

# Genetic Factors in Type 2 Diabetes

## All in the (Lipin) Family

Karen Reue and Jimmy Donkor

**T**ype 2 diabetes was once referred to as a “geneticist’s nightmare” (1) due to difficulties stemming from the nature of the disease and the strategies available for genetic analysis. Two key genetic approaches previously utilized—linkage analysis and candidate gene association studies—each have limitations that have been difficult to overcome in the study of type 2 diabetes. Linkage studies have been hampered by difficulties in obtaining well-defined pedigrees because of the late onset of the disease, imprecise diagnostic criteria, and genetic heterogeneity. Association studies are limited in scope to the consideration of known genes that have an established biological link to diabetes.

One approach to overcome some of these difficulties is to couple genome-wide linkage analysis in genetically isolated populations with high-resolution typing of genetic variations across the linkage region. This was shown to be a viable approach for the identification of novel diabetes genes with the discovery of variants in *TCF7L2*, a gene encoding a ubiquitous transcription factor with no previous functional connection to diabetes (2). Importantly, subsequent studies have revealed a previously unknown role for *TCF7L2* in pancreatic  $\beta$ -cells, with the risk allele leading to altered *TCF7L2* expression levels and reduced insulin secretion (3), although the mechanism by which the intronic polymorphism functions is not clear.

In this issue of *Diabetes*, a similar combined genetic linkage–association strategy has identified an association between *LPIN2* and insulin sensitivity and BMI (4). Previous genome-wide linkage studies identified a region of chromosome 18p11 linked to type 2 diabetes in populations from Finland, Sweden, and the Netherlands (5,6). In the current report, markers across this region were typed and the strongest association with diabetes localized to a single nucleotide polymorphism (SNP) residing in the 3′ untranslated region of *LPIN2*. Interestingly, this variant was shown to interact with BMI in determination of type 2 diabetes. Thus, the common allele was associated with

increased diabetes risk in individuals with high BMI but with neutral or protective effects in lean individuals (4).

*LPIN2* encodes one of three members of the lipin protein family, which have dual functions as phosphatidate phosphatase-1 enzymes required for triglyceride and phospholipid biosynthesis and as transcriptional coactivators for peroxisome proliferator–activated receptor nuclear receptors (7–9). The founding member of the family, lipin-1, was identified in a mutant mouse model of lipodystrophy characterized by adipose tissue deficiency and insulin resistance (10). In humans, *LPIN1* polymorphisms are associated with insulin levels and BMI (11). Lipin-1 is expressed at high levels in adipose tissue and skeletal muscle, and enhanced expression in either tissue leads to obesity but with opposite effects on insulin sensitivity (12). In mice and humans, lipin-1 levels in adipose tissue are correlated with insulin sensitivity, whereas lipin-1 levels in mouse muscle correlate with insulin resistance (11–13). Thus, it appears that lipin-1 levels in multiple tissues influence glucose homeostasis. Lipin-2 appears to have molecular functions similar to those of lipin-1 but exhibits a distinct tissue expression pattern, with higher levels in liver and lower levels in brain, small intestine, kidney, and lung (7). The fact that lipin-1–deficient mice have normal hepatic phosphatidate phosphatase-1 activity suggests that lipin-2 and/or lipin-3 may be responsible for this activity in liver.

What are the implications regarding lipin-2 in the pathogenesis of type 2 diabetes? It is tempting to speculate that the genetic polymorphism identified may influence hepatic triglyceride levels and potentially the degree of hepatic steatosis and insulin resistance in conditions such as obesity. Lipin-2 may also have an important role in regulation of the inflammatory response, as revealed by *LPIN2* mutations in Majeed syndrome. Majeed syndrome is an autoinflammatory disorder with a constellation of symptoms including recurrent fever, sterile osteomyelitis, cutaneous inflammation, and anemia (14,15). The mechanism by which lipin-2 mutations cause these symptoms is not known, and no information regarding insulin resistance or diabetes in Majeed patients has been reported.

The physiological roles of lipin-2 in lipid metabolism and inflammation make *LPIN2* an intriguing and plausible diabetes gene. However, further studies will be required to establish whether the SNP identified is functionally associated with diabetes or is simply in linkage disequilibrium with the causal variant in *LPIN2* or a neighboring gene. The initial studies failed to detect any effect of the *LPIN2* polymorphism on mRNA levels in white blood cells or in micro-RNA binding to a predicted target sequence that contains the SNP (4). These issues can be resolved in future genetic, molecular, and physiological studies. For example, additional analysis of

From the Departments of Human Genetics and Medicine, David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, California.

Address correspondence and reprint requests to Karen Reue, Department of Human Genetics, 6506A, David Geffen School of Medicine at UCLA, 695 Charles E. Young Drive South, Los Angeles, CA 90095. E-mail: reuek@ucla.edu.

Received for publication 10 September 2007 and accepted in revised form 11 September 2007.

SNP, single nucleotide polymorphism.

DOI: 10.2337/db07-1288

© 2007 by the American Diabetes Association.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

the potential effects of the *LPIN2* SNP on mRNA levels and function should be performed in relevant cell types, such as cultured hepatocytes or liver from mouse models. Further analysis of the region via deep sequencing can be used to identify all common and potential functional variants, and physiological studies of lipin-2 function in diabetes can be carried out in genetically manipulated mouse models.

The implication of two members of the lipin gene family as determinants of insulin sensitivity serves to underscore the close relationship between lipid homeostasis and diabetes. Now, what about lipin-3?

## REFERENCES

1. Neel JV: Diabetes Mellitus. In *The Genetics and Epidemiology of Chronic Disease*. Neel JV, Shaw MW, Schull WJ, Eds. Washington, U.S. Public Health Services Publications, 1965, p. 105–132
2. Grant SF, Thorleifsson G, Reynisdottir I, Benediktsson R, Manolescu A, Sainz J, Helgason A, Stefansson H, Emilsson V, Helgadóttir A, Styrkarsdóttir U, Magnusson KP, Walters GB, Palsdóttir E, Jonsdóttir T, Gudmundsdóttir T, Gylfason A, Saemundsdóttir J, Wilensky RL, Reilly MP, Rader DJ, Bagger Y, Christiansen C, Gudnason V, Sigurdsson G, Thorsteinsdóttir U, Gulcher JR, Kong A, Stefansson K: Variant of transcription factor 7-like 2 (*TCF7L2*) gene confers risk of type 2 diabetes. *Nat Genet* 38:320–323, 2006
3. Lyssenko V, Lupi R, Marchetti P, Del Guerra S, Orbo-Melander M, Almgren P, Sjogren M, Ling C, Eriksson KF, Lethagen AL, Mancarella R, Berglund G, Tuomi T, Nilsson P, Del Prato S, Groop L: Mechanisms by which common variants in the *TCF7L2* gene increase risk of type 2 diabetes. *J Clin Invest* 117:2155–2163, 2007
4. Aulchenko YS, Pullen J, Kloosterman WP, Yazdanpanah M, Hofman A, Vaessen N, Snijders PJLM, Zubakov D, Mackay I, Olavesen M, Sidhu B, Smith VE, Carey A, Berezikov E, Uttenlinden AG, Plasterk RHA, Oostra BA, van Duijn CM: *LPIN2* is associated with type 2 diabetes, glucose metabolism, and body composition. *Diabetes* 56:3020–3026, 2007
5. Aulchenko YS, Vaessen N, Heutink P, Pullen J, Snijders PJ, Hofman A, Sandkuijl LA, Houwing-Duistermaat JJ, Edwards M, Bennett S, Oostra BA, van Duijn CM: A genome-wide search for genes involved in type 2 diabetes in a recently genetically isolated population from the Netherlands. *Diabetes* 52:3001–3004, 2003
6. Parker A, Meyer J, Lewitzky S, Rennich JS, Chan G, Thomas JD, Orho-Melander M, Lehtovirta M, Forsblom C, Hyrkko A, Carlsson M, Lindgren C, Groop LC: A gene conferring susceptibility to type 2 diabetes in conjunction with obesity is located on chromosome 18p11. *Diabetes* 50:675–680, 2001
7. Donkor J, Sariahmetoglu M, Dewald J, Brindley DN, Reue K: Three mammalian lipins act as phosphatidate phosphatases with distinct tissue expression patterns. *J Biol Chem* 282:3450–3457, 2007
8. Finck BN, Gropler MC, Chen Z, Leone TC, Croce MA, Harris TE, Lawrence JC Jr, Kelly DP: Lipin 1 is an inducible amplifier of the hepatic PGC-1alpha/PPARalpha regulatory pathway. *Cell Metab* 4:199–210, 2006
9. Han GS, Wu WI, Carman GM: The *Saccharomyces cerevisiae* Lipin homolog is a Mg<sup>2+</sup>-dependent phosphatidate phosphatase enzyme. *J Biol Chem* 281:9210–9218, 2006
10. Péterfy M, Phan J, Xu P, Reue K: Lipodystrophy in the *fld* mouse results from mutation of a new gene encoding a nuclear protein, lipin. *Nat Genet* 27:121–124, 2001
11. Suviolahti E, Reue K, Cantor RM, Phan J, Gentile M, Naukkarinen J, Soro-Paavonen A, Oksanen L, Kaprio J, Rissanen A, Salomaa V, Kontula K, Taskinen MR, Pajukanta P, Peltonen L: Cross-species analyses implicate Lipin 1 involvement in human glucose metabolism. *Hum Mol Genet* 15:377–386, 2006
12. Phan J, Reue K: Lipin, a lipodystrophy and obesity gene. *Cell Metab* 1:73–83, 2005
13. Yao-Borengasser A, Rasouli N, Varma V, Miles LM, Phanavanh B, Starks TN, Phan J, Spencer HJ 3rd, McGehee RE Jr, Reue K, Kern PA: Lipin expression is attenuated in adipose tissue of insulin-resistant human subjects and increases with peroxisome proliferator-activated receptor  $\gamma$  activation. *Diabetes* 55:2811–2818, 2006
14. Ferguson PJ, Chen S, Tayeh mK, Ochoa L, Leal SM, Pelet A, Munnich A, Lyonnet S, Majeed HA, El-Dhanti H: Homozygous mutations in *LPIN2* are responsible for the syndrome of chronic recurrent osteomyelitis and congenital dyserythropoietic anaemia (Majeed syndrome). *J Med Genet* 42:551–557, 2005
15. Majeed HA, Al-Tarawna M, El-Shanti H, Kamel B, Al-Khalaileh F: The syndrome of chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anaemia: report of a new family and a review. *Eur J Pediatr* 160:705–710, 2001