Archivum Immunologiae et Therapiae Experimentalis (2020) 68:14
https://doi.org/10.1007/s00005-020-00572-8

ORIGINAL ARTICLE

HLA-A and -B Type and Haplotype Frequencies in IgG Subclass Deficiency Subgroups

James C. Barton[1,2,3] · Jackson C. Barton[2] · Luigi F. Bertoli[2,3] · Ronald T. Acton[2,4]

Received: 7 May 2019 / Accepted: 5 February 2020 / Published online: 20 April 2020

Abstract

We sought to determine whether HLA-A and -B type and haplotype frequencies differ between subgroups of adults with IgG subclass deficiency (IgGSD). We retrospectively compared type and haplotype frequencies of three subgroups of 269 unrelated adult IgGSD patients (70 subnormal IgG1; 121 subnormal IgG3; 78 subnormal IgG1/IgG3) and controls (1,321 for types; 751 for haplotypes). We selected types and haplotypes because their uncorrected frequencies differed significantly from controls in a previous adult IgGSD/common variable immunodeficiency cohort: A*24; B*14; B*35; B*40; B*49; B*50; B*58; B*62; A*01,B*08; A*02,B*44; A*02,B*60; A*03,B*07; A*03,B*14; A*03,B*44; A*31,B*40; and A*32,B*14. We used χ^2 analysis (2 × 4 tables) to identify frequency differences across three subgroups and controls. If the null hypothesis was rejected ($p < 0.05$), we computed 2 × 2 χ^2 tables to compare six combinations of subgroup and control frequencies [Bonferroni $p < 0.0083$ (< 0.05/6)]. Mean age was 48 ± 13 years; 82.2% were women. B*35 and B*40 frequencies were higher in subnormal IgG1 than subnormal IgG3 patients (0.1000 vs. 0.0248 and 0.0571 vs. 0.0083, respectively; $p \leq 0.0061$). B*62 frequencies were lower in three IgGSD subgroups than controls ($p < 0.0001$, respectively). A*02, B*44 frequency was higher in subnormal IgG1/IgG3 patients than controls (0.1282 vs. 0.0632, respectively; $p = 0.0024$). A*02, B*60 frequency was lower in subnormal IgG3 patients than controls (0.0 vs. 0.0233, respectively; $p = 0.0051$). HLA-B*35 and -B*40 frequencies differ significantly between some IgGSD subgroups. B*62, A*02, B*44, and A*02, B*60 frequencies differ significantly between some IgGSD subgroups and controls.

Keywords Common variable immunodeficiency · HLA-A*02, B*44 · HLA-B*35 · HLA-B*40 · HLA-B*62 · Major histocompatibility complex

Abbreviations

CVID	Common variable immunodeficiency
HLA	Human leukocyte antigen
Ig	Immunoglobulin
IgGSD	IgG subclass deficiency
MHC	Major histocompatibility complex
SD	Standard deviation

✉ James C. Barton
bartonjames336@gmail.com

[1] Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA

[2] Southern Iron Disorders Center, Birmingham, AL, USA

[3] Department of Medicine, Brookwood Medical Center, Birmingham, AL, USA

[4] Department of Microbiology, University of Alabama at Birmingham, Birmingham, AL, USA

Introduction

Immunoglobulin (Ig) G subclass deficiency (IgGSD) in adults is characterized by frequent or severe respiratory tract infection, unexplained subnormal IgG subclass levels, decreased IgG responsiveness to pneumococcal polysaccharides, and a predominance of women (Barton et al. 2014; Bousfiha et al. 2018). Many adults with IgGSD also have autoimmune conditions or atopy (Abrahamian et al. 2010; Barton et al. 2014; Lacombe et al. 1997; Oxelius et al. 1986). Characteristics of persons diagnosed to have IgGSD or common variable immunodeficiency (CVID) in adulthood are similar, except that patients with CVID have subnormal total IgG and IgA (by definition) and greater risk of autoimmune conditions (Barton et al. 2014).

Frequencies of some human leukocyte antigen (HLA)-A and -B types and haplotypes in unrelated adults with IgGSD or CVID differ significantly from those of control subjects (Barton et al. 2003b). Many adults with IgGSD

or CVID have first-degree family members with IgGSD or CVID (Barton et al. 2003b; Oxelius et al. 1986; Vorechovsky et al. 2000). HLA-A and -B haplotypes segregate with IgGSD or CVID immunophenotypes in many adult patients and their first-degree family members (Barton et al. 2003b; Vorechovsky et al. 2000). In one study of adults with CVID, the majority inherited the haplotype HLA-*DQ2, *DR7,*DR3(17), *B08 and/or *B44 (Waldrep et al. 2009). These observations suggest that one or more IgGSD or CVID susceptibility loci are linked to the major histocompatibility complex (MHC) (Barton et al. 2003b; Schroeder Jr. et al. 2004; Vorechovsky et al. 2000; Waldrep et al. 2009).

In a retrospective study of 269 unrelated adult patients with IgGSD, we sought to determine whether frequencies of HLA-A and -B types and haplotypes differ between patients with subnormal IgG1, subnormal IgG3, and subnormal IgG1/IgG3. We analyzed HLA-A and -B types and haplotypes, uncorrected frequencies of which differed significantly between an aggregate cohort of adults with IgGSD or CVID and controls (Barton et al. 2003b). We compared these frequencies in subgroups of the present 269 adults with IgGSD with those of population controls. We discuss our findings in the context of previous reports of HLA associations in patients diagnosed to have either IgGSD and CVID in adulthood.

Materials and Methods

Patient Selection

We studied consecutive, unrelated, self-identified non-Hispanic white adults (ages ≥ 18 years) referred to a single outpatient referral practice because they had frequent or severe upper or lower respiratory tract infection and were subsequently diagnosed to have IgGSD, underwent HLA typing and haplotyping, and had no first-degree relatives with IgGSD previously known to this practice (Barton et al. 2014; Bousfiha et al. 2018). Subnormal IgG4 level alone was not a criterion for IgGSD diagnosis. Upper respiratory tract infection was defined as reports of sinusitis, otitis media, mastoiditis, pharyngitis, and tonsillitis. Lower respiratory tract infection was defined as reports of bronchitis, pneumonia, and bronchiectasis. Frequent infection was defined as four or more episodes per year that required antibiotic therapy. Severe infection was defined as an infection that required in-hospital treatment. Autoimmune condition(s) and atopy (allergic asthma, allergic rhinitis, and allergic dermatitis/eczema) were diagnosed by referring physicians. Other allergy manifestations included urticaria, angioedema, or anaphylaxis that occurred with or without exposure to specific medications, foods, or environmental allergens (Barton et al. 2003b).

Laboratory Methods

Serum IgG levels at diagnosis were measured using standard methods (Laboratory Corporation of America, Burlington, NC, USA). We defined mean ± 2 standard deviations (SD) as reference limits (Barton et al. 2003b): IgG 7.0–16.0 g/L (700–1600 mg/dL); IgG1 4.2–12.9 g/L (422–1292 mg/dL); IgG2 1.2–7.5 g/L (117–747 mg/dL); IgG3 0.4–1.3 g/L (41–129 mg/dL); IgG4 0–2.9 g/L (1–291 mg/dL); IgA 700–4000 mg/L (70–400 mg/dL); and IgM 400–2300 mg/L (40–230 mg/dL). Subnormal Ig levels were defined as those below the corresponding lower reference limits.

HLA-A and -B types of patients were detected using low-resolution DNA-based typing (polymerase chain reaction/sequence-specific oligonucleotide probe) as previously described (Barton et al. 2003b). In each patient in whom a single A or B type was detected, we verified the type(s) and set phase to ascertain haplotypes using HLA analyses of appropriate family members (Barton et al. 2003b). Haplotypes were defined only by A and B types.

We used data from 1321 unrelated Alabama non-Hispanic whites who had undergone HLA-A and -B typing as part of paternity testing to estimate allele frequencies. HLA frequencies were calculated using observations from unrelated men and women regardless of whether the man was determined to be the father of the child in question or not. Thus, there were more men than women (Acton et al. 1993; Barton et al. 2003a). We ascertained HLA-A and -B haplotypes in 751 unrelated Alabama non-Hispanic whites who had undergone testing to establish paternity by assessing HLA-A and -B types in children and their respective mothers or putative fathers. An equal number of men and women were used to ascertain haplotypes (Acton et al. 1993; Barton et al. 2003b). Frequencies of major HLA-A and -B haplotypes observed in controls were similar to those of Caucasians enrolled in a national bone marrow donor program (Boucher et al. 1998).

We studied selected HLA-A and -B types and haplotypes because their uncorrected frequencies in an aggregate cohort of adult IgGSD and CVID patients differed significantly from those of controls (Barton et al. 2003b). The types were: A*24; B*14; B*35; B*40; B*49; B*50; B*58; and B*62. The haplotypes were: A*01, B*08; A*02, B*44; A*02, B*60; A*03, B*07; A*03, B*14; A*03, B*44; A*31,B*40; and A*32, B*14 (Barton et al. 2003b).

Statistics

The analytic data set consisted of complete observations of 269 patients. Descriptive data are displayed as enumerations, percentages, or mean ± 1 SD. We computed

frequencies of the selected HLA-A and -B types and haplotypes in patient subgroups (70 subnormal IgG1; 121 subnormal IgG3; 78 subnormal IgG1/IgG3) and controls (1321 for types; 751 for haplotypes). We used χ^2 analysis (2×4 tables) to test the null hypothesis that there were no significant differences between respective HLA type and haplotype frequencies in three patient subgroups and controls. If the null hypothesis was rejected ($p<0.05$), we computed six corresponding 2×2 χ^2 tables to compare each possible combination of patient and control type and haplotype frequencies. In the latter analyses, we controlled the type I error rate by defining Bonferroni $p<0.0083$ ($<0.05/6$) as significant. Similar analyses were performed to detect differences in the prevalence of sex, autoimmune condition(s), atopy, and other allergy across the three IgGSD subgroups. Mean age values across the three IgGSD subgroups were compared using a one-way analysis of variance test. We performed logistic regressions on subnormal IgG, subnormal IgG3, and subnormal IgG1/IgG3 subgroups, HLA-B*35, B*40, B*62, A*02,B*44, and A*02,B*60 using age, sex, autoimmune condition(s), atopy, and other allergy as independent variables. Significant associations are expressed as odds ratios [95% confidence interval]. Analyses were performed with Excel 2000® (Microsoft Corp., Redmond, WA, USA) and GB-Stat® (v. 10.0, 2003, Dynamic Microsystems, Inc., Silver Spring, MD, USA).

Results

Characteristics of 269 Patients with IgGSD

Mean age was 48 ± 13 years (SD). There were 221 women (82.2%). Prevalences (n) of the respective subnormal IgG immunophenotypes were: IgG1 26.0% (70); IgG3 45.0% (121); and IgG1/IgG3 29.0% (78). Characteristics of patients in IgGSD subgroups are displayed in Table 1. Autoimmune conditions were more prevalent in patients with subnormal IgG1 than subnormal IgG3 ($p=0.0078$). Atopy was more prevalent in patients with subnormal IgG1 or subnormal IgG3 than in patients with subnormal IgG1/IgG3 ($p=0.0022$ and $p=0.0460$, respectively). Other allergy was more prevalent in patients with subnormal IgG1 than subnormal IgG1/IgG3 ($p=0.0021$).

Logistic regressions on subnormal IgG, subnormal IgG3, and subnormal IgG1/IgG3 subgroups using age, sex, autoimmune condition(s), atopy, and allergy as independent variables revealed a single significant (negative) association: male sex and subnormal IgG3 ($p=0.0108$; odds ratio 0.40 [95% confidence interval 0.20, 0.81]). Logistic regressions on HLA-B*35, B*40, B*62, A*02, B*44, and A*02, B*60 using age, sex, autoimmune condition(s), atopy, and other allergy as independent variables revealed no significant associations.

Frequencies of HLA-A and -B Types

HLA-A and -B type frequencies for three patient subgroups and controls are displayed in Table 2. The null hypothesis that there were no differences between the frequencies of types in subgroups of patients and controls in 2×4 χ^2 analyses was rejected for A*24, B*35, B*40, B*50, B*58, and B*62 (Table 1). Thus, we performed six corresponding 2×2 χ^2 analyses for each of these types to identify differences between the respective subgroup frequencies.

Frequencies of HLA types B*35 and B*40 were significantly higher in subnormal IgG1 patients than subnormal IgG3 patients (Table 3). The frequency of B*35 was significantly lower in subnormal IgG3 patients than controls. Frequencies of B*58 were significantly lower in subnormal IgG3 and subnormal IgG1/IgG3 than controls, although these differences were not significant after Bonferroni correction. Frequencies of B*62 were significantly lower in each of the three IgGSD subgroups than controls ($p<0.0001$, respectively) (Table 3).

Table 1 Characteristics of 269 adults with IgG subclass deficiency

Characteristic	Subnormal IgG1′ ($n=70$)	Subnormal IgG3 ($n=121$)	Subnormal IgG1/IgG3 ($n=78$)	Value of p[a]
Age, mean (1 SD)	50 ± 14	47 ± 13	50 ± 13	0.2844
Male, % (n)	20.0 (14)	12.4 (15)	21.8 (17)	0.1724
Autoimmune condition(s), % (n)	41.4 (29)	23.1 (28)	34.6 (27)	<0.0001
Atopy, % (n)	20.0 (14)	29.8 (36)	43.6 (34)	0.0075
Other allergy, % (n)	30.0 (21)	41.3 (50)	55.1 (43)	0.0081

[a]Mean age values were compared using a one-way analysis of variance test. Proportions were compared using χ^2 analysis (2×4 tables) to test the null hypothesis that HLA type frequencies in patient subgroups and controls did not differ significantly

Table 2 HLA-A and -B frequencies in IgG subclass deficiency patients and control subjects

Type	Subnormal IgG1 (140 chromosomes)	Subnormal IgG3 (242 chromosomes)	Subnormal IgG1/IgG3 (156 chromosomes)	Controls (n chromosomes)	Value of p[a]
A*24	0.0929 (13)	0.0826 (20)	0.0577 (9)	0.1304 (165/1265)	0.0396
B*14	0.0500 (7)	0.0579 (14)	0.0256 (4)	0.0639 (84/1314)	0.2703
B*35	0.1000 (14)	0.0248 (6)	0.0705 (11)	0.1406 (184/1309)	<0.0001
B*40	0.0571 (8)	0.0083 (2)	0.0321 (5)	0.0265 (35/1321)	0.0408
B*49	0.0071 (1)	0.0041 (1)	0.0256 (4)	0.0171 (21/1230)	0.2622
B*50	0.0071 (1)	0 (0)	0.0321 (5)	0.0140 (17/1212)	0.0463
B*58	0 (0)	0.0041 (1)	0 (0)	0.0256 (26)	0.0082
B*62	0.0143 (2)	0.0041 (1)	0 (0)	0.1285 (151)	<0.0001

[a]These values were obtained using χ^2 analysis (2×4 tables) to test the null hypothesis that HLA type frequencies in patient subgroups and controls did not differ significantly. Bonferroni $p < 0.0083$ ($< 0.05/6$) was defined as significant for these 2×2 χ^2 analyses

Table 3 Frequency comparisons for HLA-A and -B types

Type	Frequency comparisons	Value of p[a]
B*35	0.1000 subnormal IgG1 vs. 0.0248 subnormal IgG3	0.0015
	0.0705 subnormal IgG3 vs. 0.1406 controls	< 0.0001
B*40	0.0571 subnormal IgG1 vs. 0.0083 subnormal IgG3	0.0061
B*58	0.0041 subnormal IgG3 vs. 0.0256 controls	0.0382
	0 subnormal IgG1/IgG3 vs. 0.0256 controls	0.0431
B*62	0.0143 subnormal IgG1 vs. 0.1285 controls	< 0.0001
	0.0041 subnormal IgG3 vs. 0.1285 controls	< 0.0001
	0 subnormal IgG1/IgG3 vs. 0.1285 controls	< 0.0001

There were no significant subgroup differences associated with A*24. B*14, B*15, B*49, and B*50 (data not shown)

[a]Bonferroni $p < 0.0083$ ($< 0.05/6$) was defined as significant for these 2×2 χ^2 analyses

Frequencies of HLA-A and -B Haplotypes

Haplotype frequencies for three patient subgroups and controls are displayed in Table 4. The null hypothesis that there were no differences between the frequencies of HLA haplotypes in patients in three subgroups and controls in 2×4 χ^2 analyses was rejected for A*02, B*44, A*02, B*60, and A*32, B*14 (Table 4). Thus, we performed six corresponding 2×2 χ^2 analyses for each of these haplotypes to identify differences between the respective subgroup and control frequencies. These differences were significant: A*02, B*44 (0.1282 subnormal IgG1/IgG3 vs. 0.0632 controls; $p = 0.0024$); and A*02, B*60 (0.0 subnormal IgG3 vs. 0.0233 controls; $p = 0.0051$). Differences associated with A*32, B*14 were not significant (Table 4). HLA-A and -B

Table 4 HLA haplotype frequencies in IgG subclass deficiency patients and control subjects

Haplotype	Subnormal IgG1 (140 chromosomes)	Subnormal IgG3 (242 chromosomes)	Subnormal IgG1/IgG3 (156 chromosomes)	Controls (1502 chromosomes)	Value of p[a]
A*01, B*08	0.1286 (18)	0.0992 (24)	0.1026 (16)	0.0925 (139)	0.5876
A*02, B*44	0.0429 (6)	0.0826 (20)	0.1282 (20)	0.0632 (95)	0.0095[b]
A*02, B*60	0.0071 (1)	0 (0)	0 (0)	0.0233 (35)	0.0044[b]
A*03, B*07	0.0214 (3)	0.0702 (17)	0.0641 (10)	0.0546 (82)	0.2234
A*03, B*14	0.0143 (2)	0.0124 (3)	0.0064 (1)	0.0113 (17)	0.9249
A*03, B*44	0.0214 (3)	0.0083 (2)	0.0064 (1)	0.0126 (19)	0.6256
A*31, B*40	0.0071 (1)	0.0041 (1)	0.0064 (1)	0.0013 (2)	0.3462
A*32, B*14	0.0071 (1)	0.0041 (1)	0.0064 (1)	0 (0)	0.0288[b]

[a]These values were obtained using χ^2 analysis (2×4 tables) to test the null hypothesis that HLA haplotype frequencies in patient subgroups and controls did not differ significantly

[b]We performed six corresponding 2×2 χ^2 analyses for each of these haplotypes to identify differences between the respective subgroup and control frequencies. These differences were significant: A*02, B*44 (0.1282 subnormal IgG1/IgG3 vs. 0.0632 controls; $p = 0.0024$); and A*02, B*60 (0.0 subnormal IgG3 vs. 0.0233 controls; $p = 0.0051$). Differences associated with A*32, B*14 were not significant. Bonferroni $p < 0.0083$ ($< 0.05/6$) was defined as significant for these 2×2 χ^2 analyses

haplotype frequencies did not differ significantly across IgGSD patient subgroups.

Discussion

These results demonstrate that there are significant differences between the frequencies of HLA-A and -B types in immunophenotype subgroups of adult patients with IgGSD. Frequencies of B*35 and B*40 were significantly higher in subnormal IgG1 patients than subnormal IgG3 patients. In contrast, we detected no significant differences in frequencies of A*24, B*58, and B*62 between subnormal IgG1, subnormal IgG3, and subnormal IgG1/IgG3 patients.

HLA-A and -B type and haplotype frequencies differed significantly between IgGSD subgroups and controls, consistent with previous observations (Barton et al. 2003b). The frequency of B*35 was significantly lower in subnormal IgG3 patients than controls. The frequency of B*62 was significantly lower in IgGSD subgroups than controls. The frequency of A*02, B*44 was significantly higher in patients with subnormal IgG1/IgG3 than controls, whereas the frequency of A*02, B*60 was significantly lower in patients with subnormal IgG3 than controls. HLA-A and -B haplotype frequencies did not differ significantly across IgGSD subgroups.

The frequency of HLA-A*02, B*44 was significantly higher in the present subnormal IgG1/IgG3 patients than controls. The ancestry of non-Hispanic whites who reside in central Alabama is predominantly British Isles nations and other countries of Western Europe (Acton et al. 2004; Barton et al. 2004). In the present controls, the frequency of A*02, B*44 is consistent with that of controls in the corresponding geographic regions of Europe (Finch et al. 1997; Middleton et al. 2000; Sasazuki et al. 1992; Schipper et al. 1996). IgGSD or CVID segregated with A*02, B*44 in 8 of 26 Alabama kinships (31%) (Barton et al. 2003b). In contrast, the frequency of A*02 was significantly lower in the present IgGSD immunophenotype subgroups than controls. These observations suggest that IgGSD immunophenotypes are more closely associated with B*44 than A*02.

In this study, there was no significant association of HLA-A*03,B*07 with subnormal IgG immunophenotype subgroups, although IgGSD or CVID segregated with A*03, B*07 in 2 of 26 Alabama kinships (8%) (Barton et al. 2003b). Subnormal IgG3 occurs in 30% of hemochromatosis probands homozygous for *HFE* p.C282Y (chromosome 6p21.3), most of whom did not report frequent or severe respiratory tract infection (Barton et al. 2003a). Many hemochromatosis probands inherit part or all of the ancestral hemochromatosis haplotype that includes A*03, B*07, D6S105(8), and *HFE* p.C282Y (Barton et al. 1996, 2005). These observations suggest that a locus linked to A*03,B*07 in some kinships decreases IgG or IgG subclass levels, especially IgG3.

HLA-A*03, B*07 was associated with higher IgE levels in another study of non-Hispanic white Alabama adults with IgGSD, after adjustment for other factors (Barton et al. 2004). In the same study, HLA-A*29, B*44 was observed only in IgGSD patients who had normal or elevated IgE (Barton et al. 2017). IgE levels were associated with HLA-A, HLA-G, and HLA-DQA2 in a Framingham genome-wide study (Granada et al. 2012). Thus, determinants of IgE levels are linked to the MHC in adults with and without IgGSD diagnoses.

In another study, HLA-A and -B type and haplotype frequencies in unrelated Alabama non-Hispanic white adult patients with CVID or IgGSD ($n=34$ and $n=398$, respectively) did not differ significantly (Barton et al. 2014). These observations are consistent with previous observations that CVID and IgGSD immunophenotypes segregate with the same HLA-A and -B haplotypes in some kinships (Barton et al. 2003b). In another study, only one of 63 adults with CVID characterized by MHC class I types (including HLA-B*08 and -B*44) and class II susceptibility types had *TACI* p.A181E (exon 4) (chromosome 7q21.3) (Waldrep et al. 2009) typically associated with childhood-onset CVID (Castigli et al. 2005; Salzer et al. 2005). Thus, CVID in adults is more closely associated with the MHC than *TACI* p.A181E.

Clinical characteristics of the present patients include mean age 48 years and predominance of women (82%), consistent with previous reports (Abrahamian et al. 2010; Barton et al. 2003b, 2014). Subnormal IgG3 alone accounted for 45% of the present patients. Autoimmune conditions were more prevalent in patients with subnormal IgG1 than subnormal IgG3. Atopy was more prevalent in patients with subnormal IgG1 or subnormal IgG3 than in patients with subnormal IgG1/IgG3. Other allergy was more prevalent in patients with subnormal IgG1 than subnormal IgG1/IgG3. Logistic regressions on subnormal IgG, subnormal IgG3, and subnormal IgG1/IgG3 subgroups using age, sex, autoimmune condition(s), atopy, and other allergy as independent variables revealed a single significant (negative) association: male sex and subnormal IgG3. Logistic regressions on HLA-B*35, B*40, B*62, A*02, B*44, and A*02, B*60 using age, sex, autoimmune condition(s), atopy, and other allergy as independent variables revealed no significant associations, after adjustment for other variables.

Strengths of this study include large sample sizes of IgGSD patient (70 subnormal IgG1; 121 subnormal IgG3; 78 subnormal IgG1/IgG3) and control subjects (1321 for types; 751 for haplotypes) and stringent statistical criteria. Our HLA-A and -B control data were obtained from non-Hispanic whites residing in the same geographic area as the present IgGSD patients. HLA types and haplotypes differ across populations (Grubic et al. 2016; Mack et al. 2009).

Thus, significant HLA types and haplotype associations in adults with IgGSD in other geographic regions may differ from those of the present patients. Limitations of this study include the possibility that molecular subtyping could reveal heterogeneity within HLA-A and -B types and haplotypes we detected (Song et al. 2013) and decreased statistical power to detect significant differences in HLA type or haplotype prevalence between small IgGSD subgroups and comparator groups. The present results do not exclude the possibility that HLA-A and -B types or haplotypes not analyzed herein are also associated with IgGSD in some kinships. Determining the efficacy of IgG replacement therapy or treatment of autoimmune conditions(s), atopy, or other allergy in the present men or women according to IgGSD subgroup or performing family studies and MHC class II typing were beyond the scope of the present study.

Conclusions

We conclude that HLA-B*35 and -B*40 frequencies differ significantly between some IgGSD subgroups. B*62, A*02,B*44, and A*02,B*60 frequencies differ significantly between some IgGSD subgroups and controls.

Acknowledgements This work was supported in part by Southern Iron Disorders Center.

Author contributions All authors contributed equally to this work. JCB and LFB conceived the study. JaCB and JCB compiled patient data and performed statistical analyses. RTA contributed control data. JCB drafted the manuscript. All authors contributed to the manuscript and approved its final form.

Compliance with ethical standards

Conflicts of interests None of the authors has a conflict of interest to report.

Ethical approval This work was performed according to the principles of the Declaration of Helsinki (World Medical Association 2013). Western Institutional Review Board provided an exemption under 45 CFR 46.101(b) (4) pertinent to this study on 18 October 2018 (submission 2535878-44170911; 2 October 2018). Obtaining informed consent was not required because this study involved retrospective chart review and analyses of observations recorded in routine medical care and does not include personal identifier information.

References

Abrahamian F, Agrawal S, Gupta S (2010) Immunological and clinical profile of adult patients with selective immunoglobulin subclass deficiency: response to intravenous immunoglobulin therapy. Clin Exp Immunol 159:344–350

Acton RT, Harman L, Go RC et al (1993) Comparison of HLA phenotypes among African Americans from Alabama, Maryland, and North Carolina. Transplant Proc 25:2404–2407

Acton RT, Barton EH, Hollowell WW et al (2004) Ancestry reported by white adults with cutaneous melanoma and control subjects in central Alabama. BMC Cance 4:47

Barton JC, Harmon L, Rivers C et al (1996) Hemochromatosis: association of severity of iron overload with genetic markers. Blood Cells Mol Dis 22:195–204

Barton JC, Bertoli LF, Acton RT (2003a) Common variable immunodeficiency and IgG subclass deficiency in central Alabama hemochromatosis probands homozygous for *HFE* C282Y. Blood Cells Mol Dis 31:102–111

Barton JC, Bertoli LF, Acton RT (2003b) HLA-A and -B alleles and haplotypes in 240 index patients with common variable immunodeficiency and selective IgG subclass deficiency in central Alabama. BMC Med Genet 4:3

Barton EH, Barton JC, Hollowell WW et al (2004) Countries of ancestry reported by hemochromatosis probands and control subjects in central Alabama. Ethn Dis 14:73–81

Barton JC, Wiener HW, Acton RT et al (2005) HLA haplotype A*03-B*07 in hemochromatosis probands with *HFE* C282Y homozygosity: frequency disparity in men and women and lack of association with severity of iron overload. Blood Cells Mol Dis 34:38–47

Barton JC, Bertoli LF, Barton JC (2014) Comparisons of CVID and IgGSD: referring physicians, autoimmune conditions, pneumovax reactivity, immunoglobulin levels, blood lymphocyte subsets, and HLA-A and -B typing in 432 adult index patients. J Immunol Res 2014:542706

Barton JC, Barton JC, Bertoli LF (2017) Hypogammaglobulinemia E in 216 adults with IgG subclass deficiency and respiratory tract infections. Ann Allergy Asthma Immunol 119:292–294

Boucher K, Mori M, Milford E et al (1998) Estimation of HLA-A, -B, -DR haplotype frequencies in five racial groups represented in the NMDP donor file. In: Gjertson DW, Terasaki PI (eds) HLA 1998. American Society for Histocompatibility and Immunogenetics, Lenexa, pp 57–78

Bousfiha A, Jeddane L, Picard C et al (2018) The 2017 IUIS phenotypic classification for primary immunodeficiencies. J Clin Immunol 38:129–143

Castigli E, Wilson SA, Garibyan L et al (2005) *TACI* is mutant in common variable immunodeficiency and IgA deficiency. Nat Genet 37:829–834

Finch T, Lawlor E, Borton M et al (1997) Distribution of HLA-A, B and DR genes and haplotypes in the Irish population. Exp Clin Immunogenet 14:250–263

Granada M, Wilk JB, Tuzova M et al (2012) A genome-wide association study of plasma total IgE concentrations in the Framingham Heart Study. J Allergy Clin Immunol 129:840–845.e21

Grubic Z, Maskalan M, Svilicic D et al (2016) Determination of HLA-A, -B, and -DRB1 allele and haplotype frequencies in the Croatian population based on a family study. Arch Immunol Ther Exp 64(Suppl 1):83–88

Lacombe C, Aucouturier P, Preud'homme JL (1997) Selective IgG1 deficiency. Clin Immunol Immunopathol 84:194–201

Mack SJ, Tu B, Lazaro A et al (2009) HLA-A, -B, -C, and -DRB1 allele and haplotype frequencies distinguish Eastern European Americans from the general European American population. Tissue Antigens 73:17–32

Middleton D, Williams F, Hamill MA et al (2000) Frequency of HLA-B alleles in a Caucasoid population determined by a two-stage PCR-SSOP typing strategy. Hum Immunol 61:1285–1297

Oxelius VA, Hanson LA, Björkander J et al (1986) IgG3 deficiency: common in obstructive lung disease. Hereditary in families with

immunodeficiency and autoimmune disease. Monogr Allergy 20:106–115

Salzer U, Chapel HM, Webster AD et al (2005) Mutations in *TNFRSF13B* encoding TACI are associated with common variable immunodeficiency in humans. Nat Genet 37:820–828

Sasazuki T, Tsuji K, Aizawa M (1992) HLA 1991: Proceedings of the Eleventh International Histocompatibility Workshop and Conference, held in Yokohama, Japan, 6–13 November, 1991. Oxford University Press, New York

Schipper RF, Schreuder GM, D'Amaro J et al (1996) HLA gene and haplotype frequencies in Dutch blood donors. Tissue Antigens 48:562–574

Schroeder HW Jr, Schroeder HW III, Sheikh SM (2004) The complex genetics of common variable immunodeficiency. J Investig Med 52:90–103

Song S, Han M, Zhang H et al (2013) Full screening and accurate subtyping of HLA-A*02 alleles through group-specific amplification and mono-allelic sequencing. Cell Mol Immunol 10:490–496

Vorechovsky I, Cullen M, Carrington M et al (2000) Fine mapping of *IGAD1* in IgA deficiency and common variable immunodeficiency: identification and characterization of haplotypes shared by affected members of 101 multiple-case families. J Immunol 164:4408–4416

Waldrep ML, Zhuang Y, Schroeder HW Jr (2009) Analysis of *TACI* mutations in CVID & RESPI patients who have inherited HLA B*44 or HLA*B8. BMC Med Genet 10:100

World Medical Association (2013) Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 310:2191–2194