

Variants in FGF10 cause isolated neonatal lung developmental disorder

Katharina Schuetz¹, Axel Schmidt², Nicolaus Schwerk¹, Diane Renz³, Benedicte Gerard⁴, Elise Schaefer⁴, Maria Cristina Antal⁵, Sophia Peters², Matthias Griesse⁶, Christina Katharina Rapp⁶, Hartmut Engels², Kirsten Cremer², Anke Katharina Bergmann³, Gunnar Schmidt³, Bernd Auber³, Jan C. Kamp⁷, Florian Laenger⁸, and Sandra von Hardenberg³

¹Medizinische Hochschule Hannover Klinik für Padiatrische Pneumologie Allergologie und Neonatologie

²Universitätsklinikum Bonn Institut für Humangenetik

³Hannover Medical School

⁴Hopital Universitaire Robert-Debre Unite fonctionnelle de genetique clinique

⁵Les Hopitaux Universitaires de Strasbourg Hopital de Hautepierre

⁶Dr von Haunersches Kinderspital Kinderklinik und Kinderpoliklinik der Ludwig Maximilian Universität München

⁷Deutsches Zentrum für Lungenforschung e V

⁸Medizinische Hochschule Hannover Institut für Pathologie

May 23, 2023

Abstract

Fibroblast growth factor 10 (FGF10) is a signaling molecule with a well-established role for lung branching morphogenesis. Rare heterozygous, deleterious variants in the *FGF10* gene are known causes of the lacrimo-auriculo-dento-digital (LADD) syndrome as well as aplasia of lacrimal and salivary glands (ALSG). Previous studies indicate that pathogenic variants in *FGF10* can cause lethal human developmental disorders of the lung, but reports on diffuse lung disease caused by pathogenic variants in the *FGF10* gene are lacking. We describe four children with postnatal onset of severe diffuse lung disease and heterozygous variants in *FGF10*, each detected by whole exome or whole genome sequencing. All children presented with postnatal respiratory failure. Two children died within the first 2 days of life, one patient died at age of 12 years and one patient is alive at age of six years, but still symptomatic. One patient presented signs of severe dental caries suggestive for ALSG or LADD-syndrome. Histopathological analysis of lung biopsies from the two children with early postpartum demise revealed diffuse developmental disorder representing acinar dysplasia. Sequential biopsies of the child with survival until the age of 12 years revealed alveolar simplification and progressive interstitial fibrosis. Our report extends the phenotype of *FGF10*-related disorders to diffuse developmental disorders of the lung and early onset lung fibrosis. Therefore, *FGF10*-related disorder should be considered even without previously described syndromic stigmata in children with postnatal respiratory distress, not only when leading to death in the neonatal period but also in case of persistent respiratory complaints.

Hosted file

FGF10_final main body.docx available at <https://authorea.com/users/424277/articles/644892-variants-in-fgf10-cause-isolated-neonatal-lung-developmental-disorder>