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Association of CD40 gene polymorphisms rs1883832 and rs4810485 with familial mediterranean fever in pediatric patients

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ABSTRACT

Background: Familial Mediterranean fever (FMF) is a recessively inherited autoinflammatory disease characterized by a combination of multiple clinical symptoms potentially associated with numerous genetic and non-genetic risk factors. The CD40 gene, which plays an essential role in inflammatory responses and immune system regulation, contains single-nucleotide polymorphisms (SNPs) that have been linked to various diseases. This research aimed to examine potential associations between CD40 SNPs and FMF in pediatric patients.

Methods: Data regarding common MEFV gene mutations in the patient cohort were analyzed using pyrosequencing techniques. For both patient and control groups, CD40 gene SNPs were genotyped using real-time PCR with rs1883832 and rs4810485 Taq-Man genotyping probes.

Results: The analysis of the CD40 gene's rs1883832 SNP revealed the following distribution in the patient group: CC genotype at 43.0%, CT genotype at 56.0%, and TT genotype at 1.0%. In comparison, the control group showed CC genotype in 47.0% and CT genotype in 53.0% of cases. For the rs4810485 SNP of the CD40 gene, the patient group exhibited GG genotype in 43.0%, GT genotype in 43.0%, and TT genotype in 14.0% of cases. The control group showed distributions of 47.0% for GG genotype, 45.0% for GT genotype, and 8.0% for TT genotype.

Conclusions: The study found no statistically significant correlations between FMF disease and either the rs1883832 or rs4810485 SNPs of the CD40 gene.

Keywords: CD40, familial mediterranean fever, polymorphism, rs1883832, rs4810485, single nucleotide

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INTRODUCTION

Familial Mediterranean fever (FMF) presents as an autoinflammatory disease marked by periodic fever episodes, serositis, joint involvement, erysipelas-like skin manifestations, and kidney complications. The disease's etiology stems from genetic alterations in the Mediterranean fever (MEFV) gene, following an autosomal recessive inheritance pattern [1]. FMF predominantly affects populations residing in the Mediterranean region and is widely distributed in Turkish, Jewish, Arab, and Armenian populations. Within the Mediterranean basin, it shows a relatively lower prevalence in the societies of Spain, Italy, and Greece. Nevertheless, due to the surge in immigration witnessed in recent decades, FMF has evolved into a globalised health concern [2,3].

The MEFV gene, which has been identified as the causative agent of familial Mediterranean fever (FMF), is responsible for encoding the protein known as pyrin, an immune-regulatory protein composed of 781 amino acids. This protein serves a vital function in the innate immune system by interacting with caspase-1 and other inflammasome complex components to regulate the production of interleukin-1β (IL-1β). Research has demonstrated that these components are instrumental in triggering inflammatory responses [4,5]. Within the pyrin protein, the PYD domain controls IL-1β production by forming a bond with ASC (apoptosis-associated speck-like protein with a CARD), an inflammatory adaptor protein, thereby enabling caspase-1 activation. Additionally, it regulates apoptosis through Nuclear factor kappa B (NF-κB) activation, either in an ASC-dependent or ASC-independent manner [6]. The NF-κB transcription factor exhibits significant influence over numerous genes, particularly those associated with inflammatory cytokines [7].

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The relationship between genotype and phenotype in FMF disease demonstrates considerable complexity, with multiple genetic and non-genetic risk factors playing influential roles. The pathogenesis of the disease encompasses not only ethnic and environmental elements but also various genetic components [8].

Cluster of differentiation 40 (CD40), which is categorized as a type II cytokine within the tumor necrosis factor (TNF) superfamily, is expressed on a diverse array of cellular types, encompassing immune cells, platelets, fibroblasts, epithelial cells, smooth muscle cells, mast cells, and dendritic cells. CD40 plays a significant role in both localized and systemic inflammatory responses, augments the proliferation and differentiation of immune cells, and upholds essential regulatory functions within the immune system [9].

CD40, functioning as a transmembrane receptor protein, appears extensively across diverse cell types, including antigen-presenting cells. The engagement of CD40 with its corresponding ligand (CD40L/CD154) predominantly augments the synthesis of cytokines, chemokines, matrix metalloproteinases (MMPs), growth factors, and adhesion molecules via the activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [10]. NF-κB represents the paramount transcription factor activated by the CD40-CD40L signaling pathway, as it triggers the initiation of inflammatory pathways via the synthesis of diverse cytokines and adhesion molecules [11]. Numerous research studies have established connections between CD40 SNPs and various immune-inflammatory conditions [12].

FMF manifests through a diverse array of clinical symptoms, with its development influenced by both environmental factors and genetic alterations across multiple genes. MEFV and CD40 gene expression and their role in modulating inflammatory responses via the NF-κB signaling pathway, this research seeks to explore how specific single nucleotide polymorphisms (SNPs) within the CD40 gene might influence the pathogenesis of Familial Mediterranean Fever (FMF). Our research findings will serve as a foundation for future investigations in this domain. Notably, this study represents the first investigation of the relationship between FMF and CD40 single-nucleotide polymorphisms specifically within the Turkish pediatric population, making it particularly valuable for advancing our understanding of this association.

METHODS

Patients

The study comprised 100 participants aged 0 to 18 years who were referred to the Department of Pediatrics of Dicle University Hospital with suspected familial Mediterranean fever (FMF) disease. The cohort of patients encompassed individuals in whom genetic mutations were identified subsequent to the execution of common mutation analysis for FMF in patients who were referred under a preliminary diagnosis of FMF, in accordance with the Tel Hashomer criteria by Livneh et al. [13]. The patient group comprised 43 males and 57 females. The control cohort comprised individuals in a state of optimal health who bore no familial connection to the patients, exhibited no clinical manifestations characteristic of FMF, and were devoid of any mutations in the analysis of common FMF mutations. The control group included 100 healthy individuals between the ages of 0–18 years. The control group consisted of 54 males and 46 females. The guardians of each participant were comprehensively apprised of the methodology of the study, and written informed consent was duly acquired from them. The individuals incorporated into the study were of Turkish descent and were inhabitants of the southeastern region of Turkey. Approval for the research protocol was received from Dicle University Faculty of Medicine Non-Interventional Research Ethics Committee (2019/139 date: 30 May 2019).

Genotyping

Genomic DNA was extracted from whole blood obtained from FMF patients and control groups using the EZ1 Advanced DNA Blood Kit (Qiagen, Hilden, Germany), adhering strictly to the manufacturer's protocol. The extracted samples were preserved at −20 °C. Common MEFV gene mutations in the patient group were analyzed using the FMF Pyrosequencing Kit (Qiagen, Hilden, Germany) with the manufacturer's instructions. Genotyping was performed by using the TaqMan allelic discrimination assay (Thermo Fisher, Waltham, MA, USA) with the manufacturer's instructions. PCR was performed in a 25 µL final volume containing 12.5 µL of TaqMan Genotyping Master Mix (2×), 0.625 µL of TaqMan probe (40×), 2 µL of genomic DNA, and 9.875 µL of PCR buffer according to the manufacturer's following protocols: AmpliTaq Gold Enzyme Activation at 95 °C for 10 min; initial denaturation at 95 °C for 10 s and 40 cycles of annealing at 60 °C for 1 min. For rs1883832: 5′-ACCATGCCTCCTCCCGTAC-3′ (sense) and 5′-CCACTCCCAACTCCCGTCT-3′ (antisense) primers were used. GTCC TGCCGCCGCCTGGTCTCACCTCGC[C/T]ATGGTTCGTCTGCCTCTGCCTCTGCAGTGCG context sequence was analyzed for nucleotide variation. For rs4810485: 5′-ATCCCCCAAGTACCTGGCTCCT-3′ (sense) and 5′-CCTTTGCTGCTGCTTCCCTTGCTTTC-3′ (antisense) primers were used. CCTACTTTTAGAGGGCTGTAGATTCC[G/T]GCCTGAAGCCTGGGCAGGAATGACC context sequence was analyzed for nucleotide variation.

Statistical Analysis

The computer software SPSS version 26.0 (Chicago, IL, USA) was used for all statistical analyses of the data. The genotype distributions and allele frequencies of FMF patients and controls were compared using Fisher's exact Chi-square (2) test and analyzed for Hardy–Weinberg equilibrium (HWE). The odds ratio (OR) and 95% confidence intervals (CIs) were calculated. Statistical significance was defined as when *p* values were 0.05 or less.

RESULTS

The characteristic features of both the FMF patient and healthy control groups are given in Table 1. The patients and the control group did not exhibit any significant differences in terms of age and gender (p=0.749 and p=0.776).

Table 2 provides a detailed overview of the identified mutations, along with their respective prevalence within the MEFV patient group.

Table 3 provides a summary of the genotype and allele frequencies of the CD40 gene rs1883832 and rs4810485 SNPs in comparison to healthy controls and patients. When comparing the patients and healthy controls for the CD40 gene rs1883832 and rs4810485 SNPs, there was no statistically significant difference in genotype and allele frequency (p>0.05 for all). It was found that the genotype distributions of the rs1883832 and rs4810485 SNPs in both the patient and control groups are compatible with HWE (p>0.05 for all).

Analysis of combined genotype frequencies between patients and healthy controls revealed no statistically significant differences (p>0.05 for all; Table 4).

Table 1. Features of FMF patients and healthy controls

Feature	Control (n = 100)	Patients (n = 100)	*p* value
Age (years)	7.80 ± 4.45	8.11 ± 4.62	0.749
Gender (female)	54	57	0.776
Fever	-	43/100	
Abdominal Pain	-	58/100	
Amyloidosis	-	34/100	
Erythema	-	7/100	
Arthritis	-	19/100	
Chest pain	-	7/100	
Family history	-	8/100	
Thoracic Pain	-	2/100	
Myalgia	-	11/100	
Anemia	-	5/100	
Rheumatic heart disease	-	6/100	

Table 2. MEFV gene mutations in FMF patients

MEFV mutation	Prevalence
E148Q/wt	32/100
M694V/wt	14/100
P369S/wt	8/100
R761H/wt	7/100
V726A/wt	6/100
M694V/M694V	4/100
E148Q/R761H	3/100
M694V/V726A	3/100
E148Q/P369S	2/100
M680I(G>C)/M694V	2/100
M680I(G>C)/V726A	2/100
M694I/wt	2/100
A744S/wt	1/100
E148Q/E148Q	1/100
E148Q/K695R	1/100
E148Q/M694V	1/100
E148Q/M680I(G>C)	1/100
E148Q/V726A	1/100
M680I (G>C)/wt	1/100
M680I(G>A)/wt	1/100
M680I(G>A)/M680I(G>C)	1/100
M680I(G>C)/R761H	1/100
M694I/M694I	1/100
M694V/K695R	1/100
M694V/M694I	1/100
P369S/R761H	1/100
R761H/R761H	1/100

DISCUSSION

FMF is an autoinflammatory disease that stems from mutations in the MEVF gene, characterized by the activation of various inflammatory cascades. Despite ongoing research, its etiopathogenesis remains incompletely understood [14]. Traditionally viewed as a monogenic disorder, recent scientific discourse has challenged this perspective, suggesting that FMF might be better classified as a syndrome rather than a disease. This reconsideration stems from the diverse clinical manifestations that occur simultaneously and the potential influence of environmental factors in its development. Furthermore, the condition may be linked to yet-undiscovered genetic mutations across various genes [8].

Modifier genes such as MIF, IL-1β, IL-4, MTHFR, MBL, SAA1, ABCB1 (MDR1), TNF-α, and CD-14 associated with multiple genetic factors may influence the phenotypic and genotypic manifestations of Familial Mediterranean Fever (FMF) [14-18,27,36,38]. Erken et al. demonstrated that the MBL R52C (C>T) and G54D (G>A) polymorphisms exhibited no significant correlation with susceptibility to Familial Mediterranean Fever (FMF) and its associated clinical manifestations [36]. Ozel et al. indicated that the FAS-671 (A>G) and FASLG-844 (C>T) polymorphisms were not found to be associated with FMF [35]. Nursal

Table 3. Genotype and allele distribution of CD40 polymorphisms in FMF patients and healthy controls

	Patients (n = 100) (%)	Controls (n = 100) (%)	*p* value	x^2	OR (%95 CI)
CD40 rs1883832					
Genotype					
CC	43 (43.0)	47 (47.0)	0.669	0.182	0.851 (0.487–1.486)
CT	56 (56.0)	53 (53.0)	0.776	0.081	1.129 (0.647–1.970)
TT	1 (1.0)	0 (0)	1.000	0	-
Allele					
C	142 (0.710)	147 (0.735)	0.655	0.200	1.133 (0.731–1.754)
T	58 (0.290)	53 (0.265)	0.655	0.200	1.133 (0.731–1.754)
Hardy–Weinberg Equilibrium	$p > 0.05$	$p > 0.05$			
CD40 rs4810485					
Genotype					
GG	43 (43.0)	47 (47.0)	0.669	0.182	0.851 (0.487–1.486)
GT	43 (43.0)	45 (45.0)	0.886	0.020	0.922 (0.527–1.612)
TT	14 (14.0)	8 (8.0)	0.258	1.277	1.872 (0.748–4.684)
Allele					
G	129 (0.645)	139 (0.695)	0.338	0.916	0.797 (0.525–1.211)
T	71 (0.355)	61 (0.305)	0.338	0.916	0.797 (0.525–1.211)
Hardy–Weinberg Equilibrium	$p > 0.05$	$p > 0.05$			

Table 4. Combined genotype distribution of CD40 rs1883832 and rs4810485 polymorphisms

Combined Genotype	FMF patients (n = 100)	Healthy controls (n = 100)	*p* value	x^2	OR (%95 CI)
CC-GG	42	47	0.569	0.324	0.817 (0.655–1.219)
CC-GT	0	0	-	-	-
CC-TT	1	0	1.000	-	-
CT-GG	1	0	1.000	-	-
CT-GT	43	45	0.886	0.020	0.922 (0.527–1.612)
CT-TT	12	8	0.479	0.500	1.568 (0.612–4.019)
TT-GG	0	0	-	-	-
TT-GT	0	0	-	-	-
TT-TT	1	0	1.000	-	-

et al. established a significant association between the MTHFR C677T and IL-4 VNTR polymorphisms and the occurrence of FMF disease [14,33]. Yiğit et al. identified that the IL-4 70 bp VNTR, MIF -173 (G/C), and ACE I/D polymorphisms represent genetic risk factors for FMF [8,38]. A selection of studies investigating gene polymorphisms related to FMF disease is presented in Table 5. In the present investigation, the allelic distribution of CD40 single nucleotide polymorphisms (SNPs) was systematically examined among familial Mediterranean fever (FMF) patients within a Turkish cohort to evaluate its potential involvement in the pathophysiological mechanisms underlying FMF.

The CD40 gene variations and associated changes in serum CD40 levels have emerged as significant areas of research in oncological therapeutics and as potential therapeutic targets across various pathological conditions. These include autoimmune disorders such as Graves' disease, multiple sclerosis, rheumatoid arthritis, and cerebrovascular conditions [39]. The expression of CD40 is influenced by the efficiency of its translation, which is determined by the location of the polymorphism within the gene. These genetic variations may occur within coding regions, affecting amino acid sequences, or within non-coding regions, potentially impacting processes such as gene splicing, binding sites for transcription factors, messenger RNA degradation, or sequences of non-coding RNA [40].

Numerous functional investigations have elucidated that individuals harboring the CT and TT genotypes within the rs1883832 polymorphism display diminished serum CD40 concentrations on the surfaces of monocyte-derived activated dendritic cells (Mo-DC) and B lymphocytes. On the other hand, people with the CC genotype have been shown to induce Graves' disease due to the irregular excessive production of autoimmune antibodies [39]. Numerous investigations have documented a correlation between the rs1883832 polymorphism and serum CD40 concentrations in relation to diverse pathological conditions. These studies have indicated that

Table 5. Studies investigating the association of gene polymorphisms with FMF disease

Gene	Polymorphism	Association	Year	Reference
ABCB1 (MDR1)	3435 (C>T)	Yes	2007	Tufan et al. [15]
CD14	C159T	No	2007	Keskin et al. [16]
TNF-α	TNF-α/238 promoter TNF-α/308 promoter	No No	2007	Kobak et al. [17]
IL-1β	IL-1β-511(C/T) IL-1β+3953 (C/T)	No No	2008	Balci-Peynircioğlu et al. [18]
L-1Ra	VNTR	No		
ABCB1 (MDR1)	3435 (C>T) G2677 (T/A)	Yes No	2009	Bezalel et al. [19]
C5aR	450 (C>T)	Yes	2010	Erken et al. [20]
ABCB1 (MDR1)	3435 (C>T)	Yes	2011	Ozen et al. [21]
ABCB1 (MDR1)	C1236T 3435 (C>T)	No Yes	2011	Rüstemoglu et al. [22]
TNF-α	TNF-α/308(G/A)promoter TNF-α/1031(T/C)promoter	Yes No	2012	Bonyadi et al. [23]
TNF-α	TNF-α/308 promoter	No	2013	Dundar et al. [24]
PAI-1	PAI-1 4G/5G	Yes		
CTLA-4	promoter-318 (C/T) promoter +49 (A/G)	No No	2013	Gunesacar et al. [25]
ABCB1 (MDR1)	3435 (C>T) -1 (A>G) 61 (A>G) 1199 (G>A) 1236 (C>T) 2677 (G>A) 2677 (G>T)	No No No No No No No	2013	Dogruer et al. [26]
CYP3A4	21896 (C>T) 15713 (T>Cb) -392 (A>G) 15615 (T>Ca,b) 23171 (T>C)	No No No No No		
SAA1	-13 (C/T) 2995 (C/T) 3010 (C/T)	Yes Yes Yes	2013	Migita et al. [27]
IL-1β	-511 (C/T)	No		
L-1Ra	VNTR	No		
SAA2	rs2468844	No		
IL-4	70 bp VNT	Yes	2014	Yigit et al. [8]
ACE	I/D variants	Yes		
PON1	Q/R192	No	2014	Öktem et al. [28]
GPX	Pro197Leu	No		
CTLA-4	-1661 (A/G)	No	2015	Hawary et al. [29]
IL-1β	-511 (C/T) -31 (T/C) -3954 (T/C)	No Yes Yes	2015	Ibrahim et al. [30]
IL-1Ra	VNTR	No		
SAA1	2995 (C/T) 3010 (C/T)	No No	2016	Wilson et al. [31]
IL-6	-174 (G/C)	No	2016	Ozer et al. [32]
IL-1Ra	VNTR	No	2016	Nursal et al. [33]
IL-4	VNTR	Yes		
PTPN22	C1858T	No	2016	Kucuksahin et al. [34]
FAS	-671 (A>G)	No	2017	Ozel et al. [35]
FASLG	-844 (C>T)	No		
MBL	R52C (C>T) G54D (G>A)	No No	2017	Erken et al. [36]
MTHFR	C677T A1298C	Yes No	2017	Nursal et al. [14]
IL-4	rs7907187	No	2018	Marzouk et al. [37]
MIF	-173 (G/C)	Yes	2024	Yigit et al. [38]

genotypic differences and allele frequencies are associated with this polymorphism in diseases such as Graves' disease, breast cancer, knee osteoarthritis (KOA), sepsis, atherosclerosis, multiple sclerosis (MS), primary immune thrombocytopenia (pITP), laryngeal cancer and endothelial dysfunction in a pro-diabetic microenvironment [12,41-48]. Statistically significant differences were not reported for studies conducted on diseases such as cervical cancer, Behçet's disease, Hashimoto's thyroiditis, immune thrombocytopenic purpura (ITP) and neuromyelitis optica spectrum disorders (NMOSD) [39,42,49-51]. Our study analysis revealed no significant differences between FMF patients and control subjects regarding rs1883832 polymorphism genotypes (CC-CT-TT) and alleles (C-T) (p>0.05).

The rs4810485 polymorphism, situated within the intron-1 segment of the CD40 gene has been documented to influence the modulation of CD40 gene expression through splicing mechanisms in the non-coding region. The T alleles of rs4810485 have been found to trigger irregular splicing patterns [43,52]. Various studies have identified associations between the rs4810485 polymorphism and serum CD40 levels in multiple diseases. Genotypic differences and allele frequencies have been linked to diseases such as breast cancer, knee osteoarthritis (KOA), multiple sclerosis (MS), Kawasaki disease and rheumatoid arthritis (RA) [12,43,45,53,54]. Studies on diseases such as cervical cancer, cervical squamous cell carcinoma, Behçet's disease, immune thrombocytopenic purpura (ITP) and neuromyelitis optica spectrum disorders (NMOSD) have not reported any statistically significant differences [39,49-51,55]. Analysis of our study data indicated no significant differences between FMF patients and control subjects regarding rs4810485 polymorphism genotypes (GG-GT-TT) and alleles (G-T) (p>0.05).

Nursal et al. elucidated a correlation associated with the inheritance of the combined genotypes for the two MTHFR polymorphisms in patients diagnosed with Familial Mediterranean Fever (FMF). Their findings indicate that individuals exhibiting the TT homozygous genotype at the C677T locus and the AC heterozygous genotype at the A1298C locus are at an elevated risk of developing FMF [14]. Concurrently, Rüstemoglu et al. and Gunesacar et al. also documented a significant association between the combined genotypes of the polymorphisms and FMF [22,25]. İnal and colleagues performed a study examining the combined genotypes of two single-nucleotide polymorphisms (SNPs)—rs1883832 (C/T) and rs4810485 (G/T)—in Behçet's disease. Their investigation revealed no significant differences between these polymorphisms [49]. Our study yielded similar results, showing no statistically significant variations in the combined genotypes between FMF patients and the control group (p>0.05).

This research represents a preliminary exploration of the relationship between CD40 single nucleotide polymorphisms and FMF, based on currently available data. Nevertheless, our study faces certain limitations. The limitations noted in this study may stem from the relatively small sample size, which could limit the statistical power and generalizability of the results, along with the inadequate body of research related to CD40 polymorphisms and FMF. Since we investigated only two SNPs of the CD40 gene, we were unable to fully explore all potential connections between the CD40 gene and FMF. In addition to the CD40 single nucleotide polymorphisms (SNPs) investigated within the context of our research, alternative SNPs (e.g. rs1800686, rs3765459, rs3765459, rs1535045) associated with the CD40 gene were also scrutinized regarding their correlation with autoinflammatory diseases [39,42,53,56]. It has been observed in the aforementioned studies that SNPs in the CD40 gene may function as a genetic biomarker indicative of susceptibility to autoinflammatory disorders. Additionally, our research was confined to the Turkish population within specific age ranges, suggesting that results might differ across other ethnic and age groups.

CONCLUSIONS

Our findings indicate that the two CD40 gene SNPs — rs1883832 and rs4810485 — do not show an association with FMF, though factors such as geographical variations, ethnic differences, distinct disease pathogenesis, and environmental influences may have contributed to these results. Further investigations involving diverse ethnic populations and additional CD40 gene SNPs are necessary to fully understand the precise relationship between FMF and the CD40 gene.

ABBREVIATIONS

ABCB1 – ATP-binding Cassette B1

ACE – Angiotensin-Converting Enzyme

ASC – apoptosis-associated speck-like protein with a CARD

C5aR – C5a receptor

CD14 – Cluster of differentiation 14

CD40 – Cluster of differentiation 40

CTLA-4 – Cytotoxic T lymphocyte-associated antigen-4

CYP3A4 – Cytochrome P450 3A4

FMF – Familial Mediterranean fever

GPX – Glutathione peroxidase

IL-1β – interleukin-1β

IL-4 – Interleukin-4

IL-6 – Interleukin-6

L-1Ra – Interleukin-1β receptor antagonist

MBL – Mannose Binding Lectin

MDR1 – multidrug resistance gene-1

MEFV – Mediterranean fever

MIF – Macrophage migration inhibitory factor

MTHFR – Methylenetetrahydrofolate reductase

NF-κB – Nuclear factor kappa B

PAI-1 – Plasminogen activator inhibitor 1

PON1 – Paraoxonas 1

PTPN22 – Protein tyrosine phosphatase non-receptor type 22

SAA1 – Serum amyloid A 1

SAA2 – Serum amyloid A 2

SNPs – single-nucleotide polymorphisms

TNF-α – Tumor necrosis factor-alpha

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AUTHORS' CONTRIBUTION

MB – Conceptualization; methodology, validation, formal analysis, writing—original draft preparation, visualization, investigation

İY – Validation; writing—original draft preparation, writing—review and editing

ST – Methodology; Validation, project administration, funding acquisition

DO – Data curation, visualization, validation

MB – Supervision; writing—review and editing

SK – Resources; formal analysis, data curation

CONFLICT OF INTEREST

None to declare.

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