Brief Genetics Report

Genetic Heterogeneity in Association of the *SUMO4* M55V Variant With Susceptibility to Type 1 Diabetes

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Association studies are a potentially powerful approach to identifying susceptibility variants for common multifactorial diseases such as type 1 diabetes, but the results are not always consistently reproducible. The *IDDM5* locus has recently been narrowed to an ~200-kb interval on chromosome 6q25 by two independent groups. These studies demonstrated that alleles at markers in the mitogen-activating protein kinase 7 interacting protein 2 (*MAP3K7IP2*)/*SUMO4* region were associated with susceptibility to type 1 diabetes. Subsequent studies, however, showed inconsistency in the association of the *SUMO4* gene with type 1 diabetes. To clarify the contribution of the M55V polymorphism of the *SUMO4* gene to type 1 diabetes susceptibility, 541 type 1 diabetic patients and 768 control subjects were studied in Asian populations. The M55V polymorphism was significantly associated with type 1 diabetes in Asian populations (summary odds ratio [OR] 1.46, $P = 0.00083$, Mantel-Haenszel test). Meta-analysis of published studies and the present data confirmed a highly significant association in Asian populations (summary OR 1.29, $P = 7.0 \times 10^{-6}$) but indicated heterogeneity in the genetic effect of the *SUMO4/MAP3K7IP2* locus on type 1 diabetes among diverse ethnic groups. These data indicate that the *MAP3K7IP2/SUMO4* locus in the *IDDM5* interval is associated with type 1 diabetes in Asian populations. *Diabetes* 54:3582–3586, 2005

Type 1 diabetes is a common multifactorial disease caused by the autoimmune destruction of insulin-producing β-cells of the pancreas. Previous studies have suggested that >20 genetic intervals are associated with susceptibility to type 1 diabetes (1,2). Of these, four loci have been identified and replicated as disease susceptibility genes by genetic association studies: the *HLA* class II genes (*IDDM1*) (3), *INS* gene (*IDDM2*) (4), *CTLA4* gene (*IDDM12*) (5), and *PTPN22* gene (6). Recently, the *IDDM5* locus has been narrowed down to an ~200-kb interval on chromosome 6q25 by two independent groups (7,8). Several single nucleotide polymorphisms (SNPs) that were in linkage disequilibrium in the *SUMO4*/mitogen-activating protein kinase 7 interacting protein 2 (*MAP3K7IP2*) region were found to be associated with susceptibility to type 1 diabetes (7,9). The *SUMO4* gene, encoding small ubiquitin-like modifier 4, is a posttranslational modifier, which has recently been identified as a novel member of the SUMO family and is suggested to modify immune response through the putative substrate, inhibitor of nuclear factor-κBα, a suppressor of nuclear factor-κB (NF-κB) (7). *SUMO4* is located entirely within the sixth intron of the *MAP3K7IP2* gene (Fig. 1), whose product indirectly regulates the activation of NF-κB in response to interleukin-1 stimulation (10,11).

Among the disease-associated SNPs in the *SUMO4*/*MAP3K7IP2* gene, a common nonsynonymous SNP (rs237025) encoding a methionine-to-valine substitution at codon 55 (M55V) of *SUMO4* was proposed as the causative variant of *IDDM5* by two groups but with alleles with opposite risk (7,9). The original report by Guo et al. (7) with subjects from diverse ethnic groups and the subsequent study by Park et al. (12) in Korean subjects showed that possession of the G allele was significantly associated with increased risk for type 1 diabetes, whereas studies in Caucasian subjects of European descent showed no association (13–15) or even an association of the A allele with the disease (9).

Of note is the positive association in studies with subjects from Asian populations (7,12) in contrast to the lack of association in subjects of European descent (13,14) and a tendency for an opposite association in British subjects (7,9). Genetic heterogeneity as well as gene-gene and gene-environment interactions have been suggested as possible reasons for these discrepancies observed among different populations. This prompted us to study the association of the M55V variant in *SUMO4* with type 1 diabetes in Asian populations. To this end, a total of 1,284 East Asian subjects consisting of 1,113 Japanese and 171 Korean subjects were studied. Our data were integrated into a meta-analysis to estimate the population-wide effects of genetic risk factors on type 1 diabetes in inconsistent studies (16,17).

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MAP3K7IP2, mitogen-activating protein kinase 7 interacting protein 2; NF-κB, nuclear factor-κB; SNP, single nucleotide polymorphism; TDT, transmission disequilibrium test.

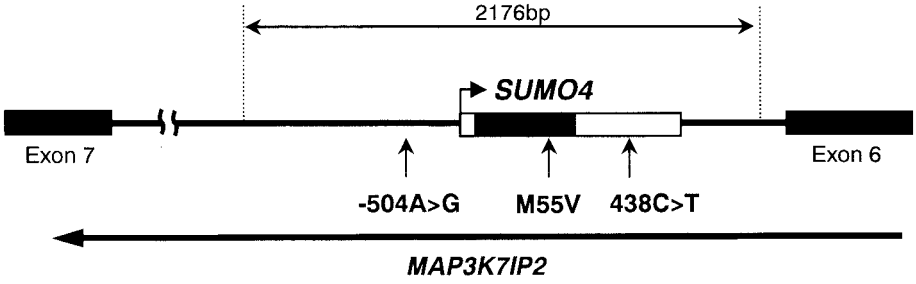

FIG. 1. Localization of SNPs in the *SUMO4* locus. The horizontal black line depicts the 2,176-bp DNA segment of chromosome 6q25 analyzed in our Japanese samples.

RESEARCH DESIGN AND METHODS

All subjects were of Japanese origin, belonging to the Eastern Asian ethnic group. The 472 case and 641 control subjects were recruited from three geographical areas in Japan (two areas from western Japan and one from eastern Japan). The mean age at onset of the type 1 diabetic subjects was 27.1 ± 17.9 years (range 1–75), and the mean age of the control subjects was 42.5 ± 11.3 years. Genomic DNA samples of 69 Korean case and 102 control subjects were obtained in the Teague area in South Korea. All subjects of Korean origin belonged to the Eastern Asian ethnic group. All the patients were ketosis prone and lacked endogenous insulin secretion as judged by a C-peptide level of <3.3 nmol/day. Control subjects had no clinical diabetes, no family history of diabetes, and no other autoimmune diseases. All DNA samples were collected after approval from the relevant research ethics committees, and informed consent was obtained from the participants.

Genotyping and sequencing. Genotyping was undertaken using TaqMan (Applied Biosystems, Tokyo, Japan), with probes and primers described in a previous report (13). To avoid genotyping error, all genotyping was reproduced by PCR–restriction fragment–length polymorphism methods with a second nonpolymorphic cutting site in the same PCR products using restriction enzyme TspRI (New England Biolab, Ipswich, MA), and a part of them was confirmed by direct sequencing using an ABI 3100 capillary sequencer. No discrepancy was observed between the three methods. The genotype frequency of GG, GA, and AA of subjects was 10.2, 41.4, and 48.4%, respectively, and the distribution was compatible with the Hardy-Weinberg equilibrium. Haplotypes were estimated using the expectation-maximization algorithm with Haploview v2.03. *HLA-DRB1* and *DQB1* were also genotyped. *DRB1*0405-DQB1*0401*, *DRB1*0405-DQB1*0401*, *DRB1*0405-DQB1*0401/DRB1*0901-DQB1*0303*, and *DRB1*0901-DQB1*0303/DRB1*0901-DQB1*0303* were considered high-risk HLA for the Japanese population and *DRB1*0405*, *DRB1*0901*, and *DRB1*0301* for the Korean population (8).

Selection of associations for meta-analysis. To perform a meta-analysis, the published literature was searched using PubMed with the key words SUMO4 and diabetes, followed by a complimentary search of the reference list of the selected articles.

Statistical analysis. The significance of differences in the distribution of alleles and genotypes between case and healthy control subjects was determined by the χ^2 method. Statistical significance was defined as $P < 0.05$. For calculation of the summary OR according to the genotype groups from case-control studies, we adopted a fixed model using the Mantel-Haenszel method (18). The 95% CI and I^2 value (19) for assessing the heterogeneity of the strength of the association were also calculated. The odds ratio estimate and the 95% CI were obtained from a study on integrating case-control and transmission disequilibrium test (TDT) studies (20).

RESULTS

Resequencing of the *SUMO4* gene in Japanese subjects. To identify polymorphisms in Japanese subjects, a 2,176-bp interval of the chromosome 6q25 region, including the whole *SUMO4* gene, was sequenced in 16 type 1 diabetic and 16 healthy control subjects. In addition to the M55V polymorphism (rs237025), one novel SNP in the promoter region (−504A>G) and another in 3′-untranslated region (438C>T, rs237024) were identified (Fig. 1). Three haplotypes were estimated for these three SNPs, and these three SNPs were in strong linkage disequilibrium (D′: 1.0 for a single pair of SNPs), suggesting that this locus across three SNPs is a single block. The 438C>T SNP in 3′-untranslated region was in complete linkage disequilibrium with the M55V polymorphism.

Association of the *SUMO4* gene with type 1 diabetes in Eastern Asian populations. The Japanese case and control subjects were recruited from three geographical areas in Japan: Saitama, Osaka, and Nagasaki. Subjects were independently genotyped in these three panels. Similar allele and genotype frequencies were observed in each geographical area (I^2: 0.0%), suggesting homogeneity of the Japanese data in this study. In total, the frequency of subjects with the G allele (encoding Val55) was significantly higher in type 1 diabetic than in control subjects (0.59 vs. 0.50; OR 1.43 [95% CI 1.12–1.81], $P < 0.005$, χ^2 test, Table 1). A similar tendency was observed in Korean subjects (0.58 vs. 0.44; 1.75 [0.94–3.24]). In the combined data from Japanese and Korean subjects, the G allele was significantly associated with type 1 diabetes (1.46 [1.17–1.83], $P = 0.00083$, Mantel-Haenszel test, Table 1). Stratification of case subjects by high-risk and low-risk HLA genotypes showed no difference in the association of GG + GA genotypes with type 1 diabetes (data not shown). The SNP in the promoter region (−504A>G) was not associated with susceptibility to type 1 diabetes (data not shown).

TABLE 1
Meta-analysis of the *SUMO4* M55V variant in Japanese and Korean subjects

	Japanese		Korean				
	Type 1 diabetic subjects	Control subjects	Type 1 diabetic subjects	Control subjects	I^2	OR (95% CI)	P
n (%)	472	641	69	102			
GG	43 (9)	64 (10)	9 (13)	11 (11)			
GA	234 (50)	256 (40)	31 (45)	34 (33)			
AA	195 (41)	321 (50)	29 (42)	57 (56)			
G	320 (34)	384 (30)	49 (36)	56 (27)			
A	624 (66)	898 (70)	89 (64)	148 (73)	0.0	1.23 (1.04–1.46)	0.0016
GG + GA	277 (59)	320 (50)	40 (58)	45 (44)			
AA	195 (41)	321 (50)	29 (42)	57 (56)	0.0	1.46 (1.17–1.83)	0.00083

Data are n (%), unless otherwise indicated. Mantel-Haenszel test.

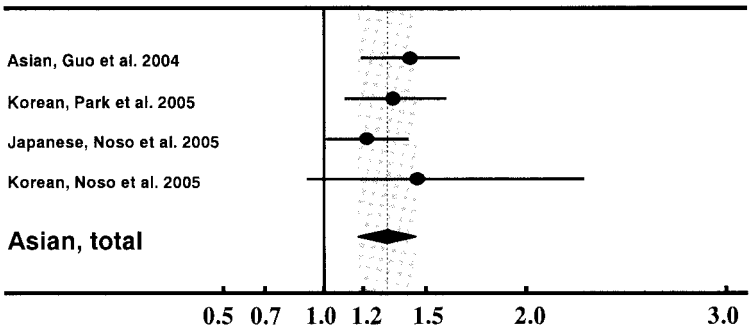

FIG. 2. Estimates of OR for type 1 diabetes according to the M55V (A163G) variant of the *SUMO4* gene in Asian populations. Values >1 imply an increased OR for type 1 diabetes associated with the G allele. The 95% CIs are expressed by bars (for each group) and ♦ (for combined studies). Broken vertical lines represent the summary OR of combined studies for Asian populations. Data from case-control and TDT studies were integrated as described in a previous study (20).

Meta-analysis of association of the *SUMO4* gene. To test whether the M55V variant of the *SUMO4* gene has a population-wide effect in its association with type 1 diabetes, we performed a meta-analysis of published studies including the present study. From seven articles detected by PubMed search, six sets of data (7,9,12–15,21), including the present results, were available. Two sets of data (9,15) were excluded from the meta-analysis because some of the subjects from the Human Biological Data Interchange and the Warren Repository overlapped with those in another large-scale association study (13). Korean subjects of the case-control study from the original report (7), which may be overlapped with the data published by Park et al. (12), were also excluded from meta-analysis. Since data were available from both case-control and TDT studies, an OR estimate and its associated SE were calculated to obtain a combined estimate from case-control and TDT studies (20,22). Meta-analysis of all Asian data from previous studies (7,12) and this study (1,126 case and 1,675 control subjects for case-control studies and 129 families for TDT studies) showed a significant association of the G allele with type 1 diabetes (OR 1.29 [95% CI 1.15–1.44], $P = 7.0 \times 10^{-6}$) with very homogenous data (P value for heterogeneity: 0.29, NS, Fig. 2). In contrast, the summary OR for European subjects (4,053 case and 5,273 control subjects for case-control studies and 2,810 families for TDT studies) was 1.02 (0.98–1.07; P value for heterogeneity within European subjects: 4.0×10^{-8}), with no overlap in the 95% CI with that of Asian data (Table 2). As a result, when both data were combined, the summary OR was reduced to 1.05 (1.01–1.09; $P = 0.0087$), although significant heterogeneity (P value for heterogeneity: 1.0×10^{-11}) across these datasets was also indicated (Table 2).

DISCUSSION

Linkage analyses by several groups (1,2,23,24) have consistently identified a type 1 diabetes susceptibility locus, *IDDM5*, on chromosome 6q25, and recent fine mapping by two independent groups (7,8) further narrowed the interval to an ~200-kb region. Two candidate genes, *SUMO4* and *MAP3K7IP2*, are located in the interval, and both products are suggested to be involved in alteration of NF-κB activity (7,10,11). In terms of disease pathogenesis, accumulating lines of evidence indicate involvement of the NF-κB pathway in the development of type 1 diabetes in humans (15) and mice (25–28), further supporting the hypothesis that the *SUMO4/MAP3K7IP2* locus is responsible for susceptibility to type 1 diabetes.

The present study demonstrated strong evidence for an association of the M55V variant of the *SUMO4* gene with type 1 diabetes in Eastern Asian populations ($P = 7.0 \times 10^{-6}$) and suggested that possession of the G allele contributes to disease susceptibility in a dominant fashion. However, a meta-analysis of published studies including both Caucasian and Asian descents with our own data indicated only a weak association (summary OR 1.05 [95% CI 1.01–1.09], $P = 0.0087$) of the G allele with type 1 diabetes, but significant heterogeneity was also observed in the genetic effect of the locus on type 1 diabetes ($P = 1.0 \times 10^{-11}$). The heterogeneity of the data across diverse ethnic groups could be explained by the marked difference in the association of the *SUMO4* locus between Eastern Asian and Caucasian populations, which was clearly demonstrated by the 95% CIs without overlap. This hypothesis is also supported by the fact that exclusion of the Caucasian data removed the heterogeneity (P value for heterogeneity = 0.290).

The human population is not homogeneous in terms of

TABLE 2
Distribution of allele frequencies of the *SUMO4* M55V variant in previously published reports and present study

	TDT		Association (Allele)				
			Case subjects		Control subjects		
	Transmitted	Untransmitted	G	A	G	A	OR (95% CI)
Caucasian (total)	2,414	2,365	4,008	4,098	5,185	5,361	1.02 (0.98–1.07)
U.K., Smyth et al., 2005	1,473	1,534	3,319	3,565	3,706	3,870	0.97 (0.92–1.01)
Canadian, Paterson et al., 2005	376	387	NA	NA	NA	NA	0.97 (0.84–1.12)
Caucasian, Guo et al., 2004	565	444	689	533	1,479	1,491	1.29 (1.18–1.41)
Asian (total)	39	23	802	1,450	1,016	2,334	1.29 (1.15–1.44)
Asian, Guo et al., 2004	39	23	142	256	230	528	1.35 (1.07–1.70)
Korean, Park et al., 2005	NA	NA	291	481	346	760	1.33 (1.10–1.61)
Japanese, Noso et al., 2005*	NA	NA	320	624	384	898	1.20 (1.00–1.44)
Korean, Noso et al., 2005*	NA	NA	49	89	56	148	1.46 (0.91–2.32)
Total	2,453	2,388	4,810	5,548	6,201	7,695	1.05 (1.01–1.09)

*Present study. NA, not applicable.

risk of disease (e.g., the causes and prevalence of disease). This is possibly due to differences in the genetic constitution and nongenetic or environmental characteristics acquired during life. One of the best examples of a gene that affects a complex disease is *APOE* in Alzheimer's disease. A susceptible allele, *APOE* ϵ4 is relatively common and is seen in all ethnic groups with different frequencies, ranging from 9% in Japanese populations to 14% in Caucasian populations and 19% in African-American populations (29). A recent meta-analysis has demonstrated that the effect of *APOE* ϵ4 on the risk of Alzheimer's disease varies according to ethnicity (29). Another illustration, which may support genetic heterogeneity across populations, is the ethnic difference in allele frequency, haplotype structure, and linkage disequilibrium (30–32). These population-genetic studies have reconfirmed the classical definition of ethnic groups based on continental ancestry, namely African, Caucasian, Asian, Pacific Islander, and Native American. However, separation of the studies by ethnicity did not remove the heterogeneity from the Caucasian populations, and further investigation will be required to clarify the association of the M55V variant in the *SUMO4* gene with type 1 diabetes in other populations.

When the case subjects in the present study were stratified by HLA haplotypes, no difference in the frequency of GG + GA genotypes was observed between high-risk and low-risk type 1 diabetic subjects, indicating no interaction of the *SUMO4* M55V variant with *IDDM1*. A factor(s) that interacts with the *SUMO4/MAP3K7IP2* locus could be other type 1 diabetes loci, except for *IDDM1*, or environmental factors.

In conclusion, the present study indicated significant genetic heterogeneity in the association of the *SUMO4* M55V variant with type 1 diabetes and an Eastern Asian–specific association of the *SUMO4/MAP3K7IP2* locus with type 1 diabetes, suggesting that genetic heterogeneity should be taken into consideration to validate an association with inconsistent results.

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