

The most frequent ABCA3 nonsense mutation -p.Tyr1515* (Y1515X) causing lethal neonatal respiratory failure in a term neonate

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Abstract:

Defects in the surfactant biosynthesis are associated with respiratory distress syndrome, commonly occurring in premature infants due to lung immaturity. However, interstitial lung diseases have also been observed in full-term infants with mutations in the SFTPC, SFTPB, NKX2-1, or ABCA3 genes, involved in the surfactant metabolism. Herein, we report a newborn baby with neonatal respiratory distress and diffuse lung disease caused by ABCA3 mutation. The baby died at 5 weeks of age after developing pulmonary hypertension. Genomic DNA was analyzed for four genes involved in surfactant metabolism out of which the c. 4545C>G (p.Tyr1515*) homozygous mutation in exon 29 of ABCA3 was identified which is one of the most frequent mutation causing lethal neonatal respiratory failure in a term neonate. This case study emphasizes the importance of raising awareness about this diagnosis in the clinical settings for fruitful outcomes in health-care delivery.

Keywords:

Interstitial lung disease, neonatal respiratory failure, pediatric pulmonology

Defects in the surfactant biosynthesis are associated with respiratory distress syndrome, which commonly occurs in premature infants due to lung immaturity. However, inherited surfactant metabolism disorders may cause a similar presentation in full-term newborns along with interstitial lung diseases (ILDs) in older children and adults. ILD have been observed in full-term infants with mutations in the *SFTPC*, *SFTPB*, *NKX2-1*, or *ABCA3* genes, which are involved in the surfactant biosynthesis.^[1,2] ABCA3 is a member of the ATP-binding cassette (ABC) transporter family which encodes membrane proteins involved in the transport of compounds across biologic membranes. ABCA3 is a 1704-amino-acid protein highly expressed in alveolar epithelial cells at the limiting membrane of lamellar bodies^[3] and is crucial for AT2 cells homeostasis, lipid composition (importation of phospholipids in lamellar bodies) and protein maturation of surfactant.^[4] More than 150 recessive mutations of the *ABCA3* gene have been reported in newborn babies with respiratory failure and

in older children or adults with ILD.^[5] We report here a full-term infant with severe respiratory failure after 8 days of life, in whom we identified an *ABCA3* null mutation at the homozygous state, namely, p.Tyr1515* (Y1515X). This truncating mutation causes a total loss of function of the ABCA3 protein.

Case Report

Our patient was from a consanguineous family (parents were first cousins) originating from Saudi Arabia. One older sister was asymptomatic, but there was a familial history since one sibling had died at 5 days of life due to meconium aspiration syndrome and bilateral pneumothorax with persistent pulmonary hypertension of the newborn [Figure 1].

The index patient was a full-term baby boy delivered normally with a weight of 3.74 kg after an uneventful pregnancy. Within the first few hours of life, he developed severe respiratory

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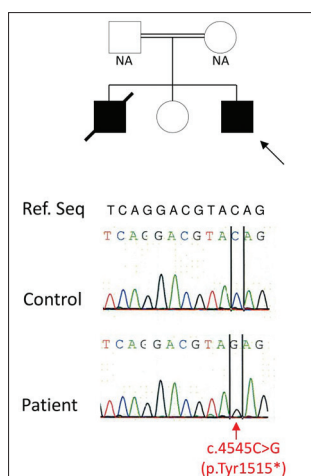


Figure 1: Pedigree of the family and identification of the homozygous mutation

distress and required invasive ventilation. Chest radiograms at first few hours showed diffuse reticular granularity and air bronchograms [Figure 2] due to which the baby received three doses of exogenous surfactant (4 ml/kg) as standard first-line treatment but with only transient improvement. Although the blood cultures were negative, the boy remained ventilated with worsening of the chest radiogram and developed pulmonary hypertension despite receiving intravenous corticosteroids (dexamethasone) treatment (0.1 mg/kg/dose once daily for 2 weeks). As the baby's condition worsened, the respiratory failure occurred due to the hypoxemia initially and at later stages due to CO₂ retention. Ultimately, he needed more respiratory support and was put on high-frequency ventilation with inhaled nitric oxide at 20 ppm.

Due to the family history, genetic analysis of genes associated with surfactant metabolism disorders was performed. Informed consent was obtained from the parents according to the current regulations. Genomic DNA was extracted from a peripheral blood ethylenediaminetetraacetic acid sample. The four genes involved in surfactant metabolism deficiency were explored by Sanger sequencing of all coding exons and their intronic flanking regions: *SFTPC* (NM_003018.3), *SFTPB* (NM_00542.3), *NKX2-1* (NM_001079668), and *ABCA3* (NM_001089.2). Sequence variations' pathogenicity was evaluated *in silico* on Alamut Visual version 2.7 software (Interactive Biossoftwares, Rouen, France). No mutation was detected in the *SFTPC*, *SFTPB*, and *NKX2-1* genes, however, we identified the c.4545C>G (p.Tyr1515*) mutation in homozygosity in exon 29 of *ABCA3* [Figure 1]. This substitution of a tyrosine codon by a premature stop codon is predicted to lead to a truncated protein.

After the genetic result of *ABCA3*-related surfactant metabolism disorder was obtained, another course of dexamethasone was given without any further improvement. The baby deceased at the age of 5 weeks.

Discussion

Pulmonary surfactant constitutes a tensioactive film covering the alveolar lumen and is necessary to avoid alveolar collapse during dynamic compression and decompression. The hydrophobic surfactant proteins SP-B and SP-C play a role in

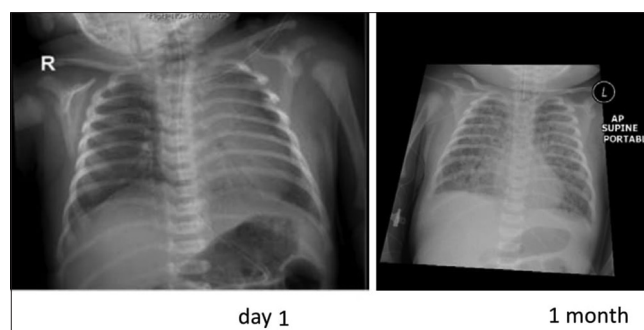


Figure 2: The chest X-ray images of the neonate

innate host lung defense and are transported to and stored in lamellar bodies—the secretory organelles of AT2 cells where they undergo posttranslational maturation before secretion at the epithelial surface.^[4] Mature SP-B and SP-C interact with phospholipids to confer tension-active properties to the pulmonary surfactant.

Four genes have mainly been implicated in genetic abnormalities of the surfactant: *SFTPB*, *SFTPC*, *NKX2-1*, and *ABCA3*, encoding respectively the specific proteins of the surfactant SP-B and SP-C, the transcription factor *NKX2-1* which regulates the transcription of *SFTPB*, *SFTPC*, and *ABCA3* genes. As with SP-B deficiency, *ABCA3* deficiency is now recognized as the most frequent cause of genetic surfactant metabolism disorder^[6] and should be suspected in full-term infants with severe neonatal respiratory distress syndrome refractory to conventional treatment^[5,7,8] *ABCA3* deficiency leads to abnormal lamellar bodies' structure and abnormal surfactant lipid composition, associated with impaired processing of SP-B and SP-C protein.^[9,10] Total loss of function leads to dramatic progress with neonatal distress syndrome and death within the 1st year of life whereas residual *ABCA3* function is associated with milder disease.^[5] Most mutations are unique, which can make the genetic counseling difficult in the families, especially in the case of missense mutations (amino acid substitution) where phenotype-genotype correlation is unknown. However, some are considered "frequent," as they have been reported among multiple patients as is the case for the p.Glu292Val (E292V) mutation which is the most frequent mutation in a population of European descent.^[11] Similarly, p.Tyr1515* mutation in the *ABCA3* gene seemed to be more frequent in the Middle East,^[5] as it was recently described in 18 consanguineous families originating from Middle East region. In our extensive study, although it was considered as a null mutation (no residual function of *ABCA3*) no functional study was performed. Unfortunately, no bronchoalveolar lavage was available for our patient hence neither mRNA nor SP studies could be carried out to determine if nonsense-mediated mRNA decay degraded abnormal transcribed mRNA or if it was translated into a truncated protein. However, this mutation was located at the end of the functional nucleotide binding domain 2, which binds adenosine triphosphate and allows channel gating and lipid transport. Such mutation at the homozygous state is thought to cause a complete absence of functional *ABCA3* protein and thus a severe defect in surfactant biosynthesis.

Neonate respiratory distress due to impaired surfactant metabolism is a rare condition, and most clinical centers

examine very few cases. Therefore, the ChILD-EU (ILD in children) collaboration recently published guidelines to diagnose the disease and to treat it when it is possible.^[12] Besides oxygen therapy, usual treatment suggestions include methylprednisolone, hydroxychloroquine, and azithromycin. However, in case of neonatal presentation, where rapid intubation and ventilation is required, respiratory failure often leads to death or lung transplantation is performed where available. Our case drew similarities to all 19 p.Tyr1515* homozygous patients described recently with patients presenting with severe respiratory distress syndrome and death before 3 months of age.^[5] Since *ABCA3* is a large gene of 30 coding exons, so the molecular analysis is time-consuming. In such cases with a frequent mutation according to geographic origin, the mutation could be searched for as a first rapid step of the study, followed by analysis of all exons. This could help expedite the therapeutic approach or the ending of the care resulting in the reduced burden on the health-care resources of a country. This case also illustrates the need for genetic analysis in patients presenting with ILD. Indeed, in this consanguineous family, two children died of surfactant metabolism deficiency before 1 month of life. Elucidating the molecular cause of the disease in families is of tremendous importance for genetic counseling and mandatory prenatal diagnosis to prevent further pregnancies and toward achieving better health outcomes. Genetic studies of all SPs, not only ABCD3, should be studied in suspected cases because the presentations of the different SPs deficiencies may be overlapping. Moreover, *ABCA3* gene mutation is important because it might ultimately obviate the need for lung biopsy with improved patient outcomes in these cases.^[13]

The findings from this case report emphasize the need to perform genetic analysis in newborns with severe respiratory distress to adapt a better therapeutic approach along with timely genetic counseling.

Conclusions

p.Tyr1515* (Y1515X) is one of the most frequent mutations in exon 29 of *ABCA3*, usually leading to death within the 1st months. Appropriate prenatal diagnosis will help to deliver specific patient care and better outcomes. Similarly, mandatory genetic counseling is of remarkable importance to prevent further pregnancies and hence achieve better health outcomes. This case study aims to act as stepping stone to raise awareness of genetic counseling among parents as well as health-care providers.

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Conflicts of interest

There are no conflicts of interest.

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