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NOTE

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# A homozygous variant in *ABCA3* is associated with severe respiratory distress and early neonatal death

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Congenital disorders of the surfactant system are a group of life-threatening disorders associated with deficiency in surfactant proteins lining lung cells. Respiratory distress syndrome (RDS) is one of those disorders where variants in ATP-binding cassette sub-family A member-3 (*ABCA3*) are known to cause neonatal respiratory failure in full-term babies and death before the end of first year of life.[1] Herein, we report the clinical course of a newborn carrying a fatal homozygous *ABCA3* variant detected through whole-exome sequencing (WES).

After 39 weeks of gestation, a male infant of consanguineous parents was born via vaginal delivery, weighing 2.75 kg. Apgar score was 8 and 9 at 1 and 5 min, respectively. The proband, eighth born in the family, had three siblings who died within the first year of life due to intractable respiratory disorder. Neonatal sepsis was first considered and consequently treated with antibiotics (ampicillin and amikacin). Blood culture was negative with normal parameter of white blood cells. Heart structure and function were normal except the presence of a tiny patent ductus arteriosus. Chest X-ray (CXR) at Day 1 showed signs of respiratory distress with diffused reticular granularity of the lungs (Figure 1(A)). The respiratory management included noninvasive ventilation and exogenous surfactant (Alveofact, Survanta). On Day 7 of life, his respiratory status deteriorated, and he required high-frequency ventilator. Systemic corticosteroid (methylprednisolone) with a dose of 2 mg/kg was administered, but without any improvement. The proband died the following day. Immediate postmortem pulmonary biopsy was performed and underwent histopathological and electron microscopic examinations. The lung tissue showed hyperplasia of Type II pneumocytes, focal intra-alveolar with abundant finely granular, periodic acid-Schiff (PAS)-positive and eosinophilic material (Figure 1(B),(C)). Electron microscopy showed a mixture of normal-appearing lamellar bodies, of which some were small and irregular. Few cells contained small compact lamellar bodies with eccentric electron dense deposits resembling fried eggs appearance (Figure 1(D)).

The proband's (II-8) WES results showed a homozygous missense variant (rs751061681) in Exon 7 of *ABCA3* gene (NM_001089.3: c.604G>A, p. G202R) (Figure 1(E)). Segregation analysis for the proband's parents and siblings showed that all members in the family were unaffected heterozygous carriers except individual II-4, who was homozygous for the wild type (Figure 1(H)). These findings are consistent with the diagnosis of surfactant metabolism dysfunction Type 3 that is inherited in an autosomal-recessive manner.

This variant has been only reported twice; once in a family of French origin in a compound heterozygous state[2] and then in 2016, when Rezaei et al. reported the same variant in its homozygous state.[3]

Missense variants in the extracellular and intracellular domains of *ABCA3* have been reported in neonates suffering RDS (Figure 1(F)).[2,4] Our variant resulted in amino acid polarity change from neutral to basic in the Position 202 (glycine to arginine). Aligning the protein domain of *ABCA3* that encompass glycine residue shows a highly conserved region through evolution across different species (Figure 1(G)). Moreover, in silico prediction tools such as PolyPhen and SIFT predict pathogenic outcome of the variant.

  

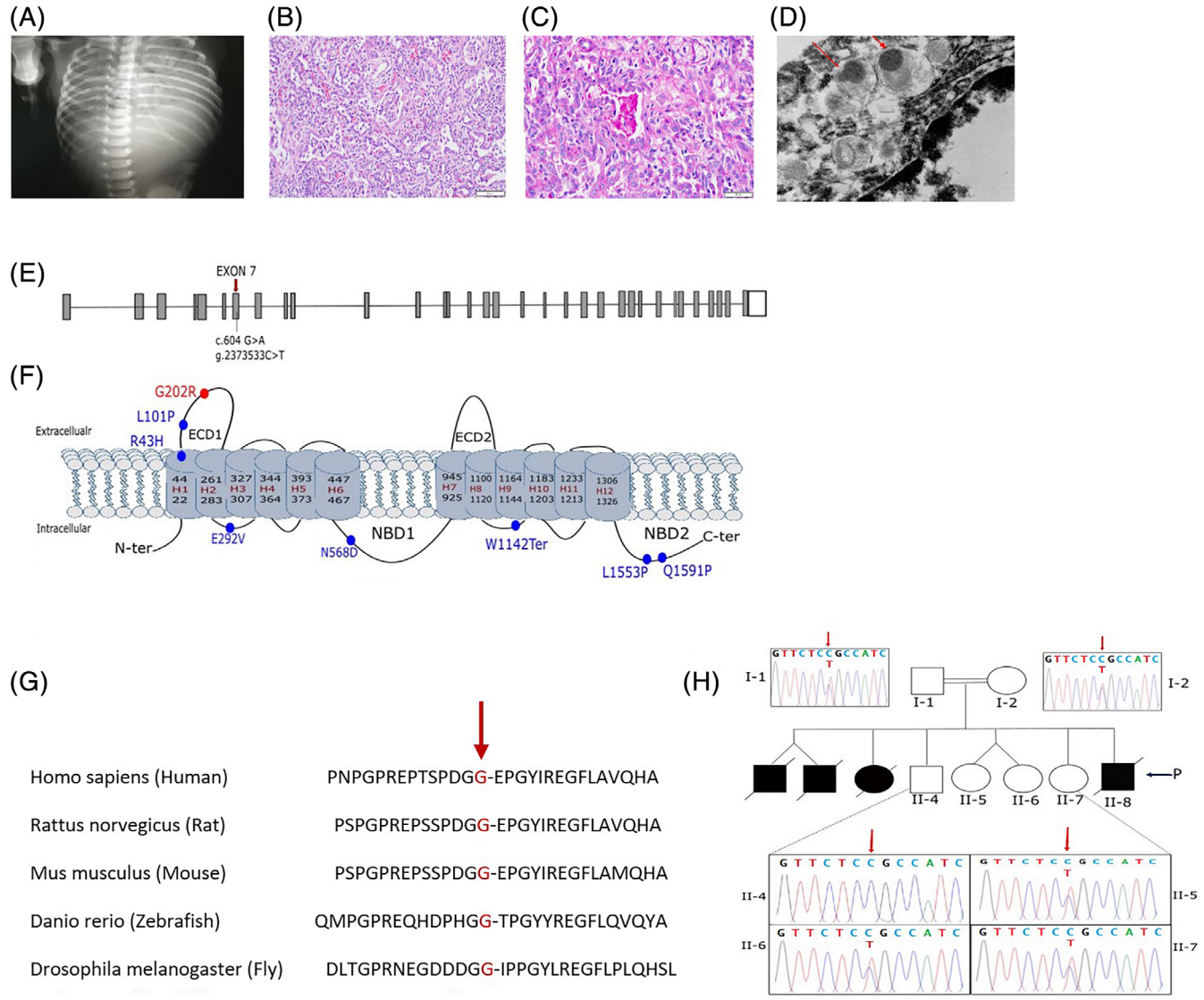


**FIGURE 1** (A) CXR at Day 1. (B) Massive pneumocyte Type II hyperplasia and desquamation of alveolar macrophages typical of desquamative interstitial pneumonia (DIP) is noted (hematoxylin–eosin ×200). (C) Interalveolar deposition of periodic acid-Schiff (PAS)-positive material (PAS ×400). (D) Electron microscopy imaging (×70 000). (E) *ABCA3* gene at Chromosome 16, variant pointed out by red arrow in Exon 7. (F) illustration of the multipass integral ABCA3 protein that contains two homologous repeats with six putative membrane-spanning helices for each. Blue dots are previously reported missense pathogenic variants in ClinVar, while the red dot is our variant. (G) The amino acid alignment of the evolutionary conservation of glycine residue 202 across different species. (H) Family pedigree and segregation analysis. Squares and circles indicate male and female members, respectively. Filled symbols, affected individuals; empty symbols, unaffected individuals; crossed symbols, deceased individuals; arrow, proband; double lines, consanguinity. The missense variant is indicated by red arrows. CXR, Chest X-ray

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Written informed consent was obtained from the patient's parents, for sharing and publishing the reported data.

## CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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