HHS Public Access

Author manuscript

Ann Allergy Asthma Immunol. Author manuscript; available in PMC 2021 November 01.

Published in final edited form as:

Ann Allergy Asthma Immunol. 2020 November ; 125(5): 614–616. doi:10.1016/j.anai.2020.07.011.

HLA-DR53 (DRB4*01) Associates with Nickel Sensitization

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Keywords

Nickel sensitization; joint replacement failure; HLA; HLADRB4*01; HLA-DR53

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All authors acknowledge they have no potential conflicts of interest including funding sources that supported their work, and any commercial associations.

In this study, Dr. Pacheco provided the clinical evaluation of all patients, established the implant components, made the diagnosis of nickel sensitization, analyzed the data and wrote the letter. Dr. Zhang designed and performed the experiments, and contributed to the data analysis and manuscript. The HLA-DR typing was performed by Drs. Anderson and Freed. All work was performed in the laboratory and under the supervision of Dr. Dai, who contributed to the experiment design, data analysis and manuscript.

Sensitization to nickel (Ni^{2+}) is the most common type IV immune response, with estimates that 17% of women and 3% of men are nickel-sensitized[1]; likely an underestimate due to unreported cases. The route and timing of nickel exposure drive sensitization. Higher rates (12.2%)[2], established by patch testing, are associated with early exposure through piercings i.e. skin and blood; early exposure orally through braces had Ni^{2+}-sensitization rates similar to baseline (2.9%). As higher dermal exposure underlies Ni^{2+}-sensitization, the EU limited nickel release from jewelry, etc. to <0.05mcg/cm^2/wk (European Directive 94/27/EC).

Ni^{2+}-sensitization is increasingly relevant in joint replacement failure. In some, Ni^{2+}-sensitization occurred through skin exposure; in others, the initial exposure is via the systemic immune system through the trauma of surgery.

In addition to route and intensity of exposure, immune determinants of Ni^{2+}-sensitization are incompletely understood. As far as we know, no particular MHC allele or isotype has been associated with Ni^{2+}-sensitization, perhaps due to the promiscuity of nickel-MHC binding, and/or the complexity of nickel exposure. However, nickel-specific T cell clones require autologous APCs for response, suggesting a role for a specific peptide, or particular MHC configuration in the metal binding site or the interaction with the TCR[3]. In one study, the relevant MHC was determined to be HLA-DR52c[4] in complex with an unknown specific peptide produced in B cells, that activated a Ni^{2+}-reactive T cell clone isolated from a contact dermatitis patient. We became interested to see if DR52c or other HLA variants associated with Ni^{2+}-sensitization in an orthopedic population.

We selected subjects from an IRB-approved cohort of 1185 enrolled participants. Subjects were referred by their orthopedic surgeon preoperatively n=464 (39%), based on a history of metal reactivity, to help select the proper implant, or postoperatively n=721 (61%) for evaluation of metal sensitization causing a failed joint replacement. Ni^{2+}-sensitization is diagnosed by patch test and/or nickel lymphocyte proliferation test (LPT). Of pre-operative patients, 206 (44%) were sensitized to nickel, compared to 124 (17%) of post-operative patients, although their Ni^{2+}sensitization status was unknown prior to implant selection. This indicates that Ni^{2+}-sensitization is relevant in a joint replacement population.

From this cohort, we selected the following groups to assess MHC usage: A) 16 with a failed nickel containing implant, of whom 8 were Ni^{2+}-sensitized and 8 were non-Ni^{2+}-sensitized; 2) 13 pre-implant, of whom 8 were Ni^{2+}-sensitized and 5 were non-Ni^{2+}-sensitized. Ni^{2+}-sensitization was diagnosed by patch test (13/16) and/or Ni^{2+}-LPT (15/16), and 13 subjects were not sensitized to Ni^{2+}. Genomic DNA was isolated from 1×10^6 of cryopreserved PBMCs by QIAamp DNA Mini-Kit #51304, and HLA-DR typed by PCR-sequence specific primers high resolution methods (ClinImmune Labs). Statistical analyses used SAS 9.4 (SAS Institute, Cary, NC) and GraphPad. Differences between the Ni^{2+}-sensitization groups were determined using χ^2 for categorical variables, and Fisher's exact when expected cell sizes were < 5. Mean age differences were evaluated by t-test. Fisher's exact or Chi-square evaluated the association of Ni^{2+}-sensitization with the HLA alleles. Significance was set at $p<0.05$.

All selected subjects were of European-American background ("Caucasian"). There were no significant differences in age, gender, or joint involved between Ni^{2+}-sensitized and non-sensitized subjects, either pre-implant or post-implant.

We compared the distribution of HLA-DRB1, 3, 4 and 5 between Ni^{2+}-sensitization groups (Table 1). There were no significant differences in the distribution of DRB3 or 5 between groups. However, in the post implant patients, 75% (6/8) Ni^{2+}-sensitized were DR53 (DRB4*01) positive, compared to 25% (2/8) of non-Ni2+-sensitized, (p=0.13), though not significant. Comparing all nickel-sensitized to all non-nickel-sensitized patients, regardless of implant status, 11/16 (69%) Ni^{2+}-sensitized were DRB4*01 positive, compared to 5/13 (38%) non-Ni^{2+}-sensitized, (p=0.1029), though not significant. In contrast, the DR53 null allele (DRB4*01:03:01:02N) was exclusively associated with lack of Ni^{2+}-sensitization. 4/13 non-Ni^{2+}-sensitized subjects had a DR53 null allele, including one with a DRB4*01 allele, compared to 0/16 Ni^{2+}-sensitized subjects, p=0.103. The DR53 null allele is expressed but aberrant due to persistence of the first exon[5], although a protein product has not been detected serologically[6]. Whether the null variant inhibits Ni^{2+}binding due to steric interference or other mechanisms is unknown. Only one subject was HLA-DR52c (DRB3*03) positive, and also HLA-DR53 positive, and was sensitized to nickel (Table 1). There was no association of other DRB3 or DRB5 alleles with Ni^{2+}-sensitization.

The DRB1 locus alleles encoding DR4 (DRB1*04), DR7 (DRB1*07), and DR9 (DRB1*09)[6] are in linkage disequilibrium with DRB4. However, DRB1*04 was not associated with Ni^{2+}-sensitization in the post-implant groups (p=0.2821). The HLA-DR53 null allele is associated with DR7 (HLA-DRB1*07:01), as reported[7]. We did not find other DRB1 alleles associated with Ni^{2+}-sensitization.

Taken together, there is potential HLA-DR53 association with Ni^{2+}-sensitization in joint replacement subjects. Whereas HLA-DR52c associated with Ni^{2+}-sensitization in one human T cell clone [4], we did not find that association in this cohort. HLA-DR52 and -DR53 are derived from two distinct lineages, and are not alleles of the same locus[8]. In a German population, the gene frequency of DR52c (DRB3*03) is 2.47%; that of DR52 (DR52a, DR52b and DR52c) is 40.13% compared to 19.75% for DR53[9]. The lack of association of DR52c and Ni^{2+}-hypersensitivity in our cohort may be due to its low gene frequency. Also possible is that DR52c associates with contact dermatitis, whereas the internal site of pathology in our joint failure population leads to a different HLA association, with potentially different antigen binding peptide(s), and coordination with Ni^{2+} and MHC II.

Of our Ni^{2+}-sensitized patients with an implant, 5/8 reported a prior history of skin reactivity to jewelry (all female), vs. 3 who did not (all male). We postulate that those without a prior history acquired Ni^{2+}-sensitization from internal contact with a nickel-containing implant: an exposure and process of sensitization different from contact dermatitis. Interestingly, HLA-DR53 also associates with several autoimmune conditions. Individuals with autoimmunity are more susceptible to metal-induced hypersensitivity [10] and HLA-DR53 may provide a link between the two conditions.

In summary, we found a potential association of HLA-DR53 (DRB4*01) with Ni^{2+}-sensitization in post-implant patients with joint failure. Presentation of nickel by DR53 may provide a critical pathway to sensitization in this immune interface.

Acknowledgements

The authors would like to gratefully acknowledge the contribution of Dr. Katherine A Pratte, who contributed to the statistical analysis.

Funding Sources:

NIH R01ES025797, R21 ES025885

Abbreviations

Ni^{2+}	nickel
LPT	lymphocyte proliferation test

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Table 1.

Distribution of HLA-DRB1, 3, 4, 5 alleles between Ni sensitized & non-Ni sensitized subjects

	Nickel sensitized				Non Nickel sensitized			
	post-implant (n=8)		pre-implant (n=8)		post-implant (n=8)		pre-implant (n=5)	
	No.	%	No.	%	No	%	No.	%
DRB1*01	1	12.5	0	0.0	0	0.0	1	20.0
DRB1*03	0	0.0	1	12.5	2	25.0	0	0.0
DRB1*04	4	50.0	4	50.0	1	12.5	2	40.0
DRB1*07	2	25.0	1	12.5	4	50.0	1	20.0
DRB1*08	1	12.5	0	0.0	1	12.5	0	0.0
DRB1*09	1	12.5	1	12.5	0	0.0	0	0.0
DRB1*11	2	25.0	3	37.5	1	12.5	1	20.0
DRB1*12	0	0.0	1	12.5	1	12.5	1	20.0
DRB1*13	3	37.5	2	25.0	1	12.5	1	20.0
DRB1*14	0	0.0	0	0.0	1	12.5	0	0.0
DRB1*15	2	25.0	1	12.5	3	37.5	2	40.0
DRB1*16	0	0.0	1	12.5	0	0.0	0	0.0
DRB3*01	2	25.0	2	25.0	3	37.5	1	20.0
DRB3*02	3	37.5	3	37.5	3	37.5	2	40.0
DRB3*03	0	0.0	1	12.5	0	0.0	0	0.0
DRB4*01 [1]	6	75.0	5	62.5	2	25.0	3	60.0
DRB4*01:03:01:02N [2]	0	0.0	0	0.0	3	37.5	1	20.0
DRB5	2	25.0	2	25.0	3	37.5	2	40.0

[1] p=0.1319 between post-implant Ni^{2+} sensitized vs. Non Ni^{2+} sensitized (Fisher's exact). p=0.1029 between Ni^{2+} sensitized (pre & post) vs. Non Ni^{2+} sensitized (pre & post) (Chi-square).

[2] p=0.1026 between Ni^{2+} sensitized (pre & post) vs. Non Ni^{2+} sensitized (pre & post) (Fisher's exact).