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Research paper

Genome-wide association study and HLA genotyping for beryllium disease susceptibility in a European descent population

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ABSTRACT

Background: Workplace exposure to beryllium can result in beryllium sensitization (BeS), a cell-mediated immune response that can progress to chronic beryllium disease (CBD), a granulomatous lung disease. DPB1-E69 is highly associated with CBD and BeS, although DRB1-E71 may also be a risk factor in the absence of DPB1-E69.
Objective: This study 1) identified novel genetic variants associated with CBD/BeS using a genome-wide association study (GWAS) approach and 2) clarified the role of DRB1-E71 in conjunction with DPB1-E69.
Methods: We performed GWAS and HLA analysis on 1626 subjects with BeS, CBD and beryllium exposure without disease.
Results: We found that rs1042140, the first base of the codon that encodes E69, was associated with CBD and BeS. We also found two single nucleotide polymorphisms (SNPs), rs56011217 and rs72636334, near *SRIP1* on chromosome 4 associated with CBD and BeS independent of rs1042140. HLA alleles DRB1*04:04 (non E71) and DQB1*06:04 were significantly associated with CBD and BeS independent of rs1042140.
Conclusions: We found both DPB1-E69 and DRB1-E71 carriers have a higher risk of CBD or BeS both independently and jointly, with DPB1-E69 status having higher impact than DRB1-E71 status. DRB1-E71 also increases the risk in subjects without DPB1-E69. Our study also implies that beyond HLA, *SRIP1* should be investigated in chronic beryllium disease pathogenesis.

1. Introduction

Exposure to beryllium particulate, usually in the workplace, may initiate a cell-mediated immune response known as beryllium sensitization (BeS). With sufficient exposure, BeS can eventually progress to chronic beryllium disease (CBD) characterized by granuloma formation in the lung. Since the early 1990s, basic science and epidemiologic studies have observed the association between DPB1-E69 and

Abbreviations: BeS, Beryllium sensitization; CBD, Chronic beryllium disease; GWAS, genome-wide association study; MHC, Major Histocompatibility Complex; SNP, Single nucleotide polymorphism.

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BeS or CBD (Richeldi et al., 1993; Richeldi et al., 1997; Wang et al., 1999; Saltini et al., 2001; Maier et al., 2003; McCanlies et al., 2004; Darlington et al., 2011; Rosenman et al., 2011; Silveira et al., 2012). Studies have shown that in CBD and in the absence of E69, a higher frequency of HLA-DRB1*13:01 has been observed (Maier et al., 2003; Rosenman et al., 2011). In another study, HLA-DRB1*13 and *BTNL2* rs3117099 homozygosity were associated with CBD (Sato et al., 2007). A recent study in the same cohort, examining the exposure–response relationship between DPB1-E69 and DRB1-E71 found that DRB1 E71 was more common in BeS than CBD after adjusting for exposure and may be a protective factor (OR 0.4, 95 % CI 0.2 to 0.9) against the progression of BeS to CBD (8). These studies identified a strong association between a glutamic acid at position 69 (E69) in the HLA-DPB1 protein and/or glutamic acid at position 71 (E71) in the HLA-1B1 protein and beryllium disease. Most studies have focused on the risk of DPB1-E69, but fewer studies have examined the relationship between having DRB1-E71, with or without carriage of DPB1-E69, and the risk of CBD or BeS. In addition, most studies focus on the HLA region, and limited studies used a candidate gene approach that identified *BTNL2* (Sato et al., 2007) and *TGFB2* (Jonth et al., 2007) variants associated with CBD. A recent study used a candidate gene approach, testing known sarcoidosis genes in a beryllium-exposed cohort, but did not find any statistically significant single nucleotide polymorphisms (SNPs) of CBD (Frye et al., 2021). Moreover, no prior genome-wide association study (GWAS) of beryllium disease exists. The main objective of this study was to 1) identify novel genetic variants associated with CBD and/or BeS using a GWAS approach and 2) clarify the role of DRB1-E71 in conjunction with DPB1-E69 and the risk for CBD or BeS.

2. Materials and Methods

2.1. Study design and population

This GWAS used a two-phase approach (Phase 1 was Discovery cohort, Phase 2 was Validation cohort) to identify genome-wide significant SNPs associated with BeS and CBD. DNA samples from CBD, BeS, and beryllium-exposed controls were obtained from National Jewish Health (NJH) (2013 Beryllium-Associated Worker Registry Summary, 2015; Former Worker Medical Screening Program, 2021), the Beryllium BioBank (BBB) (Newman et al., 2012), Cooperative Agreement with Industry (CAI) (McCanlies et al., 2004), and Michigan State University/University of Pennsylvania (MSU/UPenn) (Rosenman et al., 2011; Rosenman et al., 2005; Widyaningsih et al., 2020). The study protocol was reviewed and approved by the institutional review boards (IRB) for all sites (NJH: HS-2374; BBB: HS-2062; CAI: 03-DRDS-01; MSU/UPenn: 95-426). Written informed consent was obtained for all participants. Cases met American Thoracic Society (ATS) criteria (Balmes et al., 2014) for BeS and CBD. Specifically, BeS cases demonstrated abnormal blood beryllium lymphocyte proliferation test (BeLPT) results and/or an abnormal bronchoalveolar lavage (BAL) BeLPT with no evidence of CBD on clinical evaluation. CBD subjects had evidence of BeS along with either 1) granulomas on biopsy, 2) both an abnormal BAL BeLPT and greater than 15 % lymphocytes in BAL cells, or 3) chest radiograph consistent with CBD. Subjects with confirmed abnormal BeLPTs who did not complete a full clinical evaluation to rule out CBD were classified as BeS/CBD as their disease status is unknown. Control subjects had beryllium exposure but with normal BeLPT blood test results as part of medical surveillance or research studies. Control subjects were frequency matched to cases at each site, approximately one-to-one based on sex, race, decade of hire, and facility. To maximize power and minimize potential confounding by ancestry, we enrolled self-reported, non-Hispanic whites, as they composed most of the workers represented by the geographical areas and hiring practices of the included industries.

2.2. Genome-wide genotyping

Subjects in both phases underwent the same protocol for DNA extraction and genotyping. DNA was extracted from whole blood using the PAXgene Blood DNA kit. Genotyping was performed using the Illumina assay: Human610-Quadv1 and HumanOmniExpress-12v1-1 for the whole-genome scan portion of this study. The genome-wide association SNP genotyping was conducted at the Center for Applied Genomics at the Children's Hospital of Philadelphia (CHOP) based on the manufacturer's manual. All genotyping was performed blinded to case/control status.

2.3. Genome-wide genotyping quality control

We included only self-reported non-Hispanic white individuals and one individual among first-degree relatives based on an estimated kinship coefficient ≥ 0.177 to ensure all subjects were independent of each other. We excluded cases and controls with 1) unresolved sex mismatch between clinical and genomic data, and 2) genotype calls at less than 98 % of SNPs that pass laboratory quality control. In addition, we prioritized SNPs for follow-up based on the following criteria. We excluded SNPs with differential missingness between cases and controls based on a chi-squared test of proportions of missingness between cases and controls (p-value < 0.05). We also tested departures from Hardy–Weinberg Equilibrium (HWE) via 1-degree of freedom goodness of fit test. We prioritized SNPs with HWE p-value > 0.001 in cases and controls evaluated separately and with < 10 % missing data.

2.4. Imputation of additional genotypes and HLA variants

We imputed SNP genotypes using the combined case and control discovery samples for all 1000 genome SNPs. We used PLINK (v1.90) to harmonize study genotypes with the 1000 Genomes Phase 3 reference panel by comparing alleles, correcting strand mismatches, excluding ambiguous palindromic SNPs, and verifying alignment through allele frequency checks to ensure concordance prior to phasing and imputation. We used the multi-population reference panel data from 1000 genomes for pre-phasing using Shapeit with the default parameters (Delaneau et al., 2013; Delaneau et al., 2011). The imputation was performed using the IMPUTE2 program (Wendland and Walther, 2011; Howie et al., 2009), which involves preprocessing of genotype (liftover) and transformation of genotype data into forward–backward probabilities within the hidden Markov model framework. The Phase 1 cohort was genotyped on the Human610-Quadv1 array (Hg18), with 495,856 of 495,959 SNPs mapped after liftover to Hg19, while the Phase 2 cohort was genotyped on the HumanOmniExpress-12v1-1 array (Hg19), requiring no liftover. To further investigate the HLA region, we imputed classical HLA alleles including Class I HLA genes: HLA-A, HLA-B, HLA-C and Class II HLA genes: HLA-DRB1, HLA-DQA1, HLA-DQB1, HLA-DPB1 using the R package HLA Genotype Imputation with Attribute Bagging (HIBAG) version 1.42 (Zheng et al., 2014). The average posterior probability was derived from HIBAG using the ensemble classifier and bagging techniques. We used the European ancestry reference panel for the imputation, given that the study population is of European descent.

2.5. HLA-DPB1 and HLA-DRB1 genotyping

HLA-DPB1 and *HLA-DRB1* genotypes were determined using sequence-specific primer PCR and/or sequence-based typing. DPB1 alleles were grouped as DPB1-E69 when they had a glutamic acid at position 69 (e.g., *02:01, *02:02, *06:01, *08:01, *09:01, *10:01, *13:01, *16:01, *17:01, *19:01, *46:01, *71:01, *88:01), and non-DPB1-E69 when they did not. DRB1 alleles were grouped as DRB1-E71 when they had glutamic acid at position 71 (e.g., *01:03, *04:02, *11:02, *11:03, *13:01, *13:02) or non-DRB1-E71 when they did not. For each *HLA-DPB1* allele, we required a 2-field resolution, while for each *HLA-*

DRB1 allele, we required only the ability to determine position 71 as being a glutamic acid (E71) or not. The carriage of specific *HLA-DRB1* alleles was also investigated for the subset of subjects who had 2-field resolution. For *HLA-DPB1* and *HLA-DRB1* genotyping, the genes were evaluated for departures from HWE using the exact test (Guo and Thompson, 1992) in the CBD, BeS, and controls separately.

2.6. Statistical analysis

2.6.1. Genome-wide Single SNP association test and meta-analysis

We tested for association between each imputed and genotyped SNP and CBD/BeS using Snptest (v2) (Marchini and Howie, 2010) as described previously (Fingerlin et al., 2016). We performed a *meta*-analysis of Phase 1 and Phase 2 using summary statistical data to obtain an overall measure of association with beryllium disease. Specifically, we used the weighted inverse normal method (Fingerlin et al., 2013), which accounts for the directionality of the association. Therefore, highly significant associations with conflicting directions do not exhibit a strong statistical association in this *meta*-analysis. We used the METAL program (Willer et al., 2010) to perform our *meta*-analysis. The genome-wide statistically significant SNP threshold was defined as *meta*-analysis p-value $< 5 \times 10^{-8}$.

2.6.2. Comparing actual genotyped and HIBAG imputed HLA-DPB1/DRB1 genotypes

We compared the concordance between the *HLA-DPB1/DRB1* imputed from HIBAG and the actual genotyping results in the subset of the study population with both types of data available (69 % of the entire population).

2.6.3. HIBAG imputed classic HLA alleles analysis

We used logistic regression models to test for the association between the dosage of each imputed HLA allele and beryllium disease susceptibility. We used a p-value of less than 1.1×10^{-4} (0.05/448 HLA allele imputed and tested, Bonferroni correction) to define statistical significance.

2.6.4. Conditional models

To assess the independence of single-SNP or HLA allele effects and the most significant SNPs, we re-analyzed the data adjusted for the most significant SNPs. We included the most significant SNP into the model of the single-SNP association test and imputed classic HLA alleles analysis

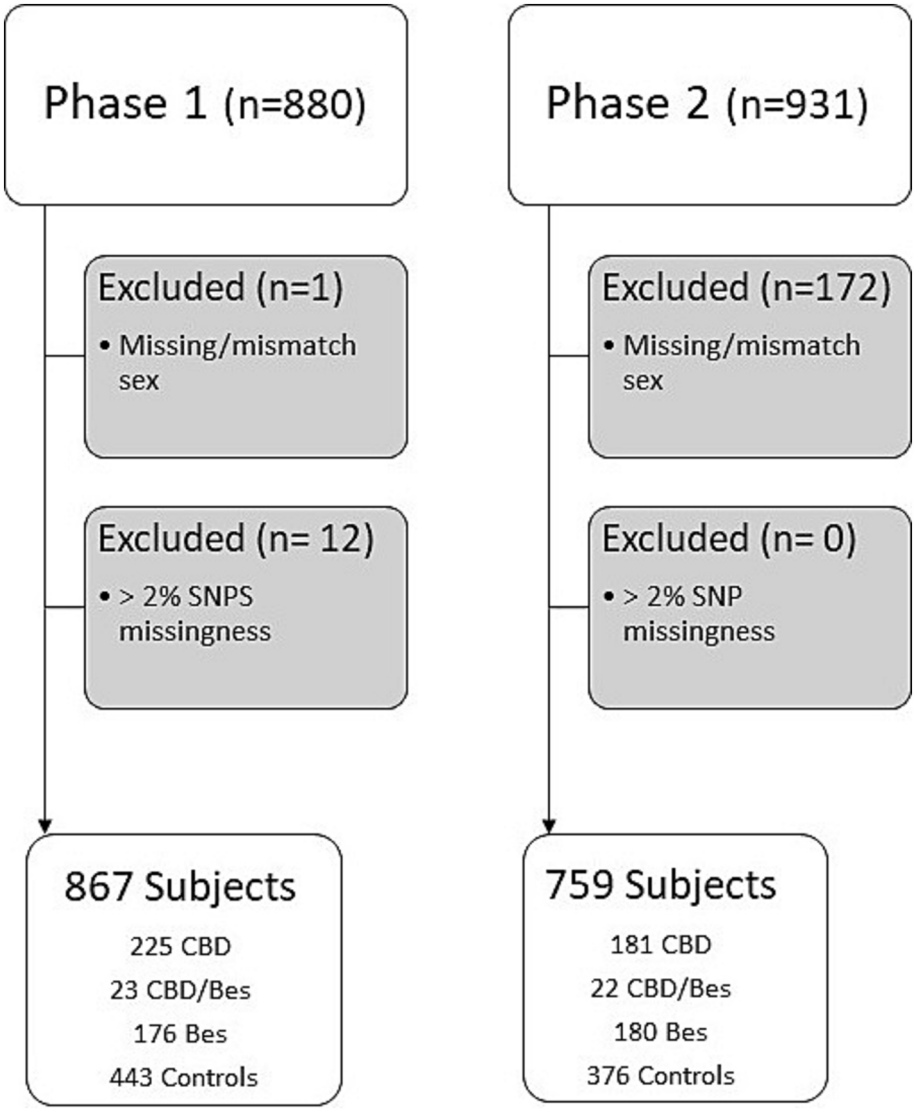

Fig. 1. CONSORT flow chart for the GWAS samples. This figure outlines the exclusion of the subject in Phase 1 and Phase 2, respectively. Before entering the flow chart, 63 individuals (by self-reported race) and 12 related subjects were removed from the Phase 1 cohort. CBD: chronic beryllium disease; BeS: Beryllium Sensitized.

as a covariate.

2.6.5. HIBAG imputed HLA-DPB1 and HLA-DRB1 association test

We used the HIBAG-imputed HLA genotyping for subsequent analysis to maximize the sample size. Multivariable logistic regression models were developed to test associations of interest between the four dichotomous outcome variables in this study: Case (CBD, BeS and CBD/BeS) vs. control, CBD vs. control, BeS vs. control, and CBD vs. BeS. The models also included an interaction term between DPB1-E69 and DRB1-E71 status/count.

3. Results

3.1. Descriptive analysis

There were 1811 non-Hispanic White and independent subjects enrolled in our GWAS. After quality control (Fig. 1), there were a total of 1626 subjects (406 CBD, 45 BeS/CBD, 356 BeS, and 819 controls) included in the analysis (Table 1); 225 CBD, 23 BeS/CBD, 176 BeS, and 443 controls in Phase 1 with 495,687 non-imputed SNPs and a total of 10,709,268 SNPs after imputation (9,340,910 info score >= 0.8). For Phase 2, we had 181 CBD, 22 BeS/CBD, 180 BeS, and 376 controls with 604,714 non-imputed SNPs and a total of 10,815,052 SNPs after imputation (9,702,730 info score >= 0.8). Among those 1626 subjects, 1118 (69 %) subjects had HLA-DPB1 and HLA-DRB1 actual genotypes available (**Tables S1 and S2**).

3.2. GWAS identifies SNPs associations with CBD and BeS

We performed GWAS analysis using four comparisons: 1) CBD + BeS vs. controls, 2) BeS vs. control, 3) CBD vs. control, and 4) CBD vs. BeS. The *meta*-analysis of Phase 1 and Phase 2 data identified the most significant SNP, rs1042140 (imputed), located in HLA-DPB1, in linkage disequilibrium with the DPB1-E69 variant known to be associated with BeS and CBD chronic beryllium disease (Maier et al., 2003). The *meta*-analysis p-values of rs1042140 are very small in all comparisons ($\sim 10^{-35}$–10^{-69}) except for CBD vs. BeS (Table 2). The Manhattan plot in Fig. 2A shows a peak around rs1042140. In subjects with both actual *HLA DPB1/DRB1* genotyping and rs1042140 genotype, we found rs1042140 was highly correlated with DPB1-E69 status but not identical (the DPB1-E69 status was based on the actual HLA genotyping with $r^2 =$ 0.81 in Phase 1 and 0.71 in Phase 2). This is likely because rs1042140 genotype was imputed (info score 0.93). To further identify SNPs independent of rs1042140, we used conditional modeling to control for rs1042140. Two SNPs, rs56011217 (.info score 0.86) (Sherry et al., 2001a) and rs72636334 (.info score 0.84) (Sherry et al., 2001b), reached the GWAS significance threshold adjusting for rs1042140 in CBD + BeS vs. controls (p-value $< 5 \times 10^{-8}$; Table 3). No other significant SNPs were found in any other comparisons. Both significant SNPs were imputed and fell in Chromosome 4, as demonstrated in Fig. 2B**,** the Manhattan plot for the SNP associations adjusted for rs1042140, and Fig. 3**,** the locus-specific plot adjusted for rs1042140. The most significant SNP, rs56011217, is near the pseudogene *SRIP1* (177.4 K base pairs apart from rs56011217). The minor allele G showed an increased risk for CBD + BeS (Phase 1 OR 4.29, 95 % CI 1.37–13.39; Phase 2 OR 18.00, 95 % CI 3.99–81.15; *meta*-analysis p-value = 3.73×10^{-8}, Table 3). The second significant SNP, rs72636334, is highly correlated with rs56011217 ($r^2 = 0.94$ in Phase 1 and 0.90 in Phase 2) and is located 20 Kb from rs56011217. The minor allele A also showed an increased risk in CBD + BeS (Phase 1 OR 3.87, 95 % CI 1.30–11.57; Phase 2 OR 18.42, 95 % CI 4.11–82.59; *meta*-analysis p-value = 4.02×10^{-8}, Table 3).

3.3. Comparing actual genotyped and HIBAG imputed HLA-DPB1/HLA-DRB1 genotype

The concordance between the imputed HLA genotype using HIBAG and the actual HLA genotyping on *HLA-DPB1/DRB1* showed a high agreement. **Fig. S1** shows the posterior probability of *HLA-DPB1/DRB1* alleles predicted by HIBAG, and Fig. S2 shows the match percentage between the HIBAG imputed posterior probability and the actual genotyped *HLA-DPB1/DRB1*. Restricted to subjects with the imputed posterior probability greater or equal to 0.5 (94 %/92 % in *HLA-DPB1/DRB1)*, the average match percentage (accuracy) of DPB1 was 0.82 (NJH 0.80, CAI 0.84, MSU/UPenn 0.89); the average match percentage of DRB1 was 0.88 (NJH 0.88, CAI 0.87, MSU/UPenn 0.89). Since the concordance was high, we used the imputed HLA genotyping for subsequent analysis to maximize the sample size. The frequency of actual genotypes at *HLA DPB1/DRB1* are shown in **Tables S1 and S2**.

3.4. HIBAG imputed classic HLA alleles are associated with CBD and BeS

The top three HLA alleles, DPB1*02:01, DPB1*04:01, and DPB1*04:02, were significantly associated with beryllium disease and not highly correlated with rs1042140 (r^2 range from 0.06 to 0.37); in fact, the *meta*-analysis p-value becomes much larger after adjusting for rs1042140 (**Table S3**). DPB1*02:01 (E69 positive) increased the risk for BeS/CBD while both DPB1*04:01 and DPB1*04:02 had a protective effect (E69 negative). To further identify novel HLA alleles independent of rs1042140, we used conditional modeling to control for rs1042140. One HLA allele, DRB1*04:04 (Phase 1 OR: 3.50, 95 % CI: 1.71–7.17; Phase 2 OR: 2.23, 95 % CI: 1.13–4.40), that reached significance threshold adjusting for rs1042140 in CBD + BeS vs. controls, showed an increased risk of CBD and BeS (Table 4). Another allele, DQB1*06:04 (Phase 1 OR: 2.38, 95 % CI: 1.38–4.12; Phase 2 OR: 1.40, 95 % CI: 0.76–2.56), which was in strong linkage disequilibrium with DRB1*13:02, while not significant after Bonferroni correction, was also positively nominally associated with CBD and BeS (Table 4).

3.5. Potential association of DRB1 alleles with CBD and BeS in a subset of the population with actual HLA DRB1/DPB1 Genotyping, controlling for DPB1-E69 status

We investigated the association of certain DRB1 alleles with CBD and BeS in a subset of the population with actual HLA-DRB1/DPB1 genotyping, controlling for DPB1-E69 status. Using data from 1118 subjects, we sought to identify novel HLA DRB1/DPB1 alleles independent of DPB1-E69 through conditional modeling. *DRB1*13:02 (E71) (OR 2.42, 95 % CI 1.49–3.92, p = 0.0004) was significantly associated (p =

Table 1
Sample size and sex of phase 1 and phase 2 genome-wide genotyping samples.

Sex	All (N = 1,626)*				Phase 1 (N = 867)				Phase 2 (N = 759)			
	CBD (n = 406)	BeS/CBD (n = 45)	BeS (n = 356)	Control (n = 819)	CBD (n = 225)	BeS/CBD (n = 23)	BeS (n = 176)	Control (n = 443)	CBD (n = 181)	BeS/CBD (n = 22)	BeS (n = 180)	Control (n = 376)
Female, n (%)	66 (16 %)	8 (18 %)	79 (22 %)	107 (13 %)	26 (12 %)	3 (13 %)	40 (23 %)	47 (11 %)	40 (22 %)	5 (23 %)	39 (22 %)	60 (16 %)
Male, n (%)	340 (84 %)	37 (82 %)	277 (78 %)	712 (87 %)	199 (88 %)	20 (87 %)	136 (76 %)	396 (89 %)	141 (78 %)	17 (77 %)	141 (78 %)	316 (84 %)

CBD: Chronic Beryllium Disease; BeS: Beryllium Sensitized; CBD/BeS: Unclassified-confirmed BeS without full clinical evaluation to rule out CBD.
*Among 1 626 subjects with genome-wide genotyping, 1 118 have actual *HLA-DPB1/DRB1* genotyping.

Table 2
Association results for rs1042140* in different comparison groups (CBD + BeS vs. Control, CBD vs. Control, BeS vs. Control, CBD vs. BeS).

Comparison	Phase1 MAF case	OR (95 % CI)	p-value	Phase 2 MAF case	OR (95 % CI)	p-value	Meta-analysis p-value
(CBD + BeS) vs. Control	0.49	4.47 (3.37, 5.92)	1.73E-30	0.50	5.38 (4.06, 7.12)	2.51E-40	6.27E-69
CBD vs. Control	0.47	5.62 (3.91, 8.07)	1.76E-26	0.50	4.90 (3.53, 6.81)	2.08E-26	4.05E-51
BeS vs. Control	0.44	3.39 (2.44, 4.72)	1.82E-14	0.49	5.03 (3.53, 7.17)	7.31E-23	2.50E-35
CBD vs. BeS	0.47	1.68 (1.17, 2.41)	4.60E-03	0.49	1.36 (0.88, 2.10)	0.174	2.37E-03**

CBD: chronic beryllium disease; BeS: Beryllium sensitized; Chr: chromosome; MAF: minor allele frequency; OR: odds ratio; CI: confidence interval.
*The minor allele of rs1042140 is the G allele.
**The test was not significant after adjusting for multiple comparisons.

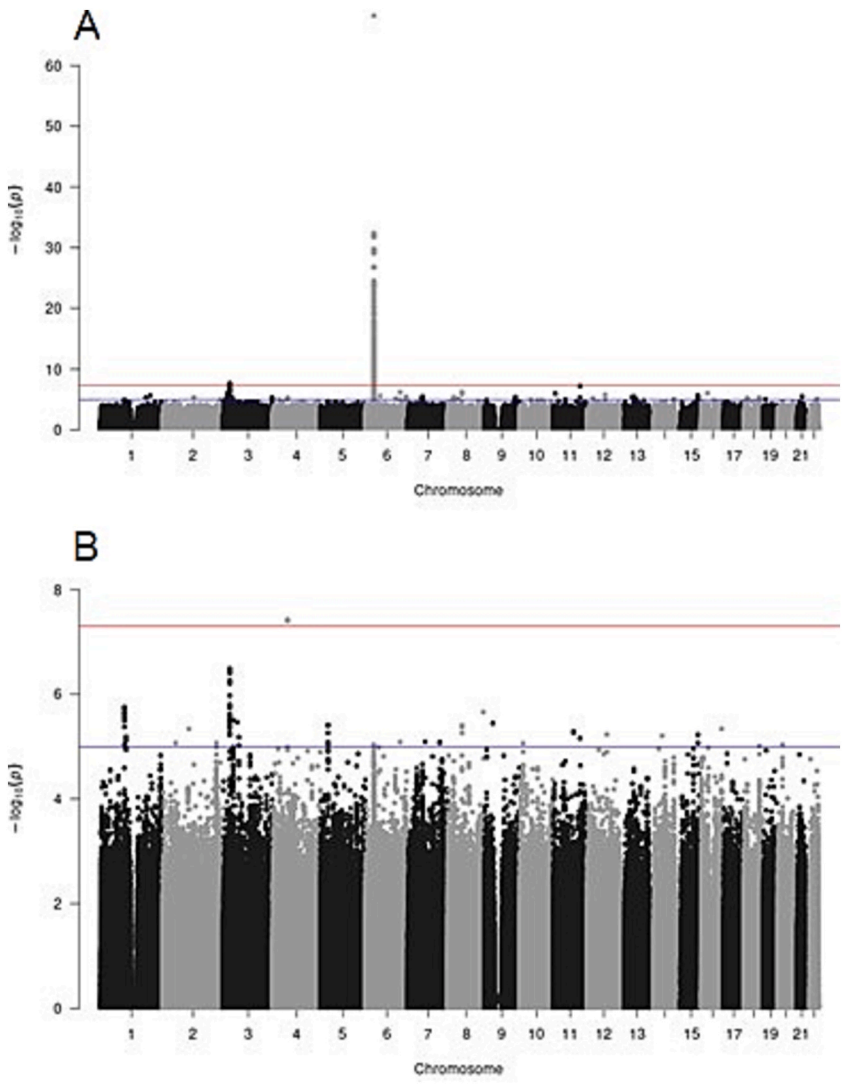

Fig. 2. Manhattan plot for SNPs associated with (chronic beryllium disease or beryllium sensitization) vs. controls. A: Manhattan plot for SNP associations; B. Manhattan plot for SNPassociations adjusted for rs1042140.

Table 3
Genome-wide significant SNPs associated with CBD + BeS adjusted for rs1042140.

SNP	Chr	Position	Minor allele	Phase1 MAF case	OR (95 % CI)	p-value	Phase 2 MAF case	OR (95 % CI)	p-value	Meta-analysis p-value
rs56011217	4	58,791,866	G	0.02	4.29 (1.37, 13.39)	0.0062	0.03	18.00 (3.99, 81.15)	6.45E-07	3.73E-08
rs72636334	4	58,811,724	A	0.02	3.87 (1.30, 11.57)	0.0086	0.03	18.42 (4.11, 82.59)	4.18E-07	4.02E-08

CBD: chronic beryllium disease; BeS: Beryllium sensitized; Chr: chromosome; MAF: minor allele frequency; OR: odds ratio; CI: confidence interval.

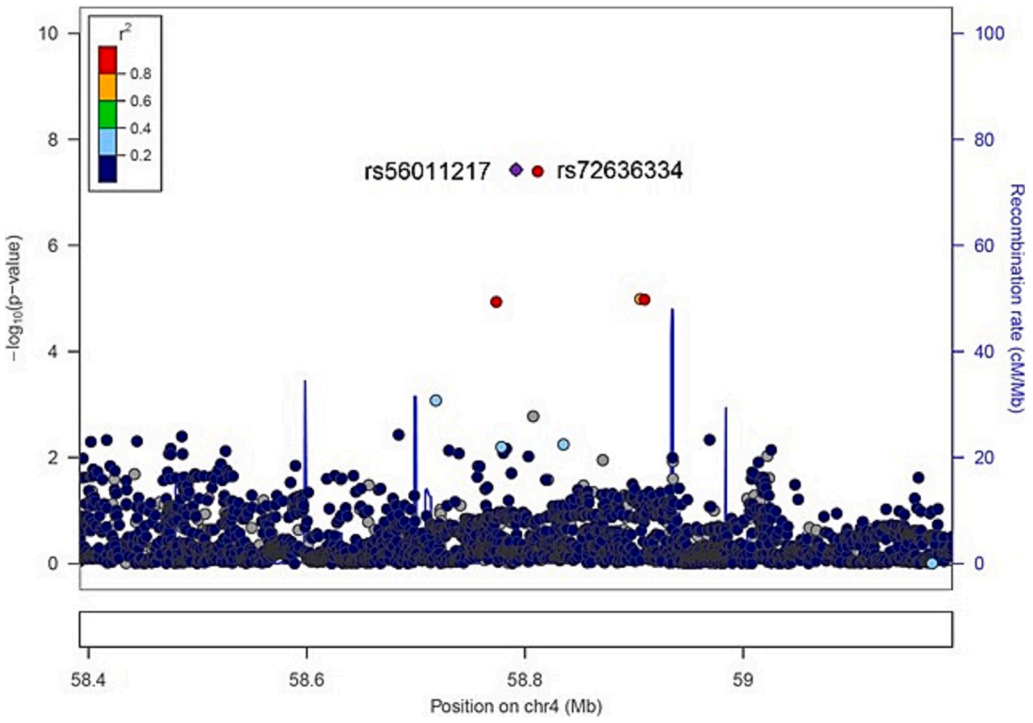

Fig. 3. Locus-zoom plot for significant SNPs associated with beryllium disease (chronic beryllium disease or beryllium sensitized) adjusted for rs1042140; rs56011217 is the most significant SNP which is in linkage disequilibrium with rs72636334.

Table 4
Top HLA alleles (imputed using HIBAG) associated with CBD/Bes adjusted for rs1042140.

	Phase 1					Phase 2					Meta-analysis
		Dosage frequency**		Univariate results			Dosage frequency		Univariate results		
HLA allele	r^2 with rs1042140	Cases	Controls	OR (95 % CI)	p-value	r^2 with rs1042140	Cases	Controls	OR (95 % CI)	p-value	p-value
DRB1*04:04	0.02	0.14	0.05	3.50 (1.71, 7.17)	6.23E-04	0.006	0.09	0.06	2.23 (1.13, 4.40)	2.13E-02	4.68E-05
DQB1*06:04	0.005	0.10	0.06	2.38 (1.38, 4.12)	1.93E-03	0.002	0.10	0.05	1.40 (0.76, 2.56)	2.76E-01	0.0026*

CBD: chronic beryllium disease; BeS: Beryllium sensitized; OR: odds ratio; CI: confidence interval.
*Did not reach the significance threshold of Bonferroni correction of 0.0001 (0.05/448).
**Dosage frequency is the weighted average of the allele count (0, 1, 2) with the weight being the probability of that allele number estimated by HiBAG.

0.0007, adjusted for 0.05/65 non-DPB1-E69 HLA alleles tested, Tables S1 and S2) when adjusting for DPB1-E69 with CBD + BeS. Another high-risk allele was *DRB1**04:04 (OR 2.01, 95 % CI 1.25–3.24, p = 0.004). The most protective allele was DRB1*08:01 (OR 0.38, 95 % CI 0.18–0.8, p = 0.01).

3.6. HIBAG imputed E69 in HLA-DPB1 and E71 in HLA-DRB1 are associated with CBD and BeS

Table 5 shows the odds ratio of different case statuses (CBD, BeS) versus controls. In Model 1, DPB1-E69 positive/DRB1-E71 negative

Table 5
Association between DPB1-E69/DRB1-E71 status/count (imputed by HIBAG) and case status (CBD, BeS) and controls.

Variable	CBD + BeS vs. Control OR (95 % CI)	p-value	CBD vs. Control OR (95 % CI)	p-value	BeS vs. Control OR (95 % CI)	p-value	CBD vs. BeS OR (95 % CI)	p-value
Model 1: Case status = β0 + β1*DPB1-E69 status + β2*DRB1-E71 status + β3*DPB1-E69 status*DRB1-E71 status								
DPB1-E69 positve|DRB1-E71 negative	5.44 (4.25,6.97)	**4.07e-41**	6.79 (4.92,9.36)	**1.71e-31**	4.56 (3.34,6.24)	**2.22e-21**	1.49 (1.01,2.18)	**0.04**
DRB1-E71 positive|DPB1-E69 negative	2.77 (1.96,3.93)	**1.04e-08**	3.09 (1.96,4.86)	**1.17e-06**	2.51 (1.61,3.93)	**5.22e-05**	1.23 (0.71,2.13)	0.46
DPB1-E69 positve|DRB1-E71 positive	2.38 (1.59,3.57)	**2.70e-05**	2.71 (1.67,4.4)	**5.48e-05**	2.13 (1.29,3.52)	**3.01e-03**	1.27 (0.74,2.18)	0.38
Model 2: In DPB1-E69 or DRB1-E71 carriers, Case status = β0 + β1*DPB1-E69 count + β2*DRB1-E71 count + β3*DPB1-E69 count*DRB1-E71 count								
DPB1-E69 count	1.83 (1.14,2.93)	**0.01**	2.12 (1.25,3.57)	**4.97e-03**	1.46 (0.82,2.60)	0.20	1.55 (0.92,2.60)	0.10
DRB1-E71 count	1.04 (0.61,1.75)	0.90	1.08 (0.59,2.00)	0.80	0.92 (0.49,1.74)	0.81	1.25 (0.66,2.35)	0.50

CBD: chronic beryllium disease; BeS: Beryllium sensitized; OR: odds ratio; CI: confidence interval; Bold: p-value < 0.05.

carrier status is defined as subjects with at least one DPB1-E69 allele and no DRB1-E71. DRB1-E71 positive/DPB1-E69 negative is defined as subjects with at least one DRB1-E71 allele and no DPB1-E69. Both DPB1-E69 and DRB1-E71 carriers have a higher risk of CBD + BeS, CBD, or BeS than controls. DPB1-E69 carriage has a higher risk of CBD or BeS than DRB1-E71 carriage with a larger OR and much smaller p-value. Comparing CBD to BeS, DPB1-E69 status but not DRB1-E71 status is associated with CBD (OR 1.49, 95 %CI 1.01–2.18, $p = 0.04$). We found a significant interaction term in Model 1: (DPB1-E69 status x DRB1-E71 status) although the risk of CBD or BeS for subjects having both DPB1-E69 and DRB1-E71 is lower than a multiplicative model. In Model 2, we explored the association between CBD or BeS risk and the DPB1-E69/DRB1-E71 count in subjects known as either DPB1-E69 or DRB1-E71 carriers. We observed subjects with increased number of DPB1-E69 alleles are associated with a higher risk of CBD + BeS than controls (OR 1.83, 95 % CI 1.14–2.93, $p = 0.01$). However, the phenomenon was not observed in subjects with an increased number of DRB1-E71 alleles.

4. Discussion

Our analyses verified that rs1042140, the first base of the codon that encodes the E69 amino acid in the DPbeta chain, was associated with CBD and BeS. We also found two SNPs, rs56011217 and rs72636334, on chromosome 4 associated with CBD and BeS independent of rs1042140. HLA alleles DRB1*04:04 and DQB1*06:04 were significantly associated with CBD or BeS independent of rs1042140. Finally, we found both DPB1-E69 and DRB1-E71 carriers have a higher risk of CBD or BeS both independently and jointly, with DPB1-E69 status having a higher impact than DRB1-E71 status. DRB1-E71 also increases risk among subjects without DPB1-E69. In subjects with DPB1-E69/DRB1-E71 carriage, there is a dose response with increasing DPB1-E69 alleles conferring increased risk of CBD or BeS risk, although this was not evident for DRB1-E71 alleles.

In our GWAS, we found rs1042140 (E69) significantly associated with CBD and BeS as expected. Before adjusting for rs1042140, we found DPB1*02:01 increased the risk of beryllium disease while DPB1*04:01 was protective against CBD and BeS, as is well established in the literature (Richeldi et al., 1993; Wang et al., 1999). We found rs1042140 (E69) likewise inversely associated with DPB1*04:01. Certainly it is clear that different E69 DP alleles carry different risk of CBD (Silveira et al., 2012), although for some studies this may not be as important since having any DPB1-E69 increases the risk of CBD overall (Van Dyke et al., 2011).

After controlling for rs1042140 (E69), we identified two genome-wide significant SNPs, rs56011217 and rs72636334, which are a novel association with BeS and CBD. The minor alleles of these two SNPs increase the risk of CBD and BeS. These two SNPs are in linkage disequilibrium and located near the *SRIP1* gene. *SRIP1* or Sorcin pseudogene 1 is located on chromosome 4. The *SRIP1* is a pseudogene and the exact function of *SRIP1* is unclear at this time. While these two SNPs have not been reported to be associated with any diseases to the best of our knowledge, the other two SNPs in *SRIP1*, rs4865309 and rs144575900, have been associated with decreased post-bronchodilator FEV1 in smokers (Lutz et al., 2015) ($p < 5x10^{-6}$). Due to incomplete pulmonary function data, we were unable to explore if there is an association with our population and lung function although this could be the focus of future studies.

We found that HLA-DRB1*04:04 significantly increases the risk of CBD or BeS using HiBAG-imputed HLA genotyping and through actual HLA genotyping. Interestingly, DRB1*04:04 was also found to increase the risk of rheumatoid arthritis (Wysocki et al., 2020) and of Vogt-Koyanagi-Harada disease, a systemic disease that affects tissues containing melanin with its ocular manifestations characterized by chronic bilateral, diffuse, granulomatous uveitis (Shi et al., 2014). In a study of Heerfordt's syndrome, a rare manifestation of sarcoidosis with uveitis, parotid or salivary gland enlargement, and cranial nerve palsy, HLA DRB1*04 (Darlington et al., 2011) including DRB1*04:01, *04:04, and *04:08 was found as a risk factor. In addition, DRB1*04:04 was associated with high titers of anti-cyclic citrullinated peptide antibodies in rheumatoid arthritis (Charpin et al., 2008). Whether this could imply that there is an autoimmune component to CBD or associated with disease is not known, although recent studies defining a peptide stimulating the TCR in CBD suggests that a self-peptide, CCL3/4 is a potential neoantigen presented by HLA-DPB1*02:01 (Falta et al., 2021). HLA-DQB1*06:04, a top HLA allele associated with CBD and BeS identified in our study, was also over-represented in first-degree relatives with sarcoidosis (Charpin et al., 2008), which may imply that people with this HLA allele are more susceptible to granuloma formation whether it be sarcoidosis or CBD.

Using HLA genotyping, we confirmed the previous association of DPB1-E69 and the risk of CBD or BeS (Rosenman et al., 2011; Richeldi et al., 1997; Wang et al., 1999; Saltini et al., 2001; Maier et al., 2003; McCanlies et al., 2004; Fontenot et al., 2006; Bill et al., 2005; Rossman et al., 2002). Similar to previous literature (Rosenman et al., 2011; McCanlies et al., 2003), a small portion of subjects with no DPB1-E69 were observed, totaling about 16 % in our study. In those DPB1-E69 absent subjects, we found that the presence of DRB1-E71 significantly increases the risk of CBD or BeS, consistent with previous literature (Rosenman et al., 2011). However, the presence of DRB1-E71 in subjects without DPB1-E69 did not increase the risk of CBD compared to BeS. Beryllium-specific oligoclonal CD4 + T lymphocytes recognize beryllium usually via DPB1-E69 or DRB1-E71 in a 'major histocompatibility complex' (MHC) class II-restricted manner (Fontenot et al., 2000). Both DPB1-E69 and DRB1-E71 play roles in the pathogenesis of the immune response in CBD and BeS, but how they interact with each other has been unclear. Our study further explored the interaction between DRB1-E71 and DPB1-E69 on CBD and BeS susceptibility. We found that either DPB1-E69 or DRB1-E71 increases risk of CBD and BeS. However, the beta estimate of the interaction term DRB1-E71*DPB1-E69 was negative, and therefore, the risk of CBD or BeS for subjects having both DPB1-E69 and DRB1-E71 does not appear to be additive let alone multiplicative.

One limitation of our study was the inability to account for beryllium exposure in our model since the exposure measurements varied across sites. Our power to identify other SNPs was limited by the overall sample size for our GWAS. Although this is the largest cohort to date, BeS and CBD prevalence ranges from < 1 % to 20 % in a relatively small population with beryllium exposure; and thus, our population with health effects is limited. We used a more restricted definition of CBD to ensure that individuals had disease and could have misclassified patients without definitive bronchoscopy results or when the patient could not undergo the procedure. Misclassification may also result due to the disease latency. Those patients we classified as exposed controls might develop CBD or BeS in the future. Similarly, BeS may progress to CBD in the future. Those misclassifications may contribute to a reduction in statistical power to explore the association between genetic effects and CBD or BeS. Another limitation of our study is that we cannot fully exclude the possibility that nearby SNPs or protective DPB1 alleles contribute to the observed dose-dependent effect of DPB1-E69 compared with DRB1-E71. However, studies to date have shown that DPB1 cell line models and transgenic mouse models recapitulate chronic beryllium disease, supporting the importance of DPB1-E69 (Falta et al., 2021; Fontenot et al., 2006).

In summary, we verified that rs1042140 was associated with CBD and BeS and can be used as a surrogate of DPB1-E69 status. We identified two SNPs, rs56011217 and rs72636334 on chromosome 4 that are associated with CBD and BeS independent of rs1042140, which expands our current knowledge of genetic factors that contribute to CBD or BeS and can be potential targets for future functional and clinical assessment. Finally, we found DRB1-E71 to increase the risk of BeS and CBD in the absence of DPB1-E69 but did not further increase the risk in combination with DPB1-E69.

CRediT authorship contribution statement

Shu-Yi Liao: Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Tasha E. Fingerlin:** Writing – review & editing, Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Sean Jacobson:** Writing – review & editing, Writing – original draft, Formal analysis. **Margaret M. Mroz:** Writing – review & editing, Writing – original draft, Project administration, Data curation. **Kenneth D. Rosenman:** Writing – review & editing, Methodology, Funding acquisition, Data curation. **Milton D. Rossman:** Writing – review & editing, Resources, Methodology, Funding acquisition, Data curation. **MAbbas Virji:** Writing – review & editing, Supervision, Project administration, Investigation, Data curation. **Erin C. McCanlies:** Writing – review & editing, Resources, Investigation, Data curation. **Christine R. Schuler:** Writing – review & editing, Resources, Project administration, Methodology, Investigation, Data curation. **Berran Yucesoy:** Writing – review & editing, Resources, Methodology, Data curation. **Joseph Glessner:** Software, Methodology, Formal analysis. **Jamie L. Duke:** Writing – review & editing, Writing – original draft, Resources, Methodology, Formal analysis. **Hakon Hakonarson:** Supervision, Methodology, Formal analysis, Data curation. **Dimitri S. Monos:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Lisa A. Maier:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Lisa Maier, MD MSPH reports financial support was provided by National Jewish Health. Christine Schuler, PhD reports financial support was provided by National Institute of Occupational Safety and Health. Dimitri Monos, PhD reports financial support was provided by Childrens Hospital of Philadelphia. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.].

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gene.2025.149820.

Data availability

Data will be made available on request.

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