Lethal lung developmental disorders (LLDDs) are rare diseases presenting with severe respiratory failure which is refractory to therapy. They include alveolar capillary dysplasia with misalignment of pulmonary veins (ACDMPV), acinar dysplasia (AcDys), congenital alveolar dysplasia (CAD), and primary pulmonary hypoplasia (PH). The vast majority of newborns with LLDD die within the first hours or days of life. Characterization of LLDDs has been hampered by their rarity, similarities in the clinical and/or histopathological features, and inconsistent use of disease definition. Despite the progress in unraveling the molecular bases of LLDD, the genetic factors underlying the disease etiology in ~35% of patients with AcDys, CAD, or PH, and ~10% of patients with ACDMPV remain unknown. Thus, analyses of more samples are crucial for better understanding LLDDs pathogenesis.

The overarching hypothesis is that LLDDs result from abnormalities involving *FOXF1*, *TBX4,* and *FGF10,* or other not yet determined genes. Their identification is necessary for precise LLDD diagnosis and for better understanding its etiology. The main aim of this proposal is to identify the causative genetic variants responsible for the LLDD and to broaden our knowledge of LLDDs. The practical goal is the implementation of LLDD diagnostic algorithm in Poland, where currently, LLDDs are underdiagnosed due to a limited access to diagnostic tools.

In this study, patients with histopathologically-verified LLDD will be molecularly tested using Sanger sequencing, whole genome sequencing and RNA sequencing to recognize the underlying factors of the disease. These planned methods are the most appropriate and accurate approaches that have proven to be successful in studying of the human genome and transcriptome. The work plan also includes a functional analyzes of variants located in the lung-specific regulatory elements at 17q23.1, reported in LLDD patients with *TBX4* or *FGF10* abnormalities. This will enable testing the previously raised hypothesis about the biallelic inheritance of selected LLDDs.

The results of this study will provide a better understanding of genetic bases of LLDD in newborns. In addition to the scientific significance, searching for the causes of LLDDs, whose clinical course is severe and mostly lethal, has also the medical and social aspects. Better understanding of etiology of LLDDs through basic research will enable improvement of their diagnostics and will provide perspectives for future therapeutic strategies. Moreover, the platform developed during this project could be used to increase the LLDD awareness and to provide a teaching environment for the medical community.