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# Genetic effects, gene-lifestyle interactions, and type 2 diabetes

**Review article**

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**Abstract:** Type 2 diabetes has become a major public health challenge worldwide. It is now widely accepted that genetic components affect the development of type 2 diabetes, in concert with environmental factors such as lifestyle and diet. Traditional linkage mapping, positional cloning, and candidate gene-based association studies have identified a few genetic variants in genes such as TCF7L2, PPARG, and KCNJ11 that are reproducibly related to the risk of type 2 diabetes. To date, about ten genome-wide association (GWA) studies have been published. These studies discovered new susceptibility genes for type 2 diabetes and provide novel insight into the diabetes etiology. In addition, data especially from lifestyle intervention trials display promising evidence that the genetic variants may interact with changes of dietary habit and physical activity in predisposing to type 2 diabetes. The gene-lifestyle interactions merit extensive exploration in large, prospective studies. The findings from these areas will substantially improve the prediction and prevention of type 2 diabetes.

**Keywords:** *Genetics • Gene-environment interactions • And type 2 diabetes*



## 1. Introduction

The prevalence of diabetes has increased in the past decades at an alarming rate in both developed and developing countries. It was projected that the number of individuals with type 2 diabetes among adults will double from the current 171 million in 2000 to 366 million in 2030 [1]. Traditional genetic research, including twin, adoption, and family studies, consistently supports that type 2 diabetes has a genetic component. During the past decades, extensive efforts have been made to detect the underlying genetic structure for type 2 diabetes. However, until very recently, the genes involved have been poorly understood. Using new technology in the form of a 'genome-wide chip' that genotypes up to hundreds of thousands of SNPs, genome-wide association (GWA) studies have recently led to the discovery of a group of novel genes that were reproducibly associated with diabetes risk [2-5].

The explanation for how genes affect type 2 diabetes, however, continues to resist understanding. It is now believed that the genetic factors may not only directly affect susceptibility but also interplay with environment (e.g., diet and lifestyle) in determining disease risk. However, little is known about the precise pattern of gene-environment interaction in predicting diabetes risk [6]. The present review discusses recent advances in genetic studies on type 2 diabetes and pioneering investigations on the gene-lifestyle interactions, as well as the implication of these findings in predicting type 2 diabetes.

### 1.1. Genetics of Type 2 Diabetes

There is substantial evidence for the heritability of type 2 diabetes. Type 2 diabetes is a well-known familial disease. Family studies have estimated that risk for type 2 diabetes increased approximately two- to fourfold when one or both parents are affected [7-9]. In addition, evidence shows a greater likelihood of diabetes in offspring of affected mothers than affected fathers, indicating an excess maternal transmission of the disease [10-12], although the data are not entirely consistent [13]. Family history

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of diabetes has a significant, independent, and graded association with the prevalence of diabetes [14]. In twin studies, very high concordance (55% to 100%) for type 2 diabetes has been reported among monozygotic (MZ) twins [15-17]. Kaprio *et al.* examined a nationwide cohort of 13,888 Finnish twin pairs, in which the probandwise and pairwise concordance rates for type 2 diabetes were 34% and 20% among MZ twins and 16% and 9% in dizygotic (DZ) twins, respectively [18]. In another study [19], Poulsen *et al.* found a probandwise concordance was 50% in MZ twins and 37% in DZ twins. Heritability estimates for type 2 diabetes range from 26% to75% [18-20].

In addition, mutations in some genes cause rare-forms of type 2 diabetes, giving additional support for the genetic roles in the etiology of the disease. For example, genes *KCNJ11* (potassium inwardly-rectifying channel, subfamily J, member 11) and *ABCC8* (ATP-binding cassette, sub-family C, member 8) carry rare mutations that cause a Mendelian form of neonatal diabetes [21,22]. Specific mutation in the mitochondrial genome was found to cause maternally inherited diabetes and deafness [23]. Maturity-onset diabetes of the young (MODY), which is characterized by high penetrance, early age at onset of hyperglycemia and defective function of β-cells in the pancreas, accounts for 1–5% of all type 2 diabetes cases. Mutations in genes encoding hepatocyte nuclear factor 4-alpha (*HNF4A*), glucokinase (*GCK*), HNF1 homeobox A (*HNF1A*), insulin promoter factor-1 (*IPF1*), hepatocyte nuclear factor-1 beta (*TCF2* or *HNF1B*), and neurogenic differentiation 1 (*NEUROD1*), cause different subtypes of MODY (MODY1-6) [24].

## 1.2. From Linkage Analysis to Association Studies

The traditional approach for mapping disease genes relies on linkage analysis in affected families followed by progressive fine-mapping of candidate linkage peaks [25]. The linkage analysis was tremendously successful in identifying mutations underpinning the rare Mendelian disorders. This approach has also been employed to detect risk genes for the common form of type 2 diabetes. As a successful example, Hanis conducted the genome-wide linkage scan in Mexican Americans and found a major susceptibility locus on chromosome 2 [26]. Subsequent positional cloning in this region led to the identification of two different haplotypes (121/112) within the *CAPN10* gene conferring higher risk for type 2 diabetes [27]. In 2006, Grant *et al*. found variants in the *TCF7L2* gene conferring 1.5-fold increased risk of type 2 diabetes in an Icelandic population [28] through fine mapping a region (chromosome 10q) identified by a previous linkage analysis [29]. The genetic effects of *TCF7L2* have been replicated with remarkable consistency across various populations [30] and stand out as having by far the biggest effect on diabetes risk. However, the vast majority of linkage studies have not led to the discovery of genes harboring the causal variants for type 2 diabetes.

Since the late 1990s, growing acknowledgement that association studies have considerably greater power than linkage analysis to detect genetic variants with moderate phenotypic effects [31] has instigated the rise of association study as the mainstream approach in the field. During the past ten years, dozens of genes have been examined for their associations with type 2 diabetes using candidate-gene based approach [20,32]. However, most of the observed associations are hard to replicate. Many reasons have been proposed to account for the low reproducibility in the association studies, including the bias introduced by population stratification, lack of power due to small sample size, confounding caused by environmental factors, and heterogeneity in genetic effects. [33]. Even though, some associations showed excellent track record and are now believed to confer 'real' genetic effects. For instance, *PPARG* Pro12Ala (P12A) and *KCNJ11* Glu23Lys (E23K) were consistently linked to the diabetes risk in various populations [34,35]. Winckler *et al.* recently reported that SNP rs757210 in *TCF2* (MODY5) gene was associated with a 12% increased risk of type 2 diabetes [36]. The genetic effect of *TCF2* variants on type 2 diabetes was confirmed by a recent GWA study [37].

## 1.3. Recent Advance in Genome-Wide Association Studies

The efforts to discover the diabetes genes were recently fuelled by GWA studies. At present, there are two general strategies for indirect GWA studies. The first uses quasi-random or anonymous SNPs spreading across the genome, and the second uses sets of LD-based tag SNPs effectively capturing most of the other unmeasured common SNPs at a pre-specified LD threshold [38]. Differing from the candidate gene approach, GWA studies have unprecedented advantage in uncovering novel genetic contributors and thus lead to insights into the etiology of the disease. The first GWA study covered 392,935 SNPs (passing quality control) [2] and identified four novel loci including *SLC30A8* (solute carrier family 30, member 8), *LOC387761*, *IDE-KIF11-HHEX* (insulin-degrading enzyme, kinesin-interacting factor 11, and homeodomain protein) and *EXT2-ALX4* (exostosin 2 and aristaless-like homeobox 4). The hetergozygotes and minor homozygotes were associated with 14%-27% and

36-53% increased diabetes risk respectively. Wellcome Trust Case Control Consortium (WTCCC) [5], Diabetes Genetics Initiative of the Broad Institute of Harvard and MIT (DGI) [39], and Finland–United States Investigation of Non–Insulin-Dependent Diabetes Mellitus Genetics (FUSION) [3] analyzed 386,731, 393,453, and 315,635 SNPs respectively. The replications were based on both GWA significance and cross-study consistency. Common variants in genes *CDKAL1* (CDK5 regulatory subunit associated protein 1-like 1), *IGF2BP2* (insulin-like growth factor 2 mRNA binding protein 2), *CDKN2A/B* (cyclin-dependent kinase inhibitor 2A/2B) were significantly associated with diabetes risk, with the allele-associated odds ratios ranging from 1.07 to 1.48. These studies also confirmed the effects of *SLC30A8* and *HHEX*.

In another GWA study [40], Steinthorsdottir *et al.* found that variant rs7756992 in the *CDKAL1* gene was significantly associated with diabetes risk in individuals of European ancestry (allele-specific OR=1.20, 95%CI 1.13-1.27) and Han Chinese ancestry (OR=1.25, 95%CI 1.11-1.40), but not in those of African ancestry. Salonen *et al.* analyzed 315,917 HapMap-derived tagging SNPs in a two-stage study of 3,073 diabetes cases and 3,273 healthy controls [4]. SNPs in the *AHI1* (Abelson helper integration site 1)-*LOC441171* region were found to confer ~30% increased risk. Three recent GWA studies genotyping 100k SNPs in the Framingham Heart Study [41], Amish [42], and American Indians [43] reported some genetic variants related to the risk of type 2 diabetes. However, these associations were not univocally observed.

## 1.4. Gene-Lifestyle Interactions: the Promising Evidence

The potential importance of the interaction between genetic susceptibility and lifestyle changes in predisposing to type 2 diabetes was first evidenced by migrant studies. In such an investigation, *PPARG* 12Pro allele was significantly related to diabetes risk among Japanese Americans who were characterized by 'westernized' lifestyle (physical inactivity and high intake of animal fat) but not in native Japanese [44]. To date, the majority of evidence for gene-lifestyle interactions on type 2 diabetes comes from lifestyle intervention trials. One of the hallmark studies, the Finnish Diabetes Prevention Study (DPS) was designed to assess the efficacy of an individually designed diet (reduced intakes of total fat and saturated fat and increased intake of fiber) and exercise program (moderate to vigorous exercise for at least 30 $min \cdot d^{-1}$) to prevent or delay the onset of type 2 diabetes in 522 middle-aged, overweight or obese subjects with IGT [45]. The variants in genes *ADRA2B* (adrenergic, alpha-2B-, receptor) [46], *PPARG* [47], *SLC2A2* (solute carrier family 2, member 2) [48], and *LEPR* (leptin receptor) [49] were significantly related to the transition from IGT to diabetes in the control group but not in the intervention group. By contrast, the variants in genes *TNF* (tumor necrosis factor) [50] and *GHRL* (ghrelin/obestatin preprohormone) [51] were associated with diabetes risk only in the intervention groups. In the Diabetes Prevention Program (DPP) [52], which was designed to test the lifestyle intervention or treatment with metformin in preventing or delaying the development of diabetes over an average of 3 years in individuals with IGT and elevated fasting glucose, the associations between the *TCF7L2* SNPs rs7903146 and rs12255372 and the diabetes risk was stronger in the placebo group than in the lifestyle-intervention groups.

Very few observational studies have addressed gene-lifestyle interactions in relation to type 2 diabetes. In a family based association study of 216 Hispanic pedigrees (1850 nuclear families) and 236 non-Hispanic white (NHW) pedigrees (1240 families), Nelson *et al.* found that the *PPARG* Pro12Ala was associated with diabetes risk only among those with low physical activity (low tertile) in non-Hispanic white. Test for the gene-physical activity interaction was significant (P=0.022) [53]. In a recent cross-sectional study of 538 subjects from a population with high intake of olive oil and Mediterranean diet, Soriguer *et al.* found that the Ala-12 allele of PPARG2 gene significantly interacted with the intake of monounsaturated fatty acids (MUFAs) in relation to the variance of the homeostasis model assessment insulin resistance index (HOMA IR) ($P_{interaction}$= 0.005) [54]. Qi *et al.* examined the interactive effects of variants (C282Y and H63D) in hemochromatosis gene (HFE) and dietary intakes of heme iron in predicting type 2 diabetes. The associations between heme iron intake and diabetes risk were stronger among women with either the H63D or C282Y variant than those with the wild genotype [55]. Test for gene-diet interaction was significant (P=0.029). A recent study indicated that the genetic variant in the alcohol dehydrogenase 1c (ADH1C) gene modified the association between alcohol consumption and type 2 diabetes. The number of ADH1C*2 alleles attenuated the lower risk of diabetes among women consuming >/=5 g alcohol/day [56].

## 1.5. Diabetes Prediction: Incorporation of the Genetic Findings

The data collected from genetic studies will help to more precisely predict disease risk. Even though information on any single variant has limited predictive value (due

to the low frequency of the risk allele and the moderate genetic effects with relative risk of 2.0 or less per allele), the same may not be true when many susceptibility genes are combined. Scott *et al.* recently tried to predict the diabetes risk in the FUSION sample using ten genetic variants identified by a GWA study, including *IGF2BP2*, *CDKAL1*, *CDKN2A/B*, *FTO*, *PPARG*, *SLC30AB*, *HHEX*, *TCF7L2*, *KCNJ11* and an intergenic region on chromosome 11 [3]. A fourfold variation in diabetes risk was found from the lowest to highest predicted risk groups characterized by the number of the risk alleles, with the proportion of diabetes cases increases from 5% in the lowest to 20% in the highest predicted risk categories. The confirmed susceptibility genes to date only explain a small proportion of the observed familial aggregation of type 2 diabetes. More risk genes are expected to be discovered in future. How to integrate the mounting genetic information to predict the disease risk will be an important issue to be explored. It is believed that the best way of addressing this question is with prospective studies [57].

In addition, to jointly examine the genetic and environmental exposures may improve the power to identify the environmental risk factors for type 2 diabetes. Bermejo *et al.* investigated the practical advantage of gene–environment over plain environmental studies in the identification of environmental risk factors and found that gene–environment studies had greater power than plain environmental studies [58]. Moreover, the observation of an interaction between the environmental factor and relevant genotype will provide additional evidence that an association between an environmental factor and disease risk is causal [59].

## 2. Conclusions

Studies in human genetics have made tremendous strides in discovering diabetes genes especially through GWA analysis. However, GWA study is only the beginning in establishing the role of genetic variants in disease etiology. This would be followed by the fine-mapping of the susceptibility region through deep sequencing in large population and the validation of causality for genetic variants in experimental settings. Efforts to define structural variants such as copy number variants (CNV) should be also included [60]. Prediction of diabetes risk using genetic information for individual patients is not straightforward and merits more attention. In addition, susceptibility to type 2 diabetes is thought to be determined by interactions between an individual's genetic make-up and environment. Thus, the increased prevalence of diabetes likely reflects the exposure of genetically susceptible individuals to unhealthy secular trends in environmental factors, such as diet and physical inactivity. Recent advances in GWA enable detailed assessment of entire genomes open up a vast new terrain in the comprehensive search for gene–lifestyle interactions. The distance from a genome variation to disease prevention is still considerable, but we are optimistic that the findings in this field will contribute to identification of 'at risk' individuals who would benefit most from individualized monitoring and care.

## References

[1] Wild S., Roglic G., Green A., Sicree R., King H., Global prevalence of diabetes: estimates for the year 2000 and projections for 2030, Diabetes Care, 2004, 27, 1047-1053

[2] Sladek R., Rocheleau G., Rung J., Dina C., Shen L., Serre D., et al., A genome-wide association study identifies novel risk loci for type 2 diabetes, Nature, 2007, 445, 881-885

[3] Scott L.J., Mohlke K.L., Bonnycastle L.L., Willer C.J., Li Y., Duren W.L., et al., A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants, Science, 2007, 316, 1341-1345

[4] Salonen J.T., Uimari P., Aalto J.M., Pirskanen M., Kaikkonen J., Todorova B., et al., Type 2 diabetes whole-genome association study in four populations: the DiaGen consortium, Am. J. Hum. Genet. 2007, 81, 338-345

[5] Zeggini E., Weedon M.N., Lindgren C.M., Frayling T.M., Elliott K.S., Lango H., et al., Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes, Science, 2007, 316, 1336-1341

[6] Hunter D.J., Gene-environment interactions in human diseases, Nat. Rev. Genet., 2005, 6, 287-298

[7] Knowler W.C., Pettitt D.J., Savage P.J., Bennett P.H., Diabetes incidence in Pima indians: contributions of obesity and parental diabetes, Am. J. Epidemiol., 1981, 113, 144-156

[8] Harris M.I., Hadden W.C., Knowler W.C., Bennett P.H., Prevalence of diabetes and impaired glucose tolerance and plasma glucose levels in U.S. population aged 20-74 yr., Diabetes, 1987, 36,

523-534
[9] Mitchell B.D., Valdez R., Hazuda H.P., Haffner S.M., Monterrosa A., Stern M.P., Differences in the prevalence of diabetes and impaired glucose tolerance according to maternal or paternal history of diabetes, Diabetes Care, 1993, 16, 1262-1267
[10] Thomas F., Balkau B., Vauzelle-Kervroedan F., Papoz L., Maternal effect and familial aggregation in NIDDM. The CODIAB Study. CODIAB-INSERM-ZENECA Study Group, Diabetes, 1994, 43, 63-67
[11] De Silva S.N., Weerasuriya N., De Alwis N.M., De Silva M.W., Fernando D.J., Excess maternal transmission and familial aggregation of Type 2 diabetes in Sri Lanka. Diabetes Res. Clin. Pract. 2002, 58, 173-177
[12] Arfa I., Abid A., Malouche D., Ben Alaya N., Azegue T.R., Mannai I., et al., Familial aggregation and excess maternal transmission of type 2 diabetes in Tunisia, Postgrad. Med. J., 2007, 83, 348-351
[13] Viswanathan M., McCarthy M.I., Snehalatha C., Hitman G.A., Ramachandran A., Familial aggregation of type 2 (non-insulin-dependent) diabetes mellitus in south India; absence of excess maternal transmission, Diabet. Med., 1996, 13, 232-237
[14] Valdez R., Yoon P.W., Liu T., Khoury M.J., Family history and prevalence of diabetes in the US population: 6-year results from the National Health and Nutrition Examination Survey (NHANES, 1999 2004), Diabetes, 2007, (in press)
[15] Newman B., Selby J.V., King M.C., Slemenda C., Fabsitz R., Friedman G.D., Concordance for type 2 (non-insulin-dependent) diabetes mellitus in male twins, Diabetologia, 1987, 30, 763-768
[16] Barnett A.H., Eff C., Leslie R.D., Pyke D.A., Diabetes in identical twins. A study of 200 pairs, Diabetologia, 1981, 20, 87-93
[17] Gottlieb M.S., Root H.F., Diabetes mellitus in twins, Diabetes, 1968, 17, 693-704
[18] Kaprio J., Tuomilehto J., Koskenvuo M., Romanov K., Reunanen A., Eriksson J., et al., Concordance for type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes mellitus in a population-based cohort of twins in Finland, Diabetologia, 1992, 35, 1060-1067
[19] Poulsen P, Kyvik K.O., Vaag A., Beck-Nielsen H., Heritability of type II (non-insulin-dependent) diabetes mellitus and abnormal glucose tolerance--a population-based twin study, Diabetologia, 1999, 42, 139-145
[20] Barroso I., Genetics of Type 2 diabetes, Diabet. Med., 2005, 22, 517-535
[21] Babenko A.P., Polak M., Cave H., Busiah K., Czernichow P., Scharfmann R., et al., Activating mutations in the ABCC8 gene in neonatal diabetes mellitus, N. Engl. J. Med., 2006, 355, 456-466.
[22] Gloyn A.L., Pearson E.R., Antcliff J.F., Proks P., Bruining G.J., Slingerland A.S., et al., Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes., N. Engl. J. Med., 2004, 350, 1838-1849
[23] van den Ouweland J.M., Lemkes H.H., Trembath R.C., Ross R., Velho G., Cohen D., et al., Maternally inherited diabetes and deafness is a distinct subtype of diabetes and associates with a single point mutation in the mitochondrial tRNA(Leu(UUR)) gene, Diabetes, 1994, 43, 746-751
[24] Fajans S.S., Bell G.I., Polonsky K.S., Molecular mechanisms and clinical pathophysiology of maturity-onset diabetes of the young, N. Engl. J. Med., 2001, 345, 971-980
[25] Collins F.S., Positional cloning: let's not call it reverse anymore, Nat. Genet., 1992, 1, 3-6
[26] Hanis C.L., Boerwinkle E., Chakraborty R., Ellsworth D.L., Concannon P., Stirling B., et al., A genome-wide search for human non-insulin-dependent (type 2) diabetes genes reveals a major susceptibility locus on chromosome 2, Nat. Genet., 1996, 13, 161-166
[27] Horikawa Y., Oda N., Cox N.J., Li X., Orho-Melander M., Hara M., et al., Genetic variation in the gene encoding calpain-10 is associated with type 2 diabetes mellitus, Nat. Genet., 2000, 26, 163-175
[28] Grant S.F., Thorleifsson G., Reynisdottir I., Benediktsson R., Manolescu A., Sainz J., et al., Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes, Nat. Genet., 2006, 38, 320-323
[29] Reynisdottir I., Thorleifsson G., Benediktsson R., Sigurdsson G., Emilsson V., Einarsdottir A.S., et al., Localization of a susceptibility gene for type 2 diabetes to chromosome 5q34-q35.2, Am. J. Hum. Genet., 2003, 73, 323-335
[30] Cauchi S., El Achhab Y., Choquet H., Dina C., Krempler F., Weitgasser R., et al., TCF7L2 is reproducibly associated with type 2 diabetes in various ethnic groups: a global meta-analysis, J. Mol. Med., 2007, 85, 777-782
[31] Risch N., Merikangas K., The future of genetic

studies of complex human diseases, Science, 1996, 273, 1516-1517

[32] Watanabe R.M., Black M.H., Xiang A.H., Allayee H., Lawrence J.M., Buchanan T.A., Genetics of gestational diabetes mellitus and type 2 diabetes, Diabetes Care, 2007, 30, Suppl 2, S134-140

[33] Newton-Cheh C., Hirschhorn J.N., Genetic association studies of complex traits: design and analysis issues, Mutat. Res., 2005, 573, 54-69

[34] Ludovico O., Pellegrini F., Di Paola R., Minenna A., Mastroianno S., Cardellini M., et al., Heterogeneous effect of peroxisome proliferator-activated receptor gamma2 Ala12 variant on type 2 diabetes risk, Obesity (Silver Spring), 2007, 15, 1076-1081

[35] Nielsen E.M., Hansen L., Carstensen B., Echwald S.M., Drivsholm T., Glumer C., et al., The E23K variant of Kir6.2 associates with impaired post-OGTT serum insulin response and increased risk of type 2 diabetes, Diabetes, 2003, 52, 573-577

[36] Winckler W., Weedon M.N., Graham R.R., McCarroll S.A., Purcell S., Almgren P., et al., Evaluation of common variants in the six known maturity-onset diabetes of the young (MODY) genes for association with type 2 diabetes, Diabetes, 2007, 56, 685-693

[37] Gudmundsson J., Sulem P., Steinthorsdottir V., Bergthorsson J.T., Thorleifsson G., Manolescu A., et al., Two variants on chromosome 17 confer prostate cancer risk, and the one in TCF2 protects against type 2 diabetes, Nat. Genet., 2007, 39, 977-983

[38] Jorgenson E., Witte J.S., A gene-centric approach to genome-wide association studies, Nat. Rev. Genet., 2006, 7, 885-891

[39] Saxena R., Voight B.F., Lyssenko V., Burtt N.P., de Bakker P.I., Chen H., et al., Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels, Science, 2007, 316, 1331-1336

[40] Steinthorsdottir V., Thorleifsson G., Reynisdottir I., Benediktsson R., Jonsdottir T., Walters G.B., et al., A variant in CDKAL1 influences insulin response and risk of type 2 diabetes, Nat. Genet., 2007, 39, 770-775

[41] Florez J.C., Manning A.K., Dupuis J., McAteer J., Irenze K., Gianniny L., et al., A 100k Genome-Wide Association Scan for Diabetes and Related Traits in the Framingham Heart Study: Replication and Integration with Other Genome-Wide Datasets, Diabetes 2007, (in press)

[42] Rampersaud E., Damcott C.M., Fu M., Shen H., McArdle P., Shi X., et al., Identification of novel candidate genes for type 2 diabetes from a genome-wide association scan in the Old Order Amish: Evidence for replication from diabetes-related quantitative traits and from independent populations, Diabetes, 2007, (in press)

[43] Hanson R.L., Bogardus C., Duggan D., Kobes S., Knowlton M., Infante A.M., A Search for Variants Associated with Young-Onset Type 2 Diabetes in American Indians in a 100k Genotyping Array, Diabetes, 2007, (in press)

[44] Nemoto M., Sasaki T., Deeb S.S., Fujimoto W.Y., Tajima N., Differential effect of PPARgamma2 variants in the development of type 2 diabetes between native Japanese and Japanese Americans, Diabetes Res. Clin. Pract., 2002, 57, 131-137

[45] Laaksonen D.E., Lindstrom J., Lakka T.A., Eriksson J.G., Niskanen L., Wikstrom K., et al., Physical activity in the prevention of type 2 diabetes: the Finnish diabetes prevention study, Diabetes, 2005, 54, 158-165

[46] Siitonen N., Lindstrom J., Eriksson J., Valle T.T., Hamalainen H., Ilanne-Parikka P., et al., Association between a deletion/insertion polymorphism in the alpha2B-adrenergic receptor gene and insulin secretion and Type 2 diabetes. The Finnish Diabetes Prevention Study, Diabetologia, 2004, 47, 1416-1424

[47] Lindi V.I., Uusitupa M.I., Lindstrom J., Louheranta A., Eriksson J.G., Valle T.T., et al., Association of the Pro12Ala polymorphism in the PPAR-gamma2 gene with 3-year incidence of type 2 diabetes and body weight change in the Finnish Diabetes Prevention Study, Diabetes, 2002, 51, 2581-2586

[48] Laukkanen O., Lindstrom J., Eriksson J., Valle T.T., Hamalainen H., Ilanne-Parikka P., et al., Polymorphisms in the SLC2A2 (GLUT2) gene are associated with the conversion from impaired glucose tolerance to type 2 diabetes: the Finnish Diabetes Prevention Study, Diabetes, 2005, 54, 2256-2260

[49] Salopuro T., Pulkkinen L., Lindstrom J., Eriksson J.G., Valle T.T., Hamalainen H., et al. Genetic variation in leptin receptor gene is associated with type 2 diabetes and body weight: The Finnish Diabetes Prevention Study, Int. J .Obes. (Lond.), 2005, 29, 1245-1251

[50] Kubaszek A., Pihlajamaki J., Komarovski V., Lindi V., Lindstrom J., Eriksson J., et al., Promoter polymorphisms of the TNF-alpha (G-308A) and IL-6 (C-174G) genes predict the conversion from impaired glucose tolerance to type 2 diabetes: the Finnish Diabetes Prevention Study, Diabetes,

2003, 52, 1872-1876
[51] Mager U., Lindi V., Lindstrom J., Eriksson J.G., Valle T.T., Hamalainen H., et al., Association of the Leu72Met polymorphism of the ghrelin gene with the risk of Type 2 diabetes in subjects with impaired glucose tolerance in the Finnish Diabetes Prevention Study, Diabetes Med., 2006, 23, 685-689
[52] Florez J.C., Jablonski K.A., Bayley N., Pollin T.I., de Bakker P.I., Shuldiner A.R., et al., TCF7L2 polymorphisms and progression to diabetes in the Diabetes Prevention Program, N. Engl. J. Med., 2006, 355, 241-250
[53] Nelson T.L., Fingerlin T.E., Moss L.K., Barmada M.M., Ferrell R.E., Norris J.M., Association of the peroxisome proliferator-activated receptor gamma gene with type 2 diabetes mellitus varies by physical activity among non-Hispanic whites from Colorado, Metabolism, 2007, 56, 388-393
[54] Soriguer F., Morcillo S., Cardona F., Rojo-Martinez G., de la Cruz Almaraz M., Ruiz de Adana Mde L., et al., Pro12Ala polymorphism of the PPARG2 gene is associated with type 2 diabetes mellitus and peripheral insulin sensitivity in a population with a high intake of oleic acid, J. Nutr., 2006, 136, 2325-2330
[55] Qi L., Meigs J., Manson J.E., Ma J., Hunter D., Rifai N., et al., HFE genetic variability, body iron stores, and the risk of type 2 diabetes in U.S. women, Diabetes, 2005, 54, 3567-3572
[56] Beulens J.W., Rimm E.B., Hendriks H.F., Hu F.B., Manson J.E., Hunter D.J., et al., Alcohol consumption and type 2 diabetes: influence of genetic variation in alcohol dehydrogenase, Diabetes, 2007, 56, 2388-2394
[57] Frayling T.M., Genome-wide association studies provide new insights into type 2 diabetes aetiology, Nat. Rev. Genet., 2007, 8, 657-662
[58] Bermejo J.L., Hemminki K., Gene-environment studies: any advantage over environmental studies? Carcinogenesis, 2007, 28, 1526-1532
[59] Willett W.C., Balancing life-style and genomics research for disease prevention. Science, 2002, 296, 695-698
[60] McCarroll S.A., Altshuler D.M., Copy-number variation and association studies of human disease, Nat. Genet., 2007, 39, S37-42