European Review for Medical and Pharmacological Sciences 2016; 20: 3255-3261

MEFV gene variation R202Q is associated with metabolic syndrome

A. BALKARLI[1], M. AKYOL[2], E. TEPELI[3], L. ELMAS[3], V. COBANKARA[4]

[1]Department of Internal Medicine, Division of Rheumatology, Antalya Training and Research Hospital, MuratpaÐa, Antalya, Turkey
[2]Department of Medical Biology, Akdeniz University Hospital, Konyaaltı, Antalya, Turkey
[3]Department of Medical Biology, Pamukkale University Hospital, Kınıklı, Denizli, Turkey
[4]Department of Internal Medicine, Division of Rheumatology, Pamukkale University Hospital, Kınıklı, Denizli, Turkey

Abstract. – OBJECTIVE: MEFV (Mediterranean fever) gene encoding pyrin regulates inflammatory responses. It has been shown that MEFV gene variations are associated with higher acute phase responses and altered course in the different inflammatory diseases. MEFV gene variations may affect the course of metabolic syndrome components.

PATIENS AND METHODS: This study included 50 patients with metabolic syndrome and 50 unrelated healthy controls. Genomic DNAs were isolated from patients and healthy controls with standard methods and analysis of exon 2 and 10 of MEFV gene was performed by using Sanger sequencing method.

RESULTS: The MEFV gene variations were detected in 21 patients with metabolic syndrome (42%) and 12 healthy controls (24%) (p=0.55). The frequency of MEFV gene variations with high penetrance (i.e. M694V, M680I, V726A) was similar between patients and healthy controls (p>0.05). We found that R202Q was more frequent in the patient group (n=11 [22%] *vs.* n=3 [6%]) and associated with metabolic syndrome (p: 0.021; OR: 4.42; CI 95%: 1.15-16.97). When patients with and without MEFV gene variations were compared, no significant difference was found in laboratory and clinical parameters.

CONCLUSIONS: To best of our knowledge, this is the first study indicating an association between MeS and R202Q mutation of MEFV gene. Familial Mediterranean fever (FMF) related MEFV gene variations may contribute to the pathogenesis of metabolic syndrome.

Key Words
Metabolic syndrome, Familial Mediterranean Fever, MEFV gene variation, Association.

Introduction

Cardinal features of the metabolic syndrome (MeS) are central obesity, hypertension, dyslipidemia, glucose intolerance, vascular inflammation, and prothrombotic state. Whether the metabolic syndrome represents a constellation of these independent risk factors or a common mechanism which can explain all of these features is highly controversial[1,2]. Several reports have speculated on the association between insulin resistance (IR) and MeS components, which is also known as insulin resistance syndrome[3,4].

IR can occur due to the defects observed at different levels of insulin signalization pathway. One of these potential mechanisms is the increase in pro-inflammatory signals. For example, free fatty acids stimulate pro-inflammatory signal through toll-like receptors (TLR), which, in turn, causes activation of kβ kinase beta inhibitor and c-Jun N-terminal kinase (JNK), resulting in increased production of TNF-alpha, IL-1β, and IL-6[5]. These serine kinases phosphorylate serine residues in the insulin receptor substrate-1 (IRS-1), leading attenuation of metabolic signaling. IL-1β decreases the expression of IRS-1 at either transcriptional or post-transcriptional level; thus, it can impair insulin signaling and its effect. Therefore, it is thought that IL-1 may contribute to IR in adipocytes[6].

Familial Mediterranean fever (FMF) is an autosomal recessive disease with unclear etiology which is characterized by fever, peritonitis, synovitis, and pleuritis[7]. The gene responsible for FMF is located in the short arm of chromosome 16, namely MEFV (Mediterranean fever) gene. The gene encodes pyrin which has an anti-inflammatory activity[8,9]. Mutations in MEFV gene cause abnormal synthesis of pyrin proteins, preventing effective suppression of inflammation. Pyrin is mainly expressed in mature granulocytes and fibroblasts, which supports its role in the activation of the inflammasome-associated IL-1β

Corresponding Author: Ayse Balkarli, MD; e-mail: drayseayan@yahoo.com.tr

activation[10]. It was shown that the serum levels of pro-inflammatory cytokines such as IL-1β, and TNF-alpha aren't only higher during acute episodes but also during remission in FMF patients when compared to healthy individuals. This was proposed as a marker of persistent subclinical inflammation[7]. Therefore, the heterozygous state for MEFV gene variations can affect the course of other inflammatory diseases. This hypothesis was tested previously by many researchers, and it was found that individuals with heterozygous MEFV gene variations had higher acute phase responses and that heterozygous MEFV gene variations alter course of different inflammatory diseases[11-13].

The prevalence of heterozygous carrier state for FMF-related MEFV gene variations was reported to be 9-20% in Turkey[10]. It is known that the MEFV gene variations cause an increase in an IL-1 which is one of the most important pro-inflammatory cytokines. Therefore, we hypothesized that heterozygous state for FMF-related MEFV gene variations can contribute to the pathogenesis of MeS. In this study, we aimed to investigate the potential association between FMF-related MEFV gene variations and MeS and their relationship with clinical features in a prospective manner.

Patients and methods

Patients

All patients with MeS who were managed in our clinic were reviewed before participation and patients with a history FMF manifestation were excluded. In addition, patients with chronic renal failure, amyloidosis, diseases other than the components of MeS, and those with family history of FMF in a first-degree relative were also excluded.

The study included 50 patients with MeS who were diagnosed according to the diagnostic criteria recommended by Turkish Endocrinology and Metabolism Committee Metabolic Syndrome Study Group, and 50 age- and sex- matched healthy volunteers without a family history of FMF. Patients were informed about the study protocol and genetic assays and gave informed consent. Venous blood samples were drawn in 10 cc tubes with EDTA. DNA was extracted immediately after sampling. All samples were stored at –70°C.

A standard data sheet was used to collect the demographical data of all subjects. Data regarding disease manifestations were also recorded in the patient group. Patients without available laboratory results at the time of study inclusion were excluded. The study was approved by Antalya Education and Training Hospital Ethical Committee. All patients gave written informed consent.

Molecular analysis

In all participants genomic DNA was isolated from peripheral blood cells by using the standard DNA extraction kit. Following amplification by polymerase chain reaction (PCR), PCR products were purified by using the kit. Alcohol precipitation was performed on PCR products obtained from Sanger sequencing reaction. Then, products were loaded on the machine by using formamide. Samples which were run on sequence analysis were also analyzed with the SeqScape. During analysis, particular attention was given to iexon 2 mutations including E148Q and R202Q and exon 10 mutations including M680I, I692del, M694V, M694I, K965R, V726A, A744S, and R761H.

Statistical Analysis

Descriptive statistics were expressed as frequency, percentage, mean, and standard deviation. Categorical variables were analyzed by Pearson chi-square and Fischer exact tests using 2x2 tables. In independent groups, normality of numeric variables in two independent groups was tested with Shapiro Wilk test. Mann-Whitney U and Student *t*-tests were used to analyze numerical variables. All statistical analyses were performed by using SPSS (**S**tatistical **P**ackage for the **S**ocial **S**ciences, SPSS Inc., Chicago, IL, USA) 21.0 package program. $p<0.05$ were considered as statistically significant.

Results

The mean age was 46.04±4.84 in the study group and 45.96±4.69 years in the control group. There were 32 women (64%) and 18 men (36%) in the patient group. Tables I and II summarizes demographic and clinical characteristics of patient and control groups. In patients with MeS, 21 participants (42%) had at least one FMF-related MEFV gene variation, while only 12 participants (24%) had these variations in healthy controls ($p=0.056$). When individual mutation frequencies were compared between study and control groups,

Table I. Demographic features of patient and control groups.

Parameter	Patients (n=50)	Controls (n=50)	p
Age, years	46.04±4.84	45.96±4.699	0.933
Gender, women/men	32/18	30/20	0.680
Body mass index (BMI)	33.94±2.25	23.13±1.46	<0.001
Waist circumference (cm)	102.82±3.05	73.72±3.05	<0.001
Systolic blood pressure (mmHg)	125.66±17.27	114±5.8	0.002
Diastolic blood pressure (mmHg)	75.46±12.33	68.7±7.2	0.007
HOMA	2.73±0.47	1.57±0.292	<0.001
Insulin	10.79±2.93	7.4±1.42	<0.001
Fasting blood glucose	104.72±18.12	86.42±4.75	<0.001

R202Q was found to be more common in patient group (p=0.021). Distribution of other FMF-related MEFV gene variations was comparable between patient and control groups. Among patients with MeS, there was R202Q homozygous variation in one, and R202Q/K965R compound heterozygous variation in another patient, while only one individual had R202Q/K965R compound heterozygous variation in healthy control group. The association was investigated between the R202Q mutation of the MEFV and MeS (p: 0.021; 4.42; 1.15-16.97) in the case control study. The presence of R202Q gene variation did not have an influence on clinical and laboratory findings in MeS patient group (p>0.05). The frequency of other mutations with high penetrance including M680I, M694V, and V726A were similar between two groups (p=0.678).

Erythrocyte sedimentation rate and CRP levels were comparable between patients with and without MEFV gene variations. Clinical characteristics and laboratory data are summarized in Table III.

Discussion

This is the first study that shows the association between R202Q mutation of FMF-related MEFV gene and MeS (p: 0.0021; OR: 4.42; CI95%: 1.15-16.97). The frequency of R202Q was significantly higher (n=11, [22%] in the study group and n= 3; [6%] in the control group). However, the presence of R202Q MEFV gene variation had no influence on the clinical and laboratory findings.

The prevalence of metabolic syndrome increases in parallel to the increased age, physical inactivity, and central obesity[14]. There are some conditions described to delineate risk factors for atherosclerotic cardiovascular disease and type 2 diabetes mellitus such as dysmetabolic syndrome X[15], deadly four[16], and dysmetabolic syndrome. Among them, the terms metabolic syndrome[17] and insulin resistance syndrome[18] are the leading ones.

Therefore, IR constitutes the main component of metabolic syndrome. In normal, when insulin binds to its membrane receptor, two

Table II. The distribution of FMF-related MEFV gene variations in patient (n=50) and healthy control (n=50) groups.

Mutation	Patient n, (%)	Control n, (%)	p (OR; CI 95%)	p (OR; CI 95%)
R202Q\-	10 (20)	3 (6)	**0.037 (3,92; 1,01-15,22)**	**0,021 (4,42 ;1,15-16,97)**
R202Q/R202Q	1 (2)	0 (0)	0.999	
E148Q/-	1 (2)	1 (2)	0.999	
V726A/-	3 (6)	1 (2)	0.617	
K965R/-	3 (6)	4 (8)	0.999	
E148Q/R761H	1 (2)	0 (0)	0.999	
R202Q/K965R	1 (2)	1 (2)	0.999	
E148Q/M694V	1 (2)	0 (0)	0.999	
E148Q/K965R	0 (0)	1 (2)	0.999	
M680I/-	0 (0)	1 (2)	0.999	
Presence of mutation with high penetrance*	4 (8)	2 (4)	0.678	
Total	**21 (42%)**	**12 (24%)**	**0.056 (2.29; 0.97-5.41)**	

Table III. Comparison of various clinical features and accompanying comorbidities according to the presence of MEFV gene variations among patients

Parameter	All patients n=50	No variations of MEFV n=29	MEFV variations present (n=21)	p
Age, years	46.04±4.84	46.38±4.37	45.57±5.51	0.672
Gender, women/men	32/18	17/12	15/6	0.352
Heigth, cm	164.82±8.136	166.52±7.54	162.48±8.51	0.360
Weight, kg	89.62±11.16	90.86±9.75	87.9±12.91	0.551
Body mass index (BMI)	33.94±2.25	33.77±2.29	34.16±2.23	0.410
Waist circumference (cm)	102.82±3.05	103.66±7.88	101.67±8.94	0.905
Systolic blood pressure (mmHg)	125.66±17.27	126.14±17.88	125±16.8	0.329
Diastolic blood pressure (mmHg)	75.46±12.33	77.03±11.74	73.29±13	0.291
Insulin resistance, n (%)	29 (58)	15 (51.7)	14 (66.7)	0.531
Diabetes mellitus, n (%)	22 (44)	14 (48.3)	8 (38.1)	
Impaired glucose tolerance, n (%)	11 (22)	7 (24.1)	4 (19)	
Hypertension, n (%)	21 (42)	13 (44.8)	8 (38.1)	0.634
Dyslipidemia, n (%)	46 (92)	27 (93.1)	19 (90.5)	0.999
Hypertriglyceridemia, n (%)	36 (72)	20 (69)	16 (76.2)	0.574
Hypolipidemia, n (%)	37 (74)	24 (82.8)	13 (61.9)	0.097
Fasting blood glucose	104.72±18.12	105.4±15.44	103.76±21.66	0.178
Total cholesterol mg/dl	200.68±52.3	197.4±45	205.19±61.8	0.859
LDL cholesterol mg/dl	120±41.89	121±34.13	118.61±51.61	0.504
Triglyceride mg/dl	210.6±91.03	200.69±84.81	224.28±99.5	0.414
HDL cholesterol	40.22±12.24	37.37±8.78	44.15±15.21	0.145
Uric acid mg/dl	8±1.19	8.14±1.25	7.8±1.1	0.320
HOMA	2.73±0.47	2.7±0.425	2.78±0.54	0.340
Sedimentation (ESR)	14.1±5.62	14.55±5.52	13.48±5.84	0.608
CRP mg/L	0.28±0.239	0.296±0.27	0.25±0.175	0.945
Insulin µIUg/ml	10.79±2.93	10.65±2.61	10.99±3.38	0.467

pathways are activated: Phosphatidyl inositol-3 kinase (PI3K) and mitogen activated protein kinase (MAPK) pathways[19,20]. In patients with IR, there is a defect in insulin receptor and post-receptor signalling, which causes blunted PI3K pathway response to insulin. However, response of MAPK pathway to insulin is normal. As a result, increased insulin levels in the metabolic syndrome (hyper-insulinemia) due to compensatory response results in the increased activity of the MAPK pathway. MeS manifests with elevated pro-inflammatory cytokines, increased synthesis of endothelial matrix proteins, and increased cellular proliferation and mitogenesis. IR is associated with the development of hypertension, dyslipidemia, coagulation abnormalities, endothelial dysfunction and albuminuria, thus, it increases the risk of cardiovascular diseases[21,22]. In the presence of MeS, the risk for coronary artery disease and death increase by three-fold[23]. Therefore, MeS constitutes an important problem in this era.

The metabolic syndrome is associated with increased mortality and closely related to inflammatory processes. Adipose tissue is not only a site of depot for fats, but also acts like an endocrine organ by synthesizing Il-6, TNF-alpha, resistin, estrogen, and leptin[23]. The adipose tissue mass increases in patients with MeS and this, in turn, leads to an increase in inflammatory molecules, namely CRP, TNF-alpha, IL-6, and IL-1[24]. Increased levels of cytokines TNF-alpha and IL-1β activate JNK and IKKB/Nf-kB. As a result, serine phosphorylation of IRS leads to disturbed insulin signaling. IL-1β genetic variants are also related with chronic inflammation and the risk of MeS development[25].

FMF is a common auto-inflammatory disease in Turkey. The frequency of heterozygous carrier state for MEFV gene variations is also high in Turkey, Israel, Armenia, and other Eastern Mediterranean countries[26,27]. The MEFV gene mutations trigger apoptosis and activate apoptosis proteins such as caspase 1 and caspase 5. Activated caspase 1, in turn, activates IL-1β which is an important inflammatory cytokine. Therefore, it has been proposed that heterozygous carriers of MEFV gene variations have higher acute phase responses and a different course of other inflammatory diseases[11-13].

Diseases characterized by fever, anemia, and increased acute phase proteins including FMF

have increased IL-1β production and bioactivity[28]. Furthermore, this group of diseases has anomalies in Nod like receptor (NLR) and signal pathways as in cryopyrinopathies. The inflammasome is a complex, which is formed after stimulation of NLR with one of its ligands[29,30].

There are some regulatory molecules, which regulate the activation of the inflammasome complex. One of these molecules is the MEFV-encoded pyrin[31]. This molecule prevents the activation of caspase-1 and negatively regulates IL-1β production[32]. Since mutations in MEFV gene disturb the structure of pyrin protein and function, the activity of inflammasome complex increases, leading to abnormally high production of IL-1β.

IL-1 decreases the expression of IRS-1 at the transcriptional and posttranscriptional level. By this effect, it may disturb insulin signaling and effect. Therefore, it has been proposed that IL-1 may contribute to IR in adipocytes[6]. IL-1β acts as a pyrogenic cytokine in blood monocytes. The synthesis and release of IL-1β are strictly regulated[33] by various mechanisms of immune system. It has been shown that various proteins (including CARD-containing proteins and pyrin) affect the production of IL-1β through caspase-1[34,35].

FMF-related MEFV gene variations cause an increase in IL-1β activation and inflammation independent from FMF clinic. Therefore, it may affect the phenotype of other inflammatory diseases[36]. There are various reports on this topic[11-13]. In one such report, healthy heterozygous carriers of MEFV gene variations had higher frequency and intensity of inflammation, which lead to alterations in health status[37]. In another study conducted on sepsis patients, there was an association between sepsis patients harboring MEFV gene variations, the frequency of poor disease outcome, and inflammatory findings. This difference was attributed to pyrin function[38]. However, heterozygous MEFV gene variation carrier state was found to be 20% in general population, and its association with metabolic syndrome hasn't been studied so far.

This is the first study investigating the frequency of MEFV gene variations in MeS patients and their impact on clinical findings. We analyzed the most frequent MEFV gene variations observed in FMF patients and general population. In patients with MeS, 21 participants (42%) had at least one FMF-related MEFV gene variation, while only 12 participants (24%) had these variations in the control group (p=0.056). No M694V mutation was found in the healthy controls, while one MeS patient had E148Q/M694V compound heterozygous variation. No R202Q mutation was found in control group, while one MeS patient expressed R202Q mutation. The study and control groups had different compound heterozygosity. In previous studies, E148Q mutation was considered as a mutation with low penetrance or polymorphism, thus when mutations with high penetrance (i.e. M694V, M680I, V726A) were assessed, 4 patients with MeS (8%) and 2 healthy controls (4%) tested positive for one mutation (p=0.678).

FMF patients have prominent acute phase response during attacks. Patients are asymptomatic during attack-free periods but studies have shown that patients during remission periods and healthy FMF mutation carriers had higher levels of acute phase proteins when compared to healthy controls[27-29]. Therefore, acute phase response during FMF attacks is only the observed portion of iceberg since these patients have persistent subclinical inflammation during remissions[3]. However, we failed to demonstrate an increased frequency of the MEFV gene variations in MeS patients when compared to healthy controls. Furthermore, the presence of such variations did not affect clinical and laboratory parameters.

We analyzed erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels as markers of inflammation but not more sensitive markers such as serum IL-1 levels. ESR and CRP levels were similar between groups. The main limitations of this study include lack of precise inflammatory markers and limited sample size. Therefore, our results should be interpreted with caution to make general assumptions about the impact of MEFV gene variations on MeS pathogenesis and clinical features.

Conclusions

The present study is the first work to show the association between MeS and R202Q mutation of MEFV gene. FMF-related MEFV gene variations may contribute to the pathogenesis of MeS. These findings are preliminary and need to be studied further with large scale trials in order to fully clarify the role of MEFV gene variations in the pathogenesis of MeS.

Conflict of Interests

The authors confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

References

1. Sundstrom J, Riserus U, Byberg L, Zethelius B, Lithell H, Lind L. Clinical value of the metabolic syndrome for long-term prediction of total and cardiovascular mortality: prospective, population-based cohort study. Br Med J 2006; 332: 878-882.
2. Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2005; 28: 2289-2304.
3. Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. European group for the study of insulin resistance (EGIR). Diabet Med 1999; 16: 442-443.
4. Einhorn D, Reaven GM, Cobin RH, Ford E, Ganda OP, Handelsman Y, Hellman R, Jellinger PS, Kendall D, Krauss RM, Neufeld ND, Petak SM, Rodbard HW,-Seibel JA, Smith DA, Wilson PW. American college of endocrinology position statement on the insulin resistance syndrome. Endocr Pract 2003; 9: 237-252.
5. Kim JA, Wei Y, Sowers JR. Role of mitochondrial dysfunction in insulin resistance. Circ Res 2008; 102: 401-414.
6. Jager J, Gremeaux T, Cormont M, Le Marchand-Brustel Y, Tanti JF. Interleukin-1β-induced insulin resistance in adipocytes through down-regulation of insulin receptor substrate-1 expression. Endocrinology 2007; 148: 241-251.
7. Celkan T, Celik M, Kasapcopur O, Ozkan A, Apak H, Ocak S, Arisoy N, Yildiz I. The anemia of familial Mediterranean fever disease. Ped Hematol Oncol 2005; 22: 657-665.
8. The International FMF Consortium: Ancient missense mutations in a new member of the RoRet gene family are likely to cause FMF. Cell 1997; 90: 797-807.
9. Drenth JPH, Van Der Meer JW. Hereditary periodic fever. N Engl J Med 2003; 345: 1748-1757.
10. Centola M, Wood G, Frucht DM, Galon J, Aringer M, Farrell C, Kingma DW, Horwitz ME, Mansfield E, Holland SM, O'Shea JJ, Rosenberg HF, Malech HL, Kastner DL. The gene for familial Mediterranean fever, MEFV, is expressed in early leukocyte development and is regulated in response to inflammatory mediators. Blood 2000; 95: 3223-3231.
11. Lachmann HJ, Sengul B, Yavuzsen TU, Booth DR, Booth SE, Bybee A, Gallimore JR, Soytürk M, Akar S, Tunca M, Hawkins PN. Clinical and subclinical inflammation in patients with familial Mediterranean fever and in heterozygous carriers of MEFV mutations. Rheumatology (Oxford) 2006; 45: 746-750.
12. Cosan F, Ustek D, Oku B, Duymaz-Tozkir J, Cakiris A, Abaci N, Ocal L, Aral O, Gül A. Association of familial Mediterranean fever-related MEFV variations with ankylosing spondylitis. Arthritis Rheum 2010; 62: 3232-3236.
13. Koca SS, Etem EO, Isik B, Yuce H, Ozgen M, Dag MS, Isik A. Prevalence and significance of MEFV gene mutations in a cohort of patients with rheumatoid arthritis. Joint Bone Spine 2010; 77: 32-35.
14. Bloomgarden ZT. American Association of Clinical Endocrinologists (AACE) consensus conference on the insulin resistance syndrome: 25-26 August 2002, Washington, DC. Diabetes Care 2003; 26: 1297-1303.
15. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988; 37: 1595-1607.
16. Kaplan NM. The deadly quartet. Upper-body obesity, glucose in tolerance, hypertriglyceridemia, and hypertension. Arch Intern Med 1989; 149: 1514-1520.
17. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998; 15: 539-553.
18. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care 1991; 14: 173-194.
19. Saltiel AR, Kahn CR. Insulin signaling and the regulation of glucose and lipid metabolism. Nature 2001; 414: 799-806.
20. Zeng G, Nystrom FH, Ravichandran LV, Cong LN, Kirby M, Mostowski H, Quon MJ. Roles for insülin receptor, PI3-kinase, and Aktin insulin-signaling pathways related to production of nitric oxide in human vascular endothelial cells. Circulation 2000; 101: 1539-1545.
21. Moreno PR, Fuster V. New aspects in the pathogenesis of diabetic atherothrombosis. J Am Coll Cardiol 2004; 44: 2293-2300.
22. Rask-Madsen C, King GL. Proatherosclerotic mechanisms involving protein kinase C in diabetes and insulin resistance. Arterioscler Thromb Vasc Biol 2005; 25: 487-496.
23. Gallagher EJ, LeRoith D, Karnieli E. The metabolic syndrome from insulin resistance to obesity and diabetes. Endocrinol Metab Clin North Am 2008; 37: 559-579.
24. Cornier MA, Dabelea D, Hernandez TL, Lindstrom RC, Steig AJ, Stob NR, Van Pelt RE, Wang H, Eckel RH. The metabolic syndrome. Endocr Rev 2008; 29: 777-822.
25. Shen J, Arnett DK, Peacock JM, Parnell LD, Kraja A, Hixson JE, Tsai MY, Lai CQ, Kabagambe EK, Straka RJ, Ordovas JM. Interleukin-1β genetic polymorphisms interact with polyunsaturated fatty acids to modulate risk of the metabolic syndrome. J Nutr 2007; 137: 1846-1851.
26. Masters SL, Simon A, Aksentijevich I, Kastner DL. Horror autoinflammaticus: the molecular pathophysiology of autoinflammatory disease. Annu Rev Immunol 2009; 27: 621-668.

27. Yilmaz E, Ozen S, Balci B, Duzova A, Topaloglu R, Besbas N, Saatci U, Bakkaloglu A, Ozguc M. Mutation frequency of familial Mediterranean fever and evidence for a high carrier rate in the Turkish population. Eur J Hum Genet 2001; 9: 553-555.

28. Coskun M, Bacanli A, Sallakci N, Alpsoy E, Yavuzer U, Yegin O. Specific interleukin-1 gene polymorphisms in Turkish patients with Behçet's disease. Exp Dermatol 2005; 14: 124-129.

29. Sidiropoulos PI, Goulielmos G, Voloudakis GK, Petraki E, Boumpas DT. Inflammasomes and rheumatic diseases: evolving concepts. Ann Rheum Dis 2008; 67: 1382-1389.

30. van de Veerdonk FL, Netea MG, Dinarello CA, Joosten LA. Inflammasome activation and IL-1β and IL-18 processing during infection. Trends Immunol 2011; 32: 110-116.

31. Mathews RJ, Sprakes MB, McDermott MF. NOD-like receptors and inflammation. Arthritis Res Ther 2008; 10: 228.

32. Stojanov S, Kastner DL. Familial autoinflammatory diseases: genetics, pathogenesis and treatment. Curr Opin Rheumatol 2005; 17: 586-599.

33. Kummer JA, Broekhuizen R, Everett H, Agostini L, Kuijk L, Martinon F, van Bruggen R, Tschopp J. Inflammasome components NALP 1 and 3 show distinct but separate expression profiles in human tissues suggesting a site-specific role in the inflammatory response. J Histochem Cytochem 2007; 55: 443-452.

34. Pay S, Erdem H, Pekel A, Simsek I, Musabak U, Sengul A, Dinc A. Snovial proinflammatory cytokines and their correlation with matrix metalloproteinase-3 expression in Behçet's dissease. Dose interleukin-1beta play a major role in Behçet's synovitis? Rheumatol Int 2006; 26: 608-613.

35. Song Q, Lu JZ, Li J. Effect of tripterygium glycosides on serum interleukin-1beta, interleukin-2, tumor necrosis factor alpha, and interferon-gamma levels in patients with Behçet's disease. Zhongguo Zhong Xi Yi Jie He Za Zhi 2010; 30: 598-600.

36. McDermott MF. A common pathway in periodic fever syndromes. Trends Immunol 2004; 25: 457-460.

37. Kalyoncu M, Celiker Acar B, Cakar N, Bakkaloglu A, Ozturk S, Dereli E, Tunca M, Kasapcopur O, Yalcinkaya F, Ozen S. Are carriers for MEFV mutations 'healty'? Clin Exp Rheumatol 2006; 24: 120-122.

38. Koc B, Oktenli C, Bulucu F, Karadurmus N, Sanisoglu SY, Gul D. The rate of pyrin mutations in critically ill patients with systemic inflammatory response syndrome and sepsis: a pilot study. J Rheumatol 2007; 34: 2070-2075.