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Fine Localization of a Major Disease-Susceptibility Locus for Diffuse Panbronchiolitis

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Summary

Diffuse panbronchiolitis affecting East Asians is strongly associated with the class I human leukocyte antigen (HLA) alleles. Recent observations suggest that a major disease-susceptibility gene may be located between the HLA-B and HLA-A loci in the class I region of the major histocompatibility complex on chromosome 6. To test this possibility, we analyzed 14 polymorphic markers in 92 Japanese patients and 93 healthy controls. Of these, seven marker alleles, including HLA-B54 and HLA-A11, were significantly associated with the disease. Maximum-likelihood haplotype analysis and subsequent direct determination of individual haplotypes identified a group of disease-associated haplotypes, one of which contained all seven disease-associated marker alleles. Another haplotype, containing HLA-B*5504, was also associated with the disease. All these haplotypes seem to have diverged from a common ancestral haplotype in East Asians and share a specific segment containing three consecutive markers between the S and TFIIH loci in the class I region. Furthermore, one of the markers within the candidate region showed the highest delta value, indicating the strongest association. Of 20 Korean patients with diffuse panbronchiolitis, 17 also shared the combination of the disease-associated marker alleles within the candidate region. These results indicate that an HLA-associated major susceptibility gene for diffuse panbronchiolitis is probably located within the 200 kb in the class I region 300 kb telomeric of the HLA-B locus on the chromosome 6p21.3.

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Introduction

Diffuse panbronchiolitis is characterized by sinobronchial infection and diffuse bilateral micronodular pulmonary lesions (Fraser et al. 1990) and is considered to be a complex genetic disease predominantly affecting East Asians, occurring with a frequency of .00011 in Japanese. This chronic airway disease was first described in Japanese patients (Homma et al. 1983) and subsequently in Koreans (Kim et al. 1992) and Chinese (Chu et al. 1992; Tsang et al. 1998), and a few cases have been reported outside Asia, notably in Asian emigrants (Høiby 1994; Corne 1996). Most of the patients are the only affected members in their pedigrees, and disease association studies have been the sole method of genetic analysis. An earlier study in the Japanese population showed that human leukocyte antigen (HLA)-B54, found only in East Asians, was strongly associated with the disease (Sugiyama et al. 1990), and this positive association was further confirmed at the nucleotide-sequence level in our larger study (Keicho et al. 1998). The disease-associated serotype HLA-B54 corresponded to a single allele of the HLA-B gene, B*5401. More recently, an HLA study in the Korean population showed that HLA-A11 was most significantly associated with the disease (Park et al. 1999). Considering the close relationship between the Japanese and Korean HLA profiles and their genetic background (Tokunaga et al. 1996; Park et al. 1998), we have hypothesized that a founder mutation of a putative disease-susceptibility gene located between the HLA-B and HLA-A loci occurred on an ancestral chromosome bearing HLA-B54 and HLA-A11 in East Asia. It is conceivable that different historical recombination events around the disease locus have resulted in disease associations with HLA-B54 in Japanese and HLA-A11 in Koreans.

When there is a founder effect in a population for simple Mendelian disorders with relatively high penetrance, such as cystic fibrosis and hereditary hemochro-

matosis in whites, linkage-disequilibrium mapping and haplotype analysis subsequent to conventional linkage analysis often have been used successfully for high-resolution mapping and cloning of the disease genes (Kerem et al. 1989; Feder et al. 1996). For complex genetic diseases, however, standard techniques for fine mapping of disease-susceptibility genes have not been established yet, mainly because the disease status of chromosomes is not defined primarily by their pedigree data, because of low penetrance and phenocopies (Lander and Schork 1994). In the present study, we used 14 genetic markers, including 9 highly polymorphic microsatellites recently described in the HLA class I region for the purpose of refined mapping of HLA-associated diseases (Tamiya et al. 1998, 1999), and attempted to identify disease-associated haplotypes and a shared identical-by-descent critical region.

Subjects and Methods

Subjects

Ninety-two unrelated Japanese patients with diffuse panbronchiolitis participated in the present study. The diagnosis of diffuse panbronchiolitis was made in Toranomon Hospital, Tenri Hospital, or Nippon Medical School Hospital, according to the criteria proposed in 1995 by the working group of the Ministry of Health and Welfare of Japan (Keicho et al. 1998). Ninety-three normal controls were healthy Japanese volunteers from the same area of Japan. Genotyping of 20 Korean patients was also done, although their pedigree data were not available.

HLA Typing

Class I HLA-A, HLA-B, and HLA-C antigens were serologically typed by the conventional NIH standard method with well-defined antisera. A part of their HLA data was previously described (Keicho et al. 1998). The presence of HLA-B*5504 encoding B55.2, a rare antigen in the Japanese population, was further confirmed by the PCR-based genotyping method (Bannai et al. 1997).

Detection of Single-Nucleotide Polymorphisms in HLA-E and Transcription-Factor IIH Genes in the Class I Region

Exon 3 of the HLA-E gene encoding a nonclassical HLA molecule and exon 1 of the general transcription-factor (TF) IIH (GTF2H4) gene encoding the 52-kilodalton subunit of the TFIIH were amplified with specific primers, and variations within the exons were genotyped by the PCR-SSCP method described previously (Bannai et al. 1997). "R" and "G" of the HLA-E gene indicate Arg-107 and Gly-107 caused by a nonsynonymous nucleotide substitution in the coding region (Geraghty et al. 1992). "T" and "C" of the TFIIH gene represent a single-nucleotide substitution within its 5′-untranslated region (GenBank accession numbers AB032121 and AB023050).

Determination of Microsatellite Alleles

C1_4_3, C1_3_2, C2_2_2, C2_4_4, C4_4_3, C4_2_7, C4_2_12, and C3_2_12 are all microsatellite markers recently identified in the HLA class I region, and they were named as follows: the first part ("C1" to "C4") represents the serial numbers of consensus genomic sequences or contigs, the second part ("_2" to "_4") indicates the number of nucleotides in repetition units, and the last part shows the serial numbers in each group. Characterization of these markers, their fluorescein-labeled PCR primers, and PCR conditions have been described elsewhere (Tamiya et al. 1998, 1999). The only exception is that PCR products of C4_4_3 were digested with *Taq*I instead of *Sau*3AI, and the fragment size was reduced to <500 bp for the subsequent allele typing. The PCR products were mixed with deionized-formamide dye and a size standard marker GENESCAN-500 TAMRA (PE Biosystems), denatured at 94°C for 4 min, and separated on a 4% polyacrylamide sequencing gel containing 8 M urea in an automated DNA sequencer ABI PRISM 377 equipped with the Genescan Software (PE Applied Biosystems). The size of each allele fragment was determined by comparison with the positions of the standard marker.

Constructing Haplotypes

Frequencies of predominant haplotypes in the disease and control populations were estimated by using a computer program presented at the 11th International Histocompatibility Workshop (Imanishi et al. 1992*a*). On the basis of the maximum-likelihood method, the program can estimate frequencies of haplotypes consisting of up to five loci when the population studied is in Hardy-Weinberg equilibrium. Furthermore, extended HLA haplotypes of nine B54 (HLA-B*5401)-positive patients and two B55.2 (HLA-B*5504)-positive patients were directly assigned on the basis of genotyping results of individual family members.

Statistical Analysis

Disease associations with markers were assessed by the χ^2 test. When any expected number in the 2 × 2 contingency table was <5, the P value was directly calculated by Fisher's exact test. The corrected P value (Pc) was calculated as the P value multiplied by the number of comparisons made. The odds ratio (OR) was defined as the cross-product ratio of the numbers shown in the 2 × 2 table. To examine whether genotype frequencies in the populations are compatible with Hardy-Weinberg

equilibrium, Hardy-Weinberg exact tests for multiple alleles provided by GENEPOP software package were done (Guo and Thompson 1992). *P* values <.05 were considered significant to show a deviation from Hardy-Weinberg equilibrium.

The degree of association was further evaluated by the original form of the delta statistic (Bengtsson and Thomson 1981). This statistic was originally proposed as a measure of associations of HLA antigens with a disease in a case-control study. This statistic is not affected by allele-frequency variation at different loci and has been reported to be more suitable than the odds ratio, for the estimation of the closest marker to the primary disease-susceptibility locus, when the specific alleles of several markers are in linkage disequilibrium with the disease allele of the susceptibility gene (Bengtsson and Thomson 1981; Devlin and Risch 1995).

Results

Disease-Associated Marker Alleles

Fourteen markers were analyzed, including nine polymorphic microsatellites, single-nucleotide substitutions within two principal genes, HLA-E and TFIIH, and serotypes of three classical HLA loci in the class I region, HLA-B, HLA-C, and HLA-A. Of these, alleles with significantly higher frequencies in the patient population than in controls ($P < .05$) are listed in table 1. As shown in our previous study (Keicho et al. 1998), the frequency of HLA-B54 was significantly increased in the patient population. The frequencies of HLA-Cw1 and HLA-A11 also were increased, but to lesser degrees. Of the other marker alleles, C1_4_3-441, C2_2_2-251, C2_4_4-231, and C4_2_12-221 were associated with the disease ($P < .05$). Disease associations with all the markers but C1_4_3-441 were robust, even after the correction for multiple testing ($Pc < .05$).

Predominant Haplotypes Estimated in the Control and Patient Populations

To examine whether the disease-associated marker alleles shown in table 1 construct a single haplotype or a group of disease-associated haplotypes, we first estimated haplotype profiles in the control and patient populations by the maximum-likelihood method. HLA-B, C2_2_2, C2_4_4, C4_2_12, and HLA-A were chosen for this five-locus analysis, because specific alleles of these loci exhibited the highest χ^2 values in table 1. The distribution of each marker did not deviate from Hardy-Weinberg equilibrium in both populations, which was a prerequisite for this analysis (data not shown). HLA-B52-A24, HLA-B44-A33, HLA-B46-A2, HLA-B7-A24, and HLA-B54-A24 haplotypes known to be most common in the Japanese population were identified in the controls as expected (CN1 to CN5 in table 2). In the patient population, the HLA-B54-A24 haplotype, HLA-B54-251-231-221-A24, was predominant (PT1 in table 2) and its frequency was estimated to be 10.9%, which was remarkably increased from 3.1% in the controls (CN5). In addition to the HLA-B54-A24 haplotype, two other B54-containing haplotypes, HLA-B54-251-231-243-A11 and HLA-B54-251-231-221-A11, also were identified in the patient population (PT4 and PT5), and their frequencies in the controls were estimated to be <1% (data not shown). Of these three haplotypes predicted in the patient population, HLA-B54-251-231-221-A11 contained all the disease-associated alleles of the tested five loci as shown in table 1, and the other two haplotypes contained four of these five alleles. In contrast, the HLA-B44-A33 haplotype demonstrated to be the second-most common haplotype in the controls (CN2) was not found in the patient population.

Table 1

Disease-Associated Marker Alleles

Marker	No. of Alleles	Allele Name[a]	No. (%) of Patients	No. (%) of Controls	χ^2	*P*	*Pc*
HLA-B	21	54	34 (37)	14 (15)	11.5	.0007	.014
HLA-C	5	1	45 (49)	28 (30)	6.8	.0089	.044
C1_4_3	11	441	43 (47)	26 (28)	7.0	.0083	.090
C1_3_2	8	…	…	…	…	…	…
C2_2_2	8	251	81 (88)	64 (69)	10.1	.0015	.011
C2_4_4	10	231	82 (89)	64 (69)	11.5	.0007	.007
C4_4_3	3	…	…	…	…	…	…
TFIIH	2	…	…	…	…	…	…
C4_2_7	12	…	…	…	…	…	…
C4_2_12	9	221	43 (47)	22 (24)	10.8	.0010	.009
HLA-E	2	…	…	…	…	…	…
C3_2_12	18	…	…	…	…	…	…
D6S265	6	…	…	…	…	…	…
HLA-A	8	11	37 (40)	19 (20)	8.6	.0034	.027

[a] Only alleles with significantly higher frequencies in patients than in controls ($P < .05$) are listed.

Individual Haplotypes Containing HLA-B54

To specify the B54-containing haplotypes characterizing the patient population, we directly determined individual haplotypes containing B54. Typing data for 14 markers in 9 patients and their family members were obtained (1–9 in table 3). B54-containing haplotypes from patients 1, 2, and probably 3 and 4 represented the pattern of HLA-B54-251-231-221-A24. Similarly, the haplotypes from patients 5 and 6 corresponded to HLA-B54-251-231-243-A11. Haplotype 7 was consistent with HLA-B54-251-231-221-A11 and contained all the disease-associated marker alleles described in table 1. Haplotypes 8 and 9 did not match any of the three patterns. All of the B54-containing haplotypes shared specific alleles from HLA-B to C4_4_3, HLA-B54-Cw1-

Table 2

Estimation of Predominant Haplotypes in Controls and Patients

	Estimated Predominant Haplotypes in									
	Controls (n = 93)					Patients (n = 92)				
Marker	CN1[a]	CN2	CN3	CN4	CN5	PT1[b]	PT2	PT3	PT4	PT5
HLA-B	52	44	46	7	54	54	7	52	54	54
C2_2_2	265	277	267	251	251	251	251	265	251	251
C2_4_4	243	259	255	231	231	231	231	243	231	231
C4_2_12	243	223	243	223	221	221	223	243	243	221
HLA-A	24	33	2	24	24	24	24	24	11	11
	Haplotype Frequency[c]									
	11.8%	9.1%	4.8%	4.3%	3.1%	10.9%	7.1%	6.0%	4.3%	3.8%

[a] CN1 to CN5 are haplotypes estimated in the control population.
[b] PT1 to PT5 are haplotypes estimated in the patient population.
[c] Only haplotype frequencies >3% are listed.

441-360-251-231-246, whereas alleles from TFIIH to HLA-A were diverse.

*Individual Haplotypes Containing HLA-B*5504*

HLA-B*5504 encoding B55.2 is a rare East Asian allele identified in 0.27% of the Japanese population. Similarities in nucleotide sequences of the B*5401 encoding B54 and B*5504 strongly suggest that these two alleles of the HLA-B gene have diverged from a common ancestral form in Asia (Bannai et al. 1997). In a previous report (Keicho et al. 1998), we showed that the frequencies of both alleles were increased in the patient population. We evaluated the presence of this allele by the genotyping method again and confirmed that its frequency was significantly increased in the patient population (4.3% in the patients vs. 0% in the controls; P = .03). Extended haplotypes of two B*5504-positive patients were also assigned on the basis of genotyping results of individual family members (10 and 11 in table 3). Although B*5504-containing haplotypes resembled the B54-containing haplotypes, the marker alleles from HLA-B to C1_3_2 in the former haplotype were different from those of the latter haplotypes. Thus, a segment shared by all the B54- and B*5504-containing haplotypes was 251-231-246 (C2_2_2, C2_4_4, and C4_4_3). Even those B54 or B*5504-positive patients whose haplotypes could not be determined all carried the combination of these three alleles (data not shown).

Strength of Associations between the Disease and Markers

As another approach to identification of the candidate region, associations between the disease and tested markers were evaluated. The top of figure 1 shows the values of the delta statistic and the odds ratio for seven marker alleles, of which frequencies were significantly increased in the patient population, as shown in table 1. The peak value of the delta statistic occurred at C2_4_4, ~300 kb telomeric of the HLA-B locus. The odds ratio also reached the peak at C2_4_4, although it was less prominent than that of the delta values.

The 14 markers used for the haplotype analysis and their relative physical locations are shown on a map at the bottom of figure 1. Also, the segment shared among the disease-associated haplotypes described earlier is exhibited as a critical region on the map.

Marker Typing of 20 Korean Patients with Diffuse Panbronchiolitis

We further genotyped 20 Korean patients with diffuse panbronchiolitis. Of the 20 patients, 17 possessed the combination of C2_2_2-251, C2_4_4-231, and C4_4_3 -246, which are shared among Japanese disease-associated haplotypes, although phase was not determined because of the lack of the patients' pedigree information (data not shown).

Discussion

We tested the hypothesis that a major disease-susceptibility gene for diffuse panbronchiolitis is located between the HLA-B and HLA-A loci and that its founder mutation occurred on an ancestral chromosome bearing HLA-B54 and A11 alleles. The present data obtained from the haplotype analysis and genetic association studies supported our hypothesis and predicted the most likely region containing the putative susceptibility gene.

First, we attempted to identify disease-associated marker alleles. Of the 14 markers tested, 7 had a single allele with a significantly higher frequency in patients than in controls. Alleles of the other seven markers did not show significant disease associations, probably because they were masked by frequent occurrence of identical-by-state alleles in other common haplotypes. Haplotype analysis by the maximum-likelihood method and

Table 3

Individual Haplotypes Containing HLA-B54 and B*5504

	B54-Containing Haplotypes									B*5504-Containing Haplotypes	
Marker	1 (SH)	2 (SS)	3 (OM)	4 (YH)	5 (MM)	6 (FT)	7 (IS)	8 (EY)	9 (KT)	10 (EY)	11 (TO)
HLA-B	54	54	54	54	54	54	54	54	54	*5504	*5504
HLA-C	1	1	1	1	1	1	1	1	1	3	3
C1_4_3	441	441	441	441	441	441	441	441	441	445	449
C1_3_2	360	360	360	360	360	360	360	360	360	342	342
C2_2_2	251[a]	251	251	251	251	251	251	251	251	251	251
C2_4_4	231	231	231	231	231	231	231	231	231	231	231
C4_4_3	246	246	246	246	246/242	246	246	246	246	246	246
TFIIH	T	T	T	C	T	T	T/C	C	T/C	T	T
C4_2_7	238	238	238	222	234	234	238	228	236/224	234	234
C4_2_12	221	221	221	221	243	243	221	223	243	243	243
HLA-E	R/G	R	R/G	G	G	G	R	R/G	G	G/R	G
C3_2_12	149	183	151	151	129	129	129	147/129	175	147	129/147
D6S265	8/6[b]	8	8/6	8/6	8	8/5	7	6/7	1	7	7
HLA-A	24	24	24/26	24/2	11	11/31	11	2	33	11	11

[a] Shared alleles among all B54 and B*5504-containing haplotypes are underlined.

[b] Alleles of the microsatellite marker D6S265 are numbered on the basis of their relative size.

subsequent direct determination of individual haplotypes identified at least three patterns of disease-associated haplotypes containing B54. The disease-associated alleles including B54 and A11 all were contained in one of the three haplotypes. Furthermore, all these haplotypes shared specific alleles of the seven centromeric markers from HLA-B to C4_4_3, whereas alleles of the seven telomeric markers from TFIIH to HLA-A were diverse. These data are consistent with our initial hypothesis that a founder mutation occurred on a B54-A11-bearing ancestral chromosome and that the present disease-associated haplotypes have diverged from their ancestral haplotype through historical recombination events. The finding that B54-containing haplotypes are distributed predominantly in Asians (Imanishi et al. 1992*b*) supports our assumption that a founder mutation occurred in East Asians and also explains why diffuse panbronchiolitis is prevalent mainly in Japanese, Koreans, and Chinese. In contrast to the B54-containing haplotype, the B44-A33 haplotype appeared to be decreased in the patient population. In fact, B44 and A33 showed negative associations with the disease in the previous study (Keicho et al. 1998). This may indicate that the B44-A33 haplotype carries a disease-resistance allele.

Next, we focused on another disease-associated allele, HLA-B*5504 encoding B55.2, since B*5401 and B*5504 probably diverged from the common ancestral form—as was deduced from the close relationship of their nucleotide sequences and regional distribution in Asia (Bannai et al. 1997). The frequency of the B*5504, a rare allele even among Japanese, was significantly increased in the patient population. Although B*5504-containing haplotypes were closely related to the B54-containing haplotypes, specific alleles of the centromeric markers from HLA-B to C1_3_2 diverged from those of the B54-containing haplotypes. Thus, a shared segment containing C2_2_2, C2_4_4, and C4_4_3 was conserved by all disease-associated haplotypes identified in this study, and the most likely region for the putative disease locus is a 200-kb segment between their flanking markers. If we consider the physical location of the nearby genes, this predicted region is roughly bordered by the S and TFIIH loci, and its center is 300 kb telomeric of the HLA-B locus.

In addition to the empirical haplotype-based approach, we further evaluated the strength of associations between the disease and marker alleles to estimate the likely location of the susceptibility gene. We applied the delta statistic as well as the odds ratio for this purpose, since the statistic is independent of allele frequencies and advantageous in the estimation of the closest marker to the disease-susceptibility gene when several marker alleles are in linkage disequilibrium with the disease-susceptibility allele (Bengtsson and Thomson 1981; Devlin and Risch 1995). The delta statistic showed the prominent peak at C2_4_4. The odds ratio was also highest at the same locus. These findings were completely consistent with our estimate of the critical region from the haplotype analysis.

We also found that a majority of Korean patients possessed the consecutive disease-associated marker alleles within the critical region. Because phase is unknown in Korean cases and because the number of those patients was relatively small for estimating haplotype frequencies by the maximum-likelihood method, we could not easily conclude that these alleles are identical by descent. However, it is likely the case, because of the close genetic relationship between Japanese and Koreans (Tokunaga

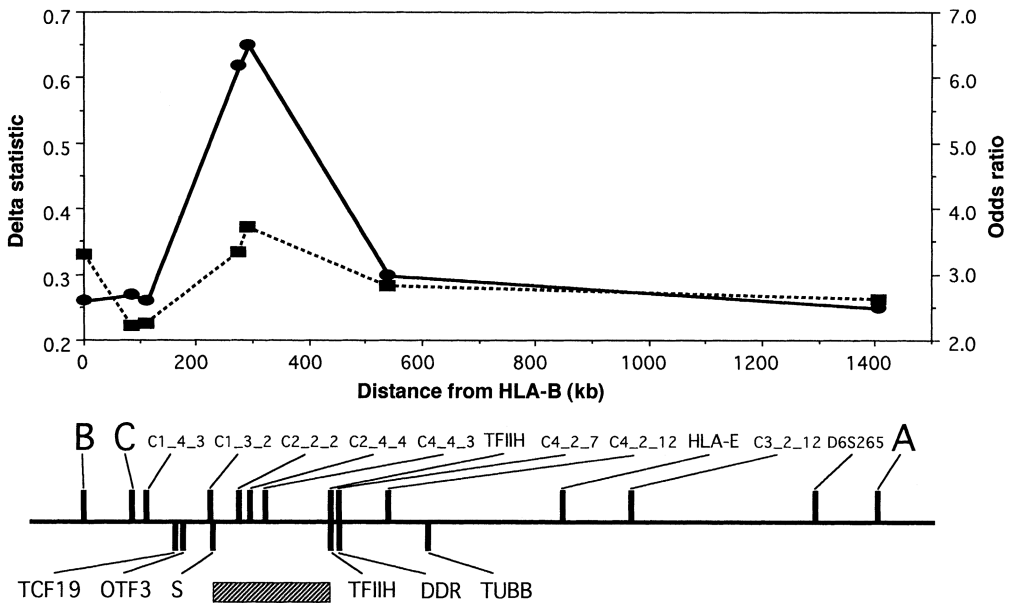

Figure 1 The delta statistic and odds ratio (*top*) and the corresponding physical map between the HLA-B and HLA-A loci on the chromosome 6p21.3 (*bottom*). On the graph, the X axis shows physical distances in kb from the HLA-B locus. Closed circles indicate the values of the delta statistic, and closed squares indicate the values of the odds ratio of seven marker alleles, of which frequencies were significantly increased in the patient population ($P < .05$). On the physical map, relative positions of 14 markers, including the other 7 markers used for the haplotype analysis, are shown. *B, C,* and *A* on the map represent the HLA-B, HLA-C, and HLA-A loci. A shaded area at the bottom of the map indicates the critical region deduced from the haplotype analysis. Relative positions of the principal genes around this region are also exhibited.

et al. 1996). This encourages us to conduct a larger study comparing disease-associated haplotypes between Japanese and Korean patients in the future. Searching for shared segments among disease-associated haplotypes in the genetically related populations may be generalized as a useful strategy to localize disease mutations, which occurred on their common ancestral chromosomes.

To our knowledge, no genes have been identified in this candidate region between the S and TFIIH loci. However, more than three potential genes are predicted by database search for expressed sequence tags. Therefore, further genetic characterization of this region is of great importance in identification of the disease-susceptibility gene.

Diffuse panbronchiolitis is considered to be a complex genetic disease, not a simple Mendelian disorder. Nevertheless, we suggest that the strategies used in the present study are helpful for fine localization of disease genes—even for more common diseases—as long as the population under study fulfills the two major prerequisites: (1) the majority of chromosomes susceptible to the disease are descended from one or a few transmitting founders, and (2) the population tested is relatively homogenous, without recent admixture. The above prerequisites are probably met in the case of diffuse panbronchiolitis in the Japanese population. The presence of a single predominant founder mutation of the susceptibility gene in East Asians is inferred from the finding that the disease is associated with mutually related Asian HLA haplotypes that presumably arose through historical recombination events. In addition, Japanese have had a relatively homogenous genetic background, being geographically isolated by the surrounding sea and without recent large immigration. In conclusion, haplotype analysis and a measure of associations enabled us to delineate the most likely region for the HLA-associated susceptibility gene for diffuse panbronchiolitis.

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Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

GenBank, http://www.ncbi.nlm.nih.gov/Genbank (for the genomic sequences of TFIIH [AB032121 and AB023050])

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