**PhD Student:** Mădălina Anciuc (Anciuc-Crauciuc)
**PhD Coordinator:** Professor Claudia Bănescu, MD, PhD

# Study of *ABCA3*, *SFTPB*, and *SFTPC* Gene Variants Involved in Surfactant Synthesis in Newborns with Respiratory Distress Syndrome

The thesis provides a comprehensive overview of neonatal respiratory distress syndrome (RDS), a significant condition associated with prematurity, characterized by pulmonary surfactant deficiency and clinical variability influenced by both genetic and non-genetic factors. Modern neonatology has advanced significantly due to improvements in intensive care, imaging, and surfactant therapy, leading to reduced mortality; however, disease severity and complications such as bronchopulmonary dysplasia persist. The work emphasizes that clinical heterogeneity among newborns of the same gestational age suggests an important role of genetic factors in the etiopathogenesis of RDS. The investigation of gene variants involved in surfactant synthesis—*ABCA3*, *SFTPB*, and *SFTPC*—is framed within the broader shift of medicine toward individualization and personalization.

The initial chapters present the historical development of neonatology, modern monitoring and treatment technologies, the impact of mechanical ventilation and antenatal corticosteroids, and the transformation of RDS management following the introduction of surfactant therapy. The onset of disease is discussed in relation to pulmonary maturation and alveolar structures, describing the transition from intrauterine to extrauterine life and the stages of lung development. Five phases of fetal lung development are highlighted—embryonic, pseudoglandular, canalicular, saccular, and alveolar—each characterized by specific molecular and cellular processes involving transcription factors (NKX2.1), signaling pathways (Wnt, BMP, Notch, Hippo), and regulatory microRNAs. Fetal breathing movements and the interplay between central mechanisms and surfactant synthesis support lung maturation and postnatal adaptation.

Extensive attention is devoted to the composition of surfactant, composed predominantly of phospholipids and specific proteins (SP-A, SP-B, SP-C, SP-D). Phospholipids, particularly dipalmitoylphosphatidylcholine, reduce surface tension, while hydrophobic proteins support alveolar film stability. SP-A and SP-D have immunological functions, whereas SP-B and SP-C are essential for alveolar expansion. Lamellar bodies, tubular myelin, and the exocytosis of type II alveolar epithelial cells (AEC2) are described to clarify normal surfactant metabolism. Disruption of these mechanisms results in RDS or interstitial lung disease.

The work broadly addresses disease etiology, differentiating between non-genetic factors—such as prematurity, maternal age, diabetes, sex, mode of delivery, race, and environmental exposure—and genetic ones. High-penetrance mutations in *ABCA3*, *SFTPB*, *SFTPC*, and *NKX2-1* may cause lethal forms of respiratory failure. Variants with minimal functional impact, such as polymorphisms in *IL-10*, *NOS3*, and genes involved in lipid metabolism, may influence susceptibility and disease severity. Epigenetic mechanisms and microRNAs are also integrated into the etiopathogenic framework.

A major chapter presents the *ABCA3*, *SFTPB*, and *SFTPC* genes in detail. The ABCA3 transporter, essential for the assembly of phospholipids within lamellar bodies, is frequently implicated in severe forms of RDS. Variants such as E292V, N568D, and L101P are described mechanistically and clinically, being associated with either neonatal mortality or interstitial lung disease. Classifications of variants (type I, II, III), their impact on protein function, and implications for genetic diagnosis, family counseling, and emerging small-molecule therapies are presented. The *SFTPB* gene encodes a hydrophobic protein essential for lamellar body formation and surfactant film stability; recessive mutations result in lethal respiratory distress. The *SFTPC* gene, involved in alveolar phospholipid structure, is frequently associated with chronic interstitial lung disease. Dominantly inherited variants that affect protein folding and alveolar homeostasis are also addressed.

In the section dedicated to original research, the thesis presents investigations of copy number variations in the *ABCA3* gene, the identification of potentially functional polymorphisms, and the exploration of *IL-10* and *NOS3* gene variants as risk factors for RDS and its progression. The methodology includes cohort studies on preterm newborns, correlating genetic variants with clinical phenotype, disease severity, complications, and treatment response. The results are discussed in relation to international literature and their relevance to clinical practice.

The thesis concludes that understanding the genetic mechanisms underlying RDS enables early identification of high-risk newborns, optimization of therapeutic strategies, and the development of personalized interventions. Research on the *ABCA3*, *SFTPB*, and *SFTPC* genes provides explanations for phenotypic variability and offers laboratory opportunities for molecular diagnosis. The originality of the studies conducted in the analyzed population and their contribution to the specialized literature are emphasized, along with future directions related to genetic therapies, family counseling, and the integration of genomic medicine in neonatology.



**Adresa:** Târgu Mureş, str. Gh. Marinescu, nr. 38, 540142, judeţul Mureş, România
**Web:** www.umfst.ro | **Email:** claudia.banescu@umfst.ro | **Tel:** +40 265 215 551, int. 184| **Fax:** +40 265 210 407