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DISEASE GENOMICS

*Trans*itioning from association to causation with eQTLs

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In the quest to identify genetic causes of disease, attention is turning increasingly to expression quantitative trait loci (eQTLs), which associate DNA sequence variation with changes in gene expression. Most efforts to identify causal eQTLs focus on *cis*-eQTLs (which affect expression of nearby genes), largely because detecting causal *trans*-eQTLs (which affect expression of distant genes) is computationally demanding. Now, two recent reports in *The American Journal of Human Genetics* describe different approaches for identifying *trans*-eQTLs and provide insight into potential gene regulatory mechanisms underlying disease.

In the first study, Yao *et al.* performed eQTL analysis on whole blood gene expression measurements from 5,257 participants in the Framingham Heart Study (FHS) and 39,165 trait-associated SNPs identified from genome-wide association studies (GWAS) databases. Of the 23,851 eQTLs identified, 2,324 were *trans*-eQTLs and included 13 *trans*-eQTL hotspots (*trans*-eQTLs that simultaneously affect the expression of many distant target genes).

Many *trans*-eQTLs were observed to be associated with both *cis* and *trans* target genes (*cis*-eGenes and *trans*-eGenes, respectively), suggesting that *cis*-eGenes might act as master regulators of a network of associated *trans*-eGenes. Mediation analysis supported this hypothesis. Indeed, subsequent causal inference testing between *trans*-eQTLs and phenotypic data identified examples of disease phenotypes in which the effect of the causal *trans*-eQTL is likely to be mediated by a *cis*-eGene. Importantly, these causal loci were not detected by traditional GWAS approaches.

A current limitation of the approach is that it is difficult to validate results because most eQTL databases do not contain information on *trans*-eQTLs. However, its utility should increase as more *trans*-eQTL data become available.

In the second study, Brynedal *et al.* adapted their previously published cross-phenotype meta-analysis (CPMA) statistic to identify *trans*-eQTL hotspots. Rather than analysing variance in expression data, this approach uses changes in the distribution of test statistics to identify (and assign *trans*-eQTL status to) SNPs that are associated with altered expression of many transcripts.

When applied to expression data from lymphoblastoid cell lines (9,085 genes, 322 individuals) and 737,867 autosomal markers across three African HapMap populations, CPMA identified 16,484 candidate *trans*-eQTL hotspots. Subsequent pairwise comparisons between populations identified eight high-confidence *trans*-eQTL hotspots for which the target gene set and their directional change in expression was reproducible across all three cohorts. Interestingly, in contrast to the study by Yao *et al.*, no *cis*-eQTL effects were detected for any of the eight hotspots.

ENCODE chromatin immunoprecipitation followed by sequencing (ChIP–seq) data and pathway annotations supported the hypothesis that, for at least some of the *trans*-eQTL hotspots, target genes are co-regulated and are involved in similar biological processes. Furthermore, protein–protein interaction analysis indicated that some target genes encode proteins that interact directly, with some forming tissue-specific subnetworks.

A potential limitation of this CPMA-based approach is that it only detect hotspots, and not *trans*-eQTLs with single (or a small number of) targets; the significance of this limitation will depend on the relative contribution of hotspots and non-hotspots to overall heritability, which is not yet known.

As higher quality data across more tissues from larger numbers of samples become available (for example, through projects like GTEx), these two complementary approaches will become increasingly useful and *trans*-eQTLs — and hopefully the genetic causes of disease — will become easier to identify.

Dorothy Clyde

ORIGINAL ARTICLES Yao, C. *et al.* Dynamic role of trans regulation of gene expression in relation to complex traits. *Am. J. Hum. Genet.* http://dx.doi.org/10.1016/j.ajhg.2017.02.003 (2017)
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FURTHER READING Albert, F. W. & Kruglyak, L.The role of regulatory variation in complex traits and disease. *Nat. Rev. Genet.* **16**, 197–212 (2015)