


Lack of mutations of the human telomerase RNA gene (hTERC) in myelodysplastic syndrome

Myelodysplastic syndrome (MDS), considered a pre-leukemic state, has recently been categorized as a subset of bone marrow failure syndromes. Unlike other subtypes of bone marrow failure syndromes, such as aplastic anemia or dyskeratosis congenita, little is known about genetic alterations of human telomerase in MDS, despite the fact that immune cells from patients with MDS frequently exhibit telomere attrition.

Human telomerase RNA (hTERC) is an essential component of the telomerase ribonucleoprotein complex, and mutations in hTERC can result in haploid insufficiency, reducing telomerase activity, leading to premature telomere shortening. Identification of mutations of hTERC in bone marrow failure syndromes, including myelodysplastic syndrome (MDS), may provide insights into the underlying molecular causes of these syndromes.

In the present study, we investigated mutations of the hTERC gene (NT 005612.14) using polymerase chain reaction-direct sequencing in 42 marrow samples from 35 consecutive MDS patients (34 to 80 years old); 19 had refractory anemia (RA), 14 had RA with excess blasts (RAEB), and two patients had RAEB in transformation. Seven RAEB patients were also studied at the time their disease transformed into acute myeloid leukemia. Blood samples were also obtained from 134 healthy volunteers (4 to 90 years old). All samples were collected from Japanese patients and healthy volunteers after obtaining informed consent. Telomere length and telomerase activity were measured as previously described in mononuclear cells.

We selected seven hTERC loci; C98T, the template region G58A, pseudoknot domain C72T and Δ110-113, CR4-CD5 domain G305A and G322A, and Box H/ACA domain G450A, to identify possible mutations of the hTERC gene. We also examined polymorphisms at 514. Direct sequencing showed no heterozygous hTERC mutations of these loci in 42 MDS samples and 134 healthy volunteers, although MDS patients had variable telomere lengths (short in 27%, normal in 69%, and long in 5% compared to normal volunteers) with low telomerase activity. We did not find allelic variations at the 514 locus in healthy populations: AA genotype (MDS 11.1% versus control 11.9%), AG genotype (MDS 55.6% versus control 51.4%), and GG genotype (MDS 33.3% versus control 36.7%) and no deviation was notable in MDS patients.