The Egyptian Journal of Medical Human Genetics (2015) 16, 227–231

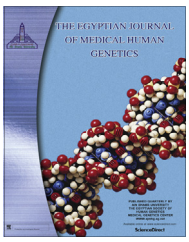
HOSTED BY

ELSEVIER

Ain Shams University

The Egyptian Journal of Medical Human Genetics

www.ejmhg.eg.net
www.sciencedirect.com



ORIGINAL ARTICLE

Lower HOMA-β values are detected among individuals with variant of E23K polymorphism of potassium inwardly-rectifying channel, subfamily J, member 11 (*KCNJ11*) gene

Raden Sunita [a,b,*], **Ahmad Hamim Sadewa** [a], **Arta Farmawati** [a]

[a] *Biochemistry Department, Faculty of Medicine, Gadjah Mada University, Yogyakarta, Indonesia*
[b] *Health Analyst Department, Poltekkes Kemenkes, Bengkulu, Indonesia*

Received 10 February 2015; accepted 23 March 2015
Available online 6 June 2015

KEYWORDS

T2DM;
E23K polymorphism of *KCNJ11*;
HOMA-β;
Individuals with family history of T2DM;
Individuals without family history of T2DM

Abstract *Background:* Type 2 Diabetes Mellitus (T2DM) is a multifactorial disease involving both genetic and also environmental factors. *Potassium inwardly-rectifying channel, subfamily J, member 11* (*KCNJ11*) gene, an ATP-sensitive potassium channel-coding gene, contributes to insulin secretion.

Objectives: This research aimed to investigate E23K polymorphism in *KCNJ11* gene and insulin secretion in individuals with family history of T2DM (cases) and without family history of T2DM (controls).

Method: This research was a case-control study involving 34 cases and 34 controls. E23K polymorphism of *KCNJ11* was detected with PCR-RFLP. All of the obtained data were statistically analyzed with *T*-test, Mann–Whitney *U*-test, Chi-Square and One-Way ANOVA.

Result: Frequency of AA genotype in individuals with family history of T2DM (41%) was higher than in individuals without family history of T2DM (6%) ($p = 0.001$). Frequency of A allele in individuals with family history of T2DM (68%) was higher than in individuals without family history of T2DM (38%) ($p = 0.001$). The risk of A allele in individuals with family history of T2DM was 3 times higher than in individuals without family history of T2DM ($p = 0.001$, OR 3.38, CI 95% 1.67–6.84). Homeostasis Model Assessment β (HOMA-β) values of AA genotype (85.44% ± 39.55) were lower than that of GA (212.20% ± 79.30) and GG (254.00% ± 61.98) genotypes ($p = 0.000$).

Conclusion: The risk of having A allele in individuals with family history of T2DM is higher than that in individuals without family history of T2DM. HOMA-β values of AA genotype are lower than that of GA and GG genotypes.

* Corresponding author at: Health Analyst Department, Polytechnic Health Ministry of Bengkulu, Indonesia.
E-mail address: zawarasunita@yahoo.co.id (R. Sunita).

Peer review under responsibility of Ain Shams University.

http://dx.doi.org/10.1016/j.ejmhg.2015.03.005

1. Introduction

Type 2 Diabetes Mellitus (T2DM) is a multifactorial disease involving both genetic and environment factors [1]. Diabetes mellitus is generally classified into 4 groups based on their pathogenesis with T2DM as the most frequent group (90–95%). T2DM is determined by the presence of insulin resistance and insulin deficiency or insulin secretions dysfunction [2]. Data from World Health Organization (WHO) showed that there were approximately 346 million individuals with DM in 2011 and would be elevated to 438 million in 2030. In Indonesia, individuals with DM were approximately 8.4 million in 2010 and is predicted to be raised to 21.3 million in 2030 [3]. Based on the data from Basic Health Research in 2013, prevalency of DM in Yogyakarta (2.6%) was the highest in number while that of Lampung was the lowest in number (0.7%) [4].

Potassium inwardly-rectifying channel, sub family J, member 11 (*KCNJ11*) is a gene encoding an ATP-sensitive potassium channel involved in the regulation of insulin secretion by pancreatic β cell [5]. K_{ATP} channels are open when extracellular glucose, and thus β cell metabolism, is low. Consequently, the cell membrane is hyperpolarized. This keeps voltage-gated Ca^{2+} channels closed, so that Ca^{2+} influx remains low and insulin secretion is inhibited. When extracellular glucose increases, metabolism generates ATP at the expense of Mg_{ADP}, there by closing K_{ATP} channels. This leads to membrane depolarization, opening of voltage-gated Ca^{2+} channels, Ca^{2+} influx and exocytosis of insulin [6].

The E23K polymorphism of *KCNJ11* gene is one of the many polymorphisms that contributes to the development of T2DM. It causes base substitution of guanine (G) to adenine (A), resulting in the alteration of amino acid encoded, i.e., glutamate (GAG) to lysine (AAG) mutation [7]. Individuals with A allele and family history of T2DM have a higher risk in the development of T2DM [8]. E23K polymorphism of *KCNJ11* gene affects K_{ATP} channel by decreasing channel closure time resulting in elevated activity of the channel and dysfunction of insulin secretion [9–11].

The objective of this research is to investigate the association of E23K polymorphism of *KCNJ11* gene and insulin secretion in individuals with family history of T2DM.

2. Subjects and methods

This research was a case control study with protocol approval by Medical and Health Research Ethics Committee (MHREC) of Faculty of Medicine (Number: KE/FK/274/EC), Gadjah Mada University. Case group consisted of 34 apparently healthy individuals with family history of T2DM, while control group consisted of 34 individuals without family history of T2DM. All of the individuals came from Diabetic Clinic of RSUP Dr. Sardjito, Yogyakarta. Inclusion criteria for case group male or female, apparently healthy, aged 19–39 years with family history of T2DM (in parents or grandparents), while controls were individuals without family history of T2DM and agreed to participate in this research. Individuals were excluded in this research if fasting blood glucose level ⩾ 126 mg/dL, obesity with body mass index ⩾ 25 kg/m^2, hypertension (systolic blood pressure ⩾ 140 mmHg, diastolic blood pressure ⩾ 90 mmHg), and in pregnancy.

Fasting blood glucose levels were determined using glucose oxydase-p-amino phenazone (GOD-PAP) spectrophotometry method, fasting blood insulin level by enzyme-linked immunosorbent assay (ELISA) obtained from DRG International, Inc. USA (EIA-2935). Homeostasis Model Assessment β (HOMA-β) value was determined using below formula to analyze fasting insulin level reflecting pancreatic-β cell function. Normal range of HOMA-β value is ⩾107% [12]. The formula [13] below is used to calculate HOMA-β value:

$$\text{HOMA-}\beta\ (\%) = \frac{\text{fasting insulin}(\mu\text{IU/mL}) \times 360}{\text{Fasting blood glucose}(\text{mg/dL}) - 63} \quad (1)$$

DNA isolation was performed using Wizard Genomic DNA Purification Kit (Promega, USA catalog number A1120). Polymorphism of *KCNJ11* E23K was analyzed with polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Partial amplification of *KCNJ11* was performed using forward primer 5′-CCA CCG AGA GGA CTC TGCA-′3 and reverse primer 5′-CTG GCG GGC ACG GTA CCT-′3 [20].

Amplification of DNA was performed in a mixture of 2 μL of DNA, 15 μL of master mix PCR (2× PCR buffer, 150 mM of dNTP, and 0.5 U of Taq DNA polymerase), 2 μL of primer (1 μL of primer forward and 1 μL of primer reverse), 11 μL of aquadest. PCR was performed as follows: an initial denaturation at 94 °C for 7 min, followed by 35 cycles of denaturation at 94 °C for 1 min, annealing at 63 °C for 1 min, extension at 72 °C for 1 min final extension at 72 °C for 7 min and cooling at 4 °C. The PCR (*Esco*) program was running for 156 min. The restriction digestion of PCR product (restriction fragment length polymorphism/RFLP) was performed in a mixture of 0.5 μL of *Ban II* endonuclease (Eco241) (*Thermo Scientific* Lot: 00184736), 1.0 μL of tango buffer, 4 μL of DNA and 4.5 μL of H_2O in a tube. Then it was spinned down for a minute at 3500 rpm. After that, the mixing formula was incubated for 16 h at 37 °C.

Electrophoresis was done with 3% of agarose for 45 min, 100 Volt, and visualized with ethidium bromide. The results

Table 1 Characteristics of individuals case and control.

Variable	Cases (n = 34)	Controls (n = 34)	p
Gender (M/F)	7/27	8/26	0.774*
Age (year)	23.94 ± 17.14	24.12 ± 3.57	0.562**
Systolic blood pressure (mmHg)	110.35 ± 9.44	110.88 ± 8.74	0.811*
Diastolic blood pressure (mmHg)	72.47 ± 6.98	75.06 ± 7.04	0.133*
Body height (cm)	158.79 ± 6.88	159.29 ± 7.31	0.772**
Body weight (kg)	52.65 ± 6.89	52.21 ± 6.80	0.791*
Body mass index (kg/m^2)	20.84 ± 1.92	20.61 ± 1.78	0.612*
Fasting blood glucose (mg/dL)	91.44 ± 12.32	90.74 ± 9.07	0.956**
Insulin (μIU/mL)	10.75 ± 6.35	16.26 ± 3.86	0.000*
Homeostasis Model Assessment β value (%)	147.09 ± 71.81	232.32 ± 88.88	0.000*

Data are expressed as Mean ± SD [30].
* Independent Sample T-test.
** Mann Whitney U-test.

were seen under UV light. GG genotype (wild type) was designated by a band at 179 bp, GA (mutant heterozygote) by three bands at 179 bp, 160 bp, and 19 bp) and AA (mutant homozygote) by two bands at 160 bp and 19 bp [20].

Data were tested for normality with Saphiro–Wilk test before being tested with Independent Sample *T*-test. If data were not normally-distributed, data transformation would be done, whereas if it is still not normally-distributed, Mann–Whitney U test would be done as an alternative test. The difference of genotype and allele frequency between with and the control group was analyzed using Chi-Square test. The risk of having A allele was determined using odds ratio. The difference of HOMA-β values between AA, GA, and GG genotypes were analyzed with One-Way ANOVA, continued with post hoc test. The *p* value of less than 0.05 was established as the significance level.

3. Results and discussion

*3.1. Frequency distribution of genotypes and alleles of E23K polymorphism in **KCNJ11** gene among individuals case and control*

Table 1 showed individuals characteristic in individuals with family history of T2DM (case) and without family history of T2DM (control) groups. Based on this data, there was no significant difference in distribution of gender, age, body weight, body height, body mass index, systolic blood pressure, diastolic blood pressure, and fasting blood glucose, between individual case and control. Fasting insulin level and HOMA-β values differed significantly between the two groups [30].

Frequency of each genotype and allele is presented in Table 2. The frequency of genotypes and alleles of E23K polymorphism in *KCNJ11* gene among case and control groups in Yogyakarta is variable due to the difference of genotype distribution in homozygote and heterozygote. Frequency of AA genotype in individuals with family history of T2DM (41%) was higher than in individuals without family history of T2DM (6%) ($p = 0.001$). Frequency of A allele in individuals with family history of T2DM (68%) was higher than in individuals without family history of T2DM (38%) ($p = 0.001$) [30].

Three genotypes (AA, GA, and GG) are shown in Fig 1.

Table 3 shows that the results of this study are in line with that of other studies done in the populations of West Asia (Palestine, Israel), East Asia (China, Japan), Middle Europe (Cekoslovakia) and West Europe (Germany). This study, along with previously mentioned studies, showed that AA genotype and A allele were highly prevalent among several different ethnicities. The difference of this study to other studies done in several other countries is that the subjects are individuals with and without family history of T2DM, where as those in another studies are normal individuals and those with T2DM.

Table 2 The distribution of genotype (AA, GA, GG) dan allele (A and G) *KCNJ11* gene in case and control groups.

		Cases ($n = 34$)	Controls ($n = 34$)	*p* OR (CI 95%)
Genotype	AA	14 (41%)	2 (6%)	0.001*
	GA	18 (53%)	22 (65%)	
	GG	2 (6%)	10 (29%)	
Genotype	AA and GA	32 (94%)	24 (71%)	0.011*
	GG	2 (6%)	10 (29%)	6.66 (1.33–33.27)
Allele	A	46 (68%)	26 (38%)	0.001*
	G	22 (32%)	42 (62%)	3.38 (1.67–6.84)

* Chi-Square test [30].

3.2. E23K polymorphism in KCNJ11 gene as risk factor of having A allele in individuals with and without family history of T2DM

Table 2 shows that individuals with family history of T2DM (case) possess 6.66 times higher risk of having AA and GA genotype than those without T2DM (controls) ($p = 0.001$, OR 6.66, 95% CI = 1.33–33.27). The risk of having A allele in cases is 3.38 times higher than that of controls ($p = 0.001$, OR 3.38, 95% CI = 1.67–6.84). The odds ratio in this study is the risk of having A allele, meanwhile those of another studies are the risk of having T2DM [30].

The individuals in this study were grouped according to the presence of A allele and the family history of T2DM. The risk stratification is as follows: (1) Low risk (no A allele and no family history of T2DM; (2) Moderate risk (no A allele, but with the presence of family history of T2DM, or having A

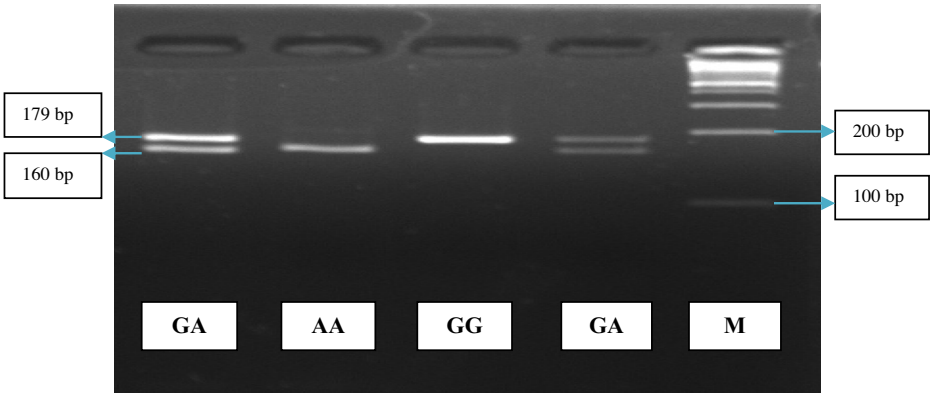


Figure 1 The genotyping results of E23K polymorphism in *KCNJ11* gene. M = marker (Geneaid); GG genotype = *wild type* (179 bp), GA = heterozygous mutant (179 bp, 160 bp, and 19 bp (unseen)) and AA = homozygous mutant (160 bp and 19 bp (unseen)) [30].

Table 3 The frequency of GG, GA, and AA genotype of E23K polymorphism in *KCNJ11* gene among different ethnicities.

Ethnicity (area)	Research individuals	Genotypes			Total *n*	*p*
		AA (%)	GA (%)	GG (%)		
Caucasian (Czech Republic and Slovakia Republic) [14]	Normal	18 (16)	47 (42)	48 (42)	113	0.05
	T2DM	4 (3)	85 (55)	66 (42)	155	
Asian (Japan) [15]	Normal	107 (12)	396 (45)	386 (43)	889	0.004
	T2DM	127 (14)	446 (49)	333 (37)	906	
Caucasian (Germany) [16]	Normal	134 (12)	492 (46)	444 (42)	1070	0.003
	T2DM	47 (15)	156 (48)	121 (37)	324	
Han (Shanghai) [17]	Normal	288 (15)	930 (49)	692 (36)	1910	0.017
	T2DM	329 (18)	863 (47)	656 (35)	1848	
Han (Beijing) [18]	Normal	57 (15)	174 (45)	156 (40)	387	0.001
	T2DM	87 (22)	189 (48)	120 (30)	396	
Ashkenazi (Israel) [19]	Normal	100 (12)	404 (48)	339 (40)	843	0.52
	T2DM	79 (14)	266 (46)	228 (40)	573	
Palestinian (Gaza) [9]	Normal	3 (3)	29 (29)	68 (68)	100	0.000
	T2DM	15 (15)	43 (43)	42 (42)	100	
Javanese (Yogyakarta) [20]	Normal	8 (20)	22 (55)	10 (25)	40	0.572
	T2DM	12 (30)	20 (55)	8 (20)	40	
Javanese* (Yogyakarta) [30]	Without T2DM History	2 (6)	22 (65)	10 (29)	34	0.001
	With T2DM history	14 (41)	18 (53)	2 (6)	34	

* Javanese: People of Java island in Indonesia [30].

allele, but no family history of T2DM); (3) High risk (having both A allele and family history of T2DM). In one study done in United States of America, the individuals were grouped based on a sole criterion of the presence of T2DM in family history. The risk stratification in that study is as follows: (1) Low risk (no family history of T2DM); (2) Moderate risk (one of the parents and also one of the grandparents has T2DM, or both grandparents in either paternal or maternal lineage have T2DM); (3) High risk (both parents have T2DM, or one of both parents plus both grandparents have T2DM) (Table 4).

3.3. The difference of HOMA-β value in individuals with AA, GA, and GG genotype in this study

The difference of HOMA-β value in this research is presented in Table 5. The value of HOMA-β with AA genotype (85.44% ± 39.55) was lower than GA genotype (212.20% ± 79.30) and GG genotype (254.00% ± 61.98). One-Way ANOVA analysis showed a significant difference of HOMA-β value between AA, GA and GG genotypes ($p = 0.000$) [30].

The insulin secretion of individuals in this study was determined using HOMA-β as a model to study pancreatic β-cell function. The results of this study showed that there was a statistically significant difference of HOMA-β values between individuals with AA, GA, and GG genotype. These results are in line with one study [24] which shows the influence of genetic factor on insulin biosynthesis and secretion. Another study [25] also shows that β-cell functional decline is associated with low HOMA-β value. The decrease in insulin secretion may be caused by several factors, and one of them is genetic factor [26]. Genetic factor has a significant contributory role on the prevalence and incidence of T2DM in a family [27].

Table 5 shows that HOMA-β value in AA genotype is lower than those of GA and GG genotypes because E23K polymorphism in *KCNJ11* gene causes amino acid change, by which glutamic acid (GAG) is substituted for lysine (AAG). The amino acid change subsequently changes its physicochemical properties (negative charge is substituted for positive charge, and acidic amino acid is substituted for basic amino acid). This electrical charge substitution causes diminished closure response of K_{ATP} channel to the presence of ATP, thus prolongs the opening of the channel. This event will eventually lead to decreased insulin secretion [28,29].

Table 4 T2DM Risk studies in several countries which are based on the presence of family history.

Countries	Study results	Data	Individuals	Total *n*
United States of America (USA) [21]	Low risk: 2.791 (64.2%) Moderate risk: 843 (19.4%) High risk: 711 (16.4%)	Questionnaire	Cases* Controls**	4.345
United States of America (USA) [22]	Low risk: 9.938 (67.5%) Moderate risk: 3.437 (23.4%) High risk: 1.340 (9.1%)	Questionnaire	Cases* Controls**	14.715
Chicago [23]	Low risk: 1.426 (61%) Moderate risk: 643 (28%) High risk: 261 (11%)	Questionnaire	Cases* Controls**	2.330
Yogyakarta (Indonesia) [30]	Low risk: 10 (14.7%) Moderate risk: 26 (38.23%) High risk: 32 (47.06%)	Questionnaire & PCR-RFLP	Cases* Controls**	68

* Individuals with family history of T2DM (cases).
** Individuals without family history of T2DM (controls) [30].

Table 5 The difference of HOMA-β among individuals in this research.

Variable	Mean ± SD			*p*
	AA (n = 16)	GA (n = 40)	GG (n = 12)	
HOMA-β (%)	85.44 ± 39.55	212.20 ± 79.30	254.00 ± 61.98	0.000*

* One-Way ANOVA [30].

4. Conclusion

The frequency of AA genotype, A allele, and risk of having A allele in the case group were higher than those in controls. The HOMA-β value in individuals having AA genotype was lower than that of individuals with GA and GG genotype.

References

[1] Weber MB, Frank RO, Staimez LR, Ali MK, Narayan KMV. Type 2 diabetes in Asians: prevalence, risk factors, and effectiveness of behavioral intervention at individual and population levels. Annu Rev Nutr 2012;32:417–39.

[2] American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2012;3(1):S64–71.

[3] Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047–53.

[4] Department of Research and development in Health of Health Ministry Republic Indonesia. Basic Health Research. 2013;1–306.

[5] Riedel MJ, Boora P, Steckley D, deVries G, Light PE. Kir6.2 polymorphism sensitize β-cell ATP-sensitive potassium channel to activation by Acyl CoAs: a possible cellular mechanism for increased susceptibility to type 2 diabetes. Diabetes 2003;52:2630–5.

[6] Proks P, Ashcroft FM. Modeling K_{ATP} channel gating and its regulation. Biophys Mol Biol 2008;99:7–19.

[7] Li YY. The KCNJ11 E23K gene polymorphism and type 2 diabetes mellitus in the Chinese Han population: a meta-analysis of 6109 individuals. Mol Biol Rep 2013;40:141–6.

[8] Abed AA, Ayesh BM, Hamdona OM. Single nucleotide polymorphism E23K of KCNJ11 gene and other risk factors associated with type-2 diabetes mellitus in Gaza. Int J Chem Life Sci 2013;02(04):1146–52.

[9] Schwanstecher C, Neugebaeur B, Schulz M, Schwanstecher M. The common single nucleotide polymorphism E23K in K(IR)6.2 sensitize β-cell ATP-sensitive potassium channels toward activation through nucleoside diphosphates. Diabetes 2002;51:363–7.

[10] Koster JC, Permutt MA, Nichols CG. Perspective in diabetes: diabetes and insulin secretion the ATP-sensitive K^+ channel (K_{ATP}) connection. Diabetes 2005;54:3065–72.

[11] Vilareal DT, Koster JC, Robertson H, Akrouh A, Miyake K, Bell GI, et al. Kir6.2 variant E23K increases ATP-sensitive K^+ channel activity and is associated with impaired insulin release and enhanced insulin sensitivity in adults with normal glucose tolerance. Diabetes 2009;58:1869–78.

[12] Ciampelli M, Leoni F, Cucinelli F, Mancuso F, Panunji S, De Gaetano A, et al. Assessment of insulin sensitivity from measurements in the fasting state and during an oral glucose tolerance test in polycystic ovary syndrome and menopausal patients. J Clin Endocrinol Metabol 2005;90:1398–406.

[13] Tabara Y, Osawa H, Kawamoto R, Onuma H, Shimizu I, Miki T, et al. Replication study of candidate genes associated with type 2 diabetes based on genome-wide screening. Diabetes 2009;58:493–8.

[14] Cejkova P, Novota P, Cerna M, Kolostova K, Novakova D, Kucera P, et al. KCNJ11 E23K polymorphism and diabetes mellitus with adult onset in Czech patients. Folia Biol (Praha) 2007;53:173–5.

[15] Sakamoto Y, Inoue H, Keshavarz P, Miyawaki K, Yamaguchi Y, Moritani M, et al. SNPs in the KCNJ11–ABCC8 gene locus are associated with type 2 diabetes and blood pressure levels in the Japanese population. J Hum Genet 2007;52:781–93.

[16] Fischer A, Fischer E, Ohlig MM, Schulze M, Hoffmann K, Weickert MO, et al. KCNJ11 E23K affects diabetes risk and is associated with the disposition index. Diabetes Care 2008;31:87–9.

[17] Zhou D, Zhang D, Liu Y, Zhao T, Chen Z, Liu Z, et al. The E23K variation in the KCNJ11 gene is associated with type 2 diabetes in Chinese and East Asian population. J Hum Genet 2009;54:433–5.

[18] Wang F, Han XY, Ren Q, Zhang XY, Han LC, Luo YY, et al. Effect of genetic variants in *KCNJ11, ABCC8, PPARG* and *HNF4A* loci on the susceptibility of type 2 diabetes in Chinese Han population. Chin Med J (Engl) 2009;122(20):2477–82.

[19] Neuman RJ, Wasson J, Atzmon G, Wainstein J, Yerushalmi Y, Cohen J, et al. Gene-gene interactions lead to higher risk for development of type 2 diabetes in an Ashkenazi Jewish population. Plos One 2010;5(3):1–6.

[20] Prabandari AS. Polimorfisme p. E23K gena potassium inwardly-rectifying channel sub family J member 11 (KCNJ11) sebagai faktor risiko diabetes melitus type 2 di Yogyakarta (thesis). Postgraduate Program, Faculty of Medicine, Gadjah Mada University 2009;1–80.

[21] Hariri S, Yoon PW, Qureshi N, Valdez R, Scheuner MT, Khoury MJ. Family history of type 2 diabetes: a population-based screening tool for prevention? Genet Med 2006;8:102–8.

[22] Valdez R, Yoon PW, Liu T, Khoury MJ. Family history and prevalence of diabetes in the U.S. population. The 6-year results from the National Health and Nutrition Examination survey (1999–2004). Diabetes Care 2007;30:2517–22.

[23] Acheson LS, Wang C, Zyzanski SJ, Lynn A, Ruffin MT, Gramling R, et al. Family history and perceptions about risk and prevention for chronic diseases in primary care: a report from the family healthware™ impact trial. Genet Med 2010;12(4):212–8.

[24] Radha V, Vimaleswaran KS, Deepa R, Mohan V. The genetics of diabetes mellitus. Indian J Med Res 2003;117:225–38.

[25] Chen G, Li M, Xu Y, Chen N, Huang H, Liang J. Impact of family history of diabetes on β-cell function and insulin resistance among Chinese with normal glucose tolerance. Diabetes Tech Therap 2012;14(6):463–8.

[26] Defronzo RA. Phatogenesis of type 2 diabetes mellitus. Med Clin N Am 2004:787–835.

[27] Bener A, Yousafzai MT, Al-hamaq A, Mohammad A, Defronzo R. Parental transmission of type 2 diabetes mellitus in a highly endogamous population. World J Diabetes 2013;4(2):40–6.

[28] Haider S, Antcliff JF, Proks P, Sansom MSP, Aschrof FM. Focus on kir6 a key component of the ATP-sensitive potassium channel. J Mol Cell Cardio 2005;38:927–36.

[29] Bryan J, Vila-Carriles W, Zhao G, Babenko AP, Agular-Bryan L. Toward linking structure with function in ATP-sensitive K^+ channels. Diabetes 2004;53(3):S104–12.

[30] Sunita. Polimorfisme E23K gen potassium inwardly rectifying channel sub family J member 11 (KCNJ11) dan sekresi insulin pada individu dengan riwayat keluarga diabetes melitus tipe 2 (thesis). Postgraduate Program, Faculty of Medicine, Gadjah Mada University 2014;1–83.