

## Pathomechanisms of Type 2 Diabetes Genes

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Type 2 diabetes mellitus is a complex metabolic disease that is caused by insulin resistance and  $\beta$ -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  $\beta$ -cell function. This favors a  $\beta$ -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)

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### 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  $\beta$ -cells (1, 2). In contrast to insulin resistance, the decline in  $\beta$ -cell function is considered a late event (3) and was shown to be, at least in part, caused by an irreversible loss of  $\beta$ -cell mass (4). It is commonly ac-

cepted 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

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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](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>). 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-breeding 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.

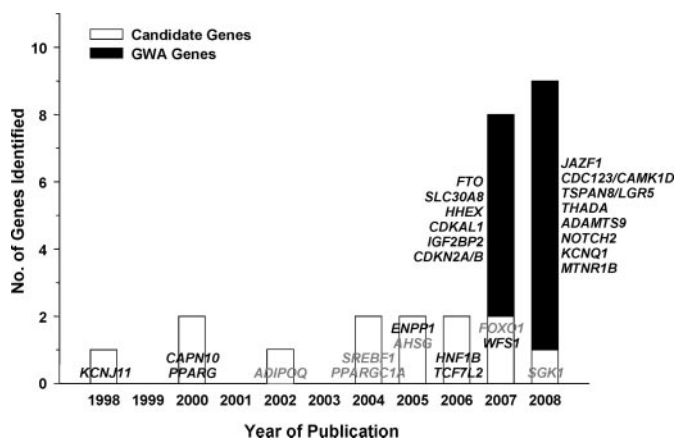
The most recent and most successful approach to identify novel risk alleles is the hypothesis-free systematic genotyping of several hundred thousand SNPs in tens of thousands of cases and controls using high-density SNP arrays. A substantial drop in the cost of these arrays initiated a revolution in 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  $\beta$ -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  $\beta$ -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  $\beta$ -cell function affected, such as insulin maturation, glucose sensitivity, or incretin sensitivity. From these rough estimates of  $\beta$ -cell function, pathomechanisms showing how these common gene variants impair  $\beta$ -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  $\beta$ -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  $\beta$ -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-ac-

tivating 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  $\beta$ -cells, and FoxO1's nuclear localization exerts inhibitory effects on insulin resistance-induced  $\beta$ -cell mass expansion and  $\beta$ -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  $\beta$ -cell proliferation and function (214). Due to this central function of FoxO1 within pancreatic  $\beta$ -cells, it appears obvious that the aforementioned SNPs (probably affecting *FOXO1* expression) exert direct effects inside the  $\beta$ -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  $\beta$ -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  $\beta$ -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
<i>ADAMTS9</i>	3	Skeletal muscle, breast, thymus, kidney, prostate, pancreas, heart, lung, spinal cord, brain, all fetal tissues	rs4607103 (80%)	Unknown
<i>CAPN10</i>	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 ↓
<i>CDC123/CAMK1D</i>	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 ↓
<i>CDKAL1</i>	6	Bone marrow, breast, liver, spleen, prostate, retina, brain, lung, kidney, thymus, pancreas, skeletal muscle	rs7754840 (30%)	Glucose-stimulated insulin secretion ↓; proinsulin conversion ↓
<i>CDKN2A/CDKN2B</i>	9	Ubiquitous/bladder, colon, lung, spleen, skin, liver, breast, skeletal muscle, prostate, kidney, brain, pancreas, adipose tissue	rs10811661 (80%)	Glucose-stimulated insulin secretion ↓
<i>ENPP1</i>	6	Thyroid gland, kidney, skeletal muscle, breast, liver, skin, thymus, salivary gland, brain capillaries	rs1044498/K121Q (10%)	Whole-body insulin sensitivity ↓; insulin secretion ↓
<i>FTO</i>	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 ↓
<i>HHEX</i>	10	Thyroid gland, brain, lymph node, spleen, liver, lung, kidney, breast, pancreas, thymus, skin, prostate, fetal pancreas	rs7923837 (60%)	Glucose-stimulated insulin secretion ↓
<i>HNF1B</i>	17	Colon, kidney, liver, thymus, retina, pancreas, prostate, lung	rs757210 (40%)	Unknown
<i>IGF2BP2</i>	3	Smooth muscle, colon, lung, retina, skeletal muscle, skin, kidney, thymus, fetal liver, fetal brain, pancreas	rs4402960 (30%)	Glucose-stimulated insulin secretion ↓
<i>JAZF1</i>	7	Lymph node, retina, pancreas, thymus, brain, skin, liver, skeletal muscle, lung, spleen, prostate	rs864745 (50%)	Insulin secretion ↓
<i>KCNJ11</i>	11	Pancreas, heart, pituitary gland, skeletal muscle, brain, smooth muscle	rs5219/E23K (50%)	Insulin secretion ↓; glucose-dependent suppression of glucagon secretion ↓
<i>KCNQ1</i>	11	Thyroid gland, bone marrow, prostate, heart, pancreas, lung, thymus, skin, liver, kidney	rs2237892 (90%), rs151290 (80%)	Insulin secretion ↓; incretin secretion ↓
<i>MTNR1B</i>	11	Retina, brain, pancreas	rs10830963 (30%), rs10830962 (40%), rs4753426 (50%)	Glucose-stimulated insulin secretion ↓
<i>NOTCH2</i>	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
<i>PPARG</i>	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 ↓
<i>SLC30A8</i>	8	Pancreas, kidney, lung, breast, amygdala	rs13266634/R325W (70%)	Glucose-stimulated insulin secretion ↓; proinsulin conversion ↓
<i>TCF7L2</i>	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
<i>THADA</i>	2	Ubiquitous	rs7578597/T1187A (90%)	Unknown
<i>TSPAN8/LGR5</i>	12	Spinal cord, colon, skeletal muscle, prostate, liver, lung, pancreas, kidney/skeletal muscle, skin, brain, spinal cord	rs7961581 (30%)	Insulin secretion ↓
<i>WFS1</i>	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  $\beta$ -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  $\beta$ -cells (228). It belongs to the calcium-dependent papain domain-containing family of cysteine proteases (228). In  $\beta$ -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 com-

ponent 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
<i>ADIPOQ</i>	3	Adipose tissue, heart, breast, thymus, brain, kidney	rs266729 (30%), rs2241766 (20%), rs1501299 (70%)	Whole-body insulin sensitivity ↓
<i>AHSG</i>	3	Liver, breast, skeletal muscle, brain	rs2077119 (50%)	Adipose tissue insulin sensitivity ↓
<i>FOXO1</i>	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 ↓
<i>PPARGC1A</i>	4	Liver, kidney, colon, heart, lung, skeletal muscle, brain, pancreas, thymus, prostate	rs8192678/G482S (40%)	Whole-body insulin sensitivity ↓ ; insulin secretion ↓
<i>SGK1</i>	6	Ubiquitous	rs9402571 (80%)	Insulin secretion ↓
<i>SREBF1</i>	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  $\beta$ -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  $\beta$ -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  $\gamma$ , coactivator 1  $\alpha$ ; OMIM entry no. 604517) gene, which encodes the amino acid exchange G482S in this gene's product PGC-1 $\alpha$ , markedly reduces human pancreatic islet *PPARGC1A* expression and concomitantly impairs glucose-stimulated insulin secretion (198). The mechanistic relevance of PGC-1 $\alpha$  for insulin secretion of human pancreatic islets was proven by downregulation 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-1 $\alpha$  as a central regulator of mitochondrial function (Ref. 234 and Section IV) and the importance of mitochondrial ATP formation for stimulus-secretion coupling in  $\beta$ -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  $\beta$ -cells is markedly enhanced by incretins. Thus, both incretin production/release by enteroendocrine cells and incretin signaling in  $\beta$ -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  $\beta$ -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  $\beta$ -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  $\beta$ -cell survival and  $\beta$ -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  $\beta$ -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  $\beta$ -cell functions: *Wfs1* knockout mice develop glucose intolerance and overt diabetes due to increased  $\beta$ -cell endoplasmic reticulum stress, reduced  $\beta$ -cell proliferation, progressive apoptotic  $\beta$ -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-chain 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  $\beta$ -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  $\beta$ -cell that has to be compensated for by increments in insulin secretion to maintain normoglycemia. Thus, genetically determined  $\beta$ -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  $\gamma$ ; 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  $\gamma$  (PPAR $\gamma$ ). Two isoforms were described, PPAR $\gamma$ 1 and PPAR $\gamma$ 2, that are formed by alternative promoter usage and divergent splicing (288). Whereas PPAR $\gamma$ 1 is expressed in a number of tissues and cell types at moderate levels, the expression of PPAR $\gamma$ 2 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 PPAR $\gamma$ 2-encoding transcript, it appears more than plausible that this variant exerts its insulin-sensitizing effect directly inside adipose tissue. That PPAR $\gamma$  is a central mediator of whole-body insulin sensitivity was clearly supported by the finding that PPAR $\gamma$  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  $\alpha$ -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  $\beta$ -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  $\alpha$  activation that induces the expression of  $\beta$ -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-1 $\alpha$ , the *PPARGC1A* gene product, is an important coactivator of nuclear receptors, such as estrogen-related receptor  $\alpha$  and peroxisome proliferator-activated receptor  $\delta$ , and, via these transcription factors, controls the expression of genes involved in oxidative phosphorylation and  $\beta$ -oxidation (323–325). In consequence of these gene-regulatory events, PGC-1 $\alpha$  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-1 $\alpha$  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* ( $\alpha 2$ -HS-glycoprotein; OMIM entry no. 138680), are functional insofar as they determine the plasma concentration of this gene's product  $\alpha 2$ -HS-glycoprotein, the human homolog of animal fetuin-A (328). Plasma  $\alpha 2$ -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  $\alpha 2$ -HS-glycoprotein's properties could explain this SNP's interference with insulin signaling in the adipocyte: first,  $\alpha 2$ -HS-glycoprotein directly binds the insulin receptor and inhibits the receptor's tyrosine kinase activity (331–335); and second,  $\alpha 2$ -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  $\beta$ -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  $\alpha$ -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  $\beta$ -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  $\alpha$ -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<sup>2</sup> 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*).

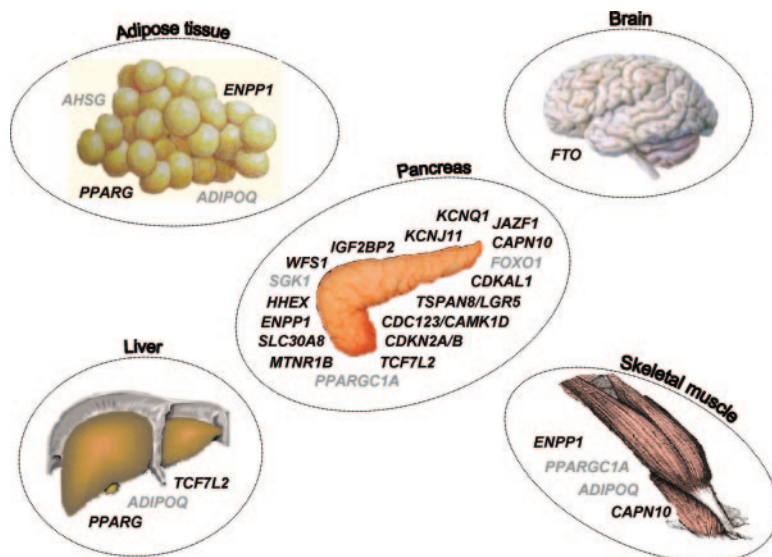
In 2008, two SNPs located 3' of a second genetic locus, the *MC4R* gene, were shown to robustly associate with variation in BMI (~0.2 kg/m<sup>2</sup> per risk allele) (380). An association with type 2 diabetes could, however, not be demonstrated. Very recently, more than 15 novel obesity loci were identified 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 con-

firmed 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  $\beta$ -cell function, and this might favor the notion that  $\beta$ -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  $\beta$ -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-de-

finer 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 therapeutic use of drugs (with their side effects) that are ineffective in certain genotypes.

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