

Genetic factors in DM

The rule of genetic factor is under scored



DR. SAAD SH. HAMDAI
DEPARTMENT OF MEDICINE

Genetics and environmental factors



Type I	Type II
a. In identical twins concordance rate of 30 – 50% higher than non identical	a. Concordance rate is 100% but no information about what is inherited



Type I

b. So environmental factors must be important for disease expression

Type II

b. The expression is modified by environmental factor



Type I

c. Although all genes not identified one is located within the insulin promoter on ch. 11 the other involve HLA region on short arm of CH 6

Type II

c. Hyperglycemia impair insulin secretion and actions known as glucose toxicity it is difficult to determine which one started the vicious cycle



Type I

HLA play dominant role the risk of DM is 15 – 20% if the sibling are identical, 5% if they have one HLA, and less than 1% if they are HLA non identical

Type II

Type II neither HLA linked nor autoimmunity

Type I



- Specific type of HLA are linked to type I DM, 90–95% express DR3 and/or DR4 class II HLA as compared with incidence of 50–60% in the general population (10 – fold)
- Another class II, HLA – DR2 has negative association
- Class II DQ (DQ8 and DQ2) more strongly associate in white individuals

Type I



F. Polymorphisms of B chain of DQ
change susceptibility, presence of
aspartic acid at position 57 protect
against DM while other AA increase.

Type II



Insulin level normal or high but not increase following CHO ingestion, this suggest a specific abnormality in recognition of glucose by the B cell, cause is unknown

Type II



- The mechanism however been defined in MODY type II, mutation in the gene encoding glucokinase, the enzyme responsible for the phosphorylation of glucose in B cell and liver

Type II



- Insulin receptors may be reduced, defects is more distal (post-receptor) play predominate role

Type II



- Glucotoxicity ;glucosamine (hexosamine pathway) induce insulin resistance by impairing insulin induced GLUT4 translocation to the cell membrane in adipocyte and skeletal muscles, activation of protein kinase C may contribute

Type II



- Loss of glucose-stimulated insulin secretion is followed by decreased expression of GLUT2, beta cell glucose transporter. This will lead to further loss of glucose stimulated insulin secretion

Type II



- Insulin is normally secreted with amyloid like protein (amylin), chronic hyper secretion of this polypeptide with insulin lead to its deposition inside cells, that lead to impaired beta cell function

Type II



- Insulin resistance is poorly understood, a defect in insulin binding to its receptors, leprechaunism (Growth retardation and insulin resistance)

Type II



- Other types of resistance; severe receptors deficiency with acanthosis nigricans, polycystic ovaries, and hirsutism, or anti-insulin receptors Abs (Acanthosis nigricans and other autoimmune phenomena)

Type II



- Abdominal obesity fat, have higher rate of lipolysis and more resistant to insulin, than fat from peripheral deposits

Type II



- Type II DM: Gene on ch2 encoding a cystine protease, calipain - 10

Type II



- Several adipokines secreted by visceral fat affect insulin action, leptin and adiponectin seem to increase sensitivity by increasing hepatic responsiveness.

Type II



- Two others, TNF- α , and resistin interfere with insulin action are high in type II

Other specific types of DM:



1. MODY; impaired glucose induced secretion of insulin
six subtypes all, have mutation of a nuclear transcription factor that regulate islet gene expression, and type 2 have glucokinase gene defect.
2. DM due to mutant insulin very rare autosomal dominant gene.
3. DM due to mutant insulin receptors.
4. DM associated with mutation of mitochondrial DNA. Only the mother transmits mitochondrial genes (with hearing loss or MELAS syndrome (myopathy + encephalopathy + lactic acidosis + stroke))
5. Wolfram's syndrome (DI, DM, OA, D)



- Syndrome X - Non diabetic with insulin resistance, low HDL, high TG& uric acid, obesity, prothromotic state

Thank You!

