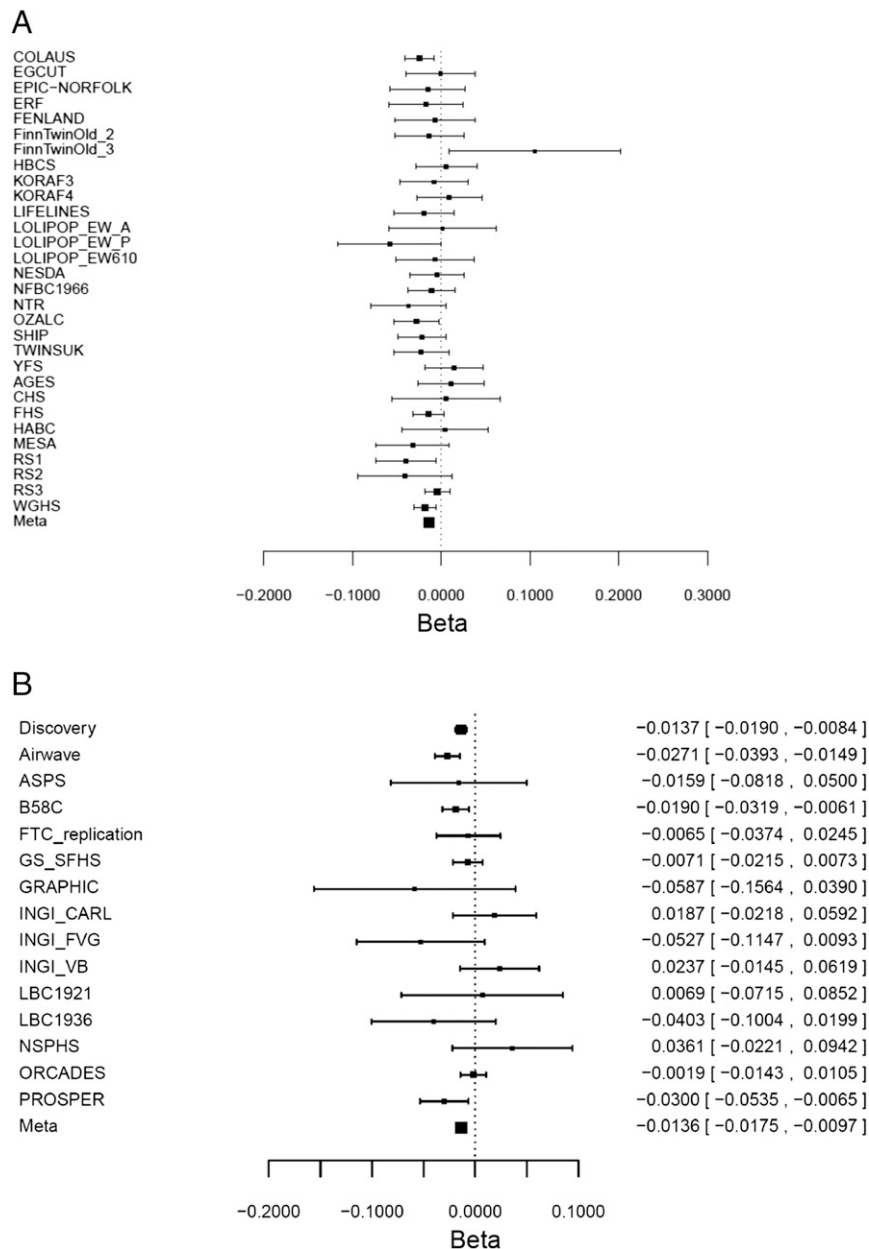


# Supporting Information

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**Fig. S1.** Forest plot for the association of rs11940694 in *KLB* with log grams per day alcohol in the discovery GWAS and replication cohorts. (A) rs11940694 in *KLB* in discovery GWAS cohorts. Discovery GWAS cohorts: the Alcohol Genome-Wide Association (AlcGen) Consortium: the Cohorte Lausannoise study (COLAUS), the Estonian Biobank Cohort (EGCUT), the European Prospective Investigation of Cancer-Norfolk study (EPIC-NORFOLK), the Erasmus Rucphen Family study (ERF), the Fenland study (FENLAND), the Older Finnish Twin Cohort\_2 (FinnTwinOld\_2), the Helsinki Birth Cohort Study (HBSC), the population-based Cooperative Health Research in the Region of Augsburg F3 Study (KORAF3), the population-based Cooperative Health Research in the Region of Augsburg F4 Study (KORAF4), the Lifelines Cohort Study & Biobank (LIFELINES), the London Life Sciences Prospective Population Study (LOLIPOP\_EW\_A, LOLIPOP\_EW\_P, and LOLIPOP\_EW610), the Older Finnish Twin Cohort\_3 (FinnTwinOld\_3), the Netherlands Study of Depression and Anxiety (NESDA), the Northern Finland Birth Cohort 1966 (NFBC1966), the Netherlands Twin Register cohort (NTR), the Australian twin-family study of alcohol use disorder (OZALC), the Study of Health in Pomerania (SHIP), the TwinsUK study (TWINSUK), and the Cardiovascular Risk in Young Finns Study (YFS); and the Cohorts for Heart and Aging Research in Genomic Epidemiology Plus (CHARGE+) Consortium: the Age, Gene/Environment Susceptibility-Reykjavik (AGES-Reykjavik) study, the Cardiovascular Health Study (CHS), the Framingham Heart Study (FHS), the Health, Aging, and Body Composition (HABC), the Multi-Ethnic Study of Atherosclerosis (MESA), the Rotterdam Study (RS1, RS2, and RS3), and the Women's Genome Health Study (WGHS). In rs11940694, the coded allele was A, and the noncoded allele was G. The allele frequency for A was ~0.42 in the entire sample. The beta/SE estimates were for A allele. (B) rs11940694 in *KLB* in discovery and replication cohorts. The coded allele was A, and the noncoded allele was G. The beta/SE estimates were for A allele.







**Table S1. Sex-specific associations of SNPs taken forward for replication from discovery GWAS**

| Alcohol phenotype | SNP        | Gene          | Chr | Position    | Effect allele | Other allele | Men     |       |                      | Women  |       |                      |
|-------------------|------------|---------------|-----|-------------|---------------|--------------|---------|-------|----------------------|--------|-------|----------------------|
|                   |            |               |     |             |               |              | Effect* | SE    | P value              | Effect | SE    | P value              |
| Log g/d           | rs780094   | <i>GCKR</i>   | 2   | 27,594,741  | T             | C            | −0.016  | 0.004 | $2.8 \times 10^{-4}$ | −0.014 | 0.003 | $2.0 \times 10^{-5}$ |
| Log g/d           | rs197273   | <i>TANK</i>   | 2   | 161,602,909 | A             | G            | −0.018  | 0.004 | $6.5 \times 10^{-5}$ | −0.010 | 0.003 | $2.1 \times 10^{-3}$ |
| Log g/d           | rs10950202 | <i>AUTS2</i>  | 7   | 69,568,034  | C             | G            | 0.022   | 0.006 | $5.7 \times 10^{-4}$ | 0.017  | 0.005 | $5.1 \times 10^{-4}$ |
| Log g/d           | rs11940694 | <i>KLB</i>    | 4   | 39,091,388  | A             | G            | −0.019  | 0.004 | $2.3 \times 10^{-5}$ | −0.011 | 0.003 | $8.9 \times 10^{-4}$ |
| Log g/d           | rs350721   | <i>ASB3</i>   | 2   | 52,833,931  | C             | G            | 0.023   | 0.007 | $5.7 \times 10^{-4}$ | 0.020  | 0.005 | $5.7 \times 10^{-5}$ |
| Log g/d           | rs6943555  | <i>AUTS2</i>  | 7   | 69,806,023  | A             | T            | −0.013  | 0.005 | $9.9 \times 10^{-3}$ | −0.011 | 0.004 | $3.3 \times 10^{-3}$ |
| Dichotomous       | rs12599112 | <i>CDH13</i>  | 16  | 81,276,212  | A             | C            | 0.053   | 0.091 | 0.561                | −0.063 | 0.015 | $2.4 \times 10^{-5}$ |
| Dichotomous       | rs10927848 | <i>TMEM82</i> | 1   | 15,948,493  | A             | G            | 0.027   | 0.036 | 0.452                | −0.023 | 0.008 | $2.5 \times 10^{-3}$ |

Chr, chromosome; EAF, effect allele frequency; *CDH13*, Cadherin 13; *TMEM82*, Transmembrane protein 82.

\*Effect refers to beta coefficient from linear regression for log grams per day alcohol phenotype and log(odds ratio) from logistic regression for dichotomous alcohol phenotype.

**Table S2. Dichotomous trait replication results**

| SNP        | Chr | Position (hg19) | Gene*         | Discovery <i>P</i>   | Replication <i>P</i> | Overall <i>P</i>     | Overall <i>N</i> |
|------------|-----|-----------------|---------------|----------------------|----------------------|----------------------|------------------|
| rs12599112 | 16  | 82,718,711      | <i>CDH13</i>  | $2.3 \times 10^{-8}$ | 0.895                | $5.0 \times 10^{-8}$ | 86,213           |
| rs10927848 | 1   | 16,075,906      | <i>TMEM82</i> | $2.6 \times 10^{-7}$ | 0.291                | $1.9 \times 10^{-7}$ | 103,219          |

Cohorts: the Airwave Health Monitoring Study (Airwave), the Austrian Stroke Prevention Study (ASPS), the British 1958 birth cohort (B58C), the Finnish Twin Cohort replication sample (FinnTwin\_replication), the Genetic Regulation of Arterial Pressure of Humans in the Community Study (GRAPHIC), the Generation Scotland: Scottish Family Health Study (GS:SFHS), the INGI- Carlantino study (INGI\_CARL), the INGI- Friuli Venezia Giulia study (INGI\_FVG), the INGI- Val Borbera study (INGI\_VB), the Lothian Birth Cohort 1921 (LBC1921), the Lothian Birth Cohort 1936 (LBC1936), and the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER). The most significant SNP per locus is displayed. Chr, chromosome; *CDH13*, Cadherin 13; *TMEM82*, Transmembrane protein 82.

\*Loci are named according to the closest gene based on the position of the most significant SNP.

**Table S3. Allele frequencies of the *KLB* SNP rs11940694 in different ethnic groups**

| Ethnicity          | Sample (2 <i>N</i> ) | Major allele frequency | Minor allele frequency |
|--------------------|----------------------|------------------------|------------------------|
| Admixture American | 694                  | A = 0.565              | G = 0.435              |
| African            | 1,322                | G = 0.570              | A = 0.430              |
| East Asian         | 1,008                | A = 0.541              | G = 0.459              |
| South Asian        | 978                  | A = 0.630              | G = 0.370              |
| European           | 1,006                | G = 0.612              | A = 0.388              |

**Table S4. Gene expression in peripheral blood in the Framingham Heart Study: Demographics for gene expression analysis**

| Phenotypes/covariates               | Offspring cohort (examination cycle 8: 2005–2008) | Third generation cohort (examination cycle 2: 2008–2011) |
|-------------------------------------|---|--|
| Gene expression analysis            | <i>n</i> = 2,222                                  | <i>n</i> = 3,014   |
| Female (%)                          | 1,221 (54.95)                                     | 1,603 (53.10)  |
| Age (y), mean (SD)                  | 66.41 (8.95)                                      | 46.88 (8.79)   |
| BMI (kg/m <sup>2</sup> ), mean (SD) | 28.04 (5.87)                                      | 28.31 (5.530)  |

BMI, body mass index.

**Table S5. Gene expression in peripheral blood in the Framingham Heart Study: Association of *KLB* SNP rs11940694 with gene expression**

| SNP        | Chr | Position   | Effect allele | Beta    | P value |
|------------|-----|------------|---------------|---------|---------|
| rs11940694 | 4   | 39,414,993 | A             | 0.00409 | 0.165   |

Chr, chromosome.

## Other Supporting Information Files

[SI Appendix \(PDF\)](#)

[Dataset S1 \(XLSX\)](#)

[Dataset S2 \(XLSX\)](#)