

Lung function in heterozygote carriers of ABCA3 mutation

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ABCA3 is a transmembrane protein exclusively expressed in the lamellar bodies of type II cells of the lung.^[1] It is a phospholipid carrier which is essential to lamellar body formation. ABCA3 mutations, resulting in abnormal lamellar body formation, have recently been associated with severe neonatal respiratory distress syndrome^[2] and infantile interstitial lung disease^[3] due to congenital surfactant deficiency. Two clinical phenotypes are associated with this mutation; the most common form is neonatal RDS which is usually fatal within 6 months and in few instances this mutation results in infantile/paediatric interstitial lung disease which leads to oxygen deficiency and progressive respiratory failure within the first year of life. The ABCA3 mutation is autosomal recessive.

Heterozygote carriers of ABCA3 mutations

In the published literature there are four series of mutations involving 26 families; nearly every family has a different mutation.^[2,3,4,5,6] Most of the reported mutations are biallelic (homozygote or double heterozygote). However, four cases affected by congenital surfactant deficiency apparently carry monoallelic mutations. The most common hypothesis for this is that there is a second undiscovered ABCA3 mutation, or a compound heterozygote mutation in another surfactant-related gene. However, an alternative theory is that the monoallelic (heterozygote) ABCA3 mutation found in these patients is actually disease-causing, for example by a dominant-negative effect.

Is there a phenotype associated with heterozygote ABCA3 mutations?

This preliminary study was designed with the aim of answering the question of whether there is a phenotype associated with heterozygote ABCA3 mutations (Figure 1). Three families of newborn infants hospitalised in the neonatal ICU with congenital surfactant deficiency had their genotype determined and lung function was studied in the index cases and in their relatives. The investigators queried whether there was a correlation between clinical phenotype, lung function and heterozygote ABCA3 mutation. Individuals ≥ 3 years old were evaluated for lower airway resistance (FEV₁), functional volume (Rv/TLC), alveolar diffusion utilising the CO

Figure 1. A,B: Lung tissue immunohistochemistry ABCA3 (green) and SP-B (red) staining in a control subject (A) and in a patient with a heterozygote ABCA3 mutation (B). While in normal subjects ABCA3 and SP-B co-localize in type II cell lamellar bodies, partial ABCA3 deficiency leads to SP-B misprocessing and intra-alveolar accumulation. C: Chest radiogram of the same patient at 3 months shows diffuse interstitial lung disease. D,E: A type II pneumocyte in a control subject (D) shows numerous lamellar bodies filled with concentric, pseudo-myelin structures corresponding to intracellular surfactant; in the ABCA3-deficient patient, type II cells lack typical pseudo-myelin structures, and lamellar bodies are smaller and denser, with one or more dense cores (E). F,G: At a higher magnification, normal lamellar bodies show regular concentric layers of surfactant (F), whereas in ABCA3 deficiency, the layers are thinner, more densely packed and irregular (G).

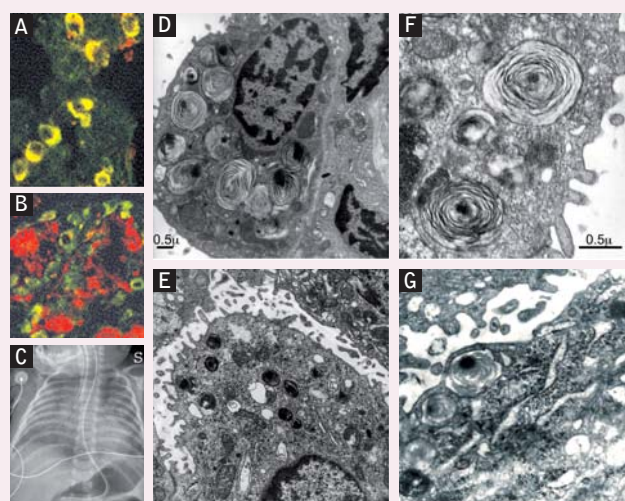


Table 1. Lung function testing results in the three pedigrees. Subjects with * are <2 year-old and underwent passive lung function testing (see text); results are reported in italic in the table. K_{CO} or PaO_2/FiO_2 are abnormal in subject 2b, 2c, 3 and 3b, indicating decreased alveolar diffusion capacity

| Case | Relation | Age | Mutations | FEV ₁ (L) tPTEF/tE* | RV/TLC Vt* | K _{CO} PaO ₂ /FiO ₂ * |
|------|-------------|-----|-----------|-----------------------------------|---------------|---|
| 1a | father | 20y | 3997delAG | 4.15 (98%) | 48 (213%) | 2.17 (121%) |
| 1b | mother | 18y | 3997delAG | 2.94 (97%) | 50 (198%) | 1.94 (95%) |
| 1c | sister* | 7d | normal | 0.27 | 7.1 | 309 |
| 1d | brother* | 8d | normal | 0.28 | 8.0 | 320 |
| 2a | father | 38y | G464A | 3.75 (101%) | 23 (81%) | 1.66 (109%) |
| 2b | mother | 33y | C439T | 2.06 (79%) | 66 (222%) | 1.28 (66%) |
| 2c | brother | 12y | C439T | 2.07 (99%) | 34 (136%) | 1.39 (67%) |
| 2d | sister | 9y | normal | 1.37 (98%) | 31 (119%) | 1.71 (81%) |
| 3 | Index case* | 1m | C743T | 0.36 | 5.0 | 115 |
| | | 16m | " | 0.37 | 2.5 | 92 |
| 3a | father | 29y | normal | 4.17 (95%) | 40 (158%) | 1.79 (106%) |
| 3b | mother | 30y | C743T | 3.06 (104%) | 32 (112%) | 1.38 (72%) |

Normal values: Age >5 years: FEV₁: 80-120%; RV/TLC: 80-120%; K_{CO}: >80% - Age <5 years: tPTEF/tE: 0.25-0.35; Vt: 5-8mL/kg; PaO₂/FiO₂: >300

single breath method and results were characterised by the percent predicted values for age, weight, and gender according to the European Respiratory Society standards (ERS93). For those aged ≤ 2 years lower airway patency (tPTEF/Te), spot tidal volume (Vt) and alveolar diffusion (PaO_2/FiO_2) were measured via ultrasound flow meter. These infants were evaluated under spontaneous sleep without any sedation (Table 1).

The first pedigree involved a newborn infant with severe RDS, unexplained by other diseases, who died at 1 month. This infant had a homozygous frame shift mutation involving total disruption of gene transcription and subsequently no ABCA3 expression. Both parents were heterozygous carriers with normal lung function, while neither of the two siblings had this mutation and both displayed normal lung function.

Pedigree 2 was a preterm infant of 35 weeks gestation with severe RDS who died of intractable lung disease at 6 months of age. This infant displayed two different heterozygous missense mutations of the ABCA3 gene. Again both parents were carriers, each carrying one of the two mutations. The sister had the same mutation as the father and both displayed normal lung function. While both the brother and mother had the same mutation and displayed normal airway resistance and lung volume, they had reduced alveolar diffusion of 66 and 67%, respectively (normal values are >80%).

The final pedigree was a term infant with a less severe phenotype who presented with unexplained oxygen requirements since birth. This infant was not intubated and at 16 months of age was awaiting a lung transplant. This infant had a heterozygous ABCA3 missense mutation, although ABCA3 protein expression appeared only slightly decreased on immunohistochemistry. No mutations were on SP-B and SP-C genes. The father and sister, who carried no mutations, had normal lung function but the mother, who carried the same mutation as the patient, had an alveolar diffusion capacity slightly reduced (72%) despite she had no respiratory complaints. While ABCA3 deficiency is usually reported as a recessive disease caused by biallelic mutations, these preliminary data show that some specific ABCA3 mutations may cause subclinical or severe alterations of the alveolar diffusion capacity in heterozygote carriers.

It has been hypothesised that ABCA3 mutations affect surfactant synthesis through various molecular mechanisms, such as aberrant gene transcription resulting in no expression (Pedigree 1), loss of function (Pedigree 2) or intracellular mislocation of ABCA3 leading to abnormal lipid metabolism.

Certain specific ABCA3 mutations may cause misprocessing of surfactant protein (SP)-B and abnormal intra-alveolar SP-B accumulation that could lead to alveolar dysfunction in a dominant negative manner.

Detailed lung function studies with a larger number of families with ABCA3 deficiencies would be necessary to confirm these preliminary findings and to define their clinical relevance.

References

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