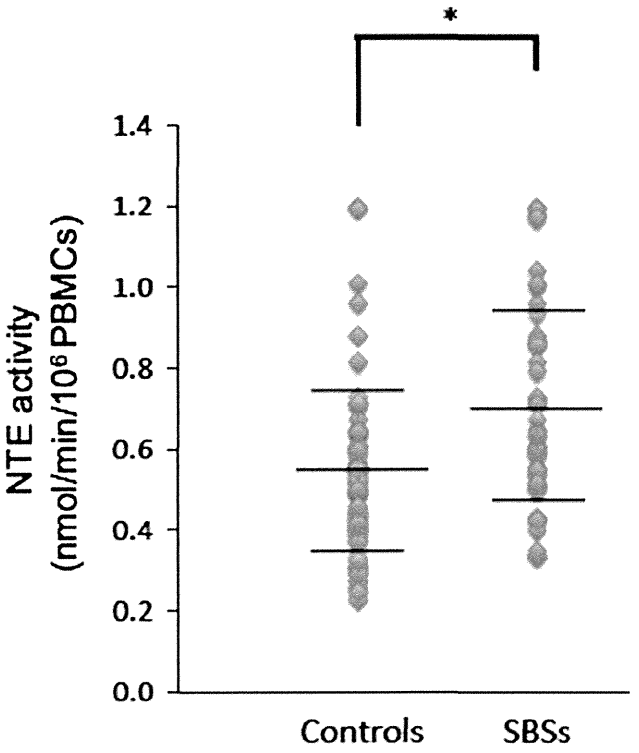

Fig. 1. NTE activity in PBMCs of SBS patients (n = 42) and controls (n = 52). Each diamonds represent individuals, and the average values and SD are shown by the long and short horizontal bars, respectively. *: $P < 0.0005$ (Mann–Whitney U-test). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

examined, and number of allele examined, respectively. The odds ratio and 95% CI (Confidence Interval) were also calculated for all SNPs. The program Haploview (MIT/Harvard Broad Institute, MA, USA) was used to estimate Pairwise linkage disequilibrium (LD) and haplotype frequency (Barrett et al., 2005). The Genetic Power Calculator was used to calculate a genetic power for association study (http://pngu.mgh.harvard.edu/~purcell/gpc/).

RESULTS

Increased Enzymatic Activity of NTE in Sick Building Syndrome Patients Group Compared to Healthy Control Group

To test our hypothesis that NTE has a role in SBS, we assessed the enzymatic activity of NTE in the PBMCs between the SBS patient group and the healthy control group. We observed a statistically significant ($P < 0.0005$, Fig. 1) higher enzymatic activity of NTE in the SBS patient group (average enzymatic activity plus minus SD was 0.70 ± 0.25 nmol/min/10^6 PBMCs) than the healthy control groups (average enzymatic activity plus minus SD was 0.54 ± 0.22 nmol/min/10^6 PBMCs).

Association Study of a Microsatellite Marker Within the *PNPLA6* Gene with Sick Building Syndrome

To investigate the genetic variations in the *PNPLA6* gene with SBS, a total of 180 Japanese patients with SBS and 370 healthy controls were enrolled for the association analysis using two potential microsatellite markers, one within intron 6 and the other located within the 3′ flanking region of the *PNPLA6* gene (Supporting Information Fig. S1). The microsatellite with the trinucleotide repeat (ATT)n positioned 1,893 bp downstream of the stop codon in the exon 35 was found to have eleven alleles with the number of repeats for allele 1 to allele 11 ranging from 9 to 19 repeats

TABLE II. Association test using microsatellite repeat polymorphism in the 3′ flanking region of PNPLA6 gene with SBS patients

Allele	PCR product length	Repeat	Patients ($2n$ = 360)	Contorls ($2n$ = 740)	OR (90% CI)[a]	P-value[b]	Pc-value[c]
Allele 1	284	9	0	0.001	–	0.485	1.000
Allele 2	287	10	0.169	0.185	0.90 (0.64 1.25)	0.525	1.000
Allele 3	290	11	0.003	0.005	0.51 (0.06 4.42)	0.543	1.000
Allele 4	293	12	0.069	0.061	1.15 (0.70 1.91)	0.582	1.000
Allele 5	296	13	0.067	0.061	1.05 (0.63 1.75)	0.842	1.000
Allele 6	299	14	0.072	0.070	1.03 (0.63 1.68)	0.906	1.000
Allele 7	302	15	0.394	0.380	1.06 (0.82 1.38)	0.638	1.000
Allele 8	305	16	0.192	0.174	1.12 (0.81 1.55)	0.482	1.000
Allele 9	308	17	0.028	0.055	0.49 (0.24 0.97)	0.041	0.409
Allele 10	311	18	0.006	0.003	2.06 (0.30 14.09)	0.461	1.000
Allele 11	314	19	0	0.001	–	0.485	1.000

[a] OR; odds ratio, CI; Confidence interval.
[b] Determined by Fisher's exact test.
[c] Determined by Bonferroni's adjustment for multiple tests.

TABLE III. Allele and genotype frequencies of SNPs in the *PNPLA6* gene and its associations for sick building syndrome

	db SNP Accession No.	Location	Allele (A/B)[a]	Patients				Controls				MAF		OR (95% CI)	*P* value	*Pc* value[c]
				AA	AB	BB	total	AA	AB	BB	total	Patients	Controls			
1	rs560849	Promoter	T/c	40	55	34	129	108	210	77	395	0.477	0.461	0.94 (0.71–1.24)	0.655	1,000
2	rs540516	intron 1	C/t	46	60	23	129	156	179	54	389	0.411	0.369	0.84 (0.63–1.12)	0.229	1,000
3	rs604959	exon 2	A/c	54	83	27	164	157	191	53	401	0.418	0.370	0.82 (0.63–1.07)	0.137	1,000
4	rs541271	intron 6	G/a	53	85	31	169	121	156	48	325	0.435	0.388	0.82 (0.63–1.07)	0.151	1,000
5	rs526411	intron 6	C/t	53	86	30	169	120	155	50	325	0.432	0.392	0.85 (0.65–1.11)	0.229	1,000
6	rs654059	intron 6	T/c	43	83	43	169	79	165	77	321	0.500	0.497	0.99 (0.76–1.29)	0.926	1,000
7	rs522750	intron 6	G/a	37	52	32	121	86	145	102	333	0.479	0.476	0.84 (0.62–1.12)	0.234	1,000
8	rs488886	intron 6	C/t	46	64	27	137	76	97	25	198	0.431	0.371	0.78 (0.57–1.07)	0.122	1,000
9	rs491518	intron 6	C/a	35	67	35	137	49	112	39	200	0.500	0.475	0.90 (0.67–1.23)	0.524	1,000
10	rs591040	exon 9	C/t	167	10	0	177	363	13	0	376	0.028	0.017	0.61 (0.26–1.38)	0.233	1,000
11	rs492092	intron 12	C/g	43	72	26	141	122	209	73	404	0.440	0.439	1.00 (0.76–1.32)	0.992	1,000
12	rs620744	intron 14	C/t	39	68	32	139	121	205	73	399	0.475	0.440	0.87 (0.66–1.14)	0.313	1,000
13	rs586551	intron 16	C/t	50	59	30	139	95	109	36	240	0.428	0.377	0.81 (0.60–1.09)	0.167	1,000
14	rs577219	intron 19	G/t	46	62	27	135	83	85	34	202	0.430	0.379	0.81 (0.59–1.11)	0.186	1,000
15	-	intron 19	DEL/a	47	63	26	136	81	85	36	202	0.423	0.389	0.87 (0.63–1.19)	0.374	1,000
16	rs473899	intron 21	A/g	60	46	30	136	95	124	43	262	0.390	0.401	0.95 (0.71–1.29)	0.762	1,000
17	rs2303177	intron 21	A/g	89	35	6	130	166	86	10	262	0.181	0.202	0.87 (0.59–1.27)	0.474	1,000
18	rs661825	intron 21	G/c	55	52	23	130	102	118	40	260	0.377	0.381	0.98 (0.72–1.34)	0.917	1,000
19	rs496380	intron 21	A/g	54	54	22	130	102	118	40	260	0.377	0.381	0.98 (0.72–1.34)	0.917	1,000
20	rs557596	intron 21	T/c	52	56	22	130	103	117	40	260	0.385	0.379	0.98 (0.72–1.33)	0.876	1,000
21	rs2432110	intron 21	T/c	40	29	22	91	57	63	31	151	0.401	0.414	0.95 (0.65–1.38)	0.781	1,000
22	rs793864	intron 21	C/g	53	26	11	90	76	53	22	151	0.267	0.321	0.77 (0.51–1.16)	0.207	1,000
23	rs1645799	intron 21	G/a	34	36	22	92	49	69	33	151	0.435	0.447	0.95 (0.66–1.38)	0.792	1,000
24	-	intron 21	C/g	21	27	20	68	51	69	32	152	0.493	0.438	0.80 (0.53–1.20)	0.283	1,000
25	-	intron 21	T/a	21	27	20	68	51	69	32	152	0.493	0.438	0.80 (0.53–1.20)	0.283	1,000
26	-	intron 21	C/g	21	27	20	68	55	65	32	152	0.493	0.424	0.76 (0.51–1.14)	0.183	1,000
27	-	intron 21	G/t	21	27	20	68	51	69	32	152	0.493	0.438	0.80 (0.53–1.20)	0.283	1,000
28	rs688348	intron 21	A/c	23	25	20	68	53	69	30	152	0.478	0.424	0.81 (0.54–1.21)	0.295	1,000
29	rs480208	intron 21	A/g	59	85	44	188	174	152	75	401	0.460	0.377	0.71 (0.55–0.91)	0.006	0,348
30	rs581698	intron 21	G/c	51	67	46	164	137	183	76	396	0.485	0.423	0.78 (0.60–1.01)	0.058	1,000
31	rs582611	intron 21	A/g	27	26	17	70	67	89	39	195	0.429	0.429	1.00 (0.68–1.48)	0.994	1,000
32	rs534758	intron 21	G/t	49	46	7	102	118	79	17	214	0.294	0.264	1.16 (0.80–1.68)	0.428	1,000
33	rs583984	intron 21	T/c	34	52	24	110	59	97	38	194	0.455	0.456	0.97 (0.69–1.35)	0.836	1,000
34	rs50874	intron 21	A/g	32	51	21	104	56	96	41	193	0.447	0.461	0.94 (0.67–1.33)	0.743	1,000
35	rs534464	intron 23	G/c	83	49	18	150	155	127	36	318	0.283	0.313	0.87 (0.64–1.17)	0.359	1,000
36	rs563266	intron 23	T/c	56	65	29	150	117	154	47	318	0.410	0.390	0.92 (0.70–1.22)	0.558	1,000
37	rs597582	intron 23	C/t	83	51	16	150	158	128	32	318	0.277	0.302	0.88 (0.65–1.20)	0.429	1,000
38	rs598023	intron 23	A/g	81	52	16	149	158	128	32	318	0.282	0.302	0.91 (0.67–1.23)	0.532	1,000

TABLE III. *(Continued)*

	db SNP Accession No.	Location	Allele (A/B)[a]	Patients				Controls				MAF		OR (95% CI)	*P* value	*Pc* value[c]
				AA	AB	BB	total	AA	AB	BB	total	Patients	Controls			
39	rs598028	intron 23	C/g	82	52	16	150	157	129	32	318	0.280	0.303	0.89 (0.66–1.21)	0.463	1,000
40	rs599328	intron 24	C/g	59	46	14	119	104	74	18	196	0.311	0.281	0.86 (0.61–1.23)	0.417	1,000
41	rs599330	intron 24	C/t	58	46	15	119	98	76	22	196	0.319	0.306	0.94 (0.66–1.33)	0.729	1,000
42	rs524530	intron 24	A/g	64	43	12	119	106	72	19	197	0.282	0.279	0.99 (0.69–1.41)	0.950	1,000
43	rs539887	intron 24	A/c	60	50	9	119	103	77	17	197	0.286	0.282	0.98 (0.69–0.98)	0.914	1,000
44	rs563826	intron 25	A/g	53	39	10	102	104	73	20	197	0.289	0.287	0.99 (0.68–1.44)	0.951	1,000
45	rs2446176	intron 29	G/a	67	49	22	138	100	74	34	208	0.337	0.341	0.98 (0.71- 1.35)	0.905	1,000
46	re1645800	intron 30	G/a	56	58	23	137	73	102	38	213	0.380	0.418	0.85 (0.62–1.16)	0.314	1,000
47	rs503336	intron 30	A/g	58	59	23	140	73	102	38	213	0.375	0.418	0.84 (0.61–1.14)	0.256	1,000
48	rs518321	intron 30	T/c	58	60	22	140	74	102	37	213	0.371	0.413	0.84 (0.62–1.14)	0.268	1,000
49	rs504934	intron 30	C/t	56	61	23	140	72	103	38	213	0.382	0.420	0.85 (0.63–1.16)	0.314	1,000
50	rs7245592	intron 30	G/a	26	29	15	70	56	66	30	152	0.421	0.414	0.97 (0.65–1.46)	0.890	1,000
51	rs521032	intron 30	T/c	27	28	16	71	61	61	30	152	0.423	0.398	0.90 (0.60–1.35)	0.623	1,000
52	rs506104	intron 30	C/a	28	28	15	71	61	63	28	152	0.408	0.391	0.93 (0.62–1.40)	0.732	1,000
53	rs538850	intron 31	C/t	50	50	20	120	69	97	33	199	0.375	0.410	0.87 (0.62–1.20)	0.388	1,000
54	rs538852	intron 31	G/a	61	50	9	120	111	75	13	199	0.283	0.254	0.86 (0.60–1.23)	0.412	1,000
55	rs577029	intron 31	T/c	49	51	20	120	67	97	34	198	0.379	0.417	0.86 (0.62–1.19)	0.350	1,000
56	rs577145	intron 31	T/c	49	51	20	120	67	96	33	196	0.379	0.413	0.87 (0.62–1.21)	0.396	1,000
57	rs541600	intron 31	C/t	49	51	20	120	67	94	33	194	0.379	0.412	0.87 (0.63–1.21)	0.409	1,000
58	rs89621	intron 31	C/t	49	51	20	120	67	94	33	194	0.379	0.412	0.87 (0.63–1.21)	0.409	1,000

[a](A/B) is Major or Minor allele.
[b]MAF: Minor allele frequencies
[c]determined by Bonferroni's adjustment for multiple tests.

TABLE IV. Genotype association between SNP (rs480208) in the *PNPLA6* gene and SBS

Genotype	Genotype frequency: Patients (n = 188)	Genotype frequency: Controls (n = 401)	OR (90% CI)[a]	P-value[b]	Pc-value[c]
A/A	0.313	0.434	0.60 (0.41 0.86)	0.005	0.580
A/G	0.452	0.379	1.35 (0.95 1.92)	0.092	1.000
G/G	0.234	0.187	1.33 (0.87 2.02)	0.185	1.000

[a] OR; odds ratio
[b] Determined by Fisher's exact test.
[c] Determined by Bonferroni's adjustment for multiple tests.

(Table II). As seen in Table II, no statistically significant association was found between SBS and the controls after a statistical correction by the Bonferroni's method. The other microsatellite marker with the tetranucleotide repeat (TTTG)n and positioned 1,092 bp downstream of the exon 6 was not polymorphic (data not shown).

SNPs Within the *PNPLA6* Gene

To address the possibility that *PNPLA6* is involved in the pathogenesis of SBS, we screened for SNPs in the *PNPLA6* gene. To search for genetic polymorphisms in the genomic sequences of the *PNPLA6* gene, PCR products separately amplified from the respective genomic regions were obtained from 10 patients with SBS and 10 healthy controls, and their nucleotide sequences were determined by direct sequencing. As a result, a total of 57 SNPs with MAFs > 0.2 were obtained in *PNPLA6* genomic region (Table III). Of them, only one SNP, rs604959, in exon 2, was located in the coding region of *PNPLA6* gene and it is not involved in an amino acid change. Also, MAF of a SNP, rs491518, in exon 9 was lower than 0.2.

Association Study of *PNPLA6* Gene Polymorphisms with Sick Building Syndrome

The association of the 58 polymorphisms in the *PNPLA6* gene was investigated in 188 patients with SBS and 401 controls subjects. Although only one SNP, rs480208 in intron 21 of the *PNPLA6* gene, was significantly associated with SBS (P = 0.006, Table III) without correction, the association between rs480208 and SBS showed no significance if the Bonferroni's adjustment is made for 58 tests (Table III). Furthermore, the AA genotype frequency of the rs480208 indicated a significant difference between SBS and controls (P = 0.005, Table IV) with the higher SNP frequency in the controls without correction. However, the association of the AA genotype with SBS is not significant if the Bonferroni's adjustment is made for 116 tests (Table IV).

Genotype-Specific Differences in the NTE Enzymatic Activity

To evaluate the functional impact of the rs480208 with respect to NTE enzymatic activity, we analyzed the relationship between the genotype of the rs480208 and the enzymatic activity of NTE. The average enzymatic activity of NTE in the people with the rs480208 homozygous AA genotype was significantly (P < 0.01) lower than in the people with the AG + GG genotypes (Fig. 2).

Genome Organization and Tissue Expression Profile of the *PNPLA6* Gene

To localize the transcription initiation site(s) of the *PNPLA6* gene, which has some transcripts with different 5′ region, a mixed oligo-capped cDNA library was constructed from various human tissues. By clustering the nucleotide sequences of the cDNAs obtained by PCR screening of the library, the 5′ ends of the *PNPLA6* mRNAs were identified in nine types of transcripts [Fig. 3(a)]. The expression of *PNPLA6* gene was

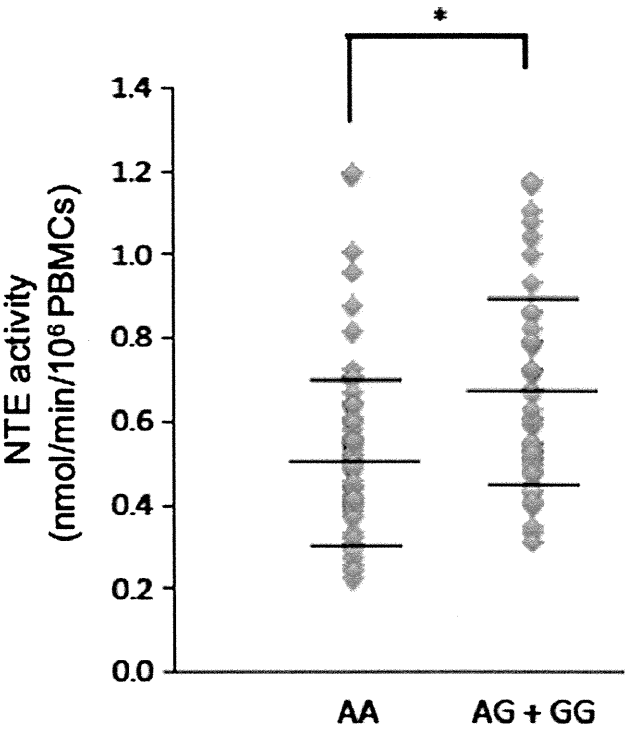

Fig. 2. NTE activity in PBMCs for the genotypes AA (n = 52) and AG + GG (n = 41) of rs480208. Each circle represents an individual, and the average values and SD are shown by the long and short horizontal bars, respectively. *: P < 0.01 (Mann–Whitney U-test). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

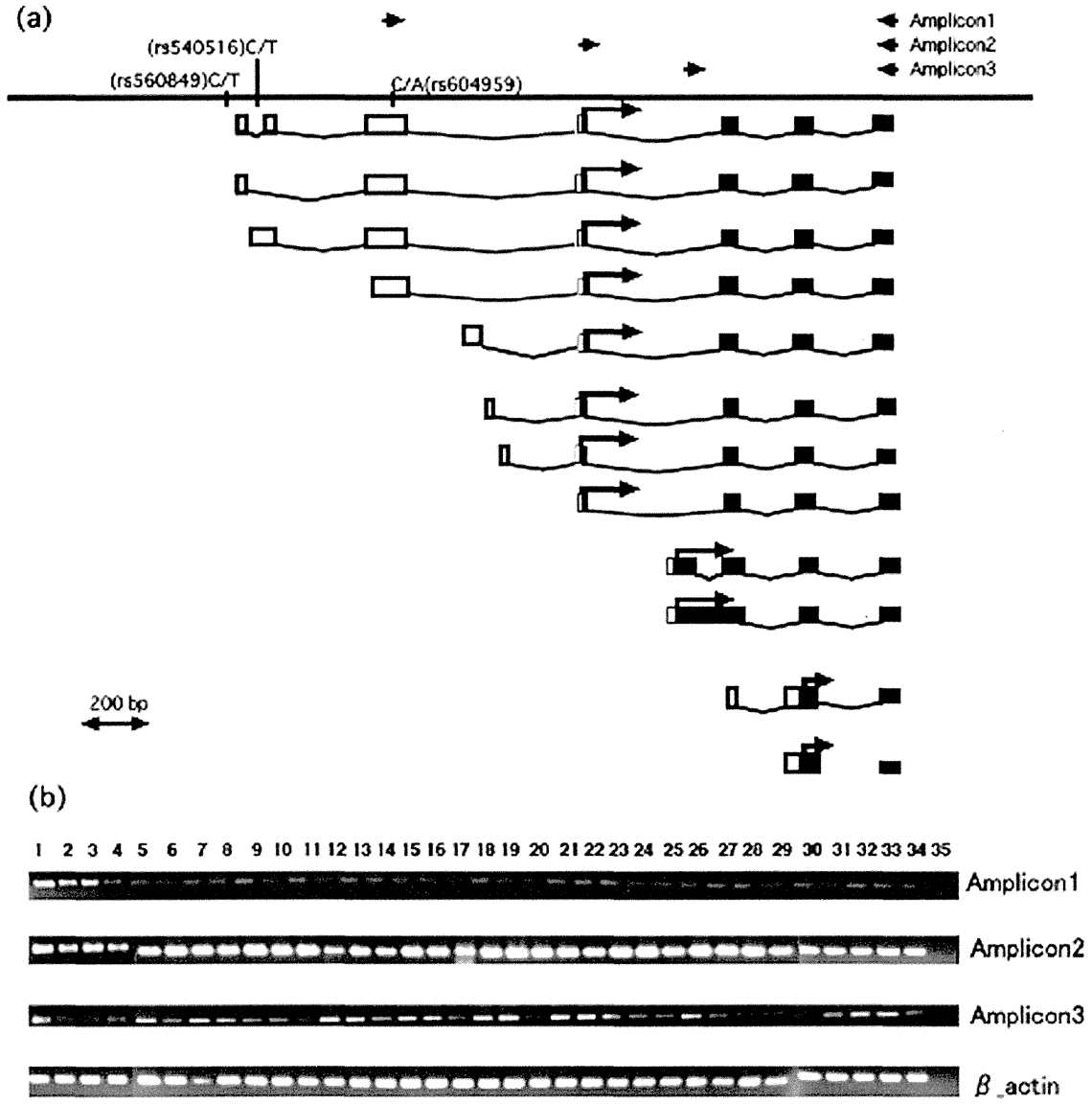

Fig. 3. The exon–intron structure around the 5′ end of the *PNPLA6* gene transcription initiation sites (a). The putative coding regions are in closed boxes and the putative non-coding region is open boxes. The deduced translational initiation methionines are shown by hooked arrows on the exons. The locations of SNP markers (registered rs No. provided) and oligonucleotide primers used for amplicon 1, 2, and 3 of RT-PCR are represented on upper line. *PNPLA6* mRNA expression (b). Each expressions in various human tissues were detected by RT-PCR. 1: amygdala, 2: cerebellum, 3: hypothalamus, 4: thalamus, 5: skin, 6: pooled skin, 7: fetal skin, 8: keratinocyte, 9: skin fibroblast, 10: dermal microvascular epidermal carcinoma cell line, 11: epidermal carcinoma cell line, 12: thymus, 13: fetal thymus, 14: bone marrow, 15: lymph node, 16: tonsil, 17: spleen, 18: periphery blood lymphocyte, 19: CD4 + activated T cells, 20: CD4 + resting T cells, 21: CD8 + activated T cells, 22: CD8 + resting T cells, 23: brain, 24: liver, 25: placenta, 26: skeletal muscle, 27: heart, 28: kidney, 29: pancreas, 30: lung, 31: stomach, 32: testis, 33: uterus, 34: cervix, and 35: negative control.

investigated by RT-PCR in various tissues. To control for the absence of genomic contamination, the primers were designed to span the introns [Fig. 3(a)]. After 40 cycles of amplification, RT-PCR generated the transcripts with the expected size in all of the 35 tissues examined [Fig. 3(b)].

DISCUSSION

The OP compounds are known to inhibit NTE activity in PBMCs by 40–80% by means of its reaction of serine residue of NTE (Lotti et al., 1986; Johnson, 1990). However, simple inhibition of NTE in PBMCs by the OP has not shown to contribute to OPIDN. Moreover, an abnormal accumulation of intrinsic substrate for NTE, PC or LPC impaires membrane integrity and disruption of phospholipid homeostasis (van Tienhoven et al., 2002; Zaccheo et al., 2004;). In our study, we found that NTE activity was significantly higher in the SBS than the control group (Fig. 1). It was also reported that NTE transcriptional activity was significantly up-regulated in the PBMCs of chronic fatigue syndrome (CFS) patients (Kaushik et al., 2005). The symptoms of CFS resemble more closely those of SBS in a lot of terms of hypersensitivity, headaches, fatigue, and sleep disturbance etc., (Zwarts et al., 2008) suggesting that SBS and CFS might have overlapping pathological causes and molecular mechanisms. Furthermore, we observed that NTE activity in the lymphocytes of Japanese with genotype AA of SNP rs480208 was significantly decreased compared to the genotypes AG+GG (Fig. 2). These results have two possibilities. One possibility is that rs480208 could directly regulate expression of *NTE* gene. Another is that mutation(s) closed to rs480208 could affect activity of NTE protein or expression of *NTE* gene. However, the AA genotype frequency of rs480208 showed no significant association with the risk of developing SBS by Bonferroni's corrections, but the frequency of the AA homozygous genotype in SBS was lower than the genotypes in the controls without the corrections for multiple testing (Table IV, $P = 0.005$, $Pc = 0.580$). It remains problematic that the statistical corrections using the Bonferroni's test may be too severe for sample size in our present study and that we may have missed biologically important genetic variant by loss of linkage disequilibrium (LD) between the disease variant and the genetic marker, which is important for the identification of susceptibility genes in association study based on common disease, common variant hypothesis. So, we evaluated the LD extension of approximately 25.4 kb of *NTE* genomic region from rs560849 to rs89621 (Supporting Information Fig. 1). We identified two LD blocks with a threshold of $\Delta = 0.7$. We numbered these blocks 1 to 2 from ATG to stop codon in *PNPLA6* gene. Blocks 1 and 2 spanned roughly 8.5 and 13.3 kb, respectively, and covered almost genomic region of *PNPLA6* gene. Furthermore, as for multifactorial and complex disease like SBS might be affected by a lot of kinds of environmental and multiple genetic factors, it is important to ensure sufficient genetic power and sample size for the detection of subtle genetic effect. So, we calculated the genetic power in our present association study. The genetic power for significant ($P = 0.001$) is 0.6042 and number of case for 80% power needs 532 of sample numbers (Supporting Information Table SII). In addtion to the by means of increasing the number of samples, the classification by environmental factors, such as OP and non-OPs, i.e. formaldehyde, toluene, xylene could overcome the problem of the detection of of susceptibility genes. Because SBS is multifactorial disease and a lot of kinds of indoor pollutants could trigger the development of this disease, it might be difficult to detect the contributions of each factors in small size of population of SBS. However, classification and combination of each molecular signaling leaded to development of SBS might be clear for each components and genetic and environmental factors of molecular mechanisms of SBS. Thus, these findings suggest that the AA homozygote might confer a degree of genetic protection or resistance in the development of SBS and a potentially important genetic connection between *PNPLA6* and SBS.

Previous studies of NTE have concentrated mostly on its sensitivity to OP and role in OPIDN (Glynn, 2003). More recent studies have investigated on the possible role of NTE in phospholipids membrane homeostasis (Vose et al., 2008). In addition, a genetic study has implicated NTE mutations with motor neuron disease (Rainier et al., 2008), whereas our study and those of others (Kaushik et al., 2005) point to a role of NTE in SBS and CFS. Futhermore, mice heterozygous *Nte* allele (*Nte*+/–) showed that a minor reduction in Nte activity can lead to a possible neuronal hyperactivity in mice (Winrow et al., 2003). However, it was reported that that reduction in NTE activity does not correlate with disease state in motor neuron disease in human tissue (Hein et al., 2010). These findings suggest that reduction of NTE enzymatic activity alone is insufficient to cause human motor neuron disease, and also other function(s) of NTE might affect the disease development. Because NTE function for a cell-signaling controlling a communication between neurons and glial cell in nervous development was proposed (Glynn, 1999, 2000). In summary, we found that NTE enzymatic activity in SBS group is significantly increased compared with controls, and that a SNP, rs480208, in *PNPLA6* gene might be directly or indirectly associated with NTE enzymatic activity. Overall, these results suggest that NTE enzymatic activity may become an important marker in the investigation of SBS. However, additional studies on different populations and genetic and environmental factors are required to further confirm its role of polymorphimsm of *PNPLA6* in the pathogenesis of SBS.

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