MedicalXpress

Mutations responsible for cleft palate and related birth defects identified

January 12 2017

Researchers located a novel gene mutation causing cleft lip and cleft palate defects, which slows the turnover of hyaluronan, an important component of the hard palate. Martina Muggenthaler working with Prof Andrew Crosby, Dr Emma Baple and colleagues at the University of Exeter (United Kingdom), and Biswajit Chowdhury working with Prof Barb Triggs-Raine of the University of Manitoba (Canada), report these findings January 12th, 2017 in *PLOS Genetics*.

Cleft lip and cleft palate (CLP) are among the most common birth defects, but the genetics underlying these conditions are poorly understood. By studying individuals with syndromic CLP from Amish and Northern Saudi Arabian families, the researchers identified the responsible mutations. Syndromic CLP is accompanied by other congenital defects such as hearing and vision problems, extra toes or fingers or heart anomalies such as cor triatriatum sinister, where the heart develops a third atrial chamber on the left side. The collaborative team mapped the condition to mutations in the HYAL2 gene, which encodes an enzyme that breaks down hyaluronan, a carbohydrate polymer found widely in connective tissue, and in the hard palate. Enzyme assays showed that the mutations reduced HYAL2 protein levels in the tissues, which likely inhibited hyaluronan turnover, ultimately impacting development of the palate and other body parts.

"This finding is important as it highlights a new molecular cause for orofacial clefting which is likely to be relevant to other as yet unidentified genetic causes of the condition", said Professor Crosby. "It

also provides the first molecular cause of the heart defect cor tritriatrium sinister", added Dr Baple.

Further experiments using mice that lack HYAL2 showed that the mice develop defects similar to human syndromic CLP, including cor triatriatum sinister.

Furthermore, the findings illustrate the fundamental importance of HYAL2 and hyaluronan turnover for normal human and mouse development. A better understanding of the factors contributing to these anomalies may contribute to the development of new treatments for these common birth defects, such as hymecromone, a drug approved in many parts of the world that blocks hyaluronan synthesis.

More information: Muggenthaler MMA, Chowdhury B, Hasan SN, Cross HE, Mark B, Harlalka GV, et al. (2016) Mutations in HYAL2, Encoding Hyaluronidase 2, Cause a Syndrome of Orofacial Clefting and Cor Triatriatum Sinister in Humans and Mice. *PLoS Genet* 12(12): e1006470. DOI: 10.1371/journal.pgen.1006470