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Telomeres are ribonucleoproteins that cap chromosome-ends and impede the activation of the DNA-damage-response (DDR). Their length is maintained by telomerase using a RNA template. Telomeric sequences are conserved across the tree of life and consist of G-rich repeated units, but variation in length and sequence is present among distant taxa. Each species is likely fine-tuned for its own telomere properties, however their quantitative contribution to fitness remains largely unexplored. In the budding yeast Saccharomyces cerevisiae, the telomerase RNA template is encoded by TLC1 and carries degenerated TG1-3 repeats. Previous studies showed that a 16-bp editing of TLC1 enables to reconfigure telomeres and generate yeasts with newly synthetised human-like T2AG3 repeats, which show an intrinsic telomere dysfunction and a chronic activation of DDR. In this work, we evolved multiple lines of humanized and wild-type yeasts to characterize the effect of telomere variation on fitness. We sequentially combined two experimental evolution paradigms: first, we evolved cells through mutation accumulation lines (MALs) to minimize selection, to investigate the cellular and genomic effects during the fitness decay driven by telomere dysfunction. Next, we submitted MALs to adaptive evolution by multiple serial transfers (STs) of large population sizes, to map mutations that counteract the fitness decline. During MALs, humanized yeasts gradually slowed their growth and shortened chronological lifespan. Whole-genome-sequencing revealed that they had increased mutation rate and genome instability, with recurrent aneuploidies on chromosome XVI. After multiple STs, most humanized lines recovered a wild-type fitness, with independent occurrence of mutations in the MRX complex, a key effector of DDR. Overall, our results show that humanized telomeres increase mutation rate and cause a severe fitness decline which is rescued by the inactivation of DDR.