Supplementary Note

Sex-biased expression at *CETP* locus: The sex-biased effect at the CETP locus on TC levels (**Figure S11**) is reflected in the eQTL signals; males show both a stronger GWAS signal and a stronger eQTL signal for gene CETP in Adipose Subcutaneous tissue.

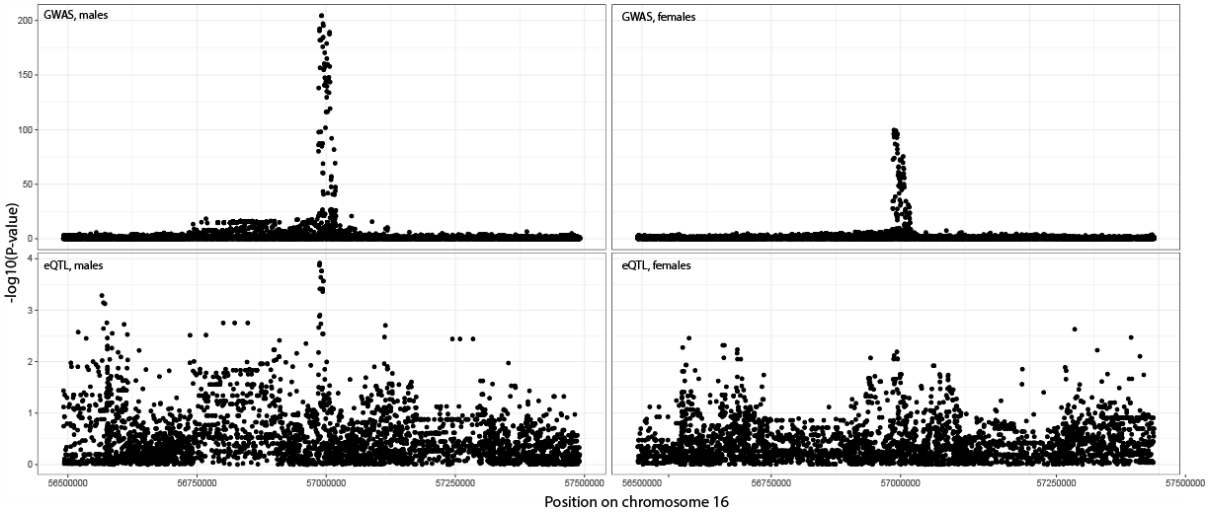

Figure S11. Sex-stratified association with TC (top) explained by a sex-stratified eQTL (bottom panels). Males (left) show a stronger GWAS and CETP eQTL signal compared to females (right). Sex-specific eQTL P-values have been computed on eQTL datasets of identical sample sizes.

Sex-biased expression at UGT2B17

The UGT2B17 locus shows a bimodal distribution of P-values. A look at this region shows the existence of a common copy number variation (CNV) in this region overlapping UGT2B17, with a frequency of the deletion allele being 33% in Europeans[1]. We hypothesize that the CNV could mediate, either fully, or partially the GWAS association at this signal.

The CNV at this region (chr4:69373811-69491113) was not genotyped or imputed either in the GWAS cohorts, or in GTEx v8. SNPs in high LD with this CNV weren't listed by GnomAD. Therefore, we studied eQTLs in GTEx v7 (a dataset with direct CNV calls) to study the regulatory effects of this CNV.

The lead CNV at this region is a significant eQTL (**Figure S12**) and shows significantly greater eQTL effect sizes in the liver in males (**Figure S13**); a decrease in copy number is associated with decreased levels of gene expression. Moreover, conditioning on this lead CNV decreases eQTL effects of the SNPs at this locus (**Figure S14**). While more data is necessary to pinpoint the true causal mechanism at this locus, these data point to the involvement of the CNV.

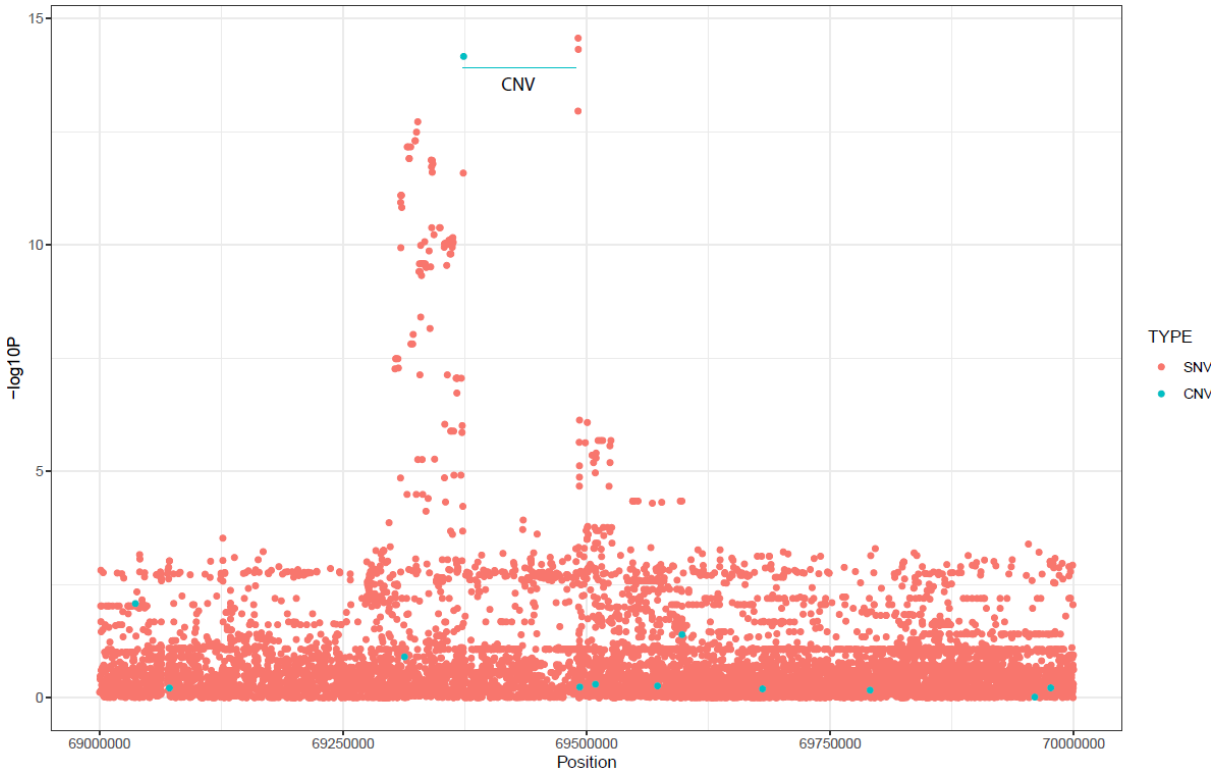

Figure S12: Manhattan plot for UGT2B17 eQTLs in the liver in GTEx v7, including both SVSs (in salmon) and CNVs (in teal). A common CNV is one of the strongest eQTL signals at this locus.

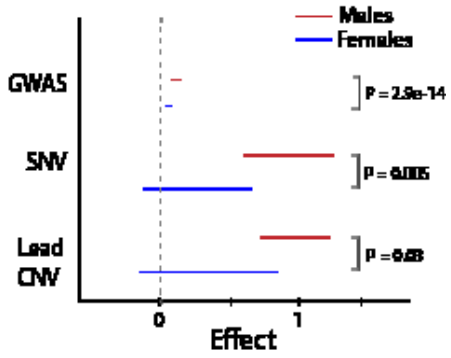

Figure S13: Effect sizes in male (red) and females (blue) at chr4: locus for TC (labelled GWAS) for lead GWAS variant. Both CNVs and the lead CNV show significantly stronger eQTL effect sizes in males.

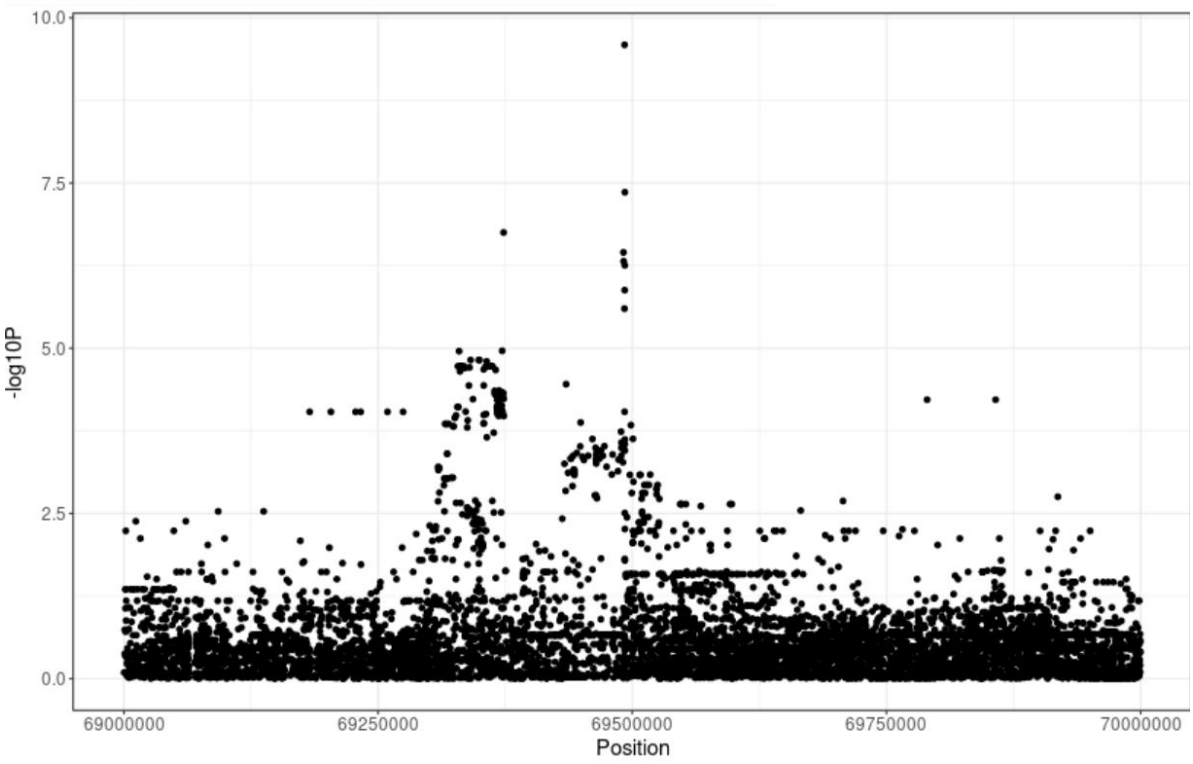

Figure S14: Conditional eQTL analysis on UGT2B17 conditioning on top CNV in GTEx shows a reduction in signal at this locus, showing at least a partial mediation effect of the CNV on SNPs in this region.

References

1. McCarroll, S.A. *et al.* Common deletion polymorphisms in the human genome. *Nat Genet* **38**, 86-92 (2006).

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Age-related diseases: Understanding Genetic and non-genetic influences - a study at the University of Regensburg

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Avon Longitudinal Study of Parents and Children (ALSPAC)

Pregnant women resident in Avon, UK with expected dates of delivery 1st April 1991 to 31st December 1992 were invited to take part in the study. The initial number of pregnancies enrolled is 14,541 (for these at least one questionnaire has been returned or a "Children in Focus" clinic had been attended by 19/07/99). Of these initial pregnancies, there was a total of 14,676 foetuses, resulting in 14,062 live births and 13,988 children who were alive at 1 year of age. When the oldest children were approximately 7 years of age, an attempt was made to bolster the initial sample with eligible cases who had failed to join the study originally. As a result, when considering variables collected from the age of seven onwards (and potentially abstracted from obstetric notes) there are data available for more than the 14,541 pregnancies mentioned above. The number of new pregnancies not in the initial sample (known as Phase I enrolment) that are currently represented on the built files and reflecting enrolment status at the age of 24 is 913 (456, 262 and 195 recruited during Phases II, III and IV respectively), resulting in an additional 913 children being enrolled. The phases of enrolment are described in more detail in the cohort profile paper and its update. The total sample size for analyses using any data collected after the age of seven is therefore 15,454 pregnancies, resulting in 15,589 foetuses. Of these 14,901 were alive at 1 year of age. Please note that the study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool" and reference the following webpage: http://www.bristol.ac.uk/alspac/researchers/our-data/. Ethical approval for the ALSPAC study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Analysis of data related to lipid traits was approved by the ALSPAC study executive. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time.

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Gene-Lifestyle Interactions and Complex Traits Involved in Elevated Disease Risk-V2

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Generation Scotland

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