# European Respiratory Society
# Annual Congress 2013

**Abstract Number:** 1066

**Publication Number:** P3125

**Abstract Group:** 3.2. Airway Cell Biology and Immunopathology

**Keyword 1:** Cell biology **Keyword 2:** Epithelial cell **Keyword 3:** Interstitial lung disease

**Title:** ABCA3 mutations disturb lipid homeostasis in alveolar epithelial cells

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**Body:** Interstitial lung diseases (ILDs) are characterized by various degrees of inflammation and fibrosis; however, the causatives are largely unknown. Among others, gene defects in the gene coding for the surfactant lipid transporter ABCA3, localized exclusively to alveolar type II cells (ATII) in the lung, were found in children presenting with ILD. Since ABCA3 is a lipid transporter, aim of this study was to determine whether ABCA3 mutations disturb lipid homeostasis of ATII. Therefore, the effects of the two clinically relevant ABCA3 mutations p.Q215K and p.E292V were investigated in A549 cells, a cell culture model system for ATII, by mass spectrometry, Oil Red O staining, qPCR, and western blotting. In A549 cells harbouring mutant ABCA3, we found accumulation of cholesterol; especially cholesterol esters (CE) were elevated approx. 2-fold compared to ABCA3-WT cells. Concurrently, the size of neutral lipid droplets, in which excess free cholesterol is stored in the form of CE, was significantly increased about 2-fold by ABCA3 mutations. Carboxylesterase 1, which plays a role in lipid droplet formation, was up-regulated more than 5000-fold in cells harbouring ABCA3 mutations. ABCA3 mutations also induced a significant reduction of several SREBP regulated genes involved in cholesterol and fatty acid metabolism. Additionally, expression of the cholesterol and phospholipid transporter ABCA1 was elevated at least 4-fold by mutant ABCA3. In conclusion, here we show that ABCA3 mutations induce intracellular cholesterol accumulation and disturb cellular lipid homeostasis. Among other factors, this ABCA3-mediated deregulation might contribute to the development of ILD in children. Supported by BMBF-GOLDnet and DFG 970/7-3.