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ABCA3 mutations in adults with interstitial lung disease: is there a link?

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ATP-binding cassette member A3 (ABCA3) is a highly conserved, transmembrane spanning protein that localizes to the limiting membrane of lamellar bodies in alveolar epithelial type II cells, transports phospholipids, and is required for pulmonary surfactant assembly (1).

Mutations in the gene encoding the ATP-binding cassette (ABC), subfamily A, member 3 (*ABCA3*) cause a broad spectrum of respiratory disorders (MIM 610921), ranging from pediatric disorders to adult forms, with an autosomal recessive hereditary transmission. Mutations in *ABCA3* are predominantly linked to neonatal and pediatric interstitial lung disease (ILD), with a minority surviving beyond puberty (2).

Biallelic pathogenic *ABCA3* variants cause severe neonatal respiratory distress syndrome or childhood interstitial lung disease. However, the *ABCA3* genotype alone does not explain the diversity in disease presentation, severity, and progression. Additionally, monoallelic *ABCA3* variants have been reported in infants and children with *ABCA3*-deficient phenotypes (3).

A potential mechanism to account for phenotypic variability among individuals with biallelic or monoallelic *ABCA3* variants may be the allele-specific expression, as suggested by Savova and colleagues (4).

Although extremely rare, patients with bi-allelic mutations in *ABCA3* may present in adulthood. Late-onset disease may be influenced by the type of mutation or environmental factors. Klay and cols. Shown a case series of three adult ILD patients with compound heterozygous *ABCA3* mutations who survived well beyond childhood. This includes three novel ABCA3 mutations and three new and six previously reported adult patients with *ABCA3* mutations (2).

Survival of patients is predominantly determined by type and combination of *ABCA3* mutations. Environmental factors, such as smoking and infection, could alter the age of presentation and disease severity.

Here, Legendre et al. show an adult patient homozygous for a complex allele encompassing the p.Ala1027Pro likely pathogenic mutation and the p.Gly974Asp variation in the *ABCA3* gene, which was followed for a late-onset, and fibrotic ILD. The patient was improved quickly and persistently for at least 6.5 years with hydroxychloroquine treatment; this is the first case of adulthood ILD with probable *ABCA3* mutation where it showed the effectiveness of hydroxychloroquine (HCQ) (5).

Many studies showed that monoallelic *ABCA3* mutations are common in infants with severe respiratory distress syndrome, childhood ILD, and adults with idiopathic pulmonary fibrosis and diffuse parenchymal lung disease (6,7).

There are no clear guidelines for treating inter-

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stitial lung disease caused by *ABCA3* mutation. Corticosteroids were shown to upregulate the expression of *ABCA3* in type II pneumocytes. In addition, several studies have proven that a combination of corticosteroids, HCQ, and macrolides like azithromycin have been effective in interstitial lung disease with genetic etiologies including genetic mutations but was still suggested to be tried through empirical observation in children with *ABCA3* mutations (8).

Most investigations have been done in pediatric ILD; case reports looking for treatments in the ILD in adulthood where *ABCA3* mutations are detected offer the opportunity to go deep into this research field. The *ABCA3* mutation may be considered in an adult if there are findings of ILD, even if there is no neonatal or childhood history of respiratory distress.

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