HORNET identifies a complex gene network underlying Alzheimer's disease risk in diverse populations.

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Background
The *ABCA7* gene in the 19p13.3 region is highly associated with both early- and late-onset Alzheimer's disease (AD) in diverse populations [1]. In vivo models suggest that *ABCA7* is involved in the clearance of amyloid beta plaques, a hallmark feature of AD pathology [2], suggesting it has a causal role in modifying AD risk. However, the 500Kb window around *ABCA7* contains 25 other genes, making formal evaluation of its causal role challenging because of complex regulatory mechanisms. Here, we searched the 1Mb region around *ABCA7* to identify genes with direct causal effects on AD risk after adjusting for inter-relationships between expression patterns of surrounding genes.

Methods
We developed the HORNET software to estimate direct causal effects of gene expression using multivariable Mendelian Randomization (MR) and GWAS summary statistics. We applied HORNET in gene expression data of European (EUR; n=31k [3]) and African American (AA; n=757 [4]) populations separately. AD GWAS summary statistics were from Jansen et al. [5] (n=455k). A network of gene regulatory relationships in this locus was constructed by applying graphical lasso to population-specific sets of cis-eQTLs.

Results
Twenty-five genes in a 1Mb window around *ABCA7* had cis-eQTLs (P<5E-8) in blood tissue in EUR and 23 in AA. The regulatory network between gene expressions was marginally denser in AA than EUR (P=0.051). For example, each gene on average either regulates or is regulated by 10 other genes in EUR and 16 in AA. The expression of these genes in blood explains approximately 95.7% of the local heritability of AD in EUR and 73.5% in AA, suggesting well-specified causal models and the appropriate tissue.

The local genetic correlation between AD risk and *ABCA7* expression was 0.93 in EUR and 0.90 in AA and its total unmediated causal effect on AD was significant (OR_{AA}=1.33, OR_{EUR}=2.40; both P<1E-100). However, after considering neighboring genes, *ABCA7* had no direct causal effect on AD risk in EUR (P=0.24) or AA (P=1.00). Our estimated regulatory network suggests that *ABCA7* expression indirectly confers AD risk by regulating nearby genes such as *KISS1R* and *ARID3A* (both P<0.05 in EUR and AA). Genetic correlations between *ABCA7* and these two mediating genes ranged in absolute value from 0.71-0.76 in EUR and 0.48-0.96 AA, potentially suggesting strong regulatory dependencies.

Conclusions/future work
This was the first application of our HORNET software which has statistical and computational advantages over existing alternatives. We found evidence that the *ABCA7* gene only indirectly

increases Alzheimer’s disease risk via the regulation of other nearby genes. This is just a single example of the complex network of regulatory relationships between genes in this locus. We plan to validate these findings using individual-level data in the UK Biobank. The need for larger AD GWAS performed in diverse populations is emphasized.

References

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