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Diet-Gene Interplay: An Insight into the Association of Diet and FADS Gene Polymorphisms

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Abstract

Fatty acid desaturases (FADS) gene polymorphisms have been implicated in cardiovascular diseases, allergies, psychiatric disorders as well as the metabolic syndrome. The relationship of genetic variation and diet is complex. Recent studies have confirmed that polymorphisms in the FADS1 and FADS2 genes are associated with fatty acid compositions which may eventually influence disease susceptibility. Dietary intake of long chain polyunsaturated fatty acids (LC-PUFAs) has been studied to influence the effects of FADS gene polymorphisms. In this review, we give an insight of the diet-gene interaction with respect to FADS gene polymorphisms.

Keywords: FADS gene polymorphisms; LC-PUFA intake; Diet-gene interaction

Introduction

In recent times, the diet-gene interactions are the front-runners in research on nutrition. Modifiable risk factors due to faulty lifestyle practices such as physical inactivity, high body mass index (BMI), smoking, alcohol use and last but not the least, unhealthy eating habits are attributed to the development of diseases [1-5]. Poor dietary habits are known to be harmful to health; additionally the numerous interactions between nutrients and genes can further modulate an individual's risk for developing disease.

The relationship of genetic variation and diet is complex. A number of genetic variations have been shown to increase the susceptibility to diet-related diseases. Numerous studies have demonstrated that diets high in refined sugars and saturated fats are associated with a higher incidence of metabolic syndrome, cardiovascular disease, cancer and autoimmune diseases [6-8].

Single nucleotide polymorphisms (SNPs) are the most common form of sequence variations that could modify an individual's response to diet. Other types of variations include nucleotide repeats, insertions and deletions [9].

Recent studies have confirmed that SNPs in the FADS1 and FADS2 genes are associated with fatty acid compositions in the human body which may eventually influence disease susceptibility [10-12].

Polyunsaturated fatty acid metabolism

Long-chain polyunsaturated fatty acids (LC-PUFAs) are important for health and maintenance of all metabolic functions. They are associated with various disorders like cardiovascular diseases, allergies, metabolic syndrome and psychiatric disorders [13,14].

Essential fatty acids (EFAs) like linoleic acid (LA) and alpha-linolenic acid (ALA) are precursors to LC-PUFAs. These precursors are further elongated and desaturated with the help of rate-limiting enzymes delta-6-desaturases (D6D) and delta-5 desaturases (D5D). LA is the precursor to arachidonic acid (AA) while ALA is the precursor to EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid). D6D and D5D catalyze both LA (omega-6) and ALA (omega-3) to their respective LC-PUFAs through a cascade of reactions [15].

SNP ID & Gene name	Genotype	Population size	Findings	References
rs174537 FADS1	G/T	1453	GG < GT, TT Increase in LA, ALA; Decrease in EDA, AA, EPA, LA, LDL and total cholesterol	
rs174545 FADS1	C/G	876	CC < CG<GG; Increase in AA, AA/LA, EPA/ALA; Decrease in LA and ALA	-21
rs174556 FADS1	C/T	658	CC < CT < TT; Increase in EDA; Decrease in AA	-39
rs174570 FADS2	C/T	727	CC< CT&TT; Increase in EDA; Decrease in GLA & AA	-39
rs174611 FADS2	T/C	876	TT < TC < CC; Increase in LA & ALA; Decrease in AA, AA/LA & EPA/ALA	-21
Rs968567 FADS2	C/T	1144	CC < CT< TT ; Increase in LA & ALA; Decrease in AA & EPA	-35

Table 1: FADS1 and FADS2 SNPs and their associations with various fatty acids.

D5D and D6D are encoded by the genes FADS1 and FADS2 respectively and are arranged in a head to head fashion to form a gene cluster on chromosome 11 (11q12-13.1) in humans (Figure 1) [16].

Contrasting roles of Omega-6 and Omega-3 PUFAS

Omega-6 and Omega-3 PUFAs compete for the rate limiting enzymes D6D and D5D to synthesize their respective products ARA and EPA, DHA. Many oxidative products of ARA are proven to be pro-inflammatory whereas a variety of omega-3 PUFA products like protectins, maresins, resolvins studied have shown anti-inflammatory activity [17-19] establishing the opposing effects of omega-6 and omega3 LC PUFAs. Their levels play a critical role in determining disease risk factors like the amount of circulating phospholipids, cholesterol and triglycerides.

Dietary changes over time

Our diet has changed over the past 10 decades with changes occurring in the type of fat and vitamins we consume. The present day "western diet" lacks a balance between omega-6 and omega-3 PUFAs with the ratio being 15/1-17/1 as opposed to the prehistoric ratio of 1/1 [20]. Genetic variations may have arisen in response to the dietary influences during evolution where there was a balance between the intake of omega-6 and omega-3 PUFAs. Today, we live in a nutritionally distinct environment from which our genetic constitution was selected [21-23]. Thus a balance of EFAs is essential for our health and development [21]. PUFA composition of cell membranes is dependent largely on both dietary intakes as well genetics. Our present day western diet has increased amounts of omega-6 fatty acids which are precursors to the inflammatory prostaglandins, thromboxanes, leukotrienes. This shifts the physiological balance giving rise to a number of inflammatory disorders.

FADS SNPs

Several FADS1 and FADS2 SNPs have been studied for their association on plasma fatty acids (Cholesterol, LDL, HDL, triglycerides etc.) [11,24-27]. These SNPs have been significantly associated with higher levels of plasma or serum fatty acids (Table 1).

Diet-FADS gene interaction

The diet-FADS gene interaction has been studied recently in several randomized studies which gives us in-depth information of the relationship between genetics and diet.

Liu et al studied the effects of dietary omega-3 PUFAs on FADS1 SNP rs174547 and coronary artery disease (CAD) risk in middle aged and elderly Chinese men. Minor T allele of rs174547 increased CAD risk (OR=1.36, 95% CIs: 1.03-1.80). However, this association held true only in individuals with lower dietary EPA intakes. Likewise, there was a significant interaction of rs174547 minor T allele and dietary DHA intake on CAD risk (OR=1.52, 95% CI: 0.95-2.42) [28]. Thus it can be concluded that elevated dietary omega-3 intakes can modify the disease risk of CAD in minor allele carriers of rs174547 in Chinese population.

In a randomized crossover design, Gillingham et al. [29] investigated the effect of flaxseed oil (FXCO) and high-oleic acid canola oil (HOCO) enriched diets and FADS gene polymorphisms on plasma fatty acid levels and [U-13C] ALA metabolism. Rs174537, rs174561, rs174545 and rs174583 were studied and minor allele carriers of all the four SNPs had lower AA in comparison to the major allele carriers. Similar results were obtained with omega-3 PUFAs with subjects homozygous for the minor alleles having lower plasma EPA levels ($p<0.05$).

Interestingly, the lower concentration of plasma EPA in the minor allele carriers for all four SNPs increased after consuming the ALA rich FXCO diet in comparison to the HOCO diet ($p=0.048$) and western diet control ($p=0.036$). Thus it can be stated that an increase in the intake in ALA increases the plasma EPA levels which in turn can be cardio protective in minor allele carriers of many of the FADS genes [29].

FADS gene polymorphisms and diet are also key regulators of erythrocyte membrane phospholipid PUFA concentrations [11,30]. Few of the SNPs are also associated with cholesterol concentrations which in turn are influenced by dietary PUFA intakes [31-36].

Imholz et al. [37] demonstrated significant interaction between FADS1 rs174546 and total and non-HDL cholesterol in the high omega-3 intake group ($p=0.006$ and 0.047 respectively) but not in the low intake group. The major allele C was associated with high cholesterol concentrations in the high omega-6 intake group which highlights the interplay of FADS1 gene polymorphisms and dietary PUFAs in Dutch adults [37].

In yet another large observational study, Hellstrand et al. [38] observed that for the 11% of the homozygous minor allele carriers of FADS1 gene SNP rs174546 high ALA and ALA/LA intake ratio was significantly associated ($p=0.04$) (after excluding participants suspected to misreport food habits) in preventing CVD and ischemic stroke.

The diet-gene interaction has been explored not only in adults but also in adolescents and infants giving us an insight of the interaction even in the early stages of life.

Dumont et al assessed whether dietary LA and ALA were associated with FADS1 rs174546 and concentrations of PUFAs in European adolescents. The subjects were grouped as per the median dietary intake of LA and ALA with 7.5 and 1.1 g/day in the low intake group and 12 and 1.8 g/day in the high intake group respectively. Serum LA levels were higher in the high LA intake group. However, ALA intake was not associated with serum ALA levels. FADS1 rs174546 minor T allele was associated with higher concentrations of ALA in both low and high ALA intake groups and also significantly associated with lower serum EPA levels in high ALA intake groups [39]. This study also showed a significant relation of FADS1 rs174546 T allele with lower serum total cholesterol and non-HDL cholesterol only in the high ALA intake group similar to Lu et al. [28] Dutch study.

Furthermore in a cross-sectional study with Danish infants, Harsløf et al. [40] studied the red blood cells (RBC) DHA status at 9 months and 3 years and genotyped four FADS SNPs rs3834458, rs1535, rs174575 and rs174448. Fish intake and information on breastfeeding was obtained by questionnaires. It was observed that FADS genotype; breastfeeding and fish intake explained 25% of the variation in the RBC DHA status of the infants. DHA fatty acid levels (FA%) was higher in infants still being breastfed at 9 months with 0.7 FA% higher DHA as compared to infants who were no longer breastfed ($p=0.001$). Homozygous minor allele carriers of FADS SNP rs1535 had an increase in DHA of 1.8 FA% in comparison to the wild type allele. The minor allele carriers of the FADS SNPs rs174575 and rs174448 had reduced FA% of 2.0 ($p=0.001$) and 1.1 ($p=0.005$), respectively. Every 10 g increment in fish intake was linked to elevated DHA status of 0.3 FA % [40]. Thus, it can be concluded that breastfeeding, FADS genotypes and fish intake are implicated in determining the DHA status in late infancy as well.

Molto-Puigmarti et al. [41] studied associations of maternal PUFA intakes in pregnancy with pregnancy durations and birth-weight as well as their associations with maternal and fetal FADS genotypes. FADS1 SNP rs174556 was genotyped in pregnant women (1516) and children (1515). Homozygous minor allele carriers of rs174556 with 75th percentile of DHA intake had infants 226 g heavier than those at 25th percentile intake (p=0.030). DHA intake was not associated significantly with infant birth-weight in major allele carriers. This study highlights the correlation of FADS gene variations on maternal and fetal fatty acid requirements [41].

Conclusion

It is long known that FADS gene polymorphisms are associated with blood PUFA levels. However, the influence of diet on this association has been studied only recently. Minor allele carriers of FADS genes have been observed to have lower levels of LC-PUFAs due to lower desaturase enzyme activity [10,42-44].

The diet-gene interaction with respect to FADS genes and PUFA intake has been very well highlighted by recent studies where the circulating PUFA levels are affected not only by the variation in FADS genes but also by the dietary intake of EFAs in adults [28,37,29]. This diet-gene interaction analysis has been extended and confirmed even in European adolescents and infants [39,40]. Moreover the modulatory effects of dietary PUFA intake on the FADS gene variation and disease risks are studied in diverse ethnic populations.

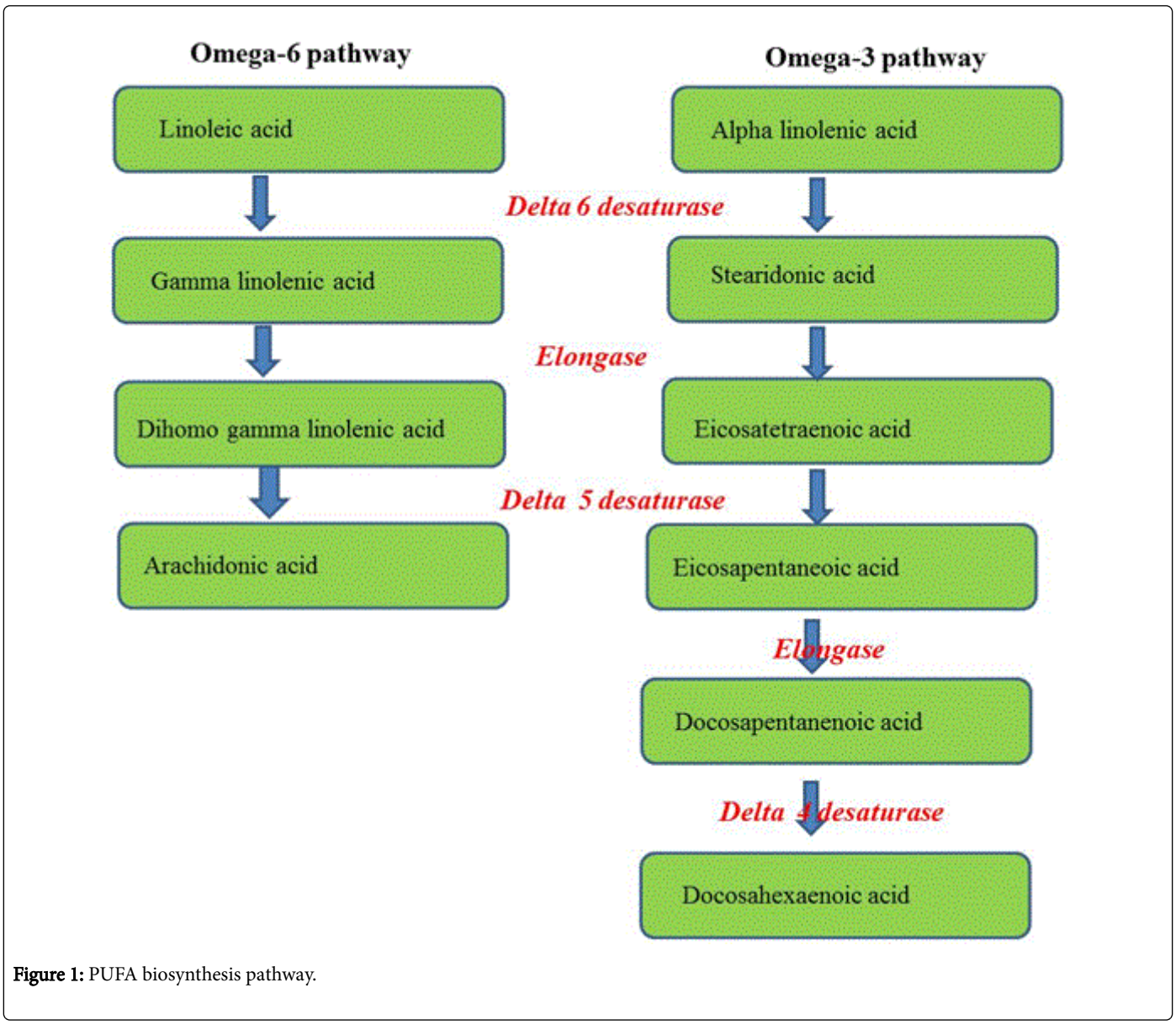

Figure 1: PUFA biosynthesis pathway.

With diet neutralizing the effects of FADS gene polymorphisms to some extent, we can hypothesize that indeed environment, in this case in the form of diet, does play a role in genetics and variation. Although the intricacies of chronic diseases are extensive, integrating the knowledge of diet-gene interactions may help us elucidate the

underlying molecular mechanisms to maintain good health and prevent the onset or progression of certain diseases.

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