

Supplemental Data

Genetic Adaptation of Fatty-Acid Metabolism: A

Human-Specific Haplotype Increasing the Biosynthesis

of Long-Chain Omega-3 and Omega-6 Fatty Acids

Adam Ameer, Stefan Enroth, Åsa Johansson, Ghazal Zaboli, Wilmar Igl, Anna C.V. Johansson, Manuel A. Rivas, Mark J. Daly, Gerd Schmitz, Andrew A. Hicks, Thomas Meitinger, Lars Feuk, Cornelia van Duijn, Ben Oostra, Peter P. Pramstaller, Igor Rudan, Alan F. Wright, James F. Wilson, Harry Campbell, and Ulf Gyllenstein

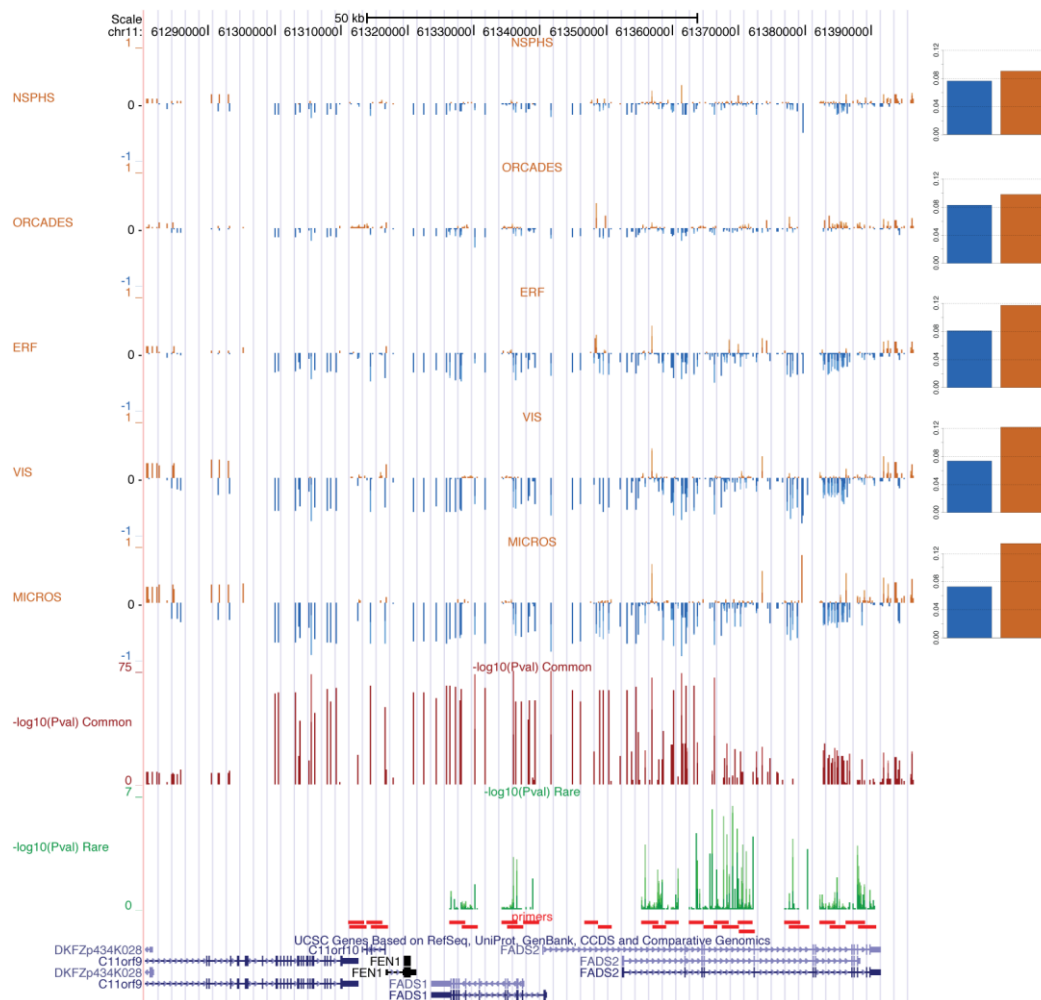


Figure S1. Overview of the Data Obtained from Genotyping, Imputation, and Resequencing of the FADS Region in the Five European Cohorts

From bottom to top; the *FADS1* and *FADS2* genes with location of the amplicons used for resequencing (red boxes). The two panels above show the individual association p -values ($-\log_{10}$) for detected rare variants (green bars) in the resequenced data and for genotypes/imputed SNPs (red bars). The five top panels show individual SNP effects (allele frequency difference between pools) on PC 36:4 for all five cohorts (NSPHS, ORCADES, ERF, VIS and MICROS). The blue and orange boxes on the side show the average PC 36:4 levels for the individuals in the low and high groups.

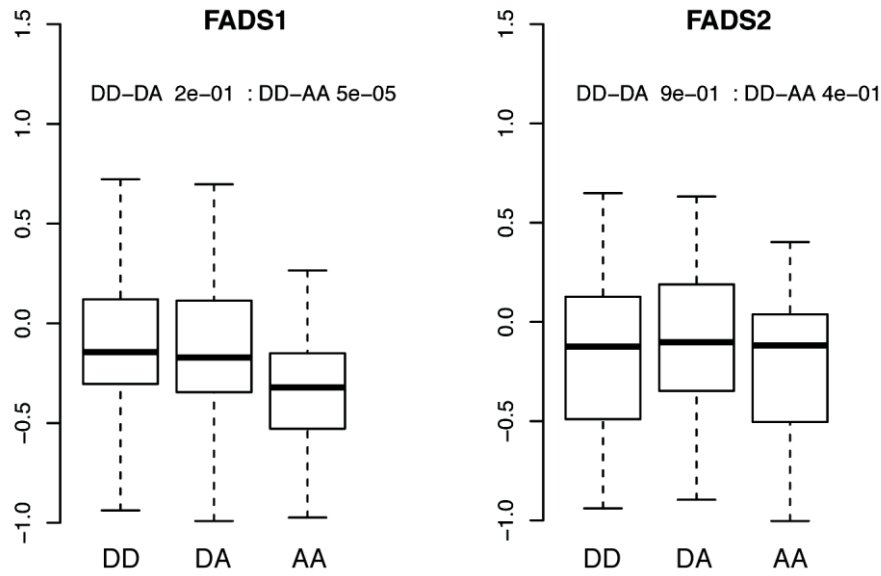


Figure S2. Expression Ratios for *FADS1* and *FADS2* in Liver Samples

The gene expression levels are based on microarray measurements in 195 individuals. Data points were grouped according to haplotype and difference in expression ratio levels between the groups was tested for significance using Wilcoxon ranked sum test. In *FADS1* the expression ratio levels of individuals homozygous for haplotype *A* have significantly lower expression (p -value = $5 \cdot 10^{-5}$) than individuals homozygous for haplotype *D*.

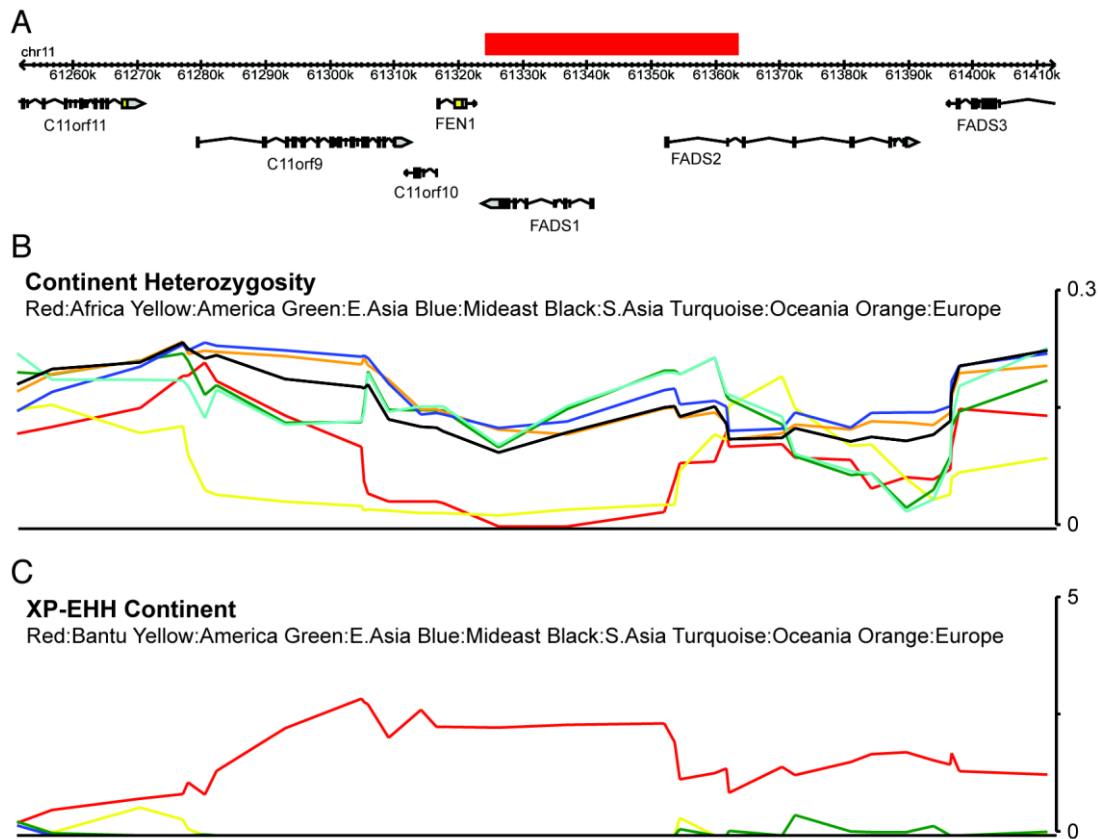


Figure S3. Evidence for a Selective Sweep for Haplotype *D* in Africa

The figure shows data from the HGDP selection browser (<http://hgdp.uchicago.edu/>).

(A) Gene coordinates (hg18 assembly version) in a 150 kb window surrounding *FADS1* and *FADS2*. The red rectangle indicates the position of the two main FADS haplotypes as defined by the 28 SNPs.

(B) Heterozygosity scores for HGDP populations on different continents. African (red line) and American populations (yellow) have almost zero heterozygosity in a region overlapping with the FADS haplotypes.

(C) Extended haplotype homozygosity (XP-EHH) scores indicate a strong positive selection in the pooled African Bantu-speaking populations (red line). The XP-EHH scores are lower for populations on other continents (other colors). The Bantu-speaking group in these calculations consists of 62 individuals (all African HGDP individuals except Pygmies, Mozabite and San).

Table S1. SNP Associations with High Levels of Phosphatidylcholine (PC) 36:4 for 134 SNPs in the FADS Region

Name	Position (hg19)	Assoc Allele	Allele Counts High/Low PC 36:4	Allele Frequencies High/Low PC 36:4	p Value	LD Block
rs174541	chr11:61565908	T	707:175, 359:503	0.802, 0.416	3.97E-61	block1
rs174544	chr11:61567753	G	733:149, 403:459	0.831, 0.468	4.00E-57	block1
rs174545	chr11:61569306	C	723:159, 364:498	0.820, 0.422	9.53E-66	block1
rs174546	chr11:61569830	C	721:161, 363:499	0.817, 0.421	2.81E-65	block1
rs174547	chr11:61570783	T	722:160, 366:496	0.819, 0.425	1.11E-64	block1
rs174548	chr11:61571348	C	733:149, 408:454	0.831, 0.473	1.40E-55	block1
rs174549	chr11:61571382	C	733:149, 408:454	0.831, 0.473	1.40E-55	block1
rs174550	chr11:61571478	T	722:160, 369:493	0.819, 0.428	1.09E-63	block1
rs4564341	chr11:61573540	C	772:52, 655:137	0.937, 0.827	6.39E-12	block1
rs174551	chr11:61573684	A	722:160, 373:489	0.819, 0.433	2.24E-62	block1
rs174553	chr11:61575158	T	723:159, 370:492	0.820, 0.429	9.36E-64	block1
rs116878346	chr11:61579381	A	868:14, 801:61	0.984, 0.929	1.61E-08	block1
rs174554	chr11:61579463	A	722:160, 369:493	0.819, 0.428	1.09E-63	block1
rs174555	chr11:61579760	T	735:147, 412:450	0.833, 0.478	4.02E-55	block1
rs174556	chr11:61580635	G	734:148, 411:451	0.832, 0.477	4.80E-55	block1
rs174559	chr11:61581656	G	748:134, 469:393	0.848, 0.544	1.88E-43	block1
rs174560	chr11:61581764	T	733:149, 408:454	0.831, 0.473	1.40E-55	block1
rs12361868	chr11:61582297	C	870:12, 823:39	0.986, 0.955	8.83E-05	block1
rs75810419	chr11:61582527	C	868:14, 801:61	0.984, 0.929	1.61E-08	block1
rs174561	chr11:61582708	A	733:149, 408:454	0.831, 0.473	1.40E-55	block1
rs116980792	chr11:61585140	C	867:15, 801:61	0.983, 0.929	3.84E-08	block1
rs174562	chr11:61585144	A	721:161, 369:493	0.817, 0.428	2.73E-63	block1
rs174564	chr11:61588305	A	721:161, 370:492	0.817, 0.429	5.80E-63	block1
rs28456	chr11:61589481	T	734:148, 410:452	0.832, 0.476	2.37E-55	block1
rs174566	chr11:61592362	T	721:161, 370:492	0.817, 0.429	5.80E-63	block1
rs174567	chr11:61593005	A	721:161, 372:490	0.817, 0.432	2.62E-62	block1
rs174568	chr11:61593816	G	721:161, 370:492	0.817, 0.429	5.80E-63	block1
rs174569	chr11:61594164	T	615:9, 508:18	0.986, 0.966	0.0272	block1
rs968567	chr11:61595564	G	790:62, 622:186	0.927, 0.770	2.40E-19	block1
rs99780	chr11:61596633	C	721:161, 370:492	0.817, 0.429	5.80E-63	block1
rs78596000	chr11:61597461	T	856:14, 778:56	0.984, 0.933	1.11E-07	block1
rs1535	chr11:61597972	T	721:161, 365:497	0.817, 0.423	1.30E-64	block1
rs174572	chr11:61598288	C	783:99, 548:314	0.888, 0.636	3.45E-35	block1
rs79976480	chr11:61598391	T	868:14, 801:61	0.984, 0.929	1.61E-08	block1
rs117553420	chr11:61599329	C	868:14, 801:61	0.984, 0.929	1.61E-08	block1
rs61897793	chr11:61599347	C	819:63, 667:195	0.929, 0.774	8.79E-20	block1
rs11230803	chr11:61599991	G	697:7, 696:26	0.990, 0.964	0.0011	block1
rs174573	chr11:61600327	C	783:99, 548:314	0.888, 0.636	3.45E-35	block1
rs174574	chr11:61600342	G	721:161, 365:497	0.817, 0.423	1.30E-64	block1
rs76498378	chr11:61601202	C	867:15, 801:61	0.983, 0.929	3.84E-08	block1
rs174575	chr11:61602003	G	782:100, 544:318	0.887, 0.631	7.64E-36	block1
rs174576	chr11:61603510	G	722:160, 373:489	0.819, 0.433	2.24E-62	block1
rs117220229	chr11:61604324	T	866:16, 793:69	0.982, 0.920	1.94E-09	block1
rs174577	chr11:61604814	G	720:162, 361:501	0.816, 0.419	1.52E-65	block1
rs174578	chr11:61605499	T	720:162, 360:502	0.816, 0.418	7.01E-66	block1
rs75992720	chr11:61605578	T	862:20, 788:74	0.977, 0.914	5.19E-09	block1
rs174579	chr11:61605613	G	774:78, 578:230	0.908, 0.715	4.69E-24	block1
rs174580	chr11:61606642	T	719:163, 359:503	0.815, 0.416	8.15E-66	block1
rs174581	chr11:61606683	G	719:163, 359:503	0.815, 0.416	8.15E-66	block1
rs77020029	chr11:61607107	C	862:20, 788:74	0.977, 0.914	5.19E-09	block1
rs174582	chr11:61607168	T	774:78, 578:230	0.908, 0.715	4.69E-24	block1
rs80349011	chr11:61607457	C	645:7, 603:13	0.989, 0.979	0.1386	block1
rs17156426	chr11:61609323	A	862:20, 788:74	0.977, 0.914	5.19E-09	block1
rs10897180	chr11:61609448	T	719:7, 709:37	0.990, 0.950	6.77E-06	block1
rs11230807	chr11:61609708	G	719:7, 709:37	0.990, 0.950	6.77E-06	block1
rs174583	chr11:61609750	G	703:167, 354:480	0.808, 0.424	8.40E-60	block1
rs75766519	chr11:61611033	T	861:21, 788:74	0.976, 0.914	1.15E-08	block1
rs174585	chr11:61611694	C	770:82, 577:231	0.904, 0.714	5.43E-23	block1

rs117702910	chr11:61611913	C	861:21, 788:74	0.976, 0.914	1.15E-08	block1
rs75321677	chr11:61612468	G	861:21, 788:74	0.976, 0.914	1.15E-08	block1
rs11601892	chr11:61612560	G	719:7, 709:37	0.990, 0.950	6.77E-06	block1
rs174587	chr11:61612830	C	775:77, 582:226	0.910, 0.720	1.84E-23	block1
rs150336394	chr11:61613137	C	861:21, 788:74	0.976, 0.914	1.15E-08	block1
rs93923	chr11:61613745	C	771:81, 581:227	0.905, 0.719	2.10E-22	block1
rs12284876	chr11:61613841	T	861:21, 788:74	0.976, 0.914	1.15E-08	block1
rs17156442	chr11:61614023	G	861:21, 788:74	0.976, 0.914	1.15E-08	block1
rs7935946	chr11:61615542	C	861:21, 788:74	0.976, 0.914	1.15E-08	block1
rs78791707	chr11:61616069	A	861:21, 788:74	0.976, 0.914	1.15E-08	block1
rs75471190	chr11:61616322	A	861:21, 788:74	0.976, 0.914	1.15E-08	block1
rs174590	chr11:61616977	C	771:81, 584:224	0.905, 0.723	9.83E-22	block1
rs115588270	chr11:61617015	C	861:21, 789:73	0.976, 0.915	1.82E-08	block1
rs55896837	chr11:61617753	T	861:21, 789:73	0.976, 0.915	1.82E-08	block1
rs61897795	chr11:61618169	A	797:55, 642:166	0.935, 0.795	3.02E-17	block1
rs916924	chr11:61619181	A	862:20, 790:72	0.977, 0.916	1.32E-08	block1
rs916925	chr11:61619294	G	862:20, 792:70	0.977, 0.919	3.31E-08	block1
rs11607437	chr11:61620079	C	863:19, 820:42	0.978, 0.951	0.002	block1
rs73487492	chr11:61621611	A	709:13, 639:59	0.982, 0.915	1.12E-08	block1
rs562172	chr11:61626167	T	73:745, 39:791	0.089, 0.047	7.00E-04	block2
rs174603	chr11:61626206	C	661:191, 485:365	0.776, 0.571	1.77E-19	block2
rs174604	chr11:61626270	G	626:226, 384:424	0.735, 0.475	2.58E-27	block2
rs174605	chr11:61626921	C	717:165, 541:321	0.813, 0.628	6.13E-18	block2
rs174606	chr11:61626973	G	553:299, 345:463	0.649, 0.427	1.13E-19	block2
rs174607	chr11:61627321	C	725:157, 570:292	0.822, 0.661	1.64E-14	block2
rs174608	chr11:61627484	T	716:166, 540:322	0.812, 0.626	6.67E-18	block2
rs174609	chr11:61627811	A	559:293, 346:462	0.656, 0.428	1.17E-20	block2
rs174610	chr11:61627833	T	558:294, 347:461	0.655, 0.429	2.94E-20	block2
rs174611	chr11:61627881	T	716:166, 540:322	0.812, 0.626	6.67E-18	block2
rs74771917	chr11:61627960	C	854:28, 815:47	0.968, 0.945	0.0191	block2
rs174612	chr11:61628266	G	553:299, 346:462	0.649, 0.428	1.78E-19	block2
rs500850	chr11:61628290	C	73:745, 43:787	0.089, 0.052	0.003	block2
rs174613	chr11:61628492	C	553:299, 346:462	0.649, 0.428	1.78E-19	block2
rs174614	chr11:61628915	A	553:299, 346:462	0.649, 0.428	1.78E-19	block2
rs174616	chr11:61629122	C	552:300, 346:462	0.648, 0.428	2.78E-19	block2
rs174617	chr11:61629166	A	553:299, 347:461	0.649, 0.429	2.80E-19	block2
rs174618	chr11:61629322	T	590:262, 403:405	0.692, 0.499	8.49E-16	block2
rs113003506	chr11:61629377	G	797:85, 725:137	0.904, 0.841	8.89E-05	block2
rs11230813	chr11:61629576	A	37:845, 34:828	0.042, 0.039	0.7911	block2
rs174620	chr11:61629747	A	590:262, 403:405	0.692, 0.499	8.49E-16	block2
rs174621	chr11:61630104	C	745:107, 571:237	0.874, 0.707	3.54E-17	block2
rs11605884	chr11:61630133	A	850:32, 815:47	0.964, 0.945	0.067	block2
rs520298	chr11:61631282	A	72:746, 43:787	0.088, 0.052	0.0039	block2
rs639394	chr11:61631331	C	73:745, 43:787	0.089, 0.052	0.003	block2
rs518511	chr11:61631454	G	73:745, 43:787	0.089, 0.052	0.003	block2
rs3168072	chr11:61631510	T	850:32, 815:47	0.964, 0.945	0.067	block2
rs3741	chr11:61631614	A	73:745, 43:787	0.089, 0.052	0.003	block2
rs174622	chr11:61631927	C	745:107, 571:237	0.874, 0.707	3.54E-17	block2
rs654226	chr11:61632298	C	73:745, 43:787	0.089, 0.052	0.003	block2
rs12577276	chr11:61632310	A	850:32, 815:47	0.964, 0.945	0.067	block2
rs482548	chr11:61633182	T	73:745, 43:787	0.089, 0.052	0.003	block2
rs11539526	chr11:61633770	C	798:84, 733:129	0.905, 0.850	5.00E-04	block2
rs77167250	chr11:61633947	C	798:84, 733:129	0.905, 0.850	5.00E-04	block2
rs113268188	chr11:61634829	A	798:84, 734:128	0.905, 0.852	7.00E-04	block2
rs17764324	chr11:61635088	G	800:82, 733:129	0.907, 0.850	3.00E-04	block2
rs17831757	chr11:61635200	T	800:82, 733:129	0.907, 0.850	3.00E-04	block2
rs174623	chr11:61635294	A	552:300, 349:459	0.648, 0.432	1.07E-18	block2
rs6591661	chr11:61635689	T	800:82, 733:129	0.907, 0.850	3.00E-04	block2
rs6591662	chr11:61635814	G	770:82, 687:121	0.904, 0.850	9.00E-04	block2
rs6591663	chr11:61635992	A	800:82, 733:129	0.907, 0.850	3.00E-04	block2
rs174625	chr11:61636013	T	553:259, 360:392	0.681, 0.479	5.08E-16	block2
rs7395424	chr11:61636017	A	798:84, 733:129	0.905, 0.850	5.00E-04	block2
rs11230815	chr11:61636126	G	800:82, 733:129	0.907, 0.850	3.00E-04	block2
rs11230816	chr11:61636253	C	800:82, 733:129	0.907, 0.850	3.00E-04	block2

rs11230817	chr11:61636255	A	800:82, 733:129	0.907, 0.850	3.00E-04	block2
rs174626	chr11:61637057	A	546:306, 345:463	0.641, 0.427	2.46E-18	block2
rs7394459	chr11:61637349	A	800:82, 733:129	0.907, 0.850	3.00E-04	block2
rs174627	chr11:61637466	C	815:67, 710:152	0.924, 0.824	2.54E-10	block2
rs174628	chr11:61637587	A	736:116, 566:242	0.864, 0.700	6.04E-16	block2
rs7104849	chr11:61638044	T	800:82, 735:127	0.907, 0.853	5.00E-04	block2
rs472031	chr11:61638420	T	72:746, 50:780	0.088, 0.060	0.0313	block2
rs508768	chr11:61639335	G	71:747, 45:785	0.087, 0.054	0.0097	block2
rs7118175	chr11:61639358	T	803:35, 741:83	0.958, 0.899	2.87E-06	block2
rs422249	chr11:61639488	C	676:206, 485:377	0.766, 0.563	1.88E-19	block2
rs174448	chr11:61639573	T	620:232, 404:404	0.728, 0.500	1.45E-21	block2
rs7481842	chr11:61639705	A	801:81, 739:123	0.908, 0.857	0.001	block2

Table S2. Nucleotide Sequences for Primates and Hominins at the 28 SNP Positions that Discriminate between Haplotypes *D* and *A*

Id	rs #	Human hg19 Position	Human Haplotypes		Rhesus	Gorilla	Chimpanzee			Denisova	Neandertal
			<i>D</i>	<i>A</i>	Ref ^a	Ref ^a	Ref ^a	SOLiD Reads1	SOLiD Reads2	Illumina Reads	Illumina Reads
1	rs174544	61567753	C	A	C	C	C	C(6)		C(21)	C(6)
2	rs174545	61569306	C	G	G	G	G	G(7)	G(7)	G(29)	G(5)
3	rs174546	61569830	C	T	T	T	T	T(9)	T(3)	T(25)	C(3),T(1)
4	rs174547	61570783	T	C	C	C	C	C(11)	C(1)	C(16)	T(2)
5	rs174548	61571348	C	G	G	G	G	G(10)	G(23)	G(36)	G(1)
6	rs174549	61571382	G	A	A	A	A	A(14)	A(26)	A(28)	G(1)
7	rs174550	61571478	T	C	C	C	C	C(9)	C(14)	C(23)	C(1)
8	rs174551	61573684	T	C	-	-	-			T(1)	
9	rs174553	61575158	A	G	G	G	G	G(6)	G(7)	G(25)	G(3)
10	rs174554	61579463	A	G	G	G	G	G(9)	G(7)	G(21)	A(1)
11	rs174555	61579760	T	C	C	C	C	C(11)	C(14)	C(33),A(1)	
12	rs174556	61580635	C	T	C	C	C	C(11)	C(11)	C(23)	C(4)
13	rs174560	61581764	T	C	-	C	C	G(8)	G(8)	C(22)	C(4)
14	rs174561	61582708	T	C	-	C	C	C(4)	C(5)	C(12)	
15	rs174562	61585144	A	G	G	G	G	G(9)	G(9)	G(20)	A(1)
16	rs174564	61588305	A	G	G	-	G	G(5)	G(5)	G(16)	A(1)
17	rs28456	61589481	A	G	G	-	A	A(2)		G(24)	A(2)
18	rs174566	61592362	A	G	A	G	G	G(7)	G(12)		G(1)
19	rs174567	61593005	A	G	G	G	G	G(5)		G(15)	G(1)
20	rs174568	61593816	C	T	T	C	C	C(11)	C(11)	C(13),T(2)	
21	rs99780	61596633	C	T	T	T	T	T(7)	T(17)	T(16)	T(3)
22	rs1535	61597972	A	G	G	G	G	G(11)	G(8)	G(22)	G(1)
23	rs174574 ^b	61600342	C	A	A	A	A	A(7)	A(4)	A(39)	A(3)
24	rs174576	61603510	C	A	A	A	A	A(17)	A(6)	A(28)	A(3)
25	rs174577	61604814	C	A	A	A	A	A(8)	A(14)	A(23)	A(2)
26	rs174578	61605499	T	A	A	A	A	A(7)		A(15)	A(3)
27	rs174580	61606642	A	G	G	G	G	G(10)	G(3)	G(20)	G(2)
28	rs174581	61606683	G	A	A	A	A	A(6)	A(8)	G(17)	A(2)

The numbers in parentheses show the read counts in support of a specific nucleotide.

Positions absent from the rhesus, gorilla or chimpanzee reference sequences are marked by hyphen signs (-). Empty cells indicates positions where there is no sequence read information, either due to insufficient coverage or because the nucleotide is missing.

^a The nucleotides in these columns are from the rhesus (rheMac2), gorilla (gorGor3) and chimpanzee (panTro2) reference assemblies.

^b The human reference sequence is identical to haplotype *D* with the only exception for rs174574 where the reference instead agrees with haplotype *A*.

Table S3. Significant Rare SNPs Detected by Targeted Resequencing of the FADS Region in of Pools of Individuals with High/Low Levels of PC 36:4

Chr:Offset (hg18)	Name (dbSNP132)	Locus	p Value, Two-Sided
chr11:61369044	rs75321677	<i>FADS2</i>	3.01e-6
chr11:61367609	rs75766519	<i>FADS2</i>	1.21e-5
chr11:61365899	rs17156426	<i>FADS2</i>	2.96e-5
chr11:61363623		<i>FADS2</i>	1.34e-4
chr11:61368286	rs117983270	<i>FADS2</i>	1.02e-4
chr11:61369713		<i>FADS2</i>	1.97e-4
chr11:61372118	rs7935946	<i>FADS2</i>	2.03e-4
chr11:61378187	rs73487492	<i>FADS2</i>	3.20e-4
chr11:61355905	rs117553420	<i>FADS2</i>	6.94e-4
chr11:61370599	rs17156442	<i>FADS2</i>	7.06e-4
chr11:61387858	rs520298	<i>FADS2</i>	2.58e-4
chr11:61380369	rs2526678	<i>FADS2</i>	4.04e-4
chr11:61371171	rs2845572	<i>FADS2</i>	9.75e-4
chr11:61365580	rs2727265	<i>FADS2</i>	7.89e-4
chr11:61335957	rs116878346	<i>FADS1</i>	5.46e-3
chr11:61336464		<i>FADS1</i>	1.73e-3
chr11:61388097	rs7928482	<i>FADS2</i>	1.35e-2
chr11:61370417	rs12284876	<i>FADS2</i>	3.04e-2
chr11:61369801		<i>FADS2</i>	1.14e-2
chr11:61363683	rs77020029	<i>FADS2</i>	2.59e-2
chr11:61360900	rs117220229	<i>FADS2</i>	2.62e-2
chr11:61357778	rs76498378	<i>FADS2</i>	1.86e-2
chr11:61366662		<i>FADS2</i>	7.25e-3
chr11:61368489	rs117702910	<i>FADS2</i>	5.05e-2

The p values were calculated using the C-alpha test, which is designed specifically to investigate the effects of rare variants in high-throughput sequencing data.

Table S4. Genotyping Results for 14 of the Predicted Rare Variants

SNP Id	Call Rate	#Genotyped Ind. Carrying SNP	# <i>AA</i> Ind.	# <i>DD</i> Ind.	MAF <i>AA</i> Group	MAF <i>DD</i> Group
rs116878346	.998	107	35	1	0.11	0.001
rs117553420	.999	107	35	1	0.11	0.001
11:61363623	.998	191	66	0	0.22	0
rs77020029	.995	139	45	1	0.14	0.001
rs2727265	.978	429	123	0	0.50	0
rs17156426	.999	139	44	1	0.13	0.001
rs75766519	1	137	45	1	0.14	0.001
rs117983270	.999	82	30	0	0.09	0
rs75321677	1	140	45	1	0.14	0.001
rs12284876	.997	144	45	2	0.14	0.002
rs17156442	.998	143	45	2	0.14	0.002
rs7935946	.997	144	45	2	0.14	0.002
rs73487492	.999	195	65	3	0.20	0.004
rs7928482	.998	39	14	0	0.04	0

In total 180 of the 1308 individuals were homozygous for haplotype *A* (*AA*) and 492 for haplotype *D* (*DD*).