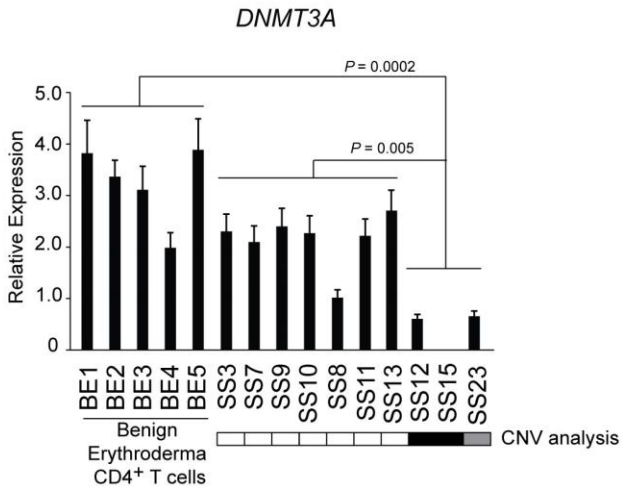
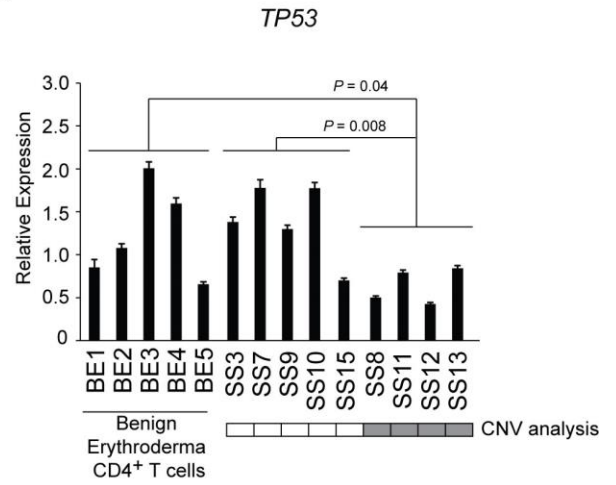
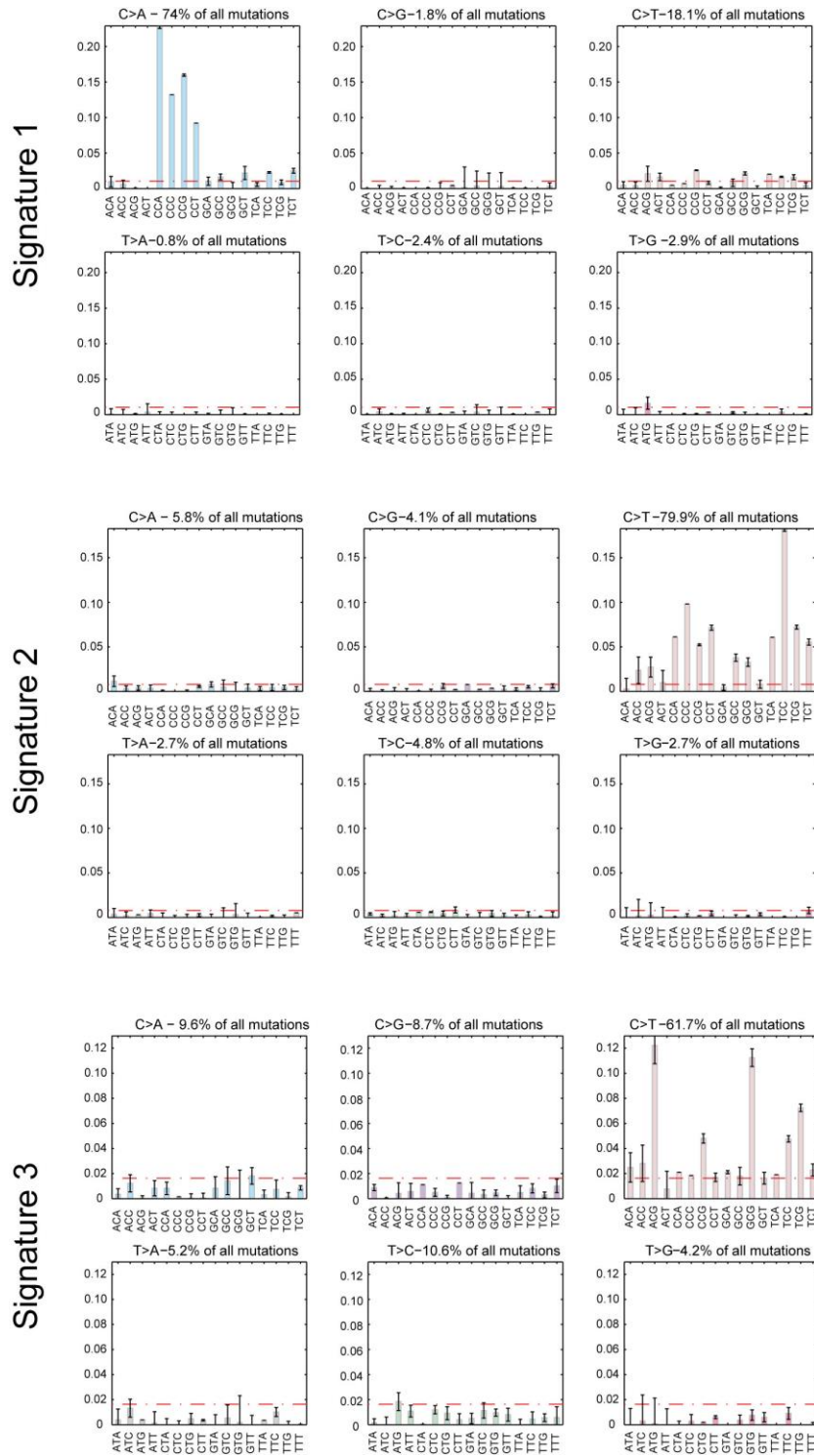


a**b**

Supplementary Figure 1

DNMT3A and TP53 expression analysis in Sézary patient samples.

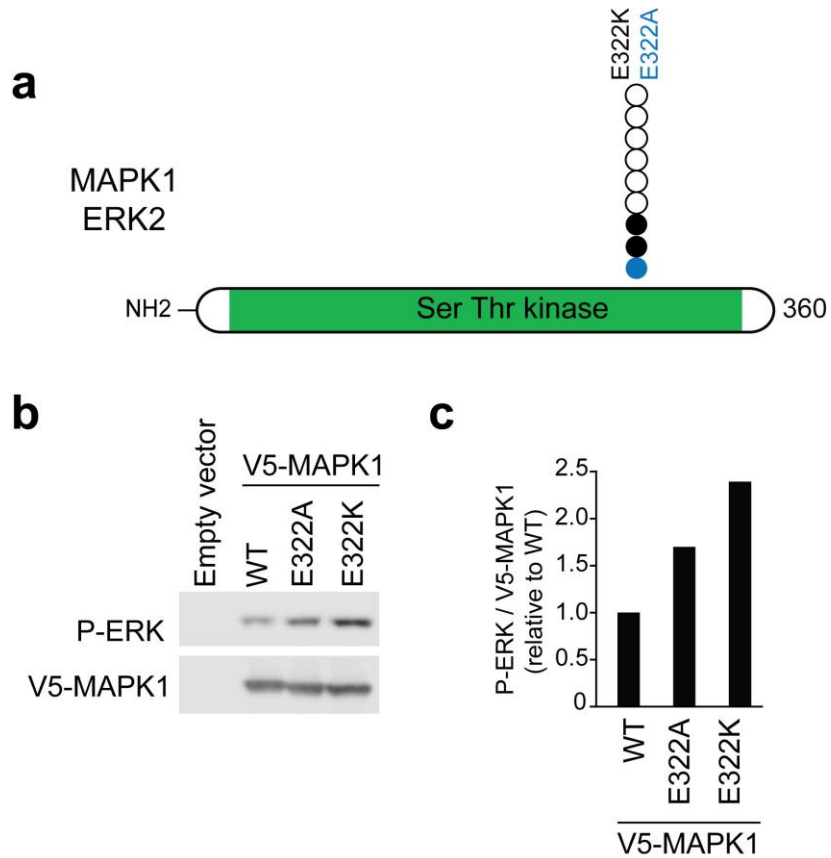
Quantitative RT-PCR analysis of CD4⁺ T-cells isolated from peripheral blood of benign erythroderma lesions and of representative cases of Sézary syndrome harboring 2p23.3 deletions (**a**) or 17p13.1 deletions (**b**). The bar graphs in **a** and **b** show the mean values from 3 technical triplicates in the qPCR reaction and error bars represent the s.d. *P* values were calculated using Student's *t* test. Grey boxes indicate heterozygous deletions. Solid boxes indicate homozygous deletions. CNV, copy number variation



Supplementary Figure 2

Signatures of mutational processes in Sézary syndrome.

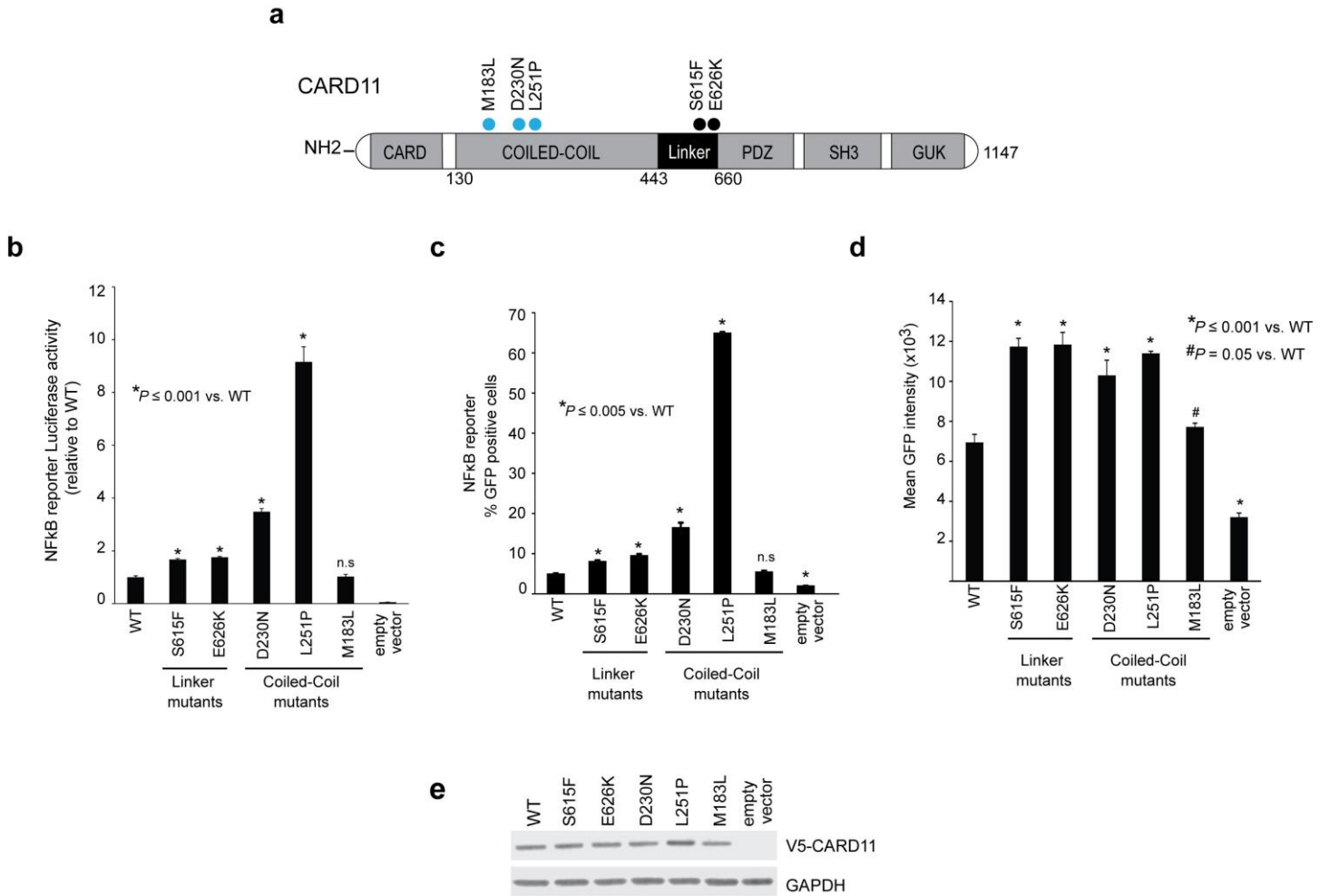
Analysis of mutational processes revealed the presence of a mutational signature characterized by C>T substitutions at NpCpG trinucleotides, as well as a high frequency of C>A substitutions at CpCpN trinucleotides and C>T substitutions at CpCpN and TpCpN trinucleotides



Supplementary Figure 3

Functional characterization of CTCL MAPK1 mutations.

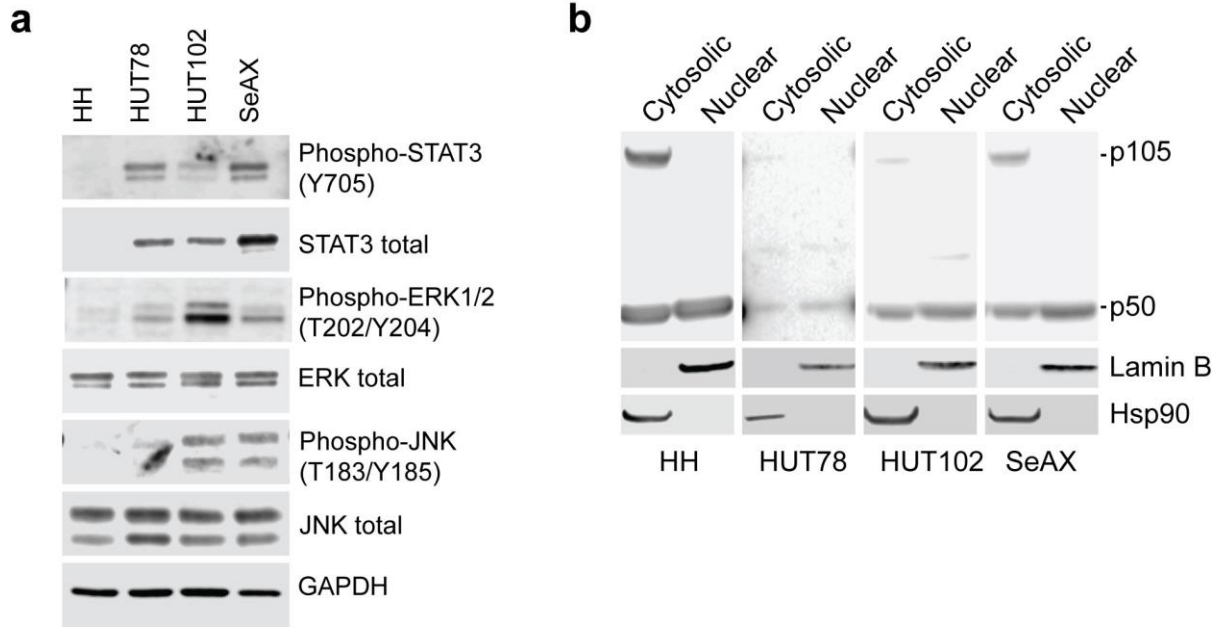
(a) Schematic representation of the structure of the MAPK1/ERK2 protein. MAPK1 mutations identified in CTCL samples are indicated with solid circles, recurrent COSMIC mutations (p.Glu322Lys) identified in solid tumors are indicated with open circles. **(b,c)** Western blot analysis **(b)** and quantification **(c)** of ERK phosphorylation in HEK293T cells expressing wild type V5-MAPK1, V5-MAPK1 E322K and V5-MAPK1 E322A. WT, wild type



Supplementary Figure 4

Comparative functional analysis of Sézary syndrome CARD11 linker domain mutations and DLBCL CARD11 Coiled-Coil domain mutations.

a) Schematic representation of the structure of the CARD11 protein. CARD11 mutations identified in the linker domain are indicated with black circles and three examples of CARD11 mutations identified in DLBCL are indicated with blue circles. **(b)** NF κ B luciferase reporter activity in HEK293-T cells transfected with V5-CARD11 wild-type, S615F, E626K, D230N, L251P, M183L or empty vector. **(c)** NF κ B-dependent GFP reporter activity in non-stimulated JURKAT cells expressing CARD11 wild type, CARD11 mutants, S615F, E626K, D230N, L251P, M183L or empty vector. Bar graphs indicate the percentage of GFP positive cells analyzed by flow cytometry. Data is representative of 3 independent experiments. **(d)** NF- κ B-dependent GFP reporter activity after stimulation for 6h with 1 μ g/ml ionomycin and 0.2 nM PMA in JURKAT cells expressing CARD11 wild type, CARD11 mutants, S615F, E626K, D230N, L251P, M183L or empty vector. Bar graphs indicate mean GFP intensity measured by flow cytometry across 3 replicates. **(e)** Analysis of the levels of V5-CARD11 protein in JURKAT NF κ B-GFP reporter cell line infected with lentiviruses driving the expression of CARD11 wild type, CARD11 mutants, S615F, E626K, D230N, L251P, M183L or empty vector. The bar graphs in **b**, **c** and **d** show the mean values and error bars represent the s.d. *P* values were calculated using Student's *t* test. WT, wild type

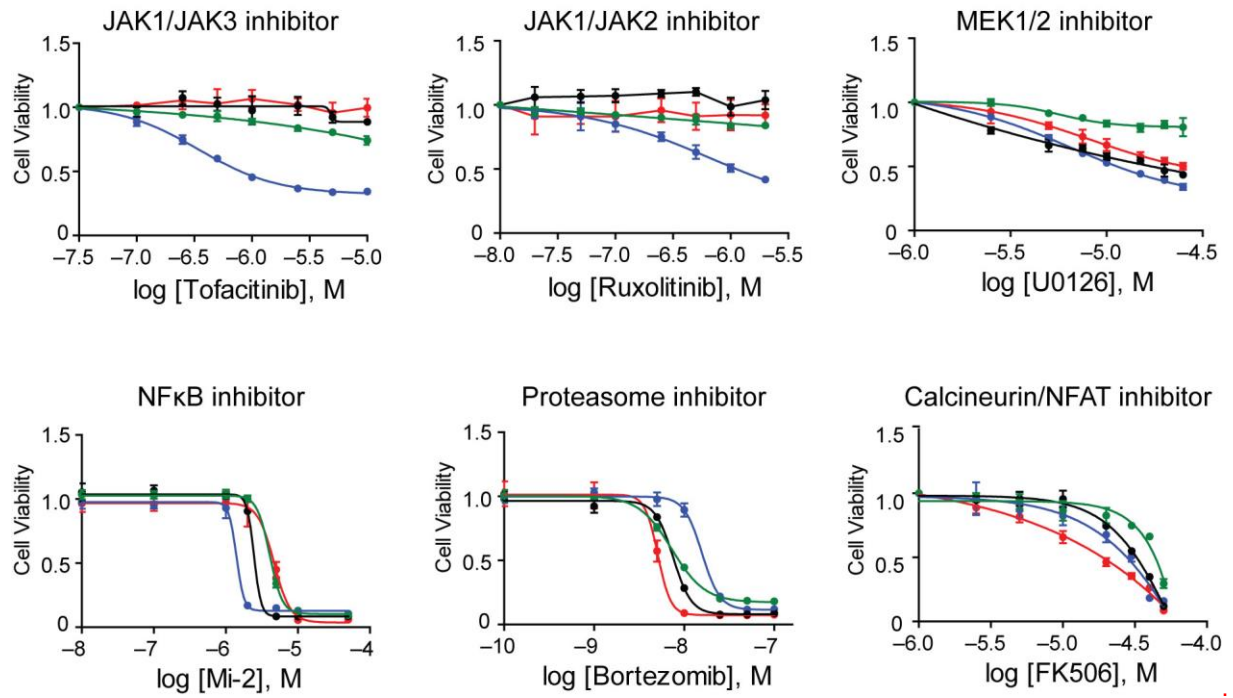


Supplementary Figure 5

Activated signaling pathways in CTCL cell lines.

(a) Western Blot analysis of STAT3, ERK1/2, and Jnk phosphorylation. **(b)** Analysis of nuclear NFkB after subcellular fractionation in CTCL cell lines.

● HH ● HUT102 ● HUT78 ● SeAX



Supplementary Figure 6

Antitumor activity of signaling inhibitors in CTCL.

Proliferation analysis of CTCL cell lines (HH, HUT78, HUT102, SeAX) after treatment with the indicated compounds for 72 h.