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Prevalence and Genetic Polymorphism of HLA-B*15 in the North Indian Population: Insights into SJS/TEN Prevention, Vaccines and Clinical Trials

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ABSTRACT

Introduction: Since HLA-B*15:02 is a biomarker for carbamazepine-induced Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in certain Asian populations, the United States food and drug administration (USFDA) recommends HLA-B*15:02 screening before carbamazepine administration in Asian and other communities. Several published reports across the globe suggested a strong association of HLA-B*15 with carbamazepine-induced hypersensitivity reactions. **Methods:** This study was conducted to estimate the prevalence and the genetic polymorphism of HLA-B*15 in the North Indian population (N=5469) by PCR sequence-specific oligonucleotide probe (SSOP) genotyping of the HLA-B locus. **Results:** The total allelic variants of HLA-B*15 identified amongst the studied samples were 17. The most frequent among these was HLA-B*15:17 (2.030%). Subsequently, HLA -B* 15:01 (1.463%) and B*15:02 (1.225%) were more frequent. Further, 185 HLA-B*15 genotypes were seen among the studied population with which the most frequent were HLA-B*15:17-40:06(0.402%), HLA-B*15:17-35:03 (0.366%) and HLA-B*15:02-40:06 (0.347%). **Conclusion:** This information highlights the prevalence and diversity of HLA-B*15 genotyping and its importance in the screening of carbamazepine-induced SJS/TEN in the North Indian population where the prevalence of HLA-B*15 allelic variants was on the higher side. Further, this baseline information could be further explored in the understanding of the pathogenesis of the disease and may contribute valuable information for designing effective vaccines and clinical trials.

INTRODUCTION

Among 24308, class I human leukocyte antigen (HLA), 8849 are contributed only by the HLA- B antigen [1]. Therefore, it is known as the most polymorphic among all the HLA antigens. The HLA-B gene has many possible variations, enabling them to react to a wide range of foreign invaders of each person's immune system and a reason behind this polymorphism. Hundreds of such allelic variants of the HLA-B gene are known, each of which is given a particular number. India is one of the mega-diversity countries comprising 4693 communities with several thousand endogamous groups [2]. Therefore, an issue like ethnic diversity, migrations, predisposition to complex disorders, or pharmaco-genomics needs to be addressed. HLA is a human version of the major histocompatibility complex (MHC). It has a genetic region that encompasses over 200 highly polymorphic genes that encode for class I (A, B, and C loci) and class II (DQ, DP, and DR loci) antigens located on the short arm of chromosome 6 [3,4]. At present more than 24,000 HLA class I alleles are known and among these, HLA- B has more than 8000 allelic variants and is hence considered as most polymorphic [1,5].

HLA association with disease is very much known for more than 30 years [6]. To understand this association in-depth testing of HLA allele is required. Several published reports suggested a strong association of HLA-B*15:02 genes with carbamazepine-induced hypersensitivity reactions [7,8,9]. The USFDA recommends testing for HLA-B*15:02 before carbamazepine treatment for inpatients of Asian ancestry, who are known to have high frequencies of the HLA-B*15:02 allele [10]. Reported alleles in the HLA-B*15 group encode molecules belonging to several serologic subgroups like B15 (B62, B63, B75, B76, B77) and B70 (B71, B72). Due to their serologic cross-reactivity resulting from structural similarity, the assignment of HLA genotyping results was big deal during the era of serology [11]. Techniques for determining HLA typing have evolved enormously since its discovery. Earlier, the serological method was used for HLA typification. Now almost universally, HLA genotyping is performed by the DNA sequence level (commonly known as the molecular method) [12]. The frequency of HLA antigen is population-specific and may vary from one population to another [13]. Further, HLA allele frequency may be useful for understanding of disease association and hence may provide valuable information for designing effective vaccines and clinical trials [14]. Anthropological study based on HLA allele polymorphism provides valuable information about ethnic diversity,

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migrations pattern, and predisposition to complex disorders [15].

The study performed here is an attempt to determine and analyze the prevalence and genetic polymorphism of the HLA-B*15 allele in the North Indian population. Further, a comparison of identifying allelic frequency was done with other populations to understand the need of testing this in the North Indian population for screening of carbamazepine-induced hypersensitivity reactions.

MATERIALS AND METHODS

Ethics Statement

A written Consent was taken from each participant before collecting the sample and included in this study. The present study was approved by the independent ethical review board "Genebandhu" in India (ECG006/2017).

Study Setting and Demographics

The samples of 5469 healthy, normal individuals from North India were examined for HLA- B locus genotyping in this study. This study only included people aged between 18 and 55 yers from Delhi, Punjab, Uttarakhand, Haryana, and Jammu & Kashmir. There were 4320 males and 1149 females in the group. The HLA- B loci were tested in all of these samples using the PCR-SSOP method on the Luminex platform. The frequency and diversity of each HLA-B*15 allele and its variants were determined through statistical analysis.

Sample Collection

From each enrolled participant, 3ml of whole blood was collected in ethylene diamine tetra acetic acid (EDTA) coated vials as per our center sample collection protocol.

DNA Extraction

DNA from each participant's blood sample was extracted by a commercial NucleoSpin® Blood DNA Extraction Kit from Machenary-Nagel (Germany). DNA extraction was done by lysis on the collected blood sample followed by adjusting the DNA binding conditions, washing of silica membrane, drying the silica membrane, and finally the elution as per the manufactures recommendation. DNA concentration was determined by measuring the intensity of absorbance with a spectrophotometer (Qubit®2.0, Invitrogen). A DNA concentration between 80-100 ng/µl is recommended for HLA genotyping.

HLA Genotyping

HLA genotyping from all the extracted DNA samples was performed by PCR-SSOP method which involved DNA amplification followed by hybridization and analysis of HLA-B by MatchIT DNA software inbuilt with Luminex system as per the manufactures recommendation (lifecodes®HLA-SSO typing, USA) [15].

Statistical Analysis of HLA- B Allele

HLA- B allele frequencies were estimated by direct counting (n/2N × 100) method in Microsoft excel 2010, Where 'n' is the number of particular alleles and 'N' is the total number of samples studied. Percent phenotype frequency, calculated as n/N × 100, where n is the number of a particular allele and N is the total number of samples studied.

RESULTS

Frequencies and Genotypes of HLA-B*15 Allelic Variants Identified

The total HLA-B allelic variants identified within these studied samples were 17. The most frequent among these was HLA-B*15:17 (2.030%). Subsequently, HLA-B*15:01 (1.463%) and B*15:02 (1.225%) were found to be the most frequent. Table 1 shows the frequencies of all HLA-B*15 alleles identified, as well as the phenotypic frequency. A total of 185 HLA-B*15 allelic combinations (genotypes) were identified as shown in Table 2. HLA-B*15:17-40:06(0.402%), HLA-B*15:17-35:03 (0.366%), and HLA-B*15:02-40:06 (0.347%) were found to be the most frequent HLA-B*15 genotypes among studied populations.

Table 1: Representing HLA B*15 allele frequency in the North Indian population (N=5469).

S. No	HLA-B*15 allelic variants	Total Number (N)	Frequency (%)	Phenotype frequency (%)
1	15:01	161	1.463	2.944
2	15:02	134	1.225	2.450
3	15:03	7	0.064	0.128
4	15:04	1	0.009	0.018
5	15:05	44	0.402	0.805
6	15:08	74	0.677	1.353
7	15:09	4	0.037	0.073
8	15:10	2	0.018	0.037
9	15:12	2	0.018	0.037
10	15:17	222	2.030	4.059
11	15:18	85	0.777	1.554
12	15:25	25	0.229	0.457
13	15:29	40	0.366	0.731
14	15:32	7	0.064	0.128
15	15:34	2	0.018	0.037
16	15:38	1	0.009	0.018
17	15:75	2	0.018	0.037

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Table 2: HLA B*15 genotypes in the studied North Indian Population (N=5469).

S.No	HLA-B* Genotypes	Total Number (N)	Genotypic Frequency
1	15:01-15:01	1	0.018
2	15:01-15:05	1	0.018
3	15:01-15:08	1	0.018
4	15:01-15:17	2	0.037
5	15:01-15:18	3	0.055
6	15:01-15:29	1	0.018
7	15:01-15:34	1	0.018
8	15:01-18:01	8	0.146
9	15:01-27:04	2	0.037
10	15:01-27:05	6	0.110
11	15:01-35:01	15	0.274
12	15:01-35:03	11	0.201
13	15:01-35:08	1	0.018
14	15:01-37:01	4	0.073
15	15:01-38:02	2	0.037
16	15:01-39:01	1	0.018
17	15:01-40:01	6	0.110
18	15:01-40:02	4	0.073
19	15:01-40:06	13	0.238
20	15:01-41:01	1	0.018
21	15:01-41:02	2	0.037
22	15:01-44:02	3	0.055
23	15:01-44:03	7	0.128
24	15:01-48:01	2	0.037
25	15:01-49:01	2	0.037
26	15:01-50:01	2	0.037
27	15:01-51:01	16	0.293
28	15:01-51:08	1	0.018
29	15:01-52:01	13	0.238
30	15:01-55:01	3	0.055
31	15:01-57:01	4	0.073
32	15:01-58:01	2	0.037
33	15:02-15:02	2	0.037
34	15:02-15:05	2	0.037
35	15:02-15:18	1	0.018
36	15:02-15:25	1	0.018
37	15:02-15:32	1	0.018
38	15:02-18:01	4	0.073
39	15:02-27:04	1	0.018
40	15:02-27:05	1	0.018
41	15:02-35:01	9	0.165
42	15:02-35:02	1	0.018
43	15:02-35:03	7	0.128
44	15:02-37:01	3	0.055
45	15:02-38:02	1	0.018
46	15:02-40:01	3	0.055
47	15:02-40:06	19	0.347
48	15:02-40:23	1	0.018
49	15:02-44:02	1	0.018
50	15:02-44:03	7	0.128
51	15:02-48:04	1	0.018
52	15:02-50:01	6	0.110
53	15:02-51:01	13	0.238
54	15:02-52:01	17	0.311
55	15:02-52:04	1	0.018
56	15:02-55:01	5	0.091
57	15:02-57:01	1	0.018
58	15:02-58:01	5	0.091
59	15:03-40:06	3	0.055
60	15:03-51:01	1	0.018
61	15:03-52:01	3	0.055
62	15:04-51:01	1	0.018
63	15:05-15:05	1	0.018
64	15:05-15:12	1	0.018
65	15:05-15:17	3	0.055
66	15:05-15:18	2	0.037
67	15:05-18:01	2	0.037
68	15:05-35:01	4	0.073
69	15:05-35:03	2	0.037
70	15:05-37:01	1	0.018
71	15:05-39:01	1	0.018
72	15:05-40:02	1	0.018
73	15:05-40:06	2	0.037
74	15:05-44:03	3	0.055
75	15:05-51:01	3	0.055
76	15:05-52:01	4	0.073
77	15:05-55:01	1	0.018
78	15:05-56:01	1	0.018
79	15:05-58:01	3	0.055
80	15:08-15:18	1	0.018
81	15:08-18:01	2	0.037
82	15:08-27:02	1	0.018
83	15:08-27:07	3	0.055
84	15:08-35:01	8	0.146
85	15:08-35:03	3	0.055
86	15:08-37:01	3	0.055
87	15:08-37:04	1	0.018
88	15:08-39:01	1	0.018
89	15:08-40:01	1	0.018
90	15:08-40:06	8	0.146
91	15:08-41:02	1	0.018
92	15:08-44:02	3	0.055
93	15:08-44:03	3	0.055
94	15:08-47:01	1	0.018
95	15:08-48:01	1	0.018
96	15:08-50:01	3	0.055
97	15:08-51:01	6	0.110
98	15:08-52:01	4	0.073
99	15:08-55:01	1	0.018
100	15:08-57:01	3	0.055
101	15:08-58:01	1	0.018
102	15:09-37:01	1	0.018
103	15:09-44:03	1	0.018
104	15:09-50:01	1	0.018
105	15:10-40:06	1	0.018
106	15:10-51:01	1	0.018
107	15:12-52:01	1	0.018
108	15:17-15:17	4	0.073
109	15:17-15:18	3	0.055
110	15:17-15:25	1	0.018
111	15:17-18:01	7	0.128
112	15:17-27:04	2	0.037
113	15:17-27:05	2	0.037
114	15:17-27:07	2	0.037
115	15:17-35:01	16	0.293
116	15:17-35:03	20	0.366
117	15:17-35:08	3	0.055
118	15:17-37:01	4	0.073
119	15:17-38:01	1	0.018
120	15:17-38:02	2	0.037
121	15:17-39:01	1	0.018
122	15:17-40:01	3	0.055

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123	15:17-40:06	22	0.402
124	15:17-41:01	6	0.110
125	15:17-41:02	2	0.037
126	15:17-44:02	4	0.073
127	15:17-44:03	12	0.219
128	15:17-47:01	1	0.018
129	15:17-49:01	2	0.037
130	15:17-50:01	6	0.110
131	15:17-51:01	15	0.274
132	15:17-52:01	15	0.274
133	15:17-52:04	1	0.018
134	15:17-55:01	7	0.128
135	15:17-56:01	1	0.018
136	15:17-57:01	12	0.219
137	15:17-58:01	4	0.073
138	15:18-15:18	1	0.018
139	15:18-15:32	1	0.018
140	15:18-18:01	3	0.055
141	15:18-27:02	1	0.018
142	15:18-27:04	1	0.018
143	15:18-35:01	1	0.018
144	15:18-35:02	1	0.018
145	15:18-35:03	9	0.165
146	15:18-37:01	1	0.018
147	15:18-40:02	1	0.018
148	15:18-40:06	6	0.110
149	15:18-41:01	1	0.018
150	15:18-44:02	1	0.018
151	15:18-44:03	9	0.165
152	15:18-51:01	7	0.128
153	15:18-52:01	9	0.165
154	15:18-56:01	1	0.018
155	15:18-57:01	2	0.037
156	15:18-58:01	3	0.055
157	15:25-15:25	1	0.018
158	15:25-35:03	1	0.018
159	15:25-35:08	1	0.018
160	15:25-37:01	1	0.018
161	15:25-40:02	1	0.018
162	15:25-40:06	1	0.018
163	15:25-44:03	5	0.091
164	15:25-48:01	2	0.037
165	15:25-50:01	1	0.018
166	15:25-51:01	2	0.037
167	15:25-52:01	2	0.037
168	15:29-15:29	1	0.018
169	15:29-18:01	4	0.073
170	15:29-35:01	1	0.018
171	15:29-35:03	1	0.018
172	15:29-37:01	1	0.018
173	15:29-40:06	4	0.073
174	15:29-44:03	2	0.037
175	15:29-50:01	4	0.073
176	15:29-51:01	2	0.037
177	15:29-52:01	2	0.037
178	15:29-55:01	1	0.018
179	15:29-57:01	1	0.018
180	15:29-58:01	1	0.018
181	15:32-52:01	3	0.055
182	15:32-57:01	1	0.018
183	15:38-35:01	1	0.018
184	15:75-27:07	1	0.018
185	15:75-44:03	1	0.018

DISCUSSION

The molecular diversity of HLA-B*15 gene polymorphism was determined in the North Indian population. In our study HLA-B*15:17 (2.030%). was found to be most prevalent. Whereas, HLA-B*15:01 and HLA-B*15:02 were amongst the list of most prevalent HLA-B antigens. HLA-B*15:02 is found to be a known risk factor for carbamazepine-induced SJS/TEN in the US population [10]. A report published by Aggarwal et al. also showed the association of HLA-B*15:02 with carbamazepine-induced SJS/TEN in the North Indian population [7]. Sukasem et al. also showed a significant HLA-B*15:02 association with carbamazepine-induced maculopapular exanthema (MPE) [9]. Several studies have shown HLA-B*15 association with carbamazepine [8,10,11,15,17]. Although, the actual mechanism of this association is not very clear, this information could be a baseline for a similar study in this region and may be utilized further for vaccine development and clinical trials.

A meta-analysis published by Tangamornsuksan *et al*. also identified a strong association between the HLA-B*15:02 allele and carbamazepine-induced SJS/ TEN in Han-Chinese, Thai, and Malaysian populations.Whereas no patients with SJS /TEN were carriers of the HLA-B*15:02 allele of white or Japanese race/ethnicity [18].This variation could be attributed to the diverse nature of HLA which is race/ethnicity specific. Population from Hong Kong, Thailand, Malaysia and certain of the Philippines is reported to be positive (more than 15%) for HLAB*15:02, compared to Taiwan (10%) and North China (4%) and could be a potential marker for carbamazepine-induced SJS/TEN. Whereas it is mostly missing in the population of Caucasians, African-Americans, Hispanics, and Native Americans [7]. Hence, USFDA recommends HLA-B*15:02 screening before carbamazepine administration in the Asian country.

The data from India is scant on this association, though the frequency and polymorphism of HLA-B*15 among Indians are most prevalent. HLA-B*15 was among the list of most frequent antigens with alleles B*15:01, B*15:02, B*15:05, B*15:08, B*15:17, and B*15:18 in a North Indian population [19]. Thus, the use of HLA-B*15 genotyping seems warranted in routine clinical use to screen carbamazepine-induced SJS/TEN. To conclude, the use of HLA-B*15 genotyping seems warranted in routine clinical use to screen carbamazepine-induced SJS/TEN in the Indian population and may provide insight into designing effective vaccines and clinical trials.

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CONFLICT OF INTEREST

The authors declare they have no conflict of interests.

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