American Journal of Respiratory and Critical Care Medicine, 2026, 212(10), 2628–2631
https://doi.org/10.1093/ajrccm/aamag320
Published: July 7, 2026
Images in Pulmonary, Critical Care, Sleep Medicine and the Sciences

From idiopathic pulmonary hemosiderosis to ENaC channelopathy: a novel *SCNN1G* mutation

Qi Peng[1,2,3,†], Zaixue Jiang[2,3,†], Yongyi Chen[4,†], Yufeng Li[4], Fangfang Zhang[2,3], Lijun Yang[5], Wei Lai[6], Xiaojun Huang[5], Linsheng Wang[2,3], Xiaomei Zeng[1,2,3], Baimao Zhong[2,3,*], Xiaomei Lu[1,2,3,*]

[1]Laboratory Department, Dongguan Eighth People's Hospital (Dongguan Children's Hospital), Dongguan, Guangdong, China
[2]Department of Medical and Molecular Genetics, Dongguan Institute of Pediatrics, Dongguan, Guangdong, China
[3]Key Laboratory for Children's Genetics and Infectious Diseases of Dongguan, Dongguan, Guangdong, China
[4]Department of Pulmonary and Critical Care Medicine, Dongguan Eighth People's Hospital (Dongguan Children's Hospital), Dongguan, Guangdong, China
[5]Department of Pathology, Dongguan Eighth People's Hospital (Dongguan Children's Hospital), Dongguan, Guangdong, China
[6]Department of Radiology, Dongguan Eighth People's Hospital (Dongguan Children's Hospital), Dongguan, Guangdong, China
*Corresponding authors: Xiaomei Lu, Laboratory Department, Dongguan Eighth People's Hospital (Dongguan Children's Hospital), Dongguan Institute of Pediatrics, No. 68, Xihu Third Road, Shilong Town, Dongguan City, Guangdong Province, China (lxm020@126.com) and Baimao Zhong, Dongguan Children's Hospital (Dongguan Eighth People's Hospital), No. 68, Xihu Third Road, Shilong Town, Dongguan City, China (zbomao@163.com).
†These authors contributed equally to this work and are considered co-first authors.

A 24-year-old woman presented with a 7-year history of recurrent hemoptysis, showed no response to immunosuppressants, and was initially misdiagnosed with idiopathic pulmonary hemosiderosis (IPH) based on hemosiderin-laden macrophages (Figure 1A, B). High-resolution computed tomography revealed acute alveolar hemorrhage without bronchiectasis (Figure 1C). Secondary causes, including autoimmune and cardiovascular etiologies, were excluded (Table S1).

Whole-exome sequencing identified a novel heterozygous variant (c.1126G>A; p.Gly376Arg) in *SCNN1G,* which encodes the γ subunit of the epithelial sodium channel (ENaC) (Figure 2A), and this was confirmed by Sanger sequencing (Figure 2B). Following confirmation of mutant γ-ENaC expression (Figure 2C) and complex assembly via α/β-subunit co-transfection (Figure 2D), patch-clamp electrophysiology revealed a gain-of-function phenotype with amplified amiloride-sensitive sodium currents (Figure 2E).

ENaC regulates airway surface liquid volume and mucociliary clearance.[1] We hypothesize a novel channelopathy wherein hyperactive ENaC might drive fluid absorption and mucociliary impairment.[2,3] Though requiring further validation, the ensuing chronic inflammation could injure the alveolar-capillary membrane, leading to recurrent alveolar hemorrhage.

Following the initiation of an exploratory regimen aimed at this mechanism—inhaled hypertonic saline (3%) targeting airway hydration, alongside oral eucalyptol and azithromycin intended to inhibit ENaC[4]—we observed a reduction in hemoptysis frequency from 41% to 17.2% over 6 months, coinciding with radiographic resolution (Figure 1D).

This case proposes a potential link between ENaC gain-of-function and alveolar hemorrhage, suggesting genetic evaluation for refractory IPH. While a temporal clinical improvement was noted, in vivo models remain essential to confirm if ENaC hyperactivity directly mediates capillary injury. Furthermore, ENaC's role in alveolar type 2 cell lineage[5] highlights its underexplored function in distal alveolar homeostasis.

Received: March 17, 2026. **Accepted:** May 11, 2026
© The Author(s) 2026. Published by Oxford University Press on behalf of the American Thoracic Society.
This is an Open Access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.

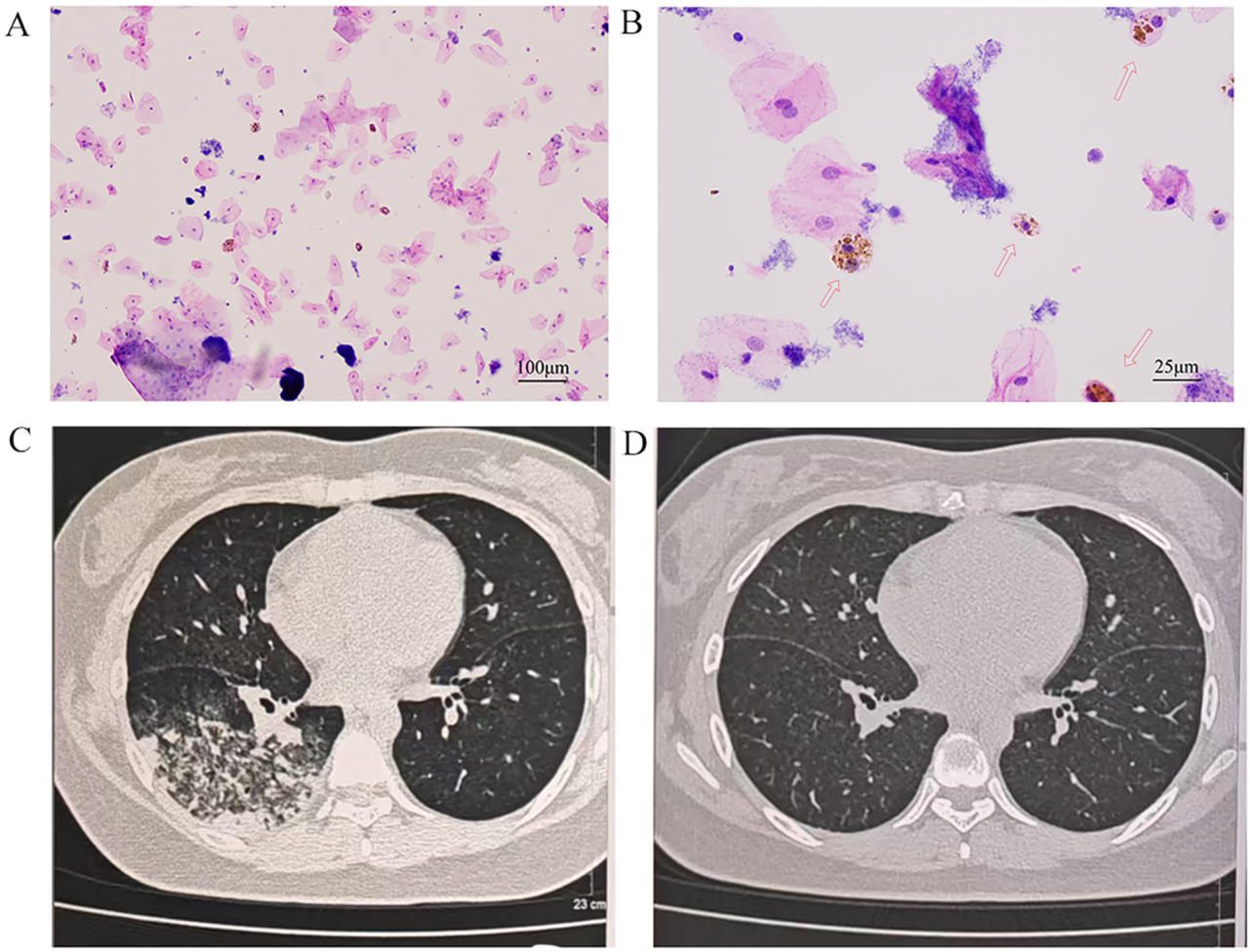


Figure 1 Cytological and radiological findings of the patient. (A) Low-magnification (100×) hematoxylin and eosin staining of the patient's bronchoalveolar lavage fluid demonstrating numerous hemosiderin-laden macrophages scattered throughout the field. Scale bar = 100 μm. (B) High-magnification (400×) image showing characteristic intracytoplasmic golden-brown hemosiderin granules (arrows). Scale bar = 25 μm. (C) High-resolution computed tomography (HRCT) at presentation, demonstrating diffuse bilateral ground-glass opacities and focal consolidation in the right lower lobe, indicating acute alveolar hemorrhage. (D) Follow-up HRCT after airway-directed therapy, showing significant resolution of the pulmonary lesions and infiltrates.

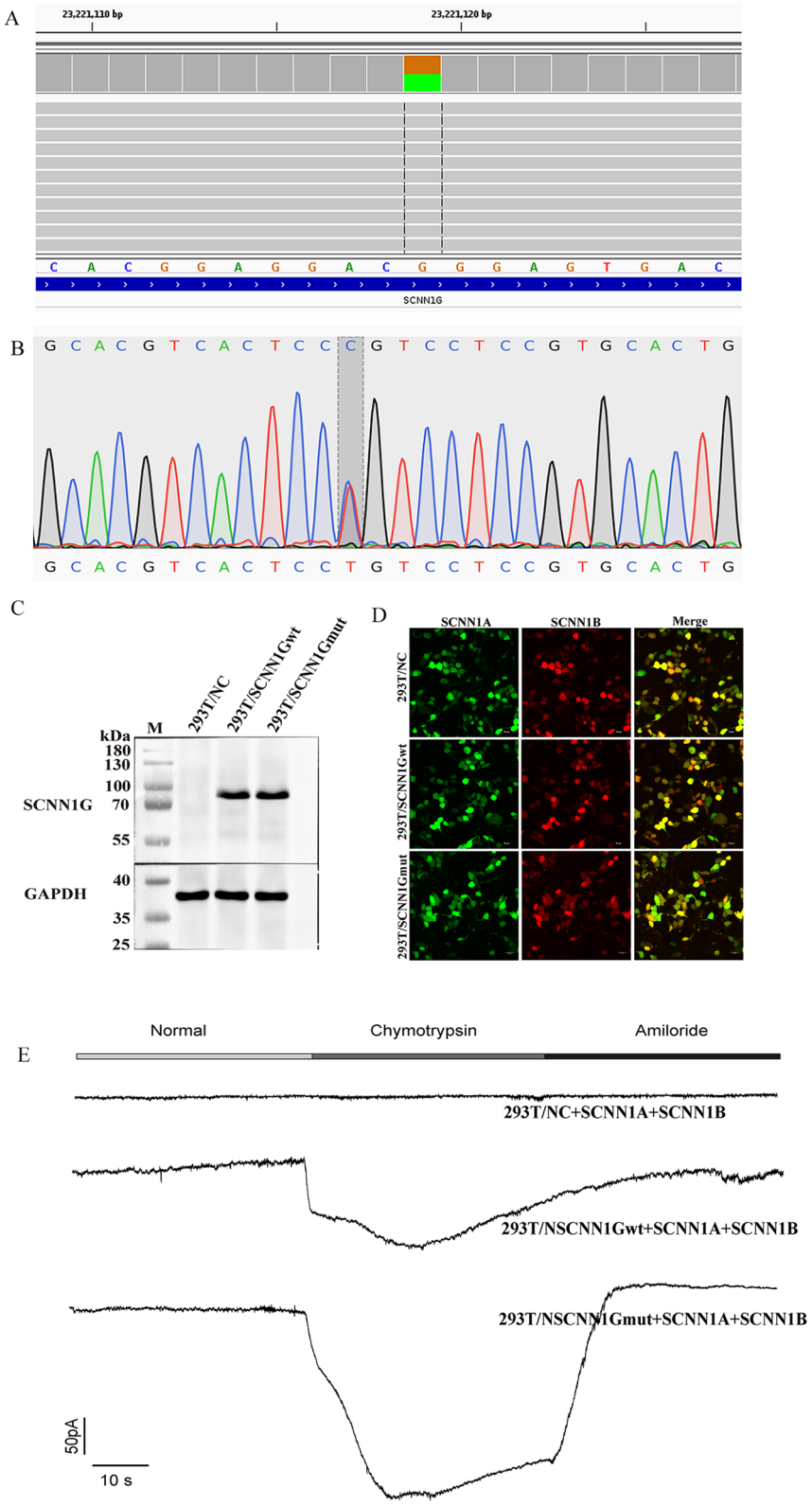


Figure 2 Genetic and functional validation of the *SCNN1G* c.1126G>A (p.Gly376Arg) variant. (A) Integrative Genomics Viewer snapshot of whole-exome sequencing data, identifying a heterozygous missense mutation (c.1126G>A, p.Gly376Arg) in the *SCNN1G* gene (NM_001039.4). (B) Sanger sequencing chromatogram confirming the heterozygous c.1126G>A variant (shaded gray box). (C). Western blot analysis of HEK293T cell lines (293T/NC, 293T/*SCNN1G* wild-type [wt], and 293T/*SCNN1G* mutant [mut]). Both wild-type and mutant γ-epithelial sodium channel (ENaC) proteins showed robust and comparable expression at approximately 75 kDa, with GAPDH as the loading control. (D) Immunofluorescence microscopy confirming the co-expression and proper membrane localization of α-ENaC (green) and β-ENaC (red) subunits in the γ-ENaC established cell lines. (E) Representative whole-cell patch-clamp electrophysiology traces. In cells co-expressing α/β subunits with mutant γ-ENaC (G376R), the amiloride-sensitive sodium current (activated by chymotrypsin and inhibited by amiloride) was significantly increased compared to the wild-type group, confirming a gain-of-function effect.

Author contributions

Q.P. and X.L. were involved in study conception and genetic analysis. Z.J., F.Z., and X.Z. performed the experimental studies. Y.C. and Y.L. contributed to clinical data acquisition and patient management. L.Y. and X.H. performed pathological examination and interpretation. W.L. provided and interpreted radiological images. L.W. assisted in electrophysiological experiments and data analysis. B.Z. and X.L. supervised the project and critically revised the manuscript. All authors reviewed and approved the final version. B.Z. and X.L. are the guarantors.

Supplementary material

Supplementary material is available at *American Journal of Respiratory and Critical Care Medicine* online.

Conflicts of interest

Please see the ICMJE disclosure forms, which have been provided as supplementary material. None declared.

Funding

This work was supported by the Guangdong Basic and Applied Basic Research Fund (Guangdong-Dongguan Joint Fund) (2024A1515140175), Dongguan Eighth People's Hospital doctoral research start-up fund project (DBBS2023003).

References

1. Hanukoglu I, Hanukoglu A. Epithelial sodium channel (ENaC) family: phylogeny, structure-function, tissue distribution, and associated inherited diseases. *Gene*. 2016;579:95-132. https://doi.org/10.1016/j.gene.2015.12.061
2. Douglas LEJ, Reihill JA, Montgomery BM, et al. Furin as a therapeutic target in cystic fibrosis airways disease. *Eur Respir Rev*. 2023;32:220256. https://doi.org/10.1183/16000617.0256-2022
3. Chen Y, Yu X, Yan Z, et al. Role of epithelial sodium channel-related inflammation in human diseases. *Front Immunol*. 2023;14:1178410. https://doi.org/10.3389/fimmu.2023.1178410
4. Fujikawa H, Kawakami T, Nakashima R, et al. Azithromycin inhibits constitutive airway epithelial sodium channel activation in vitro and modulates downstream pathogenesis in vivo. *Biol Pharm Bull*. 2020;43:725-730. https://doi.org/10.1248/bpb.b19-01091
5. Jain KG, Zhao R, Ji H-L. Delta subunit of sodium epithelial channel regulates alveolar type 2 cell lineage in mice lungs. *Am J Respir Crit Care Med*. 2025;211:A2441. https://doi.org/10.1164/ajrccm.2025.211.Abstracts.A2441

© The Author(s) 2026. Published by Oxford University Press on behalf of the American Thoracic Society.
This is an Open Access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited. American Journal of Respiratory and Critical Care Medicine 2026 212(10) 2628–2631
https://doi.org/10.1093/ajrccm/aamag320
Images in Pulmonary, Critical Care, Sleep Medicine and the Sciences