**Supplement:**

**Methods:**

**Patients and samples:**

Samples were taken after written informed consent and approved by the local ethic committee (EK98032010 / EK084/12). Blast free state/ remission at the time of sampling as an additional inclusion criterion was chosen to substantially reduce contamination of normal hematopoietic cells reflecting the germline genotype by leukemic cells since, due to the retrospective nature of the study, no non-hematopoietic tissue was available for analysis. All cases were considered *de novo* AML by the treating hematologists and all patients received an anthracycline/cytarabine based induction chemotherapy.

Sufficient DNA for genetic work up using next generation sequencing (NGS) screening was available in 26/29 patients and for TL measurement in 21/29. Of the 26 patients with available DNA, one was excluded from the overall survival analysis due to missing data.

**DNA extraction**

For NGS, 250ng genomic DNA was used per test batch. DNA isolation was carried out using standard protocols1. In three patients we were unfortunately unable to carry out any further analyses due to reduced DNA concentration. 26/29 samples underwent next-generation sequencing (NGS).

**Targeted amplicon sequencing**

NGS (MiSeqDx®, Illumina) was done as previously described1. Genetic variants and heterozygous mutations in telomere-associated and other non-TBD MNGLP associated genes were detected using a self-designed panel containing the entire coding sequences for *ACD, ANKRD26, CTC1, DDX41, DKC1, ETV6, GATA1, GATA2, LIG4, NHP2, NOP10, PARN, POT1, RPL5, RPL11, RPL15, RPL26, RPL35A, RPS7, RPS10, RPS17, RPS19, RPS24, RPS26, RTEL1, SAMD9, SAMD9L, SBDS, SRP72, TERC, TERF1, TERF2, TERT, TCAB1, USB1* and exon 6 of *TINF2*. The AmpliSeq assay (Ilumina®) was applied using the MiSeq Reagent Kit V3. After sequencing 250bp paired end, raw data was analyzed with Ilumina RTA software (version 1.18.54) on board. For alignment and variant calling, the SeqNEXT software (version 4.4.0, JSI medical systems GmbH, Ettenheim, Germany) was used. An inherited variant was considered in all patients with a variant allele frequency (VAF) between 40-60% for heterozygous variants and >90% for homozygous variants.

While screening for *CEPBA* and *RUNX1* is already recommended in current guidelines but data regarding mutations was not available, all samples were additionally tested for hereditary mutations in these two genes and for somatic mutations related to clonal hematopoiesis (*ABL, ASXL1, BARD, CALR, CBL, CEBPA, CHEK2, CSF3R, DNMT3A, ETNK1, ETV6, EZH2, IDH1, IDH2, JAK2, KIT, KRAS, MPL, NFE2, NRAS, PDGFRA, PTPN11, RUNX1, SETBP1, SF3A1, SF3B1, SH3B2 (LNK), SRSF2, TCF12, TET2, TP53, U2AF1*) by NGS using another Panel as previously described1. To detect clonal variants, we chose a VAF threshold of 5%. Since complete hematologic remission allows a blast count <5%, this approach nearly eliminates the chance of detecting mutations in residual AML-blasts. This panel is validated to detect variants with a VAF down to 5% with a mean coverage of 300 reads. Thus, a threshold of 10 (absolute) and 5% (relative) variant reads for calling a variant was chosen to reduce risk of detecting sequencing errors. Relevant transcripts are shown in Suppl. Table 1.

**Telomere length measurement:**

Telomere PCR was carried out using previously published protocols2. TL of 104 healthy blood donors were measured as a control group. Age-adaptation was carried out using linear regression and calculating the delta between measured TL and TL for the expected age. All values are given in T/S ratio.

Of note, Flow-FISH is defined as gold standard of telomere length measurement. Unfortunately, due to the retrospective design and available samples we were not able to analyze our samples by FlowFISH.

**Statistical analysis**

GraphPad Prism 5.0 (GraphPad, US) was used for statistical analysis. Statistical analysis was carried out using the Log Rank Test for comparing survival curves. P values <0.05 were considered as statistically significant.

**Supplement Table 1**



**Supplement Table 1. List of genes and used transcripts for analysis of the detected inherited class 3-5 variants**.

References:

1 Kirschner, M. *et al.* Recurrent somatic mutations are rare in patients with cryptic dyskeratosis congenita. *Leukemia* **32**, 1762-1767, doi:10.1038/s41375-018-0125-x (2018).

2 Vieri, M. *et al.* Comparable Effects of the Androgen Derivatives Danazol, Oxymetholone and Nandrolone on Telomerase Activity in Human Primary Hematopoietic Cells from Patients with Dyskeratosis Congenita. *International journal of molecular sciences* **21**, doi:10.3390/ijms21197196 (2020).