



**HAL**  
open science

## Monogenic lupus: Dissecting heterogeneity

Ommar Omarjee, Cécile Picard, Cécile Frachette, Marion Moreews, Frederic Rieux-Laucat, Pauline Soulas-Sprauel, Sebastien Viel, Jean-Christophe Lega, Brigitte Bader-Meunier, Thierry Walzer, et al.

► **To cite this version:**

Ommar Omarjee, Cécile Picard, Cécile Frachette, Marion Moreews, Frederic Rieux-Laucat, et al.. Monogenic lupus: Dissecting heterogeneity. *Autoimmunity Reviews*, 2019, 18 (10), 10.1016/j.autrev.2019.102361 . hal-03465917

**HAL Id: hal-03465917**

**<https://hal.science/hal-03465917>**

Submitted on 20 Jul 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

## Monogenic Lupus: dissecting heterogeneity

Ommar Omarjee<sup>1</sup>, Cécile Picard<sup>2</sup>, Cécile Frachette<sup>3</sup>, Marion Moreews<sup>1</sup>, Frederic Rieux Laucat<sup>4,5</sup>, Pauline Sprauel<sup>6</sup>, Sebastien Viel<sup>1,7</sup>, Jean-Christophe Lega<sup>8</sup>, Brigitte Bader-Meunier<sup>4,5,9,10</sup>, Thierry Walzer<sup>1</sup>, Anne-Laure Mathieu<sup>1</sup>, Rolando Cimaz<sup>11</sup>, Alexandre Belot<sup>1,3,10</sup>

1. CIRI, Centre International de Recherche en Infectiologie / International Center for Infectiology Research, Inserm, U1111, Ecole Normale Supérieure de Lyon, Université Lyon 1, CNRS, UMR5308, Lyon, France

2. Department of Pathology, Groupement Hospitalier Est, Hospices Civils de Lyon, UCBL Lyon 1 University, Lyon, France

3. Pediatric Nephrology, Rheumatology, Dermatology Unit, Hospices Civils de Lyon, France

4. Paris Descartes University, Sorbonne-Paris-Cité, Institut Imagine, Paris, France

5. INSERM UMR 1163, Laboratory of Immunogenetics of Pediatric Autoimmunity, Paris, France.

6. Service d'immunologie clinique, Hôpitaux Universitaires de Strasbourg, Université de Strasbourg, Strasbourg, France

7. Service d'Immunologie Biologique, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Pierre-Bénite, France

8. Department of Internal and Vascular Medicine, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Lyon, France

9. Pediatric Rheumatology and Immunology Unit, Necker hospital, Imagine Institution, Paris, France

10. National Referee Centre for Rheumatic and Autoimmune and Systemic diseases in childrEn (RAISE).

11. Department of Clinical Sciences and Community Health, University of Milan, Italy

**Corresponding author: Pr Alexandre BELOT, [alexandre.belot@chu-lyon.fr](mailto:alexandre.belot@chu-lyon.fr)**

Pediatric Nephrology, Rheumatology, Dermatology Unit, Hospices Civils de Lyon, 59 Bd Pinel, Bron F69677, FRANCE

**Abstract:**

Systemic lupus erythematosus (SLE) is a severe lifelong multisystem autoimmune disease characterized by the presence of autoantibodies targeting nuclear autoantigens, increased production of type I interferon and B cell abnormalities. Clinical presentation of SLE is extremely heterogeneous and different groups of disease are likely to exist. Recently, childhood-onset SLE (cSLE) cases have been linked to single gene mutations, defining the concept of monogenic or Mendelian lupus. Genes associated with Mendelian lupus can be grouped in at least three functional categories. First, complement deficiencies represent the main cause of monogenic lupus and its components are involved in the clearance of dying cells, a mechanism also called efferocytosis. Mutations in extracellular DNASE have been also identified in cSLE patients and represent additional causes leading to defective clearance of nucleic acids and apoptotic bodies. Second, the study of Aicardi-Goutières syndromes has introduced the concept of type-I interferonopathies. Bona fide lupus syndromes have been associated to this genetic condition, driven by defective nucleic acids metabolism or innate sensors overactivity. Interferon signaling anomalies can be detected and monitored during therapies, such as Janus-kinase (JAK) inhibitors. Third, tolerance breakdown can occur following genetic mutations in B and/or T cell expressing key immunoregulatory molecules. Biallelic mutations in *PRKCD* are associated to lupus and lymphoproliferative diseases as PKC- $\delta$  displays proapoptotic activity and is crucial to eliminate self-reactive transitional B cells. Here we review the literature of the emerging field of Mendelian lupus and discuss the physiopathological learning from these inborn errors of immunity. In addition, clinical and biological features are highlighted as well as specific therapies that have been tested in these genetic contexts.

**Keywords:** Monogenic lupus, Type-I interferonopathies, efferocytosis, complement system, PKC-delta deficiency, self-tolerance, apoptosis, systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a rare, multisystem immunological disorder characterized by the presence of autoantibodies targeting nuclear autoantigens, type I interferon production and B cell tolerance breakdown as illustrated by autoantibodies production. SLE represents an heterogeneous disease, with the diagnosis of SLE requiring the presence of 4 out of 11 defined criteria<sup>1,2,3</sup>. The pathogenesis underlying SLE remains unclear. Interestingly, familial aggregation and higher concordance rates between monozygotic (20 – 40%) relative to dizygotic twins and other full siblings (2 – 5%) suggest a major hereditary component to pathogenesis<sup>4,5</sup>. Genome-wide association studies (GWAS) have identified more than 80 loci as strongly associated with lupus<sup>6,7,8</sup>. These variants are common and confer small effects on disease susceptibility<sup>9,10</sup>. In contrast, monogenic susceptibility to SLE, for which almost 30 genes have been described in humans, are related to single mutations in DNA-coding regions of the genome<sup>11</sup>.

Mendelian inborn errors of immunity have helped unravelling the mechanisms of immune tolerance in humans, and three main pathways have been reported associated to lupus. First, defects in the complement components represent the first genetic cause of SLE identified in humans and highlight the importance of the clearance of apoptotic bodies in lupus pathogenesis<sup>12</sup>. Similarly, extracellular DNase deficiencies promote SLE secondary to defective clearance of nucleic acids in extracellular microparticles<sup>13,14</sup>. In addition, the importance of type I interferon signalling in SLE is emphasized by the association of lupus phenotype with the type I interferonopathies<sup>15</sup>. Finally, B cells are considered central in lupus pathogenesis<sup>16</sup>, with PKC $\delta$  deficiency identified as the first B cell related subset of monogenic lupus in humans<sup>17,18</sup>.

Here we report the insights arising from the molecular study of monogenic lupus forms, and illustrate their main clinical and immunological features (Table 1). Tailoring treatment with the underlying genetic molecular defect represent promising strategies.

## **Efferocytosis defects**

Every day, hundreds of billion cells die from apoptosis or specialized programs such as neutrophil cell death, defined as NETosis, a neutrophil cell death program associated to extrusion of fibrillary networks called neutrophil extracellular traps (NETs)<sup>19</sup>. Apoptotic bodies and associated extracellular nucleic acids are scavenged by tissue-resident phagocytes (macrophages and dendritic cells) or locally recruited phagocytes<sup>20</sup>. This process is important to prevent the induction of inflammation upon recognition of endogenous pathogen recognition receptors (PRR) ligands. Numerous molecules are involved in the recognition of apoptotic cells and this mechanism is also referred as efferocytosis. In humans, complement deficiencies and the DNASE1L3 deficiency define a subset of monogenic lupus due to efferocytosis defect and excess of apoptotic bodies.

### ***Complement deficiencies***

The complement system plays a role in the innate and adaptive immune response. Complement proteins act as opsonins facilitating the clearance of apoptotic bodies and immune complexes by phagocytes, as well as a lytic agent against pathogens<sup>21</sup>. The early components of the classical pathway (C1q, C1r and C1s) are mainly produced by monocytes, macrophages and dendritic cells while the other subsets are produced by hepatocytes<sup>22</sup>. Genetic defects in complement impair efferocytosis leading to the accumulation of autoantigens in the extracellular environment<sup>23</sup>. Moreover, the complement system is needed to clear immune complexes, the accumulation of which leads to inflammation and organ damage as in the case of nephritis. Complement components have additional immune regulatory functions. For example, C1q is capable to reduce type I interferon production by plasmacytoid dendritic cells<sup>24</sup> and has been recently shown to regulate adaptive immunity by modulating the mitochondrial metabolism of CD8 T cells, thereby preventing self-antigen autoreactivity and promoting viral control<sup>25</sup>. The CR1 and CR2 complement receptors that respectively recognize C1q and C4 are also potent regulators of B cell activation<sup>26,27</sup>. Genetic deficiencies of the early component of the classical pathway C1q/r/s strongly predispose to SLE, with a penetrance of up to 90%. Deficiencies or mutations in other complement proteins of the classical pathway, such as C4 and C2, also promote systemic autoimmunity such as lupus with the following risk: 10-20% in C2 deficiency and 75% in C4 deficiency<sup>28</sup>.

Complement deficiencies are associated with early-onset lupus manifestations, with a sex ratio (ie predominance in females) less biased than that of adult-onset SLE. The phenotype is severe, in particular because of recurrent life-threatening infections

such as meningitis (**Fig. 1A**). Photosensitive skin rash is very common in all complement deficiencies whereas severe arthritis is mostly seen in patients with C2 deficiency, and lupus nephritis in C4A/C4B-defective monogenic lupus. The prevalence of antinuclear antibodies (ANA) is usually high whereas only 20% of patients display anti-dsDNA. Conversely, anti-Ro/SSA antibodies are positive in 80% of patients with C1q and C4 deficiencies. Low CH50 with normal serum levels of C4 and C3 is evocative for a complement deficiency.

### ***Extracellular DNASE deficiencies***

Additional enzymes involved in digestion of extracellular nucleic acids are also critical for the maintenance of immune tolerance. DNASE1 is an extracellular DNA-degrading enzyme, which is present in both serum and urine. Dnase1-deficient mice develop ANA and glomerulonephritis<sup>29</sup>. Four SLE cases were reported with a mutation in *DNASE1* exhibiting very high levels of anti-nucleosomal antibodies<sup>30,31</sup>. DNASE1L3 is a homologue of DNASE1 containing a positively charged C-terminal peptide, which confers the ability to remove DNA chromatin associated to extracellular microparticles; Dnase1L3 deficient mice develop SLE-like phenotype<sup>14</sup>. DNASE1/DNASE1L3 deficiencies lead to the accumulation of extracellular nucleic acids which can be recognized by DNA/RNA sensors such as Toll-like receptors (TLR7 and TLR9) then promoting type I interferon production<sup>32</sup>. Moreover, circulating DNA can bind autoantibodies leading to immune complex formation with associated organ damage. DNASE1L3 deficiency was identified in familial SLE cases with the association of ANA, anti-dsDNA and ANCA and also as a form of hypocomplementemic urticarial vasculitis<sup>13,33</sup>. Lupus nephritis is frequent and beside low complement fractions C3 and C4 and positivity of ANA and anti-dsDNA antibodies, ANCA positivity is evocative<sup>34</sup>.

### ***Other defects in phagocytosis***

The X-linked form of chronic granulomatous disease (CGD) is due to *CYBB* mutations. *CYBB* encodes the 91-kD glycoprotein component of the ROS-generating enzyme NADPH oxidase or NOX2 (nicotinamide adenine dinucleotide phosphate) and has been connected to lupus phenotype. The link between *CYBB* and SLE is thought to be secondary to the increase of NETosis, releasing high amounts of intracellular DNA and self-antigens outside the cells. In mice prone to autoimmunity, *Nox2* deficiency exacerbates the disease<sup>35</sup>. Furthermore, NETs inhibition exacerbated lupus phenotype<sup>36</sup>. NOX2-derived reactive oxygen species may regulate T cell activation by oxidizing self-antigen-derived peptides limiting autoimmune arthritis, as recently proposed<sup>37</sup>. CGD is characterized by recurrent-life threatening infections by bacteria and fungi<sup>38,39</sup> and some patients also display

inflammatory manifestations ranging from Crohn's disease to discoid lupus or SLE<sup>40</sup>. X-linked carriers are at a higher risk for skin manifestations such as discoid lupus erythematosus and photosensitivity, and generally present with a strong susceptibility to recurrent infections, especially by catalase positive organisms<sup>41,42</sup>. Arthritis, glomerulonephritis and Raynaud's phenomenon were rarely described. Autoantibody screening is generally negative, even in patients with a lupus-like phenotype<sup>41,43</sup>.

### **Type I Interferonopathies**

Interferons (IFN) are cytokines with an essential role in antiviral defence and display key regulatory functions in innate and adaptive immune responses. Type I IFN represent the largest family of IFNs, including IFN $\alpha$ , which comprises 13 distinct subset and IFN- $\beta$ . Exacerbated IFN $\alpha$  signalling represents a hallmark of systemic lupus erythematosus<sup>44</sup>.

Monogenic type I interferonopathies refer to a group of diseases associated with an upregulation of type I interferon expression. Jean Aicardi and Françoise Goutières described a familial progressive neonatal encephalopathy mimicking a congenital viral infection, Interestingly, some patients with Aicardi-Goutières syndrome (AGS), also present features of systemic autoimmunity<sup>45</sup>. Patients display a wide range of neurological manifestations, from isolated cerebral calcifications to an early-onset encephalopathy, with cerebral atrophy and leukoencephalopathy. High levels of type I interferon were found in the serum and cerebrospinal fluid of these patients<sup>46</sup>. Loss of function mutations of the DNA 3' repair exonuclease 1 TREX1 were the first identified genetic cause of AGS<sup>47</sup>. This enzyme plays a crucial role in the metabolism of intracellular DNA and prevents its detection by innate immune sensors and the type I interferon activation<sup>48</sup>. Indeed, the detection of intracellular nucleic acids through various innate immune sensors leads to type I interferon production in response to the activation of regulation factors, IRF (IFN regulatory factors)<sup>43</sup>. Of note, interferon production is triggered by the detection of exogenous nucleic acids from viruses but also by intracellular nucleic acids derived from endogenous retroviral sequences present in our genome (HERV). Considering that type I interferon plays a primary pathogenic role in these disorders, Crow and colleagues proposed to group them as «Type I interferonopathies»<sup>44</sup>. Thereafter, numerous additional genes have been reported as causal for AGS and are linked to IFN signalling upregulation.

The excessive production of interferon can appear through three different pathways:

- Defect in nucleases (*TREX1*, *SAMHD1*, *ADAR1*, *RNASEH2*, *RNASEH2B*, *RNASEH2C*) leading to the accumulation of endogenous nucleic acids

- Constitutive activation or enhanced sensitivity of an innate immune sensor, for example MDA5 and RIG-I (*IFIH* and *DDX58* mutations respectively) or adaptor molecules downstream the innate sensors (such as STING, encoded by *TMEM173*, downstream the receptor cGAS)
- Defective negative feedback of the interferon pathway (*ISG15* mutations).

Type I interferons then bind to the heterodimeric receptor (IFNAR 1 and IFNAR 2) and activate the JAK-STAT signalling pathway and induce the transcription of hundreds of interferon-stimulated genes (ISG)<sup>44,51</sup>.

Type I interferonopathies manifestations are very heterogeneous and comprise overlapping phenotypes<sup>52</sup>. Herein, we review common traits associated with the different forms, as well as gene-specific features (Table 1).

Chilblain lesions as well as severe neurodevelopmental features are the most evocative manifestations of a type I interferonopathy (**Fig. 1B**). Penetrance and expressivity differ and neurological symptoms without autoimmunity or isolated type I IFN signature can be also observed in affected individuals. The frequency of lupus-like manifestations and chilblain depends on the gene involved (**Fig. 1E**). The systemic phenotype of the newly described type I interferonopathy linked to biallelic mutations in *DNASE2* is relatively broad with clinical features evocative of an autoinflammatory syndrome and various autoimmune manifestations. Transient life-threatening anemia in the neonatal period was particularly noticeable in those patients<sup>53</sup>.

Interstitial pneumonia with skin vasculitis is evocative for the STING-associated vasculitis with onset in infancy (SAVI) and interstitial lung disease represents the first symptom of the disease<sup>54,55</sup>. Tendon rupture, subluxation for the hands, reminiscent of Jaccoud's arthropathy (**Fig. 1C**) have been observed in MDA5-related type I interferonopathy<sup>56</sup>. ANA and dsDNA antibodies have been recorded in type I interferonopathies but are inconsistent.

Type I interferon protein dosage is not available in routine medical practice to date because of very low circulating levels<sup>57</sup>. However, Rice et al. showed that the type I interferon upregulation was correlated with the increased expression of a subset of six interferon stimulated genes (ISG) (*IFI27*, *IFI44L*, *IFIT1*, *ISG15*, *RSAD2* and *SIGLEC1*) in AGS patients, the so-called interferon signature<sup>58</sup>. Interferon signature can be used both for the diagnosis of type I interferonopathies and to follow disease activity, and is also very sensitive to differentiate monogenic and complex type I

Interferonopathies from inflammasomopathies. Interferon signature might be also useful to dissect the distinct monogenic lupus (**Fig. 2A**)<sup>59,60</sup>.

### **Other subsets of type I Interferonopathies**

Proteasome-associated autoinflammatory syndrome (PRAAS) is another autoinflammatory disease consisting in recurrent fever, panniculitis and lipodystrophy and is associated with positive interferon signature. *PSMB8* encodes a proteasome subunit, and its mutation leads to proteasome dysfunction, accumulation of ubiquitinated proteins and autoinflammation<sup>61</sup>. The X-linked reticulate pigmentary disorder (XLRPD) is a genodermatosis with autoinflammatory features linked to the intronic mutation of *POLA1*, which encodes a catalytic subunit of the DNA-polymerase- $\alpha$ .

Mutations in *ACP5* encoding Tartrate-resistant acid phosphatase type 5 (TRAP) are transmitted through an autosomal recessive mode and are responsible for spondyloenchondrodysplasia (SPENCD) with skeletal dysplasia, growth retardation, neurological involvement and systemic autoimmunity. The latter condition represents an increased susceptibility for Sjögren's syndrome, systemic lupus erythematosus, hemolytic anemia, thrombocytopenia, hypothyroidism, inflammatory myositis, Raynaud's syndrome and vitiligo<sup>62</sup>. TRAP is expressed in osteoclasts, macrophages and dendritic cells, thus explaining both skeletal and autoimmune involvements in SPENCD patients.

### **B and T cell tolerance breakdown**

The hallmark of SLE is the presence of a wide range of autoantibodies indicating the presence of autoreactive lymphocytes. Ineffective deletion of autoreactive T or B cells could trigger autoimmunity and disrupt self-tolerance<sup>63</sup>. The importance of apoptosis defects in human autoimmunity was underlined by the discovery of mutations in the pro-apoptotic molecule CD95/Fas defining the Autoimmune Lymphoproliferative Syndrome (ALPS). ALPS is an inherited disease characterized by a chronic non-malignant lymphadenopathy, hepatosplenomegaly, expansion of CD3<sup>+</sup>TCR $\alpha/\beta$ <sup>+</sup>CD4<sup>-</sup>CD8<sup>-</sup>double negative T (DNT) cells and other autoimmune features such as presence of autoantibodies and autoimmune cytopenia<sup>55,56</sup>. Of note, no full-blown lupus has been described so far with this specific genetic background. A few other patients have been described with homozygous *CD95L/FASL* mutations that abolish the protein function<sup>57,58</sup> or heterozygous *CD95L/FASL* mutations with a dominant negative effect<sup>59</sup>. In addition, the MRL/lpr mice represent a model of

systemic autoimmunity with a mutation in the Fas receptor gene (*lpr*)<sup>60</sup> as well as the CD95L (*gld*) deficiency<sup>61</sup>.

Another example of monogenic SLE is the protein kinase C- $\delta$  (PKC- $\delta$ ) deficiency. PKC- $\delta$  is a pro-apoptotic molecule essential in B cell survival and apoptosis, and PKC- $\delta$  knock-out mice develop systemic autoimmunity<sup>14,62,63</sup>. We identified an homozygous missense mutation in *PRKCD* in three siblings with childhood-onset SLE<sup>17</sup>. PKC- $\delta$  expression was reduced, which led to a B cell apoptosis defect and an accumulation of immature transitional B cells. Additional cases of PKC- $\delta$  deficiency have been reported, the main clinical features comprising skin lesions and alopecia, lymphoproliferative disease with lymphadenopathy, hepatosplenomegaly and mild to severe infection susceptibility, both to bacteria and viruses<sup>13,64–67</sup>. Chronic Epstein Barr virus or cytomegalovirus replication have been reported<sup>64,65</sup>. One of our patients presented at the age of 30 with severe papillomatosis illustrating the defective immune control of a wide range of viruses (**Fig. 1D**). Lupus nephritis is frequent and cerebral vasculitis has also been reported. Immunophenotyping in these patients reveals a B-cell deficiency with an expansion of transitional B cells and a decrease of memory B cells<sup>17</sup>. ANA, ENA and dsDNA antibodies are generally positive, with normal complement levels.

Another subset of disease with apoptosis dysregulation is illustrated by the RASopathies. Noonan syndrome and Noonan-related syndromes represent neurodevelopmental syndromes due to germline mutations in genes that participate in the rat sarcoma/mitogen-activated protein kinases (RAS/MAPK) pathway (PTPN11, SOS1, RAF, KRAS or NRAS, and SHOC2). Lupus phenotype has been reported in such patients and autoimmune features were not different from those presented by the general SLE population<sup>68</sup>, with polyarthritis, autoimmune cytopenia, serositis, ANA and anti dsDNA antibodies.

IKAROS mutations were also identified in 4 patients with autoimmunity including one fulfilling early-onset SLE criteria<sup>69</sup>. IKAROS mutations were reported as causal for common variable immunodeficiencies<sup>70</sup>, with decreased lymphocyte populations (B, T and NK cells). *IKZF1* encodes the IKAROS zinc finger transcription factor which is crucial in early steps of haematopoietic development, as demonstrated by a knock-out model<sup>71,72</sup>. Finally, recombination-activating 1 or 2 genes (*RAG1/2*) represents a crucial enzyme involved in the V(D)J recombination and BCR to TCR variability generation. While loss-of-function *RAG* mutations are associated with severe combined immunodeficiencies, hypomorphic mutations have been linked to autoimmunity<sup>74–76</sup>. Interestingly a *RAG2* mutation has been reported in a lupus patient<sup>82</sup>. The patient carrying the heterozygous *RAG2* mutation presented with

classical lupus-like systemic phenotype with arthritis and skin involvement, Raynaud's phenomenon, sicca syndrome, serositis and class V lupus nephritis<sup>74</sup>. She had a history of recurrent infections attributed to her medication regimen. She presented with classical lupus-associated biomarkers with high titres of ANA and dsDNA antibodies and hypocomplementemia.

Biological abnormalities from different monogenic lupus syndromes are reported in **Fig. 2B**.

### **Towards precision medicine in SLE**

SLE heterogeneity explains the so far limited success of clinical trials in lupus. With advent of NGS, our understanding of genetic causes of early-onset SLE is improving at a fast rate. This knowledge will not only allow a better stratification of patients, but also a rationale, personalized design of treatments. Moreover, the identification of causal genes may increase the number of targets for drug treatment of these diseases.

Considering the central role of type I interferon in the pathogenesis, Mendelian interferonopathies might benefit from type I interferon inhibition. JAK inhibitors are promising because they block the signalling downstream the IFN receptor. Baricitinib and ruxolitinib are both JAK1/2 inhibitors and have shown interesting preliminary results for their safety and efficacy in SAVI and CANDLE<sup>85,86</sup>, although the IFN score was not totally abrogated in SAVI patients. Anifrolumab is a fully human monoclonal antibody that neutralises the IFN $\alpha$  receptor and has been reported as effective in non-monogenic lupus, especially in the context of high IFN signatures. It is a good candidate for treatment of type I interferonopathies. The main side effect is represented by herpes zoster infections<sup>87</sup>. Finally, as the HERV are supposed to be partially responsible for the increase of intracytoplasmic nucleic acids in AGS with enzymatic defects, it has been recently suggested that reverse transcriptase inhibitors used for patients with human immunodeficiency virus (HIV) may represent an option by targeting the endogenous retroviruses and thereby decreasing the IFN signature<sup>88</sup>.

B cell targeting therapies or bone marrow transplantation may represent interesting options in B cell related monogenic lupus. Rituximab and ofatumumab have been reported as effective in siblings with PKC- $\delta$  deficiency<sup>89</sup>.

Efferocytosis defect is actually the most challenging situation. No drug can promote efferocytosis and bone marrow transplantation has been proposed in severe C1q deficiencies<sup>90</sup>.

In conclusion, monogenic lupus is a recently recognized field of diseases. Understanding better the underlying genetic causes will bring insight in the mechanisms of human immune tolerance and lupus pathogenesis, and likely lead to the discovery of novel therapeutic options to cure the disease.

## References

1. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40(9):1725.
2. Hartman EAR, van Royen-Kerkhof A, Jacobs JWG, Welsing PMJ, Fritsch-Stork RDE. Performance of the 2012 Systemic Lupus International Collaborating Clinics classification criteria versus the 1997 American College of Rheumatology classification criteria in adult and juvenile systemic lupus erythematosus. A systematic review and meta-analysis. *Autoimmun Rev* 2018;17(3):316–22.
3. Yu C, Gershwin ME, Chang C. Diagnostic criteria for systemic lupus erythematosus: a critical review. *J Autoimmun* 2014;48–49:10–3.
4. Criswell LA. The genetic contribution to systemic lupus erythematosus. *Bull NYU Hosp Jt Dis* 2008;66(3):176–83.
5. Crow YJ. Lupus: how much “complexity” is really (just) genetic heterogeneity? *Arthritis Rheum* 2011;63(12):3661–4.
6. Bentham J, Morris DL, Graham DSC, et al. Genetic association analyses implicate aberrant regulation of innate and adaptive immunity genes in the pathogenesis of systemic lupus erythematosus. *Nat Genet* 2015;47(12):1457–64.
7. Morris DL, Sheng Y, Zhang Y, et al. Genome-wide association meta-analysis in Chinese and European individuals identifies ten new loci associated with systemic lupus erythematosus. *Nat Genet* 2016;48(8):940–6.
8. Jeong DY, Lee SW, Park YH, et al. Genetic variation and systemic lupus erythematosus: A field synopsis and systematic meta-analysis. *Autoimmun Rev* 2018;17(6):553–66.
9. Chen L, Morris DL, Vyse TJ. Genetic advances in systemic lupus erythematosus: an update. *Curr Opin Rheumatol* 2017;29(5):423–433.
10. Cui Y, Sheng Y, Zhang X. Genetic susceptibility to SLE: recent progress from GWAS. *J Autoimmun* 2013;41:25–33.
11. Manolio TA, Collins FS, Cox NJ, et al. Finding the missing heritability of complex diseases. *Nature* 2009;461(7265):747–53.
12. Botto M, Dell’Agnola C, Bygrave AE, et al. Homozygous C1q deficiency causes glomerulonephritis associated with multiple apoptotic bodies. *Nat Genet* 1998;19(1):56–9.
13. Al-Mayouf SM, Sunker A, Abdwani R, et al. Loss-of-function variant in DNASE1L3 causes a familial form of systemic lupus erythematosus. *Nat Genet* 2011;43(12):1186–8.
14. Sisirak V, Sally B, D’Agati V, et al. Digestion of Chromatin in Apoptotic Cell Microparticles Prevents Autoimmunity. *Cell* 2016;166(1):88–101.
15. Crow YJ, Manel N. Aicardi-Goutières syndrome and the type I interferonopathies. *Nat Rev Immunol* 2015;15(7):429–40.
16. Lipsky PE. Systemic lupus erythematosus: an autoimmune disease of B cell hyperactivity. *Nat Immunol* 2001;2(9):764.
17. Belot A, Kasher PR, Trotter EW, et al. Protein kinase cδ deficiency causes mendelian systemic lupus erythematosus with B cell-defective apoptosis and hyperproliferation. *Arthritis Rheum* 2013;65(8):2161–71.
18. Mecklenbräuker I, Saijo K, Zheng N-Y, Leitges M, Tarakhovskiy A. Protein

kinase Cdelta controls self-antigen-induced B-cell tolerance. *Nature* 2002;416(6883):860–5.

19. Elkon KB. Review: Cell Death, Nucleic Acids, and Immunity: Inflammation Beyond the Grave. *Arthritis Rheumatol* Hoboken NJ 2018;70(6):805–16.
20. Poon IKH, Lucas CD, Rossi AG, Ravichandran KS. Apoptotic cell clearance: basic biology and therapeutic potential. *Nat Rev Immunol* 2014;14(3):166–80.
21. Leffler J, Bengtsson AA, Blom AM. The complement system in systemic lupus erythematosus: an update. *Ann Rheum Dis* 2014;73(9):1601–6.
22. Chen M, Daha MR, Kallenberg CGM. The complement system in systemic autoimmune disease. *J Autoimmun* 2010;34(3):J276–286.
23. Sullivan KE. Complement deficiency and autoimmunity. *Curr Opin Pediatr* 1998;10(6):600–6.
24. Lood C, Gullstrand B, Truedsson L, et al. C1q inhibits immune complex-induced interferon-alpha production in plasmacytoid dendritic cells: a novel link between C1q deficiency and systemic lupus erythematosus pathogenesis. *Arthritis Rheum* 2009;60(10):3081–90.
25. Ling GS, Crawford G, Buang N, et al. C1q restrains autoimmunity and viral infection by regulating CD8+ T cell metabolism. *Science* 2018;360(6388):558–63.
26. Tuveson DA, Ahearn JM, Matsumoto AK, Fearon DT. Molecular interactions of complement receptors on B lymphocytes: a CR1/CR2 complex distinct from the CR2/CD19 complex. *J Exp Med* 1991;173(5):1083–9.
27. Matsumoto AK, Kopicky-Burd J, Carter RH, Tuveson DA, Tedder TF, Fearon DT. Intersection of the complement and immune systems: a signal transduction complex of the B lymphocyte-containing complement receptor type 2 and CD19. *J Exp Med* 1991;173(1):55–64.
28. Sturfelt G, Truedsson L. Complement in the immunopathogenesis of rheumatic disease. *Nat Rev Rheumatol* 2012;8(8):458–68.
29. Napirei M, Ludwig S, Mezrhah J, Klöckl T, Mannherz HG. Murine serum nucleases – contrasting effects of plasmin and heparin on the activities of DNase1 and DNase1-like 3 (DNase1L3). *FEBS J* 2009;276(4):1059–73.
30. Yasutomo K, Horiuchi T, Kagami S, et al. Mutation of DNASE1 in people with systemic lupus erythematosus. *Nat Genet* 2001;28(4):313–4.
31. Bodaño A, Amarelo J, González A, Gómez-Reino JJ, Conde C. Novel DNASE I mutations related to systemic lupus erythematosus. *Arthritis Rheum* 2004;50(12):4070–1.
32. Roers A, Hiller B, Hornung V. Recognition of Endogenous Nucleic Acids by the Innate Immune System. *Immunity* 2016;44(4):739–54.
33. Özçakar ZB, Foster J, Diaz-Horta O, et al. DNASE1L3 mutations in hypocomplementemic urticarial vasculitis syndrome. *Arthritis Rheum* 2013;65(8):2183–9.
34. Al-Mayouf SM, Sunker A, Abdwani R, et al. Loss-of-function variant in DNASE1L3 causes a familial form of systemic lupus erythematosus. *Nat Genet* 2011;43(12):1186–8.
35. Campbell AM, Kashgarian M, Shlomchik MJ. NADPH oxidase inhibits the pathogenesis of systemic lupus erythematosus. *Sci Transl Med* 2012;4(157):157ra141.
36. Kienhöfer D, Hahn J, Stoof J, et al. Experimental lupus is aggravated in mouse

strains with impaired induction of neutrophil extracellular traps. *JCI Insight* 2017;2(10).

37. Yang M, Haase C, Viljanen J, et al. Cutting Edge: Processing of Oxidized Peptides in Macrophages Regulates T Cell Activation and Development of Autoimmune Arthritis. *J Immunol Baltim Md 1950* 2017;199(12):3937–42.
38. Baehner RL, Karnovsky ML. Deficiency of reduced nicotinamide-adenine dinucleotide oxidase in chronic granulomatous disease. *Science* 1968;162(3859):1277–9.
39. Baehner RL, Nathan DG. Quantitative nitroblue tetrazolium test in chronic granulomatous disease. *N Engl J Med* 1968;278(18):971–6.
40. De Ravin SS, Naumann N, Cowen EW, et al. Chronic granulomatous disease as a risk factor for autoimmune disease. *J Allergy Clin Immunol* 2008;122(6):1097–103.
41. Battersby AC, Braggins H, Pearce MS, et al. Inflammatory and autoimmune manifestations in X-linked carriers of chronic granulomatous disease in the United Kingdom. *J Allergy Clin Immunol* 2017;140(2):628-630.e6.
42. Sanford AN, Suriano AR, Herche D, Dietzmann K, Sullivan KE. Abnormal apoptosis in chronic granulomatous disease and autoantibody production characteristic of lupus. *Rheumatol Oxf Engl* 2006;45(2):178–81.
43. Cale CM, Morton L, Goldblatt D. Cutaneous and other lupus-like symptoms in carriers of X-linked chronic granulomatous disease: incidence and autoimmune serology. *Clin Exp Immunol* 2007;148(1):79–84.
44. Picard C, Belot A. Does type-I interferon drive systemic autoimmunity? *Autoimmun Rev* 2017;16(9):897–902.
45. Aicardi J, Goutières F. A Progressive familial encephalopathy in infancy with calcifications of the basal ganglia and chronic cerebrospinal fluid lymphocytosis: Aicardi and Goutieres: Basal Ganglia Calcifications. *Ann Neurol* 1984;15(1):49–54.
46. Lebon P, Badoual J, Ponsot G, Goutières F, Hémeury-Cukier F, Aicardi J. Intrathecal synthesis of interferon-alpha in infants with progressive familial encephalopathy. *J Neurol Sci* 1988;84(2–3):201–8.
47. Crow YJ, Hayward BE, Parmar R, et al. Mutations in the gene encoding the 3'-5' DNA exonuclease TREX1 cause Aicardi-Goutières syndrome at the AGS1 locus. *Nat Genet* 2006;38(8):917–20.
48. Sakai T, Miyazaki T, Shin D-M, et al. DNase-active TREX1 frame-shift mutants induce serologic autoimmunity in mice. *J Autoimmun* 2017;81:13–23.
49. Picard C, Mathieu A-L, Hasan U, et al. Inherited anomalies of innate immune receptors in pediatric-onset inflammatory diseases. *Autoimmun Rev* 2015;
50. Crow YJ. Type I interferonopathies: a novel set of inborn errors of immunity: Type I interferonopathies. *Ann N Y Acad Sci* 2011;1238(1):91–8.
51. Picard C, Belot A. Les interféronopathies de type I. Mise au point et revue de la littérature. *Rev Médecine Interne* 2018;39(4):271–8.
52. Rodero MP, Crow YJ. Type I interferon-mediated monogenic autoinflammation: The type I interferonopathies, a conceptual overview. *J Exp Med* 2016;213(12):2527–38.
53. Rodero MP, Tesser A, Bartok E, et al. Type I interferon-mediated autoinflammation due to DNase II deficiency. *Nat Commun* 2017;8(1):2176.
54. Picard C, Thouvenin G, Kannengiesser C, et al. Severe Pulmonary Fibrosis as the First Manifestation of Interferonopathy (TMEM173 Mutation). *Chest*

2016;150(3):e65-71.

55. Liu Y, Jesus AA, Marrero B, et al. Activated STING in a vascular and pulmonary syndrome. *N Engl J Med* 2014;371(6):507–18.
56. de Carvalho LM, Ngoumou G, Park JW, et al. Musculoskeletal Disease in MDA5-Related Type I Interferonopathy: A Mendelian Mimic of Jaccoud's Arthropathy. *Arthritis Rheumatol Hoboken NJ* 2017;69(10):2081–91.
57. Rodero MP, Decalf J, Bondet V, et al. Detection of interferon alpha protein reveals differential levels and cellular sources in disease. *J Exp Med* 2017;214(5):1547–55.
58. Rice GI, Forte GMA, Szykiewicz M, et al. Assessment of interferon-related biomarkers in Aicardi-Goutières syndrome associated with mutations in TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, and ADAR: a case-control study. *Lancet Neurol* 2013;12(12):1159–69.
59. Pescarmona R, Belot A, Villard M, et al. Comparison of RT-qPCR and Nanostring in the measurement of blood interferon response for the diagnosis of type I interferonopathies. *Cytokine* 2019;113:446–52.
60. Kim H, de Jesus AA, Brooks SR, et al. Development of a Validated Interferon Score Using NanoString Technology. *J Interferon Cytokine Res* 2018;38(4):171–85.
61. Liu Y, Ramot Y, Torrelo A, 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: Mutations in *PSMB8* Cause Candle Syndrome. *Arthritis Rheum* 2012;64(3):895–907.
62. Briggs TA, Rice GI, Daly S, et al. Tartrate-resistant acid phosphatase deficiency causes a bone dysplasia with autoimmunity and a type I interferon expression signature. *Nat Genet* 2011;43(2):127–31.
63. Peng SL. Altered T and B lymphocyte signaling pathways in lupus. *Autoimmun Rev* 2009;8(3):179–83.
64. Rieux-Laucat F, Le Deist F, Hivroz C, et al. Mutations in Fas associated with human lymphoproliferative syndrome and autoimmunity. *Science* 1995;268(5215):1347–9.
65. Straus SE, Sneller M, Lenardo MJ, Puck JM, Strober W. An inherited disorder of lymphocyte apoptosis: the autoimmune lymphoproliferative syndrome. *Ann Intern Med* 1999;130(7):591–601.
66. Magerus-Chatinet A, Stolzenberg M-C, Lanzarotti N, et al. Autoimmune lymphoproliferative syndrome caused by a homozygous null FAS ligand (FASLG) mutation. *J Allergy Clin Immunol* 2013;131(2):486–90.
67. Del-Rey M, Ruiz-Contreras J, Bosque A, et al. A homozygous Fas ligand gene mutation in a patient causes a new type of autoimmune lymphoproliferative syndrome. *Blood* 2006;108(4):1306–12.
68. 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(5):1107–13.
69. Watson ML, Rao JK, Gilkeson GS, et al. Genetic analysis of MRL-lpr mice: relationship of the Fas apoptosis gene to disease manifestations and renal disease-modifying loci. *J Exp Med* 1992;176(6):1645–56.
70. Roths JB, Murphy ED, Eicher EM. A new mutation, *gld*, that produces lymphoproliferation and autoimmunity in C3H/HeJ mice. *J Exp Med* 1984;159(1):1–

- 20.
71. Limnander A, Depeille P, Freedman TS, et al. STIM1, PKC- $\delta$  and RasGRP set a threshold for proapoptotic Erk signaling during B cell development. *Nat Immunol* 2011;12(5):425–33.
72. Miyamoto A, Nakayama K, Imaki H, et al. Increased proliferation of B cells and auto-immunity in mice lacking protein kinase Cdelta. *Nature* 2002;416(6883):865–9.
73. Kuehn HS, Niemela JE, Rangel-Santos A, et al. Loss-of-function of the protein kinase C  $\delta$  (PKC $\delta$ ) causes a B-cell lymphoproliferative syndrome in humans. *Blood* 2013;121(16):3117–25.
74. Kiykim A, Ogulur I, Baris S, et al. Potentially Beneficial Effect of Hydroxychloroquine in a Patient with a Novel Mutation in Protein Kinase C $\delta$  Deficiency. *J Clin Immunol* 2015;35(6):523–6.
75. Nanthapisa S, Omoyinmi E, Murphy C, et al. Early-Onset Juvenile SLE Associated With a Novel Mutation in Protein Kinase C  $\delta$ . *Pediatrics* 2017;139(1).
76. Salzer E, Santos-Valente E, Klaver S, et al. B-cell deficiency and severe autoimmunity caused by deficiency of protein kinase C  $\delta$ . *Blood* 2013;121(16):3112–6.
77. Bader-Meunier B, Cavé H, Jeremiah N, et al. Are RASopathies new monogenic predisposing conditions to the development of systemic lupus erythematosus? Case report and systematic review of the literature. *Semin Arthritis Rheum* 2013;43(2):217–9.
78. Hoshino A, Okada S, Yoshida K, et al. Abnormal hematopoiesis and autoimmunity in human subjects with germline IKZF1 mutations. *J Allergy Clin Immunol* 2017;140(1):223–31.
79. Kuehn HS, Boisson B, Cunningham-Rundles C, et al. Loss of B Cells in Patients with Heterozygous Mutations in IKAROS. *N Engl J Med* 2016;374(11):1032–43.
80. Nichogiannopoulou A, Trevisan M, Neben S, Friedrich C, Georgopoulos K. Defects in hemopoietic stem cell activity in Ikaros mutant mice. *J Exp Med* 1999;190(9):1201–14.
81. Wang JH, Nichogiannopoulou A, Wu L, et al. Selective defects in the development of the fetal and adult lymphoid system in mice with an Ikaros null mutation. *Immunity* 1996;5(6):537–49.
82. Walter JE, Lo MS, Kis-Toth K, 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(1):272–3.
83. Notarangelo LD, Kim M-S, Walter JE, Lee YN. Human RAG mutations: biochemistry and clinical implications. *Nat Rev Immunol* 2016;16(4):234–46.
84. Nicolas N, Moshous D, Cavazzana-Calvo M, et al. A human severe combined immunodeficiency (SCID) condition with increased sensitivity to ionizing radiations and impaired V(D)J rearrangements defines a new DNA recombination/repair deficiency. *J Exp Med* 1998;188(4):627–34.
85. Sanchez GAM, Reinhardt A, Ramsey S, et al. JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies. *J Clin Invest* 2018;
86. Frémond M-L, Rodero MP, Jeremiah N, et al. Efficacy of the Janus kinase 1/2 inhibitor ruxolitinib in the treatment of vasculopathy associated with TMEM173-activating mutations in 3 children. *J Allergy Clin Immunol* 2016;

87. Furie R, Khamashta M, Merrill JT, et al. Anifrolumab, an Anti-Interferon- $\alpha$  Receptor Monoclonal Antibody, in Moderate-to-Severe Systemic Lupus Erythematosus: ANIFROLUMAB IN MODERATE-TO-SEVERE SLE. *Arthritis Rheumatol* 2017;69(2):376–86.
88. Rice GI, Meyzer C, Bouazza N, et al. Reverse-Transcriptase Inhibitors in the Aicardi–Goutières Syndrome. *N Engl J Med* 2018;379(23):2275–7.
89. Lei L, Muhammad S, Al-Obaidi M, et al. Successful use of ofatumumab in two cases of early-onset juvenile SLE with thrombocytopenia caused by a mutation in protein kinase C  $\delta$ . *Pediatr Rheumatol Online J* 2018;16(1):61.
90. Arkwright PD, Riley P, Hughes SM, Alachkar H, Wynn RF. Successful cure of C1q deficiency in human subjects treated with hematopoietic stem cell transplantation. *J Allergy Clin Immunol* 2014;133(1):265–7.

Acknowledgements: patients and families, Pr Denis Jullien for providing some pictures

**Table 1**

<b>Pathways</b>	<b>Gene/Protein</b>	<b>Function</b>	<b>Inheritance</b>	<b>SLE manifestation</b>
Complement Deficiency	<i>C1QA, B, C/C1qA, B, C</i>	Efferocytosis	AR	Nephritis, CNS involvement, photosensitivity, arthritis, ANA
	<i>C1R/C1r-C1S/C1s</i>		AR	Nephritis, Fever, arthritis, ANA,
	<i>C4A, C4B, C4</i>		AR	Multi-organ involvement; glomerulonephritis, severe photosensitivity
	<i>C2/C2</i>		AR	Photosensitivity and arthritis, mild or absent renal, neurological or pleuropericardial involvement
	<i>C3/C3</i>		AR	Malar rash, photosensitivity, arthralgia and Raynaud's phenomenon
	<i>C5/C5, C6/C6, C7/C7, C8A/C8A, C8B/C8B, C9/C9</i>		AR	Multi-organ involvement
Auto-Antigen Excess	<i>DNASE1/DNASE1</i>	Extracellular ds/ss DNA degradation	AD	Systemic lupus, Sjögren syndrome, high levels of anti-nucleosomal antibodies
	<i>DNASE1L3/DNASE1L3</i>	DNA-chromatin degradation in	AR	Early-onset SLE, antinuclear antibodies, anti-dsDNA, ANCA

		apoptotic bleb		
Type I Interferonopathy	<i>ACP5/TRAP</i>	Regulate OPN levels though not clearly defined	AR	SPENCD, cytopenias, SLE
	<i>ADAR1/ADAR1</i>	RNA editing silencing detection by RLR	AR	AGS, DSH, BSN, SP
	<i>IFIH1/MDA5</i>	Cytoplasmic dsRNA sensor	AD	AGS, SP, SMS
	<i>RNASEH2A, B, C, RNASEH2A, B, C</i>	DNA:RNA degradation	AR	AGS
	<i>SAMHD1/SAMHD1</i>	Cytoplasmic ssRNA/DNA sensor	AR	AGS, FCL, CVD
	<i>TMEM173/STING</i>	dsDNA sensor	AD	SAVI, FCL
	<i>TREX1/TREX1</i>	Cytoplasmic Ss/dsDNA degradation	AR	AGS, FCL, SLE
Tolerance	<i>TNFRSF6/CD95</i>	Apoptosis	AR	SLE with lymphadenopathy

<i>PRKCD</i> /PKC $\delta$	B cell survival and proliferation	AR	skin and renal involvement cerebral vasculitis lymphoproliferative
<i>IKZF1</i> /KAROS	Early lymphocytes development	AD	SLE, Evans syndrome

**Table 1: Monogenic causes of SLE**

Abbreviations:

AD: Autosomal Dominant

AGS: Aicardi-Goutieres Syndrome

ANA: Anti-Nuclear Antibodies

AR: Autosomal Recessive

BSN: Bilateral strial necrosis

CNS: central nervous system

CVD: Cerebrovascular disease

DSH: Dyschromatosis symmetrica hereditaria

FCL: Familial chilblain lupus

SMS: Singleton Merten Syndrome

SPENCD: Spondyloenchondrodysplasia

SP: Spastic paraparesis

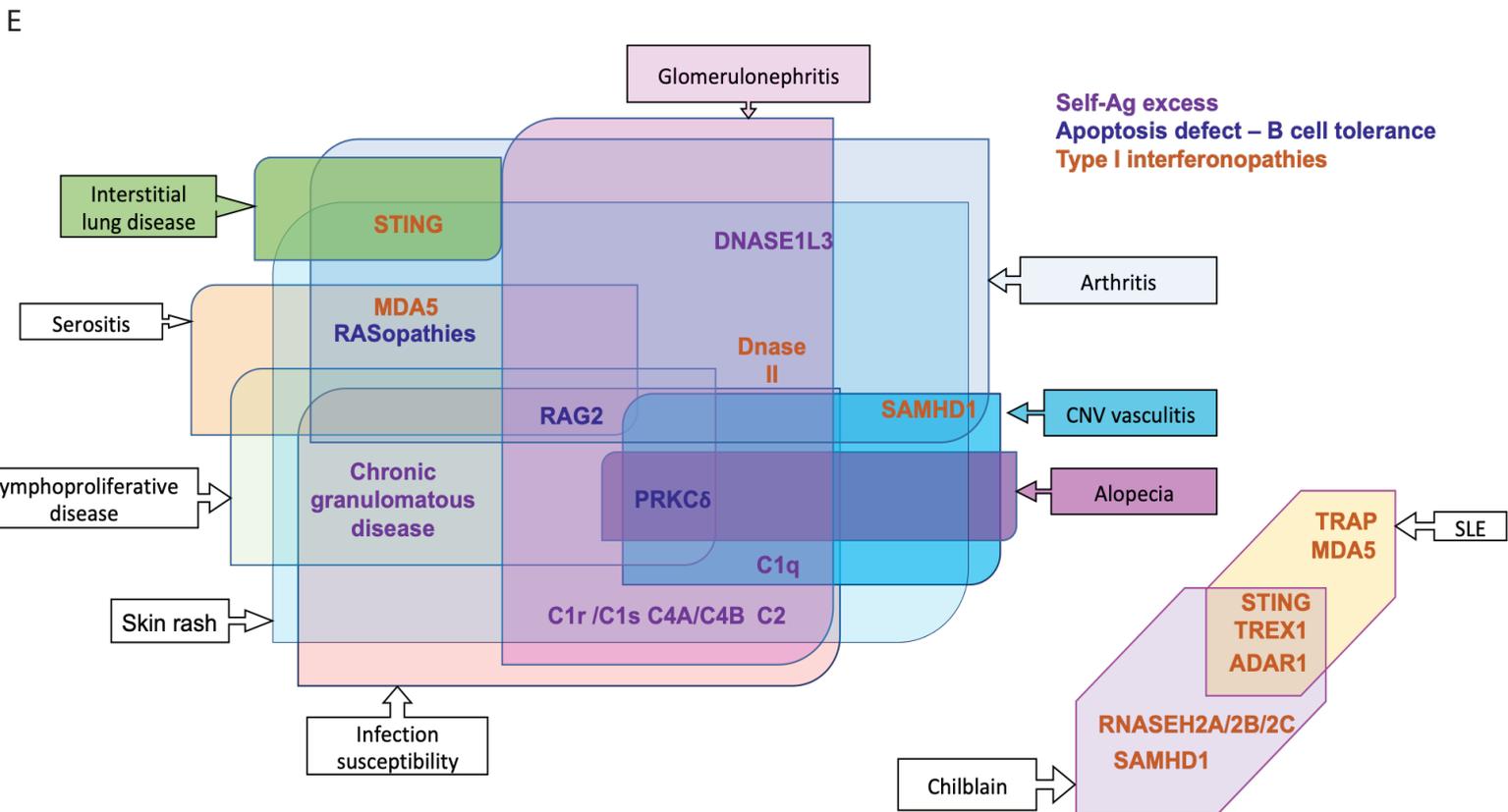
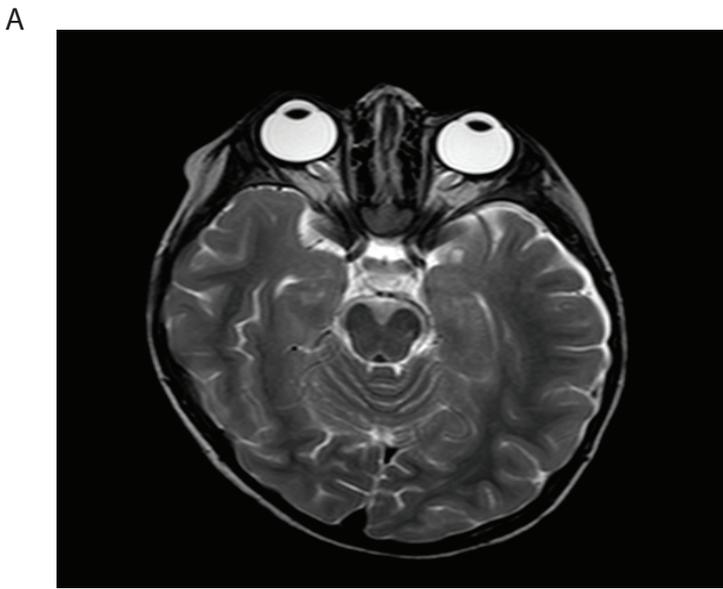
SAVI: STING-associated vasculopathy with onset in infancy

**Figure 1: Clinical features of monogenic lupus**

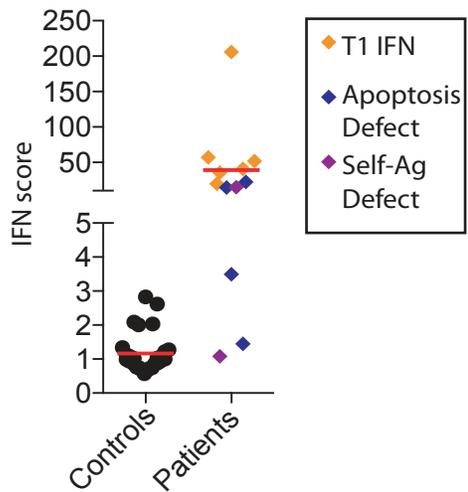
A: Cerebral MRI (T2 sequence showing temporoparietal hypersignal in a C1R deficient patient with meningitis, B: Jaccoud's arthropathy in a patient with type I interferonopathy, C: chilblain lupus in type I interferonopathy, D: papillomatosis of the hand of patient with PKC $\delta$  deficiency, E: synthesis of clinical features of monogenic lupus.

**Figure 2: Biological features of monogenic lupus**

A: Type I Interferon signature in patients with monogenic lupus, B: Synthesis of biological features of monogenic lupus.



A.



B.

