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THE GENETICS OF DIABETES

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Patogenesis of diabetes is still a mystery for medicine, the real challenge currently being the identification of genetic factors and specific mutations that cause the disease. Heterogeneity of diabetes hampers research, only a few loci inside the human genome being correlated with predisposition for disease till now.

Insulin-dependent diabetes – IDDM (T1DM) develops through autoimmune destruction of pancreatic beta cells. HLA complex on the short arm of chromosome 6 (6p21), where very important genes responsible for immunological condition of the person are located, plays a very important role in genetic predisposition for T1DM. Beside this region, there are also other loci in the human genome (on chromosomes 1, 2 and 11) where a correlation with T1DM has been shown. Correlation between HLA systems and T1DM was first described for class I alleles, but recently attention has been drawn to class II loci which seem to be the cause of primary predisposition for T1DM.

In the case of non-insulin-dependent diabetes – NIDDM (T2DM), the situation proved to be even more complex. Only a few

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genetic loci on chromosomes 11, 13 and 20 and MODY variant on chromosomes 7 and 12 have been identified by now. There are two theories about genetic basis of T2DM: the first stipulates that the genetic predisposition is determined through numerous loci, each individually responsible for a small part of predisposition; the second claims that there are a limited number of "major" genes probably functioning on a polygenic basis.

Further research in this area is definitely needed to enable an accurate calculation of the risks of the disease and possible consequences during a lifetime of a person.

Key words: genetics, diabetis, T1DM, NIDDM

I GENETIC BASIS OF INSULIN-DEPENDENT (IDDM-T1DM)

Insulin-dependent diabetes mellitus (T1DM) is an autoimmune disease that primarily occurs in people with a genetic predisposition and in about 5 % of their first-degree relatives.

Genes for type 1 diabetes provide both susceptibility towards, and protection from, the disease. Although many chromosomal loci have been located, few true genes have been identified (ATKINSON, 2001). T1DM cannot be classified according to a specific model of dominant, recessive or intermediate inheritance.

IDDM predominately occurs in people who serologically show clearly defined molecules DR3 and DR4 of class II of HLA region in the cells of immune system (figure 1). On the other hand, DR2 is in negative correlation with diabetes. DR alleles are closely related to DQ alleles and susceptibility (or resistance) to disease is closer related to specific DQ genes. Both, DR and DQ molecules are heterodimers formed from alfa and beta chains and both subunits are proteins of inner membranes.

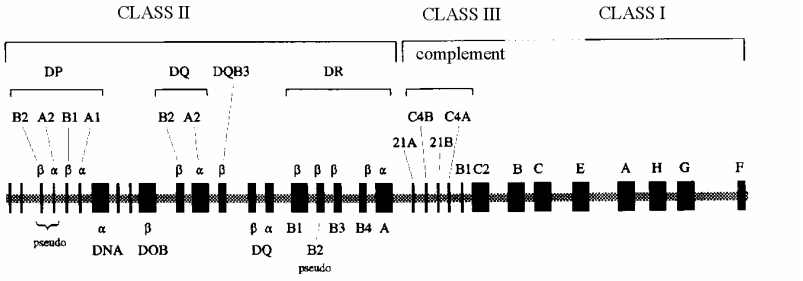

Figure 1. Genetic map of main histocompatible complex

For detection of people under risk of disease standard medical trials are administered, but they must fulfill some important rules: they must be reliable, reproducible, uninvasive and cheap. Amongst the used tests, the most popular one for searching markers is the ICA test (islet cell antibodies), i.e. the presence of antibodies in cytoplasm of the islet cell. Many studies demonstrated that the cumulative rate of appearance of IDDM in ICA positive relatives, and according to the titer of antibodies is from 34 to 100% in less than 10 years. Currently, this relatively simple test of beta cell autoimmunity presents one of the most reliable methods of diabetes risk evaluation.

HLA complex on the short arm of chromosome 6 plays a very important role in genetic predisposition for IDDM. Correlation between HLA system and IDDM was first described for class I alleles HLA-B8, B18 and B15 (with main subtype B62). The hypothesis that primary predisposition for the disease is tied to the region of class II has been supported with relatively higher risk if the connection is primarily found on DR3 with B8 and on DR4 with B62.

Polymorphic markers are not very useful for population studies because individual allele frequency is so low that comparisons do not make a lot of sense. That is why serological HLA-DR markers and DNA HLA-DQ markers are ideal for associative studies. HLA-B antigens in class I are less usable because of their polymorphism, unless a large number of people are included in such studies. Both DR and DQ markers are closely related to antigen chain from class I, and these haplotypes show a full spectrum of values in associative studies, as well as individual alleles defined by the DQ locus. In 1984, RAUM linked IDDM with four haplotypes: B8, SC01, GL02, DR3; then: B18, F1C30, DR3: then B15, SC33, DR4 and finally B38, SC21, DR4. These links are stronger than DR3 and DR4 individually.

The highest incidence of IDDM in the world is in Finland (35 out of 100,000 per annum for children up to 14 years of age). In Fennessy's extensive study (1994), based on classification HLA-A, -C, -B, -DR and DQ, 37 haplotypes were found in 84 % of subjects with diabetes.

Haplotype A2, B56, DR4 is present in 5.5 % of diabetic and in 1.1 % of non-diabetic haplotypes. This is the highest absolute risk for the occurrence of IDDM (218 out of 100,000 per annum) in comparison with other haplotypes, found in any European population.

Haplotypes with HLA-DR3 and DR4 are closely correlated to IDDM in many ethnic groups, but approximately 7 % of patients showing IDDM in Finland do not show such a correlation. One of the possible explanations would be that aspartic acid on position 57 DQ of alpha chain and other amino acids (except arginine) on position 52 DQ of alpha chain protect the patient from IDDM, and that arginine on the position 52 DQ of alpha chain and other amino acids (except aspartic) on position 57 DQ of beta chain lead towards susceptibility to IDDM. DQ heterodimer which is "susceptible" to diabetes consists of "susceptible" DQ alpha and "susceptible" DQ beta chain. In a tested population in Finland there was a great variability in the predisposition for IDDM, especially in patients that can

form a DQ heterodimer correlated with the disease, and with HLA class I alleles which are present in the haplotype.

It has been shown, regarding the participation of HLA-A region in the development of diabetes (e.g. in Japan), that HLA-A24 is correlated with acute appearance of the disease and complete loss of beta cell function. Reverse dependence of HLA-A24 with the duration of the disease development, partly dependable on A2, was increased in a South Africa patient population.

Genes which are in disequilibrium with HLA-A2 could contribute to susceptibility for the disease development, and it could be concluded that the gene (or genes) in class I linked to DQ heterodimers, which are responsible for "susceptibility" on diabetes in class II, modulate the risk for IDDM.

Probability for the appearance of IDDM in monozygotic twins is 23-35%, and in HLA identical relatives 6-19 %, which suggests that some other genes, besides the HLA-DQ region, also contribute to "susceptibility" to diabetes. Ten different loci, somehow correlated with the development of the disease, have been identified by now.

Polymorphism in insulin-ICF2- gene region (INS) on chromosome 11, beside the HLA region, has shown a correlation with the development of IDDM. According to some authors, INS polymorphism must be linked to HLA-DR4 positive people; other authors claim that INS polymorphism is independent of the HLA genotype. Gene mapping, especially studies on racial differences, contributes to our understanding of the problem of identifying genes in HLA region responsible for the primary "susceptibility" to IDDM.

Recently it has also been demonstrated (BOTTINI et al, 2006) that a single-nucleotide polymorphism (SNP) in the lymphoid tyrosine phosphatase (LYP), encoded by the PTPN 22 gene on chromosome 1P13, correlates strongly with the incidence of type 1 diabetes in two independent populations (ONENGUT & GUMUSCU, 2005).

Although the etiology of IDDM is still not clear, evaluation of the risk of the disease is of crucial importance for the members of a family. Literature data shows great variation. For example, a Danish study forecasts a risk of 6.9 % till the age of 40, and 15.9 % till 70. Anther study on a Caucasian population calculated the risk of 5.6 % till the age of 16, 5.5 % till 40 and 6.6 till 80, etc.

The vast majority of studies mainly concerns relatives of people with diagnosed diabetes, because there is scarce data on the risk assessment for patient descendents with diabetes. DEGNBOL and GREEN (1978) calculated the risk of 2.8% till the age of 20 years, 5.4 % till 35, and TILLIL and KOEBERLING (1982) calculated the risk of 4.9 till 80.

Another extensive study conducted by LORENZEN (1994) calculated the risk of IDDM in first-degree relatives on a sample of 553 persons, 46 with IDDM and 359 descendants, 18 of them with IDDM. During the study of relatives he calculated the cumulative risk at 6.4 % till age of 30, and 9.6 % till 60 years. The calculated cumulative risk for the descendants of people with IDDM was 6.3 % till the age of 34 years. If the calculation is made at the moment in which disease

appeared in proband, the risk for relatives is 12.5 % till the age of 60 years and 6.0 % for descendants till the age of 34.

According to this study, the relative risk of IDDM depends on a number of factors: the existence of at least one major gene for IDDM in HLA complex, a number of alleles HLA-B15 in class I, B8 and B18, the risk being even higher for heterozygote B15/B8.

The risk also depends on markers in class II that are closely correlated with the disease, what has been demonstrated in many ways: cellular HLA-D typing, serologic HLA-DR typization, studies of restriction fragments length polymorphism, sequencing and typization of oligonucleotides.

Further explanations will primarily be given by molecular genetics, or better said, molecular biochemistry.

II GENETIC BASIS OF NON-INSULIN DEPENDENT DIABETES (NIDDM – T2DM)

One of the serious health problems in developed and underdeveloped countries is non-insulin dependent diabetes, which represents big challenge even for clinical physicians and scientists. WHO estimated that by 2005 as many as 200-300 million people would have developed the disease. Rapid increase of the disease among children is perhaps the most alarming sign. Roughly half of the risk can be attributed to environmental exposure and the other half to genetics (HUSSAIN et al. 2006). There are many controversial opinions about the importance of genetic factor but also about the influence of environment in the pathogenesis of NIDDM. The main impression is that the interaction of these influences is essential and that only their combined activities determine the individual risk for NIDDM.

Identification of specific markers, genetic determinants which cause individual predisposition to glucose intolerance, is the focal point of research in the last years. Different steps in pathophysiological development that lead to the disease are being explained in such a way, thus both the treatment of patients and the prevention of the disease have been improved. If the number of genes involved is exactly determined, genetic markers could be used for predicting individual risk for diabetes.

It has been confirmed without any doubt that we are not dealing with a single homogenous disease, but that there is a heterogeneity in all aspects of NIDDM correlated both to the genetic and environmental influences. Genetic heterogeneity can be allelic (different alleles at the same locus) or non-allelic (involving a couple of different loci). In this second case, there is a polygenic influence on individual glucose tolerance status. Different genes, as well as combination of different genes can be very important in different types of diabetes, and situation becomes even more complicated if we consider ethnic moment.

We still do not recognize the basic defect of NIDDM. There is a possibility that it is only about different pathophysiological pathways which lead to glucose intolerance. According to one opinion the beta cell is the target cell of the

defect, the other claiming that the defect is in insulin action. It is evident that in the case of hyperglycemia, there are also defects in insulin action and in secretion. That is why further research is directed toward persons with normal glucose levels, but with higher risk for the occurrence of diabetes (e.g. descendants of a diabetic).

If we accept the hypothesis that the primary defect is in the number of beta cells, this could be the result of mutation of the gene which determines the regeneration capacity of beta cells following the attack. With regards to the existence of beta cells in large quantities, people with this type of diabetogene have normal levels of glucose, but are actually insulin-sensitive. During the life time or in the case of obesity, development of resistance to insulin occurs, inducing insufficient function of beta cells followed by hyperglycemia.

From the genetic point of view the defect of beta cell is the primary event, but irregularity that can be first clinically detected is resistance to insulin. Since correlation between defect protein and defect gene is still unknown, researches are directed toward search for mutations which can be in any way correlated to diabetes. The situation is even more complicated due to basic diagnostics of the disease, the level of glucose being relatively constant within a population, thus the diagnostic criteria being based on risk calculation from specific complications that occur in time.

If NIDDM represents a heterogeneous group of disease conditions, disease entities should first be completely clear. Careful classification could lessen this big heterogeneity and enable correlation of genotypes and phenotypes. Even basic division in two big groups, IDDM and NIDDM is now questionable because it seems that a large number of people with diagnosed NIDDM actually belong to IDDM that develops very slowly.

Correlation between NIDDM and obesity blurs the problem even further because obesity on its own is a multifactorial disease with a strong genetic component, so that search for diabetogenes is even more difficult because of the presence of genes correlated to obesity.

Loci responsible for different monogenic disturbances are usually found through “linkage” analysis. This method shows potential existence of co-segregation of locus pairs inside a family, which could mean the existence of locus with predisposition for that disease, and that the other marker is a locus on a known genome location. The term co-segregation indicates that two loci only seldom separate during meiotic recombination, meaning that they are very close in genome. Diseases which are mapped this way usually follow a simple genetic model, the classical Mendelian inheritance type.

Since “linkage” analysis proved to be very successful in monogenic diseases, simple genetic model is applied during studies of typical cases of NIDDM, disregarding the fact that in most populations under risk of NIDDM have already been shown not to comply with the laws of one locus segregation. This does not mean that the disease will definitely develop in people with diabetogene (due to insufficient penetrability), as well as that the people with the disease do not always show the presence of diabetogene. Furthermore, the fact that the

transmission of NIDDM through mother genes predominates, points to some other mechanisms that should be included in the construction of an adequate and realistic NIDDM model.

The human forkhead box O1A (FOX01A) gene on chromosome 13Q14 is a key transcription factor in insulin signaling in liver and adipose tissue and plays a central role in the regulation of key pancreatic (beta)-cell genes (KARIM et al, 2006).

There are two basic theories about the genetic basis of NIDDM (figure 2). The first theory claims that the genetic predisposition for typical form of NIDDM is determined by numerous different loci, each individually responsible for a small part of predisposition. If this was true, standard "linkage" methods would be limited as far as heterogeneity inside NIDDM is not somehow simplified.

The other theory claims that there is a limited number of "major" genes (probably functioning on a polygenic basis) individually responsible for a significant fraction of the total genetic contribution. Under such conditions, "linkage" analyses can identify them, if there are adequate numbers of families which are similar for sufficient number of polymorphic markers.

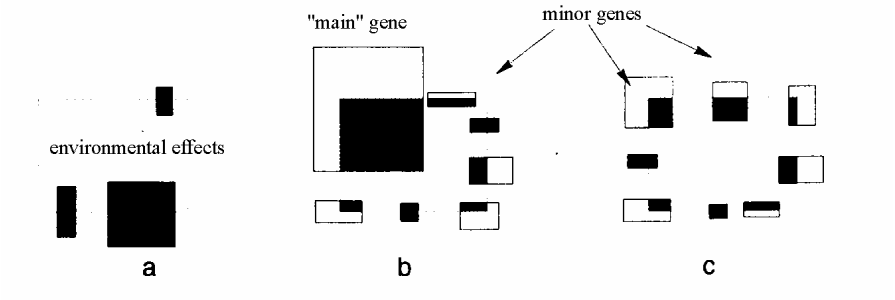

Figure 2. Possible genetic models for NIDDM

Point line represents the influence of environmental factors, and each rectangle represents one (theoretical) diabetogene, which can present itself through the disease (black areas)

a) populations with high NIDDM risk
b) typical NIDDM with "main" gene locus
c) typical NIDDM without "main" gene

Preliminary data are already available and they are in favor of the second theory, indicating that there is a main genetic locus responsible for about 40% of predisposition for disease and that it functions on a polygenic principle.

Strategy for identification NIDDM gene has two extreme approaches: screening of the total genome, or the search for candidate gene. Screening of the total genome is based on a techniques which proved to be successful in Mendelian inherited disorders. The chosen families are classified according to the method of

segregation for a large number of polymorphic markers strewn over whole genome, the regions showing a correlation with the disease being identified. For example, the correlation between glucose intolerance and locus for adenosine deaminase on chromosome 20q has been identified in such a way. Identification of chromosome region is only the first step. The next step is the search for a specific gene defect inside the region, which can be couple of megabases long, and this is very arduous task. A complementary approach is based on an animal model, based on the search of regions which cause diabetes in rodents, and these studies have given very good results.

In populations which are not under extreme risk to get the disease, studies of NIDDM are conducted through access to candidate gene. Genes with known biochemical function (for example insulin, insulin receptor, glucose carrier) are proclaimed candidates, but the selection of potential candidate for the role in the development of NIDDM is quite inaccurate. Associative studies which are applied in this process are conducted through comparison of normal people with those having diabetes and their typical polymorphic markers closely correlated to candidate gene. Any significant difference in alleles between these two groups implies that the marker is not in equilibrium with the pathogenic mutation in the next candidate gene. Accuracy of associative studies depends on the correlation between bonds of allele on marker gene and on candidate gene. For example, significant genetic defects can remain undiscovered if marker alleles and mutation of candidate gene are in balance, but mutation in disequilibrium with a rare allele of marker has possibility to discover fine genetic disbalances of disease which would stay uncovered through "linkage" analysis. These studies make sense only if the candidate gene is well chosen. Good results were also obtained in case of HLA and IDDM, but in case of NIDDM, very careful selection of control population (ethnic selection, body mass etc.) is necessary. Subphenotypisation inside NIDDM should also contribute to simplification of such a complex system. For example, comparison of diabetic and non-diabetic obese persons can strengthen the effects of genes responsible for secretion of insulin.

With regard to the molecular basis of NIDDM, single-strand conformational polymorphism is used for the search of candidate gene. In order to identify the molecular basis of each variant found, sequencing is performed. Discovery of mutation in mitochondrial genome in pedigrees with diabetes is one of the achievements of this method. The objection is that cis-mutation (upwards from gene that can influence the transcription) can not be identified if you do not search for them specifically, and there are also some difficulties in identification of the mutation. Whether the mutation in candidate gene contributes to disease obscures the problem. The fact that the mutation is more frequent in patients, is not sufficient proof, since the mutation can be in disequilibrium with mutation on some other part of the genome. To confirm the pathological role of the mutation, its consequences on secondary and tertiary protein structure also have to be monitored.

Studies of complete families with NIDDM are very rare because the disease starts developing quite late and mortality rate is high, at the same time the children are not old enough for the disease to develop.

Study by COOK et al. (1994) analysed 20 complete families, regardless of family anamnesis but in which parents and probands are alive. Seven subjects did not have parents with diabetes or with decreased glucose tolerance, 10 subjects had one sick parent (6 with diabetes and 4 with decreased glucose tolerance), and three had both parents sick (1 with diabetes and 2 with intolerance). The study analysed 697 persons with NIDDM and the same author managed to find 59 families (Figure 3), 21 proband had both parents alive. Segregation analyses were conducted through computer programs POINTER and COMDS. POINTER program is used for harmonization of individual genes, polygenic and mixed models. Mixed model considers independent contributions of main, genetic locus, polygene components and environmental influence. COMDS segregation analyses are based on a different principle, where glucose and diabetes tolerance of the whole population makes one continuum. In COMDS program, the phenotype has a higher level of hyperglycemia with different diathesis classes. This program covers models of one or two loci, but without polygenic effect.

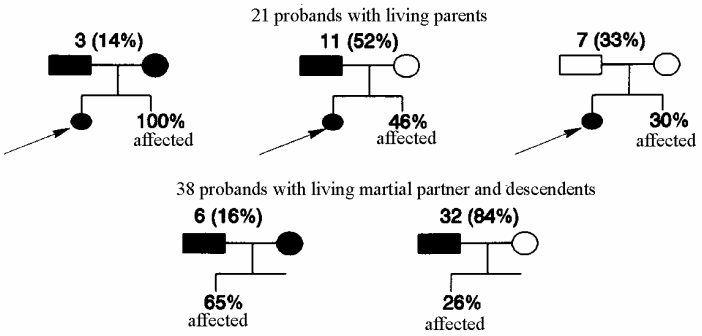

Figure 3. Graph of 59 NIDDM families
■ NIDDM or glucose intolerance
□ Normal glycemia
↑ Proband

In seven families where parents did not have diabetes, 30% of relatives were struck by the disease. In 11 families with one sick parent, 46% of relatives were also affected. In 3 families with both parents with diabetes, all analyzed relatives had decreased glucose tolerance. In families in which proband had marital partner with normal glicemy, 26% of descendants definitely develop the disease, but in cases where proband's marital partner was also sick, 65 % of descendants definitely developed the disease.

The segregation analysis in this study dismissed the recessive and the genetic component models. Best results were obtained by model of one dominant, main gene, but it is not actually possible to statistically prove that this approach is better than mixed or polygenic model. By applying COMDS program genetic frequency of 7.4 % is suggested, but the model of dominant gene with incomplete penetrability is again favored.

The other extensive study was conducted by MCCARTHY (1994) on a population in South India and both computer models were applied again. Study covered 449 persons, 64 probands, 128 parents and 257 relatives (Figure 4). Significant percentage of parents with disordered values for glucose tolerance (70% diabetics and 9% with decreased values) was discovered. COMDS analyses were in favor of diallelic gene segregation and frequency of allele predisposition for the disease was 14 %.

It was not possible to apply model of major gene adequately on the population of South India because very high frequency of NIDDM was found among diabetic parents. Since probands were chosen regardless of family anamnesis, this confirms strong family aggregations in the case of diabetes. Both programs, used on this population, can not answer how many loci contribute to the disease, but we can certainly claim that at least two of them are involved.

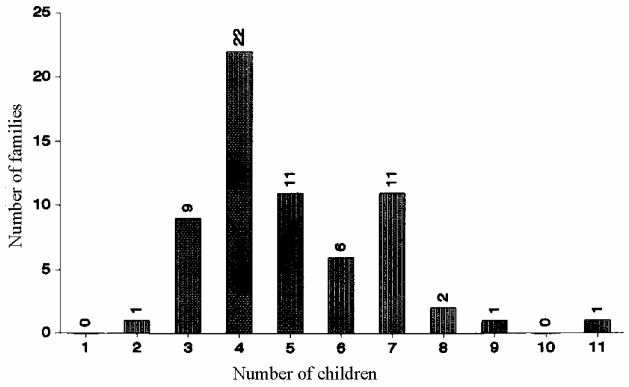

Figure 4. Survey of 449 persons in South India, classified according to the number of families and children

Segregation analysis encounters many methodological barriers when we deal with disease as complicated as NIDDM (Table 1). Problems can partly be overcome if we study probands whose parents are alive and through selection of patients who manifested the disease relatively early.

The theory of major gene is clearest in population with high NIDDM risk. Different behavior of glucose levels was noticed in couple of examined populations, for example on people who migrated from India to South Africa and it

was proof, albeit insufficient, in favor of the effect of the major gene. On the other hand, analysis of Indian Seminole families indicates that hyperglycemia is result of changes on autosomal recessive level, what again favors the theory of codominant gene. As opposed to this, the segregation studies on populations with lower risk of developing diabetes do not confirm the model of one major gene.

Table 1. Methodological barriers in NIDDM research

1.	Late development
2.	Early death
3.	Lack of biochemical markers for future diabetes
4.	Large number of undiagnosed glucose intolerances
5.	Different application of diagnostic criteria

Generally speaking, similar values of glucose values inside one family can also be explained with additional factors: similar environment and maybe some other social and cultural aspects in population.

II-A GENETIC BASIS OF MATURITY ONSET DIABETES OF THE YOUNG (MODY)

A typical form of NIDDM is characterized through resistance to insulin and disorder in function of beta cells, what is probably consequence of interaction between life style and genetic predisposition. Variant of NIDDM known as MODY (maturity-onset diabetes of the young) does not usually show resistance to insulin, opening the possibility that the problem is in fact due to a defect in insulin production.

The search for candidate gene in NIDDM caused a great deal of discussion on the role of glucokinase enzyme, glucose sensor in beta cell, because mutations correlated to this enzyme were detected in families in which MODY appeared. This type of diabetes is inherited as an autosomal dominant type and the disease is usually manifested in a light form.

FROGUEL (1993) described the existence of 16 mutation of the gene for glucokinase on chromosome 7, in 18 of 32 families with MODY. The change in gene for adenosine-deaminase on chromosome 20 has been found in other families (Figure 5).

MATSCHINSKY (1990) made an attempt to explain the involvement of the human glucokinase in the development of diabetes through the cell sensor model. According to Matschinsky, the rate of glucose metabolism and insulin secretion are closely related processes and both are determined through the concentration of glucose in the plasma. The rate of glucose metabolism in beta cells and hepatocyte is conditioned by the rate of glucose phosphorylation, catalyzed by glucokinase, one of the hexokinase enzyme families. Beta cells and hepatocyte contain also

GLUT-2, insulin-independent cell protein which intermediates in glucose transportation.

Transport capacity of GLUT-2 is quite high, thus the equilibrium between extracellular and intracellular glucose is achieved quite rapidly. Since glucose, with the assistance of GLUT-2, is transported into the cell very rapidly, the change in glucose concentration outside the cell can be noticed through glucokinase. In such a way this enzyme controls the glucose metabolism, leading to the release of insulin.

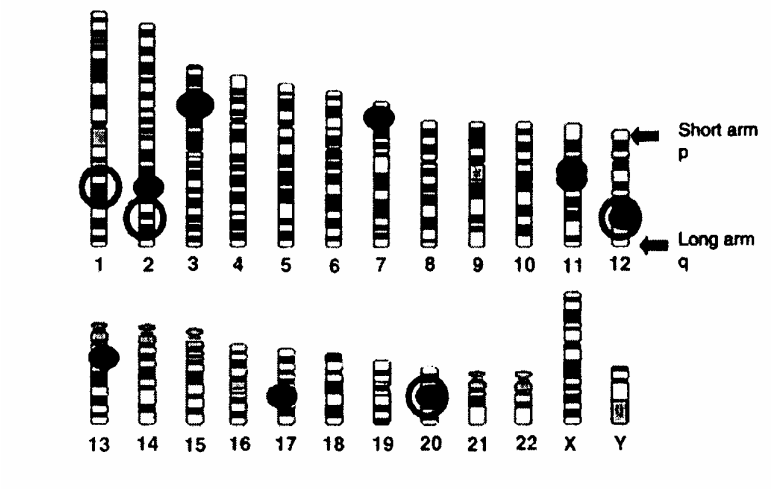

Figure 5. Chromosome regions correlated to T2DM

To understand how the deficit of glucokinase can lead to hyperglycemia, we have to view such a sensor mechanism of beta cells as a regulatory mechanism, maintaining the glucose concentration in plasma in narrow range. If one mutated allele for glucokinase is inactive, the other normal allele can provide half of the enzyme quantity to the cell (under the assumption that the compensatory mechanisms does not function), so for any concentration of glucose, glucose metabolism and the rate of insulin secretion will be decreased.

As a result of this, hypoinsulinemia have to be observed in liver and muscles, increasing glucose concentration in the liver and decreasing it in muscles, increasing the concentration of glucose in plasma. As the concentration in plasma increases, the rate of glucose metabolism in beta cells grows and reaches almost normal level.

Relatively light hyperglycemia in MODY patients probably has influence on metabolic pathways and on development of complications of diabetes in long term.

Such a benign hyperglycemia, which is result of defect in glucokinase gene, should be stable during whole life time, but certain members of some

families with MODY have much higher concentrations of glucose in plasma, requiring insulin therapy. A possible explanation for such cases would be that the genetic disorders in persons showing predisposition for NIDDM are present also in some families with MODY, so that additive effect of two or more genetic disorders arises.

ELBEIN (1994) studied glucokinase locus through "linkage" studies in a couple of families with MODY. He carried out the study using the method of single-chained conformational polymorphism, with the aim of discovering individual nucleotide substitution. Only three variants were observed, but no changes in amino-acid sequences were found.

CHIU et al. (1994) examined the glucokinase gene in 270 African women including 94 with gestational diabetes. This study could not determine a connection between alleles for glucokinase and gestational diabetes, thus further research is needed to determine the connection between glucokinase gene and diabetes.

Studies of BJORKHAUG (2000) go even further in explanation of MODY mechanism. They describe MODY type 3 which develops through mutation of hepatocyte nuclear factor (HNF)-1(alfa). During screening of Norway population on MODY two new (HNF)-1 (alfa) mutations were identified: P112L and Q466X. P112L has reduced ability to bind an HNF 1 consensus sequence and to activate transcription. Q 466X did not differ from wild type HNF-1(alpha) in DNA binding activity. Transactivation, however, was markedly reduced.

II-B MITOCHONDRIAL GENE DEFECT IN NIDDM

Mother inheritance factors have important influence in the development of NIDDM. Mitochondrial DNA in diabetes is not well examined. It is basically circular and has 16.569 base pairs which are all sequenced. Mitochondrial DNA exclusively transmits from mother and codes 13 enzyme subunits.

For the regulation of insulin production in beta cells, oxidation of mitochondrial metabolism is of special importance.

Mitochondrial myopatia represents a group of diseases that mostly shows inheritance from mother as a result of defect on mtDNA. Some of these patients demonstrate decreased glucose tolerance. Individual cases of diabetes inherited from mother correlated to deletia or point mutation on mtDNA.

According to recent studies of 200 persons with NIDDM conducted by ALCOLADO (1994), through the analyses of mutation on mtDNA, accurate data were not obtained. One patient had mutation on base pair 3243, but the expression did not match previously described syndrome. At the same time there was no patient that had the mutation on position 8344, which had previously been described as syndromes of mitochondrial encephalomyopatia.

Although a strong correlation between type-2 diabetes and obesity has been found, no comparative analyses between diabetes and obesity has been performed up to 2005 with respect to mitochondrial DNA polymorphism. (GUO et

al 2005). The results suggest that distinct mitochondrial single nucleotide polymorphism (mtSNPs) contributes to susceptibility to type-2 diabetes or obesity.

From all this we can clearly see that many additional studies are required in order to determine the potential role of defects in mitochondrial genes in the development of diabetes.

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GENETIKA DIJABETESA

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Izvod

Patogeneza šećerne bolesti još uvek predstavlja jednu od misterija medicine, a pravi izazov predstavlja identifikacija genetskih faktora i specifičnih mutacija koje uzrokuju bolest. Heterogenost dijabetesa znatno otežava istraživanja tako da se za sada sa sigurnošću zna za samo nekoliko lokusa unutar humanog genoma koji imaju vezu sa predispozicijom za bolest.

Insulin zavisni dijabetes (IDDM-T1DM) nastaje autoimunim razaranjem beta ćelija pankreasa. HLA kompleks na kratkom kraku hromozoma 6 (6p21) gde se inače nalaze veoma važni geni koji su odgovorni za imunološki status osobe, igra veoma važnu ulogu i u genetskoj predispoziciji za IDDM. Pored ovog regiona postoje i druga mesta u humanom genomu za koje je pokazano da su povezana sa IDDM i nalaze se na hromozomima 1, 2 i 11. Povezanost HLA sistema i IDDM je prvo opisana za alele u klasi I medjutim, u poslednje vreme se poseban značaj pridaje lokusima u klasi II za koje izgleda da su presudni u primarnoj predispoziciji za IDDM.

U slučaju insulin nezavisnog dijabetesa (NIDDM-T2DM) situacija je još složenija. Do sada je identifikovano nekoliko genskih lokusa i to na hromozomima 11, 13 i 20, a kod MODY varijante i na hromozomima 7 i 12. O genetskoj osnovi NIDDM postoje dve osnovne teorije: prva, da je genetska predispozicija determinisana velikim brojem lokusa od kojih je svaki individualno odgovoran za mali deo predispozicije i druga, da postoji ograničeni broj „glavnih“ gena koji verovatno funkcionišu na poligenskoj osnovi.

U svakom slučaju, potrebno je još mnogo istraživanja na ovom polju da bi se sa sigurnošću moglo pristupiti preciznom izračunavanju rizika od bolesti, kao i od mogućih pratećih komplikacija tokom života.

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