

Genome-Wide Association

Which Do You Want First: the Good News, the Bad News, or the Good News?

Kent D. Taylor,^{1,2} Jill M. Norris,³ and Jerome I. Rotter^{1,2,4}

It has long been appreciated that there is a genetic component to type 2 diabetes, but progress in gene finding has been slow because the genetic component is complex. Accumulating data on various diabetes-related phenotypes suggest that so-called “type 2 diabetes” is likely a collection of many diseases due to varying but often overlapping underlying mechanisms. As such, the search for the once hoped-for simple genetic basis of type 2 diabetes has proved elusive.

This year marks the application of the next gene-finding tool to the study of type 2 diabetes, the genome-wide association study (GWA). This type of study is the logical extension of the candidate gene association study, an approach in which a few (1–20 or so) single nucleotide polymorphisms (SNPs) within a single gene are tested for association with the phenotype of interest. By that approach, the candidate gene is chosen based on biochemistry or physiology related to that phenotype. The candidate gene approach has identified some genes but has not yielded the definitive picture of the genetic contribution to type 2 diabetes (Table 1; reviewed in [1]).

In contrast, the GWA approach tests every gene by testing the association of SNPs in every known gene (~100,000 SNPs) or in both known genes and in regions outside of genes throughout the genome (~300,000 to 1 million). The GWA is therefore not biased by a priori assumptions based on prior observations of the phenotype (e.g., kinetics of insulin signaling, glucose-mediated insulin secretion, etc). Therefore, the strength of the GWA is that it has the potential to identify genes of high genetic effect that were previously unsuspected as candidates. The latter might be because little was known about the genes previously or because investigators simply had not addressed the action of the products of these genes in prior studies of the biochemistry and physiology of type 2 diabetes.

From the ¹Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, California; the ²Department of Pediatrics, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California; the ³Department of Preventive Medicine and Biometrics, University of Colorado Health Sciences Center, Denver, Colorado; and the ⁴Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, California.

Address correspondence and reprint requests to Jerome I. Rotter, Medical Genetics Institute, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Suite 665, West Los Angeles, California 90048-1804. E-mail: jerome.rotter@cshs.org.

Received for publication 18 September and accepted in revised form 29 September 2007.

GWA, genome-wide association; SNP, single nucleotide polymorphism.

DOI: 10.2337/db07-1324

© 2007 by the American Diabetes Association.

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

In one sense, the GWA approach is driven by gene or marker location rather than by gene function and thus extends the genome-wide linkage approach. However, the advantages of the GWA approach are that it does not depend on the availability of families for study and that it can detect smaller effects than detectable by a genome-wide linkage approach. GWAs are now technically feasible because of several recent developments. First, there has been a dramatic reduction in genotyping costs, brought about by new technologies. Second, a large number of possible SNPs are now available for use in the catalog of over 12 million human SNPs in public databases (9). Third, there has been a reduction in the number of SNPs required to cover the entire human genome because of the block structure of the human genome and the ability to predict tag SNPs. Tag SNPs are SNPs that provide the most information for association studies (10,11), available from data provided by the International HapMap Project (12).

The good news is that yesterday there were twice as many confirmed type 2 diabetes genes to study compared with the number confirmed when the survey by Willer et al. (1) was published in January 2007 (Table 1). Moreover, articles in this issue both add to this list and extend GWA findings into other populations important for type 2 diabetes: Amish (39), Pima Indian (40), and Mexican American (41). As Table 1 shows, genes such as PPAR γ , KCNJ11, and TCF7L2 were also associated with type 2 diabetes, with high significance in several GWAs, thus reassuring us that GWAs do find genetic determinants of diabetes. Table 1 also shows that other genes with evidence for linkage and/or association to type 2 diabetes, such as CAPN10 and ENPP1, have not yet been found to be associated with type 2 diabetes using this tool. This is possible for several reasons: 1) Technological: the particular “chip” configuration used covered these genes poorly and so the genetic effect was missed. 2) Genetic: the genes identified using the previous tools were not detected using GWA because their quantitative contribution to type 2 diabetes is lower when ranked and compared with other genes. Such a ranking occurs in a GWA experiment study. Finally, 3) Epidemiological: the association was missed because it was not present to a great degree in a particular study sample. For example, CAPN10 and ENPP1 may yet be important within the context of a subset of metabolic disease or of a particular ethnic group.

The possibility that results are merely random is ever present in genetic analysis because subject recruitment is in fact a sampling from a population and because the path to gene finding requires statistical methods. In addition, the discipline of genetic analysis continues to mature, and we are finding out that we may have glossed over very complex problems in past work. For example, we have

TABLE 1
Genetic factors for type 2 diabetes

Gene	dbGene	Description	Studies*	GWA studies
CAPN10	11132	Calpain 10	(ref. 20)	
ENPP1	5167	Pyrophosphatase/phosphodiesterase 1	(ref. 21)	
PPARG	5468	Peroxisome proliferator-activated receptor- γ	(refs. 22–25)	(refs. 2, 4)
		Potassium inwardly rectifying channel, subfamily J, member 11	(refs. 24, 26, 27)	(refs. 2, 4)
KCNJ11	3767			
HNF4A	3172	Hepatocyte nuclear factor-4 α	(refs. 28, 29)	
TCF7L2	6934	Transcription factor 7-like 2	(refs. 30–33)	(refs. 2–6, 8, 9)
ARHGEF11	9826	Rho guanine nucleotide exchange factor (GEF)-11	(ref. 34)	
SLC30A8	169026	Solute carrier family 30 (zinc transporter), member 8		(refs. 4–8)
		Linkage disequilibrium block containing hematopoietically expressed homeobox and insulin-degrading enzyme genes		(refs. 2, 4–8)
HHEX/IDE	3087/3416			
		Linkage disequilibrium block containing exostoses and arista-like homeobox-4 genes		(ref. 5)
EXT2/ALX4	2132/60529			(2; 4; 6–8)
CDKAL1	54901	CDK5 regulatory subunit-associated protein 1-like 1		
CDKN2A/B		Linkage disequilibrium block located near cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4) and 2B (p15) genes. Region also associated with myocardial infarction.		(refs. 2, 4, 6, 7)
	1029			
IGF2BP2	10644	Insulin-like growth factor-2 mRNA binding protein-2		(refs. 2, 4, 6, 7)

*Including linkage, fine-mapping, and candidate gene studies.

made naive assumptions about populations. Recent papers have demonstrated the difficulty of genetic analysis in the “Hispanic” or “Latino” population, due to subgroups with various amounts of contribution from ancestral Native-American, West African, and European populations (35). Further, the Wellcome Trust GWA identified a substructure within the European-Caucasian population and even within the U.K. (2). It is possible that ENPP1 and CAPN10, for example, showed linkage and/or association only in particular populations. There is as yet no definitive answer on what the ENPP1 and CAPN10 candidate gene studies mean to the genetic component of type 2 diabetes as a whole.

Candidate gene studies of type 2 diabetes and complications of related physiological abnormalities will, however, remain important in the years ahead for a variety of reasons: 1) A candidate gene study may extend the results of a GWA into other ethnic groups or into groups with detailed phenotypes such as the oral glucose tolerance test, as represented by articles in this issue (39–42). 2) A candidate gene study may evaluate an association in greater depth and may include haplotype structure, population-attributable risks, and resequencing to identify specific variants. 3) A candidate gene study is more straightforward to conduct than a GWA because it is testing a specific hypothesis. 4) A candidate gene study may have greater power to detect a genetic effect and may be able to detect smaller effects because there are fewer statistical tests being performed. 5) Completion of a candidate gene study is practical for many more investigators in the research community. 6) A candidate gene study may focus on particular subgroups, e.g., minority populations, groups that do and do not respond to particular drug therapies, subgroups sharing particular clinical characteristics, or smaller numbers of patients with data from very detailed but very complicated physiological studies.

However, the bad news is that, as we have long suspected, the increase in risk for each gene remains modest, in the range of ~ 1.2 – 1.4 . Thus, the genetic analysis of type

2 diabetes by no means ends this year with the GWA, whether published earlier this year (2–8) or as reported by Florez et al. (42), Rampersaud et al. (39), Hayes et al. (41), and Hanson et al. (40).

There remains much to do. These articles show the types of approaches to be taken to disentangle type 2 diabetes genetics and to bring the changes to clinical practice promised by the genome era of medicine.

Genotyping with different SNP ensembles. Each particular GWA is performed with a particular technology using materials manufactured by a particular company, e.g., Illumina or Affymetrix. These technologies are different, and the actual list of SNPs tested by each chip type is different. This difference is due to design decisions and to which SNPs work reliably with each method. For example, the 100K chips represented by the articles in this issue focused more on including SNPs that were located within annotated genes and that changed amino acids in the protein sequence. The design of this particular chip type therefore focused more on testing all of the genes known at the time of chip manufacture rather than attempting to place SNPs within regions that had no known genes. In contrast, the design of 300K and 500K configurations have attempted to include SNPs that would tag haplotype blocks across the entire genome in the Caucasian population. Designs of 700K to 1M have attempted to include SNPs important for other populations. This latter, more genome-wide approach might well identify genetic contributions from regions that do not appear at this time to contain a gene that codes for any protein. This may be due either to our lack of knowledge of all proteins or our lack of knowledge of how regions seemingly far from a known gene may exert control over other protein-coding genes. A recent example of this is the recently identified region for myocardial infarction that is not, as of today, located within a gene annotated in the dbGene software (NCBI) (36,37). Thus, the papers in this issue focus on candidate genes (in this context, all genes) rather than on truly complete genome coverage. The usefulness of different chip designs together has been demonstrated in studies of

Crohn's disease, another complex genetic trait. An association between Crohn's disease and TNFSF15 was first detected by a 100K candidate gene approach but only by one of two 300K whole-genome approaches (13–17). The importance of autophagy and the ATG16L1 gene in Crohn's disease was demonstrated first using a collection of nonsynonymous SNPs and then observed by using a whole-genome collection (18,19), while using a whole genome collection emphasized the importance of the IL23R pathway (14).

Therefore, while the number of SNPs in the studies reported in this issue is perhaps lower than that in the other studies reported this year, the studies in this issue make a substantial contribution to identifying genetic associations with type 2 diabetes phenotypes. The four studies shared results earlier rather than later so that replication and confirmation studies could be rapidly set up and finished (39–42).

Extension into other ethnic groups. Observations of both the same and different genes across Caucasian Americans, Mexican Americans, the Amish, and Pima Indians are reported here. These differences are most likely related to the different evolutionary histories of these populations and probably contribute to the complexity of the genetics of type 2 diabetes because they affect different pathways or different pathophysiology, but all ultimately result in the clinical phenotype of type 2 diabetes. Close attention to the similarities and differences between populations definitely promises to help unravel the genetic complexity.

Analysis of subphenotypes. The definition of type 2 diabetes is arbitrary and changes every few years. It is therefore not surprising that different insights arise from examining the association between genetic variants and measurements of physiological parameters (e.g., by the oral glucose tolerance test). In the present studies, the association between SNPs and diabetes-related phenotypes are reported, and this approach will likely be powerful in gene finding. Furthermore, these studies demonstrate the great value of beginning with SNPs associated with more than one, but related, trait (for example, type 2 diabetes and fasting plasma glucose). Similarities and differences in the association of SNPs with many diabetes-related subclinical phenotypes promise to point to pathways important both in the development of subsets of patients with type 2 diabetes and in the temporal development of type 2 diabetes.

Of interest to the study of type 2 diabetes is that many, if not most, of the genes identified by earlier GWAs (2–8) appear to be involved in β -cell function rather than insulin secretion/resistance, i.e., only one of the two primary phenotypes directly predisposing to type 2 diabetes. Why might this be so? One explanation is that the variance in insulin sensitivity is due to a greater environmental component and thus that genetic risk for type 2 diabetes is indeed more related to β -cell function, development, and/or survival. A second possible explanation is that defects impairing β -cell function are less common than defects leading to insulin resistance. This would lead to a higher relative risk for β -cell defects and greater ease of identifying genes contributing to that risk. Continuing with this line of reasoning, the genes leading to insulin resistance would be many, with each contributing a slight increase in risk that would be difficult or impossible to detect reliably. These considerations may explain why identifying genes for Crohn's disease by GWA appears to require a smaller

sample and has had greater success than GWA for type 2 diabetes thus far (2). As shown in families, genes contribute more to the relative risk for Crohn's disease than to type 2 diabetes. A further implication of this line of reasoning is that, as GWAs continue to be applied and focus on traits such as insulin sensitivity/resistance, genes for this important component of type 2 diabetes may also emerge. A third possibility is that we may find, as we continue to dissect type 2 diabetes genetics, that genes related to insulin sensitivity are also genes related to β -cell function and that, therefore, the major genetic component of type 2 diabetes is indeed the genetic alteration of β -cell function, development, and/or survival acting through many different pathways. Evidence for such genetic pleiotropism has been suggested for the susceptibility contributed by CAPN10 (36).

The new vista open to type 2 diabetes genetics goes beyond the individual gene to the entire pathway related to each. This is also good news; there remains much more to do, but we have a better place to start from than we did last year.

REFERENCES

1. Willer CJ, Bonnycastle LL, Conneely KN, Duren WL, Jackson AU, Scott LJ, Narisu N, Chines PS, Skol A, Stringham HM, Petrie J, Erdos MR, Swift AJ, Enloe ST, Sprau AG, Smith E, Tong M, Doheny KF, Pugh EW, Watanabe RM, Buchanan TA, Valle TT, Bergman RN, Tuomilehto J, Mohlke KL, Collins FS, Boehnke M: Screening of 134 single nucleotide polymorphisms (SNPs) previously associated with type 2 diabetes replicates association with 12 SNPs in nine genes. *Diabetes* 56:256–264, 2007
2. Wellcome Trust Case Control Consortium: Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* 447:661–678, 2007
3. Salonen JT, Uimari P, Aalto JM, Pirskanen M, Kaikkonen J, Todorova B, Hypponen J, Korhonen VP, Asikainen J, Devine C, Tuomainen TP, Luedemann J, Nauck M, Kerner W, Stephens RH, New JP, Ollier WE, Gibson JM, Payton A, Horan MA, Pendleton N, Mahoney W, Meyre D, Delplanque J, Froguel P, Luzzatto O, Yakir B, Darvasi A: Type 2 diabetes whole-genome association study in four populations: the DiaGen consortium. *Am J Hum Genet* 81:338–345, 2007
4. Scott LJ, Mohlke KL, Bonnycastle LL, Willer CJ, Li Y, Duren WL, Erdos MR, Stringham HM, Chines PS, Jackson AU, Prokunina-Olsson L, Ding CJ, Swift AJ, Narisu N, Hu T, Pruim R, Xiao R, Li XY, Conneely KN, Riebow NL, Sprau AG, Tong M, White PP, Hetrick KN, Barnhart MW, Bark CW, Goldstein JL, Watkins L, Xiang F, Saramies J, Buchanan TA, Watanabe RM, Valle TT, Kinnunen L, Abecasis GR, Pugh EW, Doheny KF, Bergman RN, Tuomilehto J, Collins FS, Boehnke M: A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. *Science* 316:1341–1345, 2007
5. Sladek R, Rocheleau G, Rung J, Dina C, Shen L, Serre D, Boutin P, Vincent D, Belisle A, Hadjadj S, Balkau B, Heude B, Charpentier G, Hudson TJ, Montpetit A, Pshezhetsky AV, Prentki M, Posner BI, Balding DJ, Meyre D, Polychronakos C, Froguel P: A genome-wide association study identifies novel risk loci for type 2 diabetes. *Nature* 445:881–885, 2007
6. Zeggini E, Weedon MN, Lindgren CM, Frayling TM, Elliott KS, Lango H, Timpson NJ, Perry JR, Rayner NW, Freathy RM, Barrett JC, Shields B, Morris AP, Ellard S, Groves CJ, Harries LW, Marchini JL, Owen KR, Knight B, Cardon LR, Walker M, Hitman GA, Morris AD, Doney AS; Wellcome Trust Case Control Consortium (WTCCC), McCarthy MI, Hattersley AT: Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. *Science* 316:1336–1341, 2007
7. Saxena R, Voight BF, Lyssenko V, Burt NP, de Bakker PI, Chen H, Roix JJ, Kathiresan S, Hirschhorn JN, Daly MJ, Hughes TE, Groop L, Althuler D, Almgren P, Florez JC, Meyer J, Ardlie K, Bengtsson Bostrom K, Isomaa B, Lette G, Lindblad U, Lyon HN, Melander O, Newton-Cheh C, Nilsson P, Orho-Melander M, Rastam L, Speliotes EK, Taskinen MR, Tuomi T, Guiducci C, Berglund A, Carlson J, Gianniny L, Hackett R, Hall L, Holmkvist J, Laurila E, Sjogren M, Sterner M, Surti A, Svensson M, Svensson M, Tewhey R, Blumensiel B, Parkin M, Defelice M, Barry R, Brodeur W, Camarata J, Chia N, Fava M, Gibbons J, Handsaker B, Healy C, Nguyen K, Gates C, Sougnez C, Gage M, Nizzari M, Gabriel SB, Chirn GW, Ma Q, Parikh H, Richardson D, Ricke D, Purcell S: Genome-wide associ-

- ation analysis identifies loci for type 2 diabetes and triglyceride levels. *Science* 316:1331–1336, 2007
8. Steinthorsdottir V, Thorleifsson G, Reynisdottir I, Benediktsson R, Jonsdottir T, Walters GB, Styrkarsdottir U, Gretarsdottir S, Emilsson V, Ghosh S, Baker A, Snorrardottir S, Bjarnason H, Ng MC, Hansen T, Bagger Y, Wilensky RL, Reilly MP, Adeyemo A, Chen Y, Zhou J, Gudnason V, Chen G, Huang H, Lashley K, Doumatey A, So WY, Ma RC, Andersen G, Borch-Johnsen K, Jorgensen T, van Vliet-Ostaptchouk JV, Hofker MH, Wijmenga C, Christiansen C, Rader DJ, Rotimi C, Gurney M, Chan JC, Pedersen O, Sigurdsson G, Gulcher JR, Thorsteinsdottir U, Kong A, Stefansson K: A variant in CDKAL1 influences insulin response and risk of type 2 diabetes. *Nat Genet* 39:770–775, 2007
 9. Wheeler DL, Barrett T, Benson DA, Bryant SH, Canese K, Chetvernin V, Church DM, DiCuccio M, Edgar R, Federhen S, Geer LY, Kapustin Y, Khovayko O, Landsman D, Lipman DJ, Madden TL, Maglott DR, Ostell J, Miller V, Pruitt KD, Schuler GD, Sequeira E, Sherry ST, Sirotkin K, Souvorov A, Starchenko G, Tatusov RL, Tatusova TA, Wagner L, Yaschenko E: Database resources of the National Center for Biotechnology Information. *Nucleic Acid Res* 35:D5–D12, 2007
 10. Gabriel SB, Schaffner SF, Nguyen H, Moore JM, Roy J, Blumenstiel B, Higgins J, DeFelice M, Lochner A, Faggart M, Liu-Cordero SN, Rotimi C, Adeyemo A, Cooper R, Ward R, Lander ES, Daly MJ, Altshuler D: The structure of haplotype blocks in the human genome. *Science* 296:2225–2229, 2002
 11. Crawford DC, Nickerson DA: Definition and clinical importance of haplotypes. *Annu Rev Med* 56:303–320, 2005
 12. International HapMap Consortium: The International HapMap Project. *Nature* 426:789–796, 2003
 13. Yamazaki K, McGovern D, Ragoussis J, Paolucci M, Butler H, Jewell D, Cardon L, Takazoe M, Tanaka T, Ichimori T, Saito S, Sekine A, Iida A, Takahashi A, Tsunoda T, Lathrop M, Nakamura Y: Single nucleotide polymorphisms in TNFSF15 confer susceptibility to Crohn's disease. *Hum Mol Genet* 14:3499–3506, 2005
 14. Duerr RH, Taylor KD, Brant SR, Rioux JD, Silverberg MS, Daly MJ, Steinhardt AH, Abraham C, Regueiro M, Griffiths A, Dassopoulos T, Bitton A, Yang H, Targan S, Datta LW, Kistner EO, Schumm LP, Lee AT, Gregersen PK, Barnada MM, Rotter JJ, Nicolae DL, Cho JH: A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. *Science* 314:1461–1463, 2006
 15. Rioux JD, Xavier RJ, Taylor KD, Silverberg MS, Goyette P, Huett A, Green T, Kuballa P, Barnada MM, Datta LW, Shugart YY, Griffiths AM, Targan SR, Ippoliti AF, Bernard EJ, Mei L, Nicolae DL, Regueiro M, Schumm LP, Steinhardt AH, Rotter JJ, Duerr RH, Cho JH, Daly MJ, Brant SR: Genome-wide association study identifies new susceptibility loci for Crohn disease and implicates autophagy in disease pathogenesis. *Nat Genet* 39:596–604, 2007
 16. Libioulle C, Louis E, Hansoul S, Sandor C, Farnir F, Franchimont D, Vermeire S, Dewit O, de Vos M, Dixon A, Demarche B, Gut I, Heath S, Foglio M, Liang L, Laukens D, Mni M, Zelenika D, Van Gossum A, Rutgeerts P, Belaiche J, Lathrop M, Georges M: Novel Crohn disease locus identified by genome-wide association maps to a gene desert on 5p13.1 and modulates expression of PTGER4. *PLoS Genet* 3:e58, 2007
 17. Picornell Y, Mei L, Taylor K, Yang H, Targan SR, Rotter JJ: TNFSF15 is an ethnic specific IBD gene. *Inflamm Bowel Dis* 13:1333–1338, 2007
 18. Hampe J, Franke A, Rosenstiel P, Till A, Teuber M, Huse K, Albrecht M, Mayr G, De La Vega FM, Briggs J, Gunther S, Prescott NJ, Onnie CM, Hasler R, Sipos B, Folsch UR, Lengauer T, Platzer M, Mathew CG, Krawczak M, Schreiber S: A genome-wide association scan of nonsynonymous SNPs identifies a susceptibility variant for Crohn disease in ATG16L1. *Nat Genet* 39:207–211, 2007
 19. Prescott NJ, Fisher SA, Franke A, Hampe J, Onnie CM, Soars D, Bagnall R, Mirza MM, Sanderson J, Forbes A, Mansfield JC, Lewis CM, Schreiber S, Mathew CG: A nonsynonymous SNP in ATG16L1 predisposes to ileal Crohn's disease and is independent of CARD15 and IBD5. *Gastroenterology* 132:1665–1671, 2007
 20. Horikawa Y, Oda N, Cox NJ, Li X, Orho-Melander M, Hara M, Hinokio Y, Lindner TH, Mashima H, Schwarz PE, del Bosque-Plata L, Oda Y, Yoshiuchi I, Colilla S, Polonsky KS, Wei S, Concannon P, Iwasaki N, Schulze J, Baier LJ, Bogardus C, Groop L, Boerwinkle E, Hani CL, Bell GI: Genetic variation in the gene encoding calpain-10 is associated with type 2 diabetes mellitus. *Nat Genet* 26:163–175, 2000
 21. Pizzuti A, Frittitta L, Argiolas A, Baratta R, Goldfine ID, Bozzali M, Ercolino T, Scarlato G, Iacoviello L, Vigneri R, Tassi V, Trischitta V: A polymorphism (K121Q) of the human glycoprotein PC-1 gene coding region is strongly associated with insulin resistance. *Diabetes* 48:1881–1884, 1999
 22. Altshuler D, Hirschhorn JN, Klannemark M, Lindgren CM, Vohl MC, Nemesh J, Lane CR, Schaffner SF, Bolk S, Brewer C, Tuomi T, Gaudet D, Hudson TJ, Daly M, Groop L: The common PPAR γ Pro12Ala polymorphism is associated with decreased risk of type 2 diabetes. *Nat Genet* 26:76–80, 2000
 23. Deeb SS, Fajas L, Nemoto M, Pihlajamaki J, Mykkanen L, Kuusisto J, Laakso M, Fujimoto W, Auwerx J: A Pro12Ala substitution in PPAR γ 2 associated with decreased receptor activity, lower body mass index and improved insulin sensitivity. *Nat Genet* 20:284–287, 1998
 24. Hansen SK, Nielsen EM, Ek J, Andersen G, Glumer C, Carstensen B, Mouritzen P, Drivsholm T, Borch-Johnsen K, Jorgensen T, Hansen T, Pedersen O: Analysis of separate and combined effects of common variation in KCNJ11 and PPAR γ on risk of type 2 diabetes. *J Clin Endocrinol Metab* 90:3629–3637, 2005
 25. Florez JC, Jablonski KA, Sun MW, Bayley N, Kahn SE, Shamon H, Hamman RF, Knowler WC, Nathan DM, Altshuler D: Effects of the type 2 diabetes-associated PPAR γ P12A polymorphism on progression to diabetes and response to troglitazone. *J Clin Endocrinol Metab* 92:1502–1509, 2007
 26. Florez JC, Jablonski KA, Kahn SE, Franks PW, Dabelea D, Hamman RF, Knowler WC, Nathan DM, Altshuler D: Type 2 diabetes-associated missense polymorphisms KCNJ11 E23K and ABCC8 A1369S influence progression to diabetes and response to interventions in the Diabetes Prevention Program. *Diabetes* 56:531–536, 2007
 27. Gloyn AL, Weedon MN, Owen KR, Turner MJ, Knight BA, Hitman G, Walker M, Levy JC, Sampson M, Halford S, McCarthy MI, Hattersley AT, Frayling TM: Large-scale association studies of variants in genes encoding the pancreatic β -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, 2003
 28. Love-Gregory LD, Wasson J, Ma J, Jin CH, Glaser B, Suarez BK, Permutt MA: A common polymorphism in the upstream promoter region of the hepatocyte nuclear factor-4 α 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, 2004
 29. Silander K, Mohlke KL, Scott LJ, Peck EC, Hollstein P, Skol AD, Jackson AU, Deloukas P, Hunt S, Stavrides G, Chines PS, Erdos MR, Narisu N, Conneely KN, Li C, Fingerlin TE, Dhanjal SK, Valle TT, Bergman RN, Tuomilehto J, Watanabe RM, Boehnke M, Collins FS: Genetic variation near the hepatocyte nuclear factor-4 α gene predicts susceptibility to type 2 diabetes. *Diabetes* 53:1141–1149, 2004
 30. Grant SF, Thorleifsson G, Reynisdottir I, Benediktsson R, Manolescu A, Sainz J, Helgason A, Stefansson H, Emilsson V, Helgadóttir A, Styrkarsdottir U, Magnusson KP, Walters GB, Palsdóttir E, Jonsdottir T, Gudmundsdóttir T, Gylfason A, Saemundsdóttir J, Wilensky RL, Reilly MP, Rader DJ, Bagger Y, Christiansen G, Gudnason V, Sigurdsson G, Thorsteinsdottir U, Gulcher JR, Kong A, Stefansson K: Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. *Nat Genet* 38:320–323, 2006
 31. Damcott CM, Pollin TI, Reinhart LJ, Ott SH, Shen H, Silver KD, Mitchell BD, Shuldiner AR: Polymorphisms in the transcription factor 7-like 2 (TCF7L2) gene are associated with type 2 diabetes in the Amish: replication and evidence for a role in both insulin secretion and insulin resistance. *Diabetes* 55:2654–2659, 2006
 32. Florez JC, Jablonski KA, Bayley N, Pollin TI, de Bakker PI, Shuldiner AR, Knowler WC, Nathan DM, Altshuler D: TCF7L2 polymorphisms and progression to diabetes in the Diabetes Prevention Program. *N Engl J Med* 355:241–250, 2006
 33. Scott LJ, Bonycastle LL, Willer CJ, Sprau AG, Jackson AU, Narisu N, Duren WL, Chines PS, Stringham HM, Erdos MR, Valle TT, Tuomilehto J, Bergman RN, Mohlke KL, Collins FS, Boehnke M: Association of transcription factor 7-like 2 (TCF7L2) variants with type 2 diabetes in a Finnish sample. *Diabetes* 55:2649–2653, 2006
 34. Fu M, Sabra MM, Damcott C, Pollin TI, Ma L, Ott S, Shelton JC, Shi X, Reinhart L, O'Connell J, Mitchell BD, Baier LJ, Shuldiner AR: Evidence that ρ -guanine nucleotide exchange factor 11 (ARHGAP11) on 1q21 is a type 2 diabetes susceptibility gene in the Old Order Amish. *Diabetes* 56:1363–1368, 2007
 35. Price AL, Patterson N, Yu F, Cox DR, Waliszewska A, McDonald GJ, Tandon A, Schirmer C, Neubauer J, Bedoya G, Duque C, Villegas A, Bortolini MC, Salzano FM, Gallo C, Mazzotti G, Tello-Ruiz M, Riba L, Aguilar-Salinas CA, Canizales-Quinteros S, Menjivar M, Klitz W, Henderson B, Haiman CA, Winkler C, Tusie-Luna T, Ruiz-Linares A, Reich D: A genomewide admixture map for Latino populations. *Am J Hum Genet* 80:1024–1036, 2007
 36. Helgadóttir A, Thorleifsson G, Manolescu A, Gretarsdottir S, Blondal T, Jonasdóttir A, Jonasdóttir A, Sigurdsson A, Baker A, Palsson A, Masson G, Gudbjartsson DF, Magnusson KP, Andersen K, Levey AI, Backman VM, Matthiassdóttir S, Jonsdóttir T, Palsson S, Einarssdóttir H, Gunnarsdóttir S, Gylfason A, Vaccarino V, Hooper WC, Reilly MP, Granger CB, Austin H,

- Rader DJ, Shah SH, Quyyumi AA, Gulcher JR, Thorgeirsson G, Thorsteinsdottir U, Kong A, Stefansson K: A common variant on chromosome 9p21 affects the risk of myocardial infarction. *Science* 316:1491–1493, 2007
37. McPherson R, Pertsemlidis A, Kavaslar N, Stewart A, Roberts R, Cox DR, Hinds DA, Pennacchio LA, Tybjaerg-Hansen A, Folsom AR, Boerwinkle E, Hobbs HH, Cohen JC: A common allele on chromosome 9 associated with coronary heart disease. *Science* 316:1488–1491, 2007
38. Goodarzi MO, Taylor KD, Guo X, Quinones MJ, Cui J, Li Y, Saad MF, Yang H, Hsueh WA, Hodis HN, Rotter JI: Association of the diabetes gene calpain-10 with subclinical atherosclerosis: the Mexican-American Coronary Artery Disease Study. *Diabetes* 54:1228–1232, 2005
39. Rampersaud E, Damcott CM, Fu M, Shen H, McArdle P, Xiaolian Shi, Shelton J, Yin J, Chang CY, Ott SH, Zhang L, Zhao Y, Mitchell BD, O'Connell J, Shuldiner AR: Identification of novel candidate genes for type 2 diabetes from a genome-wide association scan in the Old Order Amish: evidence for replication from diabetes-related quantitative traits from independent populations. *Diabetes* 56:3053–3062, 2007
40. Hanson RL, Bogardus C, Duggan D, Kobes S, Knowlton M, Infante AM, Marovich L, Benitez D, Baier LJ, Knowler WC: A search for variants associated with young-onset type 2 diabetes in American Indians in a 100K genotyping array. *Diabetes* 56:3045–3052, 2007
41. Hayes MG, Pluzhnikov A, Miyake K, Sun Y, Ng MCY, Roe CA, Below JE, Nicolae RI, Konkashbaev A, Bell GI, Cox NJ, Hanis CL: Identification of type 2 diabetes genes in Mexican Americans through genome-wide association studies. *Diabetes* 56:3033–3044, 2007
42. Florez JC, Manning AK, Dupuis J, McAteer J, Irenze K, Gianniny L, Mirel DB, Fox CS, Cupples LA, Meigs JB: A 100K genome-wide association scan for diabetes and related traits in the Framingham Heart Study: replication and integration with other genome-wide datasets. *Diabetes* 2007. Epub 11 September 2007. DOI:10.2337/db07-0451