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The Genetics of Type 1 Diabetes

Kathleen M. Gillespie
University of Bristol
UK

1. Introduction

Type 1 diabetes (T1D) is an autoimmune disease caused by the destruction of insulin producing beta-cells in the pancreas. Individuals with T1D cannot survive without insulin replacement, and despite daily insulin treatment remain at risk of complications including nephropathy, retinopathy and coronary heart disease. Although commonly associated with onset in childhood and adolescence with a peak age at diagnosis of 12 years, many cases of T1D are diagnosed in adulthood. Epidemiological studies show that the incidence of T1D is unequally distributed in the world's population, with a high incidence rate in Caucasians (40/100 000/year in Finland) and an extremely low rate among Asian and South American populations (0.1/100 000/year) (Karvonen et al., 2000). T1D is increasingly considered a disease of "westernization" or affluence associated with improved hygiene, healthcare and living standards. The incidence of the condition has been increasing rapidly in recent decades for unknown reasons: the current rate of increase is 3% per year worldwide and it has been predicted that the incidence will be 40% higher by 2010 compared to 1998 (Onkamo et al., 1999). More recent predictions show that if present trends continue, doubling of new cases of type 1 diabetes in European children younger than 5 years will occur between 2005 and 2020, and prevalent cases younger than 15 years will rise by 70% (Patterson et al., 2009).

T1D is generally diagnosed on clinical grounds but can be confirmed by the presence of circulating antibodies in the blood (Baekkeskov et al., 1982). These antibodies are markers of ongoing autoimmune destruction (Bottazzo et al., 1985) and the best characterized are specific to the islet proteins insulin (Palmer et al., 1983), glutamic acid decarboxylase (GAD) (Baekkeskov et al., 1990), IA-2 (Christie et al., 1994) and the zinc transporter ZnT8 (Wenzlau et al., 2007, 2008). The autoimmune process begins very early in life: studies of neonatal diabetes suggest that most cases of diabetes diagnosed before 6 months are unlikely to be autoimmune, but those diagnosed after the age of 6 months have the genetic characteristics of T1D (Edghill et al., 2006) while islet autoantibodies are detectable by 5 years of age in most future T1D cases (Bonifacio et al., 2004); in many by 2 years of age (Zeigler et al., 1999), and antibodies to insulin (generally the first to appear) have been detected as early as 6 to 12 months of age (Roll et al., 1996).

T1D can be predicted accurately by the detection of multiple islet autoantibodies and their characteristics (Bingley et al. 1997; Achenbach et al., 2004a, 2004b). Trials of agents to prevent T1D however require identification of those at risk of T1D very early in life before the autoimmune process has been initiated. This is only possible by estimation of genetic risk.

2. The role of genes in susceptibility to T1D

Type 1 diabetes develops through the interaction of complex genetic and environmental influences. There are several lines of evidence indicating a strong genetic component causing susceptibility to the disease. Twin studies provide one line of evidence.

2.1 Twin studies

Concordance rates between monozygotic twins has been estimated at 30-50% compared to 10% in dizygotic twins (Olmos et al., 1988; Kaprio et al., 1992; Verge et al., 1995; Hyttinen et al., 2003) indicating that genetic mechanisms are involved but are not solely responsible for disease pathogenesis. While concordance rates do increase over the period of observation the window of greatest risk appears to be within 3 years of diagnosis of the index twin (Redondo et al. 2001). Familial clustering of type 1 diabetes provides further evidence for the role genes in T1D. The risk of developing type 1 diabetes for any individual is 0.4% (population frequency). However the risk to a sibling of someone already affected is 6%. This produces a sibling risk/population prevalence ratio (λ) of 15 (Risch et al., 1988) strongly suggesting a genetic component.

2.2 Genetic methodologies

Unraveling of genetic mechanisms underlying a complex multifactorial disease involving genetic and environmental determinants such as T1D is challenging and has been ongoing since the 1970s. Indeed studies of T1D lead the way for other complex diseases. Initially simple case control comparisons of the allele frequencies of candidate genes were used. Then, in the 1990s, linkage studies were used which search for the co-transmission in T1D families of a DNA marker with the disease. The marker locus itself usually is not directly involved in the disease process, but if it lies close to a locus that is, a disease associated allele will be observed more often in individuals with disease. This lead to the identification of more genetic loci associated with T1D but was hampered by the requirement for increased statistical power from larger patient populations.

The most recent, and successful methodologies however are genome wide association studies (GWAS). These studies have taken advantage of 1) collections of large cohorts of individuals (several thousand) with well classified disease and a similar number of matched healthy controls 2) a detailed map of the most common genetic variants in the human genome, single nucleotide polymorphisms (SNPs) and the completion of the HAPMAP (www.hapmap.org/) project which showed that not all genome wide SNPs need to be analysed to generate the maximum dataset and finally 3) improved methodologies for high throughput SNP genotyping.

Interestingly, all three methodologies identified the human leucocyte antigen (HLA) region (also known as the major histocompatibility complex(MHC)) on the short arm of chromosome 6 as the predominant genetic susceptibility factor for T1D. The HLA is crucial to immune recognition of self and non-self peptides. There are 3 classes of HLA molecules- I, II, III. Class I and II are distinct structural entities. Although there are multiple class I and II genes, all the gene products have similar overall structure. Class III is a diverse collection of more than 20 genes including those encoding complement proteins. The structure of the MHC gene cluster is shown on Figure 1.

Class I MHC molecules are found on all nucleated cells and present peptides to cytotoxic T cells. Class II MHC molecules are found on certain immune cells, chiefly macrophages, B

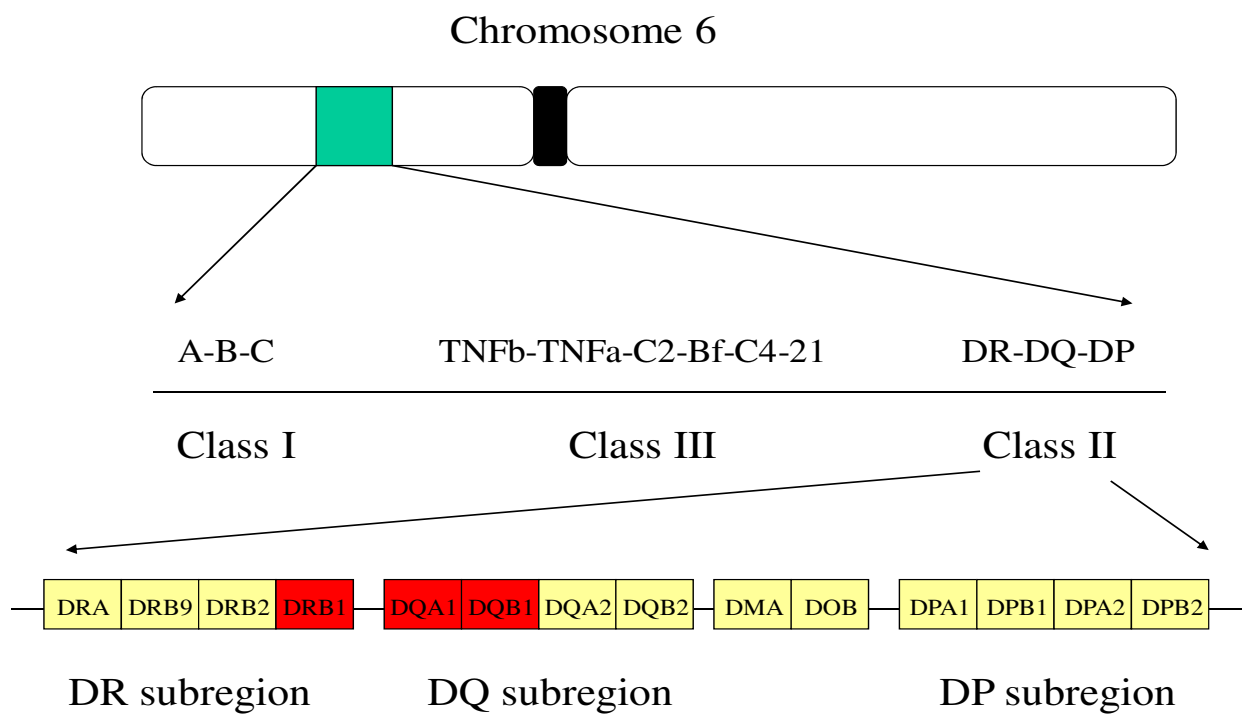


Fig. 1. The HLA region on chromosome 6 (from Mehers and Gillespie 2008). The T1D associated haplotypes are DRB1*03-DQB1*02 and DRB1*04-DQB1*0302

cells and dendritic cells, collectively known as professional antigen-presenting cells (APCs). The Class II MHC molecules on APCs present peptides to helper T cells, which stimulate an immune reaction as shown schematically on figure 2. It therefore intuitive that autoimmune diseases such as type 1 diabetes, caused by the erroneous recognition of pancreatic proteins as foreign, might involve HLA variants.

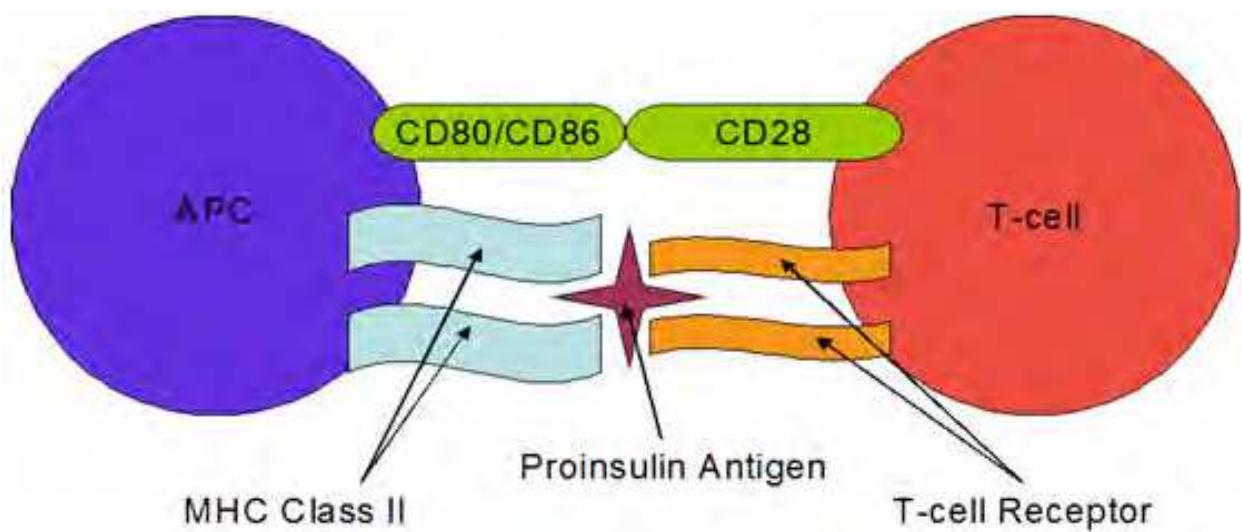


Fig. 2. A simplified schematic diagram of a proinsulin peptide being presented to a CD4 helper T cell by MHC Class II on an antigen presenting cells (from Mehers and Gillespie, 2008)

3. The HLA in susceptibility to T1D

In the early 1970s, Singal and colleagues, Nerup and colleagues and Cudworth and colleagues all independently showed that HLA class I alleles B8 and B15 were more prevalent in individuals with T1D compared to healthy individuals who lacked these antigens (Singal and Blajchman, 1973; Nerup et al., 1974; Cudworth and Woodrow, 1975). It later became clear that it was HLA class II rather than HLA class I that had the closest association with T1D. In 1987 it was shown that HLA class II DQB1 plays important role in susceptibility and resistance to T1D susceptibility (Todd et al., 1987) and in 1988, Thomson and colleagues analysed 180 Caucasoid families with at least 2 affected children and showed that there was an increase in DRB1*03/DRB1*04 genotypes in T1D patients, compared to healthy controls. They identified HLA class II DRB1*03 as the recessive allele and DRB1*04 as dominant and that the heterozygous effect of the two susceptible alleles together, produced a higher risk genotype with a synergistic effect (Thomson et al., 1988). They also demonstrated that DRB1*02 conferred a protective role in T1D susceptibility. It is now common for HLA susceptibility to T1D to be discussed in terms of HLA DRB1 (DR) and DQB1 (DQ). 90% of childhood cases have at least one of the risk haplotypes DRB1*04-DRB1*0302 (DR4-DQ8) or DRB*03-DQB1*0201 (DR3-DQ2) while the frequency of the highest risk combined genotype DRB1*04-DRB1*0302 (DR4-DQ8) and DRB*03-DQB1*0201 (DR3-DQ2) is present in almost half of children diagnosed under the age of 5 years (Cailliat

HLA class II genotype mediated absolute risk of T1D by age 15

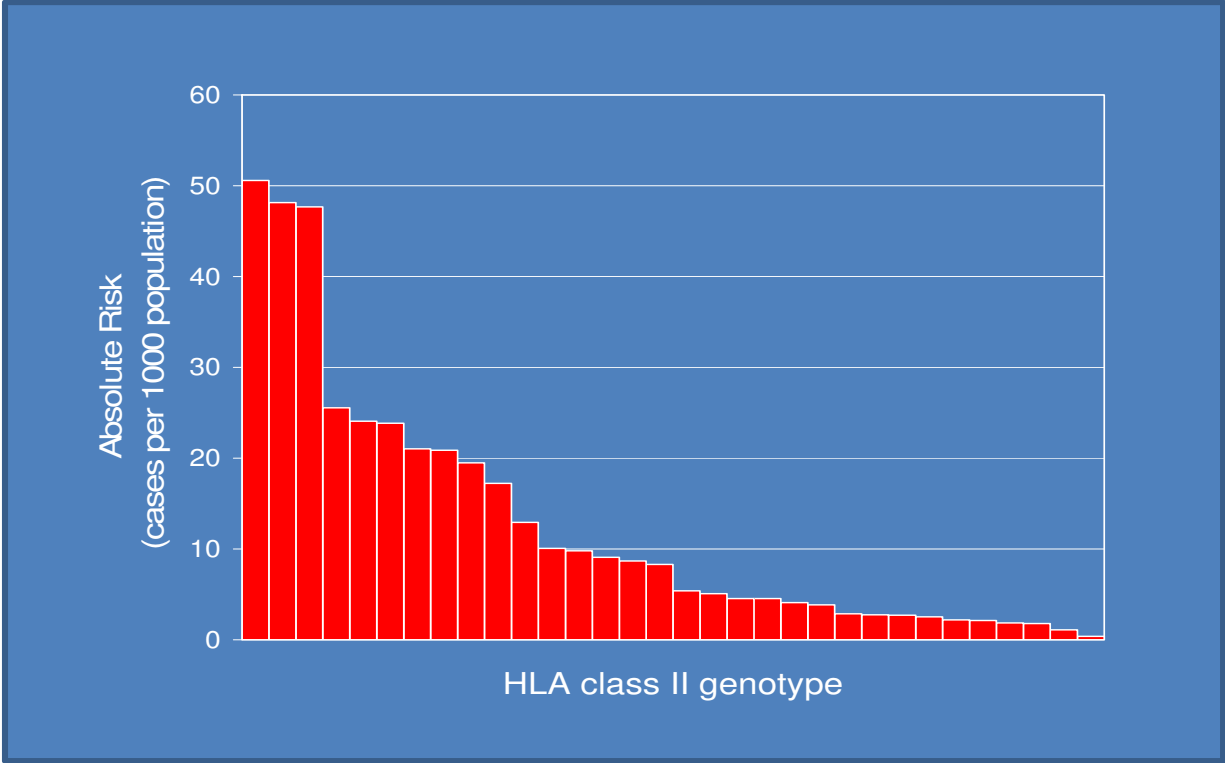


Fig. 3. Absolute risks associated with HLA class II genotypes for diagnosis of type 1 diabetes. The highest risk is associated with the genotype DRB1*03-DQB1*02/DRB1*04-DQB1*0302

Zucman et al., 1995, Gillespie et al., 2002). HLA class II haplotypes have been ranked in a risk hierarchy for T1D as shown in figure 3 (Lambert et al. 2004). Individuals with the highest risk genotype DRB1*03-DQB1*0201/DRB1*0401-DQB1*0302 have a 5% absolute risk of getting diabetes by the age of 15 years while DRB1*15-DQB1*0602 is protective (Thomson et al., 1988; Lambert et al., 2004; Pugliese et al., 1995). This haplotype is present only in about 1% of T1D cases but approximately 20% of the general population.

As the function of class II alleles is to present antigen or peptides to T cells in order to activate them, the ability of some alleles to contribute to susceptibility and others to protection is most likely to be effects on this activation pathway. Most studies have focused on the effects of different alleles on peptide binding, as it is in the peptide-binding groove where most of the HLA polymorphism is located. An early hypothesis focused on residue 57 in DQB alleles (Todd et al., 1987). All DQB1 alleles with an aspartic acid at residue 57 confer neutral to protective effects and the DQB1 alleles with alanine (*0201 and *0302) confer strong susceptibility in all ethnic groups. However this alone cannot explain all the observed associations with DQB1 alleles (Nepom et al, 1987).

A HLA class II gene which is clearly of importance in susceptibility to T1D but to a lesser extent than HLA DR and DQ is HLA DPBI. Studies have consistently shown that the DPB1*0301 allele is susceptible while the *0402 allele is protective and that these effects are independent of other HLA class II modulators (Noble et al., 2003; Cruz et al., 2004).

Intriguingly an “extreme” risk haplotype for T1D has been reported (Aly et al., 2006): siblings who share both extended high risk HLA DR3 and DR4 haplotypes identical by descent with the affected proband were shown to have a 55% risk of diabetes by the age of 12 years compared with a 7% risk of diabetes by age 12 in siblings not sharing both IBD haplotypes. These data suggest the presence of an important, and as yet recognized, modulator of risk within the HLA.

In the half century since HLA mediated susceptibility to type 1 diabetes was initially described, the HLA has consistently been replicated as the major determinant of genetic susceptibility with estimates suggesting that this gene family is responsible for 50% of susceptibility. Recent fine mapping of 8 megabases of the extended MHC region by genome wide association strategies have confirmed that the major susceptibility and resistance loci for T1D are within the HLA class II region (Nejentsev et al., 2007; Howson et al., 2009).

HLA susceptibility to T1D is dynamic

Intriguingly as the incidence of type 1 diabetes has been increasing, the frequency of HLA class II susceptibility genotypes in affected individuals has decreased (Herrman et al., 2003, Gillespie et al., 2004, Fourlanos et al., 2008). The frequency of individuals with the highest risk genotype DRB1*03-DQB1*0201/DRB1*0401-DQB1*0302 has been decreasing over the last half century while the frequency of those with the intermediate genotypes (carrying only one of the haplotypes DRB1*03-DQB1*0201 or DRB1*0401-DQB1*0302) has increased (figure 4). This was demonstrated by comparing HLA class II gene frequencies between a current T1D cohort, the Bart’s Oxford (BOX) cohort and a cohort diagnosed before 1950 known as the Golden Years cohort. As the gene pool cannot change over this time frame, it appears that increasing environmental pressure is precipitating disease in individuals with less genetic susceptibility thus contributing to the ongoing increasing numbers of children developing T1D. This dynamic in assessment of genetic risk for T1D will create difficulties for therapeutic trials where accurate assessment of risk is crucial.

3.1 The role of HLA class I genes

As indicated above HLA class II genes do not account for all of the HLA-associated contribution with type 1 diabetes. The original serological associations between the HLA and type 1 diabetes were with class I B alleles. It is increasingly clear that although the predominant effect of the HLA on susceptibility is mediated through HLA class II, these effects are modulated by HLA class I alleles. In a Finnish study of extended haplotypes it was shown that the A2, Cw1, B56, DR4, DQ8 haplotype was present in 5.5% of individuals with diabetes compared with 1.1% of controls and has the highest risk for type 1 diabetes (Tienari et al., 1992). In Finns, the Cw1, B56, DR4, DQ8 haplotype is conserved and is only associated with four HLA-A alleles. Only the A2 allele is associated with diabetes suggesting that, at least on this haplotype, the class I region contributes to susceptibility.

The effect of class I alleles was also studied in non-DR3/non-DR4 or low genetic risk individuals with T1D (Fennessy et al. 1994) who were more likely to possess two of the HLA-A alleles associated with increased disease susceptibility. The haplotypes most frequently found in type 1 diabetes were the HLA-A alleles A28, A24, A3, A2 and A1. This group went on to show elevated risks for class I alleles B13, A24 and B62 in 801 newly diagnosed Finnish children (Langholz et al., 1995). In Japanese patients with type 1 diabetes, HLA-A24 is associated with rapid onset of the disease (Nakanishi et al., 1993) and may influence age of onset and disease progression. A study of 222 diabetic multiplex families from the Human Biological Data Interchange also showed the A*2402 allele has a significant effect on the age of onset distribution of DR-DQ haplotypes occurring at a higher frequency in those individuals diagnosed younger (Valdes et al 1999) while the A*0101 was associated with older age of onset.

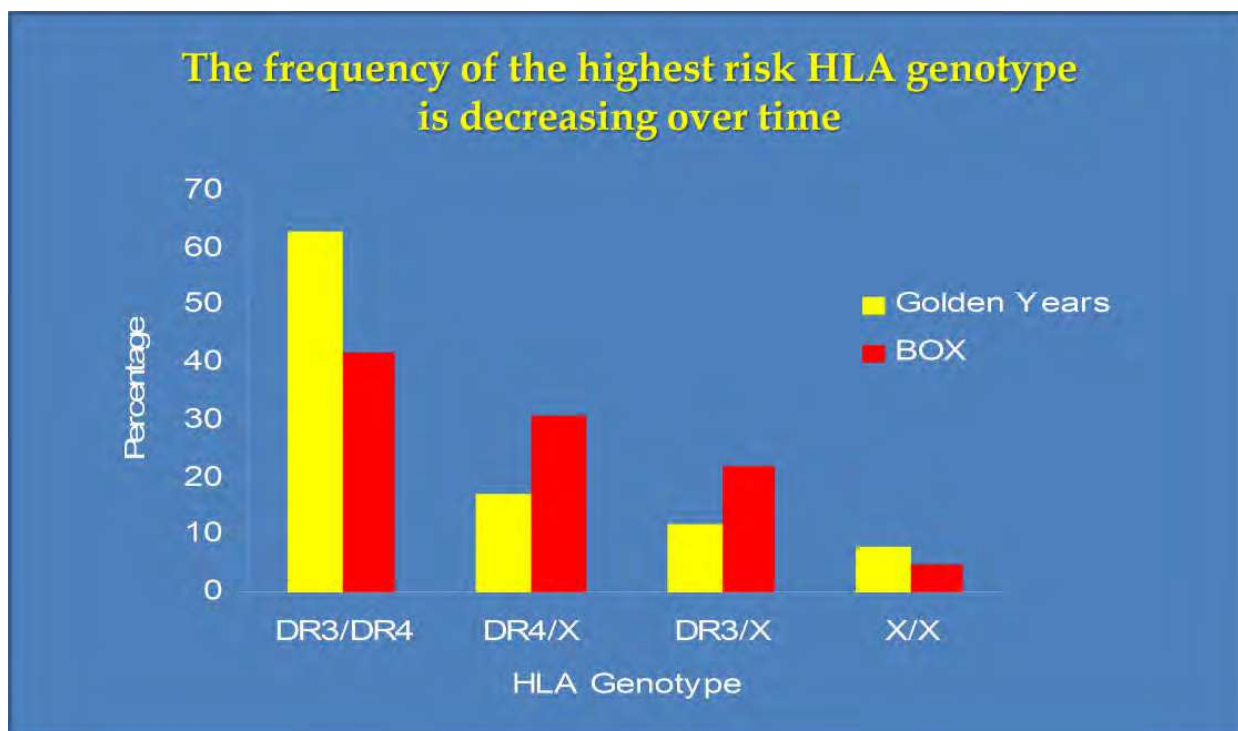


Fig. 4. The highest risk HLA DR3/DR4 genotypes is less frequent in a current T1D population (BOX) than in a population of individuals who developed T1D half a century earlier (adapted from Gillespie et al. Lancet 2004)

More recent studies by Nejentsev et al. in 2007 showed that after taking into account the effects of HLA class II, all remaining HLA effects on susceptibility to T1D are attributable to genes in HLA A and B. Most important was HLA B*39 as a susceptibility factor while the A*02 allele increases risk in individuals with the highest risk class II genotype. In the same way that HLA class II molecules present peptide to CD4 cells, HLA class I molecules present peptides to cytotoxic CD8+ T cells, increasingly accepted as the central cell in immune infiltration in human T1D pancreas and in the non-obese diabetic (NOD) mouse (discussed in section 7).

4. Non HLA genes in susceptibility to T1D

4.1 Insulin gene

In the early 1980s, a second genetic locus, the insulin gene, linked with susceptibility to T1D was identified (Bell et al., 1984). The Insulin gene (INS) on chromosome 11p15 encompasses 1430 base pairs (bp) and results in the translation of preproinsulin, the precursor of mature insulin. Preproinsulin is processed to proinsulin by removal of the signal peptide and then to mature biologically active insulin by removal of the C-peptide. It is increasingly clear that insulin is the primary autoantigen in T1D. A variable number tandem repeat (VNTR) region consisting of a 14 to 15 bp consensus sequence upstream of the INS gene, in the INS promoter, is comprised of three classes of alleles: there is a higher frequency of class I alleles with shorter repeat sequences in individuals with T1D (Bennett et al. 1995) while individuals with longer class III alleles are relatively protected from T1D. The VNTR regulates transcription rates of insulin and its precursors. Class I and Class III alleles differentially affect transcription of insulin in the thymus and pancreas (Vafiadis et al., 1997; Pugliese et al, 1997). Class III alleles result in 20% increased INS transcription in the thymus. This potentially results in more efficient negative selection of insulin reactive T cells and less susceptibility to T1D compared to class I alleles providing an attractive model for the role of the insulin gene in susceptibility to T1D but this hypothesis remains to be experimentally demonstrated.

4.2 CTLA-4

In 1996, the cytotoxic T-lymphocyte antigen-4 (CTLA-4) gene encoded on chromosome 2q33 was identified as a further T1D susceptibility gene (Nistico et al., 1996). CTLA-4 is a surface molecule found on activated T cells which produces a negative signal by inhibiting the T cell receptor signaling complex ligand interactions (blocks binding of CD80 and CD86) (Figure 2). Two major splice forms exist – encoding membrane bound and soluble forms. When CTLA-4 is knocked out, lymphoproliferative disorders result (Waterhouse et al., 1995). An A49G polymorphism in exon 1 of CTLA-4 changes the amino acid sequence resulting in reduced cell surface expression (Anjos et al., 2002). It is thought that inherited changes in CTLA-4 gene expression can increase T cell self-reactivity and therefore play an important role in autoimmune diseases such as T1D (Ueda et al., 2003).

4.3 PTPN22

More recently in 2004, protein tyrosine phosphatase non-receptor 22 (PTPN22), a gene found on chromosome 1p13 which encodes lymphoid protein tyrosine phosphatase (LYP) was found to be associated with susceptibility to T1D. Protein tyrosine phosphatases such as LYP are responsible for preventing spontaneous T cell activation and they have the ability to

prevent the response to antigen by dephosphorylating and inactivating T cell receptors. It has been demonstrated that a single nucleotide polymorphism (SNP) in the PTPN22 gene can lead to susceptibility to autoimmune diseases such as T1D because of a decrease in negative regulation of hyper-reactive T cells (Bottini et al., 2004). The first complete resequencing of the human PTPN22 gene was carried out in 2005 (Criswell et al., 2005). This sequence was further analysed for polymorphisms associated with T1D and a SNP at 1858bp in codon 620 was found. Two alleles referred to as 1858C and 1858T were identified and the 1858T variant was shown to occur more often in T1D populations: 30.6% of people with T1D compared to 21.3% healthy controls are heterozygous for the polymorphism $p = 0.0006$ (Bottini et al., 2006). LYP is expressed in other cells in addition to T cells including natural killer (NK) cells, B cells, macrophages and dendritic cells (DCs) and so could very well also have an effect on the function of several immune cells.

4.4 IL2RA/CD25

In 2005, the interleukin 2 receptor alpha (IL2RA) region on chromosome 10p15 was found to be associated with T1D (Vella et al., 2005). IL2RA encodes the α -chain of the IL-2 receptor complex (also referred to as CD25) which is responsible for binding IL-2, a key player in the proliferation of regulatory T cells. IL2R has also been associated with T1D in the non-obese diabetic (NOD) mouse (Wicker et al., 2005). Two IL-2R SNPs associated with the increased risk of T1D have been reported (Qu et al., 2007) with ss52580101 the most closely associated (Lowe et al., 2007). A recent study measuring expression of IL-2R in individuals homozygous for susceptible and protective SNPs associated with T1D demonstrated that on stimulation, higher percentages of CD69+ CD4+ memory T cells secreted IL-2 from individuals with the protective SNP compared to individuals with the susceptible SNP (Dendrou et al., 2009). More recently susceptibility genotypes were found to be associated with lower levels of soluble IL2Ralpha (sIL2Ra) (Lowe et al. 2007, Maier et al. 2009) and *in vitro* stimulation of peripheral blood mononuclear cells from individuals with T1D results in lower levels compared to healthy controls (Giordano et al. 1989).

5. Genome wide association studies

In recent years methodologies to identify susceptibility factors underlying complex disorders have improved by orders of magnitude. In particular the success of the HapMap project in identifying stretches of linkage disequilibrium decreasing the number of SNPs requiring genotyping combined with increased capacity for high throughput SNP analysis has resulted in a genetic revolution. In 2007, results of the first genome-wide association studies in seven different complex diseases was published by the Wellcome Trust Case Control Consortium (2007). Later in 2007, a further genome wide association scan was carried out and confirmed the additional associations of 12q24, 12q13, 16p13 and 18p11 with T1D (Todd et al., 2007). More recently the Type 1 Genetics Consortium (T1DGC) has published over 40 genetic loci associated with T1D (Barrett et al., 2009). A selection of the best characterized are shown on Figure 5. The genes detailed above all remain associated with T1D and most of the newly identified susceptibility genes can be positioned on immune activation pathways while some loci have yet to have the disease associated gene identified. Despite the overwhelming success of GWAS in identifying susceptibility genes for common diseases using hypothesis-free methodologies the effects of the identified genes on improved genetic risk assessments have been minimal. This is because most of the newly

identified loci make only a minimal contribution to risk with odds ratios (OR) in the range of 1.2-1.3 compared to 7 for the HLA locus (Figure 6). An OR of 1 indicates that risk is equal in healthy controls and individuals with disease. This has become known as the missing heritability and indicates, not surprisingly, that mechanisms other than common variants contribute to susceptibility to T1D. Candidates for such effects are rare variants as well as epigenetic modifications which cannot be detected by GWAS. Nevertheless the new loci identified by GWAS have informed ongoing functional studies and confirmed some interesting mechanistic loci such as IFIH1.

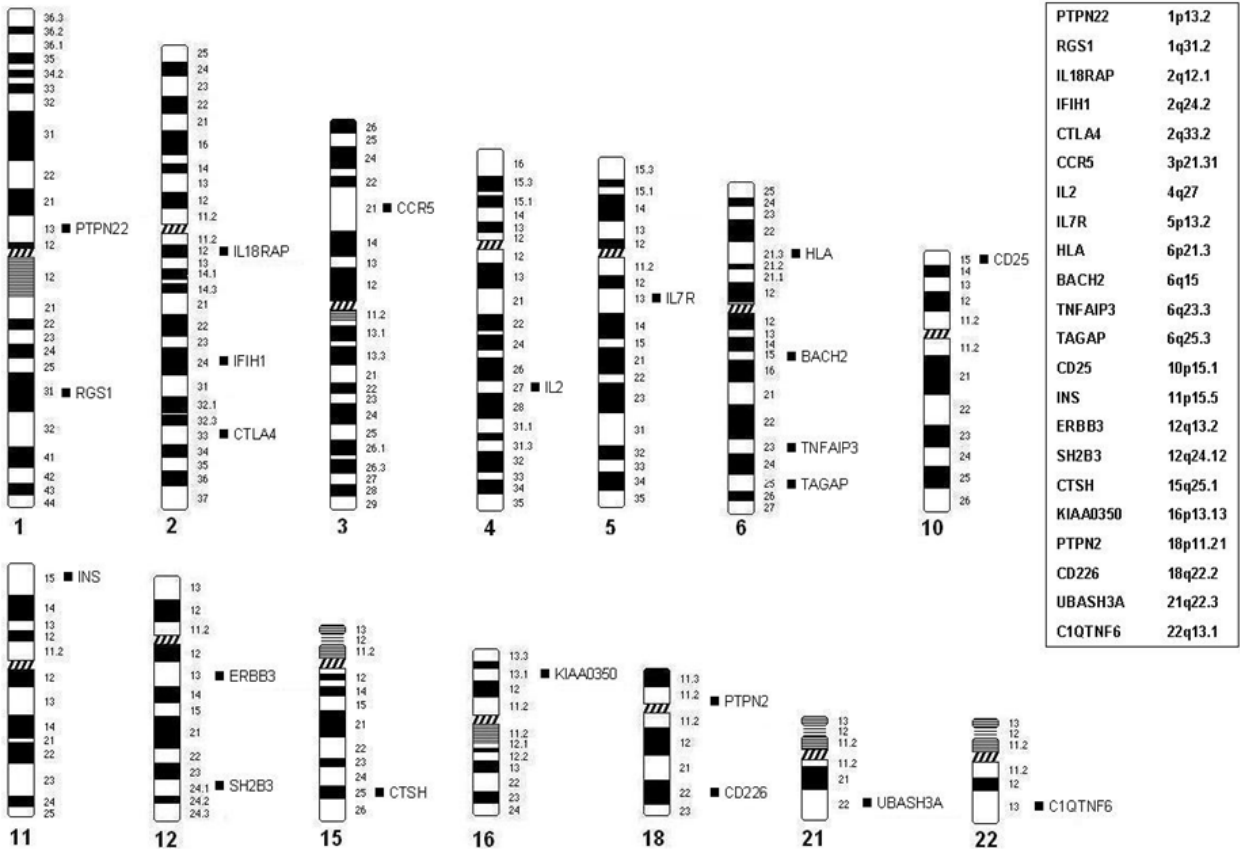


Fig. 5. Chromosomal localisation of selected T1D associated loci (adapted from Ye et al. 2010)

6. Genetic susceptibility to Type 1 diabetes in the post-GWAS era

6.1 IFIH1

In 2006, interferon induced with helicase C domain 1 (IFIH1) also known as MDA-5 on chromosome 2q24.3 was found to be strongly associated with T1D (Smyth et al., 2006) Later, in 2008, a follow up study on IFIH1 was carried out, confirming the strongest association to be with SNP rs1990760 (Qu et al., 2008). IFIH1 is particularly interesting because unlike the T1D susceptibility genes discussed so far, it is not involved in T cell activation but contributes to innate immune responses by releasing the cytokine interferon-gamma (IFN-γ) and inducing apoptosis of cells infected by picorna viruses of which enteroviruses such as coxsackie B4 which have been identified histologically in T1D pancreas (Dotta et al., 2007). This molecule may therefore provide molecular insights into the hypothesis that viral infection contributes to susceptibility to T1D as alterations in IFIH1

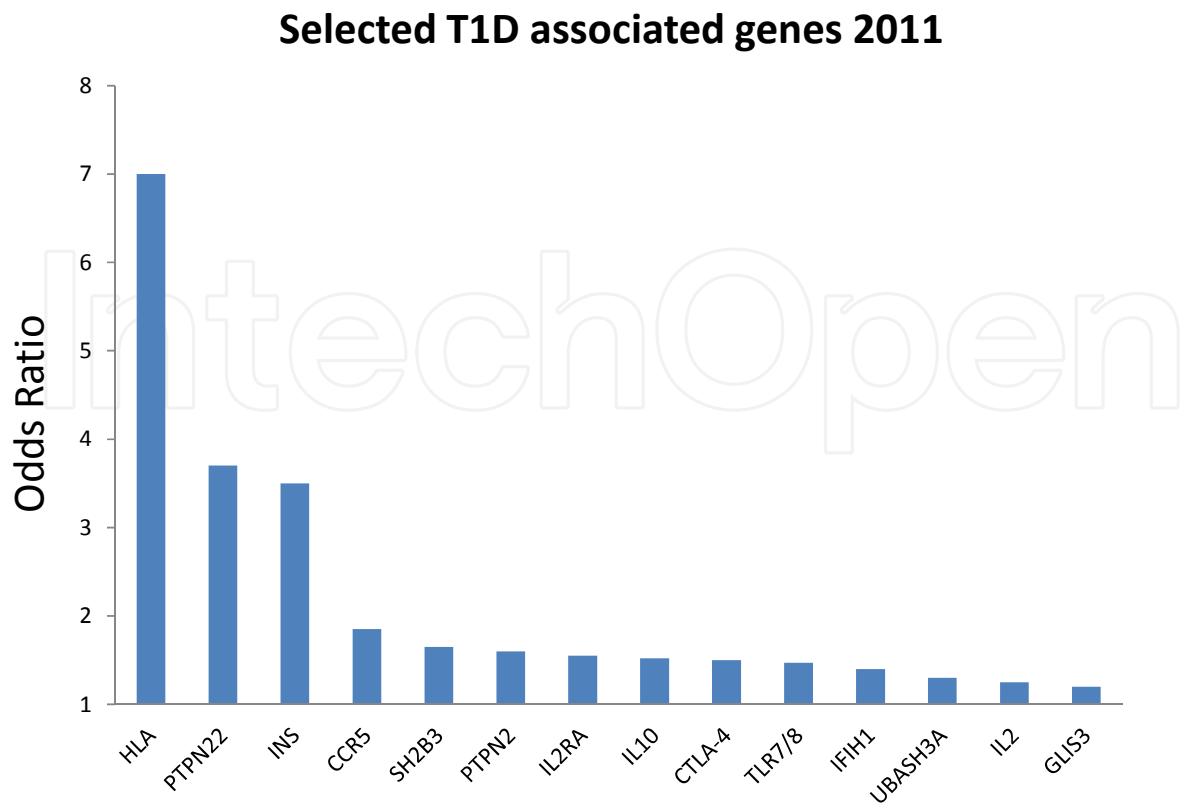


Fig. 6. The relative effect of selected T1D associated genes on susceptibility to T1D (adapted from Todd 2010)

activity could interfere with detection and clearance of virus. PBMC expression levels of IFIH1 have been reported to be higher in individuals with susceptibility genotypes (Liu et al. 2009). Recent resequencing of the IFIH1 gene identified four rare variants associated with T1D protection, which are predicted to play a role in altering the expression and structure of IFIH1 (Nejentsev et al., 2009).

6.2 TLR 7 and 8

The Toll-like receptor (TLR) family which plays a fundamental role in pathogen recognition and activation of innate immunity. TLRs are highly conserved and recognize pathogen-associated molecular patterns (PAMPs) that are expressed on infectious agents. Toll like receptors (TLR) 7 and 8 are located closely together on the X chromosome have recently been associated with T1D (Todd, 2010). TLR7 recognises single stranded RNA in endosomes, which is a common feature of viral genomes which are internalised by macrophages. Like IFIH1, the association of T1D with these receptors strengthens arguments for the involvement of viruses in the pathogenesis of disease.

6.3 CCR5

CCR5 is a chemokine receptor on the surface of several cells of the immune system including macrophages, NKT cells, CD4+ T cells and CD8+ T cells. It has been mapped to the short arm of chromosome 3 within the chemokine receptor gene cluster. Recent studies established that this gene comprises three exons spanning a region of about 6 kb. A 32bp insertion/deletion polymorphism exon 3 changes the open reading frame of CCR5 and

results in a nonfunctional protein. This polymorphism is present only in 1% of the population but deletion homozygotes are protected against HIV-1 infection (Alexander et al., 2000) as well as T1D, rheumatoid arthritis and celiac disease (Smyth et al., 2008).

6.4 UBASH3A

A chromosome 21q22.3 T1D-associated locus (rs876498) has been identified (Concannon et al. 2008) and replicated (Grant et al., 2009). The only gene in the corresponding region of linkage disequilibrium is the Ubiquitin associated and SH3 domain containing A (UBASH3A) gene which comprises 15 exons, spans 40kb, and has been shown to be expressed in spleen, bone marrow and peripheral blood lymphocytes (Wattenhoffer et al., 2009). UBASH3A suppresses T cell receptor signalling (figure 7) and may therefore provide a candidate for the increased frequency of autoimmune disease in Down syndrome (Gillespie et al., 2006).

T1D associated genes on the antigen presentation pathway

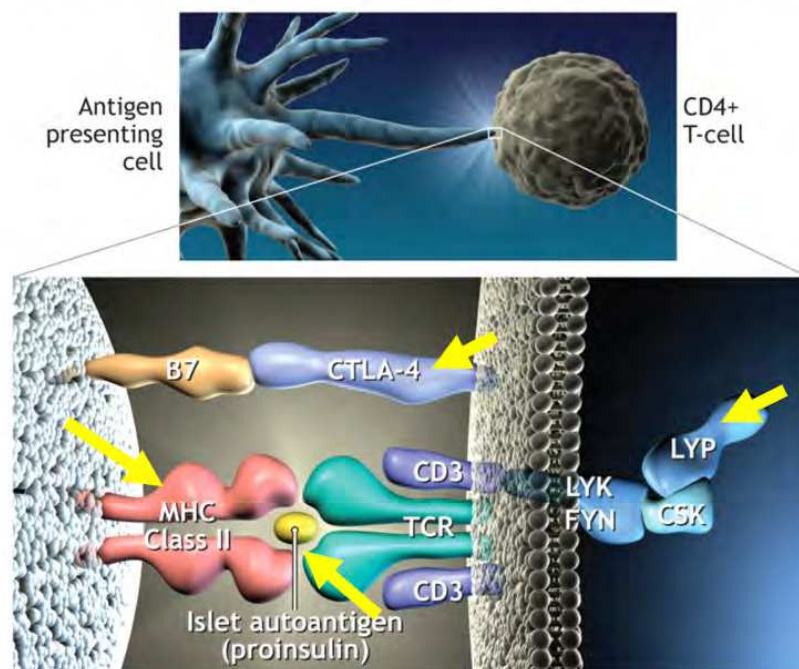


Fig. 7. Many of the T1D associated genes can be mapped onto this antigen presentation pathway when proinsulin peptide is presented to a CD4 helper T cell through the T cell receptor (TCR) this activating Lyp coded for by PTPN22 as well as PTPN2, IL2, IL2RA and UBASH3A and several others (adapted from Gillespie, 2006)

6.5 NK receptor/HLA class 1 interactions

Natural killer (NK) cells represent the first line of defence against viral infection. NK cell infiltrates have been identified in pancreas from individuals with type 1 diabetes (T1D) (Dotta et al. 2008) and increased NK cell activity has been reported in the periphery of individuals with T1D (Herold et al 1984, Nair et al 1986)]. NK cells act by either activating or inhibiting cytolysis and their activity is controlled by the balance of inhibitory and activating receptors on the cell surface. One set of human NK cell receptors are the killer immunoglobulin-like receptor (KIR) gene family on chromosome 19 [10] which consists of

16 genes; each is either inhibitory or activating in function and is polymorphic both in terms of gene content and allelic variation. Genome wide association studies of KIR in T1D are not yet available because this region of chromosome 19 does not have a high coverage SNP map but results from genetic studies of KIR in T1D increasingly show an association between T1D and the activating receptor KIR2DS2 (and its ligand, HLA C group 1). Van der Slik et al. (2003) analysed the KIR gene family and respective HLA class I ligands in 149 children diagnosed with diabetes under the age of 14 in a Dutch population and Shastry et al. (2008) carried out a similar analysis in 98 patients diagnosed with T1D under the age of 18 years compared to 70 healthy controls in a Latvian population. In addition Ramos-Lopez et al. (2009) showed, in a combined German/Belgian study of 1124 patients with T1D compared to 716 healthy controls, that a single nucleotide polymorphism (rs2756923) in exon 8 of the inhibitory gene KIR2DL2 was associated with T1D. More recent data show that activating combinations of KIR/HLA genes are more frequent in young T1D children diagnosed in the first 5 years of life suggesting that NK cell responses to viral infection are altered in this group (Mehers et al., submitted).

NK activating signals through HLA C1 increase risk of T1D

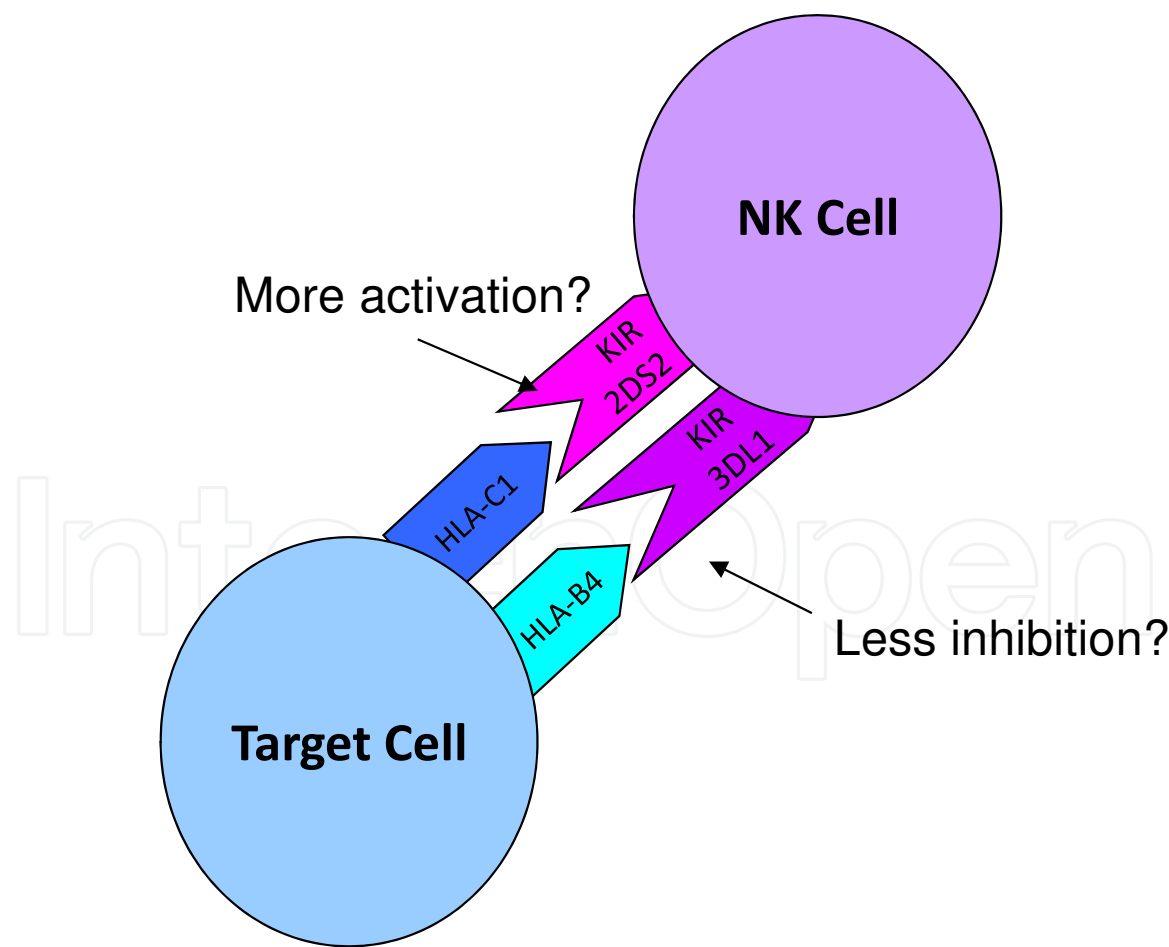


Fig. 8. Individuals with T1D more frequently express genetic combinations of NK cell activation

7. The NOD model of T1D

NOD mice, a commonly used mouse model for T1D, were generated following an experiment by Makino and colleagues in 1980 (Makino et al., 1980) where out-bred brother x sister Swiss mice were repetitively mated in order to produce a strain in which all mice developed cataracts. Mice without cataracts were found to have high blood glucose levels and were selectively bred in order to produce a mouse model strain of spontaneous diabetes development. These mice develop an autoimmune type of diabetes where pancreatic β -cells are damaged and destroyed by mononuclear cells infiltrating into the islets of langerhans (Fujino-Kurihara et al., 1985). The incidence of autoimmune diabetes in the female NOD mice varies in different colonies but generally is 60-80% and 20-30% in males (Kikutani and Makino, 1992; Atkinson and Leiter, 1999). This is in contrast to human T1D where males and females are equally affected early in life but the incidence is higher in males from adolescence onwards (Weets et al., 2001, Gale and Gillespie., 2002). Disease onset in the NOD usually occurs between 12-14 weeks in female mice and slightly later in males (Kikutani and Makino, 1992).

NOD mice are very sensitive to changes in their environment and geographical location. It has been demonstrated that changes in either of these circumstances results in a different rate of spontaneous diabetes development (Oldstone, 1988). Diabetes onset in NOD mice is prevented by administration of Complete Freund's Adjuvant (CFA), bacteria, parasites and the housing of the mice in dirty conditions, as well as many other treatments (Oldstone, 1990; Oldstone et al., 1990; Sobel et al., 1998b; Zacccone et al., 2004).

Multiple loci are involved in genetic susceptibility to autoimmune diabetes in the NOD mouse, as in humans. H-2g7, a mouse MHC haplotype, is the major genetic contributor to T1D genetic susceptibility (Kikutani and Makino, 1992; Atkinson and Leiter, 1999). Experiments investigating the MHC in the NOD mouse indicate that the MHC in mice is essential but not sufficient for β -cell destruction and development of diabetes in NOD mice (Kikutani and Makino, 1992) suggesting that, as in human T1D, other loci are important. It is increasingly clear that some susceptibility loci in humans and the NOD mouse are the same and this allows detailed functional analysis of genetic determinants of disease.

Regions of genetic association in the NOD mouse have been designated Idd numbers – for instance the MHC association is referred to as Idd1 while *ctla4* is Idd5.1. As well as the membrane bound and soluble forms of *ctla4* found in humans mice have a third form lacking a binding domain. Protection from diabetes can be mediated by over-expression of this mouse specific isoform. The IL2 signaling pathway, specifically IL2 (Lyons et al. 2000) has also been associated with diabetes in the NOD mouse (Idd3).

8. Common mechanisms of autoimmunity

More than 50 genome wide association studies have now been published and their power to identify complex gene networks that link biological pathways is increasingly clear and particularly so for autoimmunity. When data from several different forms of autoimmunity including rheumatoid arthritis, celiac disease, autoimmune thyroid disease, multiple sclerosis and type 1 diabetes are compared, common autoimmune pathways, including the HLA and genes such as PTPN22 that regulate T cell activation have become apparent. This may offer the potential for flexible therapy in the future.

9. Other genetic mechanisms underlying susceptibility to T1D

9.1 Gender and Type 1 diabetes

Unlike most other autoimmune diseases where risk is greatest in females, type I diabetes is the only major organ-specific autoimmune disorder not to show a strong female bias with risk equal between males and females in childhood. Risk in males increases in adolescence and remains higher than females thereafter. The effects of hormonal changes on risk are unknown but effects on insulin resistance could be important. Furthermore, fathers with Type I diabetes are more likely than affected mothers to transmit the condition to their offspring (Warram et al. 1988) and this observation have never been explained. Women of childbearing age are therefore less likely to develop type I diabetes, and – should this occur – are less likely to transmit it to their offspring. Parent of origin effects, precipitated by epigenetic changes to DNA are worthy of investigation.

A maternal cell in a human islet

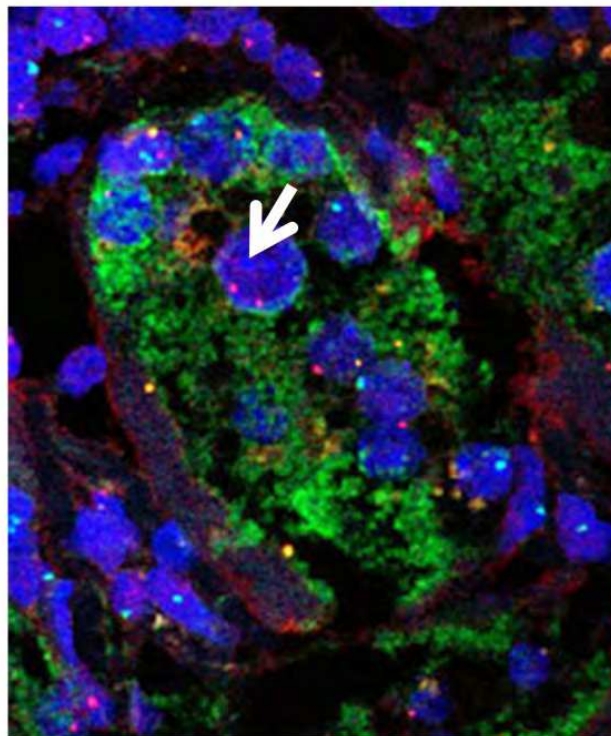


Fig. 9. A female nucleus (two red X chromosomes) in autopsy male pancreas tissue. The Y chromosome is represented as a light green dot and nuclei are stained blue with dapi. Insulin is stained green with fitc. Showing that this maternal cell lies within an islet. Adabted from van Zyl et al. 2010

9.2 Microchimerism

Some genetic mechanisms such as rare variants cannot be identified by GWAS and will be defined by high throughput next generation sequencing protocols as they increasingly become available. Other mechanisms that require further investigation are DNA methylation and other epigenetic changes to DNA that could increase risk of future type 1 diabetes. Further, over the last decade there have been several reports of associations

between maternal cells, which are known to persist in her progeny for several decades (Maloney et al. 1998). Maternal DNA is often detected by testing for the presence of the non-inherited maternal allele (NIMA) and increased levels of maternal DNA or cells have been associated with several different autoimmune diseases (reviewed by Nelson 2008). One study of 464 T1D families by Pani et al. (2002) showed that the non-transmitted HLA DR3-DQ2 and DR4-DQ8 were more frequent in mothers than in fathers of all non-DQ2/DQ8 heterozygous diabetic offspring, as well as in offspring not carrying any HLA high-risk allele. In patients with either risk allele alone, more maternal than paternal non-transmitted risk alleles complemented the constellation to DQ2/DQ8. This suggested that the non-inherited maternal allele was contributing to T1D susceptibility. This observation however could not be replicated in two other studies (Lambert et al. 2003, Herrman et al. 2003). Several years later, using a more sensitive quantitative PCR for the NIMA, Nelson et al (2007) showed that NIMA levels were increased in children with T1D compared to unaffected siblings and healthy controls. Intriguingly using fluorescence in situ hybridization (FISH) for the X and Y chromosomes, this study also showed evidence for the presence of maternal cells in autopsy pancreatic islets of individuals with T1D and healthy controls, although the frequency of maternal cells was higher.

This increased frequency of maternal cells in autopsy T1D was confirmed in a follow up study (van Zyl et al. 2010). The role of these cells in T1D is, as yet, unclear. If they are functioning beta cells could represent the target of the immune response or alternatively could be immune effector cells. Further studies are required in this new area of biology.

10. Conclusions

Type 1 diabetes is a disease of major personal, medical and financial significance. The recent rapid increase in the frequency of the disease, especially in those diagnosed under the age of 5 years is alarming. Thirty years of research have demonstrated the importance of underlying genetic susceptibility. Major improvements in identifying the genetic determinants of complex disease have resulted in an explosion of information on the genetic pathways contributing to autoimmune diabetes. While these genetic determinants have not enhanced assessment of genetic risk for participation in intervention trials (HLA mediated risk remains the most robust means of estimating genetic risk), they have identified immune and biochemical pathways that may potentially be targeted therapeutically in the future.

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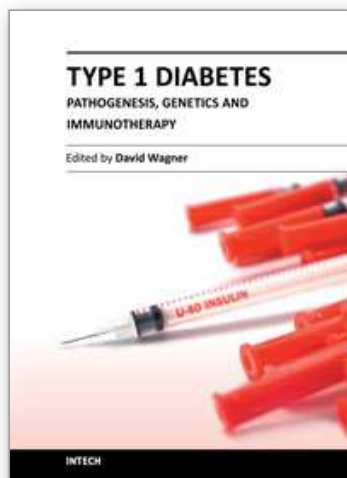
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This book is a compilation of reviews about the pathogenesis of Type 1 Diabetes. T1D is a classic autoimmune disease. Genetic factors are clearly determinant but cannot explain the rapid, even overwhelming expanse of this disease. Understanding etiology and pathogenesis of this disease is essential. A number of experts in the field have covered a range of topics for consideration that are applicable to researcher and clinician alike. This book provides apt descriptions of cutting edge technologies and applications in the ever going search for treatments and cure for diabetes. Areas including T cell development, innate immune responses, imaging of pancreata, potential viral initiators, etc. are considered.

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51000 Rijeka, Croatia
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