ANNALS OF CHILD NEUROLOGY

Original article

pISSN 2635-909X • eISSN 2635-9103
Ann Child Neurol 2019;27(2):38-45
https://doi.org/10.26815/acn.2019.00038

Association of Tumor Necrosis Factor-α Gene Promotor Variant, Not Interleukin-10, with Febrile Seizures and Genetic Epilepsy with Febrile Seizure Plus

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Received: February 3, 2019
Revised: April 9, 2019
Accepted: April 9, 2019

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Purpose: Cytokines demonstrate active roles in the occurrence of febrile seizures (FS). However, whether a genetic predisposition to inflammation is implicated in FS, febrile seizure plus (FS+) or genetic epilepsy with febrile seizure plus (GEFS+) are still unclear. Therefore we perform this study to find the association of promotor variants in pro-inflammatory cytokine tumor necrosis factor-α (*TNF-α*) genes and anti-inflammatory cytokine interleukin 10 (*IL-10*) genes either with FS, FS+, and GEFS+ in Korean children.

Methods: Fifty-seven children with FS, 32 FS+, and 12 GEFS+ patients were compared with 108 controls. The allelic and genotypic distributions were compared for *TNF-α*-238 (rs361525), -308 (rs1800629), -857 (rs1799724), -863 (rs1800630), and *IL-10*-592 (rs1800872), -819 (rs1800871), -1082 (rs1800896), and -1352 (rs1800893).

Results: Allelic and genotypic frequencies of *TNF-α* and *IL-10* promotor variants showed no significant differences between FS, FS+, and GEFS+ versus controls. However, AA genotypes at *TNF-α*-863 were present only in controls. *TNF-α*-863 (rs1800630) promoter variants showed an association with FS, FS+, and GEFS+ in a recessive mode of inheritance pattern (P<0.05).

Conclusion: Our results suggest that AA genotypes at *TNF-α*-863 may be associated with FS, FS+, and GEFS+, implicating protective roles against to development of FS, FS+, and GEFS+.

Keywords: Tumor necrosis factor-alpha; Interleukin-10; Epilepsy; Seizures, febrile; Variants

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Introduction

Febrile seizure (FS) is the most common type of seizure during childhood period, and defined as seizures provoked by fever without central nervous system (CNS) infection [1]. Febrile states are induced by pyrogenic response to various infections, and the magnitude of pyrogenic response influence the body temperature of each child. Interleukin (*IL*)-1β, *IL-6*, and tumor necrosis factor-α (*TNF-α*) are major pro-inflammatory cytokines controlling pyrogenic actions [2]. Overproduction of pro-inflammatory cytokines can boost pyrogenic action and in some children, therefore body temperatures may overwhelm the seizure threshold, provoking to develop FS.

The association between cytokine genetic variants and susceptibility to FS and epilepsy are still controversial. *IL-1β*-511 promoter variants were reported to have an association with FS [3,4]. *TNF-α*-308 genotype showed no significant association with FS in meta-analysis study [5-8]. In other studies, GG genotypes of *TNF-α*-238 were more prevalent than GA genotype among FS compared to controls in Iranian children [9]. Japanese FS study showed significant lower frequencies of the *IL-10*-592C/-819C/-1082A haplotype than controls [10]. In contrast, *IL-10*-592, -819, and -1082 showed no significant allelic association in Iranian FS study [11].

Genetic epilepsy with febrile seizure plus (GEFS+) is a familial disorder with association of FS and epilepsy and shows autosomal dominance inheritance with variable penetrance [12]. And febrile seizure plus (FS+) is a same phenotypic disorder to GEFS+ without family history. To date, sodium voltage-gated channel alpha subunit 1 (*SCN1A*), sodium voltage-gated channel beta subunit 1 (*SCN1B*), and gamma-aminobutyric acid type A receptor gamma2 subunit (*GABRG2*) are known to be disease-causing genes of GEFS+ [13]. Inheritance in GEFS+ is typically autosomal dominant with incomplete penetrance, although other complex inheritance patterns may also occur. However, whether genetic susceptibility to inflammation may be one of the genetic causes for FS or GEFS+ is still unclear.

To determine whether promotor variants of *TNF-α* and *IL-10* influence the susceptibility to FS, FS+, and GEFS+, we analysed genetic variants in the promotor region of *TNF-α* and *IL-10* among children with FS and GEFS+ patients and compared to controls.

Materials and Methods

1. Patient information

Children with FS, FS+, and GEFS+ patients were enrolled in this study from June 2008 to May 2013, visiting the emergency room of Seoul Metropolitan Government Seoul National University Boramae Medical Center with acute seizure attacks. Inclusion criteria for FS were children with seizures associated with fever above 38°C between 6-month-old to 5-year-old, without CNS infection, neurologic deficits and previous afebrile seizures [14]. Diagnosis of genetic epilepsy with febrile seizure plus (GEFSP) followed the criteria established in the 2017 International Classification of Epileptic Syndromes [15]. GEFS+ is usually diagnosed in families whose members have FSs that may continue past the usual age where these are expected to resolve and/or be accompanied by afebrile seizures that may be generalized seizures or focal seizures. FS+ are distinguished from the GEFS+ on the basis of family history. Controls were children matched for age without history of FS nor epilepsy. This study was approved by the Institutional Review Board at the Seoul Metropolitan Government Seoul National University Boramae Medical Center (20080918/06-2008-74/76). Informed consent was obtained from the parent of each child.

2. Variants selection

A total of four variants located in the promotor region of *TNF-α*, -238 (rs361525), -308 (rs1800629), -857 (rs1799724), -863 (rs1800630), and also four variants located in the promotor region of *IL-10*, -592 (rs1800872), -819 (rs1800871), -1082 (rs1800896), -1352 (rs1800893), were selected from the dbSNP database (www.ncbi.nlm.nih.gov/SNP) and the HapMap human SNP database (www.hapmap.org). For selecting variants, variants with a minor allele frequency above 0.05 were included. To estimate pairwise linkage disequilibrium of variant marker, we used Haploview v4.0 (http://www.broadinstitute.org/haploview/haploview). All variants did not show the results of the chi-square test to reject the Hardy-Weinberg equilibrium. The default confidence interval algorithm of the Haploview program revealed 1 haplotype block (Fig. 1A) of *TNF-α*-857, -863 and 1 haplotype block (Fig. 1B) of *IL-10*-592, -819, -1082, -1352, from patient group data.

3. Variant sequencing and genotyping

Probes and primers were designed with genomic sequence information. After amplifying the variant spanning fragments by polymerase chain reaction, genotyping was performed with SNaPshot (Sequenom, San Diego, CA, USA). The person analysing the genotype result was blinded to the clinical data.

4. Statistical analysis

The trend test, chi-square test, Fisher exact test and the logistic regression test were the statistical approaches used analysing the

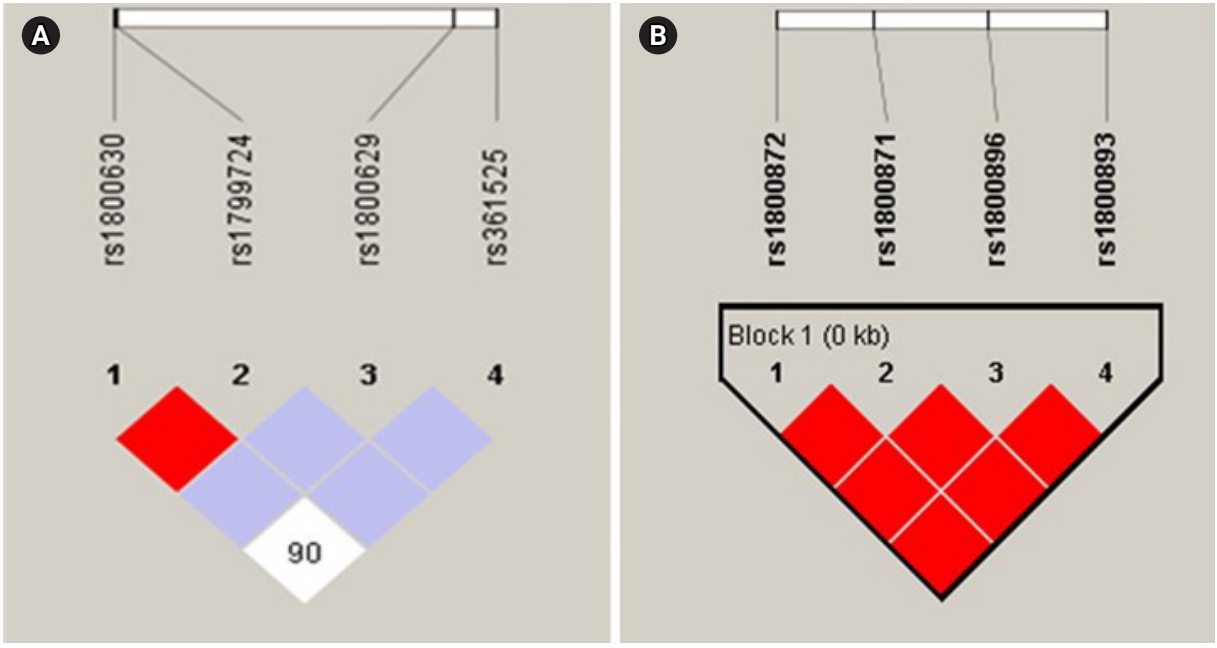

Fig. 1. Linkage disequilibrium structure of the variants in (A) tumor necrosis factor-α (*TNF-α*) and (B) interleukin 10 (*IL-10*), and haplotype blocks were analysed in the current study. The red block is a block including variants that showed significant association in single-marker analysis.

genotype distributions of patient group including FS, FS+, and GEFS+ and then comparing with controls, depending on mode of inheritance [16], such as additive, dominant and recessive, based on the minor allele of each variants. IBM SPSS statistics version 20 (IBM Co., Armonk, NY, USA) and R version 3.2.5 (http://www.r-project.org) were used to analyse the tests. The statistical significance of differences was set as $P < 0.05$ for all tests.

Results

1. Patient characteristics

Fifty-seven children with FS, 32 FS+, and 12 GEFS+ patients and 108 controls were enrolled. Semiology of FS were 46 (81%) simple types and 11 (19%) complex types. Three FS children had a history of febrile status epilepticus. All patients with FS+ and GEFS+ developed epilepsy after previous FS attacks. The children with FS, FS+, and GEFS+ patients did not show significant differences by sex, age, and laboratory findings with controls.

2. *TNF-α* allele and genotype variants

AA genotypes at *TNF-α*-863 were present only in controls. AA genotype at *TNF-α*-863 showed significant negative association with FS, FS+, and GEFS+ ($P = 0.029$) (Table 1). *TNF-α*-238, *TNF-α*-308, and *TNF-α*-857 showed no significant allelic and genotypic differences (Table 2).

3. *IL-10* allele and genotype variants

IL-10-592, -819, -1082, and -1352 failed to show significant allelic or genotypic association with FS, FS+, and GEFS+ compared to controls (Table 3 and 4).

4. Haplotype analysis: *TNF-α*-857 and *TNF-α*-863

Haplotype frequencies of block 1 consisted with *TNF-α*-863 and *TNF-α*-857 showed no significant association with patients group of FS, FS+, and GEFS+ compared to controls.

5. Haplotype analysis: *IL-10*-592, -819, -1082, and -1352

Haplotype frequencies of block 1 consisted with *IL-10*-592, -819, -1082, and -1352 showed no significant association with patients group of FS, FS+, and GEFS+ compared to controls (Table 5).

Discussion

This study demonstrates that allelic and genotypic frequencies of *TNF-α* and *IL-10* promotor variants showed no significant differences between FS, FS+, and GEFS+ versus controls in Korean children. However, AA genotypes at *TNF-α*-863 were present only in controls, therefore AA genotype at *TNF-α*-863 showed

https://doi.org/10.26815/acn.2019.00038

Table 1. Comparison of genotypic frequencies of 4 *TNF-α* SNPs between the patients with FS, FS+, and GEFS+ versus controls

Gene variants	Genotype	No. (%)		Genetic mode	*P* value
		FS, FS+, GEFS+ (n=100)	Control (n=106)		
TNF-α-238 rs361525	G/G	84 (84.0)	94 (88.7)	Additive	0.329
	G/A	16 (16.0)	12 (11.3)	Dominant	0.327
	A/A			Recessive	
TNF-α-308 rs1800629	G/G	85 (85.9)	93 (87.7)	Additive	0.852
	G/A	14 (14.1)	12 (11.3)	Dominant	0.691
	A/A	0 (0.0)	1 (0.9)	Recessive	1.000
TNF-α-857 rs1799724	C/C	71 (71.7)	73 (68.9)	Additive	0.828
	C/T	24 (24.2)	30 (28.3)	Dominant	0.656
	T/T	4 (4.0)	3 (2.8)	Recessive	0.714
TNF-α-863 rs1800630	C/C	69 (69.0)	69 (65.1)	Additive	0.203
	C/A	31 (31.0)	31 (29.2)	Dominant	0.551
	A/A	0 (0.0)	6 (5.7)	Recessive	0.029[a]

TNF-α, tumor necrosis factor-α; SNP, single nucleotide polymorphism; FS, febrile seizure; FS+, febrile seizure plus; GEFS+, genetic epilepsy with febrile seizure plus.
[a]P<0.05.

Table 2. Comparison of allelic frequencies of 4 *TNF-α* SNPs between the patients with FS, FS+, and GEFS+ versus controls

Gene variants	Genotype	No. (%)		Allelic association *P* value
		FS, FS+, GEFS+ (n=100)	Control (n=106)	
TNF-α-238 rs361525	G	184 (92)	200 (94)	0.346
	A	16 (8)	12 (6)	
TNF-α-308 rs1800629	G	184 (93)	198 (93)	0.851
	A	14 (7)	14 (7)	
TNF-α-857 rs1799724	C	166 (84)	176 (83)	0.824
	T	32 (16)	36 (17)	
TNF-α-863 rs1800630	C	169 (85)	169 (80)	0.206
	A	31 (15)	43 (20)	

TNF-α, tumor necrosis factor-α; SNP, single nucleotide polymorphism; FS, febrile seizure; FS+, febrile seizure plus; GEFS+, genetic epilepsy with febrile seizure plus.

Table 3. Comparison of genotypic frequencies of 4 *IL-10* SNPs between the patients with FS, FS+, and GEFS+ versus controls

Gene variants	Genotype	No. (%)		Genetic mode	*P* value
		FS, FS+, GEFS+ (n=100)	Control (n=106)		
IL-10-592 rs1800872	A/A	54 (54.0)	50 (47.2)	Additive	0.383
	A/C	40 (40.0)	49 (46.2)	Dominant	0.327
	C/C	6 (6.0)	7 (6.6)	Recessive	0.859
IL-10-819 rs1800871	T/T	54 (54.0)	50 (47.2)	Additive	0.383
	T/C	40 (40.0)	49 (46.2)	Dominant	0.327
	C/C	6 (6.0)	7 (6.6)	Recessive	0.859
IL-10-1082 rs1800896	A/A	86 (86.0)	95 (91.3)	Additive	0.286
	A/G	13 (13.0)	8 (7.7)	Dominant	0.228
	G/G	1 (1.0)	1 (1.0)	Recessive	1.000
IL-10-1352 rs1800893	G/G	86 (86.0)	96 (90.6)	Additive	0.361
	G/A	13 (13.0)	9 (8.5)	Dominant	0.307
	A/A	1 (1.0)	1 (0.9)	Recessive	1.000

IL, interleukin; SNP, single nucleotide polymorphism; FS, febrile seizure; FS+, febrile seizure plus; GEFS+, genetic epilepsy with febrile seizure plus.

Table 4. Comparison of allelic frequencies of 4 *IL-10* SNPs between the patients with FS, FS+, and GEFS+ versus controls

Gene variants	Allele	No. (%)		Allelic association *P* value
		FS, FS+, GEFS+ (n=100)	Control (n=106)	
IL-10-592 rs1800872	A	148 (74)	149 (70)	0.401
	C	52 (26)	63 (30)	
IL-10-819 rs1800871	T	148 (74)	149 (70)	0.401
	C	52 (26)	63 (30)	
IL-10-1082 rs1800896	A	185 (93)	198 (95)	0.257
	G	15 (7)	10 (5)	
IL-10-1352 rs1800893	G	185 (93)	201 (95)	0.335
	A	15 (7)	11 (5)	

IL, interleukin; SNP, single nucleotide polymorphism; FS, febrile seizure; FS+, febrile seizure plus; GEFS+, genetic epilepsy with febrile seizure plus.

Table 5. Haplotype frequency analysis between FS, FS+, and GEFS+ versus controls

Gene variants	Allele	No. (%)		Allelic association *P* value
		FS, FS+, GEFS+ (n=100)	Control (n=106)	
IL-10-592 rs1800872	A	148 (74)	149 (70)	0.401
	C	52 (26)	63 (30)	
IL-10-819 rs1800871	T	148 (74)	149 (70)	0.401
	C	52 (26)	63 (30)	
IL-10-1082 rs1800896	A	185 (93)	198 (95)	0.257
	G	15 (7)	10 (5)	
IL-10-1352 rs1800893	G	185 (93)	201 (95)	0.335
	A	15 (7)	11 (5)	

FS, febrile seizure; FS+, febrile seizure plus; GEFS+, genetic epilepsy with febrile seizure plus; *TNF-α*, tumor necrosis factor-α; *IL*, interleukin.

significant negative association with FS, FS+, and GEFS + compared to controls. Thus, this results may suggest that AA genotypes at *TNF-α*-863 show protective effects against FS, FS+, and GEFS+. However, our study population is small, so further study is needed with larger number of patients.

Pro-inflammatory cytokines play major actions in seizure generation and exacerbation [17]. *IL-1β* and *TNF-α* showed elevated levels in brains of experimental animals after electrical stimulation of the amygdala [18]. *TNF-α* is mostly released by microglia in the brain [19] and induces astrocytes to release glutamate [20]. An increase in extracellular glutamate may stimulate glutamatergic neurons, leading neuronal hyper-excitability. *TNF-α* upregulates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, increasing glutamatergic transmission [21]. *TNF-α* also upregulates endocytosis of gamma-Aminobutyric acid, or γ-aminobutyric acid (GABA) receptors, and eventually suppresses effects of the inhibition [22]. Altogether *TNF-α* leads to increase seizure susceptibility [22,23].

TNF-α is a potent pro-inflammatory cytokine showing implications with a large number of human diseases including many autoimmune diseases [7]. *TNF-α* shows alternate roles depending on variants of *TNF-α* gene regulating its effect and production [24]. Therefore, genetic variants that upregulate cytokine production may increase susceptibility to inflammation; subsequently, an exaggerated pro-inflammatory cytokine responses during infection may predispose in certain children to develop FS and subsequent epilepsy, especially FS+, and GEFS+. The postictal serum levels of *IL*-1β, *IL*-6, *TNF-α*, and high mobility group box 1 (HMGB1) showed significant elevation among children with FS attacks and children with epilepsy in afebrile seizure attacks, shown in our previous study [25].

TNF-α-238, -308, and -863, among promoter regions, demonstrated to alter transcriptional activity [26]. *TNF-α*-863 genotype showed a negative association with FS, FS+, and GEFS+ among Korean children in our study. AA genotype at *TNF-α*-863 correlates with a lower risk to develop FS, FS+, and GEFS+. CC genotype at *TNF-α*-863 was correlated with an increased risk of juvenile rheumatoid arthritis in Turkish patients [27]. Also, CC genotypes at *TNF-α*-863 showed higher serum levels of *TNF-α*, both pre-operatively and post-operatively after cardiac surgery in 122 German patients [28]. Taken together, CC genotype at *TNF-α*-863 is correlated with more pro-inflammatory action

https://doi.org/10.26815/acn.2019.00038

than AA genotype.

Korean Reference Genome DB KRGDB (http://coda.nih.go.kr/coda/KRGDB/index.jsp) are the free database of 1,100 Korean genomes. A allele frequency of *TNF-α*-863 is 15% and genotype frequencies are no available. In our study, A allele frequency is 15% in patients group of FS, FS+, and GEFS+ and 20% in controls; therefore, we can assume that our study population is not deviant to the general Korean population. The GG genotypes of *TNF-α*-238 were more prevalent than GA genotype among FS compared to controls in an Iranian study [9]. However, in our Korean population, there were no significant genotypic differences at *TNF-α*-238 in patient group of FS, FS+, and GEFS+ compared to controls.

TNF-α-308 is reported to have an association with higher susceptibility to asthma, atopic dermatitis, increased fatality in meningococcemia and ankylosing spondylitis [29-32]. However, in FS meta-analysis study, *TNF-α*-308 genotype showed no significant association [5-8]. Our study also showed no significant association at *TNF-α*-308 with FS, FS+, and GEFS+.

IL-10 is a major cytokine having anti-inflammatory action in immune system. *IL*-10 injected animals showed significantly higher threshold for provoking FS attacks than that in the controls, suggesting a protective effect to FS development [10]. *IL*-10 serum levels are controversial in several FS studies with some reporting increased [33] or others not increased levels [3,34].

IL-10 transmits negative feedback signals to decrease the immune system activation upon various inflammatory stimuli [35]. The *IL-10*-592, -819, and -1082 are placed in the *IL-10* promotor regions having putative regulatory actions [36]. In a study of Japanese FS patients, the frequencies of the *IL-10*-592C/-819C/-1082A haplotype were significantly lower than controls [10]. In our study, the haplotype frequencies of *IL-10*-592C/-819C/-1082A/-1352G were also decreased in patient group with FS, FS+, and GEFS+ compared to controls, although statistically insignificant (18.5% vs. 24.5%, $P=0.497$). In contrast, Iranian FS study reported that *IL-10*-592, -819, and -1082 showed no significant allelic association [11].

The limitation of our study is relatively small number of patients enrolled. Therefore, further studies with larger number of patients with different ethnicities are needed to reveal the exact association of *TNF-α* gene variants with FS, FS+, and GEFS+ in children.

In summary, allelic and genotypic frequencies of *TNF-α* and *IL-10* promotor variants showed no significant differences between FS, FS+, and GEFS+ versus controls. However, AA genotypes at *TNF-α*-863 were present only in controls; therefore, *TNF-α*-863 (rs1800630) promoter variants may be negatively associated with FS, FS+, and GEFS+. Our results support that the promotor genetic variant linked to lesser production of pro-inflammatory cytokine *TNF-α* may be implicated in the protection to fever-provoked seizures in Korean children.

Conflicts of interest

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

Acknowledgements

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (No. 2016R1A2B4009438), the Seoul National University Hospital Research Fund (No. 03-2015-0120 and No. 04-2012-0140), and the Seoul National University Boramae Hospital Research Fund (No. 03-2011-15, No.03-2013-8 and No.01-2014-11) to Jieun Choi, and by grants from the NRF funded by the Korean government (MEST) (No. 2014R1A4A1008625 and 2017R1A2B3006704) to Jeon-Soo Shin.

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