Genome-Wide Association Study Confirming a Strong Effect of HLA and Identifying Variants in *CSAD/lnc-ITGB7-1* on Chromosome 12q13.13 Associated With Susceptibility to Fulminant Type 1 Diabetes

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The first genome-wide association study of fulminant type 1 diabetes was performed in Japanese individuals. As previously reported using a candidate gene approach, a strong association was observed with multiple single nucleotide polymorphisms (SNPs) in the HLA region, and the strongest association was observed with rs9268853 in the class II DR region ($P = 1.56 \times 10^{-23}$, odds ratio [OR] 3.18). In addition, rs11170445 in *CSAD/lnc-ITGB7-1* on chromosome 12q13.13 showed an association at a genome-wide significance level ($P = 7.58 \times 10^{-9}$, OR 1.96). Fine mapping of the region revealed that rs3782151 in *CSAD/lnc-ITGB7-1* showed the lowest *P* value ($P = 4.60 \times 10^{-9}$, OR 1.97 [95% CI 1.57–2.48]). The risk allele of rs3782151 is a *cis* expression quantitative trait locus for *ITGB7* that significantly increases the expression of this gene. *CSAD/lnc-ITGB7-1* was found to be strongly associated with susceptibility to fulminant, but not classical, autoimmune type 1 diabetes, implicating this locus in the distinct phenotype of fulminant type 1 diabetes.

Type 1 diabetes is caused by the destruction of the insulin-producing β-cells of the pancreas in genetically susceptible individuals. Etiologically, type 1 diabetes consists of two subtypes: autoimmune (type 1A) and idiopathic (type 1B) (1,2). In contrast to the extensive studies on the genetics, pathogenesis, prevention, and treatment of autoimmune type 1 diabetes, studies on idiopathic type 1 diabetes are very limited owing to the heterogeneous and ambiguous nature of this subtype. Among idiopathic type 1 diabetes

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subtypes, fulminant type 1 diabetes is an established entity with well-characterized clinical phenotypes (3–5).

Fulminant type 1 diabetes is clinically distinct from autoimmune type 1 diabetes; onset is remarkably abrupt, as reflected by near-normal glycated hemoglobin (HbA_{1c}) levels despite very high blood glucose levels, which results in the complete destruction of β-cells within a few days. Diabetes-related autoantibodies are essentially negative in patients with fulminant type 1 diabetes (3). In addition to β-cells, α-cell areas are also decreased (6,7), and mononuclear cell infiltration is observed in the exocrine and endocrine pancreas in patients with recent-onset fulminant type 1 diabetes (5,7). These observations suggest that the whole pancreas is involved in fulminant type 1 diabetes, which is distinct from the selective destruction of β-cells in autoimmune type 1 diabetes.

The genetic basis of fulminant type 1 diabetes is also distinct from that of classical autoimmune type 1 diabetes. This distinction is evident from the marked difference in incidences among different populations. The frequencies of type 1 diabetes in Japan and most East Asian countries are very low; the frequency is typically less than one-tenth that in white populations of European descent (8). In contrast, most people with fulminant type 1 diabetes are from East Asian countries (4,5), and only a limited number of cases were reported in white European populations (9). However, increased attention has recently been focused on this disease because of the high frequency of fulminant type 1 diabetes in subjects undergoing cancer immunotherapy with immune checkpoint inhibitors, such as anti–PD-1 and anti–PD-L1 antibodies, in both European and Asian populations (10,11).

An accelerated immune reaction triggered by viral infection in genetically susceptible individuals has been proposed to cause the rapid and massive destruction of pancreatic islets in patients with fulminant type 1 diabetes (5,12), but the etiology of the disease remains largely unknown. The identification of susceptibility genes for fulminant type 1 diabetes is therefore important to clarify the pathogenesis and molecular mechanisms of the disease and to establish effective prediction, prevention, and intervention methods. Information on the molecular mechanisms of fulminant type 1 diabetes will also provide novel insights into the molecular mechanisms of type 1 diabetes in general, including type 1 diabetes associated with cancer immunotherapy. However, with the exception of HLA (13–15), the genetic susceptibility to fulminant type 1 diabetes is largely unknown. To identify susceptibility genes for fulminant type 1 diabetes, we performed a genome-wide association study (GWAS) in the Japanese population.

RESEARCH DESIGN AND METHODS

Study Participants

Unrelated Japanese patients with fulminant type 1 diabetes (n = 257) were recruited through a nationwide effort orchestrated by a committee of the Japan Diabetes Society. Fulminant type 1 diabetes was diagnosed by experts in diabetes according to the criteria of the Japan Diabetes Society (16) and confirmed by a review committee on fulminant type 1 diabetes, which is part of the committee on type 1 diabetes of the Japan Diabetes Society.

The diagnostic criteria for fulminant type 1 diabetes were as follows: *1*) occurrence of diabetic ketosis or ketoacidosis soon (within ~7 days) after the onset of hyperglycemic symptoms, *2*) a plasma glucose level ≥16.0 mmol/L (≥288 mg/dL) and HbA_{1c} <8.7% at the first visit, and *3*) urinary C-peptide excretion <10 μg/day or a fasting serum C-peptide level <0.3 ng/mL (<0.10 nmol/L) and <0.5 ng/mL (<0.17 nmol/L) after intravenous glucagon load (or after a meal) at onset. A diagnosis of fulminant type 1 diabetes was confirmed if all three criteria were present (16). The mean ± SD levels of these variables in the current study were as follows: plasma glucose 46.3 ± 21.6 mmol/L (833.2 ± 389.8 mg/dL), HbA_{1c} 6.57 ± 0.72% (48.3 ± 7.9 mmol/mol), urinary C-peptide excretion 3.3 ± 2.4 μg/day, and fasting C-peptide 0.031 ± 0.021 nmol/L (0.093 ± 0.062 ng/mL). The control subjects for the GWAS were 419 healthy Japanese volunteers who participated in a previous GWAS (17,18).

Patients with classical autoimmune type 1 diabetes (n = 410) were also recruited through the committee of the Japan Diabetes Society (19). The characteristics of the study participants are summarized in Supplementary Table 1.

This study was approved by the ethics committees of the Japan Diabetes Society and each institute that participated in this project. Informed consent was obtained from all the participants.

Genotyping and Data Cleaning

Genotyping for 600,307 SNPs was performed with 257 genomic DNA samples extracted from patients with fulminant type 1 diabetes using the Axiom Genome-Wide ASI 1 Array (Affymetrix, Santa Clara, CA). The genotype calls for these 600,000 SNPs obtained with genotype data from 257 patients with fulminant type 1 diabetes and 419 healthy volunteers were determined using Genotyping Console Software (version 4.2). The GWAS genotype data from the healthy volunteers were previously acquired using the Axiom Genome-Wide ASI 1 Array and are commonly used for various studies as general population data. All the samples had an overall call rate of >97%, with an average overall call rate of 99.42% (minimum 97.86; maximum 99.82), and passed a heterozygosity check. No related individuals (percent identical ≥0.1) were identified by identity-by-descent testing. A principal component analysis was carried out to check the genetic background of the 257 fulminant type 1 diabetes samples and 419 samples from healthy Japanese volunteers from the International HapMap Project (43 Japanese in Tokyo [JPT], 40 Han Chinese in Beijing [CHB], 91 Yoruba in Ibadan [YRI], and 91 Utah residents [CEPH] with Northern and Western European ancestry [CEU] samples) (Supplementary Fig. 1).

Data cleaning was performed for SNP quality control according to the following criteria: SNP call rate of ≥95% in both the case and control subjects, minor allele frequency (MAF) of ≥5% in both the case and control subjects, and no extreme departure from the Hardy-Weinberg equilibrium P value ≥0.001 in the control subjects (Supplementary Table 2). All cluster plots for SNPs with $P < 0.0001$ based on a χ^2 test of the allele frequency model were checked by visual inspection, and SNPs with ambiguous genotype calls were excluded. Of the SNPs on autosomal chromosomes, 426,851 finally passed the quality-control filters and were used for the association analysis. A quantile-quantile plot of the distribution of test statistics for the comparison of genotype frequencies in fulminant type 1 diabetes case and healthy control subjects showed that the inflation factor λ was 1.061 for all the tested SNPs, including those in the HLA region (from *HLA-F* to *KIFC1*; chromosome 6: 29,645,000–33,365,000; 3.72 Mb [hg19]), and was 1.046 when SNPs in the HLA region were excluded (Supplementary Fig. 2). Because early inflated test statistics were obtained after exclusion of the SNPs in the HLA region, we performed a logistic regression test using the top two components as covariates as well as an association test correcting for stratification using the genomic control approach (20).

Fine Mapping

We selected 13 additional SNPs in the region of the top-hit SNP on chromosome 12q13.13 based on the linkage disequilibrium (LD) and the MAF (>5%, except for rs3817537 in *ITGB7*, for which the MAF was 2.93%). The tagging SNPs were selected based on genotype data from the International HapMap Project (21) and the NBDC Human Database (National Bioscience Database Center [https://humandbs.biosciencedbc.jp/en/]). These SNPs and the three SNPs rs11170445, rs4606556, and rs2272299 (those with the lowest P values) from the GWAS, were genotyped by real-time PCR analysis with TaqMan probes (Applied Biosystems, Tokyo, Japan). The haplotypes were estimated using the PHASE program, version 2.1 (22,23).

Genotype Imputation

The imputation was conducted with the IMPUTE2 (v2.3.2) program using the haplotype reference panel from phase one of the 1000 Genomes Project without singleton sites (24). For performance of genome-wide imputation while avoiding the restrictions of the program, 10-Mbp intervals were set along the chromosomes, and imputation was repeated for all intervals.

Stratification by HLA

The association of the top-hit SNP rs3782151 in *CSAD* with fulminant type 1 diabetes was evaluated relative to HLA with the top-hit SNP, rs9268853, in the HLA-DR region in all subjects and with HLA haplotypes in a subset of subjects whose HLA genotypes were available (419 control subjects and 216 patients with fulminant type 1 diabetes). HLA-*DRB1* and -*DQB1* were genotyped by PCR using sequence-specific primers and PCR sequence-specific oligonucleotide methods as previously reported (13,15).

Resequencing of the Candidate Gene

The *CSAD* region was resequenced in 32 participants who were homozygous for the risk allele at rs3782151. A 23-kb region of *CSAD* (chromosome 12: 53,551,446–53,574,693) was sequenced with the Ion AmpliSeq technology. The target region was enriched with the AmpliSeq custom DNA panel, the Ion AmpliSeq Library Kit 2.0, and the Ion Xpress Barcode Adapters kits (Takara Bio, Inc., Kusatsu, Japan). All coding exons and exon-intron junctions and 70% of the untranslated regions (UTRs) and introns were successfully amplified and sequenced with the Ion Proton System, resulting in sequence results of 17.16-kb region (Supplementary Fig. 3 [green]). As a result of technical difficulty, sequence results in some of the introns and untranslated regions were not obtained (Supplementary Fig. 3 [red]). The alignment and identification of variants were performed using Torrent Suite Software with NCBI (National Center for Biotechnology Information) build 37 (GRCh37/hg19) as the reference human genome. The annotation of nucleotide variants was performed with Ion Reporter Software.

The His288Arg variant of *CSAD* was genotyped using real-time PCR analysis with TaqMan probes (Applied Biosystems, Tokyo, Japan) in 257 patients with fulminant type 1 diabetes, 410 patients with autoimmune type 1 diabetes, and 357 control subjects (13).

Statistical Analysis

Allele data were analyzed in 2×2 contingency tables using the χ^2 test. The LD and haplotype analyses were performed using Haploview 4.2 software (25). Here, each haplotype was assumed to be one of the alleles at a biallelic locus, and the other haplotypes were assumed to be the other allele. For example, the haplotype ACACTGAAGAGTC and the other haplotypes were designated "A allele" and "B allele," respectively. The meta-analysis was performed using the Mantel-Haenszel method (fixed effects models). The P values for the heterogeneity among the panels joined in the Mantel-Haenszel tests were all >0.05.

RESULTS

A highly significant association was observed for multiple SNPs in the HLA region on chromosome 6, and the strongest association was found for rs9268853 in the HLA class II DR region ($P = 1.56 \times 10^{-23}$, odds ratio [OR] 3.18 [95% CI 2.53–4.01]) (Fig. 1 and Supplementary Fig. 4). In addition, a total of 11 SNPs outside the HLA region showed some evidence of association ($P < 1.0 \times 10^{-5}$) (Supplementary Table 3). In particular, rs11170445 on chromosome 12q13.13 showed an association with genome-wide significance ($P = 7.58 \times 10^{-9}$, OR 1.96 [95% CI 1.56–2.46]), and this evidence provides the first

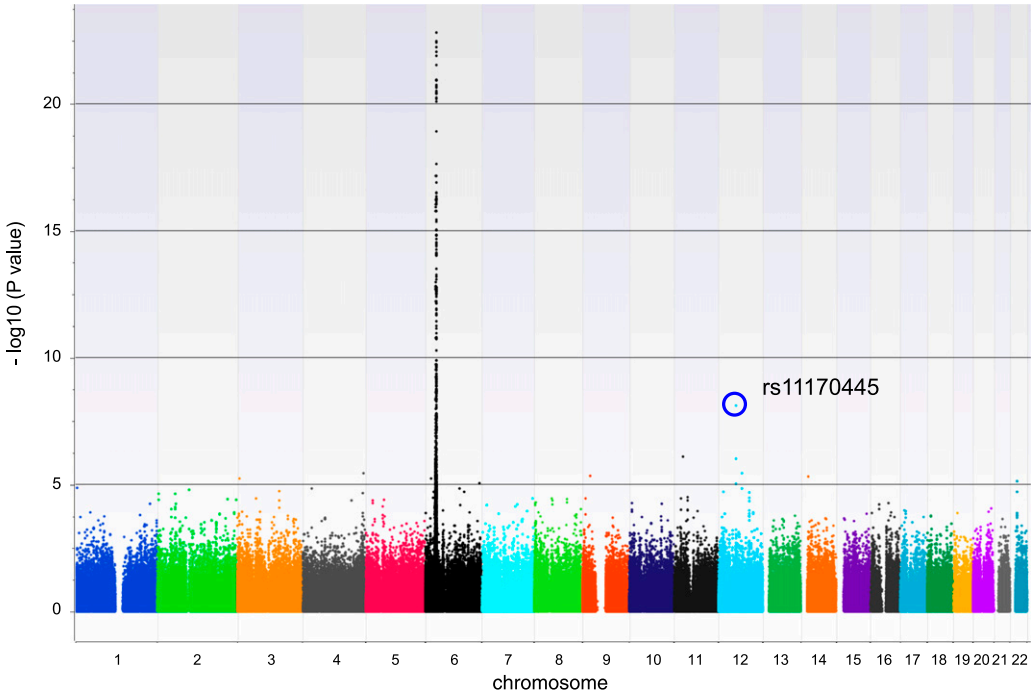

Figure 1—Manhattan plot presenting the *P* values across the genome. The $-\log_{10} P$ values from 426,851 SNPs in 257 fulminant type 1 diabetes case subjects and 419 control subjects plotted according to their physical positions on successive chromosomes. A SNP associated with fulminant type 1 diabetes with genome-wide significance outside the HLA region is circled.

indication of a region outside the HLA region that exhibits a genome-wide significant association with fulminant type 1 diabetes. Two SNPs (rs4606556 and rs2272299) located in the vicinity of rs11170445 also showed low *P* values (Supplementary Table 3). To remove a potential effect of population stratification, we performed a logistic regression test using the top two components as covariates and an association test correcting for stratification using the genomic control approach. Both analyses showed a significant association for rs11170445, with $P = 6.39 \times 10^{-8}$ and $P = 7.58 \times 10^{-9}$, respectively.

Fine mapping of the region surrounding rs11170445 identified multiple SNPs with low *P* values, and the strongest association was observed for rs3782151 ($P = 4.60 \times 10^{-9}$, OR 1.97 [95% CI 1.57–2.48]) (Table 1, Fig. 2, and Supplementary Fig. 5). Association tests using imputed genotypes with data from the 1000 Genomes Project revealed similar results (Table 1 and Supplementary Table 4). An LD analysis identified a 65-kb LD block containing three protein-coding genes (*CSAD, ZNF740*, and *ITGB7*) (Fig. 2*C* and *D* and Supplementary Fig. 6). The top-hit SNP in the GWAS, rs11170445, and that identified by fine mapping, rs3782151, are in complete LD in healthy individuals and strong LD ($r^2 = 0.98$) in patients with fulminant type 1 diabetes. When conditional analysis by controlling for rs3782151 in *CSAD* was carried out, neither rs2272299 in *ZNF740* nor rs4606556 in *ITGB7* was associated with fulminant type 1 diabetes (Supplementary Table 5). A haplotype association test using all 13 SNPs in LD block 1 showed that all the risk haplotypes associated with fulminant type 1 diabetes contained the minor A allele of rs3782151. Furthermore, no haplotypes showed a lower *P* value than the top-hit SNP, rs3782151 (Supplementary Table 6), which suggests that the minor A allele of rs3782151 in *CSAD* is primarily associated with susceptibility to fulminant type 1 diabetes.

Because HLA confers strong susceptibility to fulminant type 1 diabetes, we examined the interaction of SNPs in *CSAD* with HLA. A regression analysis using a top-hit SNP in the HLA region, rs9268853, as a covariate showed that rs11170445, a top-hit SNP outside the HLA region identified in the GWAS, exhibited a strong association with fulminant type 1 diabetes ($P = 6.23 \times 10^{-7}$) (Supplementary Fig. 7). No significant interaction was observed for rs3782151, a top-hit SNP in the *CSAD* identified in the fine mapping, with rs9268853 in the HLA region by the heterogeneity test ($P = 0.332$).

In addition to the above-mentioned comparison with the top-hit SNP in the HLA region, the interactions of rs3782151 with HLA haplotypes and genotypes were also assessed. The Asian-specific *DR4* (*DRB1*04:05-DQB1*04:01*) and *DR9* (*DRB1*09:01-DQB1*03:03*) haplotypes were significantly associated with fulminant type 1 diabetes (Supplementary Table 7), as previously reported (13–15). No heterogeneity in the strength of the association was identified depending on the presence or absence of susceptible HLA haplotypes (Supplementary Table 7). A top-hit SNP in the HLA region, rs9268853, was in LD with *DR4* and *DR9* haplotypes (Supplementary Table 7). The differences in the HLA region between patients with

Table 1—Association of SNPs on chromosome 12q13.13 with fulminant type 1 diabetes

Chr.	Position	SNP	Risk/reference allele	Gene(s) or nearby gene(s)	RAF case	RAF control	OR (95% CI)†	*P*	Imputation§ *P*	Imputation§ OR
12q13.13	53129030	rs7965802	G/A	*SOAT2*	0.471	0.35	1.65 (1.32–2.07)	1.02×10^{-5}	—	—
12q13.13	**53151908**	**rs11170445**	**T/C**	***CSAD***	**0.447**	**0.294**	**1.94 (1.55–2.44)**	$\mathbf{1.06 \times 10^{-8}}$	$\mathbf{7.58 \times 10^{-9}}$	**1.96**
12q13.13	53158691	rs12161793	G/A	*CSAD*	0.272	0.163	1.93 (1.47–2.52)	1.22×10^{-6}	1.00×10^{-6}	1.94
12q13.13	**53158877**	**rs3782151**	**A/C**	***CSAD***	**0.451**	**0.294**	**1.97 (1.57–2.48)**	$\mathbf{4.60 \times 10^{-9}}$	$\mathbf{8.82 \times 10^{-9}}$	**1.95**
12q13.13	53159448	rs2272305	C/T	*CSAD*	0.273	0.162	1.94 (1.49–2.54)	9.28×10^{-7}	1.00×10^{-6}	1.94
12q13.13	53160499	rs2272306	A/G	*CSAD*	0.175	0.129	1.43 (1.06–1.95)	0.020	0.039	1.38
12q13.13	53180119	rs2293429	C/A	*CSAD/ZNF740*	0.273	0.165	1.90 (1.45–2.48)	2.11×10^{-6}	9.84×10^{-7}	1.93
12q13.13	53181775	rs3814777	G/A	*CSAD/ZNF740*	0.276	0.164	1.94 (1.49–2.53)	8.24×10^{-7}	9.84×10^{-7}	1.93
12q13.13	53187018	rs4606556	T/G	*ZNF740*	0.275	0.163	1.94 (1.48–2.53)	9.95×10^{-7}	—	—
12q13.13	53188711	rs2272298	G/A	*ZNF740*	0.06	0.056	1.08 (0.68–1.72)	0.754	0.337	0.71
12q13.13	53193038	rs2272299	A/G	*ITGB7*	0.245	0.149	1.85 (1.40–2.44)	1.11×10^{-5}	—	—
12q13.13	53193684	rs2272300	G/T	*ITGB7*	0.245	0.15	1.85 (1.40–2.44)	1.22×10^{-5}	9.62×10^{-6}	1.86
12q13.13	53194568	rs2272301	G/C	*ITGB7*	0.18	0.134	1.42 (1.05–1.92)	0.022	0.016	1.47
12q13.13	53200147	rs3825084	C/A	*ITGB7*	0.202	0.162	1.31 (0.99–1.74)	0.061	0.078	1.31
12q13.13	53200476	rs3741435	T/C	*ITGB7*	0.246	0.16	1.71 (1.31–2.25)	9.76×10^{-5}	1.99×10^{-5}	1.82
12q13.13	53209954	rs1554753	G/A	*RARG*	0.453	0.389	1.30 (1.04–1.63)	0.020	0.220	1.29

The SNPs with genome-wide significant associations are shown in boldface type. Chr., chromosome; RAF, risk allele frequency. †OR for risk allele. §Genotype imputation using the 1000 Genomes Project data were performed using IMPUTE2 software with the default parameters.

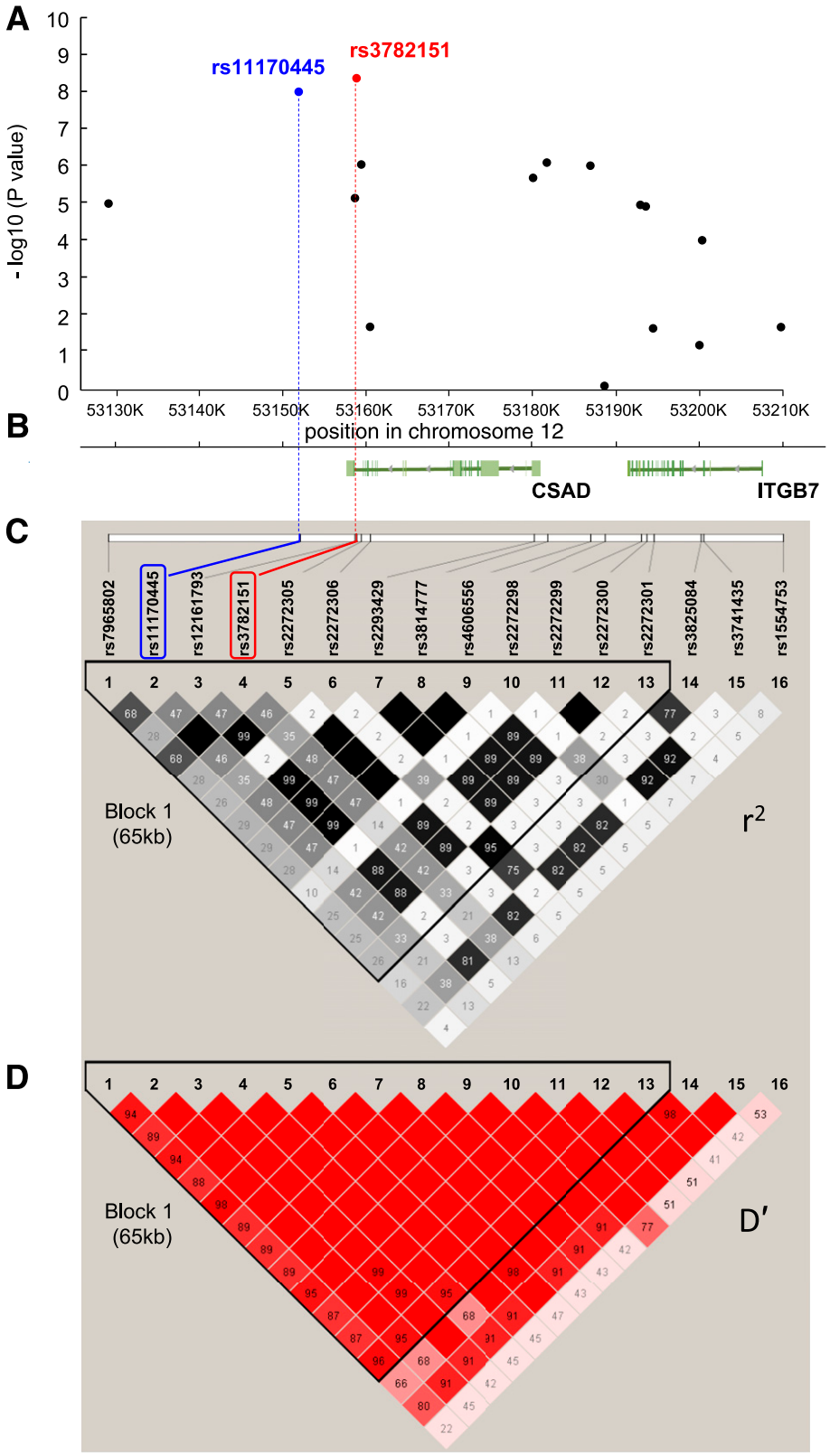

Figure 2—LD structure for the risk locus for fulminant type 1 diabetes in an ~80-kb genetic region on chromosome 12q13.13. *A*: The $-\log_{10}$ (*P* values) for 16 tagged SNPs compared between 257 patients with fulminant type 1 diabetes and 419 healthy individuals. K, thousands. *B*: Genomic location of the RefSeq genes and their intron and exon structures (NCBI). *C* and *D*: Haploview plot of the LD between markers measured based on r^2 (*C*) and D′ (*D*) in the 419 healthy individuals and LD blocks, which were defined using Gabriel's algorithm. Two SNPs associated with fulminant type 1 diabetes with genome-wide significance are highlighted.

fulminant type 1 diabetes who were or were not pregnant have previously been reported (26). To minimize the heterogeneity in fulminant type 1 diabetes, however, we included only nine pregnant patients with fulminant type 1 diabetes in the current study, and, thus, a subgroup analysis was not performed.

We also evaluated the association of rs3782151 with classical autoimmune type 1 diabetes. The association of rs3782151 with autoimmune type 1 diabetes was weak (OR 1.31, $P = 0.011$) compared with its very strong association with fulminant type 1 diabetes (OR 1.97, $P = 4.60 \times 10^{-9}$) (Table 2). The frequency of the minor allele at rs3782151 was significantly higher in fulminant type 1 diabetes compared with autoimmune type 1 diabetes (0.451 vs. 0.352, $P = 3.13 \times 10^{-4}$) (Table 2), suggesting that the association of rs3782151 in *CSAD* with type 1 diabetes is unique to the fulminant subtype.

In addition to rs3782151 in *CSAD*, we investigated the association of SNPs in *ITGB7* with type 1 diabetes because rs11170466 in *ITGB7*, which is located 33 kb distal to rs3782151, has been reported to be associated with autoimmune type 1 diabetes in populations of European descent (27). Two SNPs in *ITGB7* (rs2272299 in the current study and rs11170466 in reference 27) are in the same LD block and were in complete LD in the 419 control samples included in the current study. The association of rs3782151 in *CSAD* ($P = 4.60 \times 10^{-9}$) with fulminant type 1 diabetes was much stronger than the association of rs2272299 in *ITGB7* (Table 2). The frequencies of the minor allele at rs2272299 in *ITGB7* were not significantly different between fulminant and autoimmune type 1 diabetes ($P = 0.342$), which is in clear contrast with the above-described findings obtained for the risk allele of rs3782151 in *CSAD* in fulminant type 1 diabetes (Table 2).

To investigate the contribution of the *CSAD-ITGB7* region to type 1 diabetes in different ethnic groups, we studied rs3782151 in *CSAD* and rs2272299 in *ITGB7* in populations of European descent. Owing to the near absence of fulminant type 1 diabetes in European populations (4,5), only autoimmune type 1 diabetes was studied. Autoimmune type 1 diabetes was associated with rs2272299 in *ITGB7*, but not with rs3782151 in *CSAD*, in a large scale study of the European population in the Type 1 Diabetes Genetics Consortium (Supplementary Table 8). This tendency is similar to that found in the Japanese population, in which *ITGB7* rs2272299 (OR 1.63, $P = 0.0001$) showed a stronger association than *CSAD* rs3782151 (OR 1.31, $P = 0.011$). A meta-analysis of the two populations showed an association between rs2272299 in *ITGB7* (summary OR 1.21 [95% CI 1.10–1.34], $P = 9.68 \times 10^{-5}$), but not rs3782151 in *CSAD* (summary OR 1.05 [95% CI 1.00–1.12], NS), and autoimmune type 1 diabetes.

An analysis of the *CSAD-ITGB7* haplotypes indicated that the A-A, but not the A-G, haplotype was associated with autoimmune type 1 diabetes (Supplementary Tables 9 and 10), indicating a primary association for *ITGB7* with autoimmune type 1 diabetes. In contrast, a positive association was found for the A-A and A-G haplotypes with fulminant type 1 diabetes, but a negative association was obtained for the C-G haplotype, indicating a primary association for *CSAD* with fulminant type 1 diabetes (Supplementary Table 9). This finding suggests the existence of two distinct loci for type 1 diabetes in the *CSAD-ITGB7* region—one in *CSAD* for the fulminant subtype and the second in *ITGB7* for the autoimmune subtype. A haplotype analysis in subjects of European descent indicated that the A-A haplotype was significantly associated with susceptibility to autoimmune type 1 diabetes, similarly to the findings obtained for the Japanese population (Supplementary Tables 9 and 10). The A-G haplotype, however, was associated with protection against autoimmune type 1 diabetes in the European population, in contrast with its neutral effect on autoimmune type 1 diabetes and its association with susceptibility to fulminant type 1 diabetes in the Japanese population. The frequencies of the various haplotypes were markedly different between the two populations, with a much lower frequency of the A-A haplotype and a higher frequency of the A-G haplotype in the population of European descent compared with those in the Japanese population (Supplementary Table 10).

To clarify the contribution of *CSAD* to disease susceptibility, we sequenced the *CSAD* region in 32 individuals with fulminant type 1 diabetes who were homozygous for the risk allele at rs3782151 and identified 31 single nucleotide variants, including 1 nonsynonymous variant (chromosome 12: 53161148 [hg19], His288Arg) in the coding region (Supplementary Table 11). For study of the contribution of the chromosome 12: 53161148 (hg19) nucleotide change to susceptibility to fulminant type 1 diabetes, a total of 1,024 subjects were genotyped. The allele frequency of this variant was 0.2% in subjects with fulminant type 1 diabetes (1 of 514 chromosomes), 0% in subjects with autoimmune type 1 diabetes (0 of 820 chromosomes), and 0% in the control subjects (0 of 714 chromosomes).

The *CSAD* region encodes not only CSAD but also a long noncoding (lnc)RNA termed RP11-1136G11.7-001 (also known as lnc-ITGB7-1:1) (28). The top-hit SNP rs3782151 is located within *RP11-1136G11.7* (*lnc-ITGB7-1*) (Supplementary Fig. 8). To clarify the contribution of the *CSAD/lnc-ITGB7-1* region to the expression of nearby genes, we searched a database of *cis* expression quantitative trait loci (*cis* eQTLs). The top-hit SNP rs3782151 has been reported to be a *cis* eQTL of *ITGB7* in populations of European descent (OR 1.97, $P = 4.60 \times 10^{-9}$) (29) (Table 3). In addition, several SNPs flanking rs3782151 in the *CSAD/lnc-ITGB7-1* region have been reported to be *cis* eQTLs of *ITGB7* in the Japanese population (30,31) (Table 3 and Supplementary Fig. 8).

DISCUSSION

The first genome-wide association study of fulminant type 1 diabetes was performed in Japanese individuals. In

Table 2—Association of SNPs in the *CSAD* and *ITGB7* regions with different type 1 diabetes subtypes (fulminant and autoimmune)

SNP (gene)	Genotype	Control		Type 1 diabetes: Fulminant		Type 1 diabetes: Autoimmune		*P*			OR (95% CI)*		
		n	Frequency	*n*	Frequency	*n*	Frequency	F vs. C	A vs. C	F vs. A	F vs. C	A vs. C	F vs. A
rs3782151 (*CSAD*)	CC	210	0.502	73	0.284	174	0.424						
	CA	170	0.407	136	0.529	183	0.458						
	AA	38	0.091	48	0.187	53	0.129	2.72×10^{-8}	0.044	8.59×10^{-4}			
	Allele	*2n*	Frequency	*2n*	Frequency	*2n*	Frequency						
	C	590	0.706	282	0.549	531	0.648						
	A	246	0.294	232	0.451	289	0.352	4.60×10^{-9}	0.011	3.13×10^{-4}	1.97 (1.57–2.48)	1.31 (1.06–1.60)	1.51 (1.21–1.89)
	Genotype	*n*	Frequency	*n*	Frequency	*n*	Frequency						
rs2272299 (*ITGB7*)	GG	312	0.745	145	0.569	248	0.606						
	GA	89	0.212	95	0.373	140	0.342						
	AA	18	0.043	15	0.059	21	0.051	1.04×10^{-5}	8.33×10^{-5}	0.623			
	Allele	*2n*	Frequency	*2n*	Frequency	*2n*	Frequency						
	G	713	0.851	385	0.755	636	0.778						
	A	125	0.149	125	0.245	182	0.222	1.11×10^{-5}	1.23×10^{-4}	0.342	1.85 (1.40–2.44)	1.63 (1.27–2.10)	1.13 (0.87–1.47)

For *P* value and OR (95% CI) columns: A, autoimmune; C, control; F, fulminant. *2n*, genotype count. *OR for risk allele.

addition to HLA, which was previously identified by a candidate gene approach, variants in *CSAD/lnc-ITGB7-1* on chromosome 12q13.13 were associated with fulminant type 1 diabetes at a genome-wide significance level (Table 1 and Fig. 2).

CSAD encodes cysteine sulfinic acid decarboxylase, which is a key enzyme in taurine synthesis. Taurine has been reported to exert anti-inflammatory and cytoprotective effects by attenuating apoptosis and stimulating antioxidant activity (32–36). The contribution of taurine to the protection of pancreatic islets from destruction has been reported in both type 1 diabetes and streptozotocin-induced apoptosis (37,38), suggesting that *CSAD* variants might contribute to fulminant type 1 diabetes by impairing the protection of pancreatic islets. Since the top-hit SNP rs3782151 is located in an intronic region of *CSAD* (Fig. 2 and Supplementary Fig. 8), we sequenced the *CSAD/lnc-ITGB7-1* region and identified 31 single nucleotide variants, including 1 nonsynonymous variant (chromosome 12: 53161148 [hg19], His288Arg) in the coding region (Supplementary Table 11). This variant was found in 0.2% of patients with fulminant type 1 diabetes but was not observed in subjects with autoimmune type 1 diabetes or control subjects. In addition, the variant is not present in the Genome Aggregation Database (gnomAd) derived from 123,136 exome sequences and 15,496 whole-genome sequences from unrelated individuals sequenced as part of various disease-specific and population genetic studies (http://gnomad.broadinstitute.org/) (39), and we detected only one heterozygote among the 3,408 Japanese individuals in the Tohoku Medical Megabank, which is the largest genome database based on whole-genome sequences of the Japanese general population (https://ijgvd.megabank.tohoku.ac.jp/) (40). These findings indicate that variants in the protein-coding region of *CSAD* are unlikely to be a common cause of fulminant type 1 diabetes.

lncRNAs are generally involved in the regulation of gene expression in many biological systems, including the immune system (41,42), and the contribution of lncRNAs to inflammatory and immune-related diseases has also been reported (41–43). The top-hit SNP rs3782151 identified in this study is located within *lnc-ITGB7-1* (Supplementary Fig. 8) and is reportedly a *cis* eQTL of *ITGB7* obtained from peripheral blood in populations of European descent (29) (Table 3). In addition, recent studies of peripheral blood samples from the Japanese population found that several SNPs flanking rs3782151 in the *CSAD/lnc-ITGB7-1* region are *cis* eQTLs of *ITGB7* (30,31) (Table 3 and Supplementary Fig. 8). In contrast, the effect of these SNPs on the expression of *CSAD* is minimal (Table 3). *ITGB7* encodes integrin β subunit 7 (ITGB7), which is expressed in leukocytes and forms heterodimers with α4 or αE chains. ITGB7 is involved in the migration, entry, and adhesion of lymphocytes in inflamed organs, including the pancreas (44–48). The expression of MAdCAM-1, which is a ligand for the ITGB7 α4β7 heterodimer, has been reported to be upregulated in the inflamed pancreas (47,48).

Disease-associated minor alleles increase *ITGB7* expression (30,31), suggesting that the *CSAD/lnc-ITGB7-1* region contributes to fulminant type 1 diabetes through an increase in *ITGB7* expression and the acceleration of tissue destruction. Antibodies against ITGB7 have been explored for the treatment of inflammatory diseases (49,50). Further studies are necessary to clarify underlying mechanisms of the contribution of *ITGB7* expression to the development of fulminant type 1 diabetes.

The current study suggested the existence of two distinct loci for type 1 diabetes in the *CSAD-ITGB7* region: one in *CSAD/lnc-ITGB7-1* for the fulminant subtype and the second in *ITGB7* for the autoimmune subtype (Table 2 and Supplementary Tables 8 and 10). It is currently unknown why *CSAD/lnc-ITGB7-1* and *ITGB7*, both of which affect the expression of the same gene, are associated with distinct subtypes of type 1 diabetes. Among the possible explanations are differences in their expression levels, tissue distribution, and/or interactions with other susceptibility genes. Although coding variants in *CSAD* are unlikely to be a common cause of fulminant type 1 diabetes, the possibility that the responsible variant is located within an extended LD region of the CSAD gene cannot be excluded. Further studies are necessary to clarify these hypotheses.

In addition to *CSAD/lnc-ITGB7-1* on chromosome 12q13.13, several SNPs throughout the genome have also been suggested to be associated with fulminant type 1 diabetes (Supplementary Table 3). With the exception of *ITGB7* on chromosome 12q13.13, as described above, none of the regions that showed some evidence of association with fulminant type 1 diabetes overlapped with previously reported susceptibility loci for type 1 diabetes (ImmunoBase: www.t1dbase.org/disease/T1D/) (Supplementary Table 3). Further studies are needed to clarify the contribution of these SNPs to fulminant as well as classical type 1 diabetes.

In conclusion, we conducted the first genome-wide association study of fulminant type 1 diabetes patients and identified *CSAD/lnc-ITGB7-1* on chromosome 12q13.13 as the first non-HLA susceptibility locus for fulminant type 1 diabetes. The current study also suggested the possibility that two distinct loci for type 1 diabetes exist in the *CSAD-ITGB7* region on chromosome 12q13.13: one in *CSAD/lnc-ITGB7-1* for the fulminant subtype and the second in *ITGB7* for the autoimmune subtype. Elucidating the genetic landscape of fulminant type 1 diabetes will provide novel insights into the molecular mechanisms of not only fulminant type 1 diabetes but also type 1 diabetes in general, including type 1 diabetes associated with immune checkpoint therapy.

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Table 3—SNPs in the *CSAD* region on chromosome 12q13.13 as *cis* eQTLs of *ITGB7* and *CSAD*

Position*	SNP	Risk/reference allele	Gene or nearby gene	Association with the disease		*P* for eQTLs: *ITGB7*‡	*P* for eQTLs: *ITGB7*§	*P* for eQTLs: *CSAD*§
				OR (95% CI)†	*P*			
53129030	rs7965802	G/A	*SOAT2*	1.65 (1.32–2.07)	1.02×10^{-5}	3.96×10^{-15}	—	—
53151908	rs11170445	T/C	*CSAD*	1.94 (1.55–2.44)	1.06×10^{-8}	5.05×10^{-10}	1.48×10^{-5}	0.021
53158691	rs12161793	G/A	*CSAD*	1.93 (1.47–2.52)	7.30×10^{-6}	4.00×10^{-93}	1.89×10^{-10}	0.016
53158877	rs3782151	A/C	*CSAD*	1.97 (1.60–2.48)	4.60×10^{-9}	5.28×10^{-10}	—	—
53159448	rs2272305	C/T	*CSAD*	1.94 (1.49–2.54)	9.28×10^{-7}	—	—	—
53180119	rs2293429	C/A	*CSAD/ZNF740*	1.90 (1.45–2.48)	2.11×10^{-6}	2.43×10^{-93}	2.03×10^{-10}	0.016
53181775	rs3814777	G/A	*CSAD/ZNF740*	1.94 (1.49–2.53)	8.24×10^{-7}	2.11×10^{-95}	2.03×10^{-10}	0.016
53187018	rs4606556	T/G	*ZNF740*	1.94 (1.48–2.53)	9.95×10^{-7}	3.74×10^{-99}	2.03×10^{-10}	0.016
53193038	rs2272299	A/G	*ITGB7*	1.85 (1.40–2.44)	1.11×10^{-5}	—	1.46×10^{-10}	0.054
53193684	rs2272300	G/T	*ITGB7*	1.85 (1.40–2.44)	1.22×10^{-5}	1.06×10^{-114}	1.46×10^{-10}	0.054

A dash (—) indicates that no data were available for these SNPs. *Genome Reference Consortium Human Build 38 patch release 7 (GRCh38.p7), annotation release 108. †OR for risk allele. ‡Data for populations of European descent obtained from the Blood eQTL browser (www.genenetwork.nl/bloodeqtlbrowser/). §Data for the Japanese population obtained from the Human Genetic Variation Database (www.hgvd.genome.med.kyoto-u.ac.jp/); the data included in the database were initially obtained from peripheral blood cells.

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Author Contributions. Y.K., N.N., T.A., E.K., K.T., K.Y., and H.I. conducted the data analyses. N.N. and K.To. conducted the genotyping and data quality control. Y.K., T.A., E.K., A.I., A.S., H.O., S.T., K.Ta., M.N., H.Y., Y.U., H.K., H.M., T.K., and T.H. collected the samples and discussed the results. T.K. and T.H. managed and organized the consortium on the committee on type 1 diabetes of the Japan Diabetes Society. H.I. drafted the manuscript. H.I. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Appendix

T.A., E.K., K.Y., K.To., and H.I. are Core members for genetic analysis in the committee on type 1 diabetes, Japan Diabetes Society. T.K. and T.H. are co-chairs of the committee on type 1 diabetes, Japan Diabetes Society.

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