Table S1 Study investigators and centres contributing samples

| Country | Centre | Investigators |
|---|---|---|
| **Austria** | Department of Internal Medicine, Hospital Oberndorf, Salzburg | Christian Datz<br>Elmar Aigner |
| | First Department of Medicine, Paracelsus Medical University, Salzburg | Elmar Aigner |
| | Department of Rheumatology and Immunology, Medical University of Graz | Elizabeth Krones<br>Christian Dejaco |
| | Department of Gastroenterology, University Hospital Innsbruck, Innsbruck | Heinz Zoller |
| **England** | The Liver Unit, Addenbrooke's Hospital, Cambridge, UK | William JH Griffiths<br>Callum Wright |
| **Germany** | Department of Internal Medicine 3, University of Erlangen-Nuremberg, Erlangen | Jochen Zwerina |
| | Department of Internal Medicine IV, University Hospital Heidelberg, Heidelberg | Uta Merle<br>Karl Heinz Weiss |
| | Department of Internal Medicine, University Hospital Leipzig, Leipzig, | Janet Fischer<br>Thomas Berg |
| **Ireland** | Liver Centre, Mater Misericordiae University Hospital, Dublin | Eleanor Ryan<br>John D Ryan<br>Stephen Stewart |
| **Italy** | Medicine and Metabolic Diseases Unit, Fondazione Ca' Granda IRCCS, Policlinico Hospital University of Milan | Paola Dongiovanni<br>Anna Fracanzani |
| | Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan | Luca Valenti |
| **Switzerland** | Department of Gastroenterology and Hepatology, University Hospital of Zurich | Felix Stickel |

TABLE S2 Sequences of the primers used for each SNP

| Gene: SNP | Primer | Sequence |
|---|---|---|
| *PCSK7:* rs236918 | Forward 1 | GAAGGTCGGAGTCAACGGATTCAAGCTGCCTCACTGCTCTGC |
| | Forward 2 | GAAGGTGACCAAGTTCATGCTCAAGCTGCCTCACTGCTCTGG |
| | Reverse | CACCTCAGAACCACACAGAGAGAA |
| *PNPLA3:* rs738409 | Forward 1 | GAAGGTGACCAAGTTCATGCTCCTTGGTATGTTCCTGCTTCATC |
| | Forward 2 | GAAGGTCGGAGTCAACGGATTCCTTGGTATGTTCCTGCTTCATG |
| | Reverse | AAGGAGGGATAAGGCCACTGTAGAA |
| *TM6SF2:* rs58542926 | Forward 1 | GAAGGTCGGAGTCAACGGATTGGAAGAAGGCAGGCCTGATCTT |
| | Forward 2 | GAAGGTGACCAAGTTCATGCTGAAGAAGGCAGGCCTGATCTC |
| | Reverse | GATGCCCTCTCTCCTGCACCAT |
| *MBOAT7*: rs641738 | Forward 1 | GAAGGTGACCAAGTTCATGCTGGGGCTCCTCTAGGGG |
| | Forward 2 | GAAGGTCGGAGTCAACGGATTCCTGGGGCTCCTCTAGGGA |
| | Reverse | ATGGATCTGAGCTTCTCCTGGCATT |
| *HSD17B13:* rs72613567 | Forward 1 | GAAGGTGACCAAGTTCATGCTTTGGGTGTTCTGTGCTGTACTTAC |
| | Forward 2 | GAAGGTCGGAGTCAACGGATTATTTGGGTGTTCTGTGCTGTACTTAA |
| | Reverse | GAAGTCTGATAGATGGAATACTTACCAATA |

TABLE S3 Demographic, clinical and laboratory information in the C282Y homozygotes with available liver histology, at the time of diagnosis

| **Cohort** (n) | **Cases** (n=131) Total (n: %) | Men (n: %) | Age (yr) | Serum ferritin* (µg/l) | BMI | Obese† (n: %) | Diabetes (n:%) | **Controls** (n=299) Total (n) | Men (n: %) | Age (yr) | Serum ferritin (µg/l) | BMI | Obese† (n: %) | Diabetes (n: %) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Austria** (132) | 51 (39%) | 47 (92%) | 60 (51-67) | 2782 (1754-4184) | 26.3 (24.0-27.5) | 3/25 | 1/10 | 81 | 48 (59%) | 50 (41-59) | 1140 (628-1880) | 25.3 (24.1-28.3) | 3/26 | 1/13 |
| **England** (48) | 19(40%) | 17 (89%) | 55 (47-65) | 2628 (1300-5000) | <30 | 0/19 | 8/19 | 29 | 21 (72%) | 53 (46-63) | 1500 (1173-1859) | <30 | 0/29 | 2/25 |
| **Germany** (46) | 23 (50%) | 20 (87%) | 59 (53-64) | 3230 (2153-5250) | 28.7 (25.6-32.0) | 3/8 | 4/9 | 23 | 14 (61%) | 52 (39-65) | 1228 (669-2151) | 25.4 (23.3-27.8) | 3/19 | 0/20 |
| **Ireland** (87) | 12 (14%) | 11 (92%) | 53 (46-59) | 1650 (1186-3025) | n/a | n/a | 4/12 | 75 | 58 (77%) | 50 (42-60) | 1025 (637-1391) | n/a | n/a | 4/28 |
| **Italy** (47) | 5 (11%) | 5 (100%) | 49 (47-59) | 3090 (2353-3336) | 25.0 (24.5-26.0) | 0 | 1/5 | 42 | 29 (69%) | 45 (35-58) | 823 (524-1244) | 26.0 (24.0-29.0) | 4/21 | 1/42 |
| **Switzerland** (70) | 21 (30%) | 19 (90%) | 57 (50-63) | 3313 (2280-4940) | n/a | n/a | 5/21 | 49 | 35 (71%) | 50 (41-58) | 1073 (635-2077) | n/a | n/a | 4/48 |
| **TOTAL (430)** | **131 (30%)** | **119(91%)** | **57 (49-64)** | **2760 (1840-4380)** | **26.8 (24.1-28.7)** | **10% (6/58)** | **23% (23/99)** | **299** | **205 (69%)**** | **50* (41-59)** | **1114** (640-1621)** | **25.9 (24.0-28.3)** | **11% (10/105)** | **7%** (12/188)** |

Case-control status was confirmed by histological examination of liver biopsy material in 131 (76.6%) of the total of 171 cases and in 299 (26.0%) of the total 1148 controls. The characteristics of this subpopulation closely mirrored those of the total population

Data expressed as median (interquartile [IQR: Q1-Q3] range)
BMI: body mass index; † based on a BMI ≥30 but < 40); n/a: not available;
Significance of the differences between cases and controls * $P$ <0.001; ** $P$ <0.0001

TABLE S4 Raw genotype counts and Hardy-Weinberg equilibrium

| Gene: SNP | Cohort | Cases ( n = 171) | | Controls (n = 1148) | |
|---|---|---|---|---|---|
| | | Genotype count | HWE (*P*) | Genotype count | HWE (*P*) |
| ***PCSK7*** **rs236918** | Austria | GG/GC/CC 40/13/2 | 0.463 | GG/GC/CC 276/58/2 | 0.876 |
| | England | GG/GC/CC 15/7/0 | 0.715 | GG/GC/CC 97/28/0 | 0.361 |
| | Germany | GG/GC/CC 15/9/1 | 0.776 | GG/GC/CC 117/17/3 | 0.051 |
| | Ireland | GG/GC/CC 16/4/1 | 0.183 | GG/GC/CC 252/82/15 | **0.026** |
| | Italy | GG/GC/CC 17/8/0 | 0.742 | GG/GC/CC 124/23/3 | 0.417 |
| | Switzerland | GG/GC/CC 15/6/0 | 0.668 | GG/GC/CC 41/7/1 | 0.185 |
| ***PNPLA3*** **rs738409** | Austria | CC/CG/GG 20/25/10 | 0.683 | CC/CG/GG 172/130/29 | 0.545 |
| | England | CC/CG/GG 8/12/2 | 0.507 | CC/CG/GG 69/48/8 | 0.907 |
| | Germany | CC/CG/GG 13/11/1 | 0.819 | CC/CG/GG 63/66/9 | 0.134 |
| | Ireland | CC/CG/GG 7/11/3 | 0.829 | CC/CG/GG 224/111/14 | 0.934 |
| | Italy | CC/CG/GG 10/9/6 | 0.162 | CC/CG/GG 60/64/24 | 0.340 |
| | Switzerland | CC/CG/GG 8/10/2 | 0.817 | CC/CG/GG 26/21/2 | 0.591 |
| ***TM6SF2*** **rs58542926** | Austria | CC/CT/TT 41/14/0 | 0.385 | CC/CT/TT 289/45/1 | 0.835 |
| | England | CC/CT/TT 18/4/0 | 0.568 | CC/CT/TT 101/24/0 | 0.453 |
| | Germany | CC/CT/TT 19/2/1 | 0.069 | CC/CT/TT 112/24/0 | 0.434 |
| | Ireland | CC/CT/TT 13/5/2 | 0.119 | CC/CT/TT 298/48/2 | 0.854 |
| | Italy | CC/CT/TT 22/3/0 | 0.531 | CC/CT/TT 134/15/0 | 0.655 |
| | Switzerland | CC/CT/TT 17/4/0 | 0.572 | CC/CT/TT 40/9/0 | 0.666 |

| | | | | | |
|---|---|---|---|---|---|
| ***MBOAT7* rs641738** | Austria | CC/CT/TT 19/25/11 | 0.589 | CC/CT/TT 107/172/53 | 0.238 |
| | England | CC/CT/TT 9/10/3 | 0.825 | CC/CT/TT 42/67/16 | 0.228 |
| | Germany | CC/CT/TT 10/9/5 | 0.304 | CC/CT/TT 47/60/31 | 0.145 |
| | Ireland | CC/CT/TT 6/8/7 | 0.293 | CC/CT/TT 136/150/63 | 0.051 |
| | Italy | CC/CT/TT 2/15/7 | 0.150 | CC/CT/TT 52/66/30 | 0.277 |
| | Switzerland | CC/CT/TT 7/9/5 | 0.527 | CC/CT/TT 15/22/12 | 0.481 |
| ***HSD17B13* rs72613567** | Austria | --/-A/AA 32/16/4 | 0.429 | --/-A/AA 203/104/19 | 0.224 |
| | England | --/-A/AA 8/9/2 | 0.803 | --/-A/AA 59/40/7 | 0.900 |
| | Germany | --/-A/AA 10/8/2 | 0.809 | --/-A/AA 71/53/14 | 0.359 |
| | Ireland | --/-A/AA 11/6/2 | 0.407 | --/-A/AA 166/129/21 | 0.620 |
| | Italy | --/-A/AA 14/10/1 | 0.793 | --/-A/AA 97/37/9 | 0.056 |
| | Switzerland | --/-A/AA 17/4/0 | 0.572 | --/-A/AA 25/21/3 | 0.602 |

Abbreviation: HWE: Hardy-Weinberg Equilibrium
Significance values in bold indicate $P < 0.05$

TABLE S5 Comparison of mean allele frequencies of study populations with EUR sub-populations from 1000 Genomes Project Phase 3 (CEU, TSI, GBR, FIN, IBS)*

| Variant | Group | Groups (n) | Mean (MAF) | SD | SEM | Significance^ (*P*) | Significance ^^ (*P*) |
|---|---|---|---|---|---|---|---|
| *PCSK7*: rs236918 | EUR sub-populations | 5 | 0.128 | 0.026 | 0.012 | | |
| | Study | 6 | 0.104 | 0.030 | 0.012 | 0.186 | 0.126 |
| *PNPLA3*: rs738409 | EUR sub-populations | 5 | 0.226 | 0.034 | 0.015 | | |
| | Study | 6 | 0.279 | 0.060 | 0.024 | 0.111 | 0.126 |
| *TM6SF2*: rs58542926 | EUR sub-populations | 5 | 0.068 | 0.016 | 0.007 | | |
| | Study | 6 | 0.079 | 0.017 | 0.007 | 0.326 | 0.247 |
| *MBOAT7*: rs641738 | EUR sub-populations | 5 | 0.440 | 0.017 | 0.008 | | |
| | Study | 6 | 0.425 | 0.028 | 0.012 | 0.310 | 0.429 |
| *HSD17B13:* rs72613567 | EUR sub-populations | 5 | 0.244 | 0.018 | 0.008 | | |
| | Study | 6 | 0.251 | 0.038 | 0.016 | 0.733 | 0.662 |

MAF: mean allele frequency; SD: standard deviation; SEM: standard error of mean; EUR: European

*1000 Genome phase 3: CEU: Utah residents with Northern and Western European Ancestry; TSI: Toscani in Italy: GBR: British in England and Scotland; FIN: Finish in Finland; IBS: Iberian in Spain

^T test; ^^Independent-samples Mann-Whitney U Test

TABLE S6 Meta-analysis of the associations of the five SNPs of interest and the risk for developing cirrhosis in C282Y homozygotes†, adjusted for age and sex

| Gene: SNP | OR | 95% CI | Significance (Meta *P*) | $I^2$ (%) |
|---|---|---|---|---|
| Fixed Effect Model | | | | |
| *PCSK7*:rs236918 | 1.52 | 1.06 - 2.19 | **0.022** | 0 |
| *PNPLA3*:rs738409 | 1.60 | 1.22 - 2.11 | **$7.37 \times 10^{-4}$** | 45.5 |
| *TM6SF2*:rs58542926 | 1.94 | 1.28 - 2.95 | **$1.86 \times 10^{-3}$** | 0 |
| *MBOAT7*:rs641738 | 1.17 | 0.91 - 1.51 | 0.219 | 31.8 |
| *HSD17B13:*rs72613567 | 0.94 | 0.69 - 1.27 | 0.685 | 16.8 |
| Random Effects Model | | | | |
| **Gene: SNP** | **OR** | **95% CI** | **Significance (Meta *P*)** | ***P* heterogeneity** |
| *PCSK7*:rs236918 | 1.52 | 1.06 - 2.19 | **0.022** | 0.783 |
| *PNPLA3*:rs738409 | 1.52 | 1.04 - 2.24 | **0.032** | 0.102 |
| *TM6SF2*:rs58542926 | 1.94 | 1.28 - 2.95 | **$1.86 \times 10^{-3}$** | 0.477 |
| *MBOAT7*:rs641738 | 1.19 | 0.87 - 1.65 | 0.268 | 0.198 |
| *HSD17B13:*rs72613567 | 0.93 | 0.66 - 1.31 | 0.688 | 0.306 |

† Cases n = 158: Controls n = 1109

OR: odds ratio; CI: confidence intervals; *P* heterogeneity: P value of the Cochran's Q test for heterogeneity between cohorts

Significance values in bold indicate $P < 0.05$

TABLE S7 Sensitivity analysis of the associations of *PCSK7*:rs236918 and the risk for developing cirrhosis in C282Y homozygotes*, adjusted for age and sex

| Excluded study | Pooled OR | 95%CI | Cochran Q | Significance (Meta *P*) | *P* heterogeneity | $I^2$ (%) | $I^2$ 95% CI |
|---|---|---|---|---|---|---|---|
| Ireland^ | 1.72 | 1.15 - 2.58 | 0.58 | 0.00799 | 0.9652 | 0.00 | 0.00 - 0.00 |
| Austria | 1.49 | 0.96 - 2.31 | 2.42 | 0.07794 | 0.6593 | 0.00 | 0.00 - 65.60 |
| Germany | 1.40 | 0.93 - 2.09 | 1.50 | 0.10313 | 0.8275 | 0.00 | 0.00 - 44.37 |
| England | 1.53 | 1.04 - 2.26 | 2.45 | 0.03018 | 0.6541 | 0.00 | 0.00 - 66.01 |
| Italy | 1.50 | 1.03 - 2.18 | 2.32 | 0.03641 | 0.6771 | 0.00 | 0.00 - 64.14 |
| Switzerland | 1.53 | 1.04 - 2.23 | 2.45 | 0.02900 | 0.6528 | 0.00 | 0.00 - 66.11 |

* Cases n = 158: Controls n = 1109; ^ Hardy-Weinberg Equilibrium *P*=0.026

OR: odds ratio; CI: confidence intervals; I*P* heterogeneity: P value of the Cochran's Q test for heterogeneity between cohorts; $I^2$: between cohort heterogeneity index,

TABLE S8 Meta-analysis of the associations of the five SNPs of interest and the risk for developing cirrhosis in male C282Y homozygotes*, adjusted for age

| Gene: SNP | OR | 95% CI | Significance (Meta *P*) | $I^2$ (%) |
|---|---|---|---|---|
| Fixed Effects Model | | | | |
| *PCSK7*:rs236918 | 1.65 | 1.12 - 2.41 | **0.011** | 0 |
| *PNPLA3*:rs738409 | 1.51 | 1.12 - 2.03 | **$6.14 \times 10^{-3}$** | 54.4 |
| *TM6SF2*:rs58542926 | 1.98 | 1.25 - 3.12 | **$3.35 \times 10^{-3}$** | 0 |
| *MBOAT7*:rs641738 | 1.14 | 0.87 - 1.50 | 0.345 | 26.3 |
| *HSD17B13:*rs72613567 | 0.99 | 0.72 - 1.37 | 0.975 | 9.95 |
| Random Effects Model | | | | |
| **Gene: SNP** | **OR** | **95% CI** | **Significance (Meta *P*)** | ***P* heterogeneity** |
| *PCSK7*:rs236918 | 1.65 | 1.12 - 2.41 | **0.011** | 0.722 |
| *PNPLA3*:rs738409 | 1.40 | 0.88 - 2.21 | 0.115 | 0.052 |
| *TM6SF2*:rs58542926 | 1.98 | 1.25 - 3.12 | **$3.35 \times 10^{-3}$** | 0.450 |
| *MBOAT7*:rs641738 | 1.16 | 0.83 - 1.61 | 0.376 | 0.237 |
| *HSD17B13:*rs72613567 | 0.99 | 0.70 - 1.39 | 0.957 | 0.352 |

* Cases n = 142: Controls n = 691

OR: odds ratio; CI: confidence intervals; *P* heterogeneity: P value of the Cochran's Q test for heterogeneity between cohorts

Significance values in bold indicate $P < 0.05$

TABLE S9 Meta-analysis of the associations of the five SNPs of interest and the risk for developing cirrhosis in C282Y homozygotes* with available liver histology, adjusted for age and sex

| Gene: SNP | OR | 95% CI | Significance (Meta *P*) | $I^2$ (%) |
|---|---|---|---|---|
| Fixed Effects Model | | | | |
| *PCSK7*:rs236918 | 2.13 | 1.25 – 3.66 | **$5.80 \times 10^{-3}$** | 18.6 |
| *PNPLA3*:rs738409 | 1.80 | 1.20 – 2.68 | **$4.09 \times 10^{-3}$** | 75.6 |
| *TM6SF2*:rs58542926 | 2.06 | 1.18 – 3.61 | **0.011** | 0 |
| *MBOAT7*:rs641738 | 1.01 | 0.72 – 1.42 | 0.957 | 0 |
| *HSD17B13:*rs72613567 | 0.95 | 0.62 – 1.47 | 0.833 | 25.7 |
| Random Effects Model | | | | |
| **Gene: SNP** | **OR** | **95% CI** | **Significance (Meta *P*)** | ***P* heterogeneity** |
| *PCSK7*:rs236918 | 2.21 | 1.19 – 4.08 | **0.012** | 0.293 |
| *PNPLA3*:rs738409 | 1.59 | 0.70 – 3.65 | 0.271 | 0.001 |
| *TM6SF2*:rs58542926 | 2.06 | 1.18 – 3.61 | **0.011** | 0.718 |
| *MBOAT7*:rs641738 | 1.01 | 0.72 – 1.42 | 0.957 | 0.918 |
| *HSD17B13:*rs72613567 | 0.93 | 0.55- 1.56 | 0.774 | 0.241 |

*Cases n = 130: Controls n = 297

OR: odds ratio; CI: confidence intervals; *P* heterogeneity: P value of the Cochran's Q test for heterogeneity between cohorts

Significance values in bold indicate $P < 0.05$

TABLE S10 Sensitivity analysis of the associations *PNPLA3:*rs738409 and the risk for developing cirrhosis in C282Y homozygotes, with available liver histology*, adjusted for age and sex

| Excluded study | Pooled OR | 95%CI | Cochran Q | Significance (Meta *P*^) | *P* heterogeneity | $I^2$ (%) | $I^2$ 95% CI |
|---|---|---|---|---|---|---|---|
| Germany | 2.21 | 1.13 – 4.34 | 9.35 | 0.02054 | 0.0528 | 57.24 | 0.00 – 84.13 |
| Austria | 1.29 | 0.51 – 3.25 | 14.91 | 0.58661 | 0.0049 | 73.17 | 32.93 – 89.26 |
| England | 1.27 | 0.53 – 3.04 | 16.42 | 0.59851 | 0.0025 | 75.64 | 40.25 – 90.07 |
| Italy | 1.86 | 0.75 – 4.61 | 17.68 | 0.17907 | 0.0014 | 77.38 | 45.33 – 90.64 |
| Switzerland | 1.63 | 0.58 – 4.57 | 20.08 | 0.35276 | 0.0005 | 80.08 | 53.09 – 91.54 |
| Ireland | 1.47 | 1.52 – 4.15 | 20.26 | 0.46133 | 0.0004 | 80.26 | 53.59 – 91.60 |

*Cases n = 130: Controls n = 297

OR: odds ratio; CI: confidence intervals; *P* heterogeneity: P value of the Cochran's Q test for heterogeneity between cohorts

^ Random effects model

TABLE S11 Meta-analysis of the associations of the five SNPs of interest and the risk for developing cirrhosis in C282Y homozygotes† with available liver histology, adjusted for age sex and obesity

| Gene: SNP | OR | 95% CI | Significance (Meta *P*) | $I^2$ (%) |
|---|---|---|---|---|
| Fixed Effects Model | | | | |
| *PCSK7*:rs236918 | 3.65 | 1.18 – 11.23 | **0.024** | 0 |
| *PNPLA3*:rs738409 | 2.78 | 1.25 - 6.20 | **0.012** | 38.9 |
| *TM6SF2*:rs58542926 | 1.59 | 0.51 – 5.01 | 0.425 | 0 |
| *MBOAT7*:rs641738 | 0.85 | 0.42 - 1.72 | 0.644 | 0 |
| *HSD17B13:*rs72613567 | 1.94 | 0.94 – 4.01 | 0.075 | 0 |
| Random Effects Model | | | | |
| **Gene: SNP** | **OR** | **95% CI** | **Significance (Meta *P*)** | ***P* heterogeneity** |
| *PCSK7*:rs236918 | 3.65 | 1.18 – 11.23 | **0.024** | 0.469 |
| *PNPLA3*:rs738409 | 2.58 | 0.89 - 7.46 | 0.081 | 0.195 |
| *TM6SF2*:rs58542926 | 1.59 | 0.51 - 5.01 | 0.425 | 0.524 |
| *MBOAT7*:rs641738 | 0.85 | 0.42 - 1.72 | 0.644 | 0.495 |
| *HSD17B13:*rs72613567 | 1.94 | 0.94 - 4.01 | 0.075 | 0.853 |

† Cases n = 52: Controls n = 74 (Austria, Germany, England)

OR: odds ratio; CI: confidence intervals; *P* heterogeneity: P value of the Cochran's Q test for heterogeneity between cohorts

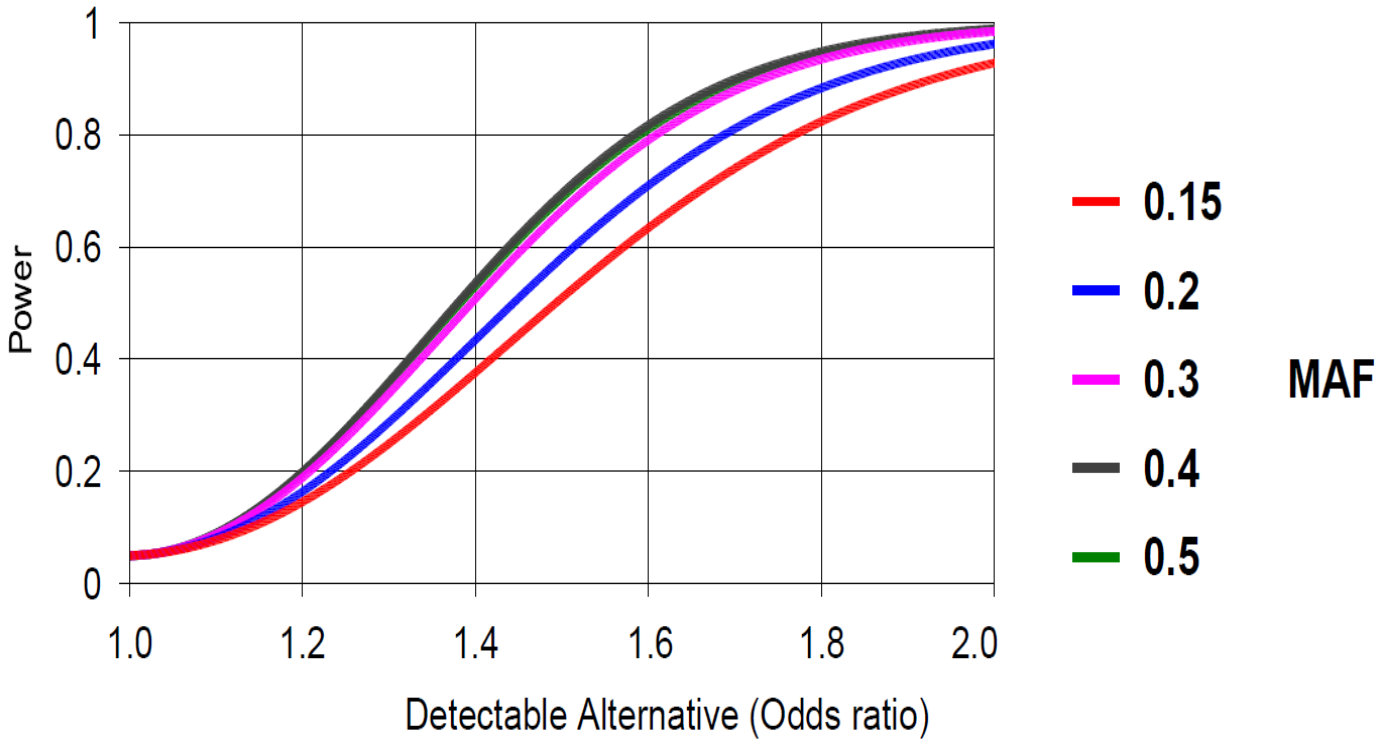
Significance values in bold indicate $P < 0.05$

TABLE S12 SNP × SNP interaction with the risk for developing cirrhosis in C282Y homozygotes

| Regression model | Risk variant | Adjusted OR (95% CI) | Significance (*P*) | SNP*SNP interaction |
|---|---|---|---|---|
| a) Two risk variant model | *PNPLA3* I148M | 1.62 (1.23 - 2.12) | 0.0006 | |
| | *TM6SF2* E167K | 1.95 (1.28 - 2.96) | 0.0018 | |
| b) Model with interaction term | *PNPLA3* I148M | 1.41 (1.04 - 1.91) | 0.028 | |
| | *TM6SF2* E167K | 1.19 (0.62 - 2.29) | 0.605 | |
| | ***PNPLA3* I148M * *TM6SF2* E167K** | **1.94 (1.02 - 3.67)** | **0.042** | **Significant** |
| a) Two risk variant model | *PNPLA3* I148M | 1.58 (1.21 - 2.07) | 0.001 | |
| | *PCSK7* rs236918 G>C | 1.57 (1.11 - 2.23) | 0.0117 | |
| b) Model with interaction term | *PNPLA3 I148M* | 1.47 (1.07 - 2.00) | 0.0167 | |
| | *PCSK7 rs236918 G>C* | 1.34 (0.83 - 2.18) | 0.2340 | |
| | ***PNPLA3* I148M * *PCSK7* rs236918** | 1.29 (0.76 - 2.20) | 0.3390 | Not significant |
| a) Two risk variant model | *PCSK7* rs236918 G>C | 1.64 (1.15 - 2.33) | 0.0063 | |
| | *TM6SF2* E167K | 1.95(1.28 - 2.97) | 0.0018 | |
| b) Model with interaction term | *PCSK7 rs236918 G>C* | 1.82 (1.25 - 2.66) | 0.0019 | |
| | *TM6SF2 E167K* | 2.28 (1.43 - 3.62) | 0.0005 | |
| | ***TM6SF2* E167K * *PCSK7* rs236918** | 0.50 (0.18 - 1.38) | 0.1810 | Not significant |

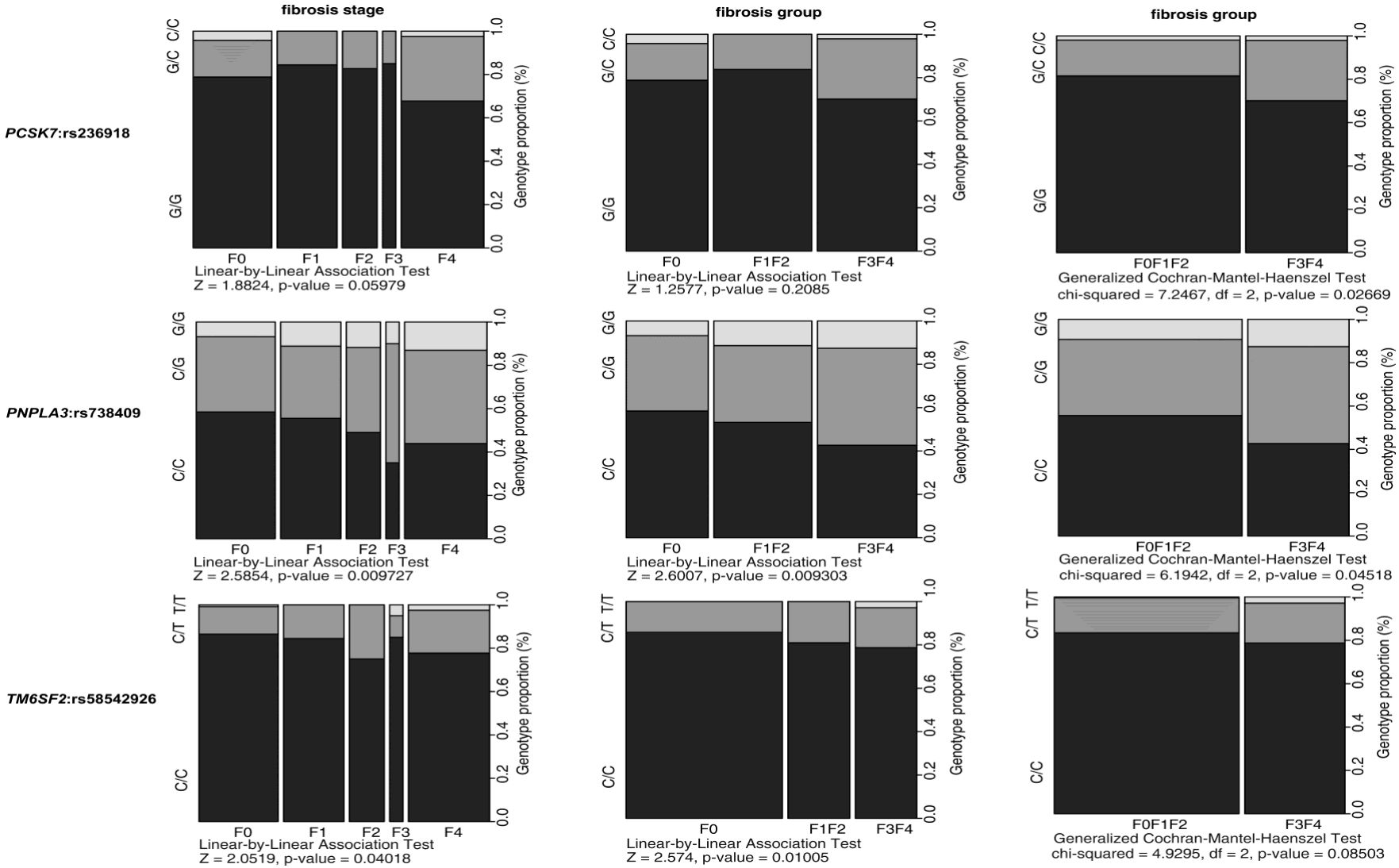
The interaction of risk variants was tested pair-wise for the allelic risk model in presence of the main SNP effect. The Table shows the risk variant estimates in a model (a) including only the two risk variants and b) the estimate of the allelic interaction effect in a model including two risk variants and the allelic interaction term. Significance was calculated using logistic regression with adjustment for age, sex and country

FIGURE S1 Power analysis of the sample used in the present study




The power of the allelic test is plotted as a function of the underlying odds ratio of the tested genetic variant. Calculations were performed using a nominal significance level of 0.05 in a two-sided test. The different colours denote the frequency of the minor allele (MAF) of the respective variant. Power increased for frequent variants and higher underlying odds. This indicates that associations with an odds ratios > 1.6 should be detectable with a power >80% for allele frequencies > 0.3. The graph was produced using PS-Power (https://vbiostatps.app.vumc.org/ps/) and shows the power as a function of the odds ratio

FIGURE S2 Genotype proportions of the *PCSK7*/*PNPLA3*/*TM6SF2* risk variants with increasing degrees of hepatic fibrosis in homozygous C282Y cases and controls with available histology




Subjects were evaluated according to single or grouped fibrosis staging scores as follows: absent fibrosis (F0), mild-moderate fibrosis (F1and F2), and severe fibrosis/cirrhosis (F3and F4). [27]