### Introduction

Severe bronchopulmonary dysplasia (sBPD) after preterm birth is associated with high late mortality and pulmonary hypertension (PH). Impaired alveolar and vascular growth with hypertensive remodeling are hallmarks of sBPD, which are features that overlap with the lethal developmental disorders, alveolar capillary dysplasia with misalignment of pulmonary veins (ACDMPV) that has been linked to loss of FOXF1 expression. As with sBPD, ACDMPV is caused by severe respiratory failure and PH, and causes death despite aggressive cardiopulmonary therapies. Past studies of ACDMPV have shown that the “MPV” are prominent bronchial veins that reflect recruitment of intrapulmonary bronchopulmonary anastomoses (IBAs), which connect the pulmonary vasculature with intrapulmonary vessels. The presence of prominent IBAs have been identified in fatal sBPD, but the potential role of impaired FOXF1 signaling in sBPD is unknown.

### Results

![Figure 1](image1.png)

**Figure 1.** Lung histopathology. A: Low power views show underdeveloped lung parenchyma with many enlarged and simplified alveoli and thick interstitium. B: Dilated alveoli are associated with double capillary layers (arrows). C: Markedly dilated and congested thin wall vessels are present within the bronchoarterial bundles (Br: bronchiole, PA: pulmonary arteries resembling those of misaligned pulmonary veins seen in alveolar capillary dysplasia (arrows). D: Pulmonary vessels connect with the bronchial microvessels consistent with bronchopulmonary shunt vessel (arrow). E: Markedly dilated peribronchial microvessel resembling those of type 1 plexiform lesion (ref: Westoo et al, Am J Physiol Lung Cell Mol Physiol. 2021). E: Extensive lymphangiectasia (asterixis) with visible lymphatic valves (arrows).

![Figure 2](image2.png)

**Figure 2.** A decrease in the expression of FOXF1 (A) and TMEM100 (B) in the proband similar to that observed in ACDMPV patients due to FOXF1 haploinsufficiency (One-way ANOVA with Tukey Test: p < 0.01). ACDMPV 179.3: paternal deletion of the FOXF1 enhancer. Error bars represent standard deviation.

### Discussion

This case of an extremely preterm infant who died with sBPD and refractory PH had striking histologic features compatible with the diagnosis of sBPD or ACDMPV but had negative genetic findings for FOXF1. These findings suggest that impaired FOXF1 signaling in sBPD may contribute to the severity of disease in the absence of a genetic diagnosis of ACDMPV.

### References