Exploration of Immunology

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Selective IgG4 deficiency and autoimmune cytopenias

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Academic Editor: Sofia Kossida, The International ImMunoGeneTics Information System, France
Received: April 1, 2025 **Accepted:** July 8, 2025 **Published:** August 7, 2025

Cite this article: Loutsou M, Giannakoulas N, Hatzipantelis E, Pergantou H, Dettoraki A, Antari V, et al. Selective IgG4 deficiency and autoimmune cytopenias. Explor Immunol. 2025;5:1003207. https://doi.org/10.37349/ei.2025.1003207

Abstract

Aim: Autoimmune cytopenias are disorders driven by immune-mediated destruction of hematopoietic cells. Recent studies have linked these conditions to inborn errors of immunity (IEI), particularly in patients with recurrent and/or chronic forms. Common variable immunodeficiency (CVID) is the most common IEI in humans, and autoimmune cytopenias represent the most prevalent autoimmune manifestations of the disease. *TNFRSF13B*/*TACI* alterations are the most common genetic defects in CVID patients. The aim of this study was to investigate both the incidence of hypogammaglobulinemia—including immunoglobulin subclass deficiencies—in patients with autoimmune cytopenias, as well as possible correlations with common *TNFRSF13B*/*TACI* defects in selective patients.

Methods: A cohort of 123 patients (110 adults and 13 children, male/female: 58/65, median age at diagnosis: 50.0 years, range: 1.5–87.0) with autoimmune cytopenias [113 with autoimmune thrombocytopenia (AIT), 8 with autoimmune hemolytic anemia (AHA), and 2 with Evans syndrome] were enrolled in the study. The main immunoglobulin types (IgG, IgM, and IgA) were measured in all patients, while serum for the estimation of IgG subclass levels was available in 84 patients. Genetic analysis of *TNFRSF13B*/*TACI* was performed by PCR and Sanger sequencing.

Results: Although no deficiency of main immunoglobulin types was detected in any patient, 8 of 84 patients (9.5%) displayed selective IgG4 deficiency (sIgG4D). Among them, three suffered from acute/newly diagnosed AIT, three from chronic AIT, and two from AHA. Interestingly, two patients with sIgG4D exhibited a family history of IEI. Furthermore, one patient (12.5%) carried a pathogenic missense mutation (c.542C>A, p.A181E, rs72553883) in a heterozygous state, while the remaining patients carried only common polymorphisms.

Conclusions: IgG4 could be considered a useful biomarker in patients with autoimmune cytopenias, while further studies may elucidate its precise role in disease pathogenesis and prognosis.

Keywords

Autoimmune cytopenias, autoimmune thrombocytopenia, autoimmune hemolytic anemia, IgG4, immunodeficiency, *TNFRSF13B*/*TACI*

Introduction

Autoimmune cytopenias represent a group of heterogenous disorders characterized by immune-mediated destruction of hematopoietic cells. The main mechanism is the production of autoantibodies directed against platelets [autoimmune thrombocytopenia (AIT)], erythrocytes [autoimmune hemolytic anemia (AHA)], and neutrophils [autoimmune neutropenia (AIN)]; however, they can also be directed simultaneously or sequentially against more than two cell lineages (Evans syndrome) [1, 2]. Autoimmune cytopenias present as either complications of other diseases—including infections, malignancies, systemic autoimmune disorders, or immunodeficiencies among others—or manifest as primary diseases [3].

In recent years, there is increasing evidence that primary immunodeficiencies, currently referred to as inborn errors of immunity (IEI), represent a significant predisposing factor of autoimmune cytopenias, particularly in patients with recurrent or chronic forms [4–6]. Among them, common variable immunodeficiency (CVID) is the most common IEI in humans, and autoimmune cytopenias represent the most prevalent autoimmune manifestation of the disease [7, 8]. Notably, more than 20% of CVID patients develop an autoimmune disorder, more often AIT accompanied by AHA, and occasionally by AIN [7]. Disease onset may occur at any age and can precede CVID diagnosis by a mean of 0.5–18.0 years, however, it may also be diagnosed concomitantly or after initiation of CVID treatment [8–10]. Data from the US Immunodeficiency Network cites that among CVID patients with a median age of 16.0 years, 4.5% suffer from AHA and 7.4% from AIT. These patients are also at higher risk of developing one or more non-infectious complications related to CVID [10]. For this reason, quantitative measurement of at minimum the three main immunoglobulins types—IgG, IgM, and IgA—should be considered essential during initial diagnosis of autoimmune cytopenias [6, 11].

Previously unpublished observations from our group revealed that some patients with autoimmune cytopenias exhibited low to undetectable levels of IgG4 immunoglobulin in peripheral blood, without evidence of overt hypogammaglobulinemia. IgG subclass deficiency is a rare type of IEI, identified by low levels of at least one or more IgG subclasses; however, its prevalence and clinical significance are rather unclear [12, 13]. Interestingly, some patients with immunoglobulin subclass deficiency (IgGScD) experience recurrent infections, autoimmunity, and atopy more frequently than the general population [14–17].

Although data in the literature are limited, previous studies suggest that IgG3 deficiency (IgG3D) is the most common IgGScD in adults, while IgG2D is more prevalent among children, with an incidence of approximately 1 in 10,000 individuals. Moreover, some patients displaying concomitant IgG2D and IgA deficiency (IgAD) exhibit a higher risk of developing CVID over their lifetime [14, 16, 18]. According to our published data, the most prevalent IgGScD in patients with IEI was selective IgG4 deficiency (sIgG4D), and affected patients displayed a notably high frequency of *TNFRSF13B*/*TACI* defects [19].

The aim of the present study was to investigate the prevalence of hypogammaglobulinemia and IgGScD in patients with autoimmune cytopenias, as well as identify the presence of *TNFRSF13B*/*TACI* defects that may contribute to disease pathogenesis and phenotype.

Materials and methods

Patients

A cohort of 123 patients (male/female: 58/65, median age: 61.5 years, range: 1.5–90.0, median age at diagnosis: 50.0 years, range: 1.5–87.0) with autoimmune cytopenias were enrolled in the study. The

majority were adults (110, male/female: 51/59, median age at diagnosis: 57.0 years, range: 17.0–87.0), while 13 patients (male/female: 7/6, median age at diagnosis: 12.0 years, range: 1.5–16) were children and adolescents. Autoimmune cytopenia diagnosis was established based on standard criteria [1, 2]. Patients with an initial diagnosis of CVID or other types of IEI, autoimmune lymphoproliferative syndrome (ALPS), hematologic malignancies, or those receiving either immunosuppressive or immunoglobulin replacement treatment were excluded from the study. Moreover, patients with AIT were further characterized according to the duration of thrombocytopenia: "acute or newly diagnosed" (duration of 0–3 months); "persistent" (duration of 3–12 months); or "chronic" (duration more than 12 months) [20].

All (13) pediatric and adolescent patients suffered from AIT, five (38.5%) from acute/newly diagnosed disease, four (30.8%) from persistent disease, and four (30.8%) from chronic disease. Among them, a female patient (five years of age) presented with AIT after a viral infection, while another male patient (one and a half years of age) developed AIT after the first dose of measles-mumps-rubella (MMR) vaccination. Moreover, one female patient (12 years of age) had a medical history of Hashimoto disease and psoriasis.

Among adult patients, 100 of 110 (90.9%) were diagnosed with AIT, including 45 (45.0%) with acute/newly diagnosed disease, 13 (13.0%) with persistent disease and 42 (42.0%) with chronic disease. Eight (7.3%) patients were diagnosed with AHA and two (1.8%) with Evans syndrome. In 13 (11.8%) patients, the diagnosis was made incidentally during blood tests performed for unrelated reasons (e.g., monitoring other conditions). A history of viral infection prior to the cytopenia emergence was reported among 16 patients (14.5%), while 12 patients (10.9%) indicated a history of systemic or organ-specific autoimmune disorders—including rheumatoid arthritis (three), lupus (one), psoriasis (four including one with additional alopecia), vitiligo (one), Graves' disease (two), and diabetes mellitus type I (one). One female patient aged 43 also suffered from Crohn's disease.

The study was approved by the institutional review boards of the University Hospital of Larissa, Greece (14/17/29.11.2022) and the Faculty of Medicine of the University of Thessaly, Greece (4/16.01.2023). Written informed consent was obtained from each individual or an accompanying relative, in the case of patients where consent was not legally applicable (e.g., children).

Immunoglobulins measurement

Peripheral blood was collected in serum separating tube (SST) and was centrifugated at 3,000× *g* for 10 minutes. It was then stored at –20°C until analysis. IgG, IgM, and IgA immunoglobulin, as well as IgG1, IgG2, IgG3, and IgG4 subclass levels, were estimated using nephelometry, according to the manufacturer's instructions (BNII System, Siemens Healthcare Diagnostic Products GmbH, Germany). IgG, IgM, and IgA levels were measured in all patients. IgG subclass measurements were performed in 84 patients (68.3%) for whom serum was available. In 39/123 patients (31.7%), immunoglobulin measurements were performed at the emergence of autoimmunity, while in the remaining 84 patients (68.3%) measurements were performed years after diagnosis.

In accordance with the literature, IgGScD was defined as the value of IgG subclass below two SD from the mean value, with normal levels of IgG, IgM, and IgA [18, 19].

Molecular studies

Genomic DNA was extracted from peripheral blood (ExtractME Genomic DNA Kit, Blirt, Gdansk, Poland) according to the manufacturer's instructions. Subsequently, a PCR amplification of all five exons was performed. The primers and conditions of all PCR reactions are displayed in Table 1. A 30-μL final volume was used for each PCR reaction, amplifying 100–200 ng of genomic DNA using 62.5 μM of each deoxynucleotide triphosphate 0.8 U of Taq polymerase (Invitrogen, UK), 1.5 mM $MgCl_2$, and 20 pmol of each primer in a buffer provided by the manufacturer. The PCR results were observed under ultraviolet light, stained with ethidium bromide, and analyzed in 2–3% TBE agarose gels. Afterward, PCR products were purified by use of a PCR purification system (GRS PCR & Gel Band Purification Kit, Grisp, Portugal) and were directly sequenced using an ABI Prism 310 genetic analyzer (Applied Biosystems, Foster City, CA, USA) and a BigDye Terminator DNA sequencing kit.

Table 1. Primers and PCR conditions used in this study

Exons	Primers	Sequence	PCR conditions	PCR product
1	1-forward	5'-GGGTGTGGCTGATTTACATCC-3'	94°C for 2 min, followed by 31 cycles (94°C for 30 s, 62°C for 30 s,72°C for 30 s), and a final elongation at 72°C for 5 min	340 bp
	1-reverse	5'-CCAGAGGCATCCAGACTCG-3'		
2	2-forward	5'-AAAGGTTGTCTGTGCGAATGT-3'	94°C for 2 min, followed by 31 cycles (94°C for 30 s, 64°C for 30 s,72°C for 30 s), and a final elongation at 72°C for 5 min	319 bp
	2-reverse	5'-CCAGAGGGTGCTCTAGGGAG-3'		
3	3-forward	5'-ATCAAAATGCAATGCAGCTAAA-3'	94°C for 2 min, followed by 31 cycles (94°C for 30 s, 62°C for 30 s,72°C for 30 s), and a final elongation at 72°C for 5 min	635 bp
	3-reverse	5'-AGACTTCTGGAAATGTTGCCTA-3'		
4	4-forward	5'-GGGGGAGTGGATCAAC-3'	94°C for 2 min, followed by 36 cycles (94°C for 30 s, 60°C for 30 s,72°C for 30 s), and a final elongation at 72°C for 5 min	540 bp
	4-reverse	5'-GTCTGCCAGGATGTCTTAACC-3'		
5	5-forward	5'-TGGCAGACAGATAACT-3'	94°C for 2 min, followed by 32 cycles (94°C for 30 s, 55°C for 30 s,72°C for 30 s), and a final elongation at 72°C for 5 min	717 bp
	5-reverse	5'-CTCTCTCCTCATATCTCTC-3'		

Statistical analysis

Disease status (AIT, AHA) and the presence (or absence) of IgGScD were treated as categorical parameters, analyzed using the chi-square test. Analysis was conducted using the free online Chi-Square Test Calculator of Social Sciences Statistics (https://www.socscistatistics.com/tests/chisquare2/default2.aspx).

Results

An overview of immunoglobulin and IgG subclass levels is presented in Table 2. No deficiencies in any of the main immunoglobulin types were detected among patients. However, among 84 patients for whom a measurement of IgG subclass was performed, eight (9.5%) displayed sIgG4D.

Table 2. Overview of immunoglobulins and IgG subclass levels in study patients

Immunoglobulins and subclasses	Total (mean ± SD)	Patients < 16 (years of age) (mean ± SD)	Patients ≥ 16 (years of age) (mean ± SD)
Immunoglobulin levels (mg/dL)	*N* = 123	*N* = 13	*N* = 110
IgG	1,065.5 ± 301.0	974.6 ± 211.6	1,076.2 ± 308.8
IgM	126.7 ± 153.4	93.6 ± 46.4	130.8 ± 161.4
IgA	195.0 ± 124.1	121.6 ± 81.8	203.9 ± 125.6
IgG subclass levels (mg/dL)	*N* = 84	*N* = 13	*N* = 71
IgG1	622.0 ±184.2	560.2 ± 176.7	632.5 ± 184.6
IgG2	311.9 ± 127.9	274.3 ±113.9	318.2 ± 129.8
IgG3	42.0 ± 44.7	38.8 ± 23.6	45.6 ± 47.5
IgG4	59.9 ± 63.7	95.1 ± 104.2	54.4 ± 53.4

Clinical and laboratory data of these patients are detailed in Table 3. Interestingly, no patient with sIgG4D displayed a medical history of systemic autoimmune disease.

Three of eight patients with sIgG4D (37.5%) suffered from chronic AIT (patients 2, 5, and 7 in Table 3), while the remaining patients suffered from acute/newly diagnosed AIT (three patients, 37.5%) or AHA (two patients, 25.0%). According to these findings, we estimated the incidence of sIgG4D was more prevalent among patients with AHA (two of eight patients, 25.0%) compared to patients with AIT (6 of 113, 5.3%) ($p = 0.030$). Moreover, sIgG4D was marginally more common among patients with chronic AIT (3 of 46 patients, 6.5%) compared to patients with acute/newly diagnosed and/or persistent disease [3 of 50 (6.0%) and none from among 17 patients, respectively]. However, these differences were not significant ($p > 0.05$, in all cases).

Table 3. Clinical, laboratory, and molecular data of patients with sIgG4D

No.	Age (years)*	Age (years)^	Sex	Disease	Medical history/Family history	IgG4 levels (mg/dL)[#]	*TNFRSF13B/TACI* defects
1	5	5	M	AIT	No/No	1.0	Wild-type
2	18	16	M	AIT	No/No	< 1.0	rs72553883-Heter (p.A181E)
							rs8072293-Heter (p.T27=)
							rs11078355-Heter (p.S277=)
							rs2274892-Heter (intronic)
3	18	18	F	AIT	No/Mother with hereditary spherocytosis	2.0	Wild-type
4	35	21	F	AIT	No/Daughter with CVID	1.0	Wild-type
5	27	27	F	AIT	No/No	2.0	rs8072293-Heter (p.T27=)
							rs11078355-Heter (p.S277=)
							rs2274892-Heter (intronic)
6	72	72	F	AHA	Urticaria/Niece with CVID	2.0	rs8072293-Homo (p.T27=)
							rs34562254-Heter (p.P251L)
							rs2274892-Heter (intronic)
							rs11652843-Heter (intronic)
							rs11652811-Heter (intronic)
7	90	84	M	AIT	DM/No	1.0	rs8072293-Heter (p.T27=)
							rs11078355-Heter (p.S277=)
							rs11652843-Heter (intronic)
							rs11652811-Heter (intronic)
8	90	87	M	AHA	Vitiligo/No	2.0	rs8072293-Heter (p.T27=)
							rs2274892-Heter (intronic)

AIT: autoimmune thrombocytopenia; AHA: autoimmune hemolytic anemia; CVID: common variable immunodeficiency; DM: diabetes mellitus; F: female; M: male; sIgG4D: selective IgG4 deficiency; Heter: heterozygous; Homo: homozygous; *: age at enrolment; ^: age at emergence (diagnosis) of autoimmune cytopenia; [#]: normal range (8–140 mg/dL)

Further molecular analysis of the *TNFRSF13B*/*TACI* gene in patients with sIgG4D revealed that only one patient (12.5%, patient 2 in Table 3) carried a pathogenic missense mutation in heterozygous state. The remaining patients carried common intronic and silent polymorphisms (Table 3). The patient carrying the pathogenic *TNFRSF13B*/*TACI* mutation (c.542C>A, p.A181E, rs72553883) displayed a persistent and stable disease (AIT) for at least one and a half years, with an initial response to corticosteroid treatment, followed by platelet counts ranging between 60–110/μL. The patient did not have a history of recurrent infections up to the age of 16, and his detailed family history revealed no IEI disease.

Interestingly, two patients with sIgGD4 and autoimmune cytopenias had additional organ-specific autoimmune manifestations: one patient with AIT and diabetes mellitus type I, and another patient with AHA and vitiligo (Table 3). Furthermore, two patients (patients 4 and 6 in Table 3) had a family history of CVID. Patient 4 (Table 3) displayed an acute/newly diagnosed AIT during pregnancy at 21 years of age. This patient was treated with corticosteroids and recovered without relapse and/or recurrent infections. Her daughter was diagnosed with CVID at the age of 15, displaying recurrent and severe respiratory infections with severe hypogammaglobulinemia; she was treated with immunoglobulin replacement therapy, initially intravenously and later subcutaneously. Patient 6 (Table 3) was diagnosed with AHA at 72 years of age, displaying severe and resistant disease. This patient's niece (daughter of her sister) was diagnosed with

CVID at 31 years of age, presenting with 10 years of recurrent respiratory infections and severe hypogammaglobulinemia, which was also treated with immunoglobulin replacement therapy. Neither patient or their relatives carried pathogenic *TNFRSF13B*/*TACI* mutations.

Discussion

To the best of our knowledge, this is the first study in the literature exploring the possible association of autoimmune cytopenias with immunoglobulin subclass levels. We clearly demonstrate that a rather high proportion of patients with autoimmune cytopenias (9.5%) display sIgG4D. Interestingly, some of these sIgG4D patients also had a family history of IEI (two of eight, 25.0%), while one patient also carried a pathogenic *TNFRSF13B*/*TACI* defect (without a family history of IEI).

Estimating immunoglobulin levels at the time of autoimmune cytopenia diagnosis is indispensable to rule out an underlying IEI [4–8]. This is particularly essential considering patients with an IEI CVID have at least a 120-fold higher incidence of developing autoimmune cytopenias compared to the general population [9]. Moreover, abnormal immunoglobulin levels have been linked to more severe clinical illness and treatment resistance in AIT, since lower IgM levels have been correlated with a lower platelet count. Elevated IgA levels have been associated with bleeding and a higher risk of resistance to first-line therapy, independent of the platelet count [21].

IgG4D represents a type of IEI, either as an isolated phenomenon (sIgG4D), or in combination with a deficiency in other immunoglobulin subclasses, usually IgG2, IgA, or IgG1 [22, 23]. The precise incidence of sIgG4D in the general population is unknown. In a study of 414 healthy Greek children, Liatsis et al. [24] found no individuals with IgG4D. Meanwhile, in the most recent and comprehensive review on IgG4-related physiology and pathology, Rispens and Huijbers [23] reported that the incidence of sIgG4D in the general population is extremely low. This contrasts with the initial study by Plebani et al. [25], which measured IgG subclasses by radial immunodiffusion and reported undetectable IgG4 levels in approximately 8% of children. Conversely, several studies have reported that sIgG4D patients display a high incidence of recurrent sinopulmonary infections, atopy, chronic diarrhea, and chronic fungal infections, especially candidiasis [22, 23, 26]. Moreover, Koutroumpakis et al. [27] retrospectively analyzed data from 1,193 patients with inflammatory bowel disease (IBD) and found that approximately 20% displayed low IgG4 levels, which were significantly correlated to disease severity and outcome. However, very low IgG4 levels in IBD patients may be induced by either steroid treatment or protein loss [28].

The present research is the only study we are aware of which indicates sIgG4D positively correlates with autoimmunity, including both AIT and AHA (Table 3). Although sIgG4D incidence was higher among patients with AHA (25.0%), this finding should be interpreted with caution, considering fewer AHA patients were enrolled compared to AIT patients (8 versus 113). Furthermore, we found that two patients with sIgG4D had a family history of CVID, suggesting a possible common genetic cause requiring further investigation.

Interestingly, we also observed that a patient with chronic AIT carried a pathogenic *TNFRSF13B*/*TACI* defect (rs72553883, Table 3). It is currently well-recognized that monoallelic (heterozygous) or biallelic (homozygous or compound heterozygous) *TNFRSF13B*/*TACI* defects represent the most common alterations in CVID, which mainly affect disease phenotype and outcome [29]. The defect found in our patient—*TNFRSF13B*-p.A181E (rs72553883)—is located within the transmembrane domain (TM) domain of the TACI receptor. Along with the *TNFRSF13B*-p.C104R defect (rs34557412), they have a more profound effect on CVID phenotype [29, 30]. TACI is a receptor on B cells that binds BAFF and APRIL, playing a crucial role in B cell survival, class-switch recombination, and, importantly, immune tolerance [31]. As mentioned above, one of the sIgG4D study patients displayed the *TNFRSF13B*/*TACI*-p.A181E defect. Previous studies demonstrate that this defect impairs *TACI* signaling—particularly through pathways like NF-kappaB and MAPK—leading to a defective deletion or anergy of autoreactive B cells, increasing susceptibility to autoimmunity [31, 32]. Moreover, impaired *TACI* function can elevate BAFF levels, which further promotes the survival of autoreactive B cells, a mechanism also implicated in diseases like systemic lupus erythematosus (SLE) [33].

Additional in vitro studies in the murine equivalent of the p.A181E defect, namely the mTACI-p.A144E, suggest that this alteration disrupts *TACI* signaling and impairs *TACI*-dependent B-cell functions [34]. The contribution of this defect in the emergence of autoimmunity is still obscure, considering that T*ACI*-knockout mice mainly exhibit a prominent autoimmune phenotype and signs of lymphoproliferation, rather than hypogammaglobulinemia [35]. Although the p.A181E defect is not fully penetrant, meaning not all carriers develop disease, it significantly increases the risk of conditions such as CVID, SLE, Sjögren's syndrome, and autoimmune cytopenias, by promoting chronic immune activation and loss of B cell tolerance [34].

In the same context, Ma et al. [36] examined CVID-related genetic defects through NGS in pediatric patients with refractory AIT, as a screening tool for suspected CVID. Notably, five of the eight patients characterized as highly suspicious for CVID carried *TNFSRF13B/TACI* mutations (two with biallelic defects and three with monoallelic defects). Peng et al. [37] analyzed two families with familial AIT and suggested that a specific *TNFRSF13B*/*TACI* defect (p.G76S) should be considered as a predisposing factor for AIT development. *TNFRSF13B*/*TACI* mutations, along with defects in other genes implicated in IEI pathogenesis, have also been identified in patients with Evans syndrome [5]. Considering other *TNFRSF13B*/*TACI* defects detected in our patients (Table 3), they are highly common in the general population [19]. Functional studies have not shown any impact on TACI protein function, signaling pathways or B cell tolerance mechanisms. Additionally, genome-wide association studies and population analyses do not link these variants to CVID or its autoimmune manifestations [29]. Therefore, without evidence of impaired receptor function, disrupted immune regulation, or disease segregation, these variants are classified as benign polymorphisms rather than pathogenetic mutations [19]. Further studies should clarify the possible contribution of *TNFRSF13B*/*TACI* defects to the emergence and prognosis of autoimmune cytopenias, even among patients without profound hypogammaglobulinemia.

According to Morell's old assumption [38] that "IgG subclasses deficiencies represent an indicator of more basic immunologic abnormalities", we suggest that measurement of IgG4 levels could be utilized as a biomarker in patients with autoimmune cytopenias. Moreover, further genetic analyses would be beneficial, distinguishing among patients with primary autoimmune cytopenias and cases of suspected CVID, for optimal follow-up and management.

In conclusion, we identified a high incidence of sIgG4D among patients with autoimmune cytopenias, whom also displayed a notable frequency of either a family history of IEI or pathogenic *TNFRSG13B/TACI* mutations. Our findings suggest that measuring IgG4 levels should be considered a useful biomarker in patients with autoimmune cytopenias. Additional studies and meta-analyses are necessary to validate our results and clarify the importance of sIgG4D in patients with autoimmune cytopenias, for their disease pathogenesis and prognosis.

Abbreviations

AHA: autoimmune hemolytic anemia

AIN: autoimmune neutropenia

AIT: autoimmune thrombocytopenia

CVID: common variable immunodeficiency

IBD: inflammatory bowel disease

IEI: inborn errors of immunity

IgAD: IgA deficiency

IgG3D: IgG3 deficiency

IgGscD: immunoglobulin subclass deficiency

sIgG4D: selective IgG4 deficiency

SLE: systemic lupus erythematosus

Declarations

Acknowledgments

Study conception and design were performed within the context of the postgraduate program "Clinical Applications of Molecular Medicine", Faculty of Medicine, School of Health Sciences, University of Thessaly, Greece. The authors express their sincere gratitude to Lemonia Anagnostopoulos for her invaluable assistance in providing important comments on the quality of the manuscript.

Author contributions

ML: Conceptualization, Investigation, Data curation, Formal analysis, Software, Methodology, Writing—original draft, Writing—review & editing. SS: Validation, Writing—review & editing, Software, Methodology, Writing—original draft, Writing—review & editing. MS: Conceptualization, Writing—original draft, Writing—review & editing, Supervision. NG, EH, HP, AD, VA, AM, and VK: Investigation, Validation, Writing—review & editing. GV, CH, and FK: Validation, Writing—review & editing. All authors read and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

The study was approved by the institutional review boards of the University Hospital of Larissa, Greece (14/17/29.11.2022) and the Faculty of Medicine of the University of Thessaly, Greece (4/16.01.2023).

Consent to participate

Written informed consent was obtained from each individual or an accompanying relative, in the case of patients where consent was not legally applicable (e.g., children).

Consent to publication

Not applicable.

Availability of data and materials

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

Funding

The study was supported by the standard budget provided by The Research Committee of the University of Thessaly to Department of Immunology & Histocompatibility, Faculty of Medicine, University of Thessaly, 41500 Larissa, Greece. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Publisher's note

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