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.

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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).