

## GENETIC ASPECTS OF DIABETES MELLITUS

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**Summary:** Practically all types of diabetes mellitus (DM) result from complex interactions of genetic and environmental factors. Multifactorial and polygenic Type 1 DM is strongly influenced by genes controlling the immune system, mainly HLA-DQ and DR. In addition to this, many other predisposition loci, interacting with each other, have some influence on susceptibility to DM. Heterogeneous Type 2 DM, accounting for about 85 % of all diabetic patients, is supposed to be induced by multiple genes defects involved in insulin action and/or insulin secretion. Other genetically influenced traits like obesity and hyperlipidemia are strongly associated with the Type 2. The group called Other specific types of DM include monogenic forms MODY 1-5 and many various subtypes of the disease, where the specific gene mutations have been identified. Both genetic and intrauterine environmental influences are likely to contribute to the abnormalities defined as Gestational DM.

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**Key words:** *Diabetes mellitus; Genetics*

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### Introduction

Practically every aspect of human biology from birth to death is more or less influenced by genetic constitution. Genes not only predict our colour of skin, hair and eyes, but also influence body weight, susceptibility to diseases or their complications, and even response to different therapies for disease.

Close connection between gene and disease is best apparent in case of inborn errors of metabolism. These mendelian autosomally or gonosomally encoded diseases represent a large group of monogenic defects, affecting transport, anabolic, catabolic or structural functions in the body. Considerable genetic heterogeneity makes sometimes the diagnostic difficult.

Much more complicated challenge is to find genes involved in diseases that have a complex pattern of inheritance, such as those that contribute to asthma, cancer, cardiovascular diseases, mental illness or diabetes. In all these cases, no one gene is responsible for the decision whether a person has a disease or not. Probably more than one mutation is required before the disease is manifest. A number of genes may each make a subtle contribution to a person's susceptibility to a disease, genes may also affect how a person reacts to environmental factors.

Both the American Diabetes Association and the World Health Organisation (WHO) working groups met separately to discuss and similar conclusions were reached so that a new classification and diagnosis system of diabetes mellitus (DM) has been accepted in 1997 (15).

This classification include *Type 1*, both autoimmune and non-autoimmune forms with beta-cell destruction, *Type 2* with varying degree of insulin resistance and insulin hyposecretion, *Other specific types of DM*, where the cause is better defined, and *Gestational DM*. Regardless of underlying cause, DM is subdivided into three groups: 1) *insulin requiring for survival* (to prevent ketoacidosis, coma and death), 2) *insulin requiring for metabolic control*, rather than survival (insufficient endogenous insulin secretion for normoglycaemia) and 3) *not insulin requiring* (non-pharmacological control or drugs other than insulin used).

All types of DM have some genetic determinants. These „diabetogenic genes (alleles)“ make some individuals more susceptible to developing diabetes than others, they make them to be more susceptible to complications and they influence diabetes-associated phenotypes as obesity and hyperlipidemia.

### Role of genetics in type 1 diabetes

Type 1a DM ( $\beta$ -cell destruction leading to absolute insulin deficiency, low C-peptide and ketosis can appear at any age, but usually in lean, younger patients) is strongly influenced by *genes controlling the immune system*. Markers of immune destruction, including islet cell antigen-2 (IA-2), glutamic acid decarboxylase (GAD65) and/or to insulin autoantibodies, are present in 85-90% of individuals with Type 1 DM. These patients may also have other autoimmune disorders, e.g. Hashimoto's thyroiditis or Addison's

disease. Especially genes for particular HLA (Human Leucocytes Antigens or transplantation antigens) DQ, DR3 and DR4 types on chromosome 6 clearly play a role, and still healthy people with those HLA outfits are in danger. Studies in both humans and mice indicate that the insulin gene on chromosome 11, the cytotoxic T-lymphocyte antigen (CTLA-4) gene on chromosome 2 and many other predisposition genes, interacting with each other, have some influence on susceptibility to DM. There exist fulminant *idiopathic* forms, Type 1b DM in some subjects of African and Asian origin with a remarkably abrupt onset, high serum pancreatic enzymes concentration and permanent insulinopenia, but without any evidence of autoimmunity, insulinitis or diabetes-related antibodies.

Another rare type with a very slow autoimmune process is called *LADA* (latent or late onset autoimmune diabetes of adults, usually adipose). Function of the  $\beta$ -cells is initially only low-grade degraded, but lately a rapid waste of insulin secretion occurs.

A genetic predisposition to autoimmune destruction of beta cells is also related to environmental factors that are still poorly defined. Type 1 DM, then, is believed to be polygenic and multifactorial disease (4,5,7,8,11,12,14-17).

### Genetic background in the development of type 2 diabetes

The most common form of diabetes, Type 2 DM (accounting for 85 % of DM patients) is a heterogeneous disease with wide variety of phenotypes. It occurs with increasing frequency with age at patients without ketosis or autoimmune phenomena, but often with a positive family history. Both environmental and genetic factors are required for clinical expression. Genetic factors play a critical role in the development of the disease and may be even more important than in Type 1. *Defect of multiple genes controlling synthesis of the proteins involved in insulin action or/and insulin secretion* is supposed. Type 2 DM is strongly associated with many other genetically influenced traits, including obesity (OBS gene on chromosome 7 involved), hyperlipidemia, accelerated atherosclerosis, hypertension, and even polycystic ovarian disease.

The polygenic (as a consequence of an ancient thrifty genotype, no more profitable in modern society) and the fetal malnutrition theory of pathogenesis of DM Type 2 has been speculated (6,9,15).

### Genetic factors in complications

Although many people with Type 1 or Type 2 diabetes will ultimately develop one or more of the devastating long-term microvascular complications of the disease, some patients are completely spared. *The risk of developing complications*, particularly damage, dysfunction and failure of various organs, especially the kidney, eye, nerves, heart and blood vessels, appears to be *genetically determined*,

described variously as Syndrome X, the Insulin Resistance Syndrome or the Metabolic Syndrome (15).

### Other specific types of DM

There exist specific genetic subtypes, clinically presenting as Type 2 DM, called *maturity-onset diabetes of the young (MODY)*, accounting for about 5 % of all DM patients. They are associated with monogenic defects in beta-cell function, usually with a dominant type of inheritance, frequently characterised by onset of mild hyperglycaemia before age 25 years. They occur in all ethnic and racial groups, although their prevalence may differ.

Here belong rare but severe post-pubertal form *MODY 1* with impaired hepatic nuclear factor-4-alpha, HNF4-alpha, insulin secretory defect and insulin resistance (chromosome 20q12-q13.1), and the *MODY 3*, caused by a mutation of hepatic transcription factor-1, TCF1 gene (chromosome 12q24.2), combined with an isolated defect of insulin secretion. Defect of glucokinase, „glucose sensor“ for  $\beta$ -cells (chromosome 7p15-p13), leading to impaired insulin secretion and decreased processing of glucose to glycogen causes rather common, mild DM of children, *MODY 2*. Both the neonatal form *MODY 4* with pancreatic agenesis, caused by insulin promoter factor, IPF1 defect (chromosome 13q12.1) and a mild diabetes *MODY 5* with impaired hepatic transcription factor-2, TCF2 (chromosome 17cen-q21.3), combined with renal diseases, are the other *MODY*-forms. Before the precise identification of mutations is made, possible new types are designed *MODY x*.

Other types include various forms of DM with *impaired  $\beta$ -cell differentiation* (an autosomal recessive congenital absence of  $\beta$ -cells with normal appearance of pancreatic islets leading to early death, defect on chromosome 6, MHC-5-cM portion).

*Mutation* in either the structural gene or some of the processing steps of *insulin receptor* may lead to insulin resistance: An impaired receptor binding with mild carbohydrate intolerance, most prominent in skeletal muscle (defect on chromosome 2q36, autosomal dominant pattern of inheritance) was described. Peroxisome proliferator-activated receptor-gamma, PPARG 1-3 (chromosome 3p25) is a member of the nuclear hormone receptor subfamily of transcription factors. PPARG is believed to be involved in adipocyte differentiation.

*Defects of insulin action* include a form often combined with acanthosis nigricans, i.e. hyperpigmentation and skin keratosis, with virilization and polycystic ovaries, former Type A insulin resistance (mutation on chromosome 19p13.2).

Leprechaunism (Donahue's) and Rabson-Mendenhall syndrome are two long-time paediatric syndromes with pineal hyperplasia, abnormalities of teeth and nails and extreme insulin resistance caused by decreased insulin binding, reduced affinity of the receptor, reduced number of receptors or defects of insulin receptor phosphorylation.

One of *variant types* of DM is induced by predisposition factors, frequent in Mexican Americans from Texas (chromosomes 2q & 15q21.1 and 13 other regions). Defect of the low-affinity glucose transporter 2 (GLUT2) (chromosome 3q26.1-q26.3), impaired neurogenic differentiation factor (chromosome 2q32), mitogen-activated protein kinase 8-interacting protein 1, MAPK8IP1 (chromosome 11p12-p11.2) and hyperproinsulinemia, inability to convert proinsulin to insulin (chromosome 11p15.1-p15.5), those are other examples of this DM subgroup. Point mutations in mitochondrial DNA (genes encoding the tRNA leucine-gene, most common at position 3243) have been found to be associated with DM and deafness. An identical lesion occurs in the MELAS syndrome (Mitochondrial myopathy, Encephalopathy, Lactic Acidosis, and Stroke-like syndrome); however, diabetes is not part of this syndrome. This is an example of different phenotypic expressions of the same genetic lesion. Rare, in about half of the affected transient, neonatal DM (mutation on chromosome 6q22-6q24), resolving at the age of 3 months often reappears as Type 2 DM later in life (3,10,13,15).

#### ***Other Genetic Syndromes Sometimes Associated with Diabetes***

Many genetic syndromes are accompanied by an increased incidence of DM. These include the chromosomal abnormalities of several syndromes e.g.:

*Barth's syndrome*, X-linked (distal Xq28) disorder characterised by cardioskeletal myopathy in males, usually fatal in childhood.

*Down's syndrome*, one of the most common genetic birth defects (frequency: 1:800-1000) is caused by an extra chromosome 21 in each of the body's cells (trisomy 21), which might be alternatively attached to another chromosome in the egg or sperm (balanced, non visible translocation). Symptomatology includes mental retardation, characteristic facial features, heart defects, visual and hearing impairment and other health problems.

*Turner's syndrome*, a rare chromosomal disorder of females (1:2500), combined with short stature, lack of sexual development at puberty, heart defects, hearing loss and other abnormalities. Possible causes: 1) genetic defect of one X chromosome (46,XX), 2) reduced number (45,X) with some Y chromosomal material attached, or 3) 45,X/46,XX mosaicism.

*Klinefelter syndrome* in males caused by an extra X chromosome (47,XXY) with frequency 1:500-1000 live male births, possible variants: XY/XXY mosaic or XXXY, XXX-XY, XXYY. Symptoms include infertility, incomplete masculinization, emotional, and mental disorders, treatable by luteinizing hormone and testosterone.

*Friedreich's ataxia*, most common inherited (autosomal recessive) ataxia with central and peripheral nervous systems and heart affection, optic atrophy, deafness, death before 25 years, incidence 1:50000. Mutations in the FRDA gene on chromosome 9q13 (or two point mutations L106X and I154F) encode the conserve mitochondrial pro-

tein frataxin. There is great clinical resemblance to mitochondrial encephalopathies or to reduced respiratory enzyme activities.

*Schmidt syndrome*, the association of diabetes mellitus, Addison disease and myxedema may be due to unusual susceptibility to immunologic derangement (particular immune-response gene linked to HLA on chromosome 6).

*Wolfram syndrome* called DIDMOAD (Diabetes Insipidus and Mellitus with Optic Atrophy and Deafness), rare autosomal recessive disorder is combined with paranoid delusions, severe dementia, hallucinations, depression and violent behaviour.

*Cystic fibrosis* is autosomal recessive disorder (chromosome 7q31-q32) with a frequency 1:3000, first occurring in newborn or infants with symptoms: growth retardation, infections, impaired glucose tolerance, pancreas and respiratory insufficiency, liver cirrhosis or fibrosis. Therapy: mucolytics, antimicrobials, heart / lung / pancreas / liver transplantation (15).

### **Gestational type of DM**

Gestational Diabetes is a disturbance of glucose metabolism that develops in around 7% of pregnancies. Individuals at high risk for gestational DM include women of higher age (*frequent gene mutations*), the *obese*, those from certain high-risk ethnic groups and those with previous history of either glucose intolerance or large for gestational age babies, both group with possible *special genetic background* (glucokinase gene, mitochondrial DNA mutations). Mothers with this type of diabetes have a markedly increased risk of developing postpartum Type 2 DM (1,2,15).

### **Conclusions**

Quite recent advances in molecular biology and genetic research might revolutionise medical research. The speed human genome-sequencing effort and explosion of new genetic technologies provide us with a great opportunity to uncover the causes of various diseases.

Practically all types of DM result from complex interactions of genetic and environmental factors. For understanding diabetes, not only the location and sequence of a gene involved both in the development and complications of the disease should be known, but also the gene's functions must be identified. Then a combined genetic and autoantibody screening for individuals in danger can be organised and the prevention or delay of the development of the disease, choosing the most useful therapy, could be initiated.

Let us hope that also diabetic patients will soon profit from the recent achievements in genetics.

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