

Genome-wide Association Study Identifies *HLA-DPB1* as a Significant Risk Factor for Severe Aplastic Anemia

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Severe aplastic anemia (SAA) is a rare disorder characterized by hypoplastic bone marrow and progressive pancytopenia. The etiology of acquired SAA is not understood but is likely related to abnormal immune responses and environmental exposures. We conducted a genome-wide association study of individuals with SAA genetically matched to healthy controls in discovery (359 cases, 1,396 controls) and validation sets (175 cases, 1,059 controls). Combined analyses identified linked SNPs in distinct blocks within the major histocompatibility complex on 6p21. The top SNP encodes p.Met76Val in the P4 binding pocket of the HLA class II gene *HLA-DPB1* (rs1042151A>G, odds ratio [OR] 1.75, 95% confidence interval [CI] 1.50–2.03, $p = 1.94 \times 10^{-13}$) and was associated with HLA-DP cell surface expression in healthy individuals ($p = 2.04 \times 10^{-6}$). Phylogenetic analyses indicate that Val76 is not monophyletic and likely occurs in conjunction with different HLA-DP binding groove conformations. Imputation of *HLA-DPB1* alleles revealed increased risk of SAA associated with Val76-encoding alleles *DPB1*03:01*, (OR 1.66, $p = 1.52 \times 10^{-7}$), *DPB1*10:01* (OR 2.12, $p = 0.0003$), and *DPB1*01:01* (OR 1.60, $p = 0.0008$). A second SNP near *HLA-B*, rs28367832G>A, reached genome-wide significance (OR 1.49, 95% CI 1.22–1.78, $p = 7.27 \times 10^{-9}$) in combined analyses; the association remained significant after excluding cases with clonal copy-neutral loss-of-heterozygosity affecting class I HLA genes (8.6% of cases and 0% of controls). SNPs in the HLA class II gene *HLA-DPB1* and possibly class I (*HLA-B*) are associated with SAA. The replacement of Met76 to Val76 in certain *HLA-DPB1* alleles might influence risk of SAA through mechanisms involving DP peptide binding specificity, expression, and/or other factors affecting DP function.

Aplastic anemia is a rare heterogeneous disorder characterized by progressive pancytopenia and bone marrow hypoplasia.^{1,2} An estimated 500 to 1,000 cases of severe aplastic anemia (SAA) occur in the United States each year.³ It occurs at all ages, and its etiology is not well understood. Acquired aplastic anemia is often immune-mediated and may occur after hepatitis or with certain drug or environmental exposures.^{1,2} A limited number of studies with small sample sizes have evaluated the potential role(s) of common single-nucleotide polymorphisms (SNPs) in aplastic anemia etiology.^{3–8} For example, a study of 170 cases and 222 controls from Pakistan found two *FAS* and two *FASL* SNPs associated with SAA.⁹ Another study evaluated four *FOXP3* SNPs in 94 aplastic anemia cases and 195 controls from Korea, and this study suggested an association with disease and response to

immunosuppressive therapy (IST).¹⁰ Aplastic anemia also occurs in individuals with rare inherited bone marrow failure syndromes caused predominantly by pathogenic germline variants in DNA-repair, ribosomal, or telomere-biology genes.¹¹ Somatic copy neutral loss of heterozygosity in chromosome 6 (chr6-CNLOH) encompassing the HLA-class I locus has been previously described in acquired SAA.^{12,13} Hematopoietic stem cells with chr6-CNLOH are thought to escape the cytotoxic T cell immune attack by deleting *HLA* alleles involved in auto-antigen presentation.¹⁴

The cytopenias in aplastic anemia may progress to a life-threatening severe disease, and affected individuals are at high risk of progression to myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML).¹⁵ In acquired SAA, allogeneic hematopoietic cell transplantation (HCT)

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is the first line of therapy for young individuals with a matched sibling donor, while IST, followed by HCT in non-responders, is recommended for all others.^{2,16,17}

We conducted a genome-wide association study (GWAS) of acquired SAA to agnostically evaluate the contribution of common germline SNPs to the etiology of this highly morbid disease. Individuals with SAA ($n = 895$) were identified from the Center for International Blood and Marrow Transplant Research (CIBMTR) database, and biorepository and germline DNA were collected prior to HCT between 1989 and 2015. CIBMTR is a research collaboration between the National Marrow Donor Program (NMDP) “Be The Match Registry” and the Medical College of Wisconsin; CIBMTR has more than 450 reporting HCT centers, and it represents one of the world’s largest databases and research repositories for HCT research. All individuals provided informed consent, and the use of the samples was approved by the NMDP Institutional Review Board (IRB-1991-0002). We excluded 93 individuals with inherited bone marrow failure based on clinical diagnoses reported to CIBMTR. Genotyping was conducted using the Illumina Infinium OmniExpress BeadChip array at the Cancer Genomics Research Laboratory (CGR) in the Division of Cancer Epidemiology and Genetics (DCEG) at the National Cancer Institute (NCI). The controls were derived from cancer-free subjects drawn from two cohort studies (the Prostate, Lung, Colon and Ovarian Cancer Prevention Trial [PLCO]¹⁸ and the American Cancer Society Cancer Prevention Study II [CPSII]¹⁹ previously scanned on the Illumina Omni 2.5M SNP microarray) as well as four other USA-based studies (Mayo Clinic Case-Control Study of Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia [MAYO];²⁰ NCI Surveillance, Epidemiology, and End Results Non-Hodgkin Lymphoma [NHL] Case-Control Study [NCI-SEER];^{21,22} Women’s Health Initiative [WHI];²³ and the Population-based Case-Control Study in Connecticut Women [YALE]²⁴) which were also scanned on the Infinium OmniExpress chip. In order to reduce the effect of population stratification, population substructure analyses using STRUCTURE and principal components analyses (PCA) were used to limit the study inclusion to individuals of European ancestry. The final analyses included 534 acquired SAA cases (359 in a discovery set and 175 in a validation set) and 2,455 controls (1,396 in the discovery set and 1,059 in the validation set). Individuals included in the validation set were independent from those in the discovery set, and all study participants were genetically proven to be unrelated. Additional details are available in [Supplementary Methods, Table S1, and Figure S1A and S1B](#).

The median age at HCT of participants with SAA was 21 years (range = 1–77), 56% were male, and the median time between SAA diagnosis and HCT was 11 months (range = 0.1–318 months). The majority of SAA-affected individuals (87%) received an unrelated donor HCT; all individuals who received a matched sibling HCT were part of the validation cohort ([Table S2](#)).

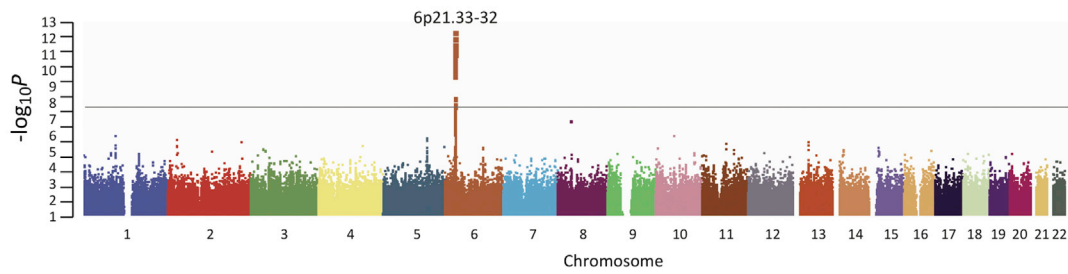
A series of strong association signals were identified across the human leukocyte antigen (*HLA*) genes encoded in the major histocompatibility complex (MHC) on chromosome 6p21 ([Figure 1](#)). Notably, 12 genotyped SNPs achieved genome-wide significance (pooled- $p < 3.46 \times 10^{-8}$; odds ratios (ORs) ranging from 1.62–1.82) ([Table 1, Figure 1, and Tables S3 and S4](#)). SNP associations with HLA class II genes were evident in two distinct regions. The top SNP, rs1042151 (pooled- $p = 1.94 \times 10^{-13}$), was in linkage disequilibrium with 18 other SNPs ($R^2 > 0.5$, chr6:33,048,661–33,064,605) that were in or near *HLA-DPB1* and *HLA-DPB2*. A second locus in HLA class II, containing 13 linked SNPs ($R^2 > 0.9$) in or near *HLA-DQA2* and *HLA-DQB2* (chr6:32,707,295–32,727,905) approached genome-wide significance (top SNP, rs9276370 T>G, pooled- $p = 5.01 \times 10^{-7}$, OR 1.41, 95% confidence interval [CI] 1.23–1.62).

The top SNP associated with SAA, rs1042151 A>G (combined OR 1.75, 95% CI 1.50–2.03, $p = 1.94 \times 10^{-13}$), encodes a nonsynonymous change of p.Met76Val (RefSeq accession number NP_002112.3) in the β -1 domain of HLA-DPB1. While dbSNP annotates rs1042151 as p.Met105Val because it includes the first 30 residues of the leader peptide, p.Met76Val is the appropriate numbering according to the WHO Nomenclature Committee for Factors of the HLA System (IPD-IMGT/HLA database, see [Web Resources](#)).²⁵ rs1042151 A>G has a minor allele frequency (MAF) of 17.5% in the non-Finnish European, 8.9% in the East Asian, and 37.6% in the African/African American gnomAD populations.²⁶ In our study participants, the MAF of rs1042151 A>G (p.Met76Val) was 18.8% in controls and 29.4% in the individuals with SAA.

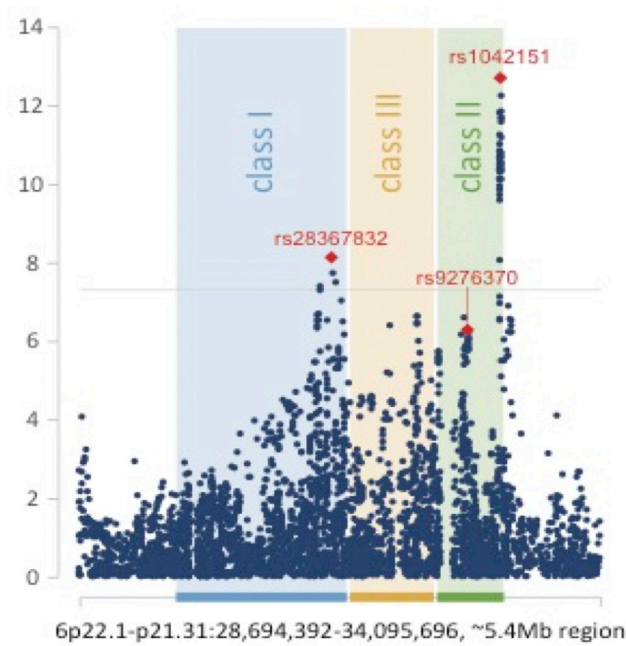
DPB1 comprises the beta strand of the HLA-DP protein heterodimer located on the cell surface of antigen-presenting cells.²⁷ Genetic variation in *HLA-DPB1* has been associated with several autoimmune diseases, including rheumatoid arthritis, Grave’s disease, and multiple sclerosis.^{28–30} Specifically, the p.Met76Val amino acid substitution caused by the rs1042151 G variant has previously been associated with risk of aspirin-exacerbated respiratory disease.³¹ Residue 76 is involved in peptide binding, forming part of the P4 pocket, and the p.Met76Val substitution is likely to influence the binding repertoire.³² Two other SNPs (rs9277534 and rs9277535), located in the 3’ UTR of *HLA-DPB1*, approximately 6 kilobases (kb) away from rs1042151 but not genotyped in our study ([Figure 1C](#)), have been previously associated with expression of *HLA-DPB1*, risk and persistence of hepatitis B virus (HBV) infection, and risk of graft-versus-host disease in HCT recipients.^{33–36}

To evaluate the possible contribution of HLA-DP cell surface expression related to the association between the rs1042151 A>G genotypes and risk of SAA, we stained CD19+ cells isolated from peripheral blood drawn from 175 healthy donors with the HLA-DP-specific monoclonal antibodies B7/21 and BrafB6^{37,38} as described previously³³ (see [Supplementary Methods in Supplemental Data](#)), and

A



B



C

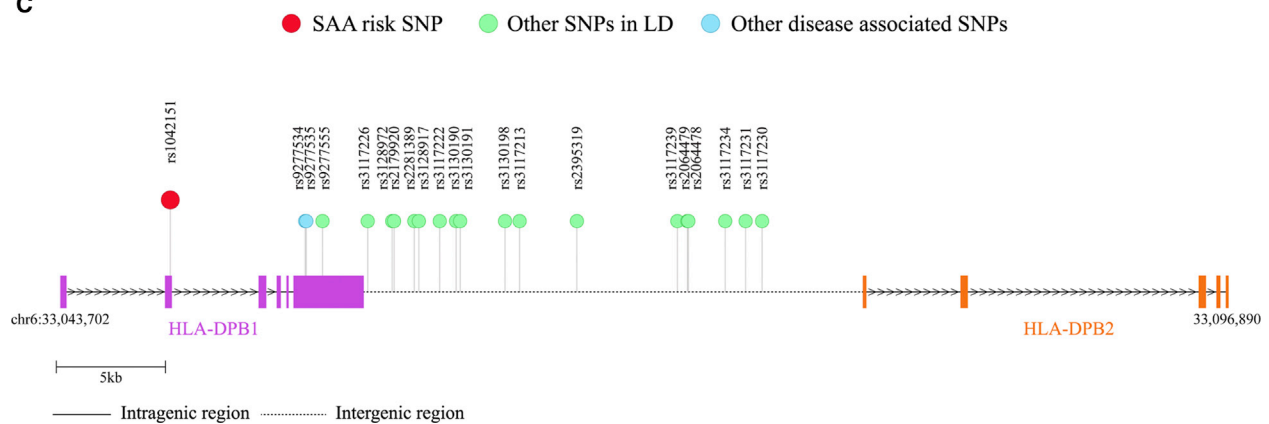


Figure 1. Genomic Locations of Single-Nucleotide Polymorphisms Associated with Severe Aplastic Anemia

(A) Manhattan plot of genome-wide association result for combined discovery and validation sets of European ancestry severe aplastic anemia cases and genomically matched controls.

(B) A portion of the Manhattan plot of the major histocompatibility complex (MHC) genomic region showing locations of SNPs in human leukocyte antigen (*HLA*) genes by HLA class.

(C) Schematic of HLA-DPB1 with SNPs of interest noted.

Table 1. Summary of combined association results for severe aplastic anemia cases and controls

dbSNP	Gene	Locus	Position	Variant	Stage	Cases	Controls	<i>p</i>	OR (95% CI)
rs1042151									
rs1042151	<i>HLA-DPB1</i>	6p21	chr6: 33048661	A > G	Discovery	356	1396	1.68E-10	1.82 (1.51-2.20)
rs1042151	<i>HLA-DPB1</i>	6p21	chr6: 33048661	A > G	Validation	175	1059	0.0015	1.52 (1.17-1.97)
rs1042151	<i>HLA-DPB1</i>	6p21	chr6: 33048661	A > G	Combined	531	2453	1.94E-13	1.75 (1.50-2.03)
rs28367832									
rs28367832	<i>HLA-B</i>	6p21	chr6: 31305731	G > A	Discovery	355	1388	3.05E-06	1.49 (1.27-1.79)
rs28367832	<i>HLA-B</i>	6p21	chr6: 31305731	rs28367832	Validation	173	1048	0.001	1.46 (1.16-1.84)
rs28367832	<i>HLA-B</i>	6p21	chr6: 31305731	rs28367832	Combined	528	2434	7.27E-09	1.49 (1.22-1.78)

SNPs shown are those with combined validation and discovery $p < 10^{-8}$

we compared the median fluorescence intensity across genotypes. The risk variant, G, was associated with a significant dose-response increase in HLA-DP cell surface expression on the CD19+ cell surface ($p = 2.04 \times 10^{-6}$) (Figure 2); this association suggests that higher cell surface expression of HLA-DP may contribute to SAA risk. However, because of the strong linkage disequilibrium across this region, it is likely that the identified risk SNP is not solely related to cell surface expression of DP. A variant previously associated with HLA-DP cell surface expression, rs9277534 A>G,³³ is also associated with SAA in our study (OR 1.64, $p = 8.2 \times 10^{-8}$). Additionally, rs1042151 is not the strongest HLA-DP eQTL, but based on GTExPortal (data accessed November 2019, see Web Resources),³⁹ it is associated with the transcript level of HLA-DPB1 in transformed fibroblasts with a p value of 1×10^{-9} .

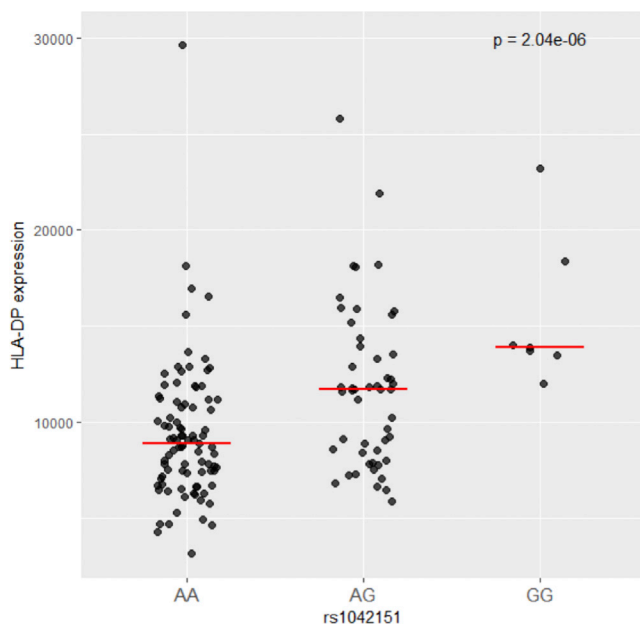


Figure 2. Cell Surface Expression of HLA-DP is Associated with rs1042151 Genotype

The cell surface expression levels of specific HLA alleles were determined in healthy individuals and plotted based on their rs1042151 genotype (see Online Methods).

To further understand the role of HLA-DPB1 in SAA etiology, we constructed a phylogenetic tree of *HLA-DPB1* through the use of the neighbor-joining method based on Kimura 2-parameter distances as implemented in MEGA7 26 to visualize the distribution pattern of HLA-DP sequences as marked by Val or Met at position 76. Our results, based on both coding regions (Figure 3) and full-length gene sequences (not shown), indicate that 76Val is not monophyletic and is found in multiple distinct clades of alleles which are likely to recognize different peptide binding motifs. We then used the HIBAG software⁴⁰ to impute *HLA-DPB1* alleles for SAA cases and controls; comparisons with high-resolution clinical typing were available for 401 individuals with SAA and showed 92.7% concordance. SAA excess risk was associated with the *HLA-DPB1* alleles containing the rs1042151 Val76 variant: *DPB1*03:01* (OR 1.66, $p = 1.52 \times 10^{-7}$), *DPB1*10:01* (OR 2.12, $p = 0.0003$), and *DPB1*01:01* (OR 1.60, $p = 0.0008$). On the other hand, an inverse association was present between the Met76-encoding alleles *DPB1*04:01* (OR = 0.78, $p = 0.01$) and *DPB1*04:02* (OR = 0.75, $p = 0.02$) (Table S5). Logistic regression analysis based upon the number of Val76 residues shows an additive effect; compared to zero copies of Val76-encoding alleles, two copies are associated with higher SAA risk (OR 2.32, $p = 3.2 \times 10^{-6}$) than one copy is (OR = 1.98, $p = 1.2 \times 10^{-11}$). Peptide repertoire specificity is not determined by the P4 pocket alone, and the phylogenetic distribution of Val76 (i.e., interspersed with Met76-encoding alleles) indicates that Val76 occurs on wide variety of antigen-binding groove configurations. Taken together, the data suggest that the p.Met76Val change might influence risk of SAA through a mechanism involving DP peptide binding specificity, *HLA-DPB1* cell surface expression levels, and/or other factors affecting DP function. For example, the P4 pocket of DRB1 has been shown to facilitate immunogenic metabolite binding,⁴¹ a scenario that may hold true for DP, as well, resulting in risk of immune-mediated diseases such as SAA.

One SNP in HLA class I, rs28367832 G>A, reached genome-wide statistical significance only in the combined analysis (pooled- $p = 7.27 \times 10^{-9}$, OR 1.49, 95% CI

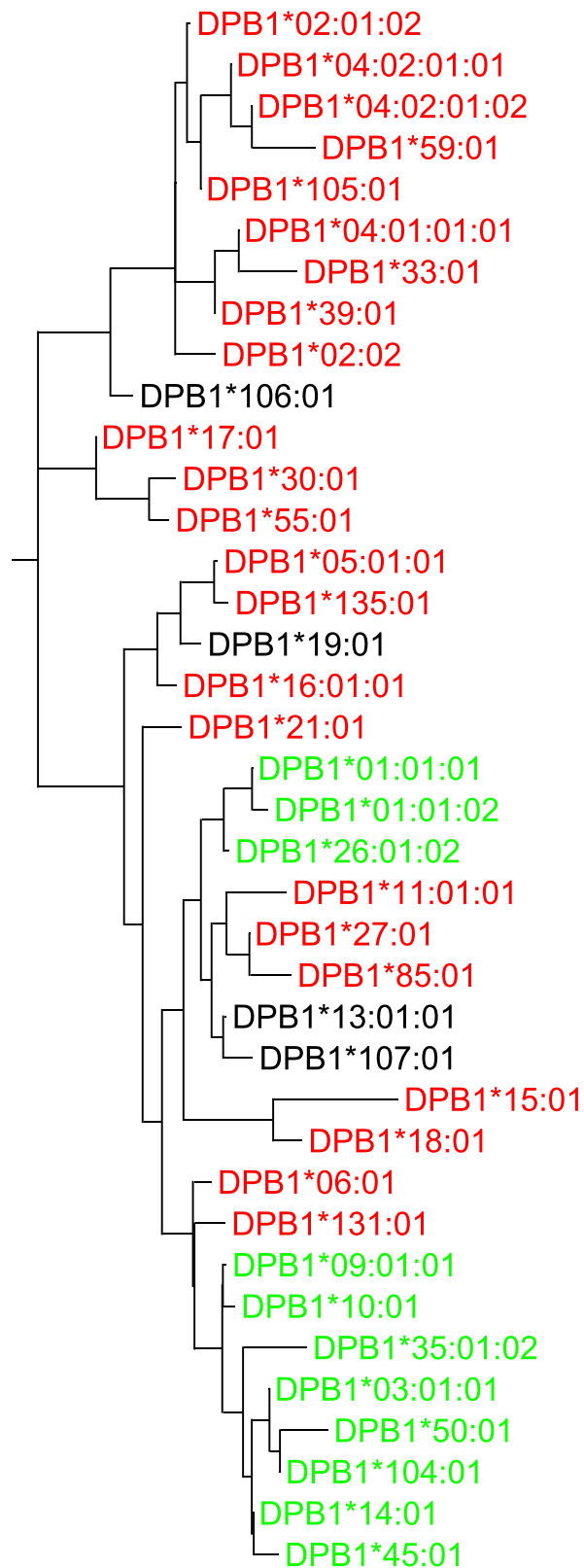


Figure 3. Phylogenetic Tree of Coding Regions of HLA-DPB1
The HLA-DPB1 alleles are color coded according to the amino acid at residue 76 as follows: red, methionine, M; black, isoleucine, I; green, valine, V. The neighbor-joining tree is based on Kimura's 2-parameter distances for the entire 777 base pair coding region.

1.22–1.78) (Table 1, Table S4). rs28367832 G>A is 15.9 kb telomeric of *HLA-B* and a common noncoding SNP with a MAF of 57.7% in the SAA cases compared with 47.5% of control in the combined analyses. This SNP was not in linkage equilibrium with our study top SNP rs1042151 ($R^2 = 0.0099$). The association remained statistically significant in conditional analysis (p for rs28367832 = 1.82×10^{-8}). Because rs28367832 G>A is located in the region possibly affected by chr6-CNLOH, we calculated the Log R ratio (LRR) and B allele frequency (BAF) in order to assess somatic chr6-CNLOH in our samples (see Figure S2 and Supplementary Methods in Supplemental Data). There were 46 individuals with SAA (8.6%) with somatic chr6-CNLOH affecting class I HLA genes (Figure S2). Next-generation sequencing of the HLA genes performed with the MIA FORA NGS kit (Immucor) confirmed these SNP array results (see Figure S3 and Supplementary Methods in Supplemental Data). Somatic chr6-CNLOH appears to be specific to SAA; none of the 2,453 controls in this study nor of 73 the individuals with Fanconi anemia in our prior work had this alteration.⁴² Persons with SAA and somatic chr6-CNLOH were more likely to carry the rs28367832 AA genotype, and this result suggests loss of the common rs28367832 G variant (56.1% versus 32.9%, $p = 0.003$). However, exclusion of SAA individuals with somatic chr6-CNLOH from the analyses did not change the germline SNP association results (data not shown).

Several additional non-HLA loci did not reach the accepted statistical genome-wide association threshold of $p < 5 \times 10^{-8}$ (Table S6). An inverse association was present between SAA and the A allele of rs7845664 on chromosome 8p11.21, a multi-allelic SNP within the *ZMAT4* gene (OR 0.70, $p = 3.07 \times 10^{-7}$). There are little data on *ZMAT4* function, but one study previously identified copy number variants (CNVs) and gene expression changes in hematologic malignancies.⁴³ We did not identify CNVs in this region in our cohort of individuals with SAA (data not shown). Four additional non-HLA loci contained SNPs with borderline p values that may warrant follow-up in a larger study: rs12753487 (OR 1.75, pooled- $p = 2.85 \times 10^{-6}$), rs1731229 (OR 0.72, pooled- $p = 5.26 \times 10^{-6}$), rs4345355 (OR 1.54, pooled- $p = 5.29 \times 10^{-6}$), and rs9533317 (OR 1.4, pooled- $p = 7.87 \times 10^{-6}$). Of these, the intragenic rs9533317 SNP is located within *EPSTI1*, a gene with functions in epithelial stromal interactions.⁴⁴ These results may warrant follow-up because they may identify a set of individuals in whom SAA is not immune mediated.

This GWAS focused on individuals with SAA who required HCT. Our data suggest that idiopathic SAA may be due, in part, to germline susceptibility due to common variants in HLA class II, and possibly class I. It remains possible that some of the identified loci are associated with disease severity or lack of response to IST rather than with the etiology of SAA because all cases required HCT for their disease. However, the agreement between results from the discovery (all received unrelated donor HCT,

mostly after failing IST) and validation sets (40% received HCT from matched sibling as a first line of therapy and did not receive IST) argues against results being associated primarily with IST response. The small sample size in this study is small in the scope of GWAS but very large in the context of a rare disease. We limited our analysis to individuals of European ancestry; analyses in populations of other racial backgrounds are of interest, particularly because SAA is more common in Asians.⁴⁵

In summary, this GWAS of acquired SAA identified a strong association at rs1042151 A>G in the *HLA-DPB1*. The rs1042151 G allele encoding HLA-DPB1 Val76 occurs on three distinct alleles, *DPB1*03:01*, *DPB1*10:01*, and *DPB1*01:01*, and this suggests that alteration of HLA-DP peptide binding specificity, as well as changes in HLA-DP cell surface expression and/or other factors affecting HLA-DP function, contribute to SAA etiology. A prospective study including the full spectrum of disease severity is warranted in order to further understand the association of HLA germline SNPs in SAA etiology.

Accession Numbers

GWAS data will be available through the dbGAP-controlled access database accession number dbGaP: phs001710.v1.p1.

Supplemental Data

Supplemental Data can be found online at <https://doi.org/10.1016/j.ajhg.2020.01.004>.

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Declaration of Interests

The authors declare no competing interests.

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Web Resources

GTExPortal, <https://www.gtexportal.org/home/gene/DPB1>
Immuno Polymorphism Database—International ImMunoGeneTics project HLA (IPD-IMGT/HLA), <https://www.ebi.ac.uk/ipd/imgt/hla/>
National Organization for Rare Disorders (NORD) Rare Disease Information on Acquired Aplastic Anemia, <https://rarediseases.org/rare-diseases/acquired-aplastic-anemia/>

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