

## 1. Supplementary Tables

### Supplementary Table 1: Description of the study cohorts and resources

*Supplementary Table 1A. Descriptive statistics and alcohol consumption assessment in participating cohorts*

*Supplementary Table 1B. Genotyping and imputation of primary GWAS cohorts in the Alcohol Genome-wide Association (AlcGen) consortium*

*Supplementary Table 1C. Genotyping and imputation of primary GWAS cohorts in the Cohorts for Heart and Aging Research in Genomic Epidemiology-Plus (CHARGE+) consortium*

*Supplementary Table 1D. Continuous trait primary GWAS cohorts - summary*

*Supplementary Table 1E. Dichotomous trait primary GWAS cohorts – summary*

*Supplementary Table 1F. Characterization of replication cohorts*

*Supplementary Table 1G. Replication studies – summary*

(See separate Excel file)

### Supplementary Table 2. Primary GWAS results for SNPs with $P < 1E-04$

*Supplementary Table 2A. Discovery GWAS results ( $P < 1E-04$ ) on log g/day alcohol intake in all samples*

*Supplementary Table 2B. Discovery GWAS results ( $P < 1E-04$ ) on dichotomous alcohol intake in all samples*

(See separate Excel file)

**Supplementary Table 3. Dichotomous trait replication results**

SNP	Chr	Position (hg19)	Gene*	Discovery <i>P</i>	Replication <i>P</i>	Overall <i>P</i>	Overall N
rs12599112	16	82718711	<i>CDH13</i>	$2.3 \times 10^{-8}$	0.895	$5.0 \times 10^{-8}$	86,213
rs10927848	1	16075906	<i>TMEM82</i>	$2.6 \times 10^{-7}$	0.291	$1.9 \times 10^{-7}$	103,219

Cohorts - Airwave, ASPS, B58C, FinnTwin\_replication, GRAPHIC, GS:SFHS, INGI\_CARL,  
INGI\_FVG, INGI\_VB, LBC1921, LBC1936, PROSPER

The most significant SNP per locus is displayed in the tables.

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

**Supplementary Table 4. Gene expression in peripheral blood in the Framingham Heart Study**

***(A) Demographics for gene expression analysis in Framingham Heart study***

<b>Phenotypes/Covariates</b>	<b>Offspring Cohort</b>	<b>Third Generation Cohort</b>
	<b>(examination cycle 8: 2005-2008)</b>	<b>(examination cycle 2: 2008-2011)</b>
<i>Gene Expression Analysis</i>	n=2,222	n=3,014
Female (%)	1,221 (54.95)	1,603 (53.10)
Age (yrs), mean (SD)	66.41 (8.95)	46.88 (8.79)
BMI (kg/m <sup>2</sup> ), mean (SD)	28.04 (5.87)	28.31 (5.5.30)

BMI: Body mass index

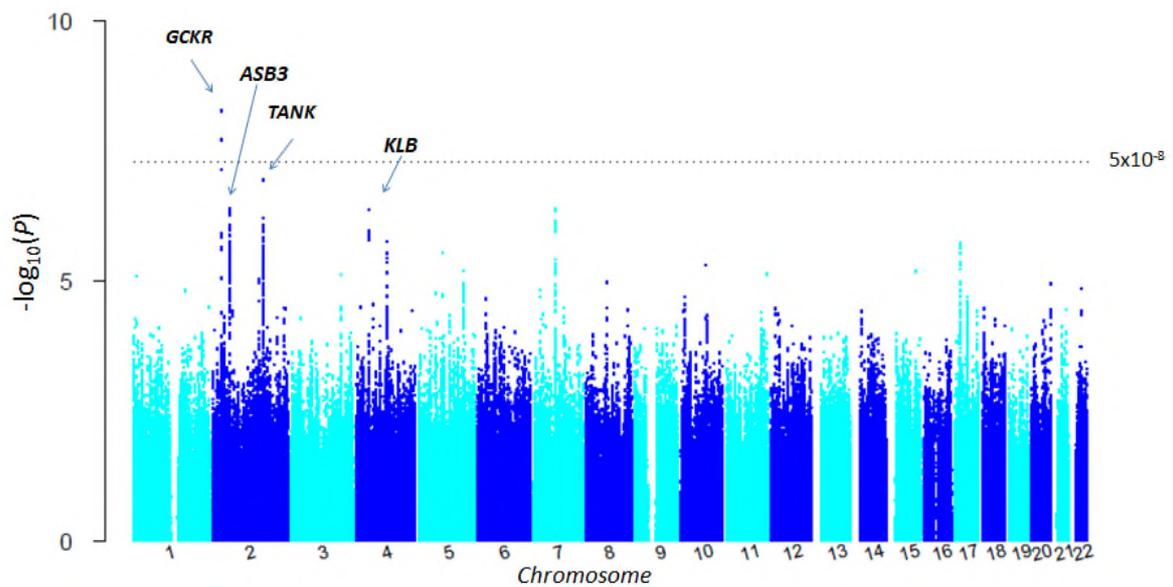
***(B) Association of KLB SNP rs11940694 with gene expression***

	<b>chr</b>	<b>position</b>	<b>Effect allele</b>	<b>Beta</b>	<b>P-value</b>
rs11940694	4	39414993	A	0.00409	0.165

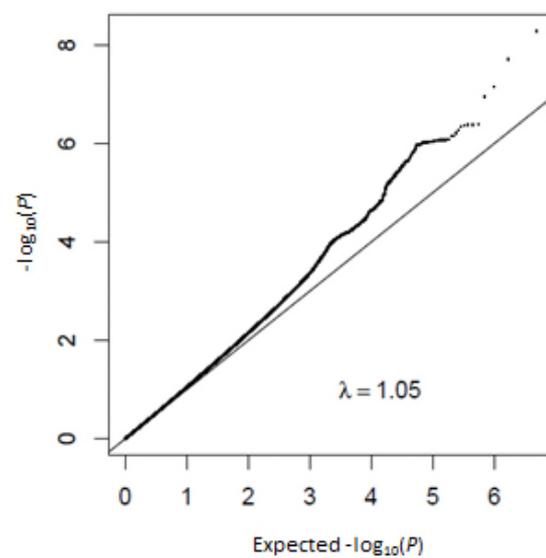
## 2. Supplementary Figures

**Supplementary Figure 1. Manhattan and QQ plots for genome-wide association analysis of log g/day alcohol in AlcGen and CHARGE+ consortia**

(A) Manhattan plot

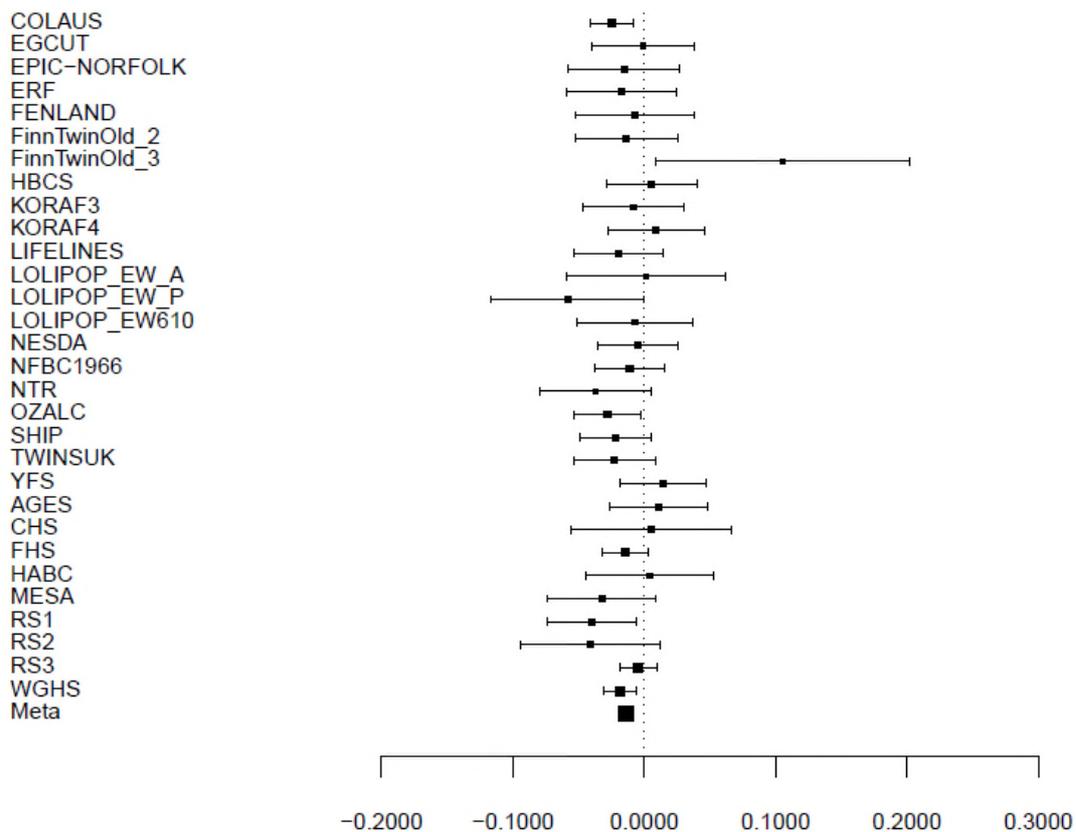


(B) QQ plot



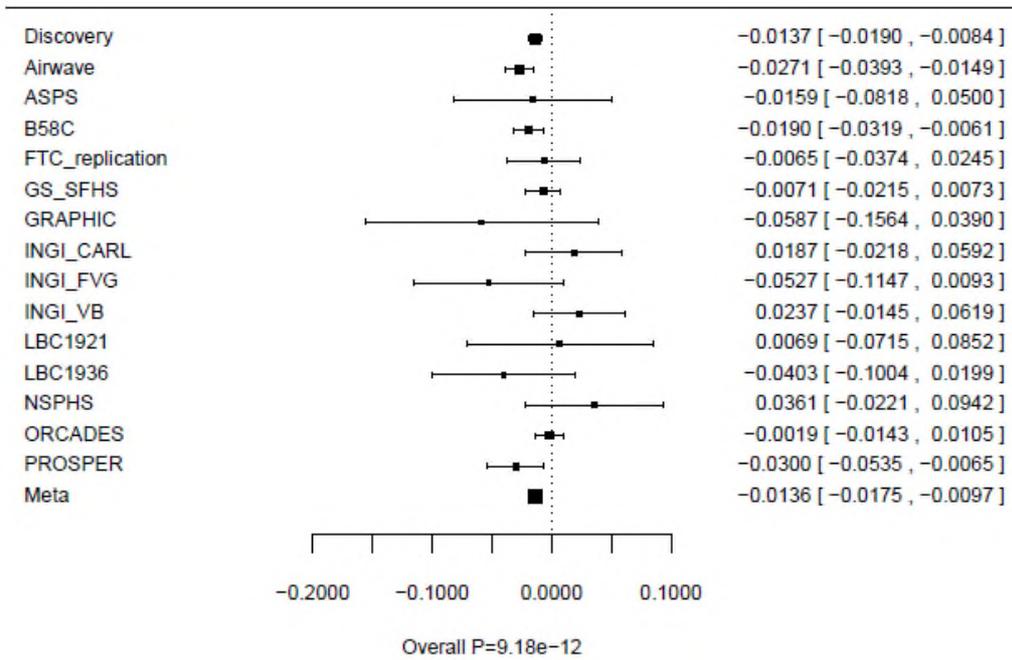
**Supplementary Figure 2. Forest plot for the association of rs11940694 in *KLB* with log g/day alcohol in the discovery GWAS and replication cohorts**

**(A) rs11940694 in *KLB* in discovery GWAS cohorts**



Discovery GWAS cohorts - AlcGen: Colaus, EGCUT, EPIC-Norfolk, ERF, Fenland, FinnTwinOld\_2, HBCS, KORA F3 and F4, Lifelines, LOLIPOP (EW A, EW P, EW610), FinnTwinOld\_3, NESDA, NFBC1966, NTR, OZALC, SHIP, TwinsUK, YFS; CHARGE+: AGES, CHS, FHS, HABC, MESA, RS1, RS2, RS2, and WGHS. In rs11940694, the coded allele was A, the non-coded allele was G. The allele frequency for A was ~ 0.42 in the entire sample. The beta/SE estimates were for A allele.

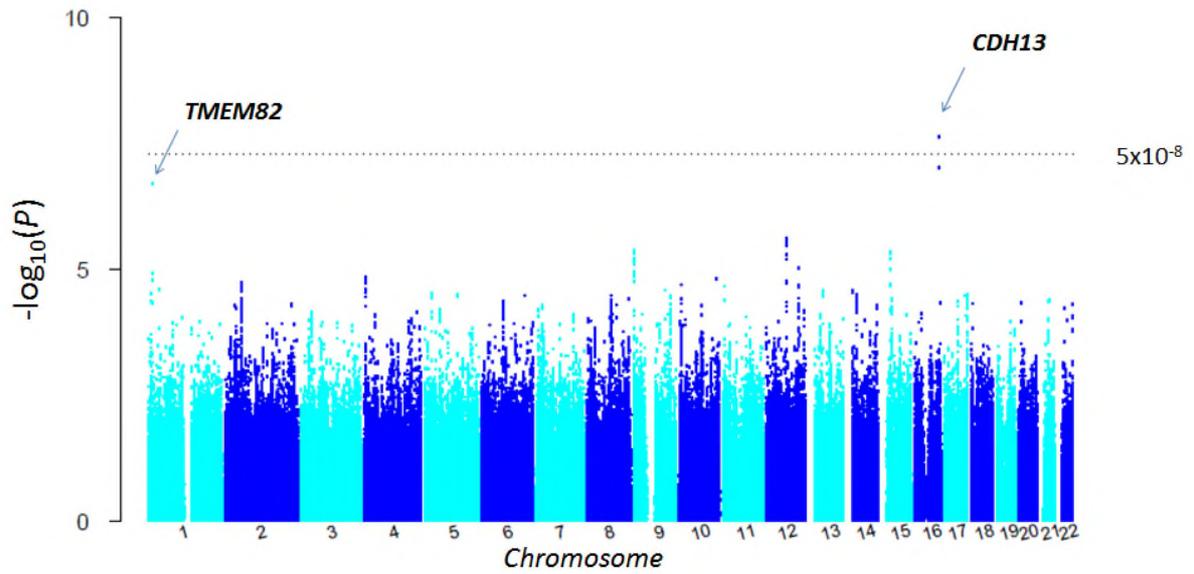
**(B) rs11940694 in KLB in discovery + replication cohorts**



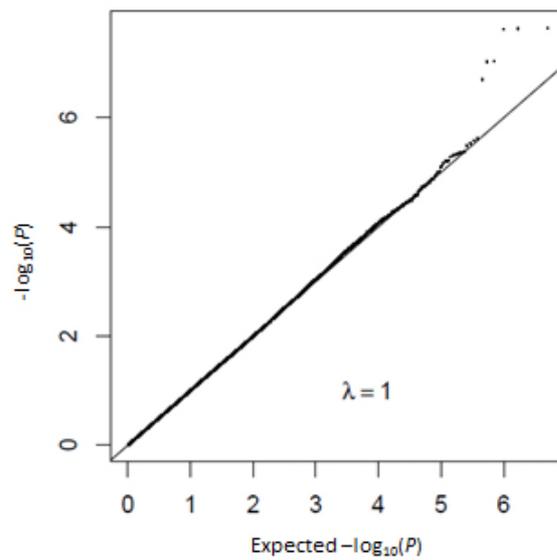
The coded allele was A, the non-coded allele was G. The beta/SE estimates were for A allele.

**Supplementary Figure 3. Manhattan and QQ plots for genome-wide association analysis of dichotomous alcohol in AlcGen and CHARGE+ consortia**

(A) Manhattan plot



(B) QQ plot



**Supplementary Figure 4. Behavior tests in brain-specific  $\beta$ -Klotho knockout mice.** Results from (A) novelty suppressed feeding, (B) elevated plus maze and (C) open field activity assays performed with control ( $Klb^{fl/fl}$ ) and brain-specific  $\beta$ -Klotho-knockout ( $Klb^{Camk2a}$ ) mice (n=15/each group). Values are the time (seconds) spent for each step of the assay.

