pISSN: 2093-940X, eISSN: 2233-4718
Journal of Rheumatic Diseases Vol. 25, No. 4, October, 2018
https://doi.org/10.4078/jrd.2018.25.4.213

Review Article

Monogenic Autoimmune Diseases

Dae Chul Jeong

Division of Pediatric Rheumatology and Clinical Immunology, Department of Pediatrics, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

Monogenic autoimmune diseases (AD) present as lupus-like clinical manifestations with recurrent fever or various vasculopathies. Recurrent fever with an elevation of acute phase reactants and various skin lesions are similar in monogenic AD and autoinflammatory disease. The molecular pathogenesis of adult systemic erythematosus can be understood through monogenic AD based on gene defects: complement, apoptosis, interferonopathy via nucleic acid sensing, tolerance, rasopathies, and others. Skin vasculopathy with chilblains and livedo reticularis, interstitial lung disease, and panniculitis are common occurrences in type I interferonopathy. Some syndromes have been reported to present with autoimmune inflammation and the general clinical findings, including cerebral calcification. Various clinical manifestations in monogenic AD present in accordance with the gene loss- or gain-of-function mutations involved. The monogenic AD for the early onset of more severe lupus-like symptoms or vasculopathy needs to be considered. Furthermore, clinical trials were conducted via targeted therapy for related molecular pathways, because conventional treatments were not effective in managing monogenic AD. **(J Rheum Dis 2018;25:213-220)**

Key Words. Autoimmune diseases, Genes, Systemic lupus erythematosus, Interferon

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, autoimmune multi-system disease with various clinical manifestations. SLE is caused by the production of autoantibodies, complement activation, and immune complex deposition [1-3]. Approximately 20% of SLE cases are diagnosed in childhood. Pediatric SLE usually presents around puberty with more severe clinical manifestations than those in adults, however, it has a significantly lower incidence before puberty, and very rare before 5 years of age [1]. The pathogenesis of SLE is associated with multi-factorial pathogenesis including environmental, genetic, or hormonal factors [3-5]. Genome wide association studies have identified genes related with SLE pathogenesis [3].

The incidence of most autoinflammatory diseases (AID) is associated with gene mutations involved in the innate immune system, autoimmune diseases (AD) is related with adaptive immunity [6]. Both AID and AD primarily result in inflammation due to chronic immune activation [7]. Many AD, including SLE, are polygenic, while AID, including familial Mediterranean fever, are identified as monogenic diseases; however, in some cases, AID can also be polygenic, AD is associated with monogenic cause [6,7]. Patients with SLE showed high levels of interferon (IFN) [1,3]. Cytokine production is dependent on activation of cell signaling pathway related with cytokine genes [3,8]. In the pathogenesis of AID or AD, high level of various cytokines was identified, and associated with uncontrolled cytokine production regardless with polygenic or monogenic causes.

Recently, a pediatric monogenic lupus-like phenotype was reported, and is called monogenic lupus in accordance with the genes involved in autoimmune inflammation [9,10]. Understanding of the pathogenesis of

Received : March 13, 2018, **Revised** : June 13, 2018, **Accepted** : June 28, 2018

Corresponding to : Dae Chul Jeong http://orcid.org/0000-0003-0934-817X
Division of Pediatric Rheumatology and Clinical Immunology, Department of Pediatrics, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea. E-mail : dcjeong@catholic.ac.kr

monogenic lupus may provide insights into SLE pathogenesis, although it is classified as an autoinflammatory disease [8,11].

Now, the present article discusses monogenic ADs based on their development and the pathogenesis of autoimmune manifestations.

MAIN SUBJECTS

Clinical manifestations

Most patients with monogenic or Mendelian lupus developed various early-onset systemic and organ-specific symptoms or signs at a young age [10,12-14]. Fever or elevation in acute phase reactants are frequently identified as systemic inflammation [9,10,14]. Skin rash is one of various manifestations resulting from gene mutations related with autoinflammatory or autoimmune responses [9,10,13-15]. In monogenic autoimmune diseases with gene mutations, organ defects or metabolic manifestations have been reported to be caused by genes involved in organ growth or development [9,10,16]. Auto-antibodies displayed a high or low titer in accordance with the gene mutation at any age [9,10]. Musculoskeletal symptoms were observed in many cases, and cardiopulmonary events including pulmonary hypertension or interstitial lung disease developed [9,10,12-15]. In some patients,

Table 1. The monogenic autoimmune diseases with corresponding pathogenesis and phenotype

Pathogenesis	Gene	Proteins	Inheritance	Phenotype
Complement/ immune clearance	*C1QA/C1QB/ C1QC*	C1q	AR	SLE with rashes, GN, CNS, ani-dsDNA often negative, recurrent infection
	C1R	C1r	AR	SLE with rashes, GN, recurrent infection
	C1S	C1s	AR	SLE with rashes, GN, recurrent infection
	C2	C2	AR	SLE with arthritis, rashes, auto-antibodies often negative, recurrent infection
	C4A, C4B	C4	AR	SLE with variable phenotype, rashes, proliferative GN, recurrent infection
Apoptosis	*TNFRSF6*	Fas	AD	Autoimmune lymphoproliferative syndrome (ALPS), autoimmune cytopenias
	FASL	FasL	AD	ALPS, SLE with lymphadenopathy
Immune clearance	*DNASE1*	DNase1	AD	SLE: high titer anti-nucleosomal antigens
	DNASE1L3	DNase1L3	AD	Anti-dsDNA antibodies, low C3/C4, GN and positive ANCA: very young age of onset
Nucleic acid sensing/Type I IFN	*TREX1*	TREX1	AR/AD	AGS: FCL: SLE with severe CNS disease
	SAMHD1	SAMHD1	AR	AGS: FCL
	ADAR1	ADAR1	AR/AD	AGS
Nucleic acid sensing/Type I IFN	*IFIH1*	IFHI1, MDA5	AD	AGS
	RNASEH (2A, 2B, 2C)	RNaseH2 complex	AR	AGS
	NEIL3	NEIL3	AR	Recurrent infection; autoimmune cytopenias
	ACP5	TRAP	AR	Spndyloenchondrodysplasia, autoimmune cytopenia; recurrent infection
Apoptosis/ Tolerance	*PRKCD*	PKC δ	AR	SLE
Tolerance	*RAG2*	RAG2	AR/AD	Leaky SCID; Omenn syndrome: autoimmune cytopenia; granuloma
Ras/MAPK	*SHOC2*	Shoc2	AD	Noonan syndrome; SLE with polyarthritis
	KRAS	K-Ras	AD	Noonan syndrome; SLE
Collagen degradation	*PEPD*	PEPD	AR	Polidase deficiency; sever leg ulcers; SLE

AR: autosomal recessive, AD: autosomal dominant, GN: glomerulonephritis, CNS: central nervous system disease, AGS: Aicardi-Goutieres syndrome, FCL: familial chilblain lupus, SCID: severe combined immunodeficiency. This table is modified and adapted from Lo, Curr Rheumatol Rep 2016;18:71 [10].

pulmonary hemorrhage with primary immune dysregulation, called COPA syndrome, has been reported to result from genetic defects deterring the transport of cargo between the Golgi complex and the endoplasmic reticulum [17]. Furthermore, recurrent infections are frequent because of gene mutations associated with the immune responses [9-11]. The clinical features of monogenic lupus include a significantly younger age at onset, and relatively lower frequency of joint manifestations in familial lupus [18].

Pathogenesis of autoimmune manifestations based on monogenic defects (Table 1)

1) Complement

Familial SLE due to complement deficiency have been reported as early as the 1950s [19]. The complement system contributes to the elimination of apoptotic cells and immune complexes on opsonization or clearance of apoptotic cells or immune complexes [9,10,16]. C1q has a role for toll-like receptor induced cytokine production and immune complex-induced IFN-1 production by dendritic cells [10,20]. C1q deficiency was reported to the result in photosensitive skin rash, nephritis, oral ulceration, and arthritis at young-age. In C1q deficiency, C3 and C4 present as normal levels; however, total hemolytic complement levels are low. Furthermore, anti-Ro antibodies were more commonly detected than anti-DNA antibodies [16,20]. C1s/1r and C2 are important for the classical pathway; C4, for complement activation [20,21]. The patients with C1s/C1r deficiency presented with severe skin disease, glomerulonephritis (GN), recurrent bacterial infections, and had anti-Ro or anti-extractable nuclear antigen (ENA) antibodies with lower titers of anti-DNA antibodies. Anti-nuclear antibodies (ANA) may not be present or may be present in low titer [21].

Patients with C4 deficiency had severe skin diseases and GN with anti-Ro antibodies [20]. The prevalence of homozygous C2 deficiency in the European population is higher than that in other races; however, only 10% to 30% of them developed SLE [22]. SLE patients with C2 deficiency have severe skin disease with cutaneous vasculitis, malar rash, discoid rash, and arthritis with anti-Ro antibodies. Some of them had anti-cardiolipin antibodies [16,23].

2) Apoptosis

Inherited mutations of Fas and Fas ligand, which play an important role in apoptosis, lead to autoimmune lymphoproliferative syndrome, characterized by immune cytopenia, GN, and autoimmune hepatitis at an early age [24,25].

Defective nucleic acid or DNA from dead cells serves as an immunogen to drive T and B cells response. DNase1, encoded by *DNASE1*, is the major endonuclease capable of cleaving ssDNA and dsDNA. Patients with *DNASE1* mutations presented with SLE phenotype with higher titers of anti-nucleosome antibodies [16,26]. In particular, DNase 1L3 is capable of translocating from the cytoplasm to the nucleus for cleaving DNA during apoptosis or necrosis [27]. Two phenotype of *DNASE1L3* mutation presented as hypocomplmentemic urticarial vasculitis, characterized by malar rash, photosensitivity, GN, raynaud phenomenon, arthritis with multiple auto-antibodies, and young-onset SLE [9,10,16].

3) Type I interferonopathy

IFNs are well described as a soluble defense factor produced by cells treated with inactivated, non-replicating viruses [12,14]. Pattern recognition receptors including Toll-like receptors detect pathogen in the cytoplasm or endosomes of infected cells. Cytosolic sensors, GMP-AMP synthetase (cGAS), interact with pathogens, and induce IFN-1 production. After apoptosis or necrosis, DNA, such as that of pathogens, bind to cGAS, and activates the adaptor protein receptor protein stimulator of IFN gene (STING), which translocates to the endoplasmic reticulum, leading to an interaction with TANK-binding kinase 1 and the subsequent phosphorylation of IFN-regulating factor-3 (IRF-3). Phosphorylated IRF-3 then translocates into the nucleus and activates the production of IFN-1 and proinflammatory cytokines [12,16,28]. Viral RNA is detected by retinoic acid inducible gene (RIG)-like receptors family including RIG-1, melanoma differentiation-associated gene 5 (MDA5) in the cytosol. Activated RIG-1 or MDA5 translocates to the mitochondria to activate mitochondrial antiviral signaling (MAV5), at the external mitochondrial membrane. Activated MAV5 interacts with TBK1 to activate IRF3 [12,16,28]. The production of IFN-1 was related with the expression of numerous genes. Type I interferonopathies result from the loss-of-function or gain-of-function mutations in genes associated with IFN production, and proteasome dysfunction (Figure 1) [12,28].

(1) Loss-of-function mutations with increased cytosolic DNA or RNA/DNA hybrid sensing. Genes related with increased cytosolic DNA are DNA 3'-repair exonuclease (*TREX1*) and control of the

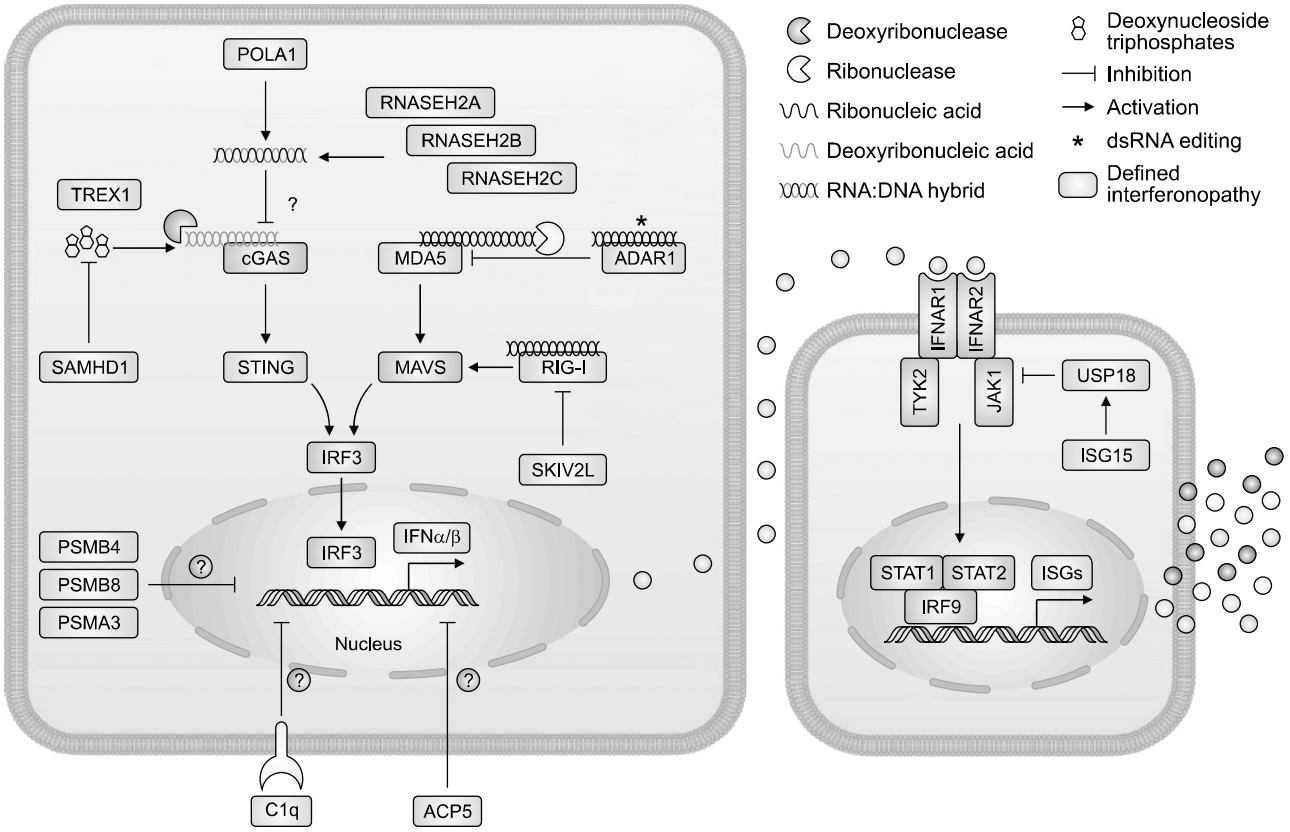

Figure 1. Type 1 interferon signaling and type 1 interferonopathies as currently assigned. This figure is adapted from Rodero et al. J Exp Med 2016;213:2527-38 [28]. ADAR1: adenosine deaminase RNA specific 1, ACP5: acid phosphatase 5, C1q: complement 1q, cGAS: GMP-AMP synthetase, IFN α/β: interferon α/β, IFNAR1: interferon alpha and beta receptor subunit 1, IFNAR2: interferon alpha and beta receptor subunit 2, JAK1: Janus kinase 1, IRF3: interferon regulatory factor 3, IRF9: interferon regulatory factor 9, ISGs: interferon-stimulating genes, ISG15: interferon-stimulating gene 15, MDA5: melanoma differentiation-associated gene 5, MAVS: mitochondrial antiviral signaling 5, POLA1: DNA polymerase 1, PSMB4: proteasome subunit beta 4, PSMB8: proteasome subunit beta 8, PSMA3: proteasome subunit beta 3, RNASEH2A: ribonuclease H2A, RNASEH2B: ribonuclease H2B, RNASEH2C: ribonuclease H2C, RIG-1: retinoic acid inducible gene-1, SAMHD1: SAM domain and HD domain containing deoxynucleoside triphosphate triphosphohydrolase 1, SKIV2L: superkiller viralicidic activity 2-like RNA helicase, STAT1: signal transducers and activators of transcription 1, STAT2: signal transducers and activators of transcription 2, TYK2: tyrosine kinase 2.

dNTP pool (*SAMHD1*). Genes with RNA/DNA hybrid sensing are ribonuclease H2 (*RNASEH2A, RNASEH2B, RNASEH2C*), and polymerase (*POLA1*).

(2) Loss-of-function mutations with a defect in RNA editing and abnormal sensing of self-nucleic acid RNA species in the cytosol, including that for RNA editing (*ADAR1*).

(3) Gain-of-function mutations with constitutive activation of cytosolic interferon signaling pathways or increased sensitivity to cytosolic nucleic acid ligands; *STING* and RIG including *MDA5*, and *RIG-1*.

(4) Loss-of-function mutations in molecules limiting IFN receptor signaling leading to uncontrolled IFN-stimulating genes (ISG) expression. Such genes are inhibitor of ISG transcription (*USP18*, and *ISG15*).

(5) Proteasome dysfunction with increased IFN signaling; *PSMA3*, *PSMA4*, and *PSMBB*.

(6) Loss-of-function mutations in TRAP/ACP5, and C1q.

4) Tolerance

PKC δ plays an important role in T or B cell activation [29], and is crucial for B cell negative selection [30]. In SLE, the autoreactive B cells are not eliminated in B cell development. A Homozygous *PRKCD* mutation is induced to reduce PKC δ expression and activity, and autoreactive B cells are not controlled through hyperproliferative responses to B cell stimulation via B cell receptor [31]. *RAG1/RAG2* genes are necessary for V(D)J recombination with T and B cell receptor, and B cell re-

ceptor editing in the bone marrow during development of lymphocytes [32]. Patient with a heterozygous mutation in *RAG2* presented with SLE manifestations including lupus nephritis, erosive arthritis, etc. [33].

5) Rasopathies

Ras is a small GTPase activated downstream of the TCR signaling pathway, and necessary for T cell maturation [34]. Some patients with Noonan syndrome are reported to have lupus-like phenotypes, and have gain-of-function mutations with constitutive stimulation of T cell proliferation and inhibition of T cell apoptosis [35].

Clinical features of monogenic molecular defects

1) Aicardi-Goutiéres Syndrome

Aicardi-Goutiéres Syndrome (AGS) resembles with congenital viral infection, in that neonatal encephalopathy with basal ganglia calcification and white matter changes are observed [36]. Patients with AGS are associated with high level of type I IFN in the serum and cerebrospinal fluid [37]. AGS patients showed neurological phenotype, and developed glaucoma, chilblains, and autoimmune symptoms [38]. Mutations are observed in the following genes in AGS: *RNASEH2B, TREX1, RNASEH2C, SAMHD1, ADAR, RNASEH2A*, and IFN-induced with helicase C domain 1 (*IFIH1*) [38,39].

(1) *TREX1*

Approximately 60% of patients with *TREX1* gene mutations had at least 1 autoimmune manifestation: thrombocytopenia, leucopenia, ANA, skin lesions, oral ulceration, arthritis, or anti-dsDNA or ENA antibodies [37]. Some patients presented with SLE phenotypes and central nervous system (CNS) disease with severe Raynaud phenomenon [40].

(2) *IFIH1* and *MDA5*

Patients with mutations in these genes presented with clinical features of AGS and lupus-like phenotype with GN and skin rash [41]. Some patients had anti-aquaporin4 antibodies, positive ANA, and anti-dsDNA antibodies [42].

(3) *SAMHD1* (approximately 13% of AGS)

The patients with *SAMHD1* mutation presented with chilblain lupus with or without CNS disease, arthritis, mental retardation and microcephaly [43].

(4) *RNaseH2*

Approximately one-third of AGS patients with *RNASEH2* variants presented with a positive ANA. Clinical features in these patients are variable from mild SLE with or without organ involvement to sever chilblains of fingers or toes with arthralgia and elevated anti-dsDNA antibodies [44].

(5) *ADAR1* (adenosine deaminase acting on RNA1)

2) Familial SLE

Familial SLE is rare; however, it has been reported in several patients with mutations in *TREX1, SAMHD1, ACP5, DNase1, DNase1L3, PRKCD*, and complements genes with C1q/r/s and C4 subunits [14].

In *TREX1* mutation, skin lesions at the extremities were presented along with chilblains after cold exposure, and other symptoms were similar to those of SLE [45]. Some patients have been reported to present with retinal vasculopathy with cerebral leukodystrophy, characterized by loss of vision, stroke, dementia, Raynaud phenomenon, and GN [46]. In *SAMHD1* mutation, lupus-like symptoms presented with chilblains, and photosensitivity [43]. In *DNASE1* mutation, affected patients presented with positive ANAs, high frequency of ANCA, and lupus nephritis [47]. In *DNASE1L3* mutations, patients presented with severe hypocomplementic urticarial vasculitis syndrome, fatigue, fever, continuous elevation of acute phase reactants, and GN [48].

3) STING associated vasculopathy with onset in infancy (SAVI)

SAVI results from gain-of-function mutations in STING, and may not be extremely uncommon [13-15]. Systemic manifestations were rash with fever and elevation of acute phase reactants, malaise, growth failure, and chronic anemia such as systemic inflammation. Skin lesions were characterized by prominent cold-sensitive acral area, presented as violaceous plaques and/or nodules, and distal ulcerations [14,15,49]. Skin lesion presented at early-onset, and characterized by livedo reticularis, or painful ulceration, and Raynaud phenomenon in some cases. The skin pathologic findings revealed diffuse endothelial inflammation with neutrophil infiltrates and microthrombosis, but no immune complex deposition [13,14]. Pulmonary involvement is not symptomatic; however, interstitial lung disease develops without vasculitis. Hilar and paratracheal lymphadenopathy are usually identified [13-15].

The auto-antibodies including ANA, anti-cardiolipin and anti-β2 glycoprotein antibodies displayed a low-titer, and anti-neutrophil cytoplasmic antibodies were detected in some cases [14,15].

4) Proteasome-associated autoinflammatory syndrome (PRAAS)

PRAAS results from loss-of-function mutations in the genes regulating proteasome function [13,14,28]. Various phenotypic diseases with disease severity were reported as joint contracture, muscular atrophy, microcytic anemia, and panniculitis-induced lipodystrophy [50], Nakajo-Nishimura syndrome with nodular erythema, elongated and thickened fingers and emacination [51], Japanese autoinflammatory syndrome with lipodystrophy, and chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome (CANDLE) [52,53].

PRAAS is characterized by early onset nodular, pernio-like, violaceous skin lesions with atypical neutrophil infiltrates, muscle atrophy, lipodystrophy, failure to thrive and deformities of hands and feet due to joint contractures resulting from chronic inflammation. Recurrent episodes of periodic fever with elevation of acute phase reactants are usually presented as autoinflammatory disease [12-14,53]. Auto-antibodies were not detected, although there were low-titers in some cases [50-53].

Diagnostic and therapeutic approaches

Most patients with monogenic autoimmune diseases experience atypical or incomplete lupus-like symptoms in infancy or at a pre-pubertal age; signs of vasculopathy such as ulceration, chilblain or stroke, panniculitis with or without lipodystrophy, and interstitial lung disease are commonly observed [9,10,14]. Furthermore, many children experienced recurrent episodes of fever with elevation of acute phase reactants, and skin rash. Therefore, we compare our clinical findings between interleukin-1-induced AID and IFN-induced AD (Table 2) [13].

There are no definite treatment strategies for monogenic autoimmune diseases because of different genetic pathways underlying their pathogenesis, although conventional treatments with steroid or disease modifying antirheumatic drugs have been used [13]. Recently, several clinical trials using targeted therapy with JAK1/2 inhibitors reported promising results for monogenic autoimmune diseases [54]. Moreover, monoclonal antibodies for IFN-α (Sifalimumab) and IFNR (Anifrolumab) have revealed preliminary positive outcomes in type I interferonopathy [55,56].

CONCLUSION

The etiology and pathogenesis of many diseases have been identified through the genetic studies using new generation sequencing. In genetic diseases on inflammation, patients experienced recurrent episodes of fever with various skin manifestations and elevation of acute phase reactants. Clinical manifestations are similar

Table 2. Differences in clinical manifestations of IL-1 and IFN-mediated autoinflammatory diseases

Organ	IL-1 mediated diseases	IFN-mediated diseases (CANDLE, SAVI, AGS)
Systemic	CRP closely correlates with disease activity Granulocytosis with flares	CRP only elevated in severe disease Lymphopenia, leucopenia with flares
CNS	Aseptic neutrophilic meningitis Arachnoid adhesion (Severe disease)	Mild lymphocyte meningitis Basal ganglion calcifications, CNS vasculopathy, white matter disease
Skin/Vessel	Neutrophilic dermatitis (urticaria-like with a mature neutrophilic infiltrate)	Panniculitis ("immature" neutrophhils), lipoatrophy, Vasculitis (chilblain-like lesion) microthrombotic disease
Lung/Heart	Serositis, pericarditis	Pulmonary fibrosis/Interstitial lung disease Hypertension, pulmonary hypertension
MSK	Osteomyelitis, bony overgrowth, fasciitis, arthralgia	Myositis, non-erosive arthritis, arthralgia
ENT	Hearing loss (inflammatory)	None
Eyes	Conjunctivitis, anterior uveitis	Glaucoma, episcleritis
Serology	40% lupus anticoagulant positive Other autoantibodies uncommon	40%～50% lupus anticoagulant positive in CANDLE/SAVI, Some with other variable/transient autoantibodies

IL-1: interleukin-1, IFN: interferon, CANDLE: Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature, SAVI: STING associated vasculopathy with onset in Infancy, AGS: Aicardi-Goutieres syndrome, CRP: C-reactive protein, CNS: central nervous system, MSK: musculoskeletal system, ENT: ear, nose, throat. This table is adapted from Kim et al. J Mol Med (Berl) 2016;94:1111-27 [13].

between AID including cryopyrin associated periodic fever syndrome and monogenic AD including monogenic lupus and type I interferonopathies. However, many monogenic autoimmune diseases may present with vasculopathies with different skin lesion compared with AID, and lupus like symptoms or findings with or without auto-antibodies. In infant or very young children with lupus like manifestations, monogenic autoimmune diseases must be considered, and further genetic studies are required for patients and their families. Furthermore, we conducted clinical trials with targeted therapy or monoclonal antibodies for monogenic autoimmune diseases.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Weiss JE. Pediatric systemic lupus erythematosus: more than a positive antinuclear antibody. Pediatr Rev 2012;33: 62-73; quiz 74.
2. Petri M, Orbai AM, Alarcon GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the systemic lupus international collaborating clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012;64: 2677-86.
3. Tsokos GC. Systemic lupus erythematosus. N Engl J Med 2011;365:2110-21.
4. Qing X, Putterman C. Gene expression profiling in the study of the pathogenesis of systemic lupus erythematosus. Autoimmun Rev 2004;3:505-9.
5. Rekvig OP, Van der Vlag J. The pathogenesis and diagnosis of systemic lupus erythematosus: still not resolved. Semin Immunopathol 2014;36:301-11.
6. Zen M, Gatto M, Domeneghetti M, Palma L, Borella E, Iaccarino L, et al. Clinical guidelines and definitions of autoinflammatory diseases: contrasts and comparisons with autoimmunity-a comprehensive review. Clin Rev Allergy Immunol 2013;45:227-35.
7. Doria A, Zen M, Bettio S, Gatto M, Bassi N, Nalotto L, et al. Autoinflammation and autoimmunity: bridging the divide. Autoimmun Rev 2012;12:22-30.
8. Moghaddas F, Masters SL. Monogenic autoinflammatory diseases: Cytokinopathies. Cytokine 2015;74:237-46.
9. Costa-Reis P, Sullivan KE. Monogenic lupus: it's all new! Curr Opin Immunol 2017;49:87-95.
10. Lo MS. Monogenic lupus. Curr Rheumatol Rep 2016;18:71.
11. de Jesus AA, Goldbach-Mansky R. Newly recognized mendelian disorders with rheumatic manifestations. Curr Opin Rheumatol 2015;27:511-9.
12. Crow YJ. Type I interferonopathies: a novel set of inborn errors of immunity. Ann N Y Acad Sci 2011;1238:91-8.
13. Kim H, Sanchez GA, Goldbach-Mansky R. Insights from mendelian interferonopathies: comparison of CANDLE, SAVI with AGS, monogenic lupus. J Mol Med (Berl) 2016;94:1111-27.
14. Volpi S, Picco P, Caorsi R, Candotti F, Gattorno M. Type I interferonopathies in pediatric rheumatology. Pediatr Rheumatol Online J 2016;14:35.
15. Liu Y, Jesus AA, Marrero B, Yang D, Ramsey SE, Sanchez GAM, et al. Activated STING in a vascular and pulmonary syndrome. N Engl J Med 2014;371:507-18.
16. Hiraki LT, Silverman ED. Genomics of systemic lupus erythematosus: insights gained by studying monogenic young-onset systemic lupus erythematosus. Rheum Dis Clin North Am 2017;43:415-34.
17. Vece TJ, Watkin LB, Nicholas S, Canter D, Braun MC, Guillerman RP, et al. Copa syndrome: a novel autosomal dominant immune dysregulatory disease. J Clin Immunol 2016;36:377-87.
18. Weill O, Decramer S, Malcus C, Kassai B, Rouvet I, Ginhoux T, et al. Familial and syndromic lupus share the same phenotype as other early-onset forms of lupus. Joint Bone Spine 2017;84:589-93.
19. Marlow AA, Peabody HD Jr, Nickel WR. Familial occurrence of systemic lupus erthematosus. JAMA 1960;173: 1641-3.
20. Leffler J, Bengtsson AA, Blom AM. The complement system in systemic lupus erythematosus: an update. Ann Rheum Dis 2014;73:1601-6.
21. Lintner KE, Wu YL, Yang Y, Spencer CH, Hauptmann G, Hebert LA, et al. Early components of the complement classical activation pathway in human systemic autoimmune diseases. Front Immunol 2016;7:36.
22. Miller EC, Atkinson JP. Overcoming C2 deficiency. Clin Immunol 2012;144:269-71.
23. Hauck F, Lee-kirsch MA, Aust D, Roesler J, Pessler F. Complement C2 deficiency disarranging innate and adaptive humoral immune responses in a pediatric patient: treatment with rituximab. Arthritis Care Res (Hoboken) 2011;63:454-9.
24. Rieux-Laucat F, Le Deist F, Hivroz C, Roberts IA, Debatin KM, Fischer A, et al. Mutations in Fas associated with human lymphoproliferative syndrome and autoimmunity. Science 1995;268:1347-9.
25. Wu J, Wilson J, He J, Xiang L, Schur PH, Mountz JD. Fas ligand mutation in a patient with systemic lupus erythematosus and lymphoproliferative disease. J Clin Invest 1996;98:1107-13.
26. Napirei M, Karsunky H, Zevnik B, Stephan H, Mannherz HG, Moroy T. Features of systemic lupus erythematosus in Dnase1-deficient mice. Nat Genet 2000;25:177-81.
27. Koyama R, Arai T, Kijima M, Sato S, Miura S, Yuasa M, et al. DNase gamma, DNase I and caspase-activated DNase cooperate to degrade dead cells. Genes Cells 2016;21:1150-63.
28. Rodero MP, Crow YJ. Type I interferon-mediated monogenic autoinflammation: The type I interferonopathies, a conceptual overview. J Exp Med 2016;213:2527-38.
29. Salzer E, Santos-Valente E, Keller B, Warnatz K, Boztug K. Protein kinase C δ : a gatekeeper of immune homeostasis. J Clin Immunol 2016;36:631-40.
30. Limnander A, Zikherman J, Lau T, Leitges M, Weiss A, Roose JP. Protein kinase C δ promotes transitional B cell-negative selection and limits proximal B cell receptor signaling to enforce tolerance. Mol Cell Biol 2014;34:

1474-85.
31. Belot A, Kasher PR, Trotter EW, Foray AP, Debaud AL, Rice GI, et al. Protein kinase cdelta deficiency causes mendelian systemic lupus erythematosus with B cell-defective apoptosis and hyperproliferation. Arthritis Rheum 2013;65: 2161-71.
32. Notarangelo LD, Kim MS, Walter JE, Lee YN. Human RAG mutations: biochemistry and clinical implications. Nat Rev Immunol 2016;16:234-46.
33. Walter JE, Lo MS, Kis-Toth K, Tirosh I, Frugoni F, Lee YN, et al. Impaired receptor editing and heterozygous RAG2 mutation in a patient with systemic lupus erythematosus and erosive arthritis. J Allergy Clin Immunol 2015;135: 272-3.
34. Mor A, Philips MR, Pillinger MH. The role of Ras signaling in lupus T lymphocytes: biology and pathogenesis. Clin Immunol 2007;125:215-23.
35. Ragotte RJ, Dhanrajani A, Pleydell-Pearce J, Del Bel KL, Tarailo-Graovac M, van Karnebeek C, et al. The importance of considering monogenic causes of autoimmunity: a somatic mutation in KRAS causing pediatric Rosai-Dorfman syndrome and systemic lupus erythematosus. Clin Immunol 2017;175:143-6.
36. Tolmie JL, Shillito P, Hughes-Benzie R, Stephenson JB. The Aicardi-Goutieres syndrome (familial, early onset encephalopathy with calcifications of the basal ganglia and chronic cerebrospinal fluid lymphocytosis). J Med Genet 1995;32: 881-4.
37. Ramantani G, Kohlhase J, Hertzberg C, Innes AM, Engel K, Hunger S, et al. Expanding the phenotypic spectrum of lupus erythematosus in Aicardi-Goutieres syndrome. Arthritis Rheum 2010;62:1469-77.
38. Crow YJ, Chase DS, Lowenstein Schmidt J, Szynkiewicz M, Forte GM, Gornall HL, et al. Characterization of human disease phenotypes associated with mutations in TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR, and IFIH1. Am J Med Genet A 2015;167A:296-312.
39. Rice GI, Forte GM, Szynkiewicz M, Chase DS, Aeby A, Abdel-Hamid MS, et al. Assessment of interferon-related biomarkers in Aicardi-Goutieres syndrome associated with mutations in TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, and ADAR: a case-control study. Lancet Neurol 2013;12:1159-69.
40. de Vries B, Steup-Beekman GM, Haan J, Bollen EL, Luyendijk J, Frants RR, et al. TREX1 gene variant in neuropsychiatric systemic lupus erythematosus. Ann Rheum Dis 2010;69:1886-7.
41. Buers I, Nitschke Y, Rutsch F. Novel interferonopathies associated with mutations in RIG-I like receptors. Cytokine Growth Factor Rev 2016;29:101-7.
42. Hacohen Y, Zuberi S, Vincent A, Crow YJ, Cordeiro N. Neuromyelitis optica in a child with Aicardi-Goutieres syndrome. Neurology 2015;85:381-3.
43. Ravenscroft JC, Suri M, Rice GI, Szynkiewicz M, Crow YJ. Autosomal dominant inheritance of a heterozygous mutation in SAMHD1 causing familial chilblain lupus. Am J Med Genet A 2011;155A:235-7.
44. Gunther C, Kind B, Reijns MA, Berndt N, Martinez-Bueno M, Wolf C, et al. Defective removal of ribonucleotides from DNA promotes systemic autoimmunity. J Clin Invest 2015;125:413-24.
45. Lee-Kirsch MA, Gong M, Schulz H, Ruschendorf F, Stein A, Pfeiffer C, et al. Familial chilblain lupus, a monogenic form of cutaneous lupus erythematosus, maps to chromosome 3p. Am J Hum Genet 2006;79:731-7.
46. Richards A, van den Maagdenberg AM, Jen JC, Kavanagh D, Bertram P, Spitzer D, et al. C-terminal truncations in human 3'-5' DNA exonuclease TREX1 cause autosomal dominant retinal vasculopathy with cerebral leukodystrophy. Nat Genet 2007;39:1068-70.
47. Al-Mayouf SM, Sunker A, Abdwani R, Abrawi SA, Almurshedi F, Alhashmi N, et al. Loss-of-function variant in DNASE1L3 causes a familial form of systemic lupus erythematosus. Nat Genet 2011;43:1186-8.
48. Ozcakar ZB, Foster J 2nd, Diaz-Horta O, Kasapcopur O, Fan YS, Yalcinkaya F, et al. DNASE1L3 mutations in hypocomplementemic urticarial vasculitis syndrome. Arthritis Rheum 2013;65:2183-9.
49. Jain A, Misra DP, Sharma A, Wakhlu A, Agarwal V, Negi VS. Vasculitis and vasculitis-like manifestations in monogenic autoinflammatory syndromes. Rheumatol Int 2018;38: 13-24.
50. Agarwal AK, Xing C, DeMartino GN, Mizrachi D, Hernandez MD, Sousa AB, et al. PSMB8 encoding the beta5i proteasome subunit is mutated in joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced lipodystrophy syndrome. Am J Hum Genet 2010;87:866-72.
51. Arima K, Kinoshita A, Mishima H, Kanazawa N, Kaneko T, Mizushima T, et al. Proteasome assembly defect due to a proteasome subunit beta type 8 (PSMB8) mutation causes the autoinflammatory disorder, Nakajo-Nishimura syndrome. Proc Natl Acad Sci U S A 2011;108:14914-9.
52. Liu Y, Ramot Y, Torrelo A, Paller AS, Si N, Babay S, et al. Mutations in proteasome subunit beta type 8 cause chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature with evidence of genetic and phenotypic heterogeneity. Arthritis Rheum 2012;64:895-907.
53. Brehm A, Liu Y, Sheikh A, Marrero B, Omoyinmi E, Zhou Q, et al. Additive loss-of-function proteasome subunit mutations in CANDLE/PRAAS patients promote type I IFN production. J Clin Invest 2015;125:4196-211.
54. Kim H, Brooks KM, Tang CC, Wakim P, Blake M, Brooks SR, et al. Pharmacokinetics, Pharmacodynamics, and Proposed Dosing of the Oral JAK1 and JAK2 Inhibitor Baricitinib in Pediatric and Young Adult CANDLE and SAVI Patients. Clin Pharmacol Ther 2018;104:364-73.
55. Merrill JT, Wallace DJ, Petri M, Kirou KA, Yao Y, White WI, et al. Safety profile and clinical activity of sifalimumab, a fully human anti-interferon alpha monoclonal antibody, in systemic lupus erythematosus: a phase I, multicentre, double-blind randomised study. Ann Rheum Dis 2011;70: 1905-13.
56. Petri M, Wallace DJ, Spindler A, Chindalore V, Kalunian K, Mysler E, et al. Sifalimumab, a human anti-interferon-alpha monoclonal antibody, in systemic lupus erythematosus: a phase I randomized, controlled, dose-escalation study. Arthritis Rheum 2013;65:1011-21.