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 hyperimmunoglobulin 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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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