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Desaturase and elongase limiting endogenous long chain polyunsaturated fatty acid biosynthesis

Ji Yao Zhang, **Kumar S.D. Kothapalli**, and **J. Thomas Brenna***

Division of Nutritional Sciences, Cornell University, Ithaca, New York 14853 USA

Abstract

Purpose of Review—Endogenous synthesis of the long chain polyunsaturated fatty acids (LCPUFA) is mediated by the fatty acid desaturase (*FADS*) gene cluster (11q12-13.1) and elongation of very long chain fatty acids 2 (*ELOVL2*) (6p24.2) and *ELOVL5* (6p12.1). Though older biochemical work identified the product of one gene, *FADS2*, rate limiting for LCPUFA synthesis, recent studies suggest that polymorphisms in any of these genes can limit accumulation of product LCPUFA.

Recent findings—Genome-wide association study (GWAS) of Greenland Inuit show strong adaptation signals within *FADS* gene cluster, attributed to high omega-3 fatty acid intake, while GWAS found *ELOVL2* associated with sleep duration, age and DNA methylation. *ELOVL5* coding mutations cause spinocerebellar ataxia 38, and epigenetic marks were associated with depression and suicide risk. Two sterol response element binding sites were found on *ELOVL5*, a SREBP-1c target gene. Minor allele carriers of a 3 single nucleotide polymorphism (SNP) haplotype in *ELOVL2* have decreased 22:6n-3 levels. Unequivocal molecular evidence shows mammalian FADS2 catalyzes direct Δ4-desaturation to yield 22:6n-3 and 22:5n-6. A SNP near *FADS1* influences the levels of 5-lipoxygenase products and epigenetic alteration.

Summary—Genetic polymorphisms within *FADS* and *ELOVL* can limit LCPUFA product accumulation at any step of the biosynthetic pathway.

Keywords

desaturase; elongase; long chain polyunsaturated fatty acids (LCPUFA); single nucleotide polymorphisms (SNPs)

INTRODUCTION

Omega3 (ω3 or n-3) and omega6 (ω6 or n-6) long chain polyunsaturated fatty acids (LCPUFA) are ubiquitous in mammalian tissue. They are key nutrients critical for growth and development, are bioactive cellular components of membrane phospholipids, serve as substrates for signaling molecules and act as direct modulators of gene expression [1, 2]. The degree of unsaturation of the biological membranes is modulated by the action of the

*Corresponding author: J. Thomas Brenna, voice (607) 255-9182, fax (607) 255-1033, jtb4@cornell.edu.

CONFLICT OF INTEREST

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desaturation and elongation enzymes mediating fatty acid biosynthesis and metabolism. In most organisms endogenous synthesis of LCPUFA from PUFA precursors is possible, but the transformations and efficiencies are specific to cell types and species. In humans, genetic variants within genes encoding for desaturation and elongation enzymes were shown to be associated with LCPUFA levels and complex disease phenotypes. Here, we present recent information gained from studies related to desaturases and elongases limiting endogenous LCPUFA synthesis.

LCPUFA BIOSYNTHESIS

LCPUFA are endogenously biosynthesized from 18:3n-3 and 18:2n-6 PUFA precursors by position-specific desaturation and carbon chain-elongation reactions, as shown in Figure 1. The two PUFA series n-3 and n-6 compete for the same enzymes in the LCPUFA biosynthetic pathway, originally worked out in rodents based on tissue composition resulting from diets rich in 18:3n-3 (alpha-linolenic acid) or 18:2n-6 (linoleic acid). The Δ6-desaturase (fatty acid desaturase 2, FADS2) metabolizes both 18:3n-3 and 18:2n-6, resulting in the synthesis of 6,9,12,15-18:4 and 6,9,12-18:3, respectively. This initial Δ6-desaturation step is widely regarded as rate limiting for LCPUFA endogenous biosynthesis based on biochemical studies, however recent data indicate that other steps in the pathway can limit LCPUFA levels and complex phenotypes. Both 20:5n-3 (eicosapentaenoic acid, EPA) and 20:4n-6 (arachidonic acid) can be further elongated and desaturated to yield 22:6n-3 (docosahexaenoic acid, DHA) and 22:5n-6, respectively. The final steps were long thought to be by direct Δ4-desaturation via 22:5n-3→22:6n-3. Biochemical data in rat liver developed in the 1990s established an alternative coupled microsomal-peroxisomal pathway via 22:5n-3→24:5n-3→24:6n-3→22:6n-3, where the last step is one round of β-oxidation in the peroxisomes [3]. Molecular studies since 2001 established that Δ4-desaturase (FADS2) is the final step in marine microorganisms (e.g.*Thraustochytrium)*, marine teleost fish, and mammals, and very recently in humans [3].

DESATURASES

Desaturase enzymes perform dehydrogenation reactions and introduce a stereospecific double bond between defined carbons of fatty acyl chains. They have evolved independently twice; the Acyl-acyl carrier protein (ACP) desaturases are soluble enzymes found in the plant plastid and most wide-spread membrane-bound desaturase enzymes found in prokaryotes and eukaryotes [4]. In humans, membrane-bound PUFA desaturases known as “front-end” desaturases introduce a nascent double bond between an existing double bond usually located between the carboxyl group and the 9^{th} carbon atoms from the terminal methyl (n-9) [5]. Front-end desaturation proceeds at the Δ4, Δ5, Δ6 and Δ8 positions and is responsible for endogenous biosynthesis of LCPUFA [3, 6, 7].

FADS1 (Δ5-desaturase), *FADS2* (Δ6-desaturase/Δ8-desaturase/Δ4-desaturase) and *FADS3* are located as a cluster within 100 kb region on the long arm of human chromosome 11 (HSA11q12-13.1), whereas, mouse *Fads* homologs with similar structural organization are localized to chromosome 19 [8, 9]. All three genes have evolved by gene duplication events,

share 12 exons and 11 introns, and contain well conserved cytochrome *b5* domain and three histidine repeats (HXXXH, HXXHH and QXXHH).

FADS2 (Δ6, Δ8, Δ4-DESATURASE)

FADS2 (OMIM#606149) in humans spans 39.1 kb of genomic DNA, encoding a 444-amino acid protein with a molecular mass of 52.3 kDa [8]. *FADS2* is a trifunctional even carbon numbered desaturase and acts on at least eleven known fatty acid substrates. In addition to humans, *Fads2* has been cloned from mouse, rat and *Caenorhabditis elegans* [10]. It introduces a double bond at the Δ6 position (between carbons 6 and 7) by acting on at least six substrates (18:2n-6 → 18:3n-6, 18:3n-3 → 18:4n-3, 24:5n-3 → 24:6n-3, 24:4n-6 → 24:5n-6, 16:0 →16:1n-10, and 18:1n-9 →18:2n-9), Δ8-desaturation by acting on 20:1n-9 → 20:2n-9, 20:2n-6 → 20:3n-6, and 20:3n-3 → 20:4n-3, and Δ4-desaturation by acting on 22:4n-6 → 22:5n-6 and 22:5n-3 → 22:6n-3 [3, 10, 11]. The Δ8-desaturase activity provides an alternative pathway to LCPUFA biosynthesis, possibly available when Δ6-desaturase activity is compromised. *FADS2* Δ8-desaturates 20:2n-6 and 20:3n-3 to eicosanoid precursors as well as to precursors of 20:4n-6 and 20:5n-3 respectively [10]. This result offers an explanation as to why 20:2n-6 has been associated with *FADS* single nucleotide polymorphisms (SNPs) in genetic studies described below.

The desaturation of saturated fatty acids (SFA) and PUFA is nearly always considered separately in mammals, with the FADS acting on PUFA and the stearoyl CoA desaturase 1 (SCD1) on SFA. However, 16:0 is the only exception, being a substrate for both Scd1 (16:0→16:1n-7) and FADS2 (16:0→16:1n-10). Human skin lipids, sebum, have long been known as unique with about 25% of fatty acids as 16:1n-10 [12]. Importantly, human and mouse skin cells handle this metabolite shift with different genes: humans use FADS2 to make 16:1n-10 and mice use Scd1 to make 16:1n-7 (Figure 2). Scd1 principally mediates desaturation of 18:0→18:1n-9 (Figure 2), however we detect no activity of FADS2 towards 18:0 in a human cell system.

A human MCF-7 cell with no detectable Δ6-desaturase (FADS2) activity stably transformed with *FADS2* mediates direct Δ4 desaturation to yield 22:6n-3 and 22:5n-6, similar to fish and many other organisms [3]. *Fads2* null mice had severe problems with fertility; once born, both female and male mice had normal viability and lifespan but were sterile [13]. The *Fads2* disruption caused an upstream deficiency in eicosanoid synthesis via reduction in 20:4n-6 substrate, unusual fatty acid biosynthesis, dermal and intestinal ulceration, reduced insulin sensitivity and perturbed cell membrane structure [14, 15]. *FADS2* is alternatively spliced to generate two isoforms (*FADS2AT1* and *FADS2AT2*, *“AT”=alternative transcript*) [16, 17]. We have shown that polypyrimidine tract binding protein (PTB, also known as *PTBP1* or *hnRNP I*) regulates alternative splicing of *Fads2*. Knock-down of PTB modulated the balance of omega-3 to omega-6 fatty acids by dramatically reducing (50% reduction) 20:5n-3 content [1].

FADS1 (Δ5-DESATURASE)

FADS1 (OMIM#606148) in humans spans 17.2 kb of genomic DNA, encodes a 444-amino acid protein with a molecular mass of 52.0 kDa and shares 61% and 52% identity with

FADS2 and *FADS3*, respectively [8]. It introduces a double bond at the Δ5 position (between carbons 5-6) by acting on at least four 20-carbon fatty acid substrates 20:3n-3, 20:4n-3, 20:2n-6 and 20:3n-6 [6]. When FADS2 is absent, FADS1 produces rare butylene-interrupted fatty acids, for instance 5,11,14-20:3 and 5,11,14,17-20:4. These and similar PUFA are observed in cell systems [6], knockout mice, and normal domestic cats [18]. In this sense, FADS1 competes successfully with FADS2 when *FADS2* expression is negligible. Disruption of the *Fads1* gene in mouse causes massive accumulation of the 20:3n-6 substrate and 1-series-derived prostaglandins, with a concurrent decrease in the product 20:4n-6 and 2-series-derived prostaglandins [19]. *Fads1* ablated mice fail to thrive beyond 12 weeks of age; the phenotype is rescued by dietary supplementation of 20:4n-6 [19]. We recently showed *FADS1* producing several mRNA and protein isoforms. One *FADS1* isoform (*FADS1AT1*) enhances desaturation activity of *FADS2*, leading to increased production of eicosanoid precursors [7].

FADS3

FADS3 (OMIM#606150) is the enigmatic third member of the *FADS* gene cluster. In humans it spans 17.9 kb of genomic DNA, presumed to encode a 445-amino acid protein with a molecular mass of 51.1 kDa [8]. *Fads3* [7, 20] is translated, but no reports exist showing *FADS3* mediating front-end desaturation analogous to *FADS1* and *FADS2*. It is extensively spliced, generating at least 8 alternative transcripts that are phylogenetically conserved in several mammalian and avian species [9]. Several FADS3 isoforms have been reported using immunoblotting [20], and are phylogenetically conserved.

Some aspects of its regulation are known and provide clues to its function. Gene transcript studies show *Fads3* is highly expressed in mouse uterus at the implantation site; in a *Fads2* null mouse, *Fads3* expression increased by 3-fold; in baboons fed 22:6n-3 and 20:4n-6 *Fads3 ATs* abundance increases while *Fads1* and *Fads2* classical transcripts decrease [9, 21]. An *in vitro* study provided evidence for *Fads3* desaturation of *trans*11-18:1 (the most abundance *trans* fatty acid in bovine milkfat) to make a conjugated isomer (*trans*11,*cis*13-18:2) by back-end desaturation at position Δ13 (between carbons 13 and 14) common in plants, though the final product structure was not positively identified [22]. We generated the first *Fads3* null mouse and found no differences in overt phenotypes (survival, fertility, growth rate) between null and wild type, but fatty acid tissue profiles support a role for *Fads3* in the synthesis of DHA during perinatal period [23]. Dosing of *trans*11-18:1 in aged wild-type mice and comparison to *Fads3* null mice provided no *in vivo* evidence for the 11,13 isomer (Zhang et al, 2015, unpublished observations).

ELONGASES

Fatty acid elongation is well known to occur in cytosol, mitochondria and predominantly microsomes. The microsomal fatty acid chain elongation system (FACES) pathway cycles through a four step process (condensation, reduction, dehydration and reduction) using fatty acids of 12 or more carbons from endogenous and exogenous sources, adding two carbons in each cycle [24]. The first, condensation step is rate limiting and is catalyzed by ELOVL family in mammals, comprised of seven members (ELOVL1-ELOVL7). Among the seven

elongases, ELOVL1, ELOVL3, ELOVL6 and ELOVL7 prefer SFA and monounsaturated fatty acids (MUFA) as substrates [24]. ELOVL2 and ELOVL5 are PUFA-specific, whereas ELOVL4 (OMIM#605512) prefer SFA and very long chain PUFA (C28-C38) [24]. A highly conserved HXXHH motif is commonly found in all 7 members [25]. Here we focus on the PUFA specific ELOVL2 and ELOVL5.

ELOVL5 (C18- 20 PUFA ELONGASE)

ELOVL5 (OMIM#611805), is expressed in several human tissues, with highest expression detected in Purkinje cells, lung, testis and adrenal gland. It is specific for 18 and 20 carbons PUFA [24–26]. Microsomes from *Elovl5* null mice failed to elongate 18:3n-6 to 20:3n-6 and 18:4n-3 to 20:4n-3 resulting in accumulation of 18:3n-6 and 18:4n-3 respectively, and significant lowering of their downstream products 20:4n-6 and 22:6n-3, respectively. These mice develop hepatic steatosis apparently as a consequence of decreased cellular 20:4n-6 and 22:6n-3 and upregulation of sterol regulatory element-binding protein 1c (*Srebp-1c*) and its target genes [24]. The expression of *ELOVL5* is transcriptionally regulated by SREBP-1c and a recent study in human showed existence of two novel sterol regulatory element (SRE) binding sites, one in the upstream region and one in the exon 1 of *ELOVL5* [25].

ELOVL2 (C20-24 PUFA ELONGASE)

ELOVL2 (OMIM#611814), is selectively expressed in human tissues, with highest expression detected in testis and liver. It has substrate specificities for 20 and 22 carbon PUFA [24, 27–29]. Rat Elovl2 converts 22:5n-3 to 24:5n-3 [28], whereas, in chickens both Elovl2 and Elovl5 convert 22:5n-3 to 24:5n-3 demonstrating species specific differences [30]. Ablation of *Elovl2* caused complete arrest of spermatogenesis, complete absence of very long chain PUFA (carbon chain length between 24 to 30) of the n-6 family in testis and significant increase in the serum levels of 20:5n-3 and 22:5n-3, with concurrent non-significant decrease in 22:6n-3 [31]. The supplementation of 22:6n-3 for 3 months was not able to restore male fertility in these mice [31]. In the follow-up study the same group found *Elovl2* deletion caused severe reduction of 22:6n-3 and 22:5n-6 and an accumulation of 22:5n-3 and 22:4n-6 in both liver and serum. These mice had increased expression of *Srebp-1c* and its target genes (*Fasn* and *Scd1*) in liver but did not develop steatosis [32].

GENETIC VARIANTS: LCPUFA LEVELS AND HUMAN PHENOTYPES

The *FADS* and *ELOVL* are among the most prominent genes associated with human phenotypes in both candidate gene study and genome-wide association study (GWAS). It has long been known that carnivores, such as cats and higher trophic level fish, have lost the metabolic ability to synthesize long chain PUFA via loss of Fads2 desaturation activity; presumably this is due to the ubiquitous presence of 20:4n-6 and 22:6n-3 in a meat based diet. In contrast, herbivores ingest very little 20:4n-6 and 22:6n-3 and must have a robust metabolic pathway to synthesize all they need, especially at life stages of high demand such as the brain growth spurt. The remarkable flexibility of humans to survive in environments that predominantly produce animal foods or plant foods suggests adaptive changes specifically in the *FADS* and *ELOVL* genes [33].

Converging evidence from candidate gene and GWAS available recently show large genetic variability in the level of fatty acid precursors 18:3n-3 and 18:2n-6 and their apparent conversion to physiologically important LCPUFA products, especially 20:5n-3 and 20:4n-6. These studies have shown strong associations between the minor allele carriers of single nucleotide polymorphisms (SNPs) within *FADS* gene cluster, *ELOVL2* and *ELOVL5* and fatty acid levels in serum, plasma, red cells, breast milk and adipose tissue [13, 34–36].

CANDIDATE (*FADS* GENE CLUSTER, *ELOVL2* AND *ELOVL5*) GENE STUDIES

A *FADS* gene cluster association study showing minor allele carriers of a 11 SNP haplotype exhibited increased levels of 18:2n-6, 20:2n-6, 20:3n-6, and 18:3n-3 and decreased levels of 18:3n-6, 20:4n-6, and 20:5n-3 in serum [34]. This finding was subsequently replicated independently by others. Genetic variability was highest (28%) for 20:4n-6 [34]. Locus specific (*FADS* gene cluster) SNPs are associated with human phenotypes, for instance, inflammation and cardiovascular disorders [13, 34], levels of blood lipids (total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LCL) and triglyceride(TG)) [37], insulin resistance in schizophrenia and bipolar patients [38], perinatal depression [13], atopic diseases [13, 34], attention/hyperactivity [13] and intelligence in children [13]. A SNP in *ELOVL5* was associated with late onset primary open-angle glaucoma [39]. Recent studies show SNPs near *FADS1* (rs174537) influencing the levels of 5-lipoxygenase products [40] and another found rs174537 associated with epigenetic alteration [41]. A minor allele of *FADS3* SNP (rs174455) was negatively associated with 22:6n-3 in erythrocyte phospholipids in the AVON longitudinal study of parents and children (ALSPAC) cohort [42]. A very distinct *FADS* haplotype was shown to be associated with enhanced ability to biosynthesize LCPUFA from PUFA precursors [43]. Major allele homozygotes of a 4 SNP haplotype showed more than 3-fold greater apparent conversion of [U-^{13}C]-18:3n-3 to [U-^{13}C]-20:5n-3 in plasma than minor allele carriers [44]. Al Saleh *et al.* [36] found minor allele carriers of 3 SNP haplotype within the *ELOVL2* gene with lower plasma 22:6n-3 than major allele carrier. An SNP within *ELOVL5* was nominally associated with decreased capacity to metabolize 20:5n-3 to 22:5n-3 [35]. Epigenetic marks within the regulatory regions of *ELOVL5* were associated with depression and suicide risk [45].

GWAS

As a complement to locus specific SNPs, several GWAS identified *FADS* and *ELOVL* loci to be associated with LCPUFA levels and human phenotypes. Traditional inhabitants of the arctic region of North America are known to subsist almost exclusively on animal foods, predominantly fish and marine mammals. GWAS show a striking adaptation of the Greenland Inuit *FADS* gene cluster attributed to high omega-3 fatty acid intake [46]. A meta-analysis of seven GWAS scans and replication with 20,623 individuals identified 30 loci including the *FADS* cluster as influencing HDL and triglyceride levels [13]. The InCHIANTI GWAS identified a minor allele of rs174537 accounted for 18.6% genetic variance in 20:4n-6 concentrations, which was confirmed in an independent sample from the GOLDN study [13] and another study found genetic variants within *FADS1* and *FADS2* to be associated with higher levels of ALA and lower levels of EPA and DPA and these

associations were similar in ancestries of European, African, Chinese and Hispanic origin [47]. Lemaitre et al.[47] also showed minor alleles of SNPs in *ELOVL2* to be associated with lower 22:6n-3 levels, however, these associations were found to be less consistent in the four ancestries. Moreover, there are numerous GWAS reports that relate *FADS* and *ELOVL* SNPs to TC-HDL-LDL-TG and lipid metabolite levels [13, 48, 49], fasting glucose homeostasis [50], and resting heart rate [51]. A few studies tried to combine GWAS with metabolomics (mGWAS) to understand gene-environment impacts on homeostasis and to address missing heritability [52]. Genetic information at the *FADS1* locus (rs174547) combined with targeted metabolomics identified 36% of the observed variance in metabolite concentrations [53], in the same study SNP (rs9393903) in *ELOVL2* accounted for 9.8% variance. Similarly, Suhre et al. [54] showed "genetically determined metabotypes" accounted for 10–60% differences in metabolite levels per allele copy in 25 loci which also includes *FADS1* and *ELOVL2*. *FADS1* SNP (rs174548) accounted for 29% of the metabolic ratio variance [13]. *ELOVL2* is associated with sleep duration [55], age and DNA methylation [56].

CODING GENETIC VARIANTS (*FADS* GENE CLUSTER, *ELOVL2* AND *ELOVL5*)

Target captured exome sequencing showed existence of 53,081 coding SNPs (cSNPs) in the human genome [57]. cSNPs may be synonymous, resulting in no change in the resulting protein primary sequence, or non-synonymous, resulting in a substitution of one amino acid for the other at the relevant position. An October 2015 check of the NCBI dbSNP database reveals several cSNPs within the *FADS* and *ELOVL* genes. No disease causing phenotypes associated with cSNPs in the FADS gene cluster and *ELOVL2* are yet known, however, a *FADS2* promoter SNP (rs968567) enhancing *FADS2* expression has been discovered [58]. Two non-synonymous mutations within *ELOVL5* causing spinocerebellar ataxia 38 (*SCA38*) has been reported in families originating from Italy and France [26].

INSERTION-DELETION (INDEL) POLYMORPHISM

GWAS and candidate gene studies target SNP(s) that are tags for haplotypes which serve only as signals close to functional variants responsible for phenotypic variation. Association strength is directly related to the physical closeness of the GWAS SNP(s) to the functional element, a basic principle underlying the Manhattan plot.

In humans, highly polymorphic small Indels (1 bp to 10,000 bp) are the second most frequent polymorphisms after SNPs and are increasingly recognized as functional contributors of genetic variation influencing multiple human phenotypes [59]. Largely due to the technical difficulties in genotyping and calling Indels from short read sequencing data, their functional effects are understood only in a few cases [59]. Recently, we discovered a 22-bp Indel polymorphic variant (rs66698963) in *FADS2* intron 1 near a SRE to be associated with desaturase expression depending on levels of SREBP-1c agonists [60]. Follow-up work showed the *FADS2* Indel strongly influencing metabolic capacity to synthesize 20:4n-6 from precursors and also showed ethnic differences in the allele frequency in general US and Indian subjects, as well as evidence for adaptive evolution

(Kothapalli et al., 2015, unpublished data). Commonly reported SNP variants within intron 1 of *FADS2* (rs174575, rs174570 and rs1535) and thus the nearby Indel are associated with increased IQ scores, blood fatty acid levels and complex diseases. rs174575 and rs174570 are within 600 and 6000 bp upstream from the *FADS2* Indel, respectively [13, 34, 46]. In humans, common SNP variants are often found to follow Indels [61], suggesting that rs174575, rs174570 and/or rs1535 are tags for the functional genomic Indel that directly modulates binding at the nearby SRE. Whether or not the Indel is the functional element or it is nearby, genotypic variation controlling basal concentrations of 20:4n-6, its immediate precursor and its products, demonstrates *in vivo* that FADS2 protein(s) is (are) a major rate limiting enzyme for LCPUFA production.

CONCLUSION

The genes mediating the endogenous synthesis of LCPUFA contribute wide variability to the efficiency of LCPUFA synthesis, likely controlled at *FADS2* but also controlled at the level of *FADS1* and the elongases depending on genotype and metabolic state. In the era of mass individual immigration and international food supplies, individuals with genotypes adapted to a food supply with high, or low, LCPUFA will find themselves exposed to diets to which they are not adapted. Precision nutrition depends on the detailed genetics controlling LCPUFA conversion efficiency, for instance, those adapted to high intakes of 20:4n-6 and 22:6n-3 via meat and fish may become deficient when consuming an otherwise heart healthy diet predominantly composed of vegetables; the risk of neurodegenerative diseases may thereby increase. Continuing mechanistic studies of genetic function are needed to address this issue.

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KEY POINTS

1. Endogenous synthesis of long chain polyunsaturated fatty acids (LCPUFA) and degree of unsaturation of the biological membranes depends largely on the action of the fatty acid desaturases (FADS1, FADS2 and putative FADS3) and elongation of very long chain fatty acids (ELOVL2 and ELOVL5).
2. While FADS2 mediated Δ6-desaturation is demonstrably rate limiting for LCPUFA synthesis in rodent biochemical studies, emerging human genomic, mouse gene ablation, and in vitro studies indicate that metabolic control over LCPUFA homeostasis is associated with FADS and ELOVL for endogenous synthesis.
3. Polymorphisms in the FADS gene cluster yield the strongest signal in genomic studies of LCPUFA eating Greenland Inuit people consistent with decades old predictions.
4. The FADS gene cluster, ELOVL2 and ELOVL5 are associated with LCPUFA levels and complex human phenotypes.
5. Novel substrate and positional desaturase specificities mediated by FADS2, Δ4 acting on 22:5n-3 and 22:4n-6, and Δ8 acting on 20:2n-6 and 20:3n-3, imply that LCPUFA endogenous synthesis is controlled at several levels.

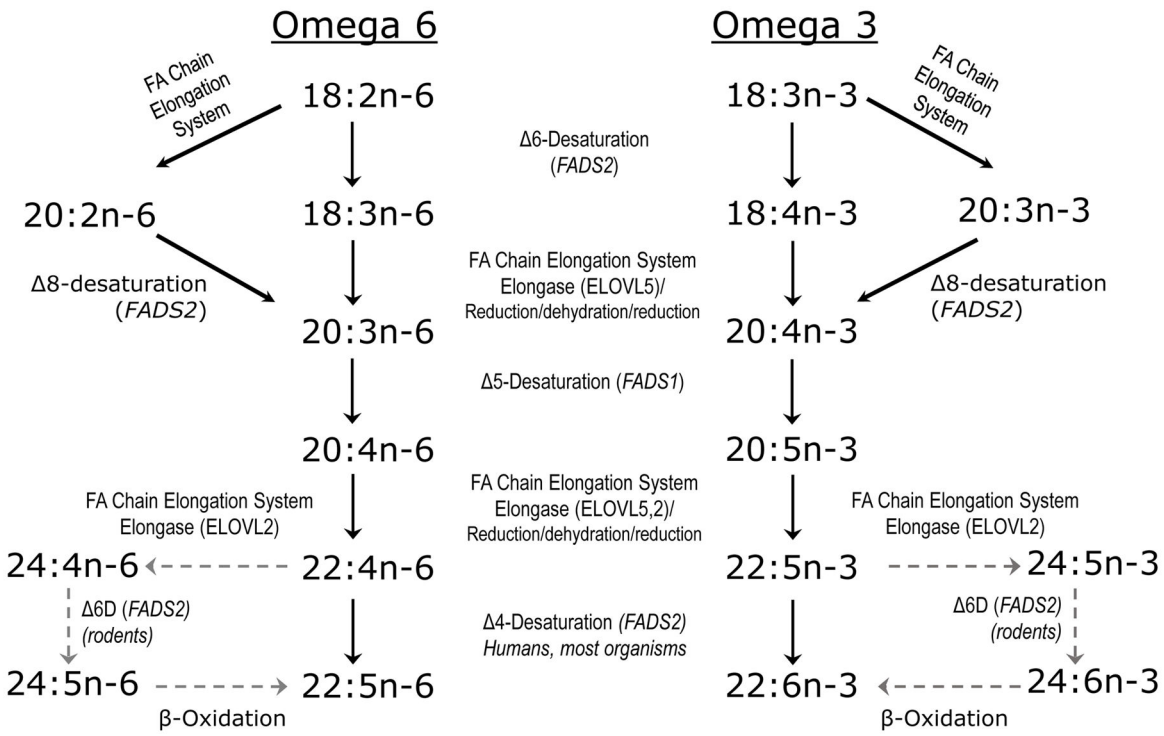

Figure 1.

LCPUFA Biosynthesis Pathway. The omega 6 (n-6) and omega 3 (n-3) fatty acids are substrates in competition for the same sets of FADS and ELOVL catalyzing desaturation and elongation, respectively. Elongation is mediated by a four enzyme coupled system; the first, rate limiting enzyme is the “elongase”.

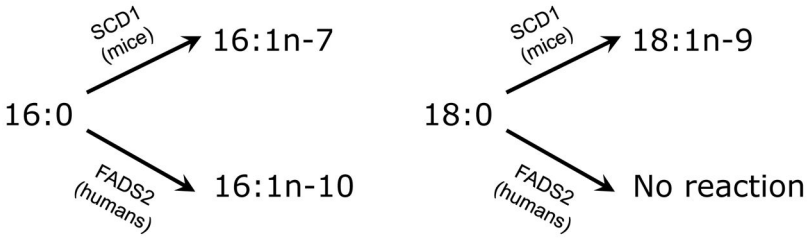

Figure 2.

Biosynthesis of monounsaturated fatty acids (MUFA) in mouse and human skin. Human skin expresses only *FADS2* while mice and all other animals' skin expresses only *Scd1*. Both *SCD1* and *FADS2* are expressed and their resulting enzymes are active in liver and other organs of both humans and mice. Mouse: Scd1 mediates 18:0 conversion to 18:1n-9 and 16:0 conversion to 16:1n-7; Human: FADS2 mediates conversion of 16:0 to 16:1n-10 but has no effect on any other saturated fatty acid (e.g. 18:0 no enzymatic activity).