

Candidate genes in adult elderly and adult Intermeddle diabetes

Abstract

The aim of this work was makes a genetic dissection proposal focusing on an exhaustive search in the literature for genetic factors (mutations and/or polymorphisms) for DM in the intermediate adult (40-64 years), as well as in the elderly (over 65 years). It deserves a dissection because in this period of life a series of progressive physiological changes related to sage-ing and aging are initiated, such as a decrease in insulin sensitivity, an increase in insulin resistance in tissues, as well as transient postprandial hyperglycemia. The involvement of chromosomes 2, 4, 3, 7, 8, 9, 10, 11, 12, 16 y 19, with 18 genes are implicated in the development of diabetes in the intermediate or older adult. These genes encodes for proteins with different functions, among them; factor transcription, insulin signaling, adipose tissue homeostasis or energy balance, inflammation, carbohydrate metabolism, insulin secretion, exocytosis, lipid transport, endocytosis as well as oxidative stress. Such factors should be corroborated in replicate epidemiological studies. NeuroD1, INSR, ABCA1, AMP1 and RET have a direct effect in development diabetes. It is interesting those genetic markers which protects again diabetes such as the polymorphism rs13266634 of the gene SLC30A8

Keywords: exocytosis, diabetes elderly, diabetes adult intermediate, insulin resistance, transcription factor

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Luis J Flores,¹ José C Hernández,² María E Aguilar-Aldrete,³ Manuel Mazariegos,⁴ José R Villafán-Bernal,⁵ Perla M Madrigal-Ruiz,¹ Rosalba Ruiz,¹ Diego Ortega-Pacheco,⁶ Eric Ramirez,⁶ José Domínguez-Rodas,² Carlos J Castro-Juárez,² Sergio A Ramirez-Garcia,^{2,6}

¹Department of Molecular Biology and Genomics, University Center of Health Sciences & University of Guadalajara, Mexico

²Institute of Public Health Research, University of the Sierra Sur, Mexico

³Departments of Public Health and Psicogeriatric College, University Center of Health Sciences & University of Guadalajara, Mexico

⁴Belchor of Medical Surgeon, University Center of Health Sciences & University of Guadalajara, Mexico

⁵Catedra CONACYT, Autonomous University of Aguascalientes, Mexico

⁶Masters program in public health, University of the Sierra Sur, Mexico

Correspondence: Sergio Alberto Ramirez Garcia, Masters program in public health, Universidad Col & Ciudad Universitaria, Mihuatlán de Porfirio Díaz, México, Tel 01(376)765-23-25, Email sergio7gentica@Hotmail.com

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Introduction

Diabetes mellitus (DM) is a complex trait that presents genetic heterogeneity, ranging from complex disease to monogenic forms. The most common is type 2 DM characterized by its complex disease pattern, in which the additive effect of the genes plus the environmental factors determine the liability or threshold for its development.¹⁻⁵ The clinical complexity of this entity is based on the multiple pathophysiological effects involved in its pathogenesis, as well as dissection of its possible overlapping genetic component in families with DM presenting different forms of inheritance in conjunction with type 2 DM. Unfortunately it is not known, even the frequency of these overlapping positions, nor have all the phenotypes of these positions been reported.¹⁻⁵ Five pure forms of DM have now been reported; DM type 1, DM type 2, DM with deafness, DM onset in young adult (MODY), DM onset in older adult and neonatal DM. The first two have a multifactorial inheritance pattern, the third mitochondrial, and the last autosomal dominant.¹⁻⁵ Familial co-inheritance of DM MODY with type 2 DM results in a variant of DM onset in the neonatal stage. Families with DM2 have been reported to develop antibodies characteristic of type 1 DM, or type 2 DM with mitochondrial component. In the Mexican population DM MODY has been described with the production of antibodies characteristic of DM1. Therefore, it is essential for physicians of all levels of health care to acquire expertise to perform a dissection of the combined forms in their captive population, as this translates into differences in metabolic control.¹⁻⁵

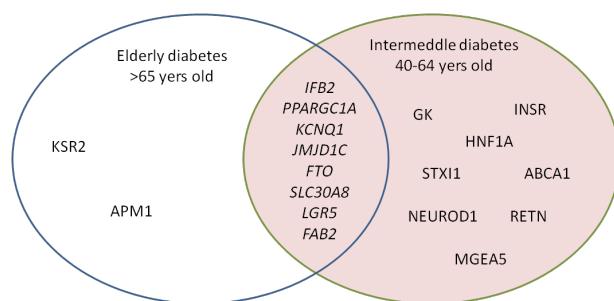
Our study group makes a genetic dissection proposal focusing on an exhaustive search in the literature for genetic factors (mutations and/or polymorphisms) for DM that starts in the intermeddle adult (40-64 years), as well as in the elderly (over 65 years). Such population deserves a detail dissection of genetic markers that lead to DM because in this period of life a series of progressive physiological changes related to sage-ing and aging are initiated, such as a decrease in insulin sensitivity, an increase in insulin resistance in tissues, Such as transient postprandial hyperglycemia.⁶

The clinical effect of these alterations results in the older adult in a modification of the renal glucose threshold that can reach up to 300mg/dl, which explains why it does not develop glucosuria until blood glucose levels are extremely high. These factors as well as a diet high in fat and low in complex carbohydrates, age-related diseases, among other situations, result in a form of diabetes and therefore require a different treatment.⁷⁻⁸ The analysis of genes responsible for and/or associated with this type of DM, includes those coding for proteins necessary for beta cell function such as NEUROD1 and GCK8 whose variants are transmitted with a dominant inheritance pattern), genes related to the Signaling of insulin as well as homeostasis of adipose tissue including INSR, APM1, RETN. Also included are the genes for pro-inflammatory cytokines involved in insulin resistance such as IFNB2 and the ABCA1 gene related to the flow of cholesterol in tissues. Other genes associated with elderly diabetes were analyzed in this document (Table 1 & Figure 1).

Table I Genes involved in diabetes of adult elderly and adult intermediate

Gene	Physiologic function	Marker	Age onset of the diabetes	Direct effect in Diabetes*	Risk factor	Protective factor	Reference
NEUROD1	Transcription factor	p.R111L	30-59	✓	✓	✗	9-Dec
INSR	Pathway Insulin	p.R331X	40-50	✓	✗	✗	13
APM1		p.G84R	50	✗	✓	✗	13
	Energetic balance	G276T	65-85	✓	✓	✗	14-18
ABCA1	Colesterol transport	p.R230C	40	✓	✗	✗	19-20
IFNB2		C174G	65 +/- 5.2	✗	✓	✗	19-20
	Inflammation	A598G	65 +/- 5.2	✓	✓	✗	24-25
RETN		C-394G	40	✗	✓	✗	24-25
		C191G	40	✗	✓	✗	24-25
		C585T	40	✗	✓	✗	24-25
	Energetic balance	-420C-G	48 +/- 12	✓	✗	✗	26-28
GCK		p.R186X	59	✓	✗	✗	26-28
	Carbohydrate metabolism	G30A	53-57	✗	✓	✗	31-32
KSR2	Pathway insulin	rs7973260	70-84	✗	✓	✗	34
PPARGC1A	Energy metabolism	rs10517030, rs10517032	40-65	✗	✓	✗	35
KCNQ1	Insulin secretion	rs163177	40-69	✗	✓	✗	36
JMD1C	DNA damage mediator	rs10761745	40-70	✗	✓	✗	36
MGEA5	Glycosylation of proteins	Tsp509I	43.5±8.9	✗	✓	✗	37
HNF1A	Transcription factor	p.G319S	50	✗	✓	✗	38
STX1A	Exocytosis	p.D68D	44.20 +/- 0.58	✗	✓	✗	39
FTO	Metabolic stress	rs9939609	40-63	✗	✓	✗	40
SLC30A8	Insulin secretion	rs13266634	40-63	✗	✗	✓	40
LGR5	Endocytosis	rs7961581	40-63	✗	✓	✗	40
FABP2	Lipid transport	rs1799883	40-63	✗	✓	✗	41

Note The genes and their polymorphisms that predispose the patient to the development DM, either as a polymorphism that in itself results in type 2 DM*, or that is considered as a mutation that as a result Risk factors such as insulin resistance, increased body mass index, among other risk factors**.

**Figure I** Genetic of adult elderly and adult intermeddle diabetes.

Candidate genes

Neurod1

NEUROD1 is a gene which has its locus in 2q32, is made up of

two exon and encodes the basic transcription factor Helix-Loop-Helix (bHLH) NEUROD1 (known as BETA2). NEUROD1 form heterodimers with bHLH which also bind to E-box. Neurod1 activates the expression of the gene for insulin and others related to its secretion mechanism, such as chromogranin A, subunits α 1C and α 1D of calcium channels as well as FOXA2 necessary for the development of β cells and hepatocytes.⁹⁻¹² This factor forms heterodimers with bHLH E47 (which is ubiquitous in the cell). It has been reported that the p.R111L mutation located in the DNA binding domain, in the heterozygote state, is responsible for the development of DM. This variant is due to a change in the nucleotide G>T, which leads to the replacement of arginine for leucine in residue 111.⁹⁻¹² Its effect results in the abolition of E-box transcriptional activation. This mutation was found in four index cases, which were two previously diagnosed with DM and the remaining two with glucose intolerance at the time of examination. The average age of the four people at the time of diagnosis with DM was 40 years.⁹⁻¹²

INSR

The INSR gene has its locus in 19p13.3-13.2, is composed of 22 exons, coding for the insulin receptor which is made up of two extracellular alpha subunits and two intracellular beta subunits.¹³ These are held together by disulfide bridges. Through this, insulin exerts its action in the target tissues through many phosphorylations of other signal amplifying molecules such as the substrate of the insulin receptor, phosphatidyl inisitol-3-kinase among others. Some mutations of this gene result in the dysfunction of its product, which causes DM.¹³ It has been reported in a 12-year Asian test with insulin resistance type A mutation in heterozygous state p.R331X. The father of the case was 40 years old and was beginning to show signs of insulin resistance. Her 66-year-old paternal grandmother had been diagnosed 15 years ago with DM. These index cases were carriers of the p.R331X mutation.¹³

APM1

Adiponectin is genetically encoded by the APM1 gene which is located on chromosome 3q27.3, consisting of 16 kb and 3 exons.¹⁴ Adiponectin is a hormone that is expressed exclusively in adipose tissue and its main function is to regulate the homeostasis of energy in the body and thus the metabolism of glucose and lipids. According to studies carried out in adiponectin gene knockout mice, which show decreased serum adiponectin levels, as well as insulin resistance in the probands, it was postulated as a risk factor for the development of DM any alteration of this gene.¹⁵ In human studies, it was demonstrated that a population of Pima Indians, who had decreased levels of serum adiponectin (compared to healthy Pima Indians with normal hormone levels), developed type 2 DM.¹⁶ According to a study carried out in the Caucasian population, the p.G84R mutation of the APM1 gene was related to low concentrations of serum adiponectin and a close relationship of the mutation to the development of DM in the elderly. It was found in three siblings diagnosed with MD, shortly after 50 years of age and two of them had decreased levels of serum adiponectin, which coincided with the presence of the p.G84R mutation of the APM1 gene. Of the three siblings, the only one who did not express the mutation was not obese¹⁶. The genotype heterozygote and homozygote T from SNP 276 (locus; intron 2), was associated with diabetes with OR >1.2 (p<0.05).¹⁷

This suggests the p.G84R polymorphism of the APM1 gene as a risk factor for developing DM. The G276T mutation of the APM1 gene has been associated with DM in the elderly and in addition to the metabolic syndrome. This was reflected in a case-control study conducted in the population aged 65 to 88 years and in which almost 50% of the test subjects had the G276T mutation.¹⁸ For all of the above, the genetic alterations of the APM1 gene are considered as an important risk factor in the development of DM in the elderly.

ABCA1

The ABCA1 gene, which is located on chromosome 9q31.1, it codes for an ATP-dependent protein that is found in the cell membrane tissues and fulfills different functions. The main one is the transport of cholesterol intracellular to the outside. This gene has been implicated in Tangier's disease, a rare disorder of lipoproteins, which runs with low levels of plasma HDL. ABCA1 has also been linked in other diseases such as Alzheimer's, Scott's syndrome and type 2 DM.¹⁹ A proposed mechanism for the pathogenesis of type 2 DM is that the dysfunction of the product produced by the ABCA1 gene produces

lipotoxicity of the beta cell, since the lipids accumulate in it producing toxicity, leading the beta cell to apoptosis and thus losing the secretion of insulin gradually.²⁰ In a study of Mexican Mestizos, it was found that the p.R230C mutation of the ABCA1 gene is not only associated with low levels of HDL but also with obesity, metabolic syndrome and type 2 DM.¹⁹

The p.R230C variant of the ABCA1 gene is located in exon 7 and this consists of a change of the nucleotide cytocine by a thymine, so that when translated into protein, a change of amino acids, arginine by cysteine occurs. An important finding of this variant is that it is associated with DM in older adults, particularly from early onset of adulthood (approximately 40 years). This was done in a study where people with the p.R230C mutation were diagnosed with type 2 DM at a mean age of 42 (+/-9.3 years).²⁰

IFNB2

Interleukin 6 (IL6), also known as interferon beta 2, is encoded by the IFNB2 gene which is found on chromosome 7p15.3. Interleukin 6 is an immunoregulatory cytokine that functions in the process of inflammation as well as in maturation of B cells and is an endogenous pyrogen. Recent studies have elucidated the fact that elevated inflammatory markers such as C-reactive protein or IL-6 are a risk factor for the development of type 2 DM.²¹ Thus IL6 alters glucose homeostasis probably by increasing Resistance to insulin in cells. It has been reported in research that the C174G polymorphism of the IFNB2 gene, up-modifies serum IL-6 concentrations as well as body mass index.²² It is well known that the risk of developing type 2 DM is significantly increased in people who are overweight, taking into account this, the C174G polymorphism is a major risk factor for the development of type 2 DM and in general, metabolic syndrome in people. According to a study of 704 older adults with two IFNB2 gene polymorphisms (C174G and -A598G), a significant association was found between the presence of these and DM, but not with insulin resistance. The synergy of these two mutations of IFNB2 gene is an independent risk factor for developing DM. The -174G and -598G alleles of these SNP, were significantly associated with type 2 diabetes (-174G: OR=1.51, p=.0096; -598G: OR=1.56, p=0.0069).²²

RETN

Resistin is a hormone synthesized mainly by adipose tissue and is primarily responsible for regulating the increase of mainly central fat tissue and as a result increased body mass. Resistin is encoded by the RETN gene which is found on chromosome 19p13.2 and is observed to be considerably over expressed during adipocyte differentiation. In a study conducted to compare serum concentrations of resistin between lean individuals and individuals with obesity, it was found that in obese individuals, resistin concentrations are significantly higher than in lean individuals.²³

To study the variability of mutations in the RETN gene and its relation to insulin resistance, a study was carried out in which 44 subjects with type 2 DM and 20 members of the families without diabetes were used. Three polymorphisms; -394C/G, C191G, and C585T were found to have a significant statistical association with insulin resistance and their interaction with body mass index (BMI), since people with those polymorphisms were found to have a BMI high (p=0.04).²⁴

In a case-control study (397 cases and 406 controls), which was performed in older adults with type 2 diabetes mellitus, it was possible to identify the participation of the -420G/G genotype in the genetic predisposition to type 2 DM (OR=1.97; p=0.008), as well as attainment Know that can accelerate the onset of diabetes 4.9 years.²³ A meta-analysis of more than 3000 subjects confirmed this association (p=0.013). Linkage disequilibrium analysis revealed that the -420G/G genotype itself was a primary variant determining T2DM susceptibility. It is known that the transcription factors Sp1 and 3 identify specific areas of DNA and among these is that of the -420C-G polymorphism. It was therefore possible to know that, in the over expression of the Sp1 or 3 transcription factors, high serum levels of resistin could be identified and therefore aggravated or predisposed to the development of type 2 DM.²⁵

GCK

The phosphorylation of glucose in the glycolysis pathway is catalyzed by a family of enzymes called hexokinases which are listed from I to IV. The hexokinase number IV is encoded by the GCK gene which is located on chromosome 7p13 composed of 12 exons and which is expressed only in liver and beta cells of the mammalian pancreas.²⁶ Any alteration of these enzymes result an inadequate metabolism of glucose.²⁷

In a study of a Japanese family, which was discovered by a previous study of a 59-year-old woman (family member) who had type 2 DM, a correlation was found between an onset of diabetes mellitus in Advanced ages and a nonsense mutation in exon five of the GCK p.R186X gene, which results in an incomplete gene product and therefore a genetic predisposing for the development of DM in the carriers of this mutation.²⁸

Recent research has shown that a -30G/A (SNP rs1799884) variant at the GCK gene promoter in the pancreatic beta cells, plus a combination of synergistic mutations with other genes results in type 2 DM in people carrying this mutation (OR=1.12, p=0.001). This case-control study was conducted in a Dutch population where cases had been diagnosed with type 2 DM between the ages of 53 and 57 years.²⁹ In particular, mutations of the GCK gene result in an ineffective hexokinase and cause a deterioration of one of the most important pathways of glucose, glycolysis.

KSR2

These gene is located in 12q24.22-q24.23, encodes by the kinase suppressor of ras-2, which regulated the pathway insulin. Different mutations are related to obesity, insulin resistance and impaired cellular fuel oxidation.³⁰ In Chinese elders aged 70-84 years from the aging arm of the Rugao Longevity and Aging Study, The pleiotropic effects of KSR2-rs7973260 on metabolic phenotypes were also explored, which were recently associated in a genome-wide association The presence of genotypes GA+AA of KSR2-rs7973260 was significantly higher in the diabetes groups than in control ones (45.8% vs. 37.9%, respectively). A allele of rs7973260 was associated with increased risk of diabetes with odds ratios of 1.384 (IC95% 1.022-1.875).³¹

PPARGC1A

The protein PGC-1 α encoded by this PPARGC1A gene (locus 4p15.2), which is a transcriptional co-activator that regulates the genes involved in energy metabolism. This protein interacts with PPAR gamma, which permits the interaction of this protein with

multiple transcription factors. PGC-1 α can regulate the activities of cAMP response element binding protein (CREB) and nuclear respiratory factors (NRFs). It stimulates and regulates mitochondrial biogenesis, and is a major factor that regulates muscle fiber. This protein may be also involved in controlling blood pressure, cholesterol homoeostasis, and the development of obesity or diabetes mellitus. Recently, in Korean population were investigated whether the PGC-1 α genotype (rs10517030 and rs10212638, rs10517032) affects the incidence DM with age range 40-65 years old. These Three variants were positively associated with T2DM prevalence. Single-nucleotide polymorphisms, rs10517030 and rs10517032, had strong association ($r^2=0.963$).³²

KCNQ1 and JMJD1C

KCNQ1 gene encodes a voltage-gated potassium channel required for depolarization phase of the cardiac action potential and beta cell. This gene is located in a region of chromosome 11p15.5-p15.4. JMJD1C with locus in 10q21.3 encoded by the protein TRIP-8, interacts with thyroid hormone receptors and contains a jumonji domain. It plays a role in the DNA-damage response pathway by demethylating the mediator of DNA damage checkpoint 1 (MDC1) protein. Data from the KoGES Study in 7,935 adults at baseline and 7,024 adults aged 40-69 show that the SNP rs10761745 (JMJD1C) and rs163177 (KCNQ1) were prospectively associated with DM, contribute to the risk of DM incidence among adults over the age of 40.³³ The G allele of SNP rs64771077 is a protector factor with OR 0.76 (p=6.06 X¹⁰⁻⁸). While the C allele of the SNP rs163177 is a risk factor with OR 1.18 (p= 9.65 X¹⁰⁻⁴).

MGEA5

The O-GlcNAc-selective N-acetyl- β -D glucosaminidase (O-GlcNAcase) is an enzyme encoded by meningioma-expressed antigen-5 (MGEA5) gene with locus on 10q24.1-q24.3. We have previously reported the linkage of type 2 diabetes and age at diabetes onset to an overlapping region on chromosome 10q in the San Antonio Family Diabetes Study. Recently in low-income Mexican Americans with type 2 diabetes. Association tests indicated significant association of the polymorphism Tsp5091 (MGEA5-14) with the traits DM (P=0.0128, relative risk= 2.77) and age at DM onset 43.5±8.9 years old (P=0.0017).³⁴

HNF1A

The protein HNF-1alpha encoded by this gene HNF1A, is a transcription factor required for the expression of several liver-specific genes. Gene HNF1A had a locus in 12q24.31. Defects in this gene are a cause of maturity onset diabetes of the young type 3 (MODY3) and also can result in the appearance of hepatic adenomas. The mutation p.G319S of the HNF1A gene increased odds of having type 2 diabetes across the whole study sample in adolescent Oji-Cree, the mutation p.G319S had specificity and positive predictive value of 97% and 95%, respectively, for developing type 2 DM by age 50, accelerated the median age of diabetes onset by about 7 yr (p<0.000).³⁵

STX1A

This gene encodes for syntaxin 1A, have a locus in 7q11.23. This gene product is a key molecule in ion channel regulation and synaptic exocytosis. Syntaxins possess a C-terminal transmembrane domain, SNARE domain (known as H3), and N-terminal regulatory domain (Habc). Syntaxin bind synaptotagmin in a calcium-dependent fashion

and interact with voltage dependent calcium and potassium channels. Syntaxin 1A is a candidate gene for type II diabetes mellitus, because it plays an important role in insulin secretion from the islet beta cells. In Japanese population it was identified and characterized coding exons of the syntaxin 1A gene and scanned the association with diabetes. Among the diabetic patients, age of onset in patients with CC genotype for the polymorphism of exon 3 (p.D68D, T to C), was lower than that in patients with the TT and TC genotypes [40.10 +/- 1.50 years old versus 44.20 +/- 0.58, p = 0.005].³⁶

FTO

This gene encode by nuclear protein of the AlkB related non-hem iron and 2-oxoglutarate-dependent oxygenase superfamily. Studies in mice and humans indicate a role in nervous and cardiovascular systems and a strong association with body mass index, obesity risk and type 2 diabetes. FTO has a locus in 16q12.2. In the Kazakh Asiatic population with DM and age range 40-63, the SNP rs9939609 of this gene, show association with ORR 1.52.³⁷

SLC30A8

The protein solute carrier family of 30 members, eight encoded by this gene, is a zinc efflux transporter. This gene had a locus in 8q24.11, is expressed at a high level only in the pancreas, particularly in islets of Langerhans. The encoded protein colocalizes with insulin in the secretory pathway granules of the secreting cell. Allelic variants confer susceptibility to DM. In the Kazakh Asiatic population with age range 40-63, the SNP rs13266634 of this gene, show association as a protector factor with ORR 0.68.³⁷

LGR5

This gene has a locus in 12q21.1. The protein encoded by this gene is a leucine-rich repeat-containing receptor (LGR) and is member of the G protein-coupled. The protein is a receptor for R-spondins and is involved in the Wnt signaling pathway, inhibiting clathrin-mediated endocytosis, plays a role in the postembryonic development. In the Kazakh Asiatic population with age range 40-63, the SNP rs7961581 of this gene, show association such as a risk factor with ORR 1.54.³⁷

FABP2

Intestinal fatty acid-binding protein 2 gene (locus 4q26) contains four exons. This gene has a polymorphism at codon 54 that identified an alanine-encoding allele and a threonine-encoding allele. Thr-54 protein is associated with increased fat oxidation and insulin resistance.³⁸ In the Kazakh Asiatic population with age range 40-63, the SNP rs1799883 of this gene, and show association such as a risk factor of DM with ORR 1.51.³⁷

Conclusion

The topic here presented is a new clinical vision for the gerontologist for learning more about the genetically aspect of DM. It allows knowing several genes involved in diabetes in the intermediate or older adult as risk factors. The present study shows the involvement of chromosomes 2, 4, 3, 7, 8, 9, 10, 11, 12, 16 and 19, with a total 18 genes implicated. These genes encodes for proteins with different functions, among them, factor transcription, insulin signaling, adipose tissue homeostasis or energy balance, inflammation, carbohydrate metabolism, insulin secretion, exocytosis, lipid transport, endocytosis as well as oxidative stress. Those factors should be corroborated in

replicate epidemiological studies. NeuroD1, INSR, ABCA1, AMP1 and RET genetic variations have a direct effect in development diabetes. How these candidate genes would be of interest to be studied in the elderly in future epidemiological research. DM in older adults can be treated in a timely manner and even prevented in people who present certain polymorphisms that cause the development of diabetes mellitus by themselves or that are at risk factor for their development, such as the rs13266634 of the gene SLC30A8 or SNP rs64771077 from JMJD1C gene, which are by diabetes a protector factor.³⁹⁻⁴¹

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None.

Conflict of interest

Authors declare that there are no conflicts of interest.

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