Chronic Beryllium Disease, Hla Dpb1 And The Dp Peptide Binding Groove

L. J. Silveira[1], E. McCanlies[2], T. Fingerlin[3], M. Van Dyke[1], P. M. Mroz[1], M. Strand[1], A. Fontenot[4], C. Schuler[2], A. Weston[2], L. Maier[5]

[1]National Jewish Health, Denver, CO, [2]National Institute for Occupational Safety and Health, Morgantown, WV, [3]University of Colorado, Denver, [4], [5]National Jewish Health, Denver

Corresponding author's email: silveiral@njhealth.org

Rationale: Multiple epidemiological studies have demonstrated associations between chronic beryllium disease (CBD), beryllium sensitization (BeS) and HLA-DPB1 alleles with a glutamic acid residue at position 69(E69). It is one of the best validated molecular epidemiologic associations. However questions remain concerning differential risk associated with specific E69 alleles. Results suggest that the less common E69 variants (non-0201 DPB1) might be associated with greater risk of CBD. Objectives: To define specific E69 carrying alleles and their amino acid sequences in the DP peptide binding grooves and their relationship to CBD and BeS risk in a large scale control study. Methods: This study included 499 BeS and CBD and 653 beryllium exposed controls from machining, nuclear or primary beryllium industries who gave informed consent for participation. Non-Hispanic white cases and controls were frequency matched by industry. HLA DPB1 genotypes were determined using sequence specific primers (SSP)-PCR. The E69 alleles were tested for association with disease individually and also grouped by amino acid structure. Comparisons for the genotype test were made by grouping genotypes with an 0201 allele, a non-0201E69 allele and two non-E69 alleles. Upper and lower bounds were developed for the odds ratios for these comparisons by placing the 0201/non-0201 E69 carrying genotypes in either the 0201 group (lower bounds) or non-0201E69 group (upper bound). Comparisons between cases and controls were modeled using logistic regression. Results: The HLA-DLP1 polymorphisms were not in Hardy Weinberg equilibrium in the cases ($p<0.0001$), so genotype tests were performed to assess the differential risk. CBD cases were more likely than controls to carry a non-0201E69 allele than an 0201E69 OR(95%CI)=lower bound 2.8(1.9-4.3), $p<0.0001$, upper bound 3.9(2.6-5.9), $p<0.0001$. In comparisons between amino acid sequences in the peptide binding groove surrounding pocket 1, those sequences present in the non-0201E69 were associated with CBD: DD vs. GG:2.4(1.5-3.7), $p=0.0002$, GD vs. GG:1.4(1.0-2.0), $p=0.04$ and this pattern was also true when comparing sequences around pocket 6, LL vs. GG:2.4(1.5-4.0), $p<0.0001$, GL vs. GG:1.1(1.5-2.0), $p=0.0074$. In addition, surface charge on the molecules coded for by E69 alleles was positively associated with CBD risk, where increasing negative charge and -9 provided an OR of 10.4(7.2-15.1) versus -7 which provided an OR of 1.8(1.3-2.3). Conclusions: There is a differential risk of CBD depending on E69 allele it appears that this allele does not confer the most risk. Whether there is a biological basis for this finding requires additional functional studies.

This abstract is funded by: 1PO1ES011810-06A1, UL1RR025780