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Original Article

Association Analysis between Genes' Variants for Regulating Mitochondrial Dynamics and Fasting Blood Glucose Level

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Maintenance of fasting blood glucose levels is important for glucose homeostasis. Disruption of feedback mechanisms are a major reason for elevations of glucose level in blood, which is a risk factor for type 2 diabetes mellitus that is mainly caused by malfunction of pancreatic beta-cell and insulin. The fasting blood glucose level has been known to be influenced by genetic and environmental factors. Mitochondria have many functions for cell survival and death: glucose metabolism, fatty acid oxidation, ATP generation, reactive oxygen species (ROS) metabolism, calcium handling, and apoptosis regulation. In addition to these functions, mitochondria change their morphology dynamically in response to multiple signals resulting in fusion and fission. In this study, we aimed to examine association between fasting blood glucose levels and variants of the genes that are reported to have functions in mitochondrial dynamics, fusion and fission, using a cohort study. A total 416 SNPs from 36 mitochondrial dynamics genes were selected to analyze the quantitative association with fasting glucose level. Among the 416 SNPs, 4 SNPs of *PRKACB*, 13 SNPs of *PPP3CA*, 6 SNPs of *PARK2*, and 3 SNPs of *GDAP1* were significantly associated. In this study, we were able to confirm an association of mitochondrial dynamics genes with glucose levels. To our knowledge our study is the first to identify specific SNPs related to fasting blood glucose level.

Key Words: Mitochondrial dynamics, Genetic variation, SNP, Glucose level, Association study

INTRODUCTION

Maintenance of fasting blood glucose levels is important for glucose homeostasis. Disruption of feedback mechanism is a major reason for elevations of glucose level in blood, which is a risk factor for type 2 diabetes mellitus that is mainly caused by malfunction of pancreatic beta-cell and insulin (Prokopenko et al., 2009; Mason et al, 2007; Jin et al, 2014). Fasting blood glucose levels are influenced by genetic and environmental factors, but genetic factors that contribute to heritability remain elusive (Watanabe et al., 1999).

Mitochondria are essential organelles in most eukaryotic cells for maintaining cellular homeostasis. Performances of mitochondria contribute to cell survival and death: glucose metabolism, fatty acid oxidation, ATP generation, reactive oxygen species (ROS) metabolism, calcium handling, and apoptosis regulation (McBride et al., 2006; In et al., 2013). Mitochondrion is also an organelle that is continually re-modeled by fusion and fission in response to a multitude of signals (Chan, 2006; Hoppins et al., 2007). Therefore, morph-

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ology of mitochondria is cycling between fusion and fission. This phenomenon is referred to as "mitochondrial dynamics", and it has been known that many regulating proteins are involved in mitochondrial dynamics (Chan, 2006; Hoppins et al., 2007). Currently, the regulating proteins are divided to five groups: 1) fusion shaping, 2) fission shaping, 3) fusion regulation, 4) fission regulation, and 5) fusion and fission regulation (Chan, 2006; Hoppins et al., 2007; Cerveny et al., 2007; Benard & Karbowski, 2009; Otera et al., 2013). In this study, we examined the association between fasting blood glucose levels and variants of the genes that are involved in mitochondrial dynamics, fusion and fission, using a cohort study.

MATERIALS AND METHODS

Subjects

Korean subjects within the Korean Association REsource (KARE) study were described in more detail by another study (Cho et al., 2009). Briefly, the participants were recruited from two community-based epidemiological cohorts; the rural community of Ansung city and the urban community of Ansan city. The cohorts are composed of 8842 people (4,183 men and 4,659 women) aged from 40 to 69 years old. Both cohorts were used for studies conducted in 2001 as part of the Korean Genome Epidemiology Study (KoGES). For accurate analysis of blood glucose, 1291 subjects who had been treated with drugs were excluded and the remaining 7551 subjects (3,747 men and 3,804 women) were finally investigated. The basic characteristics of the subjects are described in Table 2. Fasting glucose levels of the subject were obtained from the data in the KARE study. This study has been approved by the Institutional Review Board of the Korean National Institute of Health (KNIH). Written informed consent was obtained from all of subjects.

Genotyping and selection of SNPs

The detailed genotyping, quality control processes and quantitative traits were described in a previous report (Cho et al., 2009). Briefly, DNA samples were isolated from all of the participants' peripheral blood and genotyped using the Affymetrix Genome-Wide Human SNP array 5.0 (Affymetrix, Inc., Santa Clara, CA, USA). The accuracy of the genotyping was calculated by Bayesian Robust Linear Modeling using the Mahalanobis Distance (BRLMM) algorithm (Rabbee & Speed, 2006). Samples that had genotyping accuracies were lower than 98%, high missing genotype call rates (≥4%), high heterozygosity (>30%), or gender biases were excluded.

We selected candidate regulating genes for mitochondrial dynamics from several review papers (Chan, 2006; Hoppins et al., 2007; Cerveny et al., 2007; Benard and Karbowski, 2009; Otera et al., 2013). These selected 47 genes are listed in Table 1. For selection of the SNPs from the KARE data, we included gene boundary region - 5 kb upstream and downstream of the first and last exons, respectively - according to NCBI human genome build 36. Through the search processes, we were able to collect the 416 SNPs out of the 36 genes (Table 1). The clinical information and genotype data that we used were graciously provided by the Center for Genome Science, KNIH, Korea Center for Disease Control (KCDC).

Statistical analysis

Most of the statistical analyses were performed using PLINK version 1.07 (http://pngu.mgh.harvard.edu/~purcell/plink) and PASW Statistics version 18.0 (SPSS Inc., Chicago, IL, USA). The 417 SNPs selected from 37 genes were analyzed for linear regression using fasting blood glucose level as a quantitative trait. All association tests were performed under the additive genetic model. Age, gender, body mass index (BMI) and cohorts were included as covariates in the analyses. Standard statistical significance ($P < 0.05$) was determined by the two-tailed Student's *t*-test between males and females.

RESULTS

Selection of SNPs of the regulating genes for mitochondrial dynamics out of KARE data

In this association study, we collected the 47 genes that had regulating functions toward mitochondrial dynamics (fusion, fission, fusion-regulation, fission-regulation and fusion fission-regulation) based on the current literature.

Table 1. Information about the SNPs in the mitochondrial dynamics regulating genes

Function	Gene	Gene product	Gene description	Chr.	No. of SNPs*
Fusion-shaping	*MFN1*	Mfn1	Mitofusin 1	3	4
	MFN2	Mfn2	Mitofusin 2	1	1
	OPA1	Opa1	Optic atrophy 1	3	13
Fission-shaping	*DNM1L*	Drp1	Dynamin 1-like	12	12
	FIS1	Fis1	Fission 1 homolog	7	0
	MFF	Mff	Mitochondrial fission factor	2	2
Fusion-regulation	*AFG3L1*	AFG3L1	AFG3 ATPase family gene 3-like 1/m-AAA protease	16	0
	AFG3L2	AFG3L2	AFG3 ATPase family gene 3-like 2/m-AAA protease	18	6
	BCL2L1	Bcl-xL	BCL2-like 1	20	0
	LETM1	LETM1	Leucine zipper-EF-hand containing transmembrane protein 1	4	1
	MIB1	MIB	Mindbomb homolog 1	18	6
	OMA1	OMA1	OMA1 homolog, zinc metallopeptidase	1	12
	PARL	Parl	Presenilin associated, rhomboid-like	3	4
	PHB2	Prohibitin 2	Prohibitin 2	12	1
	PLD6	MitoPLD	Phospholipase D family, member 6	17	0
	SPG7	Paraplegin	Spastic paraplegia 7/m-AAA protease	16	7
	STOML2	SLP-2	Stomatic (EPB72)-like 2	9	1
	YME1L1	Yme1L	YME1-like 1	10	4
Fission-regulation	*BCL2L2*	Bcl-w	BCL2-like 2	14	1
	CAMKK1	CaM-kinase 1	Calcium/calmodulin-dependent protein kinase kinase 1, alpha	17	3
	CDK1	CDK1	Cyclin-dependent kinase 1	10	7
	CDK5	CDK5	Cyclin-dependent kinase 5	7	2
	DAP3	DAP3	Death associated protein 3	1	1
	GDAP1	GDAP1	Ganglioside-induced differentiation-associated protein 1	8	5
	GHITM	MICS1	Growth hormone inducible transmembrane protein	10	2
	MTFP1	MTFP1	Mitochondrial fission process 1	22	2
	MUL1	MAPL	Mitochondrial E3 ubiquitin protein ligase 1	1	0
	PPP3CA	Calcineurin	Protein phosphatase 3, catalytic subunit, alpha isozyme	4	47
	PPP3CB	Calcineurin	Protein phosphatase 3, catalytic subunit, beta isozyme	10	1
	PPP3CC	Calcineurin	Protein phosphatase 3, catalytic subunit, gamma isozyme	8	10
	PRKACA	PKA	Protein kinase, cAMP-dependent, catalytic, alpha	19	0
	PRKACB	PKA	Protein kinase, cAMP-dependent, catalytic, beta	1	10
	PRKACG	PKA	Protein kinase, cAMP-dependent, catalytic, gamma	9	3
	RAB32	Rab32	RAB32, member RAS oncogene family	6	1
	SENP5	SENP5	SUMO1/sentrin specific protease 5	3	0
	SH3GLB1	Bif-1/ Endophilin B1	SH3-domain GRB2-like endophilin B1	1	2
	SMCR7	MiD49	Mitochondrial dynamics protein of 49 kDa	17	0
	SMCR7L	MiD51	Mitochondrial dynamics protein of 51 kDa	22	0
	SUMO1	SUMO1	SMT3 suppressor of mif two 3 homolog 1	2	0

Table 1. Information about the SNPs in the mitochondrial dynamics regulating genes (Continued)

Function	Gene	Gene product	Gene description	Chr.	No. of SNPs*
Fission-regulation	*TIMM8A*	DDP/Timm8a	Translocase of inner mitochondrial membrane 8 homolog A	X	1
	TMEM11	TMEM11/PMI	Transmembrane protein 11	17	1
	USP30	USP30	Ubiquitin specific peptidase 30	12	2
Fusion- and fission-regulation	*BAX*	Bax	BCL2-associated X protein	19	1
	BAK1	Bak	BCL2-antagonist/killer 1	6	2
	MARCH5	MARCH-V/ MITOL	Membrane-associated ring finger (C3HC4) 5	10	4
	PINK1	Pink1	PTEN induced putative kinase 1	1	8
	PARK2	Parkin	Parkinson disease 2, parkin	6	227

Abbreviation: Chr., chromosome. *The SNPs were selected from the KARE data based on their locations within the gene boundary (5 kb upstream and downstream of the first and last exons, respectively) according to NCBI human genome build 36.

Table 2. Basic characteristics of the subjects in the KARE study cohort

Characteristics	Total	Males	Females	*P* value*
Number of subjects	7551	3747	3804	
Age (*M* years ± SD)	51.44 ± 8.78	52.17 ± 8.68	51.59 ± 8.89	0.113
Body mass index (BMI) (*M* kg/m^2 ± SD)	24.42 ± 3.07	24.14 ± 2.90	24.68 ± 3.22	< 0.0001
Fasting blood glucose (*M* mg/dl ± SD)	87.21 ± 21.51	89.89 ± 23.29	84.58 ± 19.24	< 0.0001

Abbreviations: M, mean value; SD, standard deviation.*Significant differences in characteristics between the males and females subjects were determined by the two-tailed Student's *t*-test.

Among the 47 genes, 36 genes had SNPs, which were 416 SNPs based on KARE genotype data (Table 1). Among the 36 genes, 10 genes had only one SNP each and the rest 26 genes had more than two SNPs. In particular, 227 SNPs were available in *PARK2*.

Basic subject characteristics

Basic characteristics of the 7,551 subjects in the KARE study cohort are shown in Table 1. The subjects provided the glucose level showed following characteristics: sex ratio was approximately equal, the mean age was 51.44 ± 8.78 years, mean BMI and fasting blood glucose were 24.42 ± 3.07 kg/m^2 and 87.21 ± 21.51 mg/dL, respectively. Significant differences between the males and females in BMI and fasting blood glucose were observed as determined by the two-tailed Student's *t*-test. In females, higher value of BMI and lower value of fasting blood glucose were observed compared with those of males (Table 2).

Association between the SNPs from *PRKACB*, *PPP3CA*, *PARK2* and *GDAP1* genes and the fasting blood glucose levels

We conducted statistical analyses toward the 416 SNPs of 36 genes to investigate quantitative association with fasting blood glucose levels of the KARE subjects. Through the analyses, 4 SNPs of *PRKACB*, 13 SNPs of *PPP3CA*, 6 SNPs of *PARK2*, and 3 SNPs of *GDAP1* were found to have significant association with the fasting blood glucose level (Table 3). The SNPs of the rest 32 genes were not associated with the fasting blood glucose level. Minor allele frequency, genotype counts, genotype glucose, effect size and *P* values of the associated SNPs were listed in Table 3. The three associated genes (*PRKACB*, *PPP3CA*, and *GDAP1*) have been known to have functions for fission-regulation in mito-

Table 3. The significant SNPs in the mitochondrial dynamics regulating genes associated with fasting blood glucose levels in the KARE study cohort

Gene	SNP	A1	MAF	Function & RegulomeDB results	Genotype counts			Genotype glucose (*M* mg/dl ± SD)			Additive model	
					A1/A1	A1/A2	A2/A2	A1/A1	A1/A2	A2/A2	Effect size	*P* value
PRKACB	rs6701486	C	0.409	Intron, 7	1213	3562	2593	86.78 ± 20.17	86.64 ± 20.78	88.21 ± 23.03	-1.03 ± 0.36	3.8×10^{-3}
	rs2642186	C	0.488	Intron, 6	1747	3678	1939	87.04 ± 20.49	86.62 ± 20.71	88.48 ± 23.76	-0.81 ± 0.35	0.021
	rs12723299	A	0.320	Intron, 5	740	3207	3421	86.58 ± 20.95	86.66 ± 20.74	87.87 ± 22.31	-0.99 ± 0.38	8.5×10^{-3}
	rs2134648	T	0.322	Intron, 7	745	3224	3390	86.55 ± 20.89	86.65 ± 20.74	87.91 ± 22.36	-1.04 ± 0.38	5.9×10^{-3}
PPP3CA	rs3804359	G	0.045	Intron, 7	27	606	6731	103.10 ± 54.28	88.02 ± 26.94	87.07 ± 20.70	2.11 ± 0.83	0.011
	rs2850359	T	0.340	Intron, 5	878	3285	3205	86.65 ± 18.18	86.74 ± 19.47	87.86 ± 24.17	-0.75 ± 0.37	0.041
	rs3804406	A	0.335	Intron, 7	857	3253	3256	86.71 ± 18.24	86.72 ± 19.55	87.85 ± 24.02	-0.74 ± 0.37	0.044
	rs3804408	C	0.340	Intron, 6	877	3286	3203	86.65 ± 18.19	86.73 ± 19.47	87.86 ± 24.17	-0.75 ± 0.37	0.039
	rs2583405	A	0.355	Intron, 6	955	3344	3065	86.87 ± 18.45	86.66 ± 19.47	87.93 ± 24.33	-0.72 ± 0.36	0.047
	rs2850963	C	0.458	Intron, 1f	1566	3624	2175	87.19 ± 19.52	86.46 ± 19.04	88.49 ± 26.21	-0.70 ± 0.35	0.045
	rs2850336	A	0.341	Intron, 6	880	3295	3191	86.62 ± 18.17	86.73 ± 19.45	87.89 ± 24.21	-0.78 ± 0.37	0.034
	rs1441433	T	0.460	Intron, 1f	1599	3585	2164	87.02 ± 19.23	86.53 ± 19.25	88.43 ± 25.93	-0.76 ± 0.35	0.029
	rs1530259	C	0.463	Intron, 6	1611	3613	2123	86.77 ± 19.04	86.86 ± 20.17	88.19 ± 25.23	-0.74 ± 0.35	0.033
	rs2850370	G	0.461	Intron, 6	1606	3609	2151	86.73 ± 18.99	86.86 ± 20.12	88.19 ± 25.20	-0.77 ± 0.35	0.027
	rs2583399	A	0.461	Intron, 1f	1609	3606	2152	86.71 ± 18.99	86.85 ± 20.13	88.20 ± 25.20	-0.78 ± 0.35	0.024
	rs2850371	C	0.464	Intron, 6	1623	3614	2128	86.75 ± 18.98	86.84 ± 20.14	88.22 ± 25.24	-0.77 ± 0.35	0.026
	rs2583394	G	0.464	Intron, 1f	1631	3607	2129	86.74 ± 18.95	86.83 ± 20.15	88.23 ± 25.24	-0.79 ± 0.35	0.023
PARK2	rs2209247	T	0.044	Intron, 5	13	620	6735	87.00 ± 15.53	89.02 ± 26.50	87.05 ± 21.00	1.71 ± 0.85	0.046
	rs10455889	G	0.466	Intron, 7	1622	3627	2118	86.22 ± 18.68	86.91 ± 20.32	88.50 ± 25.16	-1.14 ± 0.35	1.1×10^{-3}
	rs9365294	G	0.467	Intron, 7	1625	3630	2113	86.12 ± 18.43	86.97 ± 20.45	88.47 ± 25.14	-1.15 ± 0.35	9.1×10^{-4}
	rs9356011	T	0.205	Intron, 7	333	2349	4686	88.05 ± 29.70	87.89 ± 21.92	86.81 ± 20.59	0.88 ± 0.43	0.041
	rs9364660	G	0.489	Intron, 4	1770	3662	1935	86.65 ± 19.48	86.84 ± 19.88	88.43 ± 25.79	-0.84 ± 0.35	0.015
	rs7758475	C	0.459	Intron, 5	1551	3654	2159	86.79 ± 19.86	86.80 ± 19.69	88.21 ± 25.26	-0.70 ± 0.35	0.047

Table 3. The significant SNPs in the mitochondrial dynamics regulating genes associated with fasting blood glucose levels in the KARE study cohort (Continued)

Gene	SNP	A1	MAF	Function & RegulomeDB results	Genotype counts			Genotype glucose (*M* mg/dl ± SD)			Additive model	
					A1/A1	A1/A2	A2/A2	A1/A1	A1/A2	A2/A2	Effect size	*P* value
GDAP1	rs6993852	G	0.280	Downstream, 6	615	2927	3824	87.40 ± 20.69	88.17 ± 23.95	86.46 ± 19.55	0.90 ± 0.38	0.019
	rs4738451	A	0.279	Downstream, 7	621	2880	3823	87.38 ± 20.61	88.10 ± 23.92	86.45 ± 19.56	0.88 ± 0.38	0.022
	rs4738452	C	0.281	Downstream, 7	619	2927	3816	87.34 ± 20.65	88.17 ± 23.95	86.47 ± 19.57	0.88 ± 0.38	0.021

Age, gneder, body mass index (BMI) and cohorts were included as covariates in additive genetic model. Abbreviatins: A1, minor allele; A2, major allele; M, mean value; MAF, minor allele frequency; SD, standard deviation. RegulomeDB score were presented the changes by SNP such as 1f: eQTL+TF binding/DNase peak, 4: TF binding+DNase peak, 5: TF binding or DNase peak, and 6: other and 7: none.

chondrial dynamics, and *PARK2* gene has been known to have function for fusion- and fission-regulation (Table 1). The ratio of significantly associated SNPs out of total analyzed SNPs were 40% in *PRKACB* (4 among the 10 SNPs), 27.7% in *PPP3CA* (13 among the 47 SNPs), 2.64% in *PARK2* (6 among the 227 SNPs), and 60% in *GDAP1* (3 among the 5 SNPs). The minor allele of 4 SNPs in *PRKACB* were uniformly associated with lower glucose levels, and the minor allele of 3 SNPS in *GDAP1* were uniformly associated with higher glucose levels (Table 3).

DISCUSSION

In this study, we used 416 SNPs of 36 genes that are related to mitochondrial dynamics or shaping and found 26 SNPs of 4 genes had significant association with fasting blood glucose levels. The 4 genes are *PRKACB*, *PPP3CA*, *PARK2* and *GDAP1*. The *PRKACB* (protein kinase, cAMP-dependent, catalytic, beta) gene located on chromosome 1p36.1 encodes a catalytic subunit of cAMP (cyclic AMP)-dependent protein kinase, which mediates signaling through cAMP. And the cAMP signaling is important to a number of processes, including cell proliferation and differentiation (Gamm et al., 1996). The PRKACB are involved in the regulation of lipid and glucose metabolism as well as regulation of fission in the mitochondrial dynamics (Otera et al., 2013). But, there is no published article yet that showed association of SNPs of *PRKACB* with glucose or type 2 diabetes.

The *PPP3CA* (protein phosphatase 3 catalytic subunit alpha) gene located on chromosome 4q24 encodes calcineurin isozyme. Calcineurin is a calcium and calmodulin dependent serine/threonine protein phosphatase, and also involved in fission regulation of mitochondrial shaping (Otera et al., 2013). There is one report showed association of the genetic variation of *PPP3CA* with type 2 diabetes (Diabetes Genetics Initiative of Broad Institute of Harvard et al., 2007).

The *PARK2* (parkin RBR E3 ubiquitin protein ligase) gene located on chromosome 6q25.2-q27 encodes a component of a multiprotein E3 ubiquitin ligase complex that mediates the targeting of substrate proteins for proteasomal degradation. Mutations in this gene are known to cause Parkinson disease and autosomal recessive juvenile Parkinson disease related to mitochondrial dysfunction (Hang et al., 2015). Moreover, there are many reports that *PARK2* gene associated with various metabolic traits including insulin-related traits (Ober et al., 2009; Pollin et al., 2008; Hiura et al., 2010; Paternoster et al., 2011; Jin et al., 2014).

The *GDAP1* (ganglioside induced differentiation associated protein 1) gene located on chromosome 8q21.11 encodes a member of the ganglioside-induced differentiation-associated protein family, which may play a role in a signal transduction pathway during neuronal development. Mutations in this gene have been known to associate with various forms of Charcot-Marie-Tooth Disease and neuropathy related to mitochondrial fission (Kabzinska et al., 2014; Huber et al., 2013). There is limited article that showed association of *GDAP1* gene with the obesity-related traits (Fox et al., 2007).

It has been known that mitochondrial dynamics genes are involved in glucose metabolism. In this study, association of the genetic variants of the mitochondrial dynamics genes with fasting blood glucose level was newly analyzed. We were able to find that 4 genes (*PRKACB*, *PPP3CA*, *PARK2*, and *GDAP1*) among the mitochondrial dynamics genes might have more relationship with fasting blood glucose level the other genes. Interestingly, 3 genes (*PRKACB*, *PPP3CA*, and *GDAP1*) are involved in fission-regulation which suggests that genes for regulating mitochondrial fission may have more roles for regulating blood glucose.

There are some limitations to this current study. Since KARE is a pre-genotyping data for genome-wide association study, the 36 genes had available SNPs from the candidate 46 genes for mitochondrial dynamics. Therefore, it may be difficult to reach a definitive conclusion for all of the mitochondrial dynamics genes at this time. We hope to examine the association of the 10 unanalyzed genes when the new genotyping data becomes available. Although limited number of the genes was involved, this study presents a systemic approach concerning mitochondrial dynamics with blood glucose level.

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Conflict of interest

The authors declare that they have no competing interests.

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