

Full Length Research Paper

A narrative insight to maturity-onset diabetes of the young

Attiya Kanwal^{1*}, Sahar Fazal¹, Muhammad Ismail² and Nighat Naureen¹

¹Department of Computer Sciences and Bioinformatics, Mohammad Ali Jinnah University, Islamabad, Pakistan. ²Institute of Biomedical and Genetic Engineering (IBGE), GPO Box 2891, 24, Mauve Area, Sector G-9/1, Islamabad, Pakistan.

Accepted 23 December, 2015

The pandemic of metabolic disorders is accelerating in the urbanized world posing huge burden to health and economy. The key pioneer to most of the metabolic disorders is insulin dependent diabetes mellitus or Type 1 diabetes mellitus (T1DM) and non-insulin dependent diabetes mellitus commonly known as Type 2 diabetes mellitus (T2DM). Both of these forms of diabetes are polygenic and multifactorial. A newly discovered form of diabetes is Maturity Onset Diabetes of the Young (MODY). MODY is monogenic form of diabetes inherited as autosomal dominant anarchy. This piece of writing presents a concise portrayal to MODY. In this article this new form of diabetes is introduced, its different subtypes and clinical characteristics are discussed.

Key words: T1DM; type 1 diabetes mellitus, T2DM; type 2 diabetes mellitus, MODY; maturity onset diabetes of the young.

INTRODUCTION

MODY is the term that relies on the old classification of diabetes into juvenile-onset and maturity-onset diabetes. An etiology-based classification for diabetes has been revised and introduced by both the American Diabetes Association (ADA) and the World Health Organization (WHO). The group of "genetic defect in beta-cell function" has now included MODY as its part with its sub classification according to the gene involved (Martine and Philippe, 2008). Tattersall (U.K.) and Fajan (U.S.A.) first described MODY in 1974 (Tattersall and Fajans, 1975), after taking into account a group of young people with diabetes who were treated without insulin 2 years or more after diagnosis. Since the 1970s there has been great interest in MODY as it is a genetic form of diabetes. MODY is an ancestral form of early-onset Type 2 diabetes. It is a monogenic form of diabetes mellitus inherited in autosomal dominant mode (Anna et al., 2002; Owen and Hattersley, 2001). It is primarily an outcome of impaired beta-cells of pancreas (Anna et al., 2002; Owen and Hattersley, 2001).

MODY is not a single entity but represents genetic, metabolic, and clinical heterogeneity (Costa et al., 2000). MODY generally develops in middle age, and mainly coupled with primarily scantiness of insulin secretion (Vaxillaire and Froguel, 2006).

As MODY is a monogenic form of diabetes, most monogenic diabetes genes are fundamentally beta-cell genes. A key outcome has been that the immense mass of genes where mutations cause early-onset diabetes have condensed Beta-cell function rather than improved insulin confrontation. Heterozygous haploid insufficiency results in foremost early-onset diabetes for many beta-cell genes, including GCK, HNF1-alpha, HNF4-alpha and HNF1-beta, but this is not seen in insulin resistance genes. This shows that yet when faced with relentless insulin resistance, a strong Beta-cell is usually capable to reimburse, but there is no reparation possible when faced with marked insulin deficiency. There are many mechanisms of Beta-cell dysfunction seen in monogenic diabetes, including reduced beta-cell growth, malfunction of glucose sensing, and increased devastation of the Beta-cell (McCarthy and Hattersley, 2008).

Table 1 shows examples of some mechanisms of beta-cell dysfunction seen in monogenic diabetes (McCarthy and Hattersley, 2008).

*Corresponding author. E-mail: attiya_kanwal@yahoo.com.
Tel: +92-3325484291.

Table 1. Mechanisms of beta-cell dysfunction seen in monogenic diabetes.

Mechanism of Beta-cell dysfunction	Gene/Mutation
Reduced Beta-cell number	IPF1 homozygous
Pancreatic aplasia	PTF1A
	HNF1B
	GCK
Reduced B-cell development	Mitochondrial mutations
Reduced metabolism	HNF1A
Reduced glucose sensing	HNF1B
Reduced metabolism	HNF4A
	IPF1 heterozygous
Failure to depolarize membrane	KCNJ11
Failure to close K _{ATP} channel	ABCC8
	FOXP3
	INS
Increased destruction of B-cells	EIF2AK3
Immune-mediated destruction	WFS1
Endoplasmic reticulum stress	HNF1A
Increased apoptosis cause uncertain	HNF4A
	Mitochondrial mutations

Till 2009 eight discrete MODY genes have been acknowledged (Maciej et al., 2009). These are the genes including HNF4A, encoding hepatocyte nuclear factor 4 alpha (Yamagata et al., 1996), GCK, encoding glucokinase (Froguel et al., 1993), HNF1A, encoding hepatocyte nuclear factor 1 alpha (Yamagata et al., 1996), IPF1, encoding insulin promoter factor 1 (Stoffers et al., 1997), HNF1B, encoding hepatocyte nuclear factor 1 beta (Horikawa et al., 1997), NEUROD1, encoding neurogenic differentiation 1 (Malecki et al., 1999), KLF11, encoding for kruppel-like factor 11 (Neve et al., 2005) and CEL, encoding carboxyl-ester lipase (Helge et al., 2006). Now four further genes have been exposed that cause MODY. These genes are PAX4, encoding, paired domain gene 4 (OMIM 612225), IPF1, encoding, insulin promoter factor 1 (OMIM 606392), INS, encoding, insulin (OMIM 176730) and BLK, encoding, Tyrosine kinase, B-lymphocyte (OMIM 191305).

METHODOLOGY

All the literature for this research article was collected from online databases like Pubmed (<http://www.ncbi.nlm.nih.gov/pubmed>) and Online Mendelian Inheritance in Man (OMIM)

(<http://www.ncbi.nlm.nih.gov/omim>). PubMed comprises more than 20 million citations for biomedical literature from MEDLINE, life science journals, and online books. Citations may include links to full-text content from PubMed Central and publisher web sites.

HOW MODY DIFFERS FROM TYPE1 and TYPE 2 DIABETES

Diabetes mellitus is a state in which the pancreas no longer produces adequate insulin or when cells prevent response to the insulin that is formed so that glucose in the blood cannot be captivated into the cells of the corpse.

The affiliation and disparity between Type1 diabetes, Type 2 diabetes and Maturity onset diabetes (MODY) is given below:

- (i) Both Type 1 diabetes and Type 2 diabetes are polygenic forms of diabetes. Whereas the mode of inheritance of MODY diabetes is a monogenic.
- (ii) Type 1 diabetes is most common in children or young adults. Type 2 form of diabetes usually occurs in people who are 40, overweight and have a family history of Type 2 diabetes and MODY diabetes only appears in people under age 25.
- (iii) Only about 5 to 10% of diagnosed diabetes cases are Type 1. The frequency of Type 2 diabetes is 90 to 95% of the 18.2 million people with diabetes. MODY affects around 2 to 5% of non-insulin dependant diabetes.
- (iv) The pedigree of MODY diabetes is multi-generational where as both Type 1 and Type 2 diabetes are rarely multi-generational.
- (v) Type 1 diabetes involves a combination of genetic, environmental and autoimmune factors. Type 2 diabetes involves physical inactivity along with genetic and environmental factors whereas MODY represents genetic, metabolic and clinical heterogeneity.

DIFFERENT SUBTYPES OF MODY

Molecular genetic studies of MODY families have demonstrated that this clause is not a solo unit but is a clinically and hereditarily heterogeneous syndrome (Martine and Philippe, 2008). Mutations, deletions, or other anomalies in at least eleven genes are a root for the bulk of the MODY cases. These MODY genes encode the enzymes glucokinase (MODY 2) that is liable for the early processing of glucose in the beta-cell (Sung-Hoon et al., 2004) and copious transcription factors that modulate the expression of numerous genes concerned with the demarcation and utility of beta-cells (Sung-Hoon et al., 2004).

The first MODY gene to be documented was glucokinase (GCK) (Froguel et al., 1992), followed by

hepatocyte nuclear factors HNF1A (TCF1), HNF4A (Yamagata et al., 1996) and others.

HNF4-Alpha subtype (OMIM 125850)

MODY type 1 is caused by mutation in hepatocyte nuclear factor 4 alpha (HNF4A) gene. This gene is also known as NR2A1 (nuclear receptor subfamily 2, group A, member 1). It is a nuclear receptor encoded by HNF4A gene (Argyrokastiris et al., 1997). This gene is located on chromosome 20. HNF4-alpha is responsible for the regulation of hepatic and pancreatic β cell gene expression (Kuo et al., 1992). Heterozygous mutation in human HNF4-alpha gene results in progressive decrease in insulin production (Yamagata et al., 1996).

Heterozygous mutations in HNF4-alpha are considered a rare source of MODY compared with MODY2/ GCK and MODY3/HNF1A mutations (Pearson et al., 2005). HNF4-alpha belongs to the steroid/thyroid hormone receptor super family. Long-chain fatty acids have been shown to directly modulate the transcriptional activity of HNF4-alpha by binding as acyl-CoA thioesters to the ligand binding domain of HNF4-alpha (Hertz et al., 1998), and they could contribute to the role of dietary fats in the control of insulin secretion. This gene plays a role in development of the liver, kidney, and intestines. HNF4-alpha mutations are associated with an increase in birth weight and macrosomia and thus can be viewed as a novel cause of neonatal hypoglycemia (Pearson et al., 2007).

GCK subtype (OMIM 125851)

Glucokinase (GCK) is also called hexokinase IV. Heterozygous mutations of the glucokinase gene (GCK) result in MODY type 2 (Froguel and Velho, 1994). This gene maps to Chromosome 7. It is the most common form of MODY (Matschinsky, 1990). Unlike other MODY subtypes, the pathophysiology involves impaired glucose sensing by the pancreatic β cells, resulting in mild non-progressive hyperglycemia (5.5 to 8 mmol/L) that is often asymptomatic (Ohn et al., 2009).

It is the predominant glucose phosphorylating enzyme in the liver parenchymal cells and the β -cells of pancreatic islets, both types of cells that have to respond to changes in the blood glucose concentration. GCK acts as a candidate gene in MODY patients and families, more than 150 different mutations have been shown to cause MODY2 (Fajans et al., 2001). Compared with other subtypes of MODY, a lower prevalence of microvascular complications (retinopathy and proteinuria) was observed in MODY2 diabetic patients (Vaxillaire and Froguel, 2006). GCK mutations in the fetus result in reduced birth weight, probably by affecting insulin-mediated fetal growth, whereas maternal GCK mutations indirectly

increase the birth weight by enhancing fetal insulin secretion as a consequence of maternal hyperglycemia during fetal life (Velho et al., 2000).

HNF1A/TCF1 subtype (OMIM 600496)

Hepatocyte nuclear factor 1 alpha gene (HNF1A) accounts for a great part of the MODY type 3. This gene is located on Chromosome 12 (Velho et al., 1996). This gene is linked to a defect in the nuclear transcription factors. Patients with HNF1A mutations develop diabetes after the first decade, and it is preceded by abnormal glucose-induced insulin secretion (Stride et al., 2005). Like Type 1 MODY, it is also characterized by a progressive reduction in insulin secretion. This may require insulin and develop vascular complications for over time patients (Velho et al., 1996).

The penetrance of MODY 3 is high, although it is dependent on age, so that the probability of being diagnosed with diabetes increases steadily between 10 and 40 years of age (Pearson et al., 2001). MODY 3 is a more severe form of diabetes, often evolving toward insulin dependency, and microvascular complications of diabetes are observed in MODY 3 as in later onset diabetes (Vaxillaire and Froguel, 2006).

IPF1/PDX1 subtype (OMIM 606392)

PDX1 gene (Pancreatic and duodenal homeobox 1) is also known as insulin promoter factor 1 (IPF1). It is a transcription factor necessary for pancreatic development and β -cell maturation. Insulin promoter factor 1 (IPF1) is an orphan homeodomain protein and has been described as a master switch for both endocrine and exocrine function of pancreas. MODY type 4 is caused by mutation in IPF1 gene present on Chromosome 13 (Stoffers et al., 1997; Maestro et al., 2007). PDX1 acts as a major transcriptional regulator of endocrine pancreas-specific genes in adults, such as the Glucose transporter-2 and GCK genes in B-cells, and the somatostatin gene in B-cells (Martine and Philippe, 2008).

TCF2/HNF1B subtype (OMIM 137920)

MODY type 5 is caused by mutation in hepatocyte nuclear factor 1 beta (HNF1B) gene located on Chromosome 17. It is a rare form of MODY that is associated with kidney disease. HNF1-beta plays a major role in kidney development and nephron differentiation and is also a critical regulator of a transcriptional network that controls the specification, growth, and differentiation of the embryonic pancreas (Lindner et al., 1999).

Mutations in TCF2/HNF-1B are responsible for severe kidney disease, which may appear before the impairment

of glucose tolerance (Bellanne-Chantelot et al., 2004). This has been recognized as a discrete clinical syndrome, called renal cysts and diabetes syndrome (Bellanne-Chantelot et al., 2004; Poulin et al., 1997).

NEUROD1 subtype (OMIM 606394)

Neurogenic differentiation factor 1 (NEUROD1) is also called Beta 2 (Naya et al., 1997). It is a transcription factor of the NeuroD-type and encoded by the human gene NEUROD1. It is a member of the NeuroD family of basic-helix-loop-helix (bHLH) transcription factors and plays an important role in the development of the pancreas and the nervous system (Martine and Philippe, 2008). Mutation in transcription factor NEUROD1 results in MODY6 (Fajans et al., 2001).

This gene is involved in neuronal differentiation and development of pancreas morphology (Naya et al., 1997).

KLF11 subtype (OMIM 610508)

Krüppel-like factor 11 is a protein that in humans is encoded by the KLF11 gene (Schoy et al., 2001). MODY7 is caused by mutations in the KLF11 gene. This gene maps to Chromosome 2. KLF 11 regulates exocrine cells growth and behaves like a tumor suppressor for pancreatic malignancy (Neve et al., 2005).

CEL subtype (OMIM 609812)

Carboxyl-ester lipase gene (CEL) gene controls both exocrine and endocrine function of the pancreas. MODY8 is caused by mutation in CEL gene on Chromosome 9. It is caused by frame shift deletions in the variable number of tandem repeats (VNTR) of the carboxyl-ester lipase gene.

PAX4 subtype (OMIM 612225)

Paired box gene 4 is also known as PAX4. It is a protein which in humans is encoded by the PAX4 gene (Inoue et al., 1998). MODY9 is caused by mutations in the PAX4 gene. This gene is located on Chromosome 7. This gene is a member of the paired box (PAX) family of transcription factors. Members of this gene family typically contain a paired box domain, an octapeptide, and a paired-type homeodomain. These genes play critical roles during fetal development and cancer growth. The paired box gene 4 is involved in pancreatic islet development.

INS subtype (OMIM 176730)

Insulin is a hormone that is central to regulating energy

and glucose metabolism in the body. Insulin causes cells in the liver, muscle, and fat tissue to take up glucose from the blood, storing it as glycogen in the liver and muscle. The proinsulin precursor of insulin is encoded by the INS gene (Bell et al., 1980).

MODY type 10 is caused by mutation in INS (PROINSULIN) gene. This gene is located on Chromosome 11p15.5. It primarily defects NF-kappa-B (Dandona et al., 2001).

BLK subtype (OMIM 191305)

Tyrosine-protein kinase BLK is also known as B lymphocyte kinase. It is an enzyme that in humans is encoded by the BLK gene (Drebin et al., 1995). MODY type 11 is caused by mutation in BLK gene. This gene maps on Chromosome 8p23 to p22. It primarily defects MIN6 beta cells. This gene is a member of the SRC family of proto-oncogene and on the basis of its preferential expression in B-lymphoid cells, it is concluded that it functions in a signal transduction pathway specific to this lineage (Dymecki et al., 1990).

GENETIC CLASSIFICATION AND CLINICAL PHENOTYPES OF THE MODY SUBTYPE

Type 1

Affected gene name: HNF4 alpha
Affected protein: Hepatocyte nuclear factor 4 alpha
Locus: 20q
Gene function: Transcription factor (Nuclear factor)
Primary defect: Pancreas

Type 2

Affected gene name: GCK
Affected protein: Glucokinase
Locus: 7p15-p13
Gene function: Hexokinase IV
Primary defect: Pancreas/Liver

Type 3

Affected Gene Name: TCF1
Affected protein: Hepatocyte nuclear factor 1 alpha
Locus: 12q24.2
Gene function: Transcription factor (Homeodomain)
Primary defect: Pancreas/Kidney

Type 4

Affected gene name: IPF1

Affected protein: insulin promoter factor-1
Locus: 13q12.1
Gene function: Transcription factor (Homeodomain)
Primary defect: Pancreas

Type 5

Affected gene name: TCF2
Affected protein: Hepatocyte nuclear factor 1 beta
Locus: 17q12
Gene function: Transcription factor (Homeodomain)
Primary defect: Kidney/Pancreas

Type 6

Affected gene name: Neuro D1
Affected protein: Neurogenic differentiation factor 1
Locus: 2q
Gene function: Transcription factor (bHLH)
Primary defect: Pancreas

Type 7

Affected gene name: KLF11
Affected protein: Kruppel-like factor 11
Locus: 2p25
Gene function: Transforming growth factor-beta-inducible-early growth response 2. Primary defect: Pancreas

Type 8

Affected gene name: CEL
Affected protein: Bile salt dependent lipase
Locus: 9q34.3
Gene function: The endocrine cells of pancreas synthesize insulin and are involved in the pathogenesis of diabetes mellitus and exocrine cells are involved in the pathogenesis of pancreas.
Primary defect: Pancreas

Type 9

Affected gene name: PAX4
Affected protein: Paired domain gene 4
Locus: 7q32
Gene function: Transcription factor (paired domain gene 4)
Primary defect: Pancreas

Type 10

Affected gene name: INS

Affected protein: Insulin
Locus: 11p15.5.
Gene function: Beta cells of the islets of Langerhans
Primary defect: NF-kappa-B

Type 11

Affected gene name: BLK
Affected protein: Tyrosine kinase B-Lymphocyte specific
Locus: 8p23-p22
Gene function: Tyrosine kinase (B lymphocytes)
Primary defect: MIN6 beta cells

SIGNS AND SYMPTOMS OF MODY

The symptoms of MODY diabetes are similar to other types of diabetes as this disease affects the body similar to how other types of diabetes do. However, the absence of diabetes antibodies like anti-insulin, anti-islet, anti-GAD will distinguish MODY from Type 1 diabetes and in obese people the absence of insulin resistance will differentiate it from Type 2 diabetes. These symptoms can include Malaise, drowsiness, poor healing, blurred vision, paresthesias, peripheral neuropathy, skin ulcers, thrush, hand tingling, foot tingling, premature menopause, erectile failure, dry itchy skin, skin rashes, athlete's foot, sexual problems like nerve and circulatory problems of diabetes can disrupt normal male sexual function, resulting in impotence. Diabetes can cause specific complications in women. Women with diabetes have an increased risk of recurrent yeast infections. In terms of sexual health, diabetes may cause decreased vaginal lubrication.

COMPLICATIONS OF MODY DIABETES

No matter what kind of diabetes it is, high blood sugars damage the organs. The following are the list of complications that can be caused by MODY diabetes.

- (i) Heart and blood vessel disease.
- (ii) Nerve damage.
- (ii) Kidney damage.
- (iv) Eye damage.
- (v) Foot damage.
- (vi) Skin and mouth conditions.
- (vii) Osteoporosis.
- (Viii) Alzheimer's disease.
- (ix) Hearing problems.

DIAGNOSIS OF MODY

In a non-obese patient of any age and in an obese patient less than 50 years of age, for the patients to be

diagnosed with maturity onset diabetes of the young, they must:

- (i) Present with higher than normal blood glucose.
- (ii) Have no ketones in urine.
- (iii) Have Type 2 diabetes and not Type 1 diabetes.
- (iv) Have diabetes that does not need insulin to be controlled for a minimum of two years.
- (V) The age of onset of minimum of one family member has to be younger than 25 years of age.

TREATMENT FOR MODY DIABETES

Various treatments options for MODY diabetes are recommended depending on the severity of the diabetes. Although it is better to seek medical professional's advice about the treatment. The glucokinase type of MODY is the one most amendable to dietary control. Such patients can maintain normal blood sugar levels by restricting carbohydrates. Other types of MODY patients may be treated with very low doses of drugs that stimulate insulin secretion, if the diabetes is not controlled using oral hypoglycemic. Often sulfonylurea is considered as first line therapy. To prevent cardiovascular diseases, we should go for the aggressive treatment of complications like hyperlipidemia and hypertension. Frequent medical checkups are required for diabetes complications like peripheral neuropathy, peripheral vascular disease, eye disease and kidney disease.

CLINICAL CHARACTERISTICS OF MODY

Mody type 1

This type of MODY is mild to severe diabetes. It causes subtle liver abnormalities as defects in the HNF 4 alpha gene affect fatty acid synthesis in the liver.

Mody type 2

This type of MODY is very mild and often symptom less. Its mild insulin deficiency serves to separate it from other forms of MODY. Fortunately it rarely causes micro vascular complications. It is often picked up in obese patients or a pregnant woman with low birth weight infants who may suspect a family history.

Mody type 3

This is a progressive type of MODY. It is generally diagnosed after puberty. It may produce sufficient insulin as a child but as we get older the amount of insulin secretion decreases. MODY type 3 is susceptible to

diabetic complications such as retinopathy and neuropathy.

Mody type 4

This form of MODY diabetes produces comparatively mild. It is very rare. IPF1 gene defect causes a decrease in the kidneys re-absorption of glucose.

Mody type 5

MODY type 5 is fortunately very rare and is often diagnosed after the diagnosis for kidney disease. The defects in the HNF 1 beta protein have been known to cause renal cysts and other abnormalities for kidney disease.

Mody type 6

Mutations in the gene encoding transcription factor NeuroD1 were found in two families with autonomic dominant Type 2 diabetes. One of these families met the criteria for MODY, including (in addition to an autonomic dominant pattern of inheritance) an onset of diabetes before 25 years of age in three carriers and a requirement for insulin treatment; a finding consistent with the presence of beta-cell dysfunction in five carriers. Other types of MODY exist but are very rare.

RELATIVE PREVALENCE OF DISTINCT MODY SUBTYPE

The true relative prevalence of the eleven distinct MODY subtypes is unknown and varies substantially in different populations (Gagnoli, 2001; Barrio et al., 2002; Pruhova et al., 2003). Mutations in the genes encoding HNF1A and GCK are by far the most prevalent. Mutations in GCK (MODY 2) account for 7 to 41% (Gagnoli, 2001; Barrio et al., 2002), whereas mutations in TCF1 (MODY 3) may account for 11 to 63%, (Pruhova et al., 2003) of mutations in subjects with clinically diagnosed MODY. Mutations in HNF4A (MODY1) are less frequent and may account 2 to 5% of subjects with MODY (Pruhova et al., 2003). The prevalence of MODY patients with mutations in TCF2 (MODY 5) is considered very rare.

It may comprise up to approximately 2% (Mark et al., 2008). Mutations in IPF1 (MODY 4), NEUROD1 (MODY 6), KLF11 (MODY 7), CEL (MODY 8) and PAX4 (MODY 9) are also very rare and have been identified only 1% (McCarthy and Hattersley, 2008). The prevalence of MODY patients with mutations in INS (MODY 10) and BLK (MODY 11) are also considered only 1% (McCarthy and Hattersley, 2008).

DISCUSSION AND CONCLUSION

This paper basically provides a brief description on Maturity Onset Diabetes of the Young (MODY). MODY is nowadays a burning issue in European countries. In this paper we focus on different subtypes of MODY and their clinical characteristics. This article will help the scientific community to establish a scheme for identifying and treating MODY. In future, work can be done on identifying the unknown genes that are involved in MODY diabetes.

ACKNOWLEDGEMENT

I would like to thank Dr. Sahar Fazal for her support and corporation.

REFERENCES

- Anna LG, Sian E, Maggie S, Rodney TH, Elizabeth MP, Andrew J, Elaine RL, Andrew TH (2002). Maturity-onset Diabetes of the young Caused by a Balanced Translocation Where the 20q12 Break Point Results in Disruption Upstream of the Coding Region of Hepatocyte Nuclear Factor-4A Gene. *DIABETES*, 51: 2329-2333.
- Argyrokastiris A, Kamakari S, Kapsetaki M, Kritis A, Talianidis I, Moschonas NK (1997). Human hepatocyte nuclear factor-4 (hHNF-4) gene maps to 20q12-q13.1 between PLCG1 and D20S17. *Hum. Genet.*, 99: 233-236.
- Barrio R, Bellanne-Chantelot C, Moreno JC, Morel V, Calle H, Alonso M, Mustieles C (2002). Nine novel mutations in maturity-onset diabetes of the young (MODY) candidate genes in 22 Spanish families. *J. Clin. Endocrinol. Metab.* 87: 2532-2539.
- Bell GI, Pictet RL, Rutter WJ, Cordell B, Tischler E, Goodman HM (1980). Sequence of the human insulin gene. *Nature*, 284: 26-32.
- Bellanne-Chantelot C, Chauveau D, Gautier JF, Dubois-Laforgue D, Clauin S, Beaufils S, Wilhelm JM, Boitard C, Noe LH, Velho G, Timsit J (2004). Clinical spectrum associated with hepatocyte nuclear factor-1 Beta mutations. *Ann. Int. Med.*, 140: 510-517.
- Costa A, Bescos M, Velho G, Chevre J, Vidal J, Sesmilo G, Bellanne-Chantelot C, Froguel P, Casamitjana R, Rivera-Fillat F, Gomis R, Conget I (2000). Genetic and clinical characterization of maturity-onset diabetes of the young in Spanish families. *Eur. J. Endocrinol.*, 142: 380-386.
- Dandona P, Aljada A, Mohanty P, Ghanim H, Hamouda W, Assian E, Ahmad S (2001). Insulin inhibits intranuclear nuclear factor kappa-B and stimulates I-kappa-B in mononuclear cells in obese subjects: evidence for an anti-inflammatory effect? *J. Clin. Endocrinol. Metab.*, 86: 3257-3265.
- Drebin JA, Hartzell SW, Griffin C, Campbell MJ, Niederhuber JE (1995). Molecular cloning and chromosomal localization of the human homologue of a B-lymphocyte specific protein tyrosine kinase (blk). *Oncogene*, 10: 477-486.
- Dymecki SM, Niederhuber JE, Desiderio SV (1990). Specific expression of a novel tyrosine kinase gene, Blk, in B lymphoid cells. *Science*. 247: 332-336.
- Fajans SS, Bell GI, Polonsky KS (2001). Molecular mechanisms and clinical pathophysiology of maturity-onset diabetes of the young. *N. Engl. J. Med.* 345: 971-980
- Froguel P, Vaxillaire M, Sun F, Velho G, Zouali H, Butel MO, Lesage S, Vionnet N, Clement K, Fougereusse F, Tanizawa Y, Weissenbach J, Beckmann JS, Lathrop GM, Passa P, Permutt MA, Cohen D (1992). Close linkage of glucokinase locus on chromosome 7p to early-onset non-insulin-dependent diabetes mellitus. *Nature*. 356: 162-164.
- Froguel P, Velho G (1994). Maturity-onset diabetes of the young. *Curr. Opin. Pediatr.*, 6: 482-485.
- Froguel P, Zouali H, Vionnet N, Velho G, Vaxillaire M, Sun F, Lesage S, Stoffel M, Takeda J, Passa P, Alan MP, Jacques SB, Graeme IB, Daniel C (1993). Familial hyperglycemia due to mutations in glucokinase. Definition of a subtype of diabetes mellitus. *N. Engl. J. Med.*, 328: 697-702.
- Graglioli C (2001). Early-onset type II diabetes mellitus in Italian families due to mutations in the genes encoding hepatic nuclear factor 1 alpha and glucokinase. *Diabetologia*, 44: 1326-1329.
- Helge R, Stefan J, Pál IH, Ingrid SH, Eric M, Véronique S, Ingrid N, Stig ÅE, Louise G, Lise B, Jorn VS, Lage A, Oddmund S, Dominique L, Anders M, Pal RN (2006). Mutations in the CEL VNTR cause a syndrome of diabetes and pancreatic exocrine dysfunction. *Nat. Genet.*, 38: 54-62.
- Hertz R, Magenheimer J, Berman I, Bar-Tana J (1998). Fatty acyl-CoA thioesters are ligands of hepatic nuclear factor-4 alpha. *Nature*. 392: 512-516.
- Horikawa Y, Iwasaki N, Hara M, Furuta H, Hinokio Y, Cockburn BN, Lindner T, Yamagata K, Ogata M, Tomonaga O, Kuroki H, Kasahara T, Iwamoto Y, Bell GI (1997) Mutation in hepatocyte nuclear factor-1 beta gene (TCF2) associated with MODY. *Nat. Genet.*, 17: 384-385.
- Inoue H, Nomiya J, Nakai K, Matsutani A, Tanizawa Y, Oka Y (1998). Isolation of full-length cDNA of mouse PAX4 gene and identification of its human homologue. *Biochem. Biophys. Res. Commun.*, 243: 628-633.
- Kuo CJ, Conley PB, Chen L, Sladek FM, Darnell JE, Crabtree GR (1992). A transcriptional hierarchy involved in mammalian cell-type specification. *Nature*, 355: 457-461.
- Lindner TH, Njolstad PR, Horikawa Y, Bostad L, Bell GI, Sovik O (1999). A novel syndrome of diabetes mellitus, renal dysfunction and genital malformation associated with a partial deletion of the pseudo-POU domain of hepatocyte nuclear factor-1 Beta. *Hum. Mol. Genet.*, 8: 2001-2008.
- Maciej B, Chong WL, Ryan T, Watip B, Jiang H, Wojciech MM, Ilham EK, Sung-Hoon K, Lorella M, Stephen SR, Andrzej SK, Susan B, Arun S, Michele S, Josyf CM, Rohit NK, Alessandro D (2009). Mutations at the BLK locus linked to maturity onset diabetes of the young and B-cell dysfunction. *PNAS*, 106: 14460-14465
- Maestro MA, Cardalda C, Boj SF, Luco RF, Servitja JM, Ferrer J (2007) Distinct roles of HNF1 Beta, HNF1 alpha, and HNF4 alpha in regulating pancreas development, Beta-cell function and growth. *Endocrinology*, 12: 33-45.
- Malecki MT, Jhala US, Antonellis A, Fields L, Doria A, Orban T, Saad M, Warram JH, Montminy M, Krolewski AS (1999). Mutations in NEUROD1 are associated with the development of type 2 diabetes mellitus. *Nat. Genet.*, 23: 323-328.
- Martine V, Philippe F (2008). Monogenic Diabetes in the Young, Pharmacogenetics and Relevance to Multifactorial Forms of Type 2 Diabetes. *Endocrine Rev.*, 29: 254-264.
- Matschinsky FM (1990). Glucokinase as glucose sensor and metabolic signal generator in pancreatic beta-cells and hepatocytes. *Diabetes*. 39: 647-652.
- McCarthy MI, Hattersley AT (2008). Novel Insights arising From the Definition of Genes for Monogenic and Type 2 Diabetes. *Diabetes*, 57: 2889-2898.
- Naya FJ, Huang HP, Qiu Y, Mutoh H, DeMayo FJ, Leiter AB, Tsai MJ (1997). Diabetes, defective pancreatic morphogenesis, and abnormal enteroendocrine differentiation in BETA2/neuroD-deficient mice. *Genes Dev.*, 11: 2323-2334.
- Neve B, Fernandez-Zapico ME, Ashkenazi-Katalan V, Dina C, Hamid YH, Joly E, Vaillant E, Benmezroua Y, Durand E, Bakaher N, Delannoy V, Vaxillaire M, Cook T, Dallinga-Thie GM, Jansen H, Charles MA, Clément K, Galan P, Hercberg S, Helbecque N, Charpentier G, Prentki M, Hansen T, Pedersen O, Urrutia R, Melloul D, Froguel P (2005). Role of transcription factor KLF11 and its diabetes-associated gene variants in pancreatic beta cell function. *Proc. Natl. Acad. Sci. USA.*, 102: 4807-4812.
- Ohn N, Joyce YW, Ivan NM, Mark H, Tony H, Gary ML, David MC, Andrew MC (2009). Investigating Maturity Onset Diabetes of the Young. *Clin. Biochem.*, 30: 67-74.
- Owen K, Hattersley A (2001). Maturity-onset Diabetes of the young: from clinical description to molecular genetic characterization. In *Best Pract. Res. Clin. Endocrinol. Metabolism*, 15: 309-323.
- Pearson ER, Boj SF, Steele AM, Barrett T, Stals K, Shield JP, Ellard S,

- Ferrer J, Hattersley AT (2007). Macrosomia and hyperinsulinaemic hypoglycaemia in patients with heterozygous mutations in the HNF4-Alpha gene. *Diabetologia*, 50: 2600-2601.
- Pearson ER, Pruhova S, Tack CJ, Johansen A, Castleden HA, Lumb PJ, Wierzbicki AS, Clark PM, Lebl J, Pedersen O, Ellard S, Hansen T, Hattersley AT (2005). Molecular genetics and phenotypic characteristics of MODY caused by hepatocyte nuclear factor 4 alpha mutations in a large European collection. *Diabetologia*, 48: 878-885.
- Pearson ER, Velho G, Clark P, Stride A, Shepherd M, Frayling TM, Bulman MP, Ellard S, Froguel P, Hattersley AT (2001). Beta-Cell genes and diabetes: quantitative and qualitative differences in the pathophysiology of hepatic nuclear factor-1 alpha and glucokinase mutations. *Diabetes*, 50: 101-107.
- Poulin G, Turgeon B, Drouin J (1997). NeuroD1/beta2 contributes to cell-specific transcription of the proopiomelanocortin gene. *Mol. Cell. Biol.*, 17: 6673-6682.
- Pruhova S, Ek J, Lebl J, Sumnik Z, Saudek F, Andel M, Pedersen O, Hansen T (2003). Genetic epidemiology of MODY in the Czech Republic: new mutations in the MODY genes HNF-4 alpha, GCK and HNF-1 alpha. *Diabetologia*. 46: 291-295.
- Schohy S, Gabant P, Van RT, Hertveldt V, Dreze PL, Van VP, Riviere M, Szpirer J, Szpirer C (2001). Identification of KLF13 and KLF14 (SP6), novel members of the SP/XKLF transcription factor family. *Genomics*. 70: 93-101.
- Stoffers DA, Ferrer J, Clarke WL, Habener JF (1997). Early-onset type-II diabetes mellitus (MODY4) linked to IPF1. *Nat. Genet.* 17: 138-139.
- Stride A, Ellard S, Clark P, Shakespeare L, Salzman M, Shepherd M, Hattersley AT (2005). Beta-Cell dysfunction, insulin sensitivity, and glycosuria precede diabetes in hepatocyte nuclear factor-1 alpha mutation carriers. *Diabetes Care*. 28: 1751-1756.
- Sung-Hoon K, Xiaowei M, Stanislaw W, Tonino E, Christine P, Wojciech M, Aviva B K, James HW, Josyf M, Stephen SR, Andrzej SK, Alessandro D (2004). Identification of a locus for maturity-onset diabetes of the young on chromosome 8p23. *Diabetes*, 53: 1375-1384.
- Tattersall RB, Fajans SS (1975). A difference between the inheritance of classical juvenile-onset and maturity-onset type diabetes of young people. *Diabetes*, 24: 44-53.
- Vaxillaire M, Froguel P (2006). Genetic basis of maturity-onset diabetes of the young. *Endocrinol. Metab. Clin. North Am.*, 35: 371-384.
- Velho G, Hattersley AT, Froguel P (2000). Maternal diabetes alters birth weight in glucokinase-deficient (MODY2) kindred but has no influence on adult weight, height, insulin secretion or insulin sensitivity. *Diabetologia*, 43: 1060-1063.
- Velho G, Vaxillaire M, Boccio V, Charpentier G, Froguel P (1996). Diabetes complications in NIDDM kindreds linked to the MODY3 locus on chromosome 12q. *Diabetes Care*, 19: 915-919.
- Yamagata K, Oda N, Kaisaki PJ, Menzel S, Furuta H, Vaxillaire M, Southam L, Cox RD, Lathrop GM, Boriraj VV, Chen X, Cox NJ, Oda Y, Yano H, Le-Beau MM, Yamada S, Nishigori H, Takeda J, Fajans SS, Hattersley AT, Iwasaki N, Hansen T, Pedersen O, Polonsky KS, Turner RC, Velho G, Chèvre J, Froguel P, Bell GI (1996) Mutations in the hepatocyte nuclear factor-1_ gene in maturity-onset diabetes of the young (MODY3). *Nature*, 384: 455-458.