PRESS RELEASE

CIC bioGUNE researchers discover a relationship between Townes-Brocks Syndrome and primary cilia, cellular organelles that function as communication antennae

The findings, published in The American Journal of Human Genetics, support the hypothesis that aberrations in primary cilia function are contributing factors to the characteristics found in people affected by TBS

These findings represent a paradigm change in understanding this rare disease and open up new possibilities for treatment

Townes-Brocks Syndrome is a rare disease that occurs in one of every 350,000 live births. Affected individuals show digit, ear and kidney malformations, amongst other symptoms.

(Bilbao, 15 February 2018). Research led by Dr. Rosa Barrio from CIC bioGUNE has discovered a relationship between Townes-Brocks Syndrome (TBS) and cellular antennae, or primary cilia, thereby breaking new ground in the search for drugs to treat individuals affected by this disease.

The findings, published by The American Journal of Human Genetics, a highly prestigious journal established by the American Society of Human Genetics, elaborate on the possible molecular mechanism that underlies the symptoms of TBS, a rare disease affecting one in every 350,000 live births. Individuals affected exhibit a range of digit, ear and kidney malformations. TBS is dominantly inherited and caused by mutations in the *SALL1* gene.

Dr. Rosa Barrio, the CIC bioGUNE researcher who has led the study, explains: "Our initial observation showed that the symptoms of TBS individuals are similar to those of a family of diseases known collectively as ciliopathies, the common denominator of which is the presence of altered primary cilia. Primary cilia are small structures found in most cells which function as receiving antennae for signalling between the cells and the rest of the organism. If cilia function is defective, the signalling is altered and problems arise in the formation of the organism during embryonic development. Our team has shown that these small antennae, or cilia, are more abundant and longer in cells from individuals with Townes-Brocks Syndrome".

Many patients affected by TBS suffer serious problems, particularly progressive renal failure and hearing loss, and often require dialysis and kidney transplants. Now that the symptoms of the disease have been associated with primary cilia, new therapeutic approaches modifying cilia length, frequency, or function may be explored, a possibility

which was overlooked prior to this study. “Our findings support the hypothesis that aberrations in primary cilia function and cellular signalling are contributing factors to the characteristics found in individuals with Townes-Brocks Syndrome. This represents a paradigm change in understanding this rare disease and opens up new possibilities for treatment”, Dr. Barrio adds.

Over four years of research

The study, conducted by a multidisciplinary team of doctors and researchers from the USA (Memorial Sloan Kettering Cancer Center in New York and Saint Louis University School of Medicine in St. Louis, Missouri), Denmark (Novo Nordisk Foundation), UK (University of Oxford, Great Ormond Street Hospital in London and Ipswich Hospital NHS Trust in Ipswich) and the University of the Basque Country (Department of Genetics, Physical Anthropology and Animal Physiology in Leioa), started four years ago and has been led by CIC bioGUNE. The team has been funded by the Basque Government, the Spanish Ministry of Economy, Industry and Competitiveness and the European Union.

During this study, tissue samples from patients with TBS were obtained and cellular and molecular tools developed. Cultured cells were derived from tissue taken from TBS individuals and from a non-TBS control group, important research tools that can be used in future studies. As Dr. Barrio further emphasizes: “Using control cells, we have constructed lines which express mutant proteins found in TBS individuals; these cells develop the same characteristics as seen in TBS patient-derived cells. Furthermore, we have used the new CRISPR-Cas9 system to create a cellular model of TBS from control cells and have examined cells from a mouse model that reproduces symptoms of TBS; in both cases, cells exhibit longer, more frequent primary cilia. Finally, we applied the innovative BioID technique for proximity proteomics to identify proteins which interact with mutant SALL1 to identify potential molecular targets underlying the cilia defect”. The diagnosis and search of samples in a rare disease are challenging. The authors hope that this publication will help to rise awareness of this disease among patients, relatives and medical professionals.

About CIC bioGUNE

The Centre for Cooperative Research in Biosciences (CIC bioGUNE), located in the Bizkaia Technology Park, is a biomedical research organisation conducting cutting-edge research at the interface between structural, molecular and cell biology, with a particular focus on generating knowledge on the molecular bases of disease, for use in the development of new diagnostic methods and advanced therapies. CIC bioGUNE has been accredited as a “Severo Ochoa Centre of Excellence”, the highest level of recognition for centres of excellence in Spain.