participated in the BPRHS study and had complete data on dietary intake, anthropometry, biochemical parameters, and *MAT1A* genotype. Interviews were conducted in volunteers' homes to collect demographic and anthropometric data, and detailed data were collected on dietary intake using a questionnaire previously adapted from the NCI/Block food frequency form and validated for this population [18]. Physical activity was estimated as a physical activity score, based on the Paffenbarger questionnaire [19]. Smoking status was described in three categories: current, former, and never smoking. Alcohol consumption was defined as current drinkers and nondrinkers.

Fasting blood samples were collected the morning following health interviews in the volunteer's home [17]. Approval for the BPRHS was obtained from the Institutional Review Boards of the Tufts Medical Center and Tufts University.

Population admixture

Population admixture was calculated using STRUCTURE 2.2 based on 100 SNPs selected as ancestry informative markers specifically for Puerto Rican populations [16]. Using the estimated admixture of each subject, we adjusted for population admixture for all genotype-associated analyses.

MAT1A SNP selection and genetic analysis

A panel of eight SNPs mapping in/near the *MAT1A* gene was selected for genotyping based primarily on linkage disequilibrium analysis of HapMap data for the CEU population and the characteristics of these eight SNPs have been described [16]. Results of TAGGER [20] run with the parameters of pair-wise option, CEU population, $r^2 > 0.80$, minor allele frequency > 0.00, placed most SNPs into one of eleven blocks. Each of the SNPs chosen for genotyping falls into a different LD block within *MAT1A*, and these blocks overall span approximately 10 kbp to either side of the gene. DNA was isolated from blood samples using QIAamp DNA Blood Mini kits according to the manufacture's instructions (Qiagen, Valenic, CA). Eight SNPs were genotyped using the TaqMan SNP genotyping system (Applied Biosystems, Foster City, CA).

Linkage disequilibrium and haplotype analysis

Pair-wise linkage disequilibria among SNPs were estimated as correlation coefficients (r^2) using the haploview program. For haplotype analysis, the global association between haplotypes and plasma Hcy, and estimated haplotype frequencies we used the R software (haplo.stats package).