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The Metabolic Syndrome and *DYRK1B*

TO THE EDITOR

Keramati et al. (May 15 issue)[1] found that the gain-of-function *DYRK1B* variants R102C and H90P were associated with the metabolic syndrome. These findings probably reveal one end of the phenotypic spectrum associated with *DYRK1B* variants. The L28P variant of *DYRK1B* is predicted to be "damaging,"[2] and we have postulated that it may be a loss-of-function variant with a protective effect against the metabolic syndrome.

We performed a phenomewide association study to examine phenotypes associated with the L28P variant of *DYRK1B* in a cohort of 7800 Geisinger MyCode Project participants for whom existing genotype data (obtained with the use of the Illumina HumanExome BeadChip) were available and linked to electronic medical record data. Phenotypes associated with cardiometabolic disease were identified with the use of previously validated phenomewide association study codes.[3] Our study revealed a significant protective effect of L28P (in 42 heterozygotes) against type 2 diabetes and a trend toward a protective effect against hypertension (Table 1). Two *DYRK1B* variants (G352A and P578S) that were predicted to be benign had no significant associations in the phenomewide association study.

Some *DYRK1B* variants are associated with autosomal dominant protective effects. Electronic medical records linked to existing genomic data sets can be used to rapidly identify population-level genotype–phenotype associations.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR

Keramati et al. detected *DYRK1B* mutations in families with the metabolic syndrome. The authors state that the clinical features of affected family members cannot be explained by neurohormonal activation (the plasma levels of the five tested hormones were all within the normal ranges). However, we note that the R102C mutation induces increased expression of peroxisome-proliferator–activated receptor γ (PPAR-γ) and PPAR-γ coactivator-1 (also known as PCG-1-α), which are associated with plasma levels of adipokines (e.g., adiponectin, leptin, resistin, and fibroblast growth factor 21 [FGF-21]) that play crucial roles in the metabolic syndrome. [1–4] Therefore, these plasma adipokines are presumably more directly relevant than the five tested hormones in this special form of the metabolic syndrome. To explain the clinical features associated with neurohormonal activation, we suggest that in future studies adipokines should be taken into account as plasma biomarkers for this form of the metabolic syndrome.

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TO THE EDITOR

Keramati et al. found that *DYRK1B* mutations were associated with coinheritance of the metabolic syndrome and coronary artery disease. Considering that rare variants as well as common ones in the same gene or locus could be related to the same disease, with a variety

of effects,[1,2] we fully endorse the authors' theory that common variants in the *DYRK1B* locus could be associated with the metabolic syndrome in the general population. In the Discussion section of their article, the authors mention that linkage of the *DYRK1B* locus on 19q13 to the metabolic syndrome and type 2 diabetes has been detected in previous genomewide association studies.[3,4] However, the susceptibility loci reported in these studies (the apolipoprotein E [APOE]–C1–C4–C2 gene cluster in the metabolic syndrome and the *PEPD* gene in type 2 diabetes) are considerably distant from the *DYRK1B* locus in a different linkage disequilibrium block. To our knowledge, the *DYRK1B* locus has not thus far been shown to be associated with the metabolic syndrome or coronary artery disease in the general population.

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THE AUTHORS REPLY

Mirshahi et al. describe a relatively common nonsynonymous variant in *DYRK1B* (L28P) with an observed allele frequency of 0.53%. In silico analysis indicated that this variant was probably damaging, and it was assumed to be a loss-of-function mutation. A phenomewide association study performed with the use of electronic medical records confirmed their hypothesis and identified this allele as being protective against several metabolic traits. We agree with their statement that the mutations described in our article represent only one end of the phenotypic spectrum, and we believe there may be many more alleles with loss of function than with gain of function in this gene and most other genes. For example, gain-of-function mutations in proprotein convertase subtilisin/kexin type 9 (PCSK9) have been detected in only a handful of kindreds,[1] whereas loss-of-function protective alleles are much more prevalent in the general population.[2]

We also agree with Mirshahi et al. that the cautious use of electronic medical records is very valuable for the study of population-based genotype–phenotype associations, and we are pleased to see that their analysis independently validated our unbiased findings regarding DYRK1B regulation of metabolism.

As stated by He et al., adipokines are important disease markers for metabolic traits. DYRK1B is expressed at high levels in the brain,[3] and its paralogue Dyrk1A has been shown to play a key role in the central regulation of appetite and body weight by transmitting signals from neuropeptide Y, downstream from ghrelin and leptin.[4] Thus, as with most cases of insulin resistance and obesity, we anticipate consequential alterations in the plasma concentrations of adipokines in *DYRK1B* mutation carriers.[5] We are currently examining food intake and plasma levels of various adipokines in the extended kindreds of *DYRK1B* mutation carriers. The plasma metanephrine, normetanephrine, cortisol, renin, and aldosterone activities were initially measured because of their role in the pathogenesis of multiple metabolic traits ranging from obesity and diabetes mellitus to hypertension; our statement about neurohormones was limited to those measurements.

In our article, we described two novel and extremely rare disease-causing variants of *DYRK1B*, and as stated by Morita and Komuro, we raised the question of whether rare or common variants with a small-to-moderate effect in this gene are linked to the same metabolic traits. However, we predict that future studies will only be able to establish the association of independent rare and subthreshold variants of *DYRK1B* (such as L28P) with metabolic traits. We concur that signals on 19q13 detected in genomewide association studies are most likely linked to the *APOE–C1–C4–C2* gene cluster.

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Since publication of their article, the authors report no further potential conflict of interest.

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Table 1

Association of Clinical Conditions with the L28P Variant of *DYRK1B*, as Determined by Means of a Phenomewide Association Study.

Condition	Adjusted Odds Ratio (95% CI)	Adjusted P Value*
Diabetes mellitus	0.30 (0.12–0.71)	0.002
Essential hypertension	0.52 (0.24–1.10)	0.09
Disorders of lipid metabolism	0.68 (0.30–1.53)	0.36
Overweight and obesity	0.91 (0.36–2.29)	0.85
Hypertensive heart disease	1.32 (0.39–4.41)	0.66
Myocardial infarction	0.36 (0.05–2.66)	0.24
Pulmonary heart disease	1.71 (0.52–5.64)	0.41
Heart failure	1.59 (0.65–3.87)	0.32
Symptoms involving cardiovascular system	1.34 (0.46–3.95)	0.60

*P values were adjusted for age, sex, and study group. CI denotes confidence interval.