Supplementary Information:

Genome-wide association study of serum liver enzymes implicates diverse metabolic and liver pathology

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**Supplementary Table 1: Descriptive summary of phenotypes in UK BioBank**

| Variable | Value | N |
|---|---|---|
| Female | 54% | 390812 |
| Age (years) | 67 (8.0) | 390812 |
| Alanine aminotransferase (U/L) | 24 (14) | 390812 |
| Aspartate aminotransferase (U/L) | 24 (11) | 389565 |
| Alkaline phosphatase (U/L) | 84 (26) | 390964 |
| Triglycerides (mmol/L) | 1.5 (1.0) | 390616 |
| High-density lipoprotein (mmol/L) | 1.5 (0.38) | 358767 |
| Low-density lipoprotein (mmol/L) | 3.7 (0.82) | 321191 |
| Systolic blood pressure (mmHg) | 145 (19) | 176321 |
| Diastolic blood pressure (mmHg) | 86 (11) | 176322 |
| Body mass index (kg/m2) | 27 (4.8) | 407545 |
| Glucose (mmol/L) | 5.1 (1.2) | 358536 |
| Waist-to-hip ratio (cm/cm) | 0.87 (0.09) | 407545 |

Values are expressed as mean (standard deviation) or percentage.

**Supplementary Table 2: Genomic control parameters**

| | UK BioBank | | BioBank Japan | | Meta-analysis |
|---|---|---|---|---|---|
| **Trait** | **Lambda_GC** | **Intercept** | **Lambda_GC** | **Intercept** | **Lambda_GC** |
| Alanine aminotransferase | 1.44 | 1.26 | 1.13 | 1.02 | 1.03 |
| Aspartate aminotransferase | 1.47 | 1.31 | 1.13 | 1.01 | 1.03 |
| Alkaline phosphatase | 1.71 | 1.54 | 1.15 | 1.06 | 1.03 |

Genomic control parameters (lambda_GC) and intercept estimates for the UK BioBank, BioBank Japan, and the meta-analysis. Lambda-GC estimates are from METAL and intercept from LDpred.

**Supplementary Table 3: Alanine aminotransferase-altering alleles with heterogeneity between UK BioBank & BioBank Japan**

| CHR:POS | Variant | EA | OA | UK BioBank | | | BioBank Japan | | | Gene annotation | Nearest coding genes | P_het | Direction |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | EAF | Beta | P | EAF | Beta | P | | | | |
| 10:101912064 | rs2862954 | T | C | 0.50 | 0.071 | 2.41e-194 | 0.96 | 0.026 | 6.67e-03 | ERLIN1 (e) | ERLIN1 | 4.34e-25 | ++ |
| 19:19379549 | rs58542926 | T | C | 0.08 | 0.099 | 1.72e-106 | 0.08 | 0.034 | 9.20e-06 | TM6SF2 (e) | TM6SF2 | 1.64e-08 | ++ |
| 4:146821410 | rs4835265 | A | C | 0.16 | 0.064 | 1.21e-84 | 0.36 | 0.022 | 3.24e-08 | ZNF827 (i) | ZNF827 | 1.88e-04 | ++ |
| 11:93870338 | rs7117339 | C | T | 0.88 | 0.071 | 7.00e-80 | 0.95 | 0.038 | 3.45e-05 | PANX1 (i) | PANX1 | 3.81e-06 | ++ |
| 1:16505320 | rs1497406 | G | A | 0.58 | 0.046 | 1.38e-79 | 0.79 | 0.020 | 4.07e-05 | EPHA2, ARHGEF19 (inter) | EPHA2, ARHGEF19 | 3.53e-06 | ++ |
| 19:45411941 | rs429358 | T | C | 0.84 | 0.051 | 7.16e-54 | 0.90 | 0.016 | 1.03e-02 | APOE (e) | APOE | 9.12e-06 | ++ |
| 8:9185146 | rs2126259 | T | C | 0.10 | 0.059 | 1.08e-50 | 0.01 | 0.055 | 3.68e-03 | LOC157273 (i) | PPP1R3B, TNKS | 7.51e-05 | ++ |
| 22:36545137 | rs132642 | T | A | 0.83 | 0.051 | 7.52e-57 | 0.99 | 0.036 | 1.39e-01 | APOL3 (UTR) | APOL3 | 3.74e-08 | ++ |
| 1:220970028 | rs2642438 | G | A | 0.70 | 0.040 | 1.75e-52 | 0.83 | 0.008 | 1.37e-01 | MARC1 (e) | C1orf115, HLX | 1.73e-07 | ++ |
| 1:155106697 | rs12904 | G | A | 0.59 | 0.035 | 7.71e-46 | 0.09 | 0.018 | 7.30e-03 | EFNA1 (UTR) | EFNA1 | 1.35e-04 | ++ |
| 10:70985267 | rs2394529 | C | G | 0.70 | 0.036 | 1.19e-42 | 0.18 | 0.009 | 7.17e-02 | LOC101928994 (i) | HKDC1 | 1.61e-05 | ++ |
| 2:169834370 | rs72623176 | A | G | 0.04 | 0.047 | 4.92e-14 | 0.33 | 0.045 | 1.22e-28 | ABCB11 (i) | ABCB11 | 5.10e-09 | ++ |
| 8:145955007 | rs2467663 | T | C | 0.66 | 0.034 | 3.90e-41 | 0.31 | 0.006 | 1.63e-01 | ZNF251 (i) | ZNF251 | 5.77e-06 | ++ |
| 2:227112754 | rs2943654 | T | C | 0.65 | 0.031 | 2.59e-34 | 0.91 | 0.006 | 3.39e-01 | LOC646736, MIR5702 (inter) | NYAP2, IRS1 | 1.20e-05 | ++ |
| 8:10571491 | rs4484649 | C | A | 0.40 | 0.029 | 5.44e-32 | 0.71 | 0.005 | 2.81e-01 | C8orf74, SOX7 (inter) | C8orf74, SOX7 | 4.26e-05 | ++ |
| 2:165557318 | rs6712203 | C | T | 0.63 | 0.028 | 7.71e-29 | 0.91 | 0.006 | 3.62e-01 | COBLL1 (i) | COBLL1 | 7.42e-05 | ++ |
| 19:41333284 | rs11878604 | T | C | 0.93 | 0.026 | 2.02e-08 | 0.61 | 0.036 | 6.94e-20 | CYP2T1P, CYP2A6 (inter) | EGLN2, CYP2A6 | 4.37e-07 | ++ |
| 2:211540507 | rs1047891 | A | C | 0.32 | 0.012 | 7.65e-06 | 0.15 | 0.049 | 6.46e-18 | CPS1 (e) | CPS1 | 3.04e-07 | ++ |
| 1:150479901 | rs1815544 | C | T | 0.60 | 0.024 | 2.22e-22 | 0.72 | 0.001 | 8.47e-01 | TARS2 (UTR) | TARS2 | 7.82e-05 | ++ |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 16:53806453 | rs56094641 | G | A | 0.40 | 0.021 | 1.00e-17 | 0.20 | -0.002 | 6.54e-01 | FTO (i) | FTO | 6.80e-05 | +- |

CHR:POS, chromosome:position. EA, effect allele. OA, other allele. EAF, effect allele frequency. P_het, P value for heterogeneity between UK BioBank and BioBank Japan. Gene tags: (e) exonic, (i) intronic, (u) upstream, (d) downstream, (inter) intergenic, (UTR) untranslated region. Direction: + indicates that the variant increases the liver enzyme while - indicates that the variant decreases the liver enzyme. Direction of effect in UK BioBank is shown first, followed by effect in BioBank Japan.

**Supplementary Table 4: Aspartate aminotransferase-altering alleles with heterogeneity between UK BioBank & BioBank Japan**

| | | | | UK BioBank | | | BioBank Japan | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CHR:POS | Variant | EA | OA | EAF | Beta | P | EAF | Beta | P | Gene annotation | Nearest coding genes | P_het | Direction |
| 10:101912064 | rs2862954 | T | C | 0.50 | 0.056 | 2.60e-113 | 0.96 | 0.039 | 3.29e-05 | ERLIN1 (e) | ERLIN1 | 1.13e-09 | ++ |
| 19:19379549 | rs58542926 | T | C | 0.08 | 0.076 | 3.73e-59 | 0.08 | 0.029 | 1.38e-04 | TM6SF2 (e) | TM6SF2 | 2.25e-04 | ++ |
| 3:58380465 | rs11714574 | A | T | 0.59 | 0.045 | 2.43e-71 | 0.24 | 0.005 | 2.70e-01 | PXK (i) | PXK | 4.96e-11 | ++ |
| 1:165108894 | rs36086195 | T | C | 0.58 | 0.041 | 8.37e-59 | 0.77 | 0.017 | 4.72e-04 | EPHA2, ARHGEF19 (inter) | EPHA2, ARHGEF19 | 8.72e-05 | ++ |
| 8:8661681 | rs12544992 | G | C | 0.47 | 0.033 | 1.91e-39 | 0.72 | 0.006 | 1.74e-01 | MFHAS1 (i) | MFHAS1 | 1.13e-05 | ++ |
| 11:116648917 | rs964184 | G | C | 0.13 | 0.043 | 8.54e-32 | 0.28 | 0.006 | 1.75e-01 | ZPR1 (UTR) | ZPR1 | 1.42e-04 | ++ |
| 2:113841030 | rs6734238 | A | G | 0.60 | 0.028 | 1.11e-28 | 0.95 | 0.003 | 6.98e-01 | IL1F10, IL1RN (inter) | IL1F10, IL1RN | 1.48e-05 | ++ |
| 10:70985267 | rs2394529 | C | G | 0.70 | 0.029 | 5.40e-26 | 0.18 | 0.002 | 7.28e-01 | LOC101928994 (i) | HKDC1 | 3.69e-05 | ++ |
| 22:36545137 | rs132642 | T | A | 0.83 | 0.035 | 9.13e-27 | 0.99 | -0.008 | 7.40e-01 | APOL3 (UTR) | APOL3 | 2.06e-06 | +- |
| 1:66141502 | rs1938500 | T | G | 0.19 | 0.032 | 2.69e-23 | 0.76 | 0.001 | 8.87e-01 | LEPR, PDE4B (inter) | LEPR, PDE4B | 5.30e-05 | ++ |
| 10:18263873 | rs508196 | C | T | 0.56 | 0.088 | 1.72e-270 | 0.45 | 0.015 | 1.12e-04 | SLC39A12 (i) | SLC39A12 | 6.81e-31 | ++ |
| 6:32582601 | rs34656207 | T | C | 0.36 | 0.071 | 1.86e-159 | 0.46 | 0.029 | 6.04e-12 | HLA-DRB1, HLA-DQA1 (inter) | HLA-DRB1, HLA-DQA1 | 1.44e-08 | ++ |
| 9:136141870 | rs2519093 | C | T | 0.81 | 0.055 | 1.34e-66 | 0.72 | 0.014 | 6.32e-04 | ABO (i) | ABO | 9.19e-06 | ++ |
| 16:58770897 | rs11643959 | T | G | 0.91 | 0.081 | 1.13e-75 | 0.99 | 0.011 | 5.96e-01 | GOT2, APOOP5 (inter) | GOT2, CDH8 | 3.67e-13 | ++ |

CHR:POS, chromosome:position. EA, effect allele. OA, other allele. EAF, effect allele frequency. P_het, P value for heterogeneity between UK BioBank and BioBank Japan. Gene tags: (e) exonic, (i) intronic, (u) upstream, (d) downstream, (inter) intergenic, (UTR) untranslated region. Direction: + indicates that the variant increases the liver enzyme while - indicates that the variant decreases the liver enzyme. Direction of effect in UK BioBank is shown first, followed by effect in BioBank Japan.

**Supplementary Table 5: Alkaline phosphatase-altering alleles with heterogeneity between UK BioBank & BioBank Japan**

| | | | | UK BioBank | | | BioBank Japan | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CHR:POS | Variant | EA | OA | EAF | Beta | P | EAF | Beta | P | Gene annotation | Nearest coding genes | P_het | Direction |
| 1:21895061 | rs1256330 | T | C | 0.31 | 0.108 | 1.59E-298 | 0.23 | 0.124 | 2.84E-124 | ALPL (i) | ALPL | 3.87e-11 | ++ |
| 10:65350383 | rs10822186 | G | A | 0.49 | 0.102 | <1e-300 | 0.49 | 0.039 | 6.35E-19 | REEP3 (i) | REEP3 | 2.10e-09 | ++ |
| 12:121423659 | rs9738226 | A | G | 0.38 | 0.086 | 1.82E-207 | 0.48 | 0.021 | 1.57E-06 | HNF1A (i) | HNF1A | 7.05e-12 | ++ |
| 2:27730940 | rs1260326 | T | C | 0.39 | 0.071 | 4.02E-146 | 0.56 | 0.014 | 1.12E-03 | GCKR (e) | GCKR | 1.84e-10 | ++ |
| 19:54677189 | rs8736 | T | C | 0.44 | 0.066 | 4.58E-131 | 0.22 | 0.019 | 2.61E-04 | MBOAT7 (UTR) | MBOAT7 | 2.67e-08 | ++ |
| 11:296255 | rs12277152 | A | G | 0.05 | 0.115 | 1.25E-73 | 0.28 | 0.064 | 2.72E-38 | PGGHG (d) | PGGHG, IFITM5 | 1.62e-05 | ++ |
| 19:19379549 | rs58542926 | C | T | 0.92 | 0.127 | 3.84E-136 | 0.92 | 0.017 | 4.92E-02 | TM6SF2 (e) | TM6SF2 | 1.06e-12 | ++ |
| 19:45421877 | rs484195 | A | G | 0.38 | 0.066 | 4.51E-120 | 0.59 | 0.018 | 5.09E-04 | APOC1 (i) | APOC1 | 9.65e-08 | ++ |
| 11:61592362 | rs174566 | G | A | 0.35 | 0.063 | 3.57E-109 | 0.39 | 0.020 | 7.98E-06 | FADS2 (i) | FADS2 | 3.69e-05 | ++ |
| 8:10665444 | rs6601527 | C | A | 0.41 | 0.061 | 6.75E-108 | 0.66 | 0.011 | 1.74E-02 | PINX1 (i) | PINX1 | 6.34e-09 | ++ |
| 2:169893419 | rs2161037 | G | A | 0.45 | 0.056 | 5.33E-94 | 0.29 | 0.008 | 1.14E-01 | ABCB11, DHRS9 (inter) | ABCB11, DHRS9 | 2.88e-09 | ++ |
| 15:58678720 | rs261290 | C | T | 0.65 | 0.055 | 1.93E-82 | 0.57 | 0.010 | 1.90E-02 | AQP9, LIPC (inter) | AQP9, LIPC | 1.32e-06 | ++ |
| 4:100065509 | rs1800759 | T | G | 0.39 | 0.052 | 1.61E-78 | 0.16 | 0.007 | 2.58E-01 | LOC100507053 (i) | ADH4, ADH6 | 1.40e-08 | ++ |
| 16:72217113 | rs7202323 | G | T | 0.23 | 0.051 | 1.11E-55 | 0.37 | 0.005 | 3.16E-01 | PMFBP1, LINC01572 (inter) | PMFBP1, ZFHX3 | 2.50e-06 | ++ |
| 1:20894442 | rs12137738 | A | T | 0.90 | 0.056 | 2.29E-35 | 0.99 | 0.000 | 9.86E-01 | FAM43B, CDA (inter) | FAM43B, CDA | 1.15e-05 | +- |
| 9:136140462 | rs1633513 | C | T | 0.27 | 0.118 | <1e-300 | 0.27 | 0.137 | 1.06E-173 | ABO (i) | ABO | 3.28e-22 | ++ |
| 8:9194978 | rs13274716 | C | T | 0.12 | 0.162 | <1e-300 | 0.01 | 0.106 | 1.02E-06 | LOC157273, TNKS (inter) | PPP1R3B, TNKS | 1.81e-21 | ++ |
| 8:126500031 | rs28601761 | C | G | 0.58 | 0.100 | 1.35E-286 | 0.84 | 0.021 | 7.51E-04 | TRIB1, LINC00861 (inter) | TRIB1, POU5F1B | 2.32e-23 | ++ |
| 20:25296970 | rs6083799 | T | G | 0.56 | 0.067 | 1.92E-134 | 0.08 | 0.023 | 8.19E-03 | ABHD12 (i) | ABHD12 | 7.68e-11 | ++ |
| 14:24871926 | rs11621792 | C | T | 0.55 | 0.044 | 1.17E-58 | 0.95 | 0.006 | 5.29E-01 | NYNRIN (i) | NYNRIN | 2.36e-07 | ++ |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4:69326683 | rs4694077 | C | T | 0.68 | 0.042 | 1.26E-47 | 0.91 | 0.011 | 1.98E-01 | TMPRSS11E (i) | TMPRSS11E | 5.27e-05 | ++ |
| 12:53727545 | rs930900 | C | T | 0.69 | 0.037 | 2.56E-37 | 0.99 | 0.006 | 8.10E-01 | SP7 (i) | SP7 | 1.71e-05 | ++ |
| 12:46061688 | rs2970818 | T | A | 0.90 | 0.050 | 3.06E-29 | 1.00 | -0.011 | 8.02E-01 | C12orf4 (i) | C12orf4 | 3.15e-05 | +- |
| 6:116418112 | rs4946137 | A | G | 0.40 | 0.026 | 1.45E-20 | 0.69 | -0.003 | 4.67E-01 | FRK, NT5DC1 (inter) | FRK, NT5DC1 | 1.06e-04 | +- |

CHR:POS, chromosome:position. EA, effect allele. OA, other allele. EAF, effect allele frequency. P_het, P value for heterogeneity between UK BioBank and BioBank Japan. Gene tags: (e) exonic, (i) intronic, (u) upstream, (d) downstream, (inter) intergenic, (UTR) untranslated region. Direction: + indicates that the variant increases the liver enzyme while - indicates that the variant decreases the liver enzyme. Direction of effect in UK BioBank is shown first, followed by effect in BioBank Japan.

**Supplementary Table 6: Alanine aminotransferase-altering alleles: BioBank Japan only**

| CHR:POS | Variant | EA | OA | BioBank Japan | | | UK BioBank | | | Gene annotation | Nearest coding genes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | EAF | Beta | P | EAF | Beta | P | | |
| 12:113548243 | rs1902955 | T | C | 0.81 | 0.029 | 1.90e-09 | 0.61 | 0.0024 | 3.31e-01 | RASAL1 (i) | RASAL1 |
| 6:33860843 | rs185355701 | T | G | 0.055 | 0.047 | 3.43e-08 | 0.057 | 0.0031 | 5.48e-01 | LINC01016 (i) | MLN, GRM4 |

CHR:POS, chromosome:position. EA, effect allele. OA, other allele. EAF, effect allele frequency. Gene tags: (e) exonic, (i) intronic, (u) upstream, (d) downstream, (inter) intergenic, (UTR) untranslated region.

**Supplementary Table 7: Aspartate aminotransferase-altering alleles: BioBank Japan only**

| CHR:POS | Variant | EA | OA | BioBank Japan | | | UK BioBank | | | Gene annotation | Nearest coding genes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | EAF | Beta | P | EAF | Beta | P | | |
| 19:41333284 | rs11878604 | T | C | 0.61 | 0.03 | 2.14e-14 | 0.93 | 0.0074 | 1.29e-01 | CYP2T1P, CYP2A6 (inter) | EGLN2, CYP2A6 |
| 7:80174361 | rs139761834 | T | C | 0.95 | 0.08 | 3.45e-14 | | | | GNAT3, CD36 (inter) | GNAT3, CD36 |
| 4:79619199 | rs75759936 | C | A | 0.82 | 0.032 | 1.58e-08 | | | | LINC01094, BMP2K (inter) | ANXA3, BMP2K |
| 7:50258479 | rs4598207 | A | T | 0.57 | 0.022 | 2.82e-08 | 0.69 | -0.0035 | 1.93e-01 | C7orf72, IKZF1 (inter) | ZPBP, IKZF1 |
| 12:110069190 | rs11067592 | G | T | 0.92 | 0.04 | 3.49e-08 | | | | MVK, FAM222A (inter) | MVK, FAM222A |

CHR:POS, chromosome:position. EA, effect allele. OA, other allele. EAF, effect allele frequency. Gene tags: (e) exonic, (i) intronic, (u) upstream, (d) downstream, (inter) intergenic, (UTR) untranslated region.

**Supplementary Table 8: Alanine aminotransferase-altering alleles with heterogeneity between men and women in UK BioBank**

| CHR:POS | Variant | EA | OA | Male | | | Female | | | Gene annotation | Nearest coding genes | P_het | Direction |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | EAF | Beta | P | EAF | Beta | P | | | | |
| 9:117146043 | rs7041363 | C | G | 0.51 | 0.07 | 8.19E-88 | 0.51 | 0.049 | 3.17E-51 | AKNA (i) | AKNA | 1.09E-04 | ++ |
| 8:126482077 | rs2954021 | A | G | 0.49 | 0.064 | 1.45E-74 | 0.49 | 0.035 | 5.05E-27 | TRIB1, LINC00861 (inter) | TRIB1, FAM84B | 5.45E-08 | ++ |
| 4:146821410 | rs4835265 | A | C | 0.16 | 0.045 | 5.41E-21 | 0.16 | 0.075 | 1.68E-64 | ZNF827 (i) | ZNF827 | 3.59E-05 | ++ |
| 1:155106697 | rs12904 | G | A | 0.59 | 0.019 | 1.89E-07 | 0.59 | 0.046 | 5.12E-44 | EFNA1 (UTR) | EFNA1 | 4.89E-07 | ++ |
| 10:70985267 | rs2394529 | C | G | 0.70 | 0.012 | 1.37E-03 | 0.70 | 0.055 | 6.44E-54 | LOC101928994 (i) | HKDC1 | 3.19E-13 | ++ |
| 16:80497341 | rs28650012 | G | C | 0.27 | 0.017 | 1.25E-05 | 0.27 | 0.041 | 7.13E-29 | LOC102724084 (i) | MAF, DYNLRB2 | 9.35E-05 | ++ |
| 16:83980529 | rs4782568 | C | G | 0.55 | 0.035 | 2.01E-23 | 0.55 | 0.015 | 2.60E-06 | MLYCD, OSGIN1 (inter) | MLYCD, OSGIN1 | 2.35E-04 | ++ |

CHR:POS, chromosome:position. EA, effect allele. OA, other allele. EAF, effect allele frequency. P_het, P value for heterogeneity between men and women. Gene tags: (e) exonic, (i) intronic, (u) upstream, (d) downstream, (inter) intergenic, (UTR) untranslated region. Direction: + indicates that the variant increases the liver enzyme while - indicates that the variant decreases the liver enzyme. Direction of effect in UK BioBank male is shown as effect in men followed by effect in women.

**Supplementary Table 9: Aspartate aminotransferase-altering alleles with heterogeneity between men and women in UK BioBank**

| | | | | Male | | | Female | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CHR:POS | Variant | EA | OA | EAF | Beta | P | EAF | Beta | P | Gene annotation | Nearest coding genes | P_het | Direction |
| 1:155106697 | rs12904 | G | A | 0.59 | 0.014 | 8.98E-05 | 0.59 | 0.040 | 8.16E-34 | EFNA1 (UTR) | EFNA1 | 3.07E-06 | ++ |
| 11:116648917 | rs964184 | G | C | 0.13 | 0.063 | 5.74E-33 | 0.13 | 0.022 | 2.69E-06 | ZPR1 (UTR) | ZPR1 | 3.47E-07 | ++ |
| 10:70985267 | rs2394529 | C | G | 0.70 | 0.0071 | 6.93E-02 | 0.70 | 0.044 | 2.69E-35 | LOC101928994 (i) | HKDC1 | 5.12E-10 | ++ |
| 4:77416627 | rs12500824 | A | G | 0.35 | 0.029 | 9.59E-15 | 0.35 | 0.0056 | 9.53E-02 | SHROOM3 (i) | SHROOM3 | 4.00E-05 | ++ |
| 19:55824332 | rs7246479 | G | T | 0.51 | 0.002 | 5.82E-01 | 0.51 | 0.024 | 3.02E-13 | TMEM150B (e) | TMEM150B | 6.53E-05 | ++ |

CHR:POS, chromosome:position. EA, effect allele. OA, other allele. EAF, effect allele frequency. P_het, P value for heterogeneity between men and women. Gene tags: (e) exonic, (i) intronic, (u) upstream, (d) downstream, (inter) intergenic, (UTR) untranslated region. Direction: + indicates that the variant increases the liver enzyme while - indicates that the variant decreases the liver enzyme. Direction of effect in UK BioBank male is shown as effect in men followed by effect in women.

**Supplementary Table 10: Alkaline phosphatase-altering alleles with heterogeneity between men and women in UK BioBank**

| CHR:POS | Variant | EA | OA | Male | | | Female | | | Gene annotation | Nearest coding genes | P_het | Direction |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | EAF | Beta | P | EAF | Beta | P | | | | |
| 19:19379549 | rs58542926 | C | T | 0.92 | 0.15 | 3.35E-96 | 0.92 | 0.084 | 3.27E-42 | TM6SF2 (e) | TM6SF2 | 1.52E-08 | ++ |
| 9:136140462 | rs1633513 | C | T | 0.26 | 0.13 | 9.70E-205 | 0.27 | 0.10 | 1.00E-162 | ABO (i) | ABO | 1.75E-05 | ++ |
| 19:49164952 | rs281392 | A | G | 0.33 | 0.11 | 2.40E-164 | 0.33 | 0.081 | 3.00E-117 | NTN5 (e) | NTN5 | 6.07E-06 | ++ |
| 8:126500031 | rs28601761 | C | G | 0.58 | 0.12 | 1.80E-204 | 0.58 | 0.067 | 4.23E-88 | TRIB1, LINC00861 (inter) | TRIB1, FAM84B | 7.47E-17 | ++ |
| 20:25296970 | rs6083799 | T | G | 0.56 | 0.076 | 2.35E-90 | 0.56 | 0.046 | 3.68E-45 | ABHD12 (i) | ABHD12 | 6.77E-07 | ++ |
| 4:69326683 | rs4694077 | C | T | 0.68 | 0.053 | 2.09E-38 | 0.68 | 0.023 | 6.23E-11 | TMPRSS11E (i) | TMPRSS11E | 4.13E-06 | ++ |
| 6:25783315 | rs3923 | T | C | 0.42 | 0.039 | 7.19E-25 | 0.42 | 0.015 | 3.72E-06 | SLC17A1 (UTR) | SLC17A1 | 7.14E-05 | ++ |
| 5:88364958 | rs6886306 | T | C | 0.47 | 0.036 | 6.88E-22 | 0.47 | 0.014 | 3.14E-05 | MEF2C-AS1 (i) | MEF2C, CETN3 | 1.48E-04 | ++ |

CHR:POS, chromosome:position. EA, effect allele. OA, other allele. EAF, effect allele frequency. P_het, P value for heterogeneity between men and women. Gene tags: (e) exonic, (i) intronic, (u) upstream, (d) downstream, (inter) intergenic, (UTR) untranslated region. Direction: + indicates that the variant increases the liver enzyme while - indicates that the variant decreases the liver enzyme. Direction of effect in UK BioBank male is shown as effect in men followed by effect in women.

**Supplementary Table 11: Phenome-wide association studies of alanine aminotransferase-increasing alleles**

| Variant | Trait | EA | OA | EAF | Beta | P | Gene annotation |
|---|---|---|---|---|---|---|---|
| rs1277930 | E78 Disorders of lipoprotein metabolism and other lipidaemias | A | G | 0.81 | 0.01 | 1.22e-55 | PSRC1 (d) |
| rs1002436 | I10 Essential (primary) hypertension | G | A | 0.56 | -0.0041 | 3.44e-08 | PKN2-AS1 (i) |
| rs1277930 | I20 Angina pectoris | A | G | 0.81 | 0.0042 | 2.46e-17 | PSRC1 (d) |
| rs1277930 | I21 Acute myocardial infarction | A | G | 0.81 | 0.002 | 2.06e-09 | PSRC1 (d) |
| rs1277930 | I25 Chronic ischaemic heart disease | A | G | 0.81 | 0.0059 | 4.30e-25 | PSRC1 (d) |
| rs1538742 | K42 Umbilical hernia | A | C | 0.54 | -0.0015 | 2.04e-13 | LOC102723886 (i) |
| rs6712203 | E11 Non-insulin-dependent diabetes mellitus | C | T | 0.7 | 0.0031 | 1.51e-13 | COBLL1 (i) |
| rs2943654 | E11 Non-insulin-dependent diabetes mellitus | T | C | 0.71 | 0.0037 | 4.25e-18 | LOC646736, MIR5702 (inter) |
| rs11887534 | E78 Disorders of lipoprotein metabolism and other lipidaemias | C | G | 0.051 | -0.0083 | 2.03e-13 | ABCG8 (e) |
| rs11887534 | K80 Cholelithiasis | C | G | 0.051 | 0.026 | 7.59e-257 | ABCG8 (e) |
| rs11887534 | K81 Cholecystitis | C | G | 0.051 | 0.0041 | 5.93e-34 | ABCG8 (e) |
| rs11887534 | K82 Other diseases of gallbladder | C | G | 0.051 | 0.0034 | 1.92e-35 | ABCG8 (e) |
| rs11887534 | K83 Other diseases of biliary tract | C | G | 0.051 | 0.0022 | 4.36e-14 | ABCG8 (e) |
| rs645040 | I10 Essential (primary) hypertension | T | G | 0.79 | 0.005 | 1.02e-08 | MSL2, PCCB (inter) |
| rs645040 | I21 Acute myocardial infarction | T | G | 0.79 | 0.0019 | 2.87e-08 | MSL2, PCCB (inter) |
| rs78900599 | K80 Cholelithiasis | A | G | 0.92 | 0.0048 | 3.51e-11 | TM4SF1-AS1, TM4SF4 (inter) |
| rs40270 | E11 Non-insulin-dependent diabetes mellitus | C | A | 0.61 | 0.0028 | 1.07e-08 | LINC01948, C5orf67 (inter) |
| rs1468615 | K80 Cholelithiasis | T | C | 0.8 | 0.0036 | 2.60e-13 | ABCB4 (i) |
| rs2954021 | E78 Disorders of lipoprotein metabolism and other lipidaemias | A | G | 0.48 | 0.0068 | 8.90e-35 | TRIB1, LINC00861 (inter) |
| rs4484649 | I10 Essential (primary) hypertension | C | A | 0.47 | 0.0055 | 2.98e-13 | C8orf74, SOX7 (inter) |
| rs2954021 | I25 Chronic ischaemic heart disease | A | G | 0.48 | 0.0028 | 3.74e-09 | TRIB1, LINC00861 (inter) |
| rs687621 | E78 Disorders of lipoprotein metabolism and other lipidaemias | G | A | 0.36 | 0.0034 | 2.00e-08 | ABO (i) |
| rs687621 | I26 Pulmonary embolism | G | A | 0.36 | 0.0028 | 3.71e-42 | ABO (i) |
| rs687621 | I80 Phlebitis and thrombophlebitis | G | A | 0.36 | 0.0036 | 4.15e-62 | ABO (i) |
| rs687621 | I84 Haemorrhoids | G | A | 0.36 | -0.0041 | 1.63e-15 | ABO (i) |
| rs687621 | K57 Diverticular disease of intestine | G | A | 0.36 | -0.0039 | 2.73e-13 | ABO (i) |
| rs687621 | M79 Other soft tissue disorders, not elsewhere classified | G | A | 0.36 | 0.0024 | 4.19e-10 | ABO (i) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| rs1051713 | K80 Cholelithiasis | C | T | 0.86 | -0.0038 | 1.23e-14 | ALOX5 (i) |
| rs4766462 | E03 Other hypothyroidism | A | T | 0.64 | 0.0029 | 1.35e-10 | SH2B3 (i) |
| rs4766462 | I10 Essential (primary) hypertension | A | T | 0.64 | 0.0058 | 1.07e-10 | SH2B3 (i) |
| rs864899 | I83 Varicose veins of lower extremities | G | A | 0.52 | -0.002 | 2.38e-09 | ATF1, TMPRSS12 (inter) |
| rs11061602 | M16 Coxarthrosis [arthrosis of hip] | T | G | 0.51 | -0.0019 | 1.80e-08 | MLXIP (i) |
| rs56094641 | E11 Non-insulin-dependent diabetes mellitus | G | A | 0.35 | 0.0044 | 6.85e-26 | FTO (i) |
| rs56094641 | E66 Obesity | G | A | 0.35 | 0.004 | 3.00e-33 | FTO (i) |
| rs56094641 | I10 Essential (primary) hypertension | G | A | 0.35 | 0.0048 | 9.48e-11 | FTO (i) |
| rs17138478 | K80 Cholelithiasis | C | A | 0.85 | -0.0031 | 4.72e-08 | HNF1B (i) |
| rs429358 | G30-G32 Other degenerative diseases of the nervous system | T | C | 0.86 | -0.0022 | 4.15e-54 | APOE (e) |
| rs58542926 | E78 Disorders of lipoprotein metabolism and other lipidaemias | T | C | 0.076 | -0.0088 | 9.56e-17 | TM6SF2 (e) |
| rs429358 | E78 Disorders of lipoprotein metabolism and other lipidaemias | T | C | 0.86 | -0.014 | 1.81e-74 | APOE (e) |
| rs429358 | F05 Delirium, not induced by alcohol and other psychoactive substances | T | C | 0.86 | -0.00076 | 1.86e-12 | APOE (e) |
| rs429358 | I20 Angina pectoris | T | C | 0.86 | -0.0046 | 1.12e-15 | APOE (e) |
| rs429358 | I21 Acute myocardial infarction | T | C | 0.86 | -0.0024 | 7.00e-10 | APOE (e) |
| rs429358 | I25 Chronic ischaemic heart disease | T | C | 0.86 | -0.0059 | 2.49e-19 | APOE (e) |
| rs58542926 | K76 Other diseases of liver | T | C | 0.076 | 0.0021 | 8.23e-09 | TM6SF2 (e) |
| rs7599 | K80 Cholelithiasis | A | G | 0.33 | 0.0022 | 6.85e-09 | TMEM147 (UTR) |
| rs738409 | I85 Oesophageal varices | G | C | 0.28 | 0.00068 | 2.97e-14 | PNPLA3 (e) |
| rs738409 | K70 Alcoholic liver disease | G | C | 0.28 | 0.00088 | 1.98e-14 | PNPLA3 (e) |
| rs738409 | K74 Fibrosis and cirrhosis of liver | G | C | 0.28 | 0.00076 | 2.25e-11 | PNPLA3 (e) |
| rs738409 | K76 Other diseases of liver | G | C | 0.28 | 0.0022 | 4.77e-22 | PNPLA3 (e) |

CHR:POS, chromosome:position. EA, effect allele. OA, other allele. EAF, effect allele frequency. Traits are represented as International Classification of Diseases code followed by disease name. Gene tags: (e) exonic, (i) intronic, (u) upstream, (d) downstream, (inter) intergenic, (UTR) untranslated region.

**Supplementary Table 12: Phenome-wide association studies of aspartate aminotransferase-increasing alleles**

| Variant | Trait | EA | OA | EAF | Beta | P | Gene annotation |
|---|---|---|---|---|---|---|---|
| rs1002436 | I10 Essential (primary) hypertension | G | A | 0.56 | -0.0041 | 3.44e-08 | PKN2-AS1 (i) |
| rs6547692 | E11 Non-insulin-dependent diabetes mellitus | G | A | 0.47 | -0.0022 | 4.53e-08 | GCKR (i) |
| rs2943654 | E11 Non-insulin-dependent diabetes mellitus | T | C | 0.71 | 0.0037 | 4.25e-18 | LOC646736, MIR5702 (inter) |
| rs6547692 | E78 Disorders of lipoprotein metabolism and other lipidaemias | G | A | 0.47 | 0.0041 | 2.46e-13 | GCKR (i) |
| rs6547692 | K80 Cholelithiasis | G | A | 0.47 | -0.0024 | 4.74e-10 | GCKR (i) |
| rs6547692 | M10 Gout | G | A | 0.47 | 0.0012 | 6.31e-11 | GCKR (i) |
| rs2594973 | I10 Essential (primary) hypertension | C | G | 0.37 | -0.005 | 6.75e-11 | ATG7 (i) |
| rs6894249 | J45 Asthma | A | G | 0.55 | -0.0032 | 1.66e-10 | C5orf56 (i) |
| rs13212562 | E03 Other hypothyroidism | A | G | 0.89 | -0.0034 | 8.80e-10 | VN1R10P, ZNF204P (inter) |
| rs13212562 | E05 Thyrotoxicosis [hyperthyroidism] | A | G | 0.89 | -0.0013 | 5.10e-10 | VN1R10P, ZNF204P (inter) |
| rs13212562 | E10 Insulin-dependent diabetes mellitus | A | G | 0.89 | -0.0015 | 4.41e-09 | VN1R10P, ZNF204P (inter) |
| rs6916318 | I83 Varicose veins of lower extremities | T | A | 0.52 | -0.0018 | 3.86e-08 | MIR588, RSPO3 (inter) |
| rs13212562 | K40 Inguinal hernia | A | G | 0.89 | 0.0035 | 1.65e-09 | VN1R10P, ZNF204P (inter) |
| rs9372475 | K40 Inguinal hernia | T | C | 0.35 | 0.0023 | 1.36e-08 | RFX6, VGLL2 (inter) |
| rs13212562 | K90 Intestinal malabsorption | A | G | 0.89 | -0.0059 | 6.94e-152 | VN1R10P, ZNF204P (inter) |
| rs13212562 | N40 Hyperplasia of prostate | A | G | 0.89 | 0.0077 | 5.15e-13 | VN1R10P, ZNF204P (inter) |
| rs2954027 | E78 Disorders of lipoprotein metabolism and other lipidaemias | T | A | 0.52 | 0.0068 | 6.26e-34 | TRIB1, LINC00861 (inter) |
| rs12544992 | I10 Essential (primary) hypertension | G | C | 0.53 | 0.0047 | 2.16e-10 | MFHAS1 (i) |
| rs4841436 | I10 Essential (primary) hypertension | C | A | 0.48 | 0.0061 | 3.73e-16 | LOC102723313 (i) |
| rs2954027 | I25 Chronic ischaemic heart disease | T | A | 0.52 | 0.0028 | 2.28e-09 | TRIB1, LINC00861 (inter) |
| rs113895159 | K80 Cholelithiasis | T | C | 0.59 | -0.0025 | 5.94e-10 | SDCBP (i) |
| rs1800978 | E78 Disorders of lipoprotein metabolism and other lipidaemias | C | G | 0.85 | 0.0052 | 1.08e-09 | ABCA1 (UTR) |
| rs2519093 | E78 Disorders of lipoprotein metabolism and other lipidaemias | C | T | 0.79 | -0.0057 | 2.63e-15 | ABO (i) |
| rs2519093 | I26 Pulmonary embolism | C | T | 0.79 | -0.0037 | 2.29e-49 | ABO (i) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| rs2519093 | I80 Phlebitis and thrombophlebitis | C | T | 0.79 | -0.0041 | 3.52e-57 | ABO (i) |
| rs2519093 | I84 Haemorrhoids | C | T | 0.79 | 0.0036 | 6.03e-09 | ABO (i) |
| rs2519093 | K57 Diverticular disease of intestine | C | T | 0.79 | 0.0036 | 2.51e-08 | ABO (i) |
| rs2519093 | M79 Other soft tissue disorders, not elsewhere classified | C | T | 0.79 | -0.0028 | 7.57e-10 | ABO (i) |
| rs964184 | E78 Disorders of lipoprotein metabolism and other lipidaemias | G | C | 0.17 | 0.0096 | 1.00e-31 | ZPR1 (UTR) |
| rs705699 | E03 Other hypothyroidism | G | A | 0.63 | -0.0022 | 1.57e-09 | RAB5B (i) |
| rs705699 | J33 Nasal polyp | G | A | 0.63 | -0.001 | 4.13e-08 | RAB5B (i) |
| rs705699 | J45 Asthma | G | A | 0.63 | -0.0031 | 5.48e-10 | RAB5B (i) |
| rs217184 | E78 Disorders of lipoprotein metabolism and other lipidaemias | T | C | 0.8 | 0.0039 | 3.83e-08 | HPR (i) |
| rs17138478 | K80 Cholelithiasis | C | A | 0.85 | -0.0031 | 4.72e-08 | HNF1B (i) |
| rs58542926 | E78 Disorders of lipoprotein metabolism and other lipidaemias | T | C | 0.076 | -0.0088 | 9.56e-17 | TM6SF2 (e) |
| rs439401 | E78 Disorders of lipoprotein metabolism and other lipidaemias | C | T | 0.58 | 0.0046 | 3.36e-15 | APOE, APOC1 (inter) |
| rs11882796 | E78 Disorders of lipoprotein metabolism and other lipidaemias | T | A | 0.42 | 0.0038 | 7.62e-12 | RASIP1 (i) |
| rs11882796 | I10 Essential (primary) hypertension | T | A | 0.42 | 0.0045 | 5.56e-10 | RASIP1 (i) |
| rs58542926 | K76 Other diseases of liver | T | C | 0.076 | 0.0021 | 8.23e-09 | TM6SF2 (e) |
| rs11882796 | K80 Cholelithiasis | T | A | 0.42 | 0.0029 | 3.12e-14 | RASIP1 (i) |
| rs738409 | I85 Oesophageal varices | G | C | 0.28 | 0.00068 | 2.97e-14 | PNPLA3 (e) |
| rs738409 | K70 Alcoholic liver disease | G | C | 0.28 | 0.00088 | 1.98e-14 | PNPLA3 (e) |
| rs738409 | K74 Fibrosis and cirrhosis of liver | G | C | 0.28 | 0.00076 | 2.25e-11 | PNPLA3 (e) |
| rs738409 | K76 Other diseases of liver | G | C | 0.28 | 0.0022 | 4.77e-22 | PNPLA3 (e) |

CHR:POS, chromosome:position. EA, effect allele. OA, other allele. EAF, effect allele frequency. Traits are represented as International Classification of Diseases code followed by disease name. Gene tags: (e) exonic, (i) intronic, (u) upstream, (d) downstream, (inter) intergenic, (UTR) untranslated region.

**Supplementary Table 13: Phenome-wide association studies of alkaline phosphatase-increasing alleles**

| Variant | Trait | EA | OA | EAF | Beta | P | Gene annotation |
|---|---|---|---|---|---|---|---|
| rs1260326 | E11 Non-insulin-dependent diabetes mellitus | T | C | 0.43 | -0.0027 | 1.88e-10 | GCKR (e) |
| rs1260326 | E78 Disorders of lipoprotein metabolism and other lipidaemias | T | C | 0.43 | 0.0048 | 3.09e-17 | GCKR (e) |
| rs1260326 | K80 Cholelithiasis | T | C | 0.43 | -0.0026 | 9.37e-12 | GCKR (e) |
| rs1260326 | M10 Gout | T | C | 0.43 | 0.0014 | 2.81e-14 | GCKR (e) |
| rs687339 | I10 Essential (primary) hypertension | T | C | 0.78 | 0.0049 | 2.38e-08 | MSL2, PCCB (inter) |
| rs687339 | I21 Acute myocardial infarction | T | C | 0.78 | 0.0019 | 2.56e-08 | MSL2, PCCB (inter) |
| rs12633863 | K80 Cholelithiasis | A | G | 0.54 | -0.0033 | 2.82e-18 | TM4SF4 (i) |
| rs2290846 | K80 Cholelithiasis | G | A | 0.71 | -0.004 | 1.16e-21 | LRBA (e) |
| rs2728102 | M10 Gout | T | C | 0.79 | -0.0027 | 9.96e-24 | PKD2 (i) |
| rs3923 | E83 Disorders of mineral metabolism | T | C | 0.47 | 0.0023 | 4.41e-52 | SLC17A1 (UTR) |
| rs764284 | E83 Disorders of mineral metabolism | G | A | 0.56 | 0.001 | 8.38e-12 | VN1R10P, ZNF204P (inter) |
| rs6912283 | I10 Essential (primary) hypertension | A | G | 0.58 | -0.0045 | 8.04e-10 | ZNF318, ABCC10 (inter) |
| rs3923 | K90 Intestinal malabsorption | T | C | 0.47 | 0.0015 | 6.60e-23 | SLC17A1 (UTR) |
| rs764284 | K90 Intestinal malabsorption | G | A | 0.56 | 0.0016 | 2.96e-25 | VN1R10P, ZNF204P (inter) |
| rs28601761 | E78 Disorders of lipoprotein metabolism and other lipidaemias | C | G | 0.63 | 0.0076 | 4.43e-40 | TRIB1, LINC00861 (inter) |
| rs6601527 | I10 Essential (primary) hypertension | C | A | 0.46 | 0.0058 | 4.15e-15 | PINX1 (i) |
| rs28601761 | I25 Chronic ischaemic heart disease | C | G | 0.63 | 0.0033 | 1.03e-11 | TRIB1, LINC00861 (inter) |
| rs1633513 | I80 Phlebitis and thrombophlebitis | C | T | 0.27 | -0.0018 | 1.38e-15 | ABO (i) |
| rs10900229 | K80 Cholelithiasis | C | T | 0.78 | -0.0036 | 2.13e-17 | ZFAND4 (i) |
| rs10822186 | K80 Cholelithiasis | G | A | 0.49 | 0.0022 | 9.47e-09 | REEP3 (i) |
| rs174566 | J45 Asthma | G | A | 0.36 | -0.003 | 9.23e-09 | FADS2 (i) |
| rs174566 | K80 Cholelithiasis | G | A | 0.36 | 0.0023 | 7.15e-09 | FADS2 (i) |
| rs2073950 | E03 Other hypothyroidism | C | T | 0.79 | 0.0029 | 6.98e-11 | ATXN2 (i) |
| rs2073950 | I10 Essential (primary) hypertension | C | T | 0.79 | 0.006 | 3.28e-11 | ATXN2 (i) |
| rs9738226 | I25 Chronic ischaemic heart disease | A | G | 0.4 | 0.003 | 8.11e-10 | HNF1A (i) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| rs9738226 | K80 Cholelithiasis | A | G | 0.4 | -0.0027 | 1.26e-12 | HNF1A (i) |
| rs2941505 | J45 Asthma | A | G | 0.35 | 0.0032 | 2.39e-09 | PGAP3 (i) |
| rs58542926 | E78 Disorders of lipoprotein metabolism and other lipidaemias | C | T | 0.92 | 0.0088 | 9.56e-17 | TM6SF2 (e) |
| rs58542926 | K76 Other diseases of liver | C | T | 0.92 | -0.0021 | 8.23e-09 | TM6SF2 (e) |
| rs6088730 | C44 Other malignant neoplasms of skin | C | G | 0.57 | -0.002 | 3.50e-08 | EDEM2 (i) |
| rs17216707 | N20 Calculus of kidney and ureter | C | T | 0.17 | -0.0018 | 9.04e-10 | BCAS1, CYP24A1 (inter) |
| rs2836882 | K51 Ulcerative colitis | G | A | 0.75 | 0.0017 | 7.06e-16 | LINC01700, PSMG1 (inter) |

CHR:POS, chromosome:position. EA, effect allele. OA, other allele. EAF, effect allele frequency. Traits are represented as International Classification of Diseases code followed by disease name. Gene tags: (e) exonic, (i) intronic, (u) upstream, (d) downstream, (inter) intergenic, (UTR) untranslated region.

**Supplementary Table 14: Latent causal variable analysis of alanine aminotransferase and metabolic traits**

| Trait | GCP | GCP Z score | Rho | Rho Z score | Heritability of metabolic trait (Z score) | Heritability of liver enzyme (Z score) |
|---|---|---|---|---|---|---|
| Triglycerides | 0.65 | 2.86 | 0.18 | 1.04 | 10.08 | 12.71 |
| High-density lipoprotein | 0.53 | 2.25 | -0.31 | -5.61 | 9.26 | 12.72 |
| Body mass index | 0.65 | 2.48 | 0.40 | 6.05 | 26.27 | 12.71 |
| Waist-hip-ratio | 0.09 | 0.72 | 0.13 | 0.94 | 19.63 | 12.71 |
| Fasting glucose | -0.26 | -1.51 | 0.19 | 3.22 | 8.10 | 12.71 |
| Systolic blood pressure | -0.20 | -0.93 | 0.32 | 4.16 | 23.09 | 12.71 |
| Diastolic blood pressure | -0.19 | -0.90 | 0.29 | 3.57 | 22.83 | 12.71 |

GCP, genetic causality proportion. Significantly positive GCP implies that the metabolic trait is causal for the liver enzyme, and negative GCP implies that the liver enzyme is causal for the metabolic trait. Rho represents the estimated genetic correlation between the liver enzyme and the metabolic trait. SE, standard error.

**Supplementary Table 15: Latent causal variable analysis of aspartate aminotransferase and metabolic traits**

| Trait | GCP | GCP Z score | Rho | Rho Z score | Heritability of metabolic trait (Z score) | Heritability of liver enzyme (Z score) |
|---|---|---|---|---|---|---|
| Triglycerides | 0.24 | 0.76 | 0.02 | 0.10 | 10.08 | 11.69 |
| High-density lipoprotein | 0.34 | 1.78 | -0.02 | -0.34 | 9.26 | 11.69 |
| Body mass index | 0.37 | 0.97 | 0.17 | 1.87 | 26.27 | 11.69 |
| Waist-hip-ratio | 0.22 | 0.50 | 0.01 | 0.10 | 19.65 | 11.70 |
| Fasting glucose | 0.24 | 0.71 | -0.01 | -0.10 | 8.10 | 11.69 |
| Systolic blood pressure | -0.46 | -2.07 | 0.24 | 2.65 | 23.09 | 11.69 |
| Diastolic blood pressure | -0.41 | -1.87 | 0.19 | 1.98 | 22.83 | 11.69 |

GCP, genetic causality proportion. Significantly positive GCP implies that the metabolic trait is causal for the liver enzyme, and negative GCP implies that the liver enzyme is causal for the metabolic trait. Rho represents the estimated genetic correlation between the liver enzyme and the metabolic trait. SE, standard error.

**Supplementary Table 16: Latent causal variable analysis of alkaline phosphatase and metabolic traits**

| Trait | GCP | GCP Z score | Rho | Rho Z score | Heritability of metabolic trait (Z score) | Heritability of liver enzyme (Z score) |
|---|---|---|---|---|---|---|
| Triglycerides | 0.38 | 1.08 | -0.04 | -0.20 | 10.08 | 6.53 |
| High-density lipoprotein | 0.20 | 1.06 | -0.08 | -1.44 | 9.26 | 6.53 |
| Body mass index | 0.29 | 0.64 | 0.21 | 1.83 | 26.27 | 6.53 |
| Waist-hip-ratio | -0.57 | -2.15 | -0.09 | -0.55 | 19.63 | 6.53 |
| Fasting glucose | -0.07 | -0.09 | 0.07 | 1.07 | 8.10 | 6.53 |
| Systolic blood pressure | -0.01 | -0.02 | 0.24 | 2.19 | 23.09 | 6.55 |
| Diastolic blood pressure | -0.01 | -0.02 | 0.25 | 2.20 | 22.83 | 6.55 |

GCP, genetic causality proportion. Significantly positive GCP implies that the metabolic trait is causal for the liver enzyme, and negative GCP implies that the liver enzyme is causal for the metabolic trait. Rho represents the estimated genetic correlation between the liver enzyme and the metabolic trait. SE, standard error.

**Supplementary Table 17: Effect of all liver enzyme-increasing alleles on primary biliary cholangitis**

| CHR:POS | Variant | EA | OA | EAF | Beta | P | Proxy | R2 | Gene annotation |
|---|---|---|---|---|---|---|---|---|---|
| 3:161823590 | rs17236494 | C (T) | A (C) | 0.21 | -0.26 | 5.31E-05 | rs4679904 | 0.85 | *ARF7* |
| 4:103947120 | rs223454 | A (A) | G (C) | 0.51 | -0.21 | 7.66E-05 | rs223420 | 0.98 | *UBE2D3P* |
| 4:103797685 | rs179195 | T (A) | C (G) | 0.47 | -0.22 | 2.19E-05 | rs228614 | 0.85 | *MANBA* |

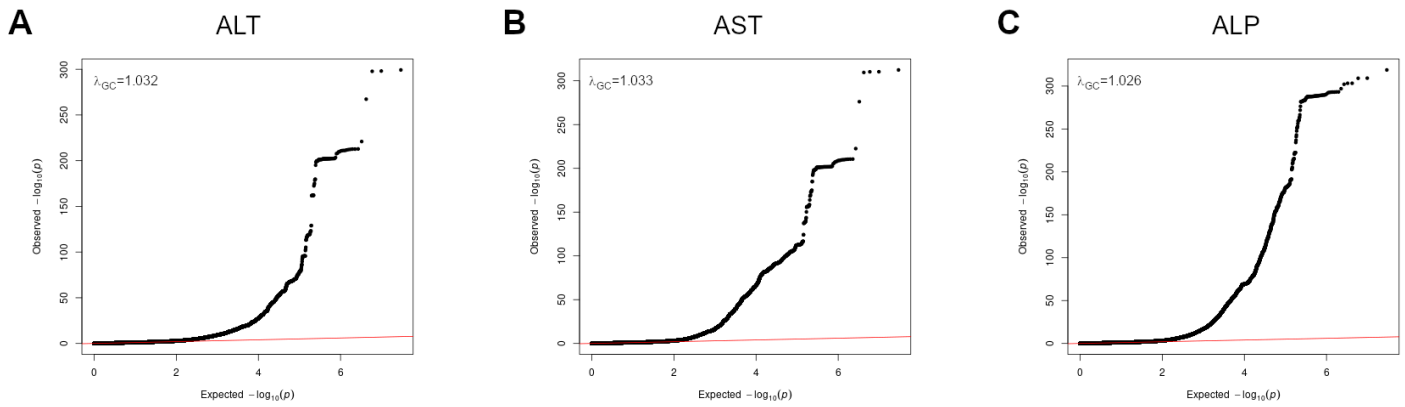
CHR:POS, chromosome:position. EA, effect allele. OA, other allele. EAF, effect allele frequency. When liver enzyme-increasing variants were not themselves available, proxy variants were used. EA and OA of proxy variants are shown in parentheses. Gene tags: (e) exonic, (i) intronic, (u) upstream, (d) downstream, (inter) intergenic, (UTR) untranslated region.

**Supplementary Table 18: Effects of polygenic risk scores on cirrhosis and hepatic steatosis in Michigan Genomics Initiative**

| | Cirrhosis | | Hepatic steatosis | |
|---|---|---|---|---|
| **Liver enzyme** | **Odds ratio** | **P value** | **Odds ratio** | **P value** |
| Alanine aminotransferase | 1.23 (1.17-1.30) | 5.10E-15 | 1.17 (1.14-1.21) | 9.60E-28 |
| Asparate aminotransferase | 1.10 (1.04-1.16) | 5.10E-04 | 1.08 (1.05-1.11) | 3.80E-08 |
| Alkaline phosphatase | 1.05 (0.99-1.10) | 8.60E-02 | 1.02 (0.99-1.05) | 1.20E-01 |

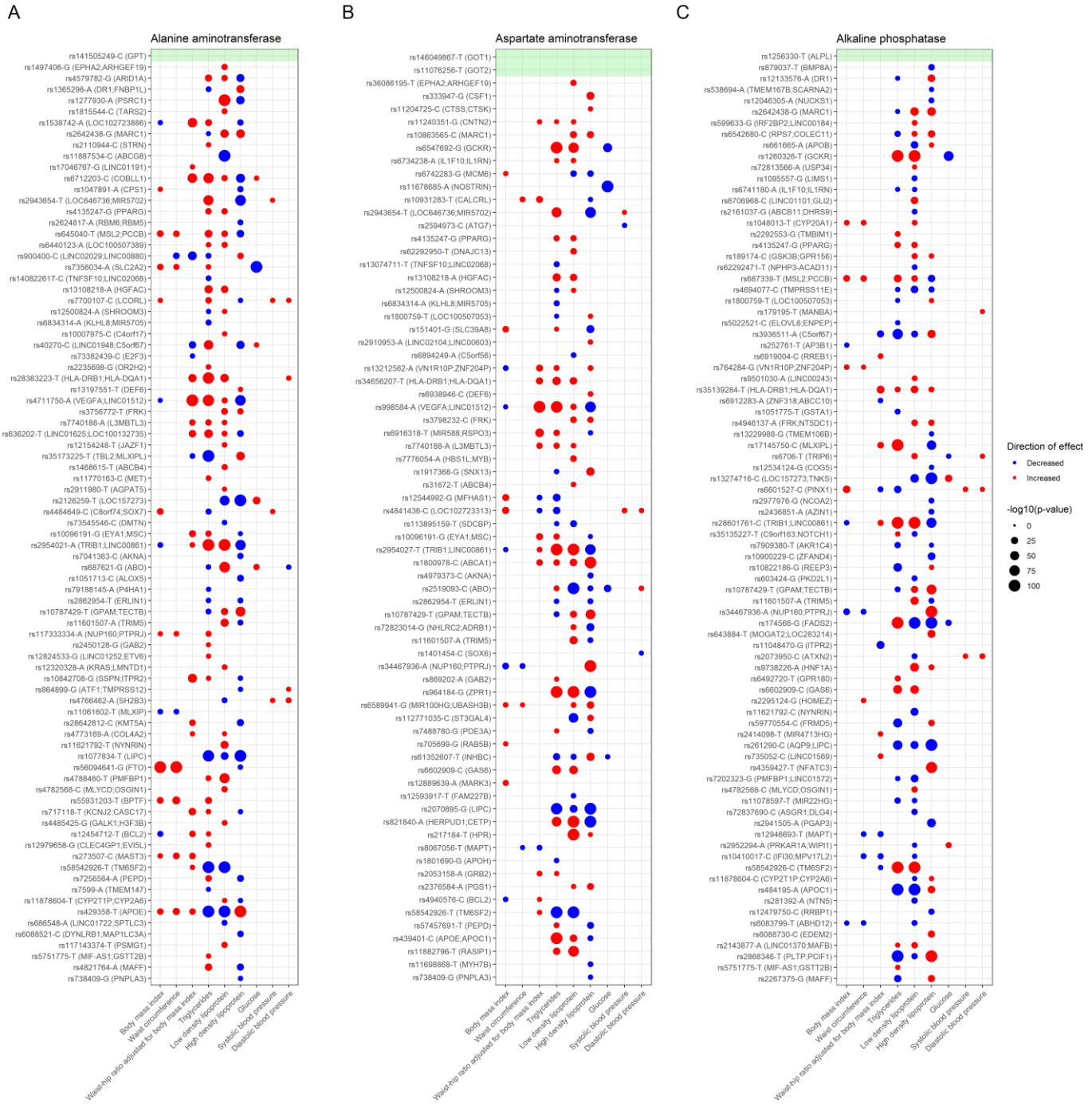
Effect of each rank unit of polygenic risk score for a specific liver enzyme on cirrhosis and hepatic steatosis. Effects are represented as odds ratio (95% confidence interval).

**Supplementary Figure 1: Quantile-quantile plots**



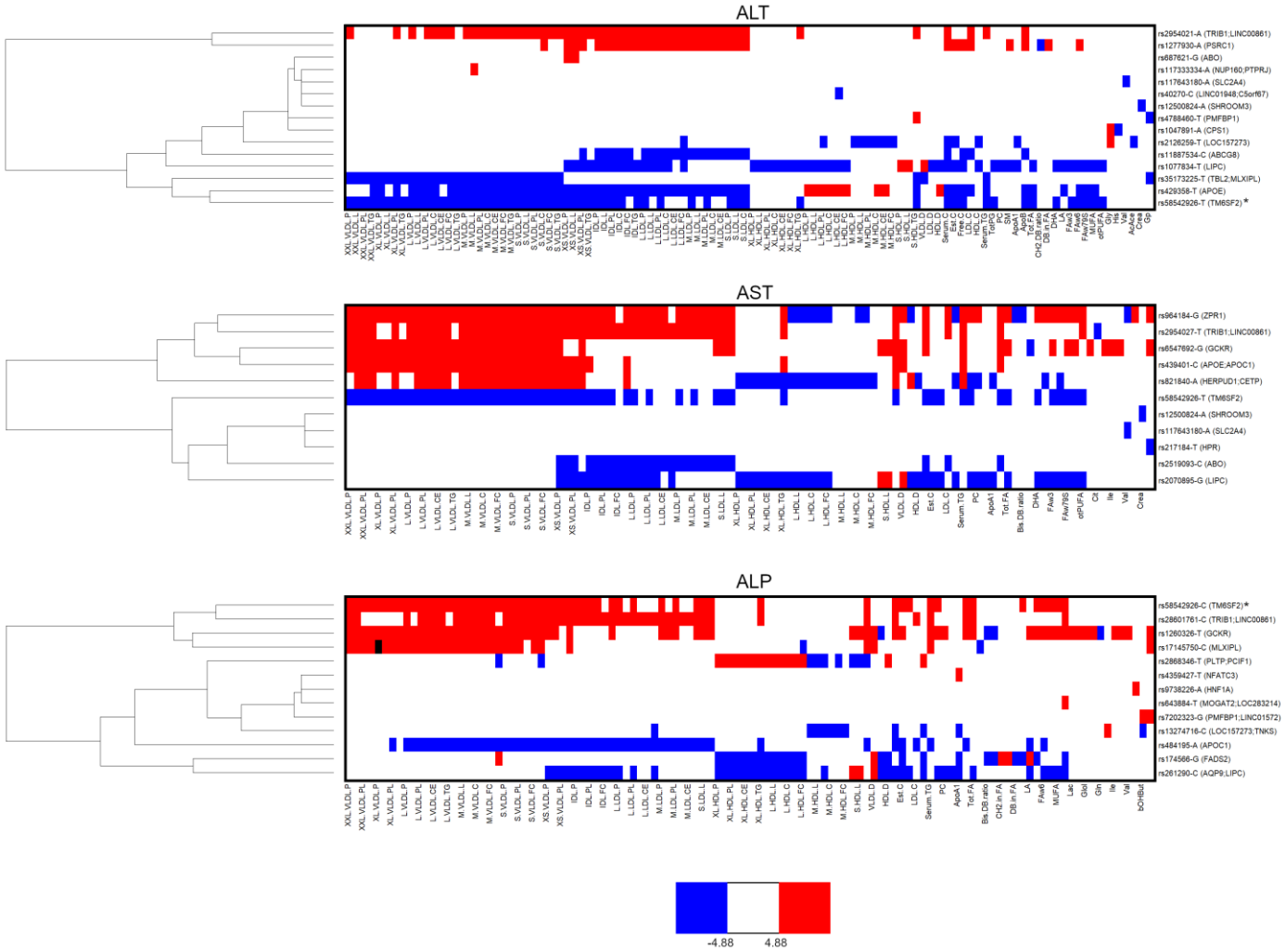

(A-C) Quantile-quantile plots for genetic variants affecting (A) alanine aminotransferase (ALT), (B) aspartate aminotransferase (AST), or (C) alkaline phosphatase (ALP).

**Supplementary Figure 2: Effects of liver enzyme-increasing variants on metabolic traits.**



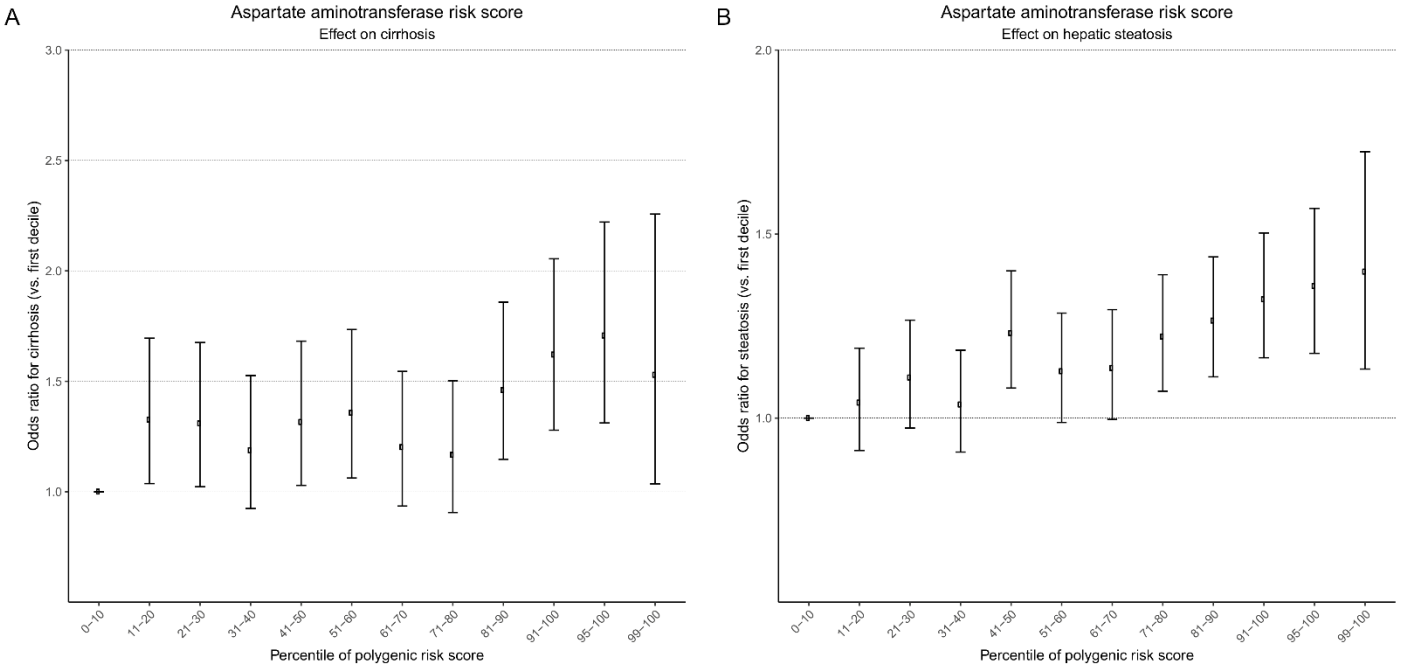

(A-C) Associations between metabolic traits and variants increasing (A) alanine aminotransferase (ALT), (B) aspartate aminotransferase (AST), or (C) alkaline phosphatase (ALP). For all panels, only genome wide-significant associations ($p < 5 \times 10^{-8}$) are shown. Red indicates that the liver enzyme-increasing allele increases the trait, while blue indicates that it decreases it. Larger circles indicate lower p value. Data are from genome-wide association studies in UK BioBank. Green highlighting indicates variants that affect the liver enzymes themselves.

**Supplementary Figure 3: Effects of liver enzyme-increasing variants on serum/plasma metabolites.**




Associations between variants associated with alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) and serum/plasma metabolites. Data on associations between genetic variants and serum/plasma metabolite concentrations are from [17]. Red indicates that the liver enzyme-increasing allele increases metabolite concentration, blue that it decreases it, and white that there is no significant association. A Bonferroni correction for 123 metabolites and 378 genetic variants ($p < 1.1 \times 10^{-6}$ or $|Z| > 4.88$) was used. Hierarchical clustering of genetic variants was performed using Z scores for variant-metabolite associations as a distance matric. * rs58542926-C (*TM6SF2*) had opposite directions on ALT and ALP.

**Supplementary Figure 4: Associations between aspartate aminotransferase polygenic risk score and cirrhosis and steatosis.**




(A-B) Association between percentile of aspartate aminotransferase polygenic risk score on (A) cirrhosis or (B) steatosis. All results are depicted as odds ratios for cirrhosis or steatosis relative to individuals in the 0-10th percentile of polygenic risk score, adjusted for sex, age, age$^2$, and principal components 1-10.

**Supplementary References**


1 Berge, K. E. *et al.* Accumulation of dietary cholesterol in sitosterolemia caused by mutations in adjacent ABC transporters. *Science (New York, N.Y.)* **290**, 1771-1775, doi:10.1126/science.290.5497.1771 (2000).

2 Solca, C. *et al.* Sitosterolaemia in Switzerland: molecular genetics links the US Amish-Mennonites to their European roots. *Clinical genetics* **68**, 174-178, doi:10.1111/j.1399-0004.2005.00472.x (2005).

3 Buch, S. *et al.* A genome-wide association scan identifies the hepatic cholesterol transporter ABCG8 as a susceptibility factor for human gallstone disease. *Nature genetics* **39**, 995-999, doi:10.1038/ng2101 (2007).

4 Chong, J. X., Ouwenga, R., Anderson, R. L., Waggoner, D. J. & Ober, C. A population-based study of autosomal-recessive disease-causing mutations in a founder population. *American journal of human genetics* **91**, 608-620, doi:10.1016/j.ajhg.2012.08.007 (2012).

5 Rees, D. C. *et al.* Stomatocytic haemolysis and macrothrombocytopenia (Mediterranean stomatocytosis/macrothrombocytopenia) is the haematological presentation of phytosterolaemia. *British journal of haematology* **130**, 297-309, doi:10.1111/j.1365-2141.2005.05599.x (2005).

6 Mannucci, L. *et al.* Beta-sitosterolaemia: a new nonsense mutation in the ABCG5 gene. *European journal of clinical investigation* **37**, 997-1000, doi:10.1111/j.1365-2362.2007.01880.x (2007).

7 Rios, J., Stein, E., Shendure, J., Hobbs, H. H. & Cohen, J. C. Identification by whole-genome resequencing of gene defect responsible for severe hypercholesterolemia. *Human molecular genetics* **19**, 4313-4318, doi:10.1093/hmg/ddq352 (2010).

8 Tsutsumi, S. *et al.* The novel gene encoding a putative transmembrane protein is mutated in gnathodiaphyseal dysplasia (GDD). *American journal of human genetics* **74**, 1255-1261, doi:10.1086/421527 (2004).

9 Marconi, C. *et al.* A novel missense mutation in ANO5/TMEM16E is causative for gnathodiaphyseal dyplasia in a large Italian pedigree. *European journal of human genetics : EJHG* **21**, 613-619, doi:10.1038/ejhg.2012.224 (2013).

10 Bolduc, V. *et al.* Recessive mutations in the putative calcium-activated chloride channel Anoctamin 5 cause proximal LGMD2L and distal MMD3 muscular dystrophies. *American journal of human genetics* **86**, 213-221, doi:10.1016/j.ajhg.2009.12.013 (2010).

11 Finckh, U. *et al.* Prenatal diagnosis of carbamoyl phosphate synthetase I deficiency by identification of a missense mutation in CPS1. *Human mutation* **12**, 206-211, doi:10.1002/(sici)1098-1004(1998)12:3<206::aid-humu8>3.0.co;2-e (1998).

12 Aoshima, T. *et al.* Novel mutations (H337R and 238-362del) in the CPS1 gene cause carbamoyl phosphate synthetase I deficiency. *Human heredity* **52**, 99-101, doi:10.1159/000053360 (2001).

13 Kurokawa, K. *et al.* Molecular and clinical analyses of Japanese patients with carbamoylphosphate synthetase 1 (CPS1) deficiency. *Journal of human genetics* **52**, 349-354, doi:10.1007/s10038-007-0122-9 (2007).

14 Klaus, V. *et al.* Highly variable clinical phenotype of carbamylphosphate synthetase 1 deficiency in one family: an effect of allelic variation in gene expression? *Clinical genetics* **76**, 263-269, doi:10.1111/j.1399-0004.2009.01216.x (2009).

15 Hu, L. *et al.* Recurrence of carbamoyl phosphate synthetase 1 (CPS1) deficiency in Turkish patients: characterization of a founder mutation by use of recombinant CPS1 from insect cells expression. *Molecular genetics and metabolism* **113**, 267-273, doi:10.1016/j.ymgme.2014.09.014 (2014).

16 Hamada, T. *et al.* Lipoid proteinosis maps to 1q21 and is caused by mutations in the extracellular matrix protein 1 gene (ECM1). *Human molecular genetics* **11**, 833-840, doi:10.1093/hmg/11.7.833 (2002).

17 Novarino, G. *et al.* Exome sequencing links corticospinal motor neuron disease to common neurodegenerative disorders. *Science (New York, N.Y.)* **343**, 506-511, doi:10.1126/science.1247363 (2014).

18 Santos-Cortez, R. L. *et al.* Autosomal-Recessive Hearing Impairment Due to Rare Missense Variants within S1PR2. *American journal of human genetics* **98**, 331-338, doi:10.1016/j.ajhg.2015.12.004 (2016).

19 Siintola, E. *et al.* Cathepsin D deficiency underlies congenital human neuronal ceroid-lipofuscinosis. *Brain : a journal of neurology* **129**, 1438-1445, doi:10.1093/brain/awl107 (2006).

20 Steinfeld, R. *et al.* Cathepsin D deficiency is associated with a human neurodegenerative disorder. *American journal of human genetics* **78**, 988-998, doi:10.1086/504159 (2006).

21 Hersheson, J. *et al.* Cathepsin D deficiency causes juvenile-onset ataxia and distinctive muscle pathology. *Neurology* **83**, 1873-1875, doi:10.1212/wnl.0000000000000981 (2014).

22 Miki, Y. *et al.* A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science (New York, N.Y.)* **266**, 66-71, doi:10.1126/science.7545954 (1994).

23 Castilla, L. H. *et al.* Mutations in the BRCA1 gene in families with early-onset breast and ovarian cancer. *Nature genetics* **8**, 387-391, doi:10.1038/ng1294-387 (1994).

24 Simard, J. *et al.* Common origins of BRCA1 mutations in Canadian breast and ovarian cancer families. *Nature genetics* **8**, 392-398, doi:10.1038/ng1294-392 (1994).

25 Friedman, L. S. *et al.* Confirmation of BRCA1 by analysis of germline mutations linked to breast and ovarian cancer in ten families. *Nature genetics* **8**, 399-404, doi:10.1038/ng1294-399 (1994).

26 Gayther, S. A. *et al.* Frequently occurring germ-line mutations of the BRCA1 gene in ovarian cancer families from Russia. *American journal of human genetics* **60**, 1239-1242 (1997).

27 Liede, A. *et al.* A breast cancer patient of Scottish descent with germ-line mutations in BRCA1 and BRCA2. *American journal of human genetics* **62**, 1543-1544, doi:10.1086/301889 (1998).

28 Janezic, S. A. *et al.* Germline BRCA1 alterations in a population-based series of ovarian cancer cases. *Human molecular genetics* **8**, 889-897, doi:10.1093/hmg/8.5.889 (1999).
29 Tesoriero, A. *et al.* De novo BRCA1 mutation in a patient with breast cancer and an inherited BRCA2 mutation. *American journal of human genetics* **65**, 567-569, doi:10.1086/302503 (1999).
30 Mefford, H. C. *et al.* Evidence for a BRCA1 founder mutation in families of West African ancestry. *American journal of human genetics* **65**, 575-578, doi:10.1086/302511 (1999).
31 Dorum, A., Heimdal, K., Hovig, E., Inganas, M. & Moller, P. Penetrances of BRCA1 1675delA and 1135insA with respect to breast cancer and ovarian cancer. *American journal of human genetics* **65**, 671-679, doi:10.1086/302530 (1999).
32 Gorski, B. *et al.* Founder mutations in the BRCA1 gene in Polish families with breast-ovarian cancer. *American journal of human genetics* **66**, 1963-1968, doi:10.1086/302922 (2000).
33 Sarantaus, L. *et al.* Multiple founder effects and geographical clustering of BRCA1 and BRCA2 families in Finland. *European journal of human genetics : EJHG* **8**, 757-763, doi:10.1038/sj.ejhg.5200529 (2000).
34 Vallon-Christersson, J. *et al.* Functional analysis of BRCA1 C-terminal missense mutations identified in breast and ovarian cancer families. *Human molecular genetics* **10**, 353-360, doi:10.1093/hmg/10.4.353 (2001).
35 Bergman, A. *et al.* The western Swedish BRCA1 founder mutation 3171ins5; a 3.7 cM conserved haplotype of today is a reminiscence of a 1500-year-old mutation. *European journal of human genetics : EJHG* **9**, 787-793, doi:10.1038/sj.ejhg.5200704 (2001).
36 Vega, A. *et al.* Analysis of BRCA1 and BRCA2 in breast and breast/ovarian cancer families shows population substructure in the Iberian peninsula. *Annals of human genetics* **66**, 29-36, doi:10.1017/s0003480001001014 (2002).
37 Tischkowitz, M. *et al.* Pathogenicity of the BRCA1 missense variant M1775K is determined by the disruption of the BRCT phosphopeptide-binding pocket: a multi-modal approach. *European journal of human genetics : EJHG* **16**, 820-832, doi:10.1038/ejhg.2008.13 (2008).
38 Domchek, S. M. *et al.* Biallelic deleterious BRCA1 mutations in a woman with early-onset ovarian cancer. *Cancer discovery* **3**, 399-405, doi:10.1158/2159-8290.cd-12-0421 (2013).
39 Sawyer, S. L. *et al.* Biallelic mutations in BRCA1 cause a new Fanconi anemia subtype. *Cancer discovery* **5**, 135-142, doi:10.1158/2159-8290.cd-14-1156 (2015).
40 Freire, B. L. *et al.* Homozygous loss of function BRCA1 variant causing a Fanconi-anemia-like phenotype, a clinical report and review of previous patients. *European journal of medical genetics* **61**, 130-133, doi:10.1016/j.ejmg.2017.11.003 (2018).
41 Seo, A. *et al.* Mechanism for survival of homozygous nonsense mutations in the tumor suppressor gene BRCA1. *Proceedings of the National Academy of Sciences of the United States of America* **115**, 5241-5246, doi:10.1073/pnas.1801796115 (2018).
42 Gal, A. *et al.* Mutations in MERTK, the human orthologue of the RCS rat retinal dystrophy gene, cause retinitis pigmentosa. *Nature genetics* **26**, 270-271, doi:10.1038/81555 (2000).
43 Ebermann, I. *et al.* Truncating mutation of the DFNB59 gene causes cochlear hearing impairment and central vestibular dysfunction. *Human mutation* **28**, 571-577, doi:10.1002/humu.20478 (2007).
44 Ksantini, M., Lafont, E., Bocquet, B., Meunier, I. & Hamel, C. P. Homozygous mutation in MERTK causes severe autosomal recessive retinitis pigmentosa. *European journal of ophthalmology* **22**, 647-653, doi:10.5301/ejo.5000096 (2012).
45 Jurkat-Rott, K. *et al.* A calcium channel mutation causing hypokalemic periodic paralysis. *Human molecular genetics* **3**, 1415-1419, doi:10.1093/hmg/3.8.1415 (1994).
46 Ptacek, L. J. *et al.* Dihydropyridine receptor mutations cause hypokalemic periodic paralysis. *Cell* **77**, 863-868, doi:10.1016/0092-8674(94)90135-x (1994).
47 Chabrier, S., Monnier, N. & Lunardi, J. Early onset of hypokalaemic periodic paralysis caused by a novel mutation of the CACNA1S gene. *Journal of medical genetics* **45**, 686-688, doi:10.1136/jmg.2008.059766 (2008).
48 Ke, T., Gomez, C. R., Mateus, H. E., Castano, J. A. & Wang, Q. K. Novel CACNA1S mutation causes autosomal dominant hypokalemic periodic paralysis in a South American family. *Journal of human genetics* **54**, 660-664, doi:10.1038/jhg.2009.92 (2009).
49 Kung, A. W., Lau, K. S., Fong, G. C. & Chan, V. Association of novel single nucleotide polymorphisms in the calcium channel alpha 1 subunit gene (Ca(v)1.1) and thyrotoxic periodic paralysis. *The Journal of clinical endocrinology and metabolism* **89**, 1340-1345, doi:10.1210/jc.2003-030924 (2004).
50 Yoneda, Y. *et al.* De novo and inherited mutations in COL4A2, encoding the type IV collagen alpha2 chain cause porencephaly. *American journal of human genetics* **90**, 86-90, doi:10.1016/j.ajhg.2011.11.016 (2012).
51 Ruiz-Perez, V. L. *et al.* Mutations in a new gene in Ellis-van Creveld syndrome and Weyers acrodental dysostosis. *Nature genetics* **24**, 283-286, doi:10.1038/73508 (2000).
52 Ye, X. *et al.* A novel heterozygous deletion in the EVC2 gene causes Weyers acrofacial dysostosis. *Human genetics* **119**, 199-205, doi:10.1007/s00439-005-0129-2 (2006).
53 Shen, W., Han, D., Zhang, J., Zhao, H. & Feng, H. Two novel heterozygous mutations of EVC2 cause a mild phenotype of Ellis-van Creveld syndrome in a Chinese family. *American journal of medical genetics. Part A* **155a**, 2131-2136, doi:10.1002/ajmg.a.34125 (2011).

54 D'Asdia, M. C. *et al.* Novel and recurrent EVC and EVC2 mutations in Ellis-van Creveld syndrome and Weyers acrofacial dyostosis. *European journal of medical genetics* **56**, 80-87, doi:10.1016/j.ejmg.2012.11.005 (2013).
55 Keller, M. D. *et al.* Mutation in IRF2BP2 is responsible for a familial form of common variable immunodeficiency disorder. *The Journal of allergy and clinical immunology* **138**, 544-550.e544, doi:10.1016/j.jaci.2016.01.018 (2016).
56 Lopez-Herrera, G. *et al.* Deleterious mutations in LRBA are associated with a syndrome of immune deficiency and autoimmunity. *American journal of human genetics* **90**, 986-1001, doi:10.1016/j.ajhg.2012.04.015 (2012).
57 Alangari, A. *et al.* LPS-responsive beige-like anchor (LRBA) gene mutation in a family with inflammatory bowel disease and combined immunodeficiency. *The Journal of allergy and clinical immunology* **130**, 481-488.e482, doi:10.1016/j.jaci.2012.05.043 (2012).
58 Charbonnier, L. M. *et al.* Regulatory T-cell deficiency and immune dysregulation, polyendocrinopathy, enteropathy, X-linked-like disorder caused by loss-of-function mutations in LRBA. *The Journal of allergy and clinical immunology* **135**, 217-227, doi:10.1016/j.jaci.2014.10.019 (2015).
59 Pinz, H. *et al.* De novo variants in Myelin regulatory factor (MYRF) as candidates of a new syndrome of cardiac and urogenital anomalies. *American journal of medical genetics. Part A* **176**, 969-972, doi:10.1002/ajmg.a.38620 (2018).
60 Chitayat, D. *et al.* An Additional Individual with a De Novo Variant in Myelin Regulatory Factor (MYRF) with Cardiac and Urogenital Anomalies: Further Proof of Causality: Comments on the article by Pinz et al. (). *American journal of medical genetics. Part A* **176**, 2041-2043, doi:10.1002/ajmg.a.40360 (2018).
61 Qi, H. *et al.* De novo variants in congenital diaphragmatic hernia identify MYRF as a new syndrome and reveal genetic overlaps with other developmental disorders. *PLoS genetics* **14**, e1007822, doi:10.1371/journal.pgen.1007822 (2018).
62 Wang, K., Zhou, B., Kuo, Y. M., Zemansky, J. & Gitschier, J. A novel member of a zinc transporter family is defective in acrodermatitis enteropathica. *American journal of human genetics* **71**, 66-73, doi:10.1086/341125 (2002).
63 Kury, S. *et al.* Identification of SLC39A4, a gene involved in acrodermatitis enteropathica. *Nature genetics* **31**, 239-240, doi:10.1038/ng913 (2002).
64 Nakano, A., Nakano, H., Nomura, K., Toyomaki, Y. & Hanada, K. Novel SLC39A4 mutations in acrodermatitis enteropathica. *The Journal of investigative dermatology* **120**, 963-966, doi:10.1046/j.1523-1747.2003.12243.x (2003).
65 Saleheen, D. *et al.* Human knockouts and phenotypic analysis in a cohort with a high rate of consanguinity. *Nature* **544**, 235-239, doi:10.1038/nature22034 (2017).
66 Diodato, D. *et al.* VARS2 and TARS2 mutations in patients with mitochondrial encephalomyopathies. *Human mutation* **35**, 983-989, doi:10.1002/humu.22590 (2014).
67 Taylor, R. W. *et al.* Use of whole-exome sequencing to determine the genetic basis of multiple mitochondrial respiratory chain complex deficiencies. *Jama* **312**, 68-77, doi:10.1001/jama.2014.7184 (2014).