Received: 5 August 2024 | Accepted: 7 October 2024

DOI: 10.1111/bjh.19838

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

SHORT REPORT

Platelets, Thrombosis and Haemostasis

Association of human leucocyte antigen loci with vaccine-induced immune thrombotic thrombocytopenia: Potential role of the interaction between platelet factor 4-derived peptides and MHC-II

Eleonora Petito[1] | Loredana Bury[1] | Lilian Antunes Heck[2] | Brooke Sadler[2] | Erica De Candia[3] | Gian Marco Podda[4] | Anna Falanga[5] | Lucia Stefanini[6] | Andrea Boccatonda[7] | Patrizia Sciancalepore[8] | Igor Florio[9] | Egidio Imbalzano[10] | Rossella Marcucci[11] | Patrizia Noris[12,13] | Marta Panella[14] | Rita Carlotta Santoro[15] | Maria Costanza Turi[16] | Gaetano Vaudo[17] | Jorge Di Paola[2] | Matthew T. Rondina[18,19,20,21] | Paolo Gresele[1]

Correspondence
Paolo Gresele, Section of Internal and Cardiovascular Medicine, Department of Medicine and Surgery, University of Perugia, Centro Didattico – Edificio B piano 1, Strada vicinale Via delle Corse, Perugia 06132, Italy.
Email: paolo.gresele@unipg.it

Funding information
Fondazione Umberto Veronesi

Summary
No risk factors have been identified for vaccine-induced immune thrombotic thrombocytopenia (VITT) so far. The aim of this study was to identify human leucocyte antigen (HLA) alleles potentially associated with VITT susceptibility. Specific HLA class II alleles were detected with significantly higher frequency in VITT patients compared with Italian controls: *DPB1*17:01*, *DQA1*05:01*, and *DRB1*11:04*. In silico analysis revealed increased affinity of *DRB1*11:04* for a platelet factor 4 (PF4)-derived peptide, ITSLEVIKA, that contains two amino acids present in the specific binding site of anti-PF4 antibodies from VITT patients. Our findings show for the first time a genetic predisposition to developing anti-PF4 antibodies in response to Ad-vector vaccines.

KEYWORDS
HLA, PF4, VITT

INTRODUCTION

Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a rare, but life-threatening autoimmune complication of adenoviral (Ad) vector COVID-19 vaccines due to the generation of anti-platelet factor 4 (PF4) antibodies.[1–3]

No specific predisposing risk factors for VITT have been identified so far and the higher incidence initially reported in young women was not confirmed in later series.[1]

Human leucocyte antigen (HLA) class I and II present protein fragments to $CD8^+$ and $CD4^+$ T cells, respectively, to trigger the immune response. HLA is the most polymorphic gene cluster of the human genome and it is an important genetic predisposition factor for autoimmune diseases. In fact, some HLA alleles, particularly those of class II, have been associated with the risk of autoimmune disorders like thrombotic thrombocytopenic purpura (TTP), heparin-induced thrombocytopenia (HIT) and immune thrombocytopenia (ITP).[4] These conditions show similarities with VITT, as they are all characterized by thrombocytopenia and thrombosis and are caused by immune mechanisms.[4] Anti-PF4 antibodies activating platelets and neutrophils

Eleonora Petito, Loredana Bury and Lilian Antunes Heck share the first authorship.

For affiliations refer to page 4.

have been shown to be present in both HIT and VITT, even if directed against different PF4 epitopes.[5,6] Anti-platelet autoantibodies detected in ~60% of patients with ITP, have also been found in 30% of patients with VITT[7] and in 42% of anti-COVID-19 Ad vector-vaccinated subjects.[8]

To the best of our knowledge, no HLA studies have been reported so far in VITT patients. We aimed to identify gene variants associated with VITT susceptibility in the Italian population with a special focus on the HLA system.

METHODS

Patients

Sixteen patients who survived an acute VITT event were enrolled in a multicentre study involving 14 Italian centres. The section on Internal and Cardiovascular Medicine of the University of Perugia centralized samples and analysis. The study was approved by the local Ethics Committees (CER Umbria n. 3656/20 and the Bioethics Committee of the University of Perugia n. 222848) and each study participant or their legally authorized representative gave written informed consent to study enrollment in accordance with the Declaration of Helsinki. Demographic and clinical variables were collected at enrollment, as well as all the relevant clinical and laboratory data on the VITT episode.[3] VITT was classified as definite or probable according to the consensus diagnostic criteria for VITT developed by the UK Haematology Expert Group.[3]

Samples

Peripheral venous blood was collected either in ACD-A or in 0.18% K3EDTA, as previously reported.[8] ACD-A-anticoagulated whole blood was immediately stored at −20°C and later used for DNA extraction, whole exome sequencing (WES) (Data S1) and HLA typing.

HLA typing by targeted sequencing

DNA samples of VITT patients were analysed by DKMS Life Science Lab gGmbH (LSL). The sequencing involved consecutive PCRs followed by next-generation sequencing using the MiSeq platform.[9] All subjects were genotyped for *HLA-A*, *-B*, and *-C*, *-DRB1*, *-DQA1*, *-DQB1*, *-DPA1*, and *–DPB1* obtaining a three-field resolution. The typing was based on the regions covering the peptide binding domains and exon 3 for HLA class II genes.

Anti-PF4/heparin antibodies

The search for anti-PF4/heparin antibodies and their ability to induce platelet activation was carried out by the enrolling centres at the time of patient hospitalization for VITT (Data S1).

Prediction of peptide binding by in silico analysis

To identify the interaction between human PF4-derived peptides and the HLA genotypes identified, an in silico peptide binding assay was performed using NetMHCIIpan-4.3 for MHC class II (https://services.healthtech.dtu.dk/services/NetMHCIIpan-4.3/).[10,11] The software calculates the prediction binding affinity of human PF4 protein-derived peptides to the identified VITT-related HLA alleles using artificial neural networks. The amino acid sequence of human PF4 was obtained from UniProt (P02776) (https://www.uniprot.org/uniprotkb/P02776/entry) (Data S1).

Statistical analysis

We compared HLA class I allele frequencies at each locus (*HLA-A*, *-B*, and *-C*) of VITT patients with those of Italian controls available in allelefrequencies.net, a freely accessible repository of the immune gene frequencies in different worldwide populations.[12] Given that not all the HLA class I loci were analysed in all the Italian populations reported in allelefrequencies.net, we selected the population for which the typing of all the HLA class I alleles identified in our VITT patients was analysed: the 'Italy pop 5 population' comprising 975 subjects (1950 alleles). We compared HLA class II allele frequencies at each locus (*HLA-DPB1*, *-DQA1*, *-DQB1*, and *-DRB1*) of VITT patients with those of Italian controls available in allelefrequencies.net. Given that not all the HLA class II loci were analysed in all the Italian populations reported in allelefrequencies.net, we merged the two Italian populations for which the typing of all the HLA class II alleles identified in our VITT patients was carried out: the 'Italy Bergamo population', comprising 101 subjects, and the 'Italy North pop 3', comprising 97 subjects, for a total of 198 subjects (396 alleles). *HLA-DPA1* allele frequencies are not available from the reference population databases, therefore, this locus was excluded from the analysis.[13] Alleles not exceeding 5% frequency in VITT patients were not considered as relevant for further analysis.

HLA allele frequencies of VITT patients and the Italian control populations were compared with the Fisher's exact test, and we report only the significant p-values. False-discovery rate (FDR) was controlled at 5% using the Benjamini–Hochberg procedure. All analyses were performed using the GraphPad Prism 10.2.3 for Windows software (GraphPad Software, San Diego, CA, USA, www.graphpad.com).

RESULTS

Characteristics of VITT patients

Sixteen unrelated Caucasian Italian VITT patients were enrolled in this study. Patients were enrolled 180.0 ± 15.0 days (min 72–max 284) after the acute VITT episode. Mean age

was 51.6 ± 3.2 years (range, 33–73 years) and 43.7% were males (Table S1). Fourteen patients (87.5%) suffered VITT following ChAdOx1, whilst 2 (12.5%) following Ad26.COV2.S vaccination. Eleven patients (68.75%) were classified as definite, and five (31.25%) as probable VITT.[3] Clinical and laboratory diagnostic criteria at the time of the acute VITT event are reported in Tables S2 and S3.

Whole exome sequencing

Exome sequencing data were obtained from the 16 unrelated individuals with VITT and 402 unrelated control subjects at the McDonnel Genome Institute (MGI, Washington University in St. Louis). We did not identify differences in the number of gene variants between VITT patients and controls in the gene burden analysis, therefore, no genes turned out to be associated with an increased risk of suffering from VITT.

Comparison of allele frequencies between VITT and healthy Italian individuals

HLA genotyping of the individual VITT patients is reported in Table S4.

The distribution of HLA class I and II genotypes for VITT patients is shown in Figure 1A–H. All the HLA class I alleles had the same frequency in VITT patients and Italian controls. We found three HLA class II alleles with an increased frequency in VITT patients compared with controls: *HLA-DPB1*17:01* (0.125 in VITT vs. 0.002 in controls, $p = 0.0009$), *-DQA1*05:01* (0.375 in VITT vs. 0.085 in controls, $p = 0.00015$), and *-DRB1*11:04* (0.218 in VITT vs. 0.053 in controls, $p = 0.03380$) alleles (Table 1A). In addition to these three HLA class II alleles, when we analysed only the 11 VITT patients with a definite diagnosis, we found also an increased frequency of the *HLA-DQB1*02:01* allele (0.318 in definite VITT patients vs. 0.080 in controls, $p = 0.01680$) compared with Italian controls (Table S5), and an even higher statistical significance for *-DPB1*17:01* and *-DRB1*11:04*.

All the 11 VITT patients with a definite diagnosis enrolled in our study were carriers of at least one of the four HLA alleles identified to be more frequent in VITT patients with a definite diagnosis compared with Italian controls (Table S4).

MHC-peptide in silico binding predictions

In silico analysis showed increased affinity of DRB1*11:04 for the PF4-derived peptides identified by the NetMHCIIpan-4.3 software (Table 1B). Among them, ITSLEVIKA was a strong binder for DRB1*11:04, showing that this peptide has a high likelihood to be presented by DRB1*11:04.

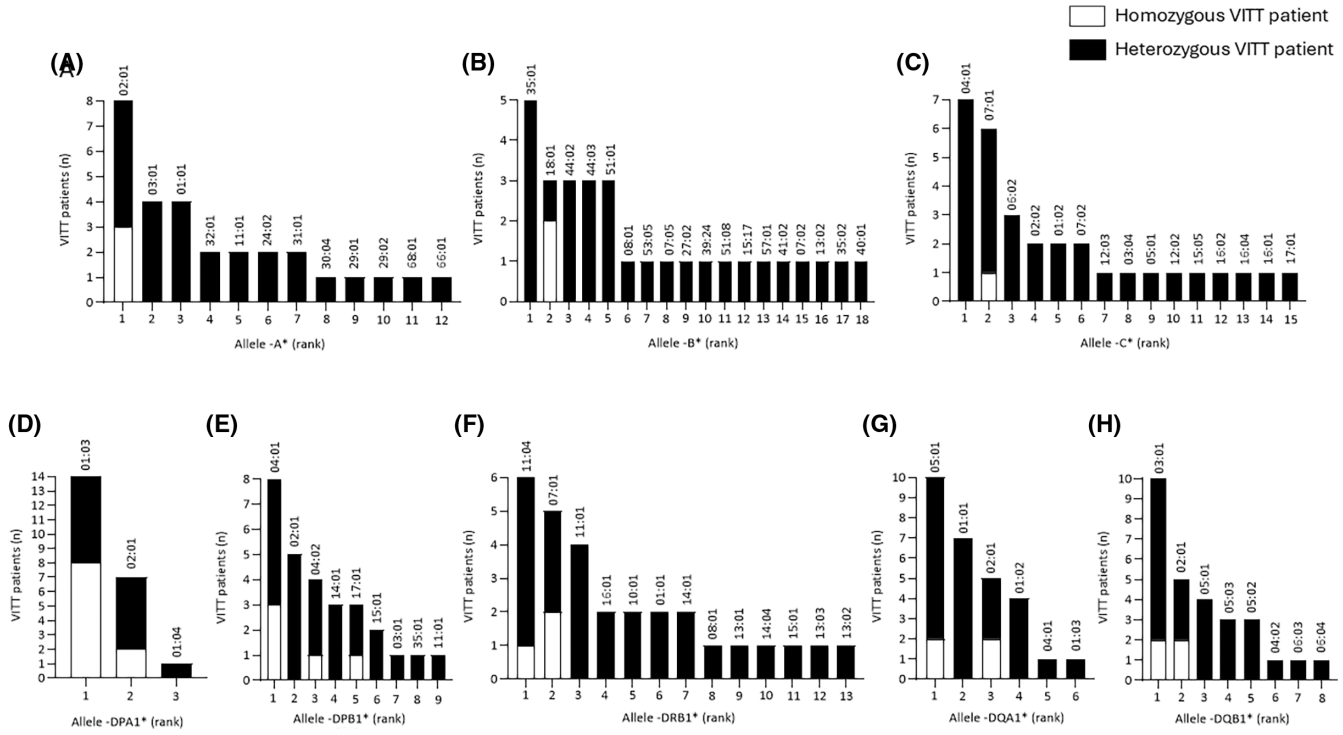

FIGURE 1 **VITT patients by their HLA alleles**. VITT patients according to their class I *HLA-A* (**A**), *-B* (**B**) and *-C* (**C**) alleles, and to their class II *HLA-DPA1* (**D**), *-DPB1* (**E**), *-DRB1* (**F**), *-DQA1* (**G**) and *-DQB1* (**H**) alleles, with alleles ordered from most to least frequent. Patients homozygous for each HLA locus reported are indicated in white, in black the heterozygous. HLA, human leucocyte antigen; VITT, vaccine-induced immune thrombotic thrombocytopenia.

TABLE 1 HLA class II alleles in VITT patients.

(A) Comparison of HLA class II allele frequencies between VITT patients and Italian control population

Allele	Freq case	Freq control	*p*-Value	*p* Value (FDR)	Reciprocal of OR [95% CI]	Control cohort (total AC)
*DPB1*17:01*	0.125	0.002	0.000124	0.00090	0.0170 [0.00144–0.11580]	396
*DQA1*05:01*	0.375	0.085	0.000026	0.00015	0.1565 [0.07048–to 0.35790]	396
*DRB1*11:04*	0.218	0.053	0.002581	0.03380	0.2000 [0.07866–to 0.51320]	396

(B) In silico peptide binding analysis of human PF4-derived peptides to HLA-DRB1*11:04

HLA type	Peptide sequence	Core sequence	% Rank	Predicted binding
	PRHITSLEVIKAGPH	ITSLEVIKA	0.80	Strong binder
	RPRHITSLEVIKAGP	ITSLEVIKA	1.30	Weak binder
*DRB1*11:04*	RHITSLEVIKAGPHC	ITSLEVIKA	3.25	Weak binder
	VRPRHITSLEVIKAG	ITSLEVIKA	3.72	Weak binder
	PTAQLIATLKNGRKI	LIATLKNGR	4.08	Weak binder

Note: Total AC in VITT patients = 32. Freq case: frequency of HLA allele in cases; Freq control: frequency of HLA allele in controls; *p*-value: *p*-value without multiple testing correction using Fisher's exact test; *p*-value (FDR): multiple testing corrected *p*-value using Benjamini–Hochberg false-discovery rate.

Abbreviations: AC, allele count; CI, confidence interval; HLA, human leucocyte antigen; OR, odds ratio; VITT, vaccine-induced immune thrombotic thrombocytopenia.

DISCUSSION

We show for the first time that specific HLA class II alleles are significantly more frequent in VITT patients compared with Italian control populations, and namely *-DPB1*17:01*, *-DQA1*05:01*, and *-DRB1*11:04*. None of these HLA alleles was previously associated with HIT and ITP, while one (*HLA-DRB1*11*) was previously reported to be higher in TTP in several European studies focused on Caucasian people.[14–16] This suggests the existence of a peculiar HLA-loci distribution in the immune reaction of VITT compared with other immune thrombotic thrombocytopenic disorders.

The in silico peptide binding assay identified one PF4-derived peptide (ITSLEVIKA) as a strong binder of the HLA-DRB1*11:04. This peptide contained two amino acids present in the previously identified binding site of VITT anti-PF4 antibodies,[5,6] Glu28 and Ala32 (Figure S1).

We acknowledge that our study has limitations. First, the low number of VITT cases studied. However, VITT is a rare event with an incidence ranging from 1.7 to 16.1 cases every 100 000 vaccinated subjects[1] and previous studies showing that HLA alleles are susceptibility factors for rare autoimmune disorders, such as TTP, primary antiphospholipid syndrome, autoimmune encephalitis, and Guillain-Barré syndrome, were performed in similar small cohorts.[14,15,17–20] Second, attempts to estimate haplotypes using Hapl-o-Mat[21] were unsuccessful because the number of samples was too small. However, also other studies which identified HLA association with other autoimmune diseases did not estimate haplotypes.[14,15,17–20]

Ours is the first study to identify that specific HLA alleles may predispose to the development of an abnormal immune response to Ad-vector vaccines increasing the susceptibility to develop VITT, probably by presenting PF4-derived peptides towards which anti-PF4 antibodies are directed[5,6] (Figure S2). Whilst mass HLA typing of subjects candidate to Ad-vector vaccines is likely unfeasible, our results may be of help to prevent thrombotic complications related to the use of adenoviral vector platforms for gene therapies.[22] Future studies in larger cohorts are warranted to further confirm the relationship between specific HLA alleles and VITT.

AUTHOR CONTRIBUTIONS

P.G. designed the study; E.P., L.B., L.A.H., B.S., and M.T.R. performed the experiments and analysed data; E.P., L.B., L.A.H., and P.G. wrote the manuscript; P.G., J.D.P., and M.T.R. critically revised the manuscript; E.D.C., G.M.P., A.F., L.S., A.B., P.S., I.F., E.I., R.M., P.N., M.P., R.C.S., M.C.T., and G.V. contributed patients to the study; E.P., L.B., and P.G. centralized samples.

AFFILIATIONS

[1]Section of Internal and Cardiovascular Medicine, Department of Medicine and Surgery, University of Perugia, Perugia, Italy
[2]Department of Pediatrics, Washington University School of Medicine, St. Louis, Missouri, USA
[3]Hemorrhagic and Thrombotic Diseases Center, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[4]Medicina III, ASST Santi Paolo e Carlo, Department of Health Sciences, University of Milan, Milano, Italy
[5]Division of Immunohematology and Transfusion Medicine, Hospital Papa Giovanni XXIII, Bergamo, Italy
[6]Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy
[7]Internal Medicine, Azienda USL di Bologna, Bologna, Italy
[8]Haemostasis and Thrombosis Center, Azienda Ospedaliera SS. Antonio e Biagio, Alessandria, Italy
[9]Unit of Neurology and Stroke Unit, Azienda Ospedaliera di Bolzano, Bolzano, Italy
[10]Section of Internal Medicine, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy
[11]Department of Clinical and Experimental Medicine, University of Florence, Firenze, Italy
[12]Department of Internal Medicine, University of Pavia, Pavia, Italy

[13]IRCCS Policlinico San Matteo Foundation, Pavia, Italy
[14]Department of Neuroscience, University Hospital of tor Vergata, Rome, Italy
[15]Haemophilia and Thrombosis Center, Pugliese-Ciaccio Hospital, Catanzaro, Italy
[16]Division of Pulmonary Disease, SS. Annunziata Hospital of Chieti, Chieti, Italy
[17]Unit of Internal Medicine, Terni University Hospital, Terni, Italy
[18]Division of Hematology and Hematologic Malignancies, Department of Internal Medicine, University of Utah Health, Salt Lake City, Utah, USA
[19]Division of Microbiology and Immunology, The Department of Pathology, University of Utah Health, Salt Lake City, Utah, USA
[20]University of Utah Molecular Medicine Program, University of Utah Health, Salt Lake City, Utah, USA
[21]The Department of Medicine and the Geriatric Research, Education, and Clinical Center (GRECC), George E. Wahlen VAMC, Salt Lake City, Utah, USA

ACKNOWLEDGEMENTS

The authors acknowledge the contribution of Silvia Sorrentino (Hemorrhagic and Thrombotic Diseases Center, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy), Mariangela Scavone (Medicina III, ASST Santi Paolo e Carlo, Department of Health Sciences, University of Milan, Italy), Marina Marchetti (Division of Immunohematology and Transfusion Medicine, Hospital Papa Giovanni XXIII, Bergamo, Italy), Luca Barcella (Division of Immunohematology and Transfusion Medicine, Hospital Papa Giovanni XXIII, Bergamo, Italy), Stefania Basili (Department of Translational and Precision Medicine, Sapienza University of Rome, Italy), Laura Contino (Haemostasis and Thrombosis Center, Azienda Ospedaliera SS. Antonio e Biagio, Alessandria, Italy), Angela Rogolino (Department of Clinical and Experimental Medicine, University of Florence, Italy), Rosa Curcio (Unit of Internal Medicine, Terni University Hospital, Italy) for patient enrollment.

FUNDING INFORMATION

This work was supported in part by a fellowship from Fondazione Umberto Veronesi to Eleonora Petito.

CONFLICT OF INTEREST STATEMENT

The authors declare no relevant conflicts of interest.

DATA AVAILABILITY STATEMENT

Data are available upon request to the corresponding author.

ORCID

Eleonora Petito https://orcid.org/0000-0003-4921-8687
Loredana Bury https://orcid.org/0000-0003-0333-0948
Erica De Candia https://orcid.org/0000-0003-0942-2819
Patrizia Noris https://orcid.org/0000-0002-3374-7325
Paolo Gresele https://orcid.org/0000-0001-5365-8445

REFERENCES

1. Petito E, Gresele P. Vaccine-induced immune thrombotic thrombocytopenia two years later: should it still be on the scientific agenda? Thromb Haemost. 2023. https://doi.org/10.1055/a-2107-0891
2. Gresele P, Momi S, Marcucci R, Ramundo F, De Stefano V, Tripodi A. Interactions of adenoviruses with platelets and coagulation and the vaccine-induced immune thrombotic thrombocytopenia syndrome. Haematologica. 2021;106(12):3034–45.
3. Pavord S, Scully M, Hunt BJ, Lester W, Bagot C, Craven B, et al. Clinical features of vaccine-induced immune thrombocytopenia and thrombosis. N Engl J Med. 2021;385(18):1680–9.
4. Amin Asnafi A, Jalali MT, Pezeshki SMS, Jaseb K, Saki N. The association between human leukocyte antigens and ITP, TTP, and HIT. J Pediatr Hematol Oncol. 2019;41(2):81–6.
5. Huynh A, Kelton JG, Arnold DM, Daka M, Nazy I. Antibody epitopes in vaccine-induced immune thrombotic thrombocytopaenia. Nature. 2021;596(7873):565–9.
6. Huynh A, Arnold DM, Michael JV, Clare R, Smith JW, Daka M, et al. Characteristics of VITT antibodies in patients vaccinated with Ad26.COV2.S. Blood Adv. 2023;7(2):246–50.
7. Nicolai L, Leunig A, Pekayvaz K, Esefeld M, Anjum A, Rath J, et al. Thrombocytopenia and splenic platelet-directed immune responses after IV ChAdOx1 nCov-19 administration. Blood. 2022;140(5):478–90.
8. Petito E, Colonna E, Falcinelli E, Mezzasoma AM, Cesari E, Giglio E, et al. Anti-severe acute respiratory syndrome coronavirus-2 adenoviral-vector vaccines trigger subclinical antiplatelet autoimmunity and increase of soluble platelet activation markers. Br J Haematol. 2022;198(2):257–66.
9. Schöfl G, Lang K, Quenzel P, Böhme I, Sauter J, Hofmann JA, et al. 2.7 Million samples genotyped for HLA by next generation sequencing: lessons learned. BMC Genomics. 2017;18(1):161.
10. Nilsson JB, Kaabinejadian S, Yari H, Kester MGD, van Balen P, Hildebrand WH, et al. Accurate prediction of HLA class II antigen presentation across all loci using tailored data acquisition and refined machine learning. Sci Adv. 2023;9(47):eadj6367.
11. Sakai K, Kuwana M, Tanaka H, Hosomichi K, Hasegawa A, Uyama H, et al. HLA loci predisposing to immune TTP in Japanese: potential role of the shared ADAMTS13 peptide bound to different HLA-DR. Blood. 2020;135(26):2413–9.
12. Gonzalez-Galarza FF, McCabe A, Santos EJMD, Jones J, Takeshita L, Ortega-Rivera ND, et al. Allele frequency net database (AFND) 2020 update: gold-standard data classification, open access genotype data and new query tools. Nucleic Acids Res. 2020;48(D1):D783–D788.
13. Crocchiolo R, Gallina AM, Pani A, Campisi D, Cento V, Sacchi N, et al. Polymorphism of the HLA system and weak antibody response to BNT162b2 mRNA vaccine. HLA. 2022;99(3):183–91.
14. Lombardi AM, Pulini S, Passeri C, Iuliani O, Salutari P, Businaro A, et al. Familial acquired thrombotic thrombocytopenic purpura: immunogenetic link with HLA-DRB1*11 and DQB1*03 antigens. Br J Haematol. 2018;183(2):317–9.
15. Joly BS, Loiseau P, Darmon M, Leblanc T, Chambost H, Fouyssac F, et al. HLA-DRB1*11 is a strong risk factor for acquired thrombotic thrombocytopenic purpura in children. Haematologica. 2020;105(10):e531.
16. Coppo P, Busson M, Veyradier A, Wynckel A, Poullin P, Azoulay E, et al. HLA-DRB1*11: a strong risk factor for acquired severe ADAMTS13 deficiency-related idiopathic thrombotic thrombocytopenic purpura in Caucasians. J Thromb Haemost. 2010;8(4):856–9.
17. Amirzargar AA, Tabasi A, Khosravi F, Kheradvar A, Rezaei N, Naroueynejad M, et al. Optic neuritis, multiple sclerosis and human leukocyte antigen: results of a 4-year follow-up study. Eur J Neurol. 2005;12(1):25–30.
18. Hasan ZN, Zalzala HH, Mohammedsalih HR, Mahdi BM, Abid LA, Shakir ZN, et al. Association between human leukocyte antigen-DR and demylinating Guillain-Barre syndrome. Neurosciences (Riyadh). 2014;19(4):301–5.
19. Camps MT, Cuadrado MJ, Ocón P, Alonso A, Gutierrez A, Guil M, et al. Association between HLA class II antigens and primary antiphospholipid syndrome from the south of Spain. Lupus. 1995;4(1):51–5.
20. Chang H, Shin YW, Keam B, Kim M, Im SA, Lee ST. HLA-B27 association of autoimmune encephalitis induced by PD-L1 inhibitor. Ann Clin Transl Neurol. 2020;7(11):2243–50.

21. Schäfer C, Schmidt AH, Sauter J. Hapl-o-Mat: open-source software for HLA haplotype frequency estimation from ambiguous and heterogeneous data. BMC Bioinformatics. 2017;18(1):284.
22. Benemei S, Gatto F, Marcucci R, Gresele P. Emerging thrombotic disorders associated with virus-based innovative therapies: from VITT to AAV-gene therapy-related thrombotic microangiopathy. Thromb Haemost. 2024. https://doi.org/10.1055/a-2413-4345

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: Petito E, Bury L, Antunes Heck L, Sadler B, De Candia E, Podda GM, et al. Association of human leucocyte antigen loci with vaccine-induced immune thrombotic thrombocytopenia: Potential role of the interaction between platelet factor 4-derived peptides and MHC-II. Br J Haematol. 2024;00:1–6. https://doi.org/10.1111/bjh.19838