Genetics of type 2 diabetes. On overview

LEIF GROOP AND VALERIYA LYSSENKO

Department of Clinical Sciences/Diabetes & Endocrinology and Lund University Diabetes Centre. Lund University. University Hospital Malmoe. Malmoe. Sweden.

INTRODUCTION

While the genetic causes of monogenic disorders have been successfully identified in the past, the success in dissecting the genetics of complex polygenic diseases has until now been limited. The picture has dramatically changed in 2007 with the introduction of whole genome wide association studies (WGAS) and today variants in at least 18 genes are consitently been associated with T2D. This probably only represents the tip of the iceberg and refined tools will over the next few years provide a more complete picture of the genetic complexity of T2D.

TYPE 2 DIABETES IS AN INHERITED DISEASE

There is ample evidence that type 2 diabetes (T2D) is an inherited disease. The life-time risk of developing T2D is about 40% in offspring of one parent with the disease. A first-degree relative of a patient with T2D has a 3-fold increased risk of developing the disease, this value is often referred to as the sibling-relative risk (λs)[1].

It is clear that 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, during which period our genes have not changed. This does not exclude an important role for genes in the rapid increase in T2D, since genes or variation in them explain how we respond to changes in the environment and the environment always imposes a selective pressure on genes.

Low level of physical activity, abdominal obesity and presence of the metabolic syndrome also confer an increased risk of T2D. In addition, elevated glucose concentrations per se are strong predictors of future T2D. In a prospective study of 2115 non-diabetic individuals followed for 6 years within the Botnia study we could show that individuals with a family-history of T2D, body mass index (BMI) $\geq$ 30, and fasting plasma glucose concentration $\geq$ 5.5 mmol/l had a 16-fold increased risk of developing T2D[1]. In the Botnia study, presence of a family history of T2D was confirmed

Correspondence: Prof. Dr. L. Groop.
Department of Clinical Sciences/Diabetes & Endocrinology.
Lund University. University Hospital Malmoe.
20502 Malmoe. Sweden.
E-mail: Leif.Groop@med.lu.se

by oral glucose tolerance tests in the parents. In general practice this is rarely the case and the value of a family history of T2D for predicting future diabetes is attenuated. Whether a family history of diabetes can be replaced by genetic testing in the prediction of T2D will be discussed later.

MAPPING GENETIC VARIABILITY

Linkage

The traditional way of mapping a disease gene has been to search for linkage between a chromosomal region and a disease by genotyping a large number (about 400-500) of polymorphic markers (microsatellites) in affected family members. If the affected family members would share an allele more often than expected by non-random Mendelian inheritance, there is evidence of excess allele sharing. The most likely explanation for excess allele sharing is that a disease-causing gene is in close proximity to the genotyped marker.

The first and thus far the only T2D gene identified by a linkage study in families was the calpain 10 (*CAPN10)* gene[2]. Calpain 10, a cystein protease with largely unknown functions in glucose metabolism, is 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[3]. Carriers of the risk G allele of SNP43 show decreased expression of the gene in skeletal muscle and insulin resistance. How this translates into increased risk of T2D is not known. Unfortunately none of the WGAS could find association between T2D and variants in the *CAPN10* gene. One reason might be that association studies detect common variants with modest effects while linkage most likely detects rare variants with stronger effects–such variants are rarely shared between a large number of patients with T2D.

Association studies and candidate genes

A number of studies have reported on association (or lack of it) between functional or positional candidate genes for T2D. Until 2007 only 3 genes could be consistently associated with T2D, namely PPARG, KCJN11 and TCF7L2.

– PPPARG: the gene encodes for a nuclear receptor PPARγ, 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 in an initial study shown to be associated with increased transcriptional activity, increased insulin sensitivity and protection against T2D[4]. Subsequently, there were a number of studies, which could not replicate the initial finding. Using a family-based association approach (transmission disequilibrium test, TDT) we could show excess transmission of the Pro allele to the affected offspring[5]. We thereafter performed a meta-analysis combining the results from all published studies showing a highly significant association with type 2 diabetes. The individual risk reduction conferred by the Ala allele is moderate, about 15% but since the risk allele Pro is so common, it

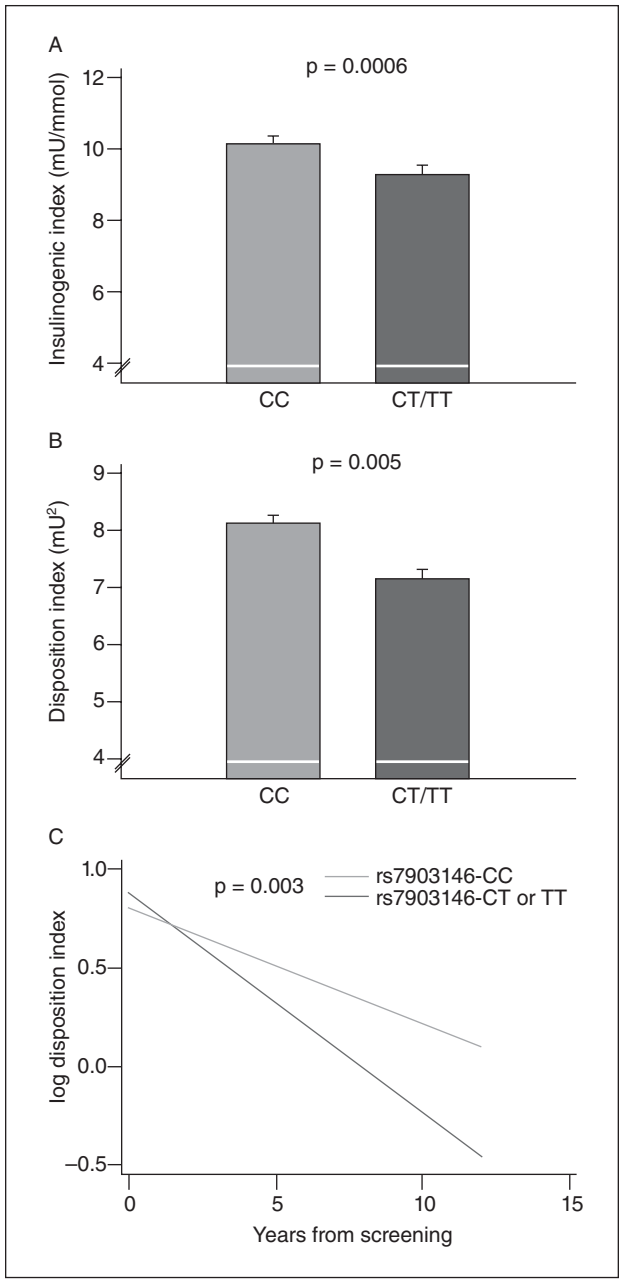

Fig. 1. Insulin secretion according to different TCF7L2 rs 7903146 genotypes. A) Insuliniogenic index, i.e. incremental insulin response to oral glucose. B) Disposition index represents the insulinogenic index adjusted for insulin sensitivity. C) Change in insulin secretion (disposition index) over time in subjects who converted to T2D in the Botnia cohort. (Lyssenko et al[9].)

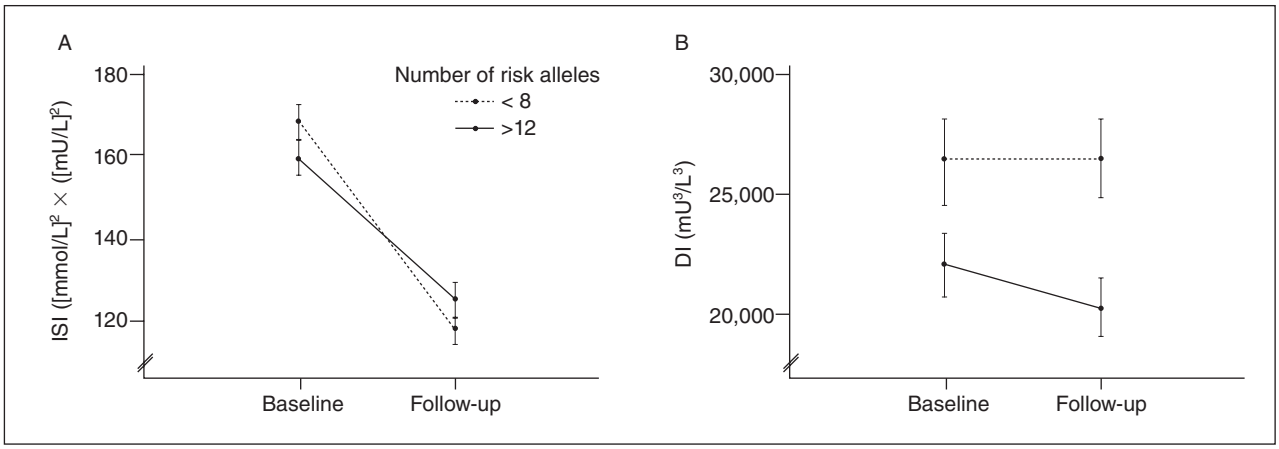

Fig. 2. Change in, insulin sensitivity (ISI) and glucose-stimulated insulin secretion adjusted for insulin sensitivity (ISI), i.e. disposition index (DI) over time in carriers of top and bottom 20% of risk genotypes for T2D.

translates into a population attributable risk of 25%.

– KCNJ11: the ATP-sensitive potassium channel Kir 6.2 (KCNJ11) forms together with the sulfonylurea receptor SUR1 (ABCC8) an octamer protein that regulates transmembrane potential and thereby glucose-stimulated insulin secretion in pancreatic beta-cells. Closure of the K- channel is a prerequisite for insulin secretion. A Glu23Lys polymorphism (E23K) has been associated with T2D and a modest impairment in insulin secretion[6]. In addition, an activating mutation in the gene causes a severe form of neonatal diabetes[7]. 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.
– TCF7L2: by far the strongest association with T2D is seen for SNPs in the gene encoding for the transcription factor-7-like 2 (*TCF7L2)*[8]. *TCF7L2* encodes for a transcription factor involved in Wnt signalling. Heterodimerization of *TCF7L2* with β-catenin induces transcription of a number of genes including intestinal proglucagon. 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[9]. It is also possible that the gene is involved in proliferation of β-cells in response to increased demands.

WHOLE GENOME ASSOCIATION STUDIES

The rapid improvement in high throughput technology for single nucleotide polymorphism (SNP) genotyping and thereby decreasing costs per genotype (in 10 years the cost has decreased by a factor of 10) has open new possibilities for both linkage and association studies. In 2007 several WGAS using DNA chips with > 500,000 SNPs in a large number of patients with T2D and controls have been performed and published[10]. In our collaborative study with the Broad Institute and Novartis (Diabetes Genetic Initiative, DGI) we performed a WGAS 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. We only considered positive results, which were seen and replicated in all three studies, i.e. together with replication samples the results were based upon DNA from 32,000 individuals! In a follow-up meta-analysis of more than 60,000 individuals another 6 variants were identified[11].

Together these studies identified 16 genes/loci for T2D. Notably, TCF7L2 was on top of each WGAS with a joint p value in the three scans of 10^{-50}. Several of the new genes seem to influence β-cell proliferation by interfering with the cell cycle e.g.CDKAL1 and CDKN2A/CDKN2B on chromosome 9. Carriers of high-risk genotypes cannot increase their insulin secretion to meet the demands imposed by insulin resistance[12]. Intriguingly, the same region on chromosome 9, which showed association with T2D, was associated with increased risk of myocardial infarction in three independent WGAS[13]. However, there are most likely different SNPs operative for T2D and myocardial infarction. FTO is an obesity gene, which increases the risk of T2D through obesity[14]. It is therefore not surprising that FTO was not detected as associated with T2D in the WGAS, which matched for BMI.

A Japanese WGAS identified variants in another ATP dependent potassium channel gene, KCNQ1 as being associated with T2D[15]. Mutations in the same gene are known to cause the long QT syndrome. We could show that it was associated with impaired insulin secretion and T2D also in Europeans. The main reason

why it was missed in the WGAS was that the risk allele was not very polymorphic in Caucasians.

More recently, focus has been on analyzing intermediate traits like glucose and insulin. Surprisingly, a variant in the melatonin receptor B1 (MTNRB1) was associated with elevated fasting glucose, impaired insulin secretion and risk of T2D[16]. Risk genotype carriers had increased expression of MTNR1B in islets and treatment of beta-cells with melatonin resulted in impaired insulin secretion. Therapeutic inhibition of melatonin effects in islets could thus represent a novel approach to treat T2D.

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

Genetics of T2D is still complicated but no longer the nightmare once proposed. The WGAs in 2007 represented an important milestone and were by Science called Breakthrough of the Year.

However, the 18 T2D 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 genetic variants detected represent common variants shared by a large number of individuals but with modest effects. It is premature to start to use these genetic variants for individual predictions[12]. However, it may be possible to use them to reduce the number of individuals needed to be included in trials aiming at prevention of T2D

Conflict of interest

The authors declare they have no conflict of interest.

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