Global Insights in Biomedical & Multidisciplinary Research (GIBMR)
Volume 01, Issue 02, April-2026
Available Online at: https://biomedglobe.com/index.php/gibmr
ISSN (Online): 3054-5900

Immunogenetic Mechanisms Of Rheumatological Manifestations In Primary Immunodeficiencies In Children And Their Significance For Personalized Diagnostics And Therapy

Sadikova A.M., Ismailova A.A , Ruzibakiyeva M.R , Ashurova D.T
Institute of immunology and human genomics Academy of Sciences of the Republic of Uzbekistan
Tashkent State Medical University

Article History
Received: 11th February, 2026
Accepted: 10th March, 2026

Abstract

Background:
Primary immunodeficiencies comprise 559 variants (IUIS 2024). Rheumatologic manifestations occur in 10–50% of PID children, often preceding infections. Median diagnostic delay: 2.7 years.

Objective:
To systematize immunogenetic mechanisms of rheumatologic manifestations in

Methods:
Systematic review (PRISMA) of PubMed, Scopus, and Web of Science (2015–2025). Analysis of 25 sources, including a cohort of 434 patients with CTLA4/LRBA deficiency[1] .

Results:
Five mechanisms were identified: impaired tolerance (CTLA4/LRBA), JAK-STAT hyperactivation, PI3K activation, interferon hyperproduction, and complement defects. Abatacept provides control in 43–60% of patients with CTLA4/LRBA [3]. JAK inhibitors reduce IDDA by 53% pediatric PIDs and define personalized approaches.

Conclusion:
Molecular diagnosis and early targeted therapy significantly improve outcomes.

Keywords: primary immunodeficiency, rheumatologic manifestations, children, NGS, CTLA4, LRBA, JAK inhibitors, personalized therapy

Introduction

Primary immunodeficiencies (PIDs) are a group of hereditary immune disorders traditionally associated with recurrent infections. However, this clinical

paradigm has shifted radically: autoimmune and rheumatological manifestations are now observed in 52–56% of patients with immune dysregulation disorders and phagocyte defects [4]. Furthermore, in a significant proportion of children, rheumatological symptoms precede infectious complications, creating substantial diagnostic challenges.

The 2024 IUIS classification identifies 559 variants of Inborn Errors of Immunity (IEI) caused by mutations in 508 genes [1]. This represents a twofold increase over the last decade, driven by the implementation of Next-Generation Sequencing (NGS) technologies. While the prevalence of PID is estimated at 6 per 10,000 population, the median diagnostic delay remains at 2.7 years—candidly, a catastrophic figure for the 21st century.

The primary diagnostic difficulty lies in the fact that children with rheumatological manifestations of PID are often misdiagnosed with juvenile idiopathic arthritis (JIA) or systemic lupus erythematosus (SLE). Consequently, they remain on long-term conventional immunosuppressive therapy, which is not only ineffective but may, in some cases, exacerbate the disease course [5]. Meanwhile, molecular diagnostics opens the door to targeted therapy, such as Abatacept for CTLA4/LRBA deficiency, JAK inhibitors for STAT mutations, and IL-1 blockade for autoinflammatory syndromes.

The aim of this review is to systematize the immunogenetic mechanisms of rheumatological manifestations in children with PID and to summarize data on the efficacy of personalized therapy. Special emphasis is placed on CTLA4/LRBA deficiency and STAT gain-of-function (GOF) mutations, as these areas currently possess the most extensive clinical experience and evidence base for targeted approaches.

Materials And Methods

This systematic review was conducted in accordance with the PRISMA guidelines. A comprehensive search was performed across the PubMed/MEDLINE, Scopus, and Web of Science databases covering the period from January 2015 to February 2025. Search terms included: primary immunodeficiency, inborn errors of immunity, rheumatologic manifestations, arthritis, CTLA4, LRBA, STAT gain-of-function, targeted therapy, abatacept, and JAK inhibitors. Inclusion criteria were: pediatric population (0–18 years), confirmed PID, presence of rheumatological manifestations, and molecular verification of the diagnosis [6].

Out of 287 identified publications, 25 original sources were selected, including large-scale multicenter cohorts, systematic reviews, and clinical trials on targeted therapy. Immunological evaluation included quantitative determination of immunoglobulins, immunophenotyping (CD3/4/8/19/NK, Treg-FOXP3+, double-negative T-cells), complement system assessment (C3/C4/CH50/AH50), and functional tests (DHR-test, interferon signature).

Genetic diagnostics were based on Next-Generation Sequencing (NGS), with subsequent variant classification according to ACMG criteria.

Limitations of the Review

Several important limitations should be noted. First, the heterogeneity of diagnostic methods across different centers makes a direct comparison of immunological parameters difficult. Second, for rare syndromes (such as interferonopathies), only small case series are available, which precludes the possibility of drawing statistically robust conclusions. Third, there is a potential publication bias, as severe and unusual cases are published more frequently, which may distort the perception of a typical disease course. Finally, for relatively new agents (such as leniolisib for APDS and JAK inhibitors for interferonopathies), long-term safety and efficacy data are currently lacking; most existing studies are limited to 2–3 years of follow-up.

Results

Immunogenetic Mechanisms of Rheumatological Manifestations

Literature analysis allowed for the identification of five core pathogenetic mechanisms underlying the rheumatological manifestations in PID:

1. Impairment of Peripheral Tolerance (CTLA4/LRBA): This is perhaps the most well-studied mechanism. CTLA4 functions as a critical inhibitory checkpoint by counteracting CD28 co-stimulatory signals. CTLA4 haploinsufficiency leads to uncontrolled T-cell activation [7]. A breakthrough discovery established that LRBA deficiency results in enhanced lysosomal degradation of CTLA4, clinically presenting with a similar phenotype. The largest comparative study of 434 patients (222 CTLA4 vs. 212 LRBA) revealed key differences: LRBA deficiency has an earlier onset (median 3.5 vs. 12 years), a more severe course, and a higher frequency of arthritis (15% vs. 9%).

2. JAK-STAT Pathway Hyperactivation (STAT1/3-GOF): Gain-of-function (GOF) mutations in the STAT1 and STAT3 genes lead to constitutive activation of cytokine signaling pathways. A multicenter study of 191 patients with STAT3-GOF showed a median age of onset at 2.3 years, while the median age at diagnosis was 12 years—a colossal delay [8]. Interestingly, arthritis occurs in 35% of patients and vasculitis in one-third. An increase in double-negative (CD4-CD8-) T-cells (>20%) is observed in 83% of those tested, serving as a valuable diagnostic marker. STAT1-GOF is characterized by chronic candidiasis in >90% of patients combined with autoimmune manifestations.

3. Constitutive PI3K-AKT-mTOR Activation (APDS): Activating mutations in PIK3CD (most commonly p.E1021K) cause Activated PI3K-delta Syndrome (APDS), characterized by lymphoproliferation, recurrent infections, and arthritis in 20–30% of patients [9]. Notably, there is an increased risk of B-cell lymphomas, requiring heightened oncological vigilance.

4. Excessive Production of Type I Interferons (Interferonopathies): Mutations in genes such as TREX1, RNASEH2A/B/C, SAMHD1, ADAR, and TMEM173 (STING) lead to the accumulation of cytoplasmic nucleic acids and activation of the cGAS-STING pathway, inducing an interferon response [10]. Clinically, this manifests as vasculitis, arthritis, and an early-onset SLE-like phenotype. The interferon signature in peripheral blood (elevated expression of IFI27, IFI44L, IFIT1, ISG15) serves as a screening biomarker.

5. Impaired Clearance of Apoptotic Cells (Complement Defects): Deficiencies in the early components of the classical pathway (C1q, C1r/C1s, C2, C4) are the most potent genetic risk factors for Systemic Lupus Erythematosus (SLE). C1q deficiency is associated with SLE development in 93% of homozygous carriers, and C4 deficiency in 75% [11]. The mechanism involves impaired clearance of apoptotic cells, leading to the exposure of autoantigens and the production of antinuclear antibodies.

Clinical Case Study from the Literature

A notable case described by Lo et al. (2015) illustrates these points [3]: A 6-year-old girl presented with progressive enteropathy, recurrent pneumonia, and polyarthritis resistant to methotrexate and infliximab. The findings of lymphopenia, hypogammaglobulinemia, and a reduction in switched memory B-cells suggested an underlying Primary Immunodeficiency (PID).

NGS (Next-Generation Sequencing) identified a biallelic mutation in LRBA, resulting in a total absence of the protein. Following the initiation of Abatacept, the patient's diarrhea resolved, infections ceased, and remission of arthritis was achieved. Within six months, the patient gained 4.5 kg, and follow-up endoscopy showed normalization of the intestinal mucosa. This case vividly demonstrates how molecular diagnostics can fundamentally transform management strategies.

Targeted Therapies in PID and Autoimmunity

Abatacept in CTLA4/LRBA Deficiency: A Turkish study of 98 patients showed that traditional immunosuppression provides only partial or no control in 72% of patients with LRBA deficiency [12]. Abatacept (soluble CTLA4-Ig) achieves complete control in 43% of LRBA patients and 60% of those with CTLA4 haploinsufficiency. Early initiation is critical: patients with prolonged disease activity prior to Abatacept administration demonstrate significantly poorer responses. In our view, this represents one of the few examples of true precision medicine in pediatric rheumatology.

JAK Inhibitors in STAT-GOF and Interferonopathies: A multicenter study of 10 pediatric patients with STAT1-GOF treated with ruxolitinib demonstrated a reduction in the IDDA activity index from a median of 15.99 to 7.55 [13]. Autoimmune cytopenias and candidiasis respond within 1–8 weeks, while keratitis and hepatitis show slower improvement (4–8 months). In interferonopathies, the effect is variable: some patients show a reduction in the interferon signature and improved neuromotor skills, though outcomes depend on starting therapy before irreversible neurological deficits develop.

IL-1 Blockade in Autoinflammatory Diseases: In randomized controlled trials for CAPS, Canakinumab (anti-IL-1β) showed a complete response in 97% of patients with Muckle-Wells syndrome and 71% with NOMID/CINCA [14]. In colchicine-resistant Familial Mediterranean Fever (FMF), canakinumab ensures complete attack control in 61% of patients vs. 6% in the placebo group ($p < 0.001$). Long-term follow-up confirmed the prevention of amyloidosis and the preservation of hearing.

PI3K Inhibitors in APDS: In an open-label Phase II study of 31 patients, Leniolisib (a selective PI3Kδ inhibitor) administered at 70 mg twice daily led to

a lymph node response (≥50% reduction) in 47% of patients by week 12 [15]. The normalization of CD19+ B-cells and switched memory B-cells allowed some patients to discontinue immunoglobulin replacement therapy. The safety profile is acceptable, with upper respiratory tract infections, headache, and diarrhea being predominantly mild.

Diagnostic Algorithm

Based on the literature analysis, a five-stage algorithm is proposed for practicing pediatric rheumatologists:

Step 1. Clinical "Red Flags": Onset before 6 years of age; combination of infections and autoimmunity; recurrent febrile attacks with arthritis; familial episodes of fever; resistance to NSAIDs/GCS/methotrexate; and chronic candidiasis.

Step 2. Basic Screening: CBC (identify lymphopenia and thrombocytopenia!); immunoglobulins (IgG/A/M/E); lymphocyte subpopulations (CD3/4/8/19/NK); and complement components (C3/C4/CH50/AH50). In case of abnormalities, immediate consultation with an immunologist is required.

Step 3. Advanced Evaluation: Expanded immunophenotyping (Treg, double-negative T-cells, cTfh); DHR-test (if CGD is suspected); interferon signature; and post-vaccination antibody titers.

Step 4. Genetics: NGS panel for PID (including CTLA4, LRBA, PIK3CD, STAT1, STAT3, FOXP3, MEFV, NLRP3, C1QA, TREX1, RNASEH2B, etc.) or Whole Exome Sequencing (WES) for atypical phenotypes.

Step 5. Multidisciplinary Interpretation: Joint consultation between an immunologist and a rheumatologist; variant classification according to ACMG guidelines; and development of a personalized clinical protocol.

Global Insights in Biomedical & Multidisciplinary Research (GIBMR)
Volume 01, Issue 02, April-2026
Available Online at: https://biomedglobe.com/index.php/gibmr
ISSN (Online): 3054-5900

TABLE

Table 1A. Primary Immunodeficiencies with Immune Dysregulation

PID	Gene	Rheumatological manifestations
CTLA-4 insufficiency / haploinsufficiency	CTLA4	Arthritis, vasculitis, granulomas, autoimmune cytopenia
LRBA-deficiency	LRBA	Chronic arthritis, autoimmune vasculitis, enterocolitis
APDS (PI3Kδ)	PIK3CD/PIK3R1	Arthralgia, arthritis, lymphoproliferation, autoimmunity
CVID + autoimmunity	Various	Arthritis, vasculitis, sarcoid-like granulomas
IPEX	FOXP3	Arthritis (less common), dermatitis, multiorgan autoimmunity
STAT3-GOF	STAT3	Early-onset vasculitis, arthritis (35%), autoimmune cytopenia, risk of lymphoma
STAT1-GOF	STAT1	Arthritis, vasculitis, chronic candidiasis >90%

Table 1B. Autoinflammatory Syndromes with Rheumatological Features

Desease	Gene	Rheumatological manifestations
FMF (ССЛ)	MEFV	Acute mono- and oligoarthritis, serositis, abdominal crises
TRAPS	TNFRSF1A	Migratory arthritis, myalgia, persistent fevers
MKD/HIDS	MVK	Arthritis, cervical lymphadenopathy, rash
NLRP3-CAPS	NLRP3	Chronic urticaria+arthritis+fever, CNS involvement
Blau Syndrome	NOD2	Granulomatous arthritis, uveitis

Table 1C. Complement System Defects with Rheumatological and Autoimmune Manifestations

Deficiency	Rheumatological manifestations

C1q, C1r, C1s, C2, C4	Early-onset SLE-like syndrome, arthritis, vasculitis, glomerulonephritis
Complement Factor H/I Deficiency	Vasculitis, atypical Hemolytic Uremic Syndrome (aHUS) phenotype

Table 1D. Combined Immunodeficiencies and Phagocyte Defects

PID	Gene	Rheumatological manifestations
Wiskott-Aldrich (WAS)	WAS	Vasculitis, arthritis, SLE-like manifestations
DiGeorge (22q11.2)	TBX1	Autoimmune arthritis, vasculitis
Omenn Syndrome	RAG1/2	Erythroderma, autoimmune manifestations
CGD	CYBB, CYBA, NCF1	Granulomatous arthropathies, vasculitis, colitis
LAD	ITGB2	Chronic skin inflammation, ulcers, impaired wound healing

Global Insights in Biomedical & Multidisciplinary Research (GIBMR)
Volume 01, Issue 02, April-2026
Available Online at: https://biomedglobe.com/index.php/gibmr
ISSN (Online): 3054-5900

Table 2A. Interpretation of Immunoglobulin Abnormalities in PID Diagnosis

Abnormality	Suspected PID	Comment
Low IgG	CVID, XLA, Combined Immunodeficiencies	Recurrent infections and autoimmunity
Low IgA	CVID, selective IgA deficiency	Arthritis and vasculitis
High IgM + low IgG/IgA	Hyper-IgM (CD40L, AID, UNG)	Autoimmune cytopenias
IgE >1000–2000 IU/ml	STAT3-HIES, DOCK8, PGM3	Cutaneous manifestations and autoimmunity
High IgG and IgA	NLRP3-CAPS, FMF, STAT1-GOF	Mimics autoimmunity

Table 2B. Lymphocyte Subpopulations

Abnormality	Suspected PID	Clinical Significance
Low CD19+ B-cells	XLA (BTK), CVID, APDS	Infections and arthritis
High CD19+	APDS, CD21L-deficiency	Lymphadenopathy and autoimmunity
ДН-Т (CD4-CD8-) >20%	STAT3-GOF, ALPS	High-risk marker for lymphoma!
CD4/CD8 < 1	ALPS, STAT3-GOF, CTLA4/LRBA	Autoimmune cytopenia and splenomegaly
Low Treg (FOXP3+)	IPEX, CTLA4, LRBA	Arthritis, enteropathy, and cytopenias

Table 2C. Complement System and Functional Assays in PID Diagnosis

Assay	Suspected PID	Clinical Phenotype
Low CH50	C1q, C1r/C1s, C2, C4-deficieny	Systemic autoimmune/vasculitic phenotype.
Low AH50 (Normal CH50)	Alternative pathway defects	Atypical HUS (aHUS), vasculitis.

Low C3 ↓ (Normal C4)	Factor H / Factor I deficiency	HUS-like syndrome, vasculitis.
High Interferon Signature ↑	TREX1, RNASEH2B, SAMHD1, TMEM173	Early-onset SLE, vasculitis, arthritis.
DHR Test (No oxidative burst)	CGD (CYBB, CYBA, NCF1)	Granulomatous arthropathies, colitis.

Table 3. Targeted Therapy Based on Specific Molecular Defects in PID

CID	Targeted Agent	Therapeutic Efficacy
CTLA4/LRBA	Abatacept	Full control in **43–60%**; survival rates comparable to HSCT.
STAT1/3-GOF	Ruxolitinib, Baricitinib	**53% reduction** in IDDA score; clinical response within 1–8 weeks.
APDS	Leniolisib	**47% reduction** in lymphadenopathy by week 12; B-cell normalization.
CAPS (NLRP3)	Canakinumab	Complete response: **MWS 97%**, **NOMID 71%**, **FCAS 100%**.
ССЛ (MEFV)	Colchicine → Canakinumab	In colchicine resistance: **61% vs. 6%** (placebo) response rate.
Interferonopathies	JAK inhibitors	Reduction in **IFN-signature**; variable CNS response observed.

Conclusion

The literature analysis demonstrates that rheumatological manifestations in children with primary immunodeficiencies (PID) are not a rarity, but rather the rule for specific genetic defects. A median diagnostic delay of 2.7 years is unacceptable in the era of accessible Next-Generation Sequencing (NGS) and targeted therapy [16]. A critical factor is the heightened clinical suspicion of pediatric rheumatologists regarding PID in cases of atypical presentation, early onset, or resistance to standard therapy.

Five primary pathogenetic mechanisms have been established, each of which dictates the approach to targeted therapy. The results in CTLA4/LRBA deficiency are particularly impressive: Abatacept does not merely control symptoms but achieves survival rates comparable to Hematopoietic Stem Cell Transplantation (HSCT), without the associated transplant toxicity. JAK inhibitors have ushered in a new era for treating STAT-GOF mutations and interferonopathies, although their long-term safety profiles require further investigation.

The developed five-stage diagnostic algorithm is practical and ready for implementation into routine pediatric rheumatology practice. Basic immunological screening is accessible in most centers; upon detecting abnormalities, timely consultation with an immunologist and NGS diagnostics enable a molecular diagnosis and the initiation of pathogenetic therapy.

Conclusions

1. Rheumatological manifestations occur in 10–50% of children with primary immunodeficiency (PID), depending on the genetic defect, and often precede infectious complications, creating diagnostic challenges for practicing rheumatologists.
2. Five primary immunogenetic mechanisms have been identified: impaired peripheral tolerance (CTLA4/LRBA), JAK-STAT hyperactivation (STAT1/3-GOF), PI3K-AKT-mTOR activation (APDS), type I interferon hyperproduction (interferonopathies), and complement defects (C1q/C4).
3. Molecular diagnostics enables personalized targeted therapy, which significantly outperforms traditional immunosuppression in terms of efficacy and safety.
4. Abatacept achieves complete control in 43–60% of patients with CTLA4/LRBA deficiency; JAK inhibitors reduce the IDDA score by 53% in cases of STAT-GOF; and canakinumab demonstrates a 97% complete response rate in CAPS.
5. A five-stage diagnostic algorithm (clinical flags - basic screening - advanced evaluation – NGS - multidisciplinary interpretation) allows for a reduction in the median diagnostic delay and the timely initiation of targeted therapy.

References

1. Tangye SG, Al-Herz W, Bousfiha A, Cunningham-Rundles C, Franco JL, Holland SM, Klein C, Morio T, Oksenhendler E, Picard C, Puel A, Puck J, Seppänen MRJ, Somech R, Su HC, Sullivan KE, Torgerson TR, Meyts I. Human inborn errors of immunity: 2024 update on the classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2024;44(Suppl 1):44. doi: 10.1007/s10875-024-01755-0
2. Bousfiha A, Moundir A, Tangye SG, et al. The 2024 update of IUIS phenotypic classification of human inborn errors of immunity. J Hum Immun. 2025;1(1):e20250002.
    a. doi:10.70962/jhi.20250002
3. Lo B, Zhang K, Lu W, et al. Patients with LRBA deficiency show CTLA4 loss and immune dysregulation responsive to abatacept therapy. Science. 2015;349(6246):436-440. doi:10.1126/science.aaa1663
4. Fischer A, Provot J, Jais JP, et al. Autoimmune and inflammatory manifestations occur frequently in patients with primary immunodeficiencies. J Allergy Clin Immunol. 2017;140(5):1388-1393. doi:10.1016/j.jaci.2016.12.978
5. Saeidi Z, Mahdaviani S, Bemanian MH, et al. Rheumatologic manifestations in children with underlying inborn errors of immunity. BMC Rheumatol. 2025;9(1):57. doi:10.1186/s41927-025-00508-9
6. Tangye SG, Al-Herz W, Bousfiha A, et al. Human Inborn Errors of Immunity: 2022 Update on the Classification from the IUIS Expert Committee. J Clin Immunol. 2022;42(7):1473-1507. doi:10.1007/s10875-022-01289-3
7. Jamee M, Azizi G, Baris S, et al. Comprehensive comparison between 222 CTLA-4 haploinsufficiency and 212 LRBA deficiency patients: a systematic review. Clin Exp Immunol. 2021;205(1):28-43. doi:10.1111/cei.13600
8. Leiding JW, Vogel TP, Santarlas VGJ, et al. Monogenic early-onset lymphoproliferation and autoimmunity: natural history of STAT3 gain-of-function syndrome. J Allergy Clin Immunol. 2022;150(5):1081-1096. doi:10.1016/j.jaci.2022.05.014
9. Tangye SG, Bier J, Lau A, et al. Immune dysregulation and disease pathogenesis due to activating mutations in PIK3CD. J Clin Immunol. 2019;39(6):520-539. doi:10.1007/s10875-019-00692-9
10. Crow YJ, Manel N. Aicardi-Goutieres syndrome and the type I interferonopathies. Nat Rev Immunol. 2015;15(7):429-440. doi:10.1038/nri3850

11. Botto M, Dell'Agnola C, Bygrave AE, et al. Homozygous C1q deficiency causes glomerulonephritis associated with multiple apoptotic bodies. Nat Genet. 1998;19(1):56-59. doi:10.1038/ng0598-56
12. Egg D, Rump IC, Mitsuiki N, et al. Therapeutic options in CTLA-4 insufficiency. J Allergy Clin Immunol. 2022;149(2):736-746. doi:10.1016/j.jaci.2021.04.039
13. Deya-Martinez A, Martinez-Saavedra MT, Duckers G, et al. Impact of JAK inhibitors in pediatric patients with STAT1 gain of function mutations. J Clin Immunol. 2022;42(5):1071-1082. doi:10.1007/s10875-022-01264-y
14. Lachmann HJ, Kone-Paut I, Kuemmerle-Deschner JB, et al. Use of canakinumab in the cryopyrin-associated periodic syndrome. N Engl J Med. 2009;360(23):2416-2425. doi:10.1056/NEJMoa0810787
15. 15Rao VK, Webster S, Dalm VASH, Šedivá A, van Hagen PM, Holland S, Rosenzweig SD, Christ AD, Sloth B, Cabanski M, Joshi AD, de Buck S, Doucet J, Guerini D, Kalis C, Pylvaenaeinen I, Soldermann N, Kashyap A, Uzel G, Lenardo MJ, Patel DD, Lucas CL, Burkhart C. Effective "activated PI3Kδ syndrome"-targeted therapy with the PI3Kδ inhibitor leniolisib. Blood. 2017;130(21):2307-2316. doi: 10.1182/blood-2017-08-801191
16. Meyts I, Bousfiha A, Dbaibo G, et al. Primary immunodeficiencies: a decade of progress and a promising future. Front Immunol. 2021;12:625753. doi:10.3389/fimmu.2021.625753
17. Milner JD, Vogel TP, Forbes L, et al. Early-onset lymphoproliferation and autoimmunity caused by germline STAT3 gain-of-function mutations. Blood. 2015;125(4):591-599. doi:10.1182/blood-2014-09-602763
18. Baris S, Alroqi F, Kiykim A, et al. Severe early-onset combined immunodeficiency due to heterozygous gain-of-function mutations in STAT1. J Clin Immunol. 2016;36(7):641-648. doi:10.1007/s10875-016-0312-3
19. Kuehn HS, Ouyang W, Lo B, et al. Immune dysregulation in human subjects with heterozygous germline mutations in CTLA4. Science. 2014;345(6201):1623-1627. doi:10.1126/science.1255904
20. Azarsiz E, Keles S, Baskin E, et al. Autoimmune and inflammatory manifestations in pediatric patients with primary immunodeficiencies. Allergol Immunopathol. 2021;49(1):61-68. doi:10.15586/aei.v49i1.132
21. Liu Y, Jesus AA, Marrero B, et al. Activated STING in a vascular and pulmonary syndrome. N Engl J Med. 2014;371(6):507-518. doi:10.1056/NEJMoa1312625

22. Ozen S, Kone-Paut I, Gul A. Colchicine resistance and intolerance in familial Mediterranean fever. Semin Arthritis Rheum. 2017;47(1):115-120. doi:10.1016/j.semarthrit.2017.03.006
23. De Benedetti F, Gattorno M, Anton J, et al. Canakinumab for the treatment of autoinflammatory recurrent fever syndromes. N Engl J Med. 2018;378(20):1908-1919. doi:10.1056/NEJMoa1706314
24. Yang Y, Chung EK, Wu YL, et al. Gene copy-number variation and associated polymorphisms of complement component C4 in human SLE. Am J Hum Genet. 2007;80(6):1037-1054. doi:10.1086/518257
25. Gadina M, Le MT, Schwartz DM, et al. Janus kinases to jakinibs: from basic insights to clinical practice. Rheumatology. 2019;58(Suppl 1):i4-i16. doi:10.1093/rheumatology/key432