Researchers discover cause of rare congenital lung malformations

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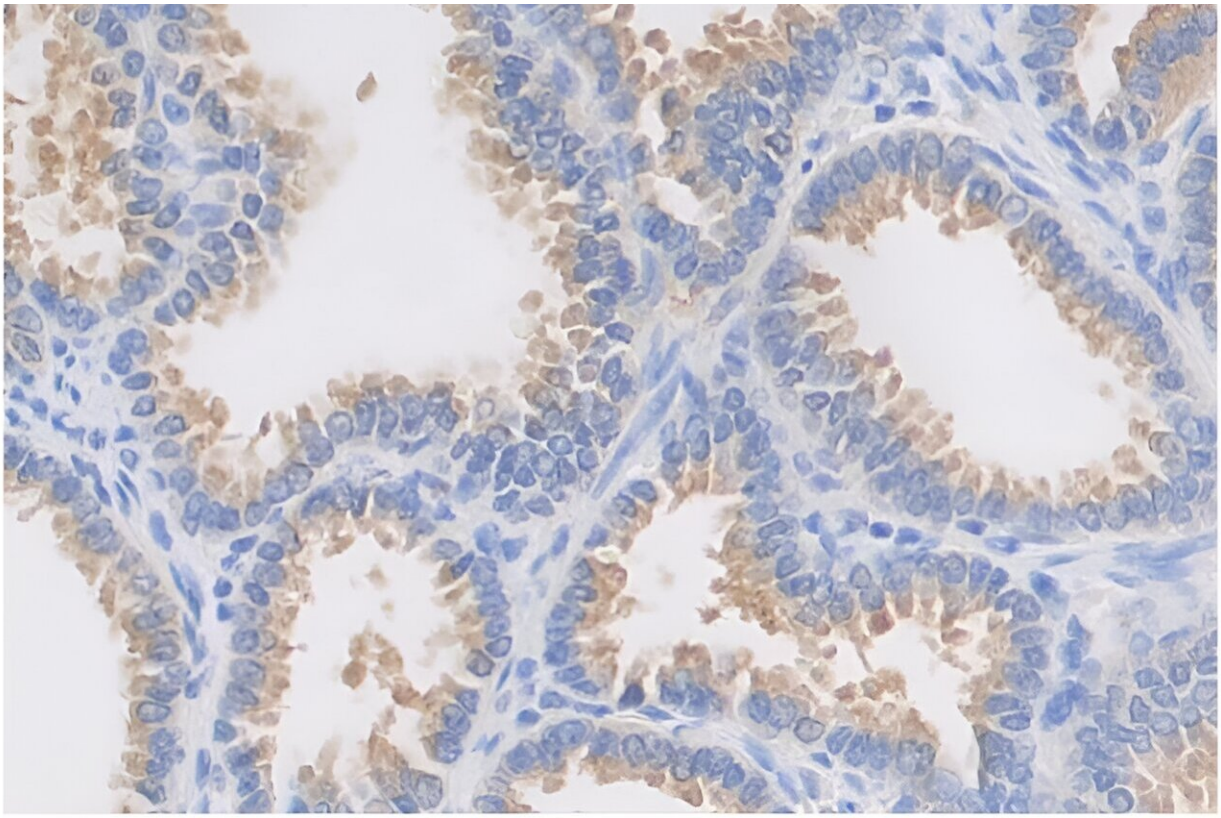

Somatic mosaic BRAF mutation in congenital pulmonary airway malformation type 3. (200 x, immunohistochemistry BRAF p.V600E specific antibody, abcam 228461). The lining epithelium of the congenital pulmonary airway malformation type 3 shows a cuboidal to columnar morphology and a diffuse expression of mutant BRAF protein mostly in the apical cytoplasm. Credit: *American Journal of Respiratory and Critical Care Medicine* (2024). DOI: 10.1164/rccm.202311-2163LE

Most rare diseases are congenital—including CPAM (congenital pulmonary airway malformations). These are airway malformations of the lungs that can lead to severe breathing problems in some affected newborns and can be associated with an increased risk of lung cancer. Researchers at Hannover Medical School (MHH) and Magdeburg University Hospital (UMMD) have now succeeded in identifying the genetic causes of the disease.

Although CPAM is rare, it is one of the most common congenital lung malformations. There are different types of the disease, which develops during the embryonic phase in the womb. In the most common form, the lung tissue is riddled with large cysts, the growth of which can have a negative impact on the newborn's blood circulation and breathing. When this occurs, the affected children must be operated on at an early age.

In the search for the cause of CPAM, the research team pursued the following hypothesis: Variants in cancer-associated genes of the so-called RAS-MAPK signaling pathway, which occur in the lung epithelium during prenatal lung development, are responsible for the lung malformations. These variants disrupt normal lung development and lead to maldevelopment in affected lung sections, resulting in a malformation of the lung.

Hypothesis confirmed: Jonas Windrich (left) and Professor Kratz now know more about the cause of congenital lung malformations. Credit: Karin Kaiser / MHH

In their study, the scientists examined CPAM tissue samples from a total of 43 children histologically and genetically. All of these children had undergone surgery for CPAM at the Department of Pediatric Surgery at the MHH over the past 20 years. Surgery for lung malformations is one of the clinic's core competencies.

The result of the genetic analysis showed that variants in genes of the RAS-MAPK signaling pathway were detected in the tissue samples of almost 60% of the young patients—confirming the research team's hypothesis. The KRAS gene in particular was affected by variants. The

children with a KRAS variant had a statistically more severe course of the disease than children without it.

The study has been published in the *American Journal of Respiratory and Critical Care Medicine*. "The results are clinically important, they contribute to a better diagnosis of CPAM and may also improve the treatment of the disease," explains Professor Dr. Christian Kratz, Director of the Department of Pediatric Hematology and Oncology and initiator of the study. "The publication was only possible thanks to the fantastic collaboration between the many people involved from different institutes and clinics," he emphasizes.

Dr. Denny Schanze, Head of Laboratory at the Institute of Human Genetics Magdeburg, adds, "The use of modern ultra-deep NGS sequencing methods was essential for the successful elucidation of the genetic cause of the disease."

The first author of the study is Jonas Windrich, a 10th-semester medical student. The work was carried out as part of his doctorate. "I learned a lot about scientific work from the project and I definitely want to combine my future work as a doctor with research," says Windrich.

More information: Jonas Windrich et al, RAS-MAPK Pathway Mutations in Congenital Pulmonary Airway Malformations, *American Journal of Respiratory and Critical Care Medicine* (2024). DOI: 10.1164/rccm.202311-2163LE

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