NOTE

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

Short title: WES reveals rare inherited variant in *ABCA3*

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/cga.12437

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 minutes, 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 1A). The respiratory management included non-invasive ventilation and exogenous surfactant (Alveofact, Survanta). On day-7 of life, his respiratory status deteriorated, and he required high frequency ventilator. Methylprednisolone with a dose of 2mg/kg was administered but without any improvement. The proband died the following day. Immediate post-mortem pulmonary biopsy was performed and underwent histopathological and electron microscopic examination. The lung tissue showed hyperplasia of type II pneumocytes, focal intra alveolar with abundant finely granular, PAS+ and eosinophilic material (Figure 1B+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 1D).

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 1E). 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 1H). 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]. Then in 2016 when Rezaei F et al. reported the same variant in its homozygous state [3].

Missense variants in the extra and intra-cellular domains of ABCA3 have been reported in neonates suffering RDS (Figure 1F) [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 1G). Moreover, in-silico prediction tools such as PolyPhen and SIFT predict pathogenic outcome of the variant.

Acknowledgements

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

Funding:

None.

Disclosures:

None.

References:

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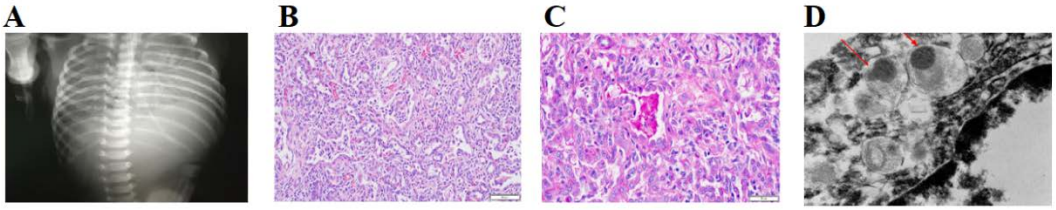
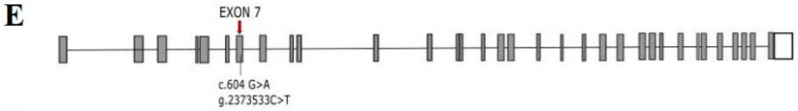
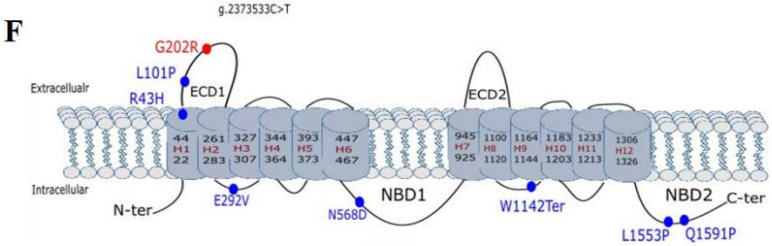
Figure 1

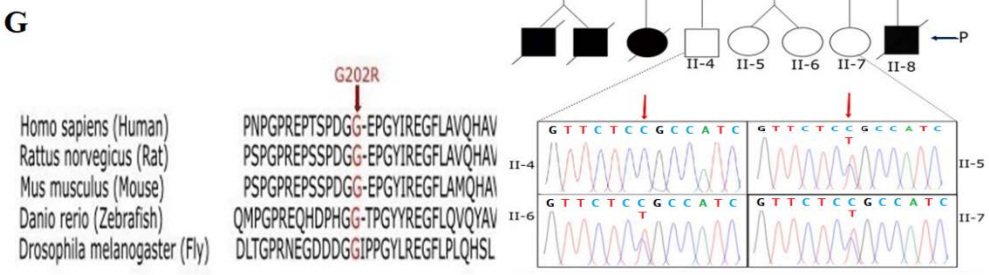
A: CXR at Day-1. B: Massive pneumocyte type II hyperplasia and desquamation of alveolar macrophages typical of DIP is noted (Hematoxylin-Eosin X 200). C: Interalveolar deposition of PAS-positive material (PAS X 400). D: Electron microscopy imaging (X 70000).

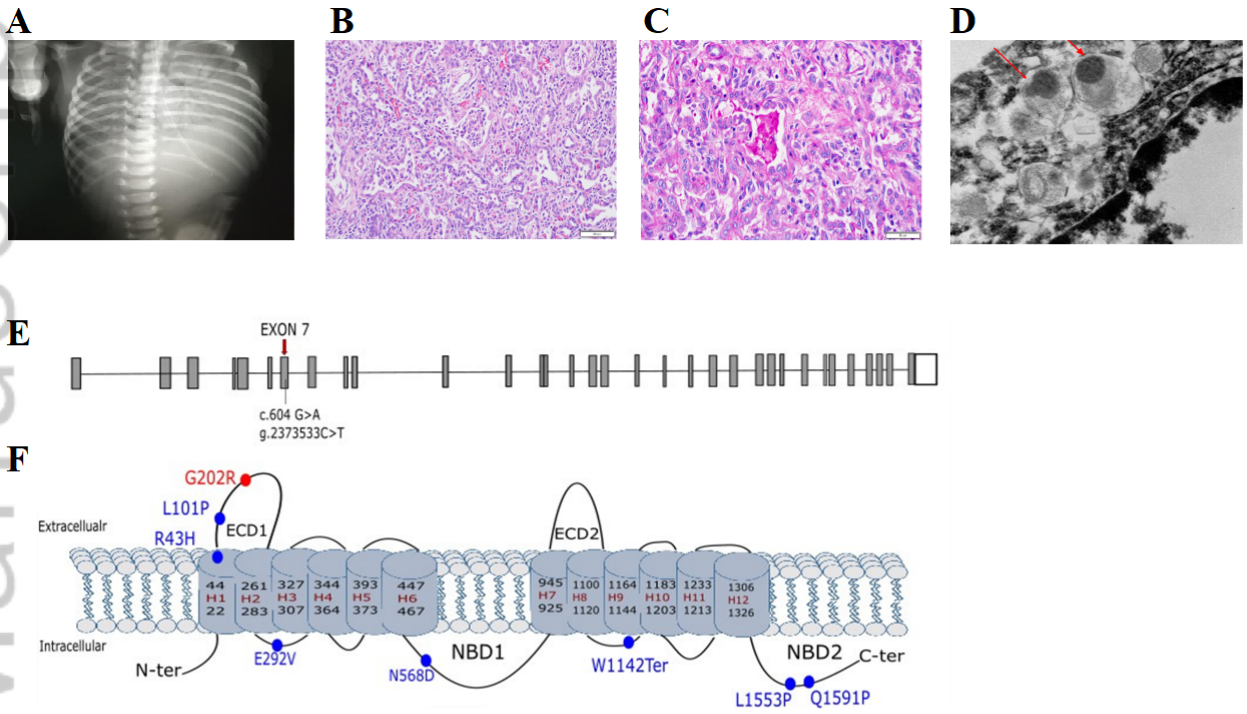
E: *ABCA3* gene at chromosome 16, variant pointed out by red arrow in exon 7. F: illustration of the multi-pass integral ABCA3 protein that contains two homologous repeats with 6 putative membrane-spanning helices for each. Blue dots are previously reported missense pathogenic variants in ClinVar, while 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.











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