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Polyunsaturated fatty acid biosynthesis pathway and genetics. implications for interindividual variability in prothrombotic, inflammatory conditions such as COVID-19☆,☆☆,★,★★

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ABSTRACT

COVID-19 symptoms vary from silence to rapid death, the latter mediated by both a cytokine storm and a thrombotic storm. SARS-CoV (2003) induces Cox-2, catalyzing the synthesis, from highly unsaturated fatty acids (HUFA), of eicosanoids and docosanoids that mediate both inflammation and thrombosis. HUFA balance between arachidonic acid (AA) and other HUFA is a likely determinant of net signaling to induce a healthy or runaway physiological response. AA levels are determined by a non-protein coding regulatory polymorphisms that mostly affect the expression of *FADS1*, located in the FADS gene cluster on chromosome 11. Major and minor haplotypes in Europeans, and a specific functional insertion-deletion (Indel), rs66698963, consistently show major differences in circulating AA (>50%) and in the balance between AA and other HUFA (47–84%) in free living humans; the indel is evolutionarily selective, probably based on diet. The pattern of fatty acid responses is fully consistent with specific genetic modulation of desaturation at the FADS1-mediated 20:3→20:4 step. Well established principles of net tissue HUFA levels indicate that the high linoleic acid and low alpha-linoleic acid in populations drive the net balance of HUFA for any individual. We predict that fast desaturators (insertion allele at rs66698963; major haplotype in Europeans) are predisposed to higher risk and pathological responses to SARS-CoV-2 could be reduced with high dose omega-3 HUFA.

Introduction

The global COVID-19 pandemic caused by the SARS-CoV-2 virus is an enigma in part because of its extraordinary range of symptoms, from complete silence that may include person-to-person through-air transmissibility to respiratory failure and death within days of diagnosis. The term “cytokine storm”, previously limited to technical journals, has made its way into the popular press because of the severity of runaway inflammation [1]. An additional defining event is widespread thrombosis, with pathological manifestations in the lung similar to SARS and MERS [2]. Platelet–fibrin thrombi in small arterial vessels are consistent with a coagulopathy. In the end stage, multiple organ failure with severe liver damage is found, consistent with thrombotic microangiopathy [3, 4]. Both inflammation and thrombosis are mediated by signaling molecules derived from highly unsaturated fatty acids (HUFA) or more precisely the relative mix of them present at any one time in membranes.

Beyond the general inflammatory/prothrombotic potential of the HUFA milieu, the spike protein of the (2003) SARS-CoV virus induces cylooxygenase-2 (COX-2), one of the key synthetic enzymes for eicosanoid synthesis [5]. Moreover, induction of COX-2 may be required for efficient early stage replication of mouse hepatitis virus, also a coronavirus [6]. Insofar as this is true for SARS-CoV-2, individuals with a robust COX-2 response to viral COX-2 induction and thus supportive of the rapid replication of the virus, would be particularly susceptible to a prothrombotic/proinflammatory HUFA milieu. Inhibition of COX-2 via known inhibitors (e.g. celecoxib (Celebrex®)) at the early infection stage would be expected to reduce viral replication. Selective COX-2 inhibitors are effective against arthritis as are high dose omega-3 HUFA [7], and randomized controlled trial (RCT) evidence indicates regular consumption of omega-3 rich salmon in the context of an “anti-inflammatory diet portfolio” reduces rheumatoid arthritis symptoms [8].

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Most selective COX-2 inhibitors were removed from the market because of enhanced thrombotic events, ascribed to rebalancing of the eicosanoid milieu toward thromboxanes [9] and thromboxane A2 production via COX-1 [10]. Because severe COVID-19 appears to be an inherently prothrombotic event, we would not expect selective COX-2 inhibitors to be effective against it and possibly exacerbate symptoms. However, a balanced HUFA milieu may be particularly important for avoidance of a COX-2-enhanced cytokine storm or the hypercoagulopathy with features characteristic of a thrombotic storm [7]. Inherited genetic risk factors can enhance or have an additive effect in increasing the risk of thrombotic events during hypercoagulable periods such as severe COVID-19. For instance, increased risk of thrombotic events and recurrence occur in patients with homozygous and compound heterozygous for Factor V Leiden (FVL) and prothrombin G20210A mutations [11, 12]. Patients with FVL mutation displayed higher levels of D-dimer and fibrinogen-fibrin degradation products in plasma [13].

We review here some of the latest genetic, nutritional, and related factors that drive the balance of membrane HUFA toward or away from proinflammatory, prothrombotic potential, that may contribute to the severity of disease.

HUFA function as components to impart physiochemical properties in membranes and lipid droplets, and as precursors for signaling molecules. Physicochemical properties are most important for support of normal membrane function. Phospholipid molecular profiles adapt based on the nutritional supply of the energetically precious fatty acids according to principles yet to be fully determined; changes in dietary fatty acids certainly influence the fatty acid profile of the membrane. Signaling is mediated by HUFA release from membranes via phospholipases. In some cases this is the rate limiting step for synthesis, while in others the free fatty acid (FFA) milieu precedes activation of the synthetic enzymes [14]. In either case, the mixture of precursor HUFA for eicosanoid and other oxylipin signaling molecules is critical as they are competitive substrates for biosynthesis.

Oxylipins, more specifically eicosanoids and docosanoids, modulate many aspects of overall physiological function. The relative mixture of circulating HUFA has long been known to mediate clotting and inflammation via eicosanoids. In the last two decades, the role of docosanoids in the resolution phase of inflammation has been at least partially elucidated. Based on numerous well established principles, the relative mix of membrane HUFA shifts the balance on the continuum of pro- vs anti-inflammatory state. HUFA-derived signaling also influence thrombotic tendency.

Among the HUFA, a guiding principle is that arachidonic acid (AA) is precursor to mostly prothrombotic/pro-inflammatory signaling molecules, while the omega-3 HUFA eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA) are generally antithrombotic/anti-inflammatory. The omega-3 s generally inhibit AA conversion to signaling molecules, and the omega-3 s are themselves converted to mediators that promote the resolution phase of inflammation. Also generally antagonistic to the actions of AA-derived products is the omega-6 HUFA 20:3n-6, dihomo-gamma-linolenic acid (DGLA), the immediate precursor of AA via FADS1-catalyzed 5-desaturation; it is also precursor to the anti-inflammatory [15, 16], potently vasodilatory, PGE1 [17]. We recognize that the concept that excess AA predisposes to disease while omega-3 s counteract this effect is a simplification of complex biochemistry for which studies of intermediate markers are ambiguous, especially for inflammation with respect to cardiovascular disease [18, 19], though recent high dose studies such as with EPA show important effects [20]. However, strong and consistent evidence supports the contention that diet and genetics influence the HUFA tissue profile as well as the biosynthesis of HUFA.

The biochemical pathways from precursor 18 carbon polyunsaturated fatty acids (PUFA) linoleic acid (LA, 18:2n-6) and alpha-linolenic acid (ALA, 18:3n-3) are presented in Fig. 1. Representations of the PUFA families transformed by the pathway in parallel are common and aptly illustrate that the two HUFA families are subject to the same sets of genes/enzymes and are thus in competition. A misleading aspect of this representation leads to the incorrect assumption that an increase in any upstream precursor causes an increase in products. From a net tissue content point of view, this is not the case. Many studies continue to be designed only to rediscover what has been known for decades.

- Omega-3. In apparently healthy, well-nourished adult humans, no amount of ALA or any precursor of DHA increases circulating [21] or breastmilk [22] DHA when LA is constant. Most of the precursors 18:3 (ALA), 18:4, and 20:5 have been tested multiple times [21], DPA at least once [23]. In other words, when ALA is increased against constant LA, the ratio of LA to ALA changes but circulating DHA does not. In rodents, increases in tissue DHA are small, tissue dependent, and is greater for HUFA [24-26] than ALA [27]. Clearly then, it is not true that the amount of HUFA depends on the omega-6 to omega-3 ratio, whether or not HUFA are present.
- Omega-6. Similarly, changes in dietary LA cause, at most, minor changes in tissue AA [27].

However, neither the amount of DHA nor AA is “tightly regulated”, in the same sense as for instance calcium concentrations are tightly regulated. Both DHA and AA concentrations are easily altered over wide ranges by dietary intervention without acute effects, and even by genotype.

- DHA, DPA, and EPA circulating concentrations and LA respond reciprocally. Reduction in dietary LA increases all omega-3 HUFA including DHA [28, 29].
- AA concentrations decrease in response to decrease in LA below about 4% of calories, depending on the ratio of LA to ALA [29].

Put another way, only 2 ways are known to increase circulating DHA status in humans: 1) consume (preformed) DHA, or 2) lower dietary LA.

The levels of specific tissue fatty acids are maintained by numerous mechanisms within broad ranges. Mammalian PUFA requirements arise because the capacity to introduce double bonds between the n-6 and n-7 positions, and the n-3 and n-4 positions in any normal (straight chain) fatty acid present in plants and lower animals has been lost in mammals (n is the number of carbons in the linear chain), presumably because mammalian diets always contain sufficient quantities of these precursors. The inaccurately named “essential fatty acids” linoleic acid (18:2n-6; LA) and alpha-linolenic acid (18:3n-3; ALA) supply most of this part of the molecule because of their prevalence in the food supply. They are inaccurately named for many reasons [30-32], among which unlike other nutrients labeled “essential” they can be completely replaced in a healthy diet [33, 34]. Functional characterization molecular studies in the last 20 years have shown that the fatty acid desaturase (FADS1 and FADS2, located at 11q12–13.1) and elongase genes (ELOVL2 at 6p24.2 and ELOVL5 at 6p12.1) mediate the endogenous biosynthesis of HUFA. A third similar gene, FADS3 (also at 11q13.1), introduces a *cis* double bond into a 4(E) (trans) ceramide at the 14–15 position to yield sphingadienine [35], and may have some role in altering fatty acid levels in development [36]. Our purpose is to integrate the known biochemical and genetic control of HUFA levels to describe in part how changes in diet in the context of genotype alter the mixture of HUFA available for signaling, thereby defining the range of inflammatory and thrombotic potential of individuals, with an eye toward possible relevance to insults such as COVID-19. We first review modern genetics relevant to HUFA biosynthesis.

Human FADS and ELOVL genomic localization and structure

The paralogous FADS gene cluster evolved by gene duplication events, and localizes to the long arm of human chromosome 11 at the cytogenetic location 11q12–13.1 [37]. The three FADS (FADS1, FADS2

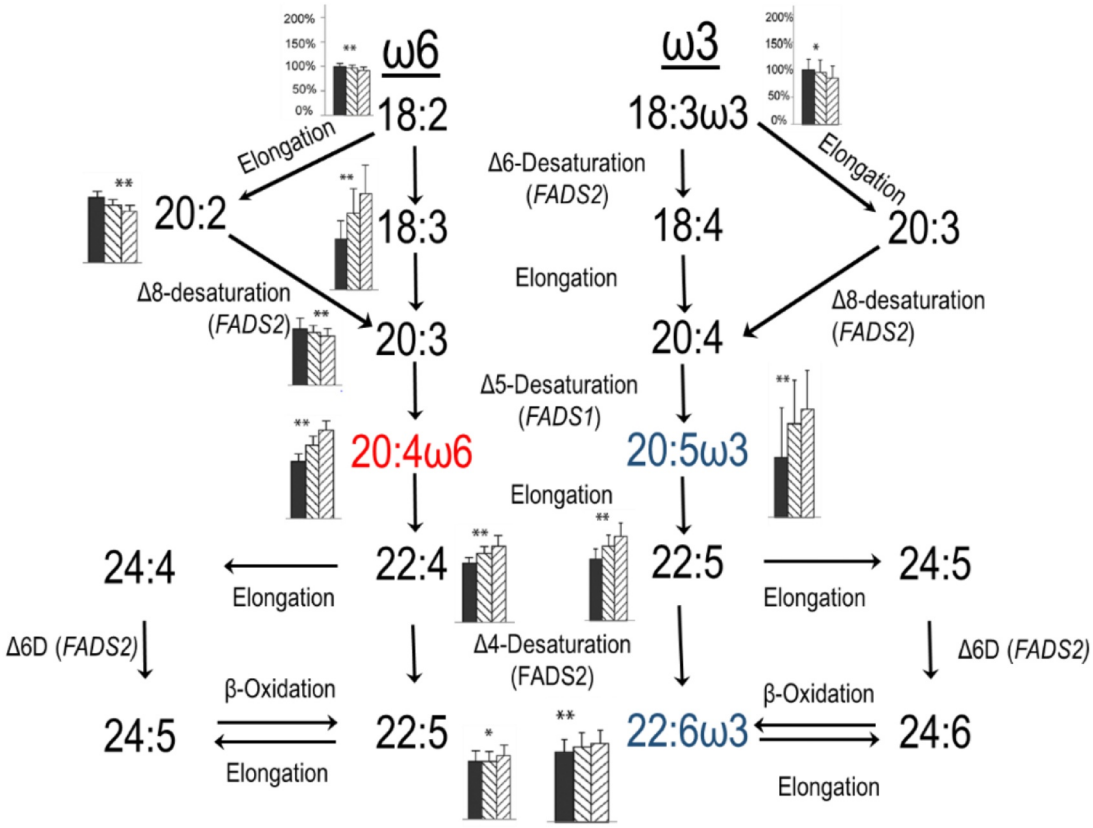

Fig. 1. Biochemical pathways for biosynthesis of highly unsaturated fatty acids from the 18 carbon precursors. The bar graphs alongside fatty acids are the relative amounts in plasma PL in the three genotypes (DD, ID, II, left to right) at the ra66698963 Indel locus in a population of 1504 free living participants in Beijing. $^{**}p < 0.05$ for all bars different from one another; $^{*}p < 0.05$ for ID different than II.

and FADS3), cluster within 92.6 kb genomic region flanked by FEN1 and RAB3IL1 (NCBI release# GRCh38.p13). FADS1 spans 17.3 kb, FADS2 spans 51.1 kb and FADS3 spans 18.7 kb of genomic DNA (NCBI release# GRCh38.p13). The classical, functional, FADS1 and FADS2 both consist of 12 exons and encode 444-amino acid (aa) peptides with estimated molecular mass of 52.0 kDa and 52.3 kDa, respectively [37-39]. A high degree of polypeptide sequence identity exists between FADS1 and FADS2 (61%). In the current NCBI database, human FADS1 (GenBank accession NM_013402) is represented by 501-aa protein (NP_037534.5), which is 57-aa more than the functional and classical FADS1 (444 aa). The function of 501-aa protein is not yet characterized. FADS3, is the third member of the FADS gene family, also with 12 exons and encoding a putative protein of 445-aa with estimated molecular mass of 51.1 kDa [37]. All three FADS contain the N-terminal highly conserved cytochrome b5 domain (HPGG) as electron donor and three histidine motifs HDFGH, HFQHH, QIEHH (FADS1); HDYGH, HFQHH, QIEHH (FADS2); and HDLGH, HFQHH, QIEHH (FADS3). All three FADS are extensively spliced and the splice variants are evolutionarily conserved [40-43].

The elongation of very long chain fatty acids-like (ELOVL) family consists of seven enzymes (ELOVL 1–7). ELOVL2 and ELOVL5 are involved in the biosynthesis of HUFA less than 24 carbons in length [44]. ELOVL2 localizes to the short arm of chromosome 6 at the cytogenetic location 6p24.2, spans 64 kb of genomic DNA, encodes 296-aa protein (NM_017770.4; NP_060240.3). In silico analysis of the protein sequence of ELOVL2 using a simple modular architecture research tool (SMART) software [45, 46] shows seven transmembrane regions (spanning residues 28–50, 62–84, 116–135, 142–164, 179–201, 208–225, and 235–254). ELOVL2 includes four amino acid motifs characteristic of elongases (KSVEFLDT, HVYHH, HILMYSYY and TQAQLVQ). ELOVL5 localizes to the short arm of chromosome 6 at the cytogenetic location 6p12.1, spans 82 kb of genomic DNA, encodes 299-aa protein (NM_021814.5; NP_068586.1). In silico analysis of peptide sequence of ELOVL5 using SMART software shows seven transmembrane regions (spanning residues 26–48, 65–87, 110–132, 139–158, 168–187, 207–224, and 229–251). ELOVL5 includes four amino acid motifs characteristic of elongases (KLIEFMDT, HVYHH, HVLMYSYY and TQGQLLQ).

FADS and ELOVL biochemical functions

Fatty acid desaturases (FADS2, FADS1) perform dehydrogenation reactions with strict stereo and regioselectivity resulting in the introduction of *cis* (Z) double bonds (DB) into fatty acid hydrocarbon chains [47-49]. The classical FADS2 is a multifunctional enzyme (Table 1) which catalyzes even numbered Δ4-, Δ6- and Δ8-desaturation towards normal even chain fatty acids (n-ECFA), normal odd chain fatty acid (n-OCFA) and monomethyl branched chain fatty acids (BCFA) substrates including eight polyunsaturates, two monounsaturates, one saturate, one n-OCFA, and four BCFA [44, 49-53]. Human FADS2 mediates the conversion of 16:0 to 16:1n-10 but has no enzymatic activity towards 18:0 [44]. FADS1 has shown Δ5-desaturation activity towards five polyunsaturates and Δ7-desaturation activity towards one monounsaturate [44, 52, 53] . ELOVL2 has substrate specificity for four PUFA with chain lengths 20 and 22 carbons [54], while ELOVL5 has substrate specificity for four PUFA with chain lengths 18 and 20 carbons [54].

11q13 Genomic Region. Human chromosome 11q13 is known to contain hotspots for viral integration, harbor fragile sites, copy number variations (CNV), and several disease phenotypes, including several types of cancers [55-58]. The 11q13 locus is well known to contain fragile sites that are prone to breakage. This region has a high frequency

Table 1
FADS2 catalyzes reactions of at least 16 substrates at three positions.

Desaturation Position	Substrate
Δ4-desaturation	*22:5n-3→22:6n-3*
	22:4n-6→22:5n-6
Δ6-desaturation	*18:3n-3→18:4n-3*
	18:2n-6→18:3n-6
	18:1n-9→18:2n-9
	24:5n-3→24:6n-3
	24:4n-6→24:5n-6
	16:0→16:1n-10
	17:0→17:1n-11
	iso*16:0*→iso*6Z-16:1*
	iso*18:0*→iso*6Z-18:1*
	iso*17:0*→iso*6Z-17:1*
	*ante*iso*17:0→ante*iso*6Z-17:1*
Δ8-desaturation	*20:1n-9→20:2n-9*
	20:3n-3→20:4n-3
	20:2n-6→20:3n-6

of repeats, low GC content, two folate-sensitive fragile sites, potential secondary structures, and a high incidence of cytogenetic and molecular alterations in several cancers [55, 58-61]. Structural variations (SV), which alter chromosomal structure and the DNA copy number, are increasingly recognized as major contributors to genome variability [62]. Copy number changes at 11q13 region are associated with several cancer phenotypes such as primary melanoma [63], breast cancer [64-70], head and neck cancers [71-73], bladder, lung, oral squamous cell, liver and esophageal cancers [57, 74], cervical cancer [61], endocrine tumors (ETs) of pancreas and duodenum [75], ovarian cancer [74] and prostate cancer [76]. In certain disease conditions, the 11q13 copy number changes span several mega bases (Mb) of DNA [77, 78]. Recently, our prediction of an alternative FADS2 mediated MUFA pathway [149] was confirmed in liver and lung cancer cells [79]. FADS2 mediated the production of sapienic acid (16:1n-10) [79, 80]. Anomalous loss of PUFA desaturase activity has been reported in several cancer cells, including MCF7, HeLa and K562 [53, 81, 82]. The loss of FADS2 activity causes cancer cells to shut down HUFA biosynthesis thereby affecting eicosanoid and docosanoid precursor synthesis and normal cell signaling [53, 81]. Earlier we have shown that this metabolic defect can be corrected by transfection of functional FADS2 [53]. Despite the key importance of FADS2 and the loss of its function in several cancer cells, the consequences of FADS2 loss have not been investigated despite the emergence of 11q13 amplicon.

***FADS* and *ELOVL* Genetics.** Candidate gene studies and genome-wide association studies (GWAS) both yield strong evidence that *FADS* and *ELOVL* genes are related to PUFA levels [83-90] and human disease phenotypes, e.g. cardiovascular disease (CVD) [91, 92], major depressive disorder [93, 94], metabolic syndrome [88, 95], obesity [96], atopic dermatitis [83], aging [97, 98], spinocerebellar ataxia 38 (SCA38) [99]. FADS genetic studies also showed population differences in the capacity to biosynthesize HUFA [95, 100]. Traditional human populations have been described that are analogous to herbivores (vegans) and carnivores (Natives of the Canadian Arctic) [101]. Due to the loss of FADS2 activity, carnivores, such as cats, have lost the metabolic capacity to synthesize HUFA, presumably due to the ubiquitous presence of AA and DHA in a meat-based diet. In contrast, herbivores intake very little AA and DHA and must have a robust metabolic capacity to synthesize all they need, especially at life stages of high demand such as the brain growth spurt.

Evidence from FADS genetic studies indicates that the regulatory non-protein coding SNPs are strongly associated with interindividual differences in converting precursors to physiologically active HUFA, especially AA, EPA and DHA [85]. We cite a handful of examples. A *FADS* association study showed a 11 SNP haplotype found in 26% participants is associated with 29% of the variation in AA levels [83, 85], subsequently replicated by many other groups [85, 95, 102-106]. A distinct *FADS* haplotype defined by 28 SNPs is associated with an enhanced ability to biosynthesize HUFA [107]. *FADS* SNPs are associated with maternal, infant, and child health phenotypes, for instance, plasma lipids in infants [108], gestational duration [109], perinatal depression [110], attention/hyperactivity and learning [111, 112], cognition and intelligence [113, 114] and blood pressure in young children [115]. A recent study showed mothers who were heterozygous or homozygous for the minor alleles of FADS1 and FADS2 SNPs had infants with a greater head circumference and birth weight [116]. A GWAS showed a striking adaptation of the Greenland Inuits attributed to high n-3 FA intake [117], recently expanded to the first Americas [118]. The InCHIANTI GWAS identified a minor allele of rs174537 accounting for 18.6% genetic variance in AA levels, confirmed in an independent sample from the GOLDN study [119]. A *FADS2*-promoter SNP (rs968567) enhancing *FADS2* expression was discovered [120]. A whole genome analysis of the Chinese population showed rs28456 to be associated with AA [121]. ELOVL2 and ELOVL5 maternal genetic variants were associated with PUFA levels in breast milk [89]. Taken together these disparate studies all point to HUFA pathway polymorphisms as key modulators of health.

Insertion-Deletion (Indel) Polymorphisms and rs66698963. In humans, highly polymorphic insertion/deletions (Indel) are the second most frequent polymorphisms after SNPs and are increasingly recognized as functional contributors of genetic variation influencing human phenotypes [122]. Largely because of the technical difficulties in genotyping and calling Indels from short-read sequencing, their functional effects are understudied [122]. One example in the FADS gene cluster appears to be a very strong modulator of circulating PUFA levels and is under selective pressure, presumably by diet. The rs66698963 is a 22 base pair (bp) regulatory polymorphism in FADS2 intron 1 nearby a sterol response element (SRE), discovered by our group [123]. Experimentally determined rs66698963 genotype frequencies from our two clinical trials [100, 124] show among South Asian Indians that II alleles are found in 67.5%, in Chinese 45.8%, whereas in a US population it was only 18% (Table 2). Commonly reported non-protein coding SNPs within *FADS2* (rs174575, rs174570 and rs1535), and thus the nearby Indel rs66698963 are associated with increased IQ scores, blood FA levels and complex diseases. SNPs rs174575 and rs174570 are within 600 and 6000 bp upstream from the *FADS2* Indel, respectively [84, 117, 125]. In humans, common SNP variants are often found to follow Indels [126], suggesting that rs174575, rs174570 and/or rs1535 are tags for the functional genomic Indel that directly modulates binding at the nearby SRE. Our early data established that under basal conditions, human lymphoblasts with the DD genotype had the lowest expression of FADS1, with II the highest and ID in the middle [123]. Subsequent studies of circulating PUFA in free living humans, that is, apparently healthy individuals sampled but not enrolled in any study, confirmed the prediction that the reaction catalyzed by FADS1, 20:3→20;4 (DGLA→AA), DD would favor precursors and II favor products [100, 124].

Importantly, genotype at this locus exerts positive selectivity likely based on the PUFA in their diets, whether primarily plant-based 18 carbon precursors that must be converted to HUFA, or ample HUFA consumed from animal and seafood [100]. Positive selectivity directly indicates that those with a genotype mismatched to their conditions of

Table 2
Experimentally determined rs66698963 genotype frequencies from three countries.

	I/I (%)	I/D (%)	D/D (%)
Indians (South Asia)	67.5	29.5	3
Americans	18	39	43
Chinese	45.8	42.4	11.8

existence leave fewer offspring. From a contemporary health perspective, we interpret this to mean that genotypes mismatched to diet are dangerous, whether due to chronic disease or pandemic events.

We return to the human endogenous biosynthesis pathway from 18:2n-6 and 18:3n-3 PUFA to HUFA (Fig. 1). Using data from a study in 1504 participants in Beijing [124], we post next to each PUFA the experimentally determined plasma PL FA levels for each rs66698963 genotype normalized to the DD genotype (Fig. 1). The genes mediating the synthesis of HUFA contribute wide variability to the efficiency of HUFA synthesis. The Δ6-desaturase [D6D coded by FADS2] metabolizes both 18:2n-6 and 18:3n-3, resulting in the synthesis of 6,9,12–18:3 and 6,9,12,15–18:4, respectively. This initial D6D step is widely regarded as the rate-limiting for HUFA biosynthesis, however, recent data indicate that other steps in the pathway can limit HUFA levels [44]. Both AA and EPA can be further elongated and desaturated to yield 22:5n-6 and DHA, respectively. We established that the last step is via Δ4-desaturation [51], also mediated by FADS2 similar to many other organisms [127, 128]; the widely accepted peroxisomal pathway worked out in rodents is also shown and is likely to operate as well [129].

Clear patterns are evident from rs66698963 genotypes (Fig. 1). The n-6 PUFA 18:2, 20:2, and 20:3, and n-3 PUFA 18:3 all decrease from DD to ID to II, which we refer to as a *precursor* pattern. In contrast, all other measured PUFA increase from DD to ID to II, a *product* pattern. Organized another way, the precursor-product pattern pairs are observed in the reactions mediated by FADS2 (18:2n-6→18:3n-6) and FADS1 (20:3n-6→20:4n-6), but not the desaturations of the C22 HUFA. We previously showed that the I allele is associated with an increase in FADS1 gene expression but activation of the nearby SRE (sterol response element) caused both FADS1 and FADS2 expression to increase [123], which predicts the precursor-product pattern if expression is taken as a proxy for activity. Taken together, these data are consistent with the I allele increasing desaturase activity in a dose dependent manner for FADS1.,

Fig. 2A and 2B are a hypothetical merging of experiment with theory to explain the role of human genetics on circulating AA (20:4) levels in individuals. Studied in rats [29], panel A shows the response of plasma phospholipid AA with increasing dietary LA, at a dietary ratio of LA to ALA (omega-6 to omega-3) of about 9.4. This latter value is similar to the LA/ALA ratio in the edible oil supply of industrialized nations consuming primarily seed oils rich in LA, including all industrialized nations at the close of the 20th century, and most developing nations at the present time. PL AA rises rapidly from 5% to over 15% where it plateaus at 3–4% of diet LA. The current intake of LA in the US is about 17 g/d for adult men [US DGA 2015] or 7.6 en%, down from a peak of 20 g/d or 9 en% in 2011–2012 [130]. Ascribing this decrease to the introduction of high oleic oils, as is likely, ALA is also lower in most high oleic oils and thus the ratio of about 9.4 likely holds and the curves apply to the changed levels. In rats, these data show that circulating AA levels would not have changed with this reduction, illustrating the central point that not all changes in precursor fatty acids result in a change in tissue fatty acids. Though no data of similar density of LA intake are available for humans, the similarity of the enzymes between rats and humans, and the similar response of human plasma AA to reductions in LA, is strong support for the hypothesis that the human curve is similar [131].

The rs66698963 indel polymorphism appears to be unique to modern humans. Both Neanderthal and Denisovan DNA has the I/I (insertion) genotype [100]. Models of its response must either study the polymorphism directly or rely on hypothetical inferences about responses from well controlled animal studies.

Noting the strong relationship between circulating AA and the indel genotype, we cast a hypothesis about the relative response of the three human genotypes (panel B). Data on AA levels for free-living humans (n = 1504) in the Beijing China region showed a strong relationship to genotype (panel C). The ratio of 20:4/(20:5 + 22:6) is 32% greater for I/I compared to D/D. We note that the measured level of plasma phospholipid LA averaged 36% which is higher than most Western populations (e.g. [132]) and thus suggests that their intake of LA is well into the AA plateau region, above about 4% LA. Bridging the two datasets are hypothetical curves intended to describe the plasma PL AA response as a function of dietary LA intake directed by genotype. Our hypothetical curves predict that at a LA/ALA ratio of 9.4 or greater, AA levels measured for the three genotypes reflect plateau AA levels. This hypothesis also explains why the relationship of AA to genotype is remarkably strong.

As noted in the introduction, the relative amounts of AA and other HUFA is regarded as a key determinant of net signaling for inflammation and thrombosis. We calculate the relative ratios of AA (20:4) vs its FADS1 mediated precursor and vs all downstream HUFA (Fig. 3A and 3B). Our results show that the ratio of 20:4 to 20:3 nearly doubles, increasing 84% from DD to II genotype. Similarly, but less intuitively obvious, the ratio of 20:4 to the sum of other HUFA increases by 47% from DD to II. The extent to which these differences predispose free living humans toward or away from disease is not known, but presents the compelling hypothesis to test whether one homozygous genotype predisposes to chronic disease.

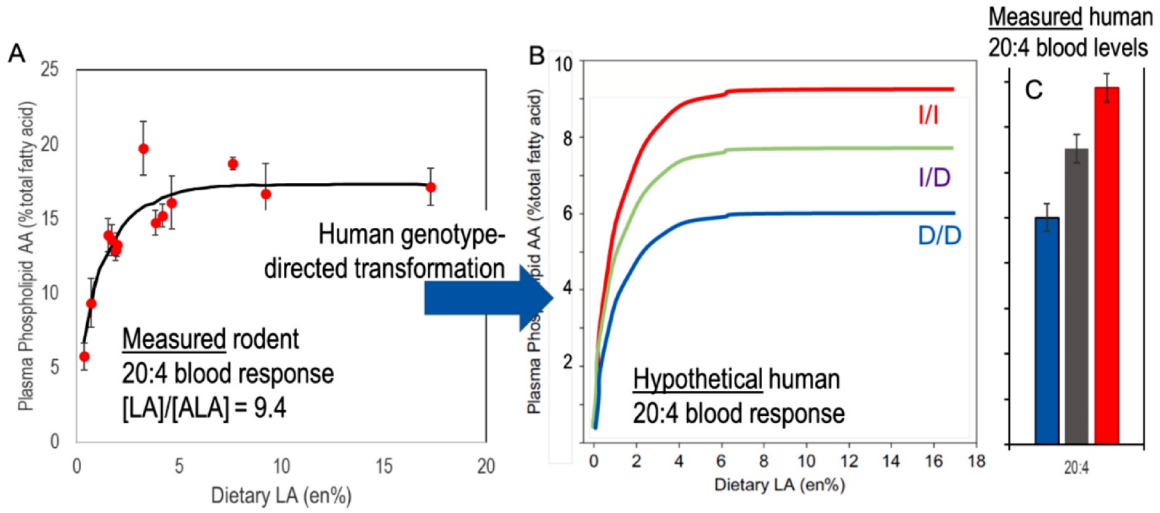

Fig. 2. A) Measured response of rat plasma PL AA (20:4n-6) as a function of dietary PUFA, LA and ALA in a fixed proportion of 9.4:1. The plasma AA rises to reach a plateau at 3–4%en (energy). B) Hypothetical response of the three rs66698963 Indel genotypes to increasing dietary PUFA. Three different plateau levels are achieved corresponding to C) the measured blood levels found in the Chinese cohort. Panel A redraw from Gibson, PLEFA 2013.

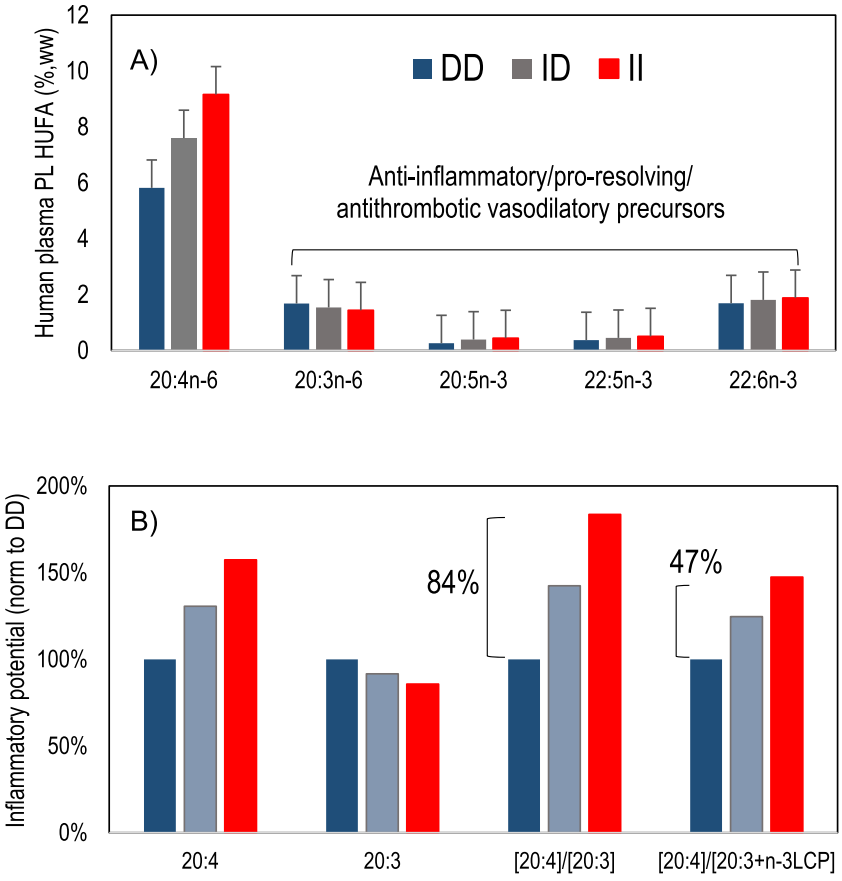

Fig. 3. Human plasma HUFA relative to rs66698963 Indel genotype and inflammatory potential. A) AA (20:4n-6) increases dramatically by genotype (similar to Fig. P1C), as well as all n-3 HUFA), while 20:3n-6 decreases. B) Normalized to their respective DD labels, the ratio of AA to precursor 20:3 is different by 84% while the ratio of 20:4 to the sum of all anti-inflammatory/proresolving precursors increases by 47%. High dietary 18:2n-6 drives the excess 20:4 increase for the I allele.

Why *FADS* genotypes are important: *translation*

It is widely assumed that human endogenous biosynthesis of DHA from precursors is inherently near zero. This is not correct: the factor driving very low DHA synthesis is high intakes of LA in the background diets in all studies – abnormal compared to any known human diet prior to industrialization and the rise of high LA seed oils. LA is antagonistic with the last steps of DHA biosynthesis competing for FADS2 for the last desaturation prior to DHA synthesis by either accepted pathway. Reduction of LA removes an effective block and circulating DHA rises. Key data from our RCT in Malawi [133] demonstrate that a conventional ready-to-use-therapeutic food (RUTF) high in LA causes a 25% drop in DHA over 4 weeks, while a high oleic (HO)-RUTF with balanced LA and ALA and with oleic acid replacing LA stabilizes DHA and causes a 60% increase in EPA, by reducing metabolism competition of LA with ω3.

We envision that individuals with II genotype will have a greater drop in DHA when put on diets high in LA, similar to conventional RUTF. Twentieth century commercially produced conventional seed oils, sunflower, safflower, peanut, grapeseed, cottonseed and corn, contain high levels of LA; individuals with a genetic make-up that rapidly converts precursors to products are likely to be vulnerable to AA-related ill-health when adopting a diet rich in LA which severely reduces the synthesis of anti-inflammatory ω3 HUFA. As importantly, n-6 PUFA compete with, and antagonize against, incorporation of ω3 PUFA into tissues [134], inhibiting incorporation of structural n-3 PUFA that are especially concentrated in neural tissue [135]. A re-evaluation of the traditional diet-heart hypothesis shows that with LA rich oils cholesterol decreases but the risk of death *increases* (-30 mg/dl cholesterol = +22% CVD death) [136]. Population differences at the 11q13 genomic locus exist and can contribute to significant genetic variability. RCT studies should take into consideration this important factor. Finally, the 21st century has seen widespread and increasing use of conventionally bred HO oilseeds with oleic acid replacing LA; the sole exception is HO canola in which oleic replaces ALA. Nearly 100% of US sunflower oil is HO, many peanuts (used in M&Ms® [137], for instance), and the major US oilseed crop, soybean, is rapidly increasing. These changes are driven mostly by the increased shelf-life and frying life of high oleic oils, though improved ω3 status through lower LA is likely an advantage.

Though ELOVL5 and ELOVL2 both elongate polyunsaturates, ELOVL2 is specific to elongation of C20 and C22[138]. The expression of the *ELOVL2* gene is different between European and Chinese populations in at least one GWAS [139], and ELOVL2 polymorphisms improve the correlation with circulating fatty acid levels [119, 140]. Importantly, considerable work has implicated methylation as a silencer of ELOVL2 expression [97, 141]. Methylation is tissue specific [142] and has recently been revealed as a molecular regulator of aging in the HUFA-rich retina [143]. Methylation at the ELOVL2 locus has been proposed as a measure of again in forensics [98] and the principle appears to be similar for chimpanzees[144]. The plasma kinetics of ^{13}C-DHA is strongly related to age[145], while EPA is only slightly related to age and AA is not [146, 147]. While these fatty acids are not immediate products of ELOVL2, it is tempting to speculate that methylation of this gene with aging plays a role. To our knowledge, no other gene in the biochemical pathway has been repeatedly related to aging.

Conclusions

Regulatory non-coding SNPs and rs66698963 Indel within FADS and ELOVL genes mediating the endogenous synthesis of HUFA are strongly associated with inter-individual differences in converting essential fatty acid precursors to physiologically active HUFA. Methylation clearly has a role in ELOVL2 function that would influence synthesis of EPA and possibly DHA.

Covid clearly is more dangerous as individuals age, and as well as

those with preexisting illnesses. Although omega-3 status is higher in older Americans, rising each decade to plateau in after age 60 [148], effects on metabolism with aging may compromise HUFA metabolism during illness. The weight of evidence suggests that HUFA balance has some role to play in most illnesses and especially those that are known to be related to HUFA-derived signaling molecules such as inflammation and thrombosis. The shift of modern diets to higher n-6 over n-3 is recognized as a major risk factor for lifestyle-related diseases, such as cardiovascular disease and diabetes via inflammation and specific issues. More importantly, n-6 LA in many seed oils never present in human diets prior to industrialization overwhelm and suppress synthesis, tissue incorporation, and downstream signaling of n-3 EPA and DHA. Individuals with high-converting genotypes (e.g. II genotype = fast desaturators) are likely to show a marked increase in proinflammatory, prothrombotic ω6 AA, possibly based on other genetic factors. They are particularly at risk.

Author statement

All authors contributed equally to this work.

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