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

Michael T. Lam^{1,2,3}, Simona Coppola⁴, Oliver H. Krumbach⁵, Giusi Prencipe⁶, Antonella Insalaco⁶, Cristina Cifaldi^{7,8}, Immacolata Brigida⁹, Serena Scala⁹, Marcello Niceta¹⁰, Andrea Ciolfi¹⁰, Alexandre Carisey^{1,2}, Mohammad Akbarzadeh⁵, Andrea Finocchi^{7,8}, Franco Locatelli¹¹, Caterina Cancrini^{7,8}, Alessandro Aiuti^{9,12,13}, Reza Ahmadian⁵, Jordan S. Orange², Fabrizio De Benedetti⁶, Marco Tartaglia¹⁰.
¹Baylor College of Medicine, Department of Pediatrics, Houston, United States of America; ²Columbia University, Irving Medical Center, Department of Pediatrics, Houston, United States of America; ³Translational Biology and Molecular Medicine Graduate Program and Medical Scientist, Baylor College of Medicine, Houston, United States of America; ⁴National Center for Rare Diseases, Istituto Superiore di Sanità, Rome, Italy; ⁵Institute of Biochemistry and Molecular Biology II, Medical Faculty of the Heinrich-Heine, Dusseldorf, Germany; ⁶Ospedale Pediatrico Bambino Gesù, IRCCS, Division of Rheumatology, Rome, Italy; ⁷Ospedale Pediatrico Bambino Gesù, IRCCS, Department of Pediatrics, Rome, Italy; ⁸University of Rome Tor Vergata, Department of Systems Medicine, Rome, Italy; ⁹San Raffaele Telethon Institute for Gene Therapy (SR-TIGET), IRCCS San Raffaele Scientific Institute, Milan, Italy; ¹⁰Genetics and Rare Diseases Research Division, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy; ¹¹Ospedale Pediatrico Bambino Gesù, IRCCS, Department of Pediatric Hematology and Oncology, Rome, Italy; ¹²San Raffaele Scientific Institute, Pediatric Immunohematology, Milan, Italy; ¹³Vita Salute, San Raffaele University, Milan, Italy

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 dyshematopoiesis, 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*IFN γ , 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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