Pathomechanisms of Type 2 Diabetes Genes

Harald Staiger, Fausto Machicao, Andreas Fritsche, and Hans-Ulrich Häring

Department of Internal Medicine, Division of Endocrinology, Diabetology, Angiology, Nephrology, and Clinical Chemistry, University Hospital Tübingen, D-72076 Tübingen, Germany

Type 2 diabetes mellitus is a complex metabolic disease that is caused by insulin resistance and β-cell dysfunction. Furthermore, type 2 diabetes has an evident genetic component and represents a polygenic disease. During the last decade, considerable progress was made in the identification of type 2 diabetes risk genes. This was crucially influenced by the development of affordable high-density single nucleotide polymorphism (SNP) arrays that prompted several successful genome-wide association scans in large case-control cohorts. Subsequent to the identification of type 2 diabetes risk SNPs, cohorts thoroughly phenotyped for prediabetic traits with elaborate *in vivo* methods allowed an initial characterization of the pathomechanisms of these SNPs. Although the underlying molecular mechanisms are still incompletely understood, a surprising result of these pathomechanistic investigations was that most of the risk SNPs affect β-cell function. This favors a β-cell-centric view on the genetics of type 2 diabetes. The aim of this review is to summarize the current knowledge about the type 2 diabetes risk genes and their variants' pathomechanisms. **(*Endocrine Reviews* 30: 557–585, 2009)**

I. Introduction

Type 2 diabetes mellitus is characterized by chronic hyperglycemia due to insulin resistance of peripheral tissues (skeletal muscle, liver, adipose tissue) and probably also the brain and insufficient compensatory insulin secretion by pancreatic β-cells (1, 2). In contrast to insulin resistance, the decline in β-cell function is considered a late event (3) and was shown to be, at least in part, caused by an irreversible loss of β-cell mass (4). It is commonly accepted that type 2 diabetes results, on the one hand, from population aging and, on the other hand, from adverse environmental factors of the modern world (*i.e.*, high-caloric diets, physical inactivity, and a sedentary lifestyle) which favor the development of obesity. In fact, excess body weight represents a major risk factor for type 2 diabetes (5–7). However, some 10% of type 2 diabetic patients display normal weight, and many obese subjects never develop type 2 diabetes, indicating that type 2 diabetes is not exclusively caused by environmental factors.

Because recent genome-wide association (GWA) studies revealed convincing evidence for the contribution of genes to the pathogenesis of type 2 diabetes (8) and subsequent efforts in thoroughly and uniquely phenotyped cohorts provided first insights into these genes' pathomechanistic roles (9), it is the purpose of this review to summarize the currently available information about (confirmed and potential) type 2 diabetes risk genes and to describe the current understanding of their pathomechanisms.

II. Genetics of Type 2 Diabetes

Type 2 diabetes clearly represents a multifactorial disease, and several findings indicate that genetics is an important

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/er.2009-0017 Received April 27, 2009. Accepted July 24, 2009.
First Published Online September 11, 2009.

Abbreviations: BMI, Body mass index; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide 1; GWA, genome-wide association; MODY, maturity onset diabetes of the young; OGTT, oral glucose tolerance test; PC-1, plasma cell glycoprotein 1; PPAR, peroxisome proliferator-activated receptor; SNP, single nucleotide polymorphism.

contributing factor. First, certain ethnic minorities and indigenous groups with low population admixture (*e.g.*, Pima Indians, Micronesians and other Pacific Islanders, Australian Aborigines, and Mexican-Americans) show exceptionally high type 2 diabetes prevalence (up to 21% in Pima Indians) (10–12). Second, type 2 diabetes clusters within families and first-degree relatives have, compared with the general population, an up to 3.5-fold higher risk to develop the disease (13, 14). Finally, twin studies demonstrated a markedly higher concordance for type 2 diabetes in monozygotic compared with dizygotic twins (~70 *vs.* 10%) (15). Type 2 diabetes does not follow simple Mendelian inheritance and, therefore, is considered a polygenic disease. According to the generally accepted common variant-common disease hypothesis (16), complex diseases, such as type 2 diabetes, are caused by the simultaneous occurrence of common DNA sequence variations (minor allele frequencies >5%) in many genes. Each of these DNA alterations is supposed to exert only moderate effects on the affected genes' function and/or expression, but in their sum, these variations confer an increased susceptibility toward the adverse environmental factors mentioned above. Single nucleotide polymorphisms (SNPs), exchanges of single base pairs, cover approximately 90% of the sequence variation within the human genome (SNP Fact Sheet of the Human Genome Project; available at http://www.ornl.gov/sci/techresources/Human_Genome/faq/snps.shtml) and are therefore regarded as the major determinants of the individual predisposition to complex diseases. Thus, strong efforts are currently ongoing to map and catalog these sequence variations (The International HapMap Project at http://www.hapmap.org/index.html.en). However, the less frequent copy number variations (due to deletion and/or duplication of DNA segments one kilobase to several megabases in size) and smaller DNA insertions, deletions, duplications, and inversions may also play a role. All of these findings initiated an intensive search for the genes, or better gene variants, responsible for the genetic predisposition to type 2 diabetes.

Two main approaches dominate the search for type 2 diabetes genes: the candidate gene approach and the hypothesis-free GWA scan (13). Candidate genes usually arise from diverse research directions (see below). They are combed through for common genetic variants, and these variants' allele frequencies are finally analyzed for being altered in type 2 diabetes cases compared with healthy controls. Areas generating candidate genes include:

- Basic research: a plethora of cell and mouse studies on insulin action, insulin secretion, obesity, mitochondrial dysfunction, *etc.*, provided several *bona fide* biological candidates. Among these, *PPARG* on chromosome 3p25 (17–35) and *KCNJ11* on chromosome 11p15.1 (23, 28–30, 33, 34, 36–46) currently represent the best replicated diabetes risk genes confirmed by recent GWA studies. Another well-replicated biological candidate gene that was not yet confirmed by GWA studies or large meta-analyses and, therefore, has still to be classified as a potential diabetes risk gene is *ADIPOQ* on chromosome 3q27 (25, 47–61). Other recently identified SNPs in the biological candidates *SREBF1* on chromosome 17p11.2 (62–65), *PPARGC1A* on chromosome 4p15.1 (66–73), *AHSG* on chromosome 3q27.3 (74, 75), *FOXO1* on chromosome 13q14.1 (76, 77), and *SGK1* on chromosome 6q23 (78, 79) also appear to represent very promising potential type 2 diabetes risk variants that await further replication in other populations and across different ethnicities and confirmation by large meta-analyses or GWA studies.
- Rodent genetics: positional cloning of genes identified by cross-breading experiments between diabetes-prone and diabetes-resistant mouse and rat strains and translational assessment of their role in humans represent this approach's rationale. Recently, with *Sorcs1* (human homolog on chromosome 10q23-q25) (80, 81), *Tbc1d1* (human homolog on chromosome 4p14) (82), and *Ll* (human homolog on chromosome 1q24.1) (83), first candidate genes were reported, but their importance for human type 2 diabetes still has to be established.
- Genetics of rare monogenic forms of human diabetes: common variants located in or near genes, in which rare mutations are known to exert strong effects and cause monogenic forms of diabetes [maturity onset diabetes of the young (MODY), Wolfram syndrome, *etc.*], represent plausible risk variants for the more common form of type 2 diabetes. Such common variants with confirmed evidence for robust association with typical type 2 diabetes were recently identified in the *HNF1B* (MODY5) gene on chromosome 17q12 (84–86) and the *WFS1* (Wolfram syndrome) gene on chromosome 4p16.1 (34, 87–89). Common variants in the *HNF1A* (MODY3) gene on chromosome 12q24.31 (26, 84, 85, 90–96) and the *HNF4A* (MODY1) gene on chromosome 20q13.12 (84, 92, 96–108) have been extensively studied, but no consistent results were obtained, pointing to very weak, if any, effects of these variants on type 2 diabetes risk.
- Human family linkage studies: positional cloning of genes located between or near diabetes-linked chromosomal markers turned out to be difficult due to: 1) the non-Mendelian mode of inheritance of human type 2 diabetes; and 2) the size of the chromosomal areas identified in this way that often encompass up to hundreds

of genes. Nevertheless, common diabetes-associated variants in *CAPN10* on chromosome 2q37.3 (109–118), *ENPP1* on chromosome 6q22-q23 (26, 32, 119–127), and *TCF7L2* on chromosome 10q25.3 (28–31, 34, 35, 45, 89, 128–161) were identified by this labor-intensive approach and replicated in several populations and ethnicities, and were confirmed in prospective studies and meta-analyses. *TCF7L2* was additionally confirmed by GWA studies. With an overall allelic relative risk of 1.56 (9), *TCF7L2* currently represents the most convincing diabetes risk gene.

The most recent and most successful approach to identify novel risk alleles is the hypothesis-free systematic genotyping of several hundred thousand SNPs in tens of thousands of cases and controls using high-density SNP arrays. A substantial drop in the cost of these arrays initiated a revolution in the genetics of complex diseases. Until now, the most frequently used arrays had approximately 500,000 SNPs spotted and covered nearly 65% of all known informative SNPs in the human genome with $r^2 > 0.8$ (http://www.illumina.com/downloads/GWASArrayWhitePaper.pdf). In these GWA studies, the frequency of all these genotyped SNPs was then compared between cases and controls, and alleles significantly more frequent in cases than in controls (commonly assumed genome-wide significance level, $P < 5 \cdot 10^{-8}$) are considered risk alleles. In early 2007, Sladek *et al.* (144) were the first not only to confirm *TCF7L2*, but also to identify four novel type 2 diabetes risk loci, namely *SLC30A8* (chromosome 8q24.11), *HHEX* (chromosome 10q23.33), *EXT2* (chromosome 11p12-p11), and the hypothetical gene LOC387761 (chromosome 11p12) using this methodology. Among these, *SLC30A8* (28–30, 34, 46, 89, 162–166) and *HHEX* (28–31, 34, 46, 161, 163, 164, 167–171) could be confirmed as diabetes risk genes in several subsequent case-control and prospective studies, whereas the association of variants in or near *EXT2* (31, 46, 166, 169) and LOC387761 (46, 166) with type 2 diabetes could not be replicated. Using SNP arrays, *FTO* on chromosome 16q12.2 was the next gene to be characterized as a reliable obesity and type 2 diabetes risk gene (28, 30, 31, 34, 35, 89, 162, 163, 169, 172, 173). Just a few months later, three back-to-back publications not only reported replication and, thus, confirmation of *HHEX*, *SLC30A8*, *TCF7L2*, *FTO*, *KCNJ11*, and *PPARG*, but also revealed, by GWA analysis, three novel diabetes risk loci: *CDKAL1* (chromosome 6p22.2), *IGF2BP2* (chromosome 3q27.2), and a genomic region between *CDKN2A* and *CDKN2B* on chromosome 9p21 (28–30). Robust replication of these new loci was provided shortly after (31, 34, 35, 46, 89, 161–164, 166, 167, 169, 174–178).

In 2008, a meta-analysis of GWA scans with data from a total of approximately 60,000 subjects delivered six additional risk loci with probably low effect sizes (odds ratios, 1.09–1.13), *i.e.*, *JAZF1* (chromosome 7p15.2-p15.1), *THADA* (chromosome 2p21), *ADAMTS9* (chromosome 3p14.1), *NOTCH2* (chromosome 1p13-p11), and two intergenic regions, one between *CDC123* and *CAMK1D* on chromosome 10p13 and another between *TSPAN8* and *LGR5* on chromosome 12q21-q22 (33). Among these, only *JAZF1*, *ADAMTS9*, and *NOTCH2* could be verified in two prospective studies up to now (34, 89). Very recently, confirmed diabetes risk alleles of *KCNQ1* on chromosome 11p15.5 were reported in Asian GWA studies that also included European replication cohorts (177, 179, 180). Finally, a meta-analysis of 13 GWA scans (~83,000 subjects) revealed common variation in the *MTNR1B* gene on chromosome 11q21-q22 that confers an increased risk for type 2 diabetes (181), and this was verified in cross-sectional and prospective studies published back to back (182, 183).

All of these genetic research efforts of the last decade have led to the identification of at least 27 (confirmed and potential) type 2 diabetes susceptibility genes, and their time-course of discovery or initial publication is depicted in Fig. 1.

III. Gene Variants Affecting Insulin Secretion

Insulin secretion is regulated by different humoral stimuli that activate respective molecular pathways within pancreatic β-cells. The two most important physiological stimuli are glucose and incretins. Glucose triggers insulin release via a complex series of cellular events (184): glu-

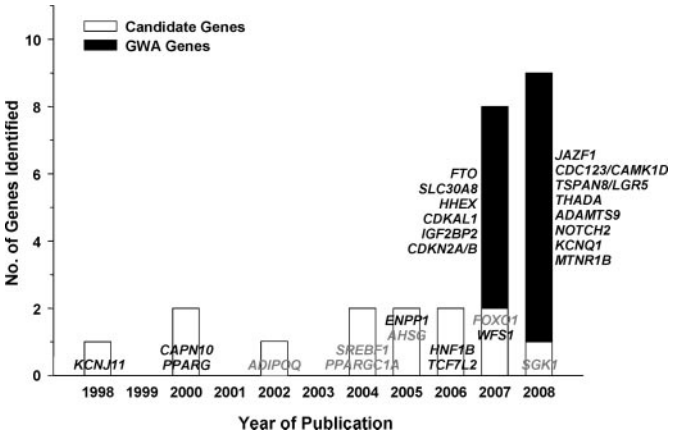

FIG. 1. Time-course of the discovery/initial publication of confirmed and potential type 2 diabetes risk genes. The numbers of genes identified by candidate gene approaches are represented by *white bars* and those of genes derived from GWA studies by *black bars*. Confirmed risk genes are given in *black letters* and potential risk genes in *gray letters*.

cose is taken up via glucose transporters, phosphorylated by glucokinase, and metabolized via the glycolytic pathway and the tricarboxylic acid cycle; during glucose catabolism, ATP is generated that causes closure of the ATP-sensitive potassium channel; this provokes membrane depolarization and subsequent opening of a voltage-dependent calcium channel; calcium influx raises the cytosolic calcium concentration, and this promotes exocytosis of insulin granules. Incretins, like glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP), enhance (in the presence of glucose) insulin secretion via binding to specific G protein-coupled transmembrane receptors; this activates adenylyl cyclase and leads to cAMP formation; cAMP activates protein kinase A, which in turn mediates induction of the insulin gene and exocytosis of insulin granules (185).

It has been hypothesized for a while that individual differences in insulin secretion capacity are predominantly determined by genetics (186, 187). This is now clearly strengthened by the finding that, among the 27 confirmed (Table 1) and potential (Table 2) diabetes risk genes mentioned above, 18 genes affect β-cell function, namely *CAPN10* (188), *CDC123/CAMK1D* (189), *CDKAL1* (166, 174, 190–193), *CDKN2A/B* (34, 167, 193), *ENPP1* (194), *FOXO1* (77), *HHEX* (167, 190, 193, 195, 196), *IGF2BP2* (34, 166, 167), *JAZF1* (189), *KCNJ11* (38, 41, 193), *KCNQ1* (180, 197), *MTNR1B* (181–183), *PPARGC1A* (198), *SGK1* (79), *SLC30A8* (34, 166), *TCF7L2* (129, 134, 138, 160, 193, 199, 200), *TSPAN8/LGR5* (189), and *WFS1* (201–203). This was revealed by calculating fasting state- and oral glucose tolerance test (OGTT)-derived (plasma insulin- and C-peptide-based) surrogate indices for insulin secretion that do not allow further dissection of the aspects of β-cell function affected, such as insulin maturation, glucose sensitivity, or incretin sensitivity. From these rough estimates of β-cell function, pathomechanisms showing how these common gene variants impair β-cell function were only proposed for the biological candidates *KCNJ11*, *FOXO1*, and *SGK1*, which have been well studied *in vitro* as well as in mice *in vivo*.

KCNJ11 (potassium inwardly-rectifying channel, subfamily J, member 11; OMIM entry no. 600937) encodes the pore-forming subunit Kir6.2 of the ATP-sensitive potassium channel of β-cells, which couples glucose sensing with membrane depolarization and exocytosis of insulin granules. The best studied and confirmed diabetes risk variant E23K (rs5219) was shown *in vitro* to increase the probability of the channel's open state, to enhance its activity, and to impair its ATP sensitivity, thereby inhibiting β-cell excitability and insulin release (204, 205). Furthermore, the same variant was suggested to impair insulin secretion due to its enhanced response to the channel-activating effect of intracellular acyl coenzyme As, fatty acid metabolites known to be elevated in obese and type 2 diabetic subjects (206).

By scanning the *FOXO1* (forkhead box O1; OMIM entry no. 136533) locus for common genetic variation associated with prediabetic traits, we very recently identified two weakly linked intronic SNPs (rs2721068 and rs17446614; $r^2 = 0.5$) that were associated with reduced insulin secretion (77). The *FOXO1* gene encodes a transcription factor of the forkhead box family, and its product FoxO1 is known to mediate insulin actions in liver, skeletal muscle, and adipose tissue (207). In addition, *FOXO1* is expressed in pancreatic β-cells, and FoxO1's nuclear localization exerts inhibitory effects on insulin resistance-induced β-cell mass expansion and β-cell proliferation via repression of *PDX1* (208–210). Insulin- or incretin-stimulated activation of the serine/threonine kinase Akt, via insulin receptor substrate 2 and phosphatidylinositol 3′-kinase, promotes FoxO1 phosphorylation and nuclear exclusion followed by *PDX1* induction (209, 211–213). *PDX1* expression stimulates β-cell proliferation and function (214). Due to this central function of FoxO1 within pancreatic β-cells, it appears obvious that the aforementioned SNPs (probably affecting *FOXO1* expression) exert direct effects inside the β-cell, although their molecular functionality remains to be proven.

The biological candidate and potential diabetes risk gene *SGK1* (serum/glucocorticoid-regulated kinase 1; OMIM entry no. 602958) encodes the ubiquitously expressed serine/threonine kinase Sgk1 which displays highest expression levels in the pancreas (215). Sgk1 participates in glucose homeostasis by regulating cellular glucose transport (216–219), insulin signaling (220), and insulin secretion (221, 222). In β-cells, Sgk1 stimulates the activity of voltage-gated potassium channels, which in turn reduces calcium influx and inhibits insulin release (221). Another Sgk1-dependent molecular mechanism that impairs insulin secretion is activation of the sodium/potassium ATPase during plasma membrane repolarization (222). In support of these functions in β-cells, a SNP in the 3′-flanking region of the *SGK1* gene (rs9402571) was recently shown to affect insulin secretion and diabetes risk in different European populations (79).

A. SNP effects on glucose-stimulated insulin secretion

The procedures best suited to assess glucose sensitivity of insulin secretion *in vivo* are measurement of plasma insulin, or even better C-peptide (insulin is rapidly cleared by the liver), levels during a frequently sampled iv glucose tolerance test or a hyperglycemic clamp. These state-of-the art methods allow determination of the individual's insulin secretion capacity in response to glucose and in the absence of interfering incretin effects. Based on these tech-

TABLE 1. Effects of SNPs in confirmed type 2 diabetes genes on prediabetic traits

Gene	Chr.	Tissue expression (reproductive system not included)	Variants (app. RAF in Europeans)	Risk allele effects
ADAMTS9	3	Skeletal muscle, breast, thymus, kidney, prostate, pancreas, heart, lung, spinal cord, brain, all fetal tissues	rs4607103 (80%)	Unknown
CAPN10	2	Thymus, colon, bladder, brain, spleen, prostate, skeletal muscle, pancreas, heart, lymph node, lung, kidney	rs3792267 (70%), rs3842570 (40%), rs5030952 (90%)	Glucose-stimulated insulin secretion ↓; proinsulin conversion ↓; whole-body insulin sensitivity ↓
CDC123/CAMK1D	10	Bone marrow, smooth muscle, kidney, prostate, colon, bladder, spleen, lung, lymph node, skin, breast, brain, liver, thymus/skin, retina, spleen, skeletal muscle, lung	rs12779790 (20%)	Insulin secretion ↓
CDKAL1	6	Bone marrow, breast, liver, spleen, prostate, retina, brain, lung, kidney, thymus, pancreas, skeletal muscle	rs7754840 (30%)	Glucose-stimulated insulin secretion ↓; proinsulin conversion ↓
CDKN2A/CDKN2B	9	Ubiquitous/bladder, colon, lung, spleen, skin, liver, breast, skeletal muscle, prostate, kidney, brain, pancreas, adipose tissue	rs10811661 (80%)	Glucose-stimulated insulin secretion ↓
ENPP1	6	Thyroid gland, kidney, skeletal muscle, breast, liver, skin, thymus, salivary gland, brain capillaries	rs1044498/K121Q (10%)	Whole-body insulin sensitivity ↓; insulin secretion ↓
FTO	16	Brain, pancreas, skeletal muscle, prostate, retina, heart, skin, breast, lung, kidney, liver, thymus, fetal brain, fetal kidney, fetal liver	rs8050136 (40%), rs9939609 (40%)	Overall fat mass ↑; energy intake ↑; cerebrocortical insulin sensitivity ↓
HHEX	10	Thyroid gland, brain, lymph node, spleen, liver, lung, kidney, breast, pancreas, thymus, skin, prostate, fetal pancreas	rs7923837 (60%)	Glucose-stimulated insulin secretion ↓
HNF1B	17	Colon, kidney, liver, thymus, retina, pancreas, prostate, lung	rs757210 (40%)	Unknown
IGF2BP2	3	Smooth muscle, colon, lung, retina, skeletal muscle, skin, kidney, thymus, fetal liver, fetal brain, pancreas	rs4402960 (30%)	Glucose-stimulated insulin secretion ↓
JAZF1	7	Lymph node, retina, pancreas, thymus, brain, skin, liver, skeletal muscle, lung, spleen, prostate	rs864745 (50%)	Insulin secretion ↓
KCNJ11	11	Pancreas, heart, pituitary gland, skeletal muscle, brain, smooth muscle	rs5219/E23K (50%)	Insulin secretion ↓; glucose-dependent suppression of glucagon secretion ↓
KCNQ1	11	Thyroid gland, bone marrow, prostate, heart, pancreas, lung, thymus, skin, liver, kidney	rs2237892 (90%), rs151290 (80%)	Insulin secretion ↓; incretin secretion ↓
MTNR1B	11	Retina, brain, pancreas	rs10830963 (30%), rs10830962 (40%), rs4753426 (50%)	Glucose-stimulated insulin secretion ↓
NOTCH2	1	Lung, skin, thyroid gland, skeletal muscle, smooth muscle, kidney, bladder, lymph node, breast, colon, prostate, spleen, brain, thymus, heart, liver, pancreas	rs10923931 (10%)	Unknown
PPARG	3	Adipose tissue, colon, lung, kidney, breast, spleen, skin, prostate, bone marrow, brain, skeletal muscle, liver	rs1801282/P12A (80%)	Whole-body insulin sensitivity ↓; adipose tissue insulin sensitivity ↓; insulin clearance ↓
SLC30A8	8	Pancreas, kidney, lung, breast, amygdala	rs13266634/R325W (70%)	Glucose-stimulated insulin secretion ↓; proinsulin conversion ↓
TCF7L2	10	Brain, lung, bone marrow, thyroid gland, colon, pancreas, skin, breast, kidney, liver, thymus, prostate	rs7903146 (30%), rs12255372 (30%), rs7901695 (30%)	Incretin-stimulated insulin secretion ↓; proinsulin conversion ↓; whole-body insulin sensitivity ↓; hepatic insulin sensitivity ↓

(*Continued*)

TABLE 1. Continued

Gene	Chr.	Tissue expression (reproductive system not included)	Variants (app. RAF in Europeans)	Risk allele effects
THADA	2	Ubiquitous	rs7578597/T1187A (90%)	Unknown
TSPAN8/LGR5	12	Spinal cord, colon, skeletal muscle, prostate, liver, lung, pancreas, kidney/skeletal muscle, skin, brain, spinal cord	rs7961581 (30%)	Insulin secretion ↓
WFS1	4	Ubiquitous	rs10010131 (60%)	Incretin-stimulated insulin secretion ↓

Genes are listed in alphabetical order. Chr., Chromosome; RAF, risk allele frequency.

niques, it was demonstrated that glucose sensitivity of β-cells is influenced by variants in *CAPN10* (223), *CDKAL1* (192, 224), *CDKN2A/B* (167), *HHEX* (195, 225), *IGF2BP2* (167, 224), *MTNR1B* (182, 226), and *SLC30A8* (195, 227).

Three unlinked intronic polymorphisms in *CAPN10* (calpain 10; OMIM entry no. 605286), *i.e.*, SNP rs3792267 (formerly UCSNP-43), the insertion/deletion polymorphism rs3842570 (formerly UCSNP-19), and SNP rs5030952 (formerly UCSNP-63), as well as haplotype combinations thereof probably confer a modest risk of type 2 diabetes. The most investigated confirmed diabetes risk SNP rs3792267 was shown to alter glucose-stimulated insulin secretion (223), and it is conceivable that this is mediated by altered *CAPN10* expression. Calpain 10 is an important molecule in peripheral glucose-sensing cells as well as in pancreatic β-cells (228). It belongs to the calcium-dependent papain domain-containing family of cysteine proteases (228). In β-cells, calpain 10 overexpression enhances insulin secretion (229). Molecularly, calpain 10 was suggested to function as a calcium sensor that, upon increments in cytosolic calcium, triggers actin reorganization and stimulates exocytosis of insulin granules by proteolytic cleavage of synaptosomal-associated protein of 25 kDa, an essential component of the granule/target membrane docking and fusion machinery (229, 230).

In recent GWA studies, the *HHEX* (hematopoietically expressed homeobox; OMIM entry no. 604420) locus was newly identified and confirmed as a diabetes risk locus, and a SNP (rs7923837) located in the 3′-flanking region of the gene was subsequently found to associate with glucose-stimulated insulin secretion (195, 225). *HHEX* encodes a transcription factor that is expressed in the embryonic ventral-lateral foregut that gives rise to the ventral pancreas and the liver (231). *Hhex* knockout in mice was shown to impair proliferation of endodermal epithelial cells, positioning of ventral foregut endoderm cells relative to the mesoderm, and budding and morphogenesis of the ventral pancreas (231). This genetic manipulation finally provoked lethality during mid-gestation (231). Although its functionality remains to be established, the association of SNP rs7923837 with differences in glucose-stimulated insulin release could arise from mild alterations in the embryonic organogenesis of the ventral pancreas. This suggestion, however, awaits further physiological and molecular clarification.

SLC30A8 [solute carrier family 30 (zinc transporter), member 8; OMIM entry no. 611145] displays prominent

TABLE 2. Effects of SNPs in selected potential type 2 diabetes genes on prediabetic traits

Gene	Chr.	Tissue expression (reproductive system not included)	Variants (app. RAF in Europeans)	Risk allele effects
ADIPOQ	3	Adipose tissue, heart, breast, thymus, brain, kidney	rs266729 (30%), rs2241766 (20%), rs1501299 (70%)	Whole-body insulin sensitivity ↓
AHSG	3	Liver, breast, skeletal muscle, brain	rs2077119 (50%)	Adipose tissue insulin sensitivity ↓
FOXO1	13	Lymph node, retina, bladder, kidney, bone marrow, thyroid gland, skin, pancreas, prostate, liver, lung, skeletal muscle, brain, heart, thymus, breast	rs2721068 (30%), rs17446614 (20%)	Insulin secretion ↓
PPARGC1A	4	Liver, kidney, colon, heart, lung, skeletal muscle, brain, pancreas, thymus, prostate	rs8192678/G482S (40%)	Whole-body insulin sensitivity ↓; insulin secretion ↓
SGK1	6	Ubiquitous	rs9402571 (80%)	Insulin secretion ↓
SREBF1	17	Thymus, brain, prostate, skin, retina, bladder, pancreas, thyroid gland, breast, kidney, lung, spleen, adipose tissue, adrenal gland	rs1889018 (30%)	Whole-body insulin sensitivity ↓

Genes are listed in alphabetical order. Chr., Chromosome; RAF, risk allele frequency.

expression in the pancreas, and its product ZnT-8 acts as a zinc transporter in the secretory granules of β-cells providing zinc for insulin maturation and storage (232, 233). This important molecular function, together with the confirmed association of the *SLC30A8* variant R325W (rs13266634) with type 2 diabetes, renders this gene a very plausible candidate for β-cell dysfunction. In keeping with this, implication of the R325W variant in glucose-stimulated insulin secretion could clearly be demonstrated (195, 227). Interestingly, the same authors reported lack of association with insulin secretion as measured during an OGTT. Thus, R325W could also exert additional insulin secretion-modulating effects that mask this variant's direct effect on glucose-stimulated insulin secretion. These alternative mechanisms remain to be established.

Although confirming *in vivo* data are still lacking, a study published in 2008 provided convincing *ex vivo* evidence that the potential type 2 diabetes risk SNP rs8192678 in the *PPARGC1A* (peroxisome proliferator-activated receptor γ, coactivator 1 α; OMIM entry no. 604517) gene, which encodes the amino acid exchange G482S in this gene's product PGC-1α, markedly reduces human pancreatic islet *PPARGC1A* expression and concomitantly impairs glucose-stimulated insulin secretion (198). The mechanistic relevance of PGC-1α for insulin secretion of human pancreatic islets was proven by down-regulation of *PPARGC1A* expression using RNA interference (198). The effect of the G482S variant on glucose-stimulated insulin secretion was explained by the role of PGC-1α as a central regulator of mitochondrial function (Ref. 234 and *Section IV*) and the importance of mitochondrial ATP formation for stimulus-secretion coupling in β-cells (235).

The molecular pathways by which the novel GWA-derived confirmed diabetes risk SNPs in or near *CDKAL1* (rs7754840), *IGF2BP2* (rs4402960), *CDKN2A/B* (rs10811661), and *MTNR1B* (rs10830963, rs10830962, rs4753426) affect glucose-stimulated insulin secretion, as reported (167, 182, 192, 224, 226), are currently unclear due to these genes' broad expression profile and/or unknown pancreas-specific functions.

B. SNP effects on incretin sensitivity or incretin secretion

The secretory response of pancreatic β-cells is markedly enhanced by incretins. Thus, both incretin production/release by enteroendocrine cells and incretin signaling in β-cells represent important determinants of insulin secretion.

Recently, two moderately linked intronic SNPs (rs7903146 and rs12255372; $r^2 = 0.7$) in the confirmed diabetes risk gene *TCF7L2* [transcription factor 7-like 2 (T-cell-specific, HMG-box); OMIM entry no. 602228] were shown to affect GLP-1 responsiveness of β-cells, as evidenced by a hyperglycemic clamp combined with GLP-1 infusion (199). This was confirmed by comparison of the effect of the representative SNP rs7903146 on insulin secretion upon an oral *vs.* an iv glucose load (200). Plasma GLP-1 levels were not different between the genotypes (199, 200). *TCF7L2* encodes a component of the bipartite transcription factor complex β-catenin/transcription factor 7-like 2 that is involved in the Wnt signaling pathway (236). Using knockdown by RNA interference and overexpression by transfection, it was demonstrated, in human and murine islets, that *TCF7L2* is required for β-cell survival and β-cell proliferation as well as for glucose- and incretin-stimulated insulin secretion (237). Furthermore, expression of the insulin gene was found to strongly correlate with *TCF7L2* expression (200) and was decreased after *TCF7L2* knockdown, suggesting that the insulin gene represents a direct target gene of transcription factor 7-like 2 (238). Importantly, novel results of Maedler's group (239) revealed that the expression of GLP-1 and GIP receptors in human islets likewise depends on the presence of transcription factor 7-like 2 providing a plausible explanation for this gene's involvement in incretin responsiveness of β-cells.

Using the hyperglycemic clamp method combined with GLP-1 infusion, we could very recently show also that an intronic SNP (rs10010131) in the confirmed diabetes risk gene *WFS1* [Wolfram syndrome 1 (wolframin); OMIM entry no. 606201] affects GLP-1-induced insulin secretion (203). Again, this was not associated with altered plasma incretin levels (203). Although the molecular role of the ubiquitously expressed *WFS1* gene in incretin responsiveness is far from being understood, its product wolframin clearly controls β-cell functions: *Wfs1* knockout mice develop glucose intolerance and overt diabetes due to increased β-cell endoplasmic reticulum stress, reduced β-cell proliferation, progressive apoptotic β-cell loss, and hence insufficient insulin secretion (240–242).

Confirmed diabetes risk SNPs in the *KCNQ1* (potassium voltage-gated channel, KQT-like subfamily, member 1; OMIM entry no. 607542) gene were recently found to associate with insulin secretion after an OGTT, but not an iv glucose tolerance test (197). Interestingly, one of these intronic SNPs (rs151290) was the first diabetes risk variant described to affect plasma GIP and GLP-1 levels (197). Whether this gene's product, a voltage-gated potassium channel, plays a role in incretin production/secretion of enteroendocrine cells remains to be shown in mouse models and *in vitro* experiments.

C. SNP effects on proinsulin conversion

The insulin gene encodes a monomeric precursor protein called proinsulin that comprises, from the N to the C terminus, the insulin B-cain sequence, the C-peptide, and

the A-chain sequence. During insulin maturation in the endoplasmic reticulum and Golgi complex, proinsulin is cleaved by proprotein convertases 1 and 2 and carboxypeptidase E and converted into the mature heterodimeric insulin molecule consisting of one A- and one B-chain (and C-peptide produced in equimolar ratios) (243). Only a small part (<10%) of the newly synthesized proinsulin escapes from this conversion process and gets into the circulation upon β-cell degranulation. The plasma proinsulin-to-insulin ratio therefore represents an estimate for the efficiency of proinsulin conversion.

First evidence of the existence of gene variants that determine the individual's efficiency of insulin maturation came from studies on the *CAPN10* gene (see *Section III.A*): using the poststimulus proinsulin-to-insulin ratio assessed during a hyperglycemic clamp, it was demonstrated that the genotype of SNP rs3792267 is associated with proinsulin conversion (223). With proinsulin-to-insulin ratios derived from the fasting state or an OGTT, also SNPs in the *TCF7L2* (158, 244–246), *SLC30A8* (245), and *CDKAL1* (245) loci were shown to affect proinsulin conversion. A suggestion about how these genes are involved in the insulin maturation process is up to now only available for *TCF7L2* (see *Section III.B*): the genes encoding proprotein convertase 1 and 2 (*PCSK1* and *PCSK2*) contain *bona fide* binding sites for transcription factor 7-like 2 in their promoters (244).

IV. Gene Variants Affecting Insulin Sensitivity

Insulin resistance provokes a critical challenge for the pancreatic β-cell that has to be compensated for by increments in insulin secretion to maintain normoglycemia. Thus, genetically determined β-cell defects may only become apparent in the presence of insulin resistance (9, 247). Insulin resistance is therefore considered an early and crucial step in the pathogenesis of type 2 diabetes. Undoubtedly, insulin resistance is strongly associated with obesity. Although the cause-effect relationship is far from being clear, insulin resistance is often suggested to result from obesity and to be predominantly caused by environmental factors, such as high-caloric diet and/or physical inactivity (248, 249). However, the genetic investigations of the last 10 yr revealed that certain gene variants impair insulin sensitivity without influencing the overall fat mass. Recent advances in the field, mainly based on candidate gene approaches, also strengthen the role of genetics in the establishment of insulin resistance.

Among the confirmed and potential type 2 diabetes risk genes described in Tables 1 and 2, eight genes influence whole-body or peripheral insulin sensitivity: *ADIPOQ* (47, 52, 250–257), *AHSG* (75, 258), *CAPN10* (259–264), *ENPP1* (265–271), *PPARG* (272–283), *PPARGC1A* (284, 285), *SREBF1* (65), and *TCF7L2* (133, 151, 286, 287).

A. SNP effects on peripheral insulin sensitivity

Whole-body insulin sensitivity can be assessed either by using rough estimates derived from plasma glucose and insulin levels in the fasting state or, more state of the art, by calculating (plasma glucose- and insulin-based) indices derived from an OGTT or a hyperinsulinemic-euglycemic clamp. The measurement of tissue-specific insulin sensitivity is more intricate and requires tracer methods with stable isotopes or *ex vivo* investigations using freshly isolated tissue specimens.

The most intensely studied and confirmed diabetes risk SNP (rs1801282) with clear and obesity-independent effects on whole-body insulin sensitivity (272–283) is located in exon 2 of the *PPARG* (peroxisome proliferator-activated receptor γ; OMIM entry no. 601487) gene and results in the amino acid exchange P12A. *PPARG* encodes the lipid-activated nuclear receptor and transcription factor peroxisome proliferator-activated receptor γ (PPARγ). Two isoforms were described, PPARγ1 and PPARγ2, that are formed by alternative promoter usage and divergent splicing (288). Whereas PPARγ1 is expressed in a number of tissues and cell types at moderate levels, the expression of PPARγ2 is prominent in, but also largely restricted to, adipose tissue, where it represents a master regulator of fat cell differentiation (289). Because exon 2, harboring the P12A variant, is only present in the PPARγ2-encoding transcript, it appears more than plausible that this variant exerts its insulin-sensitizing effect directly inside adipose tissue. That PPARγ is a central mediator of whole-body insulin sensitivity was clearly supported by the finding that PPARγ is the specific molecular target of thiazolidinediones, a clinically relevant class of insulin-sensitizing drugs (290, 291). The major allele of P12A, representing the risk allele, was shown to have a higher affinity to PPAR response elements and a higher ability to transactivate responsive promoters (272). How such a gain-of-function mutation can be reconciled with reduced antilipolytic insulin sensitivity of adipose tissue (275) is still a matter of debate. Nevertheless, increased release of fatty acids as a consequence of impaired adipose tissue insulin sensitivity represents an attractive molecular mechanism of this SNP because fatty acids are well known to impair insulin sensitivity of skeletal muscle and liver (292, 293).

The nonsynonymous confirmed diabetes risk SNP K121Q (rs1044498) in the *ENPP1* (ectonucleotide pyrophosphatase/phosphodiesterase 1; OMIM entry no. 173335) gene represents a functional variant with replicated effects on whole-body insulin sensitivity (265–271). *ENPP1* encodes a class II transmembrane glycoprotein that is identical to nucleotide diphosphatase (EC 3.6.1.9),

phosphodiesterase I (EC 3.1.4.1), and plasma cell glycoprotein 1 (PC-1). PC-1 was reported to directly interact with the insulin receptor α-subunit and to inhibit the insulin receptor tyrosine kinase activity in human cells (294–297). Moreover, *Enpp1* overexpression in rodents provokes insulin resistance and hyperglycemia *in vivo* (298, 299). Finally, the PC-1 content of skeletal muscle and adipose tissue was shown to negatively correlate with whole-body insulin sensitivity and insulin receptor tyrosine kinase activity in humans (300, 301). The finding that the K121Q amino acid exchange results in a PC-1 molecule with stronger inhibitory effects on the insulin receptor tyrosine kinase (302) provides a plausible explanation for the reported SNP effects.

SNPs in *CAPN10* affect glucose-stimulated insulin secretion and proinsulin conversion (see *Sections III.A and III.C*). In addition, the *CAPN10* SNPs rs3792267, rs3842570, and rs5030952 affect whole-body insulin sensitivity (259–264). In accordance with this clinical observation, the risk allele of SNP rs3792267 was shown in Pima Indians to associate with reduced *CAPN10* mRNA levels in skeletal muscle (259, 303). Furthermore, pharmacological inhibition (304) and RNA interference-mediated knockdown (305) of calpain-10 in human skeletal muscle cells blocked insulin-stimulated glucose uptake downstream of Akt without affecting glycogen synthesis. Because calpain-10 is necessary to reorganize actin filaments and to stimulate exocytosis of intracellular vesicles, as was shown in pancreatic β-cells (see *Section III.A*) and 3T3-L1 adipocytes (306), impaired *CAPN10* expression was suggested to prevent the exocytosis of glucose transporter 4-containing vesicles, thus provoking insulin resistance of skeletal muscle and adipose tissue glucose uptake (307).

The *ADIPOQ* (adiponectin, C1Q, and collagen domain containing; OMIM entry no. 605441) gene encodes the adipocyte-derived hormone (adipokine) adiponectin. Adiponectin has potent antisteatotic, insulin-sensitizing, antiinflammatory, and atheroprotective properties (308), and its plasma levels are inversely correlated with overall and, in particular, visceral fat mass (309–313). Adiponectin's antisteatotic and insulin-sensitizing effects in skeletal muscle and liver were shown *in vitro* as well as in mice *in vivo* to be mediated by 1) the AMP-activated protein kinase/acetyl-coenzyme A carboxylase/carnitin-palmitoyl transferase 1 pathway that enhances fatty acid import into mitochondria, and 2) peroxisome proliferator-activated receptor α activation that induces the expression of β-oxidative genes (314–317). The diabetes risk alleles of several SNPs located within the promoter region (with SNP rs266729 being the best explored), of the silent SNP rs2241766 in exon 2, and of SNP rs1501299 in intron 2 associate with decreased plasma adiponectin levels (48, 52, 57, 318–322). In line with the aforementioned molecular data from mouse and *in vitro* studies, hypoadiponectinemia due to these SNPs is associated with reduced whole-body insulin sensitivity (47, 52, 251, 255, 256).

The potential type 2 diabetes risk variant G482S (rs8192678) of the *PPARGC1A* gene (see *Section III.A*) was reported to decrease whole-body insulin sensitivity (284, 285) and to diminish exercise-induced increments in aerobic physical fitness (285). PGC-1α, the *PPARGC1A* gene product, is an important coactivator of nuclear receptors, such as estrogen-related receptor α and peroxisome proliferator-activated receptor δ, and, via these transcription factors, controls the expression of genes involved in oxidative phosphorylation and β-oxidation (323–325). In consequence of these gene-regulatory events, PGC-1α modulates mitochondrial activity, mitochondriogenesis, and the fiber-type composition of skeletal muscle (234). Thus, the impact of SNP G482S on aerobic physical fitness reflects the importance of PGC-1α for mitochondrial function of skeletal muscle. The growing body of evidence pointing to a close connection between mitochondrial dysfunction, excess intramyocellular lipid deposition, and insulin resistance (326, 327) finally provides a plausible rationale for the effect of this SNP on insulin sensitivity.

We recently reported that several tagging SNPs, covering the complete common genetic variation (with $r^2 > 0.8$) in the potential diabetes risk locus *AHSG* (α2-HS-glycoprotein; OMIM entry no. 138680), are functional insofar as they determine the plasma concentration of this gene's product α2-HS-glycoprotein, the human homolog of animal fetuin-A (328). Plasma α2-HS-glycoprotein levels are positively associated with whole-body insulin resistance and ectopic lipid deposition in the liver, the main site of its production (329, 330). Furthermore, SNP rs2077119 in the promoter region of the gene, probably affecting this gene's transcription rate, was shown to confer a reduction in adipose tissue insulin sensitivity, as evidenced by an impairment of insulin-stimulated lipogenesis and insulin-suppressed lipolysis (75, 258). At least two of α2-HS-glycoprotein's properties could explain this SNP's interference with insulin signaling in the adipocyte: first, α2-HS-glycoprotein directly binds the insulin receptor and inhibits the receptor's tyrosine kinase activity (331–335); and second, α2-HS-glycoprotein decreases the expression of the insulin-sensitizing adipokine adiponectin probably via induction of an inflammatory response in adipocytes and macrophages (336). How SNP rs2077119 ultimately affects adipose tissue insulin sensitivity remains to be molecularly elucidated.

A recent report in the literature also provided first evidence that the intronic SNP rs1889018 in the potential

type 2 diabetes risk gene *SREBF1* (sterol regulatory element-binding transcription factor 1; OMIM entry no. 184756), encoding the transcription factors sterol regulatory element-binding protein 1a and 1c, alters whole-body insulin sensitivity (65). Both gene products arise from the differential use of alternative transcription start sites and display broad tissue expression including all insulin-sensitive tissues (337). Although these transcription factors appear to play an essential role in lipogenesis (337) and insulin-dependent gene regulation (337–342), the exact molecular mechanism by which SNP rs1889018 impairs insulin sensitivity is still unknown.

Interestingly, SNPs in *TCF7L2* that were convincingly shown to affect β-cell function (see *Sections III.B and III.C*) concomitantly appear to influence whole-body (133, 151, 286) and hepatic insulin sensitivity (287). The molecular pathways underlying this observation are to date unclear, and future work should shed more light on this issue.

B. SNP effects on insulin clearance

The main sites of insulin clearance are the insulin-degrading, enzyme-expressing organs liver and kidney (343). Insulin clearance can be measured *in vivo* using C-peptide- and insulin-based indices from the hyperinsulinemic-euglycemic clamp (reflecting hepatic and peripheral insulin clearance) or from the OGTT or hyperglycemic clamp (both reflecting predominantly hepatic insulin extraction). The only SNP currently known to affect insulin clearance, as assessed with all three methods, is the P12A variation in the *PPARG* gene (see *Section IV.A*) (344). Because this SNP most probably exerts a direct role in adipose tissue, the idea of metabolic and/or humoral cross-talk between adipose tissue and the liver appears very attractive (344). In this respect, adipose tissue-derived fatty acids represent promising candidate mediators of this SNP's effect on insulin clearance because 1) P12A affects adipose tissue lipolysis (275), and 2) fatty acids promote hepatic steatosis and hepatic insulin resistance, which are close inverse correlates of hepatic insulin clearance (345).

C. SNP effects on cerebrocortical insulin sensitivity

A growing body of evidence indicates that the brain belongs to the insulin-sensitive organs, and insulin receptor expression was detected in the olfactory bulb, hypothalamus, cerebral cortex, cerebellum, and hippocampus (346, 347). Elegant studies in rodent models demonstrated that insulin blocks the release of orexigenic and stimulates the release of anorexigenic neuropeptides from hypothalamic neurons of the arcuate nucleus, thus inducing satiety and inhibiting food intake (348). Moreover, insulin appears to be involved in the regulation of neuronal survival, learning, and memory (349). In humans, we were recently able to show that insulin stimulates cerebrocortical activity, as measured by magnetoencephalography, in lean, but not in obese, subjects (350). These data point to a potential modulation of cerebrocortical functions, such as vision, audition, touch, or control of voluntary movements, by insulin, and they demonstrate that cerebrocortical insulin resistance is a close reflection of obesity. In subsequent studies, we could furthermore demonstrate that the intronic confirmed diabetes risk SNP rs8050136 in the obesity gene *FTO* (see *Section VI*) impairs insulin-stimulated cerebrocortical activity, and interestingly, this was seen even after correction for body mass index (BMI) (351). This finding therefore provides first evidence that cerebrocortical insulin resistance results not only from environmental factors but also from obesity-independent effects of genetic variation.

V. Gene Variants Affecting Glucagon Secretion

Dysregulated hepatic glucose production, arising from increments in gluconeogenesis and/or glycogenolysis, represents another pathomechanism provoking hyperglycemia and type 2 diabetes (352). Hepatic glucose production is controlled by hormones: insulin suppresses, whereas glucagon (and catecholamines) stimulates both gluconeogenesis and glycogenolysis. Therefore, it is conceivable that, in addition to impaired insulin secretion and reduced hepatic insulin sensitivity, increased glucagon secretion and/or enhanced hepatic glucagon sensitivity contribute to the dysregulation of glucose production (353). In fact, one SNP, namely the *KCNJ11* E23K variant (see *Section III*), was shown to impair glucose-dependent suppression of glucagon secretion, thereby causing elevated plasma glucagon levels during a hyperglycemic clamp (354). This finding is in good agreement with the presence of ATP-sensitive potassium channels in pancreatic α-cells (355, 356) and the recently reported role of these channels in glucose-dependent suppression of glucagon secretion (357): increased glucose metabolism, via ATP formation, promotes closure of the ATP-sensitive potassium channel triggering membrane depolarization. In contrast to the situation in β-cells, membrane depolarization does not open a voltage-dependent calcium channel, but it inactivates an N-type calcium channel. This blocks the exocytosis of glucagon granules. Because the E23K variant of the potassium channel's Kir6.2 subunit leads to reduced ATP sensitivity (204, 205), the polymorphism probably blunts α-cell excitability and, in this way, favors activation of N-type calcium channels and glucagon secretion.

VI. Gene Variants Affecting Adiposity

Obesity is a major risk factor for type 2 diabetes mellitus (see *Section I*). Hence, genetic variation affecting adiposity is expected to likewise influence the diabetes risk. Indeed, a set of SNPs (including the representative SNPs rs8050136 and rs9939609) in the first intron of the *FTO* (fat mass- and obesity-associated; OMIM entry no. 610966) gene was recently found and, in the meantime, repeatedly confirmed to affect both overall adiposity (163, 172, 173, 358–373) and type 2 diabetes risk (28, 31, 34, 35, 89, 162, 163, 172, 173, 363) in cross-sectional and prospective studies and across several ethnic groups. As reported, the association with type 2 diabetes was abolished by adjustment for BMI (172, 173, 363), clearly demonstrating that the association of these SNPs with type 2 diabetes is fully explained by their effect on adiposity. On average, *FTO* SNP carriers display an increase in BMI of 0.4 kg/m^2 per risk allele (172). The *FTO* gene encodes a nuclear Fe(II)- and 2-oxoglutarate-dependent DNA demethylase (374) and, hence, could play a role in the reactivation of genes silenced by DNA methylation. In mice and humans, *FTO* expression was found to be most abundant in the brain, particularly in the hypothalamic nuclei governing energy balance (172, 374), and in mice, its hypothalamic expression was shown to be regulated by feeding and fasting (374). In accordance with this gene's hypothalamic expression, recent *in vivo* findings in humans provided clear evidence that *FTO* SNPs increase food intake (but not energy expenditure) (374–379). That the *FTO* gene is indeed of importance for human brain functions is additionally underscored by its reported impact on cerebrocortical insulin sensitivity (see *Section IV.C*).

In 2008, two SNPs located 3′ of a second genetic locus, the *MC4R* gene, were shown to robustly associate with variation in BMI (~0.2 kg/m^2 per risk allele) (380). An association with type 2 diabetes could, however, not be demonstrated. Very recently, more than 15 novel obesity loci were identified by GWA analyses, and four of them (*GNPDA2*, *TMEM18*, *BCDIN3D/FAIM2*, and *NCR3/AIF1/BAT2*) also tended to associate with type 2 diabetes (381–383). This, however, awaits further confirmation by replication.

VII. Summary and Perspective

During the last decade, at least 27 (confirmed and potential) diabetes susceptibility genes were identified (Fig. 1 and Tables 1 and 2), and the greatest success in type 2 diabetes genetics arose from the development and use, in large case-control cohorts, of high-density SNP arrays. Most of the genes, or better gene variants, could be confirmed in many ethnicities (*e.g.*, *TCF7L2*, *SLC30A8*, *HHEX*, *CDKAL1*, *CDKN2A/B*, *IGF2BP2*, and *FTO*), whereas others, probably due to divergent risk allele frequencies, may have higher relevance for certain ethnic groups [*e.g.*, *ENPP1* for African-Americans (384, 385)]. Recent studies also provided evidence that diabetes risk SNPs act in an additive manner to increase the diabetes risk (up to 4-fold, when assessing the GWA-derived SNPs only) (163, 386). Although significantly contributing to the type 2 diabetes risk, these gene-gene interactions do, however, not yet allow a substantially better disease prediction than clinical risk factors (*e.g.*, BMI, age, gender, family history of diabetes, fasting glucose level, blood pressure, and plasma triglycerides) alone (34, 388, 389), nor do they explain the heritability of type 2 diabetes (386). These flaws may possibly be overcome by 1) the identification of further robust risk genes by applying new methods and strategies (see below), and 2) the fine-mapping, by "deep sequencing", of the known genes' causal variants, which are supposed to be in linkage with and to display greater effect sizes than the array-derived "lead SNPs". Notably, no gender-specific differences in the known genes' impact on the diabetes risk were observed. Furthermore, many of the identified SNPs are intronic or located in the 5′- or 3′-flanking regions of genes. How such noncoding SNPs influence the genes' function is not clear, but alteration of binding sites for transcription factors and enhancer-binding proteins with respective changes in the genes' transcription rate represents a conceivable and plausible hypothesis.

Subsequent to the identification of the risk SNPs, very elaborate *in vivo* methods and thoroughly phenotyped human cohorts enabled the initial characterization of their pathomechanisms (Tables 1 and 2). From Fig. 2, which depicts these gene variants' anatomical sites of action, it is evident that the majority affects β-cell function, and this might favor the notion that β-cell dysfunction is primarily determined by genetics, whereas insulin resistance predominantly results from environmental influences (9, 390). Of course, this could be true, and statistical heritability estimates (h^2) from twin studies indeed suggest a stronger heritability of insulin secretion (ranging from 0.35 to 0.84) compared with insulin sensitivity (ranging from 0.28 to 0.55) (187, 391, 392). On the other hand, some reasons for insulin resistance genes appearing underrepresented among the identified type 2 diabetes susceptibility genes are conceivable: 1) There may indeed be fewer insulin resistance genes or risk alleles that, however, upon accumulation could confer a substantial increase in diabetes risk, but this remains to be determined. 2) The insulin resistance genes may strictly depend on the interaction with specific environmental factors to cause type 2

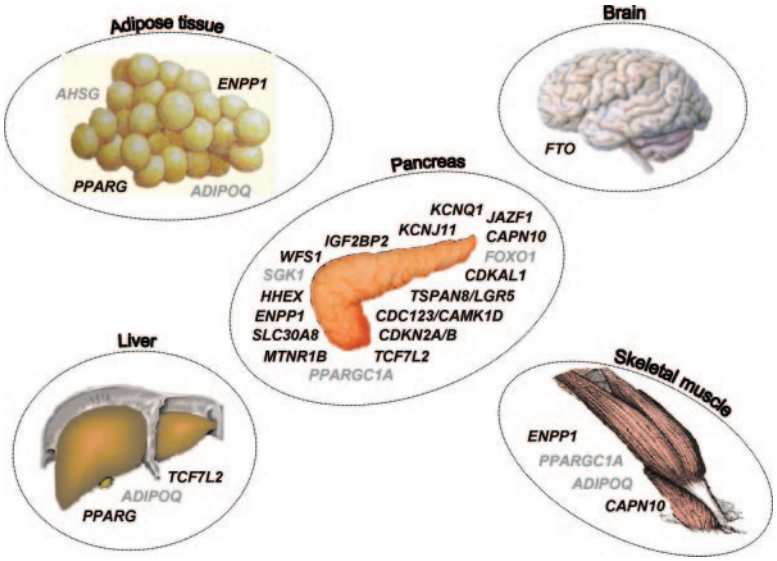

FIG. 2. Principal anatomical sites of action of confirmed and potential type 2 diabetes SNPs. Effects of type 2 diabetes risk SNPs were described in brain, pancreas, liver, skeletal muscle, and adipose tissue (see text for details). Most SNPs affect pancreatic β-cell function. Gene symbols represent SNPs in or near these gene loci. Confirmed risk genes are given in *black letters*, and potential risk genes in *gray letters*.

diabetes. These factors may be still unknown and, therefore, may not have been appropriately accounted for in previous studies. 3) Insulin resistance genes may be underrepresented on the SNP arrays used in the published GWA studies. The development of arrays with higher SNP densities and near-complete genome coverage will soon overcome this issue. 4) There may be a plethora of insulin resistance genes with each single one exerting only a very tiny effect. Their detection would require huge well-defined case-control cohorts encompassing several hundred thousand cases or, alternatively, large cohorts of several thousand subjects thoroughly phenotyped for whole-body or tissue-specific insulin sensitivity using very elaborate and time-consuming state-of-the-art measures, such as the hyperinsulinemic-euglycemic clamp or *in vivo* tracer methods, respectively.

As estimated from the currently achieved genome coverage, the next generation of high-density SNP arrays is expected to provide about half a dozen novel type 2 diabetes risk loci in the near future using the same case-control setting. Alternative settings, such as correlational analyses with state-of-the-art measures for glucose- and incretin-stimulated insulin secretion, whole-body and tissue-specific insulin sensitivity, will probably further increase this number. Moreover, future studies on the role of copy number variants, with their obvious impact on gene dosage, could once more extend our appreciation of the genetic component of type 2 diabetes. Finally, taking into account that gene-environment interactions contribute to the development of type 2 diabetes (393, 394), well-defined intervention studies have a good potential to discover risk variants that remain cryptic in cross-sectional settings. The current emergence of diabetes-relevant genes susceptible to persistent and partly inheritable epigenetic regulations, *i.e.*, DNA methylation and histone modifications, further underscores the importance of gene-environment interactions and the complexity of type 2 diabetes genetics (198, 395, 396). Because epigenetic modifications clearly affect gene expression, the establishment of diabetes-related gene expression profiles of metabolically relevant tissues or easily available surrogate "tissues", such as lymphocytes, could help identify novel candidate genes for type 2 diabetes.

What will be the clinical benefit of all this genetic knowledge beyond its use for prediction of the individual's type 2 diabetes risk? One major advantage of knowing an at-risk person's genotype could be to offer an individually tailored lifestyle intervention program to prevent or, at least, to significantly retard the onset of overt diabetes. This aim requires extensive future work to understand the interaction between risk genes and lifestyle modifications, such as diet (this research area is called nutrigenomics) and exercise regimens (this research area is called physiogenomics). In this regard, data from the Diabetes Prevention Program provided evidence that behavioral intervention can mitigate or even abolish the diabetes risk conferred by *TCF7L2* or *ENPP1*, respectively (127, 129). In the Finnish Diabetes Prevention Study, physical activity was shown to reduce the type 2 diabetes risk of *PPARG* risk allele carriers (387). Another advantage of the genetic knowledge could be to offer type 2 diabetic patients an individually tailored pharmacological therapy with currently available or newly developed, *e.g.*, risk gene-targeting, antidiabetic drugs. Thus, future pharmacogenomic studies have to thoroughly investigate the interaction between risk genes and drugs. Understanding these interactions appears important also because it could help to reduce the therapeutical use of drugs (with their side effects) that are ineffective in certain genotypes.

Acknowledgments

Address all correspondence and requests for reprints to: Prof. Hans-Ulrich Häring, Internal Medicine IV, Medical Clinic Tübingen, Otfried-Müller-Str. 10, D-72076 Tübingen, Germany. E-mail: hans-ulrich.haering@med.uni-tuebingen.de.

Disclosure Summary: The authors have nothing to disclose.

References

1. **Matthaei S, Stumvoll M, Kellerer M, Häring HU** 2000 Pathophysiology and pharmacological treatment of insulin resistance. Endocr Rev 21:585–618
2. **Wajchenberg BL** 2007 β-Cell failure in diabetes and preservation by clinical treatment. Endocr Rev 28:187–218
3. **Martin BC, Warram JH, Krolewski AS, Bergman RN, Soeldner JS, Kahn CR** 1992 Role of glucose and insulin resistance in development of type 2 diabetes mellitus: results of a 25-year follow-up study. Lancet 340:925–929
4. **Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC** 2003 β-Cell deficit and increased β-cell apoptosis in humans with type 2 diabetes. Diabetes 52:102–110
5. **Hossain P, Kawar B, El Nahas M** 2007 Obesity and diabetes in the developing world–a growing challenge. N Engl J Med 356:213–215
6. **Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M** 2001 Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 344:1343–1350
7. **Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM** 2002 Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 346:393–403
8. **Doria A, Patti ME, Kahn CR** 2008 The emerging genetic architecture of type 2 diabetes. Cell Metab 8:186–200
9. **Florez JC** 2008 Newly identified loci highlight β cell dysfunction as a key cause of type 2 diabetes: where are the insulin resistance genes? Diabetologia 51:1100–1110
10. **Knowler WC, Bennett PH, Hamman RF, Miller M** 1978 Diabetes incidence and prevalence in Pima Indians: a 19-fold greater incidence than in Rochester, Minnesota. Am J Epidemiol 108:497–505
11. **Zimmet PZ, McCarty DJ, de Courten MP** 1997 The global epidemiology of non-insulin-dependent diabetes mellitus and the metabolic syndrome. J Diabetes Complications 11: 60–68
12. **Stern MP** 1999 Genetic and environmental influences on type 2 diabetes mellitus in Mexican Americans. Nutr Rev 57:S66–S70
13. **Gloyn AL, McCarthy MI** 2001 The genetics of type 2 diabetes. Best Pract Res Clin Endocrinol Metab 15:293–308
14. **Weires MB, Tausch B, Haug PJ, Edwards CQ, Wetter T, Cannon-Albright LA** 2007 Familiality of diabetes mellitus. Exp Clin Endocrinol Diabetes 115:634–640
15. **Elbein SC** 1997 The genetics of human noninsulin-dependent (type 2) diabetes mellitus. J Nutr 127:1891S–1896S
16. **Collins FS, Guyer MS, Charkravarti A** 1997 Variations on a theme: cataloging human DNA sequence variation. Science 278:1580–1581
17. **Hara K, Okada T, Tobe K, Yasuda K, Mori Y, Kadowaki H, Hagura R, Akanuma Y, Kimura S, Ito C, Kadowaki T** 2000 The Pro12Ala polymorphism in PPAR γ2 may confer resistance to type 2 diabetes. Biochem Biophys Res Commun 271:212–216
18. **Mori H, Ikegami H, Kawaguchi Y, Seino S, Yokoi N, Takeda J, Inoue I, Seino Y, Yasuda K, Hanafusa T, Yamagata K, Awata T, Kadowaki T, Hara K, Yamada N, Gotoda T, Iwasaki N, Iwamoto Y, Sanke T, Nanjo K, Oka Y, Matsutani A, Maeda E, Kasuga M** 2001 The Pro12→Ala substitution in PPAR-γ is associated with resistance to development of diabetes in the general population: possible involvement in impairment of insulin secretion in individuals with type 2 diabetes. Diabetes 50:891–894
19. **Evans D, de Heer J, Hagemann C, Wendt D, Wolf A, Beisiegel U, Mann WA** 2001 Association between the P12A and c1431t polymorphisms in the peroxisome proliferator activated receptor γ (PPAR γ) gene and type 2 diabetes. Exp Clin Endocrinol Diabetes 109:151–154
20. **Doney AS, Fischer B, Cecil JE, Boylan K, McGuigan FE, Ralston SH, Morris AD, Palmer CN** 2004 Association of the Pro12Ala and C1431T variants of PPARG and their haplotypes with susceptibility to type 2 diabetes. Diabetologia 47:555–558
21. **Kilpeläinen TO, Lakka TA, Laaksonen DE, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Lindi V, Tuomilehto J, Uusitupa M, Laakso M** 2008 SNPs in PPARG associate with type 2 diabetes and interact with physical activity. Med Sci Sports Exerc 40:25–33
22. **Ghoussaini M, Meyre D, Lobbens S, Charpentier G, Clément K, Charles MA, Tauber M, Weill J, Froguel P** 2005 Implication of the Pro12Ala polymorphism of the PPAR-γ 2 gene in type 2 diabetes and obesity in the French population. BMC Med Genet 6:11
23. **Hansen SK, Nielsen EM, Ek J, Andersen G, Glümer C, Carstensen B, Mouritzen P, Drivsholm T, Borch-Johnsen K, Jørgensen T, Hansen T, Pedersen O** 2005 Analysis of separate and combined effects of common variation in KCNJ11 and PPARG on risk of type 2 diabetes. J Clin Endocrinol Metab 90:3629–3637
24. **Moon MK, Cho YM, Jung HS, Park YJ, Yoon KH, Sung YA, Park BL, Lee HK, Park KS, Shin HD** 2005 Genetic polymorphisms in peroxisome proliferator-activated receptor γ are associated with type 2 diabetes mellitus and obesity in the Korean population. Diabet Med 22:1161–1166
25. **Jaziri R, Lobbens S, Aubert R, Péan F, Lahmidi S, Vaxillaire M, Porchay I, Bellili N, Tichet J, Balkau B, Froguel P, Marre M, Fumeron F** 2006 The PPARG Pro12Ala polymorphism is associated with a decreased risk of developing hyperglycemia over 6 years and combines with the effect of the APM1 G-11391A single nucleotide polymorphism: the Data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR) study. Diabetes 55:1157–1162
26. **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** 2007 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
27. **Florez JC, Jablonski KA, Sun MW, Bayley N, Kahn SE, Shamoon H, Hamman RF, Knowler WC, Nathan DM, Altshuler D** 2007 Effects of the type 2 diabetes-associated PPARG P12A polymorphism on progression to diabetes and response to troglitazone. J Clin Endocrinol Metab 92: 1502–1509
28. **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 2007 A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. Science 316:1341–1345

29. **Saxena R, Voight BF, Lyssenko V, Burtt NP, de Bakker PI, Chen H, Roix JJ, Kathiresan S, Hirschhorn JN, Daly MJ, Hughes TE, Groop L, Altshuler D, Almgren P, Florez JC, Meyer J, Ardlie K, Bengtsson Boström K, Isomaa B, Lettre G, Lindblad U, Lyon HN, Melander O, Newton-Cheh C, Nilsson P, Orho-Melander M, Råstam L, Speliotes EK, Taskinen MR, Tuomi T, Guiducci C, Berglund A, Carlson J, Gianniny L, Hackett R, Hall L, et al.** 2007 Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. Science 316:1331–1336
30. **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, McCarthy MI, Hattersley AT** 2007 Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. Science [Erratum (2007) 317:1035–1036] 316:1336–1341
31. **Herder C, Rathmann W, Strassburger K, Finner H, Grallert H, Huth C, Meisinger C, Gieger C, Martin S, Giani G, Scherbaum WA, Wichmann HE, Illig T** 2008 Variants of the PPARG, IGF2BP2, CDKAL1, HHEX, and TCF7L2 genes confer risk of type 2 diabetes independently of BMI in the German KORA studies. Horm Metab Res 40:722–726
32. **Gaulton KJ, Willer CJ, Li Y, Scott LJ, Conneely KN, Jackson AU, Duren WL, Chines PS, Narisu N, Bonnycastle LL, Luo J, Tong M, Sprau AG, Pugh EW, Doheny KF, Valle TT, Abecasis GR, Tuomilehto J, Bergman RN, Collins FS, Boehnke M, Mohlke KL** 2008 Comprehensive association study of type 2 diabetes and related quantitative traits with 222 candidate genes. Diabetes 57:3136–3144
33. **Zeggini E, Scott LJ, Saxena R, Voight BF, Marchini JL, Hu T, de Bakker PI, Abecasis GR, Almgren P, Andersen G, Ardlie K, Boström KB, Bergman RN, Bonnycastle LL, Borch-Johnsen K, Burtt NP, Chen H, Chines PS, Daly MJ, Deodhar P, Ding CJ, Doney AS, Duren WL, Elliott KS, Erdos MR, Frayling TM, Freathy RM, Gianniny L, Grallert H, Grarup N, Groves CJ, Guiducci C, Hansen T, Herder C, Hitman GA, Hughes TE, Isomaa B, et al.** 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
34. **Lyssenko V, Jonsson A, Almgren P, Pulizzi N, Isomaa B, Tuomi T, Berglund G, Altshuler D, Nilsson P, Groop L** 2008 Clinical risk factors, DNA variants, and the development of type 2 diabetes. N Engl J Med 359:2220–2232
35. **Sanghera DK, Ortega L, Han S, Singh J, Ralhan SK, Wander GS, Mehra NK, Mulvihill JJ, Ferrell RE, Nath SK, Kamboh MI** 2008 Impact of nine common type 2 diabetes risk polymorphisms in Asian Indian Sikhs: PPARG2 (Pro12Ala), IGF2BP2, TCF7L2 and FTO variants confer a significant risk. BMC Med Genet 9:59
36. **Hani EH, Boutin P, Durand E, Inoue H, Permutt MA, Velho G, Froguel P** 1998 Missense mutations in the pancreatic islet β 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
37. **Gloyn AL, Hashim Y, Ashcroft SJ, Ashfield R, Wiltshire S, Turner RC** 2001 Association studies of variants in promoter and coding regions of β-cell ATP-sensitive K-channel genes SUR1 and Kir6.2 with type 2 diabetes mellitus (UKPDS 53). Diabet Med 18:206–212
38. **Nielsen EM, Hansen L, Carstensen B, Echwald SM, Drivsholm T, Glümer C, Thorsteinsson B, Borch-Johnsen K, Hansen T, Pedersen O** 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
39. **Love-Gregory L, Wasson J, Lin J, Skolnick G, Suarez B, Permutt MA** 2003 E23K single nucleotide polymorphism in the islet ATP-sensitive potassium channel gene (Kir6.2) contributes as much to the risk of type II diabetes in Caucasians as the PPARγ Pro12Ala variant. Diabetologia 46:136–137
40. **Barroso I, Luan J, Middelberg RP, Harding AH, Franks PW, Jakes RW, Clayton D, Schafer AJ, O'Rahilly S, Wareham NJ** 2003 Candidate gene association study in type 2 diabetes indicates a role for genes involved in β-cell function as well as insulin action. PLoS Biol 1:E20
41. **Florez JC, Burtt N, de Bakker PI, Almgren P, Tuomi T, Holmkvist J, Gaudet D, Hudson TJ, Schaffner SF, Daly MJ, Hirschhorn JN, Groop L, Altshuler D** 2004 Haplotype structure and genotype-phenotype correlations of the sulfonylurea receptor and the islet ATP-sensitive potassium channel gene region. Diabetes 53:1360–1368
42. **Laukkanen O, Pihlajamäki J, Lindström J, Eriksson J, Valle TT, Hämäläinen H, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Tuomilehto J, Uusitupa M, Laakso M** 2004 Polymorphisms of the SUR1 (ABCC8) and Kir6.2 (KCNJ11) genes predict the conversion from impaired glucose tolerance to type 2 diabetes. The Finnish Diabetes Prevention Study. J Clin Endocrinol Metab 89:6286–6290
43. **Doi Y, Kubo M, Ninomiya T, Yonemoto K, Iwase M, Arima H, Hata J, Tanizaki Y, Iida M, Kiyohara Y** 2007 Impact of Kir6.2 E23K polymorphism on the development of type 2 diabetes in a general Japanese population: the Hisayama Study. Diabetes 56:2829–2833
44. **Sakamoto Y, Inoue H, Keshavarz P, Miyawaki K, Yamaguchi Y, Moritani M, Kunika K, Nakamura N, Yoshikawa T, Yasui N, Shiota H, Tanahashi T, Itakura M** 2007 SNPs in the KCNJ11-ABCC8 gene locus are associated with type 2 diabetes and blood pressure levels in the Japanese population. J Hum Genet 52:781–793
45. **Vaxillaire M, Veslot J, Dina C, Proença C, Cauchi S, Charpentier G, Tichet J, Fumeron F, Marre M, Meyre D, Balkau B, Froguel P** 2008 Impact of common type 2 diabetes risk polymorphisms in the DESIR prospective study. Diabetes 57:244–254
46. **Omori S, Tanaka Y, Takahashi A, Hirose H, Kashiwagi A, Kaku K, Kawamori R, Nakamura Y, Maeda S** 2008 Association of CDKAL1, IGF2BP2, CDKN2A/B, HHEX,

SLC30A8, and KCNJ11 with susceptibility to type 2 diabetes in a Japanese population. Diabetes 57:791–795
47. **Hara K, Boutin P, Mori Y, Tobe K, Dina C, Yasuda K, Yamauchi T, Otabe S, Okada T, Eto K, Kadowaki H, Hagura R, Akanuma Y, Yazaki Y, Nagai R, Taniyama M, Matsubara K, Yoda M, Nakano Y, Tomita M, Kimura S, Ito C, Froguel P, Kadowaki T** 2002 Genetic variation in the gene encoding adiponectin is associated with an increased risk of type 2 diabetes in the Japanese population. Diabetes 51:536–540
48. **Vasseur F, Helbecque N, Dina C, Lobbens S, Delannoy V, Gaget S, Boutin P, Vaxillaire M, Leprêtre F, Dupont S, Hara K, Clément K, Bihain B, Kadowaki T, Froguel P** 2002 Single-nucleotide polymorphism haplotypes in both the proximal promoter and exon 3 of the APM1 gene modulate adipocyte-secreted adiponectin hormone levels and contribute to the genetic risk for type 2 diabetes in French Caucasians. Hum Mol Genet 11:2607–2614
49. **Gu HF, Abulaiti A, Ostenson CG, Humphreys K, Wahlestedt C, Brookes AJ, Efendic S** 2004 Single nucleotide polymorphisms in the proximal promoter region of the adiponectin (APM1) gene are asociated with type 2 diabetes in Swedish Caucasians. Diabetes 53(Suppl 1):S31–S35
50. **Gibson F, Froguel P** 2004 Genetics of the APM1 locus and its contribution to type 2 diabetes susceptibility in French Caucasians. Diabetes 53:2977–2983
51. **Zacharova J, Chiasson JL, Laakso M** 2005 The common polymorphisms (single nucleotide polymorphism [SNP] +45 and SNP +276) of the adiponectin gene predict the conversion from impaired glucose tolerance to type 2 diabetes: the STOP-NIDDM trial. Diabetes 54:893–899
52. **Vasseur F, Helbecque N, Lobbens S, Vasseur-Delannoy V, Dina C, Clément K, Boutin P, Kadowaki T, Scherer PE, Froguel P** 2005 Hypoadiponectinaemia and high risk of type 2 diabetes are associated with adiponectin-encoding (ACDC) gene promoter variants in morbid obesity: evidence for a role of ACDC in diabesity. Diabetologia 48: 892–899
53. **Tso AW, Sham PC, Wat NM, Xu A, Cheung BM, Rong R, Fong CH, Xu JY, Cheng KK, Janus ED, Lam KS** 2006 Polymorphisms of the gene encoding adiponectin and glycaemic outcome of Chinese subjects with impaired glucose tolerance: a 5-year follow-up study. Diabetologia 49:1806–1815
54. **Schwarz PE, Govindarajalu S, Towers W, Schwanebeck U, Fischer S, Vasseur F, Bornstein SR, Schulze J** 2006 Haplotypes in the promoter region of the ADIPOQ gene are associated with increased diabetes risk in a German Caucasian population. Horm Metab Res 38:447–451
55. **Yang WS, Yang YC, Chen CL, Wu IL, Lu JY, Lu FH, Tai TY, Chang CJ** 2007 Adiponectin SNP276 is associated with obesity, the metabolic syndrome, and diabetes in the elderly. Am J Clin Nutr 86:509–513
56. **Liu H, Chen S, Zhang S, Xiao C, Ren Y, Tian H, Li X** 2007 Adiponectin gene variation −4522C/T is associated with type 2 diabetic obesity and insulin resistance in Chinese. J Genet Genomics 34:877–884
57. **Li LL, Kang XL, Ran XJ, Wang Y, Wang CH, Huang L, Ren J, Luo X, Mao XM** 2007 Associations between 45T/G polymorphism of the adiponectin gene and plasma adiponectin levels with type 2 diabetes. Clin Exp Pharmacol Physiol 34:1287–1290
58. **Gable DR, Matin J, Whittall R, Cakmak H, Li KW, Cooper J, Miller GJ, Humphries SE** 2007 Common adiponectin gene variants show different effects on risk of cardiovascular disease and type 2 diabetes in European subjects. Ann Hum Genet 71:453–466
59. **Vimaleswaran KS, Radha V, Ramya K, Babu HN, Savitha N, Roopa V, Monalisa D, Deepa R, Ghosh S, Majumder PP, Rao MR, Mohan V** 2008 A novel association of a polymorphism in the first intron of adiponectin gene with type 2 diabetes, obesity and hypoadiponectinemia in Asian Indians. Hum Genet 123:599–605
60. **Yang M, Qiu CC, Chen W, Xu LL, Yu M, Xiang HD** 2008 Identification of a regulatory single nucleotide polymorphism in the adiponectin (APM1) gene associated with type 2 diabetes in Han nationality. Biomed Environ Sci 21:454–459
61. **Bostrom MA, Freedman BI, Langefeld CD, Liu L, Hicks PJ, Bowden DW** 2009 Association of adiponectin gene polymorphisms with type 2 diabetes in an African American population enriched for nephropathy. Diabetes 58:499–504
62. **Laudes M, Barroso I, Luan J, Soos MA, Yeo G, Meirhaeghe A, Logie L, Vidal-Puig A, Schafer AJ, Wareham NJ, O'Rahilly S** 2004 Genetic variants in human sterol regulatory element binding protein-1c in syndromes of severe insulin resistance and type 2 diabetes. Diabetes 53:842–846
63. **Eberlé D, Clément K, Meyre D, Sahbatou M, Vaxillaire M, Le Gall A, Ferré P, Basdevant A, Froguel P, Foufelle F** 2004 SREBF-1 gene polymorphisms are associated with obesity and type 2 diabetes in French obese and diabetic cohorts. Diabetes 53:2153–2157
64. **Felder TK, Oberkofler H, Weitgasser R, Mackevics V, Krempler F, Paulweber B, Patsch W** 2007 The SREBF-1 locus is associated with type 2 diabetes and plasma adiponectin levels in a middle-aged Austrian population. Int J Obes (Lond) 31:1099–1103
65. **Grarup N, Stender-Petersen KL, Andersson EA, Jørgensen T, Borch-Johnsen K, Sandbaek A, Lauritzen T, Schmitz O, Hansen T, Pedersen O** 2008 Association of variants in the sterol regulatory element-binding factor 1 (SREBF1) gene with type 2 diabetes, glycemia, and insulin resistance: a study of 15,734 Danish subjects. Diabetes 57:1136–1142
66. **Oberkofler H, Linnemayr V, Weitgasser R, Klein K, Xie M, Iglseder B, Krempler F, Paulweber B, Patsch W** 2004 Complex haplotypes of the PGC-1α gene are associated with carbohydrate metabolism and type 2 diabetes. Diabetes 53:1385–1393
67. **Andrulionytè L, Zacharova J, Chiasson JL, Laakso M** 2004 Common polymorphisms of the PPAR-γ2 (Pro12Ala) and PGC-1α (Gly482Ser) genes are associated with the conversion from impaired glucose tolerance to type 2 diabetes in the STOP-NIDDM trial. Diabetologia 47:2176–2184
68. **Vimaleswaran KS, Radha V, Ghosh S, Majumder PP, Deepa R, Babu HN, Rao MR, Mohan V** 2005 Peroxisome proliferator-activated receptor-γ co-activator-1α (PGC-1α) gene polymorphisms and their relationship to type 2 diabetes in Asian Indians. Diabet Med 22:1516–1521
69. **Barroso I, Luan J, Sandhu MS, Franks PW, Crowley V, Schafer AJ, O'Rahilly S, Wareham NJ** 2006 Meta-analysis of the Gly482Ser variant in PPARGC1A in type 2 diabetes and related phenotypes. Diabetologia 49:501–505

70. **Bhat A, Koul A, Rai E, Sharma S, Dhar MK, Bamezai RN** 2007 PGC-1α Thr394Thr and Gly482Ser variants are significantly associated with T2DM in two North Indian populations: a replicate case-control study. Hum Genet 121: 609–614
71. **Rai E, Sharma S, Koul A, Bhat AK, Bhanwer AJ, Bamezai RN** 2007 Interaction between the UCP2–866G/A, mtDNA 10398G/A and PGC-1α p.Thr394Thr and p.Gly482Ser polymorphisms in type 2 diabetes susceptibility in North Indian population. Hum Genet 122:535–540
72. **Zhang SL, Lu WS, Yan L, Wu MC, Xu MT, Chen LH, Cheng H** 2007 Association between peroxisome proliferator-activated receptor-γ coactivator-1α gene polymorphisms and type 2 diabetes in southern Chinese population: role of altered interaction with myocyte enhancer factor 2C. Chin Med J (Engl) 120:1878–1885
73. **Lai CQ, Tucker KL, Parnell LD, Adiconis X, García-Bailo B, Griffith J, Meydani M, Ordovás JM** 2008 PPARGC1A variation associated with DNA damage, diabetes, and cardiovascular diseases: the Boston Puerto Rican Health Study. Diabetes 57:809–816
74. **Siddiq A, Lepretre F, Hercberg S, Froguel P, Gibson F** 2005 A synonymous coding polymorphism in the α2-Heremansschmid glycoprotein gene is associated with type 2 diabetes in French Caucasians. Diabetes 54:2477–2481
75. **Andersen G, Burgdorf KS, Sparsø T, Borch-Johnsen K, Jørgensen T, Hansen T, Pedersen O** 2008 AHSG tag single nucleotide polymorphisms associate with type 2 diabetes and dyslipidemia: studies of metabolic traits in 7,683 white Danish subjects. Diabetes 57:1427–1432
76. **Böttcher Y, Tönjes A, Enigk B, Scholz GH, Blüher M, Stumvoll M, Kovacs P** 2007 A SNP haplotype of the forkhead transcription factor FOXO1A gene may have a protective effect against type 2 diabetes in German Caucasians. Diabetes Metab 33:277–283
77. **Müssig K, Staiger H, Machicao F, Stancáková A, Kuusisto J, Laakso M, Thamer C, Machann J, Schick F, Claussen CD, Stefan N, Fritsche A, Häring HU** 2009 Association of common genetic variation in the FOXO1 gene with β-cell dysfunction, impaired glucose tolerance, and type 2 diabetes. J Clin Endocrinol Metab 94:1353–1360
78. **Schwab M, Lupescu A, Mota M, Mota E, Frey A, Simon P, Mertens PR, Floege J, Luft F, Asante-Poku S, Schaeffeler E, Lang F** 2008 Association of SGK1 gene polymorphisms with type 2 diabetes. Cell Physiol Biochem 21:151–160
79. **Friedrich B, Weyrich P, Stancáková A, Wang J, Kuusisto J, Laakso M, Sesti G, Succurro E, Smith U, Hansen T, Pedersen O, Machicao F, Schäfer S, Lang F, Risler T, Ullrich S, Stefan N, Fritsche A, Häring HU** 2008 Variance of the SGK1 gene is associated with insulin secretion in different European populations: results from the TUEF, EUGENE2, and METSIM studies. PLoS ONE 3:e3506
80. **Clee SM, Yandell BS, Schueler KM, Rabaglia ME, Richards OC, Raines SM, Kabara EA, Klass DM, Mui ET, Stapleton DS, Gray-Keller MP, Young MB, Stoehr JP, Lan H, Boronenkov I, Raess PW, Flowers MT, Attie AD** 2006 Positional cloning of Sorcs1, a type 2 diabetes quantitative trait locus. Nat Genet 38:688–693
81. **Goodarzi MO, Lehman DM, Taylor KD, Guo X, Cui J, Quiñones MJ, Clee SM, Yandell BS, Blangero J, Hsueh WA, Attie AD, Stern MP, Rotter JI** 2007 SORCS1: a novel human type 2 diabetes susceptibility gene suggested by the mouse. Diabetes 56:1922–1929
82. **Chadt A, Leicht K, Deshmukh A, Jiang LQ, Scherneck S, Bernhardt U, Dreja T, Vogel H, Schmolz K, Kluge R, Zierath JR, Hultschig C, Hoeben RC, Schürmann A, Joost HG, Al-Hasani H** 2008 Tbc1d1 mutation in lean mouse strain confers leanness and protects from diet-induced obesity. Nat Genet 40:1354–1359
83. **Dokmanovic-Chouinard M, Chung WK, Chevre JC, Watson E, Yonan J, Wiegand B, Bromberg Y, Wakae N, Wright CV, Overton J, Ghosh S, Sathe GM, Ammala CE, Brown KK, Ito R, LeDuc C, Solomon K, Fischer SG, Leibel RL** 2008 Positional cloning of "Lisch-Like," a candidate modifier of susceptibility to type 2 diabetes in mice. PLoS Genet 4:e1000137
84. **Bonnycastle LL, Willer CJ, Conneely KN, Jackson AU, Burrill CP, Watanabe RM, Chines PS, Narisu N, Scott LJ, Enloe ST, Swift AJ, Duren WL, Stringham HM, Erdos MR, Riebow NL, Buchanan TA, Valle TT, Tuomilehto J, Bergman RN, Mohlke KL, Boehnke M, Collins FS** 2006 Common variants in maturity-onset diabetes of the young genes contribute to risk of type 2 diabetes in Finns. Diabetes 55:2534–2540
85. **Winckler W, Weedon MN, Graham RR, McCarroll SA, Purcell S, Almgren P, Tuomi T, Gaudet D, Boström KB, Walker M, Hitman G, Hattersley AT, McCarthy MI, Ardlie KG, Hirschhorn JN, Daly MJ, Frayling TM, Groop L, Altshuler D** 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
86. **Gudmundsson J, Sulem P, Steinthorsdottir V, Bergthorsson JT, Thorleifsson G, Manolescu A, Rafnar T, Gudbjartsson D, Agnarsson BA, Baker A, Sigurdsson A, Benediktsdottir KR, Jakobsdottir M, Blondal T, Stacey SN, Helgason A, Gunnarsdottir S, Olafsdottir A, Kristinsson KT, Birgisdottir B, Ghosh S, Thorlacius S, Magnusdottir D, Stefansdottir G, Kristjansson K, Bagger Y, Wilensky RL, Reilly MP, Morris AD, Kimber CH, et al.** 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
87. **Sandhu MS, Weedon MN, Fawcett KA, Wasson J, Debenham SL, Daly A, Lango H, Frayling TM, Neumann RJ, Sherva R, Blech I, Pharoah PD, Palmer CN, Kimber C, Tavendale R, Morris AD, McCarthy MI, Walker M, Hitman G, Glaser B, Permutt MA, Hattersley AT, Wareham NJ, Barroso I** 2007 Common variants in WFS1 confer risk of type 2 diabetes. Nat Genet 39:951–953
88. **Franks PW, Rolandsson O, Debenham SL, Fawcett KA, Payne F, Dina C, Froguel P, Mohlke KL, Willer C, Olsson T, Wareham NJ, Hallmans G, Barroso I, Sandhu MS** 2008 Replication of the association between variants in WFS1 and risk of type 2 diabetes in European populations. Diabetologia 51:458–463
89. **van Hoek M, Dehghan A, Witteman JC, van Duijn CM, Uitterlinden AG, Oostra BA, Hofman A, Sijbrands EJ, Janssens AC** 2008 Predicting type 2 diabetes based on polymorphisms from genome-wide association studies: a population-based study. Diabetes 57:3122–3128
90. **Urhammer SA, Rasmussen SK, Kaisaki PJ, Oda N, Yamagata K, Møller AM, Fridberg M, Hansen L, Hansen T, Bell GI, Pedersen O** 1997 Genetic variation in the hepatocyte nuclear

factor-1 α gene in Danish Caucasians with late-onset NIDDM. Diabetologia 40:473–475

91. **Babaya N, Ikegami H, Kawaguchi Y, Fujisawa T, Nakagawa Y, Hamada Y, Hotta M, Ueda H, Shintani M, Nojima K, Kawabata Y, Ono M, Yamada K, Shen GQ, Fukuda M, Ogihara T** 1998 Hepatocyte nuclear factor-1α gene and non-insulin-dependent diabetes mellitus in the Japanese population. Acta Diabetol 35:150–153
92. **Rissanen J, Wang H, Miettinen R, Kärkkäinen P, Kekäläinen P, Mykkänen L, Kuusisto J, Karhapää P, Niskanen L, Uusitupa M, Laakso M** 2000 Variants in the hepatocyte nuclear factor-1α and -4α genes in Finnish and Chinese subjects with late-onset type 2 diabetes. Diabetes Care 23:1533–1538
93. **Winckler W, Burtt NP, Holmkvist J, Cervin C, de Bakker PI, Sun M, Almgren P, Tuomi T, Gaudet D, Hudson TJ, Ardlie KG, Daly MJ, Hirschhorn JN, Altshuler D, Groop L** 2005 Association of common variation in the HNF1α gene region with risk of type 2 diabetes. Diabetes 54:2336–2342
94. **Weedon MN, Owen KR, Shields B, Hitman G, Walker M, McCarthy MI, Hattersley AT, Frayling TM** 2005 A large-scale association analysis of common variation of the HNF1α gene with type 2 diabetes in the U.K. Caucasian population. Diabetes 54:2487–2491
95. **Holmkvist J, Cervin C, Lyssenko V, Winckler W, Anevski D, Cilio C, Almgren P, Berglund G, Nilsson P, Tuomi T, Lindgren CM, Altshuler D, Groop L** 2006 Common variants in HNF-1 α and risk of type 2 diabetes. Diabetologia 49:2882–2891
96. **Holmkvist J, Almgren P, Lyssenko V, Lindgren CM, Eriksson KF, Isomaa B, Tuomi T, Nilsson P, Groop L** 2008 Common variants in maturity-onset diabetes of the young genes and future risk of type 2 diabetes. Diabetes 57:1738–1744
97. **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** 2004 Genetic variation near the hepatocyte nuclear factor-4α gene predicts susceptibility to type 2 diabetes. Diabetes 53:1141–1149
98. **Love-Gregory LD, Wasson J, Ma J, Jin CH, Glaser B, Suarez BK, Permutt MA** 2004 A common polymorphism in the upstream promoter region of the hepatocyte nuclear factor-4α 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
99. **Damcott CM, Hoppman N, Ott SH, Reinhart LJ, Wang J, Pollin TI, O'Connell JR, Mitchell BD, Shuldiner AR** 2004 Polymorphisms in both promoters of hepatocyte nuclear factor 4-α are associated with type 2 diabetes in the Amish. Diabetes 53:3337–3341
100. **Weedon MN, Owen KR, Shields B, Hitman G, Walker M, McCarthy MI, Love-Gregory LD, Permutt MA, Hattersley AT, Frayling TM** 2004 Common variants of the hepatocyte nuclear factor-4α P2 promoter are associated with type 2 diabetes in the U.K. population. Diabetes 53:3002–3006
101. **Hansen SK, Rose CS, Glümer C, Drivsholm T, Borch-Johnsen K, Jørgensen T, Pedersen O, Hansen T** 2005 Variation near the hepatocyte nuclear factor (HNF)-4α gene associates with type 2 diabetes in the Danish population. Diabetologia 48:452–458
102. **Winckler W, Graham RR, de Bakker PI, Sun M, Almgren P, Tuomi T, Gaudet D, Hudson TJ, Ardlie KG, Daly MJ, Hirschhorn JN, Groop L, Altshuler D** 2005 Association testing of variants in the hepatocyte nuclear factor 4α gene with risk of type 2 diabetes in 7,883 people. Diabetes 54:886–892
103. **Vaxillaire M, Dina C, Lobbens S, Dechaume A, Vasseur-Delannoy V, Helbecque N, Charpentier G, Froguel P** 2005 Effect of common polymorphisms in the HNF4α promoter on susceptibility to type 2 diabetes in the French Caucasian population. Diabetologia 48:440–444
104. **Hara K, Horikoshi M, Kitazato H, Ito C, Noda M, Ohashi J, Froguel P, Tokunaga K, Tobe K, Nagai R, Kadowaki T** 2006 Hepatocyte nuclear factor-4α P2 promoter haplotypes are associated with type 2 diabetes in the Japanese population. Diabetes 55:1260–1264
105. **Andrulionyte L, Laukkanen O, Chiasson JL, Laakso M** 2006 Single nucleotide polymorphisms of the HNF4α gene are associated with the conversion to type 2 diabetes mellitus: the STOP-NIDDM trial. J Mol Med 84:701–708
106. **Tanahashi T, Osabe D, Nomura K, Shinohara S, Kato H, Ichiishi E, Nakamura N, Yoshikawa T, Takata Y, Miyamoto T, Shiota H, Keshavarz P, Yamaguchi Y, Kunika K, Moritani M, Inoue H, Itakura M** 2006 Association study on chromosome 20q11.21–13.13 locus and its contribution to type 2 diabetes susceptibility in Japanese. Hum Genet 120:527–542
107. **Lehman DM, Richardson DK, Jenkinson CP, Hunt KJ, Dyer TD, Leach RJ, Arya R, Abboud HE, Blangero J, Duggirala R, Stern MP** 2007 P2 promoter variants of the hepatocyte nuclear factor 4α gene are associated with type 2 diabetes in Mexican Americans. Diabetes 56:513–517
108. **Johansson S, Raeder H, Eide SA, Midthjell K, Hveem K, Søvik O, Molven A, Njølstad PR** 2007 Studies in 3,523 Norwegians and meta-analysis in 11,571 subjects indicate that variants in the hepatocyte nuclear factor 4 α (HNF4A) P2 region are associated with type 2 diabetes in Scandinavians. Diabetes 56:3112–3117
109. **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, Horikawa Y, Oda Y, Yoshiuchi I, Colilla S, Polonsky KS, Wei S, Concannon P, Iwasaki N, Schulze J, Baier LJ, Bogardus C, Groop L, Boerwinkle E, Hanis CL, Bell GI** 2000 Genetic variation in the gene encoding calpain-10 is associated with type 2 diabetes mellitus. Nat Genet 26:163–175
110. **Evans JC, Frayling TM, Cassell PG, Saker PJ, Hitman GA, Walker M, Levy JC, O'Rahilly S, Rao PV, Bennett AJ, Jones EC, Menzel S, Prestwich P, Simecek N, Wishart M, Dhillon R, Fletcher C, Millward A, Demaine A, Wilkin T, Horikawa Y, Cox NJ, Bell GI, Ellard S, McCarthy MI, Hattersley AT** 2001 Studies of association between the gene for calpain-10 and type 2 diabetes mellitus in the United Kingdom. Am J Hum Genet 69:544–552
111. **Malecki MT, Moczulski DK, Klupa T, Wanic K, Cyganek K, Frey J, Sieradzki J** 2002 Homozygous combination of calpain 10 gene haplotypes is associated with type 2 diabetes mellitus in a Polish population. Eur J Endocrinol 146:695–699
112. **Cassell PG, Jackson AE, North BV, Evans JC, Syndercombe-Court D, Phillips C, Ramachandran A, Snehalatha C,**

Gelding SV, Vijayaravaghan S, Curtis D, Hitman GA 2002 Haplotype combinations of calpain 10 gene polymorphisms associate with increased risk of impaired glucose tolerance and type 2 diabetes in South Indians. Diabetes 51:1622–1628

113. **Weedon MN, Schwarz PE, Horikawa Y, Iwasaki N, Illig T, Holle R, Rathmann W, Selisko T, Schulze J, Owen KR, Evans J, Del Bosque-Plata L, Hitman G, Walker M, Levy JC, Sampson M, Bell GI, McCarthy MI, Hattersley AT, Frayling TM** 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
114. **Iwasaki N, Horikawa Y, Tsuchiya T, Kitamura Y, Nakamura T, Tanizawa Y, Oka Y, Hara K, Kadowaki T, Awata T, Honda M, Yamashita K, Oda N, Yu L, Yamada N, Ogata M, Kamatani N, Iwamoto Y, Del Bosque-Plata L, Hayes MG, Cox NJ, Bell GI** 2005 Genetic variants in the calpain-10 gene and the development of type 2 diabetes in the Japanese population. J Hum Genet 50:92–98
115. **Kang ES, Kim HJ, Nam M, Nam CM, Ahn CW, Cha BS, Lee HC** 2006 A novel 111/121 diplotype in the Calpain-10 gene is associated with type 2 diabetes. J Hum Genet 51: 629–633
116. **Tsuchiya T, Schwarz PE, Bosque-Plata LD, Geoffrey Hayes M, Dina C, Froguel P, Wayne Towers G, Fischer S, Temelkova-Kurktschiev T, Rietzsch H, Graessler J, Vcelák J, Palyzová D, Selisko T, Bendlová B, Schulze J, Julius U, Hanefeld M, Weedon MN, Evans JC, Frayling TM, Hattersley AT, Orho-Melander M, Groop L, Malecki MT, Hansen T, Pedersen O, Fingerlin TE, Boehnke M, Hanis CL, Cox NJ, Bell GI** 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
117. **Jensen DP, Urhammer SA, Eiberg H, Borch-Johnsen K, Jørgensen T, Hansen T, Pedersen O** 2006 Variation in CAPN10 in relation to type 2 diabetes, obesity and quantitative metabolic traits: studies in 6018 whites. Mol Genet Metab 89:360–367
118. **Kifagi C, Makni K, Mnif F, Boudawara M, Hamza N, Rekik N, Abid M, Rebaï A, Granier C, Jarraya F, Ayadi H** 2008 Association of calpain-10 polymorphisms with type 2 diabetes in the Tunisian population. Diabetes Metab 34: 273–278
119. **Abate N, Chandalia M, Satija P, Adams-Huet B, Grundy SM, Sandeep S, Radha V, Deepa R, Mohan V** 2005 ENPP1/PC-1 K121Q polymorphism and genetic susceptibility to type 2 diabetes. Diabetes 54:1207–1213
120. **Bacci S, Ludovico O, Prudente S, Zhang YY, Di Paola R, Mangiacotti D, Rauseo A, Nolan D, Duffy J, Fini G, Salvemini L, Amico C, Vigna C, Pellegrini F, Menzaghi C, Doria A, Trischitta V** 2005 The K121Q polymorphism of the ENPP1/PC-1 gene is associated with insulin resistance/atherogenic phenotypes, including earlier onset of type 2 diabetes and myocardial infarction. Diabetes 54:3021–3025
121. **Grarup N, Urhammer SA, Ek J, Albrechtsen A, Glümer C, Borch-Johnsen K, Jørgensen T, Hansen T, Pedersen O** 2006 Studies of the relationship between the ENPP1 K121Q polymorphism and type 2 diabetes, insulin resistance and obesity in 7,333 Danish white subjects. Diabetologia 49:2097–2104
122. **Bochenski J, Placha G, Wanic K, Malecki M, Sieradzki J, Warram JH, Krolewski AS** 2006 New polymorphism of ENPP1 (PC-1) is associated with increased risk of type 2 diabetes among obese individuals. Diabetes 55:2626–2630
123. **Meyre D, Bouatia-Naji N, Vatin V, Veslot J, Samson C, Tichet J, Marre M, Balkau B, Froguel P** 2007 ENPP1 K121Q polymorphism and obesity, hyperglycaemia and type 2 diabetes in the prospective DESIR Study. Diabetologia 50:2090–2096
124. **McAteer JB, Prudente S, Bacci S, Lyon HN, Hirschhorn JN, Trischitta V, Florez JC** 2008 The ENPP1 K121Q polymorphism is associated with type 2 diabetes in European populations: evidence from an updated meta-analysis in 42,042 subjects. Diabetes 57:1125–1130
125. **Cauchi S, Nead KT, Choquet H, Horber F, Potoczna N, Balkau B, Marre M, Charpentier G, Froguel P, Meyre D** 2008 The genetic susceptibility to type 2 diabetes may be modulated by obesity status: implications for association studies. BMC Med Genet 9:45
126. **Bouhaha R, Meyre D, Kamoun HA, Ennafaa H, Vaillant E, Sassi R, Baroudi T, Vatin V, Froguel P, Elgaaied A, Vaxillaire M** 2008 Effect of ENPP1/PC-1-K121Q and PPARγ-Pro12Ala polymorphisms on the genetic susceptibility to T2D in the Tunisian population. Diabetes Res Clin Pract 81:278–283
127. **Moore AF, Jablonski KA, Mason CC, McAteer JB, Arakaki RF, Goldstein BJ, Kahn SE, Kitabchi AE, Hanson RL, Knowler WC, Florez JC** 2009 The association of ENPP1 K121Q with diabetes incidence is abolished by lifestyle modification in the diabetes prevention program. J Clin Endocrinol Metab 94:449–455
128. **Grant SF, Thorleifsson G, Reynisdottir I, Benediktsson R, Manolescu A, Sainz J, Helgason A, Stefansson H, Emilsson V, Helgadottir A, Styrkarsdottir U, Magnusson KP, Walters GB, Palsdottir E, Jonsdottir T, Gudmundsdottir T, Gylfason A, Saemundsdottir J, Wilensky RL, Reilly MP, Rader DJ, Bagger Y, Christiansen C, Gudnason V, Sigurdsson G, Thorsteinsdottir U, Gulcher JR, Kong A, Stefansson K** 2006 Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nat Genet 38:320–323
129. **Florez JC, Jablonski KA, Bayley N, Pollin TI, de Bakker PI, Shuldiner AR, Knowler WC, Nathan DM, Altshuler D** 2006 TCF7L2 polymorphisms and progression to diabetes in the Diabetes Prevention Program. N Engl J Med 355: 241–250
130. **Groves CJ, Zeggini E, Minton J, Frayling TM, Weedon MN, Rayner NW, Hitman GA, Walker M, Wiltshire S, Hattersley AT, McCarthy MI** 2006 Association analysis of 6,736 U.K. subjects provides replication and confirms TCF7L2 as a type 2 diabetes susceptibility gene with a substantial effect on individual risk. Diabetes 55:2640–2644
131. **Zhang C, Qi L, Hunter DJ, Meigs JB, Manson JE, van Dam RM, Hu FB** 2006 Variant of transcription factor 7-like 2 (TCF7L2) gene and the risk of type 2 diabetes in large cohorts of U.S. women and men. Diabetes 55:2645–2648
132. **Scott LJ, Bonnycastle 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** 2006 Association of transcription factor 7-like 2 (TCF7L2) variants with type 2 diabetes in a Finnish sample. Diabetes 55:2649–2653
133. **Damcott CM, Pollin TI, Reinhart LJ, Ott SH, Shen H,**

Silver KD, Mitchell BD, Shuldiner AR 2006 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

134. **Saxena R, Gianniny L, Burtt NP, Lyssenko V, Giuducci C, Sjögren M, Florez JC, Almgren P, Isomaa B, Orho-Melander M, Lindblad U, Daly MJ, Tuomi T, Hirschhorn JN, Ardlie KG, Groop LC, Altshuler D** 2006 Common single nucleotide polymorphisms in TCF7L2 are reproducibly associated with type 2 diabetes and reduce the insulin response to glucose in nondiabetic individuals. Diabetes 55:2890–2895
135. **Cauchi S, Meyre D, Dina C, Choquet H, Samson C, Gallina S, Balkau B, Charpentier G, Pattou F, Stetsyuk V, Scharfmann R, Staels B, Frühbeck G, Froguel P** 2006 Transcription factor TCF7L2 genetic study in the French population: expression in human β-cells and adipose tissue and strong association with type 2 diabetes. Diabetes 55:2903–2908
136. **van Vliet-Ostaptchouk JV, Shiri-Sverdlov R, Zhernakova A, Strengman E, van Haeften TW, Hofker MH, Wijmenga C** 2007 Association of variants of transcription factor 7-like 2 (TCF7L2) with susceptibility to type 2 diabetes in the Dutch Breda cohort. Diabetologia 50:59–62
137. **Humphries SE, Gable D, Cooper JA, Ireland H, Stephens JW, Hurel SJ, Li KW, Palmen J, Miller MA, Cappuccio FP, Elkeles R, Godsland I, Miller GJ, Talmud PJ** 2006 Common variants in the TCF7L2 gene and predisposition to type 2 diabetes in UK European Whites, Indian Asians and Afro-Caribbean men and women. J Mol Med 84:1005–1014
138. **Cauchi S, Meyre D, Choquet H, Dina C, Born C, Marre M, Balkau B, Froguel P** 2006 TCF7L2 variation predicts hyperglycemia incidence in a French general population: the data from an epidemiological study on the Insulin Resistance Syndrome (DESIR) study. Diabetes 55:3189–3192
139. **Chandak GR, Janipalli CS, Bhaskar S, Kulkarni SR, Mohankrishna P, Hattersley AT, Frayling TM, Yajnik CS** 2007 Common variants in the TCF7L2 gene are strongly associated with type 2 diabetes mellitus in the Indian population. Diabetologia 50:63–67
140. **Marzi C, Huth C, Kolz M, Grallert H, Meisinger C, Wichmann HE, Rathmann W, Herder C, Illig T** 2007 Variants of the transcription factor 7-like 2 gene (TCF7L2) are strongly associated with type 2 diabetes but not with the metabolic syndrome in the MONICA/KORA surveys. Horm Metab Res 39:46–52
141. **Mayans S, Lackovic K, Lindgren P, Ruikka K, Agren A, Eliasson M, Holmberg D** 2007 TCF7L2 polymorphisms are associated with type 2 diabetes in northern Sweden. Eur J Hum Genet 15:342–346
142. **Horikoshi M, Hara K, Ito C, Nagai R, Froguel P, Kadowaki T** 2007 A genetic variation of the transcription factor 7-like 2 gene is associated with risk of type 2 diabetes in the Japanese population. Diabetologia 50:747–751
143. **Lehman DM, Hunt KJ, Leach RJ, Hamlington J, Arya R, Abboud HE, Duggirala R, Blangero J, Göring HH, Stern MP** 2007 Haplotypes of transcription factor 7-like 2 (TCF7L2) gene and its upstream region are associated with type 2 diabetes and age of onset in Mexican Americans. Diabetes 56:389–393
144. **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** 2007 A genome-wide association study identifies novel risk loci for type 2 diabetes. Nature 445:881–885
145. **Hayashi T, Iwamoto Y, Kaku K, Hirose H, Maeda S** 2007 Replication study for the association of TCF7L2 with susceptibility to type 2 diabetes in a Japanese population. Diabetologia 50:980–984
146. **Kimber CH, Doney AS, Pearson ER, McCarthy MI, Hattersley AT, Leese GP, Morris AD, Palmer CN** 2007 TCF7L2 in the Go-DARTS study: evidence for a gene dose effect on both diabetes susceptibility and control of glucose levels. Diabetologia 50:1186–1191
147. **Wang J, Kuusisto J, Vänttinen M, Kuulasmaa T, Lindström J, Tuomilehto J, Uusitupa M, Laakso M** 2007 Variants of transcription factor 7-like 2 (TCF7L2) gene predict conversion to type 2 diabetes in the Finnish Diabetes Prevention Study and are associated with impaired glucose regulation and impaired insulin secretion. Diabetologia 50:1192–1200
148. **Parra EJ, Cameron E, Simmonds L, Valladares A, McKeigue P, Shriver M, Wacher N, Kumate J, Kittles R, Cruz M** 2007 Association of TCF7L2 polymorphisms with type 2 diabetes in Mexico City. Clin Genet 71:359–366
149. **Cauchi S, El Achhab Y, Choquet H, Dina C, Krempler F, Weitgasser R, Nejjari C, Patsch W, Chikri M, Meyre D, Froguel P** 2007 TCF7L2 is reproducibly associated with type 2 diabetes in various ethnic groups: a global meta-analysis. J Mol Med 85:777–782
150. **Chang YC, Chang TJ, Jiang YD, Kuo SS, Lee KC, Chiu KC, Chuang LM** 2007 Association study of the genetic polymorphisms of the transcription factor 7-like 2 (TCF7L2) gene and type 2 diabetes in the Chinese population. Diabetes 56:2631–2637
151. **Elbein SC, Chu WS, Das SK, Yao-Borengasser A, Hasstedt SJ, Wang H, Rasouli N, Kern PA** 2007 Transcription factor 7-like 2 polymorphisms and type 2 diabetes, glucose homeostasis traits and gene expression in US participants of European and African descent. Diabetologia 50:1621–1630
152. **Ng MC, Tam CH, Lam VK, So WY, Ma RC, Chan JC** 2007 Replication and identification of novel variants at TCF7L2 associated with type 2 diabetes in Hong Kong Chinese. J Clin Endocrinol Metab 92:3733–3737
153. **Dahlgren A, Zethelius B, Jensevik K, Syvänen AC, Berne C** 2007 Variants of the TCF7L2 gene are associated with β cell dysfunction and confer an increased risk of type 2 diabetes mellitus in the ULSAM cohort of Swedish elderly men. Diabetologia 50:1852–1857
154. **Bodhini D, Radha V, Dhar M, Narayani N, Mohan V** 2007 The rs12255372(G/T) and rs7903146(C/T) polymorphisms of the TCF7L2 gene are associated with type 2 diabetes mellitus in Asian Indians. Metabolism 56:1174–1178
155. **Miyake K, Horikawa Y, Hara K, Yasuda K, Osawa H, Furuta H, Hirota Y, Yamagata K, Hinokio Y, Oka Y, Iwasaki N, Iwamoto Y, Yamada Y, Seino Y, Maegawa H, Kashiwagi A, Yamamoto K, Tokunaga K, Takeda J, Makino H, Nanjo K, Kadowaki T, Kasuga M** 2008 Association of TCF7L2 polymorphisms with susceptibility to type 2 diabetes in 4,087 Japanese subjects. J Hum Genet 53:174–180

156. **Rees SD, Bellary S, Britten AC, O'Hare JP, Kumar S, Barnett AH, Kelly MA** 2008 Common variants of the TCF7L2 gene are associated with increased risk of type 2 diabetes mellitus in a UK-resident South Asian population. BMC Med Genet 9:8
157. **Sanghera DK, Nath SK, Ortega L, Gambarelli M, Kim-Howard X, Singh JR, Ralhan SK, Wander GS, Mehra NK, Mulvihill JJ, Kamboh MI** 2008 TCF7L2 polymorphisms are associated with type 2 diabetes in Khatri Sikhs from North India: genetic variation affects lipid levels. Ann Hum Genet 72:499–509
158. **González-Sánchez JL, Martínez-Larrad MT, Zabena C, Pérez-Barba M, Serrano-Ríos M** 2008 Association of variants of the TCF7L2 gene with increases in the risk of type 2 diabetes and the proinsulin:insulin ratio in the Spanish population. Diabetologia 51:1993–1997
159. **Yan Y, North KE, Ballantyne CM, Brancati FL, Chambless LE, Franceschini N, Heiss G, Kottgen A, Pankow JS, Selvin E, West SL, Boerwinkle E** 2009 Transcription factor 7-like 2 (TCF7L2) polymorphism and context-specific risk of type 2 diabetes in African American and Caucasian adults: the Atherosclerosis Risk in Communities Study. Diabetes 58:285–289
160. **Thorsby PM, Midthjell K, Gjerlaugsen N, Holmen J, Hanssen KF, Birkeland KI, Berg JP** 2009 Comparison of genetic risk in three candidate genes (TCF7L2, PPARG, KCNJ11) with traditional risk factors for type 2 diabetes in a population-based study—the HUNT study. Scand J Clin Lab Invest 69:282–287
161. **Tabara Y, Osawa H, Kawamoto R, Onuma H, Shimizu I, Miki T, Kohara K, Makino H** 2009 Replication study of candidate genes associated with type 2 diabetes based on genome-wide screening. Diabetes 58:493–498
162. **Hertel JK, Johansson S, Raeder H, Midthjell K, Lyssenko V, Groop L, Molven A, Njølstad PR** 2008 Genetic analysis of recently identified type 2 diabetes loci in 1,638 unselected patients with type 2 diabetes and 1,858 control participants from a Norwegian population-based cohort (the HUNT study). Diabetologia 51:971–977
163. **Ng MC, Park KS, Oh B, Tam CH, Cho YM, Shin HD, Lam VK, Ma RC, So WY, Cho YS, Kim HL, Lee HK, Chan JC, Cho NH** 2008 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
164. **Horikawa Y, Miyake K, Yasuda K, Enya M, Hirota Y, Yamagata K, Hinokio Y, Oka Y, Iwasaki N, Iwamoto Y, Yamada Y, Seino Y, Maegawa H, Kashiwagi A, Yamamoto K, Tokunaga K, Takeda J, Kasuga M** 2008 Replication of genome-wide association studies of type 2 diabetes susceptibility in Japan. J Clin Endocrinol Metab 93:3136–3141
165. **Xiang J, Li XY, Xu M, Hong J, Huang Y, Tan JR, Lu X, Dai M, Yu B, Ning G** 2008 Zinc transporter-8 gene (SLC30A8) is associated with type 2 diabetes in Chinese. J Clin Endocrinol Metab 93:4107–4112
166. **Wu Y, Li H, Loos RJ, Yu Z, Ye X, Chen L, Pan A, Hu FB, Lin X** 2008 Common variants in CDKAL1, CDKN2A/B, IGF2BP2, SLC30A8, and HHEX/IDE genes are associated with type 2 diabetes and impaired fasting glucose in a Chinese Han population. Diabetes 57:2834–2842
167. **Grarup N, Rose CS, Andersson EA, Andersen G, Nielsen AL, Albrechtsen A, Clausen JO, Rasmussen SS, Jørgensen T, Sandbaek A, Lauritzen T, Schmitz O, Hansen T, Pedersen O** 2007 Studies of association of variants near the HHEX, CDKN2A/B, and IGF2BP2 genes with type 2 diabetes and impaired insulin release in 10,705 Danish subjects: validation and extension of genome-wide association studies. Diabetes 56:3105–3111
168. **Schulze MB, Al-Hasani H, Boeing H, Fisher E, Döring F, Joost HG** 2007 Variation in the HHEX-IDE gene region predisposes to type 2 diabetes in the prospective, population-based EPIC-Potsdam cohort. Diabetologia 50:2405–2407
169. **Horikoshi M, Hara K, Ito C, Shojima N, Nagai R, Ueki K, Froguel P, Kadowaki T** 2007 Variations in the HHEX gene are associated with increased risk of type 2 diabetes in the Japanese population. Diabetologia 50:2461–2466
170. **Furukawa Y, Shimada T, Furuta H, Matsuno S, Kusuyama A, Doi A, Nishi M, Sasaki H, Sanke T, Nanjo K** 2008 Polymorphisms in the IDE-KIF11-HHEX gene locus are reproducibly associated with type 2 diabetes in a Japanese population. J Clin Endocrinol Metab 93:310–314
171. **van Vliet-Ostaptchouk JV, Onland-Moret NC, van Haeften TW, Franke L, Elbers CC, Shiri-Sverdlov R, van der Schouw YT, Hofker MH, Wijmenga C** 2008 HHEX gene polymorphisms are associated with type 2 diabetes in the Dutch Breda cohort. Eur J Hum Genet 16:652–656
172. **Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, Perry JR, Elliott KS, Lango H, Rayner NW, Shields B, Harries LW, Barrett JC, Ellard S, Groves CJ, Knight B, Patch AM, Ness AR, Ebrahim S, Lawlor DA, Ring SM, Ben-Shlomo Y, Jarvelin MR, Sovio U, Bennett AJ, Melzer D, Ferrucci L, Loos RJ, Barroso I, Wareham NJ, Karpe F, Owen KR, Cardon LR, Walker M, Hitman GA, Palmer CN, Doney AS, Morris AD, Smith GD, Hattersley AT, McCarthy MI** 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
173. **Tan JT, Dorajoo R, Seielstad M, Sim XL, Ong RT, Chia KS, Wong TY, Saw SM, Chew SK, Aung T, Tai ES** 2008 FTO variants are associated with obesity in the Chinese and Malay populations in Singapore. Diabetes 57:2851–2857
174. **Steinthorsdottir V, Thorleifsson G, Reynisdottir I, Benediktsson R, Jonsdottir T, Walters GB, Styrkarsdottir U, Gretarsdottir S, Emilsson V, Ghosh S, Baker A, Snorradottir 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** 2007 A variant in CDKAL1 influences insulin response and risk of type 2 diabetes. Nat Genet 39:770–775
175. **Bronstein M, Pisanté A, Yakir B, Darvasi A** 2008 Type 2 diabetes susceptibility loci in the Ashkenazi Jewish population. Hum Genet 124:101–104
176. **Liu Y, Yu L, Zhang D, Chen Z, Zhou DZ, Zhao T, Li S, Wang T, Hu X, Feng GY, Zhang ZF, He L, Xu H** 2008 Positive association between variations in CDKAL1 and

type 2 diabetes in Han Chinese individuals. Diabetologia 51:2134–2137

177. **Lee YH, Kang ES, Kim SH, Han SJ, Kim CH, Kim HJ, Ahn CW, Cha BS, Nam M, Nam CM, Lee HC** 2008 Association between polymorphisms in SLC30A8, HHEX, CDKN2A/B, IGF2BP2, FTO, WFS1, CDKAL1, KCNQ1 and type 2 diabetes in the Korean population. J Hum Genet 53:991–998
178. **Duesing K, Fatemifar G, Charpentier G, Marre M, Tichet J, Hercberg S, Balkau B, Froguel P, Gibson F** 2008 Strong association of common variants in the CDKN2A/CDKN2B region with type 2 diabetes in French Europids. Diabetologia 51:821–826
179. **Unoki H, Takahashi A, Kawaguchi T, Hara K, Horikoshi M, Andersen G, Ng DP, Holmkvist J, Borch-Johnsen K, Jørgensen T, Sandbaek A, Lauritzen T, Hansen T, Nurbaya S, Tsunoda T, Kubo M, Babazono T, Hirose H, Hayashi M, Iwamoto Y, Kashiwagi A, Kaku K, Kawamori R, Tai ES, Pedersen O, Kamatani N, Kadowaki T, Kikkawa R, Nakamura Y, Maeda S** 2008 SNPs in KCNQ1 are associated with susceptibility to type 2 diabetes in East Asian and European populations. Nat Genet 40:1098–1102
180. **Yasuda K, Miyake K, Horikawa Y, Hara K, Osawa H, Furuta H, Hirota Y, Mori H, Jonsson A, Sato Y, Yamagata K, Hinokio Y, Wang HY, Tanahashi T, Nakamura N, Oka Y, Iwasaki N, Iwamoto Y, Yamada Y, Seino Y, Maegawa H, Kashiwagi A, Takeda J, Maeda E, Shin HD, Cho YM, Park KS, Lee HK, Ng MC, Ma RC, So WY, Chan JC, Lyssenko V, Tuomi T, Nilsson P, Groop L, Kamatani N, Sekine A, Nakamura Y, Yamamoto K, Yoshida T, Tokunaga K, Itakura M, Makino H, Nanjo K, Kadowaki T, Kasuga M** 2008 Variants in KCNQ1 are associated with susceptibility to type 2 diabetes mellitus. Nat Genet 40:1092–1097
181. **Prokopenko I, Langenberg C, Florez JC, Saxena R, Soranzo N, Thorleifsson G, Loos RJ, Manning AK, Jackson AU, Aulchenko Y, Potter SC, Erdos MR, Sanna S, Hottenga JJ, Wheeler E, Kaakinen M, Lyssenko V, Chen WM, Ahmadi K, Beckmann JS, Bergman RN, Bochud M, Bonnycastle LL, Buchanan TA, Cao A, Cervino A, Coin L, Collins FS, Crisponi L, de Geus EJ, Dehghan A, Deloukas P, Doney AS, Elliott P, Freimer N, Gateva V, et al.** 2009 Variants in MTNR1B influence fasting glucose levels. Nat Genet 41:77–81
182. **Lyssenko V, Nagorny CL, Erdos MR, Wierup N, Jonsson A, Spégel P, Bugliani M, Saxena R, Fex M, Pulizzi N, Isomaa B, Tuomi T, Nilsson P, Kuusisto J, Tuomilehto J, Boehnke M, Altshuler D, Sundler F, Eriksson JG, Jackson AU, Laakso M, Marchetti P, Watanabe RM, Mulder H, Groop L** 2009 Common variant in MTNR1B associated with increased risk of type 2 diabetes and impaired early insulin secretion. Nat Genet 41:82–88
183. **Bouatia-Naji N, Bonnefond A, Cavalcanti-Proença C, Sparsø T, Holmkvist J, Marchand M, Delplanque J, Lobbens S, Rocheleau G, Durand E, De Graeve F, Chèvre JC, Borch-Johnsen K, Hartikainen AL, Ruokonen A, Tichet J, Marre M, Weill J, Heude B, Tauber M, Lemaire K, Schuit F, Elliott P, Jørgensen T, Charpentier G, Hadjadj S, Cauchi S, Vaxillaire M, Sladek R, Visvikis-Siest S, Balkau B, Lévy-Marchal C, Pattou F, Meyre D, Blakemore AI, Jarvelin MR, Walley AJ, Hansen T, Dina C, Pedersen O, Froguel P** 2009 A variant near MTNR1B is associated with increased fasting plasma glucose levels and type 2 diabetes risk. Nat Genet 41:89–94
184. **Straub SG, Sharp GW** 2002 Glucose-stimulated signaling pathways in biphasic insulin secretion. Diabetes Metab Res Rev 18:451–463
185. **Doyle ME, Egan JM** 2007 Mechanisms of action of glucagon-like peptide 1 in the pancreas. Pharmacol Ther 113: 546–593
186. **Stumvoll M, Fritsche A, Haring HU** 2002 Clinical characterization of insulin secretion as the basis for genetic analyses. Diabetes 51(Suppl 1):S122–S129
187. **Poulsen P, Levin K, Petersen I, Christensen K, Beck-Nielsen H, Vaag A** 2005 Heritability of insulin secretion, peripheral and hepatic insulin action, and intracellular glucose partitioning in young and old Danish twins. Diabetes 54: 275–283
188. **Lynn S, Evans JC, White C, Frayling TM, Hattersley AT, Turnbull DM, Horikawa Y, Cox NJ, Bell GI, Walker M** 2002 Variation in the calpain-10 gene affects blood glucose levels in the British population. Diabetes 51:247–250
189. **Grarup N, Andersen G, Krarup NT, Albrechtsen A, Schmitz O, Jørgensen T, Borch-Johnsen K, Hansen T, Pedersen O** 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
190. **Pascoe L, Tura A, Patel SK, Ibrahim IM, Ferrannini E, Zeggini E, Weedon MN, Mari A, Hattersley AT, McCarthy MI, Frayling TM, Walker M** 2007 Common variants of the novel type 2 diabetes genes, CDKAL1 and HHEX/IDE, are associated with decreased pancreatic β-cell function. Diabetes 56:3101–3104
191. **Palmer ND, Goodarzi MO, Langefeld CD, Ziegler J, Norris JM, Haffner SM, Bryer-Ash M, Bergman RN, Wagenknecht LE, Taylor KD, Rotter JI, Bowden DW** 2008 Quantitative trait analysis of type 2 diabetes susceptibility loci identified from whole genome association studies in the Insulin Resistance Atherosclerosis Family Study. Diabetes 57:1093–1100
192. **Stancáková A, Pihlajamäki J, Kuusisto J, Stefan N, Fritsche A, Häring H, Andreozzi F, Succurro E, Sesti G, Boesgaard TW, Hansen T, Pedersen O, Jansson PA, Hammarstedt A, Smith U, Laakso M** 2008 SNP rs7754840 of CDKAL1 is associated with impaired insulin secretion in non-diabetic offspring of type 2 diabetic subjects (the EUGENE2 study) and in a large sample of men with normal glucose tolerance. J Clin Endocrinol Metab 93:1924–1930
193. **Ruchat SM, Elks CE, Loos RJ, Vohl MC, Weisnagel SJ, Rankinen T, Bouchard C, Pérusse L** 2009 Association between insulin secretion, insulin sensitivity and type 2 diabetes susceptibility variants identified in genome-wide association studies. Acta Diabetol 46:217–226
194. **Baratta R, Rossetti P, Prudente S, Barbetti F, Sudano D, Nigro A, Farina MG, Pellegrini F, Trischitta V, Frittitta L** 2008 Role of the ENPP1 K121Q polymorphism in glucose homeostasis. Diabetes 57:3360–3364
195. **Staiger H, Machicao F, Stefan N, Tschritter O, Thamer C, Kantartzis K, Schäfer SA, Kirchhoff K, Fritsche A, Häring HU** 2007 Polymorphisms within novel risk loci for type 2 diabetes determine β-cell function. PLoS ONE 2:e832
196. **Pivovarova O, Nikiforova VJ, Pfeiffer AF, Rudovich N** 2009 The influence of genetic variations in HHEX gene on

insulin metabolism in the German MESYBEPO cohort. Diabetes Metab Res Rev 25:156–162

197. **Müssig K, Staiger H, Machicao F, Kirchhoff K, Guthoff M, Schäfer SA, Kantartzis K, Silbernagel G, Stefan N, Holst JJ, Gallwitz B, Häring HU, Fritsche A** 2009 Association of type 2 diabetes candidate polymorphisms in KCNQ1 with incretin and insulin secretion. Diabetes 58:1715–1720
198. **Ling C, Del Guerra S, Lupi R, Rönn T, Granhall C, Luthman H, Masiello P, Marchetti P, Groop L, Del Prato S** 2008 Epigenetic regulation of PPARGC1A in human type 2 diabetic islets and effect on insulin secretion. Diabetologia 51:615–622
199. **Schäfer SA, Tschritter O, Machicao F, Thamer C, Stefan N, Gallwitz B, Holst JJ, Dekker JM, 't Hart LM, Nijpels G, van Haeften TW, Häring HU, Fritsche A** 2007 Impaired glucagon-like peptide-1-induced insulin secretion in carriers of transcription factor 7-like 2 (TCF7L2) gene polymorphisms. Diabetologia 50:2443–2450
200. **Lyssenko V, Lupi R, Marchetti P, Del Guerra S, Orho-Melander M, Almgren P, Sjögren M, Ling C, Eriksson KF, Lethagen AL, Mancarella R, Berglund G, Tuomi T, Nilsson P, Del Prato S, Groop L** 2007 Mechanisms by which common variants in the TCF7L2 gene increase risk of type 2 diabetes. J Clin Invest 117:2155–2163
201. **Florez JC, Jablonski KA, McAteer J, Sandhu MS, Wareham NJ, Barroso I, Franks PW, Altshuler D, Knowler WC** 2008 Testing of diabetes-associated WFS1 polymorphisms in the Diabetes Prevention Program. Diabetologia 51:451–457
202. **Sparsø T, Andersen G, Albrechtsen A, Jørgensen T, Borch-Johnsen K, Sandbaek A, Lauritzen T, Wasson J, Permutt MA, Glaser B, Madsbad S, Pedersen O, Hansen T** 2008 Impact of polymorphisms in WFS1 on prediabetic phenotypes in a population-based sample of middle-aged people with normal and abnormal glucose regulation. Diabetologia 51:1646–1652
203. **Schäfer SA, Müssig K, Staiger H, Machicao F, Stefan N, Gallwitz B, Häring HU, Fritsche A** 2009 Common genetic variation in WFS1 predicts impaired glucagon-like peptide-1-induced insulin secretion. Diabetologia 52:1075–1082
204. **Schwanstecher C, Meyer U, Schwanstecher M** 2002 K(IR)6.2 polymorphism predisposes to type 2 diabetes by inducing overactivity of pancreatic β-cell ATP-sensitive K(+) channels. Diabetes 51:875–879
205. **Schwanstecher C, Neugebauer B, Schulz M, Schwanstecher M** 2002 The common single nucleotide polymorphism E23K in K(IR)6.2 sensitizes pancreatic β-cell ATP-sensitive potassium channels toward activation through nucleoside diphosphates. Diabetes 51(Suppl 3):S363–S367
206. **Riedel MJ, Boora P, Steckley D, de Vries G, Light PE** 2003 Kir6.2 polymorphisms sensitize β-cell ATP-sensitive potassium channels to activation by acyl CoAs: a possible cellular mechanism for increased susceptibility to type 2 diabetes? Diabetes 52:2630–2635
207. **Gross DN, van den Heuvel AP, Birnbaum MJ** 2008 The role of FoxO in the regulation of metabolism. Oncogene 27:2320–2336
208. **Nakae J, Biggs 3rd WH, Kitamura T, Cavenee WK, Wright CV, Arden KC, Accili D** 2002 Regulation of insulin action and pancreatic β-cell function by mutated alleles of the gene encoding forkhead transcription factor Foxo1. Nat Genet 32:245–253
209. **Kitamura T, Nakae J, Kitamura Y, Kido Y, Biggs 3rd WH, Wright CV, White MF, Arden KC, Accili D** 2002 The forkhead transcription factor Foxo1 links insulin signaling to Pdx1 regulation of pancreatic β cell growth. J Clin Invest 110:1839–1847
210. **Okamoto H, Hribal ML, Lin HV, Bennett WR, Ward A, Accili D** 2006 Role of the forkhead protein FoxO1 in β cell compensation to insulin resistance. J Clin Invest 116:775–782
211. **Kodama S, Toyonaga T, Kondo T, Matsumoto K, Tsuruzoe K, Kawashima J, Goto H, Kume K, Kume S, Sakakida M, Araki E** 2005 Enhanced expression of PDX-1 and Ngn3 by exendin-4 during β cell regeneration in STZ-treated mice. Biochem Biophys Res Commun 327:1170-1178
212. **Buteau J, Spatz ML, Accili D** 2006 Transcription factor FoxO1 mediates glucagon-like peptide-1 effects on pancreatic β-cell mass. Diabetes 55:1190–1196
213. **Takamoto I, Terauchi Y, Kubota N, Ohsugi M, Ueki K, Kadowaki T** 2008 Crucial role of insulin receptor substrate-2 in compensatory β-cell hyperplasia in response to high fat diet-induced insulin resistance. Diabetes Obes Metab 10(Suppl 4):147–156
214. **Kaneto H, Miyatsuka T, Shiraiwa T, Yamamoto K, Kato K, Fujitani Y, Matsuoka TA** 2007 Crucial role of PDX-1 in pancreas development, β-cell differentiation, and induction of surrogate β-cells. Curr Med Chem 14:1745–1752
215. **Waldegger S, Barth P, Raber G, Lang F** 1997 Cloning and characterization of a putative human serine/threonine protein kinase transcriptionally modified during anisotonic and isotonic alterations of cell volume. Proc Natl Acad Sci USA 94:4440–4445
216. **Dieter M, Palmada M, Rajamanickam J, Aydin A, Busjahn A, Boehmer C, Luft FC, Lang F** 2004 Regulation of glucose transporter SGLT1 by ubiquitin ligase Nedd4–2 and kinases SGK1, SGK3, and PKB. Obes Res 12:862–870
217. **Grahammer F, Henke G, Sandu C, Rexhepaj R, Hussain A, Friedrich B, Risler T, Metzger M, Just L, Skutella T, Wulff P, Kuhl D, Lang F** 2006 Intestinal function of gene-targeted mice lacking serum- and glucocorticoid-inducible kinase 1. Am J Physiol Gastrointest Liver Physiol 290:G1114–G1123
218. **Palmada M, Boehmer C, Akel A, Rajamanickam J, Jeyaraj S, Keller K, Lang F** 2006 SGK1 kinase upregulates GLUT1 activity and plasma membrane expression. Diabetes 55: 421–427
219. **Jeyaraj S, Boehmer C, Lang F, Palmada M** 2007 Role of SGK1 kinase in regulating glucose transport via glucose transporter GLUT4. Biochem Biophys Res Commun 356: 629–635
220. **Lang F, Böhmer C, Palmada M, Seebohm G, Strutz-Seebohm N, Vallon V** 2006 (Patho)physiological significance of the serum- and glucocorticoid-inducible kinase isoforms. Physiol Rev 86:1151–1178
221. **Ullrich S, Berchtold S, Ranta F, Seebohm G, Henke G, Lupescu A, Mack AF, Chao CM, Su J, Nitschke R, Alexander D, Friedrich B, Wulff P, Kuhl D, Lang F** 2005 Serum- and glucocorticoid-inducible kinase 1 (SGK1) mediates glucocorticoid-induced inhibition of insulin secretion. Diabetes 54: 1090–1099
222. **Ullrich S, Zhang Y, Avram D, Ranta F, Kuhl D, Häring HU, Lang F** 2007 Dexamethasone increases Na+/K+ AT-

Pase activity in insulin secreting cells through SGK1. Biochem Biophys Res Commun 352:662–667
223. **Stumvoll M, Fritsche A, Madaus A, Stefan N, Weisser M, Machicao F, Häring H** 2001 Functional significance of the UCSNP-43 polymorphism in the CAPN10 gene for proinsulin processing and insulin secretion in nondiabetic Germans. Diabetes 50:2161–2163
224. **Groenewoud MJ, Dekker JM, Fritsche A, Reiling E, Nijpels G, Heine RJ, Maassen JA, Machicao F, Schäfer SA, Häring HU, 't Hart LM, van Haeften TW** 2008 Variants of CDKAL1 and IGF2BP2 affect first-phase insulin secretion during hyperglycaemic clamps. Diabetologia 51:1659–1663
225. **Staiger H, Stancáková A, Zilinskaite J, Vänttinen M, Hansen T, Marini MA, Hammarstedt A, Jansson PA, Sesti G, Smith U, Pedersen O, Laakso M, Stefan N, Fritsche A, Häring HU** 2008 A candidate type 2 diabetes polymorphism near the HHEX locus affects acute glucose-stimulated insulin release in European populations: results from the EUGENE2 study. Diabetes 57:514–517
226. **Staiger H, Machicao F, Schäfer SA, Kirchhoff K, Kantartzis K, Guthoff M, Silbernagel G, Stefan N, Häring HU, Fritsche A** 2008 Polymorphisms within the novel type 2 diabetes risk locus MTNR1B determine β-cell function. PLoS ONE 3:e3962
227. **Boesgaard TW, Zilinskaite J, Vänttinen M, Laakso M, Jansson PA, Hammarstedt A, Smith U, Stefan N, Fritsche A, Häring H, Hribal M, Sesti G, Zobel DP, Pedersen O, Hansen T** 2008 The common SLC30A8 Arg325Trp variant is associated with reduced first-phase insulin release in 846 non-diabetic offspring of type 2 diabetes patients—the EUGENE2 study. Diabetologia 51:816–820
228. **Turner MD, Cassell PG, Hitman GA** 2005 Calpain-10: from genome search to function. Diabetes Metab Res Rev 21:505–514
229. **Marshall C, Hitman GA, Partridge CJ, Clark A, Ma H, Shearer TR, Turner MD** 2005 Evidence that an isoform of calpain-10 is a regulator of exocytosis in pancreatic β-cells. Mol Endocrinol 19:213–224
230. **Turner MD, Fulcher FK, Jones CV, Smith BT, Aganna E, Partridge CJ, Hitman GA, Clark A, Patel YM** 2007 Calpain facilitates actin reorganization during glucose-stimulated insulin secretion. Biochem Biophys Res Commun 352:650–655
231. **Bort R, Martinez-Barbera JP, Beddington RS, Zaret KS** 2004 Hex homeobox gene-dependent tissue positioning is required for organogenesis of the ventral pancreas. Development 131:797–806
232. **Chimienti F, Devergnas S, Favier A, Seve M** 2004 Identification and cloning of a β-cell-specific zinc transporter, ZnT-8, localized into insulin secretory granules. Diabetes 53:2330–2337
233. **Chimienti F, Devergnas S, Pattou F, Schuit F, Garcia-Cuenca R, Vandewalle B, Kerr-Conte J, Van Lommel L, Grunwald D, Favier A, Seve M** 2006 In vivo expression and functional characterization of the zinc transporter ZnT8 in glucose-induced insulin secretion. J Cell Sci 119:4199–4206
234. **Scarpulla RC** 2008 Transcriptional paradigms in mammalian mitochondrial biogenesis and function. Physiol Rev 88:611–638
235. **Mulder H, Ling C** 2009 Mitochondrial dysfunction in pancreatic β-cells in type 2 diabetes. Mol Cell Endocrinol 297:34–40
236. **Jin T, Liu L** 2008 The Wnt signaling pathway effector TCF7L2 and type 2 diabetes mellitus. Mol Endocrinol 22:2383–2392
237. **Shu L, Sauter NS, Schulthess FT, Matveyenko AV, Oberholzer J, Maedler K** 2008 Transcription factor 7-like 2 regulates β-cell survival and function in human pancreatic islets. Diabetes 57:645–653
238. **Loder MK, da Silva Xavier G, McDonald A, Rutter GA** 2008 TCF7L2 controls insulin gene expression and insulin secretion in mature pancreatic β-cells. Biochem Soc Trans 36:357–359
239. **Shu L, Matveyenko AV, Kerr-Conte J, Cho JH, McIntosh CH, Maedler K** 2009 Decreased TCF7L2 protein levels in type 2 diabetes mellitus correlate with downregulation of GIP- and GLP1 receptors and impaired β-cell function. Hum Mol Genet 18:2388–2399
240. **Ishihara H, Takeda S, Tamura A, Takahashi R, Yamaguchi S, Takei D, Yamada T, Inoue H, Soga H, Katagiri H, Tanizawa Y, Oka Y** 2004 Disruption of the WFS1 gene in mice causes progressive β-cell loss and impaired stimulus-secretion coupling in insulin secretion. Hum Mol Genet 13:1159–1170
241. **Riggs AC, Bernal-Mizrachi E, Ohsugi M, Wasson J, Fatrai S, Welling C, Murray J, Schmidt RE, Herrera PL, Permutt MA** 2005 Mice conditionally lacking the Wolfram gene in pancreatic islet β cells exhibit diabetes as a result of enhanced endoplasmic reticulum stress and apoptosis. Diabetologia 48:2313–2321
242. **Yamada T, Ishihara H, Tamura A, Takahashi R, Yamaguchi S, Takei D, Tokita A, Satake C, Tashiro F, Katagiri H, Aburatani H, Miyazaki J, Oka Y** 2006 WFS1-deficiency increases endoplasmic reticulum stress, impairs cell cycle progression and triggers the apoptotic pathway specifically in pancreatic β-cells. Hum Mol Genet 15:1600–1609
243. **Steiner DF, James DE** 1992 Cellular and molecular biology of the β cell. Diabetologia 35(Suppl 2):S41–S48
244. **Loos RJ, Franks PW, Francis RW, Barroso I, Gribble FM, Savage DB, Ong KK, O'Rahilly S, Wareham NJ** 2007 TCF7L2 polymorphisms modulate proinsulin levels and β-cell function in a British Europid population. Diabetes 56:1943–1947
245. **Kirchhoff K, Machicao F, Haupt A, Schäfer SA, Tschritter O, Staiger H, Stefan N, Häring HU, Fritsche A** 2008 Polymorphisms in the TCF7L2, CDKAL1 and SLC30A8 genes are associated with impaired proinsulin conversion. Diabetologia 51:597–601
246. **Stolerman ES, Manning AK, McAteer JB, Fox CS, Dupuis J, Meigs JB, Florez JC** 2009 TCF7L2 variants are associated with increased proinsulin/insulin ratios but not obesity traits in the Framingham Heart Study. Diabetologia 52:614–620
247. **Haupt A, Guthoff M, Schäfer SA, Kirchhoff K, Machicao F, Gallwitz B, Staiger H, Stefan N, Fritsche A, Häring HU** 2009 The inhibitory effect of recent type 2 diabetes risk loci on insulin secretion is modulated by insulin sensitivity. J Clin Endocrinol Metab 94:1775–1780
248. **Qatanani M, Lazar MA** 2007 Mechanisms of obesity-associated insulin resistance: many choices on the menu. Genes Dev 21:1443–1455
249. **Østergård T, Jessen N, Schmitz O, Mandarino LJ** 2007

The effect of exercise, training, and inactivity on insulin sensitivity in diabetics and their relatives: what is new? Appl Physiol Nutr Metab 32:541–548

250. **Stumvoll M, Tschritter O, Fritsche A, Staiger H, Renn W, Weisser M, Machicao F, Häring H** 2002 Association of the T-G polymorphism in adiponectin (exon 2) with obesity and insulin sensitivity: interaction with family history of type 2 diabetes. Diabetes 51:37–41
251. **Menzaghi C, Ercolino T, Di Paola R, Berg AH, Warram JH, Scherer PE, Trischitta V, Doria A** 2002 A haplotype at the adiponectin locus is associated with obesity and other features of the insulin resistance syndrome. Diabetes 51: 2306–2312
252. **Filippi E, Sentinelli F, Trischitta V, Romeo S, Arca M, Leonetti F, Di Mario U, Baroni MG** 2004 Association of the human adiponectin gene and insulin resistance. Eur J Hum Genet 12:199–205
253. **Ukkola O, Santaniemi M, Rankinen T, Leon AS, Skinner JS, Wilmore JH, Rao DC, Bergman R, Kesäniemi YA, Bouchard C** 2005 Adiponectin polymorphisms, adiposity and insulin metabolism: HERITAGE family study and Oulu diabetic study. Ann Med 37:141–150
254. **Richardson DK, Schneider J, Fourcaudot MJ, Rodriguez LM, Arya R, Dyer TD, Almasy L, Blangero J, Stern MP, Defronzo RA, Duggirala R, Jenkinson CP** 2006 Association between variants in the genes for adiponectin and its receptors with insulin resistance syndrome (IRS)-related phenotypes in Mexican Americans. Diabetologia 49:2317–2328
255. **Petrone A, Zavarella S, Caiazzo A, Leto G, Spoletini M, Potenziani S, Osborn J, Vania A, Buzzetti R** 2006 The promoter region of the adiponectin gene is a determinant in modulating insulin sensitivity in childhood obesity. Obesity (Silver Spring) 14:1498–1504
256. **Buzzetti R, Petrone A, Zavarella S, Zampetti S, Spoletini M, Potenziani S, Leto G, Osborn J, Leonetti F** 2007 The glucose clamp reveals an association between adiponectin gene polymorphisms and insulin sensitivity in obese subjects. Int J Obes (Lond) 31:424–428
257. **Rasmussen-Torvik LJ, Pankow JS, Jacobs Jr DR, Steinberger J, Moran A, Sinaiko AR** 2009 The association of SNPs in ADIPOQ, ADIPOR1, and ADIPOR2 with insulin sensitivity in a cohort of adolescents and their parents. Hum Genet 125: 21–28
258. **Dahlman I, Eriksson P, Kaaman M, Jiao H, Lindgren CM, Kere J, Arner P** 2004 α2-Heremans-Schmid glycoprotein gene polymorphisms are associated with adipocyte insulin action. Diabetologia 47:1974–1979
259. **Baier LJ, Permana PA, Yang X, Pratley RE, Hanson RL, Shen GQ, Mott D, Knowler WC, Cox NJ, Horikawa Y, Oda N, Bell GI, Bogardus C** 2000 A calpain-10 gene polymorphism is associated with reduced muscle mRNA levels and insulin resistance. J Clin Invest 106:R69–R73
260. **Elbein SC, Chu W, Ren Q, Hemphill C, Schay J, Cox NJ, Hanis CL, Hasstedt SJ** 2002 Role of calpain-10 gene variants in familial type 2 diabetes in Caucasians. J Clin Endocrinol Metab 87:650–654
261. **Orho-Melander M, Klannemark M, Svensson MK, Ridderstråle M, Lindgren CM, Groop L** 2002 Variants in the calpain-10 gene predispose to insulin resistance and elevated free fatty acid levels. Diabetes 51:2658–2664
262. **Tripathy D, Eriksson KF, Orho-Melander M, Fredriksson J, Ahlqvist G, Groop L** 2004 Parallel manifestation of insulin resistance and β cell decompensation is compatible with a common defect in type 2 diabetes. Diabetologia 47:782–793
263. **Goodarzi MO, Taylor KD, Guo X, Quiñones MJ, Cui J, Li Y, Saad MF, Yang H, Hsueh WA, Hodis HN, Rotter JI** 2005 Association of the diabetes gene calpain-10 with subclinical atherosclerosis: the Mexican-American Coronary Artery Disease Study. Diabetes 54:1228–1232
264. **Sáez ME, González-Sánchez JL, Ramírez-Lorca R, Martínez-Larrad MT, Zabena C, González A, Morón FJ, Ruiz A, Serrano-Ríos M** 2008 The CAPN10 gene is associated with insulin resistance phenotypes in the Spanish population. PLoS ONE 3:e2953
265. **Pizzuti A, Frittitta L, Argiolas A, Baratta R, Goldfine ID, Bozzali M, Ercolino T, Scarlato G, Iacoviello L, Vigneri R, Tassi V, Trischitta V** 1999 A polymorphism (K121Q) of the human glycoprotein PC-1 gene coding region is strongly associated with insulin resistance. Diabetes 48: 1881–1884
266. **Frittitta L, Baratta R, Spampinato D, Di Paola R, Pizzuti A, Vigneri R, Trischitta V** 2001 The Q121 PC-1 variant and obesity have additive and independent effects in causing insulin resistance. J Clin Endocrinol Metab 86:5888–5891
267. **Kubaszek A, Pihlajamäki J, Karhapää P, Vauhkonen I, Laakso M** 2003 The K121Q polymorphism of the PC-1 gene is associated with insulin resistance but not with dyslipidemia. Diabetes Care 26:464–467
268. **Abate N, Carulli L, Cabo-Chan Jr A, Chandalia M, Snell PG, Grundy SM** 2003 Genetic polymorphism PC-1 K121Q and ethnic susceptibility to insulin resistance. J Clin Endocrinol Metab 88:5927–5934
269. **Böttcher Y, Körner A, Reinehr T, Enigk B, Kiess W, Stumvoll M, Kovacs P** 2006 ENPP1 variants and haplotypes predispose to early onset obesity and impaired glucose and insulin metabolism in German obese children. J Clin Endocrinol Metab 91:4948–4952
270. **Perticone F, Maio R, Di Paola R, Sciacqua A, Marucci A, De Cosmo S, Perticone M, Sesti G, Trischitta V** 2007 Role of PC-1 and ACE genes on insulin resistance and cardiac mass in never-treated hypertensive patients. Suggestive evidence for a digenic additive modulation. Nutr Metab Cardiovasc Dis 17:181–187
271. **Stolerman ES, Manning AK, McAteer JB, Dupuis J, Fox CS, Cupples LA, Meigs JB, Florez JC** 2008 Haplotype structure of the ENPP1 gene and nominal association of the K121Q missense single nucleotide polymorphism with glycemic traits in the Framingham Heart Study. Diabetes 57: 1971–1977
272. **Deeb SS, Fajas L, Nemoto M, Pihlajamäki J, Mykkänen L, Kuusisto J, Laakso M, Fujimoto W, Auwerx J** 1998 A Pro12Ala substitution in PPARγ2 associated with decreased receptor activity, lower body mass index and improved insulin sensitivity. Nat Genet 20:284–287
273. **Koch M, Rett K, Maerker E, Volk A, Haist K, Deninger M, Renn W, Häring HU** 1999 The PPARγ2 amino acid polymorphism Pro 12 Ala is prevalent in offspring of type II diabetic patients and is associated to increased insulin sensitivity in a subgroup of obese subjects. Diabetologia 42: 758–762
274. **Jacob S, Stumvoll M, Becker R, Koch M, Nielsen M, Löblein K, Maerker E, Volk A, Renn W, Balletshofer B,**

Machicao F, Rett K, Häring HU 2000 The PPARγ2 polymorphism pro12Ala is associated with better insulin sensitivity in the offspring of type 2 diabetic patients. Horm Metab Res 32:413–416

275. **Stumvoll M, Wahl HG, Löblein K, Becker R, Machicao F, Jacob S, Häring H** 2001 Pro12Ala polymorphism in the peroxisome proliferator-activated receptor-γ2 gene is associated with increased antilipolytic insulin sensitivity. Diabetes 50:876–881
276. **Ek J, Andersen G, Urhammer SA, Hansen L, Carstensen B, Borch-Johnsen K, Drivsholm T, Berglund L, Hansen T, Lithell H, Pedersen O** 2001 Studies of the Pro12Ala polymorphism of the peroxisome proliferator-activated receptor-γ2 (PPAR-γ2) gene in relation to insulin sensitivity among glucose tolerant Caucasians. Diabetologia 44:1170-1176
277. **Chuang LM, Hsiung CA, Chen YD, Ho LT, Sheu WH, Pei D, Nakatsuka CH, Cox D, Pratt RE, Lei HH, Tai TY** 2001 Sibling-based association study of the PPARγ2 Pro12Ala polymorphism and metabolic variables in Chinese and Japanese hypertension families: a SAPPHIRe study. Stanford Asian-Pacific Program in Hypertension and Insulin Resistance. J Mol Med 79:656–664
278. **González Sánchez JL, Serrano Ríos M, Fernández Perez C, Laakso M, Martínez Larrad MT** 2002 Effect of the Pro12Ala polymorphism of the peroxisome proliferator-activated receptor γ-2 gene on adiposity, insulin sensitivity and lipid profile in the Spanish population. Eur J Endocrinol 147:495–501
279. **Poulsen P, Andersen G, Fenger M, Hansen T, Echwald SM, Vølund A, Beck-Nielsen H, Pedersen O, Vaag A** 2003 Impact of two common polymorphisms in the PPARγ gene on glucose tolerance and plasma insulin profiles in monozygotic and dizygotic twins: thrifty genotype, thrifty phenotype, or both? Diabetes 52:194–198
280. **Li S, Chen W, Srinivasan SR, Boerwinkle E, Berenson GS** 2003 The peroxisome proliferator-activated receptor-γ2 gene polymorphism (Pro12Ala) beneficially influences insulin resistance and its tracking from childhood to adulthood: the Bogalusa Heart Study. Diabetes 52:1265–1269
281. **Buzzetti R, Petrone A, Ribaudo MC, Alemanno I, Zavarella S, Mein CA, Maiani F, Tiberti C, Baroni MG, Vecci E, Arca M, Leonetti F, Di Mario U** 2004 The common PPAR-γ2 Pro12Ala variant is associated with greater insulin sensitivity. Eur J Hum Genet 12:1050–1054
282. **Tavares V, Hirata RD, Rodrigues AC, Monte O, Salles JE, Scalissi N, Speranza AC, Hirata MH** 2005 Association between Pro12Ala polymorphism of the PPAR-γ2 gene and insulin sensitivity in Brazilian patients with type-2 diabetes mellitus. Diabetes Obes Metab 7:605–611
283. **Tönjes A, Scholz M, Loeffler M, Stumvoll M** 2006 Association of Pro12Ala polymorphism in peroxisome proliferator-activated receptor γ with Pre-diabetic phenotypes: meta-analysis of 57 studies on nondiabetic individuals. Diabetes Care 29:2489–2497
284. **Fanelli M, Filippi E, Sentinelli F, Romeo S, Fallarino M, Buzzetti R, Leonetti F, Baroni MG** 2005 The Gly482Ser missense mutation of the peroxisome proliferator-activated receptor γ coactivator-1 α (PGC-1 α) gene associates with reduced insulin sensitivity in normal and glucose-intolerant obese subjects. Dis Markers 21:175–180
285. **Stefan N, Thamer C, Staiger H, Machicao F, Machann J, Schick F, Venter C, Niess A, Laakso M, Fritsche A, Häring HU** 2007 Genetic variations in PPARD and PPARGC1A determine mitochondrial function and change in aerobic physical fitness and insulin sensitivity during lifestyle. J Clin Endocrinol Metab 92:1827–1833
286. **Reinehr T, Friedel S, Mueller TD, Toschke AM, Hebebrand J, Hinney A** 2008 Evidence for an influence of TCF7L2 polymorphism rs7903146 on insulin resistance and sensitivity indices in overweight children and adolescents during a lifestyle intervention. Int J Obes (Lond) 32:1521–1524
287. **Musso G, Gambino R, Pacini G, Pagano G, Durazzo M, Cassader M** 2009 Transcription factor 7-like 2 polymorphism modulates glucose and lipid homeostasis, adipokine profile, and hepatocyte apoptosis in NASH. Hepatology 49:426–435
288. **Fajas L, Auboeuf D, Raspé E, Schoonjans K, Lefebvre AM, Saladin R, Najib J, Laville M, Fruchart JC, Deeb S, Vidal-Puig A, Flier J, Briggs MR, Staels B, Vidal H, Auwerx J** 1997 The organization, promoter analysis, and expression of the human PPARγ gene. J Biol Chem 272:18779–18789
289. **Tontonoz P, Spiegelman BM** 2008 Fat and beyond: the diverse biology of PPARγ. Annu Rev Biochem 77:289–312
290. **Spiegelman BM** 1998 PPAR-γ: adipogenic regulator and thiazolidinedione receptor. Diabetes 47:507–514
291. **Stumvoll M, Häring HU** 2002 Glitazones: clinical effects and molecular mechanisms. Ann Med 34:217–224
292. **Wolf G** 2008 Role of fatty acids in the development of insulin resistance and type 2 diabetes mellitus. Nutr Rev 66:597–600
293. **Stefan N, Kantartzis K, Häring HU** 2008 Causes and metabolic consequences of fatty liver. Endocr Rev 29:939–960
294. **Maddux BA, Sbraccia P, Kumakura S, Sasson S, Youngren J, Fisher A, Spencer S, Grupe A, Henzel W, Stewart TA** 1995 Membrane glycoprotein PC-1 and insulin resistance in non-insulin-dependent diabetes mellitus. Nature 373:448–451
295. **Belfiore A, Costantino A, Frasca F, Pandini G, Mineo R, Vigneri P, Maddux B, Goldfine ID, Vigneri R** 1996 Overexpression of membrane glycoprotein PC-1 in MDA-MB231 breast cancer cells is associated with inhibition of insulin receptor tyrosine kinase activity. Mol Endocrinol 10:1318–1326
296. **Grupe A, Alleman J, Goldfine ID, Sadick M, Stewart TA** 1995 Inhibition of insulin receptor phosphorylation by PC-1 is not mediated by the hydrolysis of adenosine triphosphate or the generation of adenosine. J Biol Chem 270:22085–22088
297. **Maddux BA, Goldfine ID** 2000 Membrane glycoprotein PC-1 inhibition of insulin receptor function occurs via direct interaction with the receptor α-subunit. Diabetes 49:13–19
298. **Dong H, Maddux BA, Altomonte J, Meseck M, Accili D, Terkeltaub R, Johnson K, Youngren JF, Goldfine ID** 2005 Increased hepatic levels of the insulin receptor inhibitor, PC-1/NPP1, induce insulin resistance and glucose intolerance. Diabetes 54:367–372
299. **Maddux BA, Chang YN, Accili D, McGuinness OP, Youngren JF, Goldfine ID** 2006 Overexpression of the insulin receptor inhibitor PC-1/ENPP1 induces insulin resistance and hyperglycemia. Am J Physiol Endocrinol Metab 290:E746–E749
300. **Frittitta L, Youngren J, Vigneri R, Maddux BA, Trischitta**

V, Goldfine ID 1996 PC-1 content in skeletal muscle of non-obese, non-diabetic subjects: relationship to insulin receptor tyrosine kinase and whole body insulin sensitivity. Diabetologia 39:1190–1195

301. **Frittitta L, Youngren JF, Sbraccia P, D'Adamo M, Buongiorno A, Vigneri R, Goldfine ID, Trischitta V** 1997 Increased adipose tissue PC-1 protein content, but not tumour necrosis factor-α gene expression, is associated with a reduction of both whole body insulin sensitivity and insulin receptor tyrosine-kinase activity. Diabetologia 40:282–289
302. **Costanzo BV, Trischitta V, Di Paola R, Spampinato D, Pizzuti A, Vigneri R, Frittitta L** 2001 The Q allele variant (GLN121) of membrane glycoprotein PC-1 interacts with the insulin receptor and inhibits insulin signaling more effectively than the common K allele variant (LYS121). Diabetes 50:831–836
303. **Yang X, Pratley RE, Baier LJ, Horikawa Y, Bell GI, Bogardus C, Permana PA** 2001 Reduced skeletal muscle calpain-10 transcript level is due to a cumulative decrease in major isoforms. Mol Genet Metab 73:111–113
304. **Logie LJ, Brown AE, Yeaman SJ, Walker M** 2005 Calpain inhibition and insulin action in cultured human muscle cells. Mol Genet Metab 85:54–60
305. **Brown AE, Yeaman SJ, Walker M** 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
306. **Paul DS, Harmon AW, Winston CP, Patel YM** 2003 Calpain facilitates GLUT4 vesicle translocation during insulin-stimulated glucose uptake in adipocytes. Biochem J 376:625–632
307. **Turner MD** 2007 Coordinated control of both insulin secretion and insulin action through calpain-10-mediated regulation of exocytosis? Mol Genet Metab 91:305–307
308. **Guerre-Millo M** 2008 Adiponectin: an update. Diabetes Metab 34:12–18
309. **Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, Hotta K, Shimomura I, Nakamura T, Miyaoka K, Kuriyama H, Nishida M, Yamashita S, Okubo K, Matsubara K, Muraguchi M, Ohmoto Y, Funahashi T, Matsuzawa Y** 1999 Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun 257:79–83
310. **Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, Iwahashi H, Kuriyama H, Ouchi N, Maeda K, Nishida M, Kihara S, Sakai N, Nakajima T, Hasegawa K, Muraguchi M, Ohmoto Y, Nakamura T, Yamashita S, Hanafusa T, Matsuzawa Y** 2000 Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol 20:1595–1599
311. **Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, Tataranni PA** 2001 Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab 86:1930–1935
312. **Staiger H, Tschritter O, Machann J, Thamer C, Fritsche A, Maerker E, Schick F, Häring HU, Stumvoll M** 2003 Relationship of serum adiponectin and leptin concentrations with body fat distribution in humans. Obes Res 11:368–372
313. **Cnop M, Havel PJ, Utzschneider KM, Carr DB, Sinha MK, Boyko EJ, Retzlaff BM, Knopp RH, Brunzell JD, Kahn SE** 2003 Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. Diabetologia 46:459–469
314. **Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, Mori Y, Ide T, Murakami K, Tsuboyama-Kasaoka N, Ezaki O, Akanuma Y, Gavrilova O, Vinson C, Reitman ML, Kagechika H, Shudo K, Yoda M, Nakano Y, Tobe K, Nagai R, Kimura S, Tomita M, Froguel P, Kadowaki T** 2001 The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med 7:941–946
315. **Fruebis J, Tsao TS, Javorschi S, Ebbets-Reed D, Erickson MR, Yen FT, Bihain BE, Lodish HF** 2001 Proteolytic cleavage product of 30-kDa adipocyte complement-related protein increases fatty acid oxidation in muscle and causes weight loss in mice. Proc Natl Acad Sci USA 98:2005–2010
316. **Tomas E, Tsao TS, Saha AK, Murrey HE, Zhang Cc C, Itani SI, Lodish HF, Ruderman NB** 2002 Enhanced muscle fat oxidation and glucose transport by ACRP30 globular domain: acetyl-CoA carboxylase inhibition and AMP-activated protein kinase activation. Proc Natl Acad Sci USA 99:16309–16313
317. **Yamauchi T, Kamon J, Minokoshi Y, Ito Y, Waki H, Uchida S, Yamashita S, Noda M, Kita S, Ueki K, Eto K, Akanuma Y, Froguel P, Foufelle F, Ferre P, Carling D, Kimura S, Nagai R, Kahn BB, Kadowaki T** 2002 Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nat Med 8:1–8
318. **Menzaghi C, Ercolino T, Salvemini L, Coco A, Kim SH, Fini G, Doria A, Trischitta V** 2004 Multigenic control of serum adiponectin levels: evidence for a role of the APM1 gene and a locus on 14q13. Physiol Genomics 19:170–174
319. **Qi L, Li T, Rimm E, Zhang C, Rifai N, Hunter D, Doria A, Hu FB** 2005 The +276 polymorphism of the APM1 gene, plasma adiponectin concentration, and cardiovascular risk in diabetic men. Diabetes 54:1607–1610
320. **González-Sánchez JL, Zabena CA, Martínez-Larrad MT, Fernández-Pérez C, Pérez-Barba M, Laakso M, Serrano-Ríos M** 2005 An SNP in the adiponectin gene is associated with decreased serum adiponectin levels and risk for impaired glucose tolerance. Obes Res 13:807–812
321. **Mousavinasab F, Tähtinen T, Jokelainen J, Koskela P, Vanhala M, Oikarinen J, Keinänen-Kiukaanniemi S, Laakso M** 2006 Common polymorphisms (single-nucleotide polymorphisms SNP+45 and SNP+276) of the adiponectin gene regulate serum adiponectin concentrations and blood pressure in young Finnish men. Mol Genet Metab 87:147–151
322. **Woo JG, Dolan LM, Deka R, Kaushal RD, Shen Y, Pal P, Daniels SR, Martin LJ** 2006 Interactions between noncontiguous haplotypes in the adiponectin gene ACDC are associated with plasma adiponectin. Diabetes 55:523–529
323. **Mootha VK, Lindgren CM, Eriksson KF, Subramanian A, Sihag S, Lehar J, Puigserver P, Carlsson E, Ridderstråle M, Laurila E, Houstis N, Daly MJ, Patterson N, Mesirov JP, Golub TR, Tamayo P, Spiegelman B, Lander ES, Hirschhorn JN, Altshuler D, Groop LC** 2003 PGC-1α-responsive genes

involved in oxidative phosphorylation are coordinately downregulated in human diabetes. Nat Genet 34:267–273
324. **Mootha VK, Handschin C, Arlow D, Xie X, St Pierre J, Sihag S, Yang W, Altshuler D, Puigserver P, Patterson N, Willy PJ, Schulman IG, Heyman RA, Lander ES, Spiegelman BM** 2004 Errα and Gabpa/b specify PGC-1α-dependent oxidative phosphorylation gene expression that is altered in diabetic muscle. Proc Natl Acad Sci USA 101: 6570–6575
325. **Dressel U, Allen TL, Pippal JB, Rohde PR, Lau P, Muscat GE** 2003 The peroxisome proliferator-activated receptor β/δ agonist, GW501516, regulates the expression of genes involved in lipid catabolism and energy uncoupling in skeletal muscle cells. Mol Endocrinol 17:2477–2493
326. **Kim JA, Wei Y, Sowers JR** 2008 Role of mitochondrial dysfunction in insulin resistance. Circ Res 102:401–414
327. **Højlund K, Mogensen M, Sahlin K, Beck-Nielsen H** 2008 Mitochondrial dysfunction in type 2 diabetes and obesity. Endocrinol Metab Clin North Am 37:713–731, x
328. **Mussig K, Staiger H, Machicao F, Machann J, Hennige AM, Schick F, Claussen CD, Fritsche A, Haring HU, Stefan N** 8 April 2009 AHSG gene variation is not associated with regional body fat distribution—a magnetic resonance study. Exp Clin Endocrinol Diabetes 10.1055/s-0028–1103299
329. **Stefan N, Hennige AM, Staiger H, Machann J, Schick F, Kröber SM, Machicao F, Fritsche A, Häring HU** 2006 α2-Heremans-Schmid glycoprotein/fetuin-A is associated with insulin resistance and fat accumulation in the liver in humans. Diabetes Care 29:853–857
330. **Mori K, Emoto M, Yokoyama H, Araki T, Teramura M, Koyama H, Shoji T, Inaba M, Nishizawa Y** 2006 Association of serum fetuin-A with insulin resistance in type 2 diabetic and nondiabetic subjects. Diabetes Care 29:468
331. **Auberger P, Falquerho L, Contreres JO, Pages G, Le Cam G, Rossi B, Le Cam A** 1989 Characterization of a natural inhibitor of the insulin receptor tyrosine kinase: cDNA cloning, purification, and anti-mitogenic activity. Cell 58: 631–640
332. **Rauth G, Pöschke O, Fink E, Eulitz M, Tippmer S, Kellerer M, Häring HU, Nawratil P, Haasemann M, Jahnen-Dechent W** 1992 The nucleotide and partial amino acid sequences of rat fetuin. Identity with the natural tyrosine kinase inhibitor of the rat insulin receptor. Eur J Biochem 204:523–529
333. **Srinivas PR, Wagner AS, Reddy LV, Deutsch DD, Leon MA, Goustin AS, Grunberger G** 1993 Serum α 2-HS-glycoprotein is an inhibitor of the human insulin receptor at the tyrosine kinase level. Mol Endocrinol 7:1445–1455
334. **Mathews ST, Srinivas PR, Leon MA, Grunberger G** 1997 Bovine fetuin is an inhibitor of insulin receptor tyrosine kinase. Life Sci 61:1583–1592
335. **Mathews ST, Chellam N, Srinivas PR, Cintron VJ, Leon MA, Goustin AS, Grunberger G** 2000 α2-HSG, a specific inhibitor of insulin receptor autophosphorylation, interacts with the insulin receptor. Mol Cell Endocrinol 164: 87–98
336. **Hennige AM, Staiger H, Wicke C, Machicao F, Fritsche A, Häring HU, Stefan N** 2008 Fetuin-A induces cytokine expression and suppresses adiponectin production. PLoS ONE 3:e1765
337. **Shimomura I, Shimano H, Horton JD, Goldstein JL, Brown MS** 1997 Differential expression of exons 1a and 1c in mRNAs for sterol regulatory element binding protein-1 in human and mouse organs and cultured cells. J Clin Invest 99:838–845
338. **Guillou H, Martin PG, Pineau T** 2008 Transcriptional regulation of hepatic fatty acid metabolism. Subcell Biochem 49:3–47
339. **Streicher R, Kotzka J, Müller-Wieland D, Siemeister G, Munck M, Avci H, Krone W** 1996 SREBP-1 mediates activation of the low density lipoprotein receptor promoter by insulin and insulin-like growth factor-I. J Biol Chem 271:7128–7133
340. **Kim JB, Sarraf P, Wright M, Yao KM, Mueller E, Solanes G, Lowell BB, Spiegelman BM** 1998 Nutritional and insulin regulation of fatty acid synthetase and leptin gene expression through ADD1/SREBP1. J Clin Invest 101:1–9
341. **Fleischmann M, Iynedjian PB** 2000 Regulation of sterol regulatory-element binding protein 1 gene expression in liver: role of insulin and protein kinase B/cAkt. Biochem J 349:13–17
342. **Ribaux PG, Iynedjian PB** 2003 Analysis of the role of protein kinase B (cAKT) in insulin-dependent induction of glucokinase and sterol regulatory element-binding protein 1 (SREBP1) mRNAs in hepatocytes. Biochem J 376:697–705
343. **Valera Mora ME, Scarfone A, Calvani M, Greco AV, Mingrone G** 2003 Insulin clearance in obesity. J Am Coll Nutr 22:487–493
344. **Tschritter O, Fritsche A, Stefan N, Haap M, Thamer C, Bachmann O, Dahl D, Maerker E, Teigeler A, Machicao F, Häring H, Stumvoll M** 2003 Increased insulin clearance in peroxisome proliferator-activated receptor γ2 Pro12Ala. Metabolism 52:778–783
345. **Kotronen A, Vehkavaara S, Seppälä-Lindroos A, Bergholm R, Yki-Järvinen H** 2007 Effect of liver fat on insulin clearance. Am J Physiol Endocrinol Metab 293:E1709–E1715
346. **Havrankova J, Roth J, Brownstein M** 1978 Insulin receptors are widely distributed in the central nervous system of the rat. Nature 272:827–829
347. **van Houten M, Posner BI, Kopriwa BM, Brawer JR** 1979 Insulin-binding sites in the rat brain: *in vivo* localization to the circumventricular organs by quantitative radioautography. Endocrinology 105:666–673
348. **Plum L, Belgardt BF, Brüning JC** 2006 Central insulin action in energy and glucose homeostasis. J Clin Invest 116:1761–1766
349. **van der Heide LP, Ramakers GM, Smidt MP** 2006 Insulin signaling in the central nervous system: learning to survive. Prog Neurobiol 79:205–221
350. **Tschritter O, Preissl H, Hennige AM, Stumvoll M, Porubska K, Frost R, Marx H, Klösel B, Lutzenberger W, Birbaumer N, Häring HU, Fritsche A** 2006 The cerebrocortical response to hyperinsulinemia is reduced in overweight humans: A magnetoencephalographic study. Proc Natl Acad Sci USA 103: 12103–12108
351. **Tschritter O, Preissl H, Yokoyama Y, Machicao F, Häring HU, Fritsche A** 2007 Variation in the FTO gene locus is associated with cerebrocortical insulin resistance in humans. Diabetologia 50:2602–2603
352. **Roden M, Bernroider E** 2003 Hepatic glucose metabolism in humans—its role in health and disease. Best Pract Res Clin Endocrinol Metab 17:365–383

353. **Burcelin R, Knauf C, Cani PD** 2008 Pancreatic α-cell dysfunction in diabetes. Diabetes Metab 34(Suppl 2):S49–S55
354. **Tschritter O, Stumvoll M, Machicao F, Holzwarth M, Weisser M, Maerker E, Teigeler A, Häring H, Fritsche A** 2002 The prevalent Glu23Lys polymorphism in the potassium inward rectifier 6.2 (KIR6.2) gene is associated with impaired glucagon suppression in response to hyperglycemia. Diabetes 51:2854–2860
355. **Suzuki M, Fujikura K, Inagaki N, Seino S, Takata K** 1997 Localization of the ATP-sensitive K+ channel subunit Kir6.2 in mouse pancreas. Diabetes 46:1440–1444
356. **Bokvist K, Olsen HL, Høy M, Gotfredsen CF, Holmes WF, Buschard K, Rorsman P, Gromada J** 1999 Characterisation of sulphonylurea and ATP-regulated K+ channels in rat pancreatic A-cells. Pflugers Arch 438:428–436
357. **MacDonald PE, De Marinis YZ, Ramracheya R, Salehi A, Ma X, Johnson PR, Cox R, Eliasson L, Rorsman P** 2007 A K ATP channel-dependent pathway within α cells regulates glucagon release from both rodent and human islets of Langerhans. PLoS Biol 5:e143
358. **Scuteri A, Sanna S, Chen WM, Uda M, Albai G, Strait J, Najjar S, Nagaraja R, Orrú M, Usala G, Dei M, Lai S, Maschio A, Busonero F, Mulas A, Ehret GB, Fink AA, Weder AB, Cooper RS, Galan P, Chakravarti A, Schlessinger D, Cao A, Lakatta E, Abecasis GR** 2007 Genome-wide association scan shows genetic variants in the FTO gene are associated with obesity-related traits. PLoS Genet 3:e115
359. **Dina C, Meyre D, Gallina S, Durand E, Körner A, Jacobson P, Carlsson LM, Kiess W, Vatin V, Lecoeur C, Delplanque J, Vaillant E, Pattou F, Ruiz J, Weill J, Levy-Marchal C, Horber F, Potoczna N, Hercberg S, Le Stunff C, Bougnères P, Kovacs P, Marre M, Balkau B, Cauchi S, Chèvre JC, Froguel P** 2007 Variation in FTO contributes to childhood obesity and severe adult obesity. Nat Genet 39:724–726
360. **Hinney A, Nguyen TT, Scherag A, Friedel S, Brönner G, Müller TD, Grallert H, Illig T, Wichmann HE, Rief W, Schäfer H, Hebebrand J** 2007 Genome wide association (GWA) study for early onset extreme obesity supports the role of fat mass and obesity associated gene (FTO) variants. PLoS ONE 2:e1361
361. **Price RA, Li WD, Zhao H** 2008 FTO gene SNPs associated with extreme obesity in cases, controls and extremely discordant sister pairs. BMC Med Genet 9:4
362. **Hunt SC, Stone S, Xin Y, Scherer CA, Magness CL, Iadonato SP, Hopkins PN, Adams TD** 2008 Association of the FTO gene with BMI. Obesity (Silver Spring) 16:902–904
363. **Andreasen CH, Stender-Petersen KL, Mogensen MS, Torekov SS, Wegner L, Andersen G, Nielsen AL, Albrechtsen A, Borch-Johnsen K, Rasmussen SS, Clausen JO, Sandbaek A, Lauritzen T, Hansen L, Jørgensen T, Pedersen O, Hansen T** 2008 Low physical activity accentuates the effect of the FTO rs9939609 polymorphism on body fat accumulation. Diabetes 57:95–101
364. **Do R, Bailey SD, Desbiens K, Belisle A, Montpetit A, Bouchard C, Pérusse L, Vohl MC, Engert JC** 2008 Genetic variants of FTO influence adiposity, insulin sensitivity, leptin levels, and resting metabolic rate in the Quebec Family Study. Diabetes 57:1147–1150
365. **Grant SF, Li M, Bradfield JP, Kim CE, Annaiah K, Santa E, Glessner JT, Casalunovo T, Frackelton EC, Otieno FG, Shaner JL, Smith RM, Imielinski M, Eckert AW, Chiavacci RM, Berkowitz RI, Hakonarson H** 2008 Association analysis of the FTO gene with obesity in children of Caucasian and African ancestry reveals a common tagging SNP. PLoS ONE 3:e1746
366. **Hotta K, Nakata Y, Matsuo T, Kamohara S, Kotani K, Komatsu R, Itoh N, Mineo I, Wada J, Masuzaki H, Yoneda M, Nakajima A, Miyazaki S, Tokunaga K, Kawamoto M, Funahashi T, Hamaguchi K, Yamada K, Hanafusa T, Oikawa S, Yoshimatsu H, Nakao K, Sakata T, Matsuzawa Y, Tanaka K, Kamatani N, Nakamura Y** 2008 Variations in the FTO gene are associated with severe obesity in the Japanese. J Hum Genet 53:546–553
367. **Marvelle AF, Lange LA, Qin L, Adair LS, Mohlke KL** 2008 Association of FTO with obesity-related traits in the Cebu Longitudinal Health and Nutrition Survey (CLHNS) Cohort. Diabetes 57:1987–1991
368. **Peeters A, Beckers S, Verrijken A, Roevens P, Peeters P, Van Gaal L, Van Hul W** 2008 Variants in the FTO gene are associated with common obesity in the Belgian population. Mol Genet Metab 93:481–484
369. **Chang YC, Liu PH, Lee WJ, Chang TJ, Jiang YD, Li HY, Kuo SS, Lee KC, Chuang LM** 2008 Common variation in the fat mass and obesity-associated (FTO) gene confers risk of obesity and modulates BMI in the Chinese population. Diabetes 57:2245–2252
370. **Haupt A, Thamer C, Machann J, Kirchhoff K, Stefan N, Tschritter O, Machicao F, Schick F, Häring HU, Fritsche A** 2008 Impact of variation in the FTO gene on whole body fat distribution, ectopic fat, and weight loss. Obesity (Silver Spring) 16:1969–1972
371. **Villalobos-Comparán M, Teresa Flores-Dorantes M, Teresa Villarreal-Molina M, Rodríguez-Cruz M, García-Ulloa AC, Robles L, Huertas-Vázquez A, Saucedo-Villarreal N, López-Alarcón M, Sánchez-Muñoz F, Domínguez-López A, Gutiérrez-Aguilar R, Menjivar M, Coral-Vázquez R, Hernández-Stengele G, Vital-Reyes VS, Acuña-Alonzo V, Romero-Hidalgo S, Ruiz-Gómez DG, Riaño-Barros D, Herrera MF, Gómez-Pérez FJ, Froguel P, García-García E, Teresa Tusié-Luna M, Aguilar-Salinas CA, Canizales-Quinteros S** 2008 The FTO gene is associated with adulthood obesity in the Mexican population. Obesity (Silver Spring) 16:2296–2301
372. **Cornes BK, Lind PA, Medland SE, Montgomery GW, Nyholt DR, Martin NG** 2009 Replication of the association of common rs9939609 variant of FTO with increased BMI in an Australian adult twin population but no evidence for gene by environment (G x E) interaction. Int J Obes (Lond) 33: 75–79
373. **Lappalainen TJ, Tolppanen AM, Kolehmainen M, Schwab U, Lindström J, Tuomilehto J, Pulkkinen L, Eriksson JG, Laakso M, Gylling H, Uusitupa M** 2009 The common variant in the FTO gene did not modify the effect of lifestyle changes on body weight: the Finnish Diabetes Prevention Study. Obesity (Silver Spring) 17:832–836
374. **Gerken T, Girard CA, Tung YC, Webby CJ, Saudek V, Hewitson KS, Yeo GS, McDonough MA, Cunliffe S, McNeill LA, Galvanovskis J, Rorsman P, Robins P, Prieur X, Coll AP, Ma M, Jovanovic Z, Farooqi IS, Sedgwick B, Barroso I, Lindahl T, Ponting CP, Ashcroft FM, O'Rahilly S, Schofield CJ** 2007 The obesity-associated FTO gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase. Science 318:1469–1472
375. **Speakman JR, Rance KA, Johnstone AM** 2008 Polymor-

phisms of the FTO gene are associated with variation in energy intake, but not energy expenditure. Obesity (Silver Spring) 16:1961–1965

376. **Wardle J, Carnell S, Haworth CM, Farooqi IS, O'Rahilly S, Plomin R** 2008 Obesity associated genetic variation in FTO is associated with diminished satiety. J Clin Endocrinol Metab 93:3640–3643
377. **Wardle J, Llewellyn C, Sanderson S, Plomin R** 2009 The FTO gene and measured food intake in children. Int J Obes (Lond) 33:42–45
378. **Timpson NJ, Emmett PM, Frayling TM, Rogers I, Hattersley AT, McCarthy MI, Davey Smith G** 2008 The fat mass- and obesity-associated locus and dietary intake in children. Am J Clin Nutr 88:971–978
379. **Haupt A, Thamer C, Staiger H, Tschritter O, Kirchhoff K, Machicao F, Häring HU, Stefan N, Fritsche A** 2009 Variation in the FTO gene influences food intake but not energy expenditure. Exp Clin Endocrinol Diabetes 117:194–197
380. **Loos RJ, Lindgren CM, Li S, Wheeler E, Zhao JH, Prokopenko I, Inouye M, Freathy RM, Attwood AP, Beckmann JS, Berndt SI, Jacobs KB, Chanock SJ, Hayes RB, Bergmann S, Bennett AJ, Bingham SA, Bochud M, Brown M, Cauchi S, Connell JM, Cooper C, Smith GD, Day I, Dina C, De S, Dermitzakis ET, Doney AS, Elliott KS, Elliott P, Evans DM, Sadaf Farooqi I, Froguel P, Ghori J, Groves CJ, Gwilliam R, Hadley D, Hall AS, et al.** 2008 Common variants near MC4R are associated with fat mass, weight and risk of obesity. Nat Genet 40:768–775
381. **Thorleifsson G, Walters GB, Gudbjartsson DF, Steinthorsdottir V, Sulem P, Helgadottir A, Styrkarsdottir U, Gretarsdottir S, Thorlacius S, Jonsdottir I, Jonsdottir T, Olafsdottir EJ, Olafsdottir GH, Jonsson T, Jonsson F, Borch-Johnsen K, Hansen T, Andersen G, Jorgensen T, Lauritzen T, Aben KK, Verbeek AL, Roeleveld N, Kampman E, Yanek LR, Becker LC, Tryggvadottir L, Rafnar T, Becker DM, Gulcher J, Kiemeney LA, Pedersen O, Kong A, Thorsteinsdottir U, Stefansson K** 2009 Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. Nat Genet 41:18–24
382. **Willer CJ, Speliotes EK, Loos RJ, Li S, Lindgren CM, Heid IM, Berndt SI, Elliott AL, Jackson AU, Lamina C, Lettre G, Lim N, Lyon HN, McCarroll SA, Papadakis K, Qi L, Randall JC, Roccasecca RM, Sanna S, Scheet P, Weedon MN, Wheeler E, Zhao JH, Jacobs LC, Prokopenko I, Soranzo N, Tanaka T, Timpson NJ, Almgren P, Bennett A, Bergman RN, Bingham SA, Bonnycastle LL, Brown M, Burtt NP, Chines P, Coin L, Collins FS, et al.** 2009 Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. Nat Genet 41:25–34
383. **Meyre D, Delplanque J, Chèvre JC, Lecoeur C, Lobbens S, Gallina S, Durand E, Vatin V, Degraeve F, Proença C, Gaget S, Körner A, Kovacs P, Kiess W, Tichet J, Marre M, Hartikainen AL, Horber F, Potoczna N, Hercberg S, Levy-Marchal C, Pattou F, Heude B, Tauber M, McCarthy MI, Blakemore AI, Montpetit A, Polychronakos C, Weill J, Coin LJ, Asher J, Elliott P, Järvelin MR, Visvikis-Siest S, Balkau B, Sladek R, Balding D, Walley A, Dina C, Froguel P** 2009 Genome-wide association study for early-onset and morbid adult obesity identifies three new risk loci in European populations. Nat Genet 41:157–159
384. **Keshavarz P, Inoue H, Sakamoto Y, Kunika K, Tanahashi T, Nakamura N, Yoshikawa T, Yasui N, Shiota H, Itakura M** 2006 No evidence for association of the ENPP1 (PC-1) K121Q variant with risk of type 2 diabetes in a Japanese population. J Hum Genet 51:559–566
385. **Chandalia M, Grundy SM, Adams-Huet B, Abate N** 2007 Ethnic differences in the frequency of ENPP1/PC1 121Q genetic variant in the Dallas Heart Study cohort. J Diabetes Complications 21:143–148
386. **Lango H, Palmer CN, Morris AD, Zeggini E, Hattersley AT, McCarthy MI, Frayling TM, Weedon MN** 2008 Assessing the combined impact of 18 common genetic variants of modest effect sizes on type 2 diabetes risk. Diabetes 57:3129–3135
387. **Kilpeläinen TO, Lakka TA, Laaksonen DE, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Lindi V, Tuomilehto J, Uusitupa M, Laakso M** 2008 SNPs in PPARG associate with type 2 diabetes and interact with physical activity. Med Sci Sports Exerc 40:25–33
388. **Meigs JB, Shrader P, Sullivan LM, McAteer JB, Fox CS, Dupuis J, Manning AK, Florez JC, Wilson PW, D'Agostino Sr RB, Cupples LA** 2008 Genotype score in addition to common risk factors for prediction of type 2 diabetes. N Engl J Med 359:2208–2219
389. **Sparsø T, Grarup N, Andreasen C, Albrechtsen A, Holmkvist J, Andersen G, Jørgensen T, Borch-Johnsen K, Sandbaek A, Lauritzen T, Madsbad S, Hansen T, Pedersen O** 2009 Combined analysis of 19 common validated type 2 diabetes susceptibility gene variants shows moderate discriminative value and no evidence of gene-gene interaction. Diabetologia 52:1308–1314
390. **Perry JR, Frayling TM** 2008 New gene variants alter type 2 diabetes risk predominantly through reduced β-cell function. Curr Opin Clin Nutr Metab Care 11:371–377
391. **Lehtovirta M, Kaprio J, Forsblom C, Eriksson J, Tuomilehto J, Groop L** 2000 Insulin sensitivity and insulin secretion in monozygotic and dizygotic twins. Diabetologia 43:285–293
392. **Watanabe RM, Valle T, Hauser ER, Ghosh S, Eriksson J, Kohtamäki K, Ehnholm C, Tuomilehto J, Collins FS, Bergman RN, Boehnke M** 1999 Familiality of quantitative metabolic traits in Finnish families with non-insulin-dependent diabetes mellitus. Hum Hered 49:159–168
393. **Wareham NJ, Franks PW, Harding AH** 2002 Establishing the role of gene-environment interactions in the etiology of type 2 diabetes. Endocrinol Metab Clin North Am 31:553–566
394. **Grarup N, Andersen G** 2007 Gene-environment interactions in the pathogenesis of type 2 diabetes and metabolism. Curr Opin Clin Nutr Metab Care 10:420–426
395. **Ling C, Poulsen P, Simonsson S, Rönn T, Holmkvist J, Almgren P, Hagert P, Nilsson E, Mabey AG, Nilsson P, Vaag A, Groop L** 2007 Genetic and epigenetic factors are associated with expression of respiratory chain component NDUFB6 in human skeletal muscle. J Clin Invest 117:3427-3435
396. **Rönn T, Poulsen P, Hansson O, Holmkvist J, Almgren P, Nilsson P, Tuomi T, Isomaa B, Groop L, Vaag A, Ling C** 2008 Age influences DNA methylation and gene expression of COX7A1 in human skeletal muscle. Diabetologia 51:1159-1168