RPSAMUTATIONS IN ISOLATED CONGENITAL ASPLENIA (ICA): A RIBOSOMOPATHY UNVEILED

Barbara Bosch[1], Alexandre Bolze[1], Bertrand Boisson[1], Alexander Antipenko[1], Yuval Itan[1], Richard Copley[2], Paul Sackstein[1], Usha Kini[3] , Andrew Pollard[4], Dinakantha Kumararatne[5], Malgorzata Pac[6], Horst Von Bernuth[7], Licia Selleri[8], Anne Puel[9,10], Capucine Picard[11] , Ni zar Mahlaoui [11] and Jean-Laurent Casanova[1,11,12,13],

[1]St. Giles Laboratory of Human Genetics of Infectious Diseases, The Rockefeller University, New York, NY,
[2]Wellcome Trust Centre for Human Genetics, Oxford, United Kingdom,
[3]Department of Clinical Genetics, Oxford University Hospitals NHS Trust, Oxford, United Kingdom,
[4]Oxford Vaccine Group, University of Oxford, Oxford, United Kingdom,
[5]Department of Clinical Immunology, Addenbrookes Hospital, Cambridge, United Kingdom,
[6]Clinical Immunology, Institute Pomnik - Centrum Zdrowia Dziecka, Warsaw, Poland,
[7]Charité - Universitätsmedizin Berlin, Berlin, Germany,
[8]UCSF school of dentistry, San Francisco, CA,
[9]St Giles Laboratory of Human Genetics of Infectious Diseases, The Rockefeller University, New York, NY,
[10]Laboratory of Human Genetics of Infectious Diseases, Necker Medical School. INSERM U980 and University Paris Descartes, Paris, France,
[11]Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM U1163, Necker Hospital for Sick Children, INSERM, Paris, France,
[12]Paris Descartes University, Imagine Institute, Paris, France,
[13]Howard Hughes Medical Institute

ICA (MIM271400) is characterized by the absence of spleen at birth without any other developmental defect. In 2013, we showed that heterozygous coding mutations in ribosomal protein SA (RPSA) underlie autosomal dominant ICA in 8 kindreds. This was surprising as mutations in 13 other human ribosomal proteins, such as RPS19, cause Diamond Blackfan Anemia. None of these ribosomopathy patients have been reported with asplenia.
Since then, our cohort has doubled in size. Twenty out of the 46 ICA kindreds now included were found to carry a RPSA mutation. We identified mutations in the coding and noncoding region of the gene.
We performed a thorough clinical evaluation of patients with ICA and assessed penetrance at the splenic and infectious level. Strikingly, 6 different RPSA mutations were incompletely penetrant at both levels. Asplenic adults frequently develop auto-immunity.
We additionally carried out molecular experiments to differentiate the functional and structural impact of the observed coding and non-coding mutations on RPSA. We will present data showing human ribosomal mutations can be hypomorphic in ICA, as has been previously described for SBDS in Schwachman-Diamond Syndrome.
RPSA mutations thus consistently underlie around half of ICA cases. Of note, ICA can have incomplete penetrance and go unnoticed until adulthood.