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Association of the ABCA1 gene polymorphisms with type 2 DM in a Japanese population☆

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Abstract

To examine the association of the ATP-binding cassette transporter 1 (ABCA1) gene with type 2 diabetes (DM), we studied genetic polymorphisms of the ABCA1 gene including its linkage disequilibrium (LD) and haplotype analyses using a Japanese population. A sample set (DM:72, IGT:75, and NGT:227) was genotyped with 34 SNPs distributed from the promoter region to the last exon of the ABCA1 gene. LD between SNPs was assessed in pairwise manner. Among 13 LD blocks constructed, an LD block at the 5′-region showed a significant difference in the haplotype distribution between the study groups (NGT vs. IGT + DM: overall $p = 0.0180$; NGT vs. DM: 0.0001). Fisher's exact probability test (NGT vs. DM) showed a significant association of the haplotype 2 of the LD block ($p = 0.0001$), with an odds ratio (OR) of 2.53 (95%CI:1.62–4.12). Diplotype analysis also showed a significant association of the diplotypes with the haplotype 2 (OR:2.59, 95%CI:1.48–4.54, $p = 0.0013$).

Keywords: ABCA1; Community-based case-control study; SNP; LD block; Haplotype analysis; Diplotype analysis; Genetics; HDL cholesterol; The Funagata study

The ATP-binding cassette transporter 1 (ABCA1) gene encodes a key protein regulating the efflux of lipid from peripheral cells to HDL [1–4]. The defect of the ABCA1 gene causes rare forms of genetic HDL deficiencies such as Tangier disease and familial hypoalphalipoproteinemia (FHA) [1–9]. Many common genetic variations in the ABCA1 gene have been reported to be associated with abnormalities of serum lipid levels, especially decreased serum levels of HDL-cholesterol (HDL-C), as well as a risk of coronary artery disease/atherosclerosis (CAD) [8–15]. However, no study has been reported with regard to its association with type 2 diabetes (DM). Since decreased serum levels of HDL-C are often observed in DM and this condition is considered to be involved in the mechanisms for insulin resistance [16–19], it is natural to hypothesize that polymorphisms of the ABCA1 gene might be related to DM. In a previous study for screening SNPs in candidate genes in molecular pathways associated with DM, we found that a SNP in the ABCA1 gene is associated with DM [20]. To further exploit the association of the ABCA1 gene with DM, and to strengthen the result, we here constructed linkage disequilibrium (LD) blocks and conducted haplotype and diplotype analyses

☆ *Abbreviations:* ABCA1, ATP-binding cassette transporter 1; DM, diabetes.

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of the ABCA1 gene in a community-based case-control study of DM in a Japanese population.

Materials and methods

Subjects. Seventy-three, 75, and 227 subjects with DM, impaired glucose tolerance (IGT), and normal glucose tolerance (NGT), respectively, were recruited from the cohorts of the Funagata Study [21], which was a population-based study held in an agricultural area located about 400 km north of Tokyo. Glucose tolerance was diagnosed according to the 1985 World Health Organization criteria [22]. This study was approved by the Ethical Review Committee of Yamagata University, and written informed consent was obtained from the participants. All procedures followed the institutional guidelines. The stratification of the population seems to be minimal, since analysis using the software STRUCTURE [23] did not support the presence of any structure in this population [20]. Age and sex ratios were matched among the groups. Along with the genetic analysis, the following clinical traits were analyzed: height, body weight, 75-g oral glucose tolerance test, HbA1c, waist circumference, hip circumference, waist-to-hip ratio, BMI, percent body fat, systolic blood pressure, diastolic blood pressure, and serum levels of total cholesterol, triglycerides, and HDL-C. The details of clinical characteristics of the groups are shown in the initial analysis using the same sample set [20].

Construction of LD blocks and assignment of a haplotype combination (diplotype configuration) in each individual. Genotypes of 43 SNPs in the ABCA1 gene, which were extracted from the JSNP database (http://snp.ims.u-tokyo.ac.jp), have been analyzed with a fluorogenic polymerase chain reaction [24]. Thirty-four of them (details in Table 1 and Fig. 1) showed a more than 95% call-rate of the genotypes, and were, therefore, used for LD block construction and haplotype analyses. LD between SNPs was assessed in pairwise manner and an LD block was defined as a set of SNPs in which LOD p value between every pair in it was less than 0.01. Haplotype frequencies and diplotype configurations of individuals in each LD block were estimated using a program called LD support [25], which is based on EM algorithm. Assignments with more than an 80% posterior probability of estimation were used for the construction of the diplotype.

Statistical analysis. To assess the allelic association between each haplotype or each diplotype and disease phenotype, we performed a χ^2 test using a multi-column table. As χ^2 statistics in a multi-column contingency table do not usually show an asymptotic normal distribution, we performed a Monte Carlo Markov-Chain algorithm by using the program CLUMP [26]. The CLUMP T1 test of this program generated tables in which cell numbers were randomized with fixed marginal totals in rows and columns. The null distribution of the χ^2 statistics in 10,000 simulated tables was then obtained and used to calculate an empirical p value (overall p) corresponding to the χ^2 value in the real data set. To determine at-risk haplotype, this table collapsed to a 2×2 table and was analyzed by a Fisher's exact probability test with a Bonferroni correction. p values for the Fisher's exact test, odds ratio (OR), and 95% CI were calculated by using a 2BY2 program (http://linkage.rockefeller.edu/ott/linkutil.htm). The statistical significance of the differences of the clinical trait values between the groups was assessed by Student's t test. The independent association of the at-risk diplotype, from TG and BMI, or HDL-C was examined by multiple logistic regression analysis. A value of $p < 0.01$ was accepted as significant.

Table 1
Association of each SNP of the ABCA1 gene with IGT + DM and DM

SNP No.	JSNP ID (ssjooo-)	p value	
		NGT vs. IGT + DM	NGT vs. DM
1	rs2164560	0.441	0.104
2	rs2487031	0.437	0.111
3	rs2043664	0.457	0.655
4	1176	0.337	0.117
5	1182	0.539	0.817
6	1183	0.210	0.042
7	1184	0.142	0.060
8	1187	0.070	0.001*
9	1191	0.039	0.099
10	1194	0.054	0.060
11	1195	0.204	0.281
12	1198	0.592	0.683
13	1205	0.591	0.682
14	1209	0.643	0.690
15	1212	0.234	0.587
16	1235	0.553	0.882
17	1242	0.410	0.342
18	1259	0.410	0.342
19	1264	0.447	0.079
20	1271	0.085	0.273
21	1276	0.398	0.416
22	1279	0.457	0.279
23	1280	0.066	0.341
24	1289	0.220	0.573
25	1296	0.155	0.243
26	1300	0.336	0.498
27	1304	0.078	0.579
28	1305	0.085	0.342
29	1306	0.042	0.071
30	1311	0.037	0.036
31	1322	0.008*	0.014
32	1326	0.169	0.082
33	1333	0.631	0.768
34	1337	0.836	0.592

The description of the SNPs shown is in the web site (http://snp.ims.u-tokyo.ac.jp) under the identification number shown as "JSNP ID," except DNPs 1, 2, and 3, which are denoted by "dbSNP ID" (http://www.ncbi.nlm.gov/SNP/). p values were determined by Fisher's exact tests. p values shown in this table are the lower one in this analysis, which used dominant and recessive genetic models to evaluate the association.

* $p < 0.01$.

Results

Estimation of LD blocks

The association of each SNP with IGT + DM and with DM is shown in Table 1. As previously reported, except for the SNP31 in the intron 45, none of them showed significant association with IGT + DM [20]. When DM alone was used as the case, the SNP8 showed significant association. Analysis of the haplotype structure using the genotype data of the SNPs revealed 11 (LD block 1, 2, 3, 4, 5, 6, 7, 8, 11,12, and 13) and 12 (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, and 13) LD blocks, for the study groups, NGT, IGT, and DM (NGT + IGT + DM), and NGT and DM (NGT + DM), respectively (Fig. 1). The LD blocks 9 and 10 are a part of the LD block 11. A total of 13 LD blocks found here cover most regions of the gene.

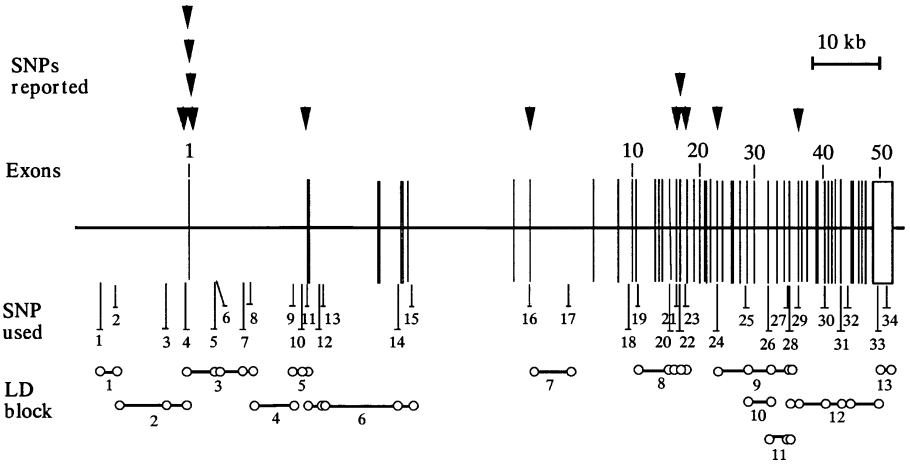

Fig. 1. The LD blocks of the ABCA1 gene estimated. The structure of the ABCA1 gene is shown in the middle. Exons are represented by vertical lines and a box. Coding region starts from the exon 2 and ends in the exon 50. SNPs used are those described in Table 1. LD blocks estimated are shown in the lower part and are represented by horizontal lines with open circles, each of which represents each corresponding SNP composing the LD block. The SNPs reported to be associated with abnormalities of serum lipid levels and/or a risk of coronary artery disease are shown in the upperpart and are represented by arrowheads.

Haplotype analysis

The differences in the haplotype distribution of each LD block are evaluated using two sets of case-control groups (NGT vs. IGT + DM and NGT vs. DM). The overall p values obtained by the CLUMP T1 test are shown in Table 2. Although we expected difference in haplotype distribution in the LD block 12 that included the SNP 31 detected to be associated with DM in the initial analysis [20], it gave only a marginal value of p (0.0669) only when the IGT and DM groups together were used as the case group. Fifteen haplotypes were determined in the LD block 12, and none of them showed significant association with DM with Fisher's exact probability test (lowest p value was 0.0985). More interestingly, the differences in the haplotype distribution of the LD blocks 3 and 4 were significant ($p = 0.0045$ and 0.0001, respectively) when DM group alone was used as the case group, and this difference of the LD block 4 was still tending to be significant ($p = 0.0180$), even when the IGT and DM groups together were used as the case group.

Table 2
Differences of haplotype distribution of the ABCA1 gene

LD block No.	Overall p	
	NGT vs. IGT + DM	NGT vs. DM
1	0.9028	0.2394
2	0.2370	0.2863
3	0.3696	0.0045*
4	0.0180	0.0001*
5	0.2121	0.8271
6	0.7567	0.4822
7	0.8636	0.6846
8	0.0824	0.1909
9	0.2955	ND
10	ND	0.5322
11	ND	0.2777
12	0.0699	0.3333
13	0.7358	0.8312

ND means analyses "not done," since the LD blocks were not estimated in the designated study population.
* $p < 0.01$.

Since the difference between the case and the control groups was more significant when the DM group alone was used as the case group, we here used this setting for the haplotype and diplotype analyses of the LD block 4, which showed strongest association with DM. The diplotypes of all samples in the LD block 4 are uniquely determined by LD Support program. As shown in Table 3, the 2×2 table from Fisher's exact probability test showed a significant association of the haplotype 2 ($p = 0.0001$), with an odds ratio (OR) of 2.58 (95% CI:1.62–4.12). The p value of the test was still very low ($p = 0.0003$), even after the Bonferroni correction.

Diplotype analysis

The distribution of the observed counts of the 6 diplotypes of the LD block 4 assigned in the observed data set is shown in a 2×6 contingency table (Table 4). The CLUMP T1 test revealed the empirical p value of 0.0006. Furthermore, Fisher's exact probability test showed a significant association of the diplotype 2/2, with an OR of 5.97. Since the haplotype 2 seems to be the at-risk haplotype, the diplotypes with the haplotype 2 were combined and designated as the at-risk diplotype, while the other diplotypes were also combined and designated as the non at-risk diplotype. A 2×2 Fisher's exact probability test using this sample set showed a significant association of the at-risk diplotype, with an OR

Table 3
Haplotype analysis of the LD block 4 in the ABCA1 gene

Haplotype	Sequence		Number		OR	95%CI	*p*	
	SNP8	SNP9	NGT	DM			Fisher	Bonferroni
1	C	A	321	84	0.51	0.34–0.75	0.0012*	0.0036*
2	C	G	55	38	2.58	1.62–4.12	0.0001*	0.0003*
3	G	A	66	22	1.05	0.62–1.78	0.8927	1

p values obtained from the 2×2 Fisher's exact probability test (Fisher) and those with Bonferroni correction (Bonferroni) are shown.
* $p < 0.01$.

Table 4
Diplotype analysis of the haplotypes of the LD block 4 in the ABCA1 gene

Diplotype	Haplotype combination		Number		OR	95%CI	*p*	
			NGT	DM			Fisher	Bonferroni
1/1	1	1	118	25	0.48	0.28–0.84	0.0103	0.06184
1/2	1	2	42	22	1.92	1.05–3.52	0.0469	0.2814
1/3	1	3	53	12	0.65	0.32–1.30	0.2544	1
2/2	2	2	4	7	5.97	1.69–21.05	0.0052*	0.0312
2/3	2	3	5	2	1.26	0.23–6.65	0.6769	1
3/3	3	3	4	4	3.26	0.80–13.4	0.0996	0.5977
With 2	—	—	51	31	2.59	1.48–4.54	0.0013*	—
Others	—	—	175	41	1	—	—	—
With 1	—	—	213	59	0.28	0.12-0.63	0.0024*	—
Others	—	—	13	13	1	—	—	—

p values obtained from the 2×2 Fisher's exact probability test (Fisher) and those with Bonferroni correction (Bonferroni) are shown.
* $p < 0.01$.

of 2.59 ($p = 0.0013$). Contrary, the haplotype 1 seems to be the protective haplotype (Table 3), and the analysis with the diplotypes with the haplotype 1 as the protective diplotype showed a significant association as well (OR:0.28, $p = 0.0024$).

Adjustment for clinical characteristics

As previously reported, the subjects of the DM group were more obese and tended to have higher serum TG levels than those of the NGT group [20]. Therefore, the haplotypes or diplotypes examined might be associated with obesity and/or a higher TG rather than DM per se. To evaluate these possibilities, we conducted multiple logistic regression analysis to examine the association of the at-risk diplotype of the LD block 4 with DM, independently from TG and BMI. After the adjustment for TG and BMI, the at-risk diplotypes still showed a significant association with DM ($p = 0.0038$, OR:2.37(1.32–4.25)).

Since several polymorphisms of the ABCA1 gene have been reported to be associated with serum levels of HDL-C [8–15], the diplotype may be similarly associated with serum levels of HDL-C. Therefore, we examined whether the serum levels of HDL-C were different between the at-risk and the non at-risk diplotype groups. However, the serum levels of HDL-C in the at-risk diplotype group were not different from those in the non at-risk diplotype group (61.7 ± 14.3 vs. 59.4 ± 15.5, $p = 0.2355$). Thus, the association of the at-risk diplotype with DM was not changed much, after the adjustment with serum levels of HDL-C ($p = 0.0008$, OR: 2.62 (1.49–4.61)).

Discussion

Case-control association study to search disease susceptibility genes sometimes shows false-positive results. When many SNPs and candidate genes were examined at once, incidence of false-positive results increases as a nature of multiple testing. An association of the ABCA1 gene with DM was found in our initial study, which used 398 SNPs derived from 120 candidate genes [20]. Therefore, the initially observed association of the ABCA1 gene (namely the SNP31) with DM seems to have a substantial risk to be a false-positive result. Thus, to further exploit the association of the ABCA1 gene with DM, we focused on the ABCA1 gene only, genotyped for 6 more SNPs to cover the whole genomic region including the promoter region, removed the genotype data that showed a less than 95% call-rate of the genotypes, constructed LD blocks, and conducted haplotype and diplotype analyses. Since haplotypes which capture the regional LD information are more informative than a single SNP, haplotype analysis is expected to improve the power of conventional single-locus analysis and to help identify disease mutations

[27–30]. Indeed, some recent studies show that haplotype analysis can improve power of the association study especially when multiple SNPs are susceptible to the disease [29,31]. Two SNPs (the SNPs8 and 31) showed significant association with DM in the single SNP association study (Table 1). Furthermore, the haplotype and diplotype analyses revealed that the haplotpe 2 of the LD block 4 (composed of the SNPs 8 and 9) is an at-risk genotype for DM. These facts strengthen the association of the ABCA1 gene with DM.

At the beginning, we hypothesized that the decreased serum levels of HDL-C might reflect the intermediate phenotype that links the ABCA1 gene and DM. However, our result did not support this hypothesis, since the serum levels of HDL-C were not lower in the at-risk diplotype group than in the non at-risk diplotype group. Therefore, ABCA1 may have some influence on pathophysiology of DM independently of serum levels of HDL-C. Furthermore, the serum levels of total cholesterol (at-risk vs. non at-risk: 202.0 ± 30.5 vs. 204.5 ± 37.5, $p = 0.576$) and TG (108.7 ± 67.3 vs. 125.1 ± 130.3, $p = 0.278$) were also not different between the groups. These facts may indicate that the mechanisms which link the ABCA1 gene to DM are not the same that link the ABCA1 gene to abnormalities of serum lipid levels.

Although many genetic variations and SNPs of the ABCA1 gene have been reported to be associated with abnormalities of serum lipid levels [5–15], several SNPs have been reported to be associated with CAD independent of changes of serum lipid levels [9,11,13]. Interestingly, the SNPs within or in the vicinity of the LD blocks 1–4 were such SNPs. Therefore, as on the development of CAD, some genetic variations within or in the vicinity of the LD block 4 of the ABCA1 gene may have an influence on glucose tolerance without a decrease in serum levels of HDL-C. Thus, these facts may indicate common pathophysiological mechanisms leading to CAD and DM, which seem to be a target to be clarified in future.

The LD block 12 is composed of 6 SNPs, one of which is the SNP31 (T/C in intron 45), which showed a significant association with DM in the previous single SNP association study [20]. However, as shown in Table 2, the haplotype distribution of the LD block 12 did not show a significant difference between the case and the control groups (NGT vs. IGT + DM: $p = 0.0699$; NGT vs. DM: 0.3333). This result may indicate that the association of the SNP31 is by chance. On the other hand, the association of the LD block 12 may not be strong enough to be detected in this study, in which the number of subjects is not large. Analysis using more subjects is needed before a conclusion can be reached.

We showed here a significant association of a haplotype in the 5′ region of the ABCA1 gene with DM independent of abnormalities of serum lipid levels in a Japanese population. Therefore, the ABCA1 gene may act as a risk factor for DM in this population. Association of the ABCA1 gene with DM is worth testing in other populations with various ethnicities.

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