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Genome-wide association study of Red Blood Cell fatty acids in the Women's Health Initiative Memory Study

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Abstract

Despite their widespread associations with a wide variety of disease phenotypes, the genetics of red blood cell fatty acids remains understudied. We present one of the first genome-wide association studies of red blood cell fatty acid levels, using the Women's Health Initiative Memory study – a prospective cohort of N=7,479 women aged 65–79. Approximately 9 million SNPs were measured directly or imputed and, in separate linear models adjusted for age and genetic principal components of ethnicity, SNPs were used to predict 28 different fatty acids. SNPs were considered genome-wide significant using a standard genome-wide significance level of $p<1\times10-8$. Twelve separate loci were identified, seven of which replicated results of a prior RBC-FA GWAS. Of the five novel loci, two have functional annotations directly related to fatty acids (ELOVL6 and ACSL6). While overall explained variation is low, the twelve loci identified provide strong evidence of direct relationships between these genes and fatty acid levels. Further studies

Author statement

JW, WSH and NT conceived of the study. CA, TDO and GCS provided substantive input on genetics of fatty acids. TO and LH provided expertise on the WHIMS cohort. JW and NT drafted the manuscript. All authors edited, revised and approved the final manuscript.

Declaration of interest

WSH owns stock in OmegaQuant Analytics, a company that offers fatty acid determinations.

are needed to establish and confirm the biological mechanisms by which these genes may directly contribute to fatty acid levels.

Keywords

fatty acids; genes; ELOVL; ACSL; FADS

1. Introduction

Red blood cell (RBC) proportions of omega-3 and omega-6 fatty acids have well established relationships with a variety of disease phenotypes and risk factors, including total mortality (1), acute coronary syndrome (2,3), serum lipid levels (4), inflammatory markers (5), cognitive function (6) and brain size (7,8) among others. Variation in RBC omega-3 fatty acid levels (i.e., proportions, expressed as a percent of total fatty acids) have been reported to possess a strong heritable component (24–70%) (4,9), suggesting that not only dietary but also genetic factors play an important role in explaining differences between individuals (10,11).

Recently genome-wide association studies (GWAS) have sought to identify common single nucleotide polymorphisms (SNPs) with fatty acid levels. Initial investigations have focused on establishing potential relationships between plasma phospholipid fatty acid proportions and common SNP variations (12–15). However, mounting evidence suggests that this fatty acid pool may be more affected by recent fat consumption (16), potentially obscuring the role of genetic variation in determining fatty acid composition (4,17). We recently conducted a GWAS using red-blood cell fatty acids in a sample of about 2600 individuals and identified multiple new loci (18). Additional studies found additional genes associated with fatty acid ratios (19), little evidence of the necessity for dietary covariate adjustment (19), and, in a companion genome-wide interaction study, modest evidence of some gene-fatty acid biomarker interaction on inflammatory biomarkers (20).

Here we report the results of a GWAS exploring relationships between the relative proportions of twenty-eight saturated, mono- and polyunsaturated RBC fatty acids with common (minor allele frequency >1%) SNPs in the Women's Health Initiative Memory Study.

2. Materials and Methods

2.1. Sample

The women's health initiative memory study (WHIMS) is a prospective cohort study of N=7,479 women which is nested within the larger Women's Health Initiative study (N=161,808). WHIMS consists of women aged 65–79 with no dementia at enrollment and followed from baseline to the present time. WHIMS examined the effects of menopausal HT on cognitive function in women aged 65–80 years (21,22). Recruitment was from 1993 to 1998. We eliminated individuals who were first degree relatives, women without fatty acid data available at baseline, women without genetic data available, and women missing

relevant covariates. Due to the limited data available on non-whites (<5%), we removed non-whites, yielding a final sample of N=5,055 white women for the analysis.

2.2 RBC fatty acid protocol

RBCs were isolated from blood drawn after a 10–12 hour fast and frozen at −80°C after collection. Gas chromatography with flame ionization detection was used to determine RBC fatty acid composition (23). After gas chromatography was completed, it was discovered that all RBC samples were inadvertently stored at −20°C for a period of approximately two weeks at the central lab during the aliquoting phase leading to oxidative degradation to the PUFAs. Experiments were undertaken to quantify the degree of degradation, and models were generated and applied to the original dataset to estimate true values. Multiple imputation was used to create a dataset containing 10 imputations of the fatty acids data for each individual (23). Subsequently, this dataset has been used in numerous peer-reviewed publications showing strong evidence of the reliability and validity of the imputation approach [E.g., (24–27)]. Our analyses considered each of the 28 measured fatty acids (C14.0, C15.0, C16.0, C16.1n7, C16.1n7t, C17.0, C18.0, C18.1c.other, C18.1n7, C18.1n9, C18.1t, C18.2n6, C18.2n6t, C18.3n3, C18.3n6, C20.0, C20.1n9, C20.2n6, C20.3n6, C20.4n6, C20.5n3, C22.0, C22.4n6, C22.5n3, C22.5n6, C22.6n3, C24.0, C24.1n9).

2.3 Single Nucleotide Polymorphisms

Our analyses focused on 9,047,113 autosomal SNPs which were measured directly or imputed. Genotyping was conducted using mix of Illumina and Affymetrix technology, with harmonization of panels prior to imputation using the 1000 genomes reference panel (28). We used consistently imputed SNP data and applied standard GWAS quality control approaches (sample call rate>0.95, SNP call rate>0.90, Hardy-Weinberg Equilibrium p-value>$1\times10^{-6,}$ MAF>0.01, imputation R^2>0.3) across all individuals to yield consistent and unbiased SNP measurements. The imputation and QC procedures for this set of SNPs is well documented and published in detail elsewhere (29).

2.4. Statistical Analysis

For each of the 28 fatty acid by SNP pairs, we fit a linear model predicting fatty acid level (percent composition; proportion) by age and the first 10 genetic principal components (as created by the parent study investigators; (28)) to account for additional ethnic substructure and cryptic relatedness. Fatty acid values were winsorized (30) so that all values for an individual fatty acid that were more than four mean absolute deviations (average distance between each value and the mean of the dataset) from the median value for that fatty acid were imputed to four means absolute deviations from the median (above or below the median as appropriate). SNPs were considered genome-wide significant using a standard genome-wide significance threshold of $p<1\times10^{-8}$. For each fatty acid, the distribution of p-values is evaluated using a Q-Q plot, and the genomic control lambda value (λGC) is estimated as median (χ^2 df=1)/0.455 where 0.455 is the expected median χ^2 df=1 value. To properly account for the imputation process for fatty acids, all statistical analyses included multiple imputation using the Amelia package in R (31), following the method of Rubin (32). To account for known systematic biases observed when analyzing multiply

imputed data in GWAS settings (33,34) we report both untransformed and results after the application of genomic control (35). All statistical analyses were performed in R (36).

3. Results

3.1. Genome-wide analysis

Table 1 provides a summary of SNP-fatty acid models meeting the genome-wide significance threshold ($p<1\times10^{-8}$) in age and PC-adjusted models. Supplemental Table 1 provides full results (all significant FA-SNP pairs). The majority of the loci (7 of 12) identified were identified in prior RBC-FA GWAS analyses. Of the five novel loci, two (ELOVL6 and ACSL6) have functional annotations directly related to fatty acids (ELOVL6 – a fatty acid elongase (37); ACSL6 catalyzes formation of acyl-CoA from fatty acids, especially in the brain (38)).

3.2. Explained variation

Table 2 provides an overview of the explained variation for SNPs identified in Table 1, organized by fatty acid (the table shows the most predictive SNP for each fatty acid). SNPs in chromosome 11 (FADS complex) show the strongest association with the omega-6 fatty acids dihomo gamma linolenic Acid (C20:3n6; partial R^2=34%), arachidonic acid (C20:4n6, R^2=15%) and linoleic acid (C18:2n6, R^2=9%). All other n3 and n6 PUFAs in the FADS region had R^2 values ≤3%. The strongest association (7% of variation) outside of the FADS region was for the LPCAT3 gene region with oleic acid (C18:1n9). Notably, all other associations outside of the FADS region had R^2<1%.

4. Discussion

In this paper we conducted a genome-wide analysis of RBC-FAs: the first such analysis in a sample other than the Framingham Offspring cohort (18). Of the twelve loci identified, seven were previously identified, with two of the novel loci in areas with direct functional connections to fatty acids despite lacking prior evidence from GWAS studies. The replication of seven loci and two novel loci with direct functional relationships suggests strong evidence of the potentially direct relationship of these genomic regions with certain fatty acid proportions.

Notably, all five of the originally detected genes/regions in the Framingham Offspring cohort (18), were replicated here (TRIM58, PCOLCE2, ELOVL2, FADS complex and LPCAT3). A follow-up analysis adjusting for dietary covariates, expanding the set of analyzed fatty acids and considering select fatty acid ratios in Framingham identified seven additional loci, two of which were replicated here (PKD2L1, NTAN1) (19). Some of these loci have also been identified by fatty acid GWAS based on plasma phospholipid (12,39–41) or whole plasma measurements (42). We will not recapitulate previous work which has provided in-depth conjectures about the biological mechanisms of action by which these genes contribute to fatty acid level variation (18,19). However, as shown before in the Framingham Heart Study and in our analysis here, notably, in most cases the explained variation is very low.

Among the novel loci, two genes with functional relationships with fatty acids (ELOVL6; ACSL6) were identified in a GWAS of fatty acids. ELOVL6 is a well-known fatty acid elongase gene, which uses malonyl-CoA as a 2-carbon donor in the first and rate-limiting step of fatty acid elongation. In this GWAS we identified a SNP in ELOVL6 associated with stearic acid (18:0) levels, which aligns with prior work in mice showing ELOVL6 as the protein converting palmitic acid (16:0) to stearic acid (18:0) (43).

ASCL6 uses magnesium as a cofactor to catalyze the formation of acyl-CoA from fatty acids, and plays a major role in fatty acid metabolism in the brain. In particular, ASCL6 has been shown to be related to brain DHA levels and cognitive decline/Alzheimer's disease (44,45). In this GWAS we identified an association between a variant in ASCL6 and DPA, which relates to prior evidence with DHA levels given the product:precursor relationship between DHA and DPA (46).

The lack of ethnic diversity in the current and previous analyses suggests the need for future studies in ethnically diverse cohorts. At the time of this publication, such analyses are ongoing using pooled data from Framingham, WHIMS and other cohorts. Additionally, novel GWAS findings for ELOVL6 and ASCL6 suggest the need to continue to pool cohorts and search for additional gene-fatty acid relationships in GWAS studies as confirmation of animal knockout experiments. Finally, future work is needed in order to establish and confirm the biological mechanisms by which all the genes identified here may directly contribute to fatty acid levels.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- One of the first GWAS of red blood cell fatty acid (RBC-FA) levels
- Many results confirmed findings of another GWAS of RBC-FA
- Twelve genes were identified including ELOVL6 and ACSL6

Table 1.

Results of genome-wide association study

Chr	Size of region (kb[3])	Chromosomal Location (kb[3])	Gene name(s)	Fatty Acid[1]	# of SNPs	P-value[1]	SNP[1]	Prior GWAS evidence[2]
1	4	248040	TRIM58, OR2W3	C18.1n9	3	4.63×10^{-18}	rs3811444	(18)
2	23	27741	GCKR	C16.1n7	4	4.08×10^{-10}	rs1260326	No
2	1 bp	196739	DNAH7	C17.0	1	5.51×10^{-10}	rs72915157	No
3	23	142642	LOC100507389 ~PAQR9 ~PCOLCE2	C20.3n6	1	4.75×10^{-09}	rs2608073	(18,19)
				C20.4n6	12	5.92×10^{-14}	rs2608073	
				C22.5n3	2	2.37×10^{-13}	rs2608073	
4	1 bp	111129	~ELOVL6	C18.0	1	4.26×10^{-09}	rs5022521	No
5	1 bp	131357	~ACSL6	C22.5n3	1	4.59×10^{-09}	rs61078674	No
6	167	11007	SYCP2L, ELOVL2, ELOVL2-AS1	C22.5n3	184	8.95×10^{-27}	rs2236212	(18,19)
				C22.5n6	164	4.06×10^{-16}	rs9368564	
				C22.6n3	84	7.19×10^{-12}	rs8523	
	115	53165	ELOVL5, RPL31P28	C22.4n6	144	5.02×10^{-11}	rs9474482	
	90	135441	HBS1L	C22.4n6	49	1.79×10^{-23}	rs9402685	
	112	161643	AGPAT4	C22.4n6	20	3.07×10^{-20}	rs75534358	
10	121	102025	CHUK, BLOC1S2, PKD2L1	C18.1n7	5	3.28×10^{-23}	rs603424	(19)
11	1 bp	58966	DTX4	C24.0	1	7.74×10^{-09}	rs138458717	No
11	714	61512	SYT7,RPLP0P2, DAGLA, MYRF, TMEM258, FEN1, FADS2, FADS1, MIR1908, FADS3, RAB3IL1, BEST1, FTH1	C18.1n9	82	1.45×10^{-21}	rs174551	(18,19)
				C18.2n6	305	7.96×10^{-112}	rs174567	
				C20.1n9	76	$9.70\times10^{-1/}$	rs174551	
				C20.2n6	249	1.36×10^{-85}	rs99780	
				C20.3n6	580	1×10^{-256}	rs174528	
				C20.4n6	354	1.77×10^{-134}	rs102275	
				C20.5n3	79	3.31×10^{-18}	rs12226877	
				C22.4n6	157	1.58×10^{-33}	rs174548	
				C22.5n3	116	6.64×10^{-33}	rs174546	
				C22.5n6	53	9.49×10^{-16}	rs61897793	
12	202	7082	SPSB2, RPL13P5, LRRC23, ENO2, PTPN6, EMG1, PHB2, LPCAT3, C1S	C18.1n9	146	4.77×10^{-91}	rs1984564	(18,19)
				C18.2n6	143	2.62×10^{-68}	rs73266713	
				C20.3n6	65	1.18×10^{-11}	rs12579776	
				C20.4n6	73	2.43×10^{-13}	rs117633233	
16	715	15481	PDXDC1, NTAN1, RRN3, NPIPP1, C16orf45, MYH11	C18.2n6	4	3.94×10^{-11}	rs12928099	(19)
				C20.3n6	68	7.85×10^{-31}	rs72789542	
20	1 bp	33146	MAP1LC3A	C20.2n6	1	7.49×10^{-09}	rs1040746	No

[1] Fatty acid, p-value and SNP are for the model showing the strongest evidence of association in the genomic region. Regions with significant associations for multiple fatty acids are depicted on separate rows.

[2] Identified in one of two prior RBC-FA genome-wide association studies.

[3] Kilobase (kb) is 1000s of base pairs (bp) and indicates the size of the region containing the significant SNPs or the number of kilobases from the end of the chromosome to the region of interest

Table 2.

Explained variation and risk allele for strongest associations[2]

Fatty Acid	Partial R-squared[1]	SNP ID (gene)	chr	Base Allele	Count Allele
C20.3n6	0.34	rs174528	11	C	T
C20.4n6	0.15	rs102275	11	C	T
C18.2n6	0.09	rs174567	11	G	A
C18.1n9	0.07	rs1984564	12	G	A
C20.2n6	0.04	rs99780	11	T	C
C22.5n3	0.03	rs174546	11	T	C
C22.4n6	0.03	rs174548	11	G	C
C18.1n7	0.01	rs603424	10	A	G
C24.0	0.01	rs138458717	11	A	C
C20.1n9	0.01	rs174551	11	C	T
C20.5n3	0.01	rs12226877	11	A	G
C17.0	0.01	rs116596919	2	T	C
C16.1n7	0.01	rs1260326	2	T	C
C18.0	0.01	rs5022521	4	C	T
C22.6n3	0.01	rs8523	6	G	A
C22.5n6	0.01	rs9368564	6	G	A

1. R^2 attributable to the SNP after adjusting for age and 10 genetic Principal Components

2. Fatty acid, p-value and SNP are for the model showing the strongest evidence of association for each fatty acid.