Association of a polymorphism of *BTN2A1* with chronic kidney disease in individuals with or without hypertension or diabetes mellitus

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Abstract. Hypertension and diabetes mellitus are important risk factors for chronic kidney disease (CKD). We previously showed that the C→T polymorphism (rs6929846) of *BTN2A1* was significantly associated with myocardial infarction. The purpose of the present study was to examine an association of rs6929846 of *BTN2A1* with CKD in individuals with or without hypertension or diabetes mellitus, thereby contributing to the personalized prevention of CKD in such individuals separately. The study population comprised 7,542 unrelated individuals, including 2,289 subjects with CKD [estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2] and 5,253 controls (eGFR ≥60 ml/min/1.73 m^2) with or without hypertension or diabetes mellitus. The Chi-square test, a multivariable logistic regression analysis with adjustment for covariates, as well as a stepwise forward selection procedure revealed that the C→T polymorphism (rs6929846) of *BTN2A1* was significantly associated with CKD in normotensive individuals, in diabetic individuals and in individuals with hypertension and diabetes mellitus, or without either condition, with the *T* allele representing a risk factor for CKD. Stratification of subjects based on hypertension or diabetes mellitus may thus be important in order to achieve personalized prevention of CKD with the use of genetic information.

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Introduction

Chronic kidney disease (CKD) is an important global public health problem because of its high morbidity in the general population. Recent studies suggest that the risk for death is increased in individuals who have impaired renal function, but do not require dialysis, compared to those who have preserved renal function (1,2). Disease prevention is an important strategy for reducing the overall burden of CKD and end-stage renal disease (ESRD), and the identification of markers for CKD risk is essential both for risk prediction and for potential intervention to reduce the chance of future cardiovascular complications (3).

Several risk factors for progression of CKD have been proposed (4), with hypertension and diabetes mellitus having been recognized as important risk factors for CKD (5-7) as well as for coronary heart disease and stroke. In addition to these conventional risk factors, recent studies have shown the importance of genetic factors and of interactions between multiple genes and environmental factors in the development of CKD (8,9). Although recent genome-wide association studies (GWASs) (10-15) have implicated several loci and candidate genes in predisposition to CKD or ESRD in Caucasians or African-American populations, the genes that contribute to genetic susceptibility to CKD in Asian populations remain to be identified definitively.

We previously showed that the C→T polymorphism (rs6929846) of *BTN2A1* was significantly associated with myocardial infarction in Japanese individuals by a GWAS (16). Given that CKD is an important risk factor for coronary heart disease, the association of rs6929846 with myocardial infarction may be attributable, at least in part, to its effect on susceptibility to CKD. We also showed that genetic variants that confer susceptibility to CKD differ between individuals with or without metabolic syndrome (17), between individuals with or without type 2 diabetes mellitus (18), between individuals with or without hypertension (8), or between individuals with different lipid profiles (19). To further examine whether the association of a genetic variant with CKD is influenced by the absence or presence of hypertension or diabetes mellitus, we performed an association study for rs6929846 of *BTN2A1* and CKD in 7,542 Japanese individuals with or without hypertension or diabetes mellitus.

Materials and methods

Study population. The study population comprised 7,542 unrelated Japanese individuals (4,382 men and 3,160 women) who either visited the outpatient clinics of or were admitted to the participating hospitals (Gifu Prefectural General Medical Center, Gifu; Gifu Prefectural Tajimi Hospital, Tajimi; Hirosaki University Hospital and Hirosaki Stroke Center, Hirosaki; Japanese Red Cross Nagoya First Hospital, Nagoya; and Inabe General Hospital, Inabe, Japan) between October 2002 and March 2009 because of various symptoms or for an annual health checkup, or who were recruited to population-based prospective cohort studies of aging and age-related diseases in Nakanojo, Kusatsu and Tokyo, Japan.

Glomerular filtration rate was estimated with the use of the simplified prediction equation derived from that in the Modification of Diet in Renal Disease Study and proposed by the Japanese Society of Nephrology (20): eGFR (ml/min/ 1.73 m^2) = 194 x [age (years)]$^{-0.287}$ x [serum creatinine (mg/dl)]$^{-1.094}$ [x 0.739 if female]. The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative guidelines recommend a diagnosis of CKD if eGFR is <60 ml/min/1.73 m^2 (3). Non-linear relations between GFR and the risk of adverse outcomes, such as death, cardiovascular events and hospitalization, have been demonstrated, with an increased risk being associated with an eGFR of <60 ml/min/1.73 m^2 (1). We thus adopted the criterion of an eGFR of <60 ml/min/1.73 m^2 for the diagnosis of CKD in the present study. On the basis of this criterion, 2,289 subjects (1,394 men and 895 women) were diagnosed with CKD. The control subjects comprised 5,253 individuals (2,988 men and 2,265 women) whose eGFR was ≥60 ml/min/1.73 m^2.

Subjects with CKD and controls either had or did not have conventional risk factors for CKD, including hypertension (systolic blood pressure of ≥140 mmHg, diastolic blood pressure of ≥90 mmHg, or taking of antihypertensive medication), diabetes mellitus [fasting plasma glucose level of ≥6.93 mmol/l, blood glycosylated hemoglobin (HbA1c) content of ≥6.5%, or taking of antidiabetes medication], or hypercholesterolemia (serum total cholesterol concentration of ≥5.72 mmol/l, or taking of lipid-lowering medication). The study protocol complied with the Declaration of Helsinki and

was approved by the Committees on the Ethics of Human Research of Mie University Graduate School of Medicine, Hirosaki University Graduate School of Medicine, Gifu International Institute of Biotechnology, Tokyo Metropolitan Institute of Gerontology and participating hospitals. Written informed consent was obtained from each participant.

Genotyping of rs6929846 single nucleotide polymorphism (SNP). Venous blood (7 ml) was collected into tubes containing 50 mmol/l ethylenediaminetetraacetic acid (disodium salt), and genomic DNA was isolated with a kit (Genomix; Talent, Trieste, Italy). Genotypes of rs6929846 of *BTN2A1* were determined at G&G Science (Fukushima, Japan) by a method that combines the polymerase chain reaction (PCR) and sequence-specific oligonucleotide probes with suspension array technology (Luminex, Austin, TX, USA). Primers, probes and other PCR conditions for the genotyping of rs6929846 have been described previously (16).

Statistical analysis. Quantitative data were compared between subjects with CKD and controls by the unpaired Student's t-test. Categorical data were compared by the Chi-square test. Allele frequencies were estimated by the gene counting method, and the Chi-square test was used to identify departures from Hardy-Weinberg equilibrium. Genotype distribution of rs6929846 was compared between subjects with CKD and controls by the Chi-square test. When a P-value for genotype distribution was <0.05, multivariable logistic regression analysis was performed with adjustment for covariates. Multivariable logistic regression analysis was thus performed with CKD as a dependent variable, and independent variables, including age, gender (0, woman; 1, man), body mass index (BMI), smoking status (0, non-smoker; 1, smoker), history of hypertension, diabetes mellitus or hypercholesterolemia (0, no history; 1, positive history) and genotype of rs6929846. P-values, odds ratios and 95% confidence intervals were calculated. Genotype was assessed according to dominant, recessive and additive genetic models. Additive models included the additive 1 (heterozygotes vs. wild-type homozygotes) and additive 2 (variant homozygotes vs. wild-type homozygotes) models, which were analyzed simultaneously with a single statistical model. We also performed a stepwise forward selection procedure to examine the effects of genotype as well as of other covariates on CKD; genotype was examined according to a dominant model on the basis of statistical significance in the multivariable logistic regression analysis. The P-levels for inclusion in and exclusion from the model were 0.25 and 0.1, respectively. A P-value of <0.05 was considered statistically significant. Statistical significance was examined by two-sided tests performed with JMP version 6.0 and JMP Genomics version 3.2 software (SAS Institute, Cary, NC, USA).

Results

Characteristics of subjects. The characteristics of the subjects are shown in Tables I-III. In all analyses, serum concentrations of creatinine were greater and eGFRs were lower in subjects with CKD than in controls. For hypertensive individuals, age and the prevalence of diabetes mellitus were greater, whereas the percentage of smokers and diastolic blood pressure were

Table I. Characteristics of subjects with chronic kidney disease (CKD) and controls among individuals with or without hypertension.

Characteristic	With hypertension			Without hypertension		
	CKD	Controls	P-value	CKD	Controls	P-value
No. of subjects	1,662	3,241		627	2,012	
Age (years)	71.0±8.7	66.9±9.7	<0.0001	70.6±9.4	63.8±11.0	<0.0001
Gender (male/female, %)	62.2/37.8	60.8/39.2	0.3409	57.4/42.6	50.6/49.4	0.0026
Body mass index (kg/m²)	23.7±3.4	23.8±3.4	0.1455	23.1±3.3	23.0±3.2	0.3631
Current or former smoker (%)	26.3	31.4	0.0002	27.3	27.9	0.7655
Systolic blood pressure (mmHg)	150±25	149±23	0.5850	121±12	122±12	0.3656
Diastolic blood pressure (mmHg)	80±15	82±14	<0.0001	70±10	71±9	0.0156
Diabetes mellitus (%)	43.5	40.1	0.0237	28.4	24.5	0.0530
Hypercholesterolemia (%)	27.7	27.2	0.7131	27.1	28.2	0.5854
Serum creatinine (μmol/l)	118.9±131.5	62.4±12.5	<0.0001	90.7±23.5	61.5±12.2	<0.0001
eGFR (ml/min/1.73 m²)	47.5±11.8	78.9±15.6	<0.0001	51.1±7.5	79.0±17.9	<0.0001

Quantitative data are the means ± SD. eGFR, estimated glomerular filtration rate.

Table II. Characteristics of subjects with chronic kidney disease (CKD) and controls among individuals with or without diabetes mellitus.

Characteristic	With diabetes mellitus			Without diabetes mellitus		
	CKD	Controls	P-value	CKD	Controls	P-value
No. of subjects	901	1,794		1,388	3,459	
Age (years)	70.1±9.2	66.9±9.6	<0.0001	71.3±8.7	65.1±10.7	<0.0001
Gender (male/female, %)	66.3/33.7	65.7/34.3	0.7799	57.4/42.6	52.3/47.7	0.0012
Body mass index (kg/m²)	23.9±3.6	23.9±3.5	0.8711	23.3±3.3	23.3±3.2	0.8712
Current or former smoker (%)	27.3	33.4	0.0011	26.1	28.3	0.1120
Hypertension (%)	80.2	72.5	<0.0001	67.7	56.1	<0.0001
Fasting plasma glucose (mmol/l)	9.08±3.68	9.15±3.62	0.4282	5.36±0.84	5.30±0.84	0.0139
Blood glycosylated hemoglobin (%)	6.67±1.76	6.65±1.76	0.4595	5.25±0.35	5.23±0.38	0.0288
Hypercholesterolemia (%)	26.2	27.7	0.4049	28.4	27.5	0.5444
Serum creatinine (μmol/l)	118.6±114.2	62.3±12.6	<0.0001	106.3±112.7	62.0±12.2	<0.0001
eGFR (ml/min/1.73 m²)	46.9±11.8	80.5±16.6	<0.0001	49.5±10.2	78.1±16.4	<0.0001

Quantitative data are the means ± SD. eGFR, estimated glomerular filtration rate.

lower in subjects with CKD than in controls. For normotensive individuals, age and the frequency of male subjects were greater, whereas diastolic blood pressure was lower in subjects with CKD than in controls (Table I).

For diabetic individuals, age and the prevalence of hypertension were greater, whereas the percentage of smokers was lower in subjects with CKD than in controls. For non-diabetic individuals, age, the frequency of male subjects, the prevalence of hypertension, fasting plasma glucose level and blood glycosylated hemoglobin content were greater in subjects with CKD than in controls (Table II).

For individuals with hypertension and diabetes mellitus, age was greater, whereas the percentage of smokers and diastolic blood pressure was lower in subjects with CKD than in controls. For individuals without hypertension or diabetes

mellitus, age and the frequency of male subjects were greater in subjects with CKD than in controls (Table III).

Association of rs6929846 of BTN2A1 with CKD. Comparison of genotype distributions by the Chi-square test revealed that the C→T polymorphism (rs6929846) of *BTN2A1* was significantly (P<0.05) associated with CKD in normotensive individuals, in diabetic individuals and in individuals with hypertension and diabetes mellitus, or without either condition (Table IV).

Multivariable logistic regression analysis with adjustment for age, gender, BMI, smoking status and the prevalence of hypertension, diabetes mellitus or hypercholesterolemia revealed that rs6929846 of *BTN2A1* was significantly associated with CKD in normotensive individuals (dominant

Table III. Characteristics of subjects with chronic kidney disease (CKD) and controls among individuals with hypertension and diabetes mellitus, or without either condition.

Characteristic	With hypertension and diabetes mellitus			Without hypertension or diabetes mellitus		
	CKD	Controls	P-value	CKD	Controls	P-value
No. of subjects	723	1,301		449	1,519	
Age (years)	70.1±9.0	67.2±9.4	<0.0001	70.6±9.1	63.1±11.3	<0.0001
Gender (male/female, %)	66.5/33.5	65.9/34.1	0.7650	54.3/45.7	45.7/54.3	0.0014
Body mass index (kg/m²)	24.0±3.6	24.1±3.5	0.2262	23.0±3.2	22.9±3.1	0.7429
Current or former smoker (%)	26.7	33.1	0.0025	26.3	25.8	0.8405
Systolic blood pressure (mmHg)	152±26	150±23	0.4352	121±12	122±12	0.3550
Diastolic blood pressure (mmHg)	80±15	82±15	0.0047	70±10	72±9	0.0637
Fasting plasma glucose (mmol/l)	9.03±3.58	9.19±3.59	0.1511	5.22±0.85	5.16±0.85	0.1251
Blood glycosylated hemoglobin (%)	6.63±1.73	6.67±1.72	0.7277	5.24±0.34	5.20±0.36	0.1464
Hypercholesterolemia (%)	27.1	28.1	0.6220	29.0	28.8	0.9396
Serum creatinine (μmol/l)	124.5±126.3	62.3±12.6	<0.0001	89.1±23.3	61.3±12.0	<0.0001
eGFR (ml/min/1.73 m²)	46.1±12.4	80.4±16.4	<0.0001	51.5±7.2	78.4±18.0	<0.0001

Quantitative data are the means ± SD. eGFR, estimated glomerular filtration rate.

Table IV. Genotype distributions of rs6929846 significantly associated with chronic kidney disease (CKD) among individuals with or without hypertension or diabetes mellitus as determined by the Chi-square test.

Gene	SNP	CKD (%)	Controls (%)	P-value
Without hypertension				
BTN2A1	C→T			0.0057
	CC	528 (84.2)	1,789 (88.9)	
	CT	93 (14.8)	215 (10.7)	
	TT	6 (1.0)	8 (0.4)	
With diabetes mellitus				
BTN2A1	C→T			0.0159
	CC	716 (79.5)	1,498 (83.5)	
	CT	174 (19.3)	286 (15.9)	
	TT	11 (1.2)	10 (0.6)	
With hypertension and diabetes mellitus				
BTN2A1	C→T			0.0488
	CC	570 (78.8)	1,075 (82.6)	
	CT	144 (19.9)	219 (16.8)	
	TT	9 (1.3)	7 (0.6)	
Without hypertension or diabetes mellitus				
BTN2A1	C→T			0.0139
	CC	382 (85.1)	1,366 (89.9)	
	CT	63 (14.0)	148 (9.7)	
	TT	4 (0.9)	5 (0.4)	

and additive 1 models), in diabetic individuals (dominant and additive 1 models) and in individuals with hypertension and diabetes mellitus (dominant model), or without either condition (dominant and additive 1 models), with the *T* allele representing a risk factor for CKD (Table V).

A stepwise forward selection procedure was performed to examine the effects of genotype for rs6929846 of *BTN2A1* as well as of age, gender, BMI, smoking and the prevalence of hypertension, diabetes mellitus or hypercholesterolemia on CKD (Table VI). For normotensive individuals, age, BMI, *BTN2A1* genotype (dominant model) and male gender, in descending order of statistical significance, were significant (P<0.05) and independent determinants of CKD. For diabetic individuals, age, hypertension, *BTN2A1* genotype (dominant model) and male gender were significant and independent determinants of CKD. For individuals with hypertension and

Table V. Multivariable logistic regression analysis of rs6929846 significantly associated with chronic kidney disease by the Chi-square test among individuals with or without hypertension or diabetes mellitus.

Gene	SNP	Dominant		Recessive		Additive 1		Additive 2	
		P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)
Without hypertension									
BTN2A1	C→T	0.0016	1.55 (1.18-2.02)	0.0983		0.0039	1.50 (1.14-1.98)	0.0805	
With diabetes mellitus									
BTN2A1	C→T	0.0149	1.30 (1.05-1.60)	0.0620		0.0345	1.26 (1.02-1.56)	0.0505	
With hypertension and diabetes mellitus									
BTN2A1	C→T	0.0440	1.27 (1.01-1.61)	0.0883		0.0856		0.0755	
Without hypertension or diabetes mellitus									
BTN2A1	C→T	0.0061	1.59 (1.14-2.20)	0.1350		0.0124	1.54 (1.09-2.14)	0.1167	

Multivariable logistic regression analysis was performed with adjustment for age, gender, body mass index (BMI), smoking status and the prevalence of diabetes mellitus and hypercholesterolemia in normotensive individuals; for age, gender, BMI, smoking status and the prevalence of hypertension and hypercholesterolemia in diabetic individuals; for age, gender, BMI, smoking status and the prevalence of hypercholesterolemia in individuals with hypertension and diabetes mellitus, or without either condition. OR, odds ratio; CI, confidence interval.

Table VI. Effects of genotype and other characteristics on chronic kidney disease among individuals with or without hypertension or diabetes mellitus determined by a stepwise forward selection procedure (P<0.05).

Variable	P-value	R^2
Without hypertension		
Age	<0.0001	0.0694
BMI	0.0002	0.0048
BTN2A1C (*CT + TT* vs. *CC*)	0.0010	0.0037
Male gender	0.0152	0.0021
With diabetes mellitus		
Age	<0.0001	0.0228
Hypertension	<0.0001	0.0050
BTN2A1C (*CT + TT* vs. *CC*)	0.0105	0.0019
Male gender	0.0242	0.0015
With hypertension and diabetes mellitus		
Age	<0.0001	0.0185
Male gender	0.0312	0.0018
BTN2A1C (*CT + TT* vs. *CC*)	0.0370	0.0016
Smoking	0.0423	0.0016
Without hypertension or diabetes mellitus		
Age	<0.0001	0.0818
BMI	0.0040	0.0039
BTN2A1C (*CT + TT* vs. *CC*)	0.0052	0.0037
Male gender	0.0169	0.0027
Smoking	0.0349	0.0021

A stepwise forward selection procedure was performed to examine the effects on CKD of the genotype for rs6929846 of *BTN2A1* as well as of age, gender, body mass index (BMI), smoking and the prevalence of diabetes mellitus and hypercholesterolemia in normotensive individuals; of age, gender, BMI, smoking and the prevalence of hypertension and hypercholesterolemia in diabetic individuals; of age, gender, BMI, smoking and the prevalence of hypercholesterolemia in individuals with hypertension and diabetes mellitus, or without either condition. R^2, contribution rate.

diabetes mellitus, age, male gender, *BTN2A1* genotype (dominant model) and smoking were significant and independent determinants of CKD. For individuals without hypertension or diabetes mellitus, age, BMI, *BTN2A1* genotype (dominant model), male gender and smoking were significant and independent determinants of CKD.

Discussion

We examined the possible relation of rs6929846 of *BTN2A1* to the prevalence of CKD in Japanese individuals with or without hypertension or diabetes mellitus. Our association study with three steps of analysis (Chi-square test, multivariable logistic regression analysis with adjustment for covariates and stepwise forward selection procedure) revealed that the C→T polymorphism (rs6929846) of *BTN2A1* was significantly associated with CKD in normotensive individuals, in diabetic individuals and in individuals with hypertension and diabetes

mellitus, or without either condition. Prediction of the risk for CKD on the basis of genetic variants is useful to decide how aggressively to target the clinical risk factors that are currently amenable to treatment.

The butyrophilin, subfamily 2, member A1 gene (*BTN2A1*) is a member of the BTN2 subfamily of genes, which encode proteins belonging to the butyrophilin protein family. While the butyrophilin family was originally identified by the ability to aid production of milk fat globules (21), many butyrophilin and butyrophilin-like family of proteins were shown to regulate immune function, and polymorphisms in the coding sequences were related to predisposition to inflammatory diseases (22). Genomic mapping of disease loci identified a SNP (rs2076530) in the butyrophilin-like 2 gene (*BTNL2*) that increases the risk for sarcoidosis (23). Polymorphisms in *BTNL2* in linkage disequilibrium with HLA-DRB were related to other inflammatory diseases, all of which can be characterized by inappropriate T-cell activation (24-26). Our previous study (16) showed that the *T* allele increased the transcription activity of *BTN2A1* and the overexpression of *BTN2A1* decreased the expression of elastin mRNA and increased the mRNA expression of matrix metallopeptidase 3 and interleukin 5. These observations suggest that the *T* allele of rs6929846 of *BTN2A1* may accelerate vascular inflammation (16).

The development of CKD is affected by various factors, including conventional risk factors, such as hypertension and diabetes mellitus, as well as oxidative stress and vascular inflammation. Dyslipidemia, that frequently coexists with renal disease, has been shown as an important factor in nephron damage (27). Large artery stiffness may also be related to the progression of CKD (28). We have now shown that the C→T polymorphism (rs6929846) of *BTN2A1* is significantly associated with CKD in Japanese normotensive individuals, in individuals with hypertension and diabetes mellitus, or without either condition. The enhancement of vascular inflammation by the *T* allele of rs6929846 may account for its association with CKD, although the underlying molecular mechanisms remain unclear.

In conclusion, our results suggest that genetic variants that confer susceptibility to CKD differ among individuals with or without hypertension or diabetes mellitus. Stratification of subjects based on hypertension or diabetes mellitus may thus be important in order to achieve personalized prevention of CKD with the use of genetic information. Validation of our findings will require their replication with independent subject panels of other ethnic groups, as well as long-term follow-up to examine the association of rs6929846 of *BTN2A1* with the prevalence of CKD.

Acknowledgements

References

1. Go AS, Chertow GM, Fan D, McCulloch CE and Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 351: 1296-1305, 2004.
2. Ruilope LM, Salvetti A, Jamerson K, *et al*: Renal function and intensive lowering of blood pressure in hypertensive participants of the hypertension optimal treatment (HOT) study. J Am Soc Nephrol 12: 218-225, 2001.
3. National Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 39 (Suppl 1): 1-266, 2002.
4. Yamagata K, Ishida K, Sairenchi T, *et al*: Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. Kidney Int 71: 159-166, 2007.
5. Norris KC, Tareen N, Martins D and Vaziri ND: Implications of ethnicity for the treatment of hypertensive kidney disease, with an emphasis on African Americans. Nat Clin Pract Nephrol 4: 538-549, 2008.
6. Sarafidis PA, Li S, Chen SC, *et al*: Hypertension awareness, treatment, and control in chronic kidney disease. Am J Med 121: 332-340, 2008.
7. James MT, Hemmelgarn BR and Tonelli M: Early recognition and prevention of chronic kidney disease. Lancet 375: 1296-1309, 2010.
8. Yoshida T, Kato K, Yokoi K, *et al*: Association of candidate gene polymorphisms with chronic kidney disease in Japanese individuals with hypertension. Hypertens Res 32: 411-418, 2009.
9. Kottgen A, Kao WH, Hwang SJ, *et al*: Genome-wide association study for renal traits in the Framingham Heart and Atherosclerosis Risk in Communities Studies. BMC Med Genet 9: 49, 2008.
10. Chambers JC, Zhang W, Lord GM, *et al*: Genetic loci influencing kidney function and chronic kidney disease. Nat Genet 42: 373-375, 2010.
11. Köttgen A, Pattaro C, Böger CA, *et al*: New loci associated with kidney function and chronic kidney disease. Nat Genet 42: 376-384, 2010.
12. Köttgen A, Glazer NL, Dehghan A, *et al*: Multiple loci associated with indices of renal function and chronic kidney disease. Nat Genet 41: 712-717, 2009.
13. Kao WH, Klag MJ, Meoni LA, *et al*; Family Investigation of Nephropathy and Diabetes Research Group: MYH9 is associated with nondiabetic end-stage renal disease in African Americans. Nat Genet 40: 1185-1192, 2008.
14. Gharavi AG, Yan Y, Scolari F, *et al*: IgA nephropathy, the most common cause of glomerulonephritis, is linked to 6q22-23. Nat Genet 26: 354-357, 2000.
15. Hanson RL, Craig DW, Millis MP, *et al*: Identification of PVT1 as a candidate gene for end-stage renal disease in type 2 diabetes using a pooling-based genome-wide single nucleotide polymorphism association study. Diabetes 56: 975-983, 2007.
16. Yamada Y, Nishida T, Ichihara S, *et al*: Association of a polymorphism of BTN2A1 with myocardial infarction in East Asian populations. Atherosclerosis (In Press).
17. Yoshida T, Kato K, Fujimaki T, *et al*: Association of a polymorphism of the apolipoprotein E gene with chronic kidney disease in Japanese individuals with metabolic syndrome. Genomics 93: 221-226, 2009.
18. Yoshida T, Kato K, Yokoi K, *et al*: Association of genetic variants with chronic kidney disease in Japanese individuals with type 2 diabetes mellitus. Int J Mol Med 23: 529-537, 2009.
19. Yoshida T, Kato K, Yokoi K, *et al*: Association of genetic variants with chronic kidney disease in individuals with different lipid profiles. Int J Mol Med 24: 233-246, 2009.
20. Matsuo S, Imai E, Horio M, *et al*: Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 53: 982-992, 2009.
21. Ogg SL, Weldon AK, Dobbie L, Smith AJ and Mather IH: Expression of butyrophilin (Btn1a1) in lactating mammary gland is essential for the regulated secretion of milk-lipid droplets. Proc Natl Acad Sci USA 101: 10084-10089, 2004.
22. Arnett HA, Escobar SS and Viney JL: Regulation of costimulation in the era of butyrophilins. Cytokine 46: 370-375, 2009.
23. Valentonyte R, Hampe J, Huse K, *et al*: Sarcoidosis is associated with a truncating splice site mutation in BTNL2. Nat Genet 37: 357-364, 2005.

24. Mochida A, Kinouchi Y, Negoro K, et al: Butyrophilin-like 2 gene is associated with ulcerative colitis in the Japanese under strong linkage disequilibrium with HLA-DRB1*1502. Tissue Antigens 70: 128-135, 2007.
25. Orozco G, Eerligh P, Sánchez E, et al: Analysis of a functional BTNL2 polymorphism in type 1 diabetes, rheumatoid arthritis, and systemic lupus erythematosus. Hum Immunol 66: 1235-1241, 2005.
26. Traherne JA, Barcellos LF, Sawcer SJ, et al: Association of the truncating splice site mutation in BTNL2 with multiple sclerosis is secondary to HLA-DRB1*15. Hum Mol Genet 15: 155-161, 2006.
27. Keane WF, Kasiske BL, O'Donnell MP and Kim Y: Hypertension, hyperlipidemia, and renal damage. Am J Kidney Dis 21 (Suppl 2): 43-50, 1993.
28. Fassett RG, D'Intini V, Healy H, et al: Assessment of arterial stiffness, oxidative stress and inflammation in acute kidney injury. BMC Nephrol 10: 15, 2009.