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# Two markers related to the alteration of the epithelial permeability in irritable bowel syndrome patients discovered

- **A study led by researchers of the University Hospital Heidelberg (Germany) and the Vall d'Hebron Institute of Research (Barcelona) identifies two microRNAs that regulate the expression of tight junction proteins, located in the jejunum, altered in patients with irritable bowel syndrome (IBS).**
- **The study outcome has the potential to facilitate biomarker development for alterations of proteins relevant to gut permeability (leaky gut) and so, to enable the diagnosis of IBS and other systemic diseases.**

**Heidelberg/Barcelona, January 25th.** Researchers of the Department of Human Molecular Genetics at the University Hospital in Heidelberg and the group of Physiology and Pathophysiology of the Digestive Tract of Vall d'Hebron Institute of Research in Barcelona have discovered novel molecular mechanisms that control the expression of crucial proteins relevant for the maintaining of the integrity of the intestinal epithelium. This finding will allow the validation of these markers for the diagnosis of IBS and other systemic diseases associated with intestinal permeability, such as diabetes or cirrhosis. The study has just been published in *Gut* and was led by Dr. Beate Niesler (Heidelberg) and Dr. Javier Santos and Dr. María Vicario (Barcelona).
The study shows how the microRNAs-16 and -125b modulate the proteins Claudin-2 and Cingulin in a different way in the intestine of patients compared to healthy controls. The function of these proteins, which are molecules of intercellular junctions, is to maintain an optimal barrier between the exterior and the interior, controlling thus the epithelial permeability and avoiding that harmful substances can cross the gut barrier. In the present study, the interdisciplinary team focused on the mechanisms that trigger the alteration of the expression of these proteins.
To perform the analysis, the team compared the biopsies of the jejunum of 43 IBS patients with the biopsies of 24 healthy people recruited at the Vall d'Hebron University Hospital in Spain. For 10 days, all subjects completed a daily questionnaire where they indicated and measured aspects such as abdominal pain and frequency and number and consistence of the depositions.
**"We checked whether or not the expression of these markers is altered in the small bowel of patients with diarrhea-predominant IBS, and not in healthy people"**, explains Dr. Vicario. In particular, the study is a follow up of an earlier study where these and other genes were found to be differentially expressed. **"Since tiny molecules, so called microRNAs, are involved in expression regulation of more than 60% of the protein coding genes, we aimed to find out whether we are able to nail down such micro RNAs and show that they are in fact responsible for the de-regulation of gene expression and make people prone to leaky gut"**, states Dr. Cristina Martinez a visiting scientist in Heidelberg and Dr. Beate Niesler adds: **"However, most challenging was first to make sense out of**

**the data, second to validate the data by sensitive methods since patient material is very precious and finally to prove the relevance of the miRNAs in gut barrier function regulation. We were successful to motivate colleagues from bioinformatics (EMBL Heidelberg), biostatistics (IMBI Heidelberg) and experts for gut barrier in vitro models from the Department of Infectiology, Virology (University Hospital Heidelberg) to team up and solve the case"**. Joining forces in this interdisciplinary team proved that if the microRNAs-16 and -125b were down regulated, the levels of the gut barrier proteins Claudin-2 and Cingulin were increased and increased intestinal permeability was observed. For this reason, Dr. Santos points out that **"the markers may be useful to diagnose the disorders of intestinal permeability (leaky gut) in the future, which we know is specially suffered by IBS patients".**

IBS is a highly prevalent chronic gastrointestinal disorder affecting up to 15% of the population in Europe. Economic, health and social impact is very high and increasing in developed countries. Nowadays, there are not agreed biological markers for IBS and the diagnosis is performed purely based on clinical criteria and after dismissing other diseases. Often the diagnosis is made late, on average it takes six years, and only between 20 and 40 per cent of the patients are correctly diagnosed, according to the estimations performed by the medical community. Therefore, IBS represents a huge burden to the socioeconomic and healthcare system and patient's quality of life is often severely impaired.

Consequently, the data generated by the team have a huge potential for biomarker generation. After the publication of the study, the researchers started a follow up study to validate if the markers are specific for IBS or general markers of diseases in which permeability is impaired such as diabetes, rheumatoid arthritis or cirrhosis. This research will be done with a cohort of 200 patients with IBS, celiac disease, inflammatory bowel disease and microscopic colitis, among other diseases.

## Collaborative study

This international and interdisciplinary study was led by researchers from the Department of Human Molecular Genetics in Heidelberg (Germany) and Vall d'Hebron Institute of Research (Barcelona). Dr. Cristina Martínez, who was a visiting scientist in Heidelberg, supervised by Dr. Niesler, performed the genetic and molecular validation of the results. In addition, the interdisciplinary team was complemented by colleagues from the EMBL, IMBI and Institute of Virology. Moreover, the research is part of the European consortium GENIEUR (the Genes in Irritable Bowel Syndrome Research Network, www.genieur.eu), funded within the COST program of the European Commission, and endorsed by the European Society of Neurogastroenterology and Motility (ESNM).

## Bibliographic reference

Martínez C, Rodiño-Janeiro BK, Lobo B, et al. Gut Published Online First: 12 January 2017 doi:10.1136/gutjnl-2016-311477

More information is available on the Web: www.GENIEUR.eu and www.ag-niesler.uni-hd.de

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