Somatic blood cell mutations at low variant allele frequency in distinct risk genes are associated with increased mortality in patients with chronic ischemic heart failure

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Background: Recurrent somatic mutations in blood stem cells cause the emergence of mutated blood cell clones, known as clonal hematopoiesis (CH). Mutations in the most prevalent driver genes DNMT3A and TET2 with a variant allele frequency (VAF)≥2% have been associated with atherosclerosis and chronic heart failure (CHF). However, the effects of mutations in other driver genes for CH with low VAF (<2%) on CHF is still unknown.

Purpose: To assess the potential prognostic significance of mutations in distinct genes other than DNMT3A and TET2 causing CH at low VAF in patients with CHF due to post-ischemic origin.

Methods: We analyzed mononuclear bone marrow and peripheral blood cells from 400 CHF patients by deep error-corrected targeted amplicon sequencing allowing for the detection of very low VAF of ≥0.5% in 56 CH driver genes and associated such with the long-term mortality in these patients.

Results: Median age of the patients was 63 and median follow-up time was 4.8 years. We detected 1116 mutations with a VAF≥0.5% in 348 of 400 patients (87%). 21% of the patients carried 1 mutation, whereas 66% showed 2 and more mutations. Only 52 (13%) patients had no detectable mutation at all. Despite a high prevalence of mutations in the most frequently mutated driver genes DNMT3A (165 patients) and TET2 (107 pts), mutations in the genes CBL (8 pts), CEBPA (10 pts), PHF6 (22 pts), SMC1A (18 pts) and SRSF2 (14 pts) were associated with increased death compared to the average death rate of all patients (18.8%). To avoid confounding effects caused by the presence of DNMT3A and TET2 CHIP mutations, we excluded patients with DNMT3A-, TET2- and other CHIP-related mutations with a VAF≥2% for further analyses. Kaplan-Meier survival curve analyses revealed a significantly higher mortality in patients with mutations in either of the five genes, combined as the CH risk gene set for CHF (Fig. 1). Patients with mutations in the risk gene set (44 pts) did not differ from patients with mutations in other CH driver genes or without mutations with respect to age, cardiovascular risk factors, disease severity or CH clone size. By multivariate Cox proportional regression analysis, including the Seattle heart failure model (SHFM) score (as tertiles), death remained independently associated with the presence of mutations in the risk gene set (HR, 2.57; 95% CI, 1.30–5.10; p=0.007), in addition to SHFM score tertiles (tertile 2, HR, 2.36; 95% CI, 0.73–7.65 and tertile 3, HR, 7.96; 95% CI, 2.77–22.90).

Conclusions: Somatic mutations with low VAF in a distinct set of genes, namely in CBL, CEBPA, PHF6, SMC1A and SRSF2, are significantly associated with mortality in CHF, independently of the classical CHIP-driver mutations DNMT3A and TET2. Mutations in the CH risk gene set are prevalent in young CHF patients and comprise an independent risk factor for the outcome of CHF, potentially providing a novel tool for cardiovascular risk assessment and precision medicine in CHF.

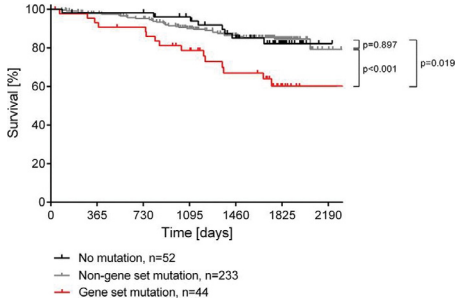

Figure 1