PRKDC mutations associated with immunodeficiency, granuloma and aire-dependent autoimmunity

Alexandre Belot1,2*, Anne-Laure Mathieu2, Estelle Veronese3, Gillian Rice4, Fanny Fouyssac5, Yves Bertrand6, Capucine Picard7, Jolan Walter8, Luigi Notarangelo9, Catharina Schuetz10, Heloise Reumaux11, Mirjam Van Der Burg12, Helen Kemp13, Isabelle Rouvet14, Christophe Malcus15, Nicole Fabien16, Yanick Crow4, Christine Menetrier-Caux3, Jean-Pierre De Villartay17, Thierry Walzer2

From 21st European Pediatric Rheumatology (PReS) Congress Belgrade, Serbia. 17-21 September 2014

Introduction
PRKDC encodes for DNA-dependent protein kinase catalytic subunit (DNA-PKcs), a kinase that forms part of a complex (DNA-PK) crucial for DNA double-strand break (DSB) repair and V(D)J recombination. In mice, DNA-PK also interacts with the transcription factor AIRE (autoimmune regulator) to promote central T cell tolerance.

Objectives
We sought to understand the causes of an inflammatory disease with granuloma and autoimmunity, associated to decreasing T and B cell counts over time diagnosed in two unrelated patients.

Methods
Genetic, molecular, and functional analyses were performed to characterize an inflammatory disease evocative of a combined immunodeficiency.

Results
We identified PRKDC mutations in both patients. These patients exhibited a defect in DNA DSB repair and V(D)J recombination. Circulating T cells had a skewed cytokine response typical of Th1 and Th2 profiles. Moreover, mutated DNA-PKcs failed to promote AIRE-dependent transcription of peripheral tissue antigens in vitro. The latter defect correlated in vivo, with the production of anti-Calcium Sensing Receptor (anti-CaSR) autoantibodies, which are usually found in AIRE-deficient patients.

Conclusion
Deficiency of DNA-PKcs, a key AIRE partner, can present as an inflammatory disease with organ-specific autoantibodies and these findings highlight the essential role of DNA-PKcs in regulating autoimmune responses and maintaining AIRE-dependent tolerance in human.

Disclosure of interest
None declared.

Authors’ details
1Pediatric Nephrology, Rheumatology and Dermatology, Hospices Civils de Lyon, France. 2U1111, INSERM, Lyon, France. 3U1052, INSERM, Lyon, France. 4Genetic Medicine, Manchester Academic Health Science Centre, University of Manchester, Manchester, UK. 5Hématologie Pédiatrique, Hôpital d’Enfants , CHU Nancy, Nancy, France. 6Institut d’hématologie et d’oncologie pédiatrique, Hospices Civils de Lyon, Lyon, France. 7Study Center for Primary Immunodeficiencies, IMAGINE, Necker, Paris, France. 8Division of Allergy/Immunology, Harvard Medical School, Boston, USA. 9Division of Immunology, Boston Children’s Hospital and Harvard Stem Cell Institute, Boston, USA. 10Department of Pediatrics and Adolescent Medicine, University Medical Center ULM, Ulm, Germany. 11Pediatric Rheumatology Unit, Jeanne de Flandre Hospital, Lille, France. 12Department of Immunology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, Netherlands. 13Department of Human Metabolism, The Medical School University of Sheffield, Sheffield, UK. 14Biotechnology, Hospices Civils de Lyon, Lyon, France. 15Immunology Department, Hospices Civils de Lyon, Lyon, France. 16Immunology, Hospices Civils de Lyon, Lyon, France. 17U1163, INSERM, Paris, France.

Published: 17 September 2014

doi:10.1186/1546-0096-12-S1-P42
Cite this article as: Belot et al.: PRKDC mutations associated with immunodeficiency, granuloma and aire-dependent autoimmunity. Pediatric Rheumatology 2014 12(Suppl 1):P42.

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