

A rare case with compound heterozygous mutations of piezo-type mechanosensitive ion channel component 2 (*PIEZO2*) induced tracheobronchomalacia

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To the Editor: Tracheobronchomalacia (TBM) is a type of disorder that is caused by malformation of cartilage; the malformation leads to a deformity of the trachea or bronchus, with a cross-sectional reduction of $\geq 50\%$ during exhalation, due to primary or secondary reasons.^[1] The severity of TBM depends on the anatomical changes of airways, which are described as mild (50%–75% reduction), moderate (75%–90% reduction), and severe ($>90\%$ reduction).^[2] According to previous studies, a set of causes have been identified to be associated with TBM.^[3] Congenital airway malacia can be a part of many rare syndromes,^[4] including chromosomal defect syndromes, *de novo* genetic mutations, mucopolysaccharidoses, and inherited connective tissue disorders. In addition, some conditions, such as tracheoesophageal fistula, vascular rings, malformation of the cardiovascular system, vitamin D deficiency, and recurrent infections, are revealed as the secondary reasons for TBM. Therefore, for TBM patients, it is important to distinguish the etiologies of TBM, which help to guide therapeutic and nursing strategies.

A 20-day-old female neonate presented to the neonatal intensive care unit (NICU) with a chief complaint of dyspnea and cyanosis. This baby is a preterm newborn with 36⁺6 gestational weeks (gravidity 2, parity 2). Previous medical history demonstrated that she was transferred into the NICU immediately following delivery, suffering a lower Apgar score of 7–9–9 at 1, 5, and 10 min. This baby had been diagnosed mainly with neonatal pneumonia and sepsis. This time, we found the baby demonstrated severe cyanosis and dyspnea with a reduced oxygen saturation at 85%. This patient suffered from severe inspiratory breath difficulty. Her bilateral breathing sounds were rough. Both feet were observed to be with talipes equinovarus. In

addition, the primitive reflex was reduced, with decreased muscle tones. Cardiac and abdominal physical examinations were negative. For this patient, we consider that she might suffer some malformations of airway structure as well as disorders in cartilage development. Therefore, all the main tests were performed to address this issue. Computerized tomography scanning demonstrated multiple fractures of the 6th to 10th left ribs, scattered patches and interstitial changes located in bilateral lungs, and enhanced thickness of the pleura. Head magnetic resonance imaging showed abnormal signals in the white matter area in the margins of bilateral lateral ventricles, indicating multiple ischemia spots. Echocardiography failed to identify any aberrant structures on the main vessels that might be related to external oppression to airways. Finally, bronchoscopy was used to observe the internal cavity structures of the trachea and bronchus. During this examination, her epiglottis always curled during the inspiration period, while the small-angle cartilage collapsed inward. In addition, significant obstruction ($>50\%$ of diameter) was identified along the main trachea and left bronchus during expiration, and some branches of the right bronchus also demonstrated obstruction (basal segment of the right lower lobe) [Figure 1A–1C]. Because severe dyspnea has been present throughout the neonate's life, several symptoms of cartilage development disorder have been revealed. Therefore, genetic mutations of cartilage catabolic and anabolic processes were suspected. Further, whole-exome sequencing (WES) using Illumina NovaSeq 6000 platform (Illumina, Inc., CA, USA) was performed for this patient. Interestingly, two mutations, c.6049C>G (father carrying) and c.3754C>T (maternal carrying), were found in the piezo-type mechanosensitive ion channel component 2 (*PIEZO2*) gene, which encodes a

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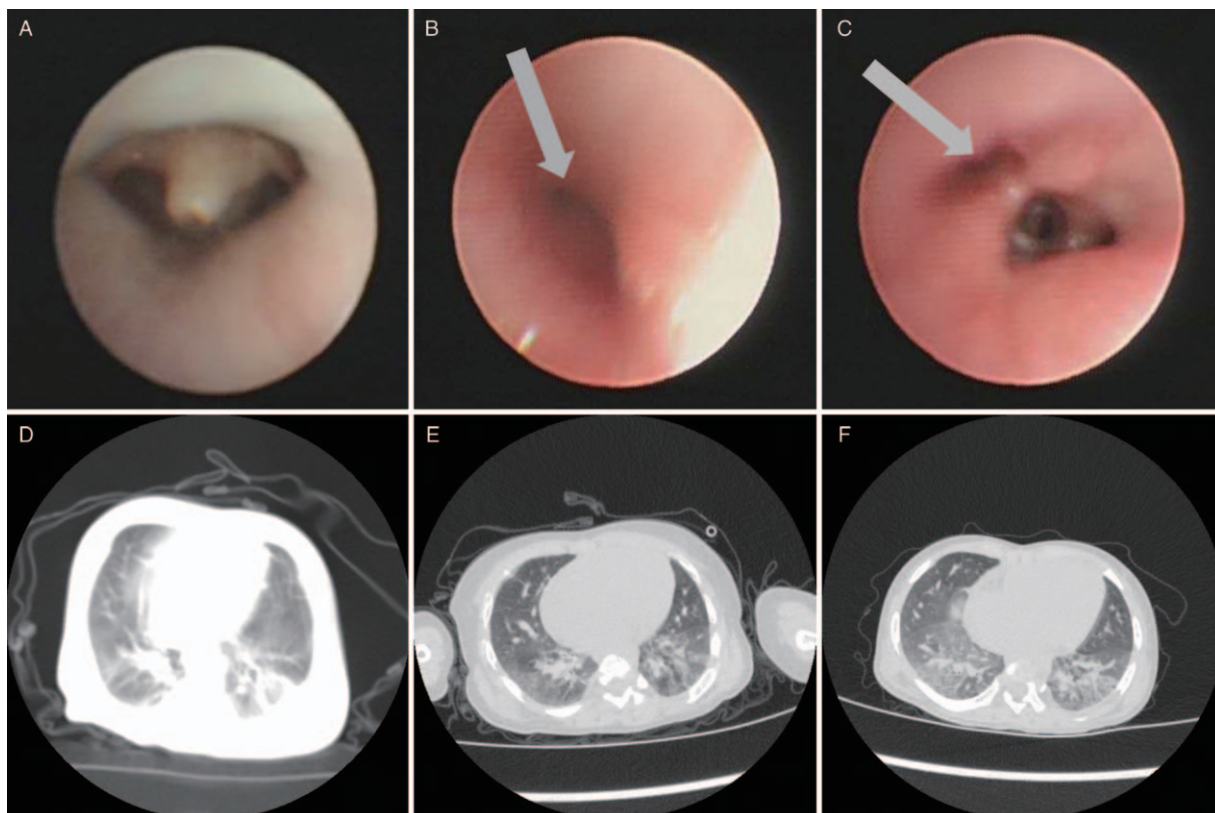


Figure 1: The bronchoscopy and CT scanning images demonstrated the obstructions of airways, caused by *PIEZO2* mutations and the recurrent infections in the lungs due to malformations of the trachea and bronchus. (A) Epiglottis curled at inspiration period. (B) Obstruction of the main trachea during the expiration phase. (C) Obstruction of the left bronchus during the expiration phase. (D–F) The CT scanning images at the ages of 3 months, 1, and 1.5 years. The arrow revealed the obstructions of airways. CT: Computerized tomography; *PIEZO2*: Piezo-type mechanosensitive ion channel component 2.

mechanosensitive calcium channel that is related to the mechanical structure of cartilage formation. This patient was finally diagnosed with TBM with a compound heterozygous mutation of *PIEZO2*.

After we obtained the genetic results, the tracheotomy was performed on this patient at 7 months of age without any hesitation, as her genetic screening indicated that cartilage formation disorder resulting in TBM was not a reversible medical issue. After that, the patient visited the hospital almost every half-a-year for several days of antibiotic therapy, and no additional ventilation support was necessary. In addition, catch-up growth was confirmed in this case both in body and motor development. However, recurrent pulmonary infections were observed during follow-up [Figure 1D–1F].

The molecular basis of TBM is the deformation of cartilage, which could be due to variants in any genes related to chondrocyte proliferation, differentiation, maturation, and maintenance of homeostasis. Taking advantage of genomic screening, a rapidly increasing number of new mutations have been identified as being associated with TBM. Chondrocytes require optimal pressure and matrix surroundings to maintain homeostasis. Among a series of mechanisms, the channelome is an essential molecule to help generate electrochemical gradients.^[5] The Ca^{2+} ion channel is the most important channel for normal cartilage development and function. *PIEZO* channels are well known

as ion channels that are directly activated by mechanical stress, which plays a critical role in trachea and bronchus structure formation and anatomy maintenance. More recently, *PIEZO1* and *PIEZO2* have been identified as transduction channels that respond to high levels of mechanical stress. Ca^{2+} influx can be inhibited by blocking *PIEZO* channels with GsMTx4, and these channels can be activated by high strain, especially in situations of overpressure load or pathological stimulation. The inhibition of *PIEZO2* genes should induce a reduction in chondrocyte proliferation and maturation, as well as cartilage tissue structure. The two mutations of c.6049C>G (Mutation Taster 0.944) and c.3754C>T (Mutation Taster 1.0) were both predicted to have protein-damaging and disease-causing effects. Therefore, for this case, the compound heterozygous mutations on *PIEZO2* would lead to the loss-of-function of this gene, indicating insensitivity to mechanical stress-inducing cartilage maturation disorder. Therefore, the inactivity of the *PIEZO2* channel would lead to deformation of the mechanical structure of chondrocyte-enriched tissues. Also, this finding helps to provide a reasonable explanation between the genotype and disease phenotype for this patient.^[5]

To conclude, it is strongly recommended to perform genomic tests for TBM cases after ruling out high-risk factors and external airway malformation. This is a rare reported case on the association between mutations of *PIEZO2* and TBM. The genetic results would not only

help to reach a diagnosis, but also help to establish the optimal nursing strategy and emphasize parents' education, which should benefit the prognosis of TBM children, avoiding repeated complications.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient's parents have given their consent for her images and other clinical information to be reported in the journal. The patient's parents understand that her name and initials will not be published and that due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Conflicts of interest

None.

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