Uncompromised ten-year survival of oldest old carrying somatic mutations in DNMT3A and TET2

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Background
Recent large-scale sequencing studies report recurrent somatic mutations in the blood of elderly individuals in genes previously linked to clonal expansion of hematopoietic stem cells [1-4]. Particularly for DNMT3A and TET2, a steep age-associated increase in the prevalence of somatic mutations is observed from middle age onward [2-4]. In addition, prospective analyses performed in predominantly middle-aged individuals show an increased risk for all-cause mortality for carriers of such mutations as compared with non-carriers [3,4]. Jointly, these data suggest a rapidly increasing vulnerability among the elderly for adverse health effects associated with clonal expansion of hematopoietic stem cells.

Aim & Approach
We investigated the association between all-cause mortality and carriership of somatic mutations in genes linked to clonal expansion of hematopoietic stem cells in a large elderly subsample (N = 864; age ≥ 80 years) derived from 2 large-scale community-dwelling Dutch cohort studies [5,6].

Main Results & Conclusions
Figure 1: Somatic mutations in genes linked to clonal expansion of hematopoietic stem cells are very common in the oldest old.

Figure 2: Unlike previous reports in predominantly middle-aged individuals, somatic mutations in genes linked to clonal expansion of hematopoietic stem cells do not compromise the 8-10 year survival in the oldest old.

Materials and Methods
We investigated whole-blood derived genomes of 646 individuals of 80 years and older from the Rotterdam Study [5] (RS; mean age at inclusion, 84.6 years; range, 80.0-105.8 years) and 218 individuals of 89 years and older from the Leiden Longevity Study [6] (LLS; mean age at inclusion, 94.0 years; range, 88.9-103.4 years). Selected elderly participants of the RS and LLS were followed for all-cause mortality for a median 8.7 and 9.2 years, respectively, which was sufficiently long to identify the age at death of 81.3% and 93.6% of the respective study subsamples.

Mutational Analysis
We analyzed DNA sequencing data for rare truncation variants and known hotspot variants in 15 genes previously reported by large-scale sequencing studies to harbor somatic mutations in the blood of normal individuals [2-4].

Characterization of somatic variants in blood of the elderly

The mutational analysis identified 39 (6.0%) and 40 (18.3%) unique carriers of, respectively, 42 and 46 mutations for the RS and LLS elderly subsamples, respectively. (A) Numbers of elderly individuals carrying a mutation, split by genes and study. (B) Prevalence of elderly carriers with somatic mutations, stratified by age categories, using data of Xie et al. [2] and the observations in the RS and LLS elderly subsample. (C) Distribution of the Variant Allele Fractions of the identified mutations. (D) Co-mutation plot of carriers with 2 independent mutations. (E) Overview of mutations in DNMT3A identified in the RS and LLS. Variants are annotated at the top with color coding (impact), shape (follow-up experiments) and border (normal: RS; thick: LLS). COSMIC, densities of somatic variants in independent mutations. (E) Overview of mutations in DNMT3A.

Uncompromised ten-year survival of elderly carriers

The Cox proportional hazards analyses in the RS and LLS.

No difference in survival was observed between carriers and non-carriers for the RS (HR = 0.96 [0.65-1.45], p = 0.61) and the LLS (HR = 0.94 [0.65-1.35], p = 0.29), nor the LLS carriers in the LLS elderly subsample. (B) Kaplan-Meier curves for the 40 mutation carriers and 168 non-carriers in the LLS elderly subsample. (C) Forest plot combining the Cox proportional hazards analyses in the RS and LLS.

References
2. Xie et al. Nat Med 2014