Supp. Methods

Clinical studies. Family 1 was evaluated as part of the Johns Hopkins Telomere Syndrome Registry, and Family 2 was evaluated at Memorial Sloan Kettering Hospital. The study was approved by the Memorial Sloan Kettering Hospital and the Johns Hopkins Medicine Institutional Review Boards. Subjects gave informed consent. Genomic DNA was extracted from either peripheral blood or primary skin fibroblasts. Telomere length was measured on lymphocytes using flow cytometry and fluorescence *in situ* hybridization from peripheral blood [Armanios, et al., 2007]. Chromosome breakage and DEB studies were performed as previously described [Auerbach, 2009].

Molecular studies. Sanger sequencing of *TERT* and *TR*, and genotyping of flanking microsatellite markers was performed as described [Armanios, et al., 2005; Armanios, et al., 2007]. We performed exome sequencing on genomic DNA using the SureSelect Human Exome 38Mb Kit (Agilent, Santa Clara, CA) and the ABI SOLiD sequencing platform (Applied Biosystems Carlsbad, CA) according to the manufacturer's instructions. Variants were called using SOLiD Bioscope software, viewed in the Integrative Genome Viewer [Robinson, et al., 2011], and verified by Sanger sequencing as described [Parry, et al., 2011]. The *DKC1* variants identified were deposited in the Telomerase Database (telomerase.asu.edu) [Podlevsky, et al., 2008]. X-inactivation analysis was performed on genomic DNA derived from peripheral blood or fibroblasts by genotyping polymorphic (CAG) repeats in the androgen receptor promoter using the HUMARA assay [Allen, et al., 1992]. Alignment was performed using ClustalW and Boxshade. TR levels were measured using quantitative real time PCR on early lymphoblastoid cells or primary fibroblasts [Parry, et al., 2011]. AG04645B cells with a known *DKC1* Ala286Thr mutation (ATCC, Manassas, VA) [Vulliamy, et al., 2006], and lymphoblasts with *TR* del375-377 were studied as controls [Alder, et al., 2011].

Supp. References

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