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THE EXPANDING SPECTRUM OF SURFACTANT ASSOCIATED DISEASE

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Mutations in critical molecules in the surfactant metabolic pathway result in acute and chronic pulmonary disease that most often presents at birth or in early infancy. In the acute neonatal presentation, term newborns develop severe respiratory failure shortly after birth that is unresponsive to intensive care interventions. This acute form is typical for infants with loss of function mutations in the genes encoding surfactant protein-B (*SFTPB*) or member A3 of the ATP Binding Cassette family of proteins (*ABCA3*), but has also been seen in a small number of infants with mutations in gene encoding surfactant protein-C (*SFTPC)* or the thyroid transcription factor (*NKX2.1*). Typically, infants with this acute presentation succumb to intractable respiratory failure or are considered for lung transplantation. A more chronic clinical presentation and variable course of disease has been seen in children with mutations in *SFTPC, ABCA3* and *NKX2.1,* in which children present in the first several months of life with gradual onset of respiratory insufficiency, failure to gain weight, and interstitial lung disease on chest radiographs. The variability in severity and course of the disease is not gene or mutation specific and precludes definitive prediction of outcome.

Heterozygous variants in these surfactant associated genes might also contribute to the risk or severity of RDS in newborns, suggesting an interaction between developmental and genetic factors in the etiology of RDS. Finally, adults with idiopathic pulmonary fibrosis have also been identified with mutations in *SFTPC* or *ABCA3*, suggesting that underlying genetic susceptibility imparted by mutations in these genes may contribute to pulmonary dysfunction across the age spectrum.

Studies investigating the population- and disease-based frequencies of these and other as yet to be identified genes will provide additional insight into the genetic contributions to newborn RDS, the mechanisms of surfactant dysfunction, and ultimately, will lead to the development of mechanism-specific interventions.