References

2004. Finishing the euchromatic sequence of the human genome. *Nature* **431:** 931-945.
2005. A haplotype map of the human genome. *Nature* **437:** 1299-1320.
2007. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* **447:** 661-678.
2008. Diagnosis and classification of diabetes mellitus. *Diabetes Care* **31 Suppl 1:** S55-60.
Abe, H., N. Yamada, K. Kamata, T. Kuwaki, M. Shimada, J. Osuga, F. Shionoiri, N. Yahagi, T. Kadowaki, H. Tamemoto, S. Ishibashi, Y. Yazaki, and M. Makuuchi. 1998. Hypertension, hypertriglyceridemia, and impaired endothelium-dependent vascular relaxation in mice lacking insulin receptor substrate-1. *J Clin Invest* **101:** 1784-1788.
Abraham, R.T. 2004. PI 3-kinase related kinases: 'big' players in stress-induced signaling pathways. *DNA Repair (Amst)* **3:** 883-887.
Accili, D., J. Drago, E.J. Lee, M.D. Johnson, M.H. Cool, P. Salvatore, L.D. Asico, P.A. Jose, S.I. Taylor, and H. Westphal. 1996. Early neonatal death in mice homozygous for a null allele of the insulin receptor gene. *Nat Genet* **12:** 106-109.
Agarwal, A.K., E. Arioglu, S. De Almeida, N. Akkoc, S.I. Taylor, A.M. Bowcock, R.I. Barnes, and A. Garg. 2002. AGPAT2 is mutated in congenital generalized lipodystrophy linked to chromosome 9q34. *Nat Genet* **31:** 21-23.
Agarwal, A.K., J.P. Fryns, R.J. Auchus, and A. Garg. 2003. Zinc metalloproteinase, ZMPSTE24, is mutated in mandibuloacral dysplasia. *Hum Mol Genet* **12:** 1995-2001.
Agarwal, A.K. and A. Garg. 2002. A novel heterozygous mutation in peroxisome proliferator-activated receptor-gamma gene in a patient with familial partial lipodystrophy. *J Clin Endocrinol Metab* **87:** 408-411.
Ahituv, N., N. Kavaslar, W. Schackwitz, A. Ustaszewska, J. Martin, S. Hebert, H. Doelle, B. Ersoy, G. Kryukov, S. Schmidt, N. Yosef, E. Ruppin, R. Sharan, C. Vaisse, S. Sunyaev, R. Dent, J. Cohen, R. McPherson, and L.A. Pennacchio. 2007. Medical sequencing at the extremes of human body mass. *Am J Hum Genet* **80:** 779-791.
Al-Mosawi, Z.S., K.K. Al-Saad, R. Ijadi-Maghsoodi, H.I. El-Shanti, and P.J. Ferguson. 2007. A splice site mutation confirms the role of LPIN2 in Majeed syndrome. *Arthritis Rheum* **56:** 960-964.
Alessi, D.R., M. Andjelkovic, B. Caudwell, P. Cron, N. Morrice, P. Cohen, and B.A. Hemmings. 1996. Mechanism of activation of protein kinase B by insulin and IGF-1. *Embo J* **15:** 6541-6551.
Alessi, D.R., S.R. James, C.P. Downes, A.B. Holmes, P.R. Gaffney, C.B. Reese, and P. Cohen. 1997. Characterization of a 3-phosphoinositide-dependent protein kinase which phosphorylates and activates protein kinase Balpha. *Curr Biol* **7:** 261-269.
Ali, S.M. and D.M. Sabatini. 2005. Structure of S6 kinase 1 determines whether raptor-mTOR or rictor-mTOR phosphorylates its hydrophobic motif site. *J Biol Chem* **280:** 19445-19448.
Altshuler, D., J.N. Hirschhorn, M. Klannemark, C.M. Lindgren, M.C. Vohl, J. Nemesh, C.R. Lane, S.F. Schaffner, S. Bolk, C. Brewer, T. Tuomi, D. Gaudet, T.J. Hudson, M. Daly, L. Groop, and E.S. Lander. 2000. The common PPARgamma Pro12Ala polymorphism is associated with decreased risk of type 2 diabetes. *Nat Genet* **26:** 76-80.
Amr, S., C. Heisey, M. Zhang, X.J. Xia, K.H. Shows, K. Ajlouni, A. Pandya, L.S. Satin, H. El-Shanti, and R. Shiang. 2007. A homozygous mutation in a novel zinc-finger protein, ERIS, is responsible for Wolfram syndrome 2. *Am J Hum Genet* **81:** 673-683.

Araki, E., B.L. Haag, 3rd, and C.R. Kahn. 1994. Cloning of the mouse insulin receptor substrate-1 (IRS-1) gene and complete sequence of mouse IRS-1. *Biochim Biophys Acta* **1221:** 353-356.

Ardlie, K.G., L. Kruglyak, and M. Seielstad. 2002. Patterns of linkage disequilibrium in the human genome. *Nat Rev Genet* **3:** 299-309.

Arthur, E.I., J. Zlotogora, I. Lerer, J. Dagan, K. Marks, and D. Abeliovich. 1997. Transient neonatal diabetes mellitus in a child with invdup(6)(q22q23) of paternal origin. *Eur J Hum Genet* **5:** 417-419.

Aulchenko, Y.S., J. Pullen, W.P. Kloosterman, M. Yazdanpanah, A. Hofman, N. Vaessen, P.J. Snijders, D. Zubakov, I. Mackay, M. Olavesen, B. Sidhu, V.E. Smith, A. Carey, E. Berezikov, A.G. Uitterlinden, R.H. Plasterk, B.A. Oostra, and C.M. van Duijn. 2007. LPIN2 is associated with type 2 diabetes, glucose metabolism, and body composition. *Diabetes* **56:** 3020-3026.

Babenko, A.P., M. Polak, H. Cave, K. Busiah, P. Czernichow, R. Scharfmann, J. Bryan, L. Aguilar-Bryan, M. Vaxillaire, and P. Froguel. 2006. Activating mutations in the ABCC8 gene in neonatal diabetes mellitus. *N Engl J Med* **355:** 456-466.

Balding, D.J. 2006. A tutorial on statistical methods for population association studies. *Nat Rev Genet* **7:** 781-791.

Barilli, A., R. Visigalli, R. Sala, G.C. Gazzola, A. Parolari, E. Tremoli, S. Bonomini, A. Simon, E.I. Closs, V. Dall'asta, and O. Bussolati. 2008. In human endothelial cells rapamycin causes mTORC2 inhibition and impairs cell viability and function. *Cardiovasc Res* **78:** 563-571.

Barrett, J.C., B. Fry, J. Maller, and M.J. Daly. 2005. Haploview: analysis and visualization of LD and haplotype maps. *Bioinformatics* **21:** 263-265.

Barroso, I. 2005. Genetics of Type 2 diabetes. *Diabet Med* **22:** 517-535.

Barroso, I., M. Gurnell, V.E. Crowley, M. Agostini, J.W. Schwabe, M.A. Soos, G.L. Maslen, T.D. Williams, H. Lewis, A.J. Schafer, V.K. Chatterjee, and S. O'Rahilly. 1999. Dominant negative mutations in human PPARgamma associated with severe insulin resistance, diabetes mellitus and hypertension. *Nature* **402:** 880-883.

Barroso, I., J. Luan, R.P. Middelberg, A.H. Harding, P.W. Franks, R.W. Jakes, D. Clayton, A.J. Schafer, S. O'Rahilly, and N.J. Wareham. 2003. Candidate gene association study in type 2 diabetes indicates a role for genes involved in beta-cell function as well as insulin action. *PLoS Biol* **1:** E20.

Barthel, A. and D. Schmoll. 2003. Novel concepts in insulin regulation of hepatic gluconeogenesis. *Am J Physiol Endocrinol Metab* **285:** E685-692.

Becker, A.B. and R.A. Roth. 1990. Insulin receptor structure and function in normal and pathological conditions. *Annu Rev Med* **41:** 99-115.

Bell, G.I., S. Horita, and J.H. Karam. 1984. A polymorphic locus near the human insulin gene is associated with insulin-dependent diabetes mellitus. *Diabetes* **33:** 176-183.

Bell, G.I., K.S. Xiang, M.V. Newman, S.H. Wu, L.G. Wright, S.S. Fajans, R.S. Spielman, and N.J. Cox. 1991. Gene for non-insulin-dependent diabetes mellitus (maturity-onset diabetes of the young subtype) is linked to DNA polymorphism on human chromosome 20q. *Proc Natl Acad Sci U S A* **88:** 1484-1488.

Berger, D., I. Barroso, M. Soos, G. Yeo, A.J. Schafer, S. O'Rahilly, and J.P. Whitehead. 2002. Genetic variants of insulin receptor substrate-1 (IRS-1) in syndromes of severe insulin resistance. Functional analysis of Ala513Pro and Gly1158Glu IRS-1. *Diabet Med* **19:** 804-809.

Berger, J., P. Bailey, C. Biswas, C.A. Cullinan, T.W. Doebber, N.S. Hayes, R. Saperstein, R.G. Smith, and M.D. Leibowitz. 1996. Thiazolidinediones produce a conformational change in peroxisomal proliferator-activated receptor-gamma:

binding and activation correlate with antidiabetic actions in db/db mice. *Endocrinology* **137:** 4189-4195.

Birnbaum, M.J. 1989. Identification of a novel gene encoding an insulin-responsive glucose transporter protein. *Cell* **57:** 305-315.

Birney, E. J.A. Stamatoyannopoulos A. Dutta R. Guigo T.R. Gingeras E.H. Margulies Z. Weng M. Snyder E.T. Dermitzakis R.E. Thurman M.S. Kuehn C.M. Taylor S. Neph C.M. Koch S. Asthana A. Malhotra I. Adzhubei J.A. Greenbaum R.M. Andrews P. Flicek P.J. Boyle H. Cao N.P. Carter G.K. Clelland S. Davis N. Day P. Dhami S.C. Dillon M.O. Dorschner H. Fiegler P.G. Giresi J. Goldy M. Hawrylycz A. Haydock R. Humbert K.D. James B.E. Johnson E.M. Johnson T.T. Frum E.R. Rosenzweig N. Karnani K. Lee G.C. Lefebvre P.A. Navas F. Neri S.C. Parker P.J. Sabo R. Sandstrom A. Shafer D. Vetrie M. Weaver S. Wilcox M. Yu F.S. Collins J. Dekker J.D. Lieb T.D. Tullius G.E. Crawford S. Sunyaev W.S. Noble I. Dunham F. Denoeud A. Reymond P. Kapranov J. Rozowsky D. Zheng R. Castelo A. Frankish J. Harrow S. Ghosh A. Sandelin I.L. Hofacker R. Baertsch D. Keefe S. Dike J. Cheng H.A. Hirsch E.A. Sekinger J. Lagarde J.F. Abril A. Shahab C. Flamm C. Fried J. Hackermuller J. Hertel M. Lindemeyer K. Missal A. Tanzer S. Washietl J. Korbel O. Emanuelsson J.S. Pedersen N. Holroyd R. Taylor D. Swarbreck N. Matthews M.C. Dickson D.J. Thomas M.T. Weirauch J. Gilbert J. Drenkow I. Bell X. Zhao K.G. Srinivasan W.K. Sung H.S. Ooi K.P. Chiu S. Foissac T. Alioto M. Brent L. Pachter M.L. Tress A. Valencia S.W. Choo C.Y. Choo C. Ucla C. Manzano C. Wyss E. Cheung T.G. Clark J.B. Brown M. Ganesh S. Patel H. Tammana J. Chrast C.N. Henrichsen C. Kai J. Kawai U. Nagalakshmi J. Wu Z. Lian J. Lian P. Newburger X. Zhang P. Bickel J.S. Mattick P. Carninci Y. Hayashizaki S. Weissman T. Hubbard R.M. Myers J. Rogers P.F. Stadler T.M. Lowe C.L. Wei Y. Ruan K. Struhl M. Gerstein S.E. Antonarakis Y. Fu E.D. Green U. Karaoz A. Siepel J. Taylor L.A. Liefer K.A. Wetterstrand P.J. Good E.A. Feingold M.S. Guyer G.M. Cooper G. Asimenos C.N. Dewey M. Hou S. Nikolaev J.I. Montoya-Burgos A. Loytynoja S. Whelan F. Pardi T. Massingham H. Huang N.R. Zhang I. Holmes J.C. Mullikin A. Ureta-Vidal B. Paten M. Seringhaus D. Church K. Rosenbloom W.J. Kent E.A. Stone S. Batzoglou N. Goldman R.C. Hardison D. Haussler W. Miller A. Sidow N.D. Trinklein Z.D. Zhang L. Barrera R. Stuart D.C. King A. Ameur S. Enroth M.C. Bieda J. Kim A.A. Bhinge N. Jiang J. Liu F. Yao V.B. Vega C.W. Lee P. Ng A. Shahab A. Yang Z. Moqtaderi Z. Zhu X. Xu S. Squazzo M.J. Oberley D. Inman M.A. Singer T.A. Richmond K.J. Munn A. Rada-Iglesias O. Wallerman J. Komorowski J.C. Fowler P. Couttet A.W. Bruce O.M. Dovey P.D. Ellis C.F. Langford D.A. Nix G. Euskirchen S. Hartman A.E. Urban P. Kraus S. Van Calcar N. Heintzman T.H. Kim K. Wang C. Qu G. Hon R. Luna C.K. Glass M.G. Rosenfeld S.F. Aldred S.J. Cooper A. Halees J.M. Lin H.P. Shulha X. Zhang M. Xu J.N. Haidar Y. Yu Y. Ruan V.R. Iyer R.D. Green C. Wadelius P.J. Farnham B. Ren R.A. Harte A.S. Hinrichs H. Trumbower H. Clawson J. Hillman-Jackson A.S. Zweig K. Smith A. Thakkapallayil G. Barber R.M. Kuhn D. Karolchik L. Armengol C.P. Bird P.I. de Bakker A.D. Kern N. Lopez-Bigas J.D. Martin B.E. Stranger A. Woodroffe E. Davydov A. Dimas E. Eyras I.B. Hallgrimsdottir J. Huppert M.C. Zody G.R. Abecasis X. Estivill G.G. Bouffard X. Guan N.F. Hansen J.R. Idol V.V. Maduro B. Maskeri J.C. McDowell M. Park P.J. Thomas A.C. Young R.W. Blakesley D.M. Muzny E. Sodergren D.A. Wheeler K.C. Worley H. Jiang G.M. Weinstock R.A. Gibbs T. Graves R. Fulton E.R. Mardis R.K. Wilson M. Clamp J. Cuff S. Gnerre D.B. Jaffe J.L. Chang K. Lindblad-Toh E.S. Lander M. Koriabine M. Nefedov K. Osoegawa Y. Yoshinaga B. Zhu and P.J. de Jong. 2007. Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project. *Nature* **447:** 799-816.

Bjorntorp, P., T. Schersten, and S.E. Fagerberg. 1967. Respiration and phosphorylation of mitochondria isolated from the skeletal muscle of diabetic and normal subjects. *Diabetologia* **3:** 346-352.

Bluher, M., M.D. Michael, O.D. Peroni, K. Ueki, N. Carter, B.B. Kahn, and C.R. Kahn. 2002. Adipose tissue selective insulin receptor knockout protects against obesity and obesity-related glucose intolerance. *Dev Cell* **3:** 25-38.

Bodmer, W. and C. Bonilla. 2008. Common and rare variants in multifactorial susceptibility to common diseases. *Nat Genet* **40:** 695-701.

Bogacka, I., B. Ukropcova, M. McNeil, J.M. Gimble, and S.R. Smith. 2005. Structural and functional consequences of mitochondrial biogenesis in human adipocytes in vitro. *J Clin Endocrinol Metab* **90:** 6650-6656.

Borecki, I.B. and M.A. Province. 2008. Linkage and association: basic concepts. *Adv Genet* **60:** 51-74.

Bottini, N., L. Musumeci, A. Alonso, S. Rahmouni, K. Nika, M. Rostamkhani, J. MacMurray, G.F. Meloni, P. Lucarelli, M. Pellecchia, G.S. Eisenbarth, D. Comings, and T. Mustelin. 2004. A functional variant of lymphoid tyrosine phosphatase is associated with type I diabetes. *Nat Genet* **36:** 337-338.

Bouatia-Naji, N., G. Rocheleau, L. Van Lommel, K. Lemaire, F. Schuit, C. Cavalcanti-Proenca, M. Marchand, A.L. Hartikainen, U. Sovio, F. De Graeve, J. Rung, M. Vaxillaire, J. Tichet, M. Marre, B. Balkau, J. Weill, P. Elliott, M.R. Jarvelin, D. Meyre, C. Polychronakos, C. Dina, R. Sladek, and P. Froguel. 2008. A polymorphism within the G6PC2 gene is associated with fasting plasma glucose levels. *Science* **320:** 1085-1088.

Brachmann, S.M., K. Ueki, J.A. Engelman, R.C. Kahn, and L.C. Cantley. 2005. Phosphoinositide 3-kinase catalytic subunit deletion and regulatory subunit deletion have opposite effects on insulin sensitivity in mice. *Mol Cell Biol* **25:** 1596-1607.

Bradburn, M.J., J.J. Deeks, and D.G. Altman. 1999. Metan - an alternative meta-analysis command. *Stata Technical Bulletin Reprints* **8:** 86-100.

Briaud, I., L.M. Dickson, M.K. Lingohr, J.F. McCuaig, J.C. Lawrence, and C.J. Rhodes. 2005. Insulin receptor substrate-2 proteasomal degradation mediated by a mammalian target of rapamycin (mTOR)-induced negative feedback down-regulates protein kinase B-mediated signaling pathway in beta-cells. *J Biol Chem* **280:** 2282-2293.

Brickwood, S., D.T. Bonthron, L.I. Al-Gazali, K. Piper, T. Hearn, D.I. Wilson, and N.A. Hanley. 2003. Wolcott-Rallison syndrome: pathogenic insights into neonatal diabetes from new mutation and expression studies of EIF2AK3. *J Med Genet* **40:** 685-689.

Brown, A.E., S.J. Yeaman, and M. Walker. 2007. Targeted suppression of calpain-10 expression impairs insulin-stimulated glucose uptake in cultured primary human skeletal muscle cells. *Mol Genet Metab* **91:** 318-324.

Bruning, J.C., M.D. Michael, J.N. Winnay, T. Hayashi, D. Horsch, D. Accili, L.J. Goodyear, and C.R. Kahn. 1998. A muscle-specific insulin receptor knockout exhibits features of the metabolic syndrome of NIDDM without altering glucose tolerance. *Mol Cell* **2:** 559-569.

Bruss, M.D., E.B. Arias, G.E. Lienhard, and G.D. Cartee. 2005. Increased phosphorylation of Akt substrate of 160 kDa (AS160) in rat skeletal muscle in response to insulin or contractile activity. *Diabetes* **54:** 41-50.

Butler, A.E., J. Janson, S. Bonner-Weir, R. Ritzel, R.A. Rizza, and P.C. Butler. 2003. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. *Diabetes* **52:** 102-110.

Calera, M.R., C. Martinez, H. Liu, A.K. Jack, M.J. Birnbaum, and P.F. Pilch. 1998. Insulin increases the association of Akt-2 with Glut4-containing vesicles. *J Biol Chem* **273:** 7201-7204.

Cann, H.M., C. de Toma, L. Cazes, M.F. Legrand, V. Morel, L. Piouffre, J. Bodmer, W.F. Bodmer, B. Bonne-Tamir, A. Cambon-Thomsen, Z. Chen, J. Chu, C. Carcassi, L. Contu, R. Du, L. Excoffier, G.B. Ferrara, J.S. Friedlaender, H. Groot, D. Gurwitz, T. Jenkins, R.J. Herrera, X. Huang, J. Kidd, K.K. Kidd, A. Langaney, A.A. Lin, S.Q. Mehdi, P. Parham, A. Piazza, M.P. Pistillo, Y. Qian, Q. Shu, J. Xu, S. Zhu, J.L. Weber, H.T. Greely, M.W. Feldman, G. Thomas, J. Dausset, and L.L. Cavalli-Sforza. 2002. A human genome diversity cell line panel. *Science* **296:** 261-262.

Cano, A., C. Rouzier, S. Monnot, B. Chabrol, J. Conrath, P. Lecomte, B. Delobel, P. Boileau, R. Valero, V. Procaccio, V. Paquis-Flucklinger, and B. Vialettes. 2007. Identification of novel mutations in WFS1 and genotype-phenotype correlation in Wolfram syndrome. *Am J Med Genet A* **143A:** 1605-1612.

Cao, H., L. Alston, J. Ruschman, and R.A. Hegele. 2008. Heterozygous CAV1 frameshift mutations (MIM 601047) in patients with atypical partial lipodystrophy and hypertriglyceridemia. *Lipids Health Dis* **7:** 3.

Cao, H. and R.A. Hegele. 2000. Nuclear lamin A/C R482Q mutation in canadian kindreds with Dunnigan-type familial partial lipodystrophy. *Hum Mol Genet* **9:** 109-112.

Cao, H. and R.A. Hegele. 2002. Identification of single-nucleotide polymorphisms in the human LPIN1 gene. *J Hum Genet* **47:** 370-372.

Cardon, L.R. and J.I. Bell. 2001. Association study designs for complex diseases. *Nat Rev Genet* **2:** 91-99.

Caux, F., E. Dubosclard, O. Lascols, B. Buendia, O. Chazouilleres, A. Cohen, J.C. Courvalin, L. Laroche, J. Capeau, C. Vigouroux, and S. Christin-Maitre. 2003. A new clinical condition linked to a novel mutation in lamins A and C with generalized lipoatrophy, insulin-resistant diabetes, disseminated leukomelanodermic papules, liver steatosis, and cardiomyopathy. *J Clin Endocrinol Metab* **88:** 1006-1013.

Chandak, G.R., C.S. Janipalli, S. Bhaskar, S.R. Kulkarni, P. Mohankrishna, A.T. Hattersley, T.M. Frayling, and C.S. Yajnik. 2007. Common variants in the TCF7L2 gene are strongly associated with type 2 diabetes mellitus in the Indian population. *Diabetologia* **50:** 63-67.

Chaturvedi, N., P.M. McKeigue, and M.G. Marmot. 1993. Resting and ambulatory blood pressure differences in Afro-Caribbeans and Europeans. *Hypertension* **22:** 90-96.

Chen, H., O. Charlat, L.A. Tartaglia, E.A. Woolf, X. Weng, S.J. Ellis, N.D. Lakey, J. Culpepper, K.J. Moore, R.E. Breitbart, G.M. Duyk, R.I. Tepper, and J.P. Morgenstern. 1996. Evidence that the diabetes gene encodes the leptin receptor: identification of a mutation in the leptin receptor gene in db/db mice. *Cell* **84:** 491-495.

Chen, L., L. Lee, B.A. Kudlow, H.G. Dos Santos, O. Sletvold, Y. Shafeghati, E.G. Botha, A. Garg, N.B. Hanson, G.M. Martin, I.S. Mian, B.K. Kennedy, and J. Oshima. 2003. LMNA mutations in atypical Werner's syndrome. *Lancet* **362:** 440-445.

Chen, W.M., M.R. Erdos, A.U. Jackson, R. Saxena, S. Sanna, K.D. Silver, N.J. Timpson, T. Hansen, M. Orru, M. Grazia Piras, L.L. Bonnycastle, C.J. Willer, V. Lyssenko, H. Shen, J. Kuusisto, S. Ebrahim, N. Sestu, W.L. Duren, M.C. Spada, H.M. Stringham, L.J. Scott, N. Olla, A.J. Swift, S. Najjar, B.D. Mitchell, D.A. Lawlor, G.D. Smith, Y. Ben-Shlomo, G. Andersen, K. Borch-Johnsen, T. Jorgensen, J. Saramies, T.T. Valle, T.A. Buchanan, A.R. Shuldiner, E. Lakatta, R.N. Bergman, M. Uda, J. Tuomilehto, O. Pedersen, A. Cao, L. Groop, K.L. Mohlke, M. Laakso,

D. Schlessinger, F.S. Collins, D. Altshuler, G.R. Abecasis, M. Boehnke, A. Scuteri, and R.M. Watanabe. 2008. Variations in the G6PC2/ABCB11 genomic region are associated with fasting glucose levels. *J Clin Invest* **118:** 2620-2628.

Chen, Y., R. Kittles, J. Zhou, G. Chen, A. Adeyemo, R.K. Panguluri, W. Chen, A. Amoah, V. Opoku, J. Acheampong, K. Agyenim-Boateng, B.A. Eghan, Jr., A. Nyantaki, J. Oli, G. Okafor, E. Ofoegbu, B. Osotimehin, F. Abbiyesuku, T. Johnson, O. Fasanmade, T. Rufus, P. Furbert-Harris, H.I. Daniel, K.A. Berg, F.S. Collins, G.M. Dunston, and C.N. Rotimi. 2005. Calpain-10 gene polymorphisms and type 2 diabetes in West Africans: the Africa America Diabetes Mellitus (AADM) Study. *Ann Epidemiol* **15:** 153-159.

Cho, H., J. Mu, J.K. Kim, J.L. Thorvaldsen, Q. Chu, E.B. Crenshaw, 3rd, K.H. Kaestner, M.S. Bartolomei, G.I. Shulman, and M.J. Birnbaum. 2001a. Insulin resistance and a diabetes mellitus-like syndrome in mice lacking the protein kinase Akt2 (PKB beta). *Science* **292:** 1728-1731.

Cho, H., J.L. Thorvaldsen, Q. Chu, F. Feng, and M.J. Birnbaum. 2001b. Akt1/PKBalpha is required for normal growth but dispensable for maintenance of glucose homeostasis in mice. *J Biol Chem* **276:** 38349-38352.

Ciafaloni, E., E. Ricci, S. Shanske, C.T. Moraes, G. Silvestri, M. Hirano, S. Simonetti, C. Angelini, M.A. Donati, C. Garcia, and et al. 1992. MELAS: clinical features, biochemistry, and molecular genetics. *Ann Neurol* **31:** 391-398.

Cohen, B., D. Novick, and M. Rubinstein. 1996. Modulation of insulin activities by leptin. *Science* **274:** 1185-1188.

Cohen, J.C., R.S. Kiss, A. Pertsemlidis, Y.L. Marcel, R. McPherson, and H.H. Hobbs. 2004. Multiple rare alleles contribute to low plasma levels of HDL cholesterol. *Science* **305:** 869-872.

Cohen, J.C., A. Pertsemlidis, S. Fahmi, S. Esmail, G.L. Vega, S.M. Grundy, and H.H. Hobbs. 2006. Multiple rare variants in NPC1L1 associated with reduced sterol absorption and plasma low-density lipoprotein levels. *Proc Natl Acad Sci U S A* **103:** 1810-1815.

Collin, G.B., J.D. Marshall, A. Ikeda, W.V. So, I. Russell-Eggitt, P. Maffei, S. Beck, C.F. Boerkoel, N. Sicolo, M. Martin, P.M. Nishina, and J.K. Naggert. 2002. Mutations in ALMS1 cause obesity, type 2 diabetes and neurosensory degeneration in Alstrom syndrome. *Nat Genet* **31:** 74-78.

Colombo, C., J.J. Cutson, T. Yamauchi, C. Vinson, T. Kadowaki, O. Gavrilova, and M.L. Reitman. 2002. Transplantation of adipose tissue lacking leptin is unable to reverse the metabolic abnormalities associated with lipoatrophy. *Diabetes* **51:** 2727-2733.

Colosimo, A., V. Guida, L. Rigoli, C. Di Bella, A. De Luca, S. Briuglia, L. Stuppia, D.C. Salpietro, and B. Dallapiccola. 2003. Molecular detection of novel WFS1 mutations in patients with Wolfram syndrome by a DHPLC-based assay. *Hum Mutat* **21:** 622-629.

Condon, J., J.E. Shaw, M. Luciano, K.O. Kyvik, N.G. Martin, and D.L. Duffy. 2008. A study of diabetes mellitus within a large sample of Australian twins. *Twin Res Hum Genet* **11:** 28-40.

Croce, M.A., J.C. Eagon, L.L. LaRiviere, K.M. Korenblat, S. Klein, and B.N. Finck. 2007. Hepatic lipin 1beta expression is diminished in insulin-resistant obese subjects and is reactivated by marked weight loss. *Diabetes* **56:** 2395-2399.

Cross, D.A., D.R. Alessi, P. Cohen, M. Andjelkovich, and B.A. Hemmings. 1995. Inhibition of glycogen synthase kinase-3 by insulin mediated by protein kinase B. *Nature* **378:** 785-789.

Cryns, K., T.A. Sivakumaran, J.M. Van den Ouweland, R.J. Pennings, C.W. Cremers, K. Flothmann, T.L. Young, R.J. Smith, M.M. Lesperance, and G. Van Camp. 2003.

Mutational spectrum of the WFS1 gene in Wolfram syndrome, nonsyndromic hearing impairment, diabetes mellitus, and psychiatric disease. *Hum Mutat* **22:** 275-287.

Cushman, S.W. and L.J. Wardzala. 1980. Potential mechanism of insulin action on glucose transport in the isolated rat adipose cell. Apparent translocation of intracellular transport systems to the plasma membrane. *J Biol Chem* **255:** 4758-4762.

Daly, M.J., J.D. Rioux, S.F. Schaffner, T.J. Hudson, and E.S. Lander. 2001. High-resolution haplotype structure in the human genome. *Nat Genet* **29:** 229-232.

Dausset, J., H. Cann, D. Cohen, M. Lathrop, J.M. Lalouel, and R. White. 1990. Centre d'etude du polymorphisme humain (CEPH): collaborative genetic mapping of the human genome. *Genomics* **6:** 575-577.

Day, N., S. Oakes, R. Luben, K.T. Khaw, S. Bingham, A. Welch, and N. Wareham. 1999. EPIC-Norfolk: study design and characteristics of the cohort. European Prospective Investigation of Cancer. *Br J Cancer* **80 Suppl 1:** 95-103.

de Bakker, P.I., R. Yelensky, I. Pe'er, S.B. Gabriel, M.J. Daly, and D. Altshuler. 2005. Efficiency and power in genetic association studies. *Nat Genet* **37:** 1217-1223.

del Bosque-Plata, L., C.A. Aguilar-Salinas, M.T. Tusie-Luna, S. Ramirez-Jimenez, M. Rodriguez-Torres, M. Auron-Gomez, E. Ramirez, M.L. Velasco-Perez, A. Ramirez-Silva, F. Gomez-Perez, C.L. Hanis, T. Tsuchiya, I. Yoshiuchi, N.J. Cox, and G.I. Bell. 2004. Association of the calpain-10 gene with type 2 diabetes mellitus in a Mexican population. *Mol Genet Metab* **81:** 122-126.

Del Guerra, S., R. Lupi, L. Marselli, M. Masini, M. Bugliani, S. Sbrana, S. Torri, M. Pollera, U. Boggi, F. Mosca, S. Del Prato, and P. Marchetti. 2005. Functional and molecular defects of pancreatic islets in human type 2 diabetes. *Diabetes* **54:** 727-735.

Delepine, M., M. Nicolino, T. Barrett, M. Golamaully, G.M. Lathrop, and C. Julier. 2000. EIF2AK3, encoding translation initiation factor 2-alpha kinase 3, is mutated in patients with Wolcott-Rallison syndrome. *Nat Genet* **25:** 406-409.

Di Paolo, S., A. Teutonico, D. Leogrande, C. Capobianco, and P.F. Schena. 2006. Chronic inhibition of mammalian target of rapamycin signaling downregulates insulin receptor substrates 1 and 2 and AKT activation: A crossroad between cancer and diabetes? *J Am Soc Nephrol* **17:** 2236-2244.

Doney, A., B. Fischer, D. Frew, A. Cumming, D.M. Flavell, M. World, H.E. Montgomery, D. Boyle, A. Morris, and C.N. Palmer. 2002. Haplotype analysis of the PPARgamma Pro12Ala and C1431T variants reveals opposing associations with body weight. *BMC Genet* **3:** 21.

Doney, A.S., B. Fischer, J.E. Cecil, K. Boylan, F.E. McGuigan, S.H. Ralston, A.D. Morris, and C.N. Palmer. 2004a. Association of the Pro12Ala and C1431T variants of PPARG and their haplotypes with susceptibility to Type 2 diabetes. *Diabetologia* **47:** 555-558.

Doney, A.S., B. Fischer, J.E. Cecil, P.T. Cohen, D.I. Boyle, G. Leese, A.D. Morris, and C.N. Palmer. 2003. Male preponderance in early diagnosed type 2 diabetes is associated with the ARE insertion/deletion polymorphism in the PPP1R3A locus. *BMC Genet* **4:** 11.

Doney, A.S., B. Fischer, S.P. Lee, A.D. Morris, G. Leese, and C.N. Palmer. 2005a. Association of common variation in the PPARA gene with incident myocardial infarction in individuals with type 2 diabetes: A Go-DARTS study. *Nucl Recept* **3:** 4.

Doney, A.S., B. Fischer, G. Leese, A.D. Morris, and C.N. Palmer. 2004b. Cardiovascular risk in type 2 diabetes is associated with variation at the PPARG locus: a Go-DARTS study. *Arterioscler Thromb Vasc Biol* **24:** 2403-2407.

Doney, A.S., S. Lee, G.P. Leese, A.D. Morris, and C.N. Palmer. 2005b. Increased cardiovascular morbidity and mortality in type 2 diabetes is associated with the glutathione S transferase theta-null genotype: a Go-DARTS study. *Circulation* **111:** 2927-2934.

Dong, C., Z. Qian, P. Jia, Y. Wang, W. Huang, and Y. Li. 2007. Gene-centric characteristics of genome-wide association studies. *PLoS ONE* **2:** e1262.

Donkor, J., M. Sariahmetoglu, J. Dewald, D.N. Brindley, and K. Reue. 2007a. Three mammalian lipins act as phosphatidate phosphatases with distinct tissue expression patterns. *J Biol Chem* **282:** 3450-3457.

Donkor, J., L.M. Sparks, H. Xie, S.R. Smith, and K. Reue. 2007b. Adipose tissue lipin-1 expression is correlated with ppar{alpha} gene expression and insulin sensitivity in healthy young men. *J Clin Endocrinol Metab*.

Dunnigan, M.G., M.A. Cochrane, A. Kelly, and J.W. Scott. 1974. Familial lipoatrophic diabetes with dominant transmission. A new syndrome. *Q J Med* **43:** 33-48.

Dupont, W.D. and W.D. Plummer, Jr. 1990. Power and sample size calculations. A review and computer program. *Control Clin Trials* **11:** 116-128.

Durocher, F., R. Faure, Y. Labrie, L. Pelletier, I. Bouchard, and R. Laframboise. 2006. A novel mutation in the EIF2AK3 gene with variable expressivity in two patients with Wolcott-Rallison syndrome. *Clin Genet* **70:** 34-38.

Easton, R.M., H. Cho, K. Roovers, D.W. Shineman, M. Mizrahi, M.S. Forman, V.M. Lee, M. Szabolcs, R. de Jong, T. Oltersdorf, T. Ludwig, A. Efstratiadis, and M.J. Birnbaum. 2005. Role for Akt3/protein kinase Bgamma in attainment of normal brain size. *Mol Cell Biol* **25:** 1869-1878.

Edwards, A.O., R. Ritter, 3rd, K.J. Abel, A. Manning, C. Panhuysen, and L.A. Farrer. 2005. Complement factor H polymorphism and age-related macular degeneration. *Science* **308:** 421-424.

Eguez, L., A. Lee, J.A. Chavez, C.P. Miinea, S. Kane, G.E. Lienhard, and T.E. McGraw. 2005. Full intracellular retention of GLUT4 requires AS160 Rab GTPase activating protein. *Cell Metab* **2:** 263-272.

Eizirik, D.L., A.K. Cardozo, and M. Cnop. 2008. The role for endoplasmic reticulum stress in diabetes mellitus. *Endocr Rev* **29:** 42-61.

Ekelund, U., P.W. Franks, S. Sharp, S. Brage, and N.J. Wareham. 2007. Increase in physical activity energy expenditure is associated with reduced metabolic risk independent of change in fatness and fitness. *Diabetes Care* **30:** 2101-2106.

El-Assaad, W., J. Buteau, M.L. Peyot, C. Nolan, R. Roduit, S. Hardy, E. Joly, G. Dbaibo, L. Rosenberg, and M. Prentki. 2003. Saturated fatty acids synergize with elevated glucose to cause pancreatic beta-cell death. *Endocrinology* **144:** 4154-4163.

Elbein, S.C., W. Chu, Q. Ren, C. Hemphill, J. Schay, N.J. Cox, C.L. Hanis, and S.J. Hasstedt. 2002. Role of calpain-10 gene variants in familial type 2 diabetes in Caucasians. *J Clin Endocrinol Metab* **87:** 650-654.

Elchebly, M., P. Payette, E. Michaliszyn, W. Cromlish, S. Collins, A.L. Loy, D. Normandin, A. Cheng, J. Himms-Hagen, C.C. Chan, C. Ramachandran, M.J. Gresser, M.L. Tremblay, and B.P. Kennedy. 1999. Increased insulin sensitivity and obesity resistance in mice lacking the protein tyrosine phosphatase-1B gene. *Science* **283:** 1544-1548.

Fan, J.B., A. Oliphant, R. Shen, B.G. Kermani, F. Garcia, K.L. Gunderson, M. Hansen, F. Steemers, S.L. Butler, P. Deloukas, L. Galver, S. Hunt, C. McBride, M. Bibikova, T. Rubano, J. Chen, E. Wickham, D. Doucet, W. Chang, D. Campbell, B. Zhang, S. Kruglyak, D. Bentley, J. Haas, P. Rigault, L. Zhou, J. Stuelpnagel, and M.S. Chee. 2003. Highly parallel SNP genotyping. *Cold Spring Harb Symp Quant Biol* **68:** 69-78.

Fanciulli, M., P.J. Norsworthy, E. Petretto, R. Dong, L. Harper, L. Kamesh, J.M. Heward, S.C. Gough, A. de Smith, A.I. Blakemore, P. Froguel, C.J. Owen, S.H. Pearce, L. Teixeira, L. Guillevin, D.S. Graham, C.D. Pusey, H.T. Cook, T.J. Vyse, and T.J. Aitman. 2007. FCGR3B copy number variation is associated with susceptibility to systemic, but not organ-specific, autoimmunity. *Nat Genet* **39:** 721-723.

Fawcett, K.A., N. Grimsey, R.J. Loos, E. Wheeler, A. Daly, M. Soos, R. Semple, H. Syddall, C. Cooper, S. Siniossoglou, S. O'Rahilly, N.J. Wareham, and I. Barroso. 2008. Evaluating the role of LPIN1 variation in insulin resistance, body weight, and human lipodystrophy in U.K. Populations. *Diabetes* **57:** 2527-2533.

Fawcett, K.A., N.J. Wareham, J. Luan, H. Syddall, C. Cooper, S. O'Rahilly, I.N. Day, M.S. Sandhu, and I. Barroso. 2006. PARL Leu262Val is not associated with fasting insulin levels in UK populations. *Diabetologia* **49:** 2649-2652.

Ferguson, P.J., X. Bing, M.A. Vasef, L.A. Ochoa, A. Mahgoub, T.J. Waldschmidt, L.T. Tygrett, A.J. Schlueter, and H. El-Shanti. 2006. A missense mutation in pstpip2 is associated with the murine autoinflammatory disorder chronic multifocal osteomyelitis. *Bone* **38:** 41-47.

Ferguson, P.J., S. Chen, M.K. Tayeh, L. Ochoa, S.M. Leal, A. Pelet, A. Munnich, S. Lyonnet, H.A. Majeed, and H. El-Shanti. 2005. Homozygous mutations in LPIN2 are responsible for the syndrome of chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anaemia (Majeed syndrome). *J Med Genet* **42:** 551-557.

Finck, B.N., M.C. Gropler, Z. Chen, T.C. Leone, M.A. Croce, T.E. Harris, J.C. Lawrence, Jr., and D.P. Kelly. 2006. Lipin 1 is an inducible amplifier of the hepatic PGC-1alpha/PPARalpha regulatory pathway. *Cell Metab* **4:** 199-210.

Flier, J.S., D.E. Moller, A.C. Moses, S. O'Rahilly, R.L. Chaiken, F. Grigorescu, D. Elahi, B.B. Kahn, J.E. Weinreb, and R. Eastman. 1993. Insulin-mediated pseudoacromegaly: clinical and biochemical characterization of a syndrome of selective insulin resistance. *J Clin Endocrinol Metab* **76:** 1533-1541.

Fonseca, S.G., M. Fukuma, K.L. Lipson, L.X. Nguyen, J.R. Allen, Y. Oka, and F. Urano. 2005. WFS1 is a novel component of the unfolded protein response and maintains homeostasis of the endoplasmic reticulum in pancreatic beta-cells. *J Biol Chem* **280:** 39609-39615.

Foti, D., E. Chiefari, M. Fedele, R. Iuliano, L. Brunetti, F. Paonessa, G. Manfioletti, F. Barbetti, A. Brunetti, C.M. Croce, A. Fusco, and A. Brunetti. 2005. Lack of the architectural factor HMGA1 causes insulin resistance and diabetes in humans and mice. *Nat Med* **11:** 765-773.

Fraenkel, M., M. Ketzinel-Gilad, Y. Ariav, O. Pappo, M. Karaca, J. Castel, M.F. Berthault, C. Magnan, E. Cerasi, N. Kaiser, and G. Leibowitz. 2008. mTOR inhibition by rapamycin prevents beta-cell adaptation to hyperglycemia and exacerbates the metabolic state in type 2 diabetes. *Diabetes* **57:** 945-957.

Frank, B., J.L. Bermejo, K. Hemminki, C. Sutter, B. Wappenschmidt, A. Meindl, M. Kiechle-Bahat, P. Bugert, R.K. Schmutzler, C.R. Bartram, and B. Burwinkel. 2007. Copy number variant in the candidate tumor suppressor gene MTUS1 and familial breast cancer risk. *Carcinogenesis* **28:** 1442-1445.

Franks, P.W., O. Rolandsson, S.L. Debenham, K.A. Fawcett, F. Payne, C. Dina, P. Froguel, K.L. Mohlke, C. Willer, T. Olsson, N.J. Wareham, G. Hallmans, I. Barroso, and M.S. Sandhu. 2008. Replication of the association between variants in WFS1 and risk of type 2 diabetes in European populations. *Diabetologia* **51:** 458-463.

Fraser, F.C. and T. Gunn. 1977. Diabetes mellitus, diabetes insipidus, and optic atrophy. An autosomal recessive syndrome? *J Med Genet* **14:** 190-193.

Frayling, T., M. Walker, M. McCarthy, J. Evans, L. Allen, S. Lynn, S. Ayres, B. Millauer, C. Turner, R. Turner, M. Sampson, G. Hitman, S. Ellard, and A. Hattersley. 1999. Parent-offspring Trios: a resource to facilitate the identification of Type 2 diabetes genes. *Diabetes* **48:** 2475-2479.

Frayling, T.M., N.J. Timpson, M.N. Weedon, E. Zeggini, R.M. Freathy, C.M. Lindgren, J.R. Perry, K.S. Elliott, H. Lango, N.W. Rayner, B. Shields, L.W. Harries, J.C. Barrett, S. Ellard, C.J. Groves, B. Knight, A.M. Patch, A.R. Ness, S. Ebrahim, D.A. Lawlor, S.M. Ring, Y. Ben-Shlomo, M.R. Jarvelin, U. Sovio, A.J. Bennett, D. Melzer, L. Ferrucci, R.J. Loos, I. Barroso, N.J. Wareham, F. Karpe, K.R. Owen, L.R. Cardon, M. Walker, G.A. Hitman, C.N. Palmer, A.S. Doney, A.D. Morris, G.D. Smith, A.T. Hattersley, and M.I. McCarthy. 2007. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science* **316:** 889-894.

Frazer, K.A. D.G. Ballinger D.R. Cox D.A. Hinds L.L. Stuve R.A. Gibbs J.W. Belmont A. Boudreau P. Hardenbol S.M. Leal S. Pasternak D.A. Wheeler T.D. Willis F. Yu H. Yang C. Zeng Y. Gao H. Hu W. Hu C. Li W. Lin S. Liu H. Pan X. Tang J. Wang W. Wang J. Yu B. Zhang Q. Zhang H. Zhao H. Zhao J. Zhou S.B. Gabriel R. Barry B. Blumenstiel A. Camargo M. Defelice M. Faggart M. Goyette S. Gupta J. Moore H. Nguyen R.C. Onofrio M. Parkin J. Roy E. Stahl E. Winchester L. Ziaugra D. Altshuler Y. Shen Z. Yao W. Huang X. Chu Y. He L. Jin Y. Liu Y. Shen W. Sun H. Wang Y. Wang Y. Wang X. Xiong L. Xu M.M. Waye S.K. Tsui H. Xue J.T. Wong L.M. Galver J.B. Fan K. Gunderson S.S. Murray A.R. Oliphant M.S. Chee A. Montpetit F. Chagnon V. Ferretti M. Leboeuf J.F. Olivier M.S. Phillips S. Roumy C. Sallee A. Verner T.J. Hudson P.Y. Kwok D. Cai D.C. Koboldt R.D. Miller L. Pawlikowska P. Taillon-Miller M. Xiao L.C. Tsui W. Mak Y.Q. Song P.K. Tam Y. Nakamura T. Kawaguchi T. Kitamoto T. Morizono A. Nagashima Y. Ohnishi A. Sekine T. Tanaka T. Tsunoda P. Deloukas C.P. Bird M. Delgado E.T. Dermitzakis R. Gwilliam S. Hunt J. Morrison D. Powell B.E. Stranger P. Whittaker D.R. Bentley M.J. Daly P.I. de Bakker J. Barrett Y.R. Chretien J. Maller S. McCarroll N. Patterson I. Pe'er A. Price S. Purcell D.J. Richter P. Sabeti R. Saxena S.F. Schaffner P.C. Sham P. Varilly D. Altshuler L.D. Stein L. Krishnan A.V. Smith M.K. Tello-Ruiz G.A. Thorisson A. Chakravarti P.E. Chen D.J. Cutler C.S. Kashuk S. Lin G.R. Abecasis W. Guan Y. Li H.M. Munro Z.S. Qin D.J. Thomas G. McVean A. Auton L. Bottolo N. Cardin S. Eyheramendy C. Freeman J. Marchini S. Myers C. Spencer M. Stephens P. Donnelly L.R. Cardon G. Clarke D.M. Evans A.P. Morris B.S. Weir T. Tsunoda J.C. Mullikin S.T. Sherry M. Feolo A. Skol H. Zhang C. Zeng H. Zhao I. Matsuda Y. Fukushima D.R. Macer E. Suda C.N. Rotimi C.A. Adebamowo I. Ajayi T. Aniagwu P.A. Marshall C. Nkwodimmah C.D. Royal M.F. Leppert M. Dixon A. Peiffer R. Qiu A. Kent K. Kato N. Niikawa I.F. Adewole B.M. Knoppers M.W. Foster E.W. Clayton J. Watkin R.A. Gibbs J.W. Belmont D. Muzny L. Nazareth E. Sodergren G.M. Weinstock D.A. Wheeler I. Yakub S.B. Gabriel R.C. Onofrio D.J. Richter L. Ziaugra B.W. Birren M.J. Daly D. Altshuler R.K. Wilson L.L. Fulton J. Rogers J. Burton N.P. Carter C.M. Clee M. Griffiths M.C. Jones K. McLay R.W. Plumb M.T. Ross S.K. Sims D.L. Willey Z. Chen H. Han L. Kang M. Godbout J.C. Wallenburg P. L'Archeveque G. Bellemare K. Saeki H. Wang D. An H. Fu Q. Li Z. Wang R. Wang A.L. Holden L.D. Brooks J.E. McEwen M.S. Guyer V.O. Wang J.L. Peterson M. Shi J. Spiegel L.M. Sung L.F. Zacharia F.S. Collins K. Kennedy R. Jamieson and J. Stewart. 2007. A second generation human haplotype map of over 3.1 million SNPs. *Nature* **449:** 851-861.

Fredriksson, R., M. Hagglund, P.K. Olszewski, O. Stephansson, J.A. Jacobsson, A.M. Olszewska, A.S. Levine, J. Lindblom, and H.B. Schioth. 2008. The obesity gene,

FTO, is of ancient origin, up-regulated during food deprivation and expressed in neurons of feeding-related nuclei of the brain. *Endocrinology* **149:** 2062-2071.

Frias, M.A., C.C. Thoreen, J.D. Jaffe, W. Schroder, T. Sculley, S.A. Carr, and D.M. Sabatini. 2006. mSin1 is necessary for Akt/PKB phosphorylation, and its isoforms define three distinct mTORC2s. *Curr Biol* **16:** 1865-1870.

Froguel, P., M. Vaxillaire, F. Sun, G. Velho, H. Zouali, M.O. Butel, S. Lesage, N. Vionnet, K. Clement, F. Fougerousse, and et al. 1992. Close linkage of glucokinase locus on chromosome 7p to early-onset non-insulin-dependent diabetes mellitus. *Nature* **356:** 162-164.

Fu, Y.H., A. Pizzuti, R.G. Fenwick, Jr., J. King, S. Rajnarayan, P.W. Dunne, J. Dubel, G.A. Nasser, T. Ashizawa, P. de Jong, and et al. 1992. An unstable triplet repeat in a gene related to myotonic muscular dystrophy. *Science* **255:** 1256-1258.

Gao, Z., X. Zhang, A. Zuberi, D. Hwang, M.J. Quon, M. Lefevre, and J. Ye. 2004. Inhibition of insulin sensitivity by free fatty acids requires activation of multiple serine kinases in 3T3-L1 adipocytes. *Mol Endocrinol* **18:** 2024-2034.

Garant, M.J., W.H. Kao, F. Brancati, J. Coresh, T.M. Rami, C.L. Hanis, E. Boerwinkle, and A.R. Shuldiner. 2002. SNP43 of CAPN10 and the risk of type 2 Diabetes in African-Americans: the Atherosclerosis Risk in Communities Study. *Diabetes* **51:** 231-237.

Garg, A., R. Wilson, R. Barnes, E. Arioglu, Z. Zaidi, F. Gurakan, N. Kocak, S. O'Rahilly, S.I. Taylor, S.B. Patel, and A.M. Bowcock. 1999. A gene for congenital generalized lipodystrophy maps to human chromosome 9q34. *J Clin Endocrinol Metab* **84:** 3390-3394.

Garofalo, R.S., S.J. Orena, K. Rafidi, A.J. Torchia, J.L. Stock, A.L. Hildebrandt, T. Coskran, S.C. Black, D.J. Brees, J.R. Wicks, J.D. McNeish, and K.G. Coleman. 2003. Severe diabetes, age-dependent loss of adipose tissue, and mild growth deficiency in mice lacking Akt2/PKB beta. *J Clin Invest* **112:** 197-208.

Gavrilova, O., B. Marcus-Samuels, D. Graham, J.K. Kim, G.I. Shulman, A.L. Castle, C. Vinson, M. Eckhaus, and M.L. Reitman. 2000. Surgical implantation of adipose tissue reverses diabetes in lipoatrophic mice. *J Clin Invest* **105:** 271-278.

George, S., J.J. Rochford, C. Wolfrum, S.L. Gray, S. Schinner, J.C. Wilson, M.A. Soos, P.R. Murgatroyd, R.M. Williams, C.L. Acerini, D.B. Dunger, D. Barford, A.M. Umpleby, N.J. Wareham, H.A. Davies, A.J. Schafer, M. Stoffel, S. O'Rahilly, and I. Barroso. 2004. A family with severe insulin resistance and diabetes due to a mutation in AKT2. *Science* **304:** 1325-1328.

Gerken, T., C.A. Girard, Y.C. Tung, C.J. Webby, V. Saudek, K.S. Hewitson, G.S. Yeo, M.A. McDonough, S. Cunliffe, L.A. McNeill, J. Galvanovskis, P. Rorsman, P. Robins, X. Prieur, A.P. Coll, M. Ma, Z. Jovanovic, I.S. Farooqi, B. Sedgwick, I. Barroso, T. Lindahl, C.P. Ponting, F.M. Ashcroft, S. O'Rahilly, and C.J. Schofield. 2007. The obesity-associated FTO gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase. *Science* **318:** 1469-1472.

Glaser, B., P. Kesavan, M. Heyman, E. Davis, A. Cuesta, A. Buchs, C.A. Stanley, P.S. Thornton, M.A. Permutt, F.M. Matschinsky, and K.C. Herold. 1998. Familial hyperinsulinism caused by an activating glucokinase mutation. *N Engl J Med* **338:** 226-230.

Gloyn, A.L., Y. Hashim, S.J. Ashcroft, R. Ashfield, S. Wiltshire, and R.C. Turner. 2001. Association studies of variants in promoter and coding regions of beta-cell ATP-sensitive K-channel genes SUR1 and Kir6.2 with Type 2 diabetes mellitus (UKPDS 53). *Diabet Med* **18:** 206-212.

Gloyn, A.L., E.R. Pearson, J.F. Antcliff, P. Proks, G.J. Bruining, A.S. Slingerland, N. Howard, S. Srinivasan, J.M. Silva, J. Molnes, E.L. Edghill, T.M. Frayling, I.K. Temple, D. Mackay, J.P. Shield, Z. Sumnik, A. van Rhijn, J.K. Wales, P. Clark, S.

Gorman, J. Aisenberg, S. Ellard, P.R. Njolstad, F.M. Ashcroft, and A.T. Hattersley. 2004. Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. *N Engl J Med* **350:** 1838-1849.

Gloyn, A.L., F. Reimann, C. Girard, E.L. Edghill, P. Proks, E.R. Pearson, I.K. Temple, D.J. Mackay, J.P. Shield, D. Freedenberg, K. Noyes, S. Ellard, F.M. Ashcroft, F.M. Gribble, and A.T. Hattersley. 2005. Relapsing diabetes can result from moderately activating mutations in KCNJ11. *Hum Mol Genet* **14:** 925-934.

Gloyn, A.L., M.N. Weedon, K.R. Owen, M.J. Turner, B.A. Knight, G. Hitman, M. Walker, J.C. Levy, M. Sampson, S. Halford, M.I. McCarthy, A.T. Hattersley, and T.M. Frayling. 2003. Large-scale association studies of variants in genes encoding the pancreatic beta-cell KATP channel subunits Kir6.2 (KCNJ11) and SUR1 (ABCC8) confirm that the KCNJ11 E23K variant is associated with type 2 diabetes. *Diabetes* **52:** 568-572.

Gomez-Zaera, M., T.M. Strom, B. Rodriguez, X. Estivill, T. Meitinger, and V. Nunes. 2001. Presence of a major WFS1 mutation in Spanish Wolfram syndrome pedigrees. *Mol Genet Metab* **72:** 72-81.

Grant, S.F., G. Thorleifsson, I. Reynisdottir, R. Benediktsson, A. Manolescu, J. Sainz, A. Helgason, H. Stefansson, V. Emilsson, A. Helgadottir, U. Styrkarsdottir, K.P. Magnusson, G.B. Walters, E. Palsdottir, T. Jonsdottir, T. Gudmundsdottir, A. Gylfason, J. Saemundsdottir, R.L. Wilensky, M.P. Reilly, D.J. Rader, Y. Bagger, C. Christiansen, V. Gudnason, G. Sigurdsson, U. Thorsteinsdottir, J.R. Gulcher, A. Kong, and K. Stefansson. 2006. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. *Nat Genet* **38:** 320-323.

Grarup, N., G. Andersen, N.T. Krarup, A. Albrechtsen, O. Schmitz, T. Jorgensen, K. Borch-Johnsen, T. Hansen, and O. Pedersen. 2008. Association testing of novel type 2 diabetes risk alleles in the JAZF1, CDC123/CAMK1D, TSPAN8, THADA, ADAMTS9, and NOTCH2 loci with insulin release, insulin sensitivity, and obesity in a population-based sample of 4,516 glucose-tolerant middle-aged Danes. *Diabetes* **57:** 2534-2540.

Gudmundsson, J., P. Sulem, V. Steinthorsdottir, J.T. Bergthorsson, G. Thorleifsson, A. Manolescu, T. Rafnar, D. Gudbjartsson, B.A. Agnarsson, A. Baker, A. Sigurdsson, K.R. Benediktsdottir, M. Jakobsdottir, T. Blondal, S.N. Stacey, A. Helgason, S. Gunnarsdottir, A. Olafsdottir, K.T. Kristinsson, B. Birgisdottir, S. Ghosh, S. Thorlacius, D. Magnusdottir, G. Stefansdottir, K. Kristjansson, Y. Bagger, R.L. Wilensky, M.P. Reilly, A.D. Morris, C.H. Kimber, A. Adeyemo, Y. Chen, J. Zhou, W.Y. So, P.C. Tong, M.C. Ng, T. Hansen, G. Andersen, K. Borch-Johnsen, T. Jorgensen, A. Tres, F. Fuertes, M. Ruiz-Echarri, L. Asin, B. Saez, E. van Boven, S. Klaver, D.W. Swinkels, K.K. Aben, T. Graif, J. Cashy, B.K. Suarez, O. van Vierssen Trip, M.L. Frigge, C. Ober, M.H. Hofker, C. Wijmenga, C. Christiansen, D.J. Rader, C.N. Palmer, C. Rotimi, J.C. Chan, O. Pedersen, G. Sigurdsson, R. Benediktsson, E. Jonsson, G.V. Einarsson, J.I. Mayordomo, W.J. Catalona, L.A. Kiemeney, R.B. Barkardottir, J.R. Gulcher, U. Thorsteinsdottir, A. Kong, and K. Stefansson. 2007. Two variants on chromosome 17 confer prostate cancer risk, and the one in TCF2 protects against type 2 diabetes. *Nat Genet* **39:** 977-983.

Guertin, D.A., D.M. Stevens, C.C. Thoreen, A.A. Burds, N.Y. Kalaany, J. Moffat, M. Brown, K.J. Fitzgerald, and D.M. Sabatini. 2006. Ablation in mice of the mTORC components raptor, rictor, or mLST8 reveals that mTORC2 is required for signaling to Akt-FOXO and PKCalpha, but not S6K1. *Dev Cell* **11:** 859-871.

Gunderson, K.L., F.J. Steemers, G. Lee, L.G. Mendoza, and M.S. Chee. 2005. A genome-wide scalable SNP genotyping assay using microarray technology. *Nat Genet* **37:** 549-554.

Haines, J.L., M.A. Hauser, S. Schmidt, W.K. Scott, L.M. Olson, P. Gallins, K.L. Spencer, S.Y. Kwan, M. Noureddine, J.R. Gilbert, N. Schnetz-Boutaud, A. Agarwal, E.A. Postel, and M.A. Pericak-Vance. 2005. Complement factor H variant increases the risk of age-related macular degeneration. *Science* **308:** 419-421.

Hamsten, A. and P. Eriksson. 2008. Identifying the susceptibility genes for coronary artery disease: from hyperbole through doubt to cautious optimism. *J Intern Med* **263:** 538-552.

Han, G.S., W.I. Wu, and G.M. Carman. 2006. The Saccharomyces cerevisiae Lipin homolog is a Mg2+-dependent phosphatidate phosphatase enzyme. *J Biol Chem* **281:** 9210-9218.

Hani, E.H., P. Boutin, E. Durand, H. Inoue, M.A. Permutt, G. Velho, and P. Froguel. 1998. Missense mutations in the pancreatic islet beta cell inwardly rectifying K+ channel gene (KIR6.2/BIR): a meta-analysis suggests a role in the polygenic basis of Type II diabetes mellitus in Caucasians. *Diabetologia* **41:** 1511-1515.

Harding, A.H., N.E. Day, K.T. Khaw, S. Bingham, R. Luben, A. Welsh, and N.J. Wareham. 2004. Dietary fat and the risk of clinical type 2 diabetes: the European prospective investigation of Cancer-Norfolk study. *Am J Epidemiol* **159:** 73-82.

Harding, H.P., H. Zeng, Y. Zhang, R. Jungries, P. Chung, H. Plesken, D.D. Sabatini, and D. Ron. 2001. Diabetes mellitus and exocrine pancreatic dysfunction in perk-/- mice reveals a role for translational control in secretory cell survival. *Mol Cell* **7:** 1153-1163.

Hardy, C., F. Khanim, R. Torres, M. Scott-Brown, A. Seller, J. Poulton, D. Collier, J. Kirk, M. Polymeropoulos, F. Latif, and T. Barrett. 1999. Clinical and molecular genetic analysis of 19 Wolfram syndrome kindreds demonstrating a wide spectrum of mutations in WFS1. *Am J Hum Genet* **65:** 1279-1290.

Harrington, L.S., G.M. Findlay, A. Gray, T. Tolkacheva, S. Wigfield, H. Rebholz, J. Barnett, N.R. Leslie, S. Cheng, P.R. Shepherd, I. Gout, C.P. Downes, and R.F. Lamb. 2004. The TSC1-2 tumor suppressor controls insulin-PI3K signaling via regulation of IRS proteins. *J Cell Biol* **166:** 213-223.

Harris, T.E., T.A. Huffman, A. Chi, J. Shabanowitz, D.F. Hunt, A. Kumar, and J.C. Lawrence, Jr. 2007. Insulin controls subcellular localization and multisite phosphorylation of the phosphatidic acid phosphatase, lipin 1. *J Biol Chem* **282:** 277-286.

Haruta, T., T. Uno, J. Kawahara, A. Takano, K. Egawa, P.M. Sharma, J.M. Olefsky, and M. Kobayashi. 2000. A rapamycin-sensitive pathway down-regulates insulin signaling via phosphorylation and proteasomal degradation of insulin receptor substrate-1. *Mol Endocrinol* **14:** 783-794.

Hattersley, A.T., R.C. Turner, M.A. Permutt, P. Patel, Y. Tanizawa, K.C. Chiu, S. O'Rahilly, P.J. Watkins, and J.S. Wainscoat. 1992. Linkage of type 2 diabetes to the glucokinase gene. *Lancet* **339:** 1307-1310.

Hayden, E.C. 2008. International genome project launched. *Nature* **451:** 378-379.

Hearn, T., G.L. Renforth, C. Spalluto, N.A. Hanley, K. Piper, S. Brickwood, C. White, V. Connolly, J.F. Taylor, I. Russell-Eggitt, D. Bonneau, M. Walker, and D.I. Wilson. 2002. Mutation of ALMS1, a large gene with a tandem repeat encoding 47 amino acids, causes Alstrom syndrome. *Nat Genet* **31:** 79-83.

Hegele, R.A., H. Cao, C. Frankowski, S.T. Mathews, and T. Leff. 2002. PPARG F388L, a transactivation-deficient mutant, in familial partial lipodystrophy. *Diabetes* **51:** 3586-3590.

Hegele, R.A., S.B. Harris, B. Zinman, A.J. Hanley, and H. Cao. 2001. Absence of association of type 2 diabetes with CAPN10 and PC-1 polymorphisms in Oji-Cree. *Diabetes Care* **24:** 1498-1499.

Heitman, J., N.R. Movva, and M.N. Hall. 1991. Targets for cell cycle arrest by the immunosuppressant rapamycin in yeast. *Science* **253:** 905-909.

Helgadottir, A., A. Manolescu, G. Thorleifsson, S. Gretarsdottir, H. Jonsdottir, U. Thorsteinsdottir, N.J. Samani, G. Gudmundsson, S.F. Grant, G. Thorgeirsson, S. Sveinbjornsdottir, E.M. Valdimarsson, S.E. Matthiasson, H. Johannsson, O. Gudmundsdottir, M.E. Gurney, J. Sainz, M. Thorhallsdottir, M. Andresdottir, M.L. Frigge, E.J. Topol, A. Kong, V. Gudnason, H. Hakonarson, J.R. Gulcher, and K. Stefansson. 2004. The gene encoding 5-lipoxygenase activating protein confers risk of myocardial infarction and stroke. *Nat Genet* **36:** 233-239.

Heller-Harrison, R.A., M. Morin, and M.P. Czech. 1995. Insulin regulation of membrane-associated insulin receptor substrate 1. *J Biol Chem* **270:** 24442-24450.

Hofmann, S. and M.F. Bauer. 2006. Wolfram syndrome-associated mutations lead to instability and proteasomal degradation of wolframin. *FEBS Lett* **580:** 4000-4004.

Hofmann, S., C. Philbrook, K.D. Gerbitz, and M.F. Bauer. 2003. Wolfram syndrome: structural and functional analyses of mutant and wild-type wolframin, the WFS1 gene product. *Hum Mol Genet* **12:** 2003-2012.

Horikawa, Y., N. Iwasaki, M. Hara, H. Furuta, Y. Hinokio, B.N. Cockburn, T. Lindner, K. Yamagata, M. Ogata, O. Tomonaga, H. Kuroki, T. Kasahara, Y. Iwamoto, and G.I. Bell. 1997. Mutation in hepatocyte nuclear factor-1 beta gene (TCF2) associated with MODY. *Nat Genet* **17:** 384-385.

Horikawa, Y., N. Oda, N.J. Cox, X. Li, M. Orho-Melander, M. Hara, Y. Hinokio, T.H. Lindner, H. Mashima, P.E. Schwarz, L. del Bosque-Plata, Y. Oda, I. Yoshiuchi, S. Colilla, K.S. Polonsky, S. Wei, P. Concannon, N. Iwasaki, J. Schulze, L.J. Baier, C. Bogardus, L. Groop, E. Boerwinkle, C.L. Hanis, and G.I. Bell. 2000. Genetic variation in the gene encoding calpain-10 is associated with type 2 diabetes mellitus. *Nat Genet* **26:** 163-175.

Hossain, P., B. Kawar, and M. El Nahas. 2007. Obesity and diabetes in the developing world--a growing challenge. *N Engl J Med* **356:** 213-215.

Hresko, R.C. and M. Mueckler. 2005. mTOR.RICTOR is the Ser473 kinase for Akt/protein kinase B in 3T3-L1 adipocytes. *J Biol Chem* **280:** 40406-40416.

Huffman, T.A., I. Mothe-Satney, and J.C. Lawrence, Jr. 2002. Insulin-stimulated phosphorylation of lipin mediated by the mammalian target of rapamycin. *Proc Natl Acad Sci U S A* **99:** 1047-1052.

Inoue, H., Y. Tanizawa, J. Wasson, P. Behn, K. Kalidas, E. Bernal-Mizrachi, M. Mueckler, H. Marshall, H. Donis-Keller, P. Crock, D. Rogers, M. Mikuni, H. Kumashiro, K. Higashi, G. Sobue, Y. Oka, and M.A. Permutt. 1998. A gene encoding a transmembrane protein is mutated in patients with diabetes mellitus and optic atrophy (Wolfram syndrome). *Nat Genet* **20:** 143-148.

Ishihara, H., S. Takeda, A. Tamura, R. Takahashi, S. Yamaguchi, D. Takei, T. Yamada, H. Inoue, H. Soga, H. Katagiri, Y. Tanizawa, and Y. Oka. 2004. Disruption of the WFS1 gene in mice causes progressive beta-cell loss and impaired stimulus-secretion coupling in insulin secretion. *Hum Mol Genet* **13:** 1159-1170.

Itani, S.I., N.B. Ruderman, F. Schmieder, and G. Boden. 2002. Lipid-induced insulin resistance in human muscle is associated with changes in diacylglycerol, protein kinase C, and IkappaB-alpha. *Diabetes* **51:** 2005-2011.

Jacinto, E., V. Facchinetti, D. Liu, N. Soto, S. Wei, S.Y. Jung, Q. Huang, J. Qin, and B. Su. 2006. SIN1/MIP1 maintains rictor-mTOR complex integrity and regulates Akt phosphorylation and substrate specificity. *Cell* **127:** 125-137.

Jacinto, E., R. Loewith, A. Schmidt, S. Lin, M.A. Ruegg, A. Hall, and M.N. Hall. 2004. Mammalian TOR complex 2 controls the actin cytoskeleton and is rapamycin insensitive. *Nat Cell Biol* **6:** 1122-1128.

James, D.E., R. Brown, J. Navarro, and P.F. Pilch. 1988. Insulin-regulatable tissues express a unique insulin-sensitive glucose transport protein. *Nature* **333:** 183-185.

James, D.E., M. Strube, and M. Mueckler. 1989. Molecular cloning and characterization of an insulin-regulatable glucose transporter. *Nature* **338:** 83-87.

Ji, W., J.N. Foo, B.J. O'Roak, H. Zhao, M.G. Larson, D.B. Simon, C. Newton-Cheh, M.W. State, D. Levy, and R.P. Lifton. 2008. Rare independent mutations in renal salt handling genes contribute to blood pressure variation. *Nat Genet* **40:** 592-599.

Jin, T. and L. Liu. 2008. The Wnt Signaling Pathway Effector TCF7L2 and Type II Diabetes Mellitus. *Mol Endocrinol*.

Joshi, R.L., B. Lamothe, N. Cordonnier, K. Mesbah, E. Monthioux, J. Jami, and D. Bucchini. 1996. Targeted disruption of the insulin receptor gene in the mouse results in neonatal lethality. *Embo J* **15:** 1542-1547.

Kadayifci, A., Y. Kepekci, Y. Coskun, and Y. Huang. 2001. Wolfram syndrome in a family with variable expression. *Acta Medica (Hradec Kralove)* **44:** 115-118.

Kadowaki, T., C.L. Bevins, A. Cama, K. Ojamaa, B. Marcus-Samuels, H. Kadowaki, L. Beitz, C. McKeon, and S.I. Taylor. 1988. Two mutant alleles of the insulin receptor gene in a patient with extreme insulin resistance. *Science* **240:** 787-790.

Kadowaki, T., H. Kadowaki, M.M. Rechler, M. Serrano-Rios, J. Roth, P. Gorden, and S.I. Taylor. 1990. Five mutant alleles of the insulin receptor gene in patients with genetic forms of insulin resistance. *J Clin Invest* **86:** 254-264.

Kakiuchi, C., M. Ishiwata, A. Hayashi, and T. Kato. 2006. XBP1 induces WFS1 through an endoplasmic reticulum stress response element-like motif in SH-SY5Y cells. *J Neurochem* **97:** 545-555.

Kamiyama, M., M. Kobayashi, S. Araki, A. Iida, T. Tsunoda, K. Kawai, M. Imanishi, M. Nomura, T. Babazono, Y. Iwamoto, A. Kashiwagi, K. Kaku, R. Kawamori, D.P. Ng, T. Hansen, P. Gaede, O. Pedersen, Y. Nakamura, and S. Maeda. 2007. Polymorphisms in the 3' UTR in the neurocalcin delta gene affect mRNA stability, and confer susceptibility to diabetic nephropathy. *Hum Genet* **122:** 397-407.

Kane, S., H. Sano, S.C. Liu, J.M. Asara, W.S. Lane, C.C. Garner, and G.E. Lienhard. 2002. A method to identify serine kinase substrates. Akt phosphorylates a novel adipocyte protein with a Rab GTPase-activating protein (GAP) domain. *J Biol Chem* **277:** 22115-22118.

Kang, E.S., H.J. Kim, M. Nam, C.M. Nam, C.W. Ahn, B.S. Cha, and H.C. Lee. 2006. A novel 111/121 diplotype in the Calpain-10 gene is associated with type 2 diabetes. *J Hum Genet* **51:** 629-633.

Karlberg, N., H. Jalanko, J. Kallijarvi, A.E. Lehesjoki, and M. Lipsanen-Nyman. 2005. Insulin resistance syndrome in subjects with mutated RING finger protein TRIM37. *Diabetes* **54:** 3577-3581.

Ke, X., S. Hunt, W. Tapper, R. Lawrence, G. Stavrides, J. Ghori, P. Whittaker, A. Collins, A.P. Morris, D. Bentley, L.R. Cardon, and P. Deloukas. 2004. The impact of SNP density on fine-scale patterns of linkage disequilibrium. *Hum Mol Genet* **13:** 577-588.

Kelley, D.E., J. He, E.V. Menshikova, and V.B. Ritov. 2002. Dysfunction of mitochondria in human skeletal muscle in type 2 diabetes. *Diabetes* **51:** 2944-2950.

Kelpe, C.L., P.C. Moore, S.D. Parazzoli, B. Wicksteed, C.J. Rhodes, and V. Poitout. 2003. Palmitate inhibition of insulin gene expression is mediated at the transcriptional level via ceramide synthesis. *J Biol Chem* **278:** 30015-30021.

Kennedy, G.C., H. Matsuzaki, S. Dong, W.M. Liu, J. Huang, G. Liu, X. Su, M. Cao, W. Chen, J. Zhang, W. Liu, G. Yang, X. Di, T. Ryder, Z. He, U. Surti, M.S. Phillips, M.T. Boyce-Jacino, S.P. Fodor, and K.W. Jones. 2003. Large-scale genotyping of complex DNA. *Nat Biotechnol* **21:** 1233-1237.

Khamzina, L., A. Veilleux, S. Bergeron, and A. Marette. 2005. Increased activation of the mammalian target of rapamycin pathway in liver and skeletal muscle of obese rats: possible involvement in obesity-linked insulin resistance. *Endocrinology* **146:** 1473-1481.

Kifagi, C., K. Makni, F. Mnif, M. Boudawara, N. Hamza, N. Rekik, M. Abid, A. Rebai, C. Granier, F. Jarraya, and H. Ayadi. 2008. Association of calpain-10 polymorphisms with type 2 diabetes in the Tunisian population. *Diabetes Metab* **34:** 273-278.

Kim, C.A., M. Delepine, E. Boutet, H. El Mourabit, S. Le Lay, M. Meier, M. Nemani, E. Bridel, C.C. Leite, D.R. Bertola, R.K. Semple, S. O'Rahilly, I. Dugail, J. Capeau, M. Lathrop, and J. Magre. 2008. Association of a homozygous nonsense caveolin-1 mutation with Berardinelli-Seip congenital lipodystrophy. *J Clin Endocrinol Metab* **93:** 1129-1134.

Kim, J.K., M.D. Michael, S.F. Previs, O.D. Peroni, F. Mauvais-Jarvis, S. Neschen, B.B. Kahn, C.R. Kahn, and G.I. Shulman. 2000. Redistribution of substrates to adipose tissue promotes obesity in mice with selective insulin resistance in muscle. *J Clin Invest* **105:** 1791-1797.

King, H. and M. Rewers. 1993. Global estimates for prevalence of diabetes mellitus and impaired glucose tolerance in adults. WHO Ad Hoc Diabetes Reporting Group. *Diabetes Care* **16:** 157-177.

Kissebah, A.H., G.E. Sonnenberg, J. Myklebust, M. Goldstein, K. Broman, R.G. James, J.A. Marks, G.R. Krakower, H.J. Jacob, J. Weber, L. Martin, J. Blangero, and A.G. Comuzzie. 2000. Quantitative trait loci on chromosomes 3 and 17 influence phenotypes of the metabolic syndrome. *Proc Natl Acad Sci U S A* **97:** 14478-14483.

Klein, R.J., C. Zeiss, E.Y. Chew, J.Y. Tsai, R.S. Sackler, C. Haynes, A.K. Henning, J.P. SanGiovanni, S.M. Mane, S.T. Mayne, M.B. Bracken, F.L. Ferris, J. Ott, C. Barnstable, and J. Hoh. 2005. Complement factor H polymorphism in age-related macular degeneration. *Science* **308:** 385-389.

Kloting, N., D. Schleinitz, K. Ruschke, J. Berndt, M. Fasshauer, A. Tonjes, M.R. Schon, P. Kovacs, M. Stumvoll, and M. Bluher. 2008. Inverse relationship between obesity and FTO gene expression in visceral adipose tissue in humans. *Diabetologia* **51:** 641-647.

Knight, B., B.M. Shields, and A.T. Hattersley. 2006. The Exeter Family Study of Childhood Health (EFSOCH): study protocol and methodology. *Paediatric And Perinatal Epidemiology* **20:** 172-179.

Kobberling, J., B. Willms, R. Kattermann, and W. Creutzfeldt. 1975. Lipodystrophy of the extremities. A dominantly inherited syndrome associated with lipatrophic diabetes. *Humangenetik* **29:** 111-120.

Korbel, J.O., A.E. Urban, J.P. Affourtit, B. Godwin, F. Grubert, J.F. Simons, P.M. Kim, D. Palejev, N.J. Carriero, L. Du, B.E. Taillon, Z. Chen, A. Tanzer, A.C. Saunders, J. Chi, F. Yang, N.P. Carter, M.E. Hurles, S.M. Weissman, T.T. Harkins, M.B. Gerstein, M. Egholm, and M. Snyder. 2007. Paired-end mapping reveals extensive structural variation in the human genome. *Science* **318:** 420-426.

Kotronen, A., A. Seppala-Lindroos, R. Bergholm, and H. Yki-Jarvinen. 2008. Tissue specificity of insulin resistance in humans: fat in the liver rather than muscle is associated with features of the metabolic syndrome. *Diabetologia* **51:** 130-138.

Kramer, H.F., C.A. Witczak, N. Fujii, N. Jessen, E.B. Taylor, D.E. Arnolds, K. Sakamoto, M.F. Hirshman, and L.J. Goodyear. 2006. Distinct signals regulate AS160 phosphorylation in response to insulin, AICAR, and contraction in mouse skeletal muscle. *Diabetes* **55:** 2067-2076.

Krebs, M., B. Brunmair, A. Brehm, M. Artwohl, J. Szendroedi, P. Nowotny, E. Roth, C. Furnsinn, M. Promintzer, C. Anderwald, M. Bischof, and M. Roden. 2007. The Mammalian target of rapamycin pathway regulates nutrient-sensitive glucose uptake in man. *Diabetes* **56:** 1600-1607.

Krook, A. and S. O'Rahilly. 1996. Mutant insulin receptors in syndromes of insulin resistance. *Baillieres Clin Endocrinol Metab* **10:** 97-122.

Kryukov, G.V., L.A. Pennacchio, and S.R. Sunyaev. 2007. Most rare missense alleles are deleterious in humans: implications for complex disease and association studies. *Am J Hum Genet* **80:** 727-739.

Kubota, N., Y. Terauchi, K. Tobe, W. Yano, R. Suzuki, K. Ueki, I. Takamoto, H. Satoh, T. Maki, T. Kubota, M. Moroi, M. Okada-Iwabu, O. Ezaki, R. Nagai, Y. Ueta, T. Kadowaki, and T. Noda. 2004. Insulin receptor substrate 2 plays a crucial role in beta cells and the hypothalamus. *J Clin Invest* **114:** 917-927.

Kubota, N., K. Tobe, Y. Terauchi, K. Eto, T. Yamauchi, R. Suzuki, Y. Tsubamoto, K. Komeda, R. Nakano, H. Miki, S. Satoh, H. Sekihara, S. Sciacchitano, M. Lesniak, S. Aizawa, R. Nagai, S. Kimura, Y. Akanuma, S.I. Taylor, and T. Kadowaki. 2000. Disruption of insulin receptor substrate 2 causes type 2 diabetes because of liver insulin resistance and lack of compensatory beta-cell hyperplasia. *Diabetes* **49:** 1880-1889.

Kubota, T., N. Kubota, M. Moroi, Y. Terauchi, T. Kobayashi, K. Kamata, R. Suzuki, K. Tobe, A. Namiki, S. Aizawa, R. Nagai, T. Kadowaki, and T. Yamaguchi. 2003. Lack of insulin receptor substrate-2 causes progressive neointima formation in response to vessel injury. *Circulation* **107:** 3073-3080.

Kulkarni, R.N., J.C. Bruning, J.N. Winnay, C. Postic, M.A. Magnuson, and C.R. Kahn. 1999. Tissue-specific knockout of the insulin receptor in pancreatic beta cells creates an insulin secretory defect similar to that in type 2 diabetes. *Cell* **96:** 329-339.

Kumar, A., T.E. Harris, S.R. Keller, K.M. Choi, M.A. Magnuson, and J.C. Lawrence, Jr. 2008. Muscle-specific deletion of rictor impairs insulin-stimulated glucose transport and enhances Basal glycogen synthase activity. *Mol Cell Biol* **28:** 61-70.

Lander, E. and L. Kruglyak. 1995. Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. *Nat Genet* **11:** 241-247.

Lander, E.S. L.M. Linton B. Birren C. Nusbaum M.C. Zody J. Baldwin K. Devon K. Dewar M. Doyle W. FitzHugh R. Funke D. Gage K. Harris A. Heaford J. Howland L. Kann J. Lehoczky R. LeVine P. McEwan K. McKernan J. Meldrim J.P. Mesirov C. Miranda W. Morris J. Naylor C. Raymond M. Rosetti R. Santos A. Sheridan C. Sougnez N. Stange-Thomann N. Stojanovic A. Subramanian D. Wyman J. Rogers J. Sulston R. Ainscough S. Beck D. Bentley J. Burton C. Clee N. Carter A. Coulson R. Deadman P. Deloukas A. Dunham I. Dunham R. Durbin L. French D. Grafham S. Gregory T. Hubbard S. Humphray A. Hunt M. Jones C. Lloyd A. McMurray L. Matthews S. Mercer S. Milne J.C. Mullikin A. Mungall R. Plumb M. Ross R. Shownkeen S. Sims R.H. Waterston R.K. Wilson L.W. Hillier J.D. McPherson M.A. Marra E.R. Mardis L.A. Fulton A.T. Chinwalla K.H. Pepin W.R. Gish S.L. Chissoe M.C. Wendl K.D. Delehaunty T.L. Miner A. Delehaunty J.B. Kramer L.L. Cook R.S. Fulton D.L. Johnson P.J. Minx S.W. Clifton T. Hawkins E. Branscomb P. Predki P. Richardson S. Wenning T. Slezak N. Doggett J.F. Cheng A. Olsen S. Lucas C. Elkin E. Uberbacher M. Frazier R.A. Gibbs D.M. Muzny S.E. Scherer J.B. Bouck E.J. Sodergren K.C. Worley C.M. Rives J.H. Gorrell M.L.

Metzker S.L. Naylor R.S. Kucherlapati D.L. Nelson G.M. Weinstock Y. Sakaki A. Fujiyama M. Hattori T. Yada A. Toyoda T. Itoh C. Kawagoe H. Watanabe Y. Totoki T. Taylor J. Weissenbach R. Heilig W. Saurin F. Artiguenave P. Brottier T. Bruls E. Pelletier C. Robert P. Wincker D.R. Smith L. Doucette-Stamm M. Rubenfield K. Weinstock H.M. Lee J. Dubois A. Rosenthal M. Platzer G. Nyakatura S. Taudien A. Rump H. Yang J. Yu J. Wang G. Huang J. Gu L. Hood L. Rowen A. Madan S. Qin R.W. Davis N.A. Federspiel A.P. Abola M.J. Proctor R.M. Myers J. Schmutz M. Dickson J. Grimwood D.R. Cox M.V. Olson R. Kaul C. Raymond N. Shimizu K. Kawasaki S. Minoshima G.A. Evans M. Athanasiou R. Schultz B.A. Roe F. Chen H. Pan J. Ramser H. Lehrach R. Reinhardt W.R. McCombie M. de la Bastide N. Dedhia H. Blocker K. Hornischer G. Nordsiek R. Agarwala L. Aravind J.A. Bailey A. Bateman S. Batzoglou E. Birney P. Bork D.G. Brown C.B. Burge L. Cerutti H.C. Chen D. Church M. Clamp R.R. Copley T. Doerks S.R. Eddy E.E. Eichler T.S. Furey J. Galagan J.G. Gilbert C. Harmon Y. Hayashizaki D. Haussler H. Hermjakob K. Hokamp W. Jang L.S. Johnson T.A. Jones S. Kasif A. Kaspryzk S. Kennedy W.J. Kent P. Kitts E.V. Koonin I. Korf D. Kulp D. Lancet T.M. Lowe A. McLysaght T. Mikkelsen J.V. Moran N. Mulder V.J. Pollara C.P. Ponting G. Schuler J. Schultz G. Slater A.F. Smit E. Stupka J. Szustakowski D. Thierry-Mieg J. Thierry-Mieg L. Wagner J. Wallis R. Wheeler A. Williams Y.I. Wolf K.H. Wolfe S.P. Yang R.F. Yeh F. Collins M.S. Guyer J. Peterson A. Felsenfeld K.A. Wetterstrand A. Patrinos M.J. Morgan P. de Jong J.J. Catanese K. Osoegawa H. Shizuya S. Choi and Y.J. Chen. 2001. Initial sequencing and analysis of the human genome. *Nature* **409:** 860-921.

Langner, C.A., E.H. Birkenmeier, O. Ben-Zeev, M.C. Schotz, H.O. Sweet, M.T. Davisson, and J.I. Gordon. 1989. The fatty liver dystrophy (fld) mutation. A new mutant mouse with a developmental abnormality in triglyceride metabolism and associated tissue-specific defects in lipoprotein lipase and hepatic lipase activities. *J Biol Chem* **264:** 7994-8003.

Lango, H., C.N. Palmer, A.D. Morris, E. Zeggini, A.T. Hattersley, M.I. McCarthy, T.M. Frayling, and M.N. Weedon. 2008. Assessing the combined impact of 18 common genetic variants of modest effect sizes on type 2 diabetes risk. *Diabetes*.

Larance, M., G. Ramm, J. Stockli, E.M. van Dam, S. Winata, V. Wasinger, F. Simpson, M. Graham, J.R. Junutula, M. Guilhaus, and D.E. James. 2005. Characterization of the role of the Rab GTPase-activating protein AS160 in insulin-regulated GLUT4 trafficking. *J Biol Chem* **280:** 37803-37813.

Lauritzen, T., S. Griffin, K. Borch-Johnsen, N.J. Wareham, B.H. Wolffenbuttel, and G. Rutten. 2000. The ADDITION study: proposed trial of the cost-effectiveness of an intensive multifactorial intervention on morbidity and mortality among people with Type 2 diabetes detected by screening. *Int J Obes Relat Metab Disord* **24 Suppl 3:** S6-11.

Laybutt, D.R., A.M. Preston, M.C. Akerfeldt, J.G. Kench, A.K. Busch, A.V. Biankin, and T.J. Biden. 2007. Endoplasmic reticulum stress contributes to beta cell apoptosis in type 2 diabetes. *Diabetologia* **50:** 752-763.

Lee, G.H., R. Proenca, J.M. Montez, K.M. Carroll, J.G. Darvishzadeh, J.I. Lee, and J.M. Friedman. 1996. Abnormal splicing of the leptin receptor in diabetic mice. *Nature* **379:** 632-635.

Lee, Y.S., B.G. Challis, D.A. Thompson, G.S. Yeo, J.M. Keogh, M.E. Madonna, V. Wraight, M. Sims, V. Vatin, D. Meyre, J. Shield, C. Burren, Z. Ibrahim, T. Cheetham, P. Swift, A. Blackwood, C.C. Hung, N.J. Wareham, P. Froguel, G.L. Millhauser, S. O'Rahilly, and I.S. Farooqi. 2006. A POMC variant implicates beta-

melanocyte-stimulating hormone in the control of human energy balance. *Cell Metab* **3:** 135-140.

Levy-Toledano, R., L.H. Caro, D. Accili, and S.I. Taylor. 1994. Investigation of the mechanism of the dominant negative effect of mutations in the tyrosine kinase domain of the insulin receptor. *Embo J* **13:** 835-842.

Lewis, J.P., N.D. Palmer, P.J. Hicks, M.M. Sale, C.D. Langefeld, B.I. Freedman, J. Divers, and D.W. Bowden. 2008. Association analysis in african americans of European-derived type 2 diabetes single nucleotide polymorphisms from whole-genome association studies. *Diabetes* **57:** 2220-2225.

Lindegaard, B., L.F. Larsen, A.B. Hansen, J. Gerstoft, B.K. Pedersen, and K. Reue. 2007. Adipose tissue lipin expression levels distinguish HIV patients with and without lipodystrophy. *Int J Obes (Lond)* **31:** 449-456.

Lohmueller, K.E., C.L. Pearce, M. Pike, E.S. Lander, and J.N. Hirschhorn. 2003. Meta-analysis of genetic association studies supports a contribution of common variants to susceptibility to common disease. *Nat Genet* **33:** 177-182.

Longo, N., Y. Wang, S.A. Smith, S.D. Langley, L.A. DiMeglio, and D. Giannella-Neto. 2002. Genotype-phenotype correlation in inherited severe insulin resistance. *Hum Mol Genet* **11:** 1465-1475.

Loos, R.J. C.M. Lindgren S. Li E. Wheeler J.H. Zhao I. Prokopenko M. Inouye R.M. Freathy A.P. Attwood J.S. Beckmann S.I. Berndt K.B. Jacobs S.J. Chanock R.B. Hayes S. Bergmann A.J. Bennett S.A. Bingham M. Bochud M. Brown S. Cauchi J.M. Connell C. Cooper G.D. Smith I. Day C. Dina S. De E.T. Dermitzakis A.S. Doney K.S. Elliott P. Elliott D.M. Evans I. Sadaf Farooqi P. Froguel J. Ghori C.J. Groves R. Gwilliam D. Hadley A.S. Hall A.T. Hattersley J. Hebebrand I.M. Heid C. Lamina C. Gieger T. Illig T. Meitinger H.E. Wichmann B. Herrera A. Hinney S.E. Hunt M.R. Jarvelin T. Johnson J.D. Jolley F. Karpe A. Keniry K.T. Khaw R.N. Luben M. Mangino J. Marchini W.L. McArdle R. McGinnis D. Meyre P.B. Munroe A.D. Morris A.R. Ness M.J. Neville A.C. Nica K.K. Ong S. O'Rahilly K.R. Owen C.N. Palmer K. Papadakis S. Potter A. Pouta L. Qi J.C. Randall N.W. Rayner S.M. Ring M.S. Sandhu A. Scherag M.A. Sims K. Song N. Soranzo E.K. Speliotes H.E. Syddall S.A. Teichmann N.J. Timpson J.H. Tobias M. Uda C.I. Vogel C. Wallace D.M. Waterworth M.N. Weedon C.J. Willer Wraight X. Yuan E. Zeggini J.N. Hirschhorn D.P. Strachan W.H. Ouwehand M.J. Caulfield N.J. Samani T.M. Frayling P. Vollenweider G. Waeber V. Mooser P. Deloukas M.I. McCarthy N.J. Wareham I. Barroso K.B. Jacobs S.J. Chanock R.B. Hayes C. Lamina C. Gieger T. Illig T. Meitinger H.E. Wichmann P. Kraft S.E. Hankinson D.J. Hunter F.B. Hu H.N. Lyon B.F. Voight M. Ridderstrale L. Groop P. Scheet S. Sanna G.R. Abecasis G. Albai R. Nagaraja D. Schlessinger A.U. Jackson J. Tuomilehto F.S. Collins M. Boehnke and K.L. Mohlke. 2008. Common variants near MC4R are associated with fat mass, weight and risk of obesity. *Nat Genet* **40:** 768-775.

Loos, R.J.F., T. Rankinen, L. Pérusse, A. Tremblay, J.-P. Després, and C. Bouchard. 2007. Association of Lipin 1 Gene Polymorphisms with Measures of Energy and Glucose Metabolism. *Obesity* **15:** 2723-2732.

Love-Gregory, L.D., J. Wasson, J. Ma, C.H. Jin, B. Glaser, B.K. Suarez, and M.A. Permutt. 2004. A common polymorphism in the upstream promoter region of the hepatocyte nuclear factor-4 alpha gene on chromosome 20q is associated with type 2 diabetes and appears to contribute to the evidence for linkage in an ashkenazi jewish population. *Diabetes* **53:** 1134-1140.

Magre, J., M. Delepine, E. Khallouf, T. Gedde-Dahl, Jr., L. Van Maldergem, E. Sobel, J. Papp, M. Meier, A. Megarbane, A. Bachy, A. Verloes, F.H. d'Abronzo, E. Seemanova, R. Assan, N. Baudic, C. Bourut, P. Czernichow, F. Huet, F.

Grigorescu, M. de Kerdanet, D. Lacombe, P. Labrune, M. Lanza, H. Loret, F. Matsuda, J. Navarro, A. Nivelon-Chevalier, M. Polak, J.J. Robert, P. Tric, N. Tubiana-Rufi, C. Vigouroux, J. Weissenbach, S. Savasta, J.A. Maassen, O. Trygstad, P. Bogalho, P. Freitas, J.L. Medina, F. Bonnicci, B.I. Joffe, G. Loyson, V.R. Panz, F.J. Raal, S. O'Rahilly, T. Stephenson, C.R. Kahn, M. Lathrop, and J. Capeau. 2001. Identification of the gene altered in Berardinelli-Seip congenital lipodystrophy on chromosome 11q13. *Nat Genet* **28:** 365-370.

Malecki, M.T., U.S. Jhala, A. Antonellis, L. Fields, A. Doria, T. Orban, M. Saad, J.H. Warram, M. Montminy, and A.S. Krolewski. 1999. Mutations in NEUROD1 are associated with the development of type 2 diabetes mellitus. *Nat Genet* **23:** 323-328.

Manmontri, B., M. Sariahmetoglu, J. Donkor, M.B. Khalil, M. Sundaram, Z. Yao, K. Reue, R. Lehner, and D.N. Brindley. 2008. Glucocorticoids and cyclic AMP selectively increase hepatic lipin-1 expression, and insulin acts antagonistically. *J Lipid Res* **49:** 1056-1067.

Manning, B.D. and L.C. Cantley. 2003. Rheb fills a GAP between TSC and TOR. *Trends Biochem Sci* **28:** 573-576.

Maraldi, N.M., C. Capanni, E. Mattioli, M. Columbaro, S. Squarzoni, W.K. Parnaik, M. Wehnert, and G. Lattanzi. 2007. A pathogenic mechanism leading to partial lipodistrophy and prospects for pharmacological treatment of insulin resistance syndrome. *Acta Biomed* **78 Suppl 1:** 207-215.

Marchetti, P., S. Del Guerra, L. Marselli, R. Lupi, M. Masini, M. Pollera, M. Bugliani, U. Boggi, F. Vistoli, F. Mosca, and S. Del Prato. 2004. Pancreatic islets from type 2 diabetic patients have functional defects and increased apoptosis that are ameliorated by metformin. *J Clin Endocrinol Metab* **89:** 5535-5541.

Marchetti, P., F. Dotta, D. Lauro, and F. Purrello. 2008. An overview of pancreatic beta-cell defects in human type 2 diabetes: implications for treatment. *Regul Pept* **146:** 4-11.

Marshall, C., G.A. Hitman, C.J. Partridge, A. Clark, H. Ma, T.R. Shearer, and M.D. Turner. 2005. Evidence that an isoform of calpain-10 is a regulator of exocytosis in pancreatic beta-cells. *Mol Endocrinol* **19:** 213-224.

Mason, T.M., T. Goh, V. Tchipashvili, H. Sandhu, N. Gupta, G.F. Lewis, and A. Giacca. 1999. Prolonged elevation of plasma free fatty acids desensitizes the insulin secretory response to glucose in vivo in rats. *Diabetes* **48:** 524-530.

Matschinsky, F., Y. Liang, P. Kesavan, L. Wang, P. Froguel, G. Velho, D. Cohen, M.A. Permutt, Y. Tanizawa, T.L. Jetton, and et al. 1993. Glucokinase as pancreatic beta cell glucose sensor and diabetes gene. *J Clin Invest* **92:** 2092-2098.

Mauvais-Jarvis, F., K. Ueki, D.A. Fruman, M.F. Hirshman, K. Sakamoto, L.J. Goodyear, M. Iannacone, D. Accili, L.C. Cantley, and C.R. Kahn. 2002. Reduced expression of the murine p85alpha subunit of phosphoinositide 3-kinase improves insulin signaling and ameliorates diabetes. *J Clin Invest* **109:** 141-149.

Mauvais-Jarvis, F., A. Virkamaki, M.D. Michael, J.N. Winnay, A. Zisman, R.N. Kulkarni, and C.R. Kahn. 2000. A model to explore the interaction between muscle insulin resistance and beta-cell dysfunction in the development of type 2 diabetes. *Diabetes* **49:** 2126-2134.

Meier, M., H.H. Klein, J. Kramer, M. Drenckhan, and M. Schutt. 2007. Calpain inhibition impairs glycogen syntheses in HepG2 hepatoma cells without altering insulin signaling. *J Endocrinol* **193:** 45-51.

Meigs, J.B., A.K. Manning, C.S. Fox, J.C. Florez, C. Liu, L.A. Cupples, and J. Dupuis. 2007. Genome-wide association with diabetes-related traits in the Framingham Heart Study. *BMC Med Genet* **8 Suppl 1:** S16.

Michael, M.D., R.N. Kulkarni, C. Postic, S.F. Previs, G.I. Shulman, M.A. Magnuson, and C.R. Kahn. 2000. Loss of insulin signaling in hepatocytes leads to severe insulin resistance and progressive hepatic dysfunction. *Mol Cell* **6:** 87-97.

Miller, M.P. and S. Kumar. 2001. Understanding human disease mutations through the use of interspecific genetic variation. *Hum Mol Genet* **10:** 2319-2328.

Minokoshi, Y., Y.B. Kim, O.D. Peroni, L.G. Fryer, C. Muller, D. Carling, and B.B. Kahn. 2002. Leptin stimulates fatty-acid oxidation by activating AMP-activated protein kinase. *Nature* **415:** 339-343.

Minton, J.A., A.T. Hattersley, K. Owen, M.I. McCarthy, M. Walker, F. Latif, T. Barrett, and T.M. Frayling. 2002. Association studies of genetic variation in the WFS1 gene and type 2 diabetes in U.K. populations. *Diabetes* **51:** 1287-1290.

Miyake, K., Y. Horikawa, K. Hara, K. Yasuda, H. Osawa, H. Furuta, Y. Hirota, K. Yamagata, Y. Hinokio, Y. Oka, N. Iwasaki, Y. Iwamoto, Y. Yamada, Y. Seino, H. Maegawa, A. Kashiwagi, K. Yamamoto, K. Tokunaga, J. Takeda, H. Makino, K. Nanjo, T. Kadowaki, and M. Kasuga. 2008. Association of TCF7L2 polymorphisms with susceptibility to type 2 diabetes in 4,087 Japanese subjects. *J Hum Genet* **53:** 174-180.

Moitra, J., M.M. Mason, M. Olive, D. Krylov, O. Gavrilova, B. Marcus-Samuels, L. Feigenbaum, E. Lee, T. Aoyama, M. Eckhaus, M.L. Reitman, and C. Vinson. 1998. Life without white fat: a transgenic mouse. *Genes Dev* **12:** 3168-3181.

Moller, D.E. and J.S. Flier. 1988. Detection of an alteration in the insulin-receptor gene in a patient with insulin resistance, acanthosis nigricans, and the polycystic ovary syndrome (type A insulin resistance). *N Engl J Med* **319:** 1526-1529.

Mootha, V.K., C.M. Lindgren, K.F. Eriksson, A. Subramanian, S. Sihag, J. Lehar, P. Puigserver, E. Carlsson, M. Ridderstrale, E. Laurila, N. Houstis, M.J. Daly, N. Patterson, J.P. Mesirov, T.R. Golub, P. Tamayo, B. Spiegelman, E.S. Lander, J.N. Hirschhorn, D. Altshuler, and L.C. Groop. 2003. PGC-1alpha-responsive genes involved in oxidative phosphorylation are coordinately downregulated in human diabetes. *Nat Genet* **34:** 267-273.

Morino, K., K.F. Petersen, S. Dufour, D. Befroy, J. Frattini, N. Shatzkes, S. Neschen, M.F. White, S. Bilz, S. Sono, M. Pypaert, and G.I. Shulman. 2005. Reduced mitochondrial density and increased IRS-1 serine phosphorylation in muscle of insulin-resistant offspring of type 2 diabetic parents. *J Clin Invest* **115:** 3587-3593.

Morino, K., K.F. Petersen, and G.I. Shulman. 2006. Molecular mechanisms of insulin resistance in humans and their potential links with mitochondrial dysfunction. *Diabetes* **55 Suppl 2:** S9-S15.

Morris, A.D., D.I. Boyle, R. MacAlpine, A. Emslie-Smith, R.T. Jung, R.W. Newton, and T.M. MacDonald. 1997. The diabetes audit and research in Tayside Scotland (DARTS) study: electronic record linkage to create a diabetes register. DARTS/MEMO Collaboration. *Bmj* **315:** 524-528.

Murphy, R., S. Ellard, and A.T. Hattersley. 2008. Clinical implications of a molecular genetic classification of monogenic beta-cell diabetes. *Nat Clin Pract Endocrinol Metab* **4:** 200-213.

Nakatani, Y., H. Kaneto, D. Kawamori, K. Yoshiuchi, M. Hatazaki, T.A. Matsuoka, K. Ozawa, S. Ogawa, M. Hori, Y. Yamasaki, and M. Matsuhisa. 2005. Involvement of endoplasmic reticulum stress in insulin resistance and diabetes. *J Biol Chem* **280:** 847-851.

Nauck, M.A., J.J. Meier, A.V. Wolfersdorff, H. Tillil, W. Creutzfeldt, and J. Kobberling. 2003. A 25-year follow-up study of glucose tolerance in first-degree relatives of type 2 diabetic patients: association of impaired or diabetic glucose tolerance with other components of the metabolic syndrome. *Acta Diabetol* **40:** 163-172.

Neve, B., M.E. Fernandez-Zapico, V. Ashkenazi-Katalan, C. Dina, Y.H. Hamid, E. Joly, E. Vaillant, Y. Benmezroua, E. Durand, N. Bakaher, V. Delannoy, M. Vaxillaire, T. Cook, G.M. Dallinga-Thie, H. Jansen, M.A. Charles, K. Clement, P. Galan, S. Hercberg, N. Helbecque, G. Charpentier, M. Prentki, T. Hansen, O. Pedersen, R. Urrutia, D. Melloul, and P. Froguel. 2005. Role of transcription factor KLF11 and its diabetes-associated gene variants in pancreatic beta cell function. *Proc Natl Acad Sci U S A* **102:** 4807-4812.

Ng, M.C., K.S. Park, B. Oh, C.H. Tam, Y.M. Cho, H.D. Shin, V.K. Lam, R.C. Ma, W.Y. So, Y.S. Cho, H.L. Kim, H.K. Lee, J.C. Chan, and N.H. Cho. 2008a. Implication of genetic variants near TCF7L2, SLC30A8, HHEX, CDKAL1, CDKN2A/B, IGF2BP2, and FTO in type 2 diabetes and obesity in 6,719 Asians. *Diabetes* **57:** 2226-2233.

Ng, P.C., S. Levy, J. Huang, T.B. Stockwell, B.P. Walenz, K. Li, N. Axelrod, D.A. Busam, R.L. Strausberg, and J.C. Venter. 2008b. Genetic variation in an individual human exome. *PLoS Genet* **4:** e1000160.

Nielsen, E.M., L. Hansen, B. Carstensen, S.M. Echwald, T. Drivsholm, C. Glumer, B. Thorsteinsson, K. Borch-Johnsen, T. Hansen, and O. Pedersen. 2003. The E23K variant of Kir6.2 associates with impaired post-OGTT serum insulin response and increased risk of type 2 diabetes. *Diabetes* **52:** 573-577.

Nistico, L., R. Buzzetti, L.E. Pritchard, B. Van der Auwera, C. Giovannini, E. Bosi, M.T. Larrad, M.S. Rios, C.C. Chow, C.S. Cockram, K. Jacobs, C. Mijovic, S.C. Bain, A.H. Barnett, C.L. Vandewalle, F. Schuit, F.K. Gorus, R. Tosi, P. Pozzilli, and J.A. Todd. 1996. The CTLA-4 gene region of chromosome 2q33 is linked to, and associated with, type 1 diabetes. Belgian Diabetes Registry. *Hum Mol Genet* **5:** 1075-1080.

Njolstad, P.R., O. Sovik, A. Cuesta-Munoz, L. Bjorkhaug, O. Massa, F. Barbetti, D.E. Undlien, C. Shiota, M.A. Magnuson, A. Molven, F.M. Matschinsky, and G.I. Bell. 2001. Neonatal diabetes mellitus due to complete glucokinase deficiency. *N Engl J Med* **344:** 1588-1592.

Novelli, G., A. Muchir, F. Sangiuolo, A. Helbling-Leclerc, M.R. D'Apice, C. Massart, F. Capon, P. Sbraccia, M. Federici, R. Lauro, C. Tudisco, R. Pallotta, G. Scarano, B. Dallapiccola, L. Merlini, and G. Bonne. 2002. Mandibuloacral dysplasia is caused by a mutation in LMNA-encoding lamin A/C. *Am J Hum Genet* **71:** 426-431.

O'Hara, L., G.S. Han, S. Peak-Chew, N. Grimsey, G.M. Carman, and S. Siniossoglou. 2006. Control of phospholipid synthesis by phosphorylation of the yeast lipin Pah1p/Smp2p Mg2+-dependent phosphatidate phosphatase. *J Biol Chem* **281:** 34537-34548.

O'Rahilly, S. 1997. Science, medicine, and the future. Non-insulin dependent diabetes mellitus: the gathering storm. *Bmj* **314:** 955-959.

Obici, S., Z. Feng, G. Karkanias, D.G. Baskin, and L. Rossetti. 2002. Decreasing hypothalamic insulin receptors causes hyperphagia and insulin resistance in rats. *Nat Neurosci* **5:** 566-572.

Ogawa, Y., H. Masuzaki, K. Hosoda, M. Aizawa-Abe, J. Suga, M. Suda, K. Ebihara, H. Iwai, N. Matsuoka, N. Satoh, H. Odaka, H. Kasuga, Y. Fujisawa, G. Inoue, H. Nishimura, Y. Yoshimasa, and K. Nakao. 1999. Increased glucose metabolism and insulin sensitivity in transgenic skinny mice overexpressing leptin. *Diabetes* **48:** 1822-1829.

Okada, T., C.W. Liew, J. Hu, C. Hinault, M.D. Michael, J. Krtzfeldt, C. Yin, M. Holzenberger, M. Stoffel, and R.N. Kulkarni. 2007. Insulin receptors in beta-cells are critical for islet compensatory growth response to insulin resistance. *Proc Natl Acad Sci U S A* **104:** 8977-8982.

Osman, A.A., M. Saito, C. Makepeace, M.A. Permutt, P. Schlesinger, and M. Mueckler. 2003. Wolframin expression induces novel ion channel activity in endoplasmic reticulum membranes and increases intracellular calcium. *J Biol Chem* **278:** 52755-52762.

Owen, K.R., A. Stride, S. Ellard, and A.T. Hattersley. 2003. Etiological investigation of diabetes in young adults presenting with apparent type 2 diabetes. *Diabetes Care* **26:** 2088-2093.

Ozcan, U., Q. Cao, E. Yilmaz, A.H. Lee, N.N. Iwakoshi, E. Ozdelen, G. Tuncman, C. Gorgun, L.H. Glimcher, and G.S. Hotamisligil. 2004. Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes. *Science* **306:** 457-461.

Ozcan, U., E. Yilmaz, L. Ozcan, M. Furuhashi, E. Vaillancourt, R.O. Smith, C.Z. Gorgun, and G.S. Hotamisligil. 2006. Chemical chaperones reduce ER stress and restore glucose homeostasis in a mouse model of type 2 diabetes. *Science* **313:** 1137-1140.

Ozes, O.N., H. Akca, L.D. Mayo, J.A. Gustin, T. Maehama, J.E. Dixon, and D.B. Donner. 2001. A phosphatidylinositol 3-kinase/Akt/mTOR pathway mediates and PTEN antagonizes tumor necrosis factor inhibition of insulin signaling through insulin receptor substrate-1. *Proc Natl Acad Sci U S A* **98:** 4640-4645.

Pan, D.A., S. Lillioja, A.D. Kriketos, M.R. Milner, L.A. Baur, C. Bogardus, A.B. Jenkins, and L.H. Storlien. 1997. Skeletal muscle triglyceride levels are inversely related to insulin action. *Diabetes* **46:** 983-988.

Paolisso, G., A. Gambardella, L. Amato, R. Tortoriello, A. D'Amore, M. Varricchio, and F. D'Onofrio. 1995. Opposite effects of short- and long-term fatty acid infusion on insulin secretion in healthy subjects. *Diabetologia* **38:** 1295-1299.

Parker, P.J., F.B. Caudwell, and P. Cohen. 1983. Glycogen synthase from rabbit skeletal muscle; effect of insulin on the state of phosphorylation of the seven phosphoserine residues in vivo. *Eur J Biochem* **130:** 227-234.

Patti, M.E., A.J. Butte, S. Crunkhorn, K. Cusi, R. Berria, S. Kashyap, Y. Miyazaki, I. Kohane, M. Costello, R. Saccone, E.J. Landaker, A.B. Goldfine, E. Mun, R. DeFronzo, J. Finlayson, C.R. Kahn, and L.J. Mandarino. 2003. Coordinated reduction of genes of oxidative metabolism in humans with insulin resistance and diabetes: Potential role of PGC1 and NRF1. *Proc Natl Acad Sci U S A* **100:** 8466-8471.

Payne, V.A., N. Grimsey, A. Tuthill, S. Virtue, S.L. Gray, E. Dalla Nora, R.K. Semple, S. O'Rahilly, and J.J. Rochford. 2008. The human lipodystrophy gene BSCL2/seipin may be essential for normal adipocyte differentiation. *Diabetes* **57:** 2055-2060.

Pederson, T.M., D.L. Kramer, and C.M. Rondinone. 2001. Serine/threonine phosphorylation of IRS-1 triggers its degradation: possible regulation by tyrosine phosphorylation. *Diabetes* **50:** 24-31.

Pende, M., S.C. Kozma, M. Jaquet, V. Oorschot, R. Burcelin, Y. Le Marchand-Brustel, J. Klumperman, B. Thorens, and G. Thomas. 2000. Hypoinsulinaemia, glucose intolerance and diminished beta-cell size in S6K1-deficient mice. *Nature* **408:** 994-997.

Perez-Carreras, M., P. Del Hoyo, M.A. Martin, J.C. Rubio, A. Martin, G. Castellano, F. Colina, J. Arenas, and J.A. Solis-Herruzo. 2003. Defective hepatic mitochondrial respiratory chain in patients with nonalcoholic steatohepatitis. *Hepatology* **38:** 999-1007.

Permutt, M.A., J.C. Wasson, B.K. Suarez, J. Lin, J. Thomas, J. Meyer, S. Lewitzky, J.S. Rennich, A. Parker, L. DuPrat, S. Maruti, S. Chayen, and B. Glaser. 2001. A genome scan for type 2 diabetes susceptibility loci in a genetically isolated population. *Diabetes* **50:** 681-685.

Perseghin, G., P. Scifo, F. De Cobelli, E. Pagliato, A. Battezzati, C. Arcelloni, A. Vanzulli, G. Testolin, G. Pozza, A. Del Maschio, and L. Luzi. 1999. Intramyocellular triglyceride content is a determinant of in vivo insulin resistance in humans: a 1H-13C nuclear magnetic resonance spectroscopy assessment in offspring of type 2 diabetic parents. *Diabetes* **48:** 1600-1606.

Pessayre, D. 2007. Role of mitochondria in non-alcoholic fatty liver disease. *J Gastroenterol Hepatol* **22 Suppl 1:** S20-27.

Peterfy, M., J. Phan, and K. Reue. 2005. Alternatively spliced lipin isoforms exhibit distinct expression pattern, subcellular localization, and role in adipogenesis. *J Biol Chem* **280:** 32883-32889.

Peterfy, M., J. Phan, P. Xu, and K. Reue. 2001. Lipodystrophy in the fld mouse results from mutation of a new gene encoding a nuclear protein, lipin. *Nat Genet* **27:** 121-124.

Peters, J.M., R. Barnes, L. Bennett, W.M. Gitomer, A.M. Bowcock, and A. Garg. 1998. Localization of the gene for familial partial lipodystrophy (Dunnigan variety) to chromosome 1q21-22. *Nat Genet* **18:** 292-295.

Petersen, K.F., D. Befroy, S. Dufour, J. Dziura, C. Ariyan, D.L. Rothman, L. DiPietro, G.W. Cline, and G.I. Shulman. 2003. Mitochondrial dysfunction in the elderly: possible role in insulin resistance. *Science* **300:** 1140-1142.

Petersen, K.F., S. Dufour, D. Befroy, R. Garcia, and G.I. Shulman. 2004. Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes. *N Engl J Med* **350:** 664-671.

Petersen, K.F., S. Dufour, and G.I. Shulman. 2005. Decreased insulin-stimulated ATP synthesis and phosphate transport in muscle of insulin-resistant offspring of type 2 diabetic parents. *PLoS Med* **2:** e233.

Phan, J., M. Peterfy, and K. Reue. 2004. Lipin expression preceding peroxisome proliferator-activated receptor-gamma is critical for adipogenesis in vivo and in vitro. *J Biol Chem* **279:** 29558-29564.

Phan, J. and K. Reue. 2005. Lipin, a lipodystrophy and obesity gene. *Cell Metab* **1:** 73-83.

Phillips, D.I., S. Caddy, V. Ilic, B.A. Fielding, K.N. Frayn, A.C. Borthwick, and R. Taylor. 1996. Intramuscular triglyceride and muscle insulin sensitivity: evidence for a relationship in nondiabetic subjects. *Metabolism* **45:** 947-950.

Plengvidhya, N., S. Kooptiwut, N. Songtawee, A. Doi, H. Furuta, M. Nishi, K. Nanjo, W. Tantibhedhyangkul, W. Boonyasrisawat, P.T. Yenchitsomanus, A. Doria, and N. Banchuin. 2007. PAX4 mutations in Thais with maturity onset diabetes of the young. *J Clin Endocrinol Metab* **92:** 2821-2826.

Poulsen, P. and A. Vaag. 2001. Glucose and insulin metabolism in twins: influence of zygosity and birth weight. *Twin Res* **4:** 350-355.

Prentki, M. and B.E. Corkey. 1996. Are the beta-cell signaling molecules malonyl-CoA and cystolic long-chain acyl-CoA implicated in multiple tissue defects of obesity and NIDDM? *Diabetes* **45:** 273-283.

Prieur, X., Y.C. Tung, J.L. Griffin, I.S. Farooqi, S. O'Rahilly, and A.P. Coll. 2008. Leptin regulates peripheral lipid metabolism primarily through central effects on food intake. *Endocrinology* **149:** 5432-5439.

Proks, P., A.L. Arnold, J. Bruining, C. Girard, S.E. Flanagan, B. Larkin, K. Colclough, A.T. Hattersley, F.M. Ashcroft, and S. Ellard. 2006. A heterozygous activating mutation in the sulphonylurea receptor SUR1 (ABCC8) causes neonatal diabetes. *Hum Mol Genet* **15:** 1793-1800.

Purcell, S., B. Neale, K. Todd-Brown, L. Thomas, M.A. Ferreira, D. Bender, J. Maller, P. Sklar, P.I. de Bakker, M.J. Daly, and P.C. Sham. 2007. PLINK: a tool set for

whole-genome association and population-based linkage analyses. *Am J Hum Genet* **81:** 559-575.

Raeder, H., S. Johansson, P.I. Holm, I.S. Haldorsen, E. Mas, V. Sbarra, I. Nermoen, S.A. Eide, L. Grevle, L. Bjorkhaug, J.V. Sagen, L. Aksnes, O. Sovik, D. Lombardo, A. Molven, and P.R. Njolstad. 2006. Mutations in the CEL VNTR cause a syndrome of diabetes and pancreatic exocrine dysfunction. *Nat Genet* **38:** 54-62.

Rahier, J., R.M. Goebbels, and J.C. Henquin. 1983. Cellular composition of the human diabetic pancreas. *Diabetologia* **24:** 366-371.

Ranade, K., M.S. Chang, C.T. Ting, D. Pei, C.F. Hsiao, M. Olivier, R. Pesich, J. Hebert, Y.D. Chen, V.J. Dzau, D. Curb, R. Olshen, N. Risch, D.R. Cox, and D. Botstein. 2001. High-throughput genotyping with single nucleotide polymorphisms. *Genome Res* **11:** 1262-1268.

Rasmussen, S.K., S.A. Urhammer, L. Berglund, J.N. Jensen, L. Hansen, S.M. Echwald, K. Borch-Johnsen, Y. Horikawa, H. Mashima, H. Lithell, N.J. Cox, T. Hansen, G.I. Bell, and O. Pedersen. 2002. Variants within the calpain-10 gene on chromosome 2q37 (NIDDM1) and relationships to type 2 diabetes, insulin resistance, and impaired acute insulin secretion among Scandinavian Caucasians. *Diabetes* **51:** 3561-3567.

Rathmann, W., B. Haastert, A. Icks, G. Giani, S. Hennings, J. Mitchell, S. Curran, and N.J. Wareham. 2001. Low faecal elastase 1 concentrations in type 2 diabetes mellitus. *Scand J Gastroenterol* **36:** 1056-1061.

Redon, R., S. Ishikawa, K.R. Fitch, L. Feuk, G.H. Perry, T.D. Andrews, H. Fiegler, M.H. Shapero, A.R. Carson, W. Chen, E.K. Cho, S. Dallaire, J.L. Freeman, J.R. Gonzalez, M. Gratacos, J. Huang, D. Kalaitzopoulos, D. Komura, J.R. MacDonald, C.R. Marshall, R. Mei, L. Montgomery, K. Nishimura, K. Okamura, F. Shen, M.J. Somerville, J. Tchinda, A. Valsesia, C. Woodwark, F. Yang, J. Zhang, T. Zerjal, J. Zhang, L. Armengol, D.F. Conrad, X. Estivill, C. Tyler-Smith, N.P. Carter, H. Aburatani, C. Lee, K.W. Jones, S.W. Scherer, and M.E. Hurles. 2006. Global variation in copy number in the human genome. *Nature* **444:** 444-454.

Reue, K., P. Xu, X.P. Wang, and B.G. Slavin. 2000. Adipose tissue deficiency, glucose intolerance, and increased atherosclerosis result from mutation in the mouse fatty liver dystrophy (fld) gene. *J Lipid Res* **41:** 1067-1076.

Reue, K. and P. Zhang. 2008. The lipin protein family: dual roles in lipid biosynthesis and gene expression. *FEBS Lett* **582:** 90-96.

Reynisdottir, I., G. Thorleifsson, R. Benediktsson, G. Sigurdsson, V. Emilsson, A.S. Einarsdottir, E.E. Hjorleifsdottir, G.T. Orlygsdottir, G.T. Bjornsdottir, J. Saemundsdottir, S. Halldorsson, S. Hrafnkelsdottir, S.B. Sigurjonsdottir, S. Steinsdottir, M. Martin, J.P. Kochan, B.K. Rhees, S.F. Grant, M.L. Frigge, A. Kong, V. Gudnason, K. Stefansson, and J.R. Gulcher. 2003. Localization of a susceptibility gene for type 2 diabetes to chromosome 5q34-q35.2. *Am J Hum Genet* **73:** 323-335.

Ricketts, C., M. Zatyka, and T. Barrett. 2006. The characterisation of the human Wolfram syndrome gene promoter demonstrating regulation by Sp1 and Sp3 transcription factors. *Biochim Biophys Acta* **1759:** 367-377.

Riggs, A.C., E. Bernal-Mizrachi, M. Ohsugi, J. Wasson, S. Fatrai, C. Welling, J. Murray, R.E. Schmidt, P.L. Herrera, and M.A. Permutt. 2005. Mice conditionally lacking the Wolfram gene in pancreatic islet beta cells exhibit diabetes as a result of enhanced endoplasmic reticulum stress and apoptosis. *Diabetologia* **48:** 2313-2321.

Risch, N. and K. Merikangas. 1996. The future of genetic studies of complex human diseases. *Science* **273:** 1516-1517.

Ritov, V.B., E.V. Menshikova, J. He, R.E. Ferrell, B.H. Goodpaster, and D.E. Kelley. 2005. Deficiency of subsarcolemmal mitochondria in obesity and type 2 diabetes. *Diabetes* **54:** 8-14.

Romeo, S., L.A. Pennacchio, Y. Fu, E. Boerwinkle, A. Tybjaerg-Hansen, H.H. Hobbs, and J.C. Cohen. 2007. Population-based resequencing of ANGPTL4 uncovers variations that reduce triglycerides and increase HDL. *Nat Genet* **39:** 513-516.

Ruvinsky, I., N. Sharon, T. Lerer, H. Cohen, M. Stolovich-Rain, T. Nir, Y. Dor, P. Zisman, and O. Meyuhas. 2005. Ribosomal protein S6 phosphorylation is a determinant of cell size and glucose homeostasis. *Genes Dev* **19:** 2199-2211.

Ryysy, L., A.M. Hakkinen, T. Goto, S. Vehkavaara, J. Westerbacka, J. Halavaara, and H. Yki-Jarvinen. 2000. Hepatic fat content and insulin action on free fatty acids and glucose metabolism rather than insulin absorption are associated with insulin requirements during insulin therapy in type 2 diabetic patients. *Diabetes* **49:** 749-758.

Sachidanandam, R., D. Weissman, S.C. Schmidt, J.M. Kakol, L.D. Stein, G. Marth, S. Sherry, J.C. Mullikin, B.J. Mortimore, D.L. Willey, S.E. Hunt, C.G. Cole, P.C. Coggill, C.M. Rice, Z. Ning, J. Rogers, D.R. Bentley, P.Y. Kwok, E.R. Mardis, R.T. Yeh, B. Schultz, L. Cook, R. Davenport, M. Dante, L. Fulton, L. Hillier, R.H. Waterston, J.D. McPherson, B. Gilman, S. Schaffner, W.J. Van Etten, D. Reich, J. Higgins, M.J. Daly, B. Blumenstiel, J. Baldwin, N. Stange-Thomann, M.C. Zody, L. Linton, E.S. Lander, and D. Altshuler. 2001. A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms. *Nature* **409:** 928-933.

Saito, K., T. Takahashi, N. Yaginuma, and N. Iwama. 1978. Islet morphometry in the diabetic pancreas of man. *Tohoku J Exp Med* **125:** 185-197.

Sako, Y. and V.E. Grill. 1990. A 48-hour lipid infusion in the rat time-dependently inhibits glucose-induced insulin secretion and B cell oxidation through a process likely coupled to fatty acid oxidation. *Endocrinology* **127:** 1580-1589.

Sakuraba, H., H. Mizukami, N. Yagihashi, R. Wada, C. Hanyu, and S. Yagihashi. 2002. Reduced beta-cell mass and expression of oxidative stress-related DNA damage in the islet of Japanese Type II diabetic patients. *Diabetologia* **45:** 85-96.

Sanchez-Pulido, L. and M.A. Andrade-Navarro. 2007. The FTO (fat mass and obesity associated) gene codes for a novel member of the non-heme dioxygenase superfamily. *BMC Biochem* **8:** 23.

Sandhu, M.S., M.N. Weedon, K.A. Fawcett, J. Wasson, S.L. Debenham, A. Daly, H. Lango, T.M. Frayling, R.J. Neumann, R. Sherva, I. Blech, P.D. Pharoah, C.N. Palmer, C. Kimber, R. Tavendale, A.D. Morris, M.I. McCarthy, M. Walker, G. Hitman, B. Glaser, M.A. Permutt, A.T. Hattersley, N.J. Wareham, and I. Barroso. 2007. Common variants in WFS1 confer risk of type 2 diabetes. *Nat Genet* **39:** 951-953.

Sano, H., S. Kane, E. Sano, C.P. Miinea, J.M. Asara, W.S. Lane, C.W. Garner, and G.E. Lienhard. 2003. Insulin-stimulated phosphorylation of a Rab GTPase-activating protein regulates GLUT4 translocation. *J Biol Chem* **278:** 14599-14602.

Santos-Rosa, H., J. Leung, N. Grimsey, S. Peak-Chew, and S. Siniossoglou. 2005. The yeast lipin Smp2 couples phospholipid biosynthesis to nuclear membrane growth. *Embo J* **24:** 1931-1941.

Sarbassov, D.D., S.M. Ali, D.H. Kim, D.A. Guertin, R.R. Latek, H. Erdjument-Bromage, P. Tempst, and D.M. Sabatini. 2004. Rictor, a novel binding partner of mTOR, defines a rapamycin-insensitive and raptor-independent pathway that regulates the cytoskeleton. *Curr Biol* **14:** 1296-1302.

Sarbassov, D.D., S.M. Ali, and D.M. Sabatini. 2005a. Growing roles for the mTOR pathway. *Curr Opin Cell Biol* **17:** 596-603.

Sarbassov, D.D., S.M. Ali, S. Sengupta, J.H. Sheen, P.P. Hsu, A.F. Bagley, A.L. Markhard, and D.M. Sabatini. 2006. Prolonged rapamycin treatment inhibits mTORC2 assembly and Akt/PKB. *Mol Cell* **22:** 159-168.

Sarbassov, D.D., D.A. Guertin, S.M. Ali, and D.M. Sabatini. 2005b. Phosphorylation and regulation of Akt/PKB by the rictor-mTOR complex. *Science* **307:** 1098-1101.

Savage, D.B., M. Agostini, I. Barroso, M. Gurnell, J. Luan, A. Meirhaeghe, A.H. Harding, G. Ihrke, O. Rajanayagam, M.A. Soos, S. George, D. Berger, E.L. Thomas, J.D. Bell, K. Meeran, R.J. Ross, A. Vidal-Puig, N.J. Wareham, S. O'Rahilly, V.K. Chatterjee, and A.J. Schafer. 2002. Digenic inheritance of severe insulin resistance in a human pedigree. *Nat Genet* **31:** 379-384.

Savage, D.B., K.F. Petersen, and G.I. Shulman. 2007. Disordered lipid metabolism and the pathogenesis of insulin resistance. *Physiol Rev* **87:** 507-520.

Savitsky, K., A. Bar-Shira, S. Gilad, G. Rotman, Y. Ziv, L. Vanagaite, D.A. Tagle, S. Smith, T. Uziel, S. Sfez, M. Ashkenazi, I. Pecker, M. Frydman, R. Harnik, S.R. Patanjali, A. Simmons, G.A. Clines, A. Sartiel, R.A. Gatti, L. Chessa, O. Sanal, M.F. Lavin, N.G. Jaspers, A.M. Taylor, C.F. Arlett, T. Miki, S.M. Weissman, M. Lovett, F.S. Collins, and Y. Shiloh. 1995. A single ataxia telangiectasia gene with a product similar to PI-3 kinase. *Science* **268:** 1749-1753.

Saxena, R., B.F. Voight, V. Lyssenko, N.P. Burtt, P.I. de Bakker, H. Chen, J.J. Roix, S. Kathiresan, J.N. Hirschhorn, M.J. Daly, T.E. Hughes, L. Groop, D. Altshuler, P. Almgren, J.C. Florez, J. Meyer, K. Ardlie, K. Bengtsson Bostrom, B. Isomaa, G. Lettre, U. Lindblad, H.N. Lyon, O. Melander, C. Newton-Cheh, P. Nilsson, M. Orho-Melander, L. Rastam, E.K. Speliotes, M.R. Taskinen, T. Tuomi, C. Guiducci, A. Berglund, J. Carlson, L. Gianniny, R. Hackett, L. Hall, J. Holmkvist, E. Laurila, M. Sjogren, M. Sterner, A. Surti, M. Svensson, M. Svensson, R. Tewhey, B. Blumenstiel, M. Parkin, M. Defelice, R. Barry, W. Brodeur, J. Camarata, N. Chia, M. Fava, J. Gibbons, B. Handsaker, C. Healy, K. Nguyen, C. Gates, C. Sougnez, D. Gage, M. Nizzari, S.B. Gabriel, G.W. Chirn, Q. Ma, H. Parikh, D. Richardson, D. Ricke, and S. Purcell. 2007. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. *Science* **316:** 1331-1336.

Scheuner, D., B. Song, E. McEwen, C. Liu, R. Laybutt, P. Gillespie, T. Saunders, S. Bonner-Weir, and R.J. Kaufman. 2001. Translational control is required for the unfolded protein response and in vivo glucose homeostasis. *Mol Cell* **7:** 1165-1176.

Scheuner, D., D. Vander Mierde, B. Song, D. Flamez, J.W. Creemers, K. Tsukamoto, M. Ribick, F.C. Schuit, and R.J. Kaufman. 2005. Control of mRNA translation preserves endoplasmic reticulum function in beta cells and maintains glucose homeostasis. *Nat Med* **11:** 757-764.

Schulz, L.O., P.H. Bennett, E. Ravussin, J.R. Kidd, K.K. Kidd, J. Esparza, and M.E. Valencia. 2006. Effects of traditional and western environments on prevalence of type 2 diabetes in Pima Indians in Mexico and the U.S. *Diabetes Care* **29:** 1866-1871.

Scott, L.J., K.L. Mohlke, L.L. Bonnycastle, C.J. Willer, Y. Li, W.L. Duren, M.R. Erdos, H.M. Stringham, P.S. Chines, A.U. Jackson, L. Prokunina-Olsson, C.J. Ding, A.J. Swift, N. Narisu, T. Hu, R. Pruim, R. Xiao, X.Y. Li, K.N. Conneely, N.L. Riebow, A.G. Sprau, M. Tong, P.P. White, K.N. Hetrick, M.W. Barnhart, C.W. Bark, J.L. Goldstein, L. Watkins, F. Xiang, J. Saramies, T.A. Buchanan, R.M. Watanabe, T.T. Valle, L. Kinnunen, G.R. Abecasis, E.W. Pugh, K.F. Doheny, R.N. Bergman, J. Tuomilehto, F.S. Collins, and M. Boehnke. 2007. A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. *Science* **316:** 1341-1345.

Sebat, J., B. Lakshmi, D. Malhotra, J. Troge, C. Lese-Martin, T. Walsh, B. Yamrom, S. Yoon, A. Krasnitz, J. Kendall, A. Leotta, D. Pai, R. Zhang, Y.H. Lee, J. Hicks, S.J. Spence, A.T. Lee, K. Puura, T. Lehtimaki, D. Ledbetter, P.K. Gregersen, J. Bregman, J.S. Sutcliffe, V. Jobanputra, W. Chung, D. Warburton, M.C. King, D. Skuse, D.H. Geschwind, T.C. Gilliam, K. Ye, and M. Wigler. 2007. Strong association of de novo copy number mutations with autism. *Science* **316:** 445-449.

Semple, R.K., V.C. Crowley, C.P. Sewter, M. Laudes, C. Christodoulides, R.V. Considine, A. Vidal-Puig, and S. O'Rahilly. 2004. Expression of the thermogenic nuclear hormone receptor coactivator PGC-1alpha is reduced in the adipose tissue of morbidly obese subjects. *Int J Obes Relat Metab Disord* **28:** 176-179.

Senee, V., C. Chelala, S. Duchatelet, D. Feng, H. Blanc, J.C. Cossec, C. Charon, M. Nicolino, P. Boileau, D.R. Cavener, P. Bougneres, D. Taha, and C. Julier. 2006. Mutations in GLIS3 are responsible for a rare syndrome with neonatal diabetes mellitus and congenital hypothyroidism. *Nat Genet* **38:** 682-687.

Seppala-Lindroos, A., S. Vehkavaara, A.M. Hakkinen, T. Goto, J. Westerbacka, A. Sovijarvi, J. Halavaara, and H. Yki-Jarvinen. 2002. Fat accumulation in the liver is associated with defects in insulin suppression of glucose production and serum free fatty acids independent of obesity in normal men. *J Clin Endocrinol Metab* **87:** 3023-3028.

Shackleton, S., D.J. Lloyd, S.N. Jackson, R. Evans, M.F. Niermeijer, B.M. Singh, H. Schmidt, G. Brabant, S. Kumar, P.N. Durrington, S. Gregory, S. O'Rahilly, and R.C. Trembath. 2000. LMNA, encoding lamin A/C, is mutated in partial lipodystrophy. *Nat Genet* **24:** 153-156.

Shah, O.J., Z. Wang, and T. Hunter. 2004. Inappropriate activation of the TSC/Rheb/mTOR/S6K cassette induces IRS1/2 depletion, insulin resistance, and cell survival deficiencies. *Curr Biol* **14:** 1650-1656.

Shield, J.P. 2000. Neonatal diabetes: new insights into aetiology and implications. *Horm Res* **53 Suppl 1:** 7-11.

Shimomura, I., R.E. Hammer, S. Ikemoto, M.S. Brown, and J.L. Goldstein. 1999. Leptin reverses insulin resistance and diabetes mellitus in mice with congenital lipodystrophy. *Nature* **401:** 73-76.

Shimomura, I., R.E. Hammer, J.A. Richardson, S. Ikemoto, Y. Bashmakov, J.L. Goldstein, and M.S. Brown. 1998. Insulin resistance and diabetes mellitus in transgenic mice expressing nuclear SREBP-1c in adipose tissue: model for congenital generalized lipodystrophy. *Genes Dev* **12:** 3182-3194.

Shiota, C., J.T. Woo, J. Lindner, K.D. Shelton, and M.A. Magnuson. 2006. Multiallelic disruption of the rictor gene in mice reveals that mTOR complex 2 is essential for fetal growth and viability. *Dev Cell* **11:** 583-589.

Silander, K., K.L. Mohlke, L.J. Scott, E.C. Peck, P. Hollstein, A.D. Skol, A.U. Jackson, P. Deloukas, S. Hunt, G. Stavrides, P.S. Chines, M.R. Erdos, N. Narisu, K.N. Conneely, C. Li, T.E. Fingerlin, S.K. Dhanjal, T.T. Valle, R.N. Bergman, J. Tuomilehto, R.M. Watanabe, M. Boehnke, and F.S. Collins. 2004. Genetic variation near the hepatocyte nuclear factor-4 alpha gene predicts susceptibility to type 2 diabetes. *Diabetes* **53:** 1141-1149.

Silva, J.P., M. Kohler, C. Graff, A. Oldfors, M.A. Magnuson, P.O. Berggren, and N.G. Larsson. 2000. Impaired insulin secretion and beta-cell loss in tissue-specific knockout mice with mitochondrial diabetes. *Nat Genet* **26:** 336-340.

Simmons, D., D.R. Williams, and M.J. Powell. 1991. The Coventry Diabetes Study: prevalence of diabetes and impaired glucose tolerance in Europids and Asians. *Q J Med* **81:** 1021-1030.

Simoneau, J.A. and D.E. Kelley. 1997. Altered glycolytic and oxidative capacities of skeletal muscle contribute to insulin resistance in NIDDM. *J Appl Physiol* **83:** 166-171.

Simoneau, J.A., J.H. Veerkamp, L.P. Turcotte, and D.E. Kelley. 1999. Markers of capacity to utilize fatty acids in human skeletal muscle: relation to insulin resistance and obesity and effects of weight loss. *Faseb J* **13:** 2051-2060.

Siniossoglou, S., H. Santos-Rosa, J. Rappsilber, M. Mann, and E. Hurt. 1998. A novel complex of membrane proteins required for formation of a spherical nucleus. *Embo J* **17:** 6449-6464.

Sladek, R., G. Rocheleau, J. Rung, C. Dina, L. Shen, D. Serre, P. Boutin, D. Vincent, A. Belisle, S. Hadjadj, B. Balkau, B. Heude, G. Charpentier, T.J. Hudson, A. Montpetit, A.V. Pshezhetsky, M. Prentki, B.I. Posner, D.J. Balding, D. Meyre, C. Polychronakos, and P. Froguel. 2007. A genome-wide association study identifies novel risk loci for type 2 diabetes. *Nature* **445:** 881-885.

Smith, C.J., P.A. Crock, B.R. King, C.J. Meldrum, and R.J. Scott. 2004. Phenotype-genotype correlations in a series of wolfram syndrome families. *Diabetes Care* **27:** 2003-2009.

Smyth, D.J., J.D. Cooper, R. Bailey, S. Field, O. Burren, L.J. Smink, C. Guja, C. Ionescu-Tirgoviste, B. Widmer, D.B. Dunger, D.A. Savage, N.M. Walker, D.G. Clayton, and J.A. Todd. 2006. A genome-wide association study of nonsynonymous SNPs identifies a type 1 diabetes locus in the interferon-induced helicase (IFIH1) region. *Nat Genet* **38:** 617-619.

Soejima, A., K. Inoue, D. Takai, M. Kaneko, H. Ishihara, Y. Oka, and J.I. Hayashi. 1996. Mitochondrial DNA is required for regulation of glucose-stimulated insulin secretion in a mouse pancreatic beta cell line, MIN6. *J Biol Chem* **271:** 26194-26199.

Song, Y., T. Niu, J.E. Manson, D.J. Kwiatkowski, and S. Liu. 2004. Are variants in the CAPN10 gene related to risk of type 2 diabetes? A quantitative assessment of population and family-based association studies. *Am J Hum Genet* **74:** 208-222.

Steemers, F.J. and K.L. Gunderson. 2007. Whole genome genotyping technologies on the BeadArray platform. *Biotechnol J* **2:** 41-49.

Steinthorsdottir, V., G. Thorleifsson, I. Reynisdottir, R. Benediktsson, T. Jonsdottir, G.B. Walters, U. Styrkarsdottir, S. Gretarsdottir, V. Emilsson, S. Ghosh, A. Baker, S. Snorradottir, H. Bjarnason, M.C. Ng, T. Hansen, Y. Bagger, R.L. Wilensky, M.P. Reilly, A. Adeyemo, Y. Chen, J. Zhou, V. Gudnason, G. Chen, H. Huang, K. Lashley, A. Doumatey, W.Y. So, R.C. Ma, G. Andersen, K. Borch-Johnsen, T. Jorgensen, J.V. van Vliet-Ostaptchouk, M.H. Hofker, C. Wijmenga, C. Christiansen, D.J. Rader, C. Rotimi, M. Gurney, J.C. Chan, O. Pedersen, G. Sigurdsson, J.R. Gulcher, U. Thorsteinsdottir, A. Kong, and K. Stefansson. 2007. A variant in CDKAL1 influences insulin response and risk of type 2 diabetes. *Nat Genet* **39:** 770-775.

Stephens, T.W., M. Basinski, P.K. Bristow, J.M. Bue-Valleskey, S.G. Burgett, L. Craft, J. Hale, J. Hoffmann, H.M. Hsiung, A. Kriauciunas, and et al. 1995. The role of neuropeptide Y in the antiobesity action of the obese gene product. *Nature* **377:** 530-532.

Stoffers, D.A., J. Ferrer, W.L. Clarke, and J.F. Habener. 1997. Early-onset type-II diabetes mellitus (MODY4) linked to IPF1. *Nat Genet* **17:** 138-139.

Storlien, L.H., A.B. Jenkins, D.J. Chisholm, W.S. Pascoe, S. Khouri, and E.W. Kraegen. 1991. Influence of dietary fat composition on development of insulin resistance in rats. Relationship to muscle triglyceride and omega-3 fatty acids in muscle phospholipid. *Diabetes* **40:** 280-289.

Stoy, J., E.L. Edghill, S.E. Flanagan, H. Ye, V.P. Paz, A. Pluzhnikov, J.E. Below, M.G. Hayes, N.J. Cox, G.M. Lipkind, R.B. Lipton, S.A. Greeley, A.M. Patch, S. Ellard, D.F. Steiner, A.T. Hattersley, L.H. Philipson, and G.I. Bell. 2007. Insulin gene mutations as a cause of permanent neonatal diabetes. *Proc Natl Acad Sci U S A* **104:** 15040-15044.

Stranger, B.E., M.S. Forrest, M. Dunning, C.E. Ingle, C. Beazley, N. Thorne, R. Redon, C.P. Bird, A. de Grassi, C. Lee, C. Tyler-Smith, N. Carter, S.W. Scherer, S. Tavare, P. Deloukas, M.E. Hurles, and E.T. Dermitzakis. 2007. Relative impact of nucleotide and copy number variation on gene expression phenotypes. *Science* **315:** 848-853.

Strom, T.M., K. Hortnagel, S. Hofmann, F. Gekeler, C. Scharfe, W. Rabl, K.D. Gerbitz, and T. Meitinger. 1998. Diabetes insipidus, diabetes mellitus, optic atrophy and deafness (DIDMOAD) caused by mutations in a novel gene (wolframin) coding for a predicted transmembrane protein. *Hum Mol Genet* **7:** 2021-2028.

Sturgess, N.C., R.Z. Kozlowski, C.A. Carrington, C.N. Hales, and M.L. Ashford. 1988. Effects of sulphonylureas and diazoxide on insulin secretion and nucleotide-sensitive channels in an insulin-secreting cell line. *Br J Pharmacol* **95:** 83-94.

Stuurman, N., S. Heins, and U. Aebi. 1998. Nuclear lamins: their structure, assembly, and interactions. *J Struct Biol* **122:** 42-66.

Suviolahti, E., K. Reue, R.M. Cantor, J. Phan, M. Gentile, J. Naukkarinen, A. Soro-Paavonen, L. Oksanen, J. Kaprio, A. Rissanen, V. Salomaa, K. Kontula, M.R. Taskinen, P. Pajukanta, and L. Peltonen. 2006. Cross-species analyses implicate Lipin 1 involvement in human glucose metabolism. *Hum Mol Genet* **15:** 377-386.

Suzuki, K. and T. Kono. 1980. Evidence that insulin causes translocation of glucose transport activity to the plasma membrane from an intracellular storage site. *Proc Natl Acad Sci U S A* **77:** 2542-2545.

Syddall, H.E., A. Aihie Sayer, E.M. Dennison, H.J. Martin, D.J. Barker, and C. Cooper. 2005. Cohort profile: the Hertfordshire cohort study. *Int J Epidemiol* **34:** 1234-1242.

Szendroedi, J., A.I. Schmid, M. Chmelik, C. Toth, A. Brehm, M. Krssak, P. Nowotny, M. Wolzt, W. Waldhausl, and M. Roden. 2007. Muscle mitochondrial ATP synthesis and glucose transport/phosphorylation in type 2 diabetes. *PLoS Med* **4:** e154.

Szymanski, K.M., D. Binns, R. Bartz, N.V. Grishin, W.P. Li, A.K. Agarwal, A. Garg, R.G. Anderson, and J.M. Goodman. 2007. The lipodystrophy protein seipin is found at endoplasmic reticulum lipid droplet junctions and is important for droplet morphology. *Proc Natl Acad Sci U S A* **104:** 20890-20895.

Takano, A., I. Usui, T. Haruta, J. Kawahara, T. Uno, M. Iwata, and M. Kobayashi. 2001. Mammalian target of rapamycin pathway regulates insulin signaling via subcellular redistribution of insulin receptor substrate 1 and integrates nutritional signals and metabolic signals of insulin. *Mol Cell Biol* **21:** 5050-5062.

Takeda, K., H. Inoue, Y. Tanizawa, Y. Matsuzaki, J. Oba, Y. Watanabe, K. Shinoda, and Y. Oka. 2001. WFS1 (Wolfram syndrome 1) gene product: predominant subcellular localization to endoplasmic reticulum in cultured cells and neuronal expression in rat brain. *Hum Mol Genet* **10:** 477-484.

Takei, D., H. Ishihara, S. Yamaguchi, T. Yamada, A. Tamura, H. Katagiri, Y. Maruyama, and Y. Oka. 2006. WFS1 protein modulates the free Ca(2+) concentration in the endoplasmic reticulum. *FEBS Lett* **580:** 5635-5640.

Tamemoto, H., T. Kadowaki, K. Tobe, T. Yagi, H. Sakura, T. Hayakawa, Y. Terauchi, K. Ueki, Y. Kaburagi, S. Satoh, and et al. 1994. Insulin resistance and growth retardation in mice lacking insulin receptor substrate-1. *Nature* **372:** 182-186.

Tan, K., W.A. Kimber, J. Luan, M.A. Soos, R.K. Semple, N.J. Wareham, S. O'Rahilly, and I. Barroso. 2007. Analysis of genetic variation in Akt2/PKB-beta in severe

insulin resistance, lipodystrophy, type 2 diabetes, and related metabolic phenotypes. *Diabetes* **56:** 714-719.

Tange, Y., A. Hirata, and O. Niwa. 2002. An evolutionarily conserved fission yeast protein, Ned1, implicated in normal nuclear morphology and chromosome stability, interacts with Dis3, Pim1/RCC1 and an essential nucleoporin. *J Cell Sci* **115:** 4375-4385.

Taniguchi, C.M., K. Ueki, and R. Kahn. 2005. Complementary roles of IRS-1 and IRS-2 in the hepatic regulation of metabolism. *J Clin Invest* **115:** 718-727.

Tartaglia, L.A., M. Dembski, X. Weng, N. Deng, J. Culpepper, R. Devos, G.J. Richards, L.A. Campfield, F.T. Clark, J. Deeds, C. Muir, S. Sanker, A. Moriarty, K.J. Moore, J.S. Smutko, G.G. Mays, E.A. Wool, C.A. Monroe, and R.I. Tepper. 1995. Identification and expression cloning of a leptin receptor, OB-R. *Cell* **83:** 1263-1271.

Tattersall, R.B. and S.S. Fajans. 1975. A difference between the inheritance of classical juvenile-onset and maturity-onset type diabetes of young people. *Diabetes* **24:** 44-53.

Tee, A.R., B.D. Manning, P.P. Roux, L.C. Cantley, and J. Blenis. 2003. Tuberous sclerosis complex gene products, Tuberin and Hamartin, control mTOR signaling by acting as a GTPase-activating protein complex toward Rheb. *Curr Biol* **13:** 1259-1268.

Temple, I.K. and J.P. Shield. 2002. Transient neonatal diabetes, a disorder of imprinting. *J Med Genet* **39:** 872-875.

Terauchi, Y., Y. Tsuji, S. Satoh, H. Minoura, K. Murakami, A. Okuno, K. Inukai, T. Asano, Y. Kaburagi, K. Ueki, H. Nakajima, T. Hanafusa, Y. Matsuzawa, H. Sekihara, Y. Yin, J.C. Barrett, H. Oda, T. Ishikawa, Y. Akanuma, I. Komuro, M. Suzuki, K. Yamamura, T. Kodama, H. Suzuki, K. Yamamura, T. Kodama, H. Suzuki, S. Koyasu, S. Aizawa, K. Tobe, Y. Fukui, Y. Yazaki, and T. Kadowaki. 1999. Increased insulin sensitivity and hypoglycaemia in mice lacking the p85 alpha subunit of phosphoinositide 3-kinase. *Nat Genet* **21:** 230-235.

Tessa, A., I. Carbone, M.C. Matteoli, C. Bruno, C. Patrono, I.P. Patera, F. De Luca, R. Lorini, and F.M. Santorelli. 2001. Identification of novel WFS1 mutations in Italian children with Wolfram syndrome. *Hum Mutat* **17:** 348-349.

Thomas, P., Y. Ye, and E. Lightner. 1996. Mutation of the pancreatic islet inward rectifier Kir6.2 also leads to familial persistent hyperinsulinemic hypoglycemia of infancy. *Hum Mol Genet* **5:** 1809-1812.

Thong, F.S., P.J. Bilan, and A. Klip. 2007. The Rab GTPase-activating protein AS160 integrates Akt, protein kinase C, and AMP-activated protein kinase signals regulating GLUT4 traffic. *Diabetes* **56:** 414-423.

Tremblay, F., A. Gagnon, A. Veilleux, A. Sorisky, and A. Marette. 2005. Activation of the mammalian target of rapamycin pathway acutely inhibits insulin signaling to Akt and glucose transport in 3T3-L1 and human adipocytes. *Endocrinology* **146:** 1328-1337.

Tremblay, F. and A. Marette. 2001. Amino acid and insulin signaling via the mTOR/p70 S6 kinase pathway. A negative feedback mechanism leading to insulin resistance in skeletal muscle cells. *J Biol Chem* **276:** 38052-38060.

Tripathy, D., E. Lindholm, B. Isomaa, C. Saloranta, T. Tuomi, and L. Groop. 2003. Familiality of metabolic abnormalities is dependent on age at onset and phenotype of the type 2 diabetic proband. *Am J Physiol Endocrinol Metab* **285:** E1297-1303.

Tsai, H.J., G. Sun, D.E. Weeks, R. Kaushal, M. Wolujewicz, S.T. McGarvey, J. Tufa, S. Viali, and R. Deka. 2001. Type 2 diabetes and three calpain-10 gene

polymorphisms in Samoans: no evidence of association. *Am J Hum Genet* **69:** 1236-1244.

Tsuchiya, T., P.E. Schwarz, L.D. Bosque-Plata, M. Geoffrey Hayes, C. Dina, P. Froguel, G. Wayne Towers, S. Fischer, T. Temelkova-Kurktschiev, H. Rietzsch, J. Graessler, J. Vcelak, D. Palyzova, T. Selisko, B. Bendlova, J. Schulze, U. Julius, M. Hanefeld, M.N. Weedon, J.C. Evans, T.M. Frayling, A.T. Hattersley, M. Orho-Melander, L. Groop, M.T. Malecki, T. Hansen, O. Pedersen, T.E. Fingerlin, M. Boehnke, C.L. Hanis, N.J. Cox, and G.I. Bell. 2006. Association of the calpain-10 gene with type 2 diabetes in Europeans: results of pooled and meta-analyses. *Mol Genet Metab* **89:** 174-184.

Turner, M.D., F.K. Fulcher, C.V. Jones, B.T. Smith, E. Aganna, C.J. Partridge, G.A. Hitman, A. Clark, and Y.M. Patel. 2007. Calpain facilitates actin reorganization during glucose-stimulated insulin secretion. *Biochem Biophys Res Commun* **352:** 650-655.

Tyrer, J., P.D. Pharoah, and D.F. Easton. 2006. The admixture maximum likelihood test: a novel experiment-wise test of association between disease and multiple SNPs. *Genet Epidemiol* **30:** 636-643.

Ueda, K., J. Kawano, K. Takeda, T. Yujiri, K. Tanabe, T. Anno, M. Akiyama, J. Nozaki, T. Yoshinaga, A. Koizumi, K. Shinoda, Y. Oka, and Y. Tanizawa. 2005. Endoplasmic reticulum stress induces Wfs1 gene expression in pancreatic beta-cells via transcriptional activation. *Eur J Endocrinol* **153:** 167-176.

Ueki, K., C.M. Yballe, S.M. Brachmann, D. Vicent, J.M. Watt, C.R. Kahn, and L.C. Cantley. 2002. Increased insulin sensitivity in mice lacking p85beta subunit of phosphoinositide 3-kinase. *Proc Natl Acad Sci U S A* **99:** 419-424.

Ukropcova, B., O. Sereda, L. de Jonge, I. Bogacka, T. Nguyen, H. Xie, G.A. Bray, and S.R. Smith. 2007. Family history of diabetes links impaired substrate switching and reduced mitochondrial content in skeletal muscle. *Diabetes* **56:** 720-727.

Um, S.H., F. Frigerio, M. Watanabe, F. Picard, M. Joaquin, M. Sticker, S. Fumagalli, P.R. Allegrini, S.C. Kozma, J. Auwerx, and G. Thomas. 2004. Absence of S6K1 protects against age- and diet-induced obesity while enhancing insulin sensitivity. *Nature* **431:** 200-205.

Unoki, H., A. Takahashi, T. Kawaguchi, K. Hara, M. Horikoshi, G. Andersen, D.P. Ng, J. Holmkvist, K. Borch-Johnsen, T. Jorgensen, A. Sandbaek, T. Lauritzen, T. Hansen, S. Nurbaya, T. Tsunoda, M. Kubo, T. Babazono, H. Hirose, M. Hayashi, Y. Iwamoto, A. Kashiwagi, K. Kaku, R. Kawamori, E.S. Tai, O. Pedersen, N. Kamatani, T. Kadowaki, R. Kikkawa, Y. Nakamura, and S. Maeda. 2008. SNPs in KCNQ1 are associated with susceptibility to type 2 diabetes in East Asian and European populations. *Nat Genet*.

van den Ouweland, J.M., H.H. Lemkes, W. Ruitenbeek, L.A. Sandkuijl, M.F. de Vijlder, P.A. Struyvenberg, J.J. van de Kamp, and J.A. Maassen. 1992. Mutation in mitochondrial tRNA(Leu)(UUR) gene in a large pedigree with maternally transmitted type II diabetes mellitus and deafness. *Nat Genet* **1:** 368-371.

van Harmelen, V., M. Ryden, E. Sjolin, and J. Hoffstedt. 2007. A role of lipin in human obesity and insulin resistance: relation to adipocyte glucose transport and GLUT4 expression. *J Lipid Res* **48:** 201-206.

Varma, S., A. Shrivastav, S. Changela, and R.L. Khandelwal. 2008. Long-term effects of rapamycin treatment on insulin mediated phosphorylation of Akt/PKB and glycogen synthase activity. *Exp Cell Res* **314:** 1281-1291.

Vaxillaire, M., V. Boccio, A. Philippi, C. Vigouroux, J. Terwilliger, P. Passa, J.S. Beckmann, G. Velho, G.M. Lathrop, and P. Froguel. 1995. A gene for maturity onset diabetes of the young (MODY) maps to chromosome 12q. *Nat Genet* **9:** 418-423.

Venter, J.C. M.D. Adams E.W. Myers P.W. Li R.J. Mural G.G. Sutton H.O. Smith M. Yandell C.A. Evans R.A. Holt J.D. Gocayne P. Amanatides R.M. Ballew D.H. Huson J.R. Wortman Q. Zhang C.D. Kodira X.H. Zheng L. Chen M. Skupski G. Subramanian P.D. Thomas J. Zhang G.L. Gabor Miklos C. Nelson S. Broder A.G. Clark J. Nadeau V.A. McKusick N. Zinder A.J. Levine R.J. Roberts M. Simon C. Slayman M. Hunkapiller R. Bolanos A. Delcher I. Dew D. Fasulo M. Flanigan L. Florea A. Halpern S. Hannenhalli S. Kravitz S. Levy C. Mobarry K. Reinert K. Remington J. Abu-Threideh E. Beasley K. Biddick V. Bonazzi R. Brandon M. Cargill I. Chandramouliswaran R. Charlab K. Chaturvedi Z. Deng V. Di Francesco P. Dunn K. Eilbeck C. Evangelista A.E. Gabrielian W. Gan W. Ge F. Gong Z. Gu P. Guan T.J. Heiman M.E. Higgins R.R. Ji Z. Ke K.A. Ketchum Z. Lai Y. Lei Z. Li J. Li Y. Liang X. Lin F. Lu G.V. Merkulov N. Milshina H.M. Moore A.K. Naik V.A. Narayan B. Neelam D. Nusskern D.B. Rusch S. Salzberg W. Shao B. Shue J. Sun Z. Wang A. Wang X. Wang J. Wang M. Wei R. Wides C. Xiao C. Yan A. Yao J. Ye M. Zhan W. Zhang H. Zhang Q. Zhao L. Zheng F. Zhong W. Zhong S. Zhu S. Zhao D. Gilbert S. Baumhueter G. Spier C. Carter A. Cravchik T. Woodage F. Ali H. An A. Awe D. Baldwin H. Baden M. Barnstead I. Barrow K. Beeson D. Busam A. Carver A. Center M.L. Cheng L. Curry S. Danaher L. Davenport R. Desilets S. Dietz K. Dodson L. Doup S. Ferriera N. Garg A. Gluecksmann B. Hart J. Haynes C. Haynes C. Heiner S. Hladun D. Hostin J. Houck T. Howland C. Ibegwam J. Johnson F. Kalush L. Kline S. Koduru A. Love F. Mann D. May S. McCawley T. McIntosh I. McMullen M. Moy L. Moy B. Murphy K. Nelson C. Pfannkoch E. Pratts V. Puri H. Qureshi M. Reardon R. Rodriguez Y.H. Rogers D. Romblad B. Ruhfel R. Scott C. Sitter M. Smallwood E. Stewart R. Strong E. Suh R. Thomas N.N. Tint S. Tse C. Vech G. Wang J. Wetter S. Williams M. Williams S. Windsor E. Winn-Deen K. Wolfe J. Zaveri K. Zaveri J.F. Abril R. Guigo M.J. Campbell K.V. Sjolander B. Karlak A. Kejariwal H. Mi B. Lazareva T. Hatton A. Narechania K. Diemer A. Muruganujan N. Guo S. Sato V. Bafna S. Istrail R. Lippert R. Schwartz B. Walenz S. Yooseph D. Allen A. Basu J. Baxendale L. Blick M. Caminha J. Carnes-Stine P. Caulk Y.H. Chiang M. Coyne C. Dahlke A. Mays M. Dombroski M. Donnelly D. Ely S. Esparham C. Fosler H. Gire S. Glanowski K. Glasser A. Glodek M. Gorokhov K. Graham B. Gropman M. Harris J. Heil S. Henderson J. Hoover D. Jennings C. Jordan J. Jordan J. Kasha L. Kagan C. Kraft A. Levitsky M. Lewis X. Liu J. Lopez D. Ma W. Majoros J. McDaniel S. Murphy M. Newman T. Nguyen N. Nguyen M. Nodell S. Pan J. Peck M. Peterson W. Rowe R. Sanders J. Scott M. Simpson T. Smith A. Sprague T. Stockwell R. Turner E. Venter M. Wang M. Wen D. Wu M. Wu A. Xia A. Zandieh and X. Zhu. 2001. The sequence of the human genome. *Science* **291:** 1304-1351.

Vionnet, N., M. Stoffel, J. Takeda, K. Yasuda, G.I. Bell, H. Zouali, S. Lesage, G. Velho, F. Iris, P. Passa, and et al. 1992. Nonsense mutation in the glucokinase gene causes early-onset non-insulin-dependent diabetes mellitus. *Nature* **356:** 721-722.

Wahlen, K., E. Sjolin, and J. Hoffstedt. 2008. The common rs9939609 gene variant of the fat mass- and obesity-associated gene FTO is related to fat cell lipolysis. *J Lipid Res* **49:** 607-611.

Walder, K., L. Kerr-Bayles, A. Civitarese, J. Jowett, J. Curran, K. Elliott, J. Trevaskis, N. Bishara, P. Zimmet, L. Mandarino, E. Ravussin, J. Blangero, A. Kissebah, and G.R. Collier. 2005. The mitochondrial rhomboid protease PSARL is a new candidate gene for type 2 diabetes. *Diabetologia* **48:** 459-468.

Wallace, H.A., F. Marques-Kranc, M. Richardson, F. Luna-Crespo, J.A. Sharpe, J. Hughes, W.G. Wood, D.R. Higgs, and A.J. Smith. 2007. Manipulating the mouse

genome to engineer precise functional syntenic replacements with human sequence. *Cell* **128:** 197-209.

Walsh, T., J.M. McClellan, S.E. McCarthy, A.M. Addington, S.B. Pierce, G.M. Cooper, A.S. Nord, M. Kusenda, D. Malhotra, A. Bhandari, S.M. Stray, C.F. Rippey, P. Roccanova, V. Makarov, B. Lakshmi, R.L. Findling, L. Sikich, T. Stromberg, B. Merriman, N. Gogtay, P. Butler, K. Eckstrand, L. Noory, P. Gochman, R. Long, Z. Chen, S. Davis, C. Baker, E.E. Eichler, P.S. Meltzer, S.F. Nelson, A.B. Singleton, M.K. Lee, J.L. Rapoport, M.C. King, and J. Sebat. 2008. Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. *Science* **320:** 539-543.

Wareham, N.J., C.D. Byrne, R. Williams, N.E. Day, and C.N. Hales. 1999. Fasting proinsulin concentrations predict the development of type 2 diabetes. *Diabetes Care* **22:** 262-270.

Wareham, N.J., S.J. Hennings, C.D. Byrne, C.N. Hales, A.M. Prentice, and N.E. Day. 1998. A quantitative analysis of the relationship between habitual energy expenditure, fitness and the metabolic cardiovascular syndrome. *Br J Nutr* **80:** 235-241.

Weedon, M., K. Owen, B. Shields, G. Hitman, M. Walker, M. McCarthy, L. Love-Gregory, M. Permutt, A. Hattersley, and T.M. Frayling. 2004. Common variants of the HNF4alpha P2 promoter are associated with type 2 diabetes in the UK population. *Diabetes* **53:** 3002-3006.

Weedon, M.N., V.J. Clark, Y. Qian, Y. Ben-Shlomo, N. Timpson, S. Ebrahim, D.A. Lawlor, M.E. Pembrey, S. Ring, T.J. Wilkin, L.D. Voss, A.N. Jeffery, B. Metcalf, L. Ferrucci, A.M. Corsi, A. Murray, D. Melzer, B. Knight, B. Shields, G.D. Smith, A.T. Hattersley, A. Di Rienzo, and T.M. Frayling. 2006. A common haplotype of the glucokinase gene alters fasting glucose and birth weight: association in six studies and population-genetics analyses. *Am J Hum Genet* **79:** 991-1001.

Weedon, M.N., P.E. Schwarz, Y. Horikawa, N. Iwasaki, T. Illig, R. Holle, W. Rathmann, T. Selisko, J. Schulze, K.R. Owen, J. Evans, L. Del Bosque-Plata, G. Hitman, M. Walker, J.C. Levy, M. Sampson, G.I. Bell, M.I. McCarthy, A.T. Hattersley, and T.M. Frayling. 2003. Meta-analysis and a large association study confirm a role for calpain-10 variation in type 2 diabetes susceptibility. *Am J Hum Genet* **73:** 1208-1212.

Weires, M.B., B. Tausch, P.J. Haug, C.Q. Edwards, T. Wetter, and L.A. Cannon-Albright. 2007. Familiality of diabetes mellitus. *Exp Clin Endocrinol Diabetes* **115:** 634-640.

Westermark, P. and E. Wilander. 1978. The influence of amyloid deposits on the islet volume in maturity onset diabetes mellitus. *Diabetologia* **15:** 417-421.

Whitman, M., C.P. Downes, M. Keeler, T. Keller, and L. Cantley. 1988. Type I phosphatidylinositol kinase makes a novel inositol phospholipid, phosphatidylinositol-3-phosphate. *Nature* **332:** 644-646.

WHO Study Group. 1999. Report of a WHO Consultation: Part 1: Diagnosis and Classification of Diabetes Mellitus. World Health Organisation, Geneva.

Wiedmann, S., M. Fischer, M. Koehler, K. Neureuther, G. Riegger, A. Doering, H. Schunkert, C. Hengstenberg, and A. Baessler. 2007. Genetic variants within the LPIN1 gene, encoding lipin, are influencing phenotypes of the metabolic syndrome in humans. *Diabetes*.

Wild, S., G. Roglic, A. Green, R. Sicree, and H. King. 2004. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* **27:** 1047-1053.

Willcocks, L.C., P.A. Lyons, M.R. Clatworthy, J.I. Robinson, W. Yang, S.A. Newland, V. Plagnol, N.N. McGovern, A.M. Condliffe, E.R. Chilvers, D. Adu, E.C. Jolly, R. Watts, Y.L. Lau, A.W. Morgan, G. Nash, and K.G. Smith. 2008. Copy number of

FCGR3B, which is associated with systemic lupus erythematosus, correlates with protein expression and immune complex uptake. *J Exp Med* **205:** 1573-1582.

Williams, D.R., N.J. Wareham, D.C. Brown, C.D. Byrne, P.M. Clark, B.D. Cox, L.J. Cox, N.E. Day, C.N. Hales, C.R. Palmer, and et al. 1995. Undiagnosed glucose intolerance in the community: the Isle of Ely Diabetes Project. *Diabet Med* **12:** 30-35.

Williams, R.C., J.C. Long, R.L. Hanson, M.L. Sievers, and W.C. Knowler. 2000. Individual estimates of European genetic admixture associated with lower body-mass index, plasma glucose, and prevalence of type 2 diabetes in Pima Indians. *Am J Hum Genet* **66:** 527-538.

Wiltshire, S., A.T. Hattersley, G.A. Hitman, M. Walker, J.C. Levy, M. Sampson, S. O'Rahilly, T.M. Frayling, J.I. Bell, G.M. Lathrop, A. Bennett, R. Dhillon, C. Fletcher, C.J. Groves, E. Jones, P. Prestwich, N. Simecek, P.V. Rao, M. Wishart, R. Foxon, G.F. Bottazzo, S. Howell, D. Smedley, L.R. Cardon, S. Menzel, and M.I. McCarthy. 2001. A genomewide scan for loci predisposing to type 2 diabetes in a U.K. population (the Diabetes UK Warren 2 Repository): analysis of 573 pedigrees provides independent replication of a susceptibility locus on chromosome 1q. *Am J Hum Genet* **69:** 553-569.

Winckler, W., M.N. Weedon, R.R. Graham, S.A. McCarroll, S. Purcell, P. Almgren, T. Tuomi, D. Gaudet, K.B. Bostrom, M. Walker, G. Hitman, A.T. Hattersley, M.I. McCarthy, K.G. Ardlie, J.N. Hirschhorn, M.J. Daly, T.M. Frayling, L. Groop, and D. Altshuler. 2007. Evaluation of common variants in the six known maturity-onset diabetes of the young (MODY) genes for association with type 2 diabetes. *Diabetes* **56:** 685-693.

Withers, D.J., D.J. Burks, H.H. Towery, S.L. Altamuro, C.L. Flint, and M.F. White. 1999. Irs-2 coordinates Igf-1 receptor-mediated beta-cell development and peripheral insulin signalling. *Nat Genet* **23:** 32-40.

Withers, D.J., J.S. Gutierrez, H. Towery, D.J. Burks, J.M. Ren, S. Previs, Y. Zhang, D. Bernal, S. Pons, G.I. Shulman, S. Bonner-Weir, and M.F. White. 1998. Disruption of IRS-2 causes type 2 diabetes in mice. *Nature* **391:** 900-904.

Wolfram DJ, W.H. 1938. Diabetes mellitus and simple optic atophy among siblings: report of four cases. *Mayo Clin. Proc.* **13:** 715-718.

World Health Organization:. 1999. Definitions, Diagnosis and Classification of Diabetes Mellitus and its Complications: Part 1: Diagnosis & Classification of Diabetes Mellitus. . World Health Organization, Geneva.

Worman, H.J. and G. Bonne. 2007. "Laminopathies": a wide spectrum of human diseases. *Exp Cell Res* **313:** 2121-2133.

Wullschleger, S., R. Loewith, and M.N. Hall. 2006. TOR signaling in growth and metabolism. *Cell* **124:** 471-484.

Xu, J., W.N. Lee, J. Phan, M.F. Saad, K. Reue, and I.J. Kurland. 2006. Lipin deficiency impairs diurnal metabolic fuel switching. *Diabetes* **55:** 3429-3438.

Yamada, E., S. Okada, T. Saito, K. Ohshima, M. Sato, T. Tsuchiya, Y. Uehara, H. Shimizu, and M. Mori. 2005. Akt2 phosphorylates Synip to regulate docking and fusion of GLUT4-containing vesicles. *J Cell Biol* **168:** 921-928.

Yamada, T., H. Ishihara, A. Tamura, R. Takahashi, S. Yamaguchi, D. Takei, A. Tokita, C. Satake, F. Tashiro, H. Katagiri, H. Aburatani, J. Miyazaki, and Y. Oka. 2006. WFS1-deficiency increases endoplasmic reticulum stress, impairs cell cycle progression and triggers the apoptotic pathway specifically in pancreatic beta-cells. *Hum Mol Genet* **15:** 1600-1609.

Yamagata, K., H. Furuta, N. Oda, P.J. Kaisaki, S. Menzel, N.J. Cox, S.S. Fajans, S. Signorini, M. Stoffel, and G.I. Bell. 1996a. Mutations in the hepatocyte nuclear

factor-4alpha gene in maturity-onset diabetes of the young (MODY1). *Nature* **384:** 458-460.

Yamagata, K., N. Oda, P.J. Kaisaki, S. Menzel, H. Furuta, M. Vaxillaire, L. Southam, R.D. Cox, G.M. Lathrop, V.V. Boriraj, X. Chen, N.J. Cox, Y. Oda, H. Yano, M.M. Le Beau, S. Yamada, H. Nishigori, J. Takeda, S.S. Fajans, A.T. Hattersley, N. Iwasaki, T. Hansen, O. Pedersen, K.S. Polonsky, G.I. Bell, and et al. 1996b. Mutations in the hepatocyte nuclear factor-1alpha gene in maturity-onset diabetes of the young (MODY3). *Nature* **384:** 455-458.

Yang, Q., K. Inoki, T. Ikenoue, and K.L. Guan. 2006. Identification of Sin1 as an essential TORC2 component required for complex formation and kinase activity. *Genes Dev* **20:** 2820-2832.

Yao-Borengasser, A., N. Rasouli, V. Varma, L.M. Miles, B. Phanavanh, T.N. Starks, J. Phan, H.J. Spencer, 3rd, R.E. McGehee, Jr., K. Reue, and P.A. Kern. 2006. 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.

Yasuda, K., K. Miyake, Y. Horikawa, K. Hara, H. Osawa, H. Furuta, Y. Hirota, H. Mori, A. Jonsson, Y. Sato, K. Yamagata, Y. Hinokio, H.Y. Wang, T. Tanahashi, N. Nakamura, Y. Oka, N. Iwasaki, Y. Iwamoto, Y. Yamada, Y. Seino, H. Maegawa, A. Kashiwagi, J. Takeda, E. Maeda, H.D. Shin, Y.M. Cho, K.S. Park, H.K. Lee, M.C. Ng, R.C. Ma, W.Y. So, J.C. Chan, V. Lyssenko, T. Tuomi, P. Nilsson, L. Groop, N. Kamatani, A. Sekine, Y. Nakamura, K. Yamamoto, T. Yoshida, K. Tokunaga, M. Itakura, H. Makino, K. Nanjo, T. Kadowaki, and M. Kasuga. 2008. Variants in KCNQ1 are associated with susceptibility to type 2 diabetes mellitus. *Nat Genet*.

Yoon, K.H., S.H. Ko, J.H. Cho, J.M. Lee, Y.B. Ahn, K.H. Song, S.J. Yoo, M.I. Kang, B.Y. Cha, K.W. Lee, H.Y. Son, S.K. Kang, H.S. Kim, I.K. Lee, and S. Bonner-Weir. 2003. Selective beta-cell loss and alpha-cell expansion in patients with type 2 diabetes mellitus in Korea. *J Clin Endocrinol Metab* **88:** 2300-2308.

Yu, C.E., J. Oshima, Y.H. Fu, E.M. Wijsman, F. Hisama, R. Alisch, S. Matthews, J. Nakura, T. Miki, S. Ouais, G.M. Martin, J. Mulligan, and G.D. Schellenberg. 1996. Positional cloning of the Werner's syndrome gene. *Science* **272:** 258-262.

Yu, J., Y. Zhang, J. McIlroy, T. Rordorf-Nikolic, G.A. Orr, and J.M. Backer. 1998. Regulation of the p85/p110 phosphatidylinositol 3'-kinase: stabilization and inhibition of the p110alpha catalytic subunit by the p85 regulatory subunit. *Mol Cell Biol* **18:** 1379-1387.

Zeggini, E., L.J. Scott, R. Saxena, B.F. Voight, J.L. Marchini, T. Hu, P.I. de Bakker, G.R. Abecasis, P. Almgren, G. Andersen, K. Ardlie, K.B. Bostrom, R.N. Bergman, L.L. Bonnycastle, K. Borch-Johnsen, N.P. Burtt, H. Chen, P.S. Chines, M.J. Daly, P. Deodhar, C.J. Ding, A.S. Doney, W.L. Duren, K.S. Elliott, M.R. Erdos, T.M. Frayling, R.M. Freathy, L. Gianniny, H. Grallert, N. Grarup, C.J. Groves, C. Guiducci, T. Hansen, C. Herder, G.A. Hitman, T.E. Hughes, B. Isomaa, A.U. Jackson, T. Jorgensen, A. Kong, K. Kubalanza, F.G. Kuruvilla, J. Kuusisto, C. Langenberg, H. Lango, T. Lauritzen, Y. Li, C.M. Lindgren, V. Lyssenko, A.F. Marvelle, C. Meisinger, K. Midthjell, K.L. Mohlke, M.A. Morken, A.D. Morris, N. Narisu, P. Nilsson, K.R. Owen, C.N. Palmer, F. Payne, J.R. Perry, E. Pettersen, C. Platou, I. Prokopenko, L. Qi, L. Qin, N.W. Rayner, M. Rees, J.J. Roix, A. Sandbaek, B. Shields, M. Sjogren, V. Steinthorsdottir, H.M. Stringham, A.J. Swift, G. Thorleifsson, U. Thorsteinsdottir, N.J. Timpson, T. Tuomi, J. Tuomilehto, M. Walker, R.M. Watanabe, M.N. Weedon, C.J. Willer, T. Illig, K. Hveem, F.B. Hu, M. Laakso, K. Stefansson, O. Pedersen, N.J. Wareham, I. Barroso, A.T. Hattersley, F.S. Collins, L. Groop, M.I. McCarthy, M. Boehnke, and D. Altshuler.

2008. Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes. *Nat Genet* **40:** 638-645.

Zhang, D., Z.X. Liu, C.S. Choi, L. Tian, R. Kibbey, J. Dong, G.W. Cline, P.A. Wood, and G.I. Shulman. 2007. Mitochondrial dysfunction due to long-chain Acyl-CoA dehydrogenase deficiency causes hepatic steatosis and hepatic insulin resistance. *Proc Natl Acad Sci U S A* **104:** 17075-17080.

Zhang, P., B. McGrath, S. Li, A. Frank, F. Zambito, J. Reinert, M. Gannon, K. Ma, K. McNaughton, and D.R. Cavener. 2002. The PERK eukaryotic initiation factor 2 alpha kinase is required for the development of the skeletal system, postnatal growth, and the function and viability of the pancreas. *Mol Cell Biol* **22:** 3864-3874.

Zhang, P., L. O'Loughlin, D.N. Brindley, and K. Reue. 2008. Regulation of lipin-1 gene expression by glucocorticoids during adipogenesis. *J Lipid Res*.

Zhang, W., S. Patil, B. Chauhan, S. Guo, D.R. Powell, J. Le, A. Klotsas, R. Matika, X. Xiao, R. Franks, K.A. Heidenreich, M.P. Sajan, R.V. Farese, D.B. Stolz, P. Tso, S.H. Koo, M. Montminy, and T.G. Unterman. 2006. FoxO1 regulates multiple metabolic pathways in the liver: effects on gluconeogenic, glycolytic, and lipogenic gene expression. *J Biol Chem* **281:** 10105-10117.

Zhang, Y., R. Proenca, M. Maffei, M. Barone, L. Leopold, and J.M. Friedman. 1994. Positional cloning of the mouse obese gene and its human homologue. *Nature* **372:** 425-432.

Zick, Y. 2001. Insulin resistance: a phosphorylation-based uncoupling of insulin signaling. *Trends Cell Biol* **11:** 437-441.

Zung, A., B. Glaser, R. Nimri, and Z. Zadik. 2004. Glibenclamide treatment in permanent neonatal diabetes mellitus due to an activating mutation in Kir6.2. *J Clin Endocrinol Metab* **89:** 5504-5507.