Published in final edited form as:
Curr Nutr Rep. 2014 June ; 3(2): 139–148. doi:10.1007/s13668-014-0079-1.

Genetic Variants in the FADS Gene: Implications for Dietary Recommendations for Fatty Acid Intake

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Abstract

Unequivocally, genetic variants within the fatty acid desaturase (*FADS*) cluster are determinants of long chain polyunsaturated fatty acid (LC-PUFA) levels in circulation, cells and tissues. A recent series of papers have addressed these associations in the context of ancestry; evidence clearly supports that the associations are robust to ethnicity. However ∼80% of African Americans carry two copies of the alleles associated with increased levels of arachidonic acid, compared to only ∼45% of European Americans raising important questions of whether gene-PUFA interactions induced by a modern western diet are differentially driving the risk of diseases of inflammation in diverse populations, and are these interactions leading to health disparities. We highlight an important aspect thus far missing in the debate regarding dietary recommendations; we content that current evidence from genetics strongly suggest that an individual's, or at the very least the population from which an individual is sampled, genetic architecture must be factored into dietary recommendations currently in place.

Keywords

polyunsaturated fatty acids; nutrition; genetic variants; fatty acid desaturase (*FADS*); single nucleotide polymorphisms; arachidonic acid; eicosanoids; inflammation; cardiovascular disease

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Compliance with Ethics Guidelines: Conflict of Interest: Rasika A. Mathias declares that she has no conflict of interest. Vrindarani Pani declares that she has no conflict of interest.
Floyd H. Chilton is an unpaid consultant for Gene Smart Health and receives no compensation or equity in this role. This information has been disclosed to Wake Forest University Health Sciences (WFUHS) and outside sponsors, as appropriate, and is institutionally managed.

Human and Animal Rights and Informed Consent: This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

Polyunsaturated fatty acids (PUFAs) and particularly LC-PUFA have a wide range of roles ranging from regulating immunity and inflammation to impacting brain and eye development and function. Key determinants of the efficiency with which long chain polyunsaturated fatty acid (LC-PUFA) are synthesize as well as LC-PUFA levels themselves have been established within the fatty acid desaturase cluster (FADS) on chromosome 11q12.2; these determinants appear to be robust to ethnicity. However, given dramatic differences in the frequencies of these critical determinants of LC-PUFA metabolism, we will highlight an important aspect thus far missing in the debate regarding dietary recommendations: the consideration of these genetic determinants.

Biosynthesis of LC-PUFAs

Figure 1 highlights a set of genes known to play key roles in the biosynthesis and metabolism of LC-PUFAs. In two parallel and competing pathways, enzymatic products from these genes convert 18-carbon (18C) n-6 or n-3 essential PUFAs (abundant in the modern western diet [MWD]) into LC-PUFA. On the n-6 arm of the pathway, arachidonic acid (ARA, 20:4n-6) is synthesized from linoleic acid (LA, 18:2n-6) utilizing three (2 desaturation and 1 elongation) enzymatic steps [1]. The primary n-3 LC-PUFAs, eicosapentaenoic acid (EPA, 20:5n-3), docosapentaenoic acid (DPA, 22:5n-3) and docosahexaenoic acid (DHA, 22:6n-3) can be synthesized from dietary α-linolenic acid (ALA, 18:3n-3). Foe example, it requires seven (3 desaturation, 3 elongation and 1 β-oxidation) enzymatic steps to synthesize DHA. Importantly, both n-6 and n-3 substrates compete for early the enzymatic steps in the pathway (described in detail below). The desaturation steps have long been recognized as the rate-limiting steps in the pathway. The initial desaturation step converts the n-6, 18C PUFA, LA and the n-3, 18C PUFA, ALA to gamma (γ)-linolenic acid (GLA, 18:3, n-6) and stearidonic acid (SDA, 18:4, n-3), respectively, by the enzyme encoded for by the gene fatty acid desaturase 2 (*FADS2*; chromosome 11q12.2) [2-4]. The second desaturation step is catalyzed by an enzyme encoded by the gene fatty acid desaturase 1 (*FADS1*; chromosome 11q12.2-q13.1); this step converts DGLA (2-:3, n-6) and ETA (20:4, n-3) to ARA (20:4, n-6) and EPA (20:5, n-3), respectively [4, 5].

Considerations for Making Dietary PUFA Recommendations in Diverse Human Populations

There are several important considerations when determining dietary recommendations for PUFAs in diverse human populations. First it is important to understand how and what quantities of PUFAs enter the biosynthetic pathways from the background human diet. There has been a dramatic (∼3-fold) increase in the dietary access to the 18C n-6 PUFA, LA (currently 6-8% of calories) in the MWD in the past 50 years with the increase in LA-containing vegetable oil products (soybean, corn, palm, and canola oils as well as margarine and shortenings [6]). In contrast, ALA levels (typically 0.5-1.5% of calories) found in green plants, nuts and botanical oils, such as flax seed oil have remained relatively constant over that same period of time (Figure 1). Given that humans ingest much lower quantities of LC-

PUFAs (typically less than 200mg/day) than 18C PUFAs, LA and ALA, the capacity to synthesize LC-PUFAs from these 18C PUFAs is critical in determining circulating and cellular levels of LC-PUFAs. Additionally, the dramatic increase of dietary LA has not only increased total PUFAs in the diet, but has dramatically shifted the ratio of LA to ALA that enters the pathway [6, 7]. Because LA and ALA compete in early steps of the pathway (Figure 1) and there is a limited synthetic capacity of the pathway, both human and animal models indicate that this shift has markedly reduced the synthesis and bioavailablity of n-3 LC-PUFAs [6, 8, 9]. It is important to note that the current levels and ratios of 18C PUFAs in the MWD are in line in in many ways resulted from with recommendations by the American Heart Association to consume 5-10% of daily calories as PUFAs [6]. For the MWD, that means these calories from PUFAs will be primarily LA and have a typical LA to ALA ratio of > 6 and more typically 10.

The second consideration for recommendations is the biological functions of n-6 and n-3 LC-PUFAs and subsequent molecular product that can result from these products. For example while a few oxidation products of ARA have been shown to be anti-inflammatory, hundreds of laboratories around the world have been able to find eicosanoids (prostaglandins and leukotrienes) at concentrations that are pharmacologically active as pro-inflammatory, and this has resulted in thousands of publications establishing the role of these ARA metabolites in inflammation [10]. Importantly there is the emerging story of n-3 LC-PUFAs and their products as anti-inflammatory, “pro-resolution” metabolites termed resolvins, protectins, and maresins [11-13]. Consequently, there is a consistent scientific literature that supports the concept that n-6 and n-3 LC-PUFAs and their products have not only different, but often opposing effects, with regard to inflammation. Many in the field of eicosanoid biology believe that this component has been underappreciated in the current recommendations by groups such as the AHA. Additionally, LC-PUFAs serve as important molecular components for disease risk factors such as circulating phospholipids, triglycerides and cholesterol esters found in lipoproteins, and thus their levels can play an important role in determining amounts and impact of these lipoproteins.

The third consideration is the type of data used to make the recommendations. For example, the current AHA dietary recommendations have been made largely based on several randomized controlled trials and population cohort studies that measured cardiovascular disease biomarkers such as serum lipids and lipoproteins [14-16]. These data show that PUFAs can have cardiovascular benefits when viewed from the perspective of measuring cardiovascular disease biomarkers such as serum lipids and lipoproteins. However, recent sets of data have raised important questions about this approach. Ramsden and colleagues recently re-examined studies utilized to support this recommendation and found that many of the oils used in the aforementioned clinical trials were mixtures of n-6 and n-3 PUFAs. Their data suggests that only substituting n-6 PUFAs for saturated and trans-fatty acids actually trended toward increased risk of death from all causes [17, 18]. This same group also recently reexamined the Sydney Diet Heart Study (458 men 30-59 with a recent coronary event), which replaced dietary saturated fatty acids with a high LA-containing life the aforementioned studies found that the LA intervention group had lower levels of total cholesterol; however, the n-6 PUFA group had unexpectedly higher rates of death than

controls [19]. These data raise the important consideration of which disease biomarker should be used to reliably predict disease and mortality.

Finally, the critical fourth consideration and the topic of this review that has not been appreciated is the potential for dietary 18C PUFAs to impact LC-PUFA biosynthesis, levels of intermediate risk factors and the incidence of human disease in dramatically different ways in diverse human populations. Most dietary PUFA recommendations made to date have been based on a simple assumption that there is a limited capacity (somewhere between 2-3% of calories) of humans to synthesize LC-PUFAs from dietary 18C PUFAs such as LA and ALA. This line of reasoning assumes that higher (than 3% calories) dietary quantities of 18C PUFAs are irrelevant since it is beyond the capacity of the PUFA biosynthetic pathway to utilize them. The second critical assumption in this line of reasoning is that the biosynthetic capacity is equivalent for all human populations. This review examines the veracity of these important assumptions by examining rapidly emerging genetic studies that point to population-associated genetic variation within or near FADS genes in the FADS cluster on chromosome 11q12-13.1 as being critical to an individual's levels of LC-PUFAs, disease biomarkers and the risk of the diseases themself.

The role of FADS genetic variants in the Biosynthesis of LC-PUFAs in the context of population diversity

As mentioned above, the desaturase enzymes encoded by genes in the FADS cluster are consistently recognized as a bottleneck that determines the levels of LC-PUFA through the biosynthetic pathway. There have been several excellent reviews on the role of FADS genetic variants as genetic determinants of PUFA levels [20, 21] and we present a birds-eye-view of the consistency of this data in Figure 2. The FADS cluster comprising three genes (FADS1, FADS2 and FADS3) is essentially a single large expanse of high linkage disequilibrium (LD) in populations of European ancestry which explains the numerous single nucleotide polymorphisms (SNPs) in the literature that have been shown to have exceedingly strong effects on PUFA metabolism (Figure 2) [22]. Subsequent to the first candidate gene study by Shaeffer et al. [23] there have been close to 20 candidate gene studies [22-43] lending support to the role these variants play, with a particular note that the dramatic effects are not only for the inter-individual variation in a single PUFA level (e.g., ARA or DGLA) but rather in those product-precursor ratios such as ARA/DGLA that specifically serve a surrogate markers for the efficiency by which PUFAs are moving through a given step (FADS1 in this case) within the biosynthetic pathway. In fact, these effects described by candidate genes studies have found strong support in the genome-wide association (GWA) approach as well; the peak associated SNP, rs174537, yielded a p-value of $p = 5.95 \times 10^{-46}$ and accounted for 18.6% of the additive variance in ARA, perhaps one the strongest GWAS-identified allelic effects to date [44]. Figure 2 documents these effects these SNPs have on both arms of the LC-PUFA metabolism pathway across numerous SNPs in the region.

In this review, these well-established effects are not the focus. Rather, we turn to the differences noted across populations. Tragically, as is typical for most diseases and traits that have been the focus of our attention in the past decade [45, 46], PUFA metabolism has

had a paucity of literature and attention in populations of African and Hispanic ancestry. For example, a recent review by Johnson and Fritsche concluded that there was little evidence that addition of LA to the diet increases the concentration of inflammatory markers in healthy humans [47]. However, this review had several critical limitations, but most importantly, only one of the fifteen studies may have utilized subjects other than European or European ancestry populations; even this one South African study did not reveal the racial composition of subjects. There have been only two recent studies in African Americans, both of which document a dramatic difference in LC-PUFA levels and product-precursor ratios (pathway efficiency) in total plasma lipids between African Americans and European Americans in the United States [22, 24], with the evidence pointing to enhanced *FADS1* efficiency ($p=9.80\times10^{-11}$ for DGLA, $p=1.35\times10^{-48}$ for ARA, and $p=2.06\times10^{-38}$ for ARA/DGLA) [22] as being a pivotal component to these differences. DGLA is lower in African Americans in contrast to ARA, which is higher in African Americans compared to European Americans [22, 24]. Similar trends were recently reported within the Multi-Ethnic Study of Atherosclerosis Risk (MESA) cohort when examining plasma phospholipids [48].

These studies confirm that variants within the region of expansive LD encompassing the FADS cluster are also key determinants of LC-PUFA metabolism in African Americans, but also highlight two critical points: (1) the studies indicate remarkably similar allelic effects in both racial group; and (2) the studies were the first insight into dramatic differences in allele frequencies between the two groups. We first showed that 79-82% of African Americans carry two copies of the G allele compared to only 42-45% of European Americans, where the G allele is the allele that has increased levels of ARA, decreased levels of DGLA and increased enzymatic efficiency (ARA/DGLA ratio) at rs174537.

There appears to be compelling evidence that the G allele at rs174537 is the *derived* allele and swept to fixation within African, is maintained at intermediate levels in Europe and European ancestry populations and at very low frequencies in Native American in the US [49]. Ameur et al. discuss that a common haplotype associated with the enhanced enzymatic efficiency of FADS1 is specific to humans appearing after the split of the common ancestor of humans and Neanderthals. Similar to our work [49], they also demonstrate that this haplotype shows evidence of positive selection in African populations [50]. Nonetheless, no matter the processes that led to these dramatic evolutionary pressures, speculated by both groups to be related to the proportionally large human brain relative to body size that is unique among primates, the present geographic distribution of the LC-PUFA enhancing alleles/haplotypes is unequivocally higher in populations of African ancestry. Coincidentally (or not), African Americans represent a fraction of the population in the United States that bears a disproportional burden of chronic diseases of inflammation [51-53]. We Believe these observations warrant a redirection of the ongoing debate surrounding the AHA's current dietary recommendations on PUFA intake away from a one-toned discussion on its appropriateness within a '*one size fits all approach*', to a more personalized argument given an individual's innate ability to synthesize LC-PUFA (with resulting molecular and clinical phenotypes at a more rapid rate given their specific genetic architecture.

The wide impact of FADS genetic variants

While it is clear that FADS variants have an important impact on LC-PUFA levels and ratios of PUFA products to precursors, it is likely that resulting additional molecular and clinical phenotypes associated with FADS variation place individuals at varying risk. For example, there are studies that document the role FADS variants in complex lipid and inflammatory phenotypes and coronary artery disease (CAD) [20, 21]. Over the past decade, genome-wide association studies (GWAS) have identified a number of genetic polymorphisms that convey increased risk for coronary artery disease, diabetes, cancer, and other common diseases, including some that implicate *FADS* variants [54, 55]. Associations have also been documented between *FADS* variants and traditional markers of cardiovascular disease, including LDL-cholesterol, triglycerides, HDL-cholesterol, and total cholesterol levels [56-59]. A recent study including ∼8,000 African Americans [60] from five cohorts leveraged the LD patterns in African Americans to identify SNPs more strongly associated with these phenotypes than previously reported GWAS SNPs in the Caucasian studies above, including for *FADS* variants, confirming FADS importance in CAD and its associated phenotypes across populations.

Associations have also been documented for phospholipid metabolites with four double bonds (i.e. ARA) for all major phospholipid species (98). Perhaps it is not surprising that strong associations are noted with *FADS* SNPs and LC-PUFA-containing glycerolipids as well as total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides given that PUFA-containing gylcerolipids are key molecular components (intermediate phenotypes) of lipoprotein particles. However, there are also now several studies that indicate specific *FADS* haplotypes favoring high desaturase activity lead to enhanced levels of inflammatory and CAD biomarkers including oxidative products of ARA (104; 116; 117). In one of the earliest studies in this area, Martinelli and colleagues demonstrated that a higher ARA/LA ratio (presumably representing more conversion of LA to ARA via the *FADS* cluster) is an independent risk factor for CAD. Additionally, they linked ARA/LA ratios to systemic inflammation by showing that concentrations of high-sensitivity C-reactive protein (CRP) increased progressively across tertiles of ARA/LA. Importantly, increases in CRP concentrations and CAD risk were related to the *FADS* haplotypes associated with higher levels ARA and ARA/LA ratios. (119) The ARA/LA ratio was also found to be higher in CAD patients and the low efficiency/capacity T allele at rs174537 was associated with a lower risk of CAD in a Chinese population. Contradictory evidence however does exist (120) which may result from the interaction between the balance of the n-6 to n-3 PUFA dietary environment and specific genotypes in the *FADS* cluster of the cohort being examined.

And then there is the important issue of gene-gene interactions between variants in the FADS cluster and variants in other genes that control LC-PUFA metabolism to eicosanoids (Figure 1). There are now numerous studies that support the concept that specific variants in genes whose activity are responsible for releasing ARA from membrane phospholipids (such as cytosolic PLA_2 alpha; *PLA2G4*) or metabolizing ARA to eicosanoids (such as 5-lipoxygenase; *ALOX5*) may further be a source of gene-diet interactions and predispose certain individuals and populations exposed to high amounts of n-6 PUFAsto enhanced

inflammation and cardiovascular disease [61-63]. For example, once ARA is released from glycerolipids via a PLA_2 cleavage, 5-lipoxygenase (*ALOX5*) becomes the rate-limiting step in leukotriene generation from ARA (Figure 2). While this group of eicosanoids were originally been identified with inflammation and bronchoconstriction associated with asthma and allergies, a large body of evidence has emerged over the past decade that demonstrates that leukotrienes play a key pro-athrogenic role particularly in CVD [64-66].

The importance of FADS variation extends well beyond the central arguments around cardiovascular disease and recommendations by the AHA, to include cancer, mental health and brain development. For example, there has been an intense focus on its role in levels of n-3 and n-6 LC-PUFAs in human milk and cognitive development in children.[67-69] [70]. Lattka et al provide an excellent review of the contradictory nature of the literature on prenatal and neonatal maternal diet and/or supplementation regarding LC-PUFA [21] and its consequent effects on measures of intelligence in the child. Many of the contradictions are speculated to be a result of the lack of consideration in maternal and child genotype at key determinants of LC-PUFA synthesis and metabolism, including *FADS*, an argument supported by gene*environment interaction studies in the field [71]. Associations of FADS variants have also been reported with attention deficit/hyperactivity disorder [72] mono- and bi-polar depression disorder [73], all of which have had previous linkage scans [74-76] that highlight this chromosomal region in families with the disorder. Pre-clinical animal and some clinical studies have provide compelling evidence that LC-PUFA levels and ARA metabolism to eicosanoids are important factors several cancers including colon, prostate and breast cancers. Interestingly, these are many of the same cancers where major disparities between African and European Americans are observed with incidence and severity being higher in African Americans. However, overall examination of epidemiologic studies provides an inconsistent picture of the associations between dietary PUFAs and cancer. Genetic variation in LC-PUFA biosynthesis and particularly within the FADS cluster have the potential to help clarify when and how LC-PUFAs play an important role in cancer.

The interplay between genes and diet

So what are we to make of all of these data and what are the major missing pieces of information necessary to make meaningful recommendations? As mentioned above, the single biggest problem in this regard is there have been few studies utilizing populations other than European and more recently Asian ancestry. For example, the question of capacity through the PUFA biosynthetic pathway needs to be addressed in African ancestry and other populations. There are at least 5 very excellent studies that show that increasing dietary LA intake above 3% of energy has no impact on circulating and tissue ARA levels [77-81]. However, these too were carried out in small numbers of volunteers from Europe (Netherlands, Spain, Germany), Canada (British Columbia) and Australia and in at least one of the studies, there were major outliers (68). We hypothesize that significantly higher concentrations of LA will be converted to ARA in African Ancestry populations where genetic variants are much more favorable (>80% carry GG at rs174537) for enhanced ARA levels. What if 6-8% of energy from LA were converted to ARA in African Americans? Would this change the dietary recommendations for PUFAs? We certainly believe it should given the role ARA and its eicosanoid product plays in human diseases and the link between

FADS variants to a variety of human disease and particularly CAD. Given the amount of data implicating variants in the rate limiting steps (enzymes encoded for in the *FADS* cluster) in LC-PUFA biosynthesis to human disease, the interplay between dietary PUFAs exposure and variants in genes that synthesize and metabolize LC-PUFAs must be better understood. Until we better understand this interplay, the association studies outlined in this review, the recent meta analyses showing substituting n-6 PUFAs (not mixed with n-3 PUFAs) for saturated and trans fatty acids actually trends toward an increase risk of death, the reexamined the Sydney Diet Heart which showed that although the LA intervention group had lower levels of total cholesterol, it had unexpectedly higher rates of death than controls, jointly indicate that we should observe great caution in making n-6 PUFA reccommendations. Understanding the relationship between PUFA exposure and *FADS* gene variants will likely provide clarity for not only cardiovascular disease, but also a range of human diseases (cognitive, mental, inflammatory and proliferative [cancer]) diseases.

Conclusions

Much of the discussion above has focused on the impact of genetic variation on LC-PUFA biosynthesis. A major limitation of the field as it currently exists is that little is known about how these SNPs work to regulate PUFA levels, shunting down and between the two arms of the pathway illustrated in Figure 1. While numerous studies use terms such as desaturase activities or efficiencies, these are not true activities (as would be measured with an isolated enzyme or subcellular fraction), but are typically ascertained by measuring PUFA precursor/product ratios within circulating or cellular lipids. There are postulated mechanisms that connect LC-PUFA exposure to the transcriptional machinery of the PUFA biosynthetic pathway [82], variants in this region have been identified as eQTLS [49], and the idea that gene expression is epigenetically modulated cannot ignored [83, 84]. For example, it is interesting to note that two recent studies show that methylation of in a promoter region of ELOVL2 to be among top 3 or 4 hits in the entire human genome with regard to association with age [85]. ELOVL2 is the first step that shows selectivity for n-3 substrates in the PUFA biosynthetic pathway. These data suggest as have other human and animal studies that age may play a critical role in LC-PUFA biosynthesis. We also know that other factors (such as sex and pregnancy status) impacts LC-PUFA biosynthesis. These raise important questions as to how these factors can be incorporated into PUFA recommendations.

The key point to highlight with this review is that the impact of genetic variants are likely to be population-specific given that frequency of the variants in PUFA biosynthetic genes and the dietary precursor PUFA environment maybe different between populations. For example, higher dietary exposure to ALA relative to LA together with high efficiency/capacity variants may markedly shift the balance from ARA towardn-3 LC-PUFAs (DHA, DPA, and EPA) and a wide array of protective n-3 containing eicosanoids and endocannabinoids (intermediate phenotypes). Alternatively, higher dietary exposure to LA relative to ALA together with a high frequency of high efficiency/capacity variants likely shifts the balance back to ARA, proinflammatory eicosanoids and endocannabinoids, inflammation and associated human disease. And if these high efficiency/capacity variants give rise to higher levels of *FADS* gene expression (as preliminary studies suggest) and protein levels, then the capacity to make ARA may increase well past 2-3% of energy

because the enzymatic capacity within cells and tissues have risen with more protein. This is the most likely explanation for what is being observed with the very strong associations between these variant and markedly higher ARA levels (particularly in populations of African ancestry). The major point of this review is that it is highly unlikely that simple dietary recommendations can be applied to diverse populations given the immense complexity and differences in genetic variation of the PUFA biosynthetic pathway in different populations. Even more important, it would be tragic if the need for simplicity drove dietary recommendations that actually harmed certain populations.

Acknowledgments

This work was supported by a grant from the National Institutes of Health, P50 AT002782.

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Abbreviations

ALA	α-linolenic acid
ARA	arachidonic acid
COX	cyclooxygenase
DGLA	dihomo γ-linolenic acid
DHA	docosahexaenoic acid
EPA	eicosapentaenoic acid
ETA	eicosatetraenoic acid
CAD	coronary artery disease
CVD	cardiovascular disease
FADS	fatty acid desaturase
GLA	γ-linolenic acid
GWAS	genome wide association study
IMT	intima-media thickness
LA	linoleic acid
Lc	long chain
LD	linkage disequilibrium
LTB4	leukotriene B4
C18	18 carbon
MWD	modern western diet
NSAID	non-steroidal anti-inflammatory drug
PC	phosphatidylcholine
PE	phosphatidylethanolamine
PI	phosphatidylinositol
PS	phosphatidylserine
PLA_2	phospholipase A_2
PUFA	polyunsaturated fatty acid
SDA	stearidonic acid

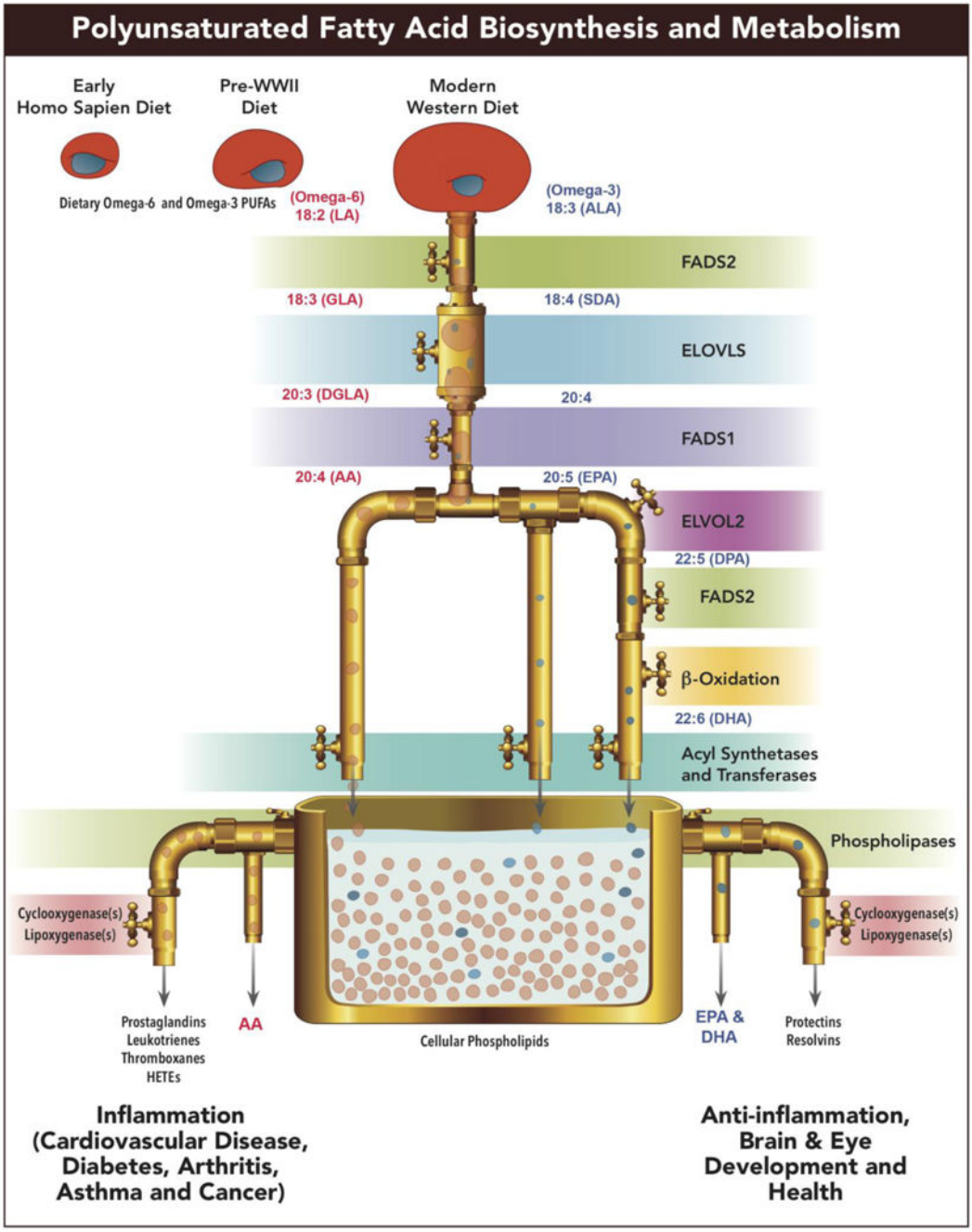

Figure 1.

Biosynthetic pathway of n3 and n6 PUFAs highlighting a set of genes known to play key roles in the biosynthesis and metabolism of LC-PUFAs in two parallel and competing pathways. Enzymatic products from these genes convert 18-carbon (18C) n-6 or n-3 essential PUFAs (abundant in the modern western diet [MWD]) into LC-PUFA.

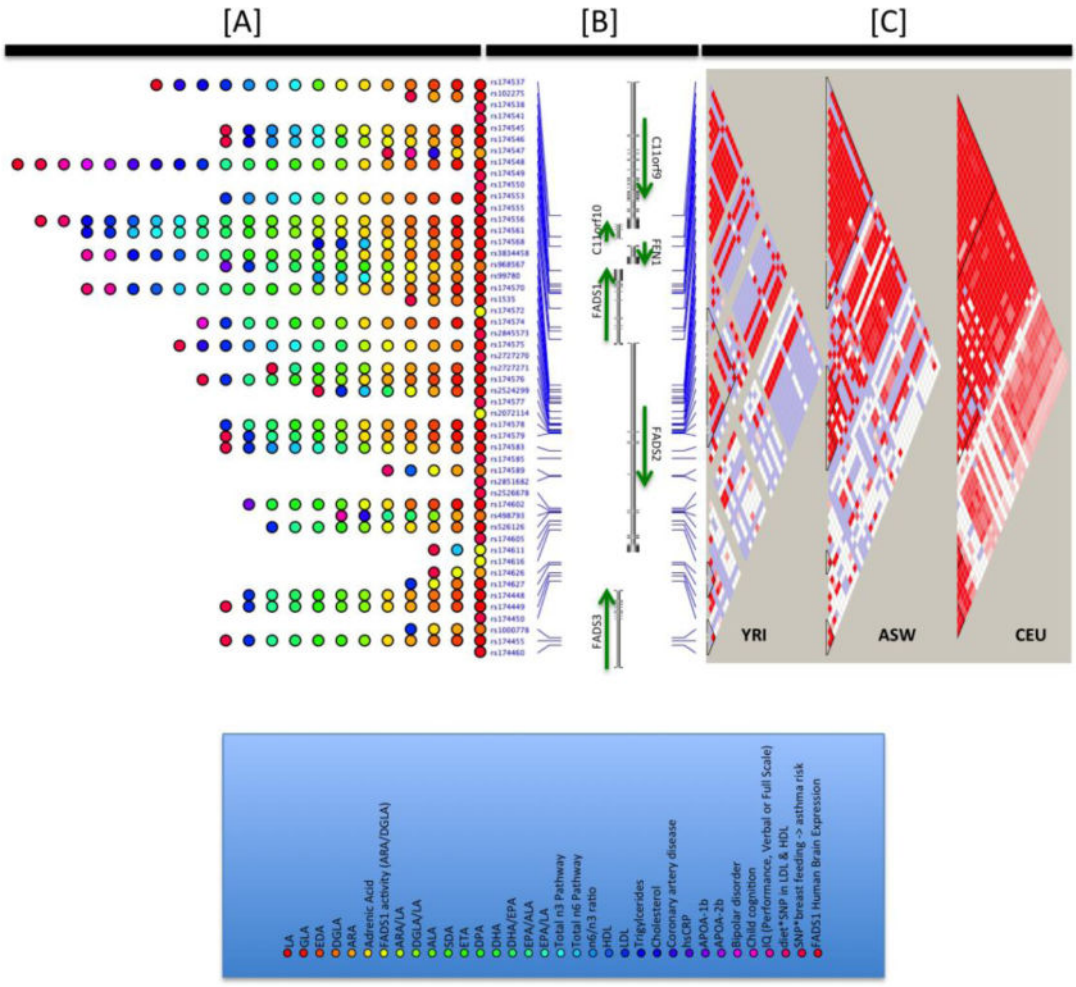

Figure 2.

Illustration of the associations observed between genetic variants within and near the FADS locus and phenotypes/traits of relevance. **Panel A** shows the orientation of genes in this regions and the SNPs implicated across the range of studies ([20-43, 56-60, 86-93]), phenotypes presented are those with $p<0.05$ in at least one reviewed study. **Panel B** illustrates the strength of linkage disequilibrium in three populations from the Thousand Genomes Project [94], including the European ancestry CEU samples, African YRI samples and the African American ASW samples. The strength of LD between variants in this region reveals an extensive block of high LD (red regions) in the European ancestry samples and smaller blocks in the African ancestry samples. **Panel C** indicates the range of phenotypes with $p<0.05$ at each SNP under consideration.