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ORIGINAL ARTICLE

The association of TNFRSF1A gene and MEFV gene mutations with adult onset Still's disease

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Abstract Adult onset Still's disease (ASD) is a systemic inflammatory disorder of unknown etiology. ASD is characterized by fever with unknown etiology, rash, arthritis, and involvement of several organ systems. FMF and TRAPS are two important autoinflammatory diseases which characterized with recurrent inflammatory attacks. We aimed in this study to investigate the MEFV gene and TNFRSF1A gene variations in ASD. Twenty consecutive Turkish ASD patients (14 female and 6 male; mean age 38.45 ± 14; mean disease duration 3.3 ± 2.3; mean age of the disease onset 35.1 ± 14.4) and 103 healthy controls of Turkish origin were analyzed. All ASD patients were genotyped for the 4 MEFV mutations (M694V, E148Q, V726A, M680I) and TNFRSF1A gene exon 2–3 and exon 4–5 by using sequence analysis. The healthy controls are genotyped using PCR–RFLP method for intron 4 variation. The results of MEFV gene mutations screening show an increase in the MEFV mutation rate in ASD group, but it was not significantly different ($p = 0.442$, OR 1.64, 95 % CI 0.409–6.589). T–C polymorphism (rs1800692) was the only variation in the intron 4 of TNFRSF1A gene that we observed at the ASD patients. The frequency of TT genotype was 15 %, TC: 45 %, and CC: 40 % in ASD patients and the frequencies were 22, 41, and 37 % in healthy controls, respectively. When we analyzed the allele difference between both groups, there was no difference ($p = 0.54$, OR 1.24, 0.619–2.496–2.654). The variations in MEFV may have role in ASD pathogenesis. Our findings suggest that there is no significant association between ASD and TNFRSF1A variations.

Keywords Adult onset Still's disease · Familial Mediterranean fever · TRAPS · TNFRSF1A gene · MEFV gene

Abbreviations

AS	Ankylosing spondylitis
ASD	Adult onset Still's disease
CAPS	Cryopyrin-associated periodic syndrome
CI	Confidence interval
CRMO	Chronic recurrent multifocal osteomyelitis
DIRA	Deficiency of the IL-1 receptor antagonist
ER	Endoplasmic reticulum
FMF	Familial Mediterranean fever
HC	Healthy control
HIDS	Hyperimmunoglobulinemia D with periodic fever syndrome
HPFS	Hereditary periodic fever syndromes
IBD	Inflammatory bowel disease
IL	Interleukin
MEFV	Mediterranean fever
NF-kappa B	Nuclear factor-kappa B
OR	Odds ratio
PAPA	Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome
PCR	Polymerase chain reaction
RA	Rheumatoid arthritis
RFLP	Restriction fraction length polymorphism
TNF	Tumor necrosing factor
TRAPS	TNF receptor-associated periodic syndrome
TNFRSF1A	Tumor necrosing factor receptor superfamily 1A

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Introduction

Hereditary periodic fever syndromes (HPFS) are a group of diseases including Familial Mediterranean fever (FMF), tumor necrosing factor receptor-associated periodic syndrome (TRAPS), cryopyrin-associated periodic syndromes (CAPSs), pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome, pediatric granulomatous arthritis, hyperimmunoglobulinemia D with periodic fever syndrome (HIDS), chronic recurrent multifocal osteomyelitis (CRMO), deficiency of the IL-1 receptor antagonist (DIRA), and deficiency of the IL-10 receptor early-onset enterocolitis (IBD) [1]. These monogenic diseases of the innate immune system are characterized with self-limited inflammatory attacks, and they are called autoinflammatory syndromes [2]. Recent years, the definition of autoinflammatory syndromes enlarged and included complex genetic disorders such as ankylosing spondylitis (AS), gout, and diabetes mellitus. Moreover, the clinical spectrum of the classical HPFSs became wider after genomic sequencing of patients with an unnamed autoinflammatory syndrome. Several clinical findings of TRAPS were reported to be associated with different mutations in the TNFRSF1A gene.

FMF (OMIM #249100) is the most common HPF and is caused by the MEFV gene mutations [3]. It was shown that individuals with MEFV mutations are at increased risk for some inflammatory diseases such as AS [4, 5], rheumatoid arthritis (RA) [6, 7], ulcerative colitis [8, 9], juvenile idiopathic arthritis [10, 11], Crohn disease [12], Henoch Schönlein purpura [13, 14], and polyarteritis nodosa [15].

TRAPS (OMIM # 142680) is an autosomal dominantly inherited autoinflammatory syndrome. The mutations in exon 2–3 and 4–5 of the TNFRSF1A gene which is located on chromosome 12p13.2 [16] are the cause of this rare syndrome. TNFRSF1A gene encodes the 55 kDa receptor for tumor necrosis factor [17]. The frequency of TRAPS is 1 per million in the UK [18], and TRAPS is not associated with ethnicity [19]. TRAPS is characterized by irregular recurrent attacks of fever, myalgia, erythematous skin rash, abdominal pain, conjunctivitis, periorbital edema, and amyloidosis. The clinical findings show great variability [20]. Attacks respond dramatically to steroids. The diagnosis is confirmed by sequencing of the TNFRSF1A gene. Because the variability of the clinical findings, genetic confirmation is required for diagnosis. TRAPS patients may present with different clinical manifestations, and several mutations have been found in association with the disease.

Adult onset Still's disease (ASD) is a systemic inflammatory disorder of unknown etiology. ASD is characterized by fever with unknown origin, erythematous rash, sore throat, arthritis or arthralgias, high glycosylated ferritin levels, and involvement of several organ systems. Steroids are used for treatment of ASD.

We aimed to investigate the role of the MEFV and TNFRSF1A gene mutations in the ASD patients, as well as their association with disease phenotype because of the similarity of the clinical findings in ASD, FMF, and TRAPS.

Methods

The study group consisted of 20 ASD patients (14 female and 6 male; mean age 38.45 ± 14; mean disease duration 3.3 ± 2.3; mean age of the disease onset 35.1 ± 14.4) and 103 healthy controls of Turkish origin. All ASD patients fulfilling the classification criteria for ASD [21] were followed up at the Kocaeli Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology. The study protocol was approved by the Local Ethics Committee of the Kocaeli Faculty of Medicine, and a written informed consent was obtained from all patients before inclusion into the study.

All ASD patients were screened for the TNFRSF1A gene variations in exons 2–3 and exons 4–5 by DNA sequencing. Genotyping for the TNFRSF1A gene was carried out with the amplification of genomic DNA for exon 2–3 by using a forward primer of 5′-AGGAC TTGAGCCAGGGAAGT-3′ and a reverse primer of 5′-CATAGACAGGCACCCACACA-3′ and for exon 4–5 by using a forward primer of 5′-GGCAGGAAGGT GTGTGTTTT-3′ and a reverse primer of 5′ ATCT GTTGCCCAGCTAATGG-3′. The healthy controls were genotyped for intron 4 polymorphism (rs1800692) using PCR–RFLP method with *Mnl*1 restriction enzyme.

The four most frequently MEFV mutations (M694V, M680I, V726A, E148Q) were genotyped in all patients and healthy controls with PCR–RFLP method according to our previously study [22].

Allele frequencies of the patients and healthy controls were compared by a Chi Square tests and odds ratios (OR) with 95 % confidence intervals (CI) were calculated by using SPSS16.0.

Results

The results of MEFV gene mutations screening were given in the Table 1. Although the mutation rate was increased in ASD group, there was no significant difference between ASD and HC groups ($p = 0.442$, OR 1.64, 95 % CI 0.409–6.589) (Fig. 1). All ASD patients have been re-examined after the mutation analysis and none of them had FMF-associated symptoms or signs.

Table 1 The distribution of MEFV mutations

Mutation	*n*
ASD	
M694V	1
M680I	1
E148Q	1
HC	
M694V	2
M680I	1
V726A	1
M694 V-E148Q	1
V726A-E148Q	1

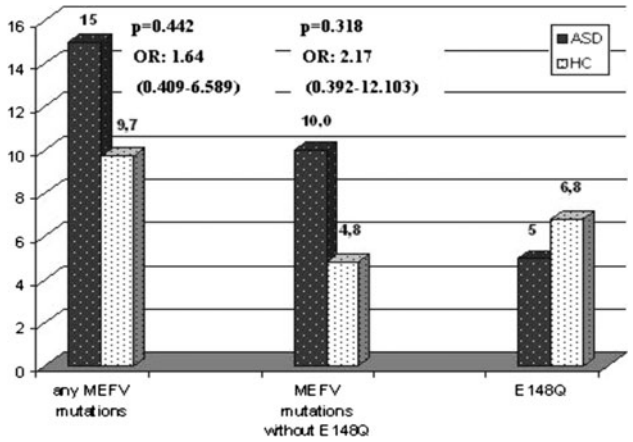

Fig. 1 The MEFV mutation distribution in HC and ASD

All patients were sequenced successfully for the exon 2–5 of the TNFRSF1A gene. No TNFRSF1A gene mutations associated with TRAPS were found in ASD patients. A common polymorphism in intron 4 (T > C, rs1800692) was the only variation found in sequencing; therefore, 103 healthy controls were genotyped by PCR–RFLP for this variation. No association for this variation was found between the ASD group and the HC group. The allele and genotype frequencies are shown in Table 2.

There was no significant difference in distribution of intron 4 polymorphism allele and genotype frequencies between the ASD group and the HC group ($p = 0.54$). Also, no significant association was observed between the alleles of this polymorphism and clinical manifestations.

Discussion

MEFV gene mutation rate was increased in ASD group, although it was not significantly different ($p = 0.442$, OR 1.64, 95 % CI 0.409–6.589). We showed only one variation in the TNFRSF1A gene, which was located in the intron 4. We screened this variation in the HC group, but we did not find any difference between both groups ($p = 0.54$, OR 1.24, 95 % CI 0.619–2.496–2.654). Our findings suggest that there is no significant association between ASD and TNFRSF1A variations. On the other hand, the variations in the MEFV gene may have role in ASD pathogenesis and should be investigated in larger ASD groups.

Table 2 Allele and genotype frequencies of the intron 4 (T > C, rs1800692) polymorphism in patients with ASD and healthy controls

	ASD		HC	
	n	%	*n*	%
Alleles				
T	15	37.5	88	42.7
C	25	62.5	118	53.3
Total	40		206	
p: 0.54, OR 1.24 (0.619–2.496)				
Genotypes				
TT	3	15	23	22..3
TC	9	45	42	40.8
CC	8	40	38	36.9
Total	20		103	

ASD is an inflammatory disease whose etiology and pathogenesis are unknown. It is characterized with strong inflammatory response to an unknown factor and good response to steroid therapy [23]. No infectious agents have been shown to be causative. ASD could be developed with one attack or non-periodical attacks, which need severe immunosuppressive therapy. Some cases could be treated with anti-TNF or anti-IL-1 therapy, even though it is unknown how these drugs affect to disease [24]. Because of the effectiveness of such therapies, we thought that some innate immune system pathways may play role in the pathogenesis. Genetic and environmental factors such as infectious agents may have role in the pathogenesis [25]. The major genetic association was found in the MHC region, and it was shown that the HLAB17, B18, B35, DR2 are associated with ASD. The other subsequently done studies have shown different HLA loci which are associated with ASD [25]. No link could be demonstrated between ASD and non-MHC gene loci.

Hereditary periodic fever syndromes constitute a rare disease group, and the most frequently seen disease of this group is FMF. In Turkey, FMF is a very frequent disease and the frequency of MEFV gene mutation was 9.7 % in our study. Because the ASD symptoms resemble the symptoms of FMF attacks, we analyzed in ASD group the common MEFV mutations. In our study, we found that the mutation rate, especially exon 10 mutations rate is

increased in ASD group without any symptoms of FMF. However, the difference was not statistically significant. Since our ASD study group was very small, the difference could be greater if the study group papulation had been larger.

MEFV gene mutations cause dysregulation of the inflammasome and increased IL-1β response [26]. This pathway is the major mechanism in FMF pathogenesis. In the populations with a high MEFV mutation carrier rate, it was shown that these mutations are associated with severe disease prognosis in the other inflammatory syndromes [3–15]. The main cause of this effect is the dysregulation of IL-1 β activation [26].

TRAPS is one of the rare hereditary autoinflammatory syndromes. TRAPS is caused by mutations in TNFRSF1A gene. TNFRSF1A, the transmembrane receptor of TNF, play the most important role in TNF-TNFRSF1A binding and therefore in the initiating of inflammation and activation of the NF-KB pathway. In consequence, inflammation is induced and apoptosis is inhibited [18]. This gene has a role in different pathways associated with inflammation, and the mutations in this gene cause in a wide range of clinical findings [27]. They may induce the expression of multiple inflammatory protein encoding genes, receptors, transcription factors, and molecules that have role in the cellular signaling pathway [28]. The clinical findings of TRAPS are variable. Although this may be due to the heterogenous mutations in TNFRSF1A, it was shown that the patients with 'TRAPS-like' symptoms are low sTNFRSF1A levels, do not have any mutations in the TNFRSF1A gene [29]. It may be suggested that the other genetic factors that decrease the TNFRSF1A levels may have a role in the pathogenesis of TRAPS. On the other hand, the pathogenesis of the diseases with symptoms similar to TRAPS may be associated with TNFRSF1A gene. It was shown that the patients with early synovitis for less than 6 months had R92Q mutation ratio 2.5 % compared to 1.04 % of HC [30]. A genomewide screening in multiplex rheumatoid arthritis families suggested that the TNFRSF1A gene may play a role in rheumatoid arthritis [31]. The clinical findings of ASD such as fever, erythematous rush, arthritis, response to steroids, and anti-TNF agents are the common characteristics of TRAPS and ASD. There is no research in the literature investigating the association between TRAPS and ASD. A case report from Japan showed that a patient with ASD-like skin manifestations had a novel mutation in the TNFRSF1A gene [32].

It is unknown how the mutations cause the disease. The common mutations are found in exon 2-4 which encode the extracellular domain of TNFRSF1A. More than 80 mutations are described in this gene [33]. The studies have shown that mutations in the extracellular domain of TNFRSF1A resulted to an impaired shedding of TNFRSF1A and so it has been described that the TNFRSF1A mutations caused elevated serum TNF-a levels [34]. The mutations in the extracellular domain of TNFRSF1A gene result the defective shedding of the extracellular part of the TNFRSF1A [35]. The other mechanisms which may have role in the pathogenesis include impaired TNF binding, a defect in the leukocyte apoptosis or a defect of the ER-stress [36–38].

In our study, we found that the intron 4 of the TNFRASF1A gene show wide variation in the Turkish population. We have shown for the first time that this part of the gene locus is variable. But our data showed that this polymorphism was not associated with the disease or any symptoms. Therefore, the variation in intron 4 seems not to be related with ASD.

Conclusion

We herein report that the TNFRSF1A exon 2–5 mutations are not associated with the pathogenesis of ASD and the MEFV gene mutations are increased in ASD group, although the difference was not statistically significant. These results may imply that being an asymptomatic carrier for MEFV mutations may increase susceptibility to ASD. It needs further investigation with larger study populations. The findings of this study suggest that there is no significant association between ASD and TNFRSF1A variations.

Conflict of interest None.

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