Genome-wide Association Study Identifies Multiple Loci Influencing Human Serum Metabolite Levels

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Nature Genetics: doi:10.1038/ng.1073

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Supplementary Note

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Nature Genetics: doi:10.1038/ng.1073

Supplementary Tables

Supplementary Table 1. Metabolite abbreviations and sample sizes used for the analyses for all metabolic traits used in this study.

Abbreviation	Full metabolite name	N (NFBC)	N (YF)	N (HBCS)	N (GenMets)	N (DILGOM)	N (Total)
AcAcO	**Acetoacetate**	4677	1889	701	568	441	*8276*
AcO	**Acetate**	4703	1904	708	572	441	*8328*
Ala	**Alanine**	4703	1904	708	572	442	*8329*
Alb	**Albumin**	4627	1889	696	562	441	*8215*
bOHBuO	**3-hydroxybutyrate**	4694	1900	704	0	439	*7737*
Cit	**Citrate**	4589	1868	659	563	441	*8120*
Crea	**Creatinine**	4698	1901	708	571	443	*8321*
DHA	**22:6, docosahexaenoic acid (DHA)**	4547	1871	619	542	432	*8011*
Est-C	**Esterified cholesterol**	4523	1866	681	549	433	*8052*
FAw3	**Omega-3 fatty acids**	4503	1874	682	548	432	*8039*
FAw67	**Omega-6 and -7 fatty acids**	4504	1873	682	548	432	*8039*
FAw9S	**Omega-9 and saturated fatty acids**	4504	1873	682	548	432	*8039*
Free-C	**Free cholesterol**	4523	1866	681	549	433	*8052*
Glc	**Glucose**	4700	1904	708	572	441	*8325*
Gln	**Glutamine**	4370	1858	261	562	441	*7492*
Glol	**Glycerol**	4698	1901	703	0	439	*7741*
Gp	**Glycoprotein acetyls, mainly a1-acid glycoprotein**	4703	1904	708	572	442	*8329*
HDL-C	**Total cholesterol in HDL**	4627	1889	696	562	441	*8215*
His	**Histidine**	4700	1898	706	572	442	*8318*
IDL-C	**Total cholesterol in IDL**	4627	1889	696	562	441	*8215*
IDL-FC	**Free cholesterol in IDL**	4627	1889	696	562	441	*8215*
IDL-L	**Total lipids in IDL**	4627	1889	696	562	441	*8215*
IDL-P	**Concentration of IDL particles**	4627	1889	696	562	441	*8215*
IDL-PL	**Phospholipids in IDL**	4627	1889	696	562	441	*8215*
IDL-TG	**Triglycerides in IDL**	4627	1889	696	562	441	*8215*
Ile	**Isoleucine**	4703	1904	708	572	441	*8328*
LA	**18:2, linoleic acid (LA)**	4554	1879	683	549	433	*8098*
Lac	**Lactate**	4687	1901	707	570	441	*8306*
LDL-C	**Total cholesterol in LDL**	4627	1889	696	562	441	*8215*
Leu	**Leucine**	4703	1902	708	572	441	*8326*
L-HDL-C	**Total cholesterol in large HDL**	4627	1889	696	562	441	*8215*
L-HDL-CE	**Cholesterol esters in large HDL**	4627	1889	696	562	441	*8215*
L-HDL-FC	**Free cholesterol in large HDL**	4627	1889	696	562	441	*8215*
L-HDL-L	**Total lipids in large HDL**	4627	1889	696	562	441	*8215*
L-HDL-P	**Concentration of large HDL particles**	4627	1889	696	562	441	*8215*
L-HDL-PL	**Phospholipids in large HDL**	4627	1889	696	562	441	*8215*

Nature Genetics: doi:10.1038/ng.1073

Abbreviation	Full metabolite name	N (NFBC)	N (YF)	N (HBCS)	N (GenMets)	N (DILGOM)	N (Total)
L-LDL-C	**Total cholesterol in large LDL**	4627	1889	696	562	441	*8215*
L-LDL-CE	**Cholesterol esters in large LDL**	4627	1889	696	562	441	*8215*
L-LDL-FC	**Free cholesterol in large LDL**	4627	1889	696	562	441	*8215*
L-LDL-L	**Total lipids in large LDL**	4627	1889	696	562	441	*8215*
L-LDL-P	**Concentration of large LDL particles**	4627	1889	696	562	441	*8215*
L-LDL-PL	**Phospholipids in large LDL**	4627	1889	696	562	441	*8215*
L-VLDL-C	**Total cholesterol in large VLDL**	4627	1889	696	562	441	*8215*
L-VLDL-CE	**Cholesterol esters in large VLDL**	4627	1889	696	562	441	*8215*
L-VLDL-FC	**Free cholesterol in large VLDL**	4627	1889	696	562	441	*8215*
L-VLDL-L	**Total lipids in large VLDL**	4627	1889	696	562	441	*8215*
L-VLDL-P	**Concentration of large VLDL particles**	4627	1889	696	562	441	*8215*
L-VLDL-PL	**Phospholipids in large VLDL**	4627	1889	696	562	441	*8215*
L-VLDL-TG	**Triglycerides in large VLDL**	4627	1889	696	562	441	*8215*
M-HDL-C	**Total cholesterol in medium HDL**	4627	1889	696	562	441	*8215*
M-HDL-CE	**Cholesterol esters in medium HDL**	4627	1889	696	562	441	*8215*
M-HDL-FC	**Free cholesterol in medium HDL**	4627	1889	696	562	441	*8215*
M-HDL-L	**Total lipids in medium HDL**	4627	1889	696	562	441	*8215*
M-HDL-P	**Concentration of medium HDL particles**	4627	1889	696	562	441	*8215*
M-HDL-PL	**Phospholipids in medium HDL**	4627	1889	696	562	441	*8215*
M-LDL-C	**Total cholesterol in medium LDL**	4627	1889	696	562	441	*8215*
M-LDL-CE	**Cholesterol esters in medium LDL**	4627	1889	696	562	441	*8215*
M-LDL-L	**Total lipids in medium LDL**	4627	1889	696	562	441	*8215*
M-LDL-P	**Concentration of medium LDL particles**	4627	1889	696	562	441	*8215*
M-LDL-PL	**Phospholipids in medium LDL**	4627	1889	696	562	441	*8215*
MobCH	**Double bond protons of mobile lipids**	4703	1904	708	572	442	*8329*
MobCH2	**CH2 groups of mobile lipids**	4703	1904	708	572	443	*8330*
MobCH3	**CH3 groups of mobile lipids**	4703	1904	708	572	443	*8330*
M-VLDL-C	**Total cholesterol in medium VLDL**	4627	1889	696	562	441	*8215*
M-VLDL-CE	**Cholesterol esters in medium VLDL**	4627	1889	696	562	441	*8215*
M-VLDL-FC	**Free cholesterol in medium VLDL**	4627	1889	696	562	441	*8215*
M-VLDL-L	**Total lipids in medium VLDL**	4627	1889	696	562	441	*8215*
M-VLDL-P	**Concentration of medium VLDL particles**	4627	1889	696	562	441	*8215*
M-VLDL-PL	**Phospholipids in medium VLDL**	4627	1889	696	562	441	*8215*
M-VLDL-TG	**Triglycerides in medium VLDL**	4627	1889	696	562	441	*8215*
PC	**Phosphatidylcholine and other cholines**	4562	1833	593	476	431	*7895*
Phe	**Phenylalanine**	4698	1902	707	572	442	*8321*
PUFA	**Other polyunsaturated fatty acids than 18:2**	4474	1855	683	546	433	*7991*
Pyr	**Pyruvate**	4678	1891	695	570	440	*8274*
Serum-C	**Serum total cholesterol**	4627	1889	696	562	441	*8215*
Serum-TG	**Serum total triglycerides**	4627	1889	696	562	441	*8215*
S-HDL-L	**Total lipids in small HDL**	4627	1889	696	562	441	*8215*
S-HDL-P	**Concentration of small HDL particles**	4627	1889	696	562	441	*8215*

Nature Genetics: doi:10.1038/ng.1073

Abbreviation	Full metabolite name	N (NFBC)	N (YF)	N (HBCS)	N (GenMets)	N (DILGOM)	N (Total)
S-HDL-TG	**Triglycerides in small HDL**	4627	1889	696	562	441	*8215*
S-LDL-C	**Total cholesterol in small LDL**	4627	1889	696	562	441	*8215*
S-LDL-L	**Total lipids in small LDL**	4627	1889	696	562	441	*8215*
S-LDL-P	**Concentration of small LDL particles**	4627	1889	696	562	441	*8215*
SM	**Sphingomyelins**	4466	1838	657	486	430	*7877*
S-VLDL-C	**Total cholesterol in small VLDL**	4627	1889	696	562	441	*8215*
S-VLDL-FC	**Free cholesterol in small VLDL**	4627	1889	696	562	441	*8215*
S-VLDL-L	**Total lipids in small VLDL**	4627	1889	696	562	441	*8215*
S-VLDL-P	**Concentration of small VLDL particles**	4627	1889	696	562	441	*8215*
S-VLDL-PL	**Phospholipids in small VLDL**	4627	1889	696	562	441	*8215*
S-VLDL-TG	**Triglycerides in small VLDL**	4627	1889	696	562	441	*8215*
Tot-C	**Total cholesterol**	4562	1879	683	549	433	*8106*
Tot-CH	**Total cholines (and other N-trimethyl compounds)**	4561	1876	683	549	433	*8102*
Tot-FA	**Total fatty acids**	4502	1873	682	548	432	*8037*
Tot-PG	**Total phosphoglycerides**	4562	1836	592	477	421	*7888*
Tot-TG	**Total triglycerides**	4559	1847	662	538	430	*8036*
Tyr	**Tyrosine**	4666	1899	641	563	441	*8210*
Urea	**Urea**	4694	1898	697	571	441	*8301*
Val	**Valine**	4702	1903	705	572	441	*8323*
VLDL-TG	**Triglycerides in VLDL**	4627	1889	696	562	441	*8215*
XL-HDL-C	**Total cholesterol in very large HDL**	4627	1889	696	562	441	*8215*
XL-HDL-CE	**Cholesterol esters in very large HDL**	4627	1889	696	562	441	*8215*
XL-HDL-FC	**Free cholesterol in very large HDL**	4627	1889	696	562	441	*8215*
XL-HDL-L	**Total lipids in very large HDL**	4627	1889	696	562	441	*8215*
XL-HDL-P	**Concentration of very large HDL particles**	4627	1889	696	562	441	*8215*
XL-HDL-PL	**Phospholipids in very large HDL**	4627	1889	696	562	441	*8215*
XL-HDL-TG	**Triglycerides in very large HDL**	4627	1889	696	562	441	*8215*
XL-VLDL-L	**Total lipids in very large VLDL**	4627	1889	696	562	441	*8215*
XL-VLDL-P	**Concentration of very large VLDL particles**	4627	1889	696	562	441	*8215*
XL-VLDL-PL	**Phospholipids in very large VLDL**	4627	1889	696	562	441	*8215*
XL-VLDL-TG	**Triglycerides in very large VLDL**	4627	1889	696	562	441	*8215*
XS-VLDL-L	**Total lipids in very small VLDL**	4627	1889	696	562	441	*8215*
XS-VLDL-P	**Concentration of very small VLDL particles**	4627	1889	696	562	441	*8215*
XS-VLDL-PL	**Phospholipids in very small VLDL**	4627	1889	696	562	441	*8215*
XS-VLDL-TG	**Triglycerides in very small VLDL**	4627	1889	696	562	441	*8215*
XXL-VLDL-L	**Total lipids in chylomicrons and largest VLDL particles**	4627	1889	696	562	441	*8215*
XXL-VLDL-P	**Concentration of chylomicrons and largest VLDL particles**	4627	1889	696	562	441	*8215*
XXL-VLDL-PL	**Phospholipids in chylomicrons and largest VLDL particles**	4627	1889	696	562	441	*8215*
XXL-VLDL-TG	**Triglycerides in chylomicrons and largest VLDL particles**	4627	1889	696	562	441	*8215*
AcO/AcAcO	**Acetate to acetoacetate ratio**	4671	1887	697	566	438	*8259*

Nature Genetics: doi:10.1038/ng.1073

Abbreviation	Full metabolite name	N (NFBC)	N (YF)	N (HBCS)	N (GenMets)	N (DILGOM)	N (Total)
Ala/Cit	**Alanine to citrate ratio**	4568	1855	651	559	439	*8072*
Ala/Glc	**Alanine to glucose ratio**	4688	1898	706	571	441	*8304*
Ala/Gln	**Alanine to glutamine ratio**	4356	1854	259	560	441	*7470*
Ala/His	**Alanine to histidine ratio**	4686	1894	705	570	442	*8297*
Ala/Ile	**Alanine to isoleucine ratio**	4702	1902	706	571	441	*8322*
Ala/Leu	**Alanine to leucine ratio**	4697	1900	708	572	440	*8317*
Ala/Phe	**Alanine to phenylalnine ratio**	4684	1900	705	571	442	*8302*
Ala/Pyr	**Alanine to pyruvate ratio**	4666	1887	694	567	439	*8253*
Ala/Tyr	**Alanine to tyrosine ratio**	4650	1894	641	562	439	*8186*
Ala/Val	**Alanine to valine ratio**	4690	1897	702	569	440	*8298*
ApoA1	**Apolipoprotein A-I (Lipido)**	4338	1837	655	534	420	*7784*
ApoB	**Apolipoprotein B (Lipido)**	4338	1837	655	534	420	*7784*
ApoBtoApoA1	**Apolipoprotein B by apolipoprotein A-I (Lipido)**	4338	1837	655	534	420	*7784*
BCAAs	**Total branched chain amino acids; Val+Leu+Ile**	4691	1901	704	572	441	*8309*
Bis/DB	**Ratio of bisallylic groups to double bonds**	4467	1849	681	546	433	*7976*
Bis/FA	**Ratio of bisallylic groups to total fatty acids**	4422	1850	682	545	432	*7931*
bOHBuO/AcAcO	**3-hydroxybutyrate to acetoacetate ratio**	4662	1885	694	0	435	*7676*
bOHBuO/AcO	**3-hydroxybutyrate to acetate ratio**	4651	1877	697	0	432	*7657*
CH2/DB	**Average number of methylene groups per a double bond**	4544	1872	681	549	433	*8079*
CH2/FA	**Average number of methylene groups in a fatty acid chain**	4500	1873	682	548	432	*8035*
Crea/Alb	**Creatinine to albumin ratio**	4622	1886	692	561	440	*8201*
DB/FA	**Average number of double bonds in a fatty acid chain**	4494	1867	680	548	432	*8021*
DHA/FAw3	**Docosahexaenoic acid to omega-3 fatty acids ratio**	4466	1843	614	537	429	*7889*
DHA/PUFA	**Docosahexaenoic acid to other polyunsaturated fatty acids than linoleic acid ratio**	4451	1829	619	537	432	*7868*
FALen	**Description of average fatty acid chain length, not actual carbon number**	4415	1844	680	545	432	*7916*
FAw3/FAw67	**Omega-3 fatty acids to omega-6 and -7 fatty acids ratio**	4473	1862	680	545	431	*7991*
FAw3/FAw9S	**Omega-3 fatty acids to omega-9 and saturated fatty acids ratio**	4478	1866	681	547	431	*8003*
FAw3/FA	**Ratio of omega-3 fatty acids to total fatty acids**	4502	1873	682	548	432	*8037*
FAw67/FAw9S	**Omega-6 and -7 fatty acids ratio to omega-9 and saturated fatty acids ratio**	4500	1871	681	547	432	*8031*
FAw67/FA	**Ratio of omega-6/7 fatty acids to total fatty acids**	4502	1873	682	548	432	*8037*
FAw9S/FA	**Ratio of omega-9 and saturated fatty acids to total fatty acids**	4502	1873	682	548	432	*8037*
FR	**Fischer's ratio; (Val+Leu+Ile)/(Phe+Tyr)**	4658	1892	637	562	440	*8189*
Free-C/Est-C	**Free cholesterol to esterified cholesterol ratio**	4493	1851	680	549	431	*8004*
Glc/Cit	**Glucose to citrate ratio**	4558	1856	651	559	439	*8063*
Glc/Pyr	**Glucose to pyruvate ratio**	4663	1888	693	567	437	*8248*
Gln/Cit	**Glutamine to citrate ratio**	4291	1810	254	550	439	*7344*
Gln/Glc	**Glutamine to glucose ratio**	4353	1853	261	562	438	*7467*

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Abbreviation	Full metabolite name	N (NFBC)	N (YF)	N (HBCS)	N (GenMets)	N (DILGOM)	N (Total)
Gln/His	**Glutamine to histidine ratio**	4365	1854	260	561	441	*7481*
Gln/Ile	**Glutamine to isoleucine ratio**	4369	1855	261	561	439	*7485*
Gln/Leu	**Glutamine to leucine ratio**	4365	1856	261	561	438	*7481*
Gln/Phe	**Glutamine to phenylalnine ratio**	4366	1855	261	561	440	*7483*
Gln/Pyr	**Glutamine to pyruvate ratio**	4340	1845	256	558	438	*7437*
Gln/Tyr	**Glutamine to tyrosine ratio**	4345	1854	259	555	439	*7452*
Gln/Val	**Glutamine to valine ratio**	4368	1854	261	561	439	*7483*
Gp/Serum-TG	**Glycoprotein acetyls to serum total triglycerides ratio**	4609	1876	688	557	438	*8168*
Gp/Tot-C	**Glycoprotein acetyls to serum total cholesterol ratio**	4552	1876	682	548	430	*8088*
HDL2-C	**Total cholesterol in HDL2 (Lipido)**	4620	1889	696	561	441	*8207*
HDL3-C	**Total cholesterol in HDL3 (Lipido)**	4620	1889	696	561	441	*8207*
HDL-D	**Mean diameter for HDL particles**	4627	1889	696	562	441	*8215*
His/Ile	**Histidine to isoleucine ratio**	4699	1893	705	569	440	*8306*
His/Leu	**Histidine to leucine ratio**	4694	1896	706	572	441	*8309*
His/Phe	**Histidine to phenylalnine ratio**	4691	1896	705	571	442	*8305*
His/Tyr	**Histidine to tyrosine ratio**	4644	1890	640	562	438	*8174*
His/Val	**Histidine to valine ratio**	4688	1895	700	572	438	*8293*
IDL-C-eFR	**Total cholesterol in IDL (Lipido)**	4622	1889	696	562	441	*8210*
Ile/Glc	**Isoleucine to glucose ratio**	4689	1899	702	570	437	*8297*
Ile/Leu	**Isoleucine to leucine ratio**	4695	1901	708	572	439	*8315*
Ile/Phe	**Isoleucine to phenylalnine ratio**	4689	1900	705	570	439	*8303*
Ile/Serum-C	**Isoleucine to serum total cholesterol ratio**	4617	1886	694	560	437	*8194*
Ile/Serum-TG	**Isoleucine to serum total triglycerides ratio**	4605	1877	689	560	438	*8169*
Ile/Tyr	**Isoleucine to tyrosine ratio**	4657	1899	639	561	438	*8194*
Ile/Val	**Isoleucine to valine ratio**	4676	1896	701	568	439	*8280*
LA/DHA	**Linoleic acid to docosahexaenoic acid ratio**	4521	1860	615	538	429	*7963*
LA/FAw67	**Linoleic acid to omega-6 and -7 fatty acids ratio**	4499	1871	678	548	430	*8026*
LA/PUFA	**Linoleic acid to other polyunsaturated fatty acids than linoleic acid ratio**	4468	1850	681	544	432	*7975*
Lac/Ala	**Lactate to alanine ratio**	4674	1889	705	569	439	*8276*
Lac/Cit	**Lactate to citrate ratio**	4552	1851	652	557	438	*8050*
Lac/Glc	**Lactate to glucose ratio**	4672	1891	705	569	438	*8275*
Lac/Gln	**Lactate to glutamine ratio**	4343	1843	260	556	437	*7439*
Lac/Pyr	**Lactate to pyruvate ratio**	4644	1879	693	565	438	*8219*
LDL-C-eFR	**Total cholesterol in LDL (Lipido)**	4622	1889	696	562	441	*8210*
LDL-D	**Mean diameter for LDL particles**	4627	1889	696	562	441	*8215*
Leu/Glc	**Leucine to glucose ratio**	4693	1900	708	571	440	*8312*
Leu/Phe	**Leucine to phenylalanine ratio**	4689	1897	707	571	441	*8305*
Leu/Serum-TG	**Leucine to serum total triglycerides ratio**	4607	1879	689	559	438	*8172*
Leu/Tyr	**Leucine to tyrosine ratio**	4653	1897	641	562	440	*8193*
Leu/Val	**Leucine to valine ratio**	4692	1891	703	570	438	*8294*

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Abbreviation	Full metabolite name	N (NFBC)	N (YF)	N (HBCS)	N (GenMets)	N (DILGOM)	N (Total)
L-HDL-C/L-HDL-PL	**Total cholesterol in large HDL to phospholipids in large HDL ratio**	4619	1887	695	562	439	*8202*
L-HDL-L/M-HDL-L	**Total lipids in large HDL to total lipids in medium HDL ratio**	4617	1887	694	561	439	*8198*
L-HDL-L/S-HDL-L	**Total lipids in large HDL to total lipids in small HDL ratio**	4620	1886	695	561	440	*8202*
M-HDL-C/M-HDL-PL	**Total cholesterol in medium HDL to phospholipids in medium HDL ratio**	4617	1887	695	562	439	*8200*
M-HDL-L/S-HDL-L	**Total lipids in medium HDL to total lipids in small HDL ratio**	4627	1889	696	561	441	*8214*
M-LDL-C/M-LDL-PL	**Total cholesterol in medium LDL to phospholipids in medium LDL ratio**	4623	1887	694	561	441	*8206*
PC/Tot-CH	**Phosphatidylcholine and other cholines to total cholines (and other N-trimethyl compounds) ratio**	4524	1828	582	472	431	*7837*
Phe/Tyr	**Phenylalanine to tyrosine ratio**	4643	1887	640	563	440	*8173*
Phe/Val	**Phenylalanine to valine ratio**	4685	1893	701	571	440	*8290*
Pyr/Cit	**Pyruvate to citrate ratio**	4543	1840	641	556	434	*8014*
Serum-TG/Glc	**Serum total triglycerides to glucose ratio**	4595	1885	694	561	436	*8171*
TG/PG	**Ratio of triglycerides to phosphoglycerides**	4559	1808	577	469	421	*7834*
Tot-C/Est-C	**Total cholesterol to esterified cholesterol ratio**	4493	1851	680	549	431	*8004*
Tyr/Val	**Tyrosine to valine ratio**	4659	1895	637	562	438	*8191*
Val/Glc	**Valine to glucose ratio**	4693	1899	705	570	440	*8307*
Val/Serum-TG	**Valine to serum total triglycerides ratio**	4609	1879	686	561	437	*8172*
VLDL-D	**Mean diameter for VLDL particles**	4627	1889	696	562	441	*8215*
VLDL-TG-eFR	**Triglycerides in VLDL (Lipido)**	4622	1889	696	562	441	*8210*
XL-HDL-L/L-HDL-L	**Total lipids in very large HDL to total lipids in large HDL ratio**	4625	1876	695	560	439	*8195*
XL-HDL-L/M-HDL-L	**Total lipids in very large HDL to total lipids in medium HDL ratio**	4607	1884	691	559	439	*8180*
XL-HDL-L/S-HDL-L	**Total lipids in very large HDL to total lipids in small HDL ratio**	4613	1884	692	560	438	*8187*

Nature Genetics: doi:10.1038/ng.1073

Supplementary Table 2. Rationale for the selection of ratios used in this study. Metabolite ratios are proxies for enzymatic activity when a pair of metabolites are closely connected to the direct substrates and products of an enzymatic conversion. The metabolites comprising the ratios are implicated in lipolysis, proteolysis, ketogenesis and glycolysis as well as reagents and products of enzymatic reactions. Table also lists the implied relations between ratios and disease end points when known.

Metabolic pathway	Ratios	Rational for the ratios
Amino acid metabolism	Ala/Gln, Ala/His, Ala/Ile, Ala/Leu, Ala/Phe, Ala/Tyr, Ala/Val, Gln/His, Gln/Ile, Gln/Leu, Gln/Phe, Gln/Tyr, Gln/Val, His/Ile, His/Leu, His/Phe, His/Tyr, His/Val, Ile/Leu, Ile/Phe, Ile/Tyr, Ile/Val, Leu/Phe, Leu/Tyr, Leu/Val, Phe/Tyr, Phe/Val, Tyr/Val	Enzymatic activity in interconversion of amino acids.
Gluconeogenesis	Ala/Cit, Ala/Pyr, Ala/Glc, Glc/Cit, Gln/Cit, Glc/Pyr, Gln/Glc, Gln/Pyr, Lac/Ala, Lac/Cit, Lac/Glc, Lac/Gln, Lac/Pyr, Pyr/Cit	Enzymatic activity in reactions implicated in glylosis and gluconeogenesis, lactic acidosis, and mitochondrial redox state.
Ketogenesis	AcO/AcAcO, bOHBuO/AcAcO, bOHBuO/AcO	Enzymatic activity in ketoacidosis, lactic acidosis, and mitochondrial redox state.
Kidney function	Crea/Alb	Estimated glomerular filtration rate.
Branched-chain amino acid link to lipid metabolism	Ile/Serum-C, Ile/Serum-TG, Leu/Serum-TG, Val/Serum-TG	Role of branched-chain amino acids in lipid metabolism[8, 16].
Branched-chain amino acid link to glucose metabolism	Ile/Glc, Leu/Glc, Val/Glc, Serum-TG/Glc	Role of branched-chain amino acids in development of insulin resistance[17], T2D[18] and obesity[16].
Glycoprotein link to lipid metabolism	Gp/Serum-TG, Gp/Tot-C	Connection between low-grade inflammation and lipid metabolism[8].
Selected lipid ratios	Free-C/Est-C, Tot-C/Est-C, L-HDL-C/L-HDL-PL, M-HDL-C/M-HDL-PL, M-LDL-C/M-LDL-PL, PC/Tot-CH, TG/PG, ApoB/ApoA1	Measures of cholesterol esterification[19], cholesterol to phosholipid balance in HDL [20, 21], phoshocholine and phosphoglycerine balance, and apolipoproteinbalance, a measure for cardiovascular risk[13].
HDL size ratios	XL-HDL-L/L-HDL-L, XL-HDL-L/M-HDL-L, XL-HDL-L/S-HDL-L, L-HDL-L/M-HDL-L, L-HDL-L/S-HDL-L, M-HDL-L/S-HDL-L	Enzymatic activity regulating lipid concentration in different HDL particle sizes[22,23].
Fatty acid saturation	Bis/DB, Bis/FA, CH2/DB, CH2/FA, DB/FA,	Cardiovascular protection [24] and risk for T2D[25]
Polyunsaturated fatty acid	DHA/FAw3, DHA/PUFA, FAw3/FA, FAw3/FAw67, FAw3/FAw9S, FAw67/FA, FAw67/FAw9S, FAw9S/FA, LA/DHA, LA/FAw67	Fatty acid saturation ratios linked with energy production, modulation of inflammation, and maintenance of cell membrane integrity[26] and the risk for cardiovascular disease[24], T2D[25], renal failure[27], and mild cognitive impairment[9].

Nature Genetics: doi:10.1038/ng.1073

Supplementary Table 3. Intraclass correlation coefficients for MZ and DZ twins, genetic and environmental raw variance estimates and heritability estimate for every phenotype.

Abbreviation	Model	ICC-MZ	ICC-DZ	A variance (95%CI)	D variance (95%CI)	C variance (95%CI)	E variance (95%CI)	Heritability (95%CI)	Variance explained
AcAcO	AE	0.506	0.24	0.497 (0.392 –0.606)	–	–	0.502 (0.425 –0.593)	0.497 (0.405 –0.578)	NA
AcO	CE	0.352	0.279	–	–	0.301 (0.220 –0.389)	0.697 (0.622 –0.783)	–	NA
AcO/AcAcO	AE	0.514	0.32	0.524 (0.424 –0.628)	–	–	0.471 (0.401 –0.555)	0.527 (0.442 –0.601)	NA
Ala	ACE	0.498	0.359	0.307 (0.054 –0.557)	–	0.185 (0.000 –0.379)	0.503 (0.422 –0.605)	0.308 (0.054 –0.553)	0.0056
Ala/Cit	ADE	0.543	0.186	0.196 (0.000 –0.573)	0.336 (0.000 –0.630)	–	0.464 (0.389 –0.557)	0.534 (0.440 –0.612)	0.0022
Ala/Glc	AE	0.52	0.339	0.540 (0.441 –0.643)	–	–	0.455 (0.388 –0.537)	0.542 (0.459 –0.614)	0.0075
Ala/Gln	ACE	0.67	0.42	0.525 (0.322 –0.735)	–	0.148 (0.000 –0.322)	0.327 (0.273 –0.395)	0.525 (0.324 –0.717)	0.031
Ala/His	AE	0.457	0.283	0.459 (0.361 –0.562)	–	–	0.533 (0.457 –0.623)	0.463 (0.374 –0.542)	0.018
Ala/Ile	AE	0.475	0.26	0.496 (0.390 –0.606)	–	–	0.506 (0.429 –0.598)	0.495 (0.402 –0.576)	NA
Ala/Leu	ACE	0.455	0.294	0.275 (0.002 –0.530)	–	0.161 (0.000 –0.375)	0.561 (0.473 –0.670)	0.276 (0.002 –0.519)	NA
Ala/Phe	AE	0.331	0.209	0.349 (0.243 –0.458)	–	–	0.650 (0.558 –0.758)	0.350 (0.248 –0.442)	0.0076
Ala/Pyr	AE	0.451	0.233	0.459 (0.352 –0.569)	–	–	0.542 (0.462 –0.639)	0.458 (0.362 –0.543)	NA
Ala/Tyr	AE	0.41	0.218	0.405 (0.300 –0.514)	–	–	0.592 (0.506 –0.694)	0.406 (0.308 –0.495)	0.003
Ala/Val	ACE	0.445	0.297	0.214 (0.000 –0.488)	–	0.202 (0.000 –0.412)	0.581 (0.492 –0.690)	0.215 (0.000 –0.483)	0.032
Alb	ACE	0.544	0.375	0.393 (0.150 –0.634)	–	0.165 (0.000 –0.355)	0.442 (0.368 –0.536)	0.393 (0.150 –0.620)	NA
ApoA1	AE	0.616	0.271	0.605 (0.500 –0.716)	–	–	0.396 (0.330 –0.476)	0.605 (0.521 –0.675)	0.058
ApoB	ADE	0.691	0.273	0.367 (0.000 –0.759)	0.338 (0.000 –0.757)	–	0.299 (0.247 –0.368)	0.702 (0.630 –0.758)	0.042
ApoB/ApoA1	ADE	0.787	0.298	0.407 (0.000 –0.812)	0.364 (0.000 –0.790)	–	0.221 (0.183 –0.271)	0.777 (0.724 –0.818)	0.077
BCAAs	AE	0.521	0.299	0.547 (0.443 –0.655)	–	–	0.455 (0.385 –0.540)	0.546 (0.459 –0.621)	0.0036
Bis/DB	AE	0.523	0.221	0.488 (0.385 –0.595)	–	–	0.507 (0.431 –0.598)	0.491 (0.399 –0.571)	0.104
Bis/FA	AE	0.507	0.26	0.489 (0.388 –0.596)	–	–	0.505 (0.430 –0.594)	0.492 (0.403 –0.571)	0.088
bOHBuO	AE	0.51	0.252	0.535 (0.422 –0.652)	–	–	0.472 (0.395 –0.566)	0.532 (0.435 –0.614)	NA
bOHBuO/AcAcO	AE	0.439	0.304	0.472 (0.364 –0.584)	–	–	0.526 (0.445 –0.623)	0.473 (0.376 –0.558)	NA
bOHBuO/AcO	AE	0.45	0.265	0.491 (0.378 –0.609)	–	–	0.514 (0.432 –0.613)	0.489 (0.389 –0.576)	NA
CH2/DB	AE	0.556	0.341	0.558 (0.460 –0.661)	–	–	0.434 (0.368 –0.513)	0.563 (0.481 –0.633)	0.048
CH2/FA	AE	0.374	0.217	0.392 (0.282 –0.505)	–	–	0.608 (0.517 –0.715)	0.392 (0.289 –0.486)	0.022
Cit	AE	0.539	0.251	0.536 (0.432 –0.644)	–	–	0.463 (0.392 –0.549)	0.536 (0.448 –0.612)	0.0005
Crea	ACE	0.584	0.372	0.412 (0.179 –0.647)	–	0.166 (0.000 –0.355)	0.418 (0.350 –0.504)	0.414 (0.180 –0.636)	NA
Crea/Alb	ACE	0.578	0.357	0.414 (0.176 –0.650)	–	0.158 (0.143 –0.650)	0.425 (0.355 –0.512)	0.416 (0.177 –0.635)	NA
DB/FA	AE	0.484	0.287	0.494 (0.391 –0.602)	–	–	0.503 (0.427 –0.593)	0.496 (0.405 –0.575)	0.044
DHA	AE	0.475	0.285	0.477 (0.376 –0.583)	–	–	0.518 (0.442 –0.609)	0.480 (0.389 –0.559)	NA
DHA/FAw3	AE	0.374	0.19	0.381 (0.270 –0.496)	–	–	0.619 (0.527 –0.729)	0.381 (0.276 –0.476)	NA
DHA/PUFA	ACE	0.446	0.326	0.282 (0.006 –0.546)	–	0.172 (0.000 –0.379)	0.545 (0.455 –0.658)	0.282 (0.006 –0.534)	0.0075
Est-C	AE	0.649	0.347	0.648 (0.551 –0.751)	–	–	0.348 (0.293 –0.416)	0.651 (0.579 –0.710)	0.057
FALen	AE	0.311	0.175	0.330 (0.215 –0.447)	–	–	0.671 (0.572 –0.789)	0.330 (0.219 –0.431)	NA
FAw3	AE	0.508	0.236	0.482 (0.379 –0.589)	–	–	0.514 (0.437 –0.605)	0.484 (0.393 –0.564)	0.017
FAw3/FA	AE	0.476	0.285	0.493 (0.388 –0.601)	–	–	0.506 (0.429 –0.598)	0.493 (0.401 –0.574)	0.028
FAw3/FAw67	AE	0.46	0.287	0.467 (0.365 –0.573)	–	–	0.528 (0.451 –0.621)	0.469 (0.378 –0.550)	0.03
FAw3/FAw9S	AE	0.493	0.286	0.509 (0.404 –0.618)	–	–	0.490 (0.415 –0.581)	0.509 (0.418 –0.589)	0.027
FAw67	AE	0.594	0.277	0.574 (0.473 –0.680)	–	–	0.423 (0.357 –0.502)	0.576 (0.493 –0.646)	0.048
FAw67/FA	ACE	0.463	0.325	0.251 (0.000 –0.521)	–	0.201 (0.000 –0.411)	0.546 (0.457 –0.655)	0.252 (0.000 –0.516)	NA
FAw67/FAw9S	CE	0.455	0.339	–	–	0.384 (0.300 –0.475)	0.614 (0.547 –0.692)	–	NA

Nature Genetics: doi:10.1038/ng.1073

Abbreviation	Model	ICC-MZ	ICC-DZ	A variance (95%CI)	D variance (95%CI)	C variance (95%CI)	E variance (95%CI)	Heritability (95%CI)	Variance explained
FAw9S	AE	0.543	0.292	0.530 (0.430 –0.635)	–	–	0.464 (0.394 –0.547)	0.533 (0.448 –0.607)	0.022
FAw9S/FA	ACE	0.476	0.326	0.280 (0.011 –0.545)	–	0.185 (0.000 –0.393)	0.532 (0.445 –0.639)	0.281 (0.011 –0.537)	NA
FR	CE	0.416	0.319	–	–	0.359 (0.274 –0.450)	0.640 (0.570 –0.722)	–	0.0082
Free-C	AE	0.641	0.33	0.644 (0.545 –0.749)	–	–	0.356 (0.299 –0.426)	0.644 (0.570 –0.706)	0.05
Free-C/Est-C	AE	0.486	0.168	0.438 (0.334 –0.546)	–	–	0.556 (0.475 –0.654)	0.440 (0.345 –0.526)	0.0044
Glc	ACE	0.492	0.373	0.253 (0.000 –0.505)	–	0.239 (0.036 –0.436)	0.507 (0.425 –0.610)	0.253 (0.000 –0.501)	0.013
Glc/Cit	AE	0.564	0.353	0.580 (0.482 –0.683)	–	–	0.414 (0.351 –0.490)	0.584 (0.505 –0.651)	0.0006
Glc/Pyr	AE	0.542	0.305	0.561 (0.459 –0.668)	–	–	0.440 (0.373 –0.522)	0.560 (0.476 –0.633)	0.021
Gln	AE	0.527	0.297	0.547 (0.445 –0.654)	–	–	0.454 (0.384 –0.537)	0.547 (0.461 –0.621)	0.014
Gln/Cit	AE	0.481	0.283	0.525 (0.418 –0.637)	–	–	0.477 (0.403 –0.568)	0.524 (0.432 –0.604)	NA
Gln/Glc	ACE	0.497	0.343	0.279 (0.020 –0.537)	–	0.209 (0.000 –0.412)	0.511 (0.429 –0.613)	0.279 (0.020 –0.533)	0.0026
Gln/His	ACE	0.504	0.372	0.339 (0.087 –0.590)	–	0.211 (0.007 –0.407)	0.459 (0.381 –0.557)	0.336 (0.086 –0.578)	0.021
Gln/Ile	AE	0.587	0.314	0.593 (0.494 –0.698)	–	–	0.406 (0.343 –0.481)	0.594 (0.515 –0.661)	0.037
Gln/Leu	AE	0.566	0.284	0.559 (0.459 –0.663)	–	–	0.438 (0.372 –0.518)	0.560 (0.478 –0.631)	0.0014
Gln/Phe	AE	0.516	0.241	0.533 (0.425 –0.644)	–	–	0.474 (0.400 –0.563)	0.529 (0.438 –0.608)	0.0013
Gln/Pyr	AE	0.499	0.31	0.548 (0.443 –0.657)	–	–	0.457 (0.387 –0.543)	0.545 (0.457 –0.621)	0.016
Gln/Tyr	AE	0.552	0.324	0.555 (0.457 –0.659)	–	–	0.439 (0.373 –0.519)	0.559 (0.477 –0.629)	0.0059
Gln/Val	ACE	0.546	0.376	0.339 (0.096 –0.582)	–	0.210 (0.009 –0.404)	0.452 (0.379 –0.545)	0.338 (0.096 –0.576)	0.016
Glol	ACE	0.567	0.431	0.331 (0.103 –0.559)	–	0.255 (0.066 –0.438)	0.415 (0.346 –0.502)	0.331 (0.103 –0.553)	NA
Gp	AE	0.541	0.298	0.527 (0.430 –0.629)	–	–	0.463 (0.395 –0.544)	0.532 (0.450 –0.605)	0.0023
Gp/Serum-TG	AE	0.635	0.288	0.626 (0.526 –0.731)	–	–	0.375 (0.316 –0.448)	0.625 (0.549 –0.689)	0.038
Gp/Tot-C	ACE	0.606	0.403	0.434 (0.208 –0.666)	–	0.185 (0.000 –0.371)	0.383 (0.318 –0.466)	0.433 (0.208 –0.657)	0.053
HDL2-C	AE	0.757	0.287	0.721 (0.627 –0.821)	–	–	0.275 (0.231 –0.330)	0.724 (0.664 –0.773)	0.059
HDL3-C	ADE	0.596	0.106	0.000 (0.000 –0.314)	0.565 (0.238 –0.669)	–	0.428 (0.360 –0.513)	0.569 (0.483 –0.641)	NA
HDL-C	AE	0.742	0.291	0.712 (0.617 –0.813)	–	–	0.286 (0.240 –0.343)	0.713 (0.652 –0.764)	0.059
HDL-D	AE	0.791	0.354	0.777 (0.686 –0.875)	–	–	0.222 (0.186 –0.267)	0.778 (0.728 –0.817)	0.077
His	ACE	0.417	0.293	0.229 (0.000 –0.497)	–	0.178 (0.000 –0.388)	0.590 (0.496 –0.704)	0.230 (0.000 –0.489)	0.0001
His/Ile	AE	0.534	0.27	0.541 (0.438 –0.649)	–	–	0.460 (0.390 –0.545)	0.540 (0.454 –0.615)	0.057
His/Leu	ACE	0.567	0.383	0.292 (0.058 –0.530)	–	0.248 (0.049 –0.440)	0.454 (0.382 –0.544)	0.294 (0.058 –0.528)	NA
His/Phe	AE	0.494	0.179	0.442 (0.342 –0.547)	–	–	0.551 (0.473 –0.644)	0.445 (0.354 –0.527)	0.0084
His/Tyr	ACE	0.417	0.291	0.235 (0.000 –0.508)	–	0.180 (0.000 –0.395)	0.585 (0.491 –0.702)	0.235 (0.000 –0.497)	0.006
His/Val	CE	0.443	0.318	–	–	0.380 (0.295 –0.472)	0.622 (0.554 –0.701)	–	0.0017
IDL-C	AE	0.635	0.341	0.657 (0.558 –0.762)	–	–	0.347 (0.292 –0.415)	0.654 (0.582 –0.714)	0.075
IDL-C-eFR	ADE	0.702	0.262	0.307 (0.000 –0.698)	0.402 (0.018 –0.772)	–	0.293 (0.244 –0.356)	0.708 (0.642 –0.760)	0.043
IDL-FC	AE	0.57	0.357	0.609 (0.509 –0.715)	–	–	0.392 (0.331 –0.467)	0.608 (0.531 –0.674)	0.086
IDL-L	AE	0.629	0.344	0.657 (0.557 –0.762)	–	–	0.348 (0.293 –0.417)	0.653 (0.581 –0.714)	0.095
IDL-P	AE	0.633	0.348	0.662 (0.562 –0.767)	–	–	0.344 (0.289 –0.412)	0.658 (0.586 –0.718)	0.095
IDL-PL	AE	0.618	0.363	0.658 (0.558 –0.762)	–	–	0.348 (0.293 –0.416)	0.654 (0.582 –0.714)	0.071
IDL-TG	AE	0.648	0.283	0.656 (0.554 –0.764)	–	–	0.354 (0.296 –0.424)	0.650 (0.575 –0.712)	0.048
Ile	AE	0.496	0.26	0.509 (0.403 –0.620)	–	–	0.493 (0.417 –0.584)	0.508 (0.416 –0.589)	0.033
Ile/Glc	AE	0.466	0.288	0.499 (0.394 –0.608)	–	–	0.502 (0.426 –0.593)	0.498 (0.406 –0.579)	0.038
Ile/Leu	AE	0.503	0.251	0.498 (0.395 –0.605)	–	–	0.501 (0.426 –0.590)	0.499 (0.409 –0.578)	NA
Ile/Phe	AE	0.469	0.232	0.488 (0.378 –0.601)	–	–	0.517 (0.438 –0.613)	0.485 (0.388 –0.570)	0.036
Ile/Serum-C	AE	0.526	0.296	0.556 (0.451 –0.666)	–	–	0.448 (0.377 –0.533)	0.554 (0.466 –0.629)	0.011
Ile/Serum-TG	AE	0.523	0.259	0.532 (0.426 –0.641)	–	–	0.471 (0.398 –0.559)	0.530 (0.440 –0.608)	0.042
Ile/Tyr	AE	0.522	0.203	0.488 (0.384 –0.597)	–	–	0.509 (0.433 –0.601)	0.489 (0.397 –0.571)	0.025
Ile/Val	AE	0.46	0.205	0.425 (0.324 –0.531)	–	–	0.570 (0.488 –0.666)	0.428 (0.334 –0.512)	NA

Nature Genetics: doi:10.1038/ng.1073

Abbreviation	Model	ICC-MZ	ICC-DZ	A variance (95%CI)	D variance (95%CI)	C variance (95%CI)	E variance (95%CI)	Heritability (95%CI)	Variance explained
LA	AE	0.645	0.267	0.619 (0.519 –0.725)	–	–	0.380 (0.319 –0.453)	0.620 (0.542 –0.685)	0.053
LA/DHA	AE	0.494	0.326	0.519 (0.418 –0.625)	–	–	0.477 (0.405 –0.564)	0.521 (0.434 –0.597)	0.027
LA/FAw67	ACE	0.46	0.371	0.257 (0.000 –0.521)	–	0.238 (0.030 –0.442)	0.509 (0.422 –0.621)	0.256 (0.000 –0.513)	0.101
LA/PUFA	AE	0.614	0.364	0.616 (0.520 –0.718)	–	–	0.377 (0.319 –0.447)	0.621 (0.546 –0.683)	0.251
Lac	ACE	0.468	0.325	0.255 (0.000 –0.521)	–	0.203 (0.000 –0.411)	0.540 (0.453 –0.647)	0.255 (0.000 –0.517)	NA
Lac/Ala	AE	0.506	0.276	0.506 (0.404 –0.612)	–	–	0.489 (0.417 –0.577)	0.508 (0.420 –0.585)	NA
Lac/Cit	AE	0.389	0.23	0.384 (0.282 –0.490)	–	–	0.612 (0.526 –0.713)	0.386 (0.289 –0.473)	0.0029
Lac/Glc	AE	0.55	0.267	0.539 (0.438 –0.644)	–	–	0.458 (0.389 –0.541)	0.541 (0.455 –0.614)	NA
Lac/Gln	ACE	0.436	0.333	0.217 (0.000 –0.486)	–	0.223 (0.011 –0.427)	0.560 (0.469 –0.673)	0.217 (0.000 –0.482)	0.0029
Lac/Pyr	AE	0.522	0.248	0.524 (0.419 –0.633)	–	–	0.477 (0.404 –0.565)	0.523 (0.433 –0.601)	NA
LDL-C	AE	0.629	0.362	0.674 (0.575 –0.780)	–	–	0.334 (0.281 –0.401)	0.668 (0.598 –0.727)	0.077
LDL-C-eFR	AE	0.603	0.344	0.622 (0.523 –0.726)	–	–	0.378 (0.319 –0.450)	0.622 (0.546 –0.686)	0.073
LDL-D	AE	0.424	0.206	0.414 (0.308 –0.523)	–	–	0.584 (0.499 –0.685)	0.415 (0.317 –0.503)	0.011
Leu	AE	0.51	0.285	0.516 (0.414 –0.623)	–	–	0.482 (0.409 –0.569)	0.517 (0.429 –0.594)	NA
Leu/Glc	AE	0.517	0.328	0.534 (0.434 –0.638)	–	–	0.462 (0.393 –0.544)	0.536 (0.452 –0.609)	NA
Leu/Phe	AE	0.433	0.295	0.458 (0.356 –0.564)	–	–	0.538 (0.460 –0.631)	0.460 (0.368 –0.541)	NA
Leu/Serum-TG	AE	0.568	0.267	0.561 (0.458 –0.668)	–	–	0.439 (0.372 –0.521)	0.561 (0.476 –0.633)	0.022
Leu/Tyr	AE	0.412	0.191	0.389 (0.285 –0.497)	–	–	0.607 (0.520 –0.709)	0.391 (0.293 –0.480)	NA
Leu/Val	AE	0.387	0.223	0.373 (0.272 –0.476)	–	–	0.622 (0.536 –0.723)	0.375 (0.280 –0.461)	0.021
L-HDL-C	AE	0.778	0.302	0.754 (0.661 –0.854)	–	–	0.247 (0.207 –0.297)	0.753 (0.699 –0.798)	0.084
L-HDL-C/L-HDL-PL	AE	0.678	0.327	0.664 (0.568 –0.765)	–	–	0.332 (0.279 –0.396)	0.667 (0.599 –0.724)	0.013
L-HDL-CE	AE	0.77	0.299	0.744 (0.651 –0.845)	–	–	0.256 (0.214 –0.307)	0.744 (0.688 –0.790)	0.086
L-HDL-FC	AE	0.783	0.301	0.758 (0.665 –0.858)	–	–	0.242 (0.203 –0.292)	0.758 (0.704 –0.801)	0.076
L-HDL-L	AE	0.778	0.31	0.754 (0.662 –0.854)	–	–	0.245 (0.205 –0.295)	0.755 (0.700 –0.799)	0.083
L-HDL-L/M-HDL-L	AE	0.796	0.344	0.787 (0.696 –0.887)	–	–	0.216 (0.181 –0.261)	0.785 (0.736 –0.824)	0.099
L-HDL-L/S-HDL-L	AE	0.793	0.349	0.780 (0.689 –0.878)	–	–	0.220 (0.184 –0.265)	0.780 (0.730 –0.819)	0.087
L-HDL-P	AE	0.776	0.31	0.751 (0.659 –0.851)	–	–	0.248 (0.207 –0.298)	0.752 (0.697 –0.796)	0.081
L-HDL-PL	AE	0.773	0.312	0.745 (0.652 –0.844)	–	–	0.252 (0.211 –0.303)	0.747 (0.692 –0.792)	0.083
L-LDL-C	AE	0.63	0.366	0.674 (0.575 –0.779)	–	–	0.334 (0.280 –0.400)	0.669 (0.598 –0.727)	0.079
L-LDL-CE	AE	0.637	0.343	0.672 (0.571 –0.777)	–	–	0.337 (0.283 –0.405)	0.666 (0.594 –0.725)	0.076
L-LDL-FC	AE	0.598	0.365	0.652 (0.552 –0.758)	–	–	0.355 (0.299 –0.426)	0.647 (0.573 –0.709)	0.08
L-LDL-L	AE	0.638	0.371	0.686 (0.587 –0.791)	–	–	0.323 (0.271 –0.388)	0.680 (0.611 –0.736)	0.078
L-LDL-P	AE	0.644	0.369	0.690 (0.591 –0.795)	–	–	0.319 (0.268 –0.383)	0.684 (0.615 –0.740)	0.077
L-LDL-PL	AE	0.638	0.363	0.685 (0.586 –0.791)	–	–	0.325 (0.272 –0.390)	0.678 (0.609 –0.735)	0.079
L-VLDL-C	AE	0.579	0.253	0.550 (0.449 –0.656)	–	–	0.446 (0.378 –0.529)	0.552 (0.467 –0.625)	0.035
L-VLDL-CE	AE	0.596	0.237	0.563 (0.461 –0.671)	–	–	0.435 (0.367 –0.517)	0.564 (0.480 –0.637)	0.04
L-VLDL-FC	AE	0.572	0.265	0.544 (0.444 –0.650)	–	–	0.450 (0.382 –0.533)	0.547 (0.463 –0.620)	0.036
L-VLDL-L	AE	0.584	0.247	0.557 (0.455 –0.665)	–	–	0.441 (0.372 –0.523)	0.558 (0.473 –0.632)	0.027
L-VLDL-P	AE	0.582	0.262	0.559 (0.457 –0.665)	–	–	0.438 (0.370 –0.519)	0.561 (0.477 –0.633)	0.024
L-VLDL-PL	AE	0.585	0.249	0.560 (0.457 –0.667)	–	–	0.438 (0.370 –0.521)	0.561 (0.476 –0.634)	0.027
L-VLDL-TG	AE	0.585	0.255	0.562 (0.459 –0.669)	–	–	0.436 (0.369 –0.518)	0.563 (0.478 –0.635)	0.011
M-HDL-C	ADE	0.668	0.23	0.277 (0.000 –0.666)	0.354 (0.000 –0.705)	–	0.355 (0.298 –0.426)	0.640 (0.566 –0.701)	0.018
M-HDL-C/M-HDL-PL	AE	0.615	0.269	0.610 (0.508 –0.717)	–	–	0.394 (0.331 –0.470)	0.608 (0.528 –0.675)	0.018

Nature Genetics: doi:10.1038/ng.1073

Abbreviation	Model	ICC-MZ	ICC-DZ	A variance (95%CI)	D variance (95%CI)	C variance (95%CI)	E variance (95%CI)	Heritability (95%CI)	Variance explained
M-HDL-CE	ADE	0.661	0.222	0.258 (0.000 –0.653)	0.367 (0.000 –0.702)	–	0.362 (0.304 –0.435)	0.633 (0.557 –0.695)	0.019
M-HDL-FC	AE	0.667	0.265	0.627 (0.529 –0.730)	–	–	0.366 (0.309 –0.436)	0.631 (0.557 –0.694)	0.014
M-HDL-L	AE	0.646	0.25	0.604 (0.505 –0.708)	–	–	0.389 (0.329 –0.463)	0.608 (0.530 –0.674)	0.01
M-HDL-L/S-HDL-L	AE	0.674	0.314	0.641 (0.546 –0.741)	–	–	0.349 (0.295 –0.414)	0.647 (0.578 –0.706)	0.024
M-HDL-P	AE	0.632	0.253	0.592 (0.493 –0.697)	–	–	0.400 (0.338 –0.475)	0.597 (0.518 –0.664)	0.0073
M-HDL-PL	AE	0.641	0.262	0.601 (0.503 –0.704)	–	–	0.391 (0.330 –0.464)	0.606 (0.529 –0.672)	0.0081
M-LDL-C	AE	0.624	0.355	0.665 (0.565 –0.771)	–	–	0.343 (0.288 –0.411)	0.660 (0.587 –0.719)	0.073
M-LDL-C/M-LDL-PL	ACE	0.486	0.362	0.307 (0.047 –0.562)	–	0.202 (0.000 –0.399)	0.494 (0.411 –0.598)	0.306 (0.047 –0.554)	0.053
M-LDL-CE	AE	0.624	0.358	0.665 (0.565 –0.771)	–	–	0.342 (0.287 –0.410)	0.660 (0.588 –0.720)	0.073
M-LDL-L	AE	0.633	0.356	0.675 (0.575 –0.781)	–	–	0.334 (0.280 –0.401)	0.669 (0.598 –0.728)	0.074
M-LDL-P	AE	0.637	0.354	0.681 (0.580 –0.786)	–	–	0.330 (0.276 –0.396)	0.674 (0.603 –0.732)	0.073
M-LDL-PL	AE	0.658	0.313	0.675 (0.574 –0.781)	–	–	0.334 (0.280 –0.402)	0.669 (0.597 –0.728)	0.067
MobCH	AE	0.581	0.218	0.547 (0.445 –0.654)	–	–	0.452 (0.383 –0.535)	0.548 (0.462 –0.622)	0.043
MobCH2	AE	0.558	0.254	0.533 (0.432 –0.639)	–	–	0.463 (0.393 –0.547)	0.535 (0.450 –0.610)	0.024
MobCH3	AE	0.593	0.231	0.555 (0.454 –0.660)	–	–	0.442 (0.375 –0.522)	0.557 (0.473 –0.629)	0.054
M-VLDL-C	AE	0.644	0.252	0.598 (0.499 –0.701)	–	–	0.396 (0.335 –0.470)	0.601 (0.524 –0.668)	0.053
M-VLDL-CE	AE	0.662	0.267	0.620 (0.522 –0.723)	–	–	0.374 (0.316 –0.444)	0.624 (0.549 –0.687)	0.065
M-VLDL-FC	AE	0.629	0.241	0.582 (0.483 –0.687)	–	–	0.412 (0.349 –0.488)	0.586 (0.506 –0.654)	0.038
M-VLDL-L	AE	0.628	0.238	0.586 (0.486 –0.691)	–	–	0.410 (0.347 –0.487)	0.588 (0.508 –0.657)	0.035
M-VLDL-P	AE	0.624	0.241	0.585 (0.485 –0.690)	–	–	0.412 (0.348 –0.489)	0.587 (0.506 –0.656)	0.034
M-VLDL-PL	AE	0.64	0.245	0.602 (0.502 –0.707)	–	–	0.395 (0.334 –0.470)	0.604 (0.525 –0.671)	0.038
M-VLDL-TG	AE	0.615	0.246	0.578 (0.478 –0.684)	–	–	0.418 (0.354 –0.496)	0.580 (0.499 –0.650)	0.031
PC	AE	0.59	0.266	0.579 (0.476 –0.687)	–	–	0.420 (0.354 –0.501)	0.580 (0.496 –0.651)	0.032
PC/Tot-CH	CE	0.317	0.314	–	–	0.322 (0.237 –0.415)	0.680 (0.605 –0.767)	–	NA
Phe	AE	0.402	0.194	0.387 (0.283 –0.495)	–	–	0.610 (0.523 –0.712)	0.389 (0.291 –0.477)	0.016
Phe/Tyr	AE	0.354	0.24	0.392 (0.282 –0.504)	–	–	0.609 (0.520 –0.716)	0.391 (0.289 –0.483)	0.0093
Phe/Val	ACE	0.408	0.269	0.222 (0.000 –0.493)	–	0.174 (0.000 –0.391)	0.604 (0.509 –0.721)	0.222 (0.000 –0.482)	0.027
PUFA	AE	0.621	0.307	0.617 (0.517 –0.723)	–	–	0.382 (0.322 –0.456)	0.618 (0.540 –0.683)	0.076
Pyr	AE	0.49	0.33	0.522 (0.421 –0.627)	–	–	0.476 (0.405 –0.560)	0.523 (0.437 –0.598)	0.018
Pyr/Cit	AE	0.491	0.161	0.451 (0.344 –0.563)	–	–	0.548 (0.465 –0.647)	0.452 (0.354 –0.539)	NA
Serum-C	AE	0.657	0.321	0.659 (0.560 –0.763)	–	–	0.343 (0.289 –0.411)	0.657 (0.586 –0.717)	0.051
Serum-TG	AE	0.639	0.255	0.611 (0.510 –0.717)	–	–	0.388 (0.327 –0.463)	0.611 (0.533 –0.678)	0.039
Serum-TG/Glc	AE	0.564	0.272	0.556 (0.454 –0.663)	–	–	0.443 (0.375 –0.526)	0.557 (0.472 –0.630)	0.034
S-HDL-L	AE	0.6	0.274	0.606 (0.502 –0.715)	–	–	0.398 (0.335 –0.476)	0.603 (0.522 –0.672)	0.0024
S-HDL-P	ADE	0.591	0.218	0.259 (0.000 –0.638)	0.335 (0.000 –0.679)	–	0.405 (0.338 –0.489)	0.595 (0.508 –0.665)	0.0028
S-HDL-TG	AE	0.665	0.336	0.661 (0.564 –0.763)	–	–	0.337 (0.284 –0.402)	0.662 (0.593 –0.720)	0.067
S-LDL-C	AE	0.608	0.349	0.657 (0.555 –0.764)	–	–	0.353 (0.296 –0.423)	0.651 (0.576 –0.712)	0.057
S-LDL-L	AE	0.616	0.341	0.659 (0.558 –0.766)	–	–	0.350 (0.294 –0.421)	0.653 (0.579 –0.714)	0.05
S-LDL-P	AE	0.633	0.341	0.663 (0.563 –0.769)	–	–	0.344 (0.289 –0.412)	0.658 (0.586 –0.718)	0.056
SM	AE	0.555	0.339	0.570 (0.471 –0.673)	–	–	0.425 (0.360 –0.503)	0.573 (0.492 –0.642)	0.0044
S-VLDL-C	AE	0.723	0.282	0.696 (0.600 –0.799)	–	–	0.304 (0.255 –0.364)	0.696 (0.631 –0.750)	0.022
S-VLDL-FC	ADE	0.71	0.255	0.359 (0.000 –0.742)	0.329 (0.000 –0.737)	–	0.305 (0.255 –0.368)	0.693 (0.627 –0.747)	0.07
S-VLDL-L	ADE	0.706	0.236	0.275 (0.000 –0.683)	0.413 (0.011 –0.760)	–	0.307 (0.256 –0.371)	0.691 (0.625 –0.745)	0.071
S-VLDL-P	ADE	0.691	0.233	0.276 (0.000 –0.684)	0.393 (0.000 –0.743)	–	0.324 (0.271 –0.391)	0.674 (0.604 –0.730)	0.062
S-VLDL-PL	ADE	0.705	0.239	0.287 (0.000 –0.695)	0.404 (0.003 –0.761)	–	0.305 (0.255 –0.369)	0.694 (0.627 –0.747)	0.081
S-VLDL-TG	AE	0.664	0.259	0.630 (0.532 –0.734)	–	–	0.367 (0.310 –0.438)	0.632 (0.557 –0.694)	0.054
TG/PG	AE	0.521	0.24	0.507 (0.401 –0.617)	–	–	0.491 (0.415 –0.582)	0.508 (0.416 –0.588)	0.002

Nature Genetics: doi:10.1038/ng.1073

Abbreviation	Model	ICC-MZ	ICC-DZ	A variance (95%CI)	D variance (95%CI)	C variance (95%CI)	E variance (95%CI)	Heritability (95%CI)	Variance explained
Tot-C	AE	0.658	0.352	0.659 (0.562 –0.762)	–	–	0.338 (0.284 –0.404)	0.661 (0.591 –0.720)	0.052
Tot-C/Est-C	AE	0.483	0.165	0.435 (0.330 –0.543)	–	–	0.560 (0.478 –0.658)	0.437 (0.341 –0.523)	0.0048
Tot-CH	AE	0.583	0.286	0.582 (0.480 –0.690)	–	–	0.417 (0.351 –0.497)	0.583 (0.500 –0.653)	0.037
Tot-FA	AE	0.567	0.281	0.544 (0.444 –0.649)	–	–	0.449 (0.381 –0.531)	0.548 (0.464 –0.620)	0.027
Tot-PG	AE	0.57	0.283	0.568 (0.465 –0.676)	–	–	0.430 (0.362 –0.512)	0.569 (0.484 –0.642)	NA
Tot-TG	AE	0.535	0.247	0.516 (0.411 –0.625)	–	–	0.482 (0.408 –0.571)	0.517 (0.426 –0.596)	0.017
Tyr	AE	0.362	0.247	0.388 (0.283 –0.497)	–	–	0.609 (0.521 –0.713)	0.389 (0.290 –0.479)	0.0044
Tyr/Val	CE	0.368	0.283	–	–	0.310 (0.229 –0.398)	0.687 (0.613 –0.773)	–	0.024
Urea	AE	0.481	0.195	0.435 (0.333 –0.541)	–	–	0.558 (0.478 –0.654)	0.438 (0.345 –0.522)	NA
Val	AE	0.429	0.277	0.445 (0.343 –0.552)	–	–	0.551 (0.472 –0.646)	0.447 (0.354 –0.530)	0.024
Val/Glc	ACE	0.408	0.316	0.259 (0.000 –0.528)	–	0.171 (0.000 –0.380)	0.571 (0.476 –0.691)	0.258 (0.000 –0.516)	0.0029
Val/Serum-TG	AE	0.553	0.226	0.528 (0.424 –0.636)	–	–	0.471 (0.399 –0.558)	0.528 (0.440 –0.605)	0.027
VLDL-D	AE	0.543	0.268	0.529 (0.428 –0.635)	–	–	0.467 (0.397 –0.551)	0.531 (0.445 –0.606)	0.0075
VLDL-TG	AE	0.627	0.247	0.594 (0.493 –0.701)	–	–	0.404 (0.341 –0.481)	0.595 (0.515 –0.664)	0.035
VLDL-TG-eFR	AE	0.639	0.28	0.616 (0.516 –0.721)	–	–	0.382 (0.322 –0.455)	0.617 (0.541 –0.682)	0.037
XL-HDL-C	AE	0.685	0.303	0.684 (0.585 –0.789)	–	–	0.322 (0.270 –0.386)	0.680 (0.611 –0.737)	0.05
XL-HDL-CE	AE	0.697	0.294	0.698 (0.598 –0.803)	–	–	0.311 (0.260 –0.374)	0.692 (0.624 –0.747)	0.049
XL-HDL-FC	AE	0.72	0.286	0.698 (0.601 –0.801)	–	–	0.303 (0.254 –0.364)	0.697 (0.632 –0.751)	0.06
XL-HDL-L	AE	0.737	0.301	0.721 (0.625 –0.823)	–	–	0.282 (0.236 –0.339)	0.719 (0.657 –0.769)	0.068
XL-HDL-L/L-HDL-L	AE	0.572	0.201	0.532 (0.429 –0.640)	–	–	0.466 (0.394 –0.552)	0.533 (0.445 –0.610)	0.001
XL-HDL-L/M-HDL-L	AE	0.702	0.275	0.690 (0.591 –0.794)	–	–	0.316 (0.265 –0.380)	0.686 (0.617 –0.742)	0.033
XL-HDL-L/S-HDL-L	AE	0.742	0.291	0.733 (0.637 –0.836)	–	–	0.274 (0.229 –0.331)	0.728 (0.667 –0.777)	0.06
XL-HDL-P	AE	0.746	0.291	0.727 (0.631 –0.829)	–	–	0.277 (0.231 –0.333)	0.724 (0.663 –0.774)	0.074
XL-HDL-PL	ADE	0.752	0.286	0.442 (0.028 –0.798)	0.288 (0.000 –0.707)	–	0.262 (0.219 –0.317)	0.736 (0.678 –0.782)	0.076
XL-HDL-TG	AE	0.626	0.366	0.643 (0.546 –0.746)	–	–	0.355 (0.300 –0.423)	0.644 (0.573 –0.704)	0.091
XL-VLDL-L	AE	0.553	0.268	0.529 (0.429 –0.635)	–	–	0.465 (0.395 –0.550)	0.532 (0.446 –0.607)	0.02
XL-VLDL-P	AE	0.557	0.263	0.529 (0.429 –0.634)	–	–	0.465 (0.395 –0.549)	0.532 (0.447 –0.607)	0.018
XL-VLDL-PL	AE	0.551	0.268	0.519 (0.420 –0.623)	–	–	0.473 (0.403 –0.557)	0.523 (0.438 –0.598)	0.02
XL-VLDL-TG	AE	0.548	0.267	0.524 (0.423 –0.629)	–	–	0.470 (0.400 –0.555)	0.527 (0.441 –0.602)	0.019
XS-VLDL-L	AE	0.626	0.26	0.608 (0.507 –0.714)	–	–	0.393 (0.331 –0.469)	0.607 (0.528 –0.674)	0.037
XS-VLDL-P	AE	0.627	0.257	0.612 (0.510 –0.719)	–	–	0.391 (0.329 –0.467)	0.610 (0.530 –0.677)	0.054
XS-VLDL-PL	AE	0.617	0.306	0.624 (0.523 –0.730)	–	–	0.379 (0.319 –0.452)	0.622 (0.545 –0.687)	0.082
XS-VLDL-TG	ADE	0.668	0.23	0.260 (0.000 –0.667)	0.408 (0.003 –0.747)	–	0.332 (0.277 –0.402)	0.668 (0.595 –0.726)	0.051
XXL-VLDL-L	AE	0.526	0.288	0.510 (0.411 –0.615)	–	–	0.482 (0.411 –0.568)	0.514 (0.428 –0.590)	0.018
XXL-VLDL-P	AE	0.454	0.311	0.493 (0.390 –0.601)	–	–	0.504 (0.429 –0.595)	0.495 (0.404 –0.574)	0.0054
XXL-VLDL-PL	AE	0.541	0.264	0.505 (0.406 –0.608)	–	–	0.486 (0.415 –0.571)	0.509 (0.424 –0.585)	0.02
XXL-VLDL-TG	AE	0.517	0.297	0.508 (0.408 –0.612)	–	–	0.485 (0.413 –0.571)	0.511 (0.425 –0.587)	0.019

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Supplementary Table 4. Sample demographics for the subsample of twin used for the heritability estimate comparison.

	MZ twins (n=106)	DZ twins(n=150)
Age (years old)	28.7 ± 3.1	28.2 ± 1.8
Sex (# men)	54	86
BMI (kg/m^2)	26.2 ± 4.8	24.4 ± 4.2

Note: The sample consist of 106 MZ and 150 DZ twins, 65 of which were evaluated in our previous round of heritability analyses.

Supplementary Table 5. Comparison of heritability estimates of NMR measured lipids and enzymatically measured lipids in 256 twins.

	Enzymatic lipid measures					**NMR lipid measures**				
Trait	ICC-MZ	ICC-DZ	A variance (95%CI)	E variance (95%CI)	Heritability (95%CI)	ICC-MZ	ICC-DZ	A variance (95%CI)	E variance (95%CI)	Heritability (95%CI)
HDL-C	0.678	0.306	0.665 (0.473 – 0.895)	0.318 (0.227 – 0.455)	0.677 (0.530 – 0.779)	0.643	0.282	0.602 (0.393 – 0.846)	0.386 (0.272 – 0.560)	0.609 (0.431 – 0.737)
LDL-C	0.634	0.435	0.731 (0.525 – 0.976)	0.282 (0.197 – 0.416)	0.722 (0.578 – 0.815)	0.591	0.441	0.734 (0.518 – 0.987)	0.286 (0.196 – 0.432)	0.720 (0.565 – 0.818)
TC	0.702	0.372	0.723 (0.521 – 0.964)	0.283 (0.199 – 0.414)	0.719 (0.577 – 0.813)	0.724	0.380	0.830 (0.614 – 1.000)	0.213 (0.144 – 0.330)	0.796 (0.669 – 0.870)
TG	0.526	0.343	0.550 (0.340 – 0.790)	0.445 (0.319 – 0.633)	0.553 (0.366 – 0.691)	0.650	0.318	0.693 (0.466 – 0.954)	0.324 (0.221 – 0.490)	0.681 (0.506 – 0.795)

A refers to additive genetic influences; E refers to specific environmental influences; 95%CI stands for 95% confidence intervals of the given estimate; heritability refers to broad sense heritability estimate.

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Supplementary Table 6. Genome wide inflation factors from the meta-analysis for each trait.

Abbreviation	Lambda	Abbreviation	Lambda
AcAcO	1.03	**L-LDL-P**	1.02
AcO	1.02	**L-LDL-PL**	1.02
Ala	1.03	**L-VLDL-C**	1.04
Alb	1.02	**L-VLDL-CE**	1.04
bOHBuO	1.05	**L-VLDL-FC**	1.03
Cit	1.03	**L-VLDL-L**	1.03
Crea	1.02	**L-VLDL-P**	1.03
DHA	1.03	**L-VLDL-PL**	1.03
Est-C	1.01	**L-VLDL-TG**	1.03
FAw3	1.03	**M-HDL-C**	1.01
FAw67	1.01	**M-HDL-CE**	1.01
FAw9S	1.02	**M-HDL-FC**	1.02
Free-C	1.02	**M-HDL-L**	1.01
Glc	1.05	**M-HDL-P**	1.02
Gln	1.02	**M-HDL-PL**	1.02
Glol	1.03	**M-LDL-C**	1.02
Gp	1.04	**M-LDL-CE**	1.02
HDL-C	1.03	**M-LDL-L**	1.02
His	1.02	**M-LDL-P**	1.02
IDL-C	1.03	**M-LDL-PL**	1.02
IDL-FC	1.03	**MobCH**	1.03
IDL-L	1.02	**MobCH2**	1.03
IDL-P	1.02	**MobCH3**	1.02
IDL-PL	1.02	**M-VLDL-C**	1.02
IDL-TG	1.03	**M-VLDL-CE**	1.02
Ile	1.04	**M-VLDL-FC**	1.02
LA	1.01	**M-VLDL-L**	1.02
Lac	1.04	**M-VLDL-P**	1.02
LDL-C	1.02	**M-VLDL-PL**	1.02
Leu	1.02	**M-VLDL-TG**	1.03
L-HDL-C	1.04	**PC**	1
L-HDL-CE	1.04	**Phe**	1.03
L-HDL-FC	1.04	**PUFA**	1.03
L-HDL-L	1.04	**Pyr**	1.01
L-HDL-P	1.04	**Serum-C**	1.02
L-HDL-PL	1.04	**Serum-TG**	1.03
L-LDL-C	1.02	**S-HDL-L**	1.01
L-LDL-CE	1.02	**S-HDL-P**	1.01
L-LDL-FC	1.02	**S-HDL-TG**	1.02

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Abbreviation	Lambda
L-LDL-L	1.02
S-LDL-L	1.02
S-LDL-P	1.02
SM	1.02
S-VLDL-C	1.02
S-VLDL-FC	1.03
S-VLDL-L	1.03
S-VLDL-P	1.03
S-VLDL-PL	1.03
S-VLDL-TG	1.03
Tot-C	1.02
Tot-CH	1
Tot-FA	1.01
Tot-PG	1.01
Tot-TG	1.03
Tyr	1.03
Urea	1
Val	1.03
VLDL-TG	1.03
XL-HDL-C	1.01
XL-HDL-CE	1.01
XL-HDL-FC	1.02
XL-HDL-L	1.02
XL-HDL-P	1.03
XL-HDL-PL	1.03
XL-HDL-TG	1.02
XL-VLDL-L	1.03
XL-VLDL-P	1.03
XL-VLDL-PL	1.03
XL-VLDL-TG	1.03
XS-VLDL-L	1.03
XS-VLDL-P	1.03
XS-VLDL-PL	1.03
XS-VLDL-TG	1.03
XXL-VLDL-L	1.03
XXL-VLDL-P	1.05
XXL-VLDL-PL	1.04
XXL-VLDL-TG	1.03
AcO/AcAcO	1.01

Abbreviation	Lambda
S-LDL-C	1.02
Ala/Ile	1.03
Ala/Leu	1.03
Ala/Phe	1.04
Ala/Pyr	1.01
Ala/Tyr	1.03
Ala/Val	1.03
ApoA1	1.01
ApoB	1.02
ApoB/ApoA1	1.04
BCAAs	1.03
Bis/DB	1.03
Bis/FA	1.03
bOHBuO/AcAcO	1.01
bOHBuO/AcO	1.01
CH2/DB	1.03
CH2/FA	1.02
Crea/Alb	1.03
DB/FA	1.03
DHA/FAw3	1.01
DHA/PUFA	1.02
FALen	1.01
FAw3/FAw67	1.03
FAw3/FAw9S	1.03
FAw3/FA	1.03
FAw67/FAw9S	1.03
FAw67/FA	1.03
FAw9S/FA	1.03
FR	1.03
Free-C/Est-C	1
Glc/Cit	1.05
Glc/Pyr	0.99
Gln/Cit	1.04
Gln/Glc	1.03
Gln/His	1.01
Gln/Ile	1.03
Gln/Leu	1.01
Gln/Phe	1.03
Gln/Pyr	1.02

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Abbreviation	Lambda
Ala/Cit	1.06
Ala/Glc	1.03
Ala/Gln	1.02
Ala/His	1.01
Gln/Tyr	1.03
Gln/Val	1.02
Gp/Serum-TG	1.04
Gp/Tot-C	1.03
HDL2-C	1.04
HDL3-C	1
HDL-D	1.03
His/Ile	1.04
His/Leu	1.02
His/Phe	1.03
His/Tyr	1.02
His/Val	1.03
IDL-C-eFR	1.02
Ile/Glc	1.03
Ile/Leu	1.02
Ile/Phe	1.02
Ile/Serum-C	1.03
Ile/Serum-TG	1.03
Ile/Tyr	1.03
Ile/Val	1.02
LA/DHA	1.03
LA/FAw67	1.03
LA/PUFA	1.03
Lac/Ala	1.04
Lac/Cit	1.02
Lac/Glc	1.02

Abbreviation	Lambda
Lac/Gln	1.04
Lac/Pyr	1.02
LDL-C-eFR	1.03
LDL-D	1.01
Leu/Glc	1.03
Leu/Phe	1.03
Leu/Serum-TG	1.03
Leu/Tyr	1.01
Leu/Val	1.01
L-HDL-C/L-HDL-PL	1.02
L-HDL-L/M-HDL-L	1.04
L-HDL-L/S-HDL-L	1.04
M-HDL-C/M-HDL-PL	1.03
M-HDL-L/S-HDL-L	1.02
M-LDL-C/M-LDL-PL	1.02
PC/Tot-CH	1
Phe/Tyr	1.02
Phe/Val	1.02
Pyr/Cit	1.03
Serum-TG/Glc	1.03
TG/PG	1.02
Tot-C/Est-C	1
Tyr/Val	1.02
Val/Glc	1.03
Val/Serum-TG	1.04
VLDL-D	1.02
VLDL-TG-eFR	1.04
XL-HDL-L/L-HDL-L	1.01
XL-HDL-L/M-HDL-L	1.01
XL-HDL-L/S-HDL-L	1.01

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Supplementary Table 7. All metabolite associations $P < 2.31 \times 10^{-10}$. **N.B! This table is provided as a separate file.**

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Supplementary Table 8. Spearman rank correlation *P*-values for expression eQTLs reaching genome wide significance ($P < 9 \times 10^{-7}$).

Gene	snp	*P*-value	Chromosome	Position
FCGR2B	1-159807481	$1.3*10^{-20}$	1	159914011
FCGR2B	1-159807481	$1.6*10^{-12}$	1	159914480
CLTCL1	rs807669	$1.8*10^{-19}$	22	17555106
PLTP	rs6065904	$2.4*10^{-8}$	20	43961028
SPRYD4	rs2638315	$3.8*10^{-13}$	12	55149894
FCGR2A	1-159807481	$3.9*10^{-10}$	1	159755560

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Supplementary Figures

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Supplementary Figure 1. Regional plots for significant loci. The green colored dot is used if the SNP has been genotyped in at least 3 study cohorts. Blue dot marks SNPs imputed from HapMap 3 reference panel and black dot represent SNPs genotyped from 1000 genomes reference panel. Red line presents the significance level $P = 2.32*10^{-10}$ and black line represents the nominal genome wide level of significance ($P < 5*10^{-8}$). Genes in the region are represented with bars in different colors and the regional candidate gene is shown in thicker black bar.

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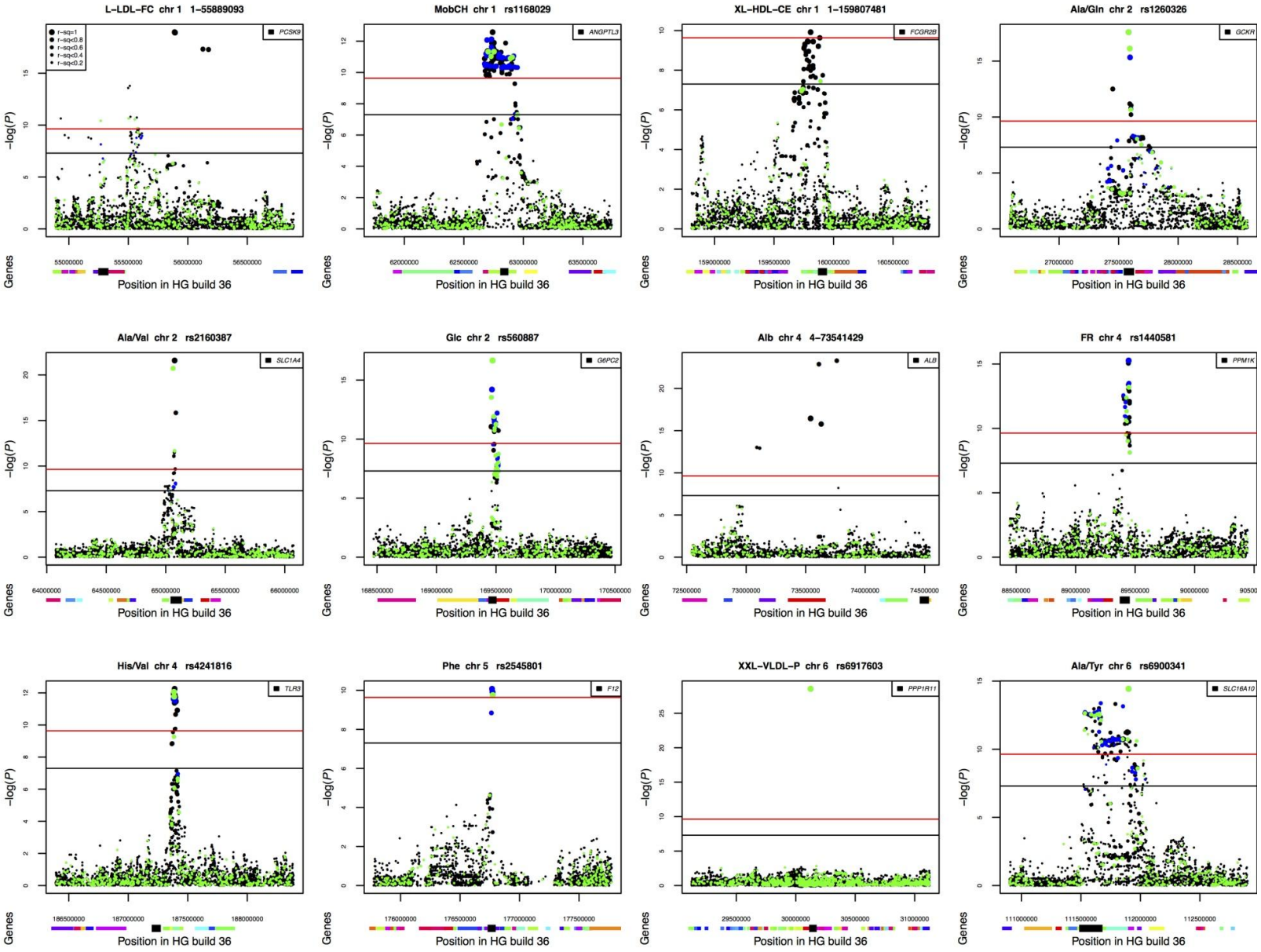

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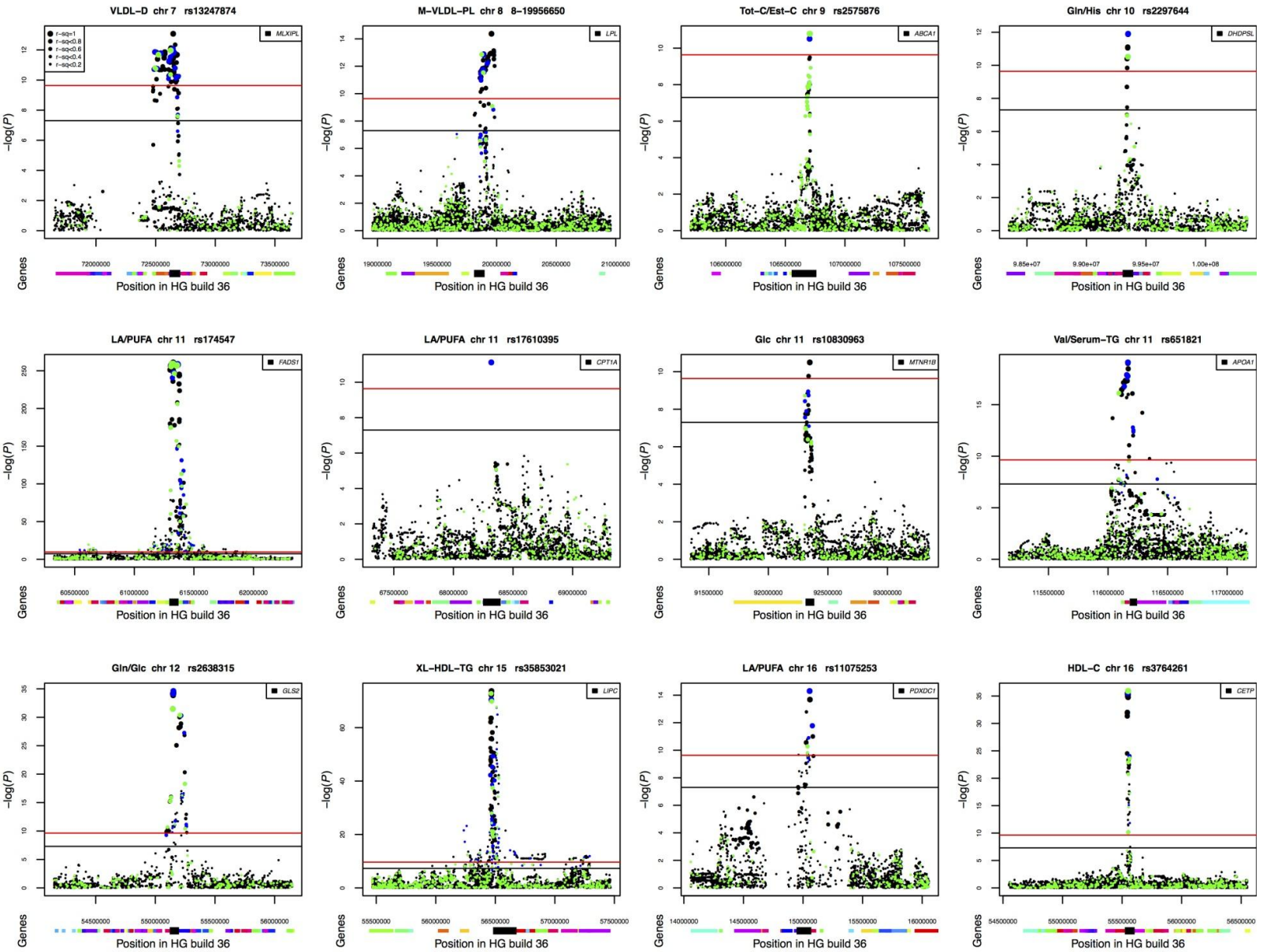

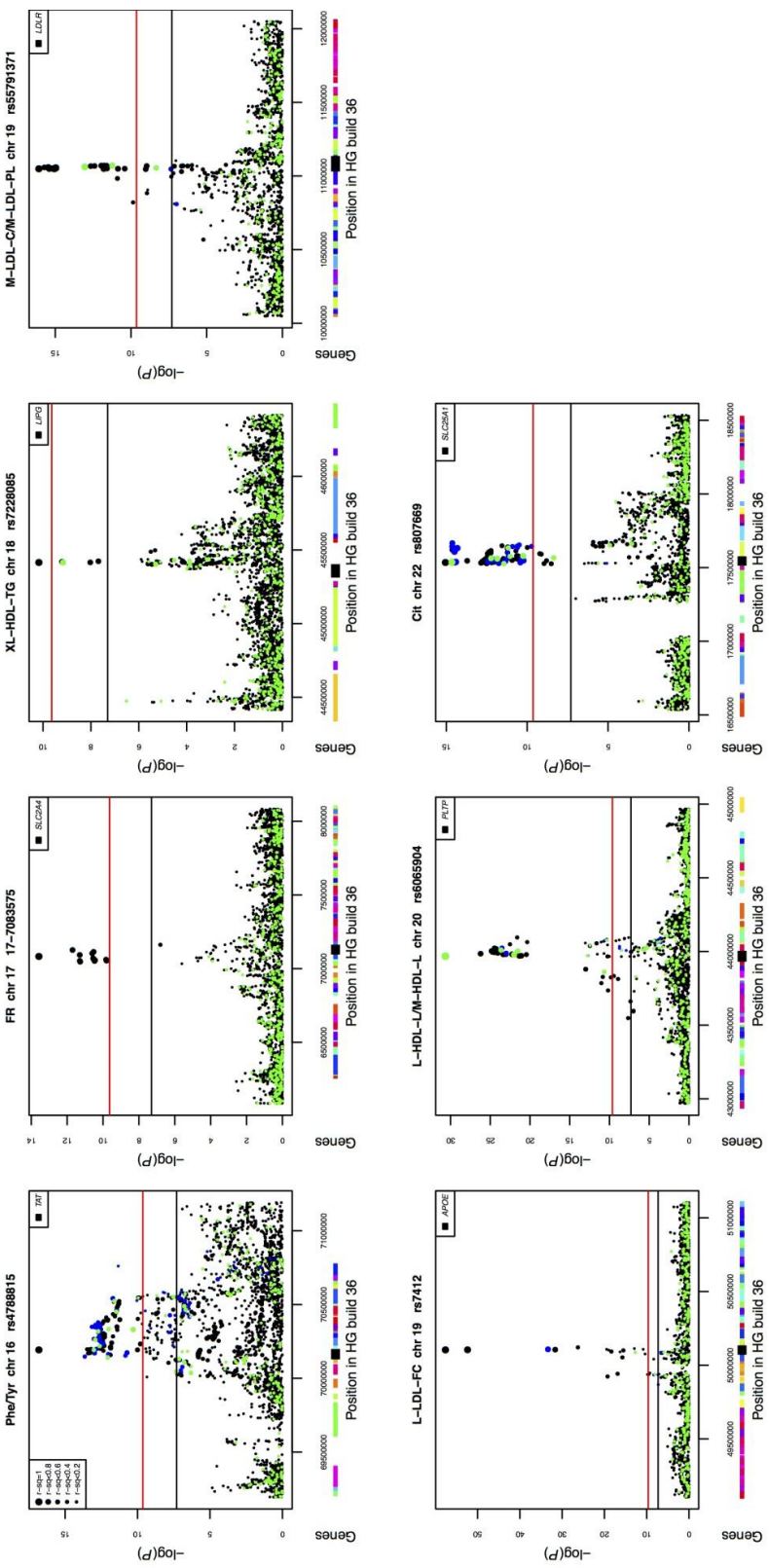

Supplementary Figure 2. Quantile-quantile (QQ) plots for the meta-analysis of the lead metabolic traits reported in **Tables 2** and **3**. Genomic control was utilized after the meta-analysis; the meta-analysis inflation factors for the traits shown were between 1.00-1.06. The expected null distribution is plotted along the diagonal as a red line and the distribution of observed *P*-values is plotted as black circles.

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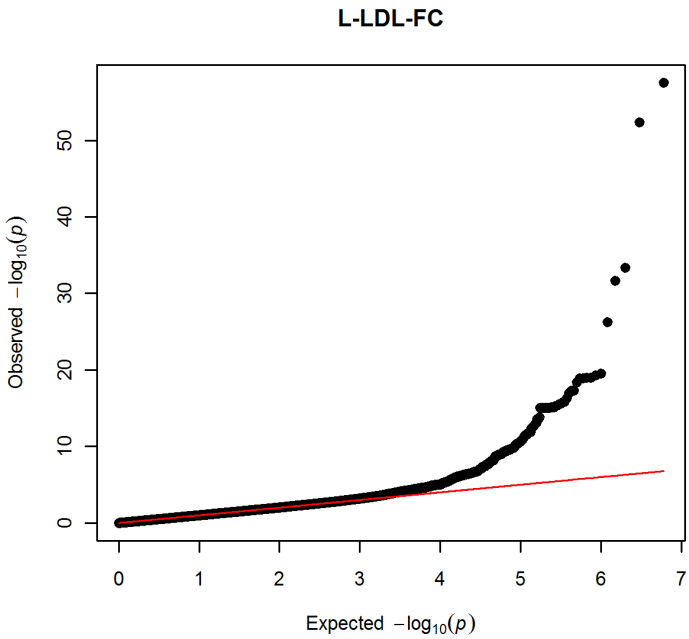

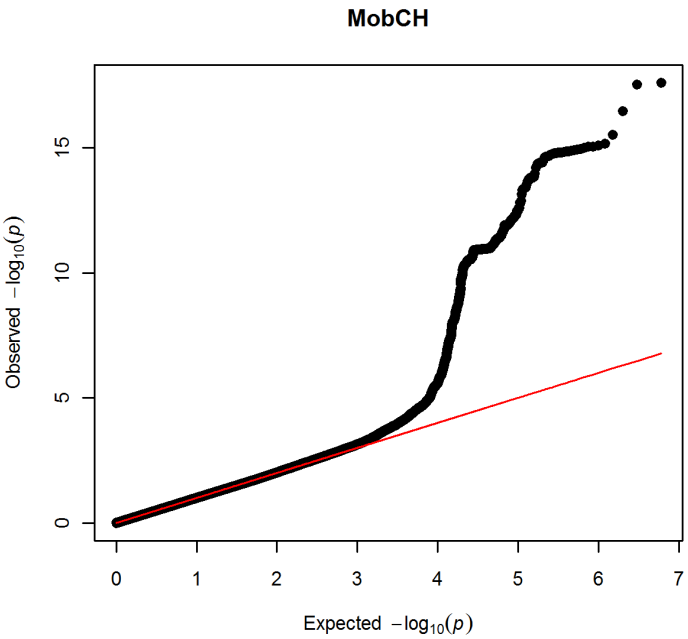

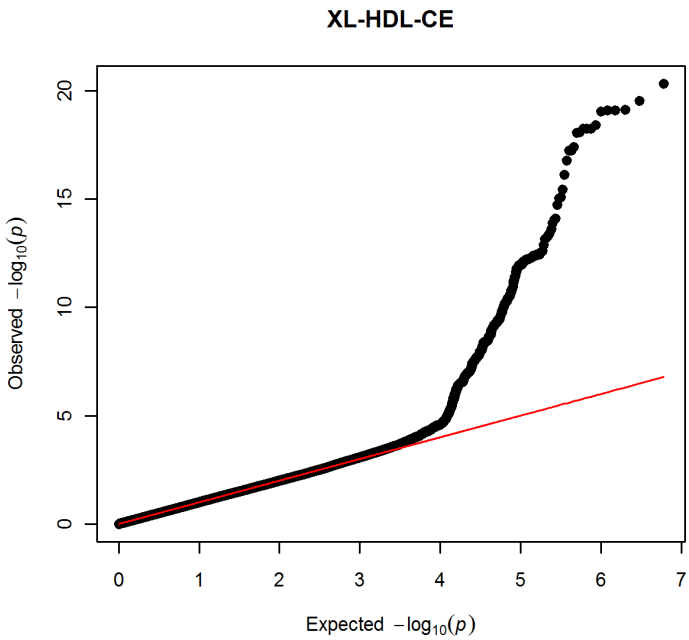

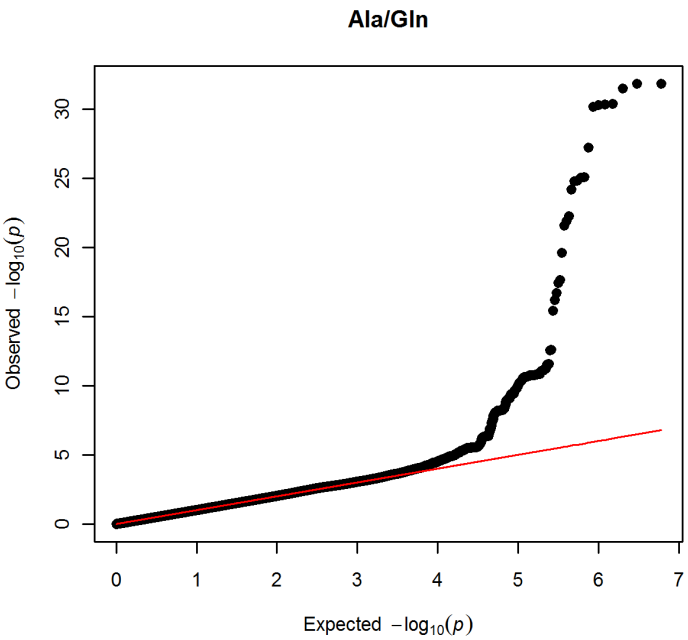

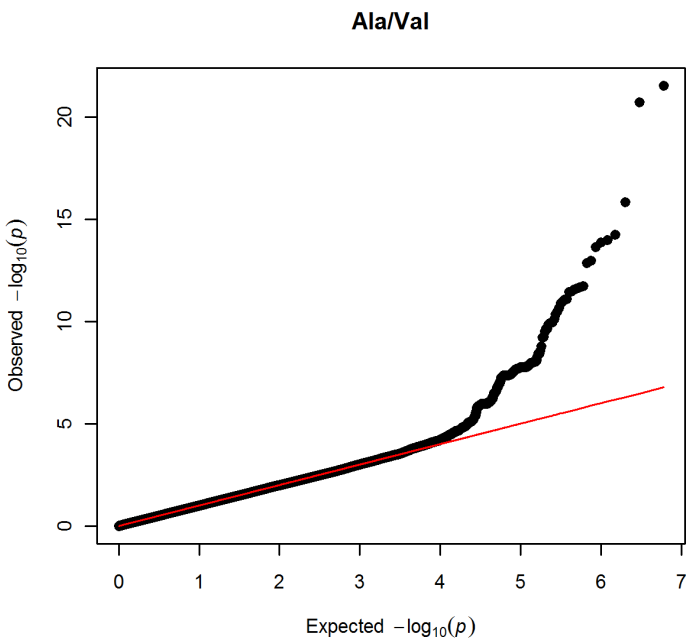

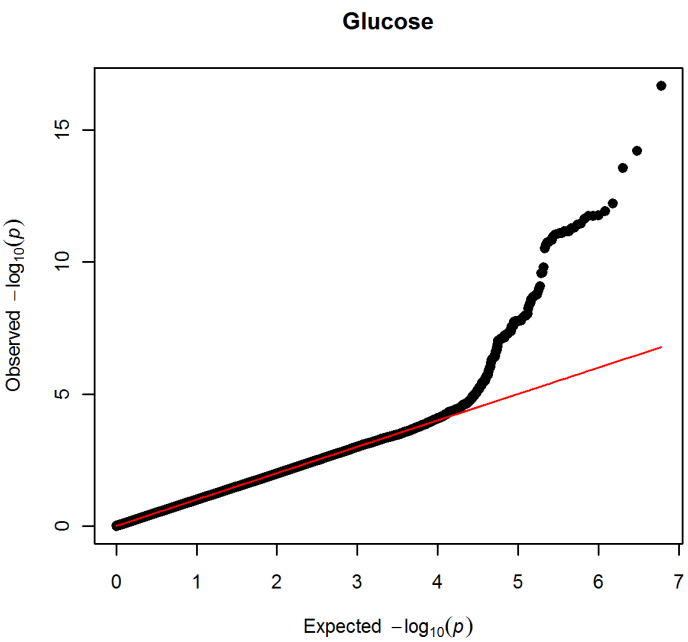

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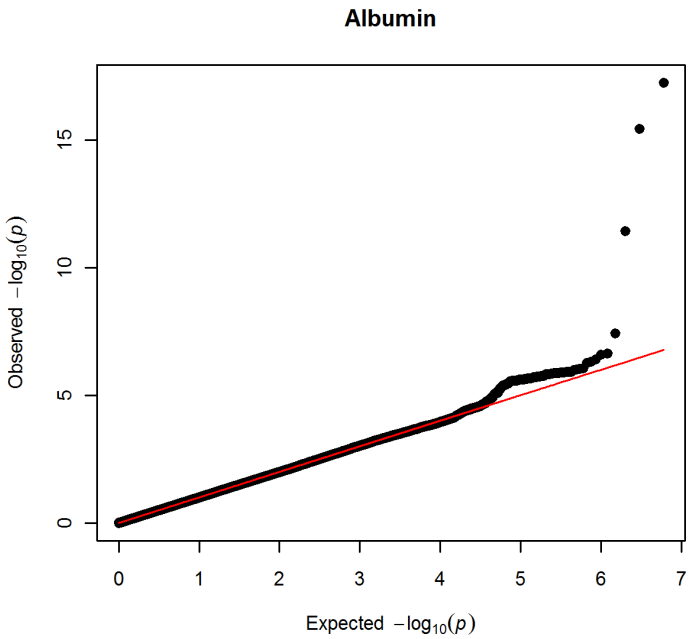
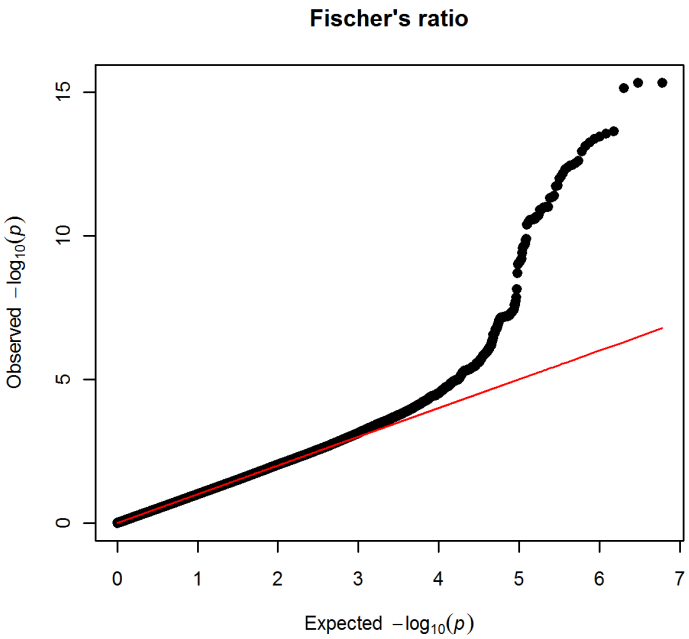
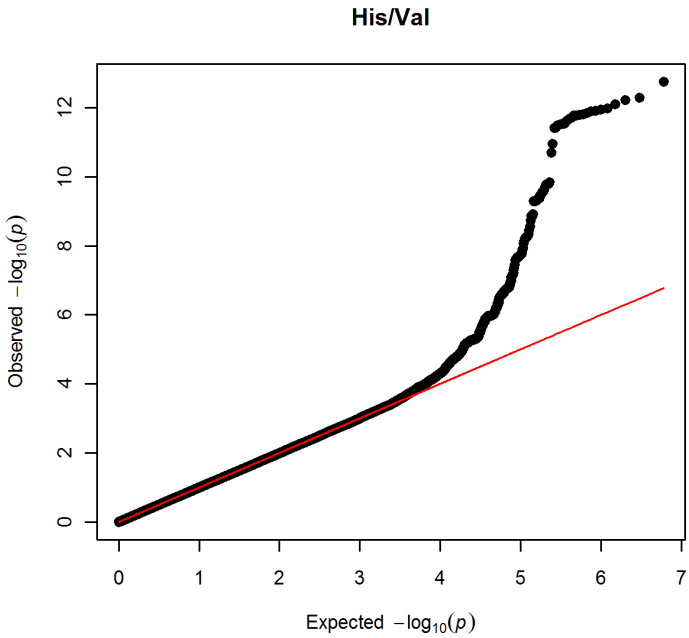
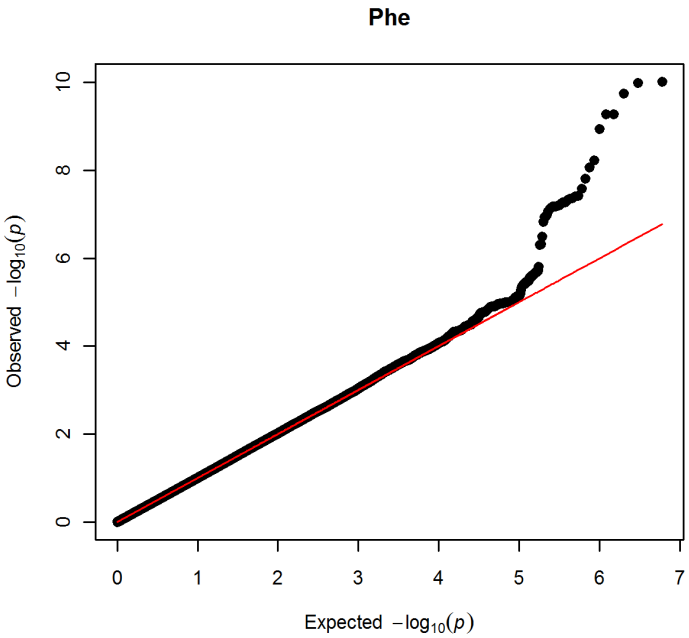
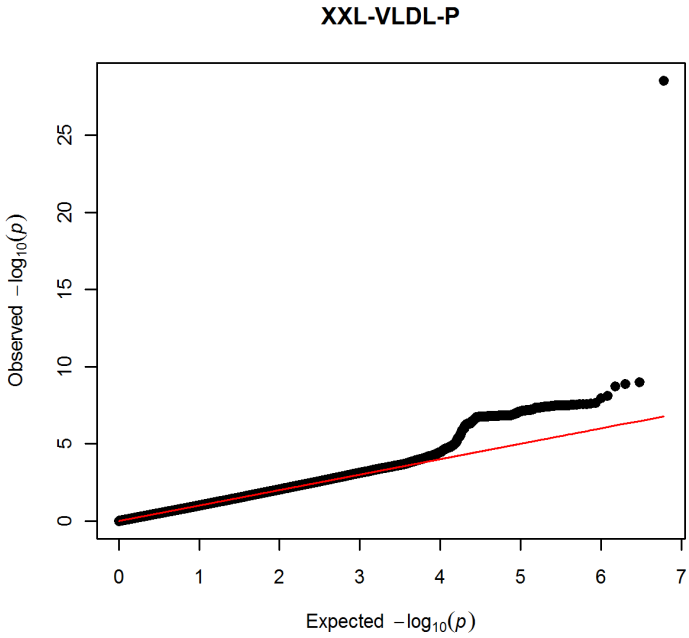
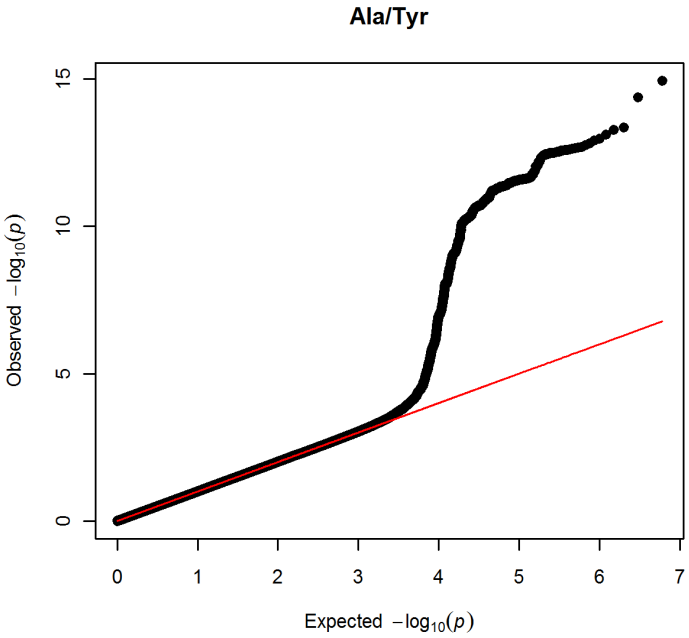

Albumin
Observed $-\log_{10}(p)$
Expected $-\log_{10}(p)$

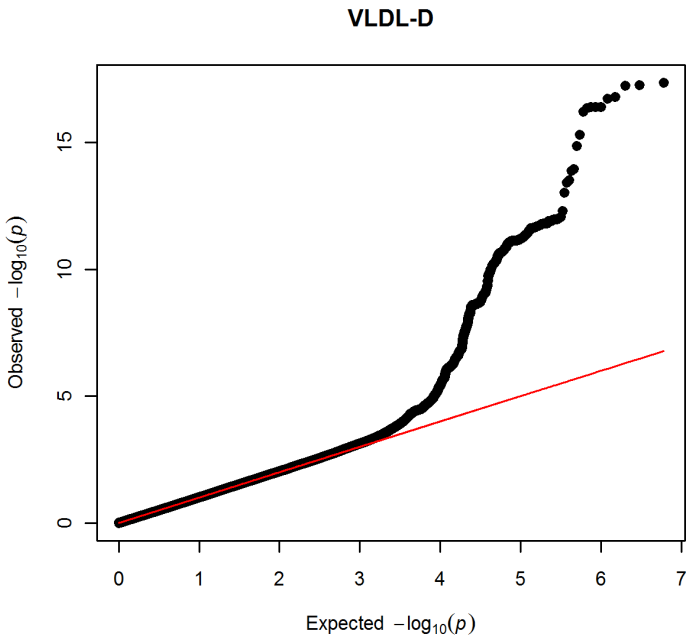

Fischer's ratio
Observed $-\log_{10}(p)$
Expected $-\log_{10}(p)$

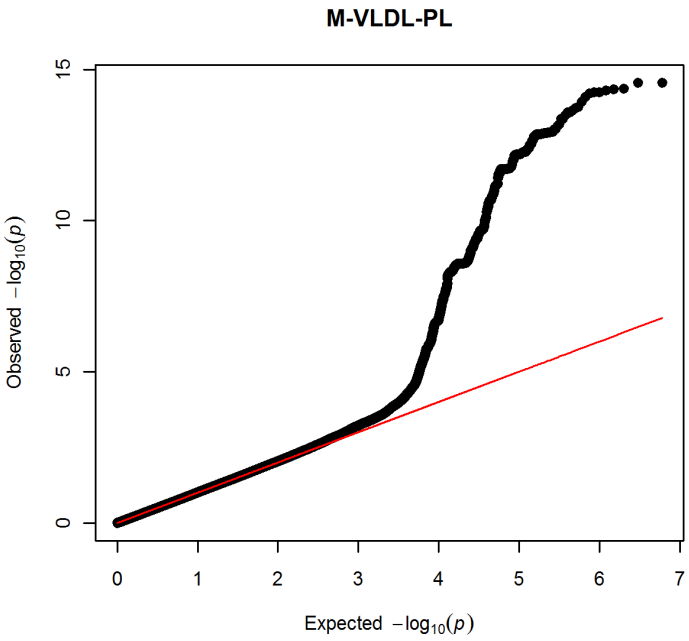

His/Val
Observed $-\log_{10}(p)$
Expected $-\log_{10}(p)$

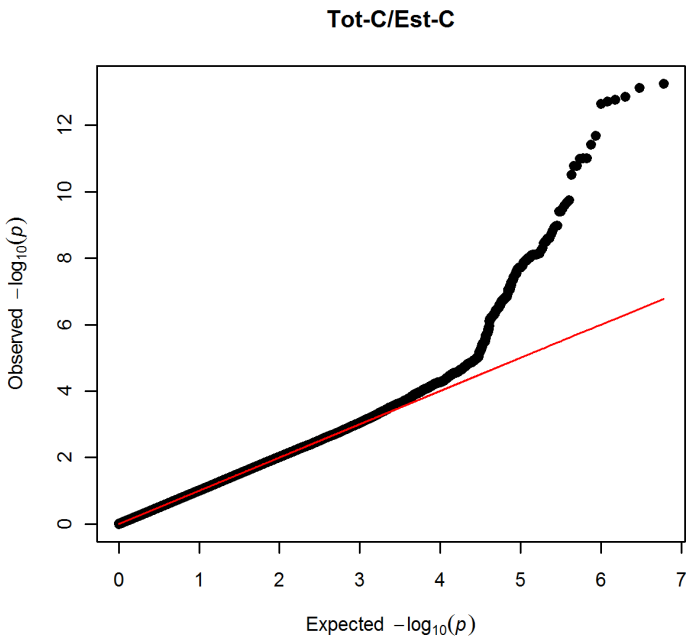

Phe
Observed $-\log_{10}(p)$
Expected $-\log_{10}(p)$

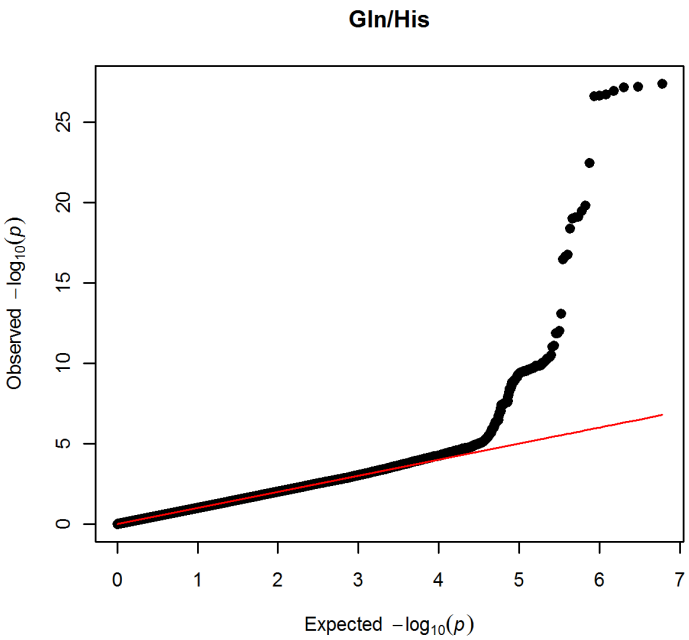

XXL-VLDL-P
Observed $-\log_{10}(p)$
Expected $-\log_{10}(p)$

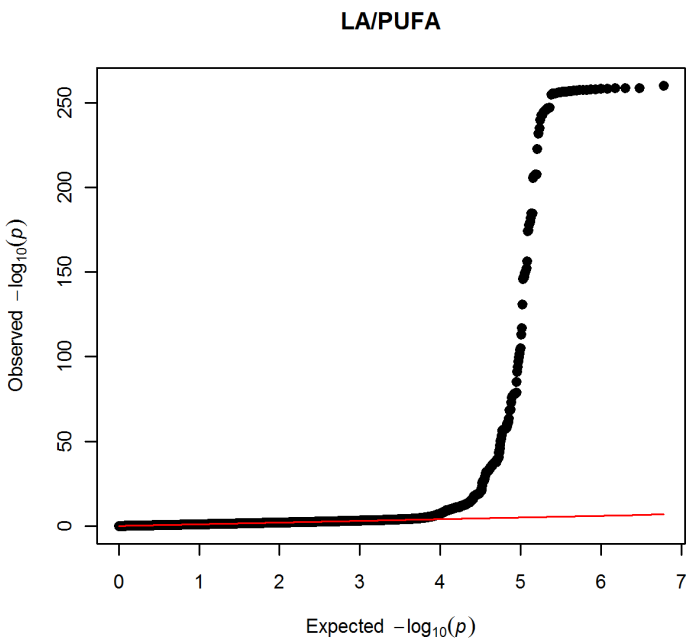

Ala/Tyr
Observed $-\log_{10}(p)$
Expected $-\log_{10}(p)$

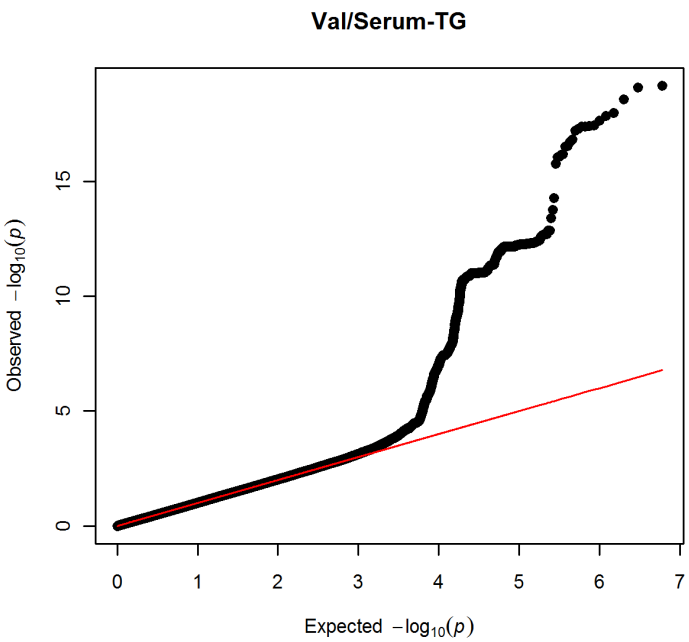












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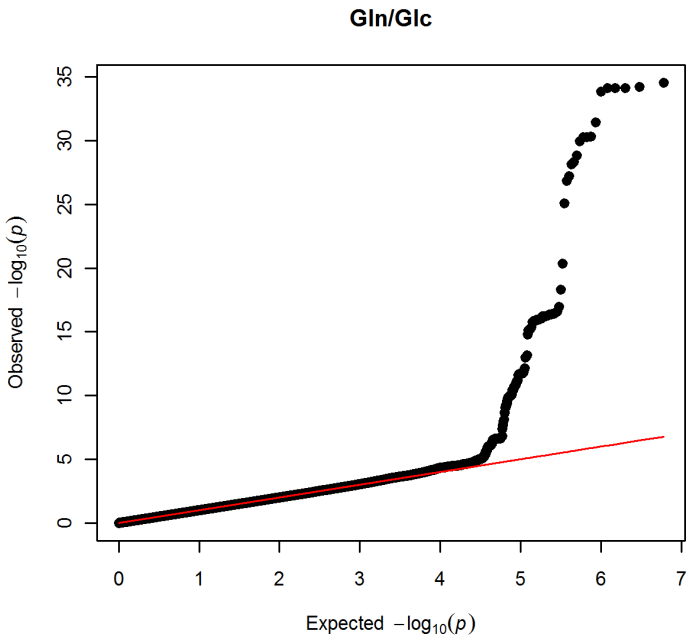
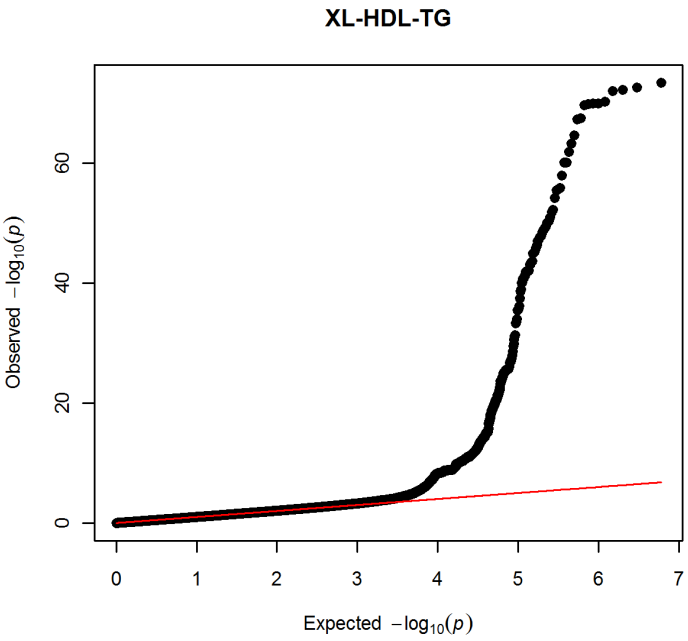
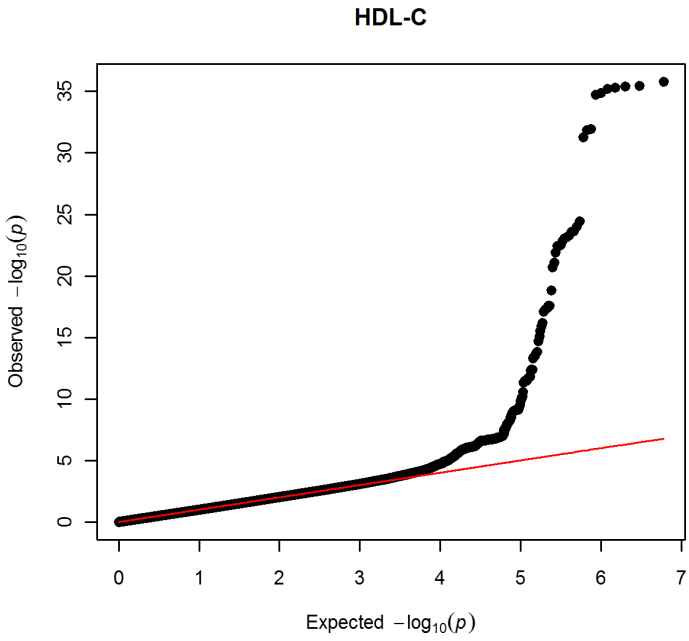
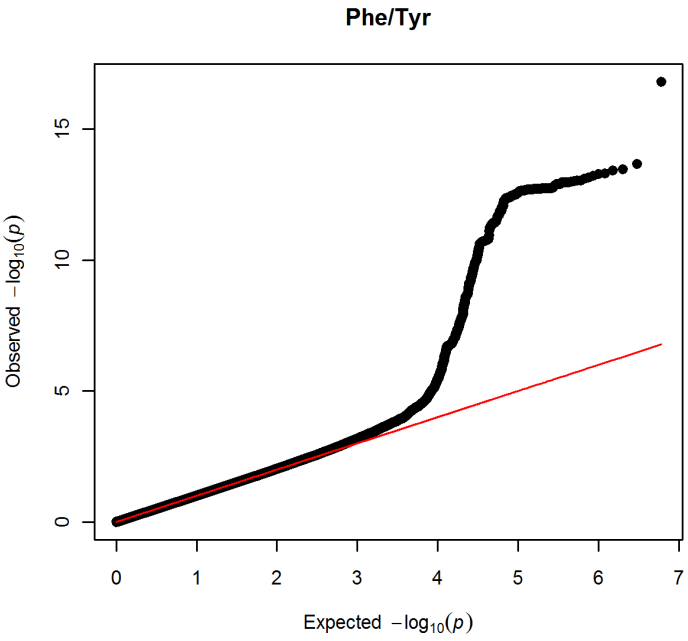
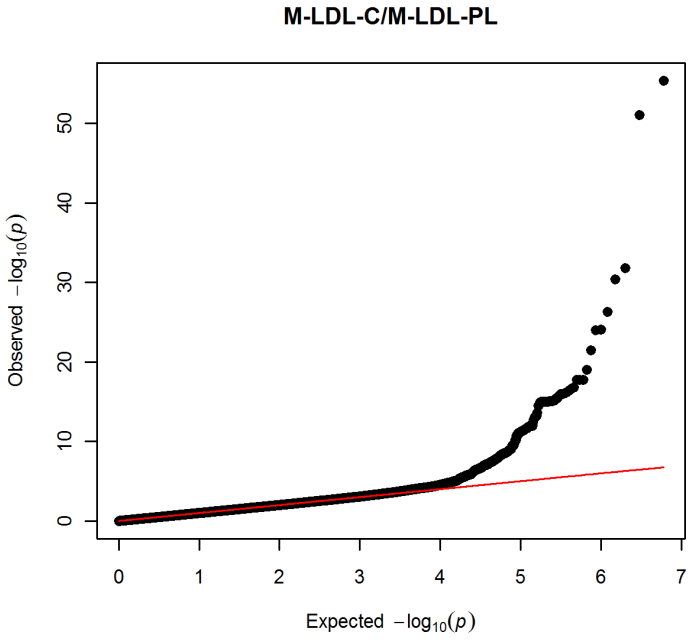
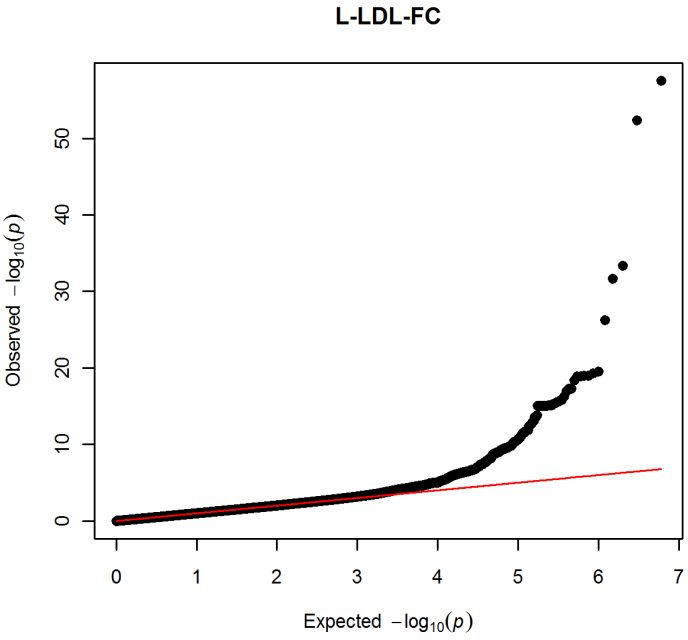

Gln/Glc
Observed $-\log_{10}(p)$
Expected $-\log_{10}(p)$

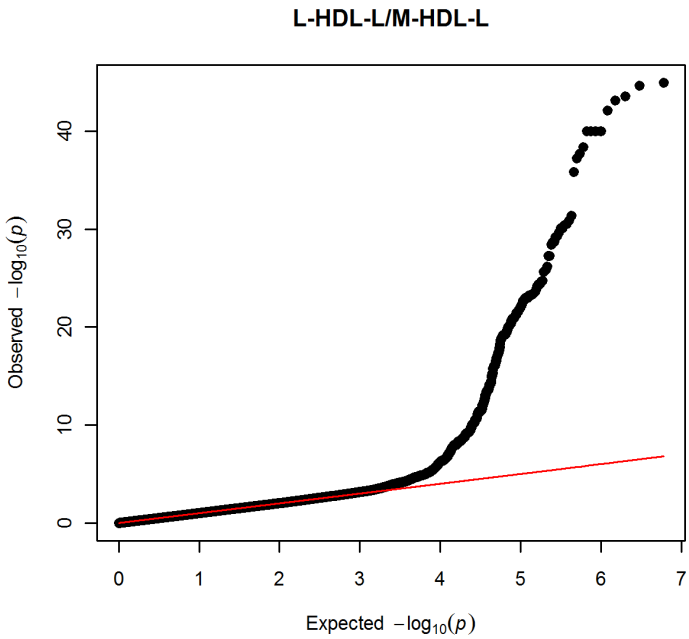

XL-HDL-TG
Observed $-\log_{10}(p)$
Expected $-\log_{10}(p)$

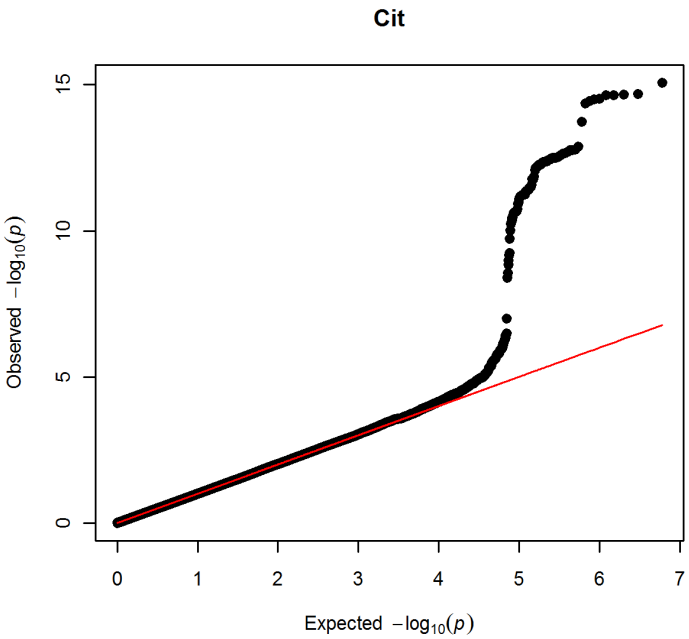

HDL-C
Observed $-\log_{10}(p)$
Expected $-\log_{10}(p)$


Phe/Tyr
Observed $-\log_{10}(p)$
Expected $-\log_{10}(p)$


M-LDL-C/M-LDL-PL
Observed $-\log_{10}(p)$
Expected $-\log_{10}(p)$


L-LDL-FC
Observed $-\log_{10}(p)$
Expected $-\log_{10}(p)$





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Supplementary Figure 3. Box plots for the lead metabolic traits reported in **Tables 2** and **3** plotted as a function of genotype (light shade: non-coded allele homozygotes, medium shade: heterozygotes, dark shade: coded allele homozygotes) and study (NFBC: green, YF: blue, HBCS: red, GenMets: turquoise, DILGOM: yellow) in chromosomal order. The plots present the untransformed and unadjusted trait values. The numbers of samples for each genotype in each cohort are indicated above the boxes. The boxes contain 50 % of the observations extending from 1st quartile (Q1) to 3rd quartile (Q3). The horizontal line indicates the median. The ends of the whiskers indicate the minimum and maximum of the data or, if extreme values are present, are drawn to the observation that is closest to, but no more than, 1.5 times the inter-quartile range (Q3-Q1) from the end of the box. The observations more distant than this are shown individually on the plots.

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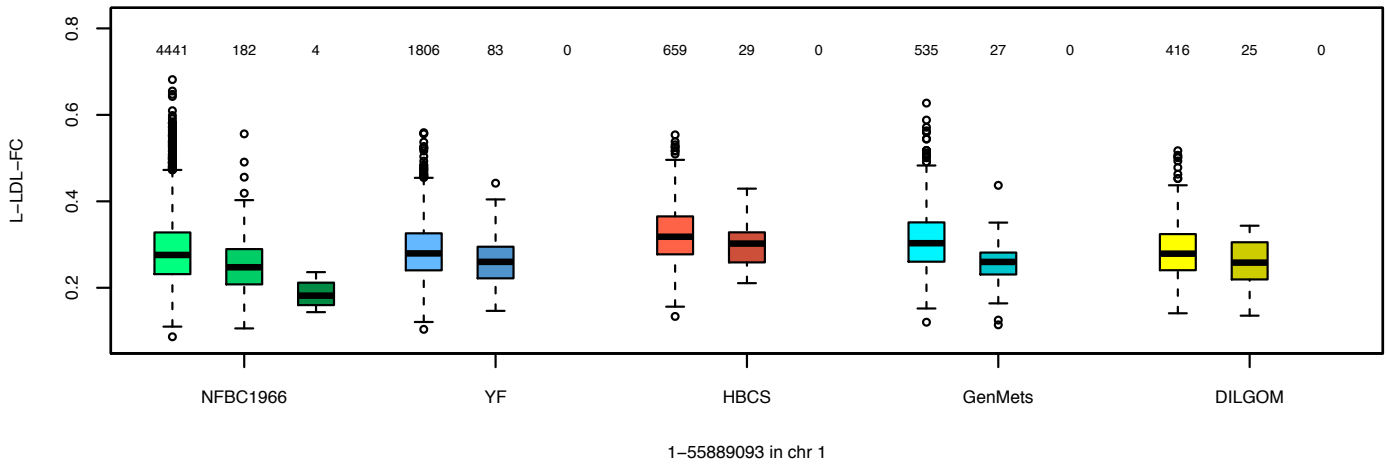
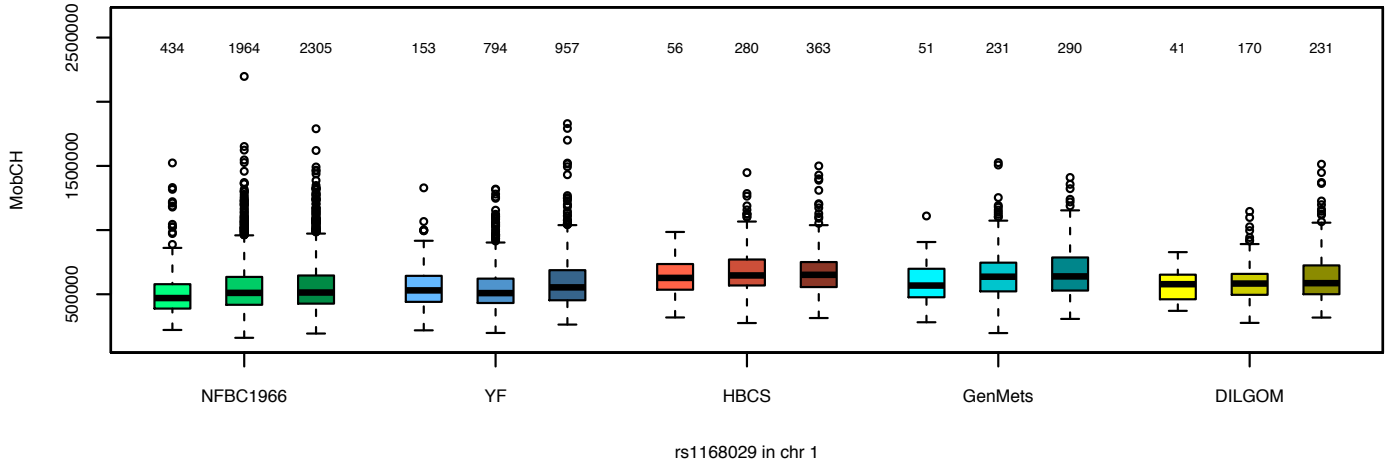
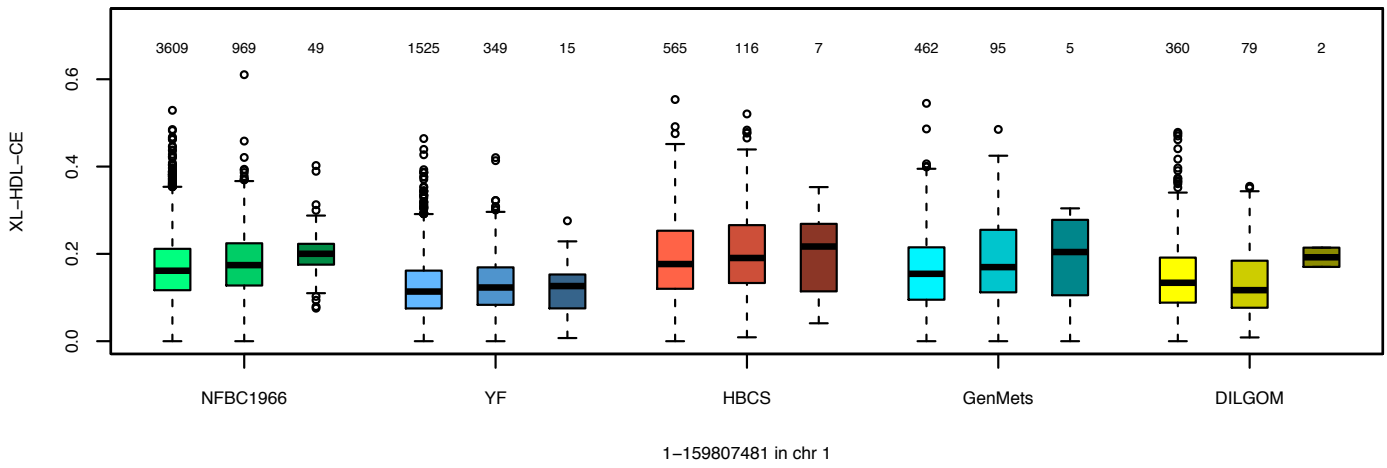


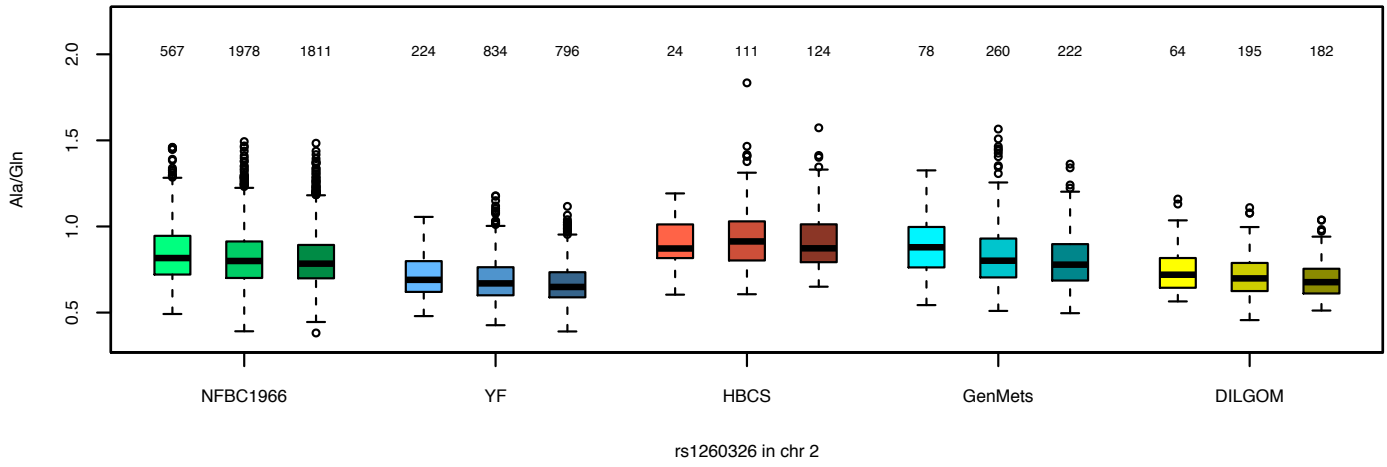
1−55889093 in chr 1



rs1168029 in chr 1



1−159807481 in chr 1



rs1260326 in chr 2

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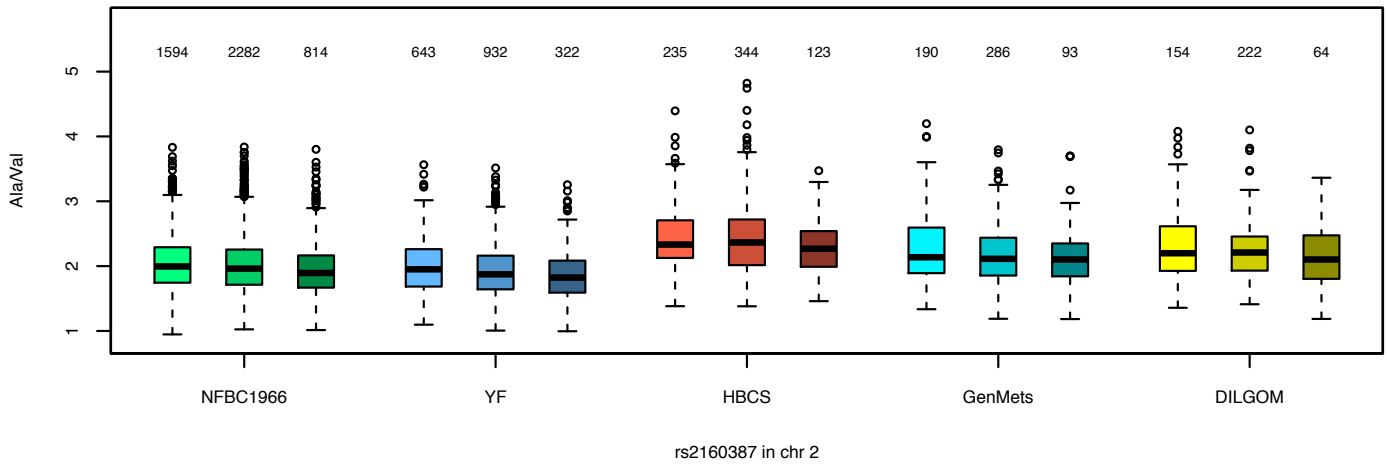
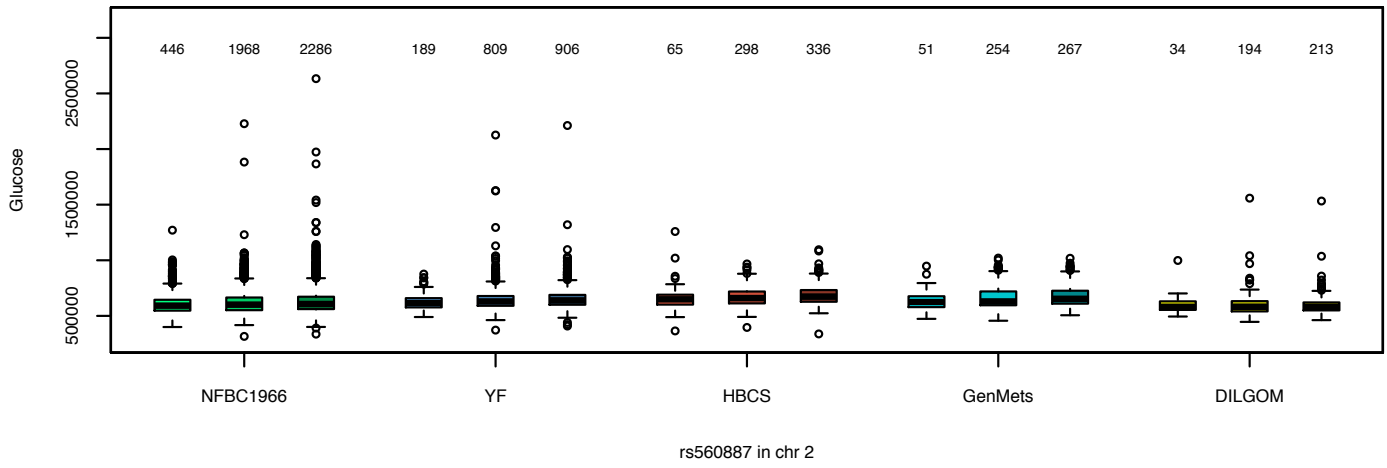
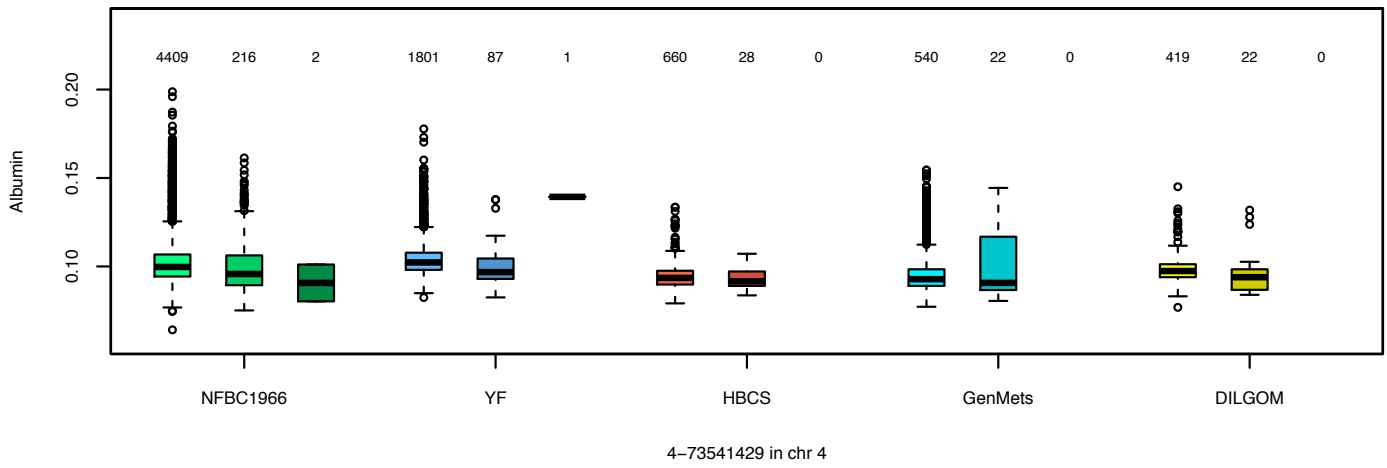


rs2160387 in chr 2



rs560887 in chr 2



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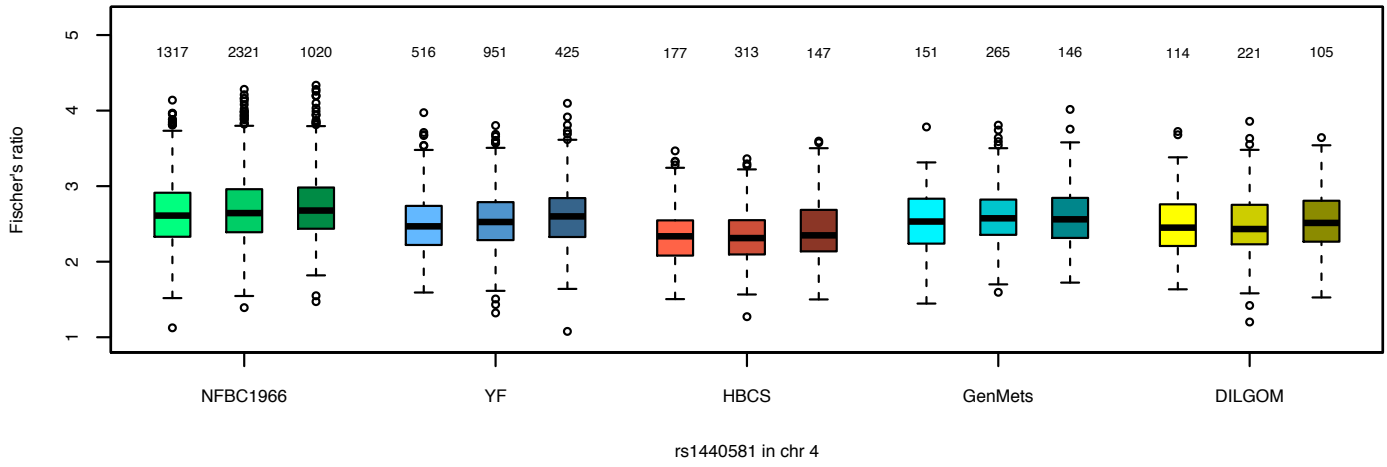

rs1440581 in chr 4

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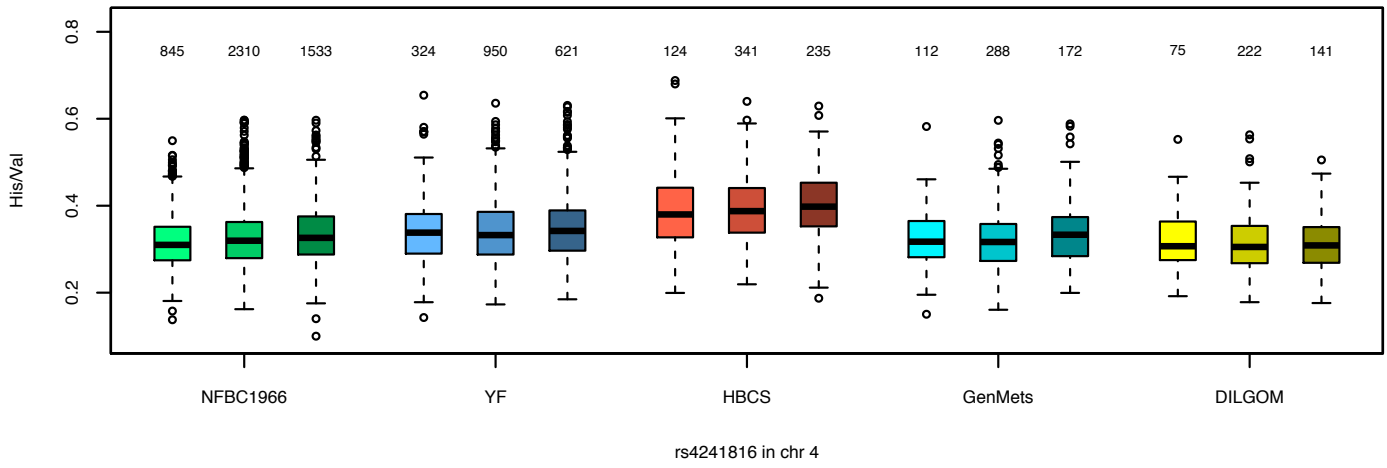

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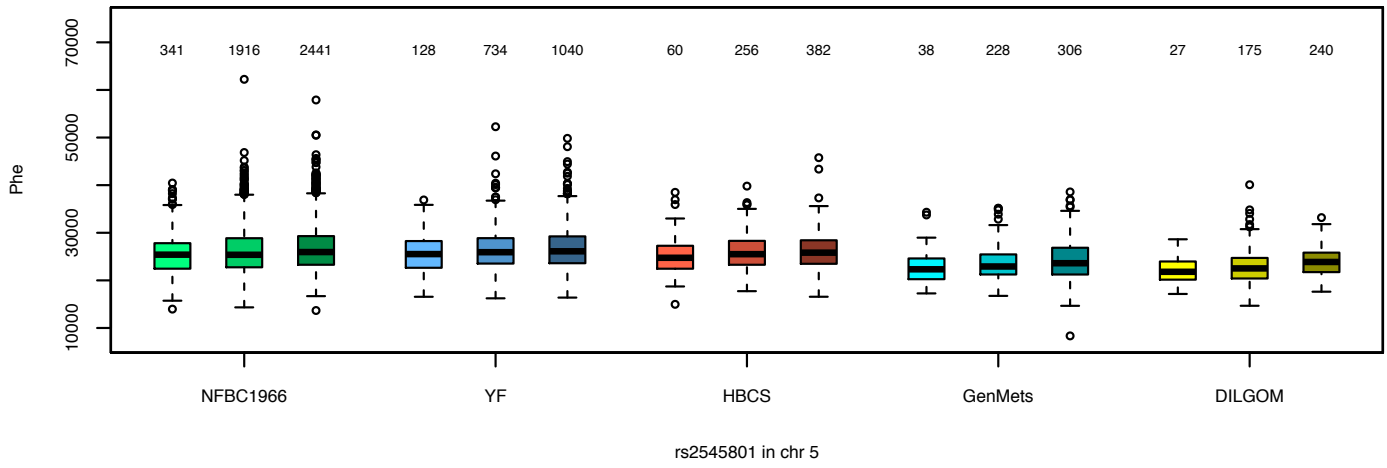

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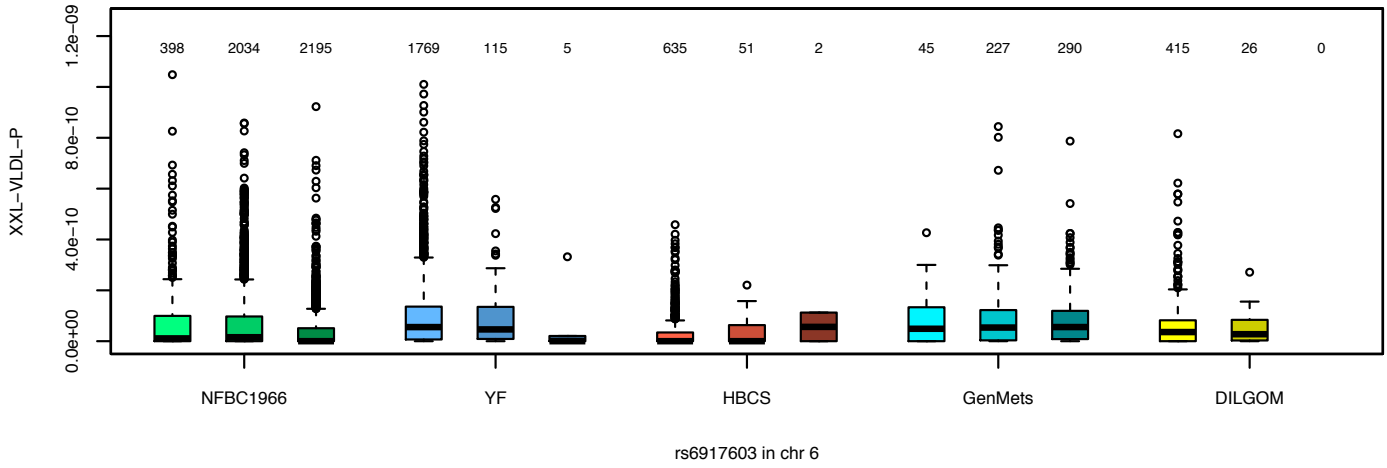
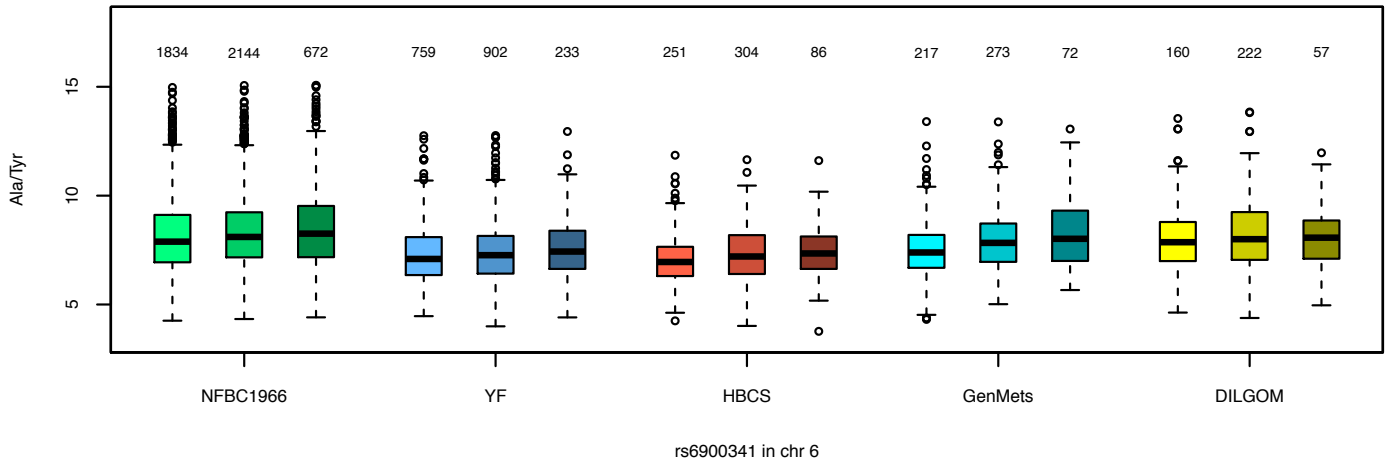


rs6917603 in chr 6



rs6900341 in chr 6

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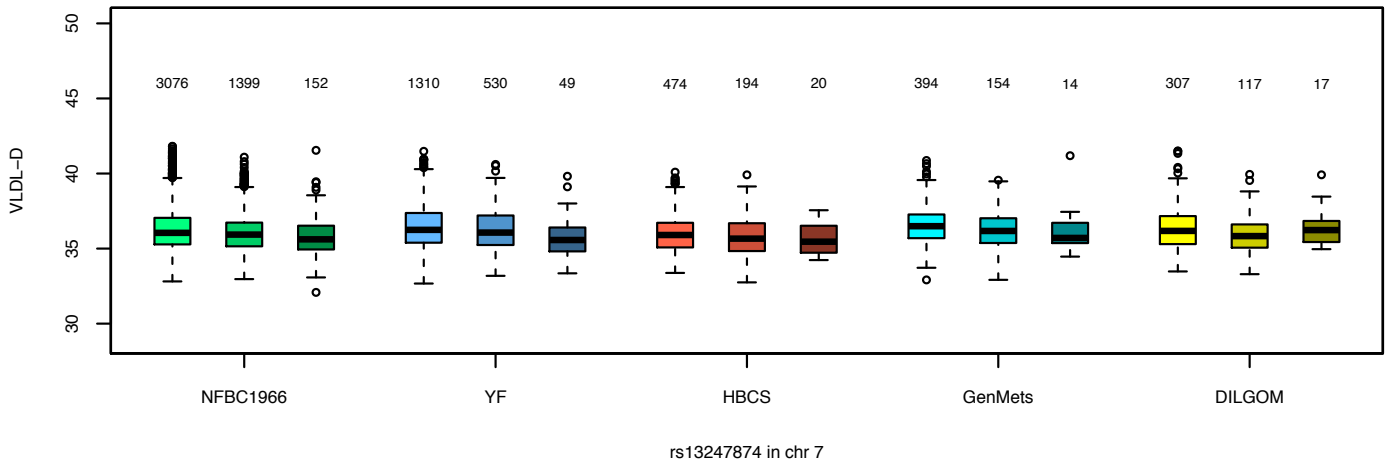
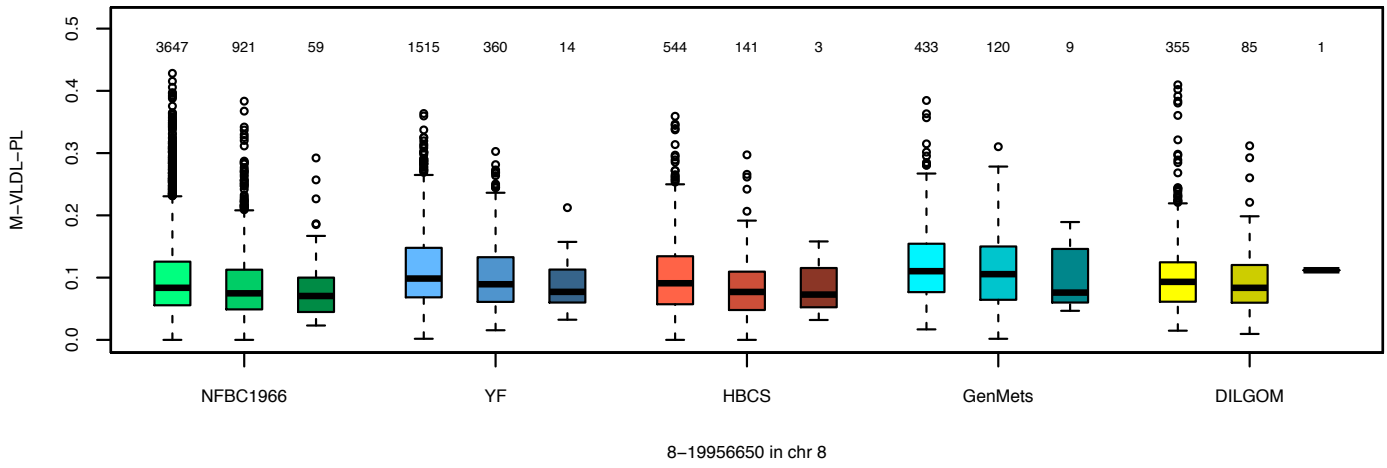
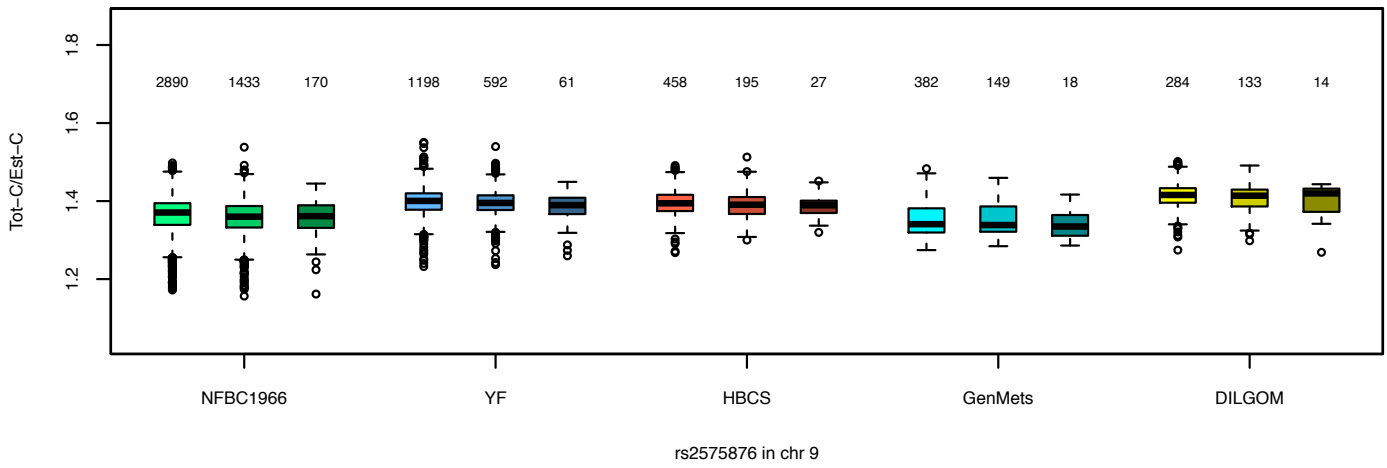


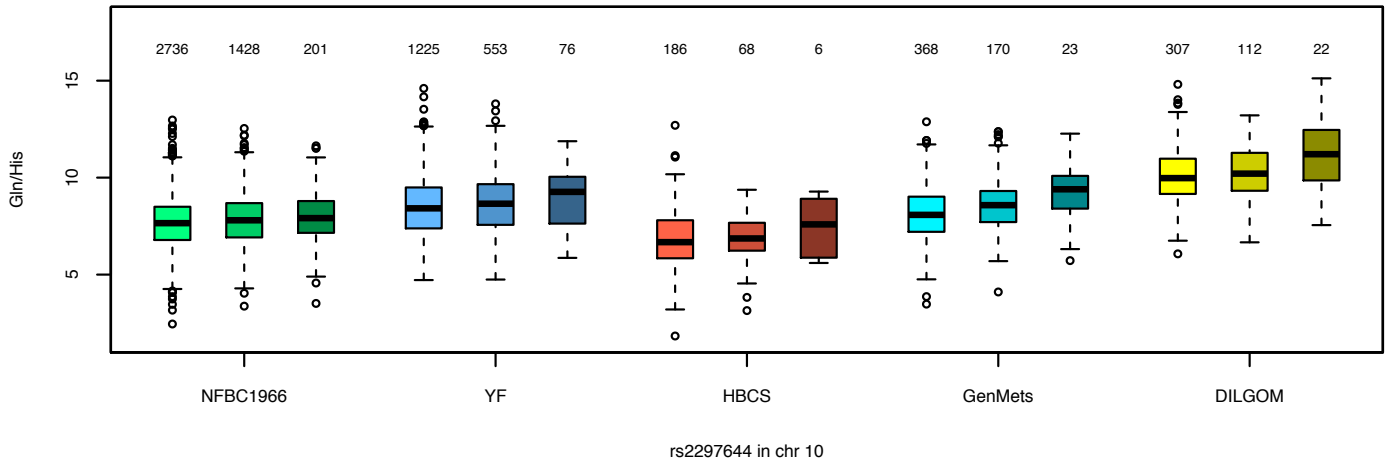
rs13247874 in chr 7



8−19956650 in chr 8



rs2575876 in chr 9



rs2297644 in chr 10

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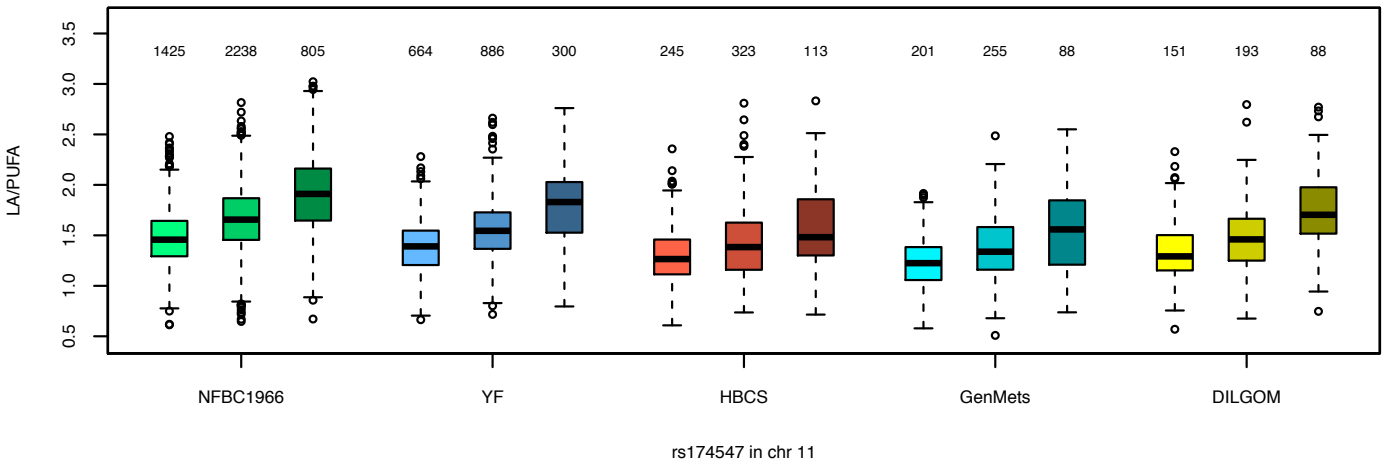
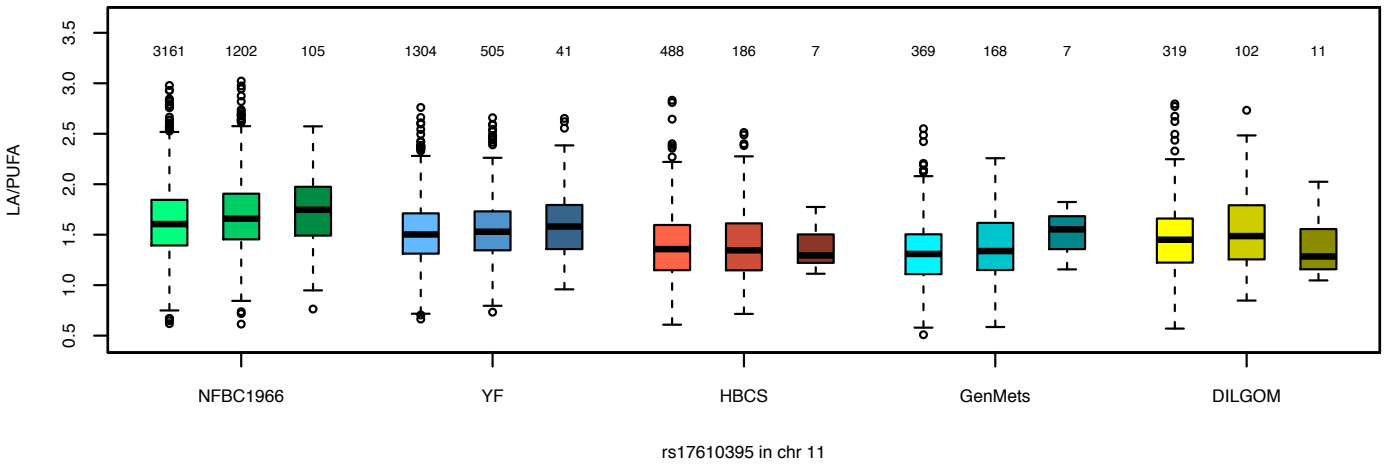


rs174547 in chr 11



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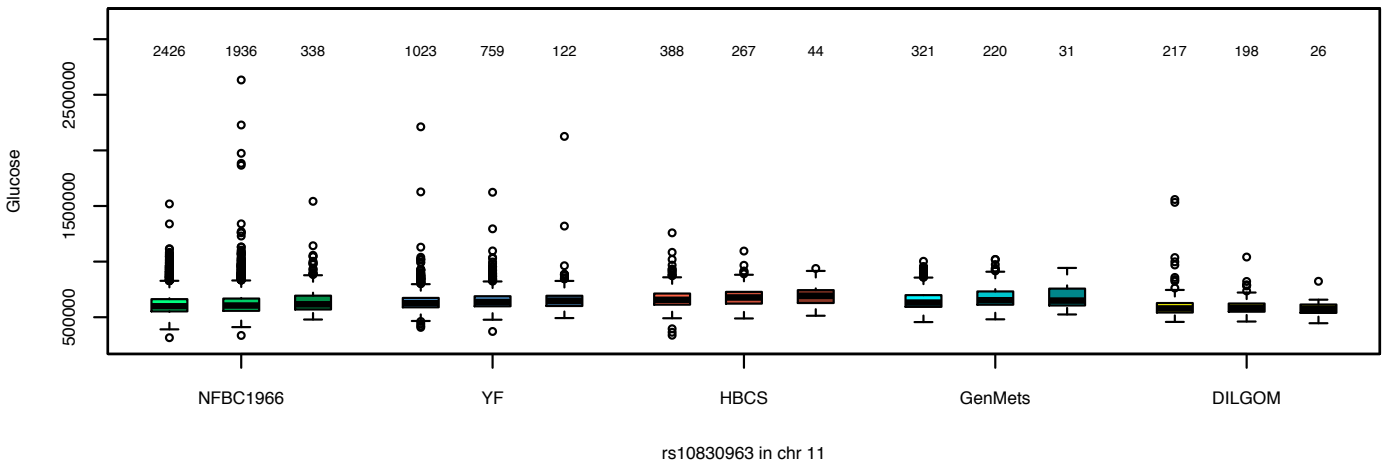

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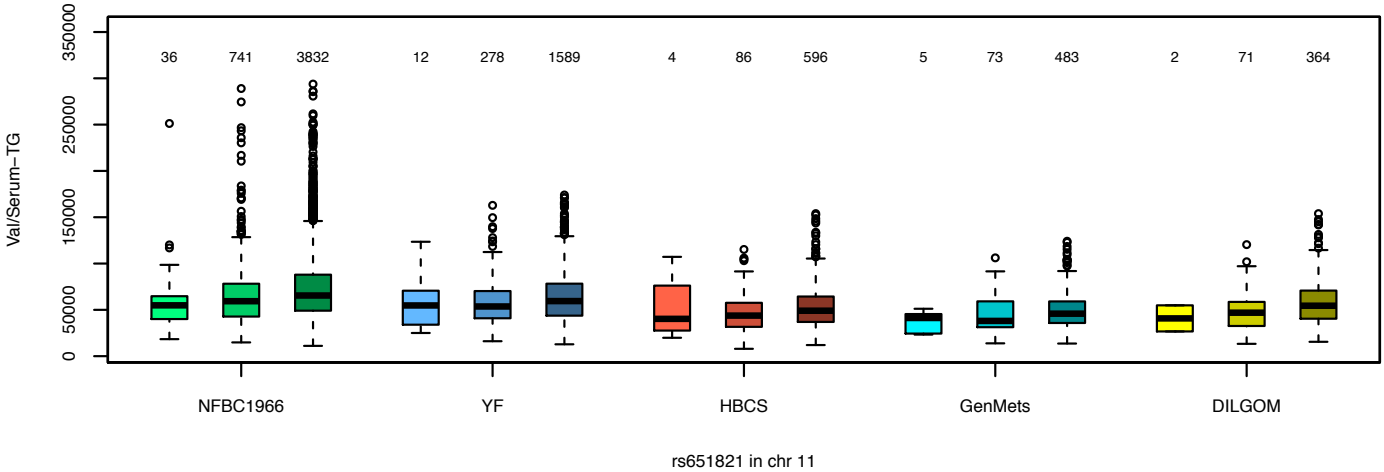
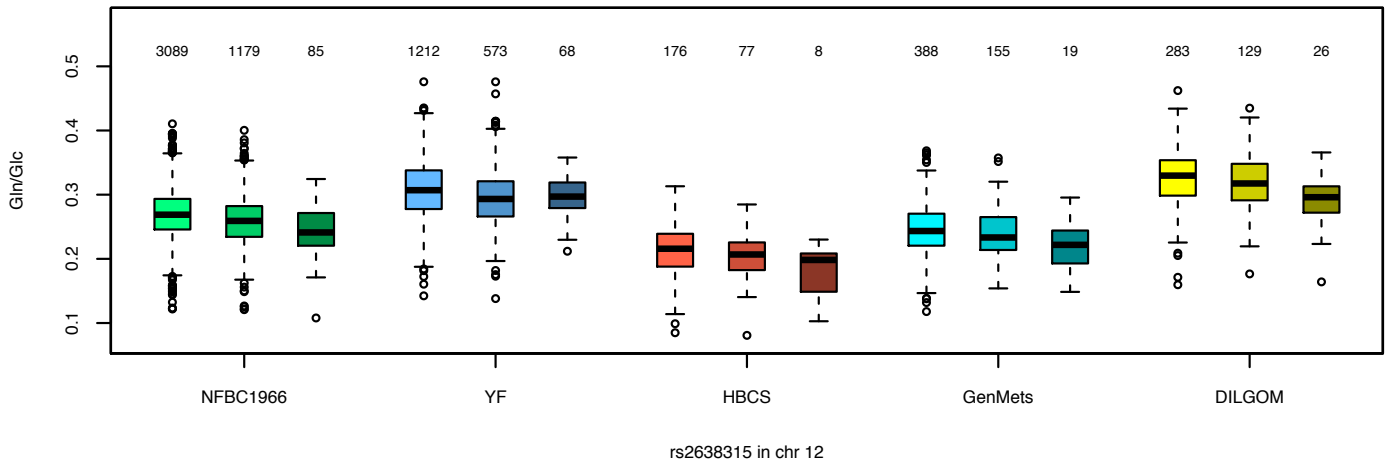
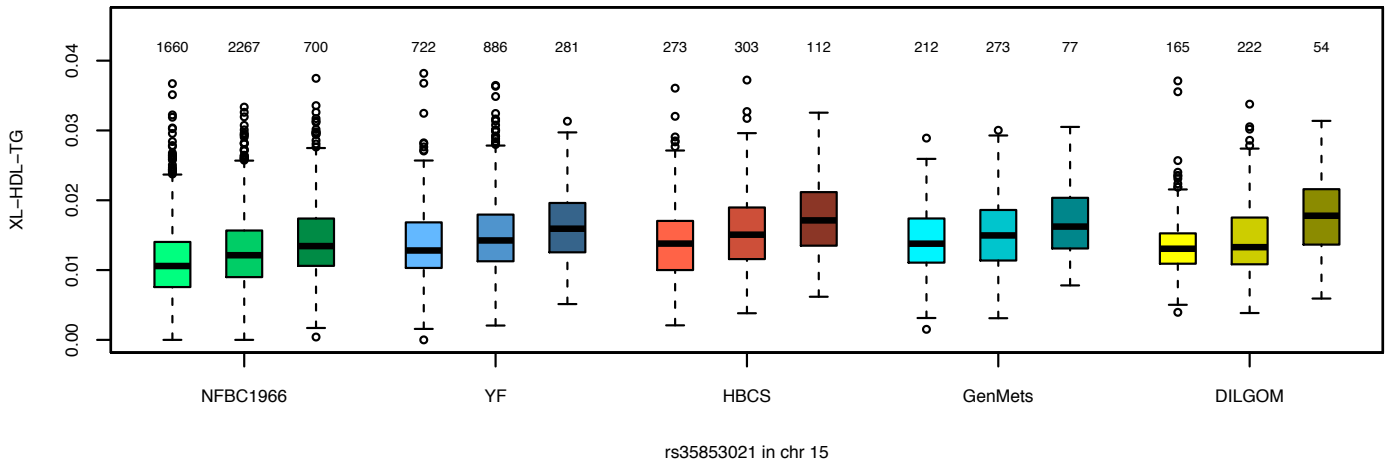


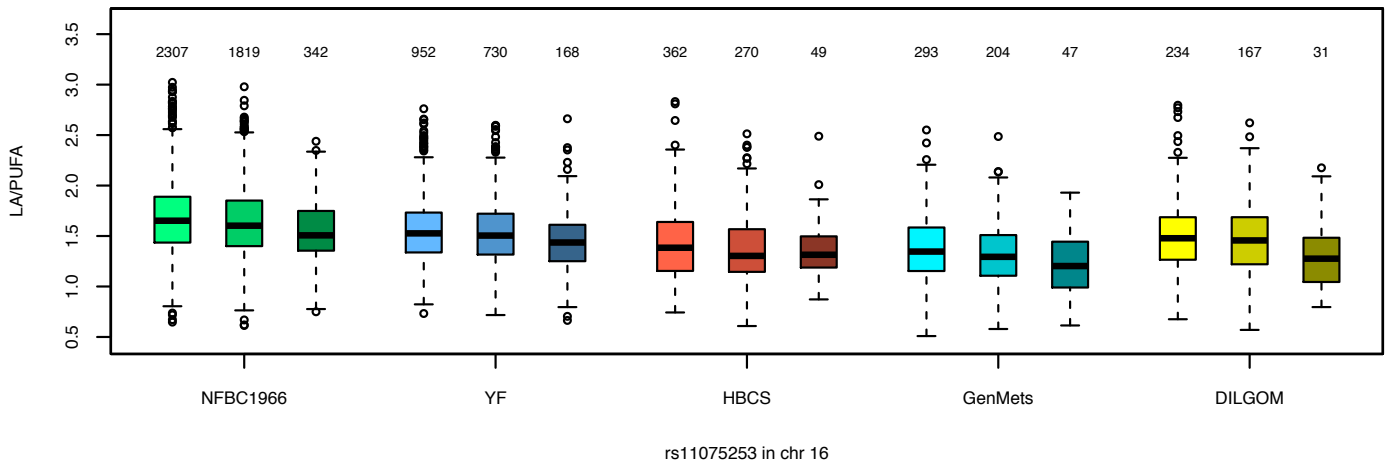
rs651821 in chr 11



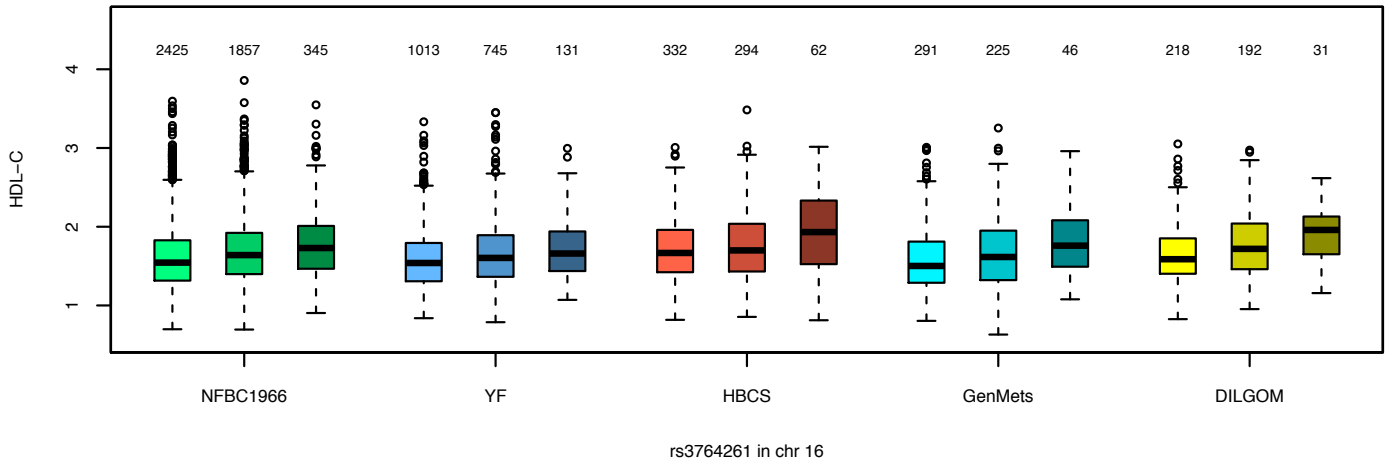
rs2638315 in chr 12



rs35853021 in chr 15



rs11075253 in chr 16



rs3764261 in chr 16

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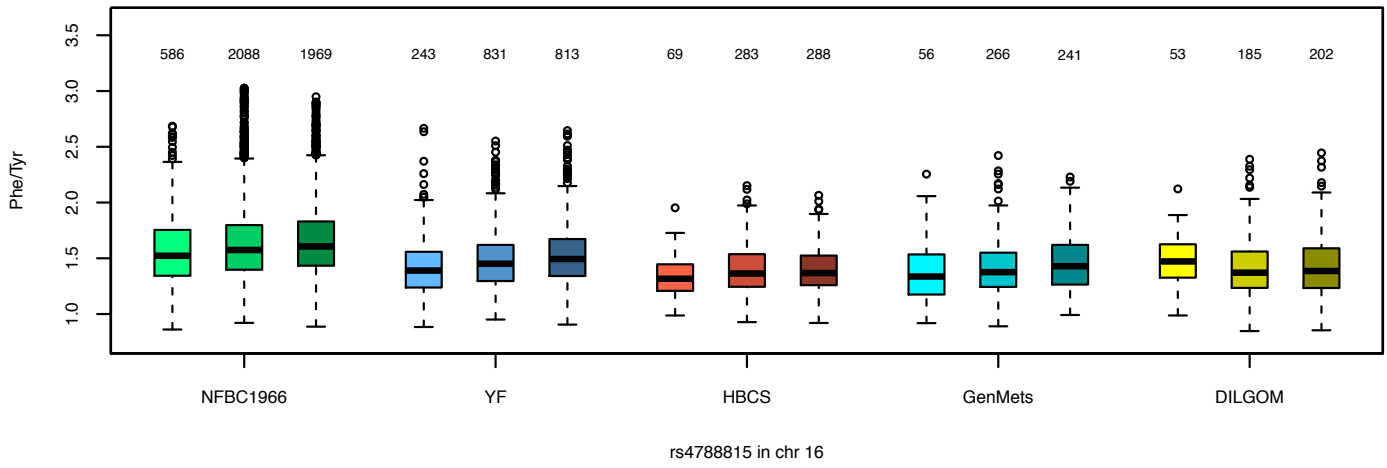
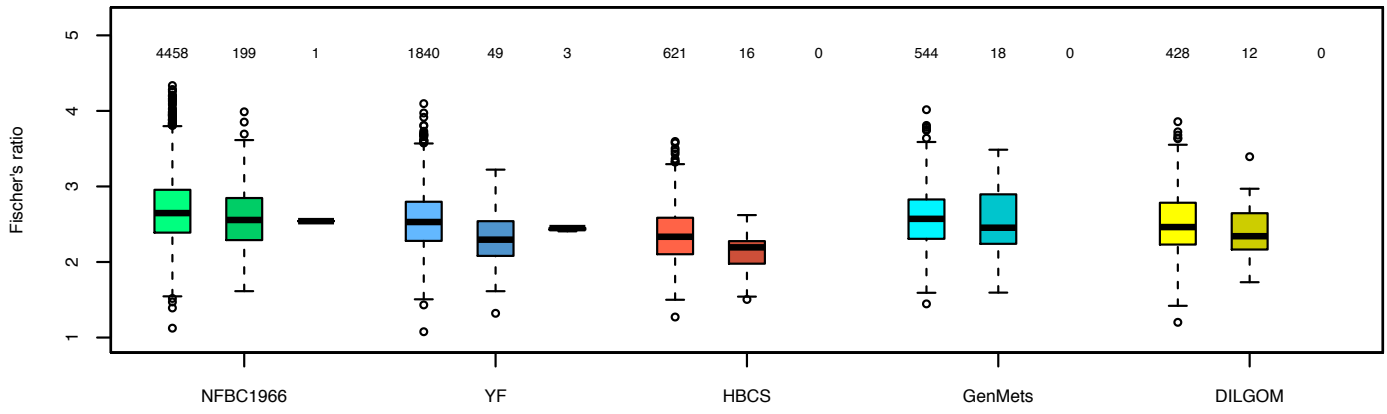
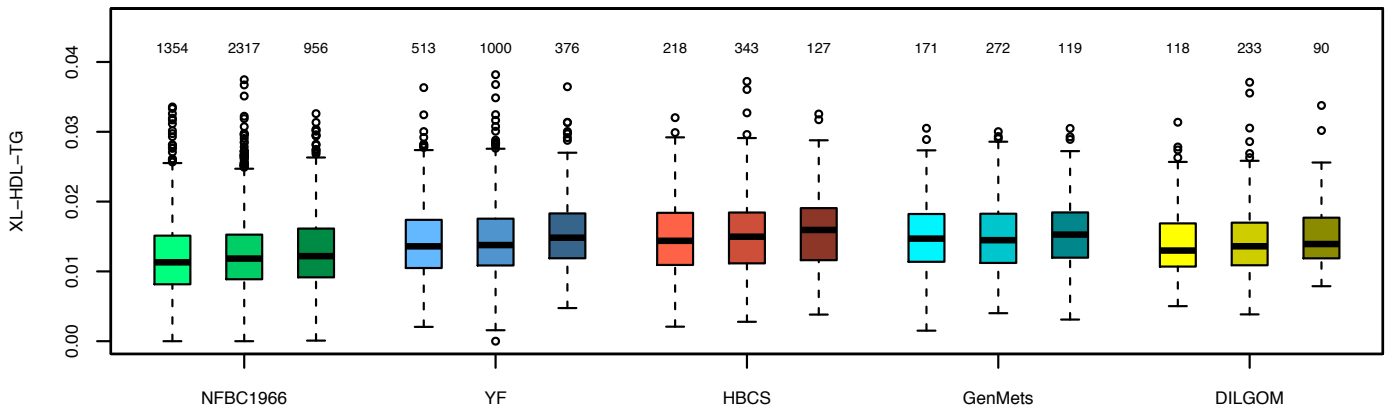


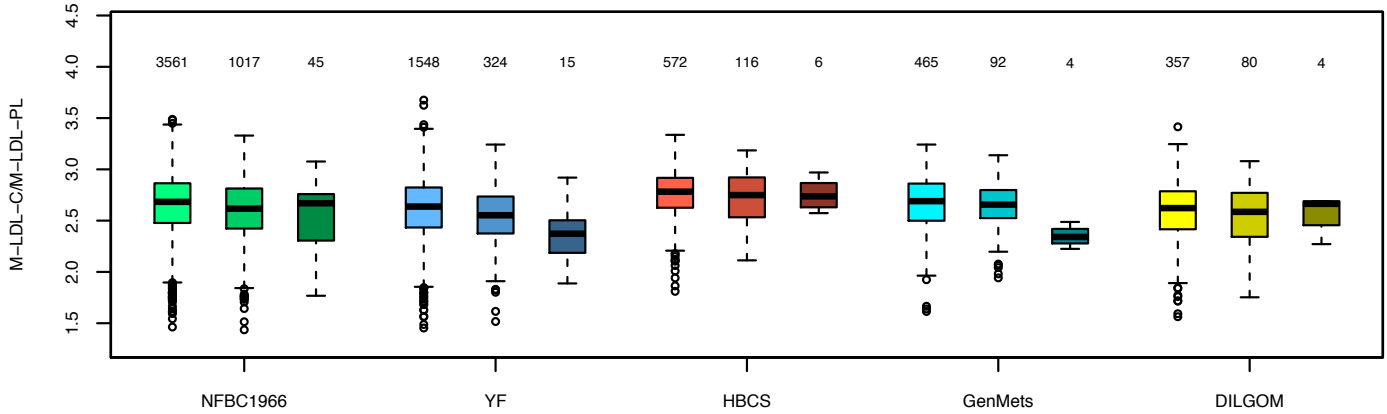
rs4788815 in chr 16



17–7083575 in chr 17



rs7228085 in chr 18



rs55791371 in chr 19

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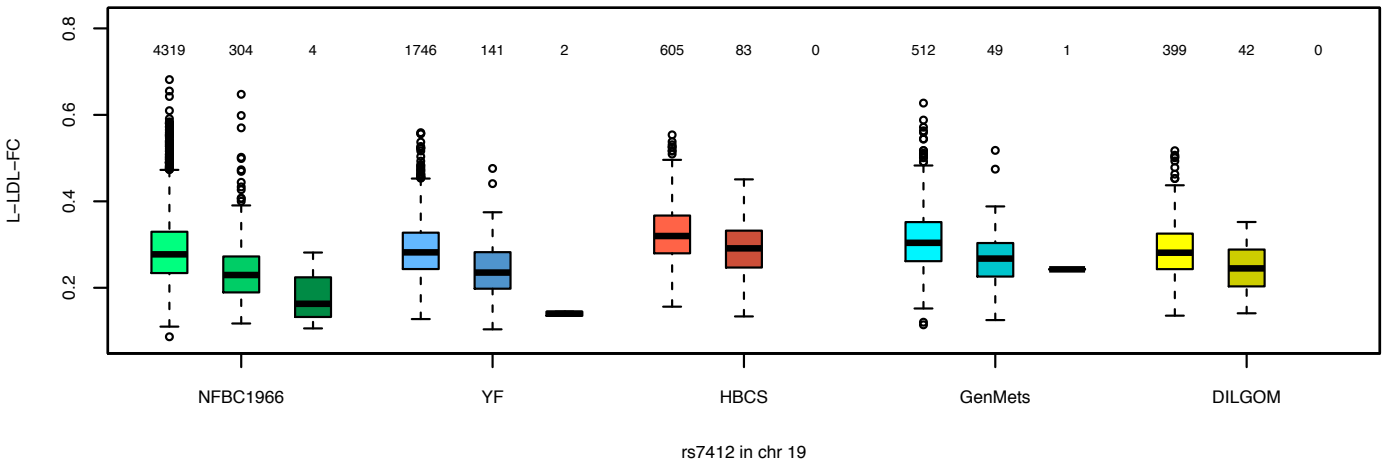
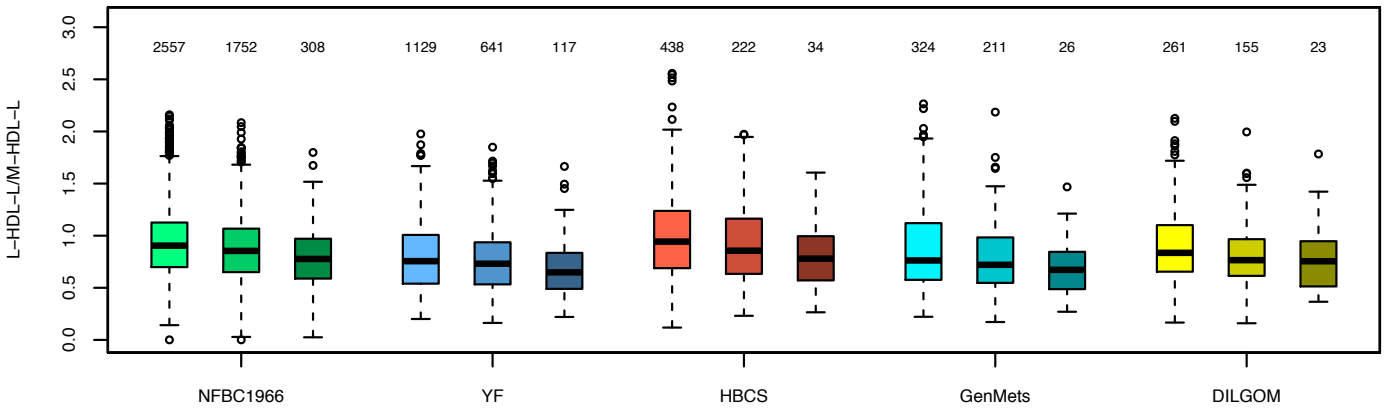
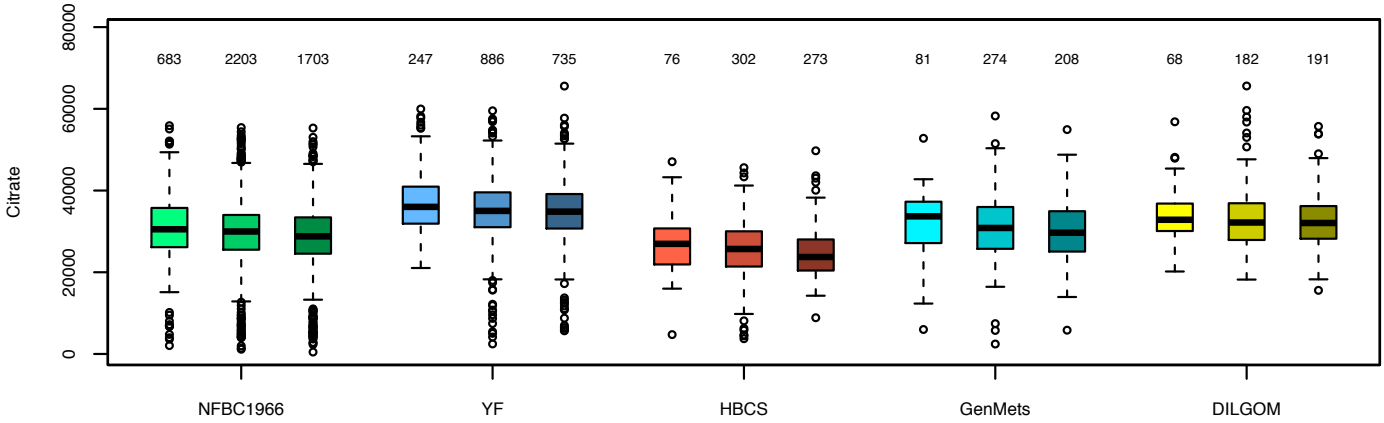


rs7412 in chr 19



rs6065904 in chr 20



rs807669 in chr 22

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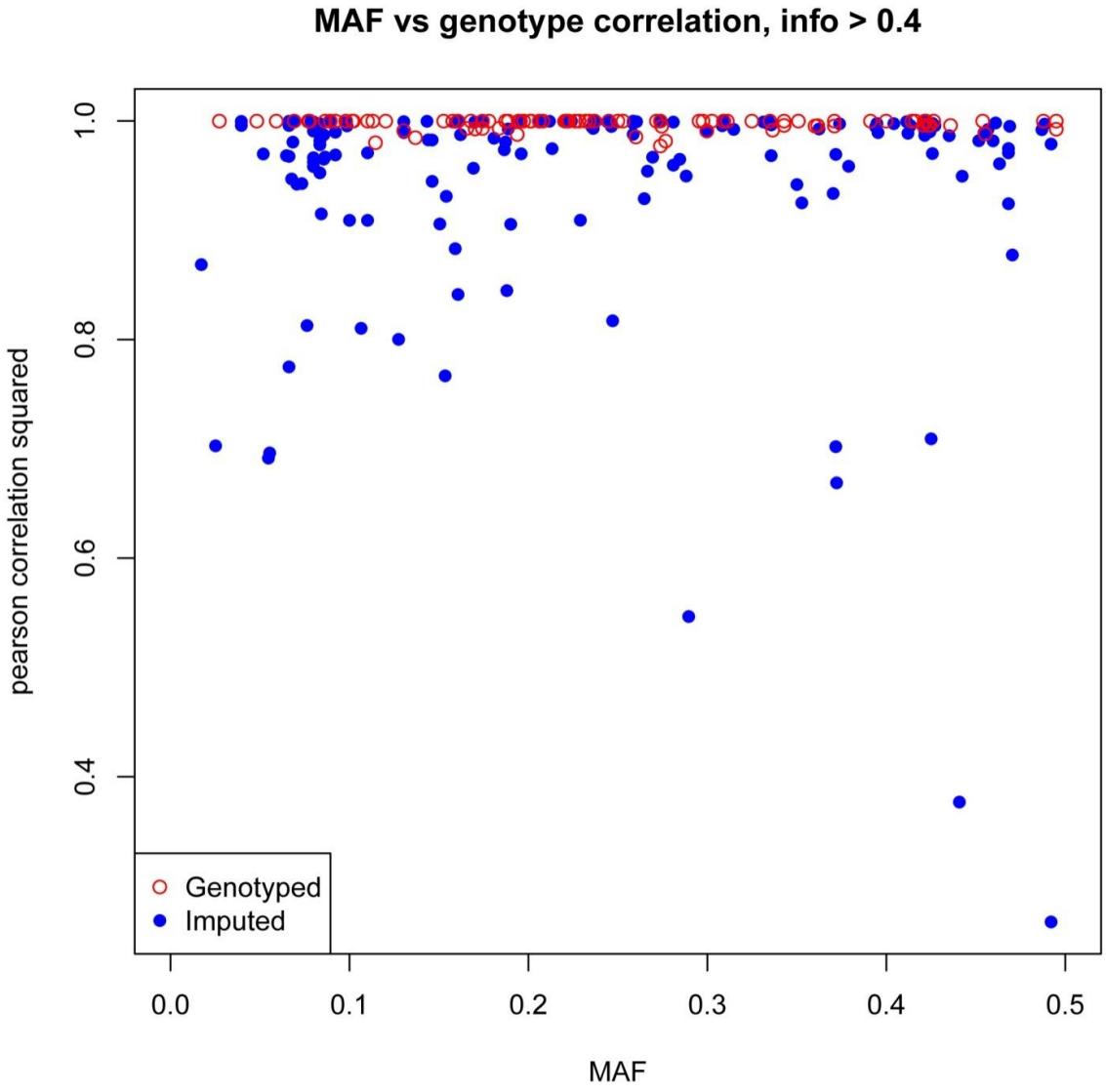
Supplementary Figure 4. Comparison of SNP genotypes which were imputed using genome wide data and genotyped in Cardiometabochip. Only SNPs which had imputation info greater than 0.4 were included. MAF = Minor allele frequency.



SUPPLEMENTARY NOTE

Study samples and phenotypes

The five studies included in the meta-analysis are described in **Table 1** in the main text and in further detail below. In addition, a twin study sample was available for estimating the heritabilities of the metabolomic measures. All participants provided informed consent, and local ethical committees at participating institutions approved individual study protocols.

Study descriptions

1. FINRISK-07 (DILGOM)

The sample has been described earlier by Inouye *et al*.[1]. In brief, the subjects (ages between 25 and 74) participated in the DIetary, Lifestyle and Genetic determinants of Obesity and Metabolic syndrome study (DILGOM) in the Helsinki region. DILGOM is a part of the FINRISK 2007 survey. FINRISK collections are performed every five years and the data are used for research projects and for national health monitoring purposes.

2. Helsinki Birth Cohort Study (HBCS)

The primary aim of the Helsinki Birth Cohort Study was to assess how growth and environmental factors acting during the fetal period and childhood are related to health in adult life. A particular focus has been the study of the early life origins of cardiovascular disease and its risk factors. Participants were born between 1934 and 1944 in Helsinki. An essential component of the project was a detailed clinical examination of over 2500 volunteers, parts of which provided data included in this study[2].

3. Health2000 GenMets Study (GenMets)

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The GenMets sample has been described in detail previously by Perttilä *et al*.[3]. Individuals in GenMets are metabolic syndrome cases and matched controls drawn from the Finnish Health2000 study, a population health survey. Persons with known diabetes were excluded. Participants included in the present study had participated in an additional survey which included drawing fasting serum samples.

4. Northern Finland Birth Cohort 1966 (NFBC1966)

The NFBC1966 has been described in detail previously by Rantakallio[4]. The original study design focused on factors affecting pre-term birth, low birth weight, and subsequent morbidity and mortality. Mothers living in the two northern-most provinces of Finland were invited to participate if they had expected delivery dates during 1966. Individuals still living in the Helsinki area or Northern Finland (N = 5923) were asked at age 31 to participate in a detailed biological and medical examination as well as a questionnaire.

5. Cardiovascular Risk in Young Finns Study (YF)

The Cardiovascular Risk in Young Finns Study (YF) is a population based prospective cohort study. It was conducted at five medical schools in Finland (Turku, Helsinki, Kuopio, Tampere and Oulu), with the aim of studying the levels of cardiovascular risk factors in children and adolescents in different parts of the country. The latest follow-up was conducted in 2007. The serum samples for this metabolomics study were collected at this latest follow up. The study and data collection protocols have been described in detail by Raitakari *et al*.[5].

6. Finnish twin cohort

Heritability analyses in this study utilized twin pairs (221 MZ and 340 DZ pairs) from the FinnTwin12 (FT12) and FinnTwin16 (FT16) cohort studies. In brief, the FT12 is a population based-cohort longitudinal study of five consecutive birth cohorts of Finnish twins born between 1983 and 1987. All twins (and their parents) were initially contacted and invited to participate by mail in the autumn of the year in which their birth cohort reached 11 years of age. Subsequent follow-up assessments were made

when the twins were aged 14, 17 and ~22 years. The FT16 is a population-based longitudinal study of five consecutive birth cohorts of Finnish twins born between 1975 and 1979. Each pair was initially approached and invited to participate by mail in the 1-2 months following the twins' 16th birthday. The baseline data collection started in 1991 and was completed in 1996, with participation of 2733 twin pairs (response rate ~ 88%). Subsequent follow-up assessments were made when the twins were 17, 18.5, and ~25 years, following a similar approach.

For both the FT12 and FT16, the baseline and follow-up assessments included surveys of health habits and attitudes, symptom checklists, personality scales, and social relationships[6]. In addition, blood samples were taken from all twins during a visit to the twin research clinic in Helsinki (Finland) at the last follow-up (young adulthood) for DNA and biochemistry analyses. All biological samples were stored at -80°C at the National Institute for Health and Welfare. Circulating metabolites were determined in 1,269 twins (FT12: n=725, 286MZ and 439DZ; FT16: n=544, 198MZ and 346DZ) using a serum NMR metabolomics platform[7, 8]. Data collection and analysis were approved by the ethics committees of the Department of Public Health of the University of Helsinki, the Helsinki and Uusimaa Hospital District and the IRB of Indiana University. Written informed consent was obtained from all participating twins.

Quantitative serum NMR metabolomics

The serum NMR metabolomics platform applied for metabolite quantification is based on three molecular windows (^{1}H NMR spectra) from each serum sample. The lipoprotein data (the LIPO window) and the low-molecular-weight metabolite data (LMWM) are acquired from native serum and the data from individual lipids (LIPID) from serum lipid extracts[9]. The experimental protocol including sample preparation and NMR spectroscopy are described in detail in Inouye *et al*.[8]. Further details of data analyses are briefly presented below.

^{1}H NMR is inherently a quantitative technique allowing for absolute metabolite quantification. The multi-metabolic nature of serum inevitably causes signal overlap, however the metabolite content and

concentrations can be extracted by appropriate computational techniques[10]. In the case of the heavily overlapping data of lipoprotein lipids in the LIPO window, we have implemented several lipoprotein subclasses (e.g., VLDL subclasses), as well as other lipoprotein (e.g., HDL-C), and serum lipid (e.g., TGs) quantification models using regression modeling. Prior to metabolite quantification the spectral data undergo pre-processing with automated baseline zeroing, peak alignments and subtraction of the albumin signal background[7]. A simplified and computationally more efficient modification of the approach presented in Vehtari *et al*. is used[11]. All the models used are cross-validated against NMR-independent high-performance liquid chromatography (HPLC) data[12]. Before applying the predictive models, we verify that the new input spectrum lies within the limits (±10%) of the training data set; otherwise, the particular sample is rejected from the subclass analyses with no outcome. The 14 lipoprotein subclass sizes determined by HPLC[12] are as follows: chylomicrons and largest VLDL particles (with particle diameters from 75nm upwards), five different VLDL subclasses, namely, very large VLDL (average particle diameter of 64.0 nm), large VLDL (53.6 nm), medium VLDL (44.5 nm), small VLDL (36.8 nm), and very small VLDL (31.3 nm); IDL (28.6 nm), three LDL subclasses as large LDL (25.5 nm), medium LDL (23.0 nm), and small LDL (18.7); and four HDL subclasses as very large HDL (14.3 nm), large HDL (12.1 nm), medium HDL (10.9 nm), and small HDL (8.7 nm). The mean R^2 between HPLC and NMR cross-validated models for lipoproteins is 0.75 (sd = 0.14). 73 % of the models had $R^2 > 0.7$. The mean size for VLDL, LDL, and HDL particles was calculated by weighting the corresponding subclass diameters with their particle concentrations. In this case, IDL particles were included in the measure of mean LDL diameter. Incorporation of the NMR measures (total and HDL cholesterol and total triglycerides) into a recently introduced extended Friedewald approach enabled estimation of apolipoprotein A-I and B as well as HDL_2-C and HDL_3-C[13].

In contrast to the LIPO window, the LMWM and LIPID windows feature sharper line shapes and less spectral overlap, which in turn ease metabolite quantification. Thus, the method of choice to quantify the low-molecular-weight metabolites in the LMWM spectra and the lipid signals in the LIPID spectra is

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iterative lineshape fitting analysis. The molecular identity of each metabolite was determined based on multidimensional spectra and literature references of chemical shifts[14]. The PERCH NMR software (Perch Solutions Ltd, Kuopio, Finland) was used in all the lineshape fitting analyses[15]. To account for the variable material loss during the serum lipid extraction procedure and to allow absolute quantification, each metabolite concentration in the LIPID spectrum is scaled via the total cholesterol concentration (from the LIPID spectrum) according to the serum total cholesterol level as quantified from the native serum (i.e., the LIPO spectrum).

Conditional analyses

In order to investigate whether the loci contain additional independent signals further association analyses were performed for loci by conditioning the analyses on the SNP reported in **Tables 2** and **3**, on the previously published SNP or significantly associated variants in the neighboring loci. The analyses using the SNP reported in **Tables 2** and **3** did not reveal additional independent signals except that the chromosome 16 region showed two independent signals. One signal was associated with serum tyrosine levels (rs4788815) and the other signal with the ratio of glycoproteins to total cholesterol (rs34042070 and rs3213423). All SNP associations remained significant after conditioning SNPs on each other. The SNP rs6917603 in the *PPP1R11*-region was conditioned with previously associated SNPs in the region (rs2247056 and rs3177928). The *CPT1A*-locus SNP, rs17610395, was conditioned on rs174547 from the *FADS*-locus.

Validation by sequencing

Nine of the eleven novel loci also showed association in the same region with a marker genotyped in at least 3 cohorts (with $P < 5 \times 10^{-8}$). For the other two loci we aimed to validate the imputed genotypes by sequencing the genomic segment containing the variant in a total of 20 individuals carrying the imputed rare allele and 40 individuals homozygous for the common allele (variants rs17610395 and 17-7083575).

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We sequenced PCR products using capillary electrophoresis with an ABI3730xl DNA Analyzer (Applied Biosystems, Foster City, CA) and BigDye v.3.1 sequencing kit (Applied Biosystems).

For rs17610395, we confirmed the presence of the rare allele, either in homozygote or heterozygote form, in 17 out of 19 successful sequencing reactions. One out of 39 individuals, who did not have an imputed heterozygous genotype in our imputed data, proved to be heterozygous after sequencing. For SNP 17-7083575, we confirmed the presence of the rare allele in a heterozygote state in 18 out of 19 imputed rare allele carriers. Three out of 40 individuals, who did not have an imputed heterozygous genotype, proved to be heterozygous after the sequencing of 17-7083575.

Heritability estimates

Heritability estimates were obtained utilizing all of the phenotypic information available from serum NMR metabolomics of the twin pairs. As the distributions of many of the NMR measures were initially highly skewed, they were standardized by age and sex and transformed using rank transformation methods, in R. This data pre-processing both achieved normality and standardized the variables so that the means and variances were independent of age and sex variability. Subsequently, we estimated the heritability of each metabolite measure using standard modeling methods: Univariate genetic models were fitted to the raw data utilizing R software with the specialized "OpenMx" package, and applying full information maximum likelihood methods. For each NMR-based phenotype, models estimating the hypothetical combinations of the different genetic and environmental sources of influence (ACE, ADE, AE, CE and E, where A is the additive genetic influence, C is the shared environmental influence, D is the dominance genetic influence, and E is the unique environmental influence) were built and tested against a saturated model, where no inference on the underlying architecture of the phenotype is assumed. As only data from MZ and DZ twins reared together were available for this study, C and D influences could not be modeled together. The simplest genetic model that fitted the data best was chosen by comparing the fit statistics (likelihood ratio test – LRT, as well as Akaike's Information Criterion – AIC)

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of the hierarchically nested, hypothetical models against that of the saturated model. A non-significant *P*-value from the LRT indicated that the hypothetical sub-model did not fit the data more poorly than the saturated model, while smaller AIC values indicated a better fit to the data. A subset of twins had both enzymatic lipoprotein measures and NMR-measures available. Those were used for the comparison of heritability estimates between enzymatic and NMR methods (**Supplementary Tables 4 and 5**).

References

1. Inouye, M. *et al*. An immune response network associated with blood lipid levels. *PLoS Genet*. **6**, e1001113 (2010).

2. Yliharsila, H. *et al*. Body mass index during childhood and adult body composition in men and women aged 56-70 y. *Am*. *J*. *Clin*. *Nutr*. **87**, 1769-1775 (2008).

3. Perttila, J. *et al*. OSBPL10, a novel candidate gene for high triglyceride trait in dyslipidemic Finnish subjects, regulates cellular lipid metabolism. *J*. *Mol*. *Med*. **87**, 825-835 (2009).

4. Rantakallio, P. Groups at risk in low birth weight infants and perinatal mortality. *Acta Paediatr*. *Scand*. **193**, Suppl 193:1+ (1969).

5. Raitakari, O. T. *et al*. Cohort profile: the cardiovascular risk in Young Finns Study. *International journal of epidemiology* **37**, 1220-6 (2008).

6. Kaprio, J., Pulkkinen, L. & Rose, R. J. Genetic and environmental factors in health-related behaviors: studies on Finnish twins and twin families. *Twin Res*. **5**, 366-371 (2002).

7. Soininen, P. *et al*. High-throughput serum NMR metabonomics for cost-effective holistic studies on systemic metabolism. *Analyst* **134**, 1781-1785 (2009).

8. Inouye, M. *et al*. Metabonomic, transcriptomic, and genomic variation of a population cohort. *Mol*. *Syst*. *Biol*. **6**, 441 (2010).

9. Tukiainen, T. *et al*. A multi-metabolite analysis of serum by 1H NMR spectroscopy: early systemic signs of Alzheimer's disease. *Biochem*. *Biophys*. *Res*. *Commun*. **375**, 356-361 (2008).

10. Ala-Korpela, M. 1H NMR spectroscopy of human blood plasma. *Prog Nucl Magn Reson Spectrosc* **27**, 475-554 (1995).

11. Vehtari, A. *et al*. A novel Bayesian approach to quantify clinical variables and to determine their spectroscopic counterparts in 1H NMR metabonomic data. *BMC Bioinformatics* **8 Suppl 2**, S8 (2007).

12. Okazaki, M. *et al*. Identification of unique lipoprotein subclasses for visceral obesity by component analysis of cholesterol profile in high-performance liquid chromatography. *Arterioscler*. *Thromb*. *Vasc*. *Biol*. **25**, 578-584 (2005).

13. Niemi, J. *et al*. Estimation of VLDL, IDL, LDL, HDL2, apoA-I, and apoB from the Friedewald inputs--apoB and IDL, but not LDL, are associated with mortality in type 1 diabetes. *Ann*. *Med*. **41**, 451-461 (2009).

14. Wishart, D. S. *et al*. HMDB: the Human Metabolome Database. *Nucleic Acids Res*. **35**, D521-6 (2007).

15. Soininen, P., Haarala, J., Vepsäläinen, J., Niemitz, M. & Laatikainen, R. Strategies for organic impurity quantification by 1H NMR spectroscopy: Constrained total-line-shape fitting. *Anal*. *Chim*. *Acta* **542**, 178-185 (2005).

16. Pietilainen, K. H. *et al*. Global transcript profiles of fat in monozygotic twins discordant for BMI: pathways behind acquired obesity. *PLoS Med*. **5**, e51 (2008).

17. Newgard, C. B. *et al*. A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. *Cell*. *Metab*. **9**, 311-326 (2009).

18. Wang, T. J. *et al*. Metabolite profiles and the risk of developing diabetes. *Nat*. *Med*. (2011).

19. Saier, E. L., Nordstrand, E., Juves, M. W. & Hartsock, R. J. The ratio of free to esterified cholesterol in serum. A new discriminant in correlating lipid metabolism with disease state. *Am*. *J*. *Clin*. *Pathol*. **71**, 83-87 (1979).

20. Steiner, A., Kendall, F. E. & Mathers, J. A. The abnormal serum lipid pattern in patients with coronary arteriosclerosis. *Circulation* **5**, 605-608 (1952).

21. Piperi, C. *et al*. The significance of serum HDL phospholipid levels in angiographically defined coronary artery disease. *Clin*. *Biochem*. **37**, 377-381 (2004).

22. Chasman, D. I. *et al*. Forty-three loci associated with plasma lipoprotein size, concentration, and cholesterol content in genome-wide analysis. *PLoS Genet*. **5**, e1000730 (2009).

23. Huuskonen, J., Olkkonen, V. M., Jauhiainen, M. & Ehnholm, C. The impact of phospholipid transfer protein (PLTP) on HDL metabolism. *Atherosclerosis* **155**, 269-281 (2001).

24. Wang, L., Folsom, A. R. & Eckfeldt, J. H. Plasma fatty acid composition and incidence of coronary heart disease in middle aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. *Nutr*. *Metab*. *Cardiovasc*. *Dis*. **13**, 256-266 (2003).

25. Rhee, E. P. *et al*. Lipid profiling identifies a triacylglycerol signature of insulin resistance and improves diabetes prediction in humans. *J*. *Clin*. *Invest*. **121**, 1402-1411 (2011).

26. Tanaka, T. *et al*. Genome-wide association study of plasma polyunsaturated fatty acids in the InCHIANTI Study. *PLoS Genet*. **5**, e1000338 (2009).

27. Yerlikaya, F. H., Mehmetoglu, I., Kurban, S. & Tonbul, Z. Plasma Fatty Acid composition in continuous ambulatory peritoneal dialysis patients: an increased omega-6/omega-3 ratio and deficiency of essential Fatty acids. *Ren*. *Fail*. **33**, 819-823 (2011).

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