

# Definition of the HLA population diversity boundaries for clinical histocompatibility practice.

Marcelo Fernández-Viña, Ph.D.  
Pedro Cano, M.D.  
MD Anderson Cancer Center  
University of Texas  
Houston, TX

HLA presents the highest degree of polymorphism of all human genetic systems. Prior knowledge of the extent of diversity is essential in the development and selection of molecular typing methods. Reliable allele frequencies are also important in allogeneic unrelated hematopoietic stem cell transplantation to determine the likelihood of finding closely HLA matched donors for each patient. Only 69 HLA-A, 162 B, 42 Cw, 82 DRB1, 25 DRB3/4/5, 23 DQB1, and 41 DPB1 alleles were identified in more than 22,000 subjects, including some only present in isolated and small ethnic groups, and 10-20% fortuitous alleles, found only once. We observed only a fraction of all the alleles so far described.

The number of alleles of loci whose products are highly expressed in the cell surface (A, B, C and DRB1) was higher than those found for the loci with low cell surface expression (DRB3/4/5, DQB1 and DPB1). A smaller percentage of described alleles were actually observed for HLA-A, B, C and DRB1 compared to the less polymorphic loci.

The catalogue of HLA alleles must distinguish well-documented alleles comprising the polymorphic HLA universe, from the nebulous set of sporadic alleles found only once. This distinction is a useful tool in routine histocompatibility practice, as decisions about addition of tests needed to resolve ambiguous assignments are made, and unnecessary tests for the resolution of ambiguities including poorly documented alleles are prevented. It is also valuable in the design of HLA typing strategies; for example development of reagents for typing DQB1 and DRB3/4/5 should focus to resolve unambiguous genotypes including the 23 and 25 alleles identified in this study at these loci. 20 DPB1 alleles cover more than 99% of the alleles of this locus, and methods to test for the presence of antibodies in the patient's serum against these alleles may turn out to be highly informative to predict risks for rejection.

In so far as the interpretation of HLA typing consists in the evaluation of a subject's HLA haplotypes under the light of the haplotype frequency distribution in a reference population, knowledge of the boundaries of the HLA polymorphic universe is essential in the interpretation of HLA typing.

Number of alleles in each locus found to account for 99% and 100% of the phenotypes in a population of 22,000 samples. The last row includes the number of alleles in the official HLA nomenclature as of Oct 2005.

	A	B	C	DRB1	DRB3/4/5	DQB1	DPB1
99%	56	111	36	59	22	18	20
100%	96	164	45	69	28	22	42
Official	414	728	210	422	73	68	120

## Catalogue of well-documented alleles:

Locus	Name	Locus	Name	Locus	Name	Locus	Name	Locus	Name	Locus	Name
A	A*01:01	B	B*07:02	Cw	Cw*02:02	DRA	DRA*01:01	DQB1	DQB1*02:01	DPB1	DPB1*01:01
A	A*01:02	B	B*07:03	Cw	Cw*02:03	DRA	DRA*01:02	DQB1	DQB1*02:02	DPB1	DPB1*01:02
A	A*01:03	B	B*07:04	Cw	Cw*02:04	DRA	DRA*01:03	DQB1	DQB1*02:03	DPB1	DPB1*01:03
A	A*01:04	B	B*07:05	Cw	Cw*02:05	DRA	DRA*01:04	DQB1	DQB1*02:04	DPB1	DPB1*01:04
A	A*01:05	B	B*07:06	Cw	Cw*02:06	DRA	DRA*01:05	DQB1	DQB1*02:05	DPB1	DPB1*01:05
A	A*01:06	B	B*07:07	Cw	Cw*02:07	DRA	DRA*01:06	DQB1	DQB1*02:06	DPB1	DPB1*01:06
A	A*01:07	B	B*07:08	Cw	Cw*02:08	DRA	DRA*01:07	DQB1	DQB1*02:07	DPB1	DPB1*01:07
A	A*01:08	B	B*07:09	Cw	Cw*02:09	DRA	DRA*01:08	DQB1	DQB1*02:08	DPB1	DPB1*01:08
A	A*01:09	B	B*07:10	Cw	Cw*02:10	DRA	DRA*01:09	DQB1	DQB1*02:09	DPB1	DPB1*01:09
A	A*01:10	B	B*07:11	Cw	Cw*02:11	DRA	DRA*01:10	DQB1	DQB1*02:10	DPB1	DPB1*01:10
A	A*01:11	B	B*07:12	Cw	Cw*02:12	DRA	DRA*01:11	DQB1	DQB1*02:11	DPB1	DPB1*01:11
A	A*01:12	B	B*07:13	Cw	Cw*02:13	DRA	DRA*01:12	DQB1	DQB1*02:12	DPB1	DPB1*01:12
A	A*01:13	B	B*07:14	Cw	Cw*02:14	DRA	DRA*01:13	DQB1	DQB1*02:13	DPB1	DPB1*01:13
A	A*01:14	B	B*07:15	Cw	Cw*02:15	DRA	DRA*01:14	DQB1	DQB1*02:14	DPB1	DPB1*01:14
A	A*01:15	B	B*07:16	Cw	Cw*02:16	DRA	DRA*01:15	DQB1	DQB1*02:15	DPB1	DPB1*01:15
A	A*01:16	B	B*07:17	Cw	Cw*02:17	DRA	DRA*01:16	DQB1	DQB1*02:16	DPB1	DPB1*01:16
A	A*01:17	B	B*07:18	Cw	Cw*02:18	DRA	DRA*01:17	DQB1	DQB1*02:17	DPB1	DPB1*01:17
A	A*01:18	B	B*07:19	Cw	Cw*02:19	DRA	DRA*01:18	DQB1	DQB1*02:18	DPB1	DPB1*01:18
A	A*01:19	B	B*07:20	Cw	Cw*02:20	DRA	DRA*01:19	DQB1	DQB1*02:19	DPB1	DPB1*01:19
A	A*01:20	B	B*07:21	Cw	Cw*02:21	DRA	DRA*01:20	DQB1	DQB1*02:20	DPB1	DPB1*01:20
A	A*01:21	B	B*07:22	Cw	Cw*02:22	DRA	DRA*01:21	DQB1	DQB1*02:21	DPB1	DPB1*01:21
A	A*01:22	B	B*07:23	Cw	Cw*02:23	DRA	DRA*01:22	DQB1	DQB1*02:22	DPB1	DPB1*01:22
A	A*01:23	B	B*07:24	Cw	Cw*02:24	DRA	DRA*01:23	DQB1	DQB1*02:23	DPB1	DPB1*01:23
A	A*01:24	B	B*07:25	Cw	Cw*02:25	DRA	DRA*01:24	DQB1	DQB1*02:24	DPB1	DPB1*01:24
A	A*01:25	B	B*07:26	Cw	Cw*02:26	DRA	DRA*01:25	DQB1	DQB1*02:25	DPB1	DPB1*01:25
A	A*01:26	B	B*07:27	Cw	Cw*02:27	DRA	DRA*01:26	DQB1	DQB1*02:26	DPB1	DPB1*01:26
A	A*01:27	B	B*07:28	Cw	Cw*02:28	DRA	DRA*01:27	DQB1	DQB1*02:27	DPB1	DPB1*01:27
A	A*01:28	B	B*07:29	Cw	Cw*02:29	DRA	DRA*01:28	DQB1	DQB1*02:28	DPB1	DPB1*01:28
A	A*01:29	B	B*07:30	Cw	Cw*02:30	DRA	DRA*01:29	DQB1	DQB1*02:29	DPB1	DPB1*01:29
A	A*01:30	B	B*07:31	Cw	Cw*02:31	DRA	DRA*01:30	DQB1	DQB1*02:30	DPB1	DPB1*01:30
A	A*01:31	B	B*07:32	Cw	Cw*02:32	DRA	DRA*01:31	DQB1	DQB1*02:31	DPB1	DPB1*01:31
A	A*01:32	B	B*07:33	Cw	Cw*02:33	DRA	DRA*01:32	DQB1	DQB1*02:32	DPB1	DPB1*01:32
A	A*01:33	B	B*07:34	Cw	Cw*02:34	DRA	DRA*01:33	DQB1	DQB1*02:33	DPB1	DPB1*01:33
A	A*01:34	B	B*07:35	Cw	Cw*02:35	DRA	DRA*01:34	DQB1	DQB1*02:34	DPB1	DPB1*01:34
A	A*01:35	B	B*07:36	Cw	Cw*02:36	DRA	DRA*01:35	DQB1	DQB1*02:35	DPB1	DPB1*01:35
A	A*01:36	B	B*07:37	Cw	Cw*02:37	DRA	DRA*01:36	DQB1	DQB1*02:36	DPB1	DPB1*01:36
A	A*01:37	B	B*07:38	Cw	Cw*02:38	DRA	DRA*01:37	DQB1	DQB1*02:37	DPB1	DPB1*01:37
A	A*01:38	B	B*07:39	Cw	Cw*02:39	DRA	DRA*01:38	DQB1	DQB1*02:38	DPB1	DPB1*01:38
A	A*01:39	B	B*07:40	Cw	Cw*02:40	DRA	DRA*01:39	DQB1	DQB1*02:39	DPB1	DPB1*01:39
A	A*01:40	B	B*07:41	Cw	Cw*02:41	DRA	DRA*01:40	DQB1	DQB1*02:40	DPB1	DPB1*01:40
A	A*01:41	B	B*07:42	Cw	Cw*02:42	DRA	DRA*01:41	DQB1	DQB1*02:41	DPB1	DPB1*01:41
A	A*01:42	B	B*07:43	Cw	Cw*02:43	DRA	DRA*01:42	DQB1	DQB1*02:42	DPB1	DPB1*01:42
A	A*01:43	B	B*07:44	Cw	Cw*02:44	DRA	DRA*01:43	DQB1	DQB1*02:43	DPB1	DPB1*01:43
A	A*01:44	B	B*07:45	Cw	Cw*02:45	DRA	DRA*01:44	DQB1	DQB1*02:44	DPB1	DPB1*01:44
A	A*01:45	B	B*07:46	Cw	Cw*02:46	DRA	DRA*01:45	DQB1	DQB1*02:45	DPB1	DPB1*01:45
A	A*01:46	B	B*07:47	Cw	Cw*02:47	DRA	DRA*01:46	DQB1	DQB1*02:46	DPB1	DPB1*01:46
A	A*01:47	B	B*07:48	Cw	Cw*02:48	DRA	DRA*01:47	DQB1	DQB1*02:47	DPB1	DPB1*01:47
A	A*01:48	B	B*07:49	Cw	Cw*02:49	DRA	DRA*01:48	DQB1	DQB1*02:48	DPB1	DPB1*01:48
A	A*01:49	B	B*07:50	Cw	Cw*02:50	DRA	DRA*01:49	DQB1	DQB1*02:49	DPB1	DPB1*01:49
A	A*01:50	B	B*07:51	Cw	Cw*02:51	DRA	DRA*01:50	DQB1	DQB1*02:50	DPB1	DPB1*01:50
A	A*01:51	B	B*07:52	Cw	Cw*02:52	DRA	DRA*01:51	DQB1	DQB1*02:51	DPB1	DPB1*01:51
A	A*01:52	B	B*07:53	Cw	Cw*02:53	DRA	DRA*01:52	DQB1	DQB1*02:52	DPB1	DPB1*01:52
A	A*01:53	B	B*07:54	Cw	Cw*02:54	DRA	DRA*01:53	DQB1	DQB1*02:53	DPB1	DPB1*01:53
A	A*01:54	B	B*07:55	Cw	Cw*02:55	DRA	DRA*01:54	DQB1	DQB1*02:54	DPB1	DPB1*01:54
A	A*01:55	B	B*07:56	Cw	Cw*02:56	DRA	DRA*01:55	DQB1	DQB1*02:55	DPB1	DPB1*01:55
A	A*01:56	B	B*07:57	Cw	Cw*02:57	DRA	DRA*01:56	DQB1	DQB1*02:56	DPB1	DPB1*01:56
A	A*01:57	B	B*07:58	Cw	Cw*02:58	DRA	DRA*01:57	DQB1	DQB1*02:57	DPB1	DPB1*01:57
A	A*01:58	B	B*07:59	Cw	Cw*02:59	DRA	DRA*01:58	DQB1	DQB1*02:58	DPB1	DPB1*01:58
A	A*01:59	B	B*07:60	Cw	Cw*02:60	DRA	DRA*01:59	DQB1	DQB1*02:59	DPB1	DPB1*01:59
A	A*01:60	B	B*07:61	Cw	Cw*02:61	DRA	DRA*01:60	DQB1	DQB1*02:60	DPB1	DPB1*01:60
A	A*01:61	B	B*07:62	Cw	Cw*02:62	DRA	DRA*01:61	DQB1	DQB1*02:61	DPB1	DPB1*01:61
A	A*01:62	B	B*07:63	Cw	Cw*02:63	DRA	DRA*01:62	DQB1	DQB1*02:62	DPB1	DPB1*01:62
A	A*01:63	B	B*07:64	Cw	Cw*02:64	DRA	DRA*01:63	DQB1	DQB1*02:63	DPB1	DPB1*01:63
A	A*01:64	B	B*07:65	Cw	Cw*02:65	DRA	DRA*01:64	DQB1	DQB1*02:64	DPB1	DPB1*01:64
A	A*01:65	B	B*07:66	Cw	Cw*02:66	DRA	DRA*01:65	DQB1	DQB1*02:65	DPB1	DPB1*01:65
A	A*01:66	B	B*07:67	Cw	Cw*02:67	DRA	DRA*01:66	DQB1	DQB1*02:66	DPB1	DPB1*01:66
A	A*01:67	B	B*07:68	Cw	Cw*02:68	DRA	DRA*01:67	DQB1	DQB1*02:67	DPB1	DPB1*01:67
A	A*01:68	B	B*07:69	Cw	Cw*02:69	DRA	DRA*01:68	DQB1	DQB1*02:68	DPB1	DPB1*01:68
A	A*01:69	B	B*07:70	Cw	Cw*02:70	DRA	DRA*01:69	DQB1	DQB1*02:69	DPB1	DPB1*01:69
A	A*01:70	B	B*07:71	Cw	Cw*02:71	DRA	DRA*01:70	DQB1	DQB1*02:70	DPB1	DPB1*01:70
A	A*01:71	B	B*07:72	Cw	Cw*02:72	DRA	DRA*01:71	DQB1	DQB1*02:71	DPB1	DPB1*01:71
A	A*01:72	B	B*07:73	Cw	Cw*02:73	DRA	DRA*01:72	DQB1	DQB1*02:72	DPB1	DPB1*01:72
A	A*01:73	B	B*07:74	Cw	Cw*02:74	DRA	DRA*01:73	DQB1	DQB1*02:73	DPB1	DPB1*01:73
A	A*01:74	B	B*07:75	Cw	Cw*02:75	DRA	DRA*01:74	DQB1	DQB1*02:74	DPB1	DPB1*01:74
A	A*01:75	B	B*07:76	Cw	Cw*02:76	DRA	DRA*01:75	DQB1	DQB1*02:75	DPB1	DPB1*01:75
A	A*01:76	B	B*07:77	Cw	Cw*02:77	DRA	DRA*01:76	DQB1	DQB1*02:76	DPB1	DPB1*01:76
A	A*01:77	B	B*07:78	Cw	Cw*02:78	DRA	DRA*01:77	DQB1	DQB1*02:77	DPB1	DPB1*01:77
A	A*01:78	B	B*07:79	Cw	Cw*02:79	DRA	DRA*01:78	DQB1	DQB1*02:78	DPB1	DPB1*01:78
A	A*01:79	B	B*07:80	Cw	Cw*02:80	DRA	DRA*01:79	DQB1	DQB1*02:79	DPB1	DPB1*01:79
A	A*01:80	B	B*07:81	Cw	Cw*02:81	DRA	DRA*01:80	DQB1	DQB1*02:80	DPB1	DPB1*01:80
A	A*01:81	B	B*07:82	Cw	Cw*02:82	DRA	DRA*01:81	DQB1	DQB1*02:81	DPB1	DPB1*01:81
A	A*01:82	B	B*07:83	Cw	Cw*02:83	DRA	DRA*01:82	DQB1	DQB1*02:82	DPB1	DPB1*01:82
A	A*01:83	B	B*07:84	Cw	Cw*02:84	DRA	DRA*01:83	DQB1	DQB1*02:83	DPB1	DPB1*01:83
A	A*01:84	B	B*07:85	Cw	Cw*02:85	DRA	DRA*01:84	DQB1	DQB1*02:84	DPB1	DPB1*01:84
A	A*01:85	B	B*07:86	Cw	Cw*02:86	DRA	DRA*01:85	DQB1	DQB1*02:85	DPB1	DPB1*01:85
A	A*01:86	B	B*07:87	Cw	Cw*02:87	DRA	DRA*01:86	DQB1	DQB1*02:86	DPB1	DPB1*01:86
A	A*01:87	B	B*07:88	Cw	Cw*02:88	DRA	DRA*01:87	DQB1	DQB1*02:87	DPB1	DPB1*01:87
A	A*01:88	B	B*07:89	Cw	Cw*02:89	DRA	DRA*01:88	DQB1	DQB1*02:88	DPB1	DPB1*01:88
A	A*01:89	B	B*07:90	Cw	Cw*02:90	DRA	DRA*01:89	DQB1	DQB1*02:89	DPB1	DPB1*01:89
A	A*01:90	B	B*07:91	Cw	Cw*02:91	DRA	DRA*01:90	DQB1	DQB1*02:90	DPB1	DPB1*01:90
A	A*01:91	B	B*07:92	Cw	Cw*02:92	DRA	DRA*01:91	DQB1	DQB1*02:91	DPB1	DPB1*01:91
A	A*01:92	B	B*07:93	Cw	Cw*02:93	DRA	DRA*01:92	DQB1	DQB1*02:92	DPB1	DPB1*01:92
A	A*01:93	B	B*07:94	Cw	Cw*02:94	DRA	DRA*01:93	DQB1	DQB1*02:93	DPB1	DPB1*01:93
A	A*01:94	B	B*07:95	Cw	Cw*02:95	DRA	DRA*01:94	DQB1	DQB1*02:94	DPB1	DPB1*01:94
A	A*01:95	B	B*07:96	Cw	Cw*02:96	DRA	DRA*01:95	DQB1	DQB1*02:95	DPB1	DPB1*01:95
A	A*01:96	B	B*07:97	Cw							

