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Editorial Comment

EDITORIAL COMMENT

Gain-of-function *TLR7* and loss-of-function *A20* gene variants identify a novel pathway for Mendelian lupus and lupus nephritis

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ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic and inflammatory autoimmune disease of unknown origin that may cause kidney disease, i.e. lupus nephritis (LN). Within a wider trend towards an expanding field of genetic causes of kidney disease, two recent reports have emphasized the role of Mendelian autoimmune disorders in causing LN both in children and in young adults. Loss-of-function (LOF) variants of tumor necrosis factor alpha–induced protein 3 (*TNFAIP3*) and gain of function (GOF) variants of Toll-like receptor 7 (*TLR7*) cause SLE and LN, respectively. Interestingly, both genes regulate the same signaling route, as A20, the protein encoded by *TNFAIP3*, inhibits nuclear factor κB (NF-κB) activation while TLR7 promoted NF-κB activation. Moreover, *TNFAIP3* and *TLR7* variants are relatively frequent, potentially contributing to polygenic risk for LN. Finally, they both may be expressed by kidney cells, potentially contributing to the severity of kidney injury in persons who have already developed autoimmunity. The fact that both genes regulate the same pathway may lead to novel therapeutic approaches targeting the shared molecular pathway.

Keywords: A20, HA20, inherited kidney disease, lupus nephritis, systemic lupus erythematosus, *TLR7*

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic and inflammatory autoimmune disease of unknown cause, characterized by the loss of immune tolerance to nuclear self-antigens, B-cell hyperreactivity and the production of autoantibodies and inflammatory cytokines, resulting in damage to several tissues and organs and in increased morbidity and mortality [1, 2]. Lupus nephritis (LN) is one of the most common severe manifestations of SLE, as up to 60% of SLE patients develop LN, mainly people with juvenile-onset SLE. The incidence and severity of LN vary according to the geographical area, race/ethnicity, sex/age and applied diagnostic criteria [3, 4]. LN is an immune complex glomerulonephritis characterized by the development of proteinuria, hematuria, leukocyturia and/or reduced kidney function. The course is characterized by relapses and remissions. LN may be the only initial manifestation of SLE [5]. Classically, evidence of LN was one of the potential

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diagnostic criteria for SLE, including persistent proteinuria (>0.5 g/24 hours) or the presence of urinary casts in the 1982 American College of Rheumatology SLE classification criteria [6] or proteinuria >0.5 g/24 hours or per gram of urinary creatinine or red blood cell casts in urinary sediment in the 2012 systemic lupus erythematosus international collaborating clinics criteria [7]. Kidney biopsy confirms the diagnosis of LN, assesses severity and helps to predict outcomes and determine treatment. The 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) LN classification and its 2018 update [8, 9] establish six histologic classes and activity and chronicity parameters of severity [3, 5, 10, 11]. The role of the kidney biopsy was recently highlighted in the 2019 European League Against RheumatismAmerican College of Rheumatology classification criteria: a positive antinuclear antibody with proteinuria >0.5 g/24 hours (or equivalent) and the presence of LN on kidney biopsy according to the 2003 ISN/RPS classification are sufficient to diagnose SLE [12].

THE EXPANDING FIELD OF GENETIC CAUSES OF KIDNEY DISEASE

Inherited kidney diseases (IKDs) are more common than previously thought. They account for at least 10% of adult CKD cases [13, 14]. Prior to the increasing availability of genetic testing, many of these patients were incorrectly classified as having hypertensive nephropathy, CKD of unknown cause or assigned a different cause of CKD. Contributing to the invisibility of IKDs, major registries only report autosomal dominant polycystic kidney disease separately as a cause of CKD, while all other causes of IKD are grouped under 'other' or, if not diagnosed, in any other category. However, when all IKDs are grouped and reported together, we get a different perspective: IKDs are the third leading cause of kidney failure in Catalonia and the fourth in Madrid, Spain [15]. This may still be an underestimation, given the low uptake of genetic diagnostic tests even when they are freely available [16]. A genetic basis for CKD was also identified for one of the most common causes of CKD, so-called hypertensive nephropathy, which in African Americans is usually an IKD *APOL1* variant nephropathy [17]. Although there is no specific treatment available for most IKDs, a correct diagnosis may prevent unnecessary invasive procedures and treatments and, as IKD can be directly attributed to the dysfunction of the responsible gene, this may lead to the design and development of specific therapies [15]. Recent reports have also provided a genetic basis for some forms of LN [18].

GENETIC CAUSES OF LUPUS

SLE is recognized as a polygenic autoimmune disease. The strong genetic component in SLE is estimated to be 66% of heritability in twin studies [19]. In recent decades, genome-wide association studies (GWASs) have identified >100 SLE susceptibility loci [20]. The proportion of phenotypic variances explained by variants in human leukocyte antigen (HLA) is 2.6% [21] and non-HLA 38% [22]. Additionally, >30 genes causing monogenic forms of SLE or SLE-like syndromes have been reported [23–25] (Table 1). Among them, deficiencies of complement factors such as C1q, C4A, B and C2 confer a high disease susceptibility [26]. Approximately 90% of people with C1q deficiency develop a lupus-like phenotype [27]. *TREX1* variants are also associated to monogenic diseases, such as familial chilblain lupus 1, a cutaneous form of SLE, and Aicardi–Goutieres syndrome, an inflammatory encephalopathy that shares features with SLE [26].

Table 1. Examples of genes whose variants are associated with human SLE and impact of the gene variants on the activity of the protein product (modified from Brown *et al.* [25])

SLE predisposition resulting from functional deficiency in protein product	SLE predisposition resulting from excess activity of protein product
TNFAIP3 [18]	*TLR7* [25]
C1QA	*TMEM173*
C1QB	*TNFSF6*
C1QC	*IFIH1*
C1R	*STAT4*
C2	
CFB	
C4A	
C4B	
DNASE1	
TREX1	
PRKCD	
DNASE1L3	
ACP5	
SOCS1	
NCKAP1L	
C1S	
C3	
SAMHD1	
ADAR1	
RNASEH2B	

The type I interferon (IFN) system also plays a major role in SLE pathogenesis [28]. GWASs have reported associations with type I IFN–induced genes, and several monogenic lupus or lupus-like diseases are associated with interferonopathy (e.g. *IFIH1*, *TNFAIP3*, *RNASEH2A*, *RNASEH2B*, *IRF7*). IFN-α-induced genes are overexpressed in the peripheral blood of 60–80% of patients with SLE [29, 30].

The HLA region is a strong predictor of genetic risk, predominately HLA class II {e.g. HLA-DR2 [hazard ratio (HR) 1.2] and HLA-DR3 [HR 2.4]} loci related to T-cell-dependent antibody responses [31–33]. Other predisposing genes involve those encoding lymphocyte signaling molecules that regulate the activation or suppression of T- or B-cell activity or survival, such as *PTPN22*, *OX40L* and *PD1* [34–37].

Lastly, in recent years, evidence suggests the role of genetic factors in both disease susceptibility and on different disease phenotypes [38]. In this regard, *ITGAM* and *FCGR2A* variants have been associated with susceptibility to skin involvement, while *ITGAM, HLDR2* and *STAT4* are associated with kidney disease [39].

Loss-of-function (LOF) variants of tumor necrosis factor alpha–induced protein 3 (*TNFAIP3*) and gain of function (GOF) variants of Toll-like receptor 7 (*TLR7*) were recently reported to underlie LN in children and adults in the *Clinical Kidney Journal* (*CKJ*) and *Nature*, respectively [18, 25].

A20, HA20 AND LN

A20 is a negative regulator of inflammation encoded by the *TNFAIP3* gene [40]. A20 inhibits nuclear factor (NF)-κB signaling and restricts the interferon regulatory factor (IRF) pathway and autophagy [41] (Figure 1). Haploinsufficiency of

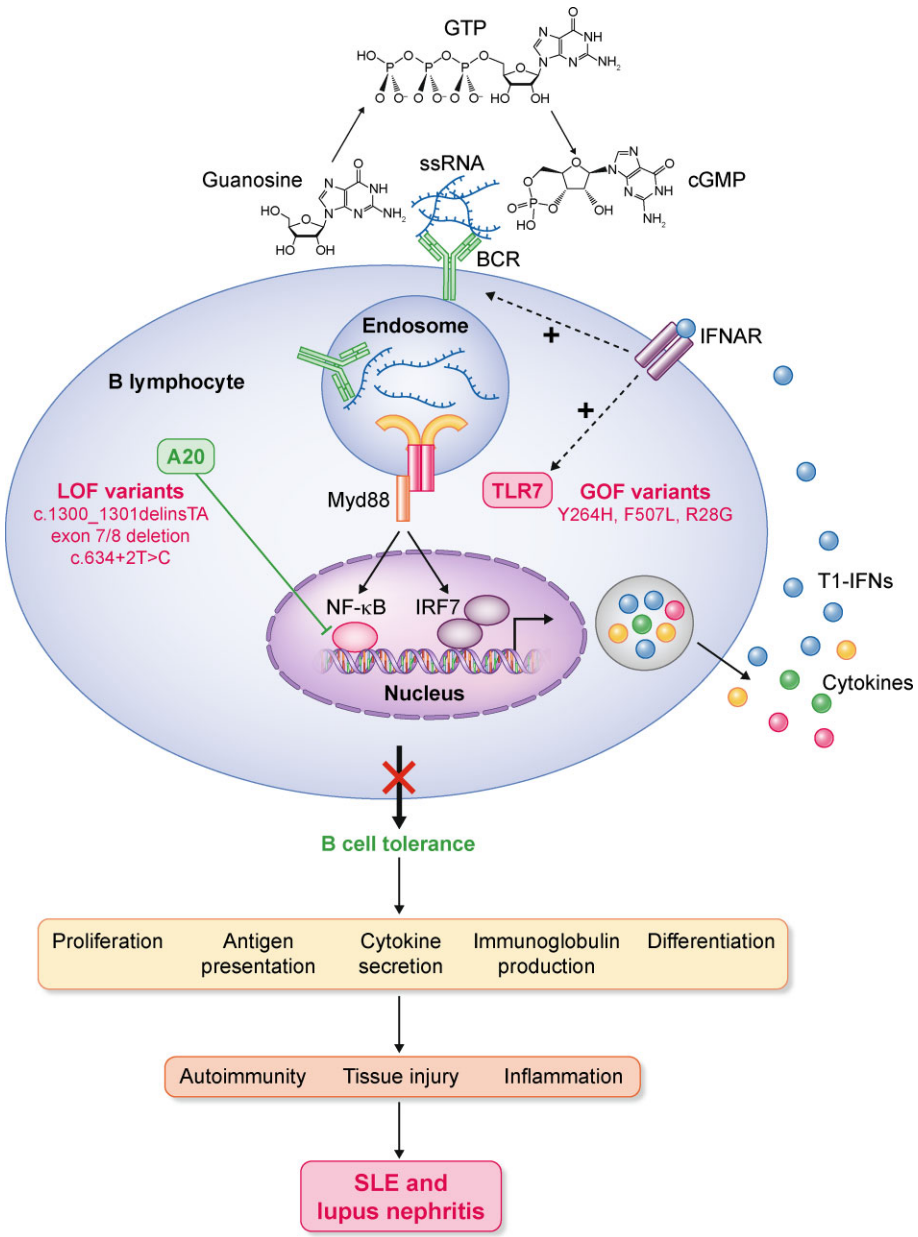

FIGURE 1: LOF *TNFAIP3* variants, GOF *TLR7* variants and LN. B lymphocytes are central players in SLE. Degradation of guanosine triphosphate (GTP) from processed ssRNA yields guanosine and 2¢,3¢-cyclophosphate guanosine monophosphate (cGMP) that are recognized by the BCR and ssRNA is endocytosed complexed with BCR and delivered to endosomes, thus allowing ssRNA interaction with TLR7. TLR7 then recruits the adaptor Myd88 and signals to activate NF-κB and IRF7, leading to synthesis and secretion of cytokines (yellow, green, red dots) and type I IFN (T1-INF, blue dots). The *TNFAIP3* gene encodes the A20 protein, a negative regulator of NF-κB (and of NF-κB association with IRF7), contributing to B-cell tolerance [58]. GOF variants of *TLR7* break B-cell tolerance, leading to SLE, as exemplified by Y264H, F507L and R28G [25]. *TLR7* GOF variants may disrupt B-cell tolerance resulting in increased proliferation of autoimmune B cells, antigen presentation to autoreactive T cells, differentiation to plasma cells and cytokine production [59, 60]. Cytokines contribute to inflammation, while T1-INF endocrine or paracrine (from activated DCs [61]) loops decisively contribute to loss of tolerance. The introduction of the TLR7-Y264H variant in mice resulted in SLE characterized by autoimmunity, tissue injury and inflammation, including LN, and this was prevented by Myd88 deficiency [25]. Also recently, LOF mutations in *TNFAIP3* decisively contribute to loss of tolerance and LN [18]. BCR: B-cell receptor; IFNAR: interferon-α/β receptor; ssRNA: single-stranded RNA.

A20 (HA20; Online Mendelian Inheritance in Man 616744) is an autosomal dominant monogenic disease caused by heterozygous LOF *TNFAIP3* variants and is characterized by early onset systemic inflammation in multiple organs [40]. Although phenotypes may vary according to specific *TNFAIP3* variants [42], the major phenotype is Behçet-like symptoms. In a literature review of clinical manifestations, the most common symptoms were oral ulcers (70%), recurrent fever (42%), gastrointestinal ulcers (40%), skin lesions (38%), genital ulcers (36%), musculoskeletal disorders (34%) and autoimmune thyroid disorder (19%). Ocular involvement, vasculitis, atrophic gastritis, kidney or liver injury, recurrent respiratory tract infection, interstitial lung disease or dental anomaly were found in <10% of patients [42]. The diverse clinical manifestations may result from variable penetrance as well as from the interaction with other genes and the environment.

Table 2. Allele distribution for gnomAD variants for *TNFAIP3* and *TLR7*

Gene	HGVS consequence	VEP annotation	Clinical significance	Allele frequency	Range of allele frequency
TNFAIP3	c.805+28A>C	Intron	Benign	6.09E-01	0.17–0.85
	c.296–15_296–13delCCT	Intron	Benign	6.05E-01	0.17–0.86
	p.Phe127Cys	Missense	Benign/Likely benign	6.17E-02	0.015–0.36
	c.805+26C>T	Intron	Benign	4.41E-02	0.001–0.10
	p.Asn102Ser	Missense	Benign	1.24E-02	0.000–0.06
	c.2089–42G>A	Intron		6.53E-03	0.000–0.01
	c.487–8C>G	Splice region	Benign	6.11E-03	0.000–0.05
	p.Thr647Pro	Missense	Conflicting interpretations of pathogenicity	1.81E-03	0.000–0.006
	p.Ala125Val	Missense	Conflicting interpretations of pathogenicity	1.65E-03	0.000–0.02
TLR7EG	p.Gln11Leu	Missense		1.79E-01	0.000–0.27
	p.Val219Ile	Missense	Benign	4.59E-03	0.000–0.03
	p.Ala448Val	Missense	Benign	3.01E-03	0.000–0.005
	p.Val222Asp	Missense	Benign	2.45E-03	0.000–0.005

HGVS: Human Genome Variation Society; VEP: variant effect predictor.
Gene variants with an allele frequency >1 in 1000 are shown. Gene changes are shown in or within 75 base pairs of a coding exon [56, 57]. The range of allele frequency refers to allele frequencies for different ethnicities.

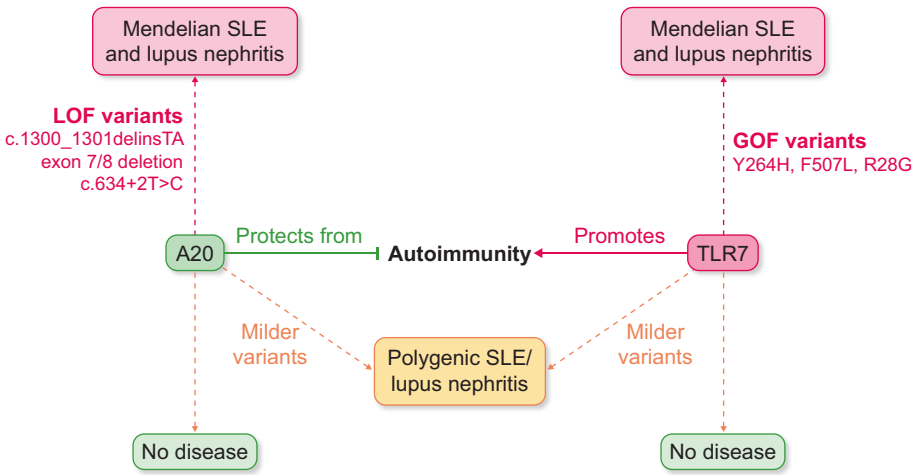

FIGURE 2: *TNFAIP3* and *TLR7* gene variants and SLE/LN. *TNFAIP3* encodes A20, an inhibitor of the pro-inflammatory transcription factor NF-κB that is activated by TLR7. This means that A20 and TLR7 can be traced to the same intracellular signaling pathway and have the potential for clinically relevant interactions. Several severe LOF *TNFAIP3* variants cause Mendelian SLE/LN, as do several GOF *TLR7* gene variants. These variants with a severe impact on function are generally associated with severe, early onset disease, but this may represent the tip of the iceberg, as milder variants may exist that cause late-onset disease that has not yet being characterized, just as familial hypocholesteremia was initially identified in patients having coronary artery disease in childhood. Additionally, even milder gene variants, with the potential to be present in genetic databases from the general population (Table 1) and that are considered benign when isolated, may contribute to polygenic risk for more classical forms of SLE/LN, especially when associated with risk variants of the other gene.

In this issue of *CKJ*, Zhang *et al.* [18]. report that HA20 is a cause of biopsy-proven LN with both early and late onset in males and females in three families with different *TNFAIP3* variants.

A male patient had late-onset (age 29 years) SLE with multiorgan involvement: alopecia, arthralgia, nephrotic proteinuria, thrombocytopenia, hypocomplementemia and positive autoantibodies. Additionally, atopy-like clinical manifestations and high immunoglobulin E levels were present. A novel heterozygous variant c.634+2T>C in the *TNFAIP3* gene affected messenger RNA (mRNA) splicing and created a frameshift mutation that removed both the Ovarian TUmor (OTU) domain and all Zinc Finger (ZnF) domains. Family members with the same genetic variant had milder involvement, including oral ulcers with or without duodenal ulcers, skin rashes, anemia and allergic history, illustrating the clinical variability even within the same family [43]. The other two patients were girls with an early onset (3 years old). One had recurrent fever, autoimmune hemolytic anemia, hepatosplenomegaly, lymphadenopathy, acute cutaneous lupus, serositis, cardiovascular compromise, mild growth retardation and kidney injury. A deletion of exons 7 and 8 in the *TNFAIP3* gene resulted in loss of both OUT and ZnF domains. The other girl also had recurrent fever, autoimmune hemolytic anemia, hepatosplenomegaly, lymphadenopathy and kidney

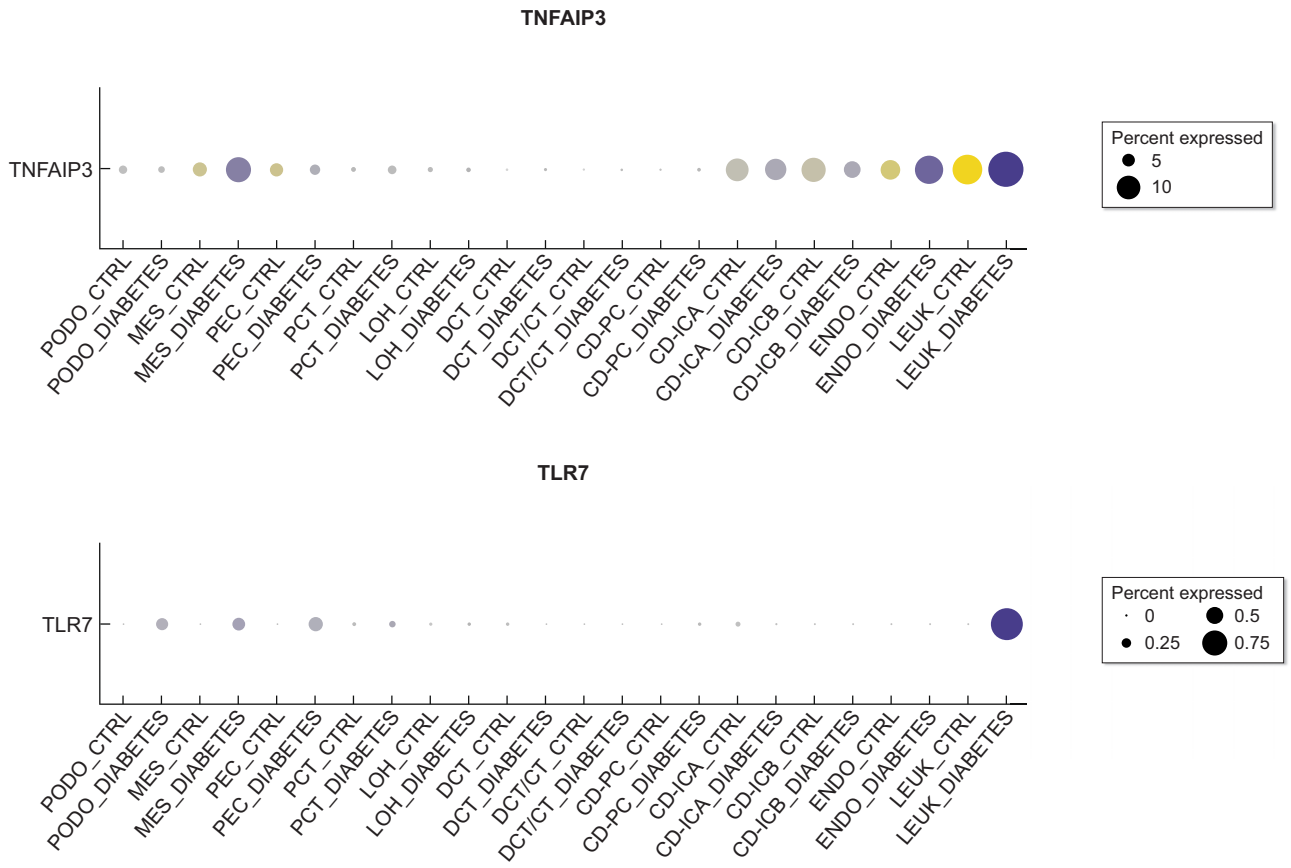

FIGURE 3: *TNFAIP3* and *TLR7* mRNA expression in human control and diabetic kidney tissue. Images from Humphreys Laboratory [62] with permission (Wilson *et al.* [63] and Wu *et al.* [64]).

injury, and additionally had oral ulcers and musculoskeletal involvement. A c.1300_1301delinsTA (p.A434*) *TNFAIP3* variant disrupted the ZnF coding region. This report adds *TNFAIP3* variants to the list of causes of Mendelian LNs. Although mainly found in children, this report illustrates that monogenic LNs may be found in adults.

TLR7

TLR7 is an intracellular receptor mainly expressed in B cells and plasmacytoid dendritic cells (pDCs) that recognizes pathogen-associated molecular patterns [44]. Overexpression of TLR7 results in more severe autoimmune responses and greater incidence of lupus-like disease [45, 46]. TLR7 is encoded by the X chromosome. Although female cells randomly inactivate one of the two X chromosomes, 15–23% of X-linked human genes escape X chromosome inactivation and both alleles are simultaneously expressed. Female B cells with biallelically expressed *TLR7* have an increased susceptibility to TLR7-dependent autoimmune syndromes [47]. In this regard, female pDCs produce more IFN-α than male pDCs upon stimulation with synthetic ligands or single-stranded RNA (ssRNA) that selectively activate TLR7 [48, 49]. Furthermore, increased IFN-α is related to exogenous and endogenous estrogens [47]. Indeed, a TLR7-dependent, IFN-independent immune activation has been proposed to be sufficient to accelerate SLE [50]. Additionally, TLR7 stimulation activates the proinflammatory transcription factor NF-κB [51] that links TLR7 and A20 on opposite sides of the same pathway. *TLR7* gene dosage also contributed to accelerating autoimmunity when a cluster of at least 16 X-linked genes is duplicated and translocated to the Y chromosome in mice (Yaa-chromosome, *Y-linked autoimmune accelerator*) [45]. Finally, in a Mexican population, an increased copy number of *TLR7* was associated with an increased risk of pediatric SLE [52].

Brown *et al.* [25] have described female patients with SLE and GOF *TLR7* variants. A 7-year-old patient had a *de novo TLR7* p.Tyr264His (Y264H) missense variant. Whole exome sequencing of additional patients with SLE identified *TLR7* p.Arg28Gly (R28G) in a young female with mucosal and hematological involvement and *TLR7* p.Phe507Leu (F507L) in a pediatric patient with optic neuritis. To explore the impact of *TLR7* gene variants, Brown *et al* [25]. overexpressed $TLR7^{Y264H}$, $TLR7^{R28G}$ and $TLR7^{F507L}$ in cultured RAW264.7 macrophages and found that these variants caused NF-κB activation. Moreover, they demonstrated that $TLR7^{Y264H}$ could cause SLE, as CRISPR-Cas9 editing into C57BL/6 mice caused splenomegaly, decreased survival, development of antinuclear antibodies, thrombocytopenia and proliferative glomerulonephritis with mesangial electron-dense deposits and increased mesangial cellularity in male or female mice carrying one or two alleles. Lymphoid cells infiltrated the liver, salivary glands and pancreas and mice displayed increased levels of IFN-γ, interleukin-6 (IL-6), IL-10 and TNF [53]. These findings are consistent with previous studies [50, 54] and confirm the role of excess TLR7 activity in the pathogenesis of SLE, including LN. This has clear therapeutic implications. In this regard, an intravenous Toll-like receptor inhibitory peptide 1 (IP1)

decreased albuminuria, kidney inflammation and mRNA expression downstream of TLR7 or TLR9 in MRL/lpr mice with SLE [54]. However, preclinical results of therapeutic interventions may be more solid if they are confirmed at multiple sites [55].

PATHOPHYSIOLOGICAL AND CLINICAL IMPACT

The unstoppable advance of kidney genetics is now expanding into immune-mediated kidney disease. *TNFAIP3* and *TLR7* should be added to the list of genes to be assessed in the evaluation of patients with LN. Interestingly, both genes regulate the same signaling route (Figure 1) and gene variants are relatively frequent (Table 2). Although most of the more common gene variants are labeled benign, this means that they are not associated with Mendelian inherited disease, but they might contribute to polygenic risk scores, and this should be explored (Figure 2). Furthermore, the identification of individual contributors to the pathogenesis of SLE and LN will allow the development of new targeted therapies. Moreover, although studies on their role in SLE have focused on the driving events of LN (i.e. autoimmunity), both genes are also expressed by kidney parenchymal cells. Thus a potential role in kidney injury, independent from the presence of autoimmunity, including a specific role in LN once autoimmunity develops, should be explored. In this regard, both *TNFAIP3* and *TLR7* may be differentially expressed in kidney parenchymal cells in the course of kidney injury (Figure 3).

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(See related article by Zhang et al. Novel loss-of-function mutations in TNFAIP3 gene in patients with lupus nephritis. *Clin Kidney J* (2022) 15: 2027–2038.)

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