Clin Rheumatol (2017) 36:831–836
DOI 10.1007/s10067-016-3466-8

ORIGINAL ARTICLE

APRIL gene polymorphism and serum sAPRIL levels in children with systemic lupus erythematosus

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Received: 10 June 2016 / Revised: 10 September 2016 / Accepted: 30 October 2016 / Published online: 23 November 2016
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Abstract Systemic lupus erythematosus (SLE) is a multifactor autoimmune disorder with diverse clinical manifestations and unclear pathogenesis. Genetic components play important roles in the incidence and development of SLE. Among these, APRIL as a cytokine has roles in the stimulation and antibody production in B cells. APRIL was hypothesized to be associated with SLE. The aim of this study was to assess the involvement of the APRIL gene in SLE susceptibility in Iranian patients. A single-nucleotide polymorphism (SNP) for rs11552708 of APRIL gene was analyzed by real-time PCR in 60 SLE Iranian children and 64 healthy controls. DNA samples of patients and healthy controls were extracted from peripheral blood leukocytes by phenol-chloroform. Serum samples obtained from 45 children with SLE and 45 healthy controls were assayed by enzyme-linked immunosorbent assay (ELISA). The G/G genotype (odds ratio (OR) 0.67, 95% confidence interval (CI) 0.22–2.07; $P = 0.68$) and G allele (OR 0.81, 95% CI 0.25–2.56; $P = 0.89$) frequencies of polymorphism at codon 67 (67G) do not differ significantly in the SLE patients compared with those in the healthy controls. The serum APRIL levels in the SLE patients (mean ± SD = 29.27 ng/ml ± 20.77, range from 0 to 55.33 ng/ml) were significantly higher than those in the healthy controls ($P = 0.02$). Our results demonstrated that rs11552708 of the APRIL gene is not associated with SLE susceptibility in Iranian children. Likewise, these findings suggest that APRIL antagonist could be a potential therapeutic target to control SLE in children.

Keywords APRIL · Single-nucleotide polymorphism · Systemic lupus erythematosus

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Introduction

Systemic lupus erythematosus (SLE) is a multi-factor autoimmune disorder with diverse clinical manifestations and unclear pathogenesis. Immunologically, the disease is diagnosed by the generation of autoantibodies against nuclear and cytoplasmic components that originated from autoreactive B cells. These autoantibodies can damage tissue either directly or as a result of immune complex deposits [1–3]. SLE occurs nine times more often in women compared to that in men [1, 2]. Among all SLE cases, 10–20% is considered as juvenile systemic lupus erythematosus (JSLE), which predominantly

begins in 12–16 years of age. Prevalence of JSLE according to ethnicity ranges from 3.3 to 24 per 100,000 children [4]. JSLE and adult-onset SLE have several similarities; however, a number of differences exist in the clinical course and severity of the disease between adult and children. Ordinarily, JSLE is more severe than the adult-onset SLE, in addition to the higher incidence of organ involvement and more rapid clinical progress [2, 4]. Genome-wide association studies and high concordance in identical twins (24–58%) versus dizygotic twins (2–5 %) have supported that genetic factors such as major histocompatibility complex (MHC), cytokines, complement components, immunoglobulin receptors (FcRs), and apoptotic molecules play important roles in the incidence and development of SLE [5–7].

A proliferation-inducing ligand (APRIL, also named TNFSF13, TALL-2, and TRDL-1) is a type II membrane-binding protein of TNF (tumor necrosis factor) superfamily [8, 9] and plays a regulatory role in tumor growth [8]. APRIL is expressed on monocytes, macrophages, and dendritic cells [10]. This protein is processed in the Golgi apparatus by cleavage at the RKRR motif with a furin protease that resulted in formation and releasing sAPRIL [11]. APRIL is involved in B lymphocyte proliferation, plasma cell survival, antibody production, and CD40L-independent isotype switching by interaction with BCMA (B cell maturation antigen) and TACI (transmembrane activator and cyclophilin interactor) on B cells [10, 12–14]. In addition, heparin sulfate proteoglycans have been characterized as APRIL-specific receptor [15–18].

The human APRIL gene is located on chromosome 17p13.3 [9]. Two single-nucleotide polymorphisms (SNPs) at codon 67 (rs11552708) and codon 96 (rs3803800) of the APRIL gene is identified [19], which G67R polymorphism is shown to have associated with SLE in Japanese [19], Hispanic, and African-American populations [20]. Subsequently, the association of codon A96S with SLE was reported and three protective (67A-96G), susceptible (67G-96A), and neutral (67G-96G) haplotypes were detected [21]. These studies suggested that both codon 67 and codon 96 contribute to SLE susceptibility.

Furthermore, raised levels of serum APRIL has been documented in SLE patients [22–26]. It has also been indicated that APRIL plays a role in other autoimmune diseases such as GBM (anti-glomerular basement membrane disease), Sjögren's syndrome, atopic dermatitis (AD), rheumatoid arthritis, and multiple sclerosis [27–32].

These investigations have indicated that APRIL is involved in the pathogenesis of adult-onset SLE. Regarding the disease similarity in the adults and children, we hypothesized that APRIL can also be effective in the incidence of SLE in children. Therefore, the aim of this study was to evaluate the hypothesis by assessment of the *APRIL* polymorphism particularly rs11552708 in addition to the serum level of APRIL in Iranian children with SLE.

Materials and methods

Participants

The study population included 60 SLE patients who were recognized in accordance with the American College of Rheumatology (ACR) criteria [2] in addition to 64 age- and sex-matched healthy controls admitted to the Children's Medical Center, Tehran, Iran. All patients were Iranian children with the mean age of 11 years (range 4–14). In addition, informed consent was obtained from all the subjects' parents.

Genomic DNA and serum samples were obtained from all the participants; both of them were stored at −20 °C until use.

Enzyme-linked immunosorbent assay (ELISA) for detection of serum APRIL levels

sAPRIL levels in the serum samples from 45 children with SLE and 45 healthy controls were measured using human sAPRIL ELISA kit (eBioscence, USA), according to the manufacturer's protocols. The absorbance was determined by an MPR4+Microplate Reader (Hiperion, Germany) at 450 nm.

Real-time PCR

DNA samples of patients and healthy controls were extracted from peripheral blood leukocytes by phenol-chloroform. Polymorphism genotyping of the samples was conducted by real-time PCR, using TaqMan probe (ABI, USA) with an ABI 7300 real-time PCR instrument (Applied Biosystems). Optical 96-well reaction plate 0.2 μl (ABI, USA) was used for the test. The total volume of 20 μl in each microwell consisted of 10 μl Master Mix (ABI, USA), 0.5 μl Assay Mix (ABI, USA), 4.5 μl deionized water, and 5 μl DNA samples with a concentration of 20 ng/ml. In order to facilitate the work, a mixture containing 1000 μl Master Mix (2×), 50 μl Assay Mix (4×), and 450 μl deionized water was prepared. Afterwards, 15 μl of prepared mixture and 5 μl DNA samples was added into each microwell. PCR conditions were as follows: 95 °C for 10 min, followed by 40 cycles of 95 °C for 15 s and 60 °C for 1 min. The results were determined using Allelic Discrimination program.

Statistical analysis

Statistical analyses were performed using SPSS software version 16.00. The chi-square (χ^2) test was used for comparison of genotypes and allele frequencies in the SLE patients and controls. Serum levels of APRIL between the two groups were assessed using unpaired *t* test. The one-way ANOVA test was used to consider association of *APRIL* gene polymorphism and sAPRIL levels.

Table 1 Comparison of *APRIL* polymorphism between children with SLE and healthy controls

Codon 67 (rs11552708)		SLE	Controls	*P* value	OR [95% CI]
Allele	A	8 (6.6 %)	7 5.5 %)	0.89	1.23 (0.39–3.93)
	G	112 (93.4 %)	121 (94.5 %)	0.89	0.81 (0.25–2.56)
Genotype	G/G	52 (86.6 %)	58 (90.6 %)	0.68	0.67 (0.22–2.07)
	G/A	8 (13.4 %)	5 (7.8 %)	0.48	1.82 (0.56–5089)
	A/A	0 (0 %)	1 (1.6 %)	0.97	

Results

Lack of association between *APRIL* polymorphism and SLE in children

We analyzed *APRIL* gene polymorphism in 124 individuals (60 children with SLE and 64 unaffected children) by real-time PCR. The genotype frequencies of the codon 67 were under Hardy-Weinberg equilibrium (HWE) within each population sample. However, the G/G genotype (odds ratio (OR) 0.67, 95% confidence interval (CI) 0.22–2.07; *P* value = 0.68) and G allele (OR) 0.81, 95% CI 0.25–2.56; *P* value = 0.89) frequencies of polymorphism at codon 67 (67G) do not differ significantly in SLE patients compared with those in healthy controls (Table 1).

Elevated sAPRIL levels in children with SLE

We measured sAPRIL levels in 45 children with SLE and 45 unaffected children using sandwich ELISA. The serum APRIL levels in SLE patients (mean ± SD = 29.27 ng/ml ± 20.77, range from 0 to 55.33 ng/ml) were significantly higher than those in healthy controls [mean ± SD = 2.61 ng/ml ± 0.24, range from 0 to 2.84 ng/ml; *P* value = 0.02] (Fig. 1). When the patients were divided into two groups, based on kidney biopsy, serum APRIL level was higher in patients with renal involvement (mean ± SD = 35.64 ng/ml ± 23.32) than that in those with no kidney manifestations [mean ± SD = 20.77 ng/ml ± 16.99, *P* = 0.05] (Fig. 2). Moreover, APRIL did not correlate with SLEDAI [Systemic Lupus Erythematosus Disease Activity Index] (Table 2) for the 15 patients (Fig. 3).

Lack of association between *APRIL* gene polymorphism and sAPRIL levels

We investigated sAPRIL levels in the SLE patients and healthy controls based on genotypes of *APRIL* polymorphism at codon 67. Expression of serum APRIL was not significantly associated with genotypes between the two groups (Fig. 4).

Discussion

Previous studies demonstrated that 67G allele (rs11552708) was associated with SLE in adults. In the current study, we investigated *APRIL* gene polymorphism at codon 67 and serum APRIL levels in Iranian children with SLE.

Ligands of the tumor necrosis factor (TNF) family are type II membrane proteins (except lymphotoxin α) [33], including TNF-α, Lymphotoxin α, LTβ, CD40L, CD30L, CD27L, OX40L, FasL, 4-1BBL, Apo2L/TRAIL [34, 35], TRANCE/RANKL [36, 37], LIGHT [38], and TWEAK [39]. Family members are involved in the biological functions such as immune regulation, inflammation, cancer, and autoimmune diseases [40]. APRIL (a proliferation-inducing ligand) and BAFF (B cell activating factor) are two members of the TNF

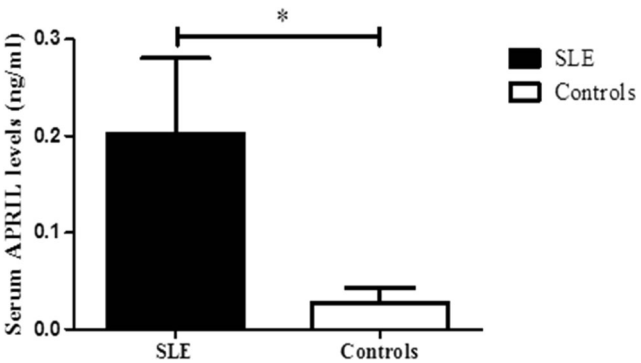

Fig. 1 sAPRIL levels in the 45 children with SLE were significantly higher than 45 healthy controls (*P* = 0.02). Data are shown as mean of serum APRIL levels

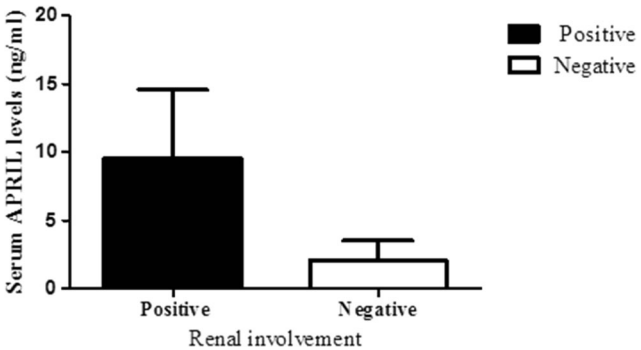

Fig. 2 sAPRIL levels in patients with SLE with renal involvement were increased compared to patients with no kidney manifestations (*P* = 0.12). Data are shown as mean of serum APRIL levels

Table 2 Clinical features of the patients with SLE

Age	
Median	11.86
Range	5 to 22
Sex	
Female	5
Male	2
SLEDAI score	
Median	18
Range	13 to 29
Clinical manifestations	
Renal involvement	57% (4/7)

SLEDAI SLE Disease Activity Index

family which share some functions in common. APRIL is closely related to BAFF [9, 13, 16].

BAFF (also known BLyS, TNFSF13B, TALL-1, zTNF-4, and THANK) is a type II transmembrane protein that cleaved by furin protease at R-X-K/R-R motif and is secreted as a soluble form [41, 42]. This protein is produced by myeloid cells (monocytes, macrophages, and dendritic cells) and non-myeloid cells (epithelial cells, astrocytes, and fibroblast-like synoviocytes) [43, 44]. The BAFF/APRIL system shares two receptors that expressed on B cells: BCMA (B cell maturation antigen) and TACI (transmembrane activator and cyclophilin ligand interactor). Additionally, BAFF can also bind to its specific receptor, BAFF-R (BR3) [9, 13, 16]. BAFF and APRIL play a regulatory role in humoral responses [14]. Besides, dendritic cells induce CD40-independent class switching recombination through BAFF and APRIL [12]. APRIL can also modulate T cell immunity through binding to TACI which was expressed on activated T cells [14]. The BAFF system is involved in the pathogenesis of autoimmune diseases, especially in SLE [45–47]. The clinical relevance of BAFF has also been supposed in other immunological fields such as chronic variable immunodeficiency (CVID), graft versus host disease (GVHD), infections, and allergy [46, 47].

The gene encoding APRIL is located on chromosome 17p13.3 [11] [a fragment spanning 2.8 kb [20]], which

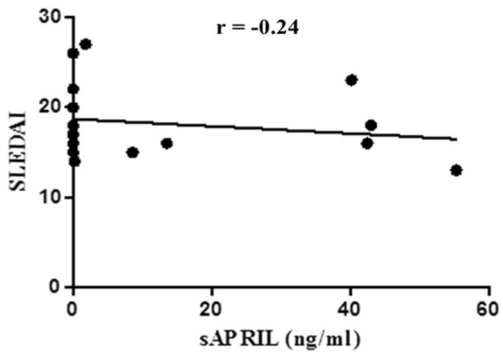

Fig. 3 No correlation was found between the serum APRIL level and the SLEDAI ($n = 15$, $P = 0.34$)

comprised six exons and five introns [20]. Two main isoforms have been reported for APRIL. The β isoform caused by alternative splicing of the exon 3 that resulted in a deletion of 16 amino acids near the cleavage site (R-K-R-R motif). The γ isoform was produced by the skipping of a part of exon 6 (181 bp) [11]. Two single-nucleotide polymorphisms have also been identified from the human APRIL gene including codon 67 (rs11552708) in exon 1 and codon 96 (rs3803800) in exon 2, which were both localized in the extracellular domain of APRIL protein. These polymorphisms lead to amino acid substitution. At codon 67, the first nucleotide G of the codon GGG for Gly was replaced by A, which resulted in an amino acid change from Gly to Arg [G67R]. At amino acid residue 96, the second nucleotide A was replaced by G, which resulted in an amino acid change from Asn (AAT) to Ser (AGT) [N96S] [20].

67G allele was associated with adult-onset SLE in Japanese [20], Hispanic, and African-American populations [23]. Furthermore, association of rs11552708 as a regulatory polymorphism was suggested with celiac disease [48]. Both polymorphisms were also associated with serum levels of IgM in a Chinese male population [49] and serum levels of NAP (non-albumin protein), IgG, IgM, and IgA in Japanese [50, 51].

Many studies presented that serum APRIL levels were increased in the adult patients with SLE [24–29]. Results of the present study also show that serum APRIL levels in children with SLE were significantly higher than those in healthy controls. The mechanism of the increased sAPRIL levels may be explained by high production of type I interferons (IFNs). Increased production of autoantigens during apoptosis (exposure to ultraviolet (UV) and/or spontaneous) results in DNA damage and increases the formation of DNA/anti-DNA immune complexes, with subsequent activation of plasmacytoid dendritic cells and generation of type I IFNs [52]. IFN secretion leads to APC stimulation which resulted in the augmented production of BAFF and APRIL. As a result of the type I IFN secretion, antigen-presenting cell (monocytes, macrophages, and conventional (myeloid) dendritic cells) stimulation occurs which results in increased production of BAFF and APRIL [12].

Another mechanism for raised serum APRIL levels in SLE may be the influence of *APRIL* gene polymorphisms. Firstly, both polymorphisms are located near the cleavage site by furin protease [53]. The amino acid substitution resulted in the induction of a new furin cleavage site (R-X-X-R) that may affect the efficiency of cleavage by furin (the enzyme) [20]. Secondly, ligands of the TNF family organize as a homotrimer; the formation of homotrimer is necessary for binding to receptors [53]. It should be mentioned that association of some other gene polymorphisms, including IL-1, IL6, IL-17F, C1q, and IRF5, with juvenile SLE have already been described [54–57]. Therefore, a systematic review and meta-analysis of all association studies are needed for a better understanding of the pathogenesis of the disease.

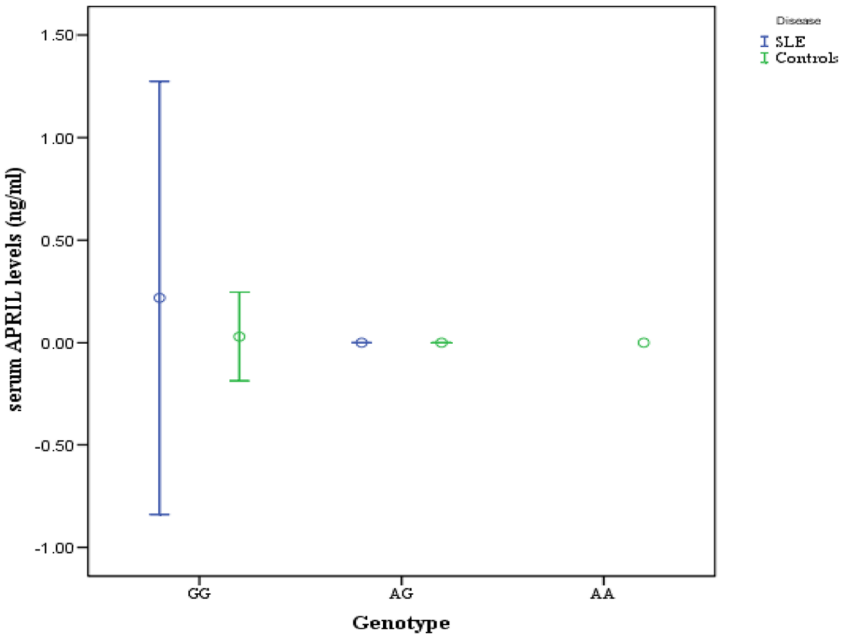

Fig. 4 Lack of association between *APRIL* gene polymorphism and sAPRIL levels. Data are shown as mean ± SD of serum APRIL levels

In conclusion, our analysis suggested that there was no association between G67R polymorphism with juvenile SLE susceptibility and serum APRIL levels in these patients. However, serum APRIL levels were increased in children with SLE the same as those with the adults' disease. Therefore, according to the role of APRIL in B cell stimulation and antibody production, it can be stated that APRIL is involved in the pathogenesis of SLE. In light of our findings, an APRIL antagonist might be suitable as a potential therapeutic target to control SLE in children.

Acknowledgements This study was supported by a grant from Tehran University of Medical Sciences (91-03-30-19288).

Compliance with ethical standards

Disclosures None.

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