Supplemental Table 1. List of mutations with a VAF ≥0.5% in 56 analysed genes

see Excel-file

Supplemental Table 2. Multivariate Cox Regression analysis for death.

| Variable	HR [95%-CI]	p-value
Death		
Gene set mutations and platelets		
Gene set mutation	3.1 [1.8-5.4]	< 0.001
Platelets	1.0 [0.9-1.0]	0.084

Abbreviations: HR, hazard ratio; CI, confidence interval.

Supplemental Table 3. Accumulation of mutations in indicated genes compared between patients with a mutation in the risk gene set and patients with a mutation in other genes.

| Gene	Mutation in „Non-gene set mutation"	Mutation in „Gene set mutation" [%]	p-value (Chi-square or exact fisher*)
DNMT3A	44	45	0.907
TET2	27	28	0.837
ABL1	0.4	2	0.348*
ASXL1	6	8	0.758*
ATRX	13	21	0.150
BCOR	3	4	0.685*
BCORL1	19	17	0.755
CALR	2	4	0.623*
CBLB	0.4	0	1.00*
CDKN2A	9	8	1.00*
CSF3R	1	9	0.008*
CUX1	9	13	0.294
ETV6	5	2	0.697*
FBXW7	0.4	2	0.348*
GATA1	1	0	1.00*
GATA2	4	4	1.00*
GNAS	1	0	1.00*
GNB1	1	5	0.174*
HRAS	2	4	0.623*
IDH1	3	0	0.599*
IKZF1	6	4	0.743*
JAK2	3	2	1.00*
KDM6A	12	8	0.470*
KIT	3	2	1.00*
KMT2A	1	0	1.00*
KRAS	1	0	1.00*
MYD88	3	2	1.00*
NOTCH1	5	8	0.498*
NRAS	1	0	1.00*
PDGFRA	2	2	1.00*
PPM1D	6	8	0.750*
RAD21	8	15	0.116
RUNX1	1	2	0.474*
SETBP1	0.4	0	1.00*
SF3B1	2	0	0.587*
SMC3	2	4	0.325*
STAG2	14	9	0.345
TP53	9	11	0.598
U2AF1	0.4	0	1.00*
WT1	0	2	0.192*
ZRSR2	9	9	0.997

Significance was tested with Chi-Square or Exact-fisher-test.

Supplemental Figure 1
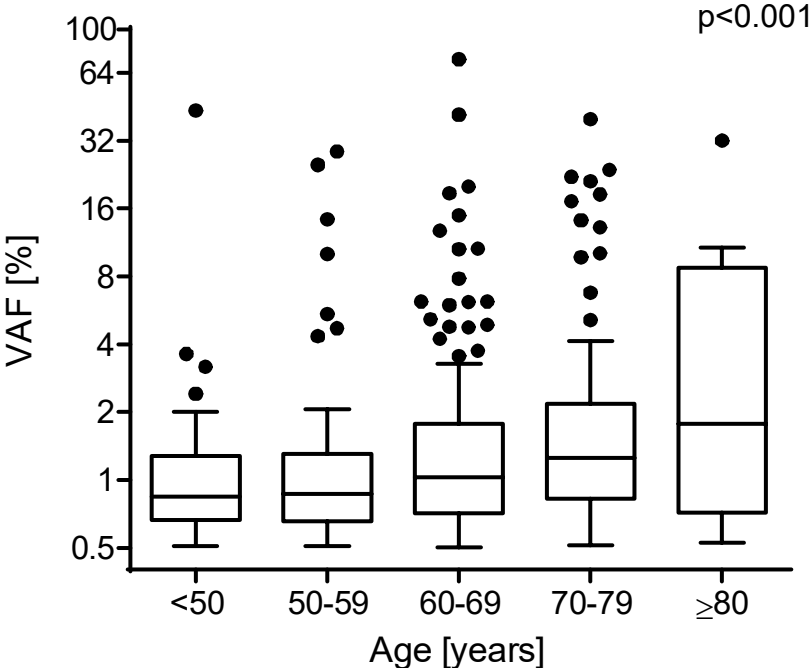
Suppl. Figure 1. VAF of recurrent mutations per age group in CHF analysed patients. VAF of identified mutations increases significantly with age. For each patient only the mutation with the highest VAF was included. Tukey Box Plot indicates the median, first and third quartiles. Correlation was tested with Spearman's correlation.
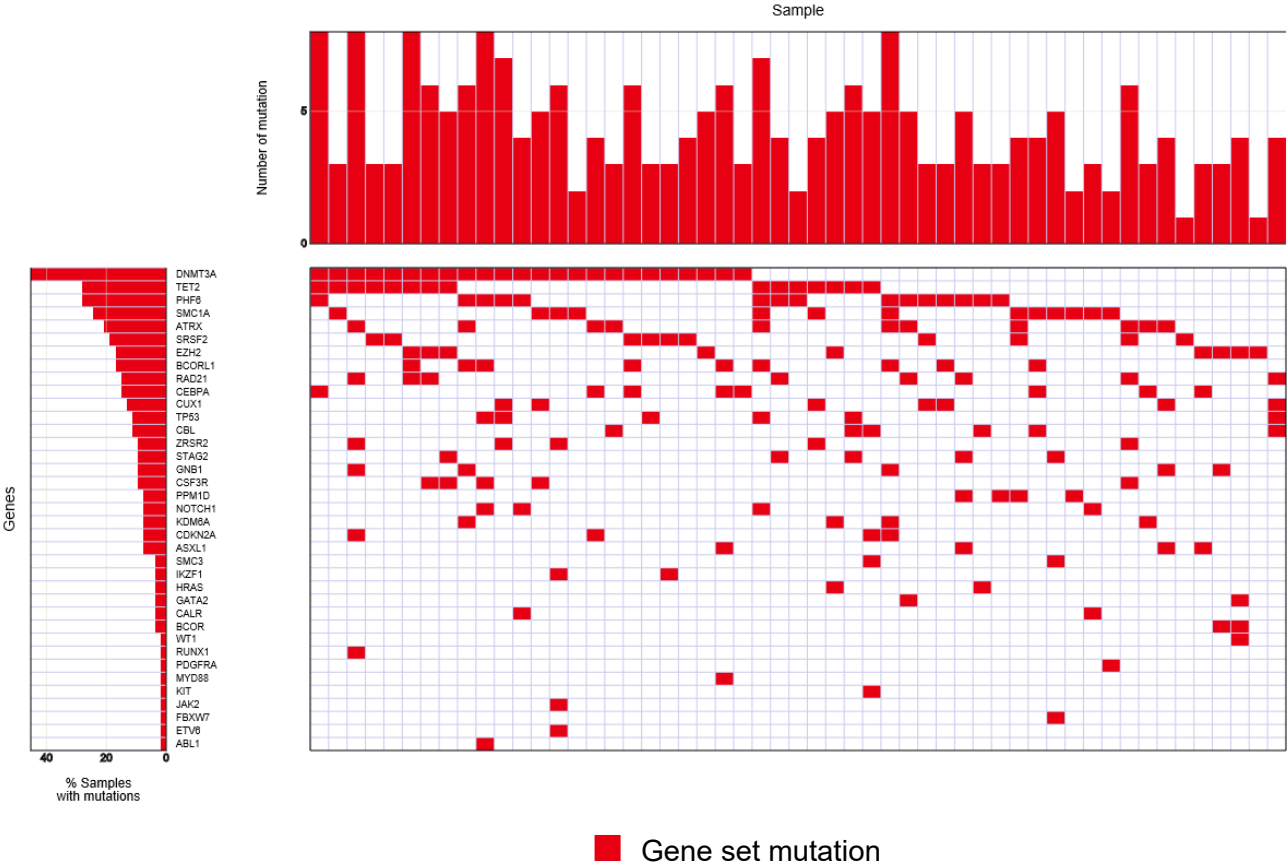
Supplemental Figure 2
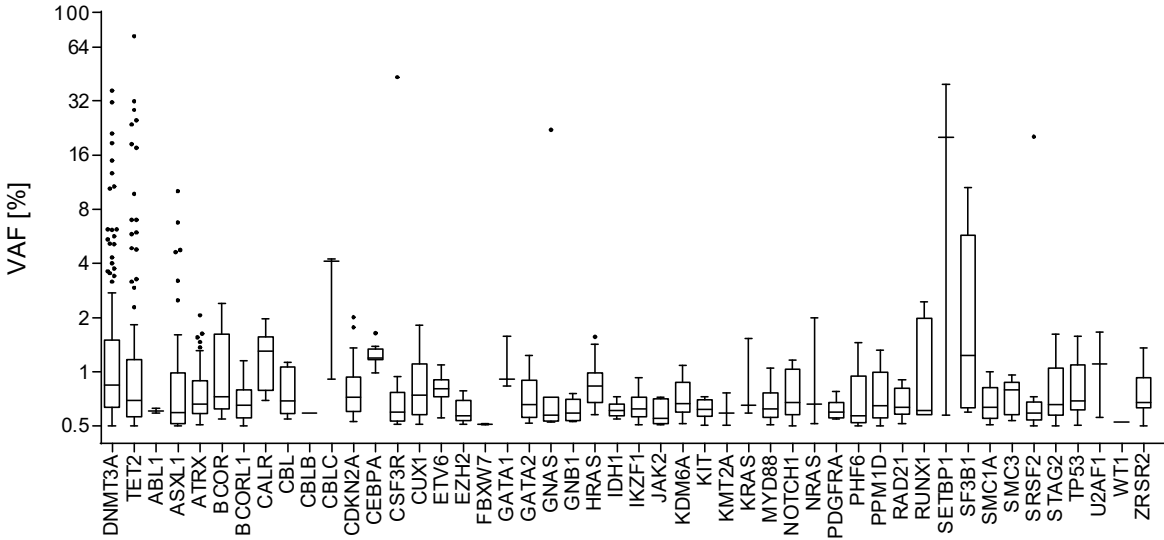
Suppl. Figure 2. VAF of somatic mutations detected in the 56 analysed genes. Tukey Box Plot indicates the median, first and third quartiles.
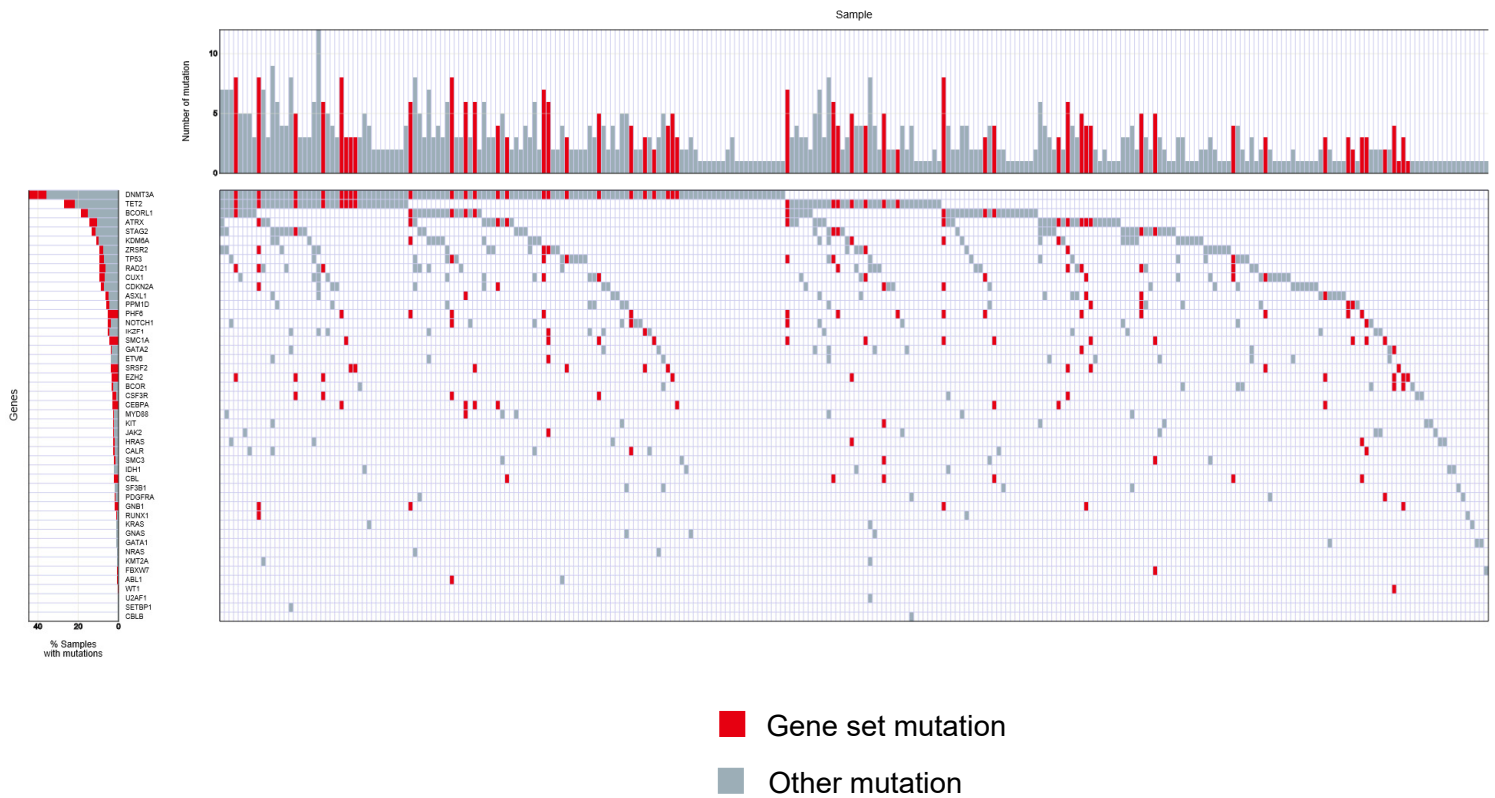
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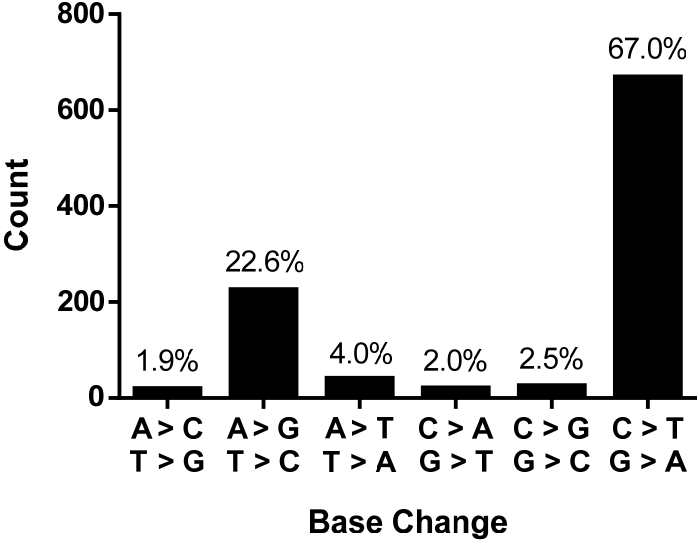
Suppl. Figure 3. Single nucleotide variants in 56 genes identified in our cohort of CHF patients. A predominance of transitions (purine–purine or pyrimidine–pyrimidine) was observed, over transversions. The most frequent C to T substitutions have been shown to represent a mutational signature characteristic of aging. Transitions, C>T and A>G; transversions, A>C, A>T, C>A, C>G.

Supplemental Figure 4

Suppl. Figure 4. Mutation matrix showing the mutated genes in 53 CHF patients with a mutation in the risk gene set (CBL, CEBPA, EZH2, GNB1, PHF6, SMC1A, and SRSF2). Patients with any mutation with a VAF ≥2% were excluded.

Suppl. Figure 5. Mutation matrix showing the mutated genes in the CHF patient cohort. Patients with mutations in the risk gene set (CBL, CEBPA, EZH2, GNB1, PHF6, SMC1A, and SRSF2) are marked in red. Patients with any mutation with a VAF ≥2% were excluded.

Supplemental Figure 6
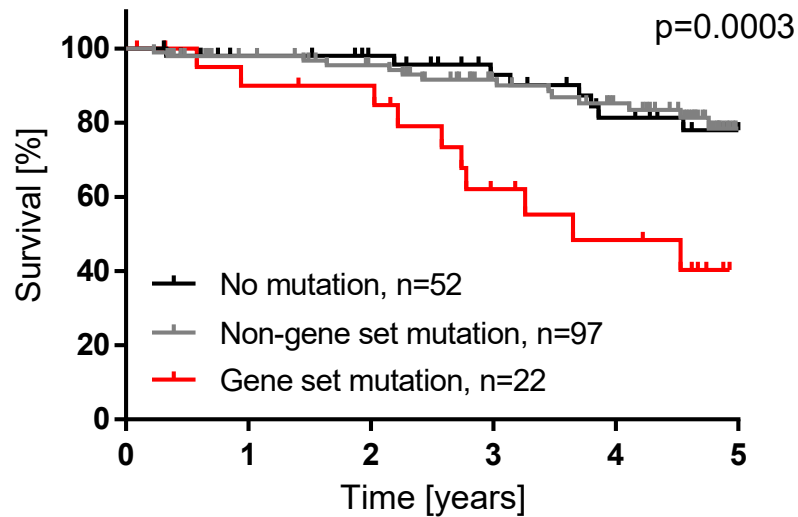
No mutation	52	51	51	49	45	44
Non-gene set mutation	97	95	93	90	86	83
Gene set mutation	22	20	20	15	13	12

Suppl. Figure 6. Kaplan-Meier survival analyses of CHF patients with a mutation in the gene set. Kaplan–Meier curves of survival, defined as the time between sample collection and death or last follow-up. All patients with a mutation in DNMT3A or TET2 above VAF ≥0.5% and patients with a mutation in any other gene with a VAF ≥2% (CHIP patients) were excluded from the analysis, to avoid any confounding gene mutations. Statistical significance was tested with Log Rank (Mantel-Cox). Survival curves are stratified according to the mutations with VAF ≥0.5% in genes of the gene set (CBL, CEBPA, EZH2, GNB1, PHF6, SMC1A, and SRSF2) in CHF patients. Non-gene set mutation, patients with mutations in any other gene; No mutation, patients without any mutation.

Supplemental Figure 7
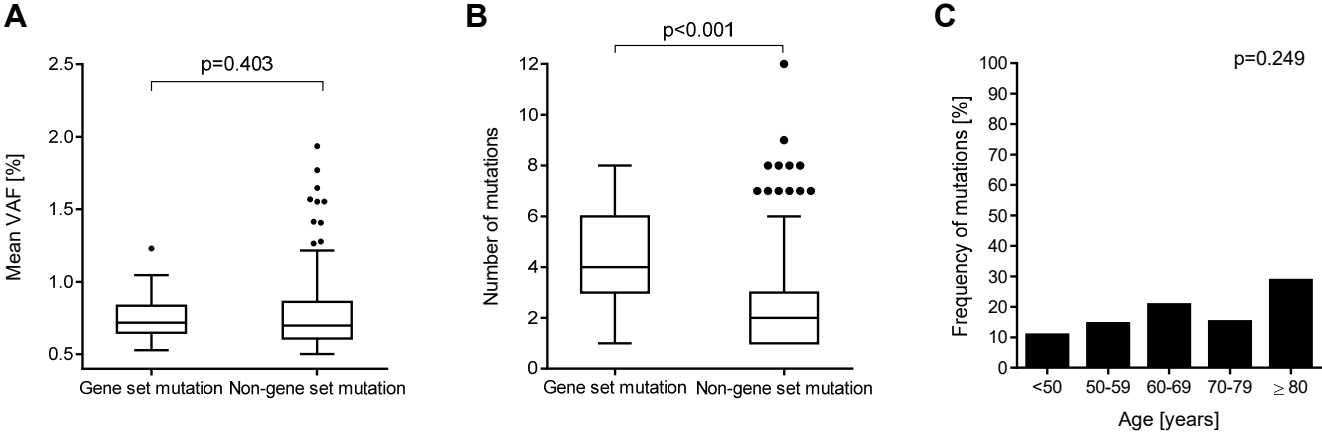
Suppl. Figure 7. Comparison of parameters between patients, who are mutated in the gene set with patients carrying a mutation in another gene. A. Tukey Box Plot showing the mean of the sum of all VAFs from each CHF-patient. Significance was tested with Mann-Whitney-U. Tukey Box Plot indicates the median, first and third quartiles. **B.** Tukey Box Plot showing the number of CH-mutations of each CHF-patient. Significance was tested with Mann-Whitney-U. Tukey Box Plot indicates the median, first and third quartiles. **C.** Prevalence of CH-associated mutations with VAF ≥0.5% in the risk gene set according to age group. Significance was tested with Spearman's correlation.