Supplementary Figures

Supplementary Figure S1. Immunohistochemical analysis of the inflammatory response in IHCA. This IHCA overexpressed SAA (**a**) and CRP (**b**) with a sharp demarcation from the non-tumoural liver (NTL). Only hepatocytes of the IHCA expressed SAA or CRP; inflammatory infiltrates are negative for these acute phase inflammation proteins (asterix). Inflammatory infiltrates are made predominantly of lymphocytes ($CD45^+$), localized around vascular axis inside the tumour (c); T lymphocytes ($CD3^+$) with CD4/CD8 (d-f) ratio around 2/1 are more numerous than B lymphocytes ($CD20^+$) (g), intermingled with $CD68^+$ histiocytes (h).

Supplementary Figure S2. Example of somatic DNA alterations identified in exon 6 of the *IL6ST* gene. Boundaries of the deletions are indicated by an arrow; mutated sequences are represented below the *IL6ST* wild-type sequence. **a,** Forward sequence of one representative case of mutated IHCA (T) and its matching non-tumour DNA (N) showing the somatic origin of the most frequent deletion identified; the nucleotide sequence deleted in tumour 382 is boxed. Amino acids (AA) and nucleotides (NT) are numbered according to *IL6ST* cDNA ORF. **b,** cDNA sequence analysis of two cases of mutated IHCA (T), showing expression of both the wild type and the mutant allele. **c**, Individual 770 is heterozygous for the polymorphism rs3729960 (697 G>C leading to G148R) located in exon 5 (arrow). The same ratio of allele is observed in normal and tumour sample both at the DNA and cDNA level. As this polymorphism is amplified in the same cDNA fragment than the mutated exon 6, these results show that the wild-type and the mutated allele are expressed at the same level in IHCA.

Supplementary Figure S3. Comparison of expression profiles between gp130 mutated inflammatory HCA and gp130 non-mutated IHCA. Comparison was carried out for the 24 genes validated by quantitative RT-PCR that were significantly differentially expressed between IHCA and non-tumour livers. Seven gp130 mutated IHCA (in black) were compared to 7 gp130 non-mutated IHCA (in grey). Results are expressed as mean ± SD; * difference between groups at $P<0.05$ (two-tailed Mann-Whitney test).

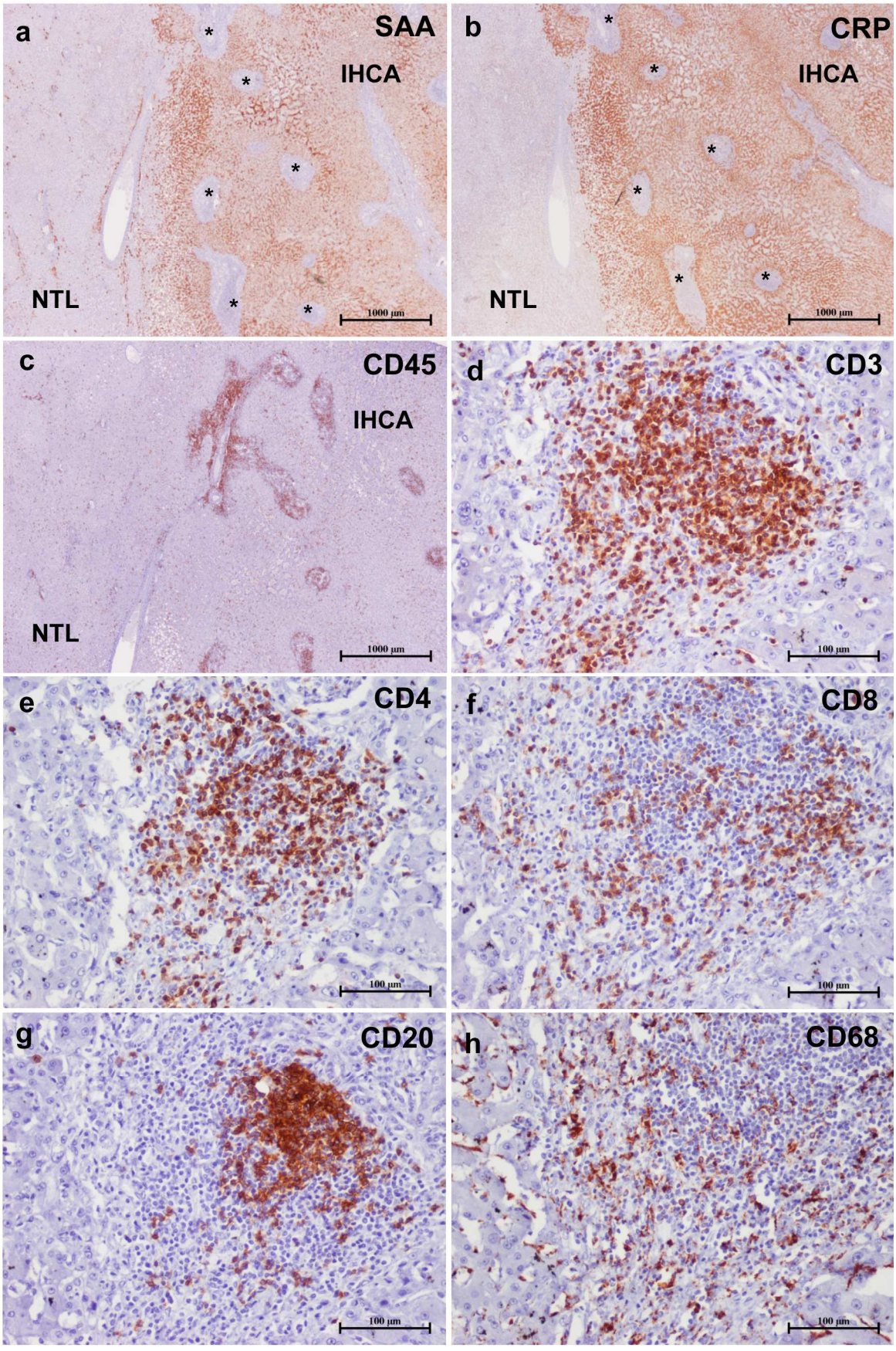
Supplementary Figure S4. Analysis of gp130 and p-STAT3 expression in inflammatory HCA. **a,** *IL6ST* mRNA level in 6 non-tumour livers (NTL) was compared with that of 7 gp130-mutated IHCA (M) and 7 gp130-non-mutated IHCA (NM), using qRT-PCR. Results are expressed as mean-fold difference ± SD, relative to NTL; ns: non significant (two-tailed Mann-Whitney test). **b,** Western-blotting analysis of gp130 protein level in 3 non-tumour livers (NTL), 2 gp130-mutated IHCA and 7 gp130-non-mutated IHCA. Red ponceau staining was used as loading control. **c**, **d**, Immunohistochemical analysis of gp130 showing

overexpression of the protein in both gp130-mutated (**c**) and gp130-non-mutated (**d**) IHCA compared to their adjacent non-tumour liver parenchyma (NTL). **e**, **f**, **g**, Immunohistochemistry of phospho-STAT3 (tyr705) in gp130-mutated (**e**) and non-mutated (**f**) IHCA showing an intense nuclear staining in tumour cells while p-STAT3 is undetectable in non-tumour liver (NTL) (**g**).

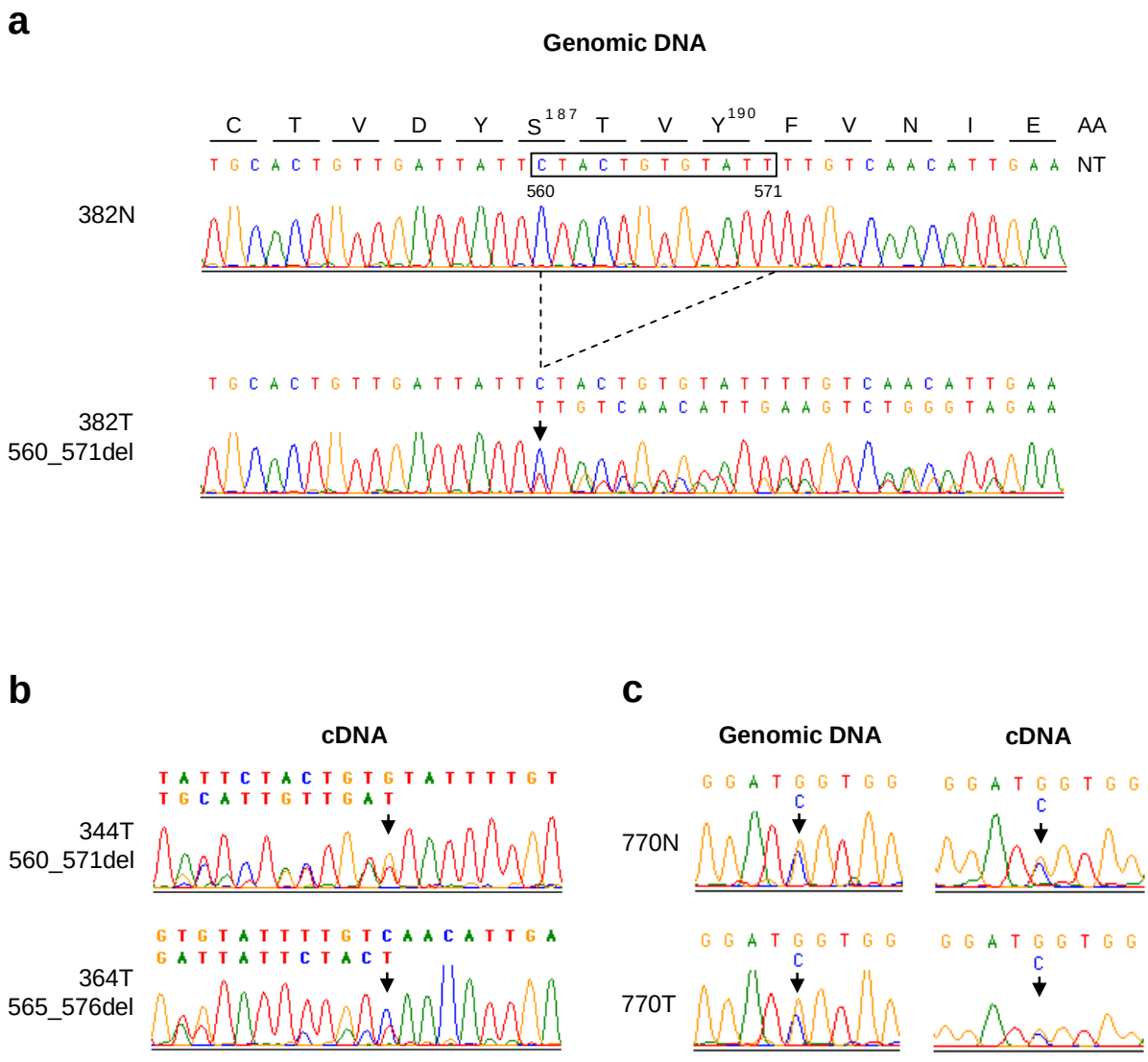
Supplementary Figure S5. **mRNA expression of *IL11* and *IL11RA* in inflammatory HCA and transfected Hep3B cells. a**, *IL11* and *IL11RA* mRNA levels were assessed using qRT-PCR in 6 non-tumour livers (NTL), 7 gp130-mutated IHCA (M) and 7 gp130-non-mutated IHCA (NM). Results are expressed as mean-fold difference ± SD, relative to NTL (mean NTL=1) *, **, difference between groups at $P<0.05$ and 0.01, respectively (two-tailed Mann-Whitney test). **b**, qRT-PCR analysis of *IL11* mRNA expression in Hep3B cells transfected either with Wt gp130 or with four IHCA mutants of gp130 (Δ) (Y186_Y190del (Y); K173_D177del (K); S187_Y190del (S) and V184_Y186del, S187A (V)), as described in Fig3. Experiments were performed in triplicate and expressed as mean ± SD in comparison to empty plasmid-transfected and untreated cells (mean=1). ns: non significant (two-tailed t-test).

Supplementary Figure S6. Western blotting analysis of ERK1/2 activation in inflammatory HCA and Hep3B cells. **a**, Expression of the phosphorylated forms of ERK1 and ERK2 was compared between 10 IHCA (including 4 cases mutated for gp130) and 6 non-tumour livers (NTL). Red ponceau staining was used as loading control. **b**, Expression of phospho-ERK1/2 was compared between Hep3B cells transfected with the wild-type (Wt) or the mutant (ΔS) gp130 (S187_Y190del). As a control cells were transfected with empty plasmid and untreated or stimulated with 100 ng/µl of IL6.

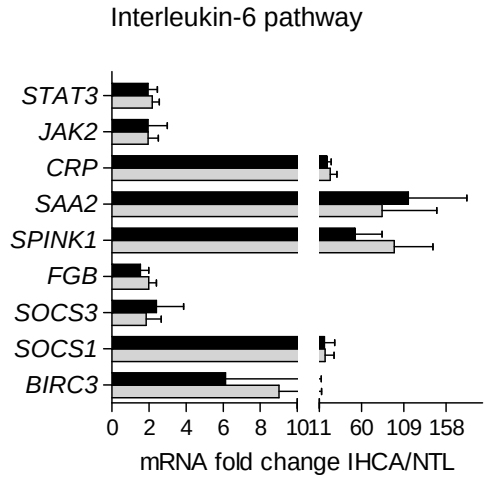
Supplementary Figure S1

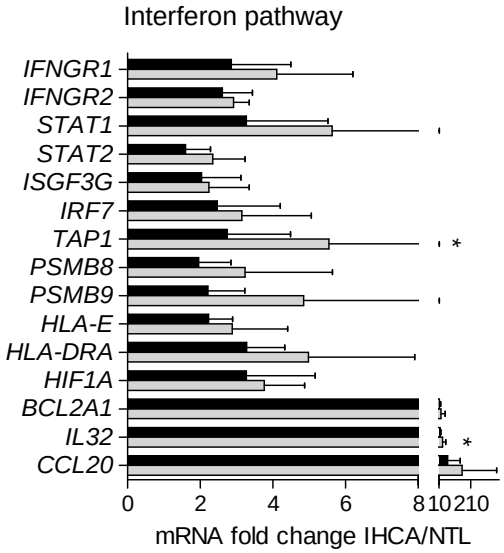


Supplementary Figure S2

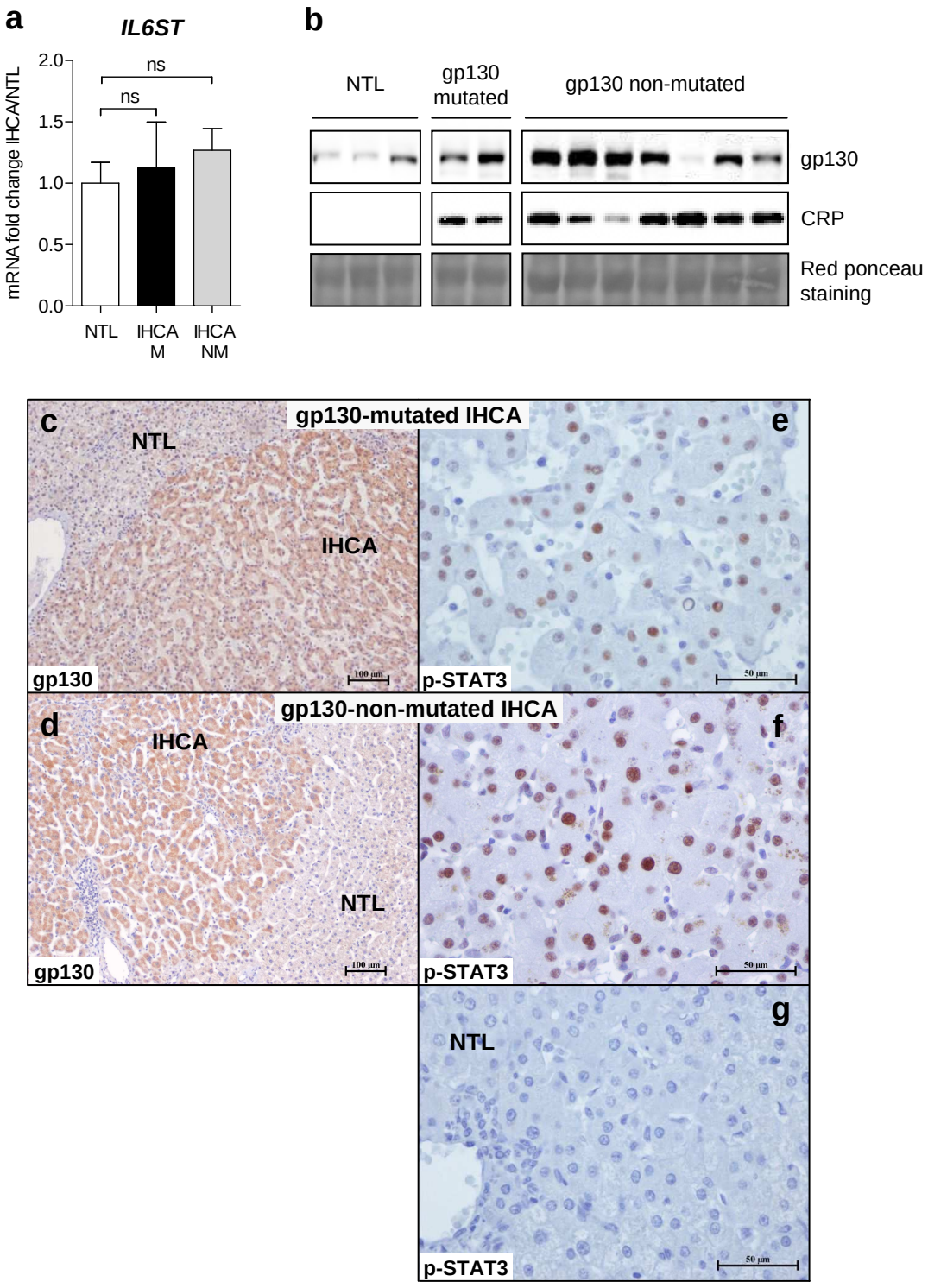


Supplementary Figure S3

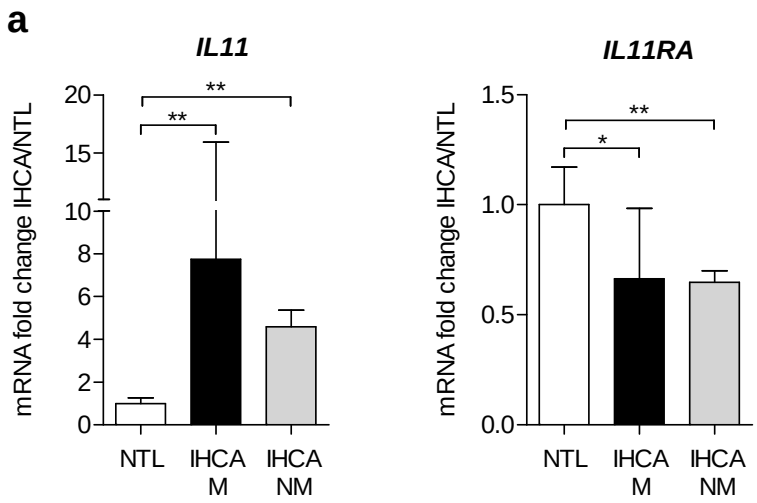


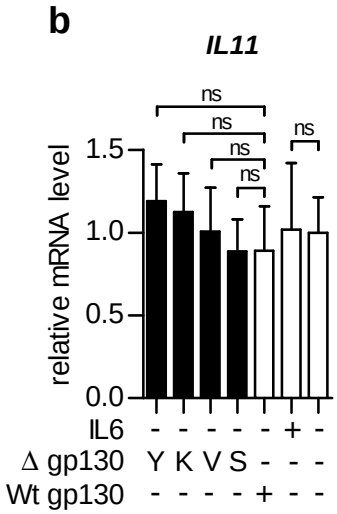


Supplementary Figure S4



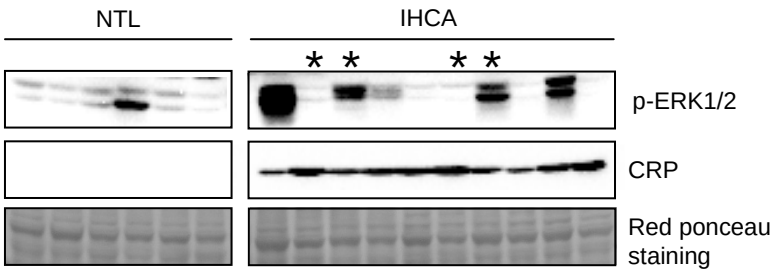
Supplementary Figure S5





Supplementary Figure S6

a



* IHCA gp130-mutated

b