FRI0556 GENETIC SCREENING IN PATIENTS WITH UNDIFFERENTIATED PERIODIC FEVER SYNDROME

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Background: Autoinflammatory diseases (AID) are a group of hereditary diseases characterised by inflammation periods accompanied with clinical findings such as fever, skin rash, lymphadenopathy, abdominal pain, musculoskeletal symptoms, and with sign of inflammation in the blood. Each disease has own typical clinical findings and they are associated with mutations in specific genes such as in MEFV gene in familial Mediterranean fever (FMF), MVK gene in hyperimmunglobulin D syndrome (HIDS), TNFRSF1A gene in tumor necrosis factor-alpha receptor associated periodic fever syndrome (TRAPS) and NLRP3 gene in cryopyrin associated periodic fever syndrome (CAPS) (1,2). Also in some patients with periodic fever syndrome (PFS), clinical signs of these diseases can be seen but no mutation can be detected in the related genes (3,4). There are also patients exhibit the incomplete phenotype of a disease or overlap signs of more than one AID. The diagnosis of these undifferentiated patients have difficult and may not be possible by a single target gene analysis (5). Screening of the periodic fever syndrome (PFS) panel including various AID genes may be beneficial to define the atypical cases. Molecular genetics has an important role for lead to diagnosis in these patients.
Objectives: The aim of this study was to investigate the genotypic diagnosis in patients with non-characteristic PFS findings for any AID.
Methods: This is a prospective study and conducted between June 2016 and December 2018. Next-generation sequencing (NGS) analysis was performed by using "Fever and AutoInflammatory Syndrome panel: Panel by Sophia Genetics" including 8 genes (MEFV, MVK, NLRP3, NLRP12, TNFRSF1A, TNFRSF11A, LPIN2 and PSTPIP1) in 30 patients with undifferentiated PFS. Clinical features and genetic results were evaluated together and final diagnoses were determined.
Results: Thirty patients included in the study did not have typical clinical features for any of the eight monogenic diseases in the PFS panel. In the result of the genetic screening; disease-causing mutation was found in MEFV gene in 12 patient, in NLRP3 gene in four patient, in NLRP12 gene in two patient and in MVK gene in one patient. Also, genetic variants of uncertain significance (VUS) in different genes were shown in five patient. No mutation was detected in remaining six patient. The final diagnosis was made by both phenotypic and genotypic data. 12 patients were diagnosed with FMF, four were FCAS, two were FCAS2, one was TRAPS and one was HIDS. Patients with negative genetic screening or had mutation as VUS, were followed as **undifferentiated** PFS.
Conclusion: Autoinflammatory diseases may not always be appear with typical clinical findings of related disease. In such patients, target gene sequencing and detection of underlying disease can be challenging. Our study has shown that the NGS analysis may help to determined the diagnosis in patients with non-characteristic PFS findings for any AID.

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FRI0557 NOVEL G-CSF RECEPTOR MUTATION CAUSING NEUTROPAENIA AND AUTO-IMMUNE DISEASE

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Background: Novel G-CSF receptor mutation causing neutropaenia and auto-immune disease:
We present 2 brothers, born to consanguineous (second cousin) parents, with persistent, moderate neutropaenia secondary to a previously undescribed mutation in the *CSF3R* gene.
Objectives: Both brothers had associated autoimmune phenomena – one with poly-articular arthritis and the other with kerato-conjunctivitis.
Methods: Patient A is a 13-year old boy who was referred with a history of recurrent knee swelling. His father described that, from an early age, whenever he had a viral illness he developed marked swelling of his knee which settled spontaneously over a few days. In between episodes he remained completely well and fully active. Growth was normal and there was no history of recurrent or unusual infections. USS & MRI confirmed the presence of large effusions in the knees during these episodes.
On examination A had clinical evidence of synovitis in his right knee which settled spontaneously over 3 weeks. However a few months later his arthritis subsequently extended to involve his other knee, both hips, elbow and shoulder. He was treated with Etanercept with good clinical response.
Patient H is the younger brother of A. He was diagnosed with severe eczema at age 3 which needed treatment with topical steroids & tacrolimus, along with oral montelukast, to control. He subsequently developed vernal kerato-conjunctivitis which required high-dose cyclosporine & steroid eye-drops to control.
Initial Investigations: Both A and H had been noted from an early age to have neutropaenia. This was initially noted during admission for a viral illness but repeat samples over several years showed persistent neutropaenia (Patient A 0.27 – 0.94, patient H 0.9 - 1.1). Patient A also had markedly raised ESR (range 27 – 120mm/hr) noted during episodes of arthritis. All other investigations were reported as normal
Results: Whole exome sequencing of patient A revealed a novel homozygous single nucleotide variant c.909C>A affecting exon 8 of the *CSF3R* gene on Chr. 1. This was confirmed by Sanger sequencing, and the same homozygous mutation was found in patient H.
CSF3R encodes the receptor for Granulocyte Colony Stimulating Factor (G-CSF). This receptor consists of an extracellular Ig-like domain, a cytokine receptor homology domain, 3 fibronectin domains, a trans-membrane domain, and a cytoplasmic domain that couples to Janus Kinases for signal transduction. The c.909C>A variant leads to a premature stop codon, p.Tyr303*. Residue Y303 is located in the 2nd extracellular fibronectin type III domain. Truncation thereafter leads to a protein that, if expressed at all, would lack its transmembrane and cytoplasmic domains. Homozygous Y303X is thus predicted to be a null mutation.
Conclusion: G-CSF is a crucial cytokine that induces proliferation, differentiation, & survival of myeloid progenitors. This variant has not, to our knowledge, been previously described. It is compatible with low level neutrophil production, as in our patients, which may be boosted by GM-CSF, but not G-CSF.
Other recessive loss-of-function mutations in *CSF3R* have been found in patients with severe congenital neutropenia. These patients are, unsurprisingly, refractory to rhG-CSF treatment.
It is not clear how this mutation is linked to autoimmunity in these 2 boys. Theoretically both G-CSF, which is likely to be circulating in high concentrations, and GM-CSF, which may be increased to stimulate neutrophil production, have been shown to have pro-inflammatory effects, and indeed are potential targets for future treatment modalities in autoimmune diseases.
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FRI0558 PREVALENCE OF SUBCLINICAL SACROILIITIS IN YOUNG PATIENTS WITH INFLAMMATORY BOWEL DISEASE REVEALED BY ENTERO-MRI

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Background: Sacroiliitis is one of the extraintestinal manifestations associated with inflammatory bowel disease (IBD), and may be underdiagnosed especially in the pediatric age. MR-enterography (Entero-MRI) is currently

the imaging gold standard to assess intestinal disease activity and to detect complications in patients with IBD. Only few studies have been conducted on adult patients with IBD in order to define the role of this technique in assessing sacroiliitis, while no data are available on pediatric patients.

Objectives: To study the prevalence of inflammatory sacroiliitis on MRI performed for intestinal investigation in an IBD pediatric population.

Methods: This is a retrospective study conducted on patients suffering from IBD followed in our gastroenterology department between 2010 and 2018 whose entero-RM (1.5 or 3 Tesla, Philips depending from year of scanning) were blindly and independently scored by two readers experienced in pediatric musculoskeletal imaging. Each sacroiliac joint was divided into 4 quadrants. Signs of sacroiliitis were identified according to the ASAS criteria, with a particular attention to the presence of bone marrow edema (using T2 weighted sequences with fat suppression), diffusion restriction in DWI sequences (Diffusion Weighted Imaging) or DWIBS (Diffusion Weighted Imaging with Background Suppression) and post-contrastographic uptake in dynamic acquisitions. Demographics, IBD characteristics, clinical, radiological, and laboratory data were recorded and a dedicated Excel database was constructed. Results were elaborated using descriptive statistics.

Results: 34 patients (10 F, 24 M, age at scanning range 5-20 yrs, median 15) were included in the study, for a total of 59 entero-MRI evaluated (some patients were subjected to more than one scan). Two out of 34 patients were affected by Ulcerative Colitis, 32 by Crohn disease. Joint examination resulted negative in all patients, and none complained of articular symptoms including back pain.

In 5 IBD patients (4 CD, 1 UC) a monolateral slight degree of sacroiliitis (grade 1) was radiologically identified. They were all males, without clinical-laboratory-radiologic inflammatory signs of intestinal activity, with the exception of a patient who presented signs of intestinal and sacroiliac inflammation at his first entero-MRI, while 18 months later, at his MRI control under pharmacological treatment, signs of sacroiliitis were still present in the absence of intestinal signs of inflammation.

Conclusion: Asymptomatic sacroiliitis was observed in about 15% of our IBD patients. Sacroiliac involvement therefore can be underdiagnosed in these patients. Entero-MRI with specific sequences could be a good tool to detect early signs of sacroiliac inflammation.

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FRI0559

VALIDATION OF NORDIC JUVENILE IDIOPATHIC ARTHRITIS CLINICAL PREDICTION MODELS IN A CANADIAN COHORT

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Background: Validation of clinical prediction tools for juvenile idiopathic arthritis (JIA) in populations different than those in which they were first developed is essential to understand their applicability across healthcare settings.

Objectives: To determine if clinical prediction tools to predict 1) non-achievement of remission off medication and 2) functional disability, developed in the Nordic cohort[1] can be directly applied to JIA patients in the Canadian Research in Arthritis in Canadian Children emphasizing Outcomes (ReACCh-Out) cohort; and to assess performance of the prediction tools if model parameters are fine-tuned to the Canadian cohort.

Methods: Since the Nordic models were developed to predict outcomes 8 years after disease onset but the follow-up of the ReACCh-Out cohort was shorter, we chose to cross-validate the tools in a subpopulation of 513 subjects at the 3 years follow-up (3.75 years after onset). Attainment of remission off medications was determined by a panel of 3 pediatric rheumatologists as previously described[2] and functional disability was defined as a Childhood Health Assessment Questionnaire Disability Index (CHAQ)>0. Missing data was handled with multiple imputation by chained equations and prediction ability was assessed with c-index and Receiver Operator Characteristic (ROC) curves. The Nordic models were first evaluated exactly as published on the entire Canadian cohort. Then we fine-tuned the model coefficients using repeated runs of cross-validation in the Canadian cohort. This way, fine-tuned models were tested in patients not included in the fine-tuning process while also minimizing the standard error of prediction.

Results: In total, 408 of 506 evaluable patients (81%) were not on remission and 137 of 361 evaluable patients (38%) had functional disability at the 3-year visit. The Nordic model for predicting non-achievement of remission had a c-index of 0.68 (95%CI 0.62-0.74) when directly applied, and a c-index of 0.74 (0.70-0.78) when it was fine-tuned for the Canadian population. The latter values are comparable to those reported in the Nordic cohort (median AUC 0.78, IQR 0.72-0.82). Table 1 shows fine-tuned coefficient values along-side the original values. The Nordic model for predicting functional disability had a c-index of 0.57 (0.50-0.63) when directly applied, and fine-tuning failed to improve its performance, a c-index of 0.53 (0.43-0.63). Figure 1 shows ROC curves for fine-tuned models in the multiple splits.

Conclusion: After fine-tuning of coefficients, the Nordic model for prediction of non-achievement of remission had similar prediction ability in Canadian patients with JIA. We could not confirm the validity of the Nordic model for prediction of functional disability in Canadian patients.

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Table 1. Prediction models for non-remission off medications 3.75 years after JIA onset

Variable	Original Nordic	Fine-tuned Canada
Constant	1.58 (SE 0.44)	0.26
Cumulative active joint count	0.04 (SE 0.05)	0.13
ESR in mm/h	0.03 (SE 0.02)	-0.01
CRP> 10 mg/L	-0.07 (SE 0.69)	0.12
Morning stiffness > 15 min	1.16 (SE 0.45)	0.36
Physician global assessment	0.16 (SE 0.46)	0.15
ANA positive	1.25 (SE 0.50)	-0.02
HLA-B27 positive	1.37 (SE 0.54)	0.84
Ankle joint arthritis	1.10 (SE 0.49)	0.67

SE= Standard Error

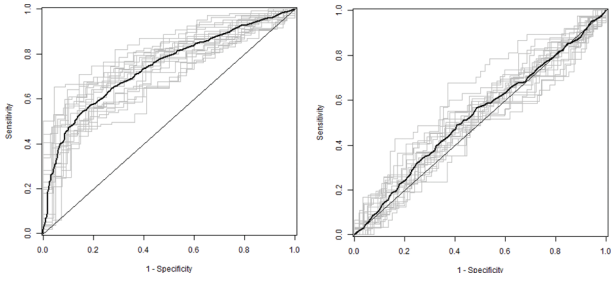

Figure 1. ROC curves for the multiple fine-tuning splits

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