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ATP binding cassette member A3 (ABCA3): coming of age

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Pathogenic variants in the ATP binding cassette member A3 (ABCA3) gene were first described in newborn infants with lethal respiratory failure in 2004.[1] Subsequent reports have expanded the clinical spectrum associated with biallelic *ABCA3* variants to include infants with the phenotype of childhood interstitial lung disease (chILD), who presented after the newborn period and had prolonged survival, even into adulthood.[2-4] A genotype–phenotype correlation has emerged with biallelic null (frameshift or nonsense) *ABCA3* variants predicting neonatal onset of respiratory failure and death prior to 1 year of age without lung transplantation, whereas the age of presentation and disease course associated with other *ABCA3* variants (missense, splicing and in-frame insertion/deletions) are less reliably predicted.[3 5] Since the original report, much of the ensuing literature has focused on identifying novel*ABCA3* variants, describing histopathological and ultrastructural features of affected lung tissue, and characterising *in vivo* and *in vitro* models of gene regulation and variant-specific disease mechanisms. Robust clinical data regarding disease progression, pulmonary outcomes and survival, particularly for those presenting or surviving beyond infancy, have been scarce. In their Thorax paper, Li *et al* provide in-depth clinical data for 44 children with ABCA3 deficiency from the chILD EU Kids Lung Register database over a 21-year period who survived beyond the first year of life.[6] This study demonstrates the power of multicentre collaboration and patient registries for defining the natural history of rare chILD disorders, as most centres follow only a few patients. The assembled cohort provides detailed genetic, radiologic, histopathological, pulmonary function data as well as medication and home oxygen use, further defining the clinical course, disease surveillance and progression beyond the first year of life. Importantly, more than 80% of children surviving beyond infancy were alive at 6 years without lung transplantation, providing affected children, families and clinicians with hope for this often life-limiting disease.

While the study provides important clinical information, there are several limitations. Most notably, the authors classified all missense *ABCA3* variants as 'hypomorphic'. Two classes of ABCA3 mutants have been recognised: type I mutants are mistrafficked and retained in the endoplasmic reticulum (ER), whereas type II mutants demonstrate reduced phospholipid

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transport.[7 8] However, the ABCA3 mutant class is not reliably predicted by the location in the gene or protein, and fewer than 10% of the over 300 reported disease-associated *ABCA3* variants have been functionally characterised *in vitro*. While type II mutants, including the most common pathogenic variant p.E292V, may be classified as 'hypomorphic', the effects of type I mutants are more difficult to determine. Type I mutants impair cleavage of the ABCA3 precursor protein, do not traffic to the lysosomally derived lamellar body membrane, and may activate intracellular stress pathways due to accumulation of mutant ABCA3 in the ER. Additionally, among type II or 'hypomorphic' *ABCA3* variants, there is likely a spectrum of impaired phospholipid transport.[9] Second, *in silico* variant prediction algorithms are limited in their ability to predict pathogenicity. Characterisation of explanted lung tissue from children who underwent lung transplantation for ABCA3 deficiency demonstrated that a missense variant near the exon–intron junction altered splicing and had a 'null' effect.[10] Studies in other genes/proteins demonstrated that even variants within the canonical splice site may not alter splicing or result in leaky splicing, and thus experimental data from lung tissue are needed to confirm alteration of splicing and 'null' effect.[11 12] Third, the authors included individuals with *ABCA3* variants (p.N124S, p.R280H, p.R288K, p.R709W, p.P766S) of uncertain pathogenicity, with conflicting in silico predictions, and some of which are identified among multiple individuals, including homozygous adults, in the genome aggregation database[13] (gnomAD, gnomad.broadinstitute. org). While the effects of these *ABCA3* variants remain uncertain, the authors provide additional clinical details for these individuals in the supplement. It is possible that some of these individuals have a pathogenic variant on only one allele, and the natural history for symptomatic individuals with monoallelic *ABCA3* variants is currently unknown.[14-16] Fourth, due to the small number of individuals who underwent chest CT and pulmonary function testing, it is unclear whether progression of CT findings correlates with genotype or pulmonary function. Fifth, while the authors reported exposure to medications for treatment of chILD (eg, steroids, hydroxychloroquine, macrolides), due to lack of time-dependent data, the impact of these therapies could not be assessed.

Despite these limitations, Li *et al* provide important longitudinal clinical information about affected individuals surviving beyond 1 year. As medical therapies for ABCA3 deficiency remain limited and not variant-specific, the clinical data provided in this manuscript may inform clinical trials and outcome metrics for current anti-inflammatory and emerging anti-fibrotic therapies.[5 17-19] Given the structural similarities between ABCA3 and the Cystic Fibrosis Transmembrane Receptor (CFTR), which is encoded by *ABCC7*, and the success of variant-specific modulator therapies for patients with cystic fibrosis, hopefully, similar therapies could be developed for patients with ABCA3 deficiency.[8 20-22] As clinicians and families consider future participation in clinical trials and therapeutic options, the limitations of this manuscript underscore the need for caution in deciding which patients should be included. Approximately 10% of *ABCA3* variants may be in *cis* with another *ABCA3* variant,[3] highlighting the need for parental samples to phase variants. With increasing availability of genetic testing, diagnostic lung biopsy is less often pursued as demonstrated in this study. Without a lung biopsy demonstrating consistent histopathology and with the large number of private *ABCA3* variants, the majority of which lack correlative functional data, there is substantial risk of making the diagnosis of ABCA3 deficiency in patients

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who may have another basis for their lung disease. Methods to increase the efficiency of functional characterisation of *ABCA3* variants and screening of repurposed or novel chemical correctors are being developed and will inform diagnosis, disease mechanisms and potential therapeutics.[8 22] Additionally, as exome and genome sequencing are increasingly being used as diagnostic tools and will result in the identification of novel variants/genes, the need for sharing genetic data through rare disease registries such as the Kids Lung Registry (chILD EU), the US chILD national registry and the Australian-New Zealand registry (chIL-DRANZ N) will facilitate the assembly of carefully phenotyped patient cohorts for clinical research and future interventions. We applaud Li *et al* for further defining the clinical characteristics of individuals with ABCA3 deficiency older than 1 year as they come of age.

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