# *HSD17B1* jointly confers risk of coronary artery and Alzheimer's diseases via gene expression in multiple tissues


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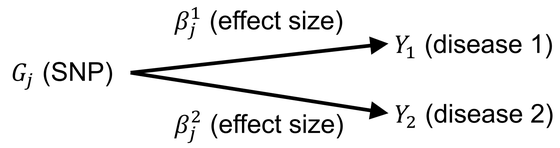
## BACKGROUND

**Vascular and Alzheimer's disease (AD) share many risk factors epidemiologically[1], but our understanding of the genetic mechanisms driving this relationship are largely unknown[2].**

We intended to detect genes associated with both coronary artery disease (CAD) and AD risk and identify the specific biological contexts in which these may genes confer risk jointly.

## METHODS

**MuGenT-Pleio detects genes associated with multiple diseases.** Consider the DAG:



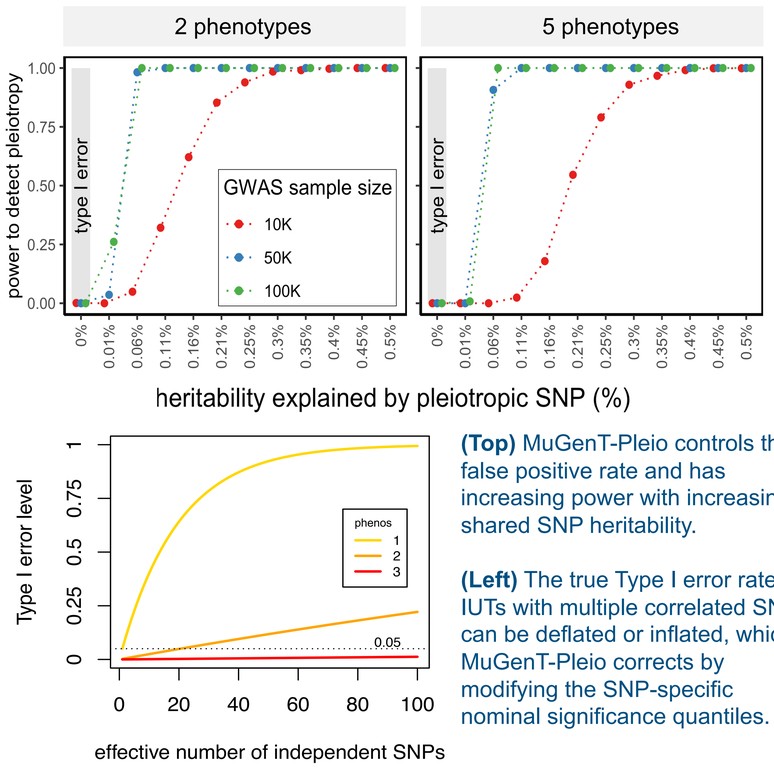

for $j = 1, \ldots, M$ correlated SNPs corresponding to a specific gene.

$$H_0\colon \cap_{j=1}^{M} \beta_{1j}\beta_{2j} = 0 \text{ vs } H_1\colon \cup_{j=1}^{M} \beta_{1j}\beta_{2j} \neq 0$$

The standard intersection-union test (IUT) applied SNP-wise can have inflated or deflated power. We correct this problem by adjusting the critical values used to test individual $H_{0j}^1\colon \beta_{1j} = 0$ and $H_{0j}^2\colon \beta_{2j} = 0$ to achieve a fixed Type I error rate $\alpha$ when applying the IUT to *k* traits and *m* effectively independent SNPs. Our corrected IUT critical value:

$$F_{\chi^2(1)}^{-1}\left\{1 - \left[1 - (1-\alpha)^{\frac{1}{2m}}\right]^{\frac{1}{k}}\right\}$$

**FIGURE 1:** Simulation and theoretical properties of MuGenT-Pleio




**(Top)** MuGenT-Pleio controls the false positive rate and has increasing power with increasing shared SNP heritability.

**(Left)** The true Type I error rate of IUTs with multiple correlated SNPs can be deflated or inflated, which MuGenT-Pleio corrects by modifying the SNP-specific nominal significance quantiles.

## RESULTS

**FIGURE 2:** *HSD17B1* is genetically correlated with multiple disease phenotypes

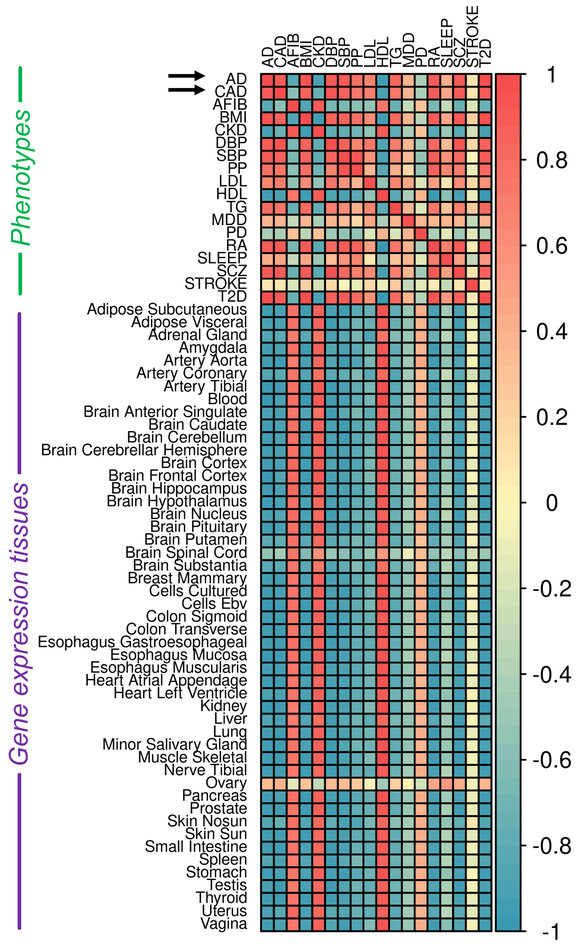



**FIGURE 3:** *HSD17B1* brain and heart eQTL signals colocalize with Alzheimer's disease signals

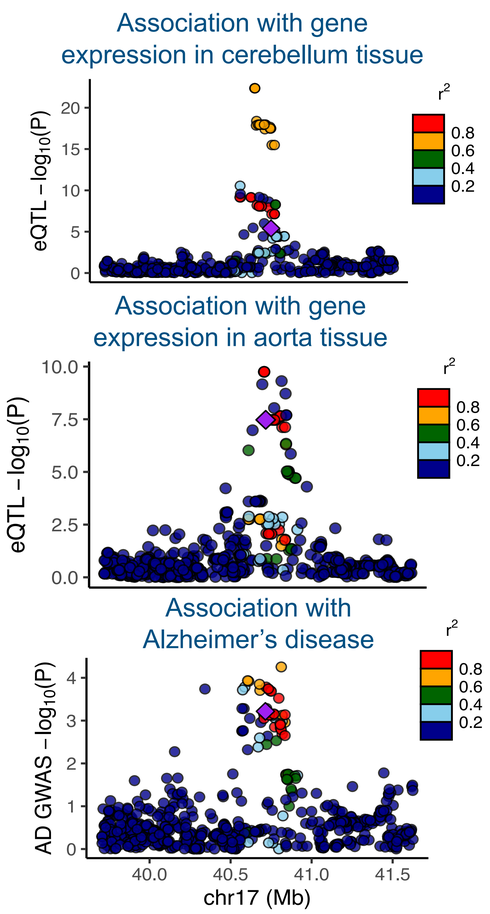



**FIGURE 4:** eQTL genetic correlations in the *HSD17B1* locus span multiple organs

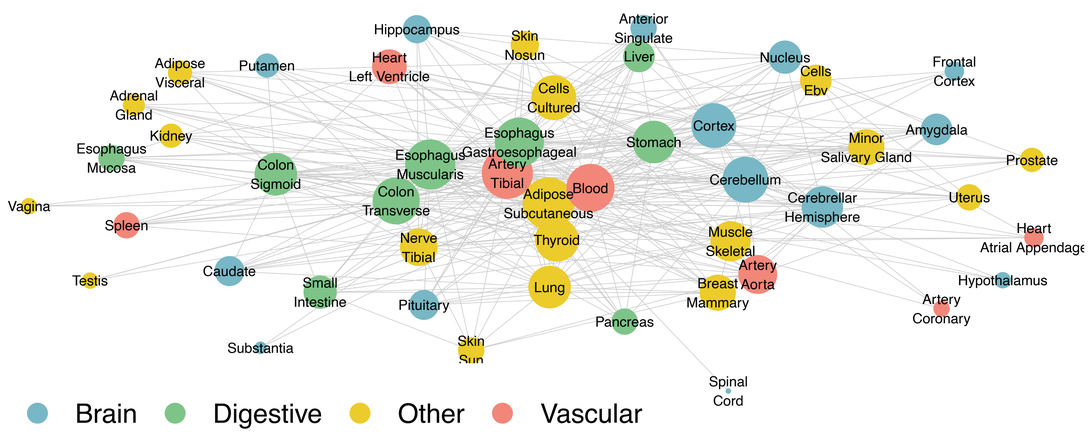
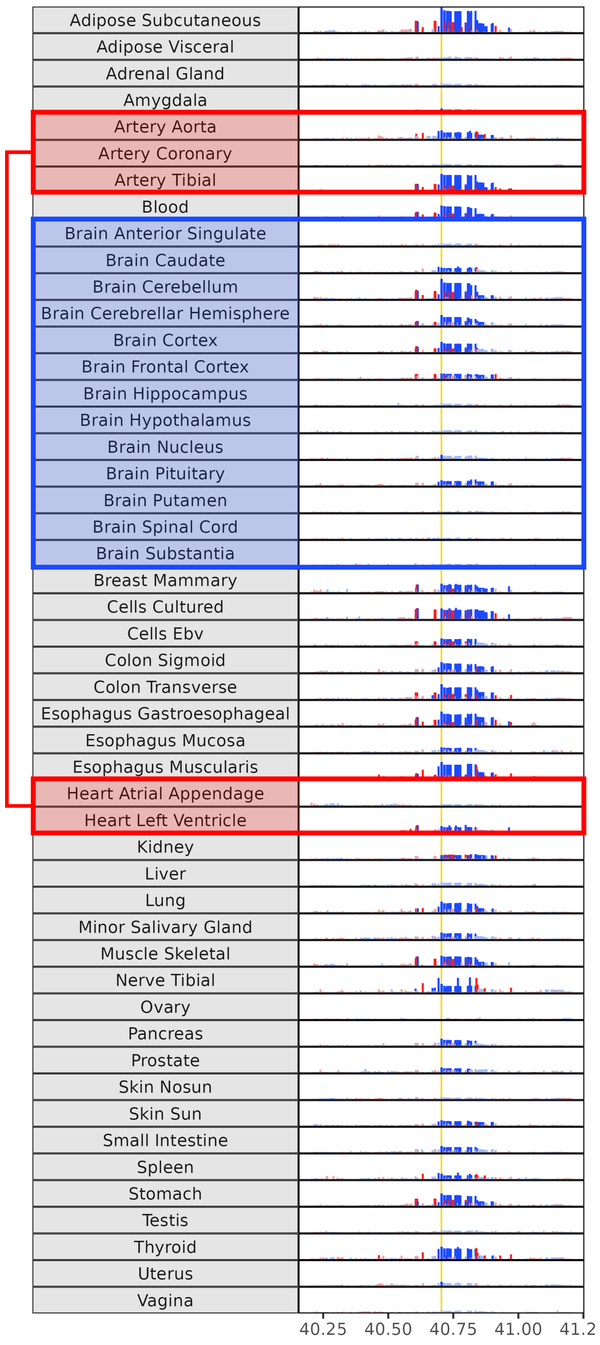



**FIGURE 5:** *HSD17B1* is expressed in multiple tissues of varying type, and SNPs explaining expression heritability are largely shared




## CONCLUSION

The *HSD17B1* gene is associated with Alzheimer's disease, coronary artery disease, and many other metabolic and vascular phenotypes. This gene is expressed in tissues spanning multiple organs with highly correlated effect sizes. Further evaluating the functional consequences of *HSD17B1* could help evaluate its viability as a gene therapy.

## ACKNOWLEDGEMENT & REFERENCES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1. [PubMed: 28886155] [CAD] and risk for cognitive impairment or dementia…
2. [PubMed: 28556832] Genetic susceptibility to cardiovascular disease and risk of dementia.


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The Alzheimer's Cell Atlas
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