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Molecular genetics of diabetes mellitus

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ABSTRACT

Diabetes mellitus (DM) is a disease that causes major public health problem worldwide. In Thailand, it was estimated that 9.6% or 2.4 million adults were affected with DM and the prevalence is increasing. The unawareness of having the disease leads to delayed treatment and development of chronic complications. The cost for management of DM and its complications is increasing enormously, causing a great economic and healthcare burden. DM is caused by both environmental and genetic factors. Although type 1 diabetes (T1D) is not a genetically predestined disease, an increased susceptibility to the disease can be inherited. Genetic factor plays a crucial role in pathogenesis and complications of type 2 diabetes (T2D) while environmental factors are also required for the disease development. Even if modifications of life-style are important for controlling T2D, the identification of susceptibility genes will lead to understanding of its complex pathogenesis and development of more effective treatment. Up to date, a number of diabetic susceptible genes are identified in Western populations. It is now the time to identify the causative and susceptibility genes of diabetes in Thai. This review aims to provide a current overview of molecular genetics of DM and some available information in Thais.

Keywords: diabetes mellitus, hyperglycemia, genetic susceptibility, pathogenesis, diabetic complication

INTRODUCTION

Diabetes mellitus (DM) is a heterogeneous metabolic disorder characterized by chronic hyperglycemia, resulting from deficiency or failure in maintenance of normal glucose homeostasis. The interaction between susceptible genetics and environmental factors is known to trigger the disease. Most patients are suffered from its complication, including retinopathy, nephropathy, coronary and peripheral vascular diseases. The vascular complications, such as ischemic heart and renal diseases are attributed to excess mortality of the disease. The cost of treatments of the disease and its complications is immense. The prevalence of DM has increased sharply in recent decades. The number of affected individual worldwide is currently estimated to be approximately 150 million and predicted to reach 220 million by 2010 and 300 million by 2025 (Zimmet *et al*., 2001). It was estimated in 2000 that 9.6% (2.4 millions) of Thai adults were affected with DM and 5.4% (1.4 millions) had impaired fasting glucose (Aekplakorn *et al*., 2003). These have indicated that DM is an

enormous global public health problem (Wolford and Vozarova de Courten, 2004) and also an increasingly significant public health problem in Thailand. Since the disease is very heterogeneous, abnormality at different biological pathways can lead to hyperglycemia and subtyping of the disease requires precise diagnostic criteria. A lot of research studies have concentrated on identifications of diabetic susceptibility genes. These efforts will facilitate a better understanding in the pathogenesis underlying each DM subtype, thereby leading to the development of effective and appropriate therapeutic approaches.

Classification and pathogenesis

DM generally presents in two major forms, type 1 diabetes (T1D) and type 2 diabetes (T2D). The former is less common while the latter is more common, accounting for approximately 10% and 90% of diabetic cases, respectively. The onset of T1D is in childhood while that of T2D is predominantly after 40 years of age and generally occurs in obese people. T1D is more severe and rapidly progressive, due to a great impairment or absolute deficiency of insulin secretion caused by an autoimmune destruction of pancreatic β-cells (Fig. 1). This destruction is mediated by both humoral (auto-antibodies) and cellular (infiltrated lymphocytes) autoimmunities which are chronic but potent to produce symptoms in childhood (Petrovsky and Schatz, 2003). However, the exact mechanism involved in the initiation and progression of β-cell destruction in T1D is still unclear. While T1D results from absolute insulin deficiency, T2D usually presents the relative insufficiency. Most often, this relative insulin insufficiency is attributable to an inability of β-cells to adequately compensate for insulin resistance (Reaven *et al.*, 1976) (Fig. 2). Generally, exogenous insulin is not required for the survival of T2D patients. This form of diabetes frequently goes undiagnosed for many years because the gradually developed hyperglycemia and at the earlier stage is often not severe enough to cause

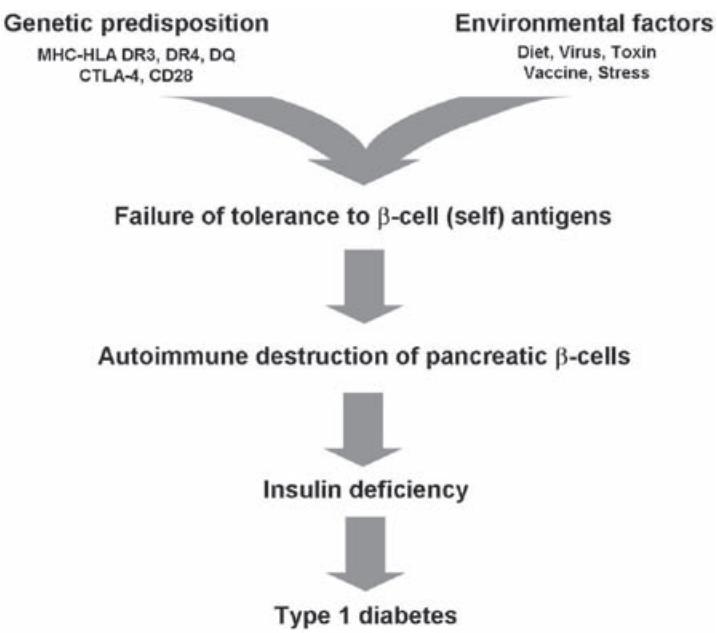

Figure 1 Pathogenesis of type 1 diabetes (T1D). Genetic predisposition and environmental factors are involved in failure of tolerance to β-cell (self) antigens and autoimmune destruction of pancreatic β-cells leading to insulin deficiency and T1D.

noticeable symptoms. Obesity is clearly demonstrated as the most common etiology of insulin resistance, although structural abnormalities of insulin and defects in insulin signaling pathway can also contribute to the resistance (Tager *et al.*, 1979; Bogardus *et al.*, 1985).

Other specific types of DM, including a monogenic form as well as non-genetic form, account for approximately 1%-2% of cases. Maturity-onset diabetes of the young (MODY) is one of monogenic form that seems to be intermediacy between T1D and T2D. Similar to T1D, it is caused by genetic abnormality which affects β-cell function but autoimmunity is not involved. In addition, diabetic symptoms are usually presented at a young age, usually less than 25 years old. However, MODY is classified as T2D subtype due to its decreased severity and the presence of insulin production. Moreover, exogenous insulin is not necessary for survival of MODY patients (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003). Other specific types of DM are very rare.

Genetic bases of DM

The evidences from family and twin studies clearly indicated the contribution of genetic components to diabetes susceptibility although the influence of environments could not be excluded. T1D shows a strong aggregation of disease within family with the risk to sibling (λ_S) of 15 folds as compared to unrelated individuals (Field, 2002). For T2D, the risk for developing disease in sibling is 4 to 6 folds higher than those of unrelated individuals. The concordance rate in monozygotic twins is much higher as compared to dizygotic twins for both T1D and T2D. For T1D, the concordance rate in monozygotic twins was estimated to range from 21%-70%, higher than 0%-13% reported in dizygotic twins (Redondo *et al.*, 2001). For T2D, the concordance rate in monozygotic twins was ranged from 34%-83% whereas it was 16%-40% in dizygotic twins (Kaprio *et al.*, 1992; Poulsen *et al.*, 1999). Majority of DM

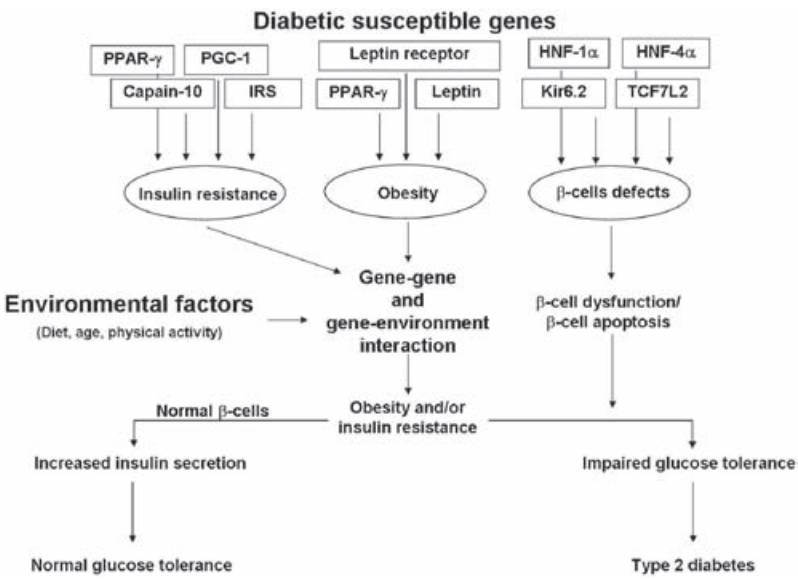

Figure 2 Pathogenesis of type 2 diabetes (T2D). The interaction of diabetic susceptible genes (causing insulin resistance, obesity, and β-cell defects) and environmental factors leads to relative insulin insufficiency. Impaired glucose tolerance and T2D are developed when pancreatic β-cells are unable to adequately compensate for the requirement of insulin in obesity and/or insulin resistance.

demonstrates familial clustering but does not show any clear pattern of Mendelian inheritance, a characteristic of multifactorial disorder. The simultaneous presence of several abnormal genes or polymorphisms together with environmental triggers, including age, sex, diet, obesity, infection, as well as physical activity, is required for the development of disease (Iselius *et al*., 1985; Bogardus *et al*., 1989; Martin *et al*., 1992). However, approximately 10% of T2D appears to segregate in a Medelian fashion, as a monogenic form with autosomal dominant inheritance pattern, known as MODY (Fajans, 1989).

Identification of diabetic susceptibility genes is said to be geneticists' nightmare (Feingold, 1976), because of its complications with a number of problems. First of all is its genetic heterogeneity. Alleles at more than one locus can individually trigger the same phenotype and such alleles may be identified in one population but not be replicated in the others. Other problems are a reduced penetrance as well as a phenocopy. The variable of onset age, leading to difficulty in defining of affected state at a particular time, is an especial problem of T2D. Studying the monogenic form of DM (i.e. MODY), which is the early-onset disease, was easier and thereby used as a clue for identifying the multifactorial form of T2D. It was believed that variants causing less functional destruction in genes responsible for MODY would be contributed to the more common and multifactorial form of T2D. For example, the G319S variant of *HNF-1a*, one of six known genes responsible for MODY, is a major susceptible gene for the common form of T2D in the Oji-Cree Native Canadian population (Triggs-Raine *et al*., 2002). This finding demonstrates that heterogeneous phenotypic of T2D might at least depend on the degree of functional impairment caused by variants in a particular gene.

To date, several diabetic susceptible genes have been identified by linkage and association approaches either in a genomic scale (genome-wide scan) or in a smaller scale by selection of only candidate chromosomal regions or candidate genes arisen from their biological function (candidate gene analysis). Recently, improvement in genotyping technology together with development in the field of bioinformatics have facilitated genome-wide scan in an easier manner. Consequently, a number of DM susceptible genes have recently been identified by genome-wide association (GWA) approach.

Candidate genes for T1D

The first T1D susceptible locus, designated as *IDDM1,* was identified by association approach (Table 1) (Florez *et al*., 2003). It is located on *human leukocyte antigen* (*HLA*) genes region, which encodes major histocompatibility complex (MHC). Fine mapping indicated that HLA-DQB1 and HLA-DRB1 are the most important alleles associated with DM. *HLA* region was later found to be a major genetic determinant of disease risk, accounting for 42% of inherited T1D. The variable number of tandem repeats (VNTR) upstream of *Insulin* (*INS*) gene was subsequently identified, designated as *IDDM*2. This locus contributes about 10% toward T1D susceptibility (Bennett *et al*., 1995). It was found that a variation of VNTR associated with the levels of insulin protein expressed in the thymus, involving in central tolerance to insulin. Both *IDDM1* and *IDDM2* were identified by the investigation of suspected genes. Afterwards, a series of chromosomal regions that may contain susceptibility genes for T1D, including *IDDM3-IDDM18* (Table 1), were identified mainly by genome-wide linkage analysis of affected sibling pairs. These regions contain several genes that encode proteins implicated with their biological functions, including pancreatic transcription factors, apoptotic proteins, and specific enzymes expressed in pancreas. Several T-cell co-stimulatory receptor encoding genes were identified in *IDDM12*, including genes encode CTLA4, CD28 and ICOS (Raffel and Rotter, 2002;

Triggs-Raine *et al*., 2002; Bain *et al*., 2003). None of suspected gene was identified in some *IDDM* regions, including *IDDM3* and *IDDM8*, even though these regions have been replicated in different data sets.

A recent GWA study has confirmed six genes/regions that previously shown a strong statistically significant association with T1D. These included genes encoding MHC, insulin, CTLA-4, and protein tyrosine phosphatase, non-receptor type 22, (PTPN22) and the regions around the interleukin 2 receptor alpha (IL2RA/CD25) and interferon-induced helicase 1 (IFIH1/MDA5) genes (The Wellcome Trust Case Control Consortium, 2007). In addition, this study showed three novel regions significantly associated with T1D including chromosomes 12q13, 12q24, and 16p13. The two regions on chromosome 12 contain several candidate genes involving in immune signaling. These included genes encoding receptor tyrosine-protein kinase erbB-3 precursor (ERBB3), SH2B adaptor protein 3 (SH2B3/LNK), TRAF-type zinc finger domain containing 1 (TRAFD1), and protein tyrosine phosphatase, non-receptor type 11 (PTPN11). In contrast, the chromosome 16p13 region consists of only two genes whose functions are unknown, i.e., KIAA0350 and dexamethasone-induced transcript. Among these novel loci, gene encoding PTPN11 is the most attractive candidate involving the major role in insulin and immune signaling (Mustelin *et al*., 2005).

Candidate genes for T2D

Chromosome 2q37.3, designated as *NIDDM1*, was the firstly identified region with a significant linkage to T2D (Hanis *et al*., 1996). Positional cloning of this region led to identification of gene encoding calpain-10, a cysteine protease

Table 1 T1D-susceptible loci identified by genome-wide linkage studies (modified from Florez *et al*., 2003).

Locus	Location	Marker/candidate gene	LOD	Population
*IDDM1**	6p21.3	*HLA*	7.3-65.8	UK,US, France, North Africa,
*IDDM2**	11p15	*INS* VNTR	2.1-4.3	UK,US
IDDM3	15q26.2	D15S107	□	□
IDDM4	11q13.3	*FGF3*	3.4	UK,US
IDDM5	6q25.1	*ESR1*	11.5-2.0	UK,US
IDDM6	18q21.2	*JK*, D18S487	1.1, 1.2	UK,US
IDDM7	2q31	*HOXD8*, D2S152	2.6	US,UK
IDDM8	6q27	D6S264	1.8-5.0	US,UK
IDDM9	3q21	D3S1576	2.4	UK
IDDM10	10p11	D10S193	1.9-4.7	UK,US
IDDM11	14q24.3	D14S67	□	□
IDDM12	2q33	*CTLA4, CD28, ICOS*	2.6	US,UK
IDDM13	2q35	D2S164	2.6	US,UK
IDDM15	6q21	D6S283	2.3, 2.4	US,UK
IDDM16	14q32.3	D14S542	□	□
IDDM17	10q25	D10S554	4.9	Bedouin
IDDM18	5q33	*IL12B*		

* Initially found by association, *HLA*; human leukocyte antigen, *INS*; insulin, *FGF3*; fibroblast growth factor 3, *ESR1*; estrogen receptor 1, *JK;* surface antigen, *HOXD3*; homeobox D3, *CTLA4*; cytotoxic T lymphocyte-associated 4, *ICOS*; inducible costimulator, *IL12B*; interleukin 12B

that plays a role in the regulation of both insulin secretion and insulin action. Further analysis in Mexican-American and European populations indicated that the disease susceptibility is best described by a combination of risk haplotypes. The second report was the linkage at chromosome 12q24.31, designated as *NIDDM2*, in Finnish Caucasian (Mahtani *et al*., 1996). This region contains *HNF1A* gene, one of six genes known to be responsible for MODY. Then, several research groups have studied the linkage of various genetic loci to T2D (Table 2) (Florez *et al*., 2003) but only few regions have been shown to have significant evidences of linkage (LOD>3.6) which could be replicated in multiple studies, including chromosomes 1q25.3, 3p24.1, 3q26-28, 10q26.13, and 18p11.22. In addition, several candidate genes which are involved in insulin sensitivity, β-cell function and obesity were investigated by association approach. More than 40 different genes have been reported to be associated with T2D but few associations have been replicated in additional populations (Florez *et al*., 2003) (Table 3). Among them, amino acid substitution of Pro12Ala of *peroxisome proliferators-activated receptor-gamma (PPARγ)*, which encodes

Table 2 Chromosomal regions and candidate genes with significant and suggestive linkage with T2D identified by genome-wide linkage studies (modified from Florez *et al*., 2003).

Location	Marker/Candidate gene	LOD	Population
1q25.3	D1S2127/ *PKLR, LMX1*	1.5-4.3	Pima India, US, France, UK
1q42.2	D1S3462	2.4	Finn
2p21	D2S2259	2.3	France
2q24.3	D2S2345	1.2, 3.0	Australia aborigines, France
2q37.3	D2S125/ *CAPN-10*	2.1-4.1	Mexican- Americans, US
3p24.1	D3S2432	1.1-3.9	Mexican-Americans, Finn
3q28	D3S1580	1.4-4.7	France, Japan, Australia Aborigines
4q34.1	D4S1539	1.3, 2.1	Ashkenazi Jews, France
5q13.3	D5S1404	1.2, 2.8	UK, Caucasians
5q31.1	D5S816	1.2, 2.4	Finn, UK
7q32.3	D7S1804-D7S500	2.0	Pima India
8p21.3	D8S258	1.3, 2.6	UK, US
9p24.2	D9S288-D9S295	2.4	Mexican-Americans
9q21.12	D9S166	2.9, 3.3	Finn, Chinese
10p14	D10S1412	2.0, 2.4	African-Americans, Chinese
10q26.13	D10S587	2.0,3.8	UK, Mexican- □Americans
11p13	D11S935	1.9, 3.1	Japan, US
12q15	D12S375	1.5, 3.1	US
12q21.32	D12S853	1.5, 2.8	Caucasians, France
12q24.31	D12S1349/*HNF-1a*	1.5-3.7	Finn, US, Pacific Islanders
18p11.22	D18S843	2.4, 4.2	US, Finn
20p12.3	D20S905	0.9, 2.0	Finn, Ashkenazi Jews
20q13.12	D20S886	2.2, 2.9	Finn, Chinese
Xq23	GATA172D05	1.7, 3.0	Japanese, Caucasians

PKLR; pyruvate kinase liver and red blood cell, *CALPN-10*; calpain-10, *HNF-4α*; hepatonuclear factor-4α

transcription factor that plays a central role in adipocyte development, is the most widely reproduced association (Altshuler *et al.*, 2000; Hara *et al.*, 2000; Douglas *et al.*, 2001; Mori *et al.*, 2001; Ardlie *et al.*, 2002). Another strong candidate gene for T2D is *an ATP-binding cassette, sub-family C, member 8 (ABCC8)* gene, which encodes the sulfonylurea receptor (SUR1), a drug target for an oral hypoglycemic agent, sulfonylurea (Thomas *et al.*, 1995). In addition, *potassium inwardly-rectifying channel, subfamily J, member 11* (*KCNJ11*) gene which encodes $K_{ir}6.2$, an essential subunit of pancreatic ATP-dependent potassium channel (K_{ATP}), and *PPAR-γcoactivator 1* (*PGC1*) gene are loci that also reproducibly associated with T2D (Hani *et al.*, 1998; Ek *et al.*, 2001; Gloyn *et al.*, 2001; Gloyn *et al.*, 2003). Other genes, which were found to be associated with T2D in more than one population, include *glucagon receptor* (*GCGR*) (Bennett *et al.*, 1995; Hager *et al.*, 1995), *glucokinase* (*GCK*) (Chiu *et al.*, 1992; McCarthy *et al.*, 1994; Takekawa *et al.*, 1994) and *solute carrier family 2 , member 1* (*SLC2A1*) (Li *et al.*, 1988; Tao *et al.*, 1995; Pontiroli *et al.*, 1996).

From the combined data of traditional candidate gene approach together with recent information from six GWA studies (Frayling *et al.*, 2007; Saxena *et al.*, 2007; Scott *et al.*, 2007;

Table 3 Candidate genes and their polymorphisms significantly associated with T2D (modified from Florez *et al.*, 2003).

Gene	Encoded protein	Polymorphism	Risk allele	*p*-value	Population
ABCC8	Sulfonylurea receptor	759C>T	T	0.0008	US/UK
				0.03	France
				0.03	Denmark
				0.01	Scandinavia
Adiponectin	Adiponectin	-11377C>G	G	0.04	France
		-11377C>G	C	0.002	Japan
		-11377C>G	G	0.04	Sweden
GCGR	Glucagon receptor	G50S	Ser	0.0001	France
				0.008	UK
GCK	Glucokinase	GCK 3'	Z+2	0.008	Mauritius-Creole
				0.0016	Finland
				0.014	Japan
KCNJ11	Potassium inward rectifier channel $K_{ir}6.2$	G23K	Lys	0.015	France
				0.024	UK
				0.01	UK
PPAR-g	Peroxisome proliferators-activated receptor-g	Pro12Ala	Pro	0.03	US Japanese-American
				0.003	Japan
				0.000054	Japan
				0.0002	Scandinavia, Quebec
SCL2A1	GLUT1 glucose transporter protein	*Xba*I	6.2 kb band	0.05	Europe and Japan
				0.0008	Japan
				0.017	Italy

Candidate genes and their polymorphisms are included in the table following the criteria of (*i*) three significant ($P<0.05$) independent studies, (*ii*) two independent studies with $P < 0.01$, or (*iii*) a single study replicating the first positive result with $P < 0.001$.

Sladek *et al*., 2007; Steinthorsdottir *et al*., 2007; Zeggini *et al*., 2007), there are now 11 regions that associated with T2D at the levels of statistical confidence required for genetic association studies (Table 4) (Frayling, 2007). Seven of them were not identified from the candidate gene approach. Common variants in *transcription factor 7-like 2* (*TCF7L*) appeared as one of the top signals in the GWA studies (Sladek *et al*., 2007). This gene encodes a transcription factor that is expressed in fetal pancreas and is involved in the WNT signaling pathway. The other six novel genes include *haematopoietically expressed homeobox* (*HHEX*), *cyclin-dependent kinase inhibitor 2A* (*CDKN2A-B*), *CDK5 regulatory subunit associated protein 1-like 1* (*CDKAL1*), *solute carrier family 30 (zinc transporter), member 8* (*SLC30A8*), *insulin-like growth factor 2 mRNA binding, protein 2* (*IGF2BP2*) and *fat mass and obesityassociated* (*FTO*) (Table 4). However, chromosome regions, probably with small effects, remain to be identified. The sample sizes of more than 10,000 cases and controls are required for finding such additional genes (Frayling, 2007).

Table 4 Single nucleotide polymorphisms (SNPs) and closet genes associated with T2D identified by genetic association studies (modified from Frayling, 2007).

Example variant	Closet gene	Previous evidence	*p*-value (Meta-analysis)	Additional evidence from human physiology	N*
rs1801282 (P12A)	*PPARG*[a]	Monogenic +drug target	2×10^{-6}	Nothing consistent	>20,000
rs5215 (E23K)	*KCNJ11*[a]	Monogenic +drug target	5×10^{-11}	Alters insulin secretion in general population	15,600
rs7901695	*TCF7L2*[b]	None	1×10^{-48}	Alters insulin secretion in general population	2,760
rs4430796	*TCF2*[a]	Monogenic	8×10^{-10}	Nothing consistent	>20,000
rs10010131	*WFS1*[a]	Monogenic	1×10^{-7}	Nothing consistent	>20,000
rs1111875	*HHEX–IDE*[c]	Some, e.g. HHEX KO mouse has disrupted pancreaticdevelopment	7×10^{-17}	Early studies indicate altered insulin secretion in general population	12,800
rs13266634	*SLC30A8*[c]	None	1×10^{-19}	Early studies indicate altered insulin secretion in general population	14,400
rs10946398	*CDKAL1*[c]	None	2×10^{-18}	Early studies indicate altered insulin secretion in general population	16,200
rs10811661	*CDKN2A–2B*[c]	Some –CDKN2A KO mouse has reduced isletproliferation	8×10^{-15}	Nothing consistent	12,400
rs4402960	*IGF2BP2*[c]	Some –binds insulin like growthFactor mRNA	9×10^{-16}	Nothing consistent	16,200
rs8050136	*FTO*[c]	None	1×10^{-12}	Alters BMI in general Population	10,400

* Total number of cases and controls needed in a 1:1 ratio to provide 80% power to detect an effect at $p = 5\times10^{-7}$, [a] gene identified by candidate approach, [b] gene identified by region-wide association, [c] gene identified by genome-wide association, *BMI, body mass index; CDKAL; CDK5 regulatory subunit associated protein 1-like 1; CDKN2, cyclin-dependent kinase inhibitor 2A; FTO, fat mass and obesityassociated; HHEX, haematopoietically expressed homeobox*; *IDE, insulin-degrading enzyme; IGF2BP2, insulin-like growth factor 2 mRNA binding, protein 2; KCNJ11, potassium inwardly-rectifying channel, subfamily J, member 11*; KO, knockout; N/C, not captured; *PPARG , peroxisome proliferator-activated receptor-γ gene*; *SLC30A8, solute carrier family 30 (zinc transporter), member 8; TCF2, transcription factor 2, hepatic; LF-B3, variant hepatic nuclear factor; TCF7L2, transcription factor 7-like 2 (T-cell specific, HMG-box); WFS1, Wolfram syndrome 1.*

Candidate genes for MODY

To date, six different genes are known to cause MODY including: *hepatocytenuclear factor-4α* (*HNF-4α*), *glucokinase* (*GCK*), *hepatocytenuclear factor-1α* (*HNF-1α*), *insulin promoting factor-1* (*IPF-1*), *hepatcyteonuclearfactor-1β*, (*HNF-1β*), and *neurogenic differentiation 1/β-cell E-box transactivator 2* (*NeuroD 1/β 2*). However, there are a number of MODY families that have no mutations in these six known genes responsible for MODY, which are referred to as MODY-X. The estimated prevalence of MODY-X is 15-20% of European families (Chevre *et al*., 1998), and 60-80% of Chinese (Plengvidhya *et al*., 2007) and Japanese families (Nishigori *et al*., 1998). Analysis of genetic variability of MODY genes in Thai diabetic patients performed by Siriraj Diabetes Research Group (SiDRG) showed that sequence variation of the six known MODY genes accounts for a small proportion of both classic MODY (19%) and early-onset type 2 diabetes patients (10%) suggesting that MODY-X is also frequent in Thai population. Recently, SiDRG has investigated the role of *PAX4,* encoding transcription factor that plays a crucial role for β-cell development, in Thai patient with MODY-X. A novel mutation, R164W, has been identified. It was segregated with diabetes in the affected family. The mutant Pax 4 protein has less repressor activity on insulin and glucagon promoters as compared to the wild type one (Plengvidhya *et al*., 2007).

Genetics of diabetic complications

In diabetes, long-term exposure to hyperglycemia leads to serious and frequently disabling or fatal complications. Diabetic complications are often categorized as microvascular (retinopathy, nephropathy), neuropathy, and macrovascular (cardiovascular and cerebrovascular). These complications can result in potential loss of vision, renal failure, foot ulcers, amputation, and Charcot joints, and autonomic neuropathy may be present with gastrointestinal and genitourinary.

Not only diabetes (T1D and T2D) but also their complications are influenced by genetic factors. There is mounting evidence for the role of genetic factors in several diabetic complications, particularly diabetic nephropathy (DN) and cardiovascular defects. The strongest evidence from epidemiological observations and family studies for the role of genetic background has been found for DN which is the most common and rapidly increasing cause of end-stage renal disease (ESRD) in the populations of developed countries. The familial clustering of overt DN and diabetic ESRD has been observed widely in multiple racial and ethnic groups, with the earliest reports of familial aggregation of diabetic kidney disease in patients with T1D. Family members with diabetes, even in the absence of clinical nephropathy, demonstrate similar patterns of glomerular involvement. The majority of data come from the studies in T1D (Seaquist *et al*., 1989; Quinn *et al*., 1996) but some were obtained from the analyses in T2D (Imperatore *et al*., 2000). Unlike for nephropathy, the epidemiological studies do not provide strong support for the role of genes in diabetic retinopathy (DR) (Leslie and Pyke, 1982). However, some clinical observations and genetic analyses in T2D (Leslie and Pyke, 1982; Imperatore *et al*., 2000) suggest that genetic influences are also involved in this microvascular complication. A study showed significant ethnic differences in the incidence of cardiovascular diseases (CAD) in T2D patients that were very likely the result of the heterogeneity of their genetic background (U.K. Prospective Diabetes Study Group, 1998).

Hundreds of loci have been studied so far in order to explain genetic susceptibility to diabetic complications. Most loci identified to date have not been replicated probably due to the complex etiologies of all diabetic complications resulting from interaction between plural genetic and clinical factors. Recent information indicating that, the most intriguing genes for further genetic studies are those encoding aldose receptor, advanced

glycation end products receptor, vascular endothelial growth factor, intercellular adhesion molecule 1, β3-adrenergic receptor gene, hemochromatosis, and α2β1 integrin. Pathways involving these gene products may represent a fruitful area for further studies aimed at investigating the genetics and pathophysiology of DN and DR. One gene that should be mentioned is that encodes aldose reductase in the polyol pathway, which is associated with DN and DR in T1D and T2D in several studies (Demaine *et al*., 2000; Moczulski *et al*., 2000; Neamat-Allah *et al*., 2001; Wang *et al*., 2003; D *et al*., 2004). Another good example is haptoglobin which is a protein in the group of antioxidant proteins that was linked to cardiovascular complications in different populations (Hochberg *et al*., 2002; Levy *et al*., 2002). Recently, the role of genetic variability of *A20*/*TNFAIP3* has been show to modulate CAD risk in T2D, which was mediated by allelic differences in *A20* expression (Boonyasrisawat *et al*., 2007).

Recent studies suggested that inflammation would be an essential component of T2D and its complications. An increased systemic and/or intra-renal inflammation in high glucose milieu is important in the pathogenesis of nephropathy in patients with T2D. The impact of inflammation on DN were studied by investigating polymorphisms in several genes encoding inflammatory cytokines and chemokines such as IL-1β, IL-1Ra, and TNF-α (Levy *et al*., 2002). The understanding of genetic factors predisposing diabetic complications would help to unveil their pathogenesis.

CONCLUSION

DM and its complications are a global health problem. Every effort must be made to minimize the development of the disease and its complications. The effective means to identify the disease at an early stage, changes of life-style, and dietary behavior are important for prevention and control of DM. Characterization of genetic factors involving in the development of DM and its complications will lead to the understanding of their pathogenesis and to develop novel therapeutic approaches. A limitation of progression in this aspect is attributable to the complicated molecular genetics of DM *per se*. Linkage analysis and association study are the traditional techniques employed to identify diabetic susceptible genes. Several candidate genes have been identified but a few genes were reproducible in additional studies in different populations. The genome-wide association (GWA) analysis has recently been carried out to identify several novel diabetic susceptible genes with small contributing effects, the roles of which are being studied. The diabetic susceptible genes in Thai population are likely to be distinct and required to be characterized.

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