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Conducting the metabolic syndrome orchestra

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Abstract

Genetic and gene expression studies have suggested an important role for *KLF14* in metabolic disease. A new study now identifies a network of genes whose expression is associated with *KLF14* variation in *trans*, providing a framework for understanding how *KLF14* influences disease risk.

Any natural population is likely to harbor many thousands of common variants influencing gene expression, just as there are common variants affecting protein sequences. Such variation can be examined globally by measuring transcript levels using microarrays or next-generation sequencing and, like other genetic traits, can be mapped using linkage or association. The loci thus identified are termed expression quantitative trait loci (eQTLs)¹. Over the past decade, eQTLs have been studied in many species and have proven particularly useful in the analysis of complex traits. For example, they have been used to model causal interactions², to prioritize candidate genes at loci identified in genome-wide association studies (GWAS)³ and to study the nature of gene-environment interactions⁴. On page 561 of this issue, Tim Spector, Mark McCarthy and colleagues⁵ report a *trans* regulatory network based on eQTL analyses that connects multiple loci for metabolic syndrome, a condition characterized by a clustering of metabolic disturbances associated with cardiovascular disease and diabetes.

Trans regulatory network

The physiological disturbances of metabolic syndrome include abdominal obesity, insulin resistance, elevated low density lipoprotein (LDL), elevated triglycerides, reduced high density lipoproteins (HDL), hypertension and type 2 diabetes (T2D). Although environmental factors, particularly caloric excess and physical inactivity, play a major role in metabolic syndrome, the traits are highly heritable⁶. GWAS have identified numerous loci influencing these traits individually, but to date, no loci have been found that affect the entire spectrum of metabolic syndrome traits.

Variants near *KLF14*, which encodes the transcription factor Krüppel-like Factor 14, have previously been associated with T2D and HDL cholesterol levels in large GWAS analyses, and the same SNPs were found to be associated with *KLF14* expression in adipose tissue, indicating the presence of a *cis* eQTL (Fig. 1a)^{7,8}. Because *KLF14* is a transcription factor, Small *et al.*⁵ reasoned that the *cis* eQTL near *KLF14* may influence the expression of

KLF14 target genes in *trans* (Fig. 1a). They examined this possibility using subcutaneous adipose biopsies from 776 female twins of European ancestry as well as a smaller replication sample. In support of their hypothesis, they identified ten genes that had genome-wide significant *trans* association with the same SNP that regulates *KLF14* expression in *cis* (Fig. 1b). Interestingly, expression levels of the ten genes were associated with a variety of metabolic syndrome traits, including obesity, dyslipidemias and measures of insulin resistance, supporting a *trans* causal link between *KLF14* expression and these ten genes. When the authors relaxed the significance threshold for their *trans* eQTL analysis, they defined a set of 46 *trans*-associated genes and found that this larger gene set was enriched for KLF transcription factor binding sites. Moreover, using large-scale GWAS data, they showed that five of the ten genes had nearby SNPs that were associated with metabolic syndrome traits at genome-wide significance (Fig. 1b). Thus, it appears that *KLF14* influences the expression of multiple genes that, in turn, mediate the effects of *KLF14* on metabolic disease. It is also noteworthy that the traits associated with the regulatory network described by Small *et al.*⁵ include all the key features of metabolic syndrome.

One of the *trans*-regulated genes, *SLC7A10*, encodes a protein that mediates the transport of neutral amino acids⁹. Notably, its expression is strongly correlated with several metabolic phenotypes. In addition, two independent SNPs in the *SLC7A10* locus are significantly associated with HDL and body mass index (BMI)-adjusted waist-hip ratio. These associations suggest an important role for *SLC7A10* in influencing a range of metabolic traits.

Exploring KLF14 function

KLF proteins are zinc-finger-containing transcription factors that play important roles in health and disease¹⁰. Seventeen KLF family members have been identified to date, but relatively little is known about KLF14. KLF14 is unusual in that it is imprinted and expressed only from the maternal allele, suggesting a possible role in growth and development. It also appears to be undergoing accelerated evolution in the human lineage, consistent with positive selection. KLF14 is highly expressed in neurons, and some of its effects may be related to metabolic control in the brain in addition to adipose tissue¹¹.

The biological function and detailed role of KLF14 in metabolic syndrome and associated clinical pathologies will need to be further elucidated. One initial challenge will be to identify the mechanism by which variants near *KLF14* affect the expression of this gene in *cis*. Moreover, the effect of *KLF14* expression on the *trans*-associated genes will have to be further examined, perhaps using adipocyte cell culture systems. Genome-wide mapping of KLF14 binding sites should help identify genes regulated by this transcription factor. Klf14 knockout mice may also be useful in understanding the role of this gene in clinical phenotypes associated with metabolic syndrome.

The study by Small *et al.*⁵ leveraged the power of integrative genomics to provide fascinating insights into the role of KLF14 in regulating metabolic syndrome traits. Looking ahead, next generation RNA sequencing approaches are likely to be especially informative in studies such as this, as they could provide information about allele-specific expression in addition to total expression levels¹². One can also think about integrating transcript levels with data from other high-throughput technologies such as chromatin immunoprecipitation sequencing (ChIP-Seq), proteomics and metabolomics. These types of integrative studies are promising avenues for exploring the mechanistic basis of complex trait associations and their underlying physiology.

References

1. Montgomery SB, Dermitzakis ET. *Nat Rev Genet.* 2011; 12:277–282.
2. Schadt EE, et al. *Nat Genet.* 2005; 37:710–717.
3. Musunuru K, et al. *Nature.* 2010; 466:714–719.
4. Romanoski CE, et al. *Am J Hum Genet.* 2010; 86:399–410.
5. Small KS, et al. *Nat Genet.* 2011; 43:561–564.
6. Lusi AJ, Attie AD, Reue K. *Nat Rev Genet.* 2008; 9:819–830. [PubMed: 18852695]
7. Teslovich TM, et al. *Nature.* 2010; 466:707–713.
8. Voight BF, et al. *Nat Genet.* 2010; 42:579–589.
9. Nakauchi J, et al. *Neurosci Lett.* 2000; 287:231–235. [PubMed: 10863037]
10. McConnell BB, Yang VW. *Physiol Rev.* 2010; 90:1337–1381.
11. Parker-Katirae L, et al. *PLoS Genet.* 2007; 3:e65.
12. Gregg C, et al. *Science.* 2010; 329:643–648.

Figure 1.

Identification of a *KLF14*-associated *trans* regulatory network. (a) Models depicting *cis* and *trans* eQTL effects. (b) Regulatory variants near *KLF14* act in *cis* to influence *KLF14* expression in adipose tissue. *KLF14*, in turn, acts in *trans* to regulate the expression of a network of genes associated with metabolic traits (shown in parentheses). Underlined traits are those showing genome-wide significant associations with local SNPs at the corresponding *trans*-regulated genes. Non-underlined traits are those associated with expression of the corresponding *trans*-regulated genes. BMI, body mass index; GLU, glucose levels; HDL, high density lipoprotein levels; HOMA, index of insulin sensitivity; INS, insulin levels; LDL, low density lipoprotein levels; TG, triglyceride levels; T2D, type 2 diabetes; WHR, waist-hip ratio.