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Fatty acid metabolism: Implications for diet, genetic variation, and disease

Janel Suburu[b], **Zhennan Gu**[a,b], **Haiqin Chen**[a], **Wei Chen**[a], **Hao Zhang**[a], and **Yong Q. Chen**[a,b,*]

Yong Q. Chen: yqchen@wakehealth.edu

[a]State Key Laboratory of Food Science and Technology, School of Food Science and Technology, Jiangnan University, Wuxi 214122, P.R. China

[b]Department of Cancer Biology, Wake Forest School of Medicine, Winston-Salem, North Carolina

Abstract

Cultures across the globe, especially Western societies, are burdened by chronic diseases such as obesity, metabolic syndrome, cardiovascular disease, and cancer. Several factors, including diet, genetics, and sedentary lifestyle, are suspected culprits to the development and progression of these health maladies. Fatty acids are primary constituents of cellular physiology. Humans can acquire fatty acids by *de novo* synthesis from carbohydrate or protein sources or by dietary consumption. Importantly, regulation of their metabolism is critical to sustain balanced homeostasis, and perturbations of such can lead to the development of disease. Here, we review *de novo* and dietary fatty acid metabolism and highlight recent advances in our understanding of the relationship between dietary influences and genetic variation in fatty acid metabolism and their role in chronic diseases.

Keywords

De novo lipogenesis; Dietary fatty acids; Genetic variation; Fatty acid metabolism

Introduction

The epidemic spread of obesity and metabolic syndrome is raising public health concerns across the globe. The factors that distinguish these diseases are also known contributors to cardiovascular disease and cancer, the two most common causes of death in the United States (Hoyert and Xu, 2012). Epidemiologic studies have shown an increased prevalence of these diseases in immigrating populations to Western societies (Nasseri and Moulton, 2011; Seeff and McKenna, 2003). One of the major hypotheses to explain this observation is the abrupt and dramatic change in diet upon emigration, particularly changes in dietary fatty acid consumption. A prevailing body of literature suggests not only the quantity, but more importantly, the quality, of dietary fat consumption modulates disease (Berquin et al., 2011; Berquin et al., 2007; Suburu and Chen, 2012). Specifically, dietary omega-6 polyunsaturated

*Corresponding author. Jiangnan University State Key Laboratory of Food Science and Technology School of Food Science and Technology, 1800 Lihu Ave Wuxi 214122, China. Tel./fax: +0086 510 8591 2155.

fatty acid (PUFA) can be pro-inflammatory mediators, while omega-3 PUFA acts as anti-inflammatory mediators (Serhan and Petasis, 2011). As such, tipping the balance of an immigrant's dietary consumption can lead to a chronic state of inflammation and promote the development and progression of cardiovascular disease and cancer.

New evidence suggests various populations may differentially metabolize dietary fatty acids (Teslovich et al., 2010), implying that the risk for chronic inflammation, metabolic syndrome, and cardiovascular disease may be inheritable. Even the progression of cancer, which is well known to be a disease of genetic alterations, can be exacerbated by pro-inflammatory lipid metabolism (Wang and Dubois, 2010). Discrepancies observed in the incidence of cardiovascular disease and cancer in various ethnic populations have been attributed to socioeconomic variance (Marmot et al., 2012). However, more recent data suggests genetic diversity in the form of single nucleotide polymorphisms (SNPs) found in several lipid metabolism genes may be a major contributing factor to these epidemiological health disparities (Illig et al., 2010; Kathiresan et al., 2009; Teslovich et al., 2010). Despite the potential inheritance of genetic risk factors for cardiovascular disease and cancer progression, advancements in the new field of metabolomics is yielding promising work to identify metabolic biomarkers of disease that may fuel diagnostic testing and/or predict health outcome. The purpose of this article is to review *de novo* and dietary fatty acid metabolism and highlight the most recent findings in genetic variation found in fatty acid metabolism genes as they relate to dietary fat consumption and various diseases.

Fatty Acids: a biological necessity

Fatty acids are fundamental molecules of cellular biology. Composed of hydrogenated carbons with a carboxyl moiety at the alpha carbon, mammalian fatty acids are divided into three major groups based on the quantity of double bonds found within the carbon chain: saturated fatty acids (SAFA), monounsaturated fatty acids (MUFA), and polyunsaturated fatty acids (PUFA). SAFA are fully hydrogenated, containing zero double bonds. They are a primary constituent of glycerolipids as well as phospholipids and sphingolipids found in cellular membrane structures. SAFA may also act as post-translational modifiers, thereby dictating the activity and location of cellular signaling proteins. MUFA contain a single double bond, most commonly found between the 9^{th} and 10^{th} carbons from the alpha carbon, and occasionally between the 7^{th} and 8^{th} carbons. MUFA are also primary constituents of cellular membrane structures and glycerolipids. PUFA have more than one, and as many as six, double bonds in their carbon chain. PUFA are found in phospholipids of membrane structures, and may also act as precursors to a variety of lipid signaling molecules. The most unique characteristic of PUFA metabolism is the inability for mammals to synthesize them *de novo*. While mammals express the necessary enzymes to convert carbohydrate and protein-derived carbons into SAFA and MUFA, they lack the desaturase enzymes required for producing the limiting substrate for PUFA synthesis. Therefore, PUFA are considered essential fatty acids that must be acquired from the diet. It is important to note that not only the degree of saturation, but also the carbon chain length can differentiate fatty acids and their biological roles. Within each class of fatty acids the carbon chain length may vary greatly, with as few as 12 and as many as 30 carbons. The chain length of fatty acids in cellular membrane can modify the membrane properties, such as fluidity and formation of microdomains and signaling platforms, ultimately altering susceptibility to cell death or survival (Iwabuchi et al., 2010; Sassa et al., 2012).

Unlike PUFA, SAFA and MUFA may be acquired from the diet or produced *de novo*. Despite identical biochemical structures, it remains unclear whether dietary and *de novo* fatty acids are equivalent or two separate pools of fatty acids used for distinct biological functions in the body. A number of features distinguishing *de novo* and dietary fatty acid

metabolism directed questions of why dietary SAFA and MUFA are likely to fall short in compensating for impaired *de novo* fatty acid synthesis. First, the major biological function of fatty acid synthesis is to store energy from carbohydrate-derived carbon precursors as compact fatty acids. This process occurs in the cytosol of cells and is performed by a series of enzymes beginning with the production of acetyl-CoA by ATP citrate lyase (ACLY). Acetyl-CoA is then metabolized by the rate limiting enzyme of the fatty acid synthesis pathway, acetyl-CoA carboxylase 1 (ACACA) to produce the limiting reagent, malonyl-CoA. The multifunctional enzyme, fatty acid synthase (FASN) then produces saturated, short (14:0) to medium (18:0) chain fatty acids by sequentially adding malonyl-CoA to the growing acyl chain through a series of biochemical reactions, with palmitate (16:0) representing about 80-90% of its total product (Jayakumar et al., 1995; Kuhajda et al., 1994). FASN-derived SAFA can be further modified by various elongation and desaturase enzymes. These *de novo* synthesized fatty acids can then be esterified and converted into triglyceride molecules for storage.

Expression of FASN is observed throughout the body, with the most prominent expression in the liver, brain, and abdominal adipose, where energy storages are important for cell survival during periods of physiological or pathological stress. In contrast, other tissues maintain a relatively low rate of fatty acid synthesis, and circulating fatty acids from the diet were believed to suffice as a sustainable source of fat for these tissue types (Jayakumar 1995 and Semenkovich 1995). However, more recent evidence suggests fatty acid synthesis plays a critical role in the function and survival of non-energy-storing tissues as well. Acylation of proteins regulates their activation, location, and propensity for receptor binding (Miura and Treisman, 2006); in particular, palmitoylation of Wnt was shown to be dependent on *de novo* fatty acid synthesis. Wnt palmitoylation facilitates its receptor binding (Janda et al., 2012) and thereby regulates its ability to activate downstream signaling proteins (Fiorentino et al., 2008). Studies of conditional, tissue-specific knockout of FASN in mice have shown that *de novo* fatty acids are constituents of endogenous lipid ligands (Chakravarthy et al., 2009a) and are required for PPARα activation in the liver (Chakravarthy et al., 2005), macrophage (Schneider et al., 2010), and hypothalamus (Chakravarthy et al., 2007). Additionally, conditional knockout of FASN in the heart of mice demonstrated that fatty acid synthesis regulates calcium signaling and adaptation to stress in the myocardium (Razani et al). Whole body knockout of FASN is embryonic lethal, as fertilized blastocysts fail to implant in the uterus (Chirala et al., 2003), suggesting fatty acid synthesis is critical for development and survival of rapidly proliferating tissues. Indeed, FASN is also critical for the proliferation and survival of most cancers (Menendez and Lupu, 2007), which utilize *de novo* fatty acids to facilitate membrane biogenesis (Swinnen et al., 2003) and prevent reactive oxygen species-induced apoptotic cell death by lipid peroxidation (Rysman et al., 2010). Whether FASN is most critical for its fatty acid products or possibly acts as a signaling protein itself is still unclear. Most *in vitro* studies can rescue the phenotype of FASN knockdown with addition of exogenous palmitate (Kridel et al., 2004; Migita et al., 2009; Rysman et al., 2010), while some cannot (Razani et al., 2011). Additionally, while dietary fat consumption can regulate *de novo* lipogenesis (Ringseis and Eder, 2011), no animal study has shown a phenotypic rescue of FASN knockout by dietary fat. This may possibly be attributed to the physiological differences between *de novo* and dietary fat metabolism.

Unlike *de novo* fatty acid metabolism where fatty acids can be immediately used inside the cell, dietary fatty acids require the presence of enzymes, transporters, and chaperone proteins to facilitate their absorption, transport, and uptake by cells in the body. Fatty acids absorbed from the gut are loaded onto lipoprotein particles in the form of triglycerides and enter circulation through the lymphatic system. Lipoprotein particles then bind to their respective receptors for cellular uptake. Release of the fatty acids from the lipoprotein

particles requires the activity of lipoprotein lipase (LPL) for fatty acid storage or energetic use in peripheral tissues, chiefly liver, muscle, adipose, and cardiac tissue; therefore, the use of dietary fatty acids by peripheral tissues is largely dependent upon the expression and activity of LPL (Mead et al., 2002; Merkel et al., 2002).

Following their release by lipase enzymes, free fatty acids can be modified by elongation or desaturation. The metabolism of *de novo* and dietary fatty acids can vary greatly; however, they may also compete as substrates for the same elongation and desaturation enzymes. Mammals possess seven known elongase enzymes (ELOVL1-7) with various substrate specificities that mediate the elongation of fatty acids through the addition of malonyl-CoA (Guillou et al., 2010). Recall that malonyl-CoA is produced by ACACA, the rate limiting enzyme of the *de novo* fatty acid synthesis pathway; hence, the activity of ACACA may contribute to both *de novo* and dietary fatty acid metabolism. Introduction of double bonds into fatty acids is mediated by the activity of the desaturase enzymes, SCD-1 (stearoly-CoA desaturase 1), FADS1 (fatty acid desaturase 1), and FADS2 (fatty acid desaturase 2), each of which insert a double bond at specific locations in the fatty acid carbon chain. Humans also possess a third FADS3 (fatty acid desaturase 3) enzyme; however, its function remains elusive. SCD-1 (also known as, delta 9 desaturase) is specific for the conversion of SAFA to MUFA, while FADS1 (delta 6 desaturase) and FADS2 (delta 5 desaturase) are specific to PUFA (Guillou et al., 2010); hence, SCD1 can metabolize both *de novo* and dietary fatty acids, while FADS1 and FADS2 are specific to dietary fatty acids. Enzymes known to be strictly responsible for *de novo* fatty acid metabolism include FASN, ELOVL1, ELOVL3, and ELOVL6, while enzymes that metabolize only dietary fatty acids include ELOVL2, ELOVL5, FADS1, and FADS2. Several enzymes participate in the metabolism of both *de novo* and dietary fatty acids, including ACLY, ACACA, SCD1, ELOVL4, and ELOVL7. Variation in any of these enzymes may lead to altered fatty acid metabolism and can modulate the propensity for the development and progression of various diseases (Guillou et al., 2010; Kihara, 2012).

Dietary Fat Metabolism Studies – The critical need for standardized methods

An exceptionally large and continuously growing body of literature has investigated the role of dietary fatty acids in disease progression, but conflicting results have lead to disparate conclusions, and for many, an elusive uncertainty of how dietary fatty acids modulate disease. Although the enzymatic pathways of dietary fatty acid metabolism are fairly well understood, new knowledge of the role of dietary fat in disease progression is hindered by several complexities in the design and methodology of research studies, consequently making it extremely difficult to identify causal roles for specific dietary fatty acids in disease. A major confounding factor throughout epidemiological research is the study design. There are two main approaches to investigating dietary and genetic influence on disease. The first approach distinguishes a population with common ailments and identifies common genetic variants and dietary habits that possibly modulate their phenotype. This approach is very common, but may unfortunately lead to biased results based on the concept of searching for significant data. An alternative to this method is the second approach, whereby the study distinguishes a population with specific genetic variants and identifies how specific dietary interventions modulate their phenotype (Perez-Martinez et al., 2012). This intervention-based approach is more controlled and can successfully address the direct influence of uniquely formulated diets (Shaw et al., 2009). It also focuses on the interaction between genetic signatures and metabolism, a topic we will return to later in this review.

Another concern for studies seeking to investigate dietary interactions with disease is that dietary fatty acids are never consumed in isolation. Whether researching humans or animal

models, the complexity of fatty acid composition in foods makes it very difficult to attribute a phenotype to any given fatty acid. Certain oils and foods may be enriched with particular fatty acids. For example, corn oil is enriched in linoleic omega-6 PUFA and olive oil is enriched in oleic MUFA (Beare-Rogers et al., 2001), but the biochemical make up of diets used in most studies is largely undisclosed, and as discussed previously, not all fatty acids are created equal. Some studies focus on a particular group or class of fatty acids and measure total consumption for correlating its role in disease. Unfortunately, such studies often ignore potential confounding factors, such as fatty acid ratios and the counterbalance of other fatty acids and/or dietary components used to make diets isocaloric, which may affect results. For example, the common use of corn oil as a common constituent of a high fat diet complicates conclusions due to the extensive research that omega-6 PUFA are pro-inflammatory and cancer promoting compared to other types of fatty acid (Greene et al., 2011; Wang and Dubois, 2010). A recent study (Baxheinrich et al., 2012) eloquently designed a dietary intervention study that accounted for both quantity and quality of dietary fatty acids consumed by patients with metabolic syndrome to determine the effects of alpha-linolenic acid (ALA) metabolic syndrome and cardiovascular disease risk factors. A health log was first recorded to identify the patients' habits. Patients were then educated and provided with detailed instructions on how to adhere to the prescribed diet, including kitchen scales, recipes, and the intervention oils. The diets of each study arm were carefully calculated to be isocaloric by measuring the same percentage of fat (38%), carbohydrate (42%), and protein (20%). Most importantly, the biochemical make up of the oils was carefully considered, such that the increased quantity of omega-6 PUFA in the high ALA rapeseed arm of the study was compensated for by the inclusion of sunflower oil in the olive oil study arm. Overall, the study concluded that energy restriction, as compared to previous dietary habits, was the largest contributor to changes in diagnostic factors for metabolic syndrome. However, because the study was adequately controlled for both quantitative and qualitative measures, ALA compared to MUFA was more effective in decreasing plasma triacylglyceride concentrations (Baxheinrich et al., 2012).

The time frame in which studies are conducted is another major contributor to controversial results of dietary fat metabolism studies. While some studies may follow subjects for just a few weeks, other studies collect data for several months or even years. A study of longer duration may allow for systemic adaptations to dietary influence and be more representative of dietary impact on disease. However, one must also consider the stringency of subject compliance and accuracy of dietary consumption from questionnaire-derived data for long term studies in humans. Acute dietary intervention may lead to transient changes in liver metabolism, circulating fatty acids, and the composition of red blood cells, but may have little effect on other organs, such as adipose, heart, and other peripheral tissues, all of which may be more relevant to the development and progression of certain chronic diseases. In contrast, chronic exposure to a diet may be more representative of lifestyle and systemic adaptation to diet and more accurately depict how these changes affect disease development and progression. Chronic exposure may even influence epigenetic changes affecting the development and progression of disease (Armitage et al., 2005).

Finally, variance in sample size and, especially, population can lead seemingly similar studies to completely different results, or conversely, repeated investigations of the same population may mislead common knowledge. Increased incidence of cancer and cardiovascular events in certain racial and ethnic populations is a common trend (Casper et al., 2003; Siegel et al., 2011) . Although many studies statistically adjust results for various criteria, it is nearly impossible to adjust for all variables. The population may, in fact, be the most significant variable among dietary research studies since populations are subject to infinite differences of socioeconomic, lifestyle, environmental, cultural, and genetic diversity around the globe. While socioeconomic factors are also becoming more

appreciated as critical factors of disease disparity (Devi, 2012), the influence of population genetics and epigenetics among epidemiologic studies has gained particular interest. It is becoming increasingly clear that genetic regulation of lipid metabolism can largely influence various diseases including cardiovascular disease, obesity, metabolic syndrome, and cancer (Illig et al., 2010; Suhre et al., 2011; Teslovich et al., 2010). Therefore, the use of genetic profiling for population studies could help target a population for dietary fat intervention studies by providing a predictive value to the research.

Genetic Variation Modifies Fatty Acid Metabolism

In an era of genomic profiling, whereby genes are well known contributors to disease, our increasing knowledge of the enzymatic pathways in *de novo* and dietary fatty acid metabolism has fostered research identifying interactions between genetic and dietary modulators of disease. The recent coming of genome-wide association studies (GWAS) has lead to the identification of several new lipid metabolism genes (Teslovich et al., 2010), although it does require extremely laborious and low-throughput functional studies to validate GWAS findings (Burkhardt et al., 2010; Musunuru et al., 2010). Even so, the development of transgenic knockout mouse models for ACLY (Beigneux et al., 2004), ACACA (Abu-Elheiga et al., 2005), FASN (Chirala et al., 2003), SCD-1 (Miyazaki et al., 2001), SCD-2 (Miyazaki et al., 2005), FADS2 (Stoffel et al., 2008; Stroud et al., 2009), ELOVL3 (Westerberg et al., 2004), ELOVL4 (Cameron et al., 2007; Harkewicz et al., 2012; Li et al., 2007), ELOVL5 (Moon et al., 2009), and ELOVL6 (Matsuzaka et al., 2007) have been instrumental in identifying the role of these enzymes in both systemic and localized lipid metabolism and homeostasis. With the continued development of spatially restricted knockout models, we can expect new studies to elucidate the tissue-specific roles of these enzymes. Nevertheless, still enthralling is the continuous discovery of genetic variants in several of these genes found in human populations, many of which have been suggested to modulate disease phenotypes. Specifically, genetic variation has been identified in FASN, SCD-1, ELOVL2, ELOVL5, ELOVL6, LPL, and most notably FADS1 and FADS2 (Garcia-Rios et al., 2011; Illig et al., 2010; Merino et al., 2010; Morcillo et al., 2011; Nguyen et al., 2010). A number of GWAS and other studies have shown that single nucleotide polymorphisms (SNPs) found within lipid metabolism genes can regulate enzyme expression and activity (Corella and Ordovas, 2012; Kihara, 2012; Merino et al., 2010), thereby affecting the efficiency of lipid metabolism. Similar studies have even been conducted in cattle as a means to predict and improve the quality, scored in part by fatty marbling, of meat consumed by humans (Li et al., 2012; Mannen, 2011; Oh et al., 2012). Here, we describe the most recent findings of genetic polymorphisms found within lipid metabolism genes in humans influencing the development and progression of lipid associated diseases, including cardiovascular disease, metabolic syndrome, and cancer.

Genetic variation in de novo fatty acid metabolism enzymes

While enzymes involved in *de novo* fatty acid metabolism have been implicated in metabolic disease (Chakravarthy et al., 2005), cardiovascular disease (Schneider et al., 2010), and cancer (Menendez and Lupu, 2007) through the use of transgenic mice, very few studies have investigated the putative role of human genetic variation in these genes and susceptibility to disease development and progression. A recent study used data from the European Prospective Investigation into Cancer (EPIC) cohort to investigate genetic variation in lipid metabolism genes and prostate cancer risk. They screened a total of 921 SNPs across 22 different genes involved in fatty acid synthesis, including *ACACA*, *FASN*, and *SREBF1*, the transcriptional regulator of fatty acid synthesis, and found no significant associations with prostate cancer risk (Campa et al., 2011). Despite this singular study, other groups have found significant associations between SNPs within FASN, ELOVL6, and

SCD-1 and characteristics of cardiovascular diseases, metabolic syndrome, and cancer (Merino et al., 2010; Morcillo et al., 2011; Moreno-Navarrete et al., 2009; Nguyen et al., 2010).

FASN is a critical mediator of atherosclerosis (Schneider et al., 2010), obesity and inflammation (Chakravarthy et al., 2009b), and cancer (Kuhajda et al., 1994; Menendez and Lupu, 2007); however, disease susceptibility due to genetic variation in *FASN* is still a nascent topic. Only 3 recent studies pertain to genetic variation in the *FASN* gene and disease risk. A study published by Campa et. al. (Campa et al., 2009) investigated 20 SNPs in the ChREBP, SREBP-1, and FASN genes of breast cancer and control patients from a Western European population. ChREBP and SREBP-1 are transcription factors known to directly regulate enzymes of the fatty acid synthesis pathway, including FASN (Eberle et al., 2004). They found no significant associations between any of the 20 SNPs and overall breast cancer risk by age or menopausal status. However, 2 SNPs in the FASN gene, rs1140616 and FAS_A0866, were found to be significantly associated with a moderately higher BMI in younger/pre-menopausal women and a marginally lower BMI in older/post-menopausal women, respectively (Campa et al., 2009). Another group (Schleinitz et al., 2010) identified 35 SNPs from sequencing the FASN gene in a German population of adults and children. A total of 4 SNPs were found to be significantly associated with obesity, but the strongest effect was observed for rs2229422, which showed significant association with BMI, waist-to-hip ratio, plasma insulin, and glucose infusion. Most striking from this study was the reaffirmation from 3 previous studies (Korner et al., 2007; Kovacs et al., 2004; Moreno-Navarrete et al., 2009) that a valine to isoleucene amino acid substitution at residue 1483 in FASN, a consequence of the minor allele SNP rs2228305, provides gender-specific protection from obesity in males (Schleinitz et al., 2010). Finally, a study from the Dana-Farber Cancer Institute (Nguyen et al., 2010) identified 4 SNPs in the FASN gene that were significantly associated with prostate cancer in white men of the Unites States. The variant alleles of SNPs rs8066956 and rs6502051 were directly associated with a decreased risk of advanced prostate cancer, and rs8066956 was associated with decreased expression of FASN in prostate tumors (Nguyen et al., 2010), which is a well described predictor of prostate cancer prognosis (Menendez and Lupu, 2007; Shurbaji et al., 1996). Additionally, the variant allele of SNP rs1127678 was associated with increased risk of advanced prostate cancer when stratified for overweight patients bearing a body mass index equal to or greater than 25, and SNP rs4246444 was associated with prostate cancer mortality (Nguyen et al., 2010).

Studies of genetic variation among the fatty acid elongase enzymes are quite sparse. In fact, with the exception of ELOVL2, which metabolizes PUFA, only ELOVL6 has been described to associate with disease on account of its genetic variation. A prospective study showed that minor allele carriers of the rs9997926 and rs6824447 SNPs in ELOVL6 from a Spanish population were at a significantly ($p \leq 0.01$) lower risk of being insulin resistant, while minor allele carriers of the rs17041272 SNP displayed an increased risk of insulin resistance. Interestingly, when adjusted for consumption of dietary oils, insulin resistance measurements significantly dropped in carriers of the minor allele for SNP rs6824447 who consumed sunflower oil as opposed to the same minor allele carriers who consumed olive oil. These results suggest the effects of ELOVL6 genetic variation on insulin resistance can be modified by dietary fat consumption (Morcillo et al., 2011). The only other study investigating genetic polymorphisms of non-PUFA metabolizing elongase enzymes described no association between ELOVL4 SNPs and adipose fatty acids, LDL cholesterol, or myocardial infarction (Aslibekyan et al., 2012). More studies are required to determine the potential role of genetic variation in the SAFA and MUFA metabolizing elongase enzymes.

The role of SCD-1 an important fatty acid desaturase enzyme in the regulation of lipid metabolism as it relates to obesity, diabetes, metabolic syndrome, and cancer, has been well characterized (Cohen and Friedman, 2004; Cohen et al., 2003; Guillou et al., 2010; MacDonald et al., 2008). Unlike other *de novo* lipogenesis enzymes, recent reviews have described numerous studies of *SCD-1* variants and dietary interactions (Bjermo and Riserus, 2010; Merino et al., 2010), as the enzyme is known to be regulated by dietary consumption (Cohen and Friedman, 2004) . However, the latest studies (Gong et al., 2011; Stryjecki et al., 2012) have confirmed previous reports of gender specific variation in *SCD-1* as a link to metabolic syndrome and inflammation in women. Two common haplotypes across 7 tagSNPs showed a significant ($P<0.01$) association with metabolic syndrome in Costa Rican women. The study observed a mildly significant association between rs1502593 and systolic blood pressure ($p=0.05$).Other metabolic characteristics, including fasting blood glucose, waist circumference, and the desaturation index of palmitate showed a similar trend (Gong et al., 2011). Additionally, the rs2060792 SNP of *SCD-1* was significantly associated ($P<0.05$) with plasma palmitate, stearate, and C reactive protein levels in European women (Stryjecki et al., 2012). Overall these studies suggest *SCD-1* polymorphisms may play a role in the development of inflammation, insulin resistance, and obesity.

Finally, a few studies have identified associations between characteristics of metabolic syndrome and genetic variants in the *ACACB* gene (Ma et al., 2011; Phillips et al., 2010; Riancho et al., 2011), the mitochondrial counterpart to ACACA involved in lipid oxidation; however, no study to date has shown similar findings for the *ACACA* gene in humans. One group identified an interaction between ACACA and the breast cancer susceptibility gene 1, BRCA1 (Magnard et al., 2002), and therefore, examined the human *ACACA* gene for sequence variation among breast cancer patients. Unfortunately, no single SNP was found to be associated with breast cancer risk.; Nonetheless, low frequency genotypes of haplotype tagging SNPs (htSNPs) across four different SNPs in breast cancer patients suggested a protective effect against breast cancer, and vice versa for the high frequency haplotype. No SNPs in this study were identified in the coding region of *ACACA*, suggesting functional conservation of the gene (Sinilnikova et al., 2004).A later study by the same group showed that BRCA1 directly regulates lipogenesis by binding to and preventing dephosphorylation of phospho-ACACA^{Ser79}, an inhibitory phosphorylation, which proposes a tumor suppressor role for BRCA1 (Moreau et al., 2006). Hence, genetic variation in the *ACACA* gene itself has yet to be identified, but other known genetic breast cancer risk factors, such as mutated *BRCA1*, may affect lipogenesis by regulating ACACA functionality and activity.

Genetic variation in dietary fatty acid metabolism enzymes

In stark contrast to enzymes responsible for *de novo* lipogenesis, the fatty acid desaturase enzymes, involved in dietary PUFA metabolism, have been extensively researched and reviewed for genetic variations and their association with disease, including dyslipidemia, coronary artery disease, metabolic syndrome, obesity, and other risk factors for cardiovascular disease (Corella and Ordovas, 2012; Cormier et al., 2012; Glaser et al., 2011; Kathiresan et al., 2009; Kim et al., 2011; Kwak et al., 2011; Lattka et al., 2010; Merino et al., 2010; Sergeant et al., 2012; Simopoulos, 2010). SNPs found within the *FADS1* and *FADS2* genes of European, Asian, African American, and North American populations have been shown to influence plasma fatty acid concentrations, which can represent desaturase activity when measured as a ratio of fatty acid product to substrate (Bokor et al., 2010; Merino et al., 2011; Sergeant et al., 2012). Even genetic variation in lipoprotein lipase, which is required to release dietary fatty acids from lipoprotein particles, has been shown to regulate plasma lipid concentrations, thereby potentiating risk for metabolic syndrome and cancer (Crous-Bou et al., 2012; Garcia-Rios et al., 2011). Instead of reiterating these well reviewed findings, we note the extensive patterns of global variation in these genes and turn

to the interesting prospect of their genetic drift among populations worldwide and the interaction between their genetic variation and regionally exclusive dietary habits.

In 2008, John Speakman proposed the ‘drifty gene hypothesis’ (Speakman, 2008) as a counter argument to James Neel's original ‘thrifty gene hypothesis’ (Neel, 1962). Whereas Neel attributes the current obesity epidemic to the now absent rise and fall of famine that genetically selected for persons of energy, or fat-storing, metabolism (Neel, 1962), Speakman describes the epidemic as a result of genetic drift by random mutation in populations following the release of the human species from predation (Speakman, 2008). More specifically, he argues that the lower intervention limit for survival, set by starvation has not changed in modern society, i.e. humans today have maintained the same survival tactics to last through a famine. On the other hand, the upper intervention limit, set by the risk of predation has dissipated, such that the loss of the body's requirement to evade predators for survival has allowed positive selection for genetic mutations that promote obesity (Speakman, 2008). Speakman also provides an alternative hypothesis to explain modern obesity, which accuses the changes in modern dietary fat consumption. He explains that individual variability in fat oxidation may currently withstand as it was in the past, but due to historically nominal fat consumption, genetic variation never lead to health disparities until humans changed their diet. As such, an increase in dietary fat consumption would lead to negative consequences in individuals of weak or low fat oxidation, driving the development of obesity and/or metabolic and cardiovascular diseases (Speakman, 2008). While Speakman's theory remains simply that, a theory, a few very recent studies published in 2012 have provided evidence to support his hypotheses by studying the genetic evolution of the FADS gene cluster.

The recently published story of the genetic evolution of the Fads gene cluster champions the concept of ecologically induced genetic diversification (Castro et al., 2012). The authors delineate an argument based on the genetic conservation and diversification of the Fads1 and Fads2 genes in various species from teleosts to amphibeans, reptiles, birds and mammals. Overall, the data suggests that the functionally diverse fatty acid desaturase enzymes found in humans today have been shaped over the course of evolution by environmental, dietary, and nutritional selective pressures in combination with genetic events, such as duplications, losses, and mutations (Castro et al., 2012).

A recent study (Ameur et al., 2012) highlighted two haplotypes found in Europeans defined by 28 SNPs that associate with very distinct measurements of long chain PUFA (LC-PUFA) product-to-substrate ratios, identified as haplotype A and D. Haplotype D was characterized as an enzymatically efficient gene signature, showing significantly increased desaturase activity, as depicted by eicosapentaenoic acid to eicosatetraenoic acid (EPA/ETA) and arachidonic acid to dihomo-γ-linolenic acid (AA/DGLA) ratios, whereas haplotype A was considered a less efficient genetic variant. The prevalence of each haplotype was then estimated for geographical ancestry based on the human genome diversity panel (Li et al., 2008). Results showed a nearly fixed population of haplotype D in Africa, while Europe and the Middle East were approximately 75% haplotype D. Eastern Asia and Oceania regions were approximately 50% D, and the Americas were nearly 100% A. To determine when the apparent genetic variation may have arisen, the authors used comparative genomic analysis to identify the haplotypes of rhesus macaques, chimpanzees, gorillas, Denisovans, Neanderthals, a Palaeo-Eskimo, and an Australian Aboriginal. Upon computational clustering they found that all appeared to be largely DD genotype, except the Eskimo and the Aboriginal, which were AA genotype. The authors ultimately concluded that the D haplotype likely appeared in modern humans following the split from Neanderthals, but before their emigration from Africa. Their speculation as to why the D haplotype has reached near fixation in Africa focuses on the requirement for LC-PUFA throughout the

sophistication of the brain in hominids. Moreover, positive selection for haplotype D may have been driven in African populations where environmental and dietary supply of AA and DHA (docosahexaenoic acid) were restrictive (Ameur et al., 2012).

Another recent publication (Mathias et al., 2012) found very similar results to the aforementioned report, yet focused on somewhat different conclusions. The group's previous findings associated genetic variants in the FADS gene cluster with a distinct discrepancy in LC-PUFA synthesis between African Americans and European Americans with diabetes or metabolic syndrome (Sergeant et al., 2012). Therefore, they sought to investigate the evolutionary patterns of these genetic variants by analyzing 1092 individuals from 14 different populations. They found that African versus non-African populations displayed decreased nucleotide diversity and large differences in allelic frequencies in the FADS1 region. They went on to identify 9 SNPs around the FADS gene cluster for which the allele associated with increased PUFA metabolism was more frequently observed in African populations compared to non-African. In particular, SNP rs174537 found in *FADS1*, which is currently reported to have the strongest p-value with LC-PUFAs in literature to date, showed near fixation for the G allele in populations of African ancestry. Computational clustering for the haplotypes revealed that only a relatively small percentage of the African populations identified with the ancestral chimpanzee haplotype. The authors estimated that the positive haplotype selection in African populations occurred approximately 85,000 years ago, prior to the emigration of humans from Africa. Similar to the report by Gyllensten's group (Ameur et al., 2012), the authors speculated that positive selection in Africa likely supported the expansion and movement of populations to more diverse ecological locations (Mathias et al., 2012). Additionally, perhaps the selective pressures following such expansion outside Africa were lost upon the emergence of hunting techniques, including fishing, and the increased technological and social capacity to acquire LC-PUFA from the environment (Mathias et al., 2012). However, in modern Western society, where food is plentiful and consumption of proinflammatory omega-6 PUFA largely outweighs that of omega-3 PUFA, these originally advantageous genetic adaptations in PUFA metabolism have become potential risk factors for metabolic and cardiovascular diseases.

Epigenetic remodeling: Diet, exercise, and metabolomic biomarkers

It is now well established that not only genes and the variation found among them, but also the epigenetic modifications, such as methylation, acetylation, and phosphorylation, on the DNA and/or histones can act as modulators of disease. It is known that even RNA, acting as micro-RNA or long, non-coding RNA, can regulate gene expression. Moreover, it is becoming ever clearer that epigenetic modifications can be readily inherited, particularly during the extremely vulnerable *in utero* stage of life, and may be predictive of health outcomes in adulthood. Maternal obesity, insulin sensitivity, adiposity, diet, and nutrition can all influence the metabolism of offspring during pregnancy and even beyond parturition. Mounting evidence suggests that epigenetic changes as a result of maternal conditioning are inherently designed to prepare the offspring for the coming environment. However, when malnutrition *in utero* is a shortcoming to the actual environment where food is plentiful, these *in utero* induced epigenetic alterations may be misleading, and rather, become susceptibility biomarkers of disease, including obesity, metabolic syndrome, inflammation, cardiovascular disease, and cancer. Now recognized as the Developmental Origins of Health and Disease (DOHaD) Hypothesis, originally postulated by Barker and colleagues (Barker, 2003), this topic has now been extensively reviewed (Armitage et al., 2005; Burdge and Lillycrop, 2010; Ellison, 2005; Gluckman and Hanson, 2004; Martinez et al., 2012; Milagro et al., 2012; Walker and Ho, 2012; Waterland and Michels, 2007).

Fortunately, unlike the genome, the epigenome appears to be quite malleable. That is, even if a mother seems to hold the reins for her child's future health risks *in utero*, healthy lifestyle choices can still minimize incurred risks. Because humans were evolutionarily adapted to obligatory physical activity, it seems only logical that the now largely sedentary cultural lifestyles are inapt for our current genome (Booth et al., 2002). Aside from diet, studies of exercise intervention suggest regular physical activity helps refine the balance of metabolic homeostasis in patients by reducing risk factors for obesity and metabolic syndrome (Davis et al., 2012; Gremeaux et al., 2012). Unfortunately, the various parameters of combined diet and exercise induced weight loss can make exercise intervention studies difficult to track the cause of the observed effects (Bianchini et al., 2012). More studies with greater power and efficiently controlled parameters are necessary to fully delineate the physiological effects of exercise on health (Metcalf et al., 2012). Nonetheless, literature suggests regular physical activity can positively impact health through a number of mechanisms, including reduced adipocyte size and number, mobilization of fatty acid stores, and modulation of lipolysis and fatty acid uptake (Thompson et al., 2012).

Finally, our understanding of genetic variation in human metabolism has largely increased in recent years due to the introduction of metabolomics. Like other "–omics" research, the ability to peruse the human metabolome has brought insightful knowledge of the functional capacity of the variation hitherto identified in the genome and epigenome. Technology now allows us to reference metabolites and their concentration ratios in GWAS, which provides a systemic perspective on genetic variation in human metabolism (Illig et al., 2010; Suhre et al., 2011). Quite up and coming is the identification of specific metabolites, such as plasma fatty acids or intermediates of the tricarboxylic acid cycle, as markers of disease or predictors of outcome (Kunesova et al., 2012; Shah et al., 2012). By cross-referencing various aspects of "–omics" research, integration of multiple high throughput methods can drive personalized medicine fitting to patient needs and predictive of therapeutic response (Chen et al., 2012).

Conclusions and future perspectives

Fatty acids are essential to life. Whether produced *de novo* or acquired by diet fatty acids play a critical role as constituents of cellular membrane, posttranslational modifications, signaling ligands, and other cellular processes. There many different kinds of fatty acids that each vary in their carbon chain length and degree of saturation, which are important characteristics that help define the biochemical properties and functions of fatty acids. The metabolism of fatty acids has become a primary focus of biomedical research. Both lipogenesis and dietary fatty acids are proven contributors to diseases such as obesity, metabolic syndrome, inflammation, cardiovascular disease, and cancer. Although the biochemical structure of *de novo* synthesized and dietary fatty acids shows no discrimination, the two sources may fulfill different biological roles. *De novo* lipogenesis can be regulated by dietary fatty acid consumption; however, no study to date has identified a compensatory role for *de novo* fatty acid synthesis by dietary fat. This may be related to the varying aspects of *de novo* versus dietary lipid metabolism.

As obesity, metabolic syndrome, cardiovascular disease, and cancer trend throughout society, intervention studies, as a means to identify clear recommendations for dietary and lifestyle changes, should take precedence. Such investigations should be well controlled, prospective, and carefully consider both dietary quality and quantity. As genetic variants affecting lipid metabolism are identified, perhaps a more personalized regimen for healthy living can be made to improve the quality of life and decrease the risk for disease. However, irrespective of genetic predisposition, evidence of epigenetic remodeling suggests we can control many of the risk factors contributing to these diseases. With rising technologies,

perhaps a high throughput screening for genetic and metabolic biomarkers will aide diagnosis and prognosis, as well as identification of a personalized treatment regimen for these diseases.

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Abbreviations

SNP	single nucleotide polymorphism
SAFA	saturated fatty acid
MUFA	monounsaturated fatty acid
PUFA	polyunsaturated fatty acid
ACLY	ATP citrate lyase
ACACA	acetyl-CoA carboxylase 1
ACACB	acetyl-CoA carboxylase 2
FASN	fatty acid synthase
ELOVL	elongation of fatty acid
LPL	lipoprotein lipase
SCD	stearoyl-CoA desaturase
FADS	fatty acid desaturase
ALA	alpha-linolenic acid
SREBF	sterol response element binding factor
SREBP	sterol response element binding protein
ChREBP	Carbohydrate response element binding protein
BRCA1	breast cancer susceptibility gene 1
EPA	eicosapentaenoic acid
ETA	eicosatetraenoic acid
AA	arachidonic acid
DGLA	dihomo-gamma-linoleic acid
LC-PUFA	long chain polyunsaturated fatty acid
DHA	docosahexaenoic acid
DNA	deoxyribonucleic acid
RNA	ribonucleic acid
DOHaD	Developmental Origins of Health and Disease
GWAS	genome wide association study

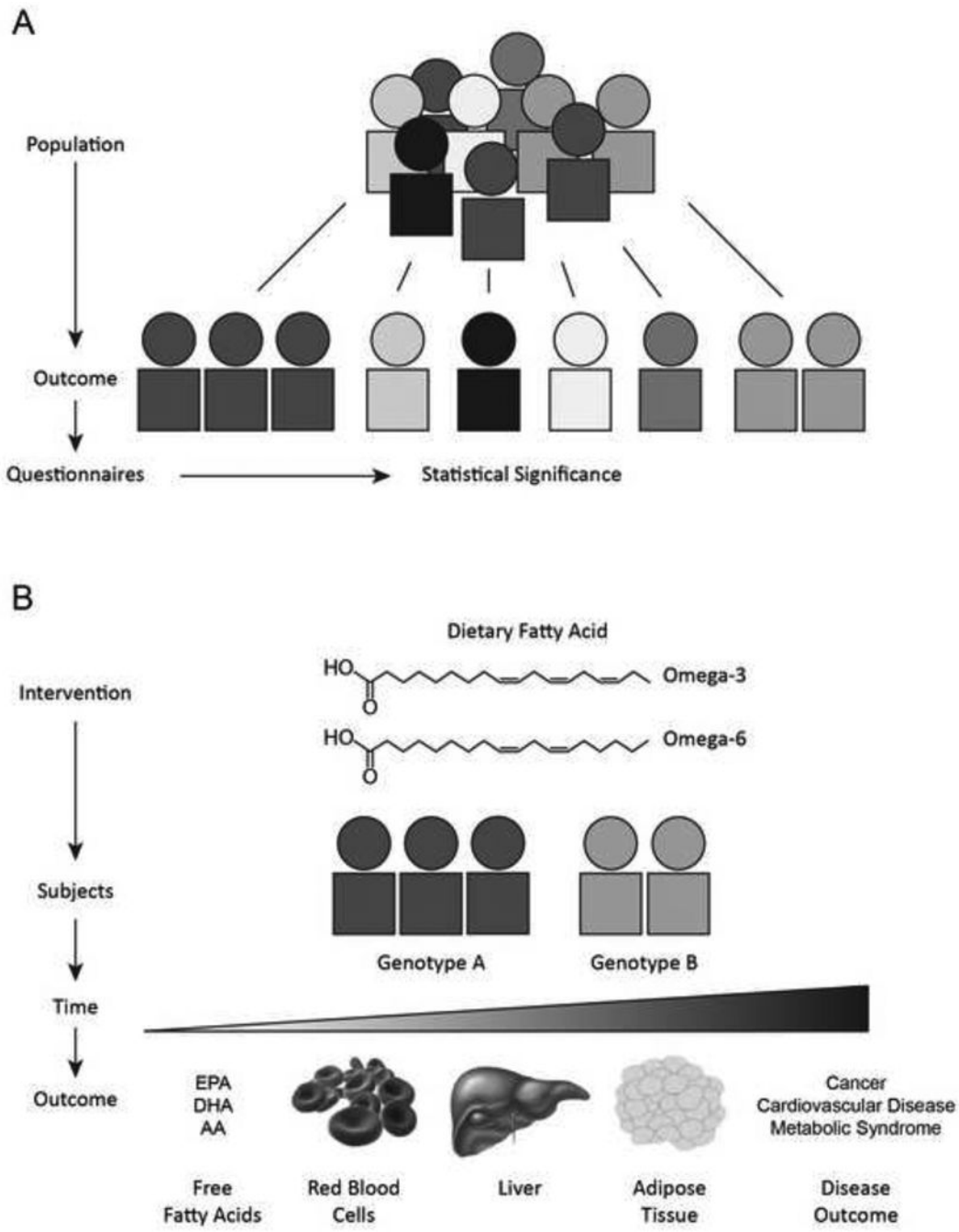

Figure 1. Standardizing Methods for Dietary Fat Studies in Humans

A. Current methodology often stratifies an isolated population by common ailments. Dietary habits are then determined by questionnaires and statistical association with genetic variation is assessed. **B.** Dietary intervention studies can directly assess the role of diet on health outcome. Here, the intervention with dietary PUFA supplement is tested on a subjects with a specific genetic profile to determine the health outcome, which is dependent on the time duration of the intervention.