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Genetic dissection of type 2 diabetes

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Abstract

Compared to the successful probing of genetic causes of monogenic disorders, dissecting the genetics of complex polygenic diseases has until recently been a fairly slow and cumbersome process. With the introduction of whole genome wide association studies (WGAS) the situation dramatically changed in 2007. The results from several recent WGAS on type 2 diabetes (T2D) and obesity have identified at least eighteen genes consistently associated with T2D. Many of the genes implicate pancreatic beta-cell function in the pathogenesis of T2D whereas only one clearly associate with insulin resistance. The identified genes most likely merely represent the tip of the iceberg in the explanation behind T2D. Refined tools will have to provide a more complete picture of the genetic complexity of T2D over the next few years. In addition to common variants increasing susceptibility for the disease, rare variants with stronger effects, copy number variations, and epigenetic effects like DNA methylation and histone acetylation will become important. Nevertheless, today we are able for the first time to anticipate that the genetics of a complex disease like T2D really can be dissected.

Key words

genetics**,** complex disease, monogenic, polygenic, linkage study, genome wide scan, association study, single nucleotide polymorphism, epigenetic, type 2 diabetes, obesity.

A disease can be inherited or acquired, or both. Some develop as a consequence of a single base pair exchange/mutation, so called monogenic diseases. The individual susceptibility to develop others depends on several genetic variants or combination of variants, so called polygenic diseases. While both common type 2 diabetes (T2D) and obesity may be considered polygenic diseases, there are several examples of clearly monogenic disorders with roughly the same phenotypic expression such as Maturity Onset Diabetes in the Young (MODY) that follow a clear Mendelian mode of inheritance. A polygenic disease is also referred to as complex because of its complex inheritance pattern. A complex disease often appears to be acquired; the development of obesity and T2D is triggered by environmental factors in genetically susceptible individuals. However, not all obese individuals develop diabetes; genetic susceptibility is a prerequisite. Given this interplay between genetic and environmental factors a complex polygenic disease may also be referred to as multifactorial.

Evidence that type 2 diabetes is inherited

There is ample evidence that T2D has a strong genetic component. The concordance of T2D in monozygotic twins is approximately 70% compared with 20-30% in dizygotic twins (1,2). Given the age-dependent penetrance of the disease, it is clear that the longer the follow-up, the higher the concordance rate (2). T2D clusters in families. The life-time risk of developing the disease is about 40% in offspring of one parent with T2D (3), greater if the mother is affected (4), the risk approaching 70% if both parents have diabetes. Translated into a λs-value, the recurrence risk for a sibling of an affected person divided by the risk for the general population, this means that a first-degree relative of a patient with type 2 diabetes has a 3-fold increased risk of developing the disease (5). Large ethnic differences in the prevalence of T2D have also been ascribed to a genetic component (6,7). The change in the environment towards a more affluent Western life style plays a key role in the epidemic increase in the prevalence of T2D worldwide. This change has occurred during the last 50 years. Clearly, our genes have not changed during this period but this does not exclude an important role for genes in the rapid increase in T2D, since genes or gene variants explain how we respond to the environment.

Thrifty genotypes or phenotypes?

A plausible explanation for the interaction between genes and environment comes from *the thrifty gene hypothesis*. Neel (8) proposed that individuals living in an environment with unstable food supply (as for hunters and nomads) would maximize their probability of survival if they could maximize storage of energy. Genetic selection would thus favor energy-conserving genotypes in such environments. Storage of energy as fat, especially as intra-abdominal fat, is a more efficient way of storing energy than as glycogen in muscle and liver. This is what we find in the insulin-resistant phenotype and explains why offspring of subjects with T2D show early accumulation of abdominal fat (4).

An alternative explanation has been proposed by which these changes can be the consequence of intrauterine programming, the so-called *thrifty phenotype hypothesis* (9). According to this hypothesis, intrauterine malnutrition would lead to a low birth weight and increased risk of the metabolic syndrome (clustering of cardiovascular risk factors like abdominal obesity, dyslipidemia, hypertension and glucose intolerance) later in life. These findings have been replicated in several studies but it has also been shown that the risk of a small birth weight is increased in families with the metabolic syndrome (10) suggesting that a small birth weight could be a phenotype for a thrifty gene.

Prediction of future type 2 diabetes

The importance of different risk factors for T2D differ between ethnic populations but the increased risk conferred by a family history of diabetes seems more constant (5), although its relative effect decreases with increasing frequency of T2D in the population. The predictive value of a family history of T2D is also relatively poor in young subjects whose parents have not yet developed the disease. A low level of physical activity, abdominal obesity and presence of the metabolic syndrome also commonly confer an increased risk of T2D (11,12). In addition, an elevated glucose concentration *per se* is a strong predictor of future T2D (5,13). In a prospective study of 2,115 non-diabetic individuals followed for six years within the Botnia study we could show that individuals with a family-history of T2D, with a BMI $\geq$ 30 kg/m^2, and fasting

plasma glucose concentration ≥ 5.5 mmol/l had a 16-fold increased risk of developing T2D (5).

Mapping genetic variability

Traditionally, two different methods have been used to discover genes that are related to a disease: analysis of genomic regions shared by relatives more often than expected (so called linkage analysis using polymorphic markers such as micro satellites or tandem repeats) and candidate gene studies, particularly by attempts to correlate biological variation (phenotype) with variation in DNA sequences (genotype) in the form of a single nucleotide polymorphism (SNP). The most straightforward approach would be to sequence the whole genome in affected and unaffected individuals but this is for practical reasons not (yet) possible. The situation may change rapidly with introduction of new large scale sequencing tools like the Solexa sequencing. Several approaches have been described to estimate whether an observed association can account for linkage (14). Without functional support it is not always possible to know whether linkage and association represent the genetic cause of the disease. For many complex disorders this may require a cumbersome sequence of *in vitro* and *in vivo* studies. In fact, the success of identifying T2D susceptibility genes by linkage has been restricted to the story of one single gene; *CAPN10*.

Calpain 10 and type 2 diabetes

In the first successful genome-wide scan of a complex disease like type 2 diabetes Graeme Bell and co-workers reported in 1996 significant linkage of T2D in Mexican American sib pairs to a locus on chromosome 2q37, which is called NIDDM1 (15). A re-examination of the data suggested an interaction with another locus on chromosome 15 (16). This enabled the researchers to narrow the telomeric region with high recombination rate down to 7 cM, which luckily represented only 1.7 megabases of physical DNA. To clone the underlying gene they genotyped 21 SNPs and identified a three-marker haplotype which was nominally associated with T2D. At the end, three intronic SNPs (43,44 and 63) in the gene coding for calpain 10 (*CAPN10*) could explain most of the linkage (17). Calpain 10, a cystein protease with largely unknown functions in glucose metabolism, was no obvious candidate gene for T2D. Despite a number of subsequent negative studies, several meta-analyses have shown consistent association

of SNPs 43 and 44 with T2D (18). Neither was it easy to understand how intronic variation in this gene could increase risk. Carrying the G allele of SNP43 is associated with decreased expression of the gene in skeletal muscle and insulin resistance (19). How this translates into increased risk of T2D is not known and will require further functional studies. *CAPN10* has not been confirmed as a candidate gene for T2D by means of GWAS.

TCF7L2: By far the strongest association with T2D is seen for SNPs in the gene encoding the transcription factor-7-like 2 (*TCF7L2)* (26). Second to *CAPN10 TCF7L2* is one of the earliest examples of a gene discovered to be associated with T2D without prior knowledge of its function as a basis for its candidacy. *TCF7L2* was identified in a follow-up analysis of a region on chromosome 10q identified through linkage analysis. TCF7L2 is involved in Wnt signaling. Heterodimerization of *TCF7L2* with β-catenin lead to nuclear translocation and induction of transcription of a number of genes including intestinal proglucagon. It is clear that risk variants in *TCF7L2* are associated with impaired insulin secretion, possibly due to an impaired incretin effect, i.e. impaired stimulatory effect of incretin hormones like GLP-1 and GIP on insulin secretion (27). It is also possible that the gene is involved in proliferation of β-cells in response to increased demands. At the onset of diabetes subjects show a 5-fold increased expression of *TCF7L2* in their islets, the higher the more copies of the risk allele. Since over-expression of TCF7L2 in human islets results in impaired insulin secretion it is unlikely that the increased expression is a consequence of a defect in the downstream pathway. It rather reflects a defect in transcription or translation of *TCF7L2* itself. It will be one of the greatest challenges to identify these mechanisms, as TCF7L2 is undoubtedly an exciting novel anti-diabetic drug target.

Common variants in MODY genes

There are at least six forms of MODY which are caused by mutations in a distinct gene. Apart from MODY2, which is caused by mutations in the glucokinase gene, most other forms of MODY are caused by mutations in different transcription factors like HNF4α (MODY1), HNF1α (MODY3), IPF-1 (MODY4), HNF1β (MODY5), and NeuroD (MODY6). Common to all of them is that they result in impaired insulin secretion and usually show strong allelic heterogeneity, i.e. different mutations cause the disease in

different families. It was therefore logical to study whether more "mild" variations in these genes could contribute to late-onset T2D. This turned out to be the case, at least for common variants in HNF1α and HNF4α (29). These studies not only emphasized the need for large sample size but also the need to consider BMI and age in the statistical analysis –genes causing subtle defects in insulin secretion are more likely to be unmasked in individuals with increased insulin needs, i.e. in insulin resistant individuals (30).

Association studies and candidate genes for type 2 diabetes

The starting point for the candidate gene approach is the potential implications that either altered expression and/or function of a particular gene product (conferred by intronic or exonic genetic variants) may have on a biological function or disease. Extending the analysis of genes implicated in monogenic forms of diabetes has proved successful also for T2D as exemplified by *PPARG*, *KCNJ11*, *TCF2/HNF1B* and *WFS1*.

PPARG: Even the screening one single gene for SNPs can represent a huge and expensive undertaking. The PPARγ gene on the short arm of chromosome 3 spans 83,000 nucleotides with 231 SNPs in public databases, seven of which are coding SNPs. The gene codes for a nuclear receptor, which is predominantly expressed in adipose tissue where it regulates transcription of genes involved in adipogenesis. In the 5' untranslated end of the gene is an extra exon B that contains a SNP changing a proline in position 12 of the protein to alanine. The rare Ala allele is seen in about 15% of Europeans and was shown to be associated with increased transcriptional activity, increased insulin sensitivity and protection against T2D in an initial study (20). Subsequently, there were a number of studies, which could not replicate the initial finding. An analysis of parent-offspring trios showed excess transmission of the Pro allele to affected offspring and a meta-analysis combining the results from all published studies a highly significant association with T2D (21). In fact, the Pro12Ala polymorphism is now one of the best-replicated genes for T2D ($p<2x10^{-10}$). The individual risk reduction conferred by the Ala allele is moderate, about 15%, but since the risk allele Pro is so common, it translates into a population attributable risk of 25% (21).

***KCNJ11*:** The ATP-sensitive potassium channel Kir 6.2 (*KCNJ11*) forms an octamer protein that regulates transmembrane potential and thereby glucose-stimulated insulin secretion in pancreatic beta-cells together with the sulfonylurea receptor SUR1 (*ABCC8*). Closure of the K-channel is a prerequisite for insulin secretion. A Glu23Lys polymorphism (E23K) in *KCNJ11* has been associated with T2D and a modest impairment of insulin secretion (22,23). In addition, an activating mutation in the gene causes a severe form of neonatal diabetes (24). Whereas these neonatal mutations result in a 10-fold activation of the ATP-dependent potassium channel, the E23K variant results in only a 2-fold increase in activity (25). *KCNQ1* encodes another potassium channel that has recently been implicated in T2D by GWAS (78,79).

***WSF-1*:** Recently 1,536 SNPs in 84 candidate genes were studied for association with T2D (28). Only one of these genes was associated with T2D; *WSF1*. The result was then replicated in 9,533 cases and 11,389 controls. *WSF1* encodes wolframin, a protein that is defective in individuals with the Wolfram syndrome. This syndrome is characterized by diabetes insipidus, juvenile diabetes, optic atrophy and deafness. Thereby WSF-1 can be considered the fourth candidate gene for T2D. The study also highlights some of the difficulties of candidate gene studies. We are limited by our own imagination and only one out of 84 candidate genes gave a positive result!

Whole genome association studies

Given the limited success with linkage studies and candidate gene studies researchers turned their hope to new tools. The rapid improvement in high throughput technology for SNP genotyping decreasing costs per genotype (in 10 years the cost has decreased by a factor of 10) has opened new possibilities for both linkage and association studies. The Hap Map provided another important tool showing that genotyping approximately 500,000 SNPs in the entire genome would cover about 75% of all common variants in the genome. Last year brought about a real breakthrough in the genetics of T2D. The reason was that several so called whole genome association studies (WGAS) using DNA chips with more than 500,000 SNPs in a large number of patients with T2D and controls have been performed and published (33-37). Robust statistical evidence of association in these studies requires *p*-values lower than $5x10^{-8}$. In our collaborative study with the Broad Institute and Novartis (Diabetes Genetic Initiative, DGI) we performed a GWAS in 1,464 patients with T2D and 1,467 non-diabetic control subjects

from Finland and Sweden. Prior to publication we shared the results with researchers from the FUSION (Finnish USA Study of NIDDM) and WTCCC (Wellcome Trust Case Control Consortium) groups (35). We only considered positive results, which were seen and replicated in all three studies based upon DNA from 32,000 individuals.

The transcription factor gene *TCF7L2* was on top of the list of each WGAS with a joint p-value in the three scans of 10^{-50}. In addition to *TCF7L2*, *PPARG*, *KCJN11* and *WSF1* the first WGAS studies have identified at least six novel genes/loci for T2D: *CDKN2A* and *CDKN2B* encoding the tumor suppressors cyclin-dependent kinase inhibitor-2A and -2B which may play a role in pancreatic islet regenerative capacity through inhibition of CDK4 and CDK6 (cyclin-dependent kinase 4 and 6), respectively; *IGF2BP2* which encodes insulin-like growth factor 2 binding protein 2, an mRNA binding protein implicated in transport of RNA targets to enable protein synthesis important for pancreas development as judged by studies in *Xenopus* and transgenic mice; *CDKAL1* which is homologous to CDK5RAP1, an inhibitor of cyclin-dependent kinase CDK5 which transduces glucotoxicity signals in pancreatic beta cells; *SLC30A8* (solute carrier family 30, member 8) encoding a pancreatic beta-cell specific zinc transporter which may affect insulin stability, storage, or secretion; and the *HHEX* (hematopoietically expressed homeobox) region which also harbors *IDE* encoding insulin degrading enzyme which has been implicated in both insulin signal and islet function. Both *HHEX*, critical for ventral pancreas development, and *IDE* are powerful biological candidates for T2D.

A central theme for many of the recently discovered genes is that many of them seem to be involved in insulin secretion, pin-pointing the pivotal role of beta-cell (dys)function in the pathogenesis of T2D. These genes include *TCF7L2*, *KCNJ11*, *HHEX*, *SLC30A8*, *CDKAL1*, *CDKN2A/2B*, *IGF2BP2* and *KCNQ1* (37,70-73,78,79). The loci seem particularly to be associated with an increased risk of developing T2D through a reduced insulin-secretory capacity. We can assume that these T2D genes only represent the tip of the iceberg, and more refined analyses will certainly yield additional genes associated with T2D. Recent analysis have also implicated *CDC123* (cell division cycle 123 homolog and *CAMK1D* (calcium/calmodulin-dependent protein kinase ID) (76). *CDC123* is regulated by nutrient availability in *S. cerevisiae* and has a role in cell cycle regulation. Taken together, evidence from GWAS implicating variants in or near

CDKAL1, *CDKN2A/B*, *CDC123* and *CAMK1D* suggests that cell cycle dysregulation may be a common pathogenetic mechanism in T2D. Several of the new genes seem to influence cell proliferation by interfering with the cell cycle as e.g.*CDKAL1* and *CDKN2A/CDKN2B* on chromosome 9. Intriguingly, the same region on chromosome 9 showing association with T2D was associated with increased risk of myocardial infarction in three independent WGAS (38-40). However, different SNPs are most likely operative for T2D and myocardial infarction.

Further recent meta-analysis efforts such as DIAGRAM have identified 6 further candidate SNPs (76-79): *JAZF1* (juxtaposed with another zinc finger gene 1) encodes a transcriptional repressor of *NR2C2* (nuclear receptor subfamily 2, group C, member 2)16. Mice deficient in Nr2c2 show growth retardation, low IGF1 serum concentrations and perinatal and early postnatal hypoglycaemia; *CDC123* and *CAMK1D* (see above); *TSPAN8* (tetraspanin 8) which encodes a cell-surface glycoprotein expressed in carcinomas of the colon, liver and pancreas; *THADA* (thyroid adenoma associated) gene; *ADAMTS9* (ADAM metallopeptidase with thrombospondin type 1 motif, 9), encoding awidely expressed and secreted metalloprotease that cleaves the proteoglycans versican and aggrecan; *NOTCH2* (Notch homolog 2 Drosophila) encoding a type 1 transmembrane receptor expressed in embryonic ductal cells of branching pancreatic buds during pancreatic organogenesis in mice and; *ADAM30* (ADAM metallopeptidase domain 30) that represents the same signal (76).

Curiously, some of the recent studies suggest a possible explanation for previous much debated epidemiological observations that men with T2D are less likely to develop prostate cancer. The same allele in *HNF1B* (or *TCF2*) that predisposes to T2DM was protective of prostate cancer (80). Moreover, different variants in *JAZF1* are associated with T2D and with prostate cancer (34-36,81). In keeping with an effect on development and transcriptional processes these findings may not come as a surprise although the exact causal relationships remain to be investigated (82).

Obesity genes and type 2 diabetes

Obesity is clearly one of the driving risk factors behind developing T2D. However, not all subjects with diabetes are obese and not all obese develop diabetes. With this scenario in mind it is important to consider whether a possible association between a

gene and T2D is in fact due to a gene associated with obesity or vice versa. *FTO*, the strongest identified obesity gene so far increases the risk of T2D (41,42). It is therefore not surprising that *FTO* was not detected as associated with T2D in the WGAS which matched for BMI. Although insulin resistance is an early detectable defect in subjects at increased risk of developing T2D, obesity, and particularly abdominal obesity, usually precedes insulin resistance in these individuals. About 40% of the variation in body fat can be attributed to genetic factors (43). The genetic influence is even more impressing for abdominal obesity. For example, genes are considered to explain 60% of the variance in abdominal fat in postmenopausal women (44,45). Abdominal fat tissue could provide a signal for the chain of events leading to skeletal muscle insulin resistance. Two such candidate signals are the adipocyte hormones leptin, and another tumor necrosis factor-α (TNF-α) (46,47). A mutation in the leptin gene results in complete absence of the protein in the fat ob/ob mouse. Treatment of the ob/ob mouse with leptin resulted in marked weight loss (48). This is another example of a monogenic disorder with a similar although exaggerated phenotype as found in common obesity. Two morbidly obese children from consanguineous parents had very low circulating leptin levels due to a frame shift mutation involving a deletion of a single guanine nucleotide in the leptin gene (49). Whereas some progress in treatment of these children with leptin has been reported, treatment of obese subjects without mutations the leptin gene has been less successful. Obese humans actually have elevated rather than decreased levels of leptin suggestive of hormonal resistance analogous to insulin resistance (50) and leptin levels show a strong positive correlation with the total fat mass (51). Moreover, contribution of common variants in the leptin receptor gene to obesity and obesity-related phenotypes including leptin levels has remained more or less elusive. Other monogenic forms of obesity implicate the gene encoding the melanocortin 4 receptor (*MC4R*) (52,53) which serves as the hypothalamic receptor for the anorexigenic peptide a-MSH (melanocyte stimulating hormone). α-MSH is derived from the product of pro-opiomelanocortin (*POMC*), which has also been associated with monogenic forms of (early-onset) obesity, either directly or indirectly (54,55). *MC4R* gene variants are expected to account for as much as 5% of severe obesity cases (56). Recently, variants close to *MC4R* were found to associate with obesity in a large study involving over 90.000 samples thus establishing *MC4R* as the second replicated obesity gene after *FTO* (74).

The list of candidate genes for both monogenic and particularly for common obesity that has been compiled through numerous one-by-one candidate gene association studies is very long (57). Unfortunately, many of these studies are underpowered and the field probably plagued by publication bias. With the advent of GWAS this has now changed although progress has been slower for obesity than for T2D. Thus far two genes (*FTO* and *MC4R*) have been identified in two different scans but several more scans including a substantial number of subjects is under way or already in press. Insulin-induced gene 2 (*INSIG2*) was identified in a low-density scan in the Framingham cohort where heritability estimates for BMI range between 37 and 54% (58). Out of 116,204 SNPs tested in 694 participants only one SNP reached overall significance. The obesity-associated *INSIG2* genotype was present in 10% of individuals, homozygotes being about one BMI unit heavier than heterozygotes or non-carriers, regardless of sex and age. The protein encoded by *INSIG2* is also a functionally attractive candidate gene for obesity since it inhibits the synthesis of fatty acids and cholesterol. Loss of function may thus need to a need for excessive storage of surplus lipid in the form of adipose tissue. The association between *INSIG2* and obesity has been replicated in some but certainly not all populations tested including meta-analysis of obesity WGAS (58,59). A stronger candidate was then found in *FTO* (41). As mentioned above, the gene predisposes to diabetes through an effect on BMI with a three-kilogram between-homozygote difference reflecting fat mass (41). The obesity-associated *FTO* risk allele is present in 16% of adults resulting in an increased risk for obesity with about 30% for one and 70% for two copies (41). The function of the gene product of *FTO* (fat mass and obesity associated) is largely unknown. A recent bioinformatics analysis suggests that it may serve as a 2-oxoglutarate-dependent nucleic acid demethylase (60). Functional data could confirm such a function and also suggested nuclear localization. The link between demethylation and fat mass remains to be elucidated. FTO genotypes seem to affect metabolic variables in line with the effect on BMI. However, we have also found association between FTO variants and measures of insulin resistance in obese children and adolescents that appear to be independent of BMI (75).

Genetic influences on age-related decline in mitochondrial dysfunction

Since genes are transcribed to RNA, RNA translated into proteins, and defects in proteins cause disease the ultimate goal would be to carry out a random search of expressed proteins in target tissues. This may not yet be completely feasible but the study of large-scale transcript profiles is. This approach has been successful in defining prognosis of cancers but for complex diseases affecting many target tissues it may not be that simple. Moreover, defining what is differentially expressed among more than 20,000 gene transcripts on a chip is a statistical challenge. Despite these problems analysis of gene expression in skeletal muscle of patients with T2D and prediabetic individuals has provided new insights into the pathogenesis of the disease applying pathway analysis rather than analysis of expression of single genes. This is based upon the assumption that if one member of the pathway shows altered expression, this will be translated into the whole pathway (61). Transcriptome analysis has shown that genes regulating oxidative phosphorylation in mitochondria exhibit a 20% coordinated down-regulation in skeletal muscle from prediabetic and diabetic individuals compared with non-diabetic controls (61,62). A similar down-regulation of the gene encoding a master regulator of oxidative phosphorylation, the PPARγ co-activator PGC-1α was also observed. Thus OXPHOS genes, has emerged as central in the pathogenesis of T2D suggesting that impaired mitochondrial function and impaired oxidation of fat may predispose to T2D diabetes through a "thrifty gene" mechanism. By studying young and elderly twins we could demonstrate that elderly carriers of a Gly482Ser polymorphism in the PGC-1α gene had decreased expression of the PGC-1α in skeletal muscle, suggesting that genetic variants determine the age-related decline in expression of key genes regulating oxidative phosphorylation (63). This study gives an example of how genetic factors, in combination with non-genetic factors, can influence gene-expression, which subsequently affects glucose and fat metabolism. The interaction between genetic and non-genetic factors may be even more complex and involve epigenetic factors such as DNA methylation and histone modifications. So far, the knowledge of the influence of epigenetic factors on the pathogenesis of T2D remains limited.

Gene-environment interactions

The rapid increase in T2D during the past 50 years must be ascribed to changes in the environment rather than to genes, as the genetic background has not changed during this period. But the genetic background determines how we respond to the environment. The PPARγ receptor is a good example of an interaction between genes and the environment. PPARγ activators have become a major new type of anti-diabetic drugs (thiazolidinediones) while dietary long-chain polyunsaturated fatty acids are supposedly natural ligands for PPARγ. The importance of the genetic variation in *PPARG* as a significant modulator of physiological responses to dietary fat in humans has been demonstrated in several studies (64-66). The different genotype carriers show different association between intake of total fat, fat subtypes, and obesity. There are also data to suggest that the protective effect of the Ala allele is influenced by the degree of saturation of ingested fat (64-66). This may not be too surprising since free fatty acids have been proposed as natural ligands for PPARγ.

Pharmacogenetics

An important goal of genetics is to use the information to improve treatment, i.e. to identify individuals who are more likely than others to respond to a specific therapy. This has been shown in neonatal diabetic patients with the *KCJN11* mutation (67). When the patients were switched from insulin to sulfonylurea their symptoms markedly improved. This was especially dramatic for the severe neurological symptoms often associated with the disease. Patients with MODY3 (HNF-1α mutations) are supersensitive to treatment with sulfonylureas whereas they respond poorly to treatment with metformin (68). It has also recently been shown that individuals with the *TCF7L2* risk genotype respond poorly to treatment with sulfonylureas, eventually as a consequence of their more severe impairment in beta-cell function (69).

Genetic prediction of type 2 diabetes

A few studies have tried to use genetic variants to predict future T2D. Lyssenko et al. showed that the Pro12Pro genotype in *PPARG* predicted future T2D in individuals with BMI ≥ 30 kg/m^2 and fasting plasma glucose > 5.5 mmol/l with an OR of 1.7 (31). The TT risk genotype of SNP 44 in *CAPN10* increased this risk in an additive manner to an OR of 2.7. More recently we showed that risk genotype carriers of *TCF7L2* had a 1.5

fold increased risk of developing future T2D in two independent studies. Combining the risk variants in *TCF7L2* with those in *PPARG* and *KCJN11* increased the OR to 3 (Lyssenko V, unpublished observations). In keeping with this observation, Weedon *et al* showed that each risk allele of these three genes increased the OR by 1.28 yielding an additive OR of 5.78 in a cross-sectional study (32). It can be expected that cross-sectional studies will give higher risk estimates than prospective studies, as they tend to include more severe cases of T2D.

Future directions

Dissecting the genetics of T2D is still a complicated task but by no means the nightmare task that it used to be. The last ten years, particularly the last two, have brought about tangible breakthroughs and we can now list at eighteen genes that consistently increase risk of T2D. We are likely to see a doubling of this number within the next one to two years. Meanwhile, these genes explain only a small proportion (≈ 0.3) of the individual risk of T2D (λs of 3). Although we now seem to cover approximately 75% of the genetic map of T2D, the variants detected most likely represent "low hanging fruit" or common variants. It is possible that there are more rare variants with stronger effects not detected with our current methodology. These variants are most likely seen in patients with early-onset forms of diabetes or in individuals with a marked β-cell dysfunction. It is unlikely that genotyping using high-density DNA arrays can detect these rare variants. Their detection will rather require sequencing. Sequencing of the whole genome was once a dream, but with new technology this dream may become true in a very near future. The role of copy number variations in the pathogenesis of disease has been highlighted in the past years but the tools to detect these CNVs have limited further exploration. This problem may be solved with the introduction of new DNA chips with a much better coverage of CNVs. We are only beginning to realize that epigenetic alteration (DNA methylation, histone acetylation and deacetylation) can introduce epigenetic changes during life-time. Such changes may influence age-related changes in gene-expression and thereby contribute to age-related diseases. Until now, DNA methylation has been studied by laborious bisulfite sequencing of single genes. In the future, the possibility of whole genome DNA methylation studies may shed new light on the extent and importance of these epigenetic effects. Dissection of the genetic complexity of T2D and obesity may thus

be possible after all. Besides these issues that are mostly related to or depend on methodology the real task will be to probe the interaction between genes, environment, and treatment and how to bring these results back to subjects who have developed T2D or are at risk of developing the disease.

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Table 1

Type 2 diabetes susceptibility genes

Year (major publication)	Gene (suggested)	Disease mechanism
2000	*PPARG*	Insulin sensitivity
2003	*CAPN10*	Glucose transport
2003	*KCNJ11*	Beta-cell dysfuncion
2006	*TCF7L2*	Beta-cell dysfuncion
2007	*CDKAL1*	Beta-cell dysfunction
2007	*CDKN2A/2B*	Beta-cell dysfuncion
2007	*HHEX/IDE*	Beta-cell dysfuncion
2007	*SLC30A8*	Beta-cell dysfuncion
2007	*IGF2BP2*	Beta-cell dysfuncion
2007	*WFS1*	Unknown
2007	*TCF2*	Unkonown
2007	*FTO*	Obesity
2008	*MC4R*	Obesity
2008	*NOTCH2*	Unknown
2008	*ADAMTS9*	Unknown
2008	*THADA*	Unknown
2008	*TSPAN8/LGR5*	Unknown
2008	*CDC123/CAMK1D*	Unknown
2008	*JAZF1*	Unknown
2008	*KCNQ1*	Beta-cell dysfuncion

PPARG, peroxisome proliferator-activated receptor gamma; *CAPN10*, calpain 10; *KCNJ11*, potassium inwardly-rectifying channel, subfamily J, member 11; *TCF7L2*, transcription factor 7-like 2; *CDKAL1*, CDK5 regulatory subunit associated protein 1-like 1; *CDKN2A/B*, cyclin-dependent kinase inhibitor 2A/B; *HHEX*, haematopoietically expressed homeobox; *IDE*, insulin-degrading enzyme; *SLC30A8*, solute carrier family 30 member 8; *IGF2BP2*, insulin-like growth factor 2 mRNA-binding protein 2; *FTO*, fat mass and obesity associated; *MC4R*, melanocortin 4 receptor; *NOTCH2*, Notch homolog 2 Drosophila; *ADAMTS9*, ADAM metallopeptidase with thrombospondin type 1 motif, 9; *THADA*, thyroid adenoma associated; *TSPAN8*, tetraspanin 8; *LGR5*, leucine-rich repeat-containing G protein-coupled receptor 5; *CDC123*, cell division cycle 123 homolog; *CAMK1D*, calcium/calmodulin-dependent protein kinase ID; *JAZF1*, juxtaposed with another zinc finger gene 1; *KCNQ1*, potassium voltage-gated channel, KQT-like subfamily, member 1.