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Eur Respir J 2013; 42: 1752–1757 | DOI: 10.1183/09031936.00140913 | Copyright ©ERS 2013

Pulmonary fibrosis in dyskeratosis congenita with *TINF2* gene mutation

To the Editor:

Dyskeratosis congenita is a rare inherited disorder of ectodermal dysplasia characterised by the classical mucocutaneous triad of abnormal skin pigmentation, nail dystrophy and leukoplakia [1–3], at least one of which is present in around 80–90% of dyskeratosis congenita cases. Bone marrow failure is another common feature, and a variety of other abnormalities (*e.g.* dental, gastrointestinal, neurological, ophthalmic, pulmonary and skeletal) have been also described [1–3]. The main causes of mortality in dyskeratosis congenita are bone marrow failure, pulmonary disease and malignancy [1]. Three modes of inheritance have been recognised: X-linked recessive, autosomal dominant and autosomal recessive [1, 3]. Eight dyskeratosis congenita genes (*DKC1* (dyskeratosis congenita 1), *TERC* (telomerase RNA component), *TERT* (telomerase reverse transcriptase), *NOP10* (nucleolar protein 10), *NHP2*, *TINF2* (TERF1-interacting nuclear factor 2), *TCAB1* and *RTEL1* (regulation of telomere elongation helicase 1)) have already been identified, and their mutations account for ~60% of all dyskeratosis congenita cases [1]. Among the dyskeratosis congenita genes, mutations in *TERC*, *TERT* and *DKC1* have recently been reported to be associated with familial pulmonary fibrosis and idiopathic pulmonary fibrosis, and pulmonary fibrosis is recognised as one of the features of dyskeratosis congenita. However, the relationship between mutations in the other dyskeratosis congenita genes and pulmonary fibrosis has not yet been clarified. To the best of our knowledge, this is the first case report describing a dyskeratosis congenita patient with pulmonary fibrosis who had a *TINF2* mutation.

A 43-year-old female visited our hospital with cough and progressive dyspnoea. She had never smoked, and had a history of aplastic anaemia, ocular pemphigoid, erythroplasia of Queyrat and infertility. Her father had been diagnosed as having aplastic anaemia and his whole body was pigmented. About 2 years ago, she complained of cough and consulted her personal doctor. Her chest radiographs showed diffuse reticular shadows in the bilateral lung fields. She was referred to a general hospital and was diagnosed with idiopathic interstitial pneumonia. Because her general condition was stable at that time, she was followed up without any specific therapy for 1 year. She was referred to our hospital due to gradual worsening of dyspnoea and admitted for further examinations. Her physical examination was remarkable for skin pigmentation on her whole body, ocular pemphigoid in the left eye and fine crackles in both lung fields. Her fingertip skin was rough but her nails were not dystrophic. Although no leukoplakia was found in the oral mucosa, she had erythroplasia of Queyrat of the vulva. Laboratory data showed elevated lactate dehydrogenase, transaminases, erythrocyte sedimentation rate and sialylated carbohydrate antigen KL-6 with thrombocytopenia. Chest radiographs demonstrated consolidation and reticular shadows in the bilateral lung fields. Furthermore, chest computed tomography revealed consolidation and reticular shadows in both lung fields, as well as bronchiectasis and cystic shadows in the left lung.

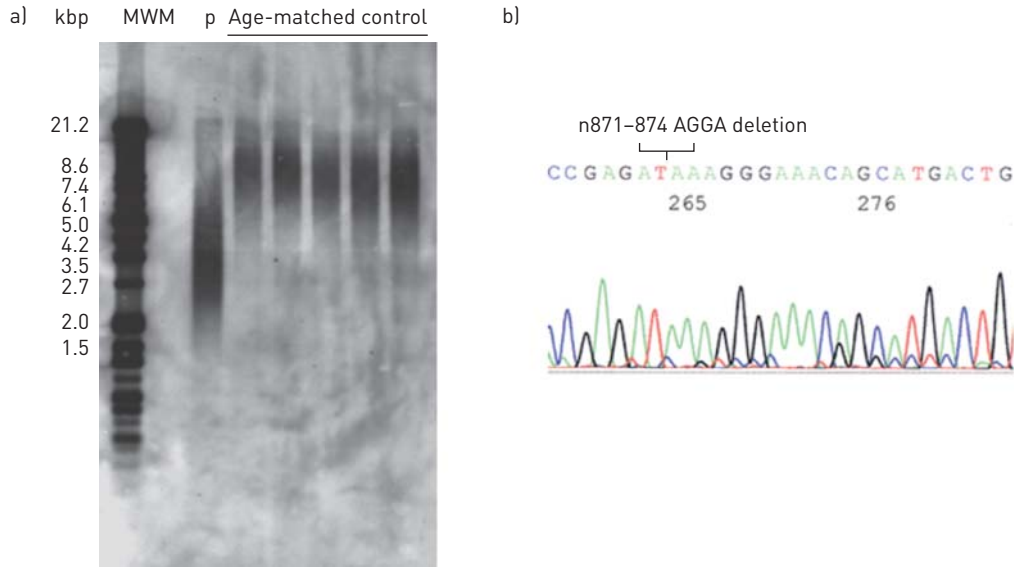

FIGURE 1 a) Southern blot analysis showed shorter telomere length of the patient (P) compared to age-matched healthy controls. MWM: molecular weight marker. b) Gene mutation analysis by direct sequencing showed n871–874 tetranucleotide AGGA deletion in *TINF2* gene.

At this point, we strongly suspected that she had dyskeratosis congenita. To make a definite diagnosis, we first examined the *TERC* and *TERT* genes by direct sequencing. However, no mutations were found in either gene. Southern blot analysis showed short telomere length (fig. 1a), therefore mutations in *TINF2* were next explored. As shown in figure 1b, because direct sequencing showed a n871–874 tetranucleotide AGGA deletion in *TINF2*, she was diagnosed as having dyskeratosis congenita with pulmonary fibrosis associated with *TINF2* mutation. As her respiratory condition progressed, steroid pulse therapy followed by oral prednisolone was conducted. However, no improvement of her symptoms was observed, and bilateral pneumothorax with mediastinal and subcutaneous emphysemas developed. She died of respiratory failure 1 year after starting the treatment.

Dyskeratosis congenita is a rare genetic ectodermal disorder characterised by skin hyperpigmentation, nail dystrophy and leukoplakia of the mucous membranes. Bone marrow failure is a frequent finding and a predisposition to malignancy has been noted. Although pulmonary manifestations of dyskeratosis congenita were believed to be uncommon, DOKAL [1] reported that abnormal pulmonary features may be seen in as many as 10–15% of patients.

Genetically, dyskeratosis congenita is heterogeneous, with three forms having been identified: X-linked recessive, autosomal dominant and autosomal recessive. In the present case, the patient's father had suffered from the same disease; therefore, we suspected that the form of dyskeratosis of this patient was autosomal dominant. The autosomal dominant form of dyskeratosis congenita is caused by heterozygous mutations in the core components of telomerase, *TERC* [4, 5] and *TERT* [6, 7], as well as in the component of the shelterin telomere protection complex, *TINF2* [3]. In this patient, mutation of *TINF2*, but not *TERC* and *TERT*, was confirmed by gene mutation analysis. It has previously been reported that mutations in *DKC1* [8], *TERC* [5] and *TERT* [6] were associated with pulmonary fibrosis in dyskeratosis congenita patients. *DKC1* was not analysed in this patient, because mutation in *DKC1* causes the X-linked form of dyskeratosis congenita. Regarding the relationship between pulmonary fibrosis and *TINF2* mutation in dyskeratosis congenita, WALNE *et al.* [3] have reported that only one patient had pulmonary fibrosis among other clinical features in 33 dyskeratosis congenita patients with *TINF2* mutations. However, they did not describe the patient in detail. To the best of our knowledge, this is the first case report showing pulmonary fibrosis in dyskeratosis congenita with *TINF2* mutation.

TINF2 mutations were reported to be heterozygous mutations in the sixth-found dyskeratosis congenita gene by SAVAGE *et al.* [9] in 2008. *TINF2* encodes TIN2, and is a component of the shelterin telomere-protection complex. The shelterin complex has at least three effects on telomeres: it determines the structure of the telomeric terminus, is implicated in the generation of t-loops and controls the synthesis of telomeric DNA by telomerase [1, 10]. Without the protective activity of shelterin, telomeres are no longer hidden from DNA repair mechanisms and chromosome ends are therefore incorrectly processed by the DNA repair pathways. Approximately 11% of all dyskeratosis congenita has been reported to be accounted for by *TINF2*

mutations and patients with these mutations have significantly shorter telomeres than those with other dyskeratosis congenita subtypes [3]. It has also been reported that most patients with dyskeratosis congenita with *TINF2* mutations have severe disease, and, compared with other dyskeratosis congenita genes, patients with *TINF2* mutations have a high incidence of aplastic anaemia before the age of 10 years [3].

Aberrant repair process by enhanced apoptosis of alveolar epithelial cells plays a critical role in the pathogenesis of pulmonary fibrosis such as idiopathic pulmonary fibrosis, although the precise mechanism is still unclear. The mechanism(s) of pulmonary fibrosis in dyskeratosis congenita has also not yet been clarified. However, because mutations in dyskeratosis congenita genes cause short telomere length with functional deficits in telomere maintenance, telomeres in alveolar epithelial cells may be short. In patients with dyskeratosis congenita, we speculate that aberrant lung repair by enhanced cell death causes pulmonary fibrosis, although the short telomere length in alveolar epithelial cells has not been directly demonstrated.

Herein, we describe the first case report of dyskeratosis congenita with pulmonary fibrosis associated with *TINF2* mutation. This report proved that mutations not only in *TERC*, *TERT* and *DKC1*, but also *TINF2*, cause pulmonary fibrosis in dyskeratosis congenita. However, we do not know why mutations in *TERC*, *TERT* and *DKC1* are frequently found in dyskeratosis congenita patients with pulmonary fibrosis in contrast to the other five genes. In addition, sex hormones, which can increase telomerase activity, are potential therapeutic drugs; however, no standard treatment has been established for pulmonary fibrosis in dyskeratosis congenita patients. Because the clinical characteristics and pathogenesis of pulmonary fibrosis in dyskeratosis congenita is not clear, the accumulation of case-based reports sheds light on the understanding of this devastating disease.

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The first reported case of a dyskeratosis congenita patient with pulmonary fibrosis and *TINF2* mutation http://ow.ly/pheRW

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Received: Aug 27 2013 | Accepted after revision: Sept 04 2013 | First published online: Sept 26 2013

Conflict of interest: None declared.

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