[Frontiers in Bioscience 14, 4535-4545, January 1, 2009]

Human genetics of diabetes mellitus in Taiwan

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TABLE OF CONTENTS

1. ABSTRACT

Diabetes mellitus (DM) is a disease defined by biochemical hyperglycemia. Currently it is classified into four major categories: type 1 DM (T1DM), type 2 DM (T2DM), gestational DM (GDM) and other DM. Within each category, the etiology is still heterogeneous. The pathogenesis of most DM is multi-factorial, including many genetic and environmental factors. T1DM, T2DM and GDM are polygenic. In the category of other DM, there are at least six maturity onset diabetes of the young (MODY) and many other genetic syndromes associated with DM, which are monogenic in origin. In this review, we briefly summarized the current status of genetics in DM, described what has been done in this specific area in Taiwan and discuss what should be done after the era of genome-wide association study.

2. INTRODUCTION

Diabetes mellitus (DM) comprises a collection of clinically and genetically heterogeneous disorders characterized by inappropriate hyperglycemia. The underlying pathophysiology is related to deficiency of insulin secretion, a reduction in the biologic effectiveness of insulin, or a combination of these two. The most recent update of DM classification system and diagnostic criteria were developed by an international workgroup sponsored by the National Diabetes Data Group of the National Institute of Health of the US in 1997 (1) and by World Health Organization Expert Committee in 1999 (2). The diagnostic criteria include: (A) symptoms of diabetes (i.e. thirst, polyuria and unexplained weight loss) plus a random plasma glucose concentration higher than 200 mg/dL (11.1mmol/L); (B) fasting plasma glucose higher than 126

mg/dL (7.0 mmol/L) after an overnight (at least 8-hour) fast; and (C) two-hour plasma glucose higher than 200 mg/dL (11.1 mmol/L) during a standard 75-gram oral glucose tolerance test. Currently, DM can be broadly categorized as 4 groups: type 1 DM (T1DM), type 2 DM (T2DM), other specific types of DM and gestational DM (GDM) (1). Any of these 4 types is still not a single homogeneous disease; for example, the "other specific types of DM" category contains tens of known disease entities, including mitochondrial diabetes, maturity-onset diabetes of the young (MODY), and other genetic or non-genetic causes.

Genetic factors play an important role in the pathogenesis of diabetes. T1DM and T2DM are complex traits with both genetic and environmental predisposition. Multiple lines of evidence, including family study and twin study, support the important role of genetic factors, most likely multiple genes, in the pathogenesis of T1DM or T2DM. Mitochondrial DM is maternally inherited and is caused by genetic variations, such as substitution or deletion, at the genes of mitochondrial genome or nuclear genes encoding mitochondrial proteins. All types of currently known MODY are single gene diseases inherited in an autosomal dominant pattern. In this article, we will briefly update the progress of human genetic study of DM worldwide and then review the work conducted in Taiwan.

3. GENETICS OF TYPE 1 DM

3.1. Summary of the current progress of type 1 DM genetics

T1DM is a chronic autoimmune disorder with the immune-mediated destruction of pancreatic beta cells (3). The disease incidence differs significantly among different geographic areas and populations, ranging from more than 20 cases/year/100,000 individuals in the Scandinavian population to around 1 case/year/100,000 individuals in Asians (4, 5). The recurrence risk λs (lambda of siblings) for T1DM is ~15 in Caucasians (6), and twin study suggests that 88% of the phenotypic variance is due to genetic factors (7).

Before the era of genomewide association study, there have been a handful of susceptibility genes identified with reasonable statistical evidence, including the human leukocyte antigen (HLA) region (8-10), insulin (*INS*) (11), protein tyrosine phosphatase, non-receptor type 22 (*PTPN22*) (12, 13), and cytotoxic T-lymphocyte associated 4 (*CTLA-4*) (14). Genome-wide association (GWA) study with a large sample size is an exciting and powerful new approach. Since 2006, several genes/regions, such as the regions around interferon-induced helicase 1 (*IFIH1/MDA5*) and chromosomes 12q13, 12q24 and 16p13, have been implicated with GWA (15). With the rapid progress of genotyping technology and sample collection, more and more plausible susceptibility genes will be identified and vigorously tested.

3.2. Review of type 1 DM genetics in Taiwan

For the Han population in Taiwan, there have been several genetic studies showing the association between HLA and T1DM. As early as 1980, with just 39 cases and 57 controls, Maeda *et al*. found that the incidence of HLA-DRw3 was increased in cases (relative risk=5.8, P=0.0027) (16). Subsequently, the increased risk of DR3/DR4 heterozygotes was demonstrated (17). When DNA-based typing techniques were introduced, researchers could conduct studies with higher precision. Overall, DR3 and DR4 were found to increase, while DR2 and DR5 were decreased in T1DM individuals in Taiwan (18). HLA DR9, when combined with DR3, increased the risk for T1DM (19). DQB-57-non-Arg is positively associated, but not sufficient to explain all the risk of T1DM (20). With 31 simplex T1DM families, Chuang et al. deduced the extended HLA haplotypes without ambiguity and showed that DRB1*0301/DQA1*0501/DQB1*0201, DRB1*0405/DQA1*0301/DQB1*0302 and DRB1*0405/DQA1*0301/DQB1*0401 were susceptibility haplotypes in Taiwan (19), which was later replicated by another group (21). The allele frequency and haplotype composition of classical HLA loci can differ significantly between populations (22, 23), which might be one of the reasons why the incidence of T1DM varies across the world.

The allele frequencies of the variable number of tandem repeats (VNTR) located 5' upstream of the insulin gene are also different across populations (24, 25). In Taiwan, Chuang *et al*. (26) could not find association between T1DM and the class I allele of VNTR (27) or other restriction fragment length polymorphism (RFLP) markers within *INS*. Association studies of T1DM and *INS* from other non-Caucasian populations have been inconsistent (25, 28).

Vitamin D receptor (*VDR*) has been tested as a candidate susceptibility gene in Taiwan. Chang *et al*. (29) recruited 157 cases and 248 controls and found that one RFLP marker in the 7th intron of VDR, with allele frequency 7.6% in cases and 3.6% in controls, was association with T1DM even after correcting for multiple testing (corrected P = 0.045).

4. GENETICS OF TYPE 2 DM

4.1. Summary of the current progress of type 2 DM genetics

T2DM is a chronic metabolic disorder characterized by insulin resistance and/or abnormal insulin secretion (30, 31). We are witnessing a global epidemic of DM, with the total number of diabetes individuals projected to rise from 171 million in 2000 to 366 million in 2030 (32). Although lifestyle, behavior and environment are important for T2DM pathogenesis, genetic factors definitely play a critical role. The estimated λs for T2DM is ~3.5 in Caucasians (33), which reflects shared environment and genetic predisposition between family members. Heritability values derived from twin studies vary, with most estimates between 30 and 70% (31).

There have been three T2DM susceptibility genes identified and repeatedly replicated, which are transcription factor 7-like 2 (*TCF7L2*) (34), inwardly-rectifying Kir6.2 component of the pancreatic beta-cell KATP channel (*KCNJ11*) (35) and peroxisomal

proliferative activated receptor gamma (*PPARG*) (36). Other genetic studies also support the roles of the following genes: calpain 10 (*CAPN10*) (37), hepatocyte nuclear factor 4-alpha (*HNF4A*) (38), lamin A/C (*LMNA*) (39), ectonucleotide pyrophosphatase phosphodiesterase 1 (*ENPP1*) (40), insulin receptor substrate 1 (*IRS1*) (41), ATP-binding cassette, subfamily C, member 8 (*ABCC8*) (42), solute carrier family 2, member 1 (*SLC2A1*) (42) and insulin (*INS*) (41). Recent genome-wide scans further implicate some other signals, such as fat-mass and obesity-associated (*FTO*), *CDK5* regulatory subunit associated protein 1-like 1 (*CDKAL1*), insulin-like growth factor 2 mRNA-binding protein 2 (*IGF2BP2*), solute carrier family 30, member 8 (*SLC30A8*), hematopoietically expressed homeobox (*HHEX*), and the region near cyclin-dependent kinase inhibitor 2A and 2B (*CDKN2A* and *CDKN2B*) (43-45).

4.2. Review of type 2 DM genetics in Taiwan

In Taiwan, there have been many candidate gene-based association reports for T2DM. Similar to the situation of the research field worldwide, the sample size of early studies tended to be small, mostly less then 500 cases. In some latest association studies conducted in Taiwan, the sample sizes could surpass 1000 cases and should have better power to detect susceptibility genes with small to moderate effect.

Glucokinase (*GCK*), the gene responsible for MODY2, was tested for association with T2DM in Taiwan by Wu *et al*. (46). Two short tandem repeat polymorphism (STRP) markers (GCK1 and GCK2) near *GCK* were genotyped, and one allele of GCK1 was found to have a lower frequency in cases than in controls (14.0% vs. 23.9%) although the P value (0.058) did not reach a statistically significant level caused by small sample size.

Chuang *et al*. collected 23 multiplex families, 89 unrelated T2DM individuals and 82 unrelated controls to test the role of *IRS1* (47). The PCR-RFLP method was used to genotype the Gly971Arg variant. They did not find evidence of association.

A mis-sense mutation, Gly40Ser, of glucagon receptor (*GCG-R*) was reported to be associated with T2DM in Caucasians with an allele frequency as high as 4.6% in France and 8.38% in Sardinia (48, 49). Huang *et al*. screened 213 T2DM subjects, 107 hypertension subjects and 121 normal controls and found none of them had this genetic variation (50). Their results demonstrated a strong genetic heterogeneity between different ethnic groups in some genomic regions.

The angiotensin-converting enzyme (*ACE*) gene has been tested for association with T2DM or other related phenotypes in Taiwan. Chuang *et al*. collected 107 subjects with T2DM, 67 with hypertension, 70 with both T2DM and coronary artery disease and 197 normal controls, and found no association of the insertion/deletion (I/D) polymorphism with any of the phenotypes they tested (51). On the other hand, Hsieh *et al*., using 336 T2DM patients and 263 matched normal controls, found an increased frequency of DD genotype in T2DM patients than in normal controls (18.2% vs. 9.1%, P<0.01) (52). Lee and Tsai showed that the *ACE* I/D polymorphism was significantly associated with the metabolic syndrome in 711 T2DM patients (P=0.001) (53). However, when Tseng and Tseng examined the relationship of this I/D polymorphism with the peripheral vascular disease complication of T2DM individuals, they did not find association (54).

A couple of immune-related genes were tested for the association with T2DM, including tumor necrosis factor-alpha (*TNF-alpha*) (55), interleukin-6 (*IL-6*) (56) and interleukin-10 (*IL-10*) (57). Up to now, none of them has been shown to be associated with T2DM in Taiwan.

The Arg16Gly polymorphism of beta2-adrenoreceptor (*ADRB2*) gene was examined by Chang *et al*. (58). With a collection of 130 patients and 130 age, gender and body mass index (BMI)-matched controls, they concluded that the homozygosity of Arg16 was associated with a higher frequency of T2DM, and also associated with an earlier onset of the disease.

Solute carrier family 2, facilitated glucose transporter, member 10 (*SLC2A10*) is another intriguing candidate gene for T2DM. Lin *et al*. performed the association study using 15 SNPs and 1 tandem repeat polymorphism in 375 cases and 377 controls, and found only a modest association signal from a haplotype of one of the four linkage disequilibrium blocks (59). They suggested that *SLC2A10* does not appear to be a major determinant for T2DM in Taiwan.

Adiponectin is a plasma glycoprotein of adipose tissue origin, and is a promising candidate T2DM gene based on its biological relevance and other previous association studies. Yang *et al*. genotyped 1793 subjects of Chinese and Japanese descendents from 601 hypertensive families, and focused on variants in the adiponectin gene and *PPARG* (60). The phenotypes they were working on were insulin concentrations and insulin resistance index. They demonstrated that adiponectin is associated with insulin sensitivity, and they also showed that interaction with *PPARG* would modify this association. Later on, Yang *et al*., based on 1438 elderly individuals (> 65 years old) in Taiwan, found that genetic variants of adiponectin is associated with T2DM, obesity and metabolic syndrome (61). The effect of adiponectin genotype on the risk of T2DM was partially independent of BMI.

The discovery of *TCF7L2* as a susceptibility gene is probably the biggest story in genetic study of T2DM (62). The association has been replicated in almost all the subsequent studies in the Caucasians, and there have been replication in other populations (63-65), although a Japanese group reported a much lower frequency of the risk allele (63). In Taiwan, Chang *et al*. genotyped 20 tagging SNPs across *TCF7L2* in 760 T2DM cases and 760 unrelated controls (66). They demonstrated that rs7903146, the SNP with highest risk in previous studies, had a much lower allele frequency (~2.3%) in our population, and was not associated with T2DM. However, they found rs290487

and haplotypes containing it, which is ~150 kb downstream of rs7903146, were significantly associated with T2DM (odds ratio: 1.26, nominal P = 0.0021) and conferred a population attributable risk fraction of 18.7%. This population-specific risk SNP/region of *TCF7L2* in our population, if confirmed in subsequent studies, will provide valuable information for both basic research and clinical application.

5. GENETICS OF MITOCHONDRIAL DM

5.1. Summary of the current progress of mitochondrial DM genetics

DM can also be caused by mitochondrial diseases. Point mutation at mitochondrial DNA m.3243A>G, which is located at the tRNA (Leu, UUR) gene, was the first discovered causative variant (67, 68). Other point mutations, such as m.14709T>C (69, 70), and deletions (71, 72) can also be responsible for diabetes. Even mitochondrial protein encoded in nucleus has been implicated to cause diabetes (73). However, little is known about the factors determining the clinical phenotypes for any particular genotype. For example, the same m.3243A>G mutation can confer a spectrum of phenotypes in different individuals, including asymptomatic; maternally inherited diabetes and deafness; chronic progressive external ophthalmoplegia; or the MELAS (mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes) syndrome (74). Mitochondrial DM is likely under-diagnosed, because of the lack in awareness among medical doctors and the lack of proper diagnostic tools. There has been no good prevalence estimate of mitochondrial diabetes. The m.3243A>G is by far the most common disease-causing mutation (74), and can account for up to 3% of all diabetes individuals in some populations (75, 76).

5.2. Review of mitochondrial DM genetics in Taiwan

In Taiwan, there were sparse studies on mitochondrial diabetes. It is difficult to estimate the prevalence and relevant importance of different variants. Chuang *et al*. screened 23 T2DM pedigrees and found one of the 23 pedigrees carried the m.3243A>G mutation (77). With a similar approach, 2 out of 84 T1DM individuals were shown to have the m.3243A>G point mutation, although one of the two individuals also carried the susceptibility HLA haplotype (78). Pang *et al*. analyzed the genotypes of 77 patients with mitochondrial diseases, and found 32 patients with m.3243A>G mutation, 9 with m.8344A>G, 18 with m.11778G>A, 1 with m.8993T>C, 2 with m.8993T>G, and 21 with deletion (79).

It is an important question to ask if the clinical severity is related to the degree of heteroplasmy or not. Two studies in Taiwan touched this issue, and the researchers found no correlation between the clinical severity and the degree of heteroplasmy in various tissues, such as leukocytes, hair follicles and muscle tissues (77, 80).

A common variant (m.16189 T>C) has been reported in patients with MELAS (81) and might be associated with insulin resistance (82, 83). In a recent study enrolling 462 T2DM patients and 592 non-DM controls in Taiwan, Liou *et al.* (84) showed that a higher proportion of T2DM patients (39.2%) carry this variant compared to the proportion in non-DM controls (30.7%), with a multivariate odds ratio of 1.38. They also reported increased BMI as an aggravating factor for development of DM in subjects harboring the variant.

6. GENETICS OF MODY AND GENETIC SYNDROMES

6.1. Summary of the current progress of MODY genetics

MODY comprises a group of monogenic, autosomal dominant diabetes, characterized by an early age of onset (usually < 25 years old) (85). Up to now, 6 genes have been identified, including hepatocyte nuclear factor (*HNF*)-4α (MODY1) (86), glucokinase (*GCK*) (MODY2) (87), *HNF-1α* (MODY3) (88), insulin promoter factor-1 (*IPF-1*) (MODY4) (89), *HNF-1β* (MODY5) (90) and neurogenic differentiation factor 1 (*NEUROD1*) (MODY6) (91). In the Caucasian population, MODY3 and MODY2 accounts for more than 80% of all MODY patients, MODY1 is less common, and all the other forms are rare (92). In Japan, however, about 80% of MODY patients cannot be explained by known MODY genes (93).

6.2. Review of MODY genetics in Taiwan

In Taiwan, very few papers related to MODY have been published. Jap *et al*. sequenced the *HNF-1α* gene of 15 unrelated loosely defined MODY patients (94). None of previously described causal variants were found. Instead, a novel mis-sense mutation, Y218C, at the DNA binding domain of the *HNF-1α* gene was found in one patient. It seems that the most common causal variants in Caucasians do not account for most of the MODY patients in Taiwan.

In Chinese population in Hong Kong, Xu *et al*. collected 146 unrelated families fulfilling the minimum criteria for MODY and screened for mutations of MODY1, MODY2 and MODY3 by direct sequencing (95). The prevalence of MODY3, MODY2 and MODY1 was only 9%, 1% and 0% respectively. Among the 12 MODY3 mutations, 4 had not been reported before this study. They concluded that the majority of Chinese MODY patients are due to defects in unknown genes.

6.3. Summary of the current progress of genetic syndrome of DM

There are more than 50 genetic syndromes related to diabetes mellitus (http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim). These syndromes are usually of Mendelian inheritance. Their phenotypes include not only DM but also many other phenotypes. Most of the time, the phenotype other than DM are much more prominent. Wolfram syndrome also referred to as DIDMOAD (diabetes insipidus, DM, optic atrophy, and deafness) is one of the examples. Mutations in *WFS1* gene confers autosomal recessive Wolfram syndrome and autosomal dominant sensorineural hearing loss (96)

6.4. Review of genetic syndrome of DM in Taiwan

Only one report by Tsai *et al.* described a Taiwanese family with a Y669H (2005T>C) mutation in exon 8 of *WFS1* gene (97). The carriers with the mutation had familial nonsyndromic low-frequency sensorineural hearing loss, but did not appear to have DM. Comprehensive review of any genetic syndrome associated with DM is beyond the scope of this article. Moreover, this area is rarely touched by scientists in Taiwan, mainly because they are relatively rare and probably under-diagnosed or under-reported by physicians.

7. PERSPECTIVES

With the advance of genotyping technology, statistic tools and large-size sample collection, genetic study of various forms of DM is, although still complicated, no longer a nightmare. The key point for future genetic study is to increase sample size and marker density. Besides, careful phenotyping to identify a more homogeneous subtype is always beneficial. Furthermore, genetic variants other than SNPs, such as copy number variation or inversion, should also be investigated. Last but not the least, population-specific susceptibility genes and/or alleles are likely to exist and should be vigorously looked for. A good example to justify the last statement is the recent discovery of different associated SNPs in *TCF7L2* for T2DM in Taiwan (66) and in Hong Kong (98).

Genetics is exciting because it not only provides tools to test hypotheses, but actually can also generate new hypothesis. Both linkage analysis and genome-wide association (GWA) study can lead researchers to find susceptibility genes/pathways that surprise everybody. The identification of *TCF7L2* as a susceptibility gene of T2DM is a good example, which can open a whole new basic research field and might guide treatment choices in the future. The next step ahead of us is to identify all the major genetic and environmental factors for diabetes. At that time, risk prediction will be possible and personalized medicine is no longer a dream.

In 2003, several leading diabetologists in Taiwan from several major medical centers, including National Taiwan University Hospital, Veteran General Hospitals at Taipei and Taichung, Chang-Gung Memorial Hospital at Taipei, and Chang-Hua Christian Hospital were summoned at Academia Sinica (AS) at Taipei for a GWA study of T2DM, a collaborative project of AS with the pharmaceutical giant GlaxoSmithKline. Unfortunately the project was not worked out as planned. The investigators in Taiwan missed a golden opportunity to participate in the international race of GWA study for T2DM. With several GWA studies published (43-45), it does not appear sensible to pursue a GWA study of T2DM in Taiwan. What we need to focus next should be population-based case-control studies of descent sample size to fully elucidate the proportion of genetic risk and the population-specific risk alleles of diabetes, respectively for T1DM, T2DM, MODY, mitochondrial DM. We also need to enhance the awareness of the genetic syndromes associated with DM among physicians and recruit more subjects to investigate the prevalence and mutation spectrum of these syndromes. We also need to investigate the genotype-phenotype correlation in our population. Furthermore, many T2DM genes discovered by GWA studies are of unknown function. Therefore, further molecular, biochemical and physiological investigation of gene functions should be performed.

8. ACKNOWLEDGEMENTS

WSY is supported by grant from National Science Council of Taiwan (#95-2314-B-002-316-MY2).

9. REFERENCES

1. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20, 1183-1197 (1997)

2. World Health Organization: Definition, Diagnosis and Classification of Diabetes mellitus and its Complications. Part 1: Diagnosis and Classification of Diabetes Mellitus (Department of Noncommunicable Disease Surveillance, Geneva, 1999) (1999)

3. G. S. Eisenbarth: Type I diabetes mellitus. A chronic autoimmune disease. N Engl J Med 314, 1360-1368 (1986)

4. Diabetes Epidemiology Research International Group: Geographic patterns of childhood insulin-dependent diabetes mellitus. Diabetes Epidemiology Research International Group. Diabetes 37, 1113-1119 (1988)

5. WHO DIAMOND PROJECT GROUP: WHO Multinational Project for Childhood Diabetes. WHO Diamond Project Group. *Diabetes Care* 13, 1062-1068 (1990)

6. N. Risch: Assessing the role of HLA-linked and unlinked determinants of disease. *Am J Hum Genet* 40, 1-14 (1987)

7. V. Hyttinen, J. Kaprio, L. Kinnunen, M. Koskenvuo, J. Tuomilehto: Genetic liability of type 1 diabetes and the onset age among 22,650 young Finnish twin pairs: a nationwide follow-up study. *Diabetes* 52, 1052-1055 (2003)

8. P. Concannon, H. A. Erlich, C. Julier, G. Morahan, J. Nerup, F. Pociot, J. A. Todd, S. S. Rich: Type 1 diabetes: evidence for susceptibility loci from four genome-wide linkage scans in 1,435 multiplex families. *Diabetes* 54, 2995-3001 (2005)

9. S. S. Rich, A. Green, N. E. Morton, J. Barbosa: A combined segregation and linkage analysis of insulin-dependent diabetes mellitus. *Am J Hum Genet* 40, 237-249 (1987)

10. J. A. Todd, J. I. Bell, H. O. McDevitt: HLA-DQ beta gene contributes to susceptibility and resistance to insulin-dependent diabetes mellitus. *Nature* 329, 599-604 (1987)
11. G. I. Bell, S. Horita, J. H. Karam: A polymorphic locus near the human insulin gene is associated with insulin-dependent diabetes mellitus. *Diabetes* 33, 176-183 (1984)

12. N. Bottini, L. Musumeci, A. Alonso, S. Rahmouni, K. Nika, M. Rostamkhani, J. MacMurray, G. F. Meloni, P. Lucarelli, M. Pellecchia, G. S. Eisenbarth, D. Comings, T. Mustelin: A functional variant of lymphoid tyrosine phosphatase is associated with type I diabetes. *Nat Genet* 36, 337-338 (2004)

13. E. Kawasaki, T. Awata, H. Ikegami, T. Kobayashi, T. Maruyama, K. Nakanishi, A. Shimada, M. Uga, S. Kurihara, Y. Kawabata, S. Tanaka, Y. Kanazawa, I. Lee, K. Eguchi: Systematic search for single nucleotide polymorphisms in a lymphoid tyrosine phosphatase gene (PTPN22): Association between a promoter polymorphism and type 1 diabetes in Asian populations. American Journal of Medical Genetics 140A:586-593 (2006). *Am J Med Genet A* 143, 1812-1813 (2007)

14. H. Ueda, J. M. Howson, L. Esposito, J. Heward, H. Snook, G. Chamberlain, D. B. Rainbow, K. M. Hunter, A. N. Smith, G. Di Genova, M. H. Herr, I. Dahlman, F. Payne, D. Smyth, C. Lowe, R. C. Twells, S. Howlett, B. Healy, S. Nutland, H. E. Rance, V. Everett, L. J. Smink, A. C. Lam, H. J. Cordell, N. M. Walker, C. Bordin, J. Hulme, C. Motzo, F. Cucca, J. F. Hess, M. L. Metzker, J. Rogers, S. Gregory, A. Allahabadia, R. Nithiyananthan, E. Tuomilehto-Wolf, J. Tuomilehto, P. Bingley, K. M. Gillespie, D. E. Undlien, K. S. Ronningen, C. Guja, C. Ionescu-Tirgoviste, D. A. Savage, A. P. Maxwell, D. J. Carson, C. C. Patterson, J. A. Franklyn, D. G. Clayton, L. B. Peterson, L. S. Wicker, J. A. Todd, S. C. Gough: Association of the T-cell regulatory gene CTLA4 with susceptibility to autoimmune disease. *Nature* 423, 506-511 (2003)

15. D. J. Smyth, J. D. Cooper, R. Bailey, S. Field, O. Burren, L. J. Smink, C. Guja, C. Ionescu-Tirgoviste, B. Widmer, D. B. Dunger, D. A. Savage, N. M. Walker, D. G. Clayton, J. A. Todd: A genome-wide association study of nonsynonymous SNPs identifies a type 1 diabetes locus in the interferon-induced helicase (IFIH1) region. *Nat Genet* 38, 617-619 (2006)

16. H. Maeda, F. Takeuchi, T. Juji, Y. Akanuma, M. Kasuga, Y. S. Lee, K. Kosaka, S. H. Tsai: HLA-DRw3 in juvenile onset diabetes mellitus in Chinese. *Tissue Antigens* 15, 173-176 (1980)

17. H. S. Huang, M. J. Huang, C. C. Huang, B. Y. Huang, P. W. Wang, J. D. Lin: A strong association of HLA-DR 3/4 heterozygotes with insulin-dependent diabetes among Chinese in Taiwan. *Taiwan Yi Xue Hui Za Zhi* 87, 1-6 (1988)

18. C. Y. Hu, M. Allen, L. M. Chuang, B. J. Lin, U. Gyllensten: Association of insulin-dependent diabetes mellitus in Taiwan with HLA class II DQB1 and DRB1 alleles. *Hum Immunol* 38, 105-114 (1993)

19. L. M. Chuang, H. P. Wu, W. Y. Tsai, B. J. Lin, T. Y. Tai: Transcomplementation of HLA DQA1-DQB1 in DR3/DR4 and DR3/DR9 heterozygotes and IDDM in Taiwanese families. *Diabetes Care* 18, 1483-1486 (1995)

20. L. M. Chuang, T. S. Jou, C. Y. Hu, H. P. Wu, W. Y. Tsai, J. S. Lee, R. P. Hsieh, K. H. Chen, T. Y. Tai, B. J. Lin: HLA-DQB1 codon 57 and IDDM in Chinese living in Taiwan. *Diabetes Care* 17, 863-868 (1994)

21. H. S. Huang, J. T. Peng, J. Y. She, L. P. Zhang, C. C. Chao, K. H. Liu, J. X. She: HLA-encoded susceptibility to insulin-dependent diabetes mellitus is determined by DR and DQ genes as well as their linkage disequilibria in a Chinese population. *Hum Immunol* 44, 210-219 (1995)

22. Y. Kawabata, H. Ikegami, Y. Kawaguchi, T. Fujisawa, M. Shintani, M. Ono, M. Nishino, Y. Uchigata, I. Lee, T. Ogihara: Asian-specific HLA haplotypes reveal heterogeneity of the contribution of HLA-DR and -DQ haplotypes to susceptibility to type 1 diabetes. *Diabetes* 51, 545-551 (2002)

23. J. Robinson, M. J. Waller, P. Parham, N. de Groot, R. Bontrop, L. J. Kennedy, P. Stoehr, S. G. Marsh: IMGT/HLA and IMGT/MHC: sequence databases for the study of the major histocompatibility complex. *Nucleic Acids Res* 31, 311-314 (2003)

24. S. T. Bennett, A. J. Wilson, F. Cucca, J. Nerup, F. Pociot, P. A. McKinney, A. H. Barnett, S. C. Bain, J. A. Todd: IDDM2-VNTR-encoded susceptibility to type 1 diabetes: dominant protection and parental transmission of alleles of the insulin gene-linked minisatellite locus. *J Autoimmun* 9, 415-421 (1996)

25. Y. Kawaguchi, H. Ikegami, G. Q. Shen, Y. Nakagawa, T. Fujisawa, Y. Hamada, H. Ueda, J. Fu, Y. Uchigata, Y. Kitagawa, Y. Omori, K. Shima, T. Ogihara: Insulin gene region contributes to genetic susceptibility to, but may not to low incidence of, insulin-dependent diabetes mellitus in Japanese. *Biochem Biophys Res Commun* 233, 283-287 (1997)

26. L. Chuang, S. Tsai, J. Juang, W. Tsai, T. Tai: Genetic epidemiology of type 1 diabetes mellitus in Taiwan. *Diabetes Res Clin Pract* 50 Suppl 2, S41-47 (2000)

27. S. T. Bennett, A. M. Lucassen, S. C. Gough, E. E. Powell, D. E. Undlien, L. E. Pritchard, M. E. Merriman, Y. Kawaguchi, M. J. Dronsfield, F. Pociot et al.: Susceptibility to human type 1 diabetes at IDDM2 is determined by tandem repeat variation at the insulin gene minisatellite locus. *Nat Genet* 9, 284-292 (1995)

28. C. H. Mijovic, M. A. Penny, D. Jenkins, K. Jacobs, J. Heward, S. W. Knight, A. Lucassen, E. Morrison, A. H. Barnett: The insulin gene region and susceptibility to insulin-dependent diabetes mellitus in four races; new insights from Afro-Caribbean race-specific haplotypes. *Autoimmunity* 26, 11-22 (1997)

29. T. J. Chang, H. H. Lei, J. I. Yeh, K. C. Chiu, K. C. Lee, M. C. Chen, T. Y. Tai, L. M. Chuang: Vitamin D receptor gene polymorphisms influence susceptibility to type 1 diabetes mellitus in the Taiwanese population. *Clin Endocrinol (Oxf)* 52, 575-580 (2000)

30. P. Zimmet, K. G. Alberti, J. Shaw: Global and societal implications of the diabetes epidemic. *Nature* 414, 782-787 (2001)

31. M. Stumvoll, B. J. Goldstein, T. W. van Haeften: Type 2 diabetes: principles of pathogenesis and therapy. *Lancet* 365, 1333-1346 (2005)

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

33. S. S. Rich: Mapping genes in diabetes. Genetic epidemiological perspective. *Diabetes* 39, 1315-1319 (1990)

34. S. F. Grant, G. Thorleifsson, I. Reynisdottir, R. Benediktsson, A. Manolescu, J. Sainz, A. Helgason, H. Stefansson, V. Emilsson, A. Helgadottir, U. Styrkarsdottir, K. P. Magnusson, G. B. Walters, E. Palsdottir, T. Jonsdottir, T. Gudmundsdottir, A. Gylfason, J. Saemundsdottir, R. L. Wilensky, M. P. Reilly, D. J. Rader, Y. Bagger, C. Christiansen, V. Gudnason, G. Sigurdsson, U. Thorsteinsdottir, J. R. Gulcher, A. Kong, K. Stefansson: Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nat Genet 38, 320-323 (2006)

35. A. L. Gloyn, M. N. Weedon, K. R. Owen, M. J. Turner, B. A. Knight, G. Hitman, M. Walker, J. C. Levy, M. Sampson, S. Halford, M. I. McCarthy, A. T. Hattersley, T. M. Frayling: Large-scale association studies of variants in genes encoding the pancreatic beta-cell KATP channel subunits Kir6.2 (KCNJ11) and SUR1 (ABCC8) confirm that the KCNJ11 E23K variant is associated with type 2 diabetes. Diabetes 52, 568-572 (2003)

36. D. Altshuler, J. N. Hirschhorn, M. Klannemark, C. M. Lindgren, M. C. Vohl, J. Nemesh, C. R. Lane, S. F. Schaffner, S. Bolk, C. Brewer, T. Tuomi, D. Gaudet, T. J. Hudson, M. Daly, L. Groop, E. S. Lander: The common PPARgamma Pro12Ala polymorphism is associated with decreased risk of type 2 diabetes. Nat Genet 26, 76-80 (2000)

37. Y. Horikawa, N. Oda, N. J. Cox, X. Li, M. Orho-Melander, M. Hara, Y. Hinokio, T. H. Lindner, H. Mashima, P. E. Schwarz, L. del Bosque-Plata, Y. Horikawa, Y. Oda, I. Yoshiuchi, S. Colilla, K. S. Polonsky, S. Wei, P. Concannon, N. Iwasaki, J. Schulze, L. J. Baier, C. Bogardus, L. Groop, E. Boerwinkle, C. L. Hanis, G. I. Bell: Genetic variation in the gene encoding calpain-10 is associated with type 2 diabetes mellitus. *Nat Genet* 26, 163-175 (2000)

38. K. Silander, K. L. Mohlke, L. J. Scott, E. C. Peck, P. Hollstein, A. D. Skol, A. U. Jackson, P. Deloukas, S. Hunt, G. Stavrides, P. S. Chines, M. R. Erdos, N. Narisu, K. N. Conneely, C. Li, T. E. Fingerlin, S. K. Dhanjal, T. T. Valle, R. N. Bergman, J. Tuomilehto, R. M. Watanabe, M. Boehnke, F. S. Collins: Genetic variation near the hepatocyte nuclear factor-4 alpha gene predicts susceptibility to type 2 diabetes. *Diabetes* 53, 1141-1149 (2004)

39. K. R. Owen, C. J. Groves, R. L. Hanson, W. C. Knowler, A. R. Shuldiner, S. C. Elbein, B. D. Mitchell, P. Froguel, M. C. Ng, J. C. Chan, W. Jia, P. Deloukas, G. A. Hitman, M. Walker, T. M. Frayling, A. T. Hattersley, E. Zeggini, M. I. McCarthy: Common variation in the LMNA gene (encoding lamin A/C) and type 2 diabetes: association analyses in 9,518 subjects. *Diabetes* 56, 879-883 (2007)

40. D. Meyre, N. Bouatia-Naji, A. Tounian, C. Samson, C. Lecoeur, V. Vatin, M. Ghoussaini, C. Wachter, S. Hercberg, G. Charpentier, W. Patsch, F. Pattou, M. A. Charles, P. Tounian, K. Clement, B. Jouret, J. Weill, B. A. Maddux, I. D. Goldfine, A. Walley, P. Boutin, C. Dina, P. Froguel: Variants of ENPP1 are associated with childhood and adult obesity and increase the risk of glucose intolerance and type 2 diabetes. *Nat Genet* 37, 863-867 (2005)

41. H. Parikh, L. Groop: Candidate genes for type 2 diabetes. *Rev Endocr Metab Disord* 5, 151-176 (2004)

42. K. E. Lohmueller, C. L. Pearce, M. Pike, E. S. Lander, J. N. Hirschhorn: Meta-analysis of genetic association studies supports a contribution of common variants to susceptibility to common disease. *Nat Genet* 33, 177-182 (2003)

43. Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, Novartis Institutes of BioMedical Research, R. Saxena, B. F. Voight, V. Lyssenko, N. P. Burtt, P. I. de Bakker, H. Chen, J. J. Roix, S. Kathiresan, J. N. Hirschhorn, M. J. Daly, T. E. Hughes, L. Groop, D. Altshuler, P. Almgren, J. C. Florez, J. Meyer, K. Ardlie, K. Bengtsson Bostrom, B. Isomaa, G. Lettre, U. Lindblad, H. N. Lyon, O. Melander, C. Newton-Cheh, P. Nilsson, M. Orho-Melander, L. Rastam, E. K. Speliotes, M. R. Taskinen, T. Tuomi, C. Guiducci, A. Berglund, J. Carlson, L. Gianniny, R. Hackett, L. Hall, J. Holmkvist, E. Laurila, M. Sjogren, M. Sterner, A. Surti, M. Svensson, M. Svensson, R. Tewhey, B. Blumenstiel, M. Parkin, M. Defelice, R. Barry, W. Brodeur, J. Camarata, N. Chia, M. Fava, J. Gibbons, B. Handsaker, C. Healy, K.

Nguyen, C. Gates, C. Sougnez, D. Gage, M. Nizzari, S. B. Gabriel, G. W. Chirn, Q. Ma, H. Parikh, D. Richardson, D. Ricke, S. Purcell: Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. *Science* 316, 1331-1336 (2007)

44. L. J. Scott, K. L. Mohlke, L. L. Bonnycastle, C. J. Willer, Y. Li, W. L. Duren, M. R. Erdos, H. M. Stringham, P. S. Chines, A. U. Jackson, L. Prokunina-Olsson, C. J. Ding, A. J. Swift, N. Narisu, T. Hu, R. Pruim, R. Xiao, X. Y. Li, K. N. Conneely, N. L. Riebow, A. G. Sprau, M. Tong, P. P. White, K. N. Hetrick, M. W. Barnhart, C. W. Bark, J. L. Goldstein, L. Watkins, F. Xiang, J. Saramies, T. A. Buchanan, R. M. Watanabe, T. T. Valle, L. Kinnunen, G. R. Abecasis, E. W. Pugh, K. F. Doheny, R. N. Bergman, J. Tuomilehto, F. S. Collins, M. Boehnke: A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. *Science* 316, 1341-1345 (2007)

45. The Wellcome Trust Case Control Consortium: Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* 447, 661-678 (2007)

46. H. P. Wu, T. Y. Tai, L. M. Chuang, K. C. Chiu, B. J. Lin: CA-repeated microsatellite polymorphism of the glucokinase gene and its association with non-insulin-dependent diabetes mellitus in Taiwanese. *Diabetes Res Clin Pract* 30, 21-26 (1995)

47. L. M. Chuang, C. S. Lai, J. I. Yeh, H. P. Wu, T. Y. Tai, B. J. Lin: No association between the Gly971Arg variant of the insulin receptor substrate 1 gene and NIDDM in the Taiwanese population. *Diabetes Care* 19, 446-449 (1996)

48. J. Hager, L. Hansen, C. Vaisse, N. Vionnet, A. Philippi, W. Poller, G. Velho, C. Carcassi, L. Contu, C. Julier et al.: A missense mutation in the glucagon receptor gene is associated with non-insulin-dependent diabetes mellitus. *Nat Genet* 9, 299-304 (1995)

49. S. C. Gough, P. J. Saker, L. E. Pritchard, T. R. Merriman, M. E. Merriman, B. R. Rowe, S. Kumar, T. Aitman, A. H. Barnett, R. C. Turner et al.: Mutation of the glucagon receptor gene and diabetes mellitus in the UK: association or founder effect? *Hum Mol Genet* 4, 1609-1612 (1995)

50. C. N. Huang, K. C. Lee, H. P. Wu, T. Y. Tai, B. J. Lin, L. M. Chuang: Screening for the Gly40Ser mutation in the glucagon receptor gene among patients with type 2 diabetes or essential hypertension in Taiwan. *Pancreas* 18, 151-155 (1999)

51. L. M. Chuang, K. C. Chiu, F. T. Chiang, K. C. Lee, H. P. Wu, B. J. Lin, T. Y. Tai: Insertion/deletion polymorphism of the angiotensin I-converting enzyme gene in patients with hypertension, non-insulin-dependent diabetes mellitus, and coronary heart disease in Taiwan. *Metabolism* 46, 1211-1214 (1997)

52. M. C. Hsieh, S. R. Lin, T. J. Hsieh, C. H. Hsu, H. C. Chen, S. J. Shin, J. H. Tsai: Increased frequency of angiotensin-converting enzyme DD genotype in patients with type 2 diabetes in Taiwan. *Nephrol Dial Transplant* 15, 1008-1013 (2000)

53. Y. J. Lee, J. C. Tsai: ACE gene insertion/deletion polymorphism associated with 1998 World Health Organization definition of metabolic syndrome in Chinese type 2 diabetic patients. *Diabetes Care* 25, 1002-1008 (2002)

54. C. H. Tseng, C. P. Tseng: Lack of association between angiotensin-converting enzyme gene polymorphism and peripheral vascular disease in type 2 diabetic patients in Taiwan. *Circ J* 66, 1014-1018 (2002)

55. M. Y. Shiau, C. Y. Wu, C. N. Huang, S. W. Hu, S. J. Lin, Y. H. Chang: TNF-alpha polymorphisms and type 2 diabetes mellitus in Taiwanese patients. *Tissue Antigens* 61, 393-397 (2003)

56. Y. H. Chang, C. N. Huang, M. Y. Shiau: The C-174G promoter polymorphism of the interleukin-6 (IL-6) gene that affects insulin sensitivity in Caucasians is not involved in the pathogenesis of Taiwanese type 2 diabetes mellitus. *Eur Cytokine Netw* 15, 117-119 (2004)

57. Y. H. Chang, C. N. Huang, C. Y. Wu, M. Y. Shiau: Association of interleukin-10 A-592C and T-819C polymorphisms with type 2 diabetes mellitus. *Hum Immunol* 66, 1258-1263 (2005)

58. T. J. Chang, M. H. Tsai, Y. D. Jiang, B. Lee, K. C. Lee, J. Y. Lin, K. C. Chiu, T. Y. Tai, L. M. Chuang: The Arg16Gly polymorphism of human beta2-adrenoreceptor is associated with type 2 diabetes in Taiwanese people. *Clin Endocrinol (Oxf)* 57, 685-690 (2002)

59. W. H. Lin, L. M. Chuang, C. H. Chen, J. I. Yeh, P. S. Hsieh, C. H. Cheng, Y. T. Chen: Association study of genetic polymorphisms of SLC2A10 gene and type 2 diabetes in the Taiwanese population. *Diabetologia* 49, 1214-1221 (2006)

60. W. S. Yang, C. A. Hsiung, L. T. Ho, Y. T. Chen, C. T. He, J. D. Curb, J. Grove, T. Quertermous, Y. D. Chen, S. S. Kuo, L. M. Chuang: Genetic epistasis of adiponectin and PPARgamma2 genotypes in modulation of insulin sensitivity: a family-based association study. *Diabetologia* 46, 977-983 (2003)

61. W. S. Yang, Y. C. Yang, C. L. Chen, I. L. Wu, J. Y. Lu, F. H. Lu, T. Y. Tai, C. J. Chang: Adiponectin SNP276 is associated with obesity, the metabolic syndrome, and diabetes in the elderly. *Am J Clin Nutr* 86, 509-513 (2007)

62. E. Zeggini, M. I. McCarthy: TCF7L2: the biggest story in diabetes genetics since HLA? *Diabetologia* 50, 1-4 (2007)

63. T. Hayashi, Y. Iwamoto, K. Kaku, H. Hirose, S. Maeda: Replication study for the association of TCF7L2 with susceptibility to type 2 diabetes in a Japanese population. *Diabetologia* 50, 980-984 (2007)

64. G. R. Chandak, C. S. Janipalli, S. Bhaskar, S. R. Kulkarni, P. Mohankrishna, A. T. Hattersley, T. M. Frayling, C. S. Yajnik: Common variants in the TCF7L2 gene are strongly associated with type 2 diabetes mellitus in the Indian population. *Diabetologia* 50, 63-67 (2007)

65. M. M. Sale, S. G. Smith, J. C. Mychaleckyj, K. L. Keene, C. D. Langefeld, T. S. Leak, P. J. Hicks, D. W. Bowden, S. S. Rich, B. I. Freedman: Variants of the transcription factor 7-like 2 (TCF7L2) gene are associated with type 2 diabetes in an African-American population enriched for nephropathy. *Diabetes* 56, 2638-2642 (2007)

66. Y. C. Chang, T. J. Chang, Y. D. Jiang, S. S. Kuo, K. C. Lee, K. C. Chiu, L. M. Chuang: Association study of the genetic polymorphisms of the transcription factor 7-like 2 (TCF7L2) gene and type 2 diabetes in the Chinese population. *Diabetes* 56, 2631-2637 (2007)

67. J. M. van den Ouweland, H. H. Lemkes, W. Ruitenbeek, L. A. Sandkuijl, M. F. de Vijlder, P. A. Struyvenberg, J. J. van de Kamp, J. A. Maassen: Mutation in mitochondrial tRNA(Leu)(UUR) gene in a large pedigree with maternally transmitted type II diabetes mellitus and deafness. *Nat Genet* 1, 368-371 (1992)

68. W. Reardon, R. J. Ross, M. G. Sweeney, L. M. Luxon, M. E. Pembrey, A. E. Harding, R. C. Trembath: Diabetes mellitus associated with a pathogenic point mutation in mitochondrial DNA. *Lancet* 340, 1376-1379 (1992)

69. M. G. Hanna, I. Nelson, M. G. Sweeney, J. M. Cooper, P. J. Watkins, J. A. Morgan-Hughes, A. E. Harding: Congenital encephalomyopathy and adult-onset myopathy and diabetes mellitus: different phenotypic associations of a new heteroplasmic mtDNA tRNA glutamic acid mutation. *Am J Hum Genet* 56, 1026-1033 (1995)

70. R. McFarland, A. M. Schaefer, J. L. Gardner, S. Lynn, C. M. Hayes, M. J. Barron, M. Walker, P. F. Chinnery, R. W. Taylor, D. M. Turnbull: Familial myopathy: new insights into the T14709C mitochondrial tRNA mutation. *Ann Neurol* 55, 478-484 (2004)

71. S. W. Ballinger, J. M. Shoffner, E. V. Hedaya, I. Trounce, M. A. Polak, D. A. Koontz, D. C. Wallace: Maternally transmitted diabetes and deafness associated with a 10.4 kb mitochondrial DNA deletion. *Nat Genet* 1, 11-15 (1992)

72. D. R. Dunbar, P. A. Moonie, R. J. Swingler, D. Davidson, R. Roberts, I. J. Holt: Maternally transmitted partial direct tandem duplication of mitochondrial DNA associated with diabetes mellitus. *Hum Mol Genet* 2, 1619-1624 (1993)

73. S. Kiechl, R. Horvath, P. Luoma, U. Kiechl-Kohlendorfer, B. Wallacher-Scholz, R. Stucka, C. Thaler, J. Wanschitz, A. Suomalainen, M. Jaksch, J. Willeit: Two families with autosomal dominant progressive external ophthalmoplegia. *J Neurol Neurosurg Psychiatry* 75, 1125-1128 (2004)

74. R. G. Whittaker, A. M. Schaefer, R. McFarland, R. W. Taylor, M. Walker, D. M. Turnbull: Prevalence and progression of diabetes in mitochondrial disease. *Diabetologia* 50, 2085-2089 (2007)

75. M. Walker, R. W. Taylor, D. M. Turnbull: Mitochondrial diabetes. *Diabet Med* 22 Suppl 4, 18-20 (2005)

76. K. Ohkubo, A. Yamano, M. Nagashima, Y. Mori, K. Anzai, Y. Akehi, R. Nomiyama, T. Asano, A. Urae, J. Ono: Mitochondrial gene mutations in the tRNA(Leu(UUR)) region and diabetes: prevalence and clinical phenotypes in Japan. *Clin Chem* 47, 1641-1648 (2001)

77. L. M. Chuang, H. P. Wu, K. C. Chiu, C. S. Lai, T. Y. Tai, B. J. Lin: Mitochondrial gene mutations in familial non-insulin-dependent diabetes mellitus in Taiwan. *Clin Genet* 48, 251-254 (1995)

78. L. M. Chuang, H. P. Wu, W. Y. Tsai, C. S. Lai, T. Y. Tai, B. J. Lin: Mitochondrial gene mutations in patients with insulin-dependent diabetes mellitus in Taiwan. *Pancreas* 12, 243-247 (1996)

79. C. Y. Pang, C. C. Huang, M. Y. Yen, E. K. Wang, K. P. Kao, S. S. Chen, Y. H. Wei: Molecular epidemiologic study of mitochondrial DNA mutations in patients with mitochondrial diseases in Taiwan. *J Formos Med Assoc* 98, 326-334 (1999)

80. C. W. Liou, C. C. Huang, Y. H. Wei: Molecular analysis of diabetes mellitus-associated A3243G mitochondrial DNA mutation in Taiwanese cases. *Diabetes Res Clin Pract* 54 Suppl 2, S39-43 (2001)

81. K. J. Morten, J. Poulton, B. Sykes: Multiple independent occurrence of the 3243 mutation in mitochondrial tRNA(leuUUR) in patients with the MELAS phenotype. *Hum Mol Genet* 4, 1689-1691 (1995)

82. J. Poulton, M. S. Brown, A. Cooper, D. R. Marchington, D. I. Phillips: A common mitochondrial DNA variant is associated with insulin resistance in adult life. *Diabetologia* 41, 54-58 (1998)

83. S. W. Weng, C. W. Liou, T. K. Lin, Y. H. Wei, C. F. Lee, H. L. Eng, S. D. Chen, R. T. Liu, J. F. Chen, I. Y. Chen, M. H. Chen, P. W. Wang: Association of mitochondrial deoxyribonucleic acid 16189 variant (T->C transition) with metabolic syndrome in Chinese adults. *J Clin Endocrinol Metab* 90, 5037-5040 (2005)

84. C. W. Liou, T. K. Lin, H. Huei Weng, C. F. Lee, T. L. Chen, Y. H. Wei, S. D. Chen, Y. C. Chuang, S. W. Weng, P. W. Wang: A common mitochondrial DNA variant and increased body mass index as associated factors for development of type 2 diabetes: Additive effects of genetic and environmental factors. *J Clin Endocrinol Metab* 92, 235-239 (2007)

85. R. B. Tattersall, S. S. Fajans: A difference between the inheritance of classical juvenile-onset and maturity-onset type diabetes of young people. *Diabetes* 24, 44-53 (1975)

86. K. Yamagata, H. Furuta, N. Oda, P. J. Kaisaki, S. Menzel, N. J. Cox, S. S. Fajans, S. Signorini, M. Stoffel, G. I. Bell: Mutations in the hepatocyte nuclear factor-4alpha gene in maturity-onset diabetes of the young (MODY1). *Nature* 384, 458-460 (1996)

87. M. Stoffel, P. Froguel, J. Takeda, H. Zouali, N. Vionnet, S. Nishi, I. T. Weber, R. W. Harrison, S. J. Pilkis, S. Lesage et al.: Human glucokinase gene: isolation, characterization, and identification of two missense mutations linked to early-onset non-insulin-dependent (type 2) diabetes mellitus. *Proc Natl Acad Sci U S A* 89, 7698-7702 (1992)

88. K. Yamagata, N. Oda, P. J. Kaisaki, S. Menzel, H. Furuta, M. Vaxillaire, L. Southam, R. D. Cox, G. M. Lathrop, V. V. Boriraj, X. Chen, N. J. Cox, Y. Oda, H. Yano, M. M. Le Beau, S. Yamada, H. Nishigori, J. Takeda, S. S. Fajans, A. T. Hattersley, N. Iwasaki, T. Hansen, O. Pedersen, K. S. Polonsky, G. I. Bell et al.: Mutations in the hepatocyte nuclear factor-1alpha gene in maturity-onset diabetes of the young (MODY3). *Nature* 384, 455-458 (1996)

89. D. A. Stoffers, J. Ferrer, W. L. Clarke, J. F. Habener: Early-onset type-II diabetes mellitus (MODY4) linked to IPF1. *Nat Genet* 17, 138-139 (1997)

90. Y. Horikawa, N. Iwasaki, M. Hara, H. Furuta, Y. Hinokio, B. N. Cockburn, T. Lindner, K. Yamagata, M. Ogata, O. Tomonaga, H. Kuroki, T. Kasahara, Y. Iwamoto, G. I. Bell: Mutation in hepatocyte nuclear factor-1 beta gene (TCF2) associated with MODY. *Nat Genet* 17, 384-385 (1997)

91. M. T. Malecki, U. S. Jhala, A. Antonellis, L. Fields, A. Doria, T. Orban, M. Saad, J. H. Warram, M. Montminy, A. S. Krolewski: Mutations in NEUROD1 are associated with the development of type 2 diabetes mellitus. *Nat Genet* 23, 323-328 (1999)

92. T. M. Frayling, J. C. Evans, M. P. Bulman, E. Pearson, L. Allen, K. Owen, C. Bingham, M. Hannemann, M. Shepherd, S. Ellard, A. T. Hattersley: beta-cell genes and diabetes: molecular and clinical characterization of mutations in transcription factors. *Diabetes* 50 Suppl 1, S94-100 (2001)

93. S. Yamada, Q. Zhu, Y. Aihara, H. Onda, Z. Zhang, L. Yu, L. Jin, Y. J. Si, H. Nishigori, H. Tomura, I. Inoue, A. Morikawa, K. Yamagata, T. Hanafusa, Y. Matsuzawa, J. Takeda: Cloning of cDNA and the gene encoding human hepatocyte nuclear factor (HNF)-3 beta and mutation screening in Japanese subjects with maturity-onset diabetes of the young. *Diabetologia* 43, 121-124 (2000)

94. T. S. Jap, Y. C. Wu, J. Y. Chiou, C. F. Kwok: A novel mutation in the hepatocyte nuclear factor-1alpha/MODY3 gene in Chinese subjects with early-onset Type 2 diabetes mellitus in Taiwan. *Diabet Med* 17, 390-393 (2000)

95. J. Y. Xu, Q. H. Dan, V. Chan, N. M. Wat, S. Tam, S. C. Tiu, K. F. Lee, S. C. Siu, M. W. Tsang, L. M. Fung, K. W. Chan, K. S. Lam: Genetic and clinical characteristics of maturity-onset diabetes of the young in Chinese patients. *Eur J Hum Genet* 13, 422-427 (2005)

96. K. Cryns, T. A. Sivakumaran, J. M. Van den Ouweland, R. J. Pennings, C. W. Cremers, K. Flothmann, T. L. Young, R. J. Smith, M. M. Lesperance, G. Van Camp: Mutational spectrum of the WFS1 gene in Wolfram syndrome, nonsyndromic hearing impairment, diabetes mellitus, and psychiatric disease. *Hum Mutat* 22, 275-287 (2003)

97. H. T. Tsai, Y. P. Wang, S. F. Chung, H. C. Lin, G. M. Ho, M. T. Shu: A novel mutation in the WFS1 gene identified in a Taiwanese family with low-frequency hearing impairment. *BMC Med Genet* 8, 26 (2007)

98. M. C. Ng, C. H. Tam, V. K. Lam, W. Y. So, R. C. Ma, J. C. Chan: Replication and identification of novel variants at TCF7L2 associated with type 2 diabetes in Hong Kong Chinese. *J Clin Endocrinol Metab* 92, 3733-3737 (2007)

Abbreviations: DM: Diabetes mellitus; T1DM: type 1 DM; T2DM: type 2 DM; GDM: gestational DM; MODY: maturity onset diabetes of the young; GWA: genome-wide association; VNTR: variable number of tandem repeats; STRP: short tandem repeat polymorphism; RFLP: restriction fragment length polymorphism; DIDMOAD: diabetes insipidus, DM, optic atrophy, and deafness

Key Words: diabetes mellitus, genetics, Taiwan, HLA, mitochondria, MODY, Syndrome, Candidate Gene, Genome-Wide Association, Review

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