Introduction: Familial Mediterranean fever (FMF) is the most common monogenic auto-inflammatory disease with peculiar ethnic predisposition. The disease occurs frequently among Mediterranean populations like Turks, Jews, Armenians, and Arabs. It was not until 2016, the Crimean Tatars, people of Turk origin, became first considered as the population with prominent incidence of FMF.
Objectives: the study examines the clinical and genetic features of FMF among children of Crimean Tatar nationality and studied the distribution of exon 10 MEFV alleles in healthy adults.
Methods: the retrospective study included data from case histories of 16 children aged 5 to 18 years. Diagnosis of FMF was based on Eurofever/PRINTO 2019 criteria. In each patient clinical characteristics including administered colchicine dose, tolerance, side effects, and biologics therapy were evaluated. All patients underwent direct Sanger sequencing of exon 10 of the MEFV gene. For population study we included 127 healthy unrelated adults without FMF and any periodic fever, whome exon 10 of the MEFV gene were analyzed.
Results: The mean age of FMF diagnosis was 9.5 (4.0; 14.2), the mean time from the first symptoms to the diagnosis was 5.5 (2.0; 9.3) years. The main clinical manifestations were fever (100%), arthritis (100%), peritonitis (50%), pleuritis (7%), and erysipeloid rash (57%). Most commonly involved joints were knee (100%) and hip (25%); in 13% of patients both joints were affected during the attack. Patients were at first diagnosed as having acute respiratory infection (n=14) or juvenile idiopathic arthritis (n=2). Genetic analysis revealed well-known pathogenic alleles of MEFV, p.M694V (88%), p.M680I (6%) and p.V726A (6%). The most common p.M694M mutation was found in heterozygous/homozygous state in 81% and 19%, respectively. Parents of 8 patients (50%) were consanguineous. Colchicine intolerance was observed in 13%, and colchicine resistance in 25% of the patients. 6 patients (38%) received biologic treatment: canakinumab - 4 (25%), and tocilizumab - 2 (13%). Colchicine treatment and biologics were effective in 100% of patients. In healthy adults from Crimean Tatar origin 13/127 (10.2%) had pathogenic exon 10 mutations: V726A (n=2, 1.6%), M694V (n=9, 7.1%), M680I (n=2, 1.6%)
Conclusion: MEFV mutations are frequent in Crimean Tatars probably due to founder effect. The main clinical features observed in the FMF patients were fever and arthritis. A high proportion of patients receives biologic therapy. Further investigations required to evaluate the characteristics of FMF in the Crimean Tatars population.

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Disclosure of Interest
None declared

P007

Multiplex long-range PCR for routine genotyping of up to nine autoinflammatory gene in a single analytical run by next generation sequencing

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Introduction: During the last decade, remarkable progress with massive sequencing has been made in the identification of disease-associated genes for AIDs using the next generation sequencing technologies (NGS). International group of experts described the ideal genetic screening method which should give information about SNVs, InDels, Copy Number Variations (CNVs), GC rich regions.
Objectives: Our aim was to develop and validate molecular diagnostic method in conjunction with NGS platform as an inexpensive, extended and uniform coverage and fast screening tool which consist of nine genes known to be associated with various AIDs.
Methods: To validation of four and nine gene containing panels, long range multiplex models were setup on 9 healthy sample without any known variations for MEFV, MVK, TNFRSF1A, NLRP3, PSTPIP1, IL1RN, NOD2, NLRP12 and LPIN2 genes. Ten patients with AIDs who had already known causative genes were sequenced for analytical validation. As a last step, multiplex models validated on 46 patients with pre-diagnosis of AIDs. All sequencing steps were performed on Illumina NGS platform. Validity steps included the selection of related candidate genes, primer design, development of screening methods, validation and verification of the product. GDPE (Gentera) bioinformatics pipeline was followed.
Results: Although there was no non-synonymous variation in 9 healthy samples, 127 synonymous variant alleles and some intronic and UTR variants were detected. In 10 patients who underwent analytical validation, beside the 11 known non-synonymous variant alleles, 9 additional non-synonymous variant alleles and a total of 110 exonic variant alleles were found. In clinical validation phase, 46 patients sequenced with multiplex panels, genetic and clinical findings were combined for diagnosis.
Conclusion: In this study, we described the development and validation of NGS-based multiplex array enables the "long-amplicon" approach for targeted sequencing of nine AIDs genes. This screening tool is less expensive and more comprehensive compared to other methods and more informative than traditional sequencing. Our panels have a great advantage compared to WES or hybridization probe equivalents in terms of CNV analysis, high sensitivity and uniformity, GC-rich region sequencing, InDel detection and intron covering.

Disclosure of Interest
None declared

P008

Adherence to colchicine treatment and colchicine resistance in a multicentric FMF national cohort

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Introduction: Colchicine is the standard treatment for Familiar Mediterranean Fever (FMF), however about 5% of patients (pts) experience colchicine resistance. There is no standard definition of colchicine resistance. Recently a panel of experts elaborated a new definition based on a Delphi consensus approach.
Objectives: We aim to describe main features of the disease and clinical outcome of a cohort of FMF pts with particular interest on the colchicine resistance and tolerability according to the definitions proposed by the recent consensus.
Methods: Since November 2009, 425 Italian pediatric and adult FMF pts from 13 centers were enrolled in a national longitudinal cohort study, using the EUROFEVER registry. Demographic, genetic and clinical data, including response to treatment, were analyzed. Supplementary information on quality of life and treatment adherence was also collected by a specific questionnaire.
Results: Complete information were available in 341 pts (M/F 189/152, 211 children and 120 adults). The median age at disease onset was 5.0 years (range 0.1-59); the median diagnostic delay was 8.7 years (0-61). The median age at enrollment was 12.1 years (0.4-82). The MEFV genotype was the following: 103 (30.2%) pts carried biallelic pathogenic (P) variants; 59 (17.3%) one P variants and one variants of unknown significance (VOUS)/likely benign (LB) variant; 27 (7.9%) had biallelic VOUS/LB variants; 97 (28.45%) were heterozygous

for P variants; 30 (8.8%) were heterozygous for VOUS/LB, 25 (7.33%) were genetically negative.
Colchicine treatment was used in 280 patients; during treatment, biologic treatment (anti-IL1) in 22 patients. 61 patients received NSAI D or steroid on demand.
We analyzed the behavior of the pts treated with colchicine according to the statements on resistance/intolerance defined by Ozen (1) (Table 1).
Conclusion: Almost 46% of FMF pts display some disease activity despite colchicine treatment. The treatment is generally under-dosed, especially in children. The adherence and the compliance to the treatment is generally good.

References

1 Ozen S et all. Recommendation on colchicine dosing and definition of colchicine resistance/intolerance in the management of FMF. Arthritis Rheumatology, 2019

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Disclosure of Interest

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Table 1 (abstract P008). See text for description

Adherence	62% displayed a total adherence (> 90% of prescription); 10.8% a good adherence (50-89% of prescriptions); 1.9% poor adherence (< 50% of prescriptions); 0.9% no adherence
Dose adjustment criteria/ Recommended maximum colchicine dose	Mean colchicine dose:
	Pts <5 years: 0.57mg/de (std. dev. 0.18)
	5-10 year: 0.77mg/die (std. dev. 0.23)
	10-18 years: 1.1mg/die (std. dev. 0.39)
	Adults : 1.16 mg/die (std. dev. 0.37)
	Pts with a dose equal or lower to the recommended starting dose:
	5-10 years: 35.3%
	10-18 years: 58.9%
	Adults: 67.6%
Resistance to Colchicine	Resistance was be defined as persistence of fever attacks, despite optimal treatment.
	54% pts had a complete disease control
	46% pts had some disease activity:
	- 30.4% pts had < 1 episode/ month for 3 months
	- 7.8 % had ≥1 episode/month for 3 months
	- 7,3% frequency not known
Inclusion of secondary amyloidosis in the definition of colchicine resistance	5 adult pts (1.5%) displayed amyloidosis
Colchicine intolerance	11 pts (3.2%) withdraw colchicine because of drug intolerance
Patient quality of life and patient-reported outcomes	20.7% of pts experience fatigue or chronic pain, 16.9% limitations in daily activities, and 16.9% have lost school/ work days.

P009

Efficacy of anakinra treatment in pediatric rheumatic diseases; a single-center experience

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Introduction: Anakinra, a recombinant IL-1 receptorantagonist, is a treatment option that acts byblocking the biological activity of IL-1 in autoinflammatory conditions. The diseases that the IL-1 was over expressed are the potential conditions for this treatment. Such as familial Mediterranean fever (FMF), cryopyrin-associated periodic syndrome (CAPS), and hyperimmunglobulin D syndrome (HIDS) with monogenic inheritance, and systemic juvenile idiopathic arthritis (SoJIA) or idiopathic recurrent pericarditis as non-Mendelian polygenic diseases, can be listed as examples of these diseases.
Objectives: We aim to report our experiences of pediatric rheumatic diseases treated with anakinra.
Methods: The study group consisted of children with pediatric rheumatic diseases followed up in the Pediatric Rheumatology Department of University of Health Sciences and treated with anakinra (anti-IL 1) for at least one month, between 1 July 2016 and 1 January 2020. The data of these patients were collected retrospectively. The disease activity of the patients at 3rd month and 12th month after the treatment were assessed.
Results: There were 28 patients treated with anakinra for the different pediatric rheumatic diseases. The diagnoses of these patients were as follows; eight were macrophage activation syndrome (MAS) complicating SoJIA, six were HIDS, four were CAPS, four were FMF, four were idiopathic recurrent pericarditis, one was deficiency of interleukin-36 receptor antagonist (DITRA), and one was undefined systemic autoinflammatory disease. 46.4% of the patients were male and 53.6% were female. The median age of diagnosis of the patients was 6.5 ((interquartile range (IQR): 4-12.7) years. The median follow-up duration of the patients was 14 (IQR: 3.7-28) months. The patients median anakinra treatment duration was 3 (IQR: 1-4) months. Fever reduced and C-reactive protein normalized within median 2 (IQR: 1-3) and 5 (IQR: 5-7) days, respectively. In the 3rd month after treatment; It was observed that 53.6% of patients achieved a complete remission (no attack was seen or MAS was improved). The frequency of attacks were decreased more than 50% in 35.7% of patients and less than 50% in 7.1%. 3.6% of patients were unresponsive to treatment. In the 12th month assessment after the initiation of treatment, it was observed that 28.6% of patients were still under anakinra treatment and in remission, 10.7% of them were in remission without anakinra treatment. In 60.7% of patients, anakinra was switch to other biological treatments for different reasons (35.7% partial response or unresponsiveness, 17.8% injection site reactions and 7.1% daily-injection difficulty). Biologic drug switch to canakinumab and tocilizumab was observed in 88.2% and 11.8% of patients , respectively. One patient developed recurrent MAS episodes when the anakinra dose was tapered, and one another patient was unresponsive to the anakinra and dead due to secondary to MAS.
Conclusion: Anakinra seems to be a successful treatment to achieve inactive disease in a significant portion of patients in the early period. The recurrence of disease attacks while drug tapering and injection site reactions were appears the main causes of treatment switch or discontinuation.

Trial registration identifying number: None

Disclosure of Interest

None declared

P010

Majeed syndrome and FMF in a lebanese patient: a case report

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