Balkan Med J 2025;42:464-8

A Rare *TERT* Mutation Associated with Idiopathic Pulmonary Fibrosis and COPD in a Chinese Family

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Background: Idiopathic pulmonary fibrosis (IPF) is a form of interstitial lung disease characterized by progressive lung scarring. It involves destruction of the alveolar architecture, thickening of the basement membrane, abnormal deposition of the extracellular matrix, inflammatory cell infiltration in the interstitial space, and formation of fibroblast foci. Mutations in *telomerase reverse transcriptase (TERT)* have been reported to be associated with IPF.

Aims: To explore the genetic cause of a family affected by IPF and chronic obstructive pulmonary disease.

Study Design: Cross-sectional study.

Methods: Whole-exome sequencing combined with IPF candidate gene filtering was used to identify the causative mutations. Sanger sequencing was applied to validate the mutation and perform c-segregation analysis. Real-time polymerase chain reaction (PCR) was conducted to analyze the telomere lengths of family members.

Results: We identified a rare mutation, c.2669G > A (p. Gly890Asp), in *TERT* (NM_198253.2) in the proband and another affected family member. Bioinformatics analysis predicted this mutation to be deleterious, and structural modeling suggested that it altered the structure and surface charge distribution of the *TERT* protein. Additionally, real-time PCR demonstrated that mutation carriers had significantly shorter telomere lengths compared with individuals of the same age. According to American College of Medical Genetics and Genomics guidelines, this rare mutation was classified as likely pathogenic.

Conclusions: This is the first reported case of IPF caused by the p. Gly890Asp mutation of *TERT* in the Chinese population. Our findings support the diagnosis of IPF in the patient and further highlight the role of *TERT* in the disease.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and one of the most common subtypes of interstitial lung disease of unknown origin. Its hallmark pathological features include abnormal thickening and stiffening of the lung tissue, accompanied by progressive fibrotic changes within the lung parenchyma.[1] These structural alterations impair the functionality of the alveolar-capillary units, leading to a marked reduction in gas exchange efficiency and subsequently causing characteristic respiratory symptoms such as progressive dyspnea and hypoxemia. Epidemiological studies indicate that the incidence of IPF is steadily increasing, with over 50,000 new cases diagnosed globally each year.[2] Genetic studies have reported that mutations in genes encoding telomere-related proteins and pulmonary surfactant proteins are implicated in the development of IPF.[3] These genetic aberrations collectively contribute to pulmonary fibrosis by disrupting cellular repair processes and alveolar homeostasis.[4]

As one of the key genes encoding telomere-associated proteins, *telomerase reverse transcriptases* (*TERT*, NM_198253.2) encodes the telomerase catalytic subunit-a ribonucleoprotein complex essential for maintaining chromosomal stability in eukaryotic cells.[5] Acting as the core enzymatic component, *TERT* facilitates telomere elongation through its reverse transcriptase (RT) activity, synthesizing telomeric repeats at chromosome ends.[6] Previous studies have indicated that *TERT* is a pivotal regulator of cellular senescence.[7] Mutations in *TERT* have been documented in patients with IPF[8,9], dyskeratosis congenita, bone marrow failure syndrome, and other related conditions.[10]

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Received: June 17, 2025 **Accepted:** August 20, 2025 **Available Online Date:** 01.09.2025 • **DOI:** 10.4274/balkanmedj.galenos.2025.2025-6-142
Available at www.balkanmedicaljournal.org

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Cite this article as: Fan LL, Feng DC, Long JY, Zhang AQ. Idiopathic Pulmonary Fibrosis and Chronic Obstructive Pulmonary Disease Caused by A Novel *TRET* Mutation in A Chinese Family. Balkan Med J. 2025; 42(5):464-8.

Here, we describe a family affected by IPF and chronic obstructive pulmonary disease (COPD), in which whole-exome sequencing and Sanger sequencing were employed to identify candidate mutations in the affected individuals.

MATERIALS AND METHODS

Subjects

A three-generation Chinese pedigree consisting of seven members affected by IPF and COPD was recruited for this study (Figure 1a). Clinical data and peripheral blood samples were collected from five members, including two affected individuals (II-1 and III-1) and two unaffected individuals (II-2 and II-3). This study was approved by the Ethics Committee of the Third Xiangya Hospital of the Central South University (approval number: 2024363, date: 28.06.2024). Informed consent was obtained prior to blood sample collection.

Whole-exome sequencing

Genomic DNA was extracted from peripheral blood lymphocytes of family members using the DNeasy Blood and Tissue Kit (Qiagen, USA). Whole-exome sequencing of the proband (II-1) was performed at the Berry Genomics Institute (Beijing, China). Exomes were captured using Agilent SureSelect Human All Exon V6 kits, and sequencing was carried out on the Illumina HiSeq X-10 platform. Subsequent steps, including read mapping, variant detection, general data filtering, and annotation, were also conducted at the Berry Genomics Institute (Beijing, China). The data filtering strategy followed our previously established methods.[11]

Sanger sequencing

Filtered variants were validated and subjected to co-segregation analysis using Sanger sequencing. The primers used for amplification were as follows: Forward 5'-AGCACCCTGCTCCAAATC-3', Reverse 5'-CCTCGTCTTCTACAGGGAAGT-3'. Polymerase chain reaction (PCR) products were analyzed on an ABI 3100 Genetic Analyzer.

Bioinformatics analysis

Bioinformatics analyses were performed as described in our previous study.[11] These included pathogenicity prediction using MutationTaster, PolyPhen-2, and SIFT, tolerance analysis using MetaDome software, and protein modeling analysis using SWISS-MODEL software.

Telomere length detection

Telomere length was compared among family members using a commercial telomere length assay kit (Biowing Telomere Detection Kit, TL100, Shanghai), which includes data from 1,500 peripheral blood samples randomly collected in Shanghai. Procedures followed the manufacturer's established protocols.[12,13] Telomere length was measured on a Fast 7500 Real-Time PCR System (Applied Biosystems) using the $2^{(-\triangle\triangle Ct)}$ method. Each measurement was performed in triplicate.

RESULTS

Clinical description

The proband (II-1), a 76-year-old male, presented with a persistent cough and expectoration lasting > 1 month and was admitted to the hospital. His symptoms had significantly worsened over the preceding 4 days, accompanied by fever. Physical examination revealed coarse breath sounds in both lungs, along with wet rales and pleural friction rubs. Laboratory tests showed a markedly elevated neutrophil count (6.33×10^9/L) on complete blood count. Lipid profile testing indicated hypertriglyceridemia, with a triglyceride level of 3.7 mmol/L. Infection markers demonstrated elevated procalcitonin (0.17 ng/mL), C-reactive protein (62.40 mg/L), and erythrocyte sedimentation rate (58 mm/h). The interferon-γ release assay was positive, while other laboratory findings were negative. Chest radiography and computed tomography of the proband revealed bilateral interstitial lung changes, with recurrent infection, emphysema, and minimal bilateral pleural effusions (Figure 1b). He also reported experiencing chest tightness and shortness of breath for > 3 years. Following multidisciplinary consultation involving two respiratory physicians, one radiologist, and one rheumatologist, the patient was diagnosed with IPF. Family history indicated that the proband's mother (I-2) had a history of hemoptysis. Radiological examination of the proband's son (III-1) showed an increased and disorganized bronchovascular pattern in

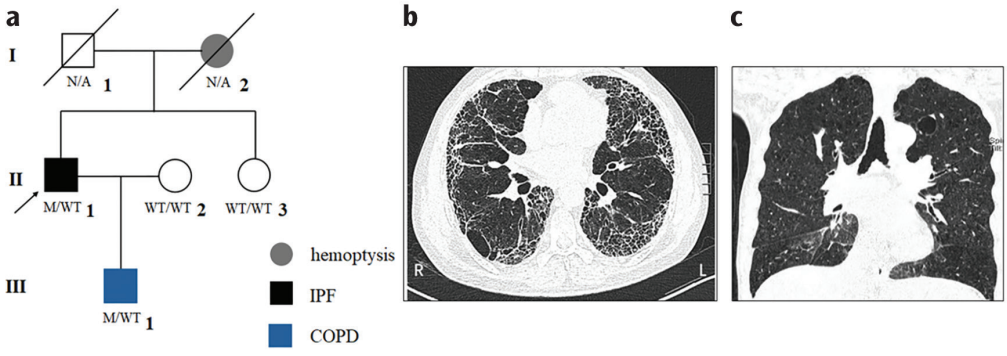

FIG. 1. Clinical and genetic analysis of the family. (a) Pedigree of the family. The arrow indicates the proband. N/A means no detection. M represents mutation. WT represents Wilde type. The HRCT of the proband (b) and the proband's son (III-1) (c) were exhibited.
IPF, idiopathic pulmonary fibrosis; COPD, chronic obstructive pulmonary disease; N/A, not available; HRCTV, high-risk clinical target volume.

both lungs, along with multiple cystic, wall-less lucencies suggestive of bronchial abnormalities complicated by emphysema (Figure 1c). Pulmonary function testing revealed an forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio of 63.90%, post-bronchodilator FEV_1/FVC ratio of 63.62%, and FEV_1 of 78.20%, consistent with moderate COPD. Both the proband and his son (III-1) denied any history of smoking.

Genetic analysis

After filtering the whole-exome sequencing data using the candidate gene table (Table S1), a rare *TERT* mutation, c.2669G > A (p. Gly890Asp), previously associated with IPF, was identified in the proband. Sanger sequencing confirmed the presence of this mutation in both the proband and his son (III-1), but not in the healthy control (II-3) (Figure 2a). This variant was absent from public databases, including 1000G, ESP6500, dnSNP155, and gnomAD. The p. Gly890Asp mutation occurred at a highly evolutionarily conserved site (Figure 2b) and within an intolerant region of *TERT* (Figure 2c). Bioinformatics tools predicted the variant to be deleterious. Protein structure modeling indicated that the mutation disrupted the α-helical conformation of the *TERT* protein (Figure 2d) and altered its surface charge distribution (Figure 2e). Telomere length analysis demonstrated that mutation carriers (II-1 and III-1) had significantly shorter telomeres compared with age-matched controls, whereas the healthy control (II-3) had telomere length in the upper range for his age group (Figure 3). According to American College of Medical Genetics and Genomics guidelines[14], the p.Gly890Asp mutation in *TERT* is classified as likely pathogenic, meeting the following criteria: PM1 (located in a well-established functional domain) + PM2 (absent from controls in the Exome Sequencing Project and 1,000 Genomes) + PP1 (co-segregation with disease in multiple affected family members) + PP3 (computational evidence supports a deleterious effect on the gene).

DISCUSSION

The association between *TERT* gene mutations and IPF has been substantiated by numerous studies.[8,9] *TERT* encodes the telomerase catalytic subunit, which maintains telomere length and thereby safeguards chromosomal stability.[5] Approximately 15% of patients with familial pulmonary fibrosis carry heterozygous *TERT* mutations.[8] In this study, we identified a rare *TERT* mutation, c.2669G > A (p. Gly890Asp), in a family with IPF and COPD. The mutation carriers exhibited shortened telomere length. This variant has also been reported in the ClinVar database (RCV005212934.1) in patients with dyskeratosis congenita and IPF; however, detailed clinical information and telomere length data were not provided. To our knowledge, this is the first report describing the p.Gly890Asp mutation in Chinese patients with IPF and COPD. Our findings support the diagnosis of IPF in the proband and further highlight the role of *TERT* in IPF pathogenesis.

The *TERT* protein consists of an N-terminal region, a central RT domain, and a C-terminal extension.[15] The RT domain contains nine essential motifs within two subdomains, which together account for its reverse transcription activity.[15] The p. Gly890Asp mutation lies within the RT domain and may impair reverse transcription activity, ultimately leading to telomere shortening in mutation carriers[16] as confirmed by our telomere length analysis. These results further underscore the functional importance of the RT domain in *TERT*.

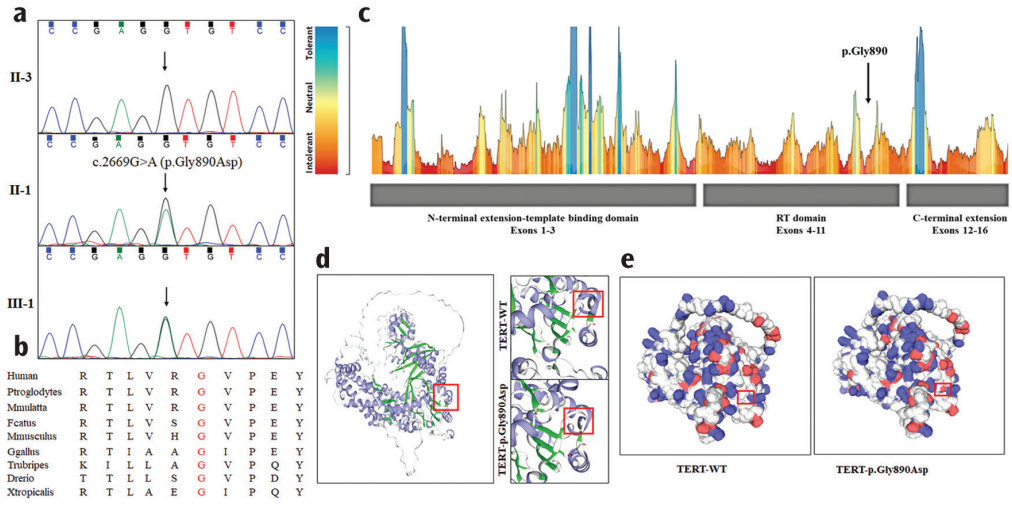

FIG. 2. Genetic analysis of the *TERT* mutation. (a) Sanger sequencing of *TERT* confirmed the c.2669G > A/p.Gly890Asp rare mutation in II-1 and III-1. (b) Alignment of multiple *TERT* protein sequences across species. The p.Gly890-affected amino acid is located in the highly conserved amino acid region in different mammals (from Ensembl). The red words represent the p.Gly890. (c) The tolerance analysis of mutant amino acid sites of *TERT* was predicted by MetaDome software. (d) The wild type *TERT* (WT) protein structure and the mutant *TERT* (p.Gly890Asp) protein structures were predicted by SWISS-MODEL online software. The blue structure represents the α -helical structure. The red squares showed the mutation altered the structure of *TERT* protein. (e) The electrostatic potential maps of wild type *TERT* (WT) protein structure and the mutant *TERT* (p.Gly890Asp) protein. The red squares indicate the changes of the surface charge distribution between WT and mutated proteins.

TERT, telomerase reverse transcriptase.

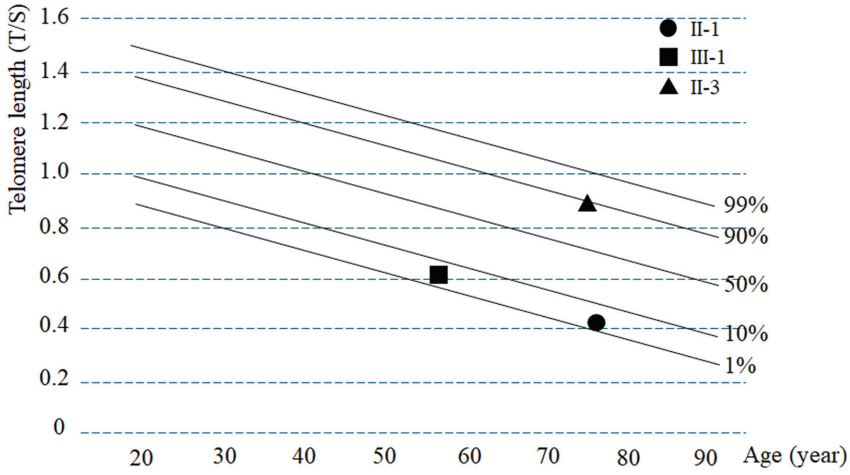

FIG. 3. Telomere length of the mutation carrier (II-1 and III-1) and healthy control (II-3). T/S represents relative telomere length. Random volunteers were recruited at different age stages, tested for telomere length by real-time PCR and established of the characteristics of the Chinese population which then lines represent the 1st, 10th, 50th, 90th, and 99th percentiles of telomere length in age-matched controls' granulocytes and lymphocytes were identified.

PCR, polymerase chain reaction; T/S, telomer/single copy gene.

The pulmonary fibrosis phenotype in *TERT* mutation carriers exhibits an age-dependent pattern. Typically, no onset is observed in carriers under the age of 40, whereas the incidence rate increases to approximately 60% among men aged 60 years and older.[17] Imaging studies have shown that 74% of pulmonary fibrosis cases associated with *TERT* mutations present with typical IPF features, such as a usual interstitial pneumonia (UIP) pattern.[17] However, a subset of patients display an atypical UIP pattern.[18] In our study, both affected individuals developed symptoms after age 50, consistent with the reported later onset in *TERT* mutation carriers.

In addition, one mutation carrier in our study was diagnosed with COPD, another chronic lung disease. Previous studies have reported that approximately 1% of severe COPD cases are attributable to telomere-related gene mutations, and COPD in patients with such mutations tends to be more severe compared with COPD in patients without these mutations.[19] In our cohort, the *TERT* mutation carrier with COPD was diagnosed with moderate disease at age 50-substantially younger than the average age of COPD onset in China.[20] Telephone follow-up revealed that his shortness of breath had worsened significantly over the past 5 years. Unfortunately, the patient declined further medical evaluation. These findings further support the role of *TERT* mutations not only in IPF but also in other chronic lung diseases, including COPD.

In summary, we identified a rare *TERT* mutation, c.2669G > A (p. Gly890Asp), in a family with IPF and COPD. Both mutation carriers exhibited markedly shortened telomere lengths compared with healthy controls. This is the first report of the p.Gly890Asp mutation in a Chinese IPF patient. Our findings support the diagnosis of IPF in the proband and further highlight the pathogenic role of *TERT* mutations in IPF.

Ethics Committee Approval: The study was approved by the Ethics Committee of the Third Xiangya Hospital of the Central South University (approval number: 2024363, date: 28.06.2024).

Informed Consent: Informed consent was obtained prior to blood sample collection.

Authorship Contributions: Concept- A.Q.Z.; Design- L.L.F.; Supervision- A.Q.Z.; Fundings- A.Q.Z.; Materials- D.C.F.; Data Collection or Processing- L.L.F.; Analysis or Interpretation- L.L.F., D.C.F., J.Y.L.; Literature Review- L.L.F., D.C.F., A.Q.Z.; Writing- L.L.F., D.C.F.; Critical Review- L.L.F., A.Q.Z.

Data Sharing Statement: The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interest: The authors declare that they have no conflict of interest.

Financial Disclosure: This work was supported by Natural Science Foundation of Hunan Province (2025JJ50518).

Supplementary: balkanmedicaljournal.org/img/files/supplementray.pdf

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