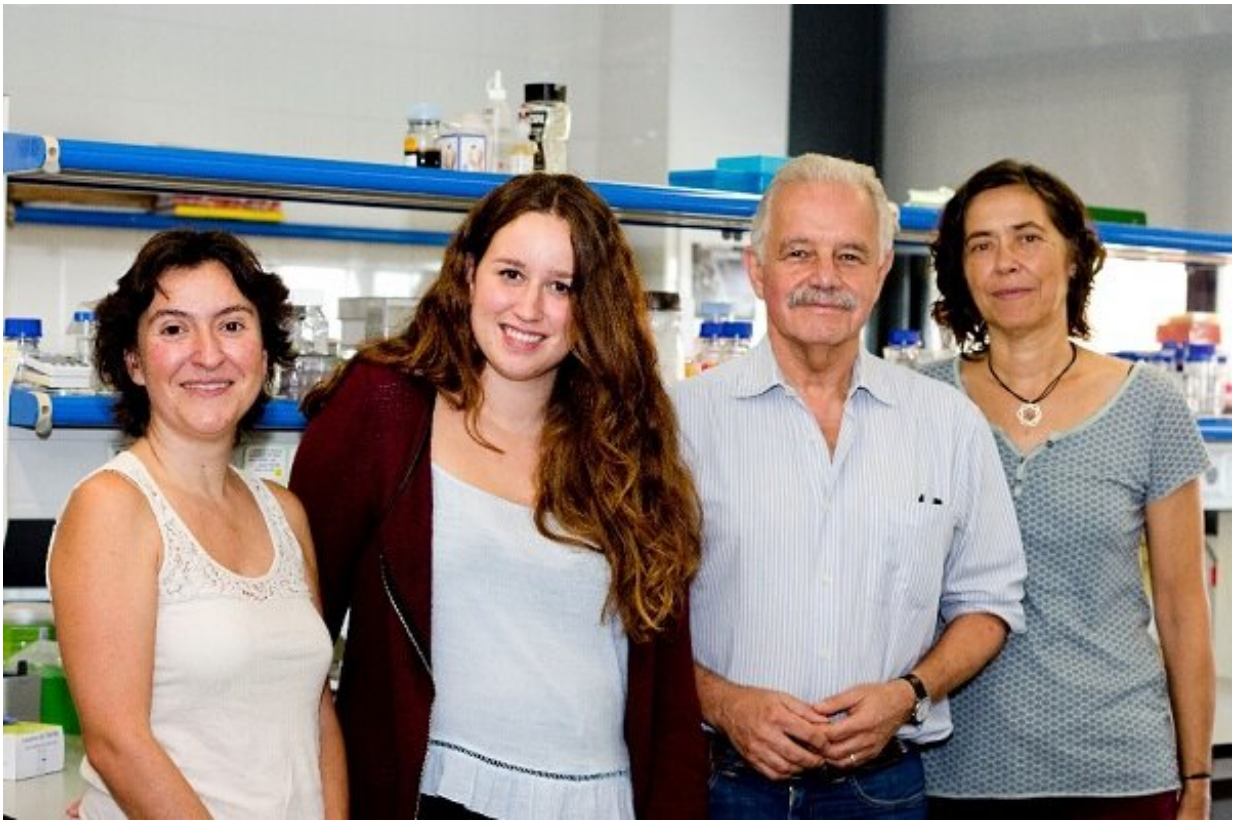
New advances to improve the genetic diagnosis of Opitz C syndrome

April 5 2019



The experts Roser Urreizti, Laura Castilla-Vallmanya, Daniel Grinberg and Susana Balcells, researchers from the Human Molecular Genetics group of the UB and the IBUB, the CIBERER and the Research Institute Sant Joan de Déu. Credit: UNIVERSITY OF BARCELONA

Opitz C syndrome (OCS), an ultra-rare disease that causes serious

physical and intellectual disabilities, has an heterogeneous genetic base that makes its medical diagnostic and therapeutic intervention difficult, according to a new study by professors Daniel Grinberg, Susanna Balcells and Roser Urreizti, from the Group on Human Molecular Genetics of the of the Faculty of Biology of the University of Barcelona and the Rare Diseases Networking Biomedical Research Centre (CIBERER).

The new study, published in the journal *Expert Opinion on Orphan Drugs*, concludes this severe and extremely rare disease could be considered a "private syndrome" for each patient.

Described in 1969 by geneticist John M. Opitz, this ultra-rare pathology, with only a few diagnosed cases worldwide, shows a great clinical variability in different levels of severity (trigonocephaly, intellectual disability, psychomotor retardation, among others). Therefore, clinical symptomatology of Opitz C syndrome can overlap other similar minority pathologies (Kleefstra, Kabuki, Bohring-Opitz syndromes, etc.).

However, despite sharing several clinical manifestations, "this disease does not show a genetic base shared by the affected people, and its hereditary transmission model is still unknown," note the authors, also members of the Institute of Biomedicine of the University of Barcelona (IBUB) and the Research Institute Sant Joan de Déu (IRSJD).

Massive sequencing technologies for a precise genetic diagnose

Since 2007, several genes have been related to this pathology, which is hard to diagnose due its wide clinical pattern (for instance, ASXL1, CD96, ASXL3 and MAGEL2). The new study broadens the knowledge of the genetic basis of this pathology, which so far does not have any

treatment, prenatal diagnosis or genetic counseling.

"In these ultra-rare diseases, the application of new massive sequencing technologies is a determining factor regarding the molecular diagnosis for patients and therefore, to progress in the exploration of therapeutic applications," the authors write.

Opitz C: when the early diagnosis is mistaken

In some cases, affected patients can receive an incomplete and overly general diagnosis that makes any therapeutic intervention difficult. This is shown by a recent research study in which the Group on Human Molecular Genetics participated, finding two mutations in the PIGT gen in a patient who had initially been diagnosed Opitz C syndrome.

This study could contribute to a precise molecular diagnosis of the causes of the real pathology. The study, published in the journal *Medicine*, was carried out in collaboration with experts from the Center for Clinical Genetics and the University of New South Wales (Australia), among other institutions.

From Malta to Yemen: genes, families and ultra-rare diseases

The international scientific collaboration has contributed to the genetic diagnosis of other cases of severe neuro-developmental disorders that had been considered to be Opitz C syndrome. In particular, the UB team has identified new genetic mutations associated with DPH1 syndrome, a minority disease with a low prevalence in the population, in patients of two different families from Malta and Yemen.

The study, published in the journal *European Journal of Human*

Genetics, analyzed the effect of the new mutations in the DPH1 gene that were identified in these patients and the ones that were previously mentioned in the scientific bibliography. Through the application of a biochemical trial and a computational model of the DPH1 protein and its variants, they could evaluate the enzymatic ability of the natural and mutated configurations of this protein related to the embryogenesis and organogenesis processes.

In this scenario of scientific challenges to improve molecular diagnosis, "the possibility to conduct family analysis with whole-exome sequencing (WES), together with international collaboration, are essential to promote the knowledge of rare neuro-developmental diseases," note the experts of the Group on Human Molecular Genetics (UB-IBUB-CIBERER-IRSJD).

More information: Roser Urreizti et al, C syndrome - what do we know and what could the future hold?, *Expert Opinion on Orphan Drugs* (2019). DOI: 10.1080/21678707.2019.1589448

Provided by University of Barcelona