

ABO, secretor, and Lewis carbohydrate histo-blood groups are associated with autoimmune neutropenia of early childhood in Danish patients

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Abstract

Background: Autoimmune neutropenia of early childhood (AIN) is caused by autoantibodies directed against antigens on the neutrophil membrane. The ABO, secretor, and Lewis histo-blood group systems control the expression of carbohydrate antigens and have previously been linked to autoimmune diseases. We aimed to investigate the association between genotypes and the risk of AIN in Danish patients.

Study Design and Methods: One hundred fifty-four antibody-positive AIN patients were included. Controls ($n = 400$) were healthy unrelated Danish blood donors. Molecular determination of ABO, secretor (*FUT2*), and Lewis (*FUT3*) genotypes were determined using real-time polymerase chain reaction (qPCR) or Sanger sequencing to infer the prevalence of Lewis antigens (Le^a and Le^b) and secretor (SeSe or Sese) or nonsecretor (sese) phenotypes.

Results: Blood type O was more common in controls (46.8%) than in AIN patients (36.4%) (OR = 0.65; $p = 0.028$). Secretors of H Le^b antigens were less frequent among AIN patients (25.2%) than controls (35.0%) (OR = 0.62; $p = 0.037$).

Discussion: ABO blood group antigens and the secretion of these antigens are associated with a diagnosis of AIN. The mechanism underlying the association between autoimmunity and interaction among ABO, secretor, and Lewis genotypes has not yet been elucidated, but several studies indicate a connection to the gut microbiota.

KEYWORDS

AIN, histo-blood group, Lewis, polymorphisms of *FUT2* and *FUT3*, secretor status

List of Abbreviations: AIN, Autoimmune neutropenia; ANC, Absolute neutrophile count; CI, 95% confidence interval; *FUT*, Fucosyltransferase; GIFT, Granulocyte immunofluorescence test; HLA, Human leukocyte antigens; HNA, Human neutrophil antigens; LD, Linkage disequilibrium; *LE*, Lewis; OR, Odds ratio; qPCR, Real-time polymerase chain reaction; rs, RefSNP number; *SE*, Secretor; SNP, Single nucleotide polymorphism.

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1 | INTRODUCTION

Primary autoimmune neutropenia (AIN) of early childhood is a frequent cause of neutropenia in children. It is caused by an increase in the peripheral destruction of neutrophils that results from an underlying autoimmune mechanism in which autoantibodies are directed against the child's own neutrophils. The disease is often self-limiting, and most patients are in complete remission after 2–3 years.¹ A previous study on Danish AIN patients found an association between HLA genes and the HNA system,² indicating a genetic association, known from other autoimmune diseases like multiple sclerosis, Crohn's disease Type 1 diabetes, or ITP.^{3,4}

The first association between the ABO histo-blood group system and disease was described by Buckwalter et al. in the 1950s,⁵ and since then, ABO types have been linked to a wide range of diseases. ABO is the major human alloantigen system and involves three carbohydrate antigens (ABH). Individuals with type A, B, or AB express glycosyltransferase activity, converting the H antigen into A or B antigens, whereas group O individuals lack such activity. ABH is widely expressed in body fluids and tissues.⁶

ABH expression in tissues and body fluids is regulated by the secretor gene (*FUT2*) and the Lewis gene (*FUT3*), which are both located on chromosome 19p13.3. *FUT2* encodes an α -1,2-fucosyltransferase that converts a type 1 precursor to an H-type 1 antigen. *FUT3* encodes an α -1,3-fucosyltransferase that converts the H-type 1 antigen

to a Lewis (Le^b) antigen, or in the absence of *FUT2*, the type 1 chain precursor is converted to a Le^a antigen (Figure 1).

Single nucleotide polymorphisms (SNPs) located in the ABO, *FUT2*, and *FUT3* genes are associated with susceptibility or resistance to various infectious and inflammatory diseases and seem to play a role in shaping the microbiome.^{8,9} Interaction between *FUT2* and ABO has been reported to increase the risk of childhood respiratory illness¹⁰ and *FUT2* and *FUT3* polymorphisms are frequent in newborns with implications for infectious disease susceptibility.¹¹

We hypothesize that the risk of developing AIN is different depending on ABO type, as seen for other autoimmune diseases. We compared the distribution of genetic variants in ABO, *FUT2*, and *FUT3* in AIN patients with a control group consisting of healthy unrelated Danish blood donors.

2 | MATERIALS AND METHODS

2.1 | Study cohort

We included 154 patients diagnosed with AIN between 2004 and 2021 at the Department of Clinical Immunology, Aalborg University Hospital, Denmark. Criteria for inclusion were the presence of neutropenia, defined as absolute neutrophil count (ANC) $< 1.5 \times 10^9$ cell/L in two repeated tests, age under 5 years at the time of diagnosis, and the presence of anti-neutrophil antibodies in

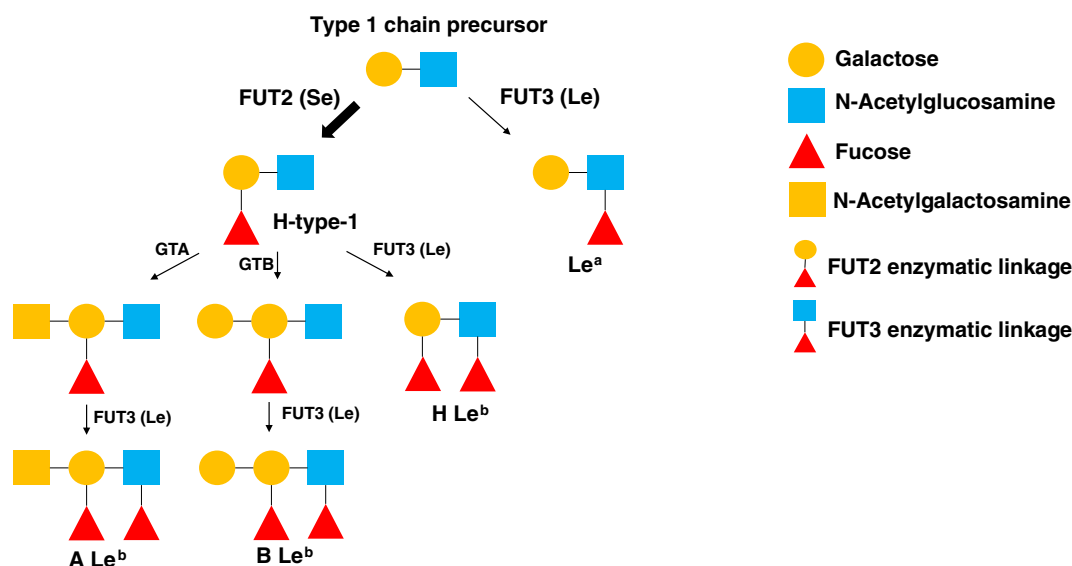


FIGURE 1 Summary of glycoconjugates profiles related to histo-blood systems ABO, secretor and Lewis. Adapted from Barbé et al. 2018.⁷ *FUT2* and *FUT3* fucosyltransferases catalyze the linkage of fucose to the Type 1 chain precursor, creating H-type 1 antigen. Glucosyltransferases specific for blood types A (GTA) and B (GTB) catalyze the linkage of N-acetylgalactosamine or galactose to the antigen. The addition of fucose to N-acetylglucosamine by *FUT3* results in Lewis antigens

the flow cytometric indirect granulocyte immunofluorescence test (Flow-GIFT) as previously described.² The Flow-GIFT was performed with repeated tests after recommendation by Bux,¹ with the use of three tests before we conclude the antibody found to be negative. 91% of our patients are positive in the first test, the remaining are found positive in a follow-up test.

Patient inclusion was made in collaboration with clinicians, excluding patients with congenital neutropenia, known somatic mutations, neutropenia related to inborn syndromes, postinfection neutropenia, or hematological malignancies. Genetic material was available for all patients for genotyping for ABO, but there was only sufficient material for the additional analyses in 143 of the 154 patients. The control group consisted of randomly selected healthy adult Danish blood donors from the Aalborg University Hospital blood bank, Aalborg, Denmark. These donors were serologically tested for ABO and genetically tested for *RhD*, *FUT2*, and *FUT3*. Both patients and controls consisted primarily of Caucasians. Consent for study participation was obtained from legal guardians and the study was approved by the local ethics committee (nr. N-20170026).

2.2 | DNA preparation

DNA was extracted from EDTA-stabilized whole blood or buccal swap using the Maxwell 16 Blood DNA Kit or the Maxwell RSC Buccal Swab Kit on the Maxwell RSC instrument (Promega, US).

2.3 | ABO, FUT2, FUT3 and RhD genotyping

Three SNPs in ABO (rs8176719 (G216del), rs7853989 (C526G) and rs8176743 (G703A)), one SNP in *FUT2* (rs601338 (G428A)) and one SNP in *FUT3* (rs3894326 (T1067A)) were genotyped using qPCR with TaqMan assay. Further, three SNPs in *FUT3* (rs28362459 (T59G), rs812936 (T202C), and rs778986 (C314T)) were analyzed

with Sanger sequencing using BigDye Direct Cycle Sequencing Kit. RhD genotyping was analyzed using qPCR as previously described by¹² (Data S1: Materials and Methods).

2.4 | Inferring secretor and Le^b status

For samples that did not carry an active Lewis gene (*LE*) regardless of an active secretor gene (*SE*), the phenotype was concluded to be the Le(a–b–) phenotype. Samples who carry *LE* but do not carry an *SE* were considered Le(a+b–). Finally, samples that carry both *LE* and *SE* were considered to have a Le(a–b+) phenotype (Table 1 and (Data S1: Materials and Methods)).

2.5 | Statistics

Alleles were counted by direct counting. Statistical analysis and interpretation of the data were carried out (Data S1: Materials and Methods).

3 | RESULTS

3.1 | Baseline characteristics

We included 154 children diagnosed with AIN with a median age at diagnosis of 14.2 months (3–54 months). The sex distribution was 48% females and 52% males. The control group consisted of 400 healthy unrelated Danish blood donors (41% females and 59% males).

3.2 | ABO and RhD

We found a significant difference ($p = 0.028$) in blood type O distribution between patients and controls (Table 1). There was a 10% decrease in the frequency of type O in the patient group compared to the control group, with an OR = 0.65 (CI = 0.44–0.95). The most

ABO type	AIN patients <i>n</i> = 154 (%)	Controls <i>n</i> = 400 (%)	<i>p</i> value ^a	OR (95% CI) ^a
A	77 (50.0)	164 (41.0)	0.057	1.43 (0.99–2.09)
B	13 (8.4)	34 (8.5)	1.000	0.99 (0.51–1.94)
AB	8 (5.2)	15 (3.8)	0.478	1.41 (0.58–3.39)
O	56 (36.4)	187 (46.8)	0.028	0.65 (0.44–0.95)

TABLE 1 ABO phenotype frequency in Danish AIN patients and controls

Abbreviations: CI, confidence interval; OR, odds ratio.

^aBold values indicate statistically significant results.

common blood group differed between patients and controls. Type A (50.0%) was the most frequent in the patient group, and type O (46.8%) was the most frequent in the control group. No significant difference was observed in the distribution of *RhD* positive between 113 patients (85%) and 400 controls (81%) ($p = 0.884$).

3.3 | Secretor status

The *SE/se* alleles coded by *FUT2* were determined by the SNP (rs601338 (G428A)) in 143 patients and 400 controls. The frequency of the mutant allele (428A) did not differ significantly between the two groups, and the distribution of nonsecretors (homozygote 428A) was 22.4% in patients and 22.3% in controls (Data S2: Table 3).

3.4 | Lewis

Genotyping of the Lewis locus (*Le/le*) included the identification of four major SNPs in the *FUT3* gene at nucleotide positions T59G (rs28362459), A1067T (rs3894326), T202C (rs812936), and C314T (rs778986) which are known to explain 90%–95% of the Le^b-negative phenotype in Caucasians.¹³ *FUT3* genotypes were successfully determined in 143 patients and 400 controls (Data S2: Table 3). Haplotypes for *FUT3* were formed as a trichotomous composite index as described by Cakir et al.¹⁴ based on molecular biological studies of the *FUT3* gene and products.^{13,15–22} The most common genotype combination was the “wild type” genotype at all four nucleotide positions, and this genotype was found to be present in 55.9% of patients and 53.5% of controls (Data S2:

TABLE 2 Genetically determined Lewis phenotypes among Danish AIN patients and controls

Lewis type	LE	SE	ABH secretors	AIN patients <i>n</i> = 143 (%)	Controls <i>n</i> = 400 (%)	<i>p</i> value	OR (95% CI)
Le(a–b–)	<i>le/le</i>	<i>se/se</i>	No	0 (0.0)	10 (2.5)	0.070	0.13 (0.00–2.23)
Le(a–b–)	<i>le/le</i>	<i>SE/se</i>	Yes	7 (4.9)	8 (2.0)	0.079	2.52 (0.90–7.09)
Le(a–b–)	<i>le/le</i>	<i>SE/SE</i>	Yes	3 (2.1)	8 (2.0)	1.000	1.05 (0.27–4.01)
Le(a+b–)	<i>LE/le</i>	<i>se/se</i>	No	9 (6.3)	29 (7.3)	0.849	0.68 (0.40–1.86)
Le(a+b–)	<i>LE/LE</i>	<i>se/se</i>	No	23 (16.1)	50 (12.5)	0.317	1.34 (0.79–2.30)
Le(a–b+)	<i>LE/le</i>	<i>SE/se</i>	Yes	30 (21.0)	70 (17.5)	0.380	1.25 (0.78–2.02)
Le(a–b+)	<i>LE/le</i>	<i>SE/SE</i>	Yes	14 (9.8)	56 (14.0)	0.245	0.67 (0.36–1.24)
Le(a–b+)	<i>LE/LE</i>	<i>SE/se</i>	Yes	35 (24.5)	94 (23.5)	0.820	1.06 (0.68–1.65)
Le(a–b+)	<i>LE/LE</i>	<i>SE/SE</i>	Yes	22 (15.4)	75 (18.8)	0.445	0.79 (0.47–1.32)

Abbreviations: CI, confidence interval; LE, Lewis gene; OR, odds ratio; SE, secretor gene.

TABLE 3 Frequencies of ABH secretor status among Danish AIN patients and controls

ABO type	Lewis type	ABH secretor	AIN patients <i>n</i> = 143 (%)	Controls <i>n</i> = 400 (%)	<i>p</i> value ^a	OR (95% CI) ^a
A	Le(a–b–)	Yes/No	4 (2.8)	10 (2.5)	0.767	1.12 (0.35–3.64)
A	Le(a+b–)	No	14 (9.8)	31 (7.8)	0.480	1.29 (0.67–2.50)
A	Le(a–b+)	Yes	53 (37.1)	123 (30.8)	0.177	1.33 (0.89–1.98)
B	Le(a–b–)	Yes/No	1 (0.7)	2 (0.5)	1.000	1.40 (0.13–15.57)
B	Le(a+b–)	No	3 (2.1)	8 (2.0)	1.000	1.05 (0.27–4.01)
B	Le(a–b+)	Yes	9 (6.3)	24 (6.0)	0.842	1.05 (0.48–2.32)
AB	Le(a–b–)	Yes/No	1 (0.7)	1 (0.3)	0.458	2.81 (0.17–45.22)
AB	Le(a+b–)	No	0 (0.0)	6 (1.5)	0.348	0.21 (0.01–3.78)
AB	Le(a–b+)	Yes	5 (3.5)	8 (2.0)	0.342	1.78 (0.57–5.52)
O	Le(a–b–)	Yes/No	4 (2.8)	13 (3.3)	1.000	0.86 (0.27–2.67)
O	Le(a+b–)	No	13 (9.1)	34 (8.5)	0.862	1.08 (0.55–2.10)
O	Le(a–b+)	Yes	36 (25.2)	140 (35.0)	0.037	0.62 (0.41–0.96)

Abbreviations: CI, confidence interval; OR, odds ratio.

^aBold values indicate statistically significant results.

Table S4). Based on the four SNPs, the study participants were divided into Lewis positive (*LE/LE*), semipositive (*LE/le*), and negative (*le/le*) groups (Table 2). Lewis-positive and semipositive individuals were divided based on their secretor status into Le^a (nonsecretor) or Le^b (secretor) individuals. The groups were further divided based on ABO blood types into ABH Le^b antigen groups. Comparison of ABH Le^b antigen groups between patients and controls showed a statistically significant difference ($p = 0.037$) in the distribution of H Le^b antigen presenters (25.2% in patients and 35.0% in controls), with an OR = 0.62 (CI = 0.41–0.96) (Table 3). These findings were significant, and the p values were below the critical value for multiple testing according to the Benjamini-Hochberg procedure (Data S2: Table S5). Although we did not establish an association for either secretor or Lewis types, we did observe a significant difference when combining the Lewis and secretor status with ABO blood types.

4 | DISCUSSION

Here, we report an association between the ABO blood group system and the risk of AIN in Danish patients. This study is, to our knowledge, the first to investigate the association between the ABO blood system and AIN. With a study population of 154 individuals, it is also one of the largest studies to date investigating genetic susceptibility to AIN. The distribution of ABO blood groups in the control group was consistent with the reported prevalence in the Danish population.²³ The most common blood type among the Danish population is blood type O. In our study, 46.8% of the control group were type O, but only 36.4% ($p = 0.028$) of the patients. In contrast, 50.0% of the patients were blood type A. The lower prevalence of blood type O among AIN patients suggests a protective effect. ABO blood groups are reported to be associated with both autoimmune diseases and the risk of various infections, and the underlying mechanism is thought to be a modulating factor of the intestinal microbiome.⁸ However, the exact mechanism for these carbohydrates in autoinflammation is not well understood. In a recently published study, Rühlemann et al. found a correlation between the ABO gene and an increase in specific bacteria in the gut microbiome.⁹ Interestingly, the prevalence of these bacteria is also associated with the *FUT2* locus, through a missense variant that is in strong linkage disequilibrium (LD) with rs601338 (G428A) encoding the *FUT2* secretor phenotype. This variant determines whether the fucosyl precursor for ABO, H-type 1, is synthesized on mucosal surfaces in secretions. The H-type 1 and Lewis antigens encoded by the *FUT3*

gene are highly expressed in the gut mucosa and are implicated in susceptibility to a range of microorganisms and other environmental stimuli.^{8,24} They are also receptors for various pathogens, including rotavirus, norovirus, *Helicobacter pylori*, and *Campylobacter jejuni*.^{25–28} Individuals homozygous for the *FUT2* missense variant display the nonsecretor phenotype and do not secrete ABO. Therefore, the pattern of antigen expression by each individual determines that person's susceptibility to infection. Rühlemann et al. also described a positive correlation between the non-O blood group and positive secretor status and the prevalence of the aforementioned bacteria and other bacteria of the intestinal bacteria flora. These findings indicate an impact of human ABO blood groups and secretor status on the human microbiome.

A recently published genome-wide association study reported that interaction between ABO and *FUT2* increases the risk of early childhood asthma and *Streptococcus pneumoniae* respiratory illnesses.¹⁰ Ahluwalia et al. identified a top SNP in the ABO locus, which is in almost complete LD with the frameshift/deletion polymorphism SNP encoding the O antigen. They found an indication that individuals with non-O blood groups have a higher risk of childhood asthma. Association at both ABO and *FUT2* raised the possibility that these associations were caused by the same mechanism: the secretion of A/B antigens. There was no effect observed from the ABO variation in nonsecretors, but there was an increasing effect observed for individuals with a functional *FUT2* allele.

These findings initiated our investigation of the *FUT2* secretor and *FUT3* Lewis status. Our findings suggest that a combined effect of these two systems with the ABO system is associated with AIN. The association was the strongest for Lewis-positive individuals who are type O, that is, individuals who secrete the H Le^b substance. These individuals seem to have a protective effect against AIN. The reason for this protection might be because of the lack of AB antigen expression. We do not know if the disposition to certain infections associated with the representation of specific carbohydrate antigens could initiate an autoimmune response in children with other genetic dispositions to autoimmune diseases, such as certain HLA genotypes. The combined effect indicated in this study is grounds for further investigations. Along with differences in methodology and genotyping techniques by which SNPs were identified, other possible explanations for our findings include population heterogeneity. Copy-number variations, deletions, and fusions (particularly in *FUT2*) are described in some populations, but they require further investigation.^{29,30} We did not observe *RhD* association, which is in accordance with other findings, that *RhD* does not have the same disease associations as ABO.³¹

In conclusion, we report associations between the ABO blood type-O and H substance secretion and AIN.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Kløve-Mogensen K, Steffensen R, Masmus TN, Glenthøj A, Haunstrup TM, Ratcliffe P, et al. ABO, secretor, and Lewis carbohydrate histo-blood groups are associated with autoimmune neutropenia of early childhood in Danish patients. *Transfusion.* 2022; 62(8):1636–42. <https://doi.org/10.1111/trf.17002>