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Severe Hypersensitivity Reactions to Biological Drugs in Children with Rheumatic Diseases.

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BACKGROUND: Hypersensitivity reactions (HSR) to biological drugs (BD) may limit their use in children with rheumatic diseases. We aimed to analyze the incidence and clinical characteristics of immediate Type I (IgE/Non-IgE) hypersensitivity reactions to BD, and the risk factors for these reactions.
METHODS: Children with rheumatic diseases using BD who were evaluated in the Pediatric Allergy Department for possible drug hypersensitivity reaction (DHR) due to BD or any other drug were included in the study.
RESULTS: One hundred and twenty-eight children [49.2% boys; 14.6 years (9.9 -16.9 years) with juvenile idiopathic arthritis (58%), familial Mediterranean fever (14%), vasculitis (14%), and other diseases (14%)] had used 8 different BD with 32,494 infusions/injections. Fifteen patients were evaluated for DHR [injection-site reactions (n=4), adverse events (n=2), drug hypersensitivity other than BD (n=3) and immediate BD hypersensitivity (n=6)]. The incidence of immediate BD HSR was 4.7%, with a clinical presentation of anaphylaxis in 3.9% [tocilizumab (n=3), rituximab (n=2), positive skin test with culprit BD (n=3)]. Among patients with BD HSR, the median follow-up was longer (84.5 vs 54 months, p=0.048), and renal (33.3% vs 4.1%, p=0.002), hematologic involvement (16.7% vs 0, p<0.001) and active disease (83.3% vs 13.9%, p<0.001) were more common. Logistic regression analysis revealed that renal involvement, more than 14 hospitalizations per lifetime and more than two different BD used were associated with BD hypersensitivity.
CONCLUSION: The frequency of severe immediate HSR due to BD was shown to be 3.9% in children with rheumatic diseases. Children with active rheumatic disease and who have exposure to multiple BD should be monitored for BD HSR, particularly during intravenous BD infusions. This article is protected by copyright. All rights reserved.

2. Rheumatology (Oxford). 2019 Aug 14. pii: kez332. doi: 10.1093/rheumatology/kez332

Improvement of MEFV gene variants classification to aid treatment decision making in familial Mediterranean fever.

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OBJECTIVE: FMF is an inherited autoinflammatory syndrome caused by mutations in the MEFV gene. MEFV variants are still largely classified as acvariant of uncertain significance, or with unresolved classification, posing significant challenges in FMF diagnosis. Rare Exome Variant Ensemble Learner (REVEL) is a recently developed variant metapredictor tool. To reduce the number of MEFV variants with ambiguous classification, we extracted REVEL scores for all missense variants present in the INFEVERS database, and analysed its correlation with expert-based classification and localization in the MEFV-encoded pyrin functional domains.
METHODS: The data set of 216 MEFV missense variants was divided into four categories (likely benign, variant of uncertain significance, likely pathogenic and unresolved). Variants were plotted onto the pyrin protein, the distribution of REVEL scores in each category was computed and means, confidence intervals, and area under the receiver operating curve were calculated.
RESULTS: We observed a non-random distribution of pathogenic variants along the pyrin functional domains. The REVEL scores demonstrated a good correlation with the consensus classification of the International Study Group for Systemic Autoinflammatory Diseases. Sensitivity, specificity and accuracy were calculated for different cut-off values of REVEL scores and a gene-specific-threshold of 0.298 was computed with confidence boundary limits. This cut-off value allowed us to propose a reclassification of 96 MEFV gene variants, thus reducing the variant of uncertain significance proportion from 61.6% to 17.6%.
CONCLUSION: The combination of available expert information with sensitive

predictor tools could result in a more accurate interpretation of clinical consequences of MEFV gene variants, and to a better genetic counselling and patient management.

3. Clin Rheumatol. 2019 Aug 10. doi: 10.1007/s10067-019-04741-9

The grandfather's fever.

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An 86-year-old Caucasian man had prior episodes of fever (up to 38 °C), mild abdominal pain, tachycardia, and malaise in the last 3 months, lasting 2-3 days. He never suffered from abdominal or chest pain, rash, or arthralgia. Major causes of fever were excluded (pulmonary, urinary, abdomen, skin infections, neoplasms, and major rheumatologic disorders). The patient was native of Altamura with a family history of familial Mediterranean fever (FMF). The genetic testing confirmed the presence of MEFV gene variants c.442G>C (E148Q) on exon 2 and c.2282G>A (R761H) on exon 10, all in heterozygosity. Mildly elevated serum transaminases suggested an ongoing form of FMF hepatitis on nonalcoholic liver steatosis. The patient started colchicine 1 mg/day that induced symptom control and normalization of inflammatory markers, hyperbilirubinemia, and markers of cholestasis. Symptoms of FMF can appear at any age in life and our patient represents a very late-onset clinical case. The Apulian region has a consistent clustering of MEFV variants and FMF families with affected individuals in multiple consecutive generations. Families show unique clinical features and rare signs of secondary amyloidosis without kidney damage. Genetic and environmental bases of this phenotypic variant are under scrutiny. Colchicine lifetime remains the mainstay of treatment in FMF patients. KEY POINTS: • Familial Mediterranean fever (FMF) is the most frequent hereditary monogenic recurrent fever syndrome, and symptoms can appear at any age in life. • Late-onset FMF approaches 30% in late adulthood, but in general, onset of FMF after the age of 40 (late onset FMF)

is rare, usually associated with M694V heterozygosity. • In a local cluster of FMF families (Altamura, Puglia, Southern Italy), we report a very late-onset FMF (variants E148Q, R761H) in an 86-year-old patient with a positive family history of FMF in two generations of descendants. • While lifetime colchicine remains the mainstay of treatment in FMF patients, prospective studies need to identify the characteristics of several phenotypic variants accounting for (very)-late onset FMF.

4. Transplant Proc. 2019 Aug 7. pii: S0041-1345(18)31751-2. doi: 10.1016/j.transproceed.2019.03.049.

Outcomes of Canakinumab Treatment in Recipients of Kidney Transplant WithFamilial Mediterranean Fever: A Case Series.

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Familial Mediterranean fever (FMF) is an important and preventable cause of chronic kidney disease due to secondary amyloidosis. Although colchicine is the first-line therapy in patients with FMF with 60% to 65% complete remission rates, 5% to 10% of patients are colchicine-resistant and 5% to 10% of them are intolerant to the therapy. Anti-interleukin-1 agents, such as anakinra and canakinumab, are safe and efficient therapeutic options in patients with colchicine resistance or intolerance. However, the data on management of these targeted agents is limited in recipients of kidney transplant (RKT). In this case series, we aim to share our experience on canakinumab therapy of 4 RKTs with FMF-related amyloidosis, who were followed up in our clinic between 2010 and 2017. All of the 4 patients with end-stage renal disease were colchicine-resistant and on other alternative therapies, which provided poor disease control. For efficient control of secondary amyloidosis, canakinumab therapy was initiated in 1 of the patients before the renal transplant, and for the remaining patients after renal transplant. Any serious adverse effect, development of proteinuria, or graft dysfunction has not been observed in any of the patients. Under the canakinumab treatment, complete clinical responses, prevent typical

familial Mediterranean fever attacks with fever and arthritis and abdominal pain, normalized serum amyloid A and C-reactive protein levels were achieved in all patients. Canakinumab treatment is a safe and effective therapeutic option for RKTs with FMF who are resistant or intolerant to colchicine and anakinra.

5. Transplant Proc. 2019 Aug 7. pii: S0041-1345(18)31742-1. doi: 10.1016/j.transproceed.2019.04.074

Long-term Results of Kidney Transplantation in Patients With Familial Mediterranean Fever and Amyloidosis.

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INTRODUCTION: Amyloid A amyloidosis is most commonly caused by familial Mediterranean fever (FMF) in Turkey. Amyloidosis secondary to FMF is an important cause of end-stage renal failure, and kidney transplantation (KT) in these cases can be complicated, with long-term results oftentimes inferior compared with organ transplant in patients without FMF. The present study aims to show the long-term results of patients with secondary amyloidosis caused by FMF undergoing KT .
METHODS: We enrolled 27 patients with a history of FMF amyloidosis undergoing KT and a control group of 614 patients undergoing KT between 2005 and 2018 at Ankara University Medical School. All data were recorded retrospectively from patients files.
RESULTS: Twenty-two patients (81.5%) were treated with triple immunosuppressive therapy consisting of mycophenolate mofetil, tacrolimus, and a steroid; 5 patients (18.5%) were treated with tacrolimus, azathioprine, and prednisolone. Acute cellular rejection was seen in 3 patients (11.1%), and acute cellular- and antibody-mediated rejection occurred in 1 patient (3.7%). During the follow-up period, graft loss due to acute cellular rejection was observed in only 1 patient. One patient was lost to follow-up.

6. Rheumatol Int. 2019 Aug 7. doi: 10.1007/s00296-019-04412-7. [Epub ahead of print]

Familial Mediterranean fever is associated with a wide spectrum of inflammatory disorders: results from a large cohort study.

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Familial Mediterranean fever (FMF) is characterized by recurrent short-lived/self-limiting inflammatory attacks. Besides these, a substantial number of patients with FMF present with a variety of other inflammatory diseases; however, this issue has not been systematically studied previously. Hence, we aimed to investigate the frequency of inflammatory comorbid diseases in a large FMF cohort. All patients were recruited from "FMF in Central Anatolia (FiCA) Cohort", comprising 971 (mean age 35.3 ± 12 years, 61.5% female) adult subjects. All patients fulfilled Tel Hashomer criteria. Demographic data, FMF disease characteristics, MEFV gene mutations, and comorbid inflammatory diseases were meticulously questioned, and laboratory features and genotype data were retrieved from hospital records. There were comorbid inflammatory diseases in 205 (21.1%) patients. The most common inflammatory disease was spondyloarthritis (12.9%). Other remarkable inflammatory disorders were psoriasis, immunoglobulin A vasculitis/Henoch-Schönlein purpura, Behçet's disease and inflammatory bowel diseases. Cryptogenic organizing pneumonia is a newly defined entity in our cohort which is seemed to be associated with FMF (0.3%). Number of patients with persistent inflammation was higher in those with comorbid diseases ($p < 0.001$). Our results suggest that FMF is commonly associated with other inflammatory

diseases. Therefore, clinicians should be cautious about comorbid inflammatory diseases in FMF patients, particularly in those with persistent inflammation. Identification of pathogenic pathways linking FMF to these diseases warrants further investigations.

7. Rheumatology (Oxford). 2019 Aug 5. pii: kez334. doi: 10.1093/rheumatology/kez334.

British kindred with dominant FMF associated with high incidence of AA amyloidosis caused by novel MEFV variant, and a review of the literature.

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OBJECTIVES: Hereditary systemic autoinflammatory diseases are rare genetic disorders, which if untreated, can be complicated by AA amyloidosis leading to renal failure and premature death. Our objective was to find a genetic cause in a British family with a dominantly inherited autoinflammatory disease complicated by AA amyloidosis.
METHODS: The index patient and his sister underwent comprehensive clinical and laboratory assessment including the next-generation sequencing panel targeting autoinflammatory genes. Subsequently, other relatives underwent clinical evaluation and genetic testing. Screening of the SAA1 gene was performed in all symptomatic cases.
RESULTS: The index case and his sister presented with proteinuria due to AA amyloidosis. They have been suffering from episodes of fever accompanied by severe abdominal and chest pain, arthritis and erythema since childhood. Their father died aged 52 years from complications following a cadaveric renal transplantation. The post-mortem examination demonstrated AA amyloidosis. The index case's grandmother, two paternal cousins and two of their children described similar symptoms. All symptomatic individuals had excellent responses to colchicine. Next-generation sequencing analysis identified a single MEFV p.P373L variant in the index case, his sister and subsequently, in symptomatic family members. Sequencing of the SAA1 gene revealed all cases were heterozygous for the SAA1.1 allele.
CONCLUSION: Typically FMF is an autosomal recessive disorder; nonetheless rare

cases of dominantly inherited disease have previously been described. Here we report a novel MEFV variant p.P373L, causing dominant FMF complicated by AA amyloidosis in four generations of a British family.

8. Med Hypotheses. 2019 Sep;130:109269. doi: 10.1016/j.mehy.2019.109269.

IL-1 blockers together with colchicine may be administered as first line therapy in familial Mediterranean fever with amyloidosis.

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Colchicine is the first choice of the treatment in familial Mediterranean fever (FMF). However, in FMF patients with amyloidosis, especially during creatinine level >1.5 mg/dL and nephrotic range proteinuria, colchicine may be ineffective. Interleukin-1 (IL-1) blockers could be used in colchicine resistant cases. However, starting IL-1 blocker treatment after colchicine failure may lose opportunity for effective treatment. Therefore, administering IL-1 blocker together with colchicine as first line therapy may increase the chance for suppressing the disease.

9. Ann Rheum Dis. 2019 Aug 3. pii: annrheumdis-2019-215258. doi: 10.1136/annrheumdis-2019-215258.

Specific changes in faecal microbiota are associated with familial Mediterranean fever.

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OBJECTIVES: Familial Mediterranean fever (FMF) can be complicated by AA amyloidosis (AAA), though it remains unclear why only some patients develop amyloidosis. We examined the gut microbiota composition and inflammatory markers in patients with FMF complicated or not by AAA.
METHODS: We analysed the gut microbiota of 34 patients with FMF without AAA, 7 patients with FMF with AAA, 19 patients with AAA of another origin, and 26 controls using 16S ribosomal RNA gene sequencing with the Illumina MiSeq platform. Associations between bacterial taxa and clinical phenotypes were evaluated using multivariate association with linear models statistical method. Blood levels of interleukin (IL)-1β, IL-6, tumour necrosis factor-α and adipokines were assessed by ELISA; indoleamine 2,3-dioxygenase (IDO) activity was determined by high-performance liquid chromatography.
RESULTS: Compared with healthy subjects, specific changes in faecal microbiota were observed in FMF and AAA groups. Several operational taxonomic units (OTUs) were associated with FMF. Moreover, two OTUs were over-represented in FMF-related AAA compared with FMF without AAA. Additionally, higher adiponectin levels and IDO activity were observed in FMF-related AAA compared with FMF without AAA ($p<0.05$).
CONCLUSION: The presence of specific changes in faecal microbiota in FMF and in FMF-related AAA suggests that intestinal microorganisms may play a role in the pathogenesis of these diseases. These findings may offer an opportunity to use techniques for gut microbiota manipulation.

10. Clin Exp Rheumatol. 2019 Jul 15. [Epub ahead of print]

Pseudodominance of autoinflammatory disease in a single Turkish family explained by co-inheritance of haploinsufficiency of A20 and familial Mediterranean fever.

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OBJECTIVES: We investigated a Turkish family with multiple patients presenting with familial Mediterranean fever (FMF) and Behçet's disease (BD)-like manifestations. The index case and the two daughters with Behçet-like disease, were previously found to have a TNFAIP3 frameshift mutation. The high number of affected cases in this expanded family could be consistent with a dominantly inherited inflammatory disease, although some individuals had clinical features more consistent with recessively inherited FMF. We sequenced DNA from members of this family to determine whether the TNFAIP3 frameshift mutation and/or MEFV variants could explain this autoinflammatory disease pedigree.
METHODS: Patients were clinically diagnosed to have FMF or BD. Sanger sequence targeting TNFAIP3 exon 5 and MEFV exon 10 was carried out.
RESULTS: The symptomatic mother of the index case and her affected maternal uncle had compound heterozygous FMF-associated MEFV mutations, p.Met680Ile and p.Arg761His. Two affected daughters of the maternal uncle also had compound heterozygous FMF-associated mutations, p.Met680Ile and p.Val726Ala. The index case and her two affected daughters had a TNFAIP3 frameshift mutation (c.799delG; p.Pro268Leufs*19), which is consistent with their HA20 diagnosis, and also carried a heterozygous MEFV p.Arg761His mutation.
CONCLUSIONS: Autoinflammatory disease manifestations in a Turkish family with multiple affected cases could be explained by co-inheritance of pathogenic MEFV variants and a heterozygous HA20-associated mutation. FMF-associated p.Arg761His allele carried with the loss of function TNFAIP3 mutation by all three HA20 patients may contribute to their autoinflammatory phenotype and could also be responsible for their favourable response to colchicine.

11. Eur J Rheumatol. 2019 Apr 1;6(2):85-88. doi: 10.5152/eurjrheum.2019.18190.

Treatment of familial mediterranean fever with canakinumab in patients who are unresponsive to colchicine.

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OBJECTIVE: Familial Mediterranean fever (FMF) is the most common inherited monogenic autoinflammatory disease worldwide. It is caused by loss-of-function

mutations in the MEFV gene, mostly affecting Eastern Mediterranean population. It is discussed if it should be considered an autosomal-dominant disease with variable penetrance, because heterozygosis mutations are associated with clinical autoinflammatory manifestations. Colchicine constitutes that the mainstay of FMF treatment should be preventing acute attacks and amyloidosis, and decreasing the chronic inflammation. In colchicine-resistant or intolerant patients, recent insights into the pathogenesis of FMF have made the anti-IL1 treatments important. We aimed to search for the retrospective results of canakinumab treatment in patients with FMF who are unresponsive to colchicine.
METHODS: In this study, 22 (13 males and nine females) patients with FMF with colchicine resistance/intolerance, age ranging from 6 to 18 years, were included in Ege University Department of Pediatric Rheumatology. After clinical and genetic diagnosis, colchicine treatment with standard doses was started. After treatment with canakinumab, complete response to treatment was determined as no acute episodes and normal level of acute phase reactants.
RESULTS: After canakinumab treatment, 22 patients with FMF who were colchicine-resistant were evaluated. After the treatment, no attack was observed in 19 patients, and the values of acute phase reactants were normal in 22 patients. In three patients, disease attack was observed 16 months after the first dose treatment. In all patients, the values of acute phase reactants were found at normal level during treatment. No drug-related side effects were observed in any patient.
CONCLUSION: Canakinumab is an effective and safe anti-IL1 agent to reduce attacks in patients with FMF with no response to colchicine and to reduce the level of high-level laboratory findings associated with FMF.

12. Rheumatol Int. 2019 Jul 27. doi: 10.1007/s00296-019-04391-9.

Evaluation of co-existing diseases in children with familial Mediterranean fever.

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Familial Mediterranean fever (FMF) is A common periodic fever syndrome. The causative gene of the FMF is named Mediterranean Fever gene (MEFV). Increased inflammation in FMF may play a role as a trigger for the development of some diseases. The objective of the study is to evaluate the frequency of comorbid disorders in children followed up with diagnosis of FMF. Additionally, we aimed to assess the association between FMF and other inflammatory conditions in a large pediatric FMF cohort. A total of 686 FMF patients were included in the cross-sectional study. A questionnaire including questions about characteristics of fever episodes, presence of arthralgia, arthritis, abdominal pain, chest pain during and co-existence of any other disease diagnosed by a physician was filled out by face-to-face interviews with patients or their parents. Female-male ratio was 0.85. Median age at the time of study, age at disease onset and at the time of diagnosis were 12.9 (1.7-22.3), 3 (0.08-17), and 6 (0.75-17) years, respectively. In 130 (18.9%) FMF patients we detected co-existing inflammatory condition. The most common co-existing diseases were: juvenile idiopathic arthritis 42 (6.1%), asthma/reactive airway disease 29 (4.2%), Henoch-Schönlein purpura 20 (2.9%), uveitis 12 (1.7%) and inflammatory bowel disease 10 (1.4%). Except for asthma/reactive airway disease and inflammatory bowel disease, there was no significant difference regarding the type of MEFV gene mutation. We have reported increased frequencies of various inflammatory conditions and decreased frequency of asthma in patients with FMF.

13. Rheumatol Int. 2019 Jul 25. doi: 10.1007/s00296-019-04362-0. [Epub ahead of print]

Performance of recently proposed periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome criteria in a region endemic for familial Mediterranean fever.

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The periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is an auto-inflammatory condition characterized by recurrent episodes of fever accompanied by aphthosis, cervical adenitis, and pharyngitis.

Diagnosis of PFAPA could be challenging due to clinic overlap with familial Mediterranean fever (FMF). An international consensus has been established recently, to define a new set of classification criteria for PFAPA syndrome. We aimed to evaluate the performance of recently proposed PFAPA criteria, to assess their utility in FMF regions. Patients diagnosed with PFAPA syndrome, FMF, and juvenile idiopathic arthritis (JIA) were included. Two investigators blindly evaluated all of patients for the newly proposed PFAPA criteria. A total of 542 patients (322 with PFAPA syndrome, 118 FMF and 102 JIA) were evaluated. Mean age of patients was 6.6 ± 2.81, 12.75 ± 3.9, and 12.42 ± 4.8 years for PFAPA, FMF, and JIA, respectively. We found quite high sensitivity (89.7%) but insufficient specificity of newly proposed PFAPA criteria (69.5%). When applied to control patients separately, specificity was found to be 61% and 79.4% for FMF and JIA patients, respectively. Positive predictive value was 81%, while negative predictive value was 82%. Recently proposed PFAPA criteria have satisfactory sensitivity, but its specificity is still under expectation. There is a need for a distinctive criterion between PFAPA syndrome and FMF, in FMF endemic regions, e.g., cryptic tonsillitis rapidly responsive to single dose of glucocorticoids. Further studies with higher patients' number in different regions are needed.

14. Inflamm Res. 2019 Jul 24. doi: 10.1007/s00011-019-01272-6. [Epub ahead of print]

Potential of miRNAs to predict and treat inflammation from the perspective of Familial Mediterranean Fever.

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AIM: microRNAs (miRNAs) are small noncoding RNAs that play critical roles in physiological networks by regulating host genome expression at the post-transcriptional level. miRNAs are known to be key regulators of various biological processes in different types of immune cells, and they are known to regulate immunological functions. Differential expression of miRNAs has been documented in several diseases, including autoinflammatory and autoimmune diseases. This review aimed to focus on miRNAs and their association with autoimmune and autoinflammatory diseases.
METHODS: All related literature was screened from PubMed, and we discussed the possible role of miRNAs in disease prediction and usage as therapeutic agents from the perspective of Familial Mediterranean Fever (FMF).

CONCLUSIONS: FMF is an inherited autosomal recessive autoinflammatory disease caused by mutations in the MEditerranean FeVer (MEFV) gene, which encodes the protein pyrin. Recent studies have demonstrated that miRNAs may be effective in the pathogenesis of FMF and offer a potential explanation for phenotypic heterogeneity. Further understanding of the role of miRNAs in the pathogenesis of these diseases may help to identify molecular diagnostic markers, which may be important for the differential diagnosis of autoinflammatory diseases. Studies have shown that in the near future, traditional therapies in autoinflammatory diseases may be replaced with novel effective, miRNA-based therapies, such as the delivery of miRNA mimics or antagonists. These approaches may be important for predictive, preventive, and personalized medicine.

15. J Autoimmun. 2019 Jul 20:102305. doi: 10.1016/j.jaut.2019.102305. [Epub ahead of print]

Autoinflammation: Lessons from the study of familial Mediterranean fever.

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Autoinflammatory disorders represent a heterogeneous group of systemic inflammatory diseases caused by genetic or acquired defects in key components of the innate immunity. Familial Mediterranean fever (FMF) is the most common among the other clinical phenotypes of the rare hereditary periodic fevers (HPFs) syndromes. FMF is associated with mutations in the MEFV gene encoding pyrin and is characterized by recurrent, often stress-provoked attacks of fever and serositis, but sometimes also by chronic subclinical inflammation. FMF is prevalent in Greece and other countries of the eastern Mediterranean region. Over the last 17 years, our group has focused on FMF as a model suitable for the research on innate immunity and particularly the role of neutrophils. Therefore, the study of Greek patients with FMF has yielded lessons across several levels:

the epidemiology of the disease in Greece, the spectrum of its clinical manifestations and potential overlaps with other idiopathic inflammatory conditions, the demonstration of its rather complex and heterogeneous genetic background and the suggestion of a novel mechanism involved in the crosstalk between environmental stress and inflammation. Mechanistically, during FMF attack, neutrophils release chromatin structures called neutrophil extracellular traps (NETs), which are decorated with bioactive IL-1β. REDD1 (regulated in development and DNA damage responses 1), that encodes a stress-related mTOR repressor, has been found to be the most significantly upregulated gene in neutrophils during disease attacks. Upon adrenergic stress, REDD1-induced autophagy triggers a pyrin-driven IL-1β maturation, and the release of IL-1β-bearing NETs. Consequently, not only the mode of action of IL-1β-targeting therapies is explained, but also new treatment prospects emerge with the evaluation of old or the design of new drugs targeting autophagy-induced NETosis. Information gained from FMF studies may subsequently be applied in more complex but still relevant inflammatory conditions, such as adult-onset Still's disease, gout, ulcerative colitis and Behçet's disease.

16. J Biochem Mol Toxicol. 2019 Jul 23:e22366. doi: 10.1002/jbt.22366. [Epub ahead of print]

Studies on hepatotoxicity and toxicokinetics of colchicine.

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Colchicine (COL) is an alkaloid existing in plants of Liliaceous colchicum. It has widely been used in the treatments of many diseases, such as gout, Familial Mediterranean Fever, and tumor. However, the adverse effects of COL are an obstacle to its safe use. The present studies explored the role of metabolic demethylation in the development of COL-induced hepatotoxicity. We found that

inhibition of CYP3A increased the susceptibility of mice to COL hepatotoxicity, and induction of CYP3A decreased the susceptibility of animals to the hepatotoxicity. The toxicokinetic study demonstrated that pretreatment with ketoconazole caused elevated area under the concentration-time curve of COL. Three demethylation metabolites of COL were found to be less hepatotoxic than the parent compound. It appears that the formation of electrophilic demethylation metabolites was not involved in the development of COL-induced liver injury.

17. Rheumatology (Oxford). 2019 Apr 28. pii: kez156. doi: 10.1093/rheumatology/kez156. [Epub ahead of print]

Short-term follow-up results of children with familial Mediterranean fever after cessation of colchicine: is it possible to quit?

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OBJECTIVE: To define the characteristics of children expressing the FMF phenotype under colchicine until it was ceased and to compare the clinical features of patients requiring colchicine again with the patients who did not need colchicine.
METHODS: Sixty-four of 1786 children with FMF in whom colchicine was stopped by the physician or patients/parents were enrolled. These patients were grouped as children who were in need of colchicine due to attacks and/or elevated acute phase reactants after cessation of colchicine (group 1) and children in whom colchicine was not necessary and not restarted (group 2).
RESULTS: Colchicine was stopped in 59.4% by the physician and in 40.6% by the patient/parents. It was ceased at a median of 10.6 years of age (range 2.1-20.5) and attack- and inflammation-free periods of 18.2 months (range 6-148). The median follow-up of 64 patients after colchicine cessation was 37.4 months (range 6.4-154.7). It was restarted in 17 patients due to attacks (n = 11) or elevated acute phase reactants (n = 6). The age at cessation of the colchicine was lower (P = 0.04) and the duration of colchicine treatment until its cessation was shorter (P = 0.007) in group 1 compared with group 2.

CONCLUSION: Life-long colchicine treatment may not be required in all FMF patients. There are no current guidelines to determine in which patients it is safe to stop colchicine. We found that younger age during cessation and shorter duration of colchicine treatment lead to a higher risk of needing to restart colchicine.

21. Rheumatol Int. 2019 Jul 19. doi: 10.1007/s00296-019-04389-3. [Epub ahead of print]

IL-1β blockade in periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome: case-based review.

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Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome and familial Mediterranean fever (FMF) are considered as inflammasome disorders associated with uncontrolled interleukin (IL)-1β production. Anti-IL1 agents are used in colchicine-resistant cases of FMF. Increase in pro-inflammatory mediators even between febrile attacks in PFAPA suggests that anti-IL1 treatment might be beneficial in these patients. We describe a child presenting with recurrent, self-limited febrile attacks at 1 year of age who was diagnosed as FMF being heterozygous for M694 V mutation. Her clinical findings were only controlled by the addition of canakinumab (2 mg/kg/8 week) to colchicine treatment. However, she developed typical PFAPA attacks during this treatment at 3 years of age. We conducted a literature search focusing on English articles with keywords including PFAPA, anakinra, canakinumab, and rilonacept.

Five children and one adult patient with PFAPA were found and evaluated. Anakinra was reported to abort PFAPA attacks in children, while the adult patient first responded and then became resistant to anakinra. Canakinumab was effective in preventing febrile attacks in this patient. Failure of canakinumab to prevent PFAPA attacks in our case may arise from the differences in the pathophysiology of PFAPA and FMF. Thus, further experience with higher doses or shorter intervals of canakinumab is needed in children with PFAPA.

22. Pan Afr Med J. 2019 May 10;33:16. doi: 10.11604/pamj.2019.33.16.18300. eCollection 2019.

[Contribution of cutaneous manifestations to early diagnosis of periodic disease:a case study].

[Article in French]

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We here report a case of chronic periodic disease diagnosed on the basis of recurrent and persistent erysipelas in plaques in a patient under antibiotic therapy. Patient's interview, genetic testing and favorable outcome of colchicine helped to reach a diagnosis.

Conflict of interest statement: Les auteurs ne déclarent aucun conflit d'intérêts.

23. Reumatismo. 2019 Jul 9;71(2):85-87. doi: 10.4081/reumatismo.2019.1141.

A new MEFV gene mutation in an Iranian patient with familial Mediterranean fever.

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Familial mediterranean fever (FMF) is an inherited autoinflammatory disorder characterized by recurrent episodes of fever and painful inflammation involving the intra-abdominal organs, the lungs and the joints, which is highly prevalent in specific ethnic groups including the Iranians. We report a 12-year-old boy from Iran, with a clinical history of recurrent fever. Based on the suggestive clinical data, mutational analysis revealed the presence of the novel c.1945C>T heterozygous variant in exon 10, which leads to a leucine to phenylalanine change at position 649 of the protein. The mutation was inherited from the mother. This novel mutation lies in exon 10 of the MEFV gene, which encodes for a domain called B30.2-SPRY, located in the C-terminal region of the pyrin protein and contains the most frequent mutations associated with FMF. The present report expands the spectrum of MEFV gene mutations associated with FMF. The uniqueness of this study, compared with other published case reports, consists in the new mutation found in the MEFV gene. In fact, new mutations in this gene are of high interest, in order to better understand the role of this gene in autoinflammation.

24. Intern Med. 2019;58(14):2025-2028. doi: 10.2169/internalmedicine.2293-18. Epub 2019 Jul 15.

Familial Mediterranean Fever with Small Bowel Stenosis.

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A 37-year-old man developed abdominal pain and the frequency of severe abdominal pain steadily increased to once a month. He was therefore admitted to our hospital. Abdominal CT showed bowel obstruction. It revealed transient stenosis in the small intestine. There were no symptoms such as fever or weight loss, it seemed unlikely that the patient had inflammatory bowel disease. Considering the history of recurrent abdominal pain, Familial Mediterranean Fever (FMF) was considered. As a result, a genetic analysis revealed mutations in exons 3 and 8 of the MEFV gene. We herein report the first known case of FMF with transient small bowel stenosis in Japan.

25. Intern Med. 2019 Jul 10. doi: 10.2169/internalmedicine.3001-19. [Epub ahead of print]

A Case of Atypical Familial Mediterranean Fever Presenting with Recurrent Migratory Polyarthritis: A Case Report.

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A 38-year-old Japanese man without any significant past medical history was referred to our clinic to undergo further examination for a "refractory infection in his joints". He suffered recurrent migratory polyarthritis starting from bilateral knees to his right elbow. Certain antibiotic therapies appeared to improve his symptoms, but the symptoms recurred due to the migratory nature of arthritis. A diagnosis of familial Mediterranean fever (FMF) was considered and diagnostic tests were performed. Not many differential diagnoses exist for migratory polyarthritis, particularly when it has a recurrent nature. The administration of antibiotics without sufficient diagnostic consideration can cause a delay in making an accurate diagnosis and thereby also cause a delay in administering appropriate treatment.

26. Adv Bioinformatics. 2019 Jun 4;2019:1651587.

Novel Deleterious nsSNPs within MEFV Gene that Could Be Used as Diagnostic Markers to Predict Hereditary Familial Mediterranean Fever: Using Bioinformatics Analysis.

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Background: Familial Mediterranean Fever (FMF) is the most common

autoinflammatory disease (AID) affecting mainly the ethnic groups originating from Mediterranean basin. We aimed to identify the pathogenic SNPs in MEFV by computational analysis software.
Methods: We carried out in silico prediction of structural effect of each SNP using different bioinformatics tools to predict substitution influence on protein structure and function.
Result: 23 novel mutations out of 857 nsSNPs are found to have deleterious effect on the MEFV structure and function.
Conclusion: This is the first in silico analysis of MEFV gene to prioritize SNPs for further genetic mapping studies. After using multiple bioinformatics tools to compare and rely on the results predicted, we found 23 novel mutations that may cause FMF disease and it could be used as diagnostic markers for Mediterranean basin populations.

27. Rheumatol Int. 2019 Jul 4. doi: 10.1007/s00296-019-04366-w. [Epub ahead of print]

Successful management of colchicine resistant familial Mediterranean feverpatients with a standardized canakinumab treatment protocol: a case series and literature review.

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Familial Mediterranean fever (FMF) is the most common monogenic auto-inflammatory disease characterized by recurrent attacks of fever and serositis. Although colchicine is the first line treatment in FMF, 5-10% of patients do not respond to colchicine. Canakinumab, an anti-IL-1β monoclonal antibody, has been reported to be effective and safe in colchicine-resistant FMF patients, but the adequate duration and interval of treatment is still a matter of debate. Aim of this study was to evaluate the success of the standardized treatment protocol for canakinumab applied in our Pediatric Rheumatology Department in colchicine-resistant FMF cases with a review of the literature. Nine patients included in this study had indications for canakinumab use as colchicine resistance and recurrent corticosteroid need for pleural/pericardial effusions. Canakinumab was administered monthly for 6 months (initial treatment), bimonthly

for 6 months (maintenance treatment), then treatment was discontinued. For the patients who developed a new attack after one-year treatment period, canakinumab was readministered with 3-month intervals (continuation treatment). The mean follow-up time beginning from the first canakinumab injection was 24.3 ± 10.2 (6-33) months. None of the patients had an attack during the first-year treatment. Four of the patients developed an attack 9.0 ± 2.9 (6-12) months after discontinuation of treatment and switched to the continuation treatment period, with no more attacks. We suggest that this standard protocol may be used successfully in colchicine-resistant FMF patients.

28. BMJ Case Rep. 2019 Jul 1;12(7). pii: e228858. doi: 10.1136/bcr-2018-228858.

Symptomatic patients with P369S-R408Q mutations: familial Mediterranean fever or mixed auto-inflammatory syndrome?

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A 51-year-old South African female of Ashkenazi Jewish descent was admitted with acute pleuritic chest pain, shortness of breath, fatigue and fever. She experienced vague abdominal and calf pains for 30 years. Her monozygotic twin was investigated independently for recurrent abdominal pain. Despite initially responding to antibiotics, treating suspected pneumonia, she developed recurrent fevers and pleuritic chest pain. After thorough investigation without significant findings, she re-attended days after discharge with similar symptoms. Familial Mediterranean fever (FMF) was suggested as she met diagnostic criteria and responded to colchicine, though FMF normally presents before 20 years old. Genetic testing showed no pathogenic mutations but heterozygous P369S and R408Q mutations. The significance of these mutations remains unclear, as they are found in asymptomatic patients, suggesting incomplete penetrance. She remains well, with full symptom resolution, but mixed auto-inflammatory syndrome may be a more appropriate diagnosis in symptomatic patients with both P369S and R408Q mutations.

Conflict of interest statement: Competing interests: MB has been sponsored to attend national and international meetings by Union Chimique Belge (UCB) celltech, Roche/Chugai, Pfizer, Abbvie, Merck, Mennarini and Eli-lilly and has received honoraria 20 for speaking and attended advisory boards with Bristol-Myers Squib, UCB Celltech, Roche/Chugai/Pfizer, Abbvie, Merck and Mennarini.

29. Neth J Med. 2019 Jun;77(5):177-182.

Familial Mediterranean Fever (FMF): a single centre retrospective study in Amsterdam.

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BACKGROUND: Familial Mediterranean Fever (FMF) is the earliest described and most prevalent hereditary auto-inflammatory disease. Its clinical presentation is diverse, leading to possible delay in diagnosis and treatment. Due to immigration, FMF became common in non-Mediterranean European regions. In the present single centre retrospective study, the clinical, demographic, and genetic characteristics of patients with FMF of different ancestry in Amsterdam are described.
METHODS: Case records of patients with FMF, who met the Tel-Hashomer diagnostic criteria, were retrospectively analysed. The international disease severity score was used.
RESULTS: Between 1990-2012, 53 patients were identified, 28 were female. Main country of origin was Turkey. The mean age at the time of analysis was 29.1 years; 13.8 years at onset of symptoms; and at time of diagnosis, 22.0 years. Most frequent symptoms were peritonitis (91%) and fever (81%). The mean C-reactive protein and erythrocyte sedimentation rate during acute attacks were 133 mg/l and 37 mm/first hour, respectively. One patient developed amyloidosis as a complication. Seventeen patients underwent abdominal surgery before diagnosis. Most patients (92%) received colchicine treatment and were responsive (81%). Most patients classified their disease as a mild disease (42%). MEFV gene mutation analysis was performed in 46 patients; most patients were compound heterozygotes (n = 17), and the most frequent mutation was M694V (n = 18).
CONCLUSION: FMF in Amsterdam is diagnosed in relatively young patients and the delay to diagnosis is 8.2 years. Disease manifestations and genetic distribution

of our FMF patients are comparable to those in Mediterranean regions, suggesting that ancestry is more important than environment.

30. J Trop Pediatr. 2019 Jun 30. pii: fmz040. doi: 10.1093/tropej/fmz040.

Assessment of Epicardial Adipose Tissue Thickness in Children with Familial Mediterranean Fever.

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BACKGROUND: Familial Mediterranean fever (FMF) is suggested to be associated with increased risk of atherosclerosis. Epicardial adipose tissue (EAT) thickness is used in prediction of atherosclerotic risk. The aim of our study was to evaluate EAT thickness in FMF patients for early detection of risk of atherosclerosis and to be compared with its level in healthy controls.
METHODS: Thirty 6- to 18-year-old children with FMF and 30 age- and sex-matched children (control group) were included in the study. Disease characteristics, disease severity and Mediterranean fever gene mutations were recorded. EAT thicknesses was measured by echocardiography.
RESULTS: EAT in patients' group was significantly greater than that of controls (5.21 ± 2.3 vs. 2.81 ± 2.96 mm, $p = 0.001$) and was correlated with cholesterol level and platelets count ($p = 0.047$ and 0.018, respectively).
CONCLUSION: This study concluded that EAT thickness was statistically increased in FMF patients than controls with a positive correlation with cholesterol level and platelet count. This finding suggests a higher risk for atherosclerosis in these patients. Follow-up study is needed to verify the effect of treatment of FMF on the EAT thickness. Further studies with larger number of patients following-up EAT are needed to verify this finding.

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PMID: 31257436

31. Semin Arthritis Rheum. 2019 May 31.

Age dependent safety and efficacy of colchicine treatment for familial mediterranean fever in children.

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OBJECTIVE: Colchicine has been found to be highly effective for the treatment of familial Mediterranean fever (FMF). However, it is FDA-approved only for children older than 4 years owing to the lack of studies in younger children. Our tertiary pediatric rheumatology department routinely uses colchicine even in very young children with FMF. The aim of the study was to evaluate its safety and efficacy in children with FMF <4 years old.
METHODS: The departmental database was searched for all children diagnosed with FMF between 2010-2018. Those who started treatment with colchicine before age 4 years were identified and matched by MEFV variant to children who started treatment at age 4-8 years. Drug efficacy was assessed by the improvement in the frequency and duration of attacks. Adverse events were assessed according to the Rheumatology Common Toxicity Criteria ver. 2.0.
RESULTS: The cohort included 89 patients with FMF: 41 first treated before age 4 years, and 48 first treated at age 4-8 years. Rates of complete response to colchicine were 61% in the younger group and 60.4% in the older group, Corresponding rates of partial remission were 24.4% and 29.2% (p = 0.77). The most frequent adverse event was diarrhea, with a prevalence of 24.4% in the younger group and22. 9% in the older group respectively (p = 0.87). There were no

significant between-group differences in other adverse events.
CONCLUSION: Colchicine is equally effective and safe for use in patients with FMF under 4 years old, with no difference in response from older pediatric patients.

35. Best Pract Res Clin Rheumatol. 2018 Oct;32(5):651-661.

Toll-like receptor 2 is overexpressed in Familial Mediterranean fever patients and is inhibited by colchicine treatment.

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AIM: To study the role of Toll-like receptor (TLR) 2 in Familial Mediterranean fever (FMF) inflammatory process.

METHODS: TLR2 expression on monocytes of FMF attack-free patients (n = 20) and the effect of sera of FMF patients with an acute attack (n = 9) on TLR2 expression on monocytes of healthy donors were studied by flow cytometry (FACS). TLR2 expression was also studied in THP-1 cells, and TLR2 downstream signaling was studied by ELISA for the secretion of IL-1β and pro-inflammatory cytokines or by western blotting to measure nuclear factor (NF)-κB.
RESULTS: FMF attack-free patients had increased CD14 + TLR2+ cell count as compared to healthy donors. High-dose colchicine treatment (≥2 mg/d) inhibited this increased expression in FMF patients. Colchicine in vitro also inhibited TLR2 expression on THP-1 cells. Sera from FMF patients with an acute attack induced TLR2 expression by both monocytes of healthy donors and THP-1 cells as well as pro-inflammatory cytokine secretion by healthy monocytes, while colchicine inhibited this induction. Pam2CSK4 increased interleukin-1β (IL-1β) secretion by peripheral blood mononuclear cells (PBMCs) of healthy donors, and this activation was inhibited by colchicine. THP-1 cells presented elevated NF-κB expression when cultured with Pam2CSK4, whereas colchicine inhibited this elevation.
CONCLUSIONS: TLR2 activation was upregulated in monocytes of FMF patients, and colchicine inhibited this upregulation both in -vitro and in -vivo. This indicates that elevated expression of TLR2 promotes the production of pro-inflammatory cytokines, which may contribute to uncontrolled inflammation in FMF.