Pulmonary fibrosis associated with *TINF2* gene mutation: is somatic reversion required?

To the Editor:

We read with great interest the case reported by FUKUHARA *et al.* [1] of a 43-year-old female patient with dyskeratosis congenita, pulmonary fibrosis and heterozygous mutation in *TINF2* (telomerase repeat binding factor 1-interacting nuclear factor 2). TIN2, the *TINF2* gene product, *TERT* (telomere reverse transcriptase) and *TERC* (telomerase RNA component) participate in the regulation of telomere elongation, in which mutations have been previously found to be associated with familial pulmonary fibrosis in adults [2]. Indeed mutations of *SFTPC*, coding for surfactant protein C, were initially described in children before being described in adults as old as 72 years of age who presented with familial pulmonary fibrosis [3].

However, we were surprised that a *TINF2* mutation could be evidenced in an adult of that age. As highlighted by FUKUHARA *et al.* [1], patients with the *TINF2* mutation present with severe haematological symptoms before 10 years of age [4]. As mentioned by FUKUHARA *et al.* [1], the identified mutation is probably not hypomorphic because it is a frame-shift deletion located in the mutational "hot spot" described previously. Furthermore, the patient presented with very short telomeres. The *TINF2* mutation was probably inherited from her father because he had abnormal skin pigmentation and aplastic anaemia [1].

Re-analysis of the gene mutation sequencing could provide new hypotheses for this late disease onset. Indeed, the electrophoregram depicted in figure 1b in the study by FUKUHARA *et al.* [1] probably comes from a PCR product sub-cloned into an expression vector [5], and does not ensure that the deletion is at the heterozygous status usually seen in our patients (fig. 1). The patient may have experienced a somatic reversion leading to a partial loss of the germline mutation in peripheral blood cells (used for sequencing analysis). Indeed, cells would take advantage of a somatic reversion to become normal, particularly in the blood which is a highly regenerating system. This situation could explain the "milder" phenotype in this patient as compared with "classical" patients with *TINF2* mutation. Of note, somatic reversion has been previously reported with *TERC* mutations [6].

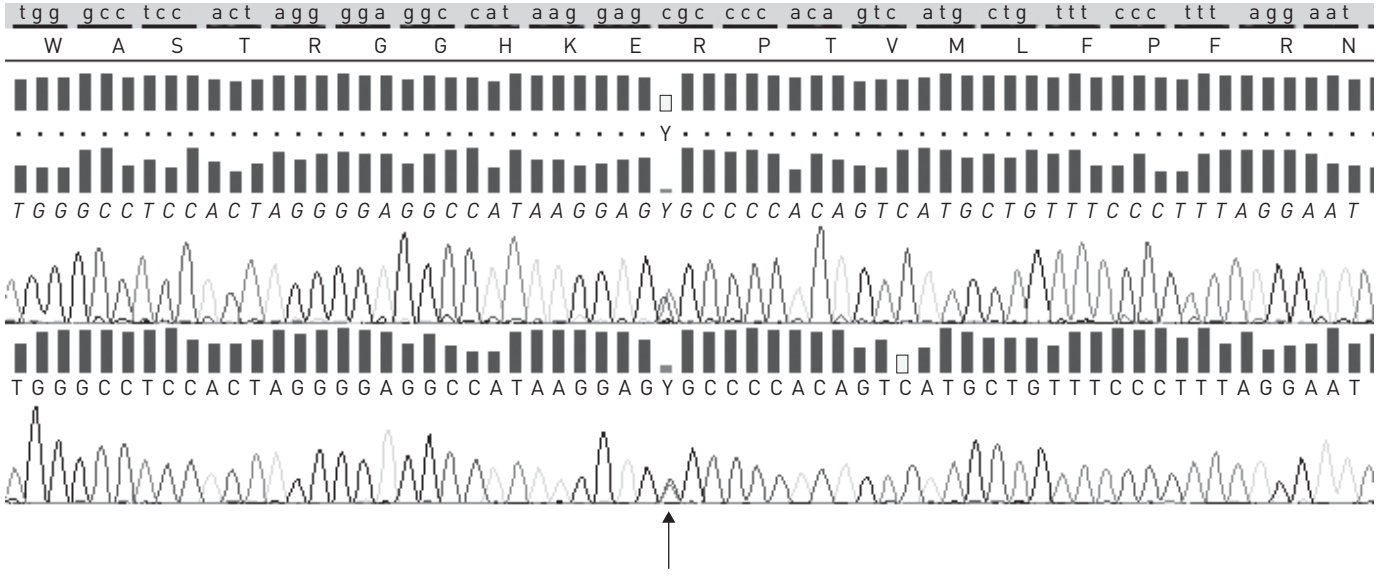

FIGURE 1 Gene mutation analysis of the *TINF2* (telomerase repeat binding factor 1-interacting nuclear factor 2) gene by direct sequencing revealed heterozygous c.814C>T, pArg282Cys (arrow) in a 7-year-old child with severe dyskeratosis congenita.

To verify this hypothesis, one could sequence the *TINF2* gene of the patient with DNA from other tissue, a buccal swab and/or a lung sample, where the mutation would probably appear as ''really'' heterozygous. In addition, high throughput sequencing (with next-generation sequencing) of *TINF2* in DNA from the patient's blood should provide precise data on the mutation frequency. However, one cannot definitely exclude the fact that *TINF2* mutations could lead to far more heterogeneous clinical phenotypes than previously described.

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A TINF2 mutation with somatic reversion may be revealed in adults with pulmonary fibrosis
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From the authors:

We would like to thank C. Kannengiesser and co-workers for their interest in our article [1] and for their patient's information and comments. They showed that their patient with the *TINF2* (telomerase repeat binding factor 1-interacting nuclear factor 2) mutation had the heterozygous mutation, which is usually seen in young patients with dyskeratosis congenita. In addition, they suggested that a somatic reversion might have occurred in our case because figure 1b showed that the deletion was not heterozygous despite the late disease onset [1].

Somatic reversion is a possible mechanism, which may explain late disease onset of dyskeratosis congenita with the *TINF2* mutation. In fact, JONGMANS *et al.* [2] described dyskeratosis congenita in a patient with somatic reversion. In this patient, the wild-type allele was observed more than the mutated allele in DNA from his peripheral blood cells despite DNA from his lung tissues revealing heterozygous mutation.

In our case, figure 1b showed n871–874 tetranucleotide AGGA deletion in *TINF2* gene [1]. However, because the mutation was a deletion mutation, TA cloning was performed for this analysis as described previously [3]. The result of gene mutation analysis by direct sequencing before TA cloning showed that the mutation was heterozygous (fig. 1). Although it may be possible that somatic reversion of the cells in the lungs led to pulmonary fibrosis in our patient, unfortunately we could not analyse DNA from lung tissues because the patient had passed away and no lung tissue had been retained.

More cases are needed to determine the exact mechanism(s) of dyskeratosis congenita by analysing each affected organ/system in detail.