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Identification of an imprinted master *trans*-regulator at the *KLF14* locus related to multiple metabolic phenotypes

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Abstract

Genome-wide association studies have identified many genetic variants associated with complex traits. However, at only a minority of loci have the molecular mechanisms mediating these associations been characterized. In parallel, whilst *cis*-regulatory patterns of gene expression have been extensively explored, the identification of *trans*-regulatory effects in humans has attracted less attention. We demonstrate that the Type 2 diabetes and HDL-cholesterol associated *cis*-acting eQTL of the maternally-expressed transcription factor *KLF14* acts as a master *trans*-regulator of adipose gene expression. Expression levels of genes regulated by this *trans*-eQTL are highly-correlated with concurrently-measured metabolic traits, and a subset of the *trans*-genes harbor variants directly-associated with metabolic phenotypes. This *trans*-eQTL network provides a mechanistic understanding of the effect of the *KLF14* locus on metabolic disease risk, providing a potential model for other complex traits.

Variants near the maternally-expressed transcription factor *KLF14* (*Kruppel-like factor 14*) are robustly associated with both Type 2 Diabetes (T2D) and HDL-cholesterol levels in large-scale genome-wide association studies (GWAS)^{1,2}. These studies have implicated a group of highly-correlated SNPs including rs4731702 and rs972283 ~14kb upstream of *KLF14*^{1,2}. *KLF14* is the regional gene most likely to be mediating these effects since the same SNPs show adipose-specific, maternally-restricted *cis*-regulatory associations with

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AUTHOR CONTRIBUTIONS KSS, ÅKH, EG GT and ACN analyzed data. GT, AK, SYS, HBR NS and CML contributed reagents/materials/analysis tools. UT, KRA, KS, ETD, PD, MIM, and TDS conceived and designed the experiments. KSS and MIM wrote the paper with contributions from ÅKH and EG. All authors read and approved the manuscript before submission.

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KLF14 expression levels, a pattern which mirrors the parent-of-origin effects for T2D-susceptibility at this locus³.

Since transcription factors such as *KLF14* typically modulate expression of other genes in *trans*, we tested for association between rs4731702 and expression levels of ~24K probes (16,663 genes) on the Illumina Human HT12 array in subcutaneous adipose tissue biopsies from a cohort of 776 healthy female twins⁴. The enrichment of rs4731702 *trans*-associations for low p-values (Figure 1, Supplemental Figure 1) suggests that *KLF14* is a master-regulator of gene expression in adipose tissue. The pattern of *trans*-associations at *KLF14* mirrors the GWAS associations (Fig 2, Suppl Fig 2), and conditioning the *trans* associations on rs4731702 abolishes the signal at all other SNPs. These findings indicate that the same set of SNPs (and presumably the same causal variant) underlies the *cis*-, *trans*- and metabolic trait-associations at this locus.

We focused on the ten genes (*TPMT*, *ARSD*, *SLC7A10*, *C8orf82*, *APH1B*, *PRMT2*, *NINJ2*, *KLF13*, *GNB1*, *MYL5*) showing genome-wide significant *trans* (GWST) associations ($p < 5 \times 10^{-8}$) driven by rs4731702. First, we sought replication of the *trans*-associations in an independent set of adipose tissue samples (deCODE Genetics; N= 589)⁵. As previously reported³, the deCODE data revealed a strong maternally-specific *cis*-association between rs4731702 and *KLF14* expression in adipose tissue ($p = 1 \times 10^{-19}$) (Table 1). This *cis* effect was not detected in the MuTHER data due to apparent problems with the *KLF14* probe represented on the Illumina HT12 array used for MuTHER (See methods). Seven of the GWST genes from the MuTHER analysis had a directionally-consistent *trans*-association with p-value <0.05 in the deCODE replication set (Table 1), and we were able to show parent-of-origin effects for the *trans*-associations consistent with the maternally-specific *cis*-effects for *KLF14* expression and T2D-risk³. In the deCODE replication data maternally inherited *trans*-associations were markedly more significant than general analyses and no paternally-inherited *trans*-associations were seen (Table 1).

The *trans*-effects explain a substantial portion of the genetically-regulated variation in GWST expression levels. Our heritability estimates of GWST-gene expression levels ranged from 0.13 to 0.79: the rs4731702 *trans*-eQTL explained between 3-7.8% of the variance in expression, corresponding to 6-25% of the heritability (Table 2). Expression levels of the ten GWST genes are moderately-correlated in adipose tissue, with a mean |pairwise rho| of 0.29 (stdev = 0.15). *SLC7A10* is the only GWST gene down-regulated by the T2D-risk allele (and hence the only transcript showing anti-correlated expression levels within the GWST genes). This pattern is consistent with the known ability of the *KLF* family of transcription factors to act as both transcription activators and repressors⁶.

Further support for the hypothesis that the *trans*-effects are mediated by *KLF14* expression comes from analysis of transcription-factor binding-sites in *trans*-associated genes using PSCAN⁷ with the JASPAR database⁸. *KLF14* itself is not represented in JASPAR, but other *KLF* family members have closely related binding sites (and in some cases have been shown to compete for the same binding site)⁹, and *KLF4* (the only *KLF* family member in the JASPAR database) and *KLF14* share highly similar DNA binding C-terminal regions¹⁰. Though we found no evidence for enrichment after correction for multiple-testing when examining the 10 GWST genes alone, inclusion of a larger number of *trans*-associated genes (46 with $\text{trans } p < 10^{-4}$ or 121 with $\text{trans } p < 10^{-3}$) revealed strong evidence of enrichment for *KLF4* binding sites. *KLF4* was the most over-represented binding site in the former set (Bonferroni-corrected $p = 0.01$) and the second most over-represented site in the latter set (Bonferroni corrected $p = 1.3 \times 10^{-7}$) after *EGR1*. These data indicate that one feature of the transcripts showing *trans*-associations with the *KLF14* SNPs is enrichment for KLF binding sites.

Having demonstrated that the same set of SNPs influences *cis*-expression of *KLF14*, *trans*-expression of members of the GWST-gene network, and a variety of metabolic traits including T2D and HDL-cholesterol, we sought to clarify the causal connections between these effects, and in particular to establish whether or not the *trans*-effects were likely to be mediating the metabolic associations at *KLF14*. First, we examined the correlations between *trans*-gene expression and concurrently-measured metabolic phenotypes. At an array-wide Bonferroni threshold of $p < 1.9 \times 10^{-6}$, expression levels of six of the ten GWST genes are associated with BMI and HDL-cholesterol, five each with triglycerides and fasting insulin levels, four with HOMA-IR (an index of insulin sensitivity) and two each with fasting glucose and adiponectin (Table 3). Compared to all genes on the array, this represents an enrichment for expression/metabolic phenotype associations, with significance ranging from $p = 0.001$ to $p = 3.3 \times 10^{-5}$. The strength of these associations is consistent with a causal link between *trans* gene expression and metabolic phenotypes, and provides clues to the biological processes in which these genes may participate.

Next we examined large-scale association data made available by trait-specific GWAS meta-analysis consortia, focusing on SNPs in the 250kb surrounding each GWST gene. The rs4731702 T2D risk-allele is associated with higher fasting insulin¹, indicating that the primary effect on diabetes-risk is mediated by decreased peripheral insulin sensitivity. Accordingly, we focused on a set of insulin-resistance related traits including fasting insulin¹¹, fasting glucose¹¹, HOMA-IR¹¹, T2D¹, lipids (HDL, LDL, triglycerides)², body fat distribution (BMI-adjusted WHR)¹² and BMI¹³. In GWAS datasets ranging in size from 22,044-123,865 individuals, we found eight associations in five genes at a study-wide significance threshold of 1.03×10^{-4} (Table 4). (See methods for threshold determination). For example, SNPs near *APH1B* are associated with HDL (rs2729787; $p = 9.8 \times 10^{-9}$) and triglycerides (rs17184382; $p = 1.5 \times 10^{-5}$), and SNPs near *KLF13* with BMI-adjusted WHR (rs4779526; $p = 1.8 \times 10^{-5}$) and LDL (rs8034505; $p = 5.8 \times 10^{-5}$). In addition, SNPs in *MSRA* (expression levels of which marginally failed to reach genome-wide significance: *trans*-association $p = 5.1 \times 10^{-8}$) have been previously associated with waist circumference¹⁰, and are here associated with triglycerides (rs615171; $p = 7.5 \times 10^{-7}$). This pattern of association signals reveals that variation involving GWST-genes has the potential to impact on insulin-resistance related traits, and thereby supports the notion that a subset of these genes are directly implicated in mediating the effects of *KLF14* variation on disease-susceptibility.

One of the more interesting transcripts revealed by these analyses is *SLC7A10*, a member of the solute carrier family that mediates transport of neutral amino acids. Adipose expression of *SLC7A10* is highly heritable ($h^2 = 0.79$) and is down-regulated by the *KLF14* T2D risk-allele. *SLC7A10* expression is strongly-associated with diverse metabolic phenotypes; negatively correlated with BMI ($p = 3 \times 10^{-48}$), insulin ($p = 1.1 \times 10^{-51}$), HOMA-IR ($p = 7 \times 10^{-48}$), glucose ($p = 6 \times 10^{-7}$), and triglycerides ($p = 1 \times 10^{-34}$) and positively correlated with HDL ($p = 7 \times 10^{-30}$) and adiponectin ($p = 1 \times 10^{-12}$) levels (Table 3). The *SLC7A10* locus contains independent ($r^2 = 0.03$) SNPs associated with HDL (rs8182584; $p = 3.2 \times 10^{-7}$), and BMI-adjusted WHR (rs7251505; $p = 3.2 \times 10^{-6}$). The former SNP (rs8182584) is weakly associated to insulin ($p = 0.002$) and BMI ($p = 1.4 \times 10^{-3}$) suggesting that this gene has a wide-ranging role in metabolism.

Our data provide convincing evidence of a *bona fide* adipose *trans*-eQTL and implicate this *trans*-expression network in the link between *KLF14* variation and risk of metabolic disease. The *trans*-regulation uncovers novel biological links between previously-identified genome-wide significant associations at *KLF14* (HDL; T2D), *APH1B* (HDL) and *MRSR* (Waist circumference) and to additional signals where metabolic trait associations have not yet been established to genome-wide significance (*SLC7A10*, *KLF13*, *C8orf82*, *NINJ2*). These links provide a framework for hypothesis-directed investigation of genetic interactions among

GWAS loci and provide an example of the power of ‘integrative genomics’ to leverage ‘omics data from multiple sources to discover new biological and functional insights.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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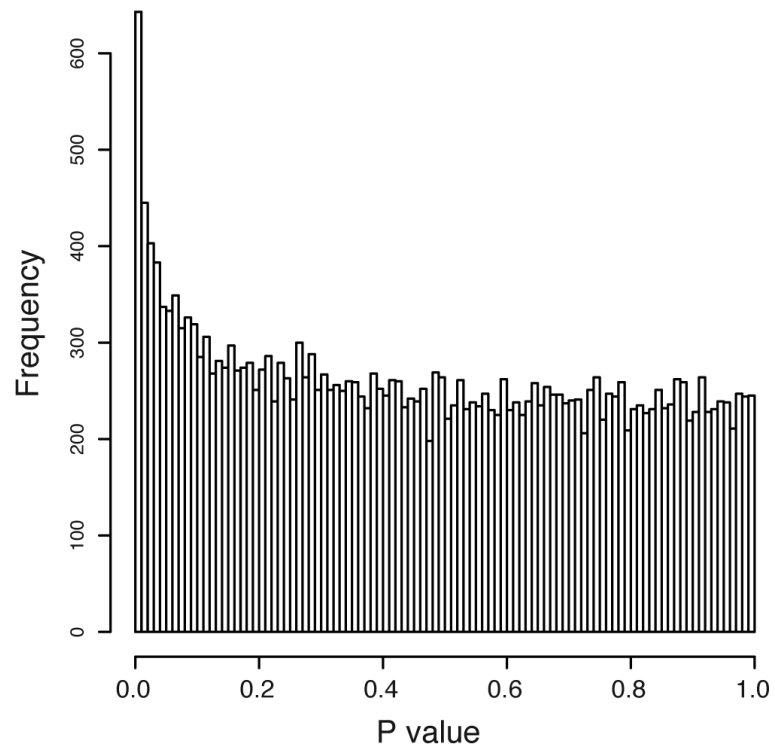


Figure 1. *KLF14* is a master regulator of gene expression in adipose tissue
p-value distribution of association between the *KLF14* cis-eQTL rs4731702 and expression levels of ~24K probes in adipose tissue.

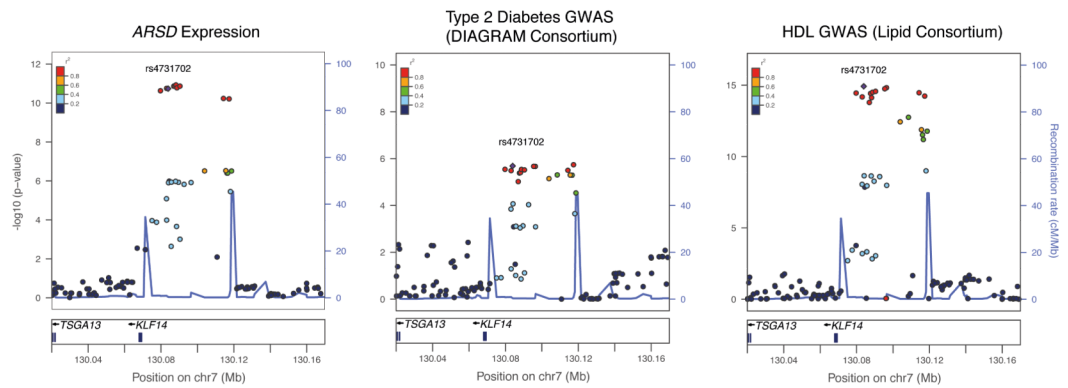


Figure 2. Regional signal plots of the *KLF14* locus

Left: signal plot of a representative *trans*-regulated gene in the MuTHER samples (N = 776). Middle: signal plot for the Type 2 Diabetes GWA meta-analysis performed by the DIAGRAM consortium¹ (stage 1 data only, effective sample size 22,044; rs972283 reached genome-wide significance after further replication). Right: signal plot for the HDL-cholesterol GWA meta-analysis performed by the Lipid Consortium (N = 99,900)². Signal plots of all 10 genome-wide significant *trans*-regulated genes are included in Supplementary Figure 2

Genome-wide significant ($p < 5 \times 10^{-8}$) associations of gene expression levels with rs4731702 at 130,083,924 (build 36) on chromosome 7. The effect allele is the Type 2 Diabetes risk allele C, which has a frequency of 55% in the HapMap CEU population.

Table 1

Gene	Chr	MuTHER Data		Decode All		Decode Maternal		Decode Paternal		Combined MuTHER + Decode Maternal		
		Effect (se)	Pvalue	Effect (se)	Pvalue	Effect (se)	Pvalue	Effect (se)	Pvalue	Zscore	Pvalue	Direction
<i>APH1B</i>	15	0.08 (0.013)	6.2E-10	0.11 (0.059)	0.08	0.17 (0.085)	0.07 (0.083)	0.07	0.44	6.2	5.5E-10	++
<i>ARSD</i>	X	0.08 (0.012)	0.24 (0.059)	9.4E-12	2.2E-04	0.51 (0.083)	2.6E-08	-0.004 (0.083)	0.96	8.7	2.6E-18	++
<i>C8orf82</i>	8	0.09 (0.014)	2.4E-10	0.28 (0.058)	8.9E-06	0.69 (0.080)	2.1E-14	-0.09 (0.082)	0.28	9.4	4.8E-21	++
<i>GNB1</i>	1	0.05 (0.009)	2.0E-08	0.23 (0.059)	1.8E-04	0.42 (0.085)	1.6E-06	0.06 (0.084)	0.51	7.3	3.0E-13	++
<i>KLF13</i>	15	0.10 (0.017)	1.1E-08	-0.01 (0.060)	0.94	0.01 (0.086)	0.89	-0.02 (0.084)	0.80	4.9	8.5E-07	++
<i>MYL5</i>	4	0.09 (0.017)	2.3E-08	0.20 (0.059)	1.3E-03	0.45 (0.083)	1.3E-07	-0.04 (0.083)	0.60	7.5	5.0E-14	++
<i>NIN2</i>	12	0.08 (0.013)	4.3E-09	0.14 (0.060)	0.03	0.24 (0.087)	0.01	0.05 (0.085)	0.59	6.3	2.2E-10	++
<i>PRMT2</i>	21	0.06 (0.010)	3.6E-09	0.18 (0.060)	0.01	0.27 (0.087)	6.7E-03	0.09 (0.085)	0.33	6.4	1.2E-10	++
<i>SLC7A10</i>	19	-0.27 (0.042)	1.4E-10	-0.21 (0.057)	7.4E-04	-0.31 (0.082)	3.3E-04	-0.11 (0.081)	0.18	-7.3	2.0E-13	--
<i>TPMT</i>	6	0.10 (0.013)	8.0E-15	-0.04 (0.060)	0.49	-0.03 (0.087)	0.78	-0.06 (0.084)	0.49	6.4	1.1E-10	+-

Table 2

Heritability and trans-eQTL variance of GWST gene expression

Probe ID	Gene	CHR	Transcription start site (b36)	%variance explained in <i>trans</i>	h^2	% h^2 explained in <i>trans</i>
ILMN_1767816	<i>APH1B</i>	15	61356801	3.1%	0.13	23.2%
ILMN_1684873	<i>ARSD</i>	X	2832010	6.6%	0.52	12.6%
ILMN_1693862	<i>C8orf82</i>	8	145722410	6.9%	0.27	25.4%
ILMN_1760320	<i>GNB1</i>	1	1706588	4.1%	0.19	21.3%
ILMN_1679929	<i>KLF13</i>	15	29406374	4.3%	0.70	6.2%
ILMN_1746948	<i>MYL5</i>	4	661710	4.0%	0.40	10.0%
ILMN_1731745	<i>NIN2</i>	12	543722	4.7%	0.48	9.8%
ILMN_1675038	<i>PRMT2</i>	21	46879954	4.9%	0.55	8.9%
ILMN_1681087	<i>SLC7A10</i>	19	38391409	5.4%	0.79	6.8%
ILMN_1740185	<i>TPMT</i>	6	18236523	7.8%	0.48	16.4%

Table 3

Association between expression of GWST genes and concurrently measured metabolic phenotypes. Values in each cell represent p value and (beta value).

Gene	Adiponectin	HDL	LDL	Triglycerides	BMI	Fasting Insulin	Fasting Glucose	HOMA-IR
<i>APH1B</i>	7.7E-07 (-0.02)	1.9E-08 (-0.11)	0.01 (0.02)	5.2E-17 (0.13)	5.2E-15 (0.01)	6.7E-18 (0.002)	0.001 (0.05)	1.2E-12 (0.05)
<i>AKSD</i>	0.02 (-0.008)	6.8E-09 (-0.10)	0.02 (0.02)	3.6E-11 (0.09)	5.3E-11 (0.01)	4.3E-16 (0.002)	4.2E-10 (0.07)	2.1E-11 (0.04)
<i>C8orf82</i>	2.8E-05 (0.02)	4.4E-08 (0.11)	0.008 (-0.03)	4.1E-05 (-0.07)	2.4E-14 (-0.01)	6.0E-05 (-0.001)	0.52 (-0.009)	0.0003 (-0.02)
<i>GNBI</i>	0.004 (-0.008)	6.1E-10 (-0.08)	0.03 (0.01)	2.1E-12 (0.08)	2.9E-21 (0.01)	8.4E-08 (0.001)	0.00053 (0.03)	9.8E-06 (0.02)
<i>KLF13</i>	0.17 (0.005)	0.11 (-0.04)	0.86 (-0.002)	0.33 (0.02)	0.93 (0)	0.87 (0)	0.02 (0.04)	0.48 (-0.0002)
<i>MYL5</i>	0.00075 (0.02)	0.00053 (0.10)	0.19 (-0.02)	0.8 (-0.005)	8.4E-05 (-0.009)	0.007 (-0.001)	0.47 (-0.01)	0.001 (-0.02)
<i>NINJ2</i>	0.85 (-0.002)	0.03 (-0.04)	0.03 (0.02)	0.00012 (0.06)	0.003 (0.005)	0.0006 (0.001)	0.51 (0.009)	0.05 (0.02)
<i>PRMT2</i>	0.04 (0.005)	0.06 (0.03)	0.56 (-0.004)	0.21 (-0.015)	1.1E-05 (-0.006)	0.008 (-0.0004)	0.3 (-0.01)	0.002 (-0.01)
<i>SLC7A10</i>	1.6E-14 (0.07)	7.8E-30 (0.65)	2.7E-05 (-0.12)	1.7E-34 (-0.55)	3.6E-48 (-0.08)	1.2E-51 (-0.01)	6.7E-07 (-0.21)	5.3E-45 (-0.27)
<i>TPMT</i>	0.0003 (-0.01)	2.3E-09 (-0.11)	0.01 (0.023)	4.9E-16 (0.12)	7.5E-24 (0.02)	7.3E-21 (0.002)	0.00057 (0.05)	6.7E-15 (0.06)

GWA meta-analysis signals ($p < 1.03 \times 10^{-4}$) within 250KB of genome-wide significant *trans* genes. This table also includes the results for MSRA for which the *trans* association marginally failed to reach genome-wide significance ($p = 5.1 \times 10^{-8}$).

Table 4

Gene	Trait	SNP	Effect Allele	Zscore	Pvalue
<i>APH1B</i>	HDL	rs2729787	T	5.73	9.81E-09
<i>APH1B</i>	Triglycerides	rs17184382	A	4.32	1.58E-05
<i>C8orf82</i>	Type 2 Diabetes	rs2294120	A	1.14 (Odds ratio)	8.43E-05
<i>NINJ2</i>	LDL	rs2302408	T	3.91	9.06E-05
<i>SLC7A10</i>	HDL	rs8182584	T	-5.11	3.19E-07
<i>SLC7A10</i>	Waist-Hip Ratio	rs7251505	A	-4.85	3.21E-06
<i>KLF13</i>	LDL	rs8034505	A	4.02	5.85E-05
<i>KLF13</i>	Waist-Hip Ratio	rs4779526	A	4.50	1.79E-05
<i>MSRA</i>	Triglycerides	rs615171	T	-4.95	7.50E-07
<i>MSRA</i>	Waist Circumference	rs7826222	G	5.75	8.89E-09