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Published in:
Pediatric Allergy and Immunology

DOI (link to publication from Publisher):
10.1111/pai.13450

Publication date:
2021

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (APA):
Nielsen, K. R., Bojsen, S. R., Masmas, T. N., Fjordside, A-L., Baech, J., Haunstrup T, T. M., & Steffensen, R. (2021). Association between human leukocyte antigens (HLAs) and human neutrophil antigens (HNAs) and autoimmune neutropenia of infancy in Danish patients. *Pediatric Allergy and Immunology*, *32*(4), 756-761. https://doi.org/10.1111/pai.13450

Received: 4 August 2020 | Revised: 9 December 2020 | Accepted: 16 December 2020

DOI: 10.1111/pai.13450

ORIGINAL ARTICLE

WILEY

Association between human leukocyte antigens (HLAs) and human neutrophil antigens (HNAs) and autoimmune neutropenia of infancy in Danish patients

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Editor: Jon Genuneit

Abstract

Background: Autoimmune neutropenia of infancy (AIN) is a frequent cause of neutropenia in children. The disease is caused by antibodies against epitopes on the immunoglobulin G (IgG) Fc receptor type 3b (FcγIIIb). We investigated the possible association of human neutrophil antigens (HNA), human leukocyte antigen (HLA)-DR, and HLA-DQ alleles with AIN and the association of these genotypes with the presence of autoantibodies.

Methods: Eighty AIN cases with a median age of 13.5 months were included. Controls were healthy unrelated Danish blood donors. Anti-HNA-1a autoantibodies were detected using a flow cytometric granulocyte immunofluorescence test (Flow-GIFT) with phenotyped donor cells for detection of antibody specificity. Molecular determination of HNA genotypes was determined using real-time polymerase chain reaction (q-PCR). High-resolution HLA-DRB1 and HLA-DQB1 were determined by next-generation sequencing.

Results: Antibodies against HNA-1a were detected in 51% (n = 41) of AIN patients, and anti-HNA-1b was detected in 3% (n = 2) of cases. In 46% of cases, the antibodies were anti-FcγIIIb-reactive. *FCGR3B*01+,*02-,*03-* was more common (odds ratio, 6.70; $P < .0001$), and *FCGR3B*01-,*02+,*03-* was less common (odds ratio, 0.30; $P < .0001$) among AIN cases. HNA-1a antibodies were significantly more frequent among AIN cases with the *FCGR3B*01+,*02-,*03-* genotype (odds ratio, 3.86; $P < .007$). The HLA-DRB1*14 - HLA-DQB1*05:03 haplotype was significantly more common (odds ratio, 7.44; $P < .0001$) in AIN patients.

Conclusion: The HLA haplotype HLA-DRB1*14 - DQB1*05:03 is associated with Danish AIN cases. Among Danish AIN patients, anti-HNA-1a is the most common autoantibody, and the antibody is more common in cases with the *FCGR3B*01+,*02-,*03-* genotype.

KEYWORDS

autoimmune, genotype, HLA, HNA, neutropenia

Abbreviations: AIN, autoimmune neutropenia of infancy; CI, 95% confidence interval; *FCGR3B*, Fc receptor type 3b gene; FcγRIIIb, Fc receptor type 3b; GIFT, granulocyte immunofluorescence test; HLA, human leukocyte antigen; HNA, human neutrophil antigen; IgG, immunoglobulin G; *ITGAL*, the integrin alpha L gene; *ITGAM*, integrin alpha M gene; OR, odds ratio; p^c, corrected p value; q-PCR, polymerase chain reaction; rs, RefSNP number; *SLC44A2*, choline transporter-like protein-2 gene.

1 | INTRODUCTION

Primary autoimmune neutropenia of infancy (AIN) is a disease in which antibodies recognize membrane antigens of neutrophils, mostly located on immunoglobulin G (IgG) Fc receptor type 3b (FcγRIIIb (CD16b)), causing their peripheral destruction and is a frequent type of severe neutropenia in children under 3-4 years of age. Five systems of neutrophil antigens (HNAs) with at least 11 antigens have to date been described. HNA-1 (FcγRIIIb) is the most immunogenic glycoprotein on the granulocyte membrane and has at least four alleles *FCGR3B**01 (HNA-1a), *FCGR3B**02 (HNA-1b,1d), and *FCGR3B**03 (HNA-1c) which constitute the principal antigens implicated in autoimmune neutropenia of infancy (AIN). Three other systems, HNA-3, HNA-4, and HNA-5, are biallelic antigens encoded by the choline transporter-like protein-2 gene (*SLC44A2*), the integrin alpha M gene (*ITGAM*), and the integrin alpha L (*ITGAL*) gene, respectively. The complete genetic background for the HNA-2 genotype remains to be elucidated.[1] The disease is often self-limiting, and most patients are in complete remission after 2-3 years.[2] The overall risk of severe invasive bacterial and fungal infections is relatively low with respect to the neutrophil count since the bone marrow function is normal.[3] The presentation of antigens to the immune system relies on the highly polymorphic human leukocyte antigens (HLAs). Specific HLA types are strongly associated with the risk of autoimmune diseases.[4] This association is often disease-specific and may represent the superiority of these HLA proteins in binding antigens with autoantigenic potential.[5] Associations with HLA-DR2 genotypes[6] and the HLA-DRB1*14 and -DQB1*05:03 genotypes[7] have previously been suggested in AIN. In the present study, we investigated the association between the HLA-DRB1 and HLA-DQB1 and HNA-1, HNA-3, HNA-4, and HNA-5 genotypes and the risk of AIN in a cohort of 80 Danish AIN patients. To obtain better insight into the relationship between AIN and HNA antibodies, we investigated the association between HNA genotypes and anti-HNA-1a antibodies, since it has previously been shown that primary AIN is more frequent in individuals with the *FCGR3B*01* (HNA-1a) allele.[8]

Key Message

Autoimmune neutropenia of infancy is a common cause of severe neutropenia in small children. The genetic background is still unknown. We report an association with certain human leukocyte antigens (HLA) and human neutrophil antigens (HNA) genotypes and with respect to disease risk.

2 | METHODS

2.1 | Study cohort

Eighty AIN patients diagnosed between 2005 and 2015 at the Department of Clinical Immunology, Aalborg University Hospital, Aalborg, Denmark, were included in the study. Inclusion criteria were the presence of neutropenia defined as absolute neutrophil count (ANC) < 1.5 × 109/L in two repeated tests, age ≤ 5 years, and the presence of anti-neutrophil antibodies in the flow cytometric indirect granulocyte immunofluorescence test (Flow-GIFT). The exclusion criteria were inborn neutropenia, neutropenia related to inborn syndromes, post-infection neutropenia, and hematological malignancies. Genetic material for HNA and HLA genotyping was available from all patients, and consent for study participation was obtained from the legal guardian. Antibody specificity was determined from the panel reactivity in the Flow-GIFT. The control group consisted of healthy Danish blood donors from the Aalborg University Hospital blood bank, Aalborg, Denmark. A group of 200 randomly selected Danish blood donors were tested for the HNA-1, HNA-3, HNA-4, and HNA-5 genotypes. The control group for HLA genotyping consisted of 298 randomly selected bone marrow donors from the Danish bone marrow registry. Both control groups consisted primarily of Caucasians. All samples were handled anonymously. The study was approved by the local ethics committee.

2.2 | Samples

Blood samples consisted of EDTA-stabilized whole blood for genotyping and blood serum for Flow-GIFT.

2.3 | DNA preparation

DNA was extracted from peripheral blood using the Maxwell16 Blood DNA Kit on the Maxwell16 Instrument (Promega Corporation).

2.4 | HNA genotyping

Real-time polymerase chain reaction using TaqMan probes was used for the genotyping of eight single-nucleotide polymorphisms in the HNA-1 (*FCGR3B*) (rs447536, rs448740, rs52820103, rs428888, and rs2290834), HNA-3 (*SLC44A2*) (rs2288904), HNA-4 (*ITGAM*) (rs1143679), and HNA-5 (*ITGAL*) (rs2230433) loci as previously described.[9] The analysis is ISO accredited (DANAK, Denmark) and validated continuously in the IGIW and INSTAND programs.

2.5 | High-resolution HLA-DRB1 and HLA-DQB1 genotyping

High-resolution HLA typing was performed by next-generation sequencing-based HLA typing using the Illumina MiSeq platform

at Histogenetics. HLA typing with 2× high resolution at the 4-digit allelic level without ambiguities for HLA class II genotyping was performed. Exons 2 and 3 were sequenced for HLA class II alleles.

2.6 | Flow-GIFT analysis

Briefly, EDTA-stabilized whole blood from HNA phenotyped donors was washed three times in PBS with 5% fetal calf serum. Packed cells were incubated for 30 minutes with patient sera at 37 degrees Celsius, washed twice, and blocked with heat-inactivated rabbit serum. After 30 minutes of incubation with polyclonal rabbit anti-human IgM and IgG antibodies (DAKO, Denmark), erythrocytes were lysed and the cells were fixed. 100 000 cells were analyzed. The samples were analyzed using a BD FACS Canto flow cytometer (Becton Dickinson). Flow-GIFT was considered positive if mean fluorescent intensity (MFI) ≥2 times the negative control using AB serum. For determination of antibody specificity, the panel cells always consisted of two HNA-1aa, two HNA-1ab, and one HNA-1bb donor. One donor in the panel was selected for the subsequent expression of HNA-1c. The donor cells were selected by genotyping and after this, a confirmatory phenotyping using sera with known specificity. The analysis was performed as part of routine clinical practice in an International Society of Blood Transfusion (ISBT) reference laboratory. The analysis is ISO accredited (DANAK, Denmark) and validated continuously in the IGIW and INSTAND programs.

2.7 | Statistical analysis

STATA software (StataCorp) and Excel (Microsoft) were used for statistical analysis. The allele frequencies were calculated by direct counting. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated, and differences between populations were tested using Fischer's exact test. The Bonferroni-corrected significance level was used in all analyses.

3 | RESULTS

3.1 | Baseline characteristics

We included 80 children (37 females (46%) and 43 males (54%)) with newly diagnosed AIN with a median age at diagnosis of 13.5 months (5-40 months).

3.2 | Neutrophil reactive antibodies

Forty-three samples contained antibodies with conclusive anti-HNA specificity. Forty-one samples (51%) had anti-HNA-1a specificity, and 2 samples (3%) had anti-HNA-1b specificity. Thirty-seven samples (46%) revealed a broad reactive pattern against the panel cells and were concluded to be anti-FcγRIIIb reactive.

3.3 | HNA genotypes and anti-HNA-1a association

The presence of *FCGR3B*01+,*02-,*03-* (OR = 6.70 (3.70-12.10)) was significantly higher in the AIN patient group compared to healthy controls, whereas the presence of *FCGR3B*01-,*02+,*03-* (OR = 0.30 (0.14-0.51)) was decreased in the AIN group compared to healthy controls. No other HNA genotypes were significantly associated with AIN (Table 1). The presence of anti-HNA-1a-specific antibodies was strongly associated with the presence of the *FCGR3B*01+,*02-,*03-* genotype (OR = 3.86 (1.53-9.75)) and the absence of the *FCGR3B*01-,*02+,*03-* genotype (OR = 0.02 (0.01-0.37)) (Table 3).

3.4 | HLA class II genotypes and anti-HNA-1a association

The distributions of all HLA-DRB1 and HLA-DQB1 alleles are reported in supplementary (Tables S1 and S2). HLA-DRB1*14 (OR = 7.44 (2.83-19.30)) and HLA-DQB1*05 (OR = 2.50 (1.64-3.80)) were significantly associated with AIN, which is well known as a DRB1*14-DQB1*05:03 haplotype previously described among Caucasian Europeans (OR = 7.44 (2.83-19.30)) (Table 2). We observed an association between the presence of the HLA-DQ*05:03 genotype and HNA-1a-specific antibodies (OR = 2.56 (1.24-5.24)) (Table S4). The HLA-DRB1*14-DQB1*05:03 haplotype was not associated with antibody specificity (Tables S3 and S4).

4 | DISCUSSION

In the present study, we investigated the possible association between HLA and HNA genotypes and AIN and discovered an association between HLA-DRB1 and -DQB1 genotypes and risk of AIN. We also found association between *FCGR3B* genotypes and autoantibody specificity.

The mechanism by which HLA antigens are involved in autoimmune diseases is still largely unknown;[4] however, antigen presentation and T-cell activation seem to be the key triggering event in most autoimmune diseases.[10] Association between certain HLA antigens and human autoimmune diseases is well established; however, the molecular mechanisms underlining this altered self-tolerance remain unclear. Proposed mechanisms are viral infections through molecular mimicry initiating the activation of autoreactive B cells and CD4 + T cells; however, recent research proposes a general deficiency in peripheral self-tolerance, primarily mediated by an altered function or number of regulatory CD4 + T cells.[11] Regulatory T cells (Tregs) are indeed activated in a HLA restricted manner, and it has been shown that certain HLA genotypes can protect or increase susceptibility

TABLE 1 Prevalence of HNA alleles

HNA system	Genotype	Patients n = 80 (%)	Controls n = 200 (%)	OR	CI	*P*[a]
HNA-1	*FCGR3B*01+,*02-,*03-*	40 (50.0)	26 (13.0)	6.70	3.70-12.10	<.0001[b]
	*FCGR3B*01+,*02+,*03-*	22 (28.0)	78 (39.0)	0.59	0.34-1.03	.07
	*FCGR3B*01-,*02+,*03-*	13 (16.0)	84 (42.0)	0.30	0.14-0.51	<.0001[b]
	*FCGR3B*01+,*02-,*03+*	2 (2.5)	4 (2.0)	1.30	0.24-5.50	.99
	*FCGR3B*01+,*02+,*03+*	2 (2.5)	8 (4.0)	0.62	0.13-2.60	.73
	*FCGR3B*01-,*02+,*03+*	1 (1.0)	0	7.566	0.31-187.70	.082
	*FCGR3B*01-,*02-,*03+*	0	0	*		
	*FCGR3B*01-,*02-,*03-*	0	0	*		
HNA-3	HNA-3aa	57 (71.0)	134 (67.0)	0.73	0.73-2.10	.51
	HNA-3ab	21 (26.0)	58 (29.0)	0.87	0.50-1.50	.68
	HNA-3bb	2 (3.0)	8 (4.0)	1.67	0.13-2.39	.75
HNA-4	HNA-4aa	65 (81.0)	156 (78.0)	1.30	0.65-2.32	.63
	HNA-4ab	15 (19.0)	42 (21.0)	1.15	0.47-1.68	.75
	HNA-4bb	0	2 (1.0)	0.37	0.02-7.21	1.00
HNA-5	HNA-5aa	46 (58.0)	106 (53.0)	1.21	0.72-2.00	.51
	HNA-5ab	29 (36.0)	78 (39.0)	0.89	0.52-1.52	.69
	HNA-5bb	5 (6.0)	16 (8.0)	0.76	0.30-2.11	.80

Abbreviation: n, number of cases.

Significance level after Bonferroni correction to $\alpha = 0.05$: $\alpha/3 = 0.02$.

[a]*P*-value using Fisher's exact test, [b]$P < .02$

TABLE 2 Significant HLA-DRB1 and HLA-DQB1 alleles

HLA DRB1/DQB1	Patients n = 80 (%)	Controls n = 298 (%)	OR	95% CI	*P*-value[a]
DRB1*14	13 (8.1)	7 (1.2)	7.44	2.83-19.30	<.0001[b]
DQB1*05	46 (28.8)	83 (13.9)	2.50	1.64-3.80	<.0001[b]

Note: Abbreviation: n, number of cases.

Significance level after Bonferroni correction to $\alpha = 0.05$: $\alpha/13 = 0.004$.

[a]*P*-value using Fisher's exact test; [b]$P < .004$.

TABLE 3 Association between HNA genotypes and the presence of anti-HNA-1a specific

HNA	Genotype	Anti-HNA-1a positive n = 41	Anti-HNA-1a negative n = 39	OR	95% CI	*P*[a]
HNA-1	*FCGR3B*01+,*02-,*03-*	27	13	3.86	1.53-9.75	.007[b]
	*FCGR3B*01+,*02+,*03-*	12	10	1.20	0.45-3.21	.80
	*FCGR3B*01-,*02+,*03-*	0	14	0.02	0.01-0.37	<.001[b]
	*FCGR3B*01+,*02-,*03+*	1	1	0.95	0.06-15.74	1.00
	*FCGR3B*01+,*02+,*03+*	1	1	0.95	0.06-15.74	1.00

Abbreviation: n, number of cases.

Significance level after Bonferroni correction to $\alpha = 0.05$: $\alpha/3 = 0.02$.

[a]*P*-value using Fisher's exact test; [b]$P < .02$.

to a number of autoimmune diseases through a regulatory T cell–mediated mechanism. In AIN, a decreased number of circulating Tregs have actually been shown by Nakamura et al,[12] supporting a possible HLA association in this disease. An unknown environmental factor is thought to trigger this HLA restricted lack of tolerance and since autoantibody production continues after the initiating environmental trigger is eliminated, epitope spreading is proposed as a underlying mechanism[13] in antibody-mediated autoimmune diseases such as AIN; however, we do not yet know the nature of this triggering mechanism in AIN. The FcγRIIIb is polymorphic and

encodes the HNA-1 phenotypes known to be associated with AIN. Bruin et. al. suggested an association between the HNA-1a homozygous state encoded by the *FCGR3B*01+,*02-,*03-* genotype and the risk of AIN.[8] Audrain et al. reported similar findings in a French AIN cohort.[3] Here, we confirmed these findings, and furthermore, we discovered that the presence of this *FCGR3B* variant appears to be responsible for all our cases of anti-HNA-1a-positive AIN. We therefore suggest that the FcγRIIIb could play an important role as an autoantigen in this disease. Since neutrophils are an essential part of the inflammatory process, we speculated whether the combination of certain neutrophil antigens, an environmental trigger, and presentation through some HLA types might explain some cases of this disease. Two former smaller studies have explored the association between the HLA system and the risk of AIN. Bux et al[6] investigated 26 children using serological HLA typing methods and found an association between AIN and the HLA-DR2 phenotype. This finding could not be reproduced by Lin et. al., who genotyped 55 AIN patients and found a strong association with the HLA-DQ*05:03 genotype in Taiwanese children.[7] Surprisingly, we discovered the exact same association in our cohort of Danish Caucasian patients, suggesting that if an environmental trigger exists, it might be the same in these genetically distant populations. These findings even seem to be unrelated to the different allele frequencies of the *FCGR3B* gene between these populations.[9] Different HLA epitopes bind autoantigens differently[4] and DQB1*05:03 allele encodes a negatively charged aspartic acid at amino acid position 57 of the b chain, replacing positively charged amino acids such as valine, serine, or alanine. The peptide binding motif is changed compared to different HLA-DQB1*05 genotypes which could explain for the genotype effect. When we looked at the association with HLA genotypes and the specificity of the autoantibodies, we did not find an association (Table S3 and S4). Antibody specificity in AIN can change from FcγRIIIb reactivity to anti-HNA-1a specificity during the disease. This finding might suggest that another autoantigen triggers the disease and the anti-HNA-1a specificity in some cases is caused by epitope spreading. The HLA-DQ genotypes have also been associated with immunization toward food antigens;[14] however, no evidence of this mechanism has been shown for AIN. Since we are now including patients prospectively for the Danish AIN cohort, we hope to update these data and hopefully add further information. We also did not investigate the binding of antigens to the HLA epitopes associated with AIN and this remains a topic for further studies. Today, truly little is known about the mechanisms leading to primary autoimmune neutropenia. We believe that our study adds further evidence to an HLA association with this disease and the possibility of a regulatory T cell–mediated mechanism. In conclusion, we report an association between certain HNA and HLA antigens and AIN. We support the findings from smaller studies and suggest that antigen presentation from HLA-DQ phenotypes might be important in solving the etiology of AIN.

CONFLICT OF INTEREST

On behalf of all authors, I hereby declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Signe Rolskov Bojsen: Conceptualization (equal); Formal analysis (equal); Investigation (equal); Writing-original draft (supporting); Writing-review & editing (supporting). **Tania Nicole Masmas:** Investigation (supporting); Methodology (supporting); Validation (lead); Writing-original draft (equal); Writing-review & editing (equal). **Anne-Louise Fjordside:** Data curation (equal); Methodology (equal); Validation (equal); Writing-original draft (supporting); Writing-review & editing (supporting). **John Baech:** Conceptualization (supporting); Formal analysis (supporting); Writing-original draft (supporting); Writing-review & editing (equal). **Thure Mors Haunstrup:** Conceptualization (supporting); Validation (equal); Writing-original draft (supporting); Writing-review & editing (equal). **Rudi Steffensen:** Conceptualization (equal); Formal analysis (equal); Methodology (equal); Writing-original draft (equal); Writing-review & editing (equal).

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/pai.13450.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Nielsen KR, Bojsen SR, Masmas TN, et al. Association between human leukocyte antigens (HLAs) and human neutrophil antigens (HNAs) and autoimmune neutropenia of infancy in Danish patients. *Pediatr Allergy Immunol*. 2021;32:756–761. https://doi.org/10.1111/pai.13450