A Nutrigenetic Overview to Human Health: Single Nucleotide Polymorphisms in Fatty Acid Desaturase (FADS) Encoding Genes

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Abstract

Long-chain polyunsaturated fatty acids (LC-PUFAs) play an important role in some physiological processes in the human body. Their level and composition are highly dependent on their intake in the diet or on the intake of fatty acid (FA) precursors. The fatty acid precursors are endogenously elongated and desaturated to physiologically active LC-PUFAs by the fatty acid desaturases (FADS), encoded by FADS gene cluster. The single nucleotide polymorphisms (SNPs) in these genes are highly associated with the concentration of ω3- and ω6-fatty acids. Beside nutrition, genetic factors also play an important role in the regulation of LC-PUFAs. Changes in desaturase activity have potentially large impacts on cellular FA content, which consequently influences numerous biological processes. A genetic variation in the LC-PUFA biosynthetic pathway, especially within the FADS gene cluster, determines the levels of circulating and tissue PUFAs and several biomarkers. In this review, we aimed to provide an nutrigenetic overview to the human health over single nucleotide polymorphisms in the fatty acid desaturase (FADS) encoding genes.

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Keywords: Desaturase, FADS gene, fatty acid, health, nutrigenetics

İnsan Sağlığına Nütrigenetik Bir Bakış: Yağ Asiti Desatüraz Enzimleri (FADS) Kodlayan Genlerde Tek Nükleotid Polimorfizmleri

Öz

Uzun Zincirli Çoklu Doymamış Yağ Asitleri (UZ-ÇDYA) insan vücudunda gerçekleşen fizyolojik süreçlerde son derece önemli roller oynayan maddelerdir. Bu maddelerin seviyeleri ve kompozisyonu diyet yoluyla direkt tayin edileceği gibi, yağ asiti prekürsörlerinin yine diyet yoluyla alımı ile belirlenebilmektedir. Yağ asiti prekürsörleri endojen olarak yağ asiti desatüraz enzimleri tarafından uzatılarak ve desatüre edilerek fizyolojik aktif UZ-ÇDYA'lerine dönüştürülürler. Yağ asit desatüraz enzimleri FADS genleri tarafından kodlanırlar. Bu gen kümesinde tek nükleotid polimorfizmlerin (SNP) ω3- ve ω6-yağ asitleri seviyeleri ile yakından ilişkisi bulunmaktadır. Beslenme olgusu yanında, genetik faktörler de UZ-ÇDYA regulasyonunu etkilemektedir. Desatüraz enzim aktivitelerindeki değişimlerin sellüler seviyede yağ asiti oranlarını ciddi şekilde etkileme potansiyelleri bulunmaktadır. Sellüler seviyede gerçekleşen yağ asiti değişimleri biyolojik süreçleri de etkilemektedir. Bu derlemede yağ asiti desatüraz enzimleri kodlayan FADS genlerinde tek nükleotid polimorfizmler üzerinden ve insan sağlığına nütrigenetik bir bakış verilmesi amaçlanmıştır.

Anahtar Sözcükler: Desatüraz, FADS geni, yağ asiti, sağlık, nütrigenetik

Introduction

Diets and dietary patterns provide better insight into relationships between nutrition and health and disease[1]. The composition of fatty acids in a diet is important because they are critical nutrients to regulate human health, and associated with obesity, cardiovascular, cognitive, cancer and else[2].

The diets rich in ω-3 polyunsaturated fatty acids (ω3-PUFAs) (alpha-linolenic acid, eicosapentaenoic acid, docosahexaenoic acid, and their corresponding metabolites) are associated with decreased incidence of diet-related diseases. In contrast to the beneficial effects of the ω3-PUFAs, the ω6-PUFAs (linoleic acid,

arachidonic acid, and their corresponding metabolites) promote inflammation[3]. Within the past three decades, the intake of ω-6 PUFAs increased and ω-3 PUFAs decreased, resulting in a ratio even upto 20:1 today in the western diets[4].

The ω3-PUFAs can be obtained directly from the diet, or synthesized endogenously from alpha-linolenic acid (ALA) by Δ-5 and Δ-6 desaturases (FADS). These enzymes play a critical role in the conversion pathway of long chain PUFAs, and could have implications for chronic disease risk, especially in the context of a long-chain PUFA deficient diet. Several studies linked polymorphisms in the FADS gene cluster to PUFA concentrations in serum phospholipids and erythrocyte cell membranes in several populations, including Caucasians, East Asians, and African Americans[5].

The FADS are encoded by FADS1 and FADS2 genes respectively[6]. These genes are located on chromosome 11 (11q12.2-q13.1), highly polymorphic with 4391 variants, predominately single nucleotide polymorphisms (SNP)[7,8].

The FADS genes are closely related to different human physiological conditions. Genetic polymorphisms within FADS can limit LC-PUFA product accumulation at any step of the biosynthetic pathway[9,10].

In this review, we aimed to provide an nutrigenetic overview to the human health over single nucleotide polymorphisms in the fatty acid desaturase (FADS) encoding genes.

Fatty Acid Desaturase (FADS) Encoding Genes in PUFA Regulation

The FADS1 and FADS2 genes code for fatty acid desaturases, which are enzymes responsible for the introduction of cis double bonds at the Δ-5 and Δ-6 positions in PUFAs, respectively. These enzymes have important roles in fatty acid (FA) biosynthesis by converting the essential dietary FAs, α-linolenic acid (ALA;18:3n-3) and linoleic acid (LA;18:2n-6), into their corresponding long-chain counterparts, eicosapentaenoic acid (EPA;20:5n-3), docosahexaenoic acid

(DHA;22:6n-3), and arachidonic acid (AA;20:4n-6). Changes in desaturase activity alter cellular FA content, which consequently influences numerous biological processes including membrane transport, ion channel modulation, eicosanoid signaling, and gene expression[11].

Genetic Make-Up of Each Individual and Nutrigenetics

Nutrigenetics refers to the role of DNA sequence variation in the responses to nutrients[12]. Technological advances have made it possible to investigate not only specific genes but also to explore in unbiased designs the whole genome-wide complement of DNA sequence variants or transcriptome[13].

The genetic make-up of each individual should be taken into consideration[14,15]. The consequences of such genetic variation can be either little change or very large changes in serum lipids and lipoproteins in response to diet, depending on an individual's genetic make-up[16]. Throughout human history, diet has affected the expression of genes[13]**.** There is an increasing demand for knowledge on genetic variation in nutrition (nutrigenetics)[17]. Thus, understanding nutrigenetics of dietary fatty acids is key to understanding the etiology, as well as prevention, of critically important diseases[3].

Single Nucleotide Polymorphisms (SNPs) in FADS Encoding Genes

The endogenous synthesis of LC-PUFAs occurs mainly in the liver in humans, via a common series of desaturation and elongation reactions. The efficiency of the pathway is inherently low in humans. Therefore any changes in bioconversion efficiency have potentially large impacts on LC-PUFA status[8].

Recently, polymorphisms of the human Δ-5 fatty acid desaturase-1 (FADS1) and Δ-6 fatty acid desaturase-2 (FADS2) genes have been described as being associated with the level of several long-chain (LC) ω3 and ω6 PUFAs in serum phospholipids[18,19].

Population-related genetic variation in the LC-PUFA biosynthetic pathway, especially within the FADS gene cluster determines the levels of circulating and tissue PUFAs and several biomarkers. Elevated TGs are highly clinically significant CVD risk factors[20]. Strong associations between variants in the human genes FADS1/FADS2 and blood levels of PUFAs and LC-PUFAs have been reported[21].

Strong associations between variants in the human genes FADS1/FADS2 and blood levels of PUFAs and LC-PUFAs have been reported. Subjects carrying the minor alleles of several SNPs had a lower prevalence of allergic rhinitis and atopic eczema. Therefore, blood levels of PUFAs and LC-PUFAs are influenced not only by diet, but to a large extent also by genetic variants common in a population[21].

FADS SNPs also modulate the risk for allergic disorders and eczema, the effect of breastfeeding n later cognitive development, and LC-PUFA levels in children and in human milk[22]. The association of polymorphisms in FADS genes with PUFAs in serum phospholipids, lipid peroxides, and coronary artery disease (CAD)[23].

Genetic Association Studies, FADS Polymorphisms and FA Concentrations

Genetic variation in the FADS gene cluster can alter desaturase activity in two populations of young Canadian adults descent (Caucasian and Asian)[24]. Dietary intake levels of different PUFAs modify the associated effect of genetic variation in FADS on LDL and HDL[25]. A Mediterranean diet indicated that FADS genotype could modify the effects of changes in dietary fat intakes on arachidonic acid concentrations in the colon[26]. FADS gene polymorphisms are likely to influence plasma fatty acid concentrations and desaturase activities in coronary artery disease patients in a Chinese Han population[27]. At present, the associations of the SNPs in the FADS1/FADS2 gene cluster with serum lipid levels and risk of cardiovascular disease have been more reported in the European populations, relatively little is known about such association in the Chinese populations, especially in Chinese south population[28]. SNPs in FADS gene increase the risk of

CAD in diabetic patients[29]. A high prevalence of SNPs that are associated with slow PUFA conversion has been described in Hispanic populations[30]. FADS2 genotype influences whole-body resting fat oxidation in young adult men. genetic variation in FADS2 is not only associated with the activity of the desaturation-elongation pathway, but also whole-body fat oxidation[31]. FADS genes are associated with Dyslipidemia in polycystic ovary syndrome[32]. The polymorphism in FADS1/2 genes associates with fatty acid metabolism and adipose tissue inflammation, leading to an interaction between weight loss and FADS1/2 genes in the regulation of adipose tissue inflammation[33].

Conclusion

The composition of fatty acids in a diet is important because genetic variation in nutrition (nutrigenetics) significantly responses to nutrients, which are responsible for regulating the human health. Nutrigenetics of dietary fatty acids is, therefore, key to preventing critically important disease such as obesity, cardiovascular, cognitive, cancer and else. Those having genetic variations in their fatty acid desaturase (FADS) encoding genes should absolutely intake diets rich in ω3-PUFAs (alpha-linolenic acid, eicosapentaenoic acid, docosahexaenoic acid, and their corresponding metabolites) associated with decreased incidence of diet-related diseases.

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