Unraveling the role of genomic imprinting at 16q24.1 in pathogenetics of alveolar capillary dysplasia with misalignment of pulmonary veins and maternal uniparental disomy 16.

Paweł Stankiewicz,[1] Avinash V Dharmadhikari,[1] Jenny J Sun,[2] Brandi Carofino[1], Kadir Caner Akdemir,[3] Claire Langston,[4] Edwina Popek,[4] Monica J Justice,[5] Mary E Dickinson,[6] Russell Ray,[2] Partha Sen,[7,8] Przemyslaw Szafranski[1]

[1]Department of Molecular and Human Genetics; [2]Department of Neuroscience, Baylor College of Medicine, Houston, Texas, USA; [3]Genomic Medicine Department, MD Anderson Cancer Center, Houston, Texas, USA; [4]Department of Pathology and Immunology, Baylor College of Medicine, Houston, Texas, USA; [5]Genetics & Genome Biology Program, SickKids, Toronto, Canada; [6]Department of Molecular Physiology & Biophysics; [7]Department of Pediatrics, Baylor College of Medicine, Houston, Texas, USA; [8]Department of Pediatrics, Northwestern University, Chicago, Illinois, USA

Alveolar capillary dysplasia with misalignment of pulmonary veins (ACDMPV) is a rare lethal developmental lung disorder caused by heterozygous SNVs or deletion CNVs of *FOXF1*. We have accumulated the largest collection of ACDMPV samples in the world (N=141 families). In ~25% of children with ACDMPV, we identified overlapping deletion CNVs, involving fetal lung-expressed long noncoding RNA genes *LINC01081* and *LINC01082* that enabled to define a tissue-specific enhancer region mapping ~ 270 kb upstream to *FOXF1*. We now describe novel deletion CNVs at the *FOXF1* locus in 14 unrelated ACDMPV patients. In aggregate, all 31 deletion CNVs, for which parental origin was determined, arose *de novo* with 30 of them occurring on the maternally inherited chromosome 16, strongly implicating genomic imprinting of the *FOXF1* locus in human lungs. Surprisingly, we also identified four ACDMPV families with pathogenic SNVs in *FOXF1* that arose on paternal chromosome 16. Interestingly, additional clinical features observed in ACDMPV (heart defects, pulmonary hypoplasia, gut malrotation, hydronephrosis, and single umbilical artery) have also been reported in patients with maternal UPD(16). In contrast, relatively normal phenotype was reported in a few patients with paternal UPD(16). Most recently, duplication CNVs involving *FOXF1* were associated with pyloric stenosis, mesenterium commune, and aplasia of the appendix. Modeling *Foxf1* overexpression in mice by knocking-in a Cre-inducible *Foxf1* allele at the *ROSA26* locus and activating it using the vascular *Tie2-cre* resulted in embryonic and perinatal lethality. MicroCT, and plethysmography analyses revealed hypoplastic lungs, abnormal breathing, gastrointestinal and vascular abnormalities in these mice. We propose that genomic imprinting at 16q24.1 plays an important role in long-range regulation of *FOXF1* expression and variable ACDMPV manifestation and may be also responsible for the key phenotypic features of maternal UPD(16).