Diabetes type 1

Overview and pathophysiology

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Diabetes type I- Features

- Juvenile diabetes or IDDM.
- Usually diagnosed in children and young adults
- When body's own immune system destroys the B-cells of the pancreas

- Life long dependency on Insulin.
- Hyperglycemia and ketoacidosis are hallmarks of T1D.

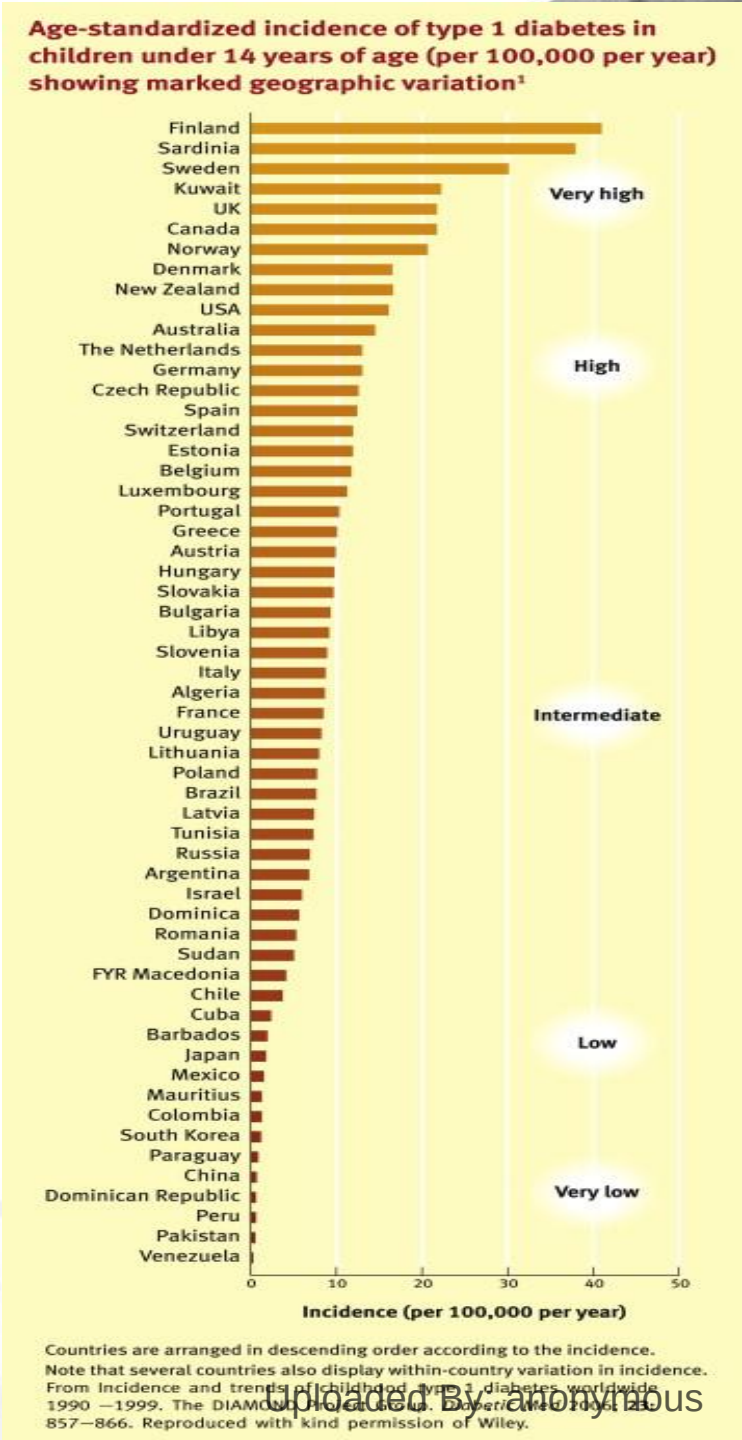
- The incidence of T1D continues to increase worldwide at a rate of nearly 3% per year.

Diabetes type I- Epidemiology

The incidence of type 1 diabetes in children varies nearly 400-fold between countries.

- Age-adjusted incidence rates ranging from 0.1 per 100,000 per year in parts of Venezuela and China **to 37.8 in Sardinia and 40.9 per 100,000/year in Finland**

Forouhi & Wareham, 2014



Diabetes type I- Epidemiology

- Type 1 diabetes can occur at any age, but in most populations the Incidence is highest between **birth and 14 years old.**

- Peak incidence is around puberty in most populations.

- incidence is higher in populations of European origin than in non-Europeans.

Forouhi & Wareham, 2014

Type 1 DM- Diagnosis & Screening

- Blood glucose rather than A1C should be used to dx type 1 diabetes in symptomatic individuals.

- Screening for type 1 diabetes with an antibody panel is recommended only in the setting of a clinical research study or in a first-degree family members of a proband with type 1 diabetes.

American Diabetes Association Standards of Medical Care in Diabetes. Classification and diagnosis of diabetes. Diabetes Care 2017; 40 (Suppl. 1): S11-S24

Diabetes type I- Aetiology

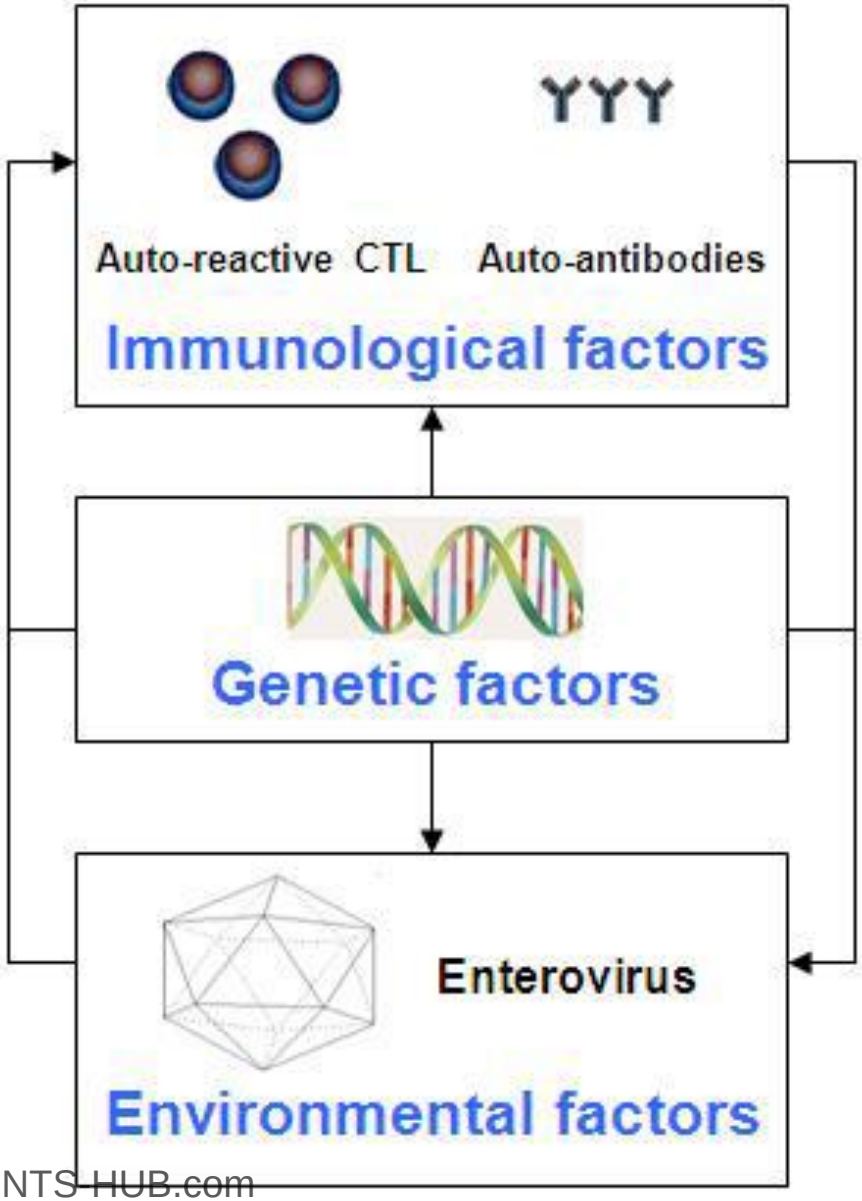
Diabetes type I- Aetiology

- Type 1 diabetes mellitus considered an autoimmune disease involving genetic, immunologic and environmental factors characterized by a direct attack to pancreatic beta cells.

- 90% of the cases are T-cell mediated autoimmune destruction.

- **Aetiology is complex and not well understood**

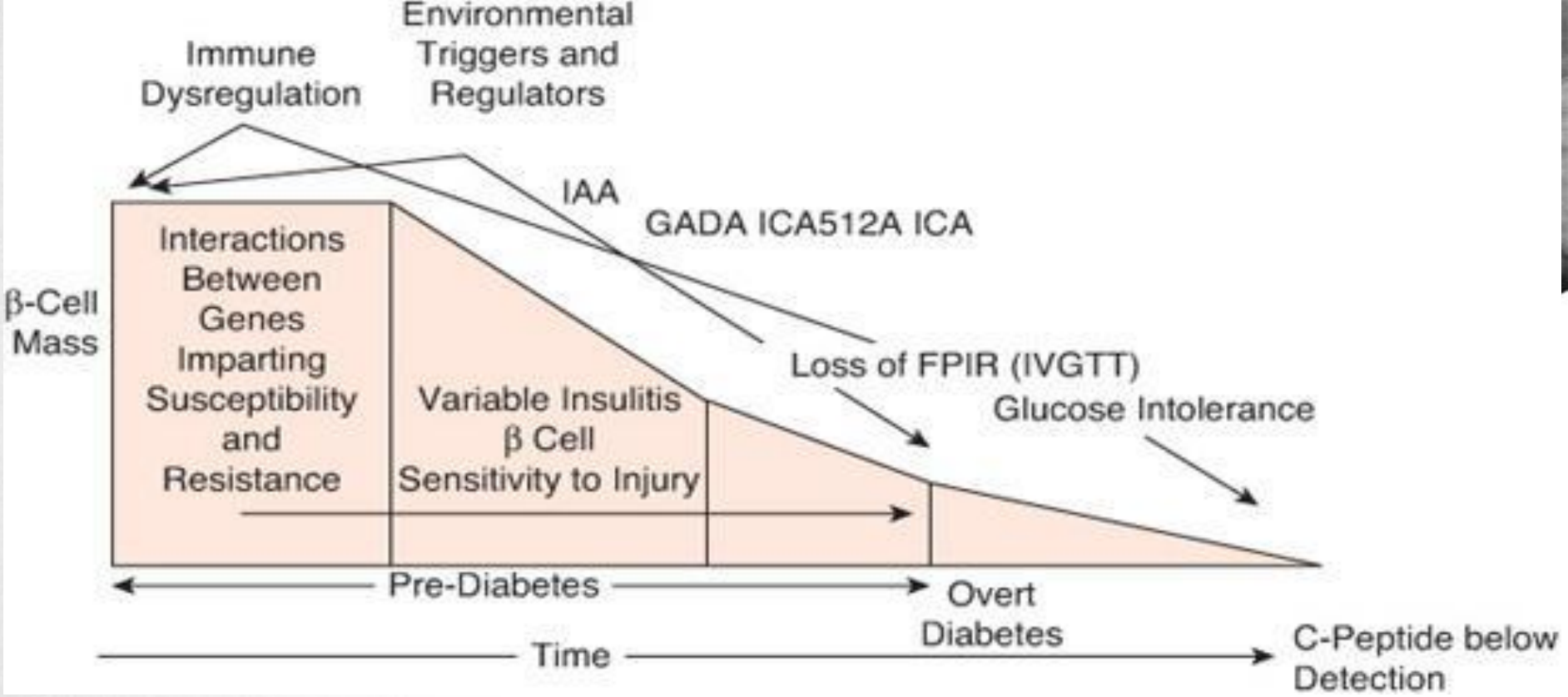
Diabetes type I- Aetiology



Pancreas

β cells

Type 1 diabetes



Model of the pathogenesis and natural history of DM I. involves the roles for genetics, immunology, and environment in the natural history of T1D.

(Adapted from Atkinson and Eisenbarth 2001)

Diabetes type I- Aetiology

- During the largely silent preclinical phase of the disease, beta-cell destruction may persist for weeks, months, or even years until insulin production is first unable to maintain normal glucose metabolism.

- More severe insulin deficiency, is unable to inhibit fatty acid metabolism

Diabetes type I- Aetiology/Genetic susceptibility

- The lifelong risk of type 1 diabetes is markedly increased in close relatives of a patient with type 1 diabetes

→Averaging about 6% in offspring, 5 % in siblings

→50 % in identical twins

- A monozygotic twin of a patient with DM I has a higher risk of diabetes than a dizygotic twin, and the risk in a dizygotic twin sibling is similar to that in non-twin siblings

Diabetes type I- Aetiology/Genetic susceptibility

- Diabetes with onset before age 5 years is a marker of high familial risk and suggests a major role for genetic factors.

→ Siblings of children with onset of T1D before the age of 5 years have a **3-to 5-fold greater** cumulative risk of diabetes by age 20years compared with siblings of children diagnosed between 5 and 15 years of age

Diabetes type I- Aetiology/Genetic susceptibility

- All these indicate strong genetic effect.
- Inheritance of susceptibility to and protection fromT1D are multifactorial and polygenic.

Diabetes type I- Aetiology/Genetic susceptibility

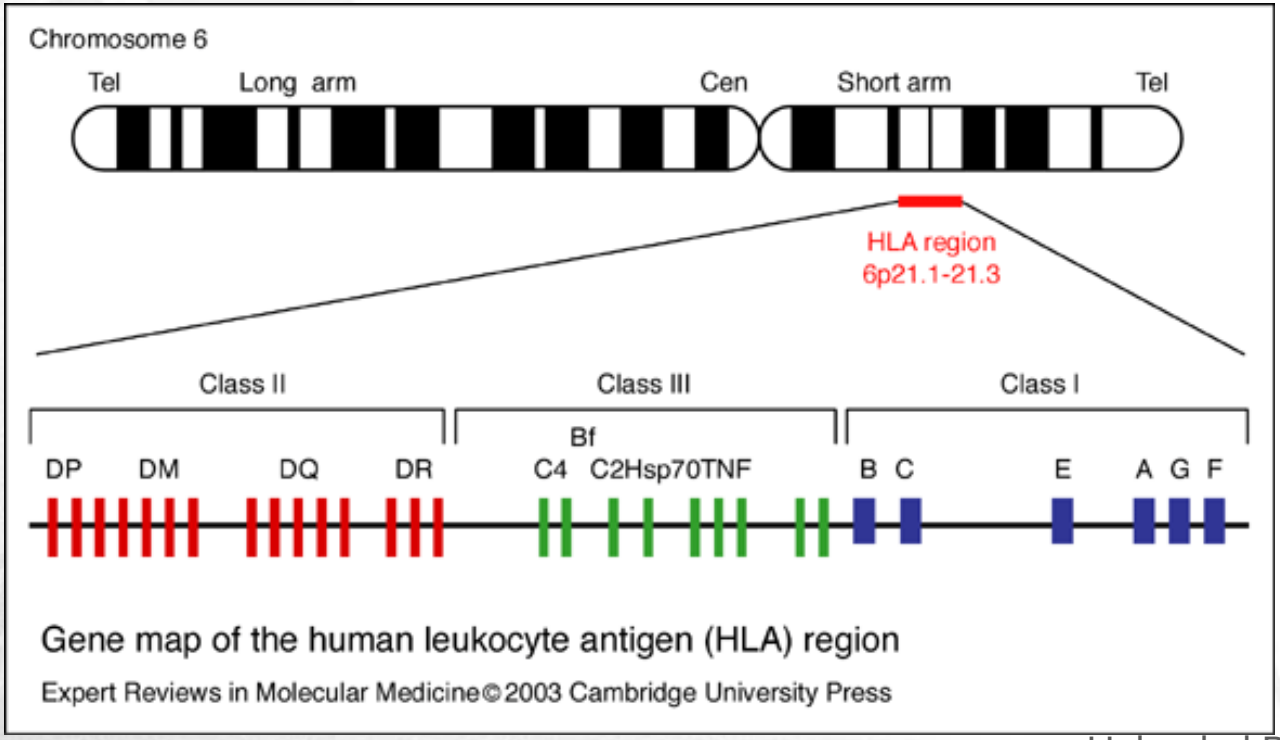
- In the mammalian system, each and every nucleated cell has **special marker molecules, expressed at the cell surface**, which help in identifying them as constituents of its own system.

- In humans it is called Human leukocyte antigen (HLA)

- HLA loci on chromosome 6p21 are the major genetic susceptibility determinants in DM I.

Diabetes type I- Aetiology/Genetic susceptibility

- The **human leukocyte antigen** (**HLA**) system is a gene complex encoding the **major cell surface proteins that are responsible for the regulation of the immune system in humans.**



Gene map of the human leukocyte antigen (HLA) region

Expert Reviews in Molecular Medicine © 2003 Cambridge University Press

Diabetes type I- Aetiology/Genetic susceptibility

- **Only some of the HLA region genes are involved in the immune response**; in particular, the genes that encode the classical **HLA class I (A, B, and C) and class II (DR, DQ, and DP) antigens.**

- **Class II genes were more strongly associated with DM I risk than class I or other genes.**

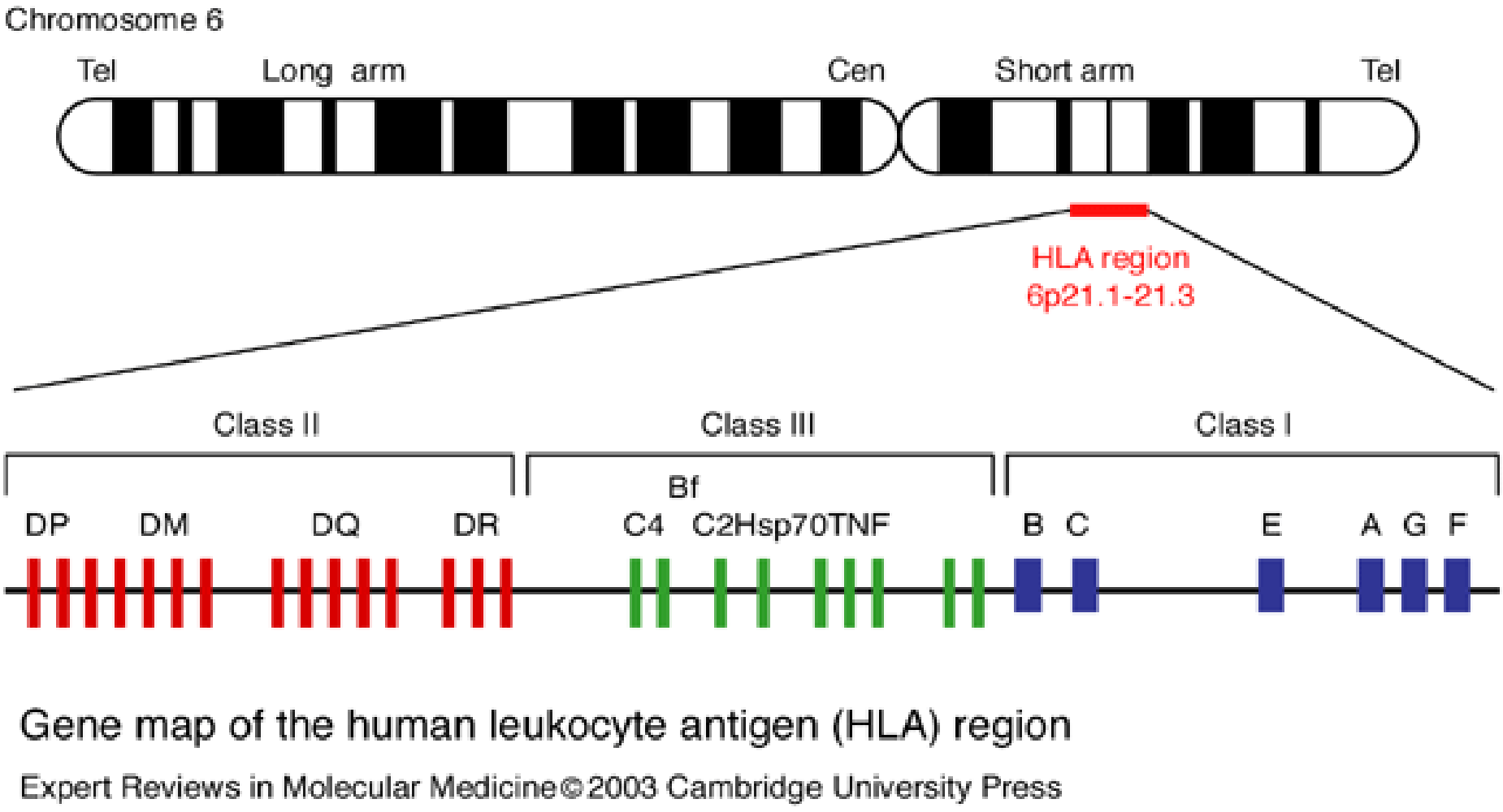
Noble & Erlich, 2012

Diabetes type I- Aetiology/Genetic susceptibility

- **Class II genes** : macrophages, T cells, dendric cells, epithelial cells of islet of Langerhans.

- Studies have shown that some variants of HLA-DQ and DR genes are involved primarily in the genetic predisposition to type 1 diabetes mellitus.

- **Among these, the HLA-DQ locus is the strongest susceptibility candidate**



Gene map of the human leukocyte antigen (HLA) region

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Diabetes type I- Aetiology/Genetic susceptibility

- Class II HLA play a role in Presenting foreign and self Antigen to T cells.

- Some polymorphisms result In **a.a substitutions** which at the end might lead to destruction of cells by T-cells.

Diabetes type I- Aetiology/Genetic susceptibility

- **The function of the HLA/peptide complex** in directing the immune response suggests **a role for HLA in both the immune response to environmental pathogens and in autoimmune disease.**

- HLA was originally identified through its role in transplant rejection

- HLA has been implicated in the etiology of >100 diseases, including, but not limited to, complex autoimmune diseases, such as type 1 diabetes, rheumatoid arthritis, and multiple sclerosis; cancers,

Noble & Erlich, 2012

Diabetes type I- Aetiology/Genetic susceptibility

- The genes known to affect T1D susceptibility can be grouped into three general categories: immune function, insulin expression, and β-cell function.

- After HLA, the strongest susceptibility locus is in the insulin gene itself, in which promoter polymorphisms affect insulin expression levels. Other candidate loci are involved in β-cell function.

Noble & Erlich, 2012

Diabetes type I- Aetiology/Autoimmunity

- Islet cell autoantibodies (ICAs) were first detected in serum from patients with autoimmune polyendocrine deficiency;
- They have subsequently been identified in 85 percent of patients with newly diagnosed type 1 diabetes and in prediabetic subjects

- Patients with more of the different types of antibodies appear to have the most accelerated islet destruction and a higher requirement for exogenous insulin during the second year of clinical disease

Diabetes type I- Aetiology/cellular immunity

- The existence of IgG immunoglobulins directed to epitopes of islet autoantigens implies the influence of T cell participation in the autoimmune response.

- The occurrence of type 1 diabetes in a 14-year-old boy with X-linked agammaglobulinemia suggests that B cells are not required for the development of the disorder and that the destruction of pancreatic beta cells is mediated principally by T cells

Diabetes type I- Aetiology/Environmental factors

- Environmental influences are another important factor in the development of type 1 diabetes.
- The best evidence for this influence is the demonstration **in multiple populations of a rapid increase in the incidence of type 1A diabetes**
- The etiology of the increase is unknown.

Diabetes type I- Aetiology/Environmental factors

- Some hypothesis:
- **The hygiene hypothesis** → relates improved "sanitation" to increasing immune mediated disorders .
- **Twin studies** indicate that not all monozygotic twins of probands with type 1 diabetes develop diabetes, although the cumulative prevalence increases with long-term follow-up.

Diabetes type I- Aetiology/Perinatal factors

- Maternal age >25 years, preeclampsia, neonatal respiratory disease, and jaundice, especially that due to ABO blood group incompatibility → **Increase the risk, but not significant.**

- Protective factors were low birth weight and short birth length.

- These associations remain unexplained.

Diabetes type I- Aetiology/Role of viruses

- Viruses can cause diabetes in animal models either by **directly** infecting and destroying beta cells or by **triggering an autoimmune attack** against these cells.

- Although isolated case reports have suggested direct viral destruction of beta cells , **this is probably extremely rare.**

- However, some unusual forms of diabetes have been associated with the presence of Coxsackie virus in a large number of beta cells

Diabetes type I- Aetiology/Role of viruses

- **The importance of autoimmune activation is also uncertain.**

- **Coxsackie B virus-specific IgM responses have been found in 39% of children with newly diagnosed type 1 diabetes, compared with only 6 % of normal children.**

  - ✓ **Coxsackie virus antibody titers** were significantly higher in pregnant women whose children developed DM I.

  - ✓ **Enteroviral infections** were almost **2X more common in siblings who developed DM I** than in siblings who remained nondiabetic.

Diabetes type I- Aetiology/Role of viruses

“These observations suggest that exposure to enteroviruses, both in utero and in childhood, can induce B-cell damage and lead to clinical diabetes.”

- The possibility of viral-induced autoimmunity or molecular mimicry is supported by long-term follow-up of infants with the congenital **rubella syndrome**.

→ Autoimmune diabetes and other autoimmune diseases may occur **5 to 20 years after infection**

Diabetes type I- Aetiology/Role of viruses

- Rat models have shown the clearest associations.

- However, there is some conflicting results between studies.

Diabetes type I- Aetiology/Childhood immunization

- There has been concern that childhood vaccination may be associated with later development of chronic diseases, including type 1 diabetes.

→ However, immunization of genetically pre-disposed infants (siblings with DMI) does not appear to be associated with an increased risk of developing DM I.

Diabetes type I- Aetiology/Diet

- Several dietary factors may influence the development of type 1 diabetes.

→ **Most attention having been paid to cow's milk.**

Diabetes type I- Aetiology/Diet-Cow's milk

- Some component of albumin in cow's milk **(bovine serum albumin),** the basis for most infant milk formulas, may trigger an autoimmune response.

- E.g. **Epidemiologic data from Finland** suggest that there is an increased risk of type 1 diabetes associated **with introduction to dairy products at an early age and with high milk consumption during childhood.**

Is it proved in literature? Conflicting results.

Diabetes type I- Aetiology/Diet-Cow's milk

- **Suggestion - a cell-mediated response to a specific cow's milk protein, beta-casein**, may be involved in the pathogenesis of DM I.

→ In one report, 36 patients with recent-onset DM I were compared with 36 normal subjects ; Exposure to bovine beta-casein **led to proliferation of peripheral blood T-cells in 51 %** of the patients with DM I verses only one (3%) of the normal subjects.

→ An epidemiological study of children **from 10 countries** revealed **a strong correlation** between the incidence of DM I and the consumption of beta-casein.

Diabetes type I- Aetiology/Diet-Vitamin D

- Might be a protective factor.

- A case- control study in seven European countries suggested that supplementation with vitamin D in early infancy can protect against development of DMI.

- A similar protective effect was noted in a birth-cohort study of over 10,000 children→ The children who regularly took vitamin D (2000 IU daily) had a reduced risk of DM I Vs. children with lower intake

Diabetes type I- Aetiology/Diet- cereals

- In high risk infants → the timing of initial exposure to cereals may affect the risk of developing **islet cell autoantibodies (IA).**

- Maybe due to gluten →

  Early introduction of gluten (<3 months of age) increases the risk of celiac disease.

- DM I and coeliac disease share disease-specific alleles.

Early introduction of solid foods ?

Diabetes type I- Aetiology/Omega-3 FA

- Inverse association between omega-3 fatty acid intake and development of islet autoimmunity.

- A case-control study from Norway → children with DM I were less likely to be given cod liver oil (containing omega-3 fatty acids and vitamin D) during infancy than children without diabetes

Diabetes type I- Aetiology/Diet- Nitrates

- Studies in Colorado and in Yorkshire (UK) have found that the incidence of DM I correlates with the concentration of nitrates in the drinking water

- The incidence is about 30% higher in areas with nitrate concentrations >14.8 mg/L compared with areas with concentrations < 3.2 mg/L.