HUMAN GENOME EPIDEMIOLOGY (HuGE) REVIEW

HLA-DPB1 and Chronic Beryllium Disease: A HuGE Review

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The human leukocyte antigen (HLA) complex is a series of genes located on chromosome 6 that are important in normal immune function. Susceptibility to chronic beryllium disease, a granulomatous lung disease that appears in workers exposed to beryllium, is modified by genetic variants of the *HLA-DP* subregion. Evaluation of *HLA-DPB1* sequence motifs in current and former beryllium workers implicated a glutamic acid residue at position 69 (*HLA-DPB1^{Glu69}*) in chronic beryllium disease. This finding has since been extended to specific *HLA-DPB1^{Glu69}* alleles. Specific job tasks have also been implicated in degree of risk, and in this paper the authors explore gene-environment interaction. The utility of this genetic information for prospective, current, and former beryllium workers must be weighed against the potential for employment and insurance discrimination. Continued research in the beryllium-exposed population will be important for improving personal risk assessment and identifying high-risk genes associated with disease progression.

berylliosis; beryllium; chronic beryllium disease; epidemiology; genetic screening; *HLA-DP* antigens; *HLA-DPB1*; occupational exposure

Abbreviations: Arg, arginine; Asp, aspartic acid; BHWCD, beryllium hypersensitivity without clinical disease; CBD, chronic beryllium disease; CI, confidence interval; Glu, glutamic acid; HLA, human leukocyte antigen; Lys, lysine; OR, odds ratio; TNF-α, tumor necrosis factor-α.

Editor's note: *This article is also available on the website of the Human Genome Epidemiology Network (http://www.cdc.gov/genomics/hugenet/default.htm).*

GENE

The human leukocyte antigen (HLA) complex comprises closely linked genes located on the short arm of chromosome 6 that include *HLA-A*, *-B*, *-C*, and *-D*. The *HLA-A*, *-B*, and *-C* loci code for class I molecules. The *HLA-D* region consists of three primary subregions designated *DP*, *DQ*, and *DR*, and these loci code for class II molecules. A map of chromosome 6p12.3 shows the relative locations of the HLA genes (figure 1) (1). Both class I and class II molecules are extremely important in immunologic processes, specifically the presentation of foreign and self antigens to the cell surface for T-cell recognition (2). Although the *HLA-DP* molecule has not been studied as extensively as *HLA-DR* or *HLA-DQ*, it shares similar functional characteristics of antigen presentation to the T-cell and induces a strong secondary proliferative response.
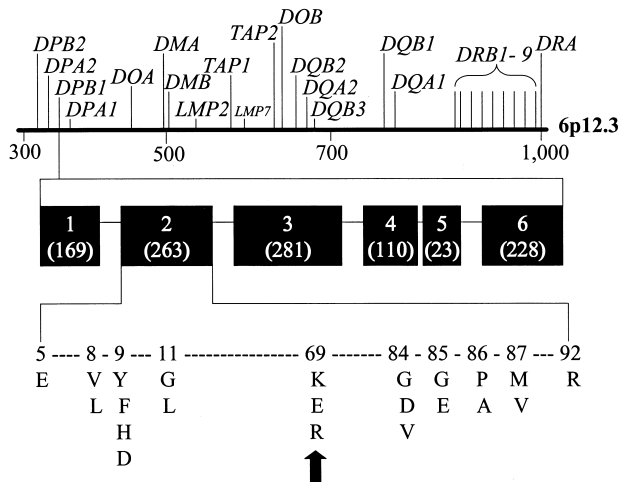
FIGURE 1. Partial map of chromosome 6p12.3 showing the relative positions of genes in the human leukocyte antigen (HLA) complex (1). *HLA-DPB1* has been expanded to show the coding region (exons 1–6 and their relative sizes in base pairs). Some of the key amino acid substitution polymorphisms are listed. The arrow indicates those at position 69 (K = lysine; E = glutamic acid; R = arginine).

GENE VARIANTS

Variations encoded in α and β chains of the *DP* molecule are located at the second exon (3). The α helical walls and the β pleated sheet floor form the peptide binding groove. Polymorphisms are generally restricted to amino acid residues that form this groove and that interact with the peptide or T-cell receptor. These polymorphic residues in the α and β chains account for most of the association of HLA with disease (3). Inheritance of certain alleles may lead to either an absent or a vigorous T-cell response to a given antigen. A strong response protects from some infectious disease, but it can also result in adverse pathologic events (3).

To date, 100 different *HLA-DPB1* alleles and 20 *HLA-DPA1* alleles have been described (3–10). Certain *HLA-DP* alleles are thought to play a role in acute graft rejection, pauciarticular juvenile rheumatoid arthritis, and sarcoidosis (11, 12). Among the Japanese, *HLA-DPB1*0501* has been found to be associated with opticospinal multiple sclerosis (13, 14). *HLA-DP* has also been found to be associated with insulin-dependent diabetes mellitus in the Japanese and Indian populations (15, 16). Furthermore, the family of *HLA-DPB1* alleles characterized by a glutamic acid residue in the 69th position has been found to be associated with hard metal disease and chronic beryllium disease (17–24). There are 34 such alleles, and it is likely that levels of risk vary by allele. This review will focus on the role of *HLA-DPB1* in chronic beryllium disease.

We searched MEDLINE using the keyword "HLA-DP" for papers published between 1993 and 2002. The search was limited to human subjects and the English language. We then identified relevant papers and critically evaluated them for inclusion in or exclusion from the current review. We

were specifically interested in identifying population frequencies for those alleles that contain a glutamic acid residue in the 69th position (table 1) (25–38).

Table 1 reports either the allelic frequency (*F*), the carrier frequency (*C*), or both for the *HLA-DPB1*02* and non-*HLA-DPB1*02* alleles reported in different populations. The alleles listed are only those for *HLA-DPB1*^{Glu69} and are not necessarily all of the alleles genotyped. Hardy-Weinberg equilibrium was estimated in four of these studies and was found to be nonsignificant (35–38). Because of the lack of data for the majority of the studies, however, neither Hardy-Weinberg equilibrium nor the frequencies associated with heterozygosity versus homozygosity could be determined (25–38). For this reason, the allelic frequencies, particularly in studies with small populations, might not represent true population frequencies. Furthermore, different laboratory methods probably introduce varying degrees of error. High-resolution allele-specific sequencing data are the most reliable, followed by sequence-specific oligonucleotide probes and dot blot hybridization. Even in light of these limitations, the results indicate that there are considerable differences in the frequency of the *HLA-DPB1*^{Glu69}-containing alleles across populations. For example, *HLA-DPB1*02* occurred most often in the Tolai people of Papua New Guinea (total *F* = 0.58), followed by Australian aboriginals from the central desert (*F* = 0.36) (27, 38). There also appear to be populations in which *HLA-DPB1*02* occurs with such a small frequency as to be almost nonexistent. This is true for natives of the Trobriand Islands (*F* = 0.006) and a large number of Colombian aboriginals (*F* = 0.00) (29, 38). Similarly, the frequencies for non-*HLA-DPB1*02* are also highly variable. *HLA-DPB1*1301* occurred with the highest frequency in a Borneo population (*F* = 0.43) (38). However, the prevalence of this same allele was greatly reduced in a Liberian population (*F* = 0.03) (35).

DISEASE(S)

Individuals who are exposed to beryllium dust or fumes are at risk of lung cancer and a granulomatous lung disease called chronic beryllium disease (CBD) (39–43). Beryllium is atomic number 4 on the periodic table of the elements. Its light weight, stability, and considerable strength make it an ideal element for numerous technological applications. It is extracted from beryl ore or bertrandite and is generally sold as beryllium oxide powder, beryllium alloys, or pure beryllium metal. Beryllium products are used in the aerospace industry, the nuclear power industry, electronics, and the manufacture of dental prostheses (39–41). Exposure to beryllium occurs primarily among workers in beryllium manufacturing plants in which welding, machining, heating, grinding, melting, and pressing of beryllia ceramics may result in the production of respirable beryllium particles (41). However, beryllium exposure and risk of CBD may also occur among secondary users of beryllium products who further adapt them by grinding, welding, or machining, which also results in respirable beryllium particles. Workers in precious metal reclamation and construction workers in beryllium-using facilities are also at risk (44). Currently, it is not known how many persons are or have been exposed to

TABLE 1. Frequency of *HLA*-DPB1^Glu69* alleles across populations in English-language studies published between 1993 and 2002

Authors and year of publication (ref. no.)	Laboratory method(s)	Study population and/or location (sample size)	HLA-DPB1*02 allele†	Allelic frequency‡ (%)	Carrier frequency‡ (%)	Non-HLA-DPB1*02 allele†	Allelic frequency‡ (%)	Carrier frequency‡ (%)
Gao et al., 1991 (25)	PCR*/dot blot	Northern Chinese (n = 88)	*0201	18		*0601	1	
			*0202	3		*0901	1	
			Total	21		*1301	5	
						*1701	6	
						Total	13	
Falco et al., 1993 (26)	PCR/dot blot	Southern Chinese (n = 99)	*0201	15		*1301	11	
			*0202	11		*1901	0.5	
			Total	26		*2101	6	
						Total	18	
Lienert et al., 1993 (27)	PCR/RFLP*	Australia						
		Caucasians (n = 50)	*0201	9		*0601	3	
						*1001	2	
						*1301	2	
						*1601	1	
						*1701	1	
						*1901	1	
						Total	10	
		Aboriginals—central desert (n = 60)	*0201	32		*0601	0.8	
			*0202	4		*1601	18	
			Total	36		*2201	2	
						Total	21	
		Aboriginals—northern coast (n = 33)	*0201	17		*1601	8	
			*0202	3		*2201	6	
			Total	20		Total	14	
Titus-Trachtenberg et al., 1994 (28)	SSOP*	Cayapa Indians, Ecuador (n = 100)	*0201	4		*1301	6	
Briceno et al., 1996 (29)	SSOP	Colombia Kogui (n = 50) Arsario (n = 50) Ijka (n = 40) Wayuu (n = 54) Vaupes (n = 46) Coreguaje (n = 45) Embera (n = 49)				*1301	28	
Ploski et al., 1996 (30)	SSOP	Caucasians, Poland (n = 158)	*0201		23	*0601		3
						*0801		1
						*0901		1
						*1001		1
						*1301		3
						*1701		5
						*1901		1
						Total		15
Trachtenberg et al., 1996 (31)	SSOP	Colombia Kogui (n = 30) Ijka (n = 30) Sikuani (n = 28) Ingano (n = 11) Coreguaje (n = 20) Nukak (n = 20) Waunana (n = 30) Embera (n = 20) Tule (n = 29)	*0201	2		*1301 *1301	23 35	

Table continues

beryllium, although estimates range from a low of 21,233 to a high of 800,000 (44–46). Estimates are important, however, because exposure confers a lifetime risk of CBD.

Since 1960, a series of epidemiologic studies have been conducted to evaluate the excess risks of lung cancer and mortality among beryllium workers (47–58). Although a number of methodological problems plagued many of the earlier studies (59), in 1980 the International Agency for Research on Cancer classified beryllium as a probable human carcinogen (class 2A) (42). This was later revised, and in 1993 beryllium and beryllium compounds were classified as human carcinogens (group 1) (43). However, CBD overshadows lung cancer as a significant problem for beryllium workers.

MORBIDITY

Exposure to beryllium triggers a cell-mediated, type IV delayed hypersensitivity reaction that results in the prolifera-

TABLE 1. Continued

Authors and year of publication (ref. no.)	Laboratory method(s)	Study population and/or location (sample size)	*HLA-DPB1*02* allele†	Allelic frequency‡ (%)	Carrier frequency‡ (%)	Non-*HLA-DPB1*02* allele†	Allelic frequency‡ (%)	Carrier frequency‡ (%)
Trachtenberg et al., 1996 (32)	SSOP	African-American Colombians						
		Cauca (*n* = 40)	*0201	3		*1301	5	
						*1701	5	
						Total	10	
		Choco (*n* = 20)	*0201	3		*0901	3	
						*3001	3	
						Total	6	
		Providencia (*n* = 20)	*0201	10		*1001	3	
						*1301	3	
						*1601	5	
						*1701	8	
						Total	19	
Just et al., 1997 (33)	SSOP	African Americans, New York City (*n* = 241)	*0201	10		*0601	1	
			*0202	0.4		*0901	0.4	
			Total	10		*1301	5	
						*1601	0.2	
						*1701	9	
						*1901	0.2	
						*2901	0.4	
						*3001	0.4	
						Total	17	
Cechova et al., 1998 (34)	RFLP	Slovak Republic (*n* = 146)	*0201	14		*0601	0.3	
			*0202	0.3		*0901	0.7	
			Total	14		*1001	1.4	
						*1601	2	
						*1701	1.7	
						Total	6	
May et al., 1998 (35)	SSOP	Nigeria (*n* = 130)	*0201	8.5		*1001	0.4	
						*1301	2.3	
						*1601	3.5	
						*1701	4.6	
						*3001	0.8	
						*3201	0.8	
						*4601	0.4	
						*5501	0.4	
						Total	13	
		Liberia (*n* = 110)	*0201	5		*0601	0.5	
						*1301	3.2	
						*1701	6.8	
						*3001	0.9	
						*3701	0.5	
						Total	12	
		Gabon (*n* = 120)	*0201	18.3		*1001	0.4	
						*0601	1.3	
						*1301	0.8	
						*1701	2.5	
						*1901	1.3	
						*2901	0.8	
						*3301	0.4	
						Total	8	

Table continues

tion of beryllium-specific T lymphocytes (60, 61). This immunologic response can be monitored in the blood using the beryllium lymphocyte proliferation test, which is used to indicate beryllium sensitization in exposed workers (62–65). Further clinical evaluation is then necessary to determine whether granuloma formation has occurred, resulting in a diagnosis of CBD.

The prevalence of beryllium sensitization among beryllium-exposed workers has been reported to be between 1 percent and 12 percent (table 2) (63–69). Part of this variation may be a result of the poor reproducibility of the beryllium lymphocyte proliferation test between and within laboratories. Higher prevalence rates are often reported when two laboratories receive split samples than when a single laboratory is used.

Of sensitized persons, 36–100 percent have evidence of granulomatous lung disease (table 2) (63–69). Currently, it is not known whether all sensitized persons will develop CBD. Individuals with CBD often develop shortness of breath, cough, chest discomfort, fatigue, and weight loss. Severe disease results in pulmonary failure (40, 70). However, in its initial stages, beryllium disease may be asymptomatic. Before the advent of beryllium lymphocyte proliferation test screening and identification of subclinical disease, the average latency period for clinical disease was reported to be 10 years (71). Shorter latency periods are evident with sensi-

TABLE 1. Continued

Authors and year of publication (ref. no.)	Laboratory method(s)	Study population and/or location (sample size)	HLA-DPB1*02 allele†	Allelic frequency‡ (%)	Carrier frequency‡ (%)	Non-HLA-DPB1*02 allele†	Allelic frequency‡ (%)	Carrier frequency‡ (%)
Poulton et al., 1998 (36)	SSOP/ sequencing	Bantu, Cameroon (n = 89)	*0201 *0202 Total		35 2 37	*1301 *1701 *1901 *2901 Total		6 6 1 2 15
Loudova et al., 1999 (37)	SSOP	Prague, Czech Republic (n = 92)	*0201	11	23	*0901 *1001 *1301 *1701 *1901 Total	0.5 1 2 2 0.5 6	1 2 4 4 1 12
Zimdahl et al., 1999 (38)	SSOP/ sequencing	Asia-Oceana						
		Trobriand Islands (n = 81)	*0201	0.6				
		Papua New Guinea						
		Roro (n = 26)	*0201	10				
		Highlands (n = 28)	*0201 *0202 Total	27 2 29				
		Tolai, New Britain (n = 48)	*0201 *0202 Total	57 1 58		*1701	2	
		Western Samoa (n = 22)	*0201	2		*4801	2	
		Java (n = 59)	*0201 *0202 Total	2.6 7.6 10		*0901 *1301 *1701 *1901 Total	20 20 1 1 42	
		Borneo (n = 21)	*0201	2		*1301	43	
		Taiwanese/Aboriginals: Ami, Atayal, Bunun, Paiwan (n = 48)	*0201	5		*1301 *2201 Total	2 1 3	

* HLA, human leukocyte antigen; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; SSOP, sequence-specific oligonucleotide probes.

† An empty cell indicates that there were no observed alleles for either HLA-DPB1*02 or non-HLA-DPB1*02.

‡ An empty cell indicates that either the allelic frequency or the carrier frequency could not be determined from the data.

tization screening and clinical evaluation of asymptomatic sensitized workers (69).

MORTALITY

Only a few studies have been conducted to evaluate mortality rates associated with CBD (56–58, 72). Among beryllium-exposed workers, excess mortality has been observed for lung cancer, heart disease, diseases of the respiratory system (e.g., beryllium disease, emphysema, pneumoconiosis), and diseases of the genitourinary system (56–58).

As of 1993, 36 percent of the persons registered in the United Kingdom Beryllium Case Registry had died from respiratory failure associated with beryllium disease (72). A similar study utilizing data from the United States Beryllium Case Registry (71, 73–75) reported that 62 percent of eligible persons had died. The primary cause of death in this cohort was reported as "pneumoconioses, other respiratory disease," a classification often used for beryllium disease (56). However, ascertainment problems may affect both the United Kingdom Beryllium Case Registry and the United States Beryllium Case Registry, resulting in inaccuracy in mortality rates. For example, prior to the advent of the beryllium lymphocyte proliferation test, it was difficult to distinguish beryllium disease from other granulomatous lung diseases, particularly sarcoidosis. Furthermore, some CBD patients may have been excluded from the registry because they were not actively sought out for registration or because their physicians did not recognize CBD or refer them for registration (71–75).

ASSOCIATIONS

The rationale for the investigation of genetic variation at HLA-DP loci was based on observations that implicated major histocompatibility complex class II antigen-bearing cells in a beryllium-specific T-lymphocyte-mediated response in CBD (19). In 1993, Richeldi et al. (19) evaluated the presence of HLA-DPB1 variants at codons 36, 55–57, and 65–69 in persons with and without CBD. No significant association was seen between CBD and variants at codon 36. However, the presence of aspartic acid and glutamic acid in positions 55 and 56, respectively, was found to occur more often in CBD cases than in controls (79 percent vs. 41

TABLE 2.   Prevalence of beryllium sensitization and chronic beryllium disease among beryllium workers in English-language studies published between 1993 and 2002

Authors and year of publication (ref. no.)	Beryllium exposure site surveyed	Sample size	Beryllium sensitization			Chronic beryllium disease		
			No. with test results*	No. sensitized	%	No. evaluated†	No. with chronic beryllium disease	%
Kreiss et al., 1989 (63)	Rocky Flats nuclear weapons facility (Denver, Colorado)	51	51	6	11.8	5	4	80
Kreiss et al., 1993 (64)	Coors Ceramics Company (Golden, Colorado)	505	505	8	1.6	8	8	100
Kreiss et al., 1993 (65)	Rocky Flats‡	895	890	17	2	16	13	81
Kreiss et al., 1996 (66)	Brush Wellman, Inc. (Tucson, Arizona)	136	136	8	5.9	7	6	86
Stange et al., 1996 (67)	Rocky Flats§	4,268	4,268	74	1.7	74	27	36
Kreiss et al., 1997 (68)	Brush Wellman, Inc. (Elmore, Ohio)	627	627	59	9.4	47	24	51
Henneberger et al., 2001 (69)	Brush Wellman, Inc. (Tucson, Arizona)¶	151	151	15	9.9	15	8	53

* Number of persons for whom beryllium lymphocyte proliferation test results were obtained.
† Number of persons who underwent complete clinical evaluation.
‡ Does not include persons surveyed by Kreiss et al. in 1989 (63).
§ Includes cases identified by Kreiss et al. in 1989 and 1993 (63, 65).
¶ Includes persons previously surveyed by Kreiss et al. in 1996 (66).

percent; $p = 0.005$) (table 3). A family of *HLA-DPB1* alleles that code for a glutamic acid residue at the 69th position in the amino acid sequence was also found to be associated with CBD (97 percent vs. 27 percent; $p = 0.0001$) (19). When allele-specific genotyping was conducted, *HLA-DPB1*0201* was found to occur significantly more often in cases than in controls (30 percent vs. 10 percent; $p = 0.05$), while *HLA-DPB1*0401*, which does not contain a glutamic acid residue at position 69, occurred less often in cases than in controls (14 percent vs. 48 percent; $p = 0.001$) (19). The association between CBD and *HLA-DPB1*[Glu69]* was later confirmed in a separate study that was also conducted by Richeldi et al. (20). They did not reevaluate the allele-specific information until 2000 (23). Prior to this, Wang et al. (21) used allele-specific DNA sequencing of *HLA-DPB1* and identified important variations at positions 8, 9, 11, 55–57, 69, and 84–87 (table 3).

This study, consisting of 20 cases and 75 controls, also found a strong association between the inheritance of *HLA-DPB1*[Glu69]* and disease risk in beryllium-exposed workers (95 percent vs. 45 percent; odds ratio (OR) = 22.9, 95 percent confidence interval (CI): 4.8, 108.2) (21). Although the small sample size resulted in large confidence intervals, haplotype determination strongly suggested that being homozygous for *HLA-DPB1*[Glu69]* (OR = 246.0, 95 percent CI: 38.0, 1,594.4) conferred a much greater risk for CBD than being heterozygous (OR = 16.2, 95 percent CI: 3.1, 84.4). Further examination of other subtypic alleles, all containing a glutamic acid residue at codon 69, found that persons with CBD were more likely to have alleles characterized by valine, histidine [or tyrosine], and leucine codons at positions 8, 9, and 11, respectively, rather than leucine, phenylalanine, and glycine (79 percent vs. 30 percent; $p =$

0.003) (21). Furthermore, persons with CBD were more likely to have alleles characterized by aspartate, glutamic acid, alanine, and valine codons at positions 84, 85, 86, and 87, respectively, rather than glycine, glycine, proline, and methionine (84 percent vs. 35 percent; $p = 0.004$) (21). On the basis of this information, the alleles defined by the supratypic marker at codon 69 that would be expected to be most closely associated with CBD are *HLA-DPB1*0601*, *0901*, *1001*, *1301*, and *1701* as opposed to *HLA-DPB1*02012*, *02013*, *02014*, *02015*, *0202*, and *1901* (or other alleles containing a glutamic acid residue at codon 69 that have not yet been reported in a beryllium exposure study, such as *HLA-DPB1*4601* and *7101*).

In 2001, Wang et al. (21, 22) once again utilized allele-specific polymerase chain reaction to evaluate the frequency of *HLA-DPB1* in 25 beryllium-sensitized persons (without CBD) and to further characterize persons with and without CBD. Twenty of the persons with CBD and 70 of the controls in this study had participated in the previous study (21). The additional controls were beryllium-exposed workers who had a negative beryllium lymphocyte proliferation test. When the presence or absence of *HLA-DPB1*[Glu69]* was evaluated, sensitized persons were significantly more likely to carry at least one *HLA-DPB1*[Glu69]* allele in comparison with the control group (88 percent vs. 37 percent; OR = 12.3, 95 percent CI: 3.5, 42.7; $p < 0.0001$). Haplotype analysis identified 30 percent of persons with CBD as being homozygous for *HLA-DPB1*[Glu69]*, as compared with 24 percent of the sensitized persons and only 3 percent of the controls ($p < 0.001$). When the frequency of non-*HLA-DPB1*0201* alleles was evaluated, sensitized persons were more likely to have at least one non-*HLA-DPB1*0201* allele than controls (52 percent vs. 13 percent; $p < 0.001$) but had

TABLE 3. Frequency of *HLA**-*DPB1* alleles among beryllium workers with and without chronic beryllium disease in English-language studies published between 1993 and 2002

Authors and year of publication (ref. no.)	Sample size		Allele	Frequency of allele (%)		*p* value
	Cases	Controls		Cases	Controls	
Richeldi et al., 1993 (19)	33	44	*HLA-DPB1* $^{Asp55/Glu56}$	79	41	0.005
			HLA-DPB1 ^{Glu69}	97	27	0.0001
			HLA-DPB1*0201*	30	10	0.05
			HLA-DPB1*0401*	14	48	0.001
Richeldi et al., 1997 (20)	6	119	*HLA-DPB1* ^{Glu69}	83	30	0.01
Wang et al., 1999 (21)	20	75	*HLA-DPB1* ^{Glu69}	95	45	0.001
			HLA-DPB1 $^{V8/H[Y]9/L11}$†	79‡	30‡	0.003
			HLA-DPB1 $^{D84/E85/A86/V87}$§	84‡	35‡	0.004
Saltini et al., 2001 (23)	22	93	*HLA-DPB1* ^{Glu69}	72‡	40‡	0.02
Rossman et al., 2002 (24)	25	82	*HLA-DPB1* ^{Glu69}	84	48	0.03

* HLA, human leukocyte antigen.

† The superscript V8/H[Y]9/L11 represents the amino acid residues valine, histidine [or tyrosine], and leucine at positions 8, 9, and 11 of the *HLA-DPB1* gene.

‡ Carrier frequencies.

§ The superscript D84/E85/A86/V87 represents the amino acid residues aspartic acid, glutamic acid, alanine, and valine at positions 84, 85, 86, and 87 of the *HLA-DPB1* gene.

such an allele less often than persons with CBD (52 percent vs. 80 percent; not significant). When the specific non-*HLA-DPB1**0201* alleles were examined, *HLA-DPB1**1701* occurred most often in both sensitized persons (16 percent) and persons with CBD (30 percent) in comparison with the control group (2 percent) ($p < 0.01$) (21, 22).

The results of this last study (22) will help in clarifying the natural history of CBD. However, concerns about the population under study also warrant further evaluation and verification of these findings. These concerns include composition of the CBD case, sensitized, and control groups and the small sample size. For example, five of the sensitized persons in the most recent study conducted by Wang et al. (22) had previously been analyzed as controls (21); 10 of the beryllium-sensitized persons did not have signs of respiratory impairment, but none were clinically evaluated for granulomatous lung disease; and two of the sensitized persons in the most recent study were not known to have been occupationally exposed to beryllium.

Using the same methods as Richeldi et al. (19, 20), Saltini et al. (23) conducted a study that analyzed the presence and absence of specific *HLA-DPB1* alleles in 22 persons with CBD, 23 persons with beryllium sensitivity (without CBD), and 93 control samples. *HLA-DPB1*^{Glu69} was significantly associated with persons with CBD in comparison with both the control group and the sensitized group. *HLA-DPB1**0501* occurred more often, though not significantly, among the sensitized in comparison with both persons with CBD and controls (11 percent in the sensitized vs. 2 percent among persons with CBD and controls). The prevalence of *HLA-DPB1**0201* was increased, also not significantly, in the CBD cases as compared with the controls (27 percent vs. 17 percent). Although frequencies were not significantly different, a number of non-*HLA-DPB1**0201* alleles were also observed to appear more often in the CBD cases than in

the controls (23). These included *HLA-DPB1**0601*, *HLA-DPB1**0901*, *HLA-DPB1**1001*, *HLA-DPB1**1701*, and *HLA-DPB1**1901*.

Rossman et al. (24) recently published information on the genetics of beryllium sensitization and CBD. The study population consisted of 137 persons who had been referred to the Hospital of the University of Pennsylvania for clinical evaluation of CBD. Fifty-five of the participants had a positive beryllium lymphocyte proliferation test and were designated as having beryllium hypersensitivity. Upon clinical examination, 25 out of 55 were determined to have CBD and 30 out of 55 were defined as having beryllium hypersensitivity without clinical disease (BHWCD). The control group consisted of 82 beryllium-exposed persons. None had positive beryllium lymphocyte proliferation test results, although 10 had abnormal chest radiographs. *HLA-DPB1* genotyping was conducted on all of the samples, and the frequencies of alleles were compared across the groups with and without disease (24). *HLA-DQB1* and *HLA-DRB1* were also evaluated but not in conjunction with *HLA-DPB1*, so they will not be discussed here.

HLA-DPB1^{Glu69} appeared more often in persons with BHWCD (90 percent) and persons with CBD (84 percent) than in those without disease (48 percent). The highest odds ratio for disease was associated with BHWCD and *HLA-DPB1*^{Glu69} (OR = 9.9, 95 percent CI: 2.8, 35.3). When the frequency of *HLA-DPB1*^{Glu69} among persons with BHWCD was compared with the frequency among persons with CBD, there was no significant difference. When specific *HLA-DPB1*^{Glu69} alleles were evaluated, none remained significant after adjustment for multiple comparisons.

The presence of lysine at position 11 (*HLA-DPB1*^{Lys11}) and the presence of aspartic acid at position 55 (*HLA-DPB1*^{Asp55}) were significantly associated with beryllium hypersensitivity, but this association remained significant only in the

TABLE 4.   Prevalence of chronic beryllium disease according to the presence of the *HLA**-*DPB1^{Glu69}* allele and employment in machining†

Presence of *HLA-DPB1^{Glu69}* allele	Employment in machining	No. of cases (*n* = 6)	No. of controls (*n* = 121)	Proportion with chronic beryllium disease	95% confidence interval
No	No	0	55	0.00	0.00, 0.06
No	Yes	1	30	0.03	0.00, 0.17
Yes	No	1	24	0.04	0.00, 0.20
Yes	Yes	4	12	0.25	0.07, 0.52

* HLA, human leukocyte antigen.

† Data were obtained from the paper by Richeldi et al. (20).

presence of *HLA-DPB1^{Glu69}*. Furthermore, there was no difference between the frequencies of *HLA-DPB1^{-Glu69 -Lys11}* and *HLA-DPB1^{-Glu69 -Asp55}* among persons with CBD or persons with BHWCD. It was concluded that *HLA-DPB1^{Glu69}* was the most important epitope in the development of beryllium hypersensitivity, but it could not be used to predict whether someone would develop CBD.

While all of the studies conducted found that *HLA-DPB1^{Glu69}* is associated with CBD, they differed in terms of the relative importance placed on the role of the *HLA-DPB1*0201* alloforms in CBD (19–24). Furthermore, it is of interest that while Wang et al. (22) and Rossman et al. (24) found a relation between *HLA-DPB1^{Glu69}* and beryllium sensitization, Saltini et al. (23) did not report this relation. This discrepancy might be a result of the different methods used to determine HLA haplotypes or differences between the populations under study. Future studies should formally address the differences observed across these studies.

The overall meaning of the reviewed studies described in tables 2 and 3 must be considered with some caution, because of sample populations known to overlap and with the potential to overlap. For example, Stange et al. (67) included beryllium cases previously identified by Kreiss et al. (63, 65). Similarly, Henneberger et al. (69) included beryllium-exposed workers previously studied by Kreiss et al. (66) (table 2). Although the studies presented in table 3 appear to be independent, there is potential for overlap across the populations studied by Rossman et al. (24) and Saltini et al. (23) (table 3). Overlap among these studies does not change the general interpretation of these results with respect to the range of prevalence and the estimates of association. However, it could affect the generalizablity of the results, since the estimates of association may not be entirely statistically independent.

INTERACTIONS

Exposure to beryllium is a requirement for developing CBD. However, *HLA-DPB1^{Glu69}* modifies an individual's risk of CBD. This was demonstrated from cross-sectional surveillance conducted at a beryllium ceramic manufacturing facility. This study established that particular job tasks (i.e., machining) conferred substantially increased risk of beryllium sensitization and disease and that this risk was further magnified in the presence of *HLA-DPB1^{Glu69}* (20).

Five of six persons with CBD were found to have machined beryllium. Similarly, five of the six CBD cases were carriers of *HLA-DPB1^{Glu69}*. When the presence of *HLA-DPB1^{Glu69}* and a history of machining was evaluated, four of the 16 machinists who were *HLA-DPB1^{Glu69}*-positive had CBD. In logistic regression analysis, the odds ratio for disease from machining alone was estimated to be 10.1 (95 percent CI: 1.1, 93.7); the odds ratio for disease from the genetic marker was estimated to be 11.8 (95 percent CI: 1.3, 108.8). On the basis of these results, the investigators reported that genetic and job factors had at least an additive effect for risk of beryllium disease in the industrial environment. We have included an additional summary of disease prevalence by *HLA-DPB1^{Glu69}* and machining job history for this study (table 4). While it was not possible to estimate odds ratios referenced to the lowest risk group because there were no observed cases, it is clear when looking at the prevalence estimates and confidence intervals that the presence of both *HLA-DPB1^{Glu69}* and a machining job history account for a remarkable proportion of cases (table 4).

Utilizing a series of 2 × 2 tables extracted from a 2 × 4 table, Saltini et al. (23) evaluated the risk of sensitization or CBD in the presence of either one or a combination of the genes *HLA-DPB1^{Glu69}*, tumor necrosis factor-α (*TNF*-α)-*308*2*, and *HLA-DR^{Arg74}*. *HLA-DR^{Arg74}* was independently associated with sensitization (OR = 4.0, 95 percent CI: 1.5, 10.1), while *HLA-DPB1^{Glu69}* was found to be associated with CBD (OR = 3.7, 95 percent CI: 1.4, 10.0) but not with sensitization. *TNF*-α-*308*2* was associated with a positive beryllium lymphocyte proliferation test result (OR = 7.8, 95 percent CI: 3.2, 19.1), regardless of disease status. When gene combinations were evaluated, the risk of sensitization was increased in the presence of both *TNF*-α-*308*2* and *HLA-DR^{Arg74}*. The risk of sensitization was also reportedly higher among persons who were *HLA-DPB1^{Glu69}*-positive but *HLA-DR^{Arg74}*-negative (23). However, scrutiny of the tabulated data revealed that sensitization was associated with *HLA-DR^{Arg74}*-positive, *HLA-DPB1^{Glu69}*-negative persons. *TNF*-α-*308*2* was independently associated with CBD (OR = 4.0; $p < 0.05$), but in the presence of *HLA-DPB1^{Glu69}*, this risk was even greater (OR = 9.7; $p < 0.05$). Interestingly, neither *HLA-DPB1^{Glu69}* alone nor *HLA-DR^{Arg74}* alone, nor both in combination, was associated with CBD. This may have been an effect of the small sample sizes created in the construction of the 2 × 4 tables. The extent to which these

analyses may have been affected by the use of different laboratory methods to determine the presence of the TNF-α-$308*2$, HLA-$DPB1^{Glu69}$, and HLA-DR^{Arg74} alleles is unknown. However, these results demonstrate that genes other than HLA-$DPB1^{Glu69}$ or genes acting in conjunction with HLA-$DPB1^{Glu69}$ may play a role in the risks of both sensitization and disease.

LABORATORY TESTS

Neither commercial kit manufacturers nor laboratories approved by the Clinical Laboratory Improvement Advisory Committee are currently offering HLA-$DPB1^{Glu69}$ genetic testing. Rather, research laboratory methods have been used to evaluate the presence and absence of HLA-$DPB1$ sequence motifs and alleles in persons with and without CBD. Heteroduplex analysis, allele-specific polymerase chain reaction, restriction fragment length polymorphism, oligonucleotide hybridization, and direct and allele-specific sequencing of polymerase chain reaction products have all been used to examine HLA-$DPB1$ variants (19–24). Each method has strengths and limitations. Allele-specific sequencing gives the least ambiguous and most complete analysis, but it is also the most labor intensive. Heteroduplex, allele-specific polymerase chain reaction and restriction fragment length polymorphism analysis may only detect a limited number of alleles. Similarly, oligonucleotide hybridization might not detect all alleles, but additionally this method potentially has a higher rate of false positives and false negatives.

POPULATION TESTING

Ethical issues surrounding the use of genetic information as a screening tool in the workplace include employment discrimination and insurance discrimination (76). These concerns have become particularly relevant given that current, former, and prospective beryllium-industry workers are being genetically characterized in research studies for HLA-$DPB1^{Glu69}$. In addition, while the odds associated with CBD in the presence of HLA-$DPB1^{Glu69}$ are quite high, because the population prevalence of HLA-$DPB1^{Glu69}$ is also high, the cross-sectional predictive value is relatively low (77).

The positive predictive value has typically been defined as the probability that an individual will have a disease given that the diagnostic test is positive. It is a function of test sensitivity, test specificity, and disease prevalence (78). For example, using the odds ratio of 23 obtained by Wang et al. (21), a population prevalence of 40 percent for HLA-$DPB1^{Glu69}$, and a prevalence of disease among beryllium workers of 5 percent, the positive predictive value is only 11.7 percent (77). Thus, HLA-$DPB1^{Glu69}$ does not fulfill the screening criteria outlined by Khoury et al. (79).

The positive predictive value can also be defined longitudinally. This definition is based on disease incidence rather than on prevalence, and it can be interpreted as the probability that an exposed individual will develop the disease subsequent to screening, given that he or she has a positive screening test (78). While prospective employees might be able to use longitudinal risk information, the disease incidence data required to estimate this risk are not yet available. The utility of risk information for people already exposed to beryllium is even less clear, since CBD risk remains even after exposure cessation. Currently, it is not known whether workers can lower their risk by leaving the industry or whether genetic characterization of sensitized or CBD cases has prognostic implications. Continued research will be important in the identification of other high-risk genes, gene-exposure interactions, and gene-gene interactions that may improve personal risk assessment and help in determining whether specific genes or alleles are more valuable as prognostic indicators. Regardless, prospective, current, and former beryllium workers must be educated about the risks and benefits associated with obtaining their genetic screening results.

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