Poster Presentations

Gastroenterology: Enteropathy (other than Coeliac Disease)

PO-G-0091

MALT -1 LOSS OF FUNCTION MUTATION: A NEW CAUSE OF EARLY ONSET AUTO-IMMUNE ENTEROPATHY

Fabienne Charbit-Henrion [1 2,*] Anja Koren Jeverica [3] Bernadette Begue [1] Patrick Nitschke [4] Christine Bole [5] Matjaz Homan [3] Tadej Avcin [3] Nadine Cerf-Bensussan [1] Frank Ruemmele [1 2]
[1]INSERM U1163 - IMAGINE Institute, [2]Hôpital Necker-Enfants Malades, Paris, France, [3]University Children's Hospital, Ljubljana, Slovenia, [4]Bioinformatics platform Université Paris-Descartes-Paris Sorbonne Centre and Institut Imagine, [5]Genomic platform, Institut Imagine, Paris, France

Objectives and Study: Whole exome sequencing (WES) was applied to identify the molecular defect causing severe auto immune enteropathy (AIE) with combined immunodeficiency in two siblings from consaguineous parents.
Methods: Mutation was identified by WES and confirmed by Sanger sequencing. mRNA expression was studied by RT-PCR and protein expression was analysed by western blot. Activation of NFkB was analysed in PHA (phytohemagglutinin)-T cell lines by flow cytometry after stimulation by Phorbol 12-myristate 13-acetate (PMA) and ionomycin.
Results: The girl (6 year-old) and her brother (4 year-old) displayed severe dermatitis and failure to thrive since birth. Progressively, they developed AIE with severe villous atrophy and an important lymphocytic infiltrate, without evidence of auto antibodies (AIE 75kD and anti-enterocytes). They displayed a wide spectrum of infections, including life-threatening pulmonary infections with adenovirus, Pneumocystis jirovecii and EBV. Immunological parameters were high IgE, low IgM, normal B cell counts but variable antibody titers to vaccination, elevated counts of activated/memory T lymphocytes, but reduced frequencies of Th1, Th2, Th17 and Treg.
WES identified a single autosomal recessive nucleotide variation (c.550G>T) in exon 4 of MALT1 predicting a deleterious p.Asp184Tyr amino acid change.
In agreement with the indispensable role of MALT-1 in the NFkB cascade downstream the T cell receptor (1), induction of interleukin-2 and degradation of IκBα in response to PMA and ionomycin were drastically impaired in PHA-T cell lines from the two siblings carrying the MALT1 D184Y mutation compared to cell lines derived from an unrelated healthy control and from both parents.
MALT1 mRNA expression was comparable in PHA-T cell lines from the two patients, their parents and an unrelated healthy control, but the protein was undetectable in the two affected children. These results indicate that the mutant MALT1 D184Y is most probably unstable and rapidly degraded.
Conclusion: We describe the third (2, 3) loss-of-function mutation in the MALT1 gene as a cause of combined immunodeficiency and AIE.
MALT1 should be now considered as a candidate gene in AIE without auto-antibodies, especially in the context of immunodeficiency and multiple infections.
References: 1. Turvey SE, et al. The Journal of allergy and clinical immunology. 2014;134(2):276-84.
2. Jabara HH, et al. The Journal of allergy and clinical immunology. 2013;132(1):151-8.
3. McKinnon ML, et al. The Journal of allergy and clinical immunology. 2014;133(5):1458-62, 62 e1-7.

Disclosure of Interest: None Declared

Gastroenterology: Enteropathy (other than Coeliac Disease)

PO-G-0092

A DEDICATED NETWORK FOR CONGENITAL DIARRHEAL DISORDERS: REPORT FROM LAST 8 YEARS OF ACTIVITY

V. Pezzella [1,*] A. Elce [2] G. Terrin [3] G. Castaldo [3] R. Berni Canani [1]
[1]University of Naples "Federico II", [2]CEINGE Biotecnologie Avanzate, [3]University of Rome "La Sapienza", Naples, Italy

Objectives and Study: Congenital diarrheal disorders (CDD, [OMIM] 251850) are a group of rare heterogeneous chronic enteropathies with clinical onset in the first hours or days of life. Dedicated network and website (http://www.congenitaldiarrhealdisorders.net) were created at University of Naples "Federico II", combining pediatric gastroenterology and clinical genetics expertise, in order to provide a rapid access to molecular analysis and other diagnostic and therapeutic procedures.
Methods: CDD patients database was investigated regarding the network activity from January 2007 to November 2014.
Results: During the study period DNA samples from patients suspected of CDD (n=95), and from their relatives (n=54) were analyzed. The molecular analysis showed mutations causative of disease in 66 patients: congenital chloride diarrhea (SLC26A3, n=44), congenital sucrase-isomaltase deficiency (SI, n=3), glucose-galactose malabsorption (SLC5A1, n=8), microvillous inclusion disease (MYO5B, n=2), congenital tufting enteropathy (EpCAM, n=2) and Shwachman-Diamond syndrome (SBDS, n=7).
Conclusion: Recent evidence in the understanding of genetics and pathophysiology of CDD are leading to significant advances in the diagnostic approach to these conditions. Molecular analysis is changing the scenario in CDD diagnosis and it is allowing to a reduction in the use of invasive and expensive diagnostic procedures. The activity of a dedicated network website made CDD molecular diagnosis readily available.

Disclosure of Interest: V. Pezzella Conflict with: Agenzia Italiana del Farmaco (AIFA), A. Elce Conflict with: Agenzia Italiana del Farmaco (AIFA), G. Terrin Conflict with: Agenzia Italiana del Farmaco (AIFA), G. Castaldo Conflict with: Agenzia Italiana del Farmaco (AIFA), R. Berni Canani Conflict with: Agenzia Italiana del Farmaco (AIFA)

Gastroenterology: Enteropathy (other than Coeliac Disease)

PO-G-0093

FUNCTIONAL ANALYSIS OF ATYPICAL MICROVILLUS INCLUSION DISEASE PATIENTS

Caroline Wiegerinck [1,*] Anke van Vugt [2] Kerstin Schneeberger [2] Hankje Escher [3] Rüdiger Adam [4] Roderick Houwen [2] Edward Nieuwenhuis [2] Sabine Middendorp [2]
[1]Pediatric gastroenterology, [2]Wilhelmina Childrens Hospital, Utrecht, [3]Sofia Childrens Hospital, Rotterdam, Netherlands, [4]University Medical Center Mannheim, Mannheim, Germany

Objectives and Study: Microvillus inclusion disease (MVID) is a rare congenital enteropathy that causes severe diarrhea resulting in dehydration, metabolic acidosis and the need for parenteral nutrition for survival. Recently, we identified that mutations in syntaxin 3 can cause atypical MVID.[1] These patients also have enterocytic subapical accumulation of vesicles, partial microvillus atrophy and microvillus inclusion bodies, however they are different from classical patients because they can endure partial enteral feeding and show basolateral inclusions. It is still unknown to what extend cell polarity and nutrient uptake is affected in these atypical patients, we are currently addressing these questions by use of an in vitro organoid model.
Methods: We established intestinal organoids from two atypical MVID patients with mutations in syntaxin 3. By confocal microscopy we are assessing apical and basal polarity. Furthermore, we study the nutrient-uptake in a 2D-monolayer model with an accessible apical and basolateral side to measure sucrose uptake in these patients.
Results: Preliminary data show that organoids can be grown in 2D monolayers and some apical proteins are mislocalized, while others are not.
Conclusion: Mutations in syntaxin 3 in MVID patients cause partial mislocalization of apical proteins.
References: 1. Wiegerinck, C.L., Janecke, A.R., Schneeberger, K., Vogel, G.F., van Haaften-Visser, D.Y. et al. **Loss of syntaxin 3 causes variant microvillus inclusion disease.** *Gastroenterology*. 2014; 147: 65–68

Disclosure of Interest: None Declared