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FRI0538

MAY SOME OF THE MEFV GENE VARIANTS CAUSE PFAPA SYNDROME LIKE SYMPTOMS?

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Background: PFAPA syndrome is characterized by periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis. As diagnosis usually depends on clinical diagnostic criteria, sometimes it can be difficult to distinguish this clinical entity from the other periodic fever syndromes, especially in regions endemic for FMF.

Objectives: The objective of the study is to evaluate the PFAPA patients' MEFV gene variation frequencies (if it was performed) and relations between detected variants and clinical manifestations in pediatric PFAPA patients.

Methods: Nine hundred and thirty-seven patients that were recorded to our database as PFAPA syndrome were evaluated. Patients were reached by phone and asked about characteristics of their fever episodes, presence of acute phase reactant elevation, pharyngitis, aphthous stomatitis/cryptic tonsillitis, cervical lymphadenopathy, arthralgia, arthritis, abdominal pain, headache, nausea or vomiting, chest pain, diarrhea, skin changes, myalgia and conjunctivitis in the course of fever attack, if they had tonsillectomy, if they were attack-free after tonsillectomy and if they had clinical response to steroid or colchicine.

Results: There were 937 PFAPA patients in our database. MEFV gene analysis was performed in 407 (%43) of PFAPA patients and 305 of them had at least one mutation. Most common MEFV mutations of patients were: R202Q heterozygotes (25,9%), M694V heterozygotes (24,2%), E148Q heterozygotes (13,4%), P369S heterozygotes (9,8%) and V726A heterozygotes (8,6%), respectively.%45.8 of detected mutations were located in exon 2,%40,3 of them were located in exon 10 and% 13,9 of them were located in exon 3 of the MEFV gene. Patients were divided into five groups according to their mutations' localization and groups were compared according to clinical features. There were significant differences between groups according to presence of pharyngitis, arthralgia, abdominal pain, myalgia and tonsillectomy history (Table 1).

Table 1. Comparison of patients according to their mutations' location and clinical features.

		Exon 2	Exon 3	Exon 10	No Mutation	MEFV study not performed	p
Pharyngitis	Yes	21	9(40,9)	45	28 (87,5)	168(87,5)	<0,05
	No	(87,5)	13 (59,1)	(80,4)	4(12,5)	24(12,5)	
Aphthous stomatitis/Cryptic tonsillitis	Yes	15	8(36,4)	21	17 (53,1)	102(53,1)	0,11
	No	(62,5)	14 (63,6)	(37,5)	15(46,9)	90(46,9)	
Cervical lymphadenopathy	Yes	10	8(36,4)	21	14(56,3)	77(40,1)	0,97
	No	(41,7)	14 (63,6)	(37,5)	18(43,7)	115(59,9)	
Arthralgia	Yes	5(20,8)	11(50)	22	19(59,4)	66(34,5)	0,02
	No	19 (79,2)	11(50)	(39,3)	13(40,6)	126(65,5)	
Abdominal Pain	Yes	17	12	27	16(50)	56(70,8)	<0,05
	No	(70,8)	(54,5)	(48,2)	16(50)	136(29,2)	
Myalgia	Yes	0(0)	8(36,4)	9(16,1)	7(21,9)	24(12,5)	0,006
	No	24(100)	14 (63,6)	47 (83,9)	25(78,1)	168(87,5)	
Tonsillectomy	Yes	14	5(22,7)	21	20(62,5)	109(57,1)	0,005
	No	(58,3)	17 (77,3)	(38,9)	12(37,5)	82(42,9)	

Conclusion: In this study, we reported increased frequency of MEFV mutations in a large PFAPA patients cohort. Frequency differences of clinical features between groups suggest that some of the MEFV gene mutations may modify phenotype of PFAPA syndrome. Furthermore, underlying MEFV gene mutations possibly lead to PFAPA like clinical presentation in FMF patients. Another remarkable finding of this study is the relatively high P369S mutation rates in patients with PFAPA syndrome.

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FRI0539

WNT6 MUTATION CAUSES AN EARLY ONSET GRANULOMATOUS INTESTINAL DISEASE WITH RECURRENT HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH)

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Background: Use of NGS in patients with unclassifiable disease lies a possible approach to the identification of novel disease causing genes.

Objectives: We report a patient with an early onset inflammatory bowel disease with granulomatous lesions and recurrent HLH episodes carrying a missense mutation in the WNT6 gene.

Methods: A trio based Whole Exome Sequencing (WES) approach was used. Cytokine levels were measured by multiplex assay and by specific ELISAs.

Results: Ten years old Caucasian boy affected by early onset pan-colitis from 9 months of age. Since the disease onset the patient is on glucocorticoid treatment with amino acid enteral nutrition and oligo antigenic diet. Because of recurrent disease relapses at any attempt of glucocorticoid withdrawal, azathioprine and cyclosporine treatments were also added. At 2 years of age he received total colectomy with ileostomy.

Because of insufficient disease control, treatment with a TNF-inhibitor (infliximab) was started with apparent improvement of intestinal symptoms. However, persistent granulomatous inflammatory disease of the distal portion of the ileus-rectal anastomosis persisted. Moreover, the patient presented recurrent HLH episodes that required high dose of glucocorticoid and cyclosporine-A treatment. Except one HLH episode related to a varicella zoster infection, the other HLH events were most likely triggered by his underlying inflammatory condition. During the HLH episodes levels of IL-18 were moderately elevated (10.880 pg/ml) the IFN-gamma induced chemokine CXCL9 was markedly high (21.871 pg/mL) and remained markedly elevated also during clinical and laboratory HLH remission (3.121 pg/ml and 9.929 pg/ml respectively). Considering the early disease onset, primary immunodeficiency and early intestinal bowel disease onset were genetically ruled out as well as chronic granulomatosis diseases through extensive NGS panels. WES revealed carriage of a private (MAF: 1/125568, TOPMED), predicted pathogenic (CADD: 31), homozygous variant of WNT6 (c.793G>C; p.(Asp265His); NM_006522.3). The patient is now partially controlled on low dose of oral glucocorticoid (0.1 mg/kg), cyclosporine-A (5mg/kg) and antimicrobial treatment.

Conclusion: WNT signalling has been primarily described as a regulatory pathway in ontogeny and homeostatic processes. Schaale et al. demonstrated that WNT6 is expressed in granulomatous lesions in the lung of *Mycobacterium tuberculosis*-infected mice. Moreover, they found that the transcription factor c-Myc is significantly induced in murine macrophages by WNT6. This identifies WNT6 as a novel factor driving macrophage polarization toward an M2-like phenotype, suggesting a role for WNT6 in macrophage differentiation. Our case suggests defective function of WNT6 might be involved in the development of a granulomatous disease. WNT6 role in macrophage differentiation and polarization might also be important in the activation of the IFN-gamma pathway and in recurrent HLH episodes.

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FRI0540

A NOVEL AUTOINFLAMMATORY DISEASE CHARACTERIZED BY NEONATAL-ONSET CYTOPENIA WITH AUTOINFLAMMATION, RASH, AND HEMOPHAGOCYTOSIS (NOCARH) DUE TO ABERRANT CDC42 FUNCTION

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Background: Despite continuous advances in the identification of novel causative genes, several patients with a clinical autoinflammatory phenotype remain unclassifiable

Objectives: to describe a novel hematological and autoinflammatory disorder in three unrelated patients caused by a *de novo* missense mutation of *CDC42*

Methods: Whole exome sequencing was used to identify the novel variant. The functional impact of altered CDC42 function on hematopoiesis and inflammation was assessed through patient peripheral blood and bone marrow analyses, protein behavior and immune and non-immune cell functioning through *in vitro* biochemical and functional assays and *in vivo* *C. elegans* modeling

Results: Patients shared the same *de novo* missense mutation of *CDC42* (NM_001791, Chr1:22417990, c.556C>T, p.R186C). Disease features included neonatal-onset cytopenia with dysmaturational dysplasia, autoinflammation, rash, and hemophagocytosis (collectively termed NOCARH syndrome) (Table). An altered hematopoietic compartment (prevalence of early differentiation elements and substantially decreased clonogenic progenitors) was demonstrated. Complementary assays documented the unique consequences of this mutation on CDC42 localization and function, and its disruptive effect on cell behavior and developmental processes, possibly linked to actin dysregulation. Increased secretion of IL-1 β , and particularly of IL-18, was observed via *ex vivo* spontaneous release from unstimulated bone marrow mononuclear cells and by high levels in bone marrow supernatants and plasma. IFN γ was also increased and correlated to CXCL9 levels which were strictly related to ferritin levels. Treatment with anakinra and emapalumab, a monoclonal antibody to IL-1 β , was identified as critical in the survival of one patient, who underwent successful hematopoietic stem cell transplantation

	Patient 1	Patient 2	Patient 3
Outcome and status	Alive, 6 yrs	Dead, 6 mos	Dead, 1.5yrs
Fever	+	+	+
Skin rash	+	+	+
Hepato-Splenomegaly	+	+	+
Hemophagocytic lymphohistiocytosis	+	+	+
Gastrointestinal symptoms	+	+	+
Cytopenia	+	+	+
Acute phase response	+	+	+
Bone marrow dysplasia	+	+	+

Conclusion: The p.R186C amino acid substitution in CDC42 underlies a novel, unique syndrome where CDC42 functional dysregulation has pleiotropic effects, causing hematopoietic disturbance, hyperinflammation, and immune impairment. Early recognition and control of HLH, through neutralization of IFN γ , followed by hematopoietic stem cell transplantation, appear to be crucial to survival.

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