News Release

Title

Clinical diagnostic value of telomere length measurement in inherited bone marrow failure syndromes

Key Points

○ Bone marrow failure (BMF) encompasses a diverse group of inherited and acquired disorders. It is important to differentiate inherited bone marrow failure syndromes (IBMFS) as a more accurate diagnosis may improve treatment outcomes.

○ This study measured TL in a cohort of BMF patients comprehensively and genetically evaluated by next-generation sequencing, and patients with IBMFS showed shorter TL than those with acquired aplastic anemia (AA).

○ This study confirms that a short TL was found in a significant proportion of patients with IBMFS, indicating the clinical diagnostic value of TL measurement in identifying patients who need further testing.

Summary

Prof. Yoshiyuki Takahashi, Dr. Hideki Muramatsu, and Dr. Atsushi Narita in Department of Pediatrics, Nagoya University Hospital, Dr. Shunsuke Miwata in Department of Pediatrics, Nagoya University Graduate School of Medicine, and their colleagues have reported that clinical diagnostic value of telomere length (TL) measurement in inherited bone marrow failure syndromes (IBMFS). Bone marrow failure (BMF) is characterized by a hypocellular marrow and encompasses a diverse group of inherited and acquired disorders. IBMFS are a heterogeneous group of disorders in which bone marrow failure is usually associated with physical abnormalities. Recent diagnostic advances using next-generation sequencing have revealed that some patients initially diagnosed with idiopathic aplastic anemia (AA) had cryptic presentations of IBMFS. This issue is important as a more accurate diagnosis may improve treatment outcomes. Telomeres are the end segments of chromosomes and are essential for genome integrity. Germline mutations in telomere biology genes can result in significantly short TL in patients with DC. Although there is a consensus on the usefulness of TL for screening DC but not for other IBMFS, several investigators have demonstrated that TL is excessively short in patients with AA and non-DC IBMFS. To assess the diagnostic value of TL, we measured TL in 133 patients with BMF and compared it in patients with DC, non-DC IBMFS, and AA. Patients with IBMFS showed shorter TL than those with AA. Furthermore, we calculated a cutoff value useful for diagnosing IBMFS. Of the total cohort, 44 patients (33%) were classified with short TL, which was more frequent in DC (91%) and non-DC IBMFS (60%) than in AA (23%). These results suggest that TL measurement is useful as a screening test for DC and as a clinical diagnostic tool for non-DC IBMFS patients.

Research Background

Bone marrow failure (BMF) is characterized by a hypocellular marrow and encompasses a diverse group

of inherited and acquired disorders. Inherited bone marrow failure syndromes (IBMFS) occur in approximately 5%–30% of patients with BMF in a pediatric cohort, including dyskeratosis congenita (DC), Fanconi anemia (FA), Diamond–Blackfan anemia (DBA), and Shwachman–Diamond syndrome (SDS). IBMFS are a heterogeneous group of disorders in which BMF is usually associated with physical abnormalities. The diagnosis of IBMFS previously relied on the recognition of characteristic clinical features. Recent diagnostic advances using next-generation sequencing have revealed that some patients initially diagnosed with idiopathic aplastic anemia (AA) had cryptic presentations of IBMFS. This issue is important as a more accurate diagnosis may improve treatment outcomes. Telomeres are the end segments of chromosomes and are essential for genome integrity. Germline mutations in telomere biology genes can result in significantly short telomere length (TL) in patients with DC. Although there is a consensus on the usefulness of TL for screening DC but not for other IBMFS, several investigators have demonstrated that TL is excessively short in patients with AA and non-DC IBMFS. To assess the diagnostic value of TL, we measured TL in 133 patients with BMF and compared it in patients with DC, non-DC IBMFS, and AA.

Research Results

This study measured TL by standard flow-FISH in a cohort of 133 BMF patients comprehensively and genetically evaluated by next-generation sequencing (**Figure 1**). The 26 IBMFS cases consisted of 11 DC, 9 FA, 4 DBA, 1 SDS, and 1 Bloom syndrome. The median TL in all 133 patients was –0.96 SD (range, −5.73 to +4.00 SD). Furthermore, median TL in the patients with DC, non-DC IBMFS, and AA were −3.50 SD (range, −5.73 to +0.83 SD), −1.89 SD (range, −4.74 to +2.05 SD), and −0.84 SD (range, −4.27 to +4.00 SD), respectively. Patients with IBMFS showed shorter TL than those with AA (**Figure 2**). The statistical analysis revealed that, for the diagnosis of patients with IBMFS, the TL cut-off value at −1.71 SD yielded an appropriate cutoff value. Of the total cohort, 44 patients (33%) had short TL, which was more frequent in DC (91%) and non-DC IBMFS (60%) than in AA (23%). These results suggest that TL measurement is useful as a screening test for DC and as a clinical diagnostic tool for non-DC IBMFS patients.

Research Summary and Future Perspective

This study confirms that measurement of TL was found in a significant proportion of patients with DC and non-DC IBMFS, indicating the clinical diagnostic value of TL measurement in identifying patients who need further testing, particularly comprehensive genetic analysis.

Publication

Shunsuke Miwata, Atsushi Narita, Yusuke Okuno, Kyogo Suzuki, Motoharu Hamada, Taro Yoshida, Masayuki Imaya, Ayako Yamamori, Manabu Wakamatsu, Kotaro Narita, Hironobu Kitazawa, Daisuke Ichikawa, Rieko Taniguchi, Nozomu Kawashima, Eri Nishikawa, Nobuhiro Nishio, Seiji Kojima, Hideki Muramatsu, Yoshiyuki Takahashi, Clinical diagnostic value of telomere length measurement in inherited bone marrow failure syndromes, Haematologica, Apr 22, 2021.
DOI : https://doi.org/10.3324/haematol.2021.278334

Japanese ver :
https://www.med.nagoya-u.ac.jp/medical_J/research/pdf/Haem_210422.pdf

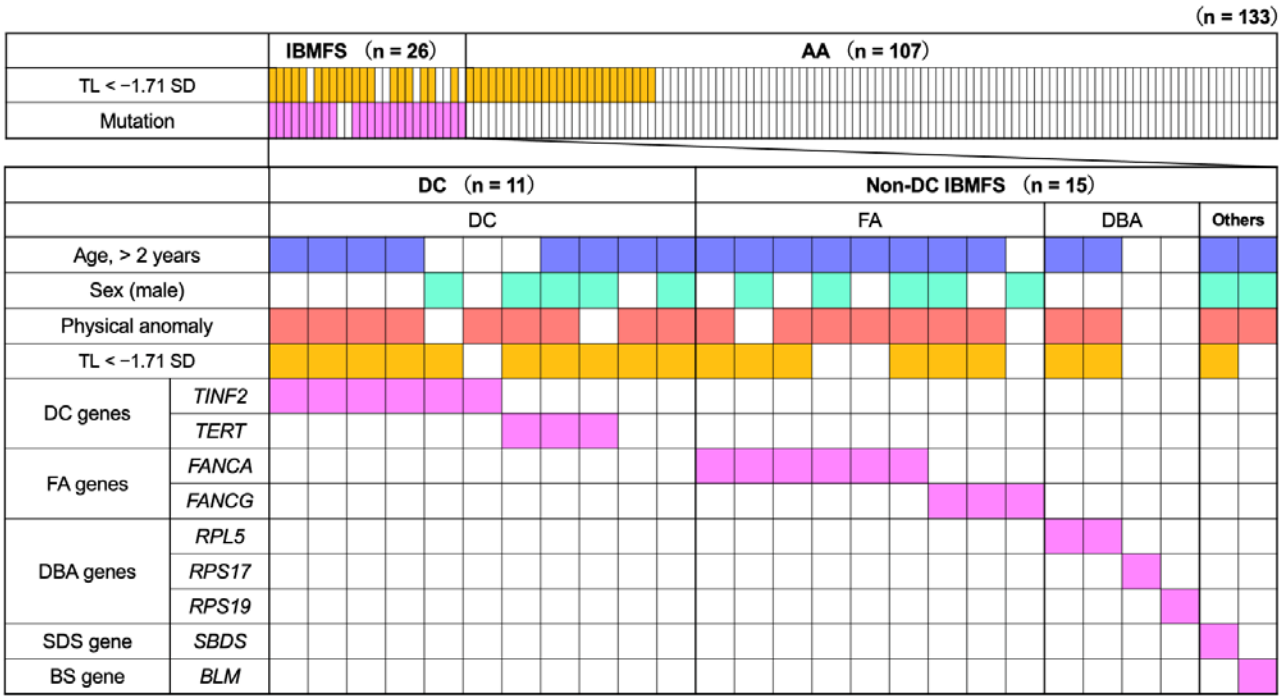

Figure 1. Clinical and genetic profiles of 133 patients with bone marrow failure (BMF). Each column indicates one patient. TL, telomere length; IBMFS, inherited bone marrow failure syndromes; AA, aplastic anemia; DC, dyskeratosis congenita; FA, Fanconi anemia; DBA, Diamond–Blackfan anemia; SDS, Shwachman–Diamond syndrome; BS, Bloom syndrome.

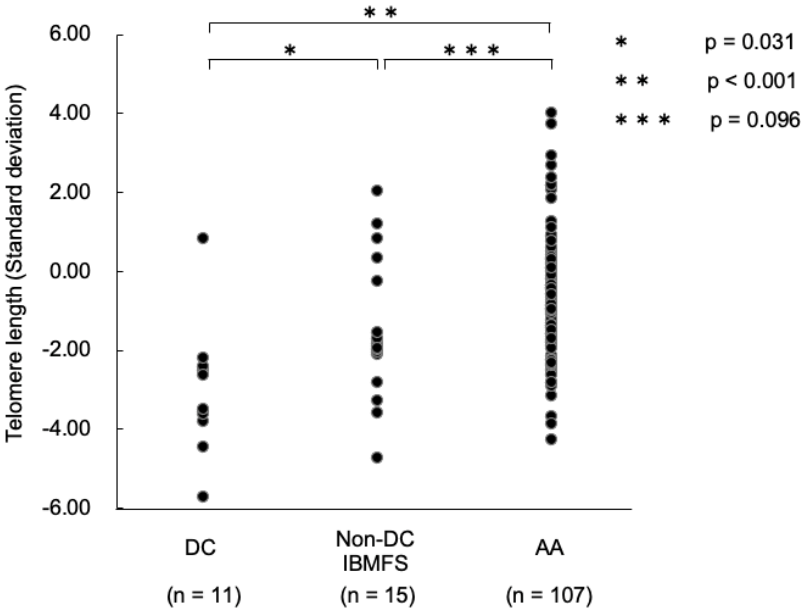

Figure 2. Comparison of Telomere length in patients with dyskeratosis congenita (DC), non-DC inherited bone marrow failure syndromes (IBMFS), and aplastic anemia (AA).