SUPPLEMENTARY MATERIAL from:

Genomic and Transcriptomic Hallmarks of Poorly-Differentiated and Anaplastic Thyroid Cancers

Landa I, Ibrahimpasic T, Boucai L, Sinha R, Knauf JA, Shah RH, Dogan S, Ricarte-Filho JC, Krishnamoorthy GP, Xu B, Schultz N, Berger MF, Sander C, Taylor BS, Ghossein R, Ganly I, Fagin JA

SUPPLEMENTARY FIGURE LEGENDS

Supplementary Figure S1. Diagrams showing mutation location, count and alteration type for common somatic variants in ATCs and PDTCs. Each graph depicts the mutations found in each gene altered in our series of 117 advanced thyroid tumors. Graphs were generated with the MutationMapper tool (v1.0.1) available at cBioPortal (http://cbioportal.org). Proteins are represented left to right from N- to C-terminal regions, with aminoacid (aa) positions shown on the X-axis and with main domains highlighted. Location of mutations in the protein are depicted as circles, the height of which represents the mutation count for that position, as measured in Y-axis. Circles are color-coded as follows: green= missense; red= truncating (nonsense, nonstop, frameshift deletion, frameshift insertion, splice site); black= in-frame (in-frame deletion, in-frame insertion), blue= promoter mutations; purple= residues affected by different mutation types in the same proportion. Where different mutation types occur at a single position, color is determined by the most frequent mutation type. The most common residue mutated for each protein is spelled out in the graph. **A.** *BRAF*; **B.** *NRAS*; **C.** *HRAS*; **D.** *KRAS*; **E.** *NF1*; **F.** *TSHR*; **G.** *STK11*; **H.** *EIF1AX*; **I.** *PIK3CA*; **J.** *PTEN*; **K.** *TERT* promoter; **L-P.** Tumor suppressor genes frequently mutated; **L.** *TP53*; **M.** *ATM*; **N.** *RB1*; **O.** *NF2*; **P.** *MEN1*; **I, J, Q-Y.** PI3K/AKT/mTOR pathway proteins; **Q.** *PIK3C2G*; **R.** *PIK3CG*; **S.** *PIK3C3*; **T.** *PIK3R1*; **U.** *PIK3R2*; **V.** *AKT3*; **W.** *TSC1*; **X.** *TSC2*; **Y.** *MTOR*; **Z-AF.** SWI/SNF complex: **Z.** *ARID1A*; **AA.** *ARID1B*; **AB.** *ARID2*; **AC.** *ARID5B*; **AD.** *SMARCB1*; **AE.** *PBRM1*; **AF.** *ATRX*; **AG-AJ.** Histone methyltransferases (HMTs): **AG.** *KMT2A*; **AH.** *KMT2C*; **AI.** *KMT2D*; **AJ.** *SETD2*; **AK-AM.** Mismatch excision repair (MMR): **AK.** *MSH2*; **AL.** *MSH6*; **AM.** *MLH1*; **AN-AQ**. Proteins involved in histone acetylation; **AN.** *CREBBP*; **AO.** *EP300*; **AP.** *BCOR*; **AQ.** *BCL6*; **AR-AV.** Receptor tyrosine kinases; **AR.** *EGFR*; **AS.** *EPHA3*; **AT.** *FLT1* (VEGFR1); **AU.** *FLT4* (VEGFR3); **AV.** *KDR* (VEGFR2); **AW-AZ.** NOTCH: **AW.** *NOTCH1*; **AX.** *NOTCH2*; **AY.** *NOTCH3*; **AZ.** *NOTCH4*; **BA.** *PRKAR1A*; **BB.** *DIS3*; **BC.** *FAT1*; **BD.** *POLE*; **BE.** *RBM10*; **BF.** *RAD54L*; **BG.** *RECQL4*; **BH.** *SF3B1*; **BI.** *CDKN1B*; **BJ.** *CDKN2A*; **BK.** *CDKN2C*; **BL.** *ERBB2*; **BM.** *PTCH1*; **BN.** *DAXX*.

Supplementary Figure S2. Tumor purity of PTCs, PDTCs and ATCs. A. Calculation of tumor purity was based on the assumption that driver mutations are clonal heterozygous events (see Methods). Graph shows percentage of tumor content for 62 PDTCs and 32 ATCs. We applied the same purity calculation method to 286 *BRAF*- or *RAS*-mutated tumors from the PTC-TCGA dataset. Horizontal blue bars show the median value for each tumor type, which is also shown in the adjacent table. p-values were derived from Mann-Whitney tests.

Supplementary Figure S3. Comparison of copy number calls in a subset of 37 frozen tumors (17 PDTCs and 20 ATCs) by array-CGH vs IMPACT with or without correction for tumor purity. Examples for chromosome 1p loss (panels **A-C**) and chromosome 20q gain (**D-F**) are shown. Copy number alterations were assessed by an array-CGH platform from Agilent (**A, D**) and by MSK-IMPACT targeted sequencing without (**B, E**) or with tumor purity-correction (**C, F**). Samples were ranked based on log-ratio values for identical regions in the respective chromosomes. Sample IDs and log-ratios corresponding to each sample are listed in the figure. **A-C:** The nine tumors with top 1p losses (mostly PDTCs with high tumor content) were similarly detected by both CGH and IMPACT, with minor changes in sample order, although IMPACT showed more negative log-ratios. **D-F:** IMPACT-detected 20q gains (an alteration enriched in ATCs) matched those with the highest log-ratios as called by array-CGH (green), and identified gains in additional highly impure specimens (black), particularly after correcting for tumor purity.

Supplementary Figure S4. Genome-wide copy number alterations in 117 advanced thyroid cancers. IGV representation of copy number gains and losses in all chromosomes in 84 PDTCs and 33 ATCs expressed as red (gain) or blue (loss), with shading intensity proportional to the log-ratio (lr) values. Samples are grouped by tumor type and sorted by genetic driver alteration: *BRAF*, *RAS*, fusions (RET/PTC, PAX8-PPARG and ALK), or none/unknown. Color key and annotations are shown on the left.

Top panel shows the eight arm-level regions recurrently gained or lost in PDTCs and ATCs, further discussed in Figure 5 and in the main text.

Supplementary Figure S5. Extended BRS heatmaps for 17 PDTCs and 20 ATCs. Heatmaps representing the complete 67-gene BRS signature applied separately to PDTCs (panel **A**) and ATCs (**B**). Expression values are displayed as Z-scores after scaling the values of each gene across the 17 and 20 tumors, respectively. Samples are sorted by ascending BRS score (*BRAF*^{V600E}-like on the left and *RAS*-like on the right, within each panel) and annotated for driver alteration. This is an expanded version of Figure 6B, which only shows 26 out of the 67 genes in the signature, and combines PDTCs and ATCs in the same heatmap.

Supplementary Figure S6. Extended M2 macrophage gene signature heatmap in 37 advanced thyroid tumors. Unsupervised clustering showing the complete 68-gene signature of "genes overexpressed in M2 macrophages" in 17 PDTCs (green) and 20 ATCs (orange). Expression values are displayed as Z-scores after scaling the values of each gene across the 37 samples. This figure is an expanded version of Figure 7A, which only shows the 11 most discriminative genes out of the total 68 genes in this signature.

Supplementary Figure S7. TDS heatmap in 37 advanced thyroid tumors. Unsupervised clustering using the 16-gene TDS signature in 17 PDTCs (green) and 20 ATCs (orange). Expression values are absolute (not scaled across samples) and they match the ones represented in the box-plots shown in Figure 7B.

SUPPLEMENTARY TABLE LEGENDS

Supplementary Table S1. Clinicopathological features of 117 advanced thyroid tumors. Detailed information of the main features of 84 poorly-differentiated (PDTC) and 33 anaplastic thyroid cancers (ATC) reported in the study. All categories and color codes depicted in Figure 1 and summarized in Table 1 are expanded here.

Supplementary Table S2. Impact of mutation burden on clinicopathological features of advanced thyroid tumors.

Supplementary Table S3. Contingency tables for the main genetic alterations found in PDTCs and ATCs. Mutation distribution and associated tests for all genes/pathways in PDTCs *vs.* ATCs, as shown in Figure 1. [1] "*RAS*" category includes *NRAS*, *HRAS* and *KRAS*; [2] "Thyroid fusions" include rearrangements of genes previously reported in thyroid tumors: RET/PTC, PAX8-PPARG and *ALK* fusions; [3] Significant p-values are highlighted in yellow; marginally significant are highlighted in grey; Abbreviations: PDTC= Poorly-Differentiated Thyroid Cancer, ATC= Anaplastic Thyroid Cancer, HMT= histone methyltransferase, MMR= mismatch excision repair.

Supplementary Table S4. Full list of single nucleotide variants (SNVs) and short indels in 341 genes in 117 advanced thyroid tumors. Complete list of all variants called in 84 poorly-differentiated (PDTC) and 33 anaplastic thyroid cancers (ATC). The following categories are listed: Tumor type= PDTC or ATC; Sample ID= identification code of each tumor; Alternate ID= alternative tumor identification code; Normal = paired or pooled normal tissue identification code; Gene_mutation summary= the first column refers to the gene and the second to the protein; Chrom= chromosome number; Coordinate start site= genomic coordinate (hg19); Ref= reference (wildtype) allele; Alt= alternative (mutant) allele; Variant Class= type of alteration, depending on its effect on the protein product; Gene= gene name (HUGO nomenclature); cDNA change= variant nomenclature, based on the complementary DNA coordinates;

AA change= variant nomenclature, based on the change in the protein (AA= aminoacid); dbSNP_ID= "rs" code from NCBI SNP database (http://www.ncbi.nlm.nih.gov/snp); COSMIC_ID= mutation code from Sanger's Catalogue of Somatic Mutations in Cancer (COSMIC, http://cancer.sanger.ac.uk/cosmic); T_Total Depth= total number of sequencing reads that include position of variant nucleotide in each sample; T_Ref Count= number of reads for the reference allele in the tumor; T_Alt Count= number of reads for the alternative allele in the tumor; T_Alt Freq= frequency of the alternative allele in the tumor (=T_Alt Count/T_Total Depth); N_Total Depth= total number of sequencing reads in the normal tissue; N_Ref Count= number of reads for the reference allele in the normal; N_Alt Count= number of reads for the alternative allele in the normal; N_Alt Freq= frequency of the alternative allele in the normal (=N_Alt Count/N_Total Depth).

Supplementary Table S5. Clinicopathological characteristics of ATCs and PDTCs according to *BRAF* and *RAS* mutation status and gene fusions.

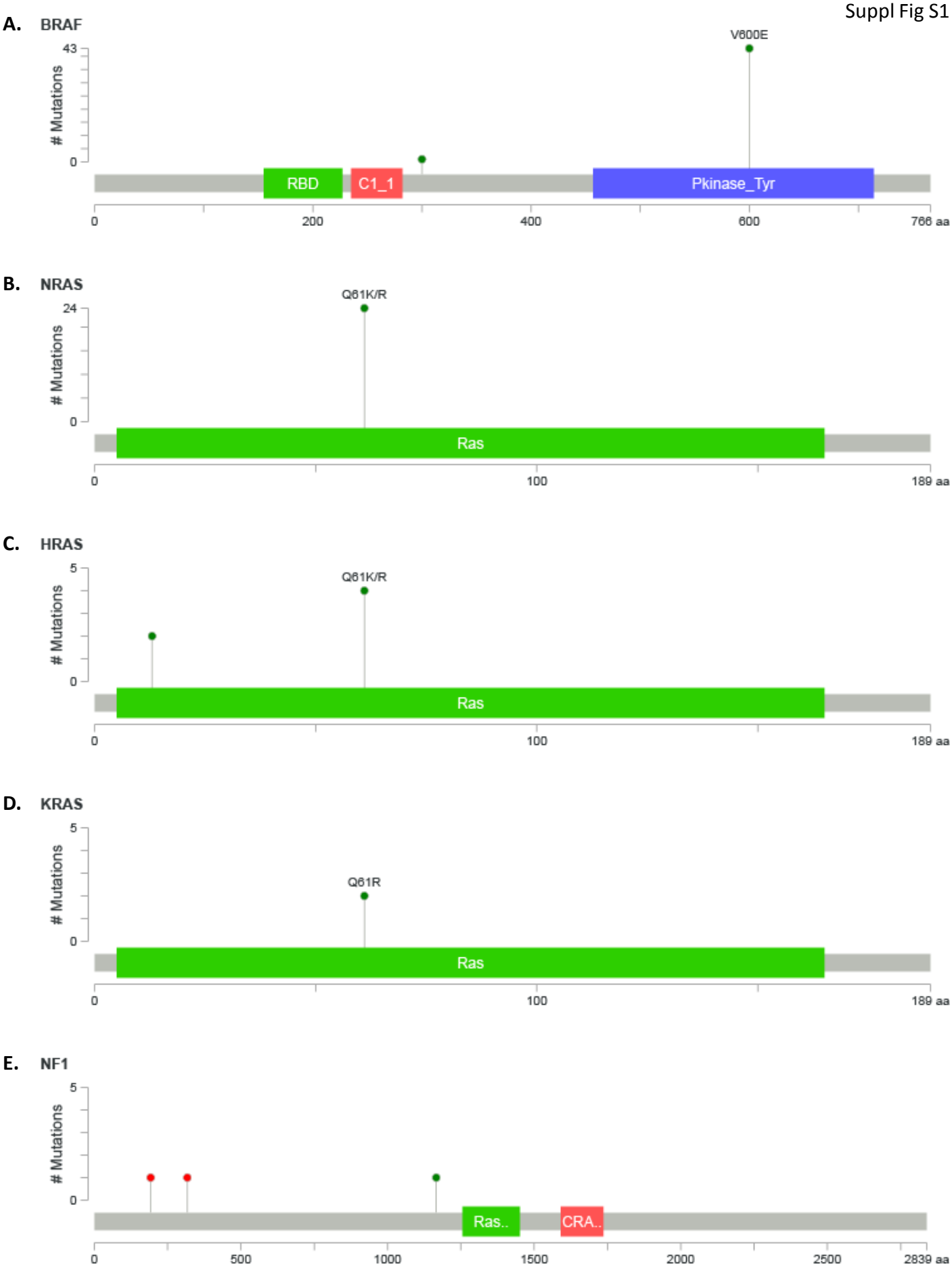
Supplementary Table S6. Clinicopathological characteristics of ATCs and PDTCs according to *EIF1AX* mutation status.

Supplementary Table S7. Clinicopathological characteristics of ATCs and PDTCs according to *TERT* promoter mutation status.

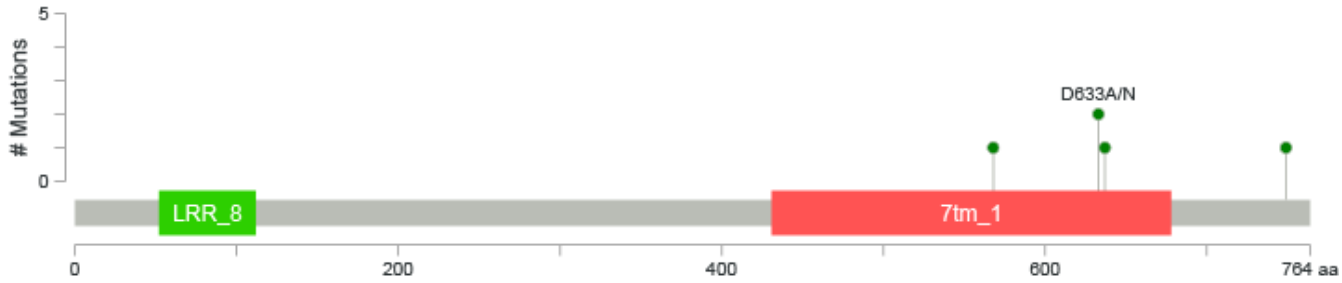
Supplementary Table S8. Prevalence of common gene mutations in advanced thyroid cancers reported in the literature. Summary of published studies reporting genetic alterations in PDTCs and/or ATCs for *BRAF*, *RAS*, RET/PTC, *TP53*, *PIK3CA*, *PTEN*, *AKT1*, *CTNNB1*, *AXIN1*, *APC*, *TERT* promoter and *EIF1AX*.

Supplementary Table S9. Tumor characteristics and gene expression results of 37 advanced thyroid tumors. Characteristics of the 17 PDTCs and 20 ATCs frozen tissues used for gene expression studies. Sample types, tumor purity and driver alterations are listed. Individual gene expression scores for the

following signatures are shown: BRAF-RAS score (BRS; see as well Figures 6B, C and Supplementary Figure S5), M2 macrophage signature (Figure 7A and Supplementary Figure S6) and the thyroid differentiation score (TDS, Figure 7B-D and Supplementary Figure S7). Average expression values are listed for all three signatures for each sample, and individual expression values (relative to all genes expressed) are given for the 16 thyroid genes that define the TDS.


A.
BRAF
V600E
43
Mutations
0
RBD
C1_1
Pkinase_Tyr
0
200
400
600
766 aa
B.
NRAS
Q61K/R
24
Mutations
0
Ras
0
100
189 aa
C.
HRAS
Q61K/R
5
Mutations
0
Ras
0
100
189 aa
D.
KRAS
Q61R
5
Mutations
0
Ras
0
100
189 aa
E.
NF1
5
Mutations
0
Ras..
CRA..
0
500
1000
1500
2000
2500
2839 aa

F. **TSHR**



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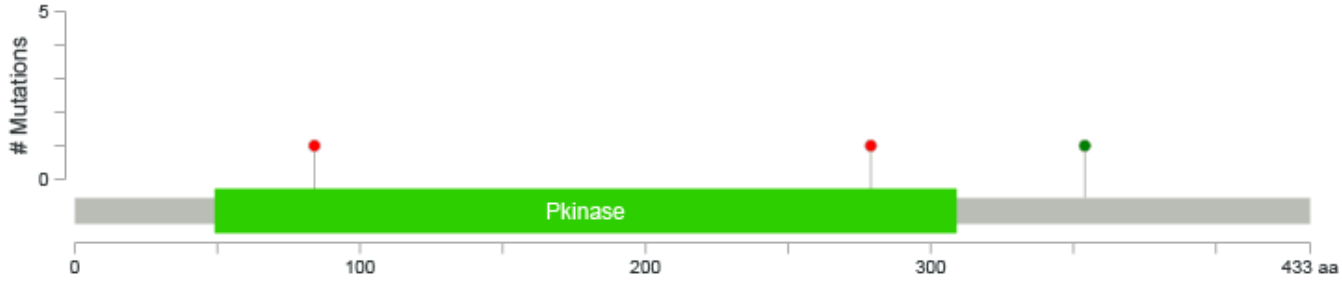
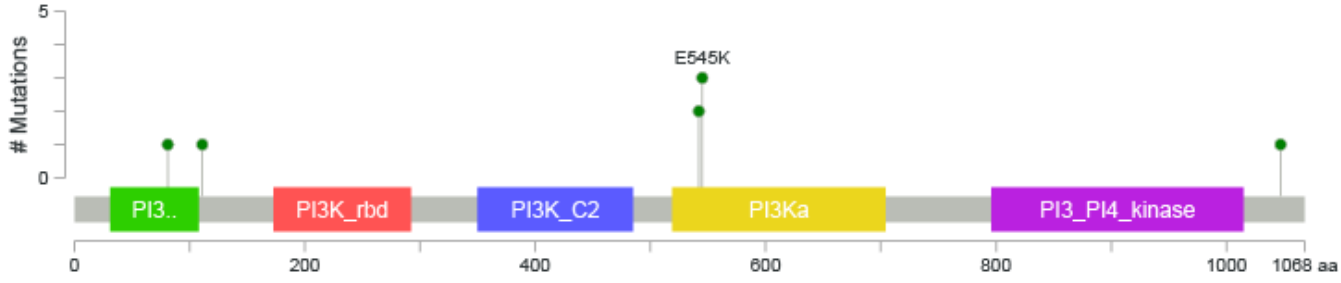


H. **EIF1AX**

I. **PIK3CA**



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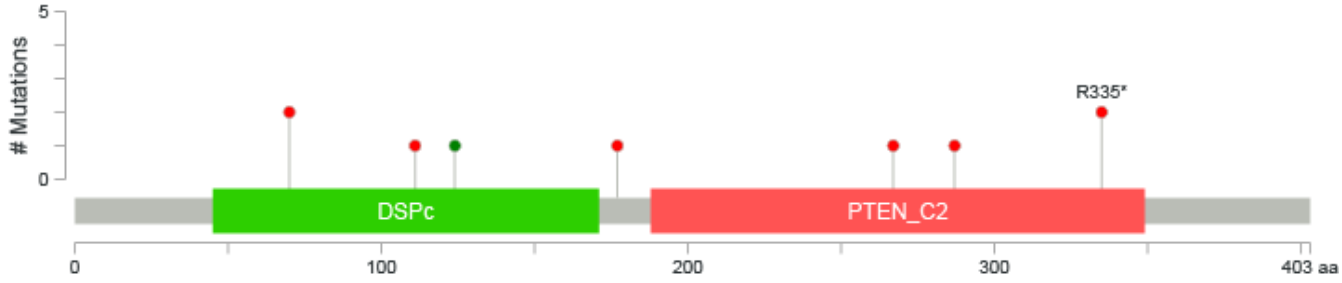

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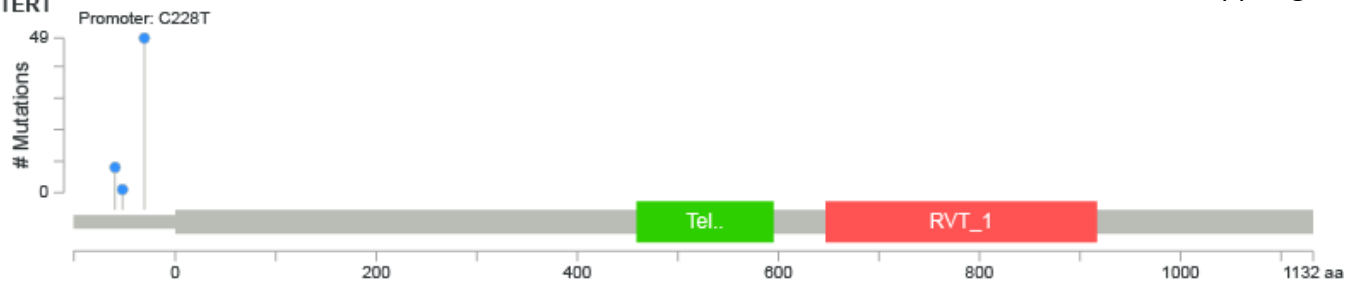

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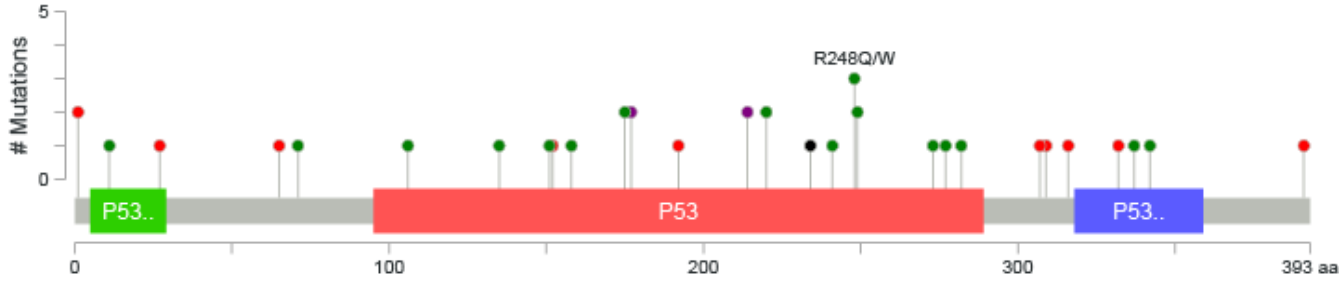

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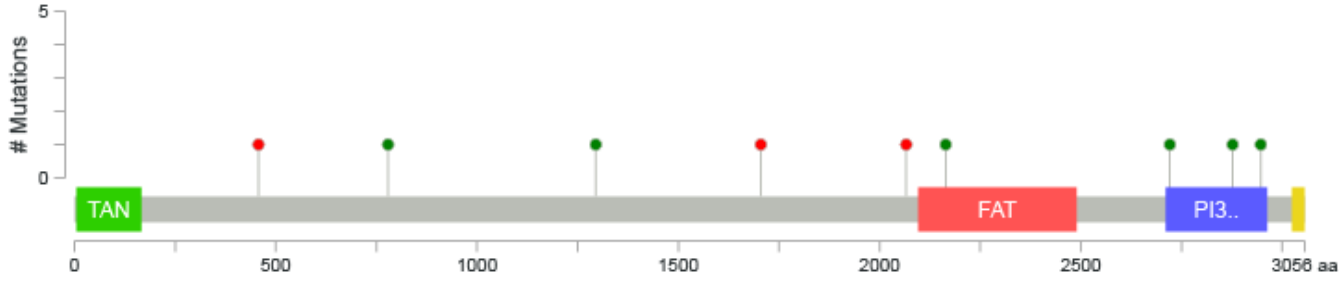

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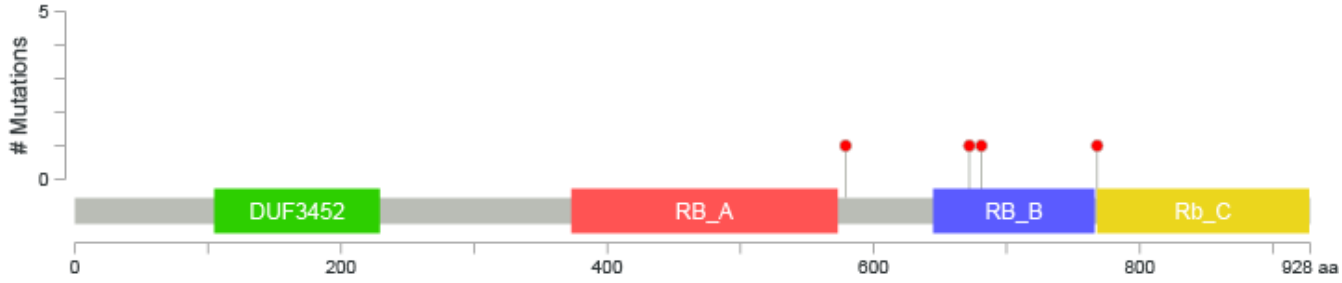

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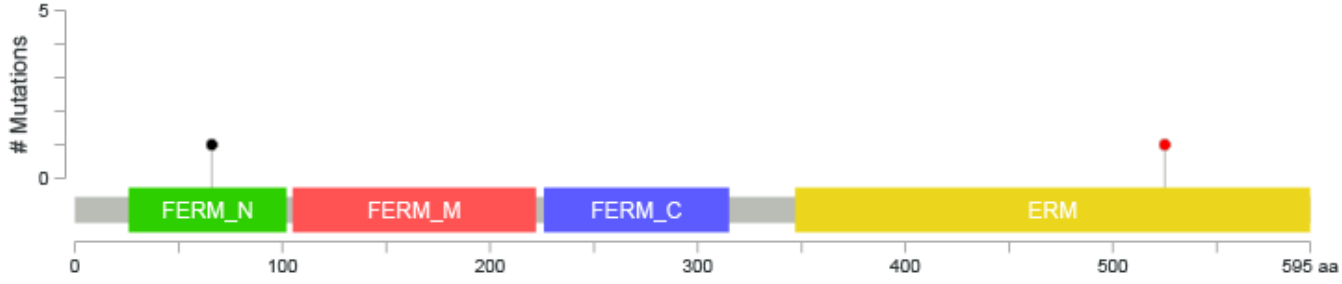

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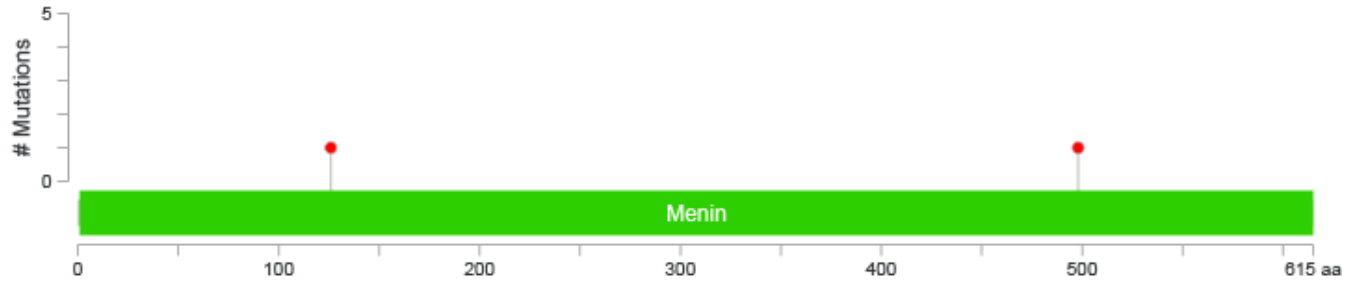

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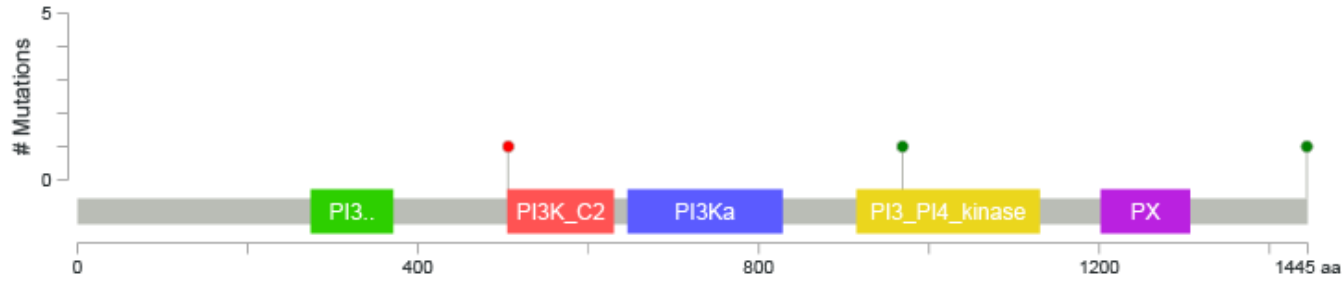

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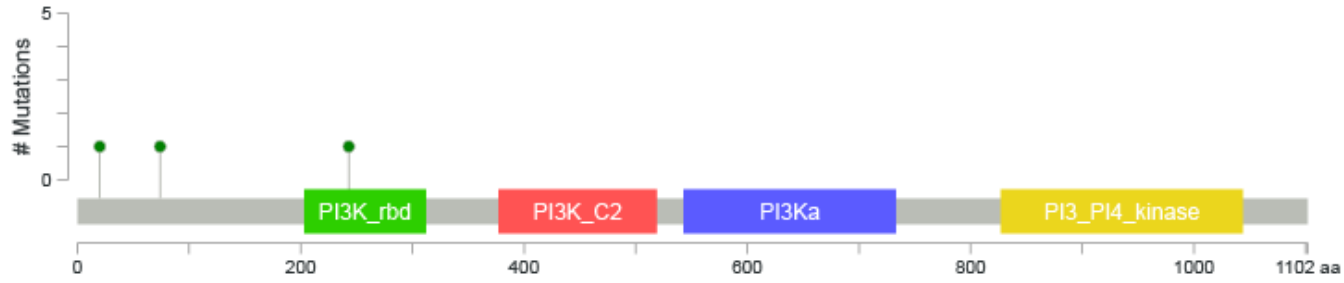

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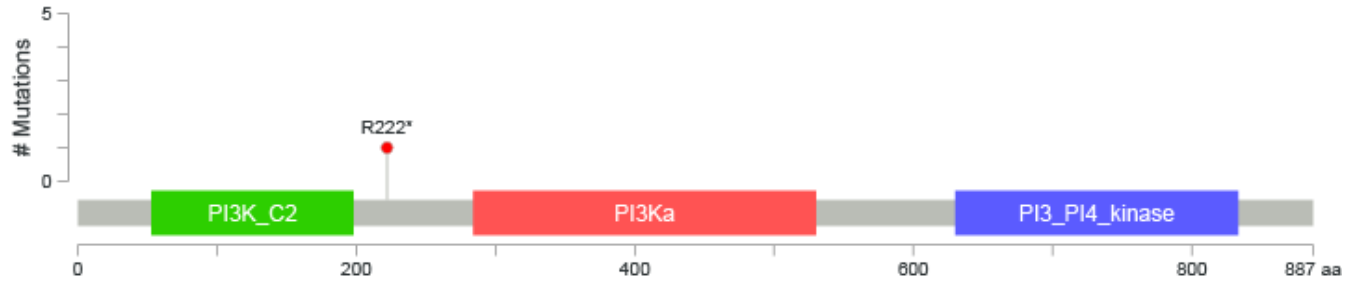

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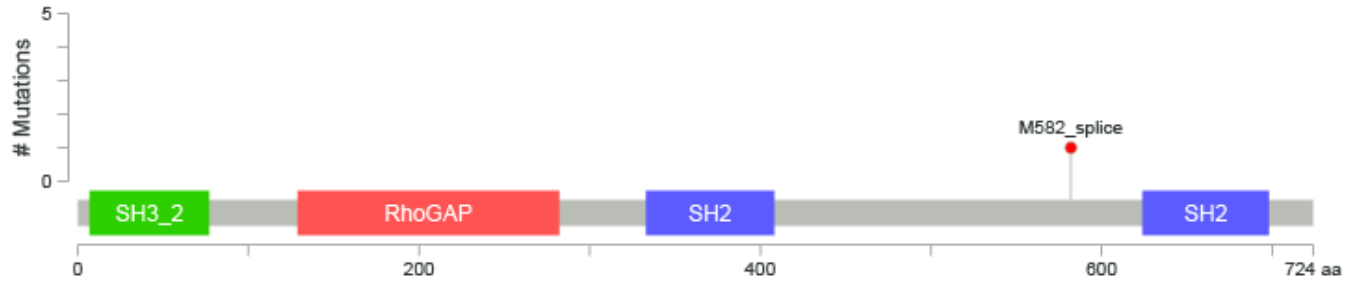

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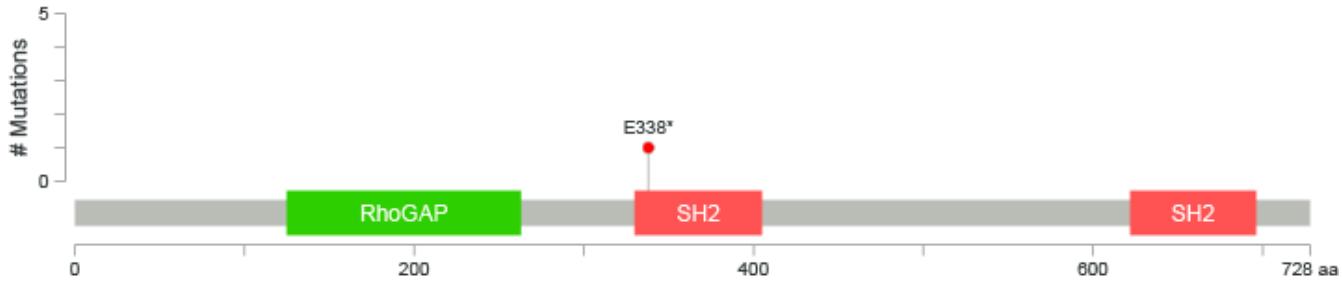

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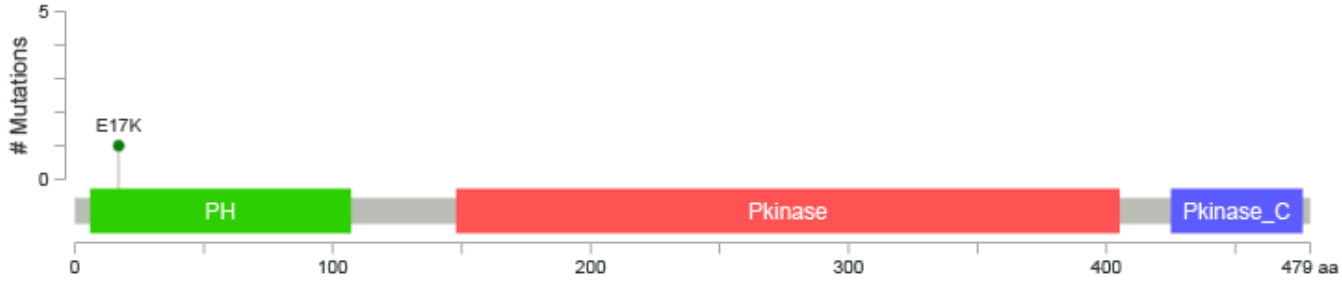

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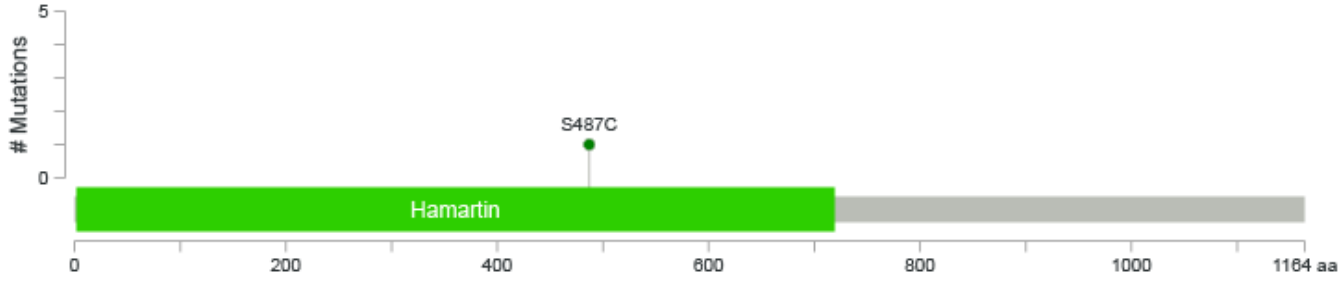

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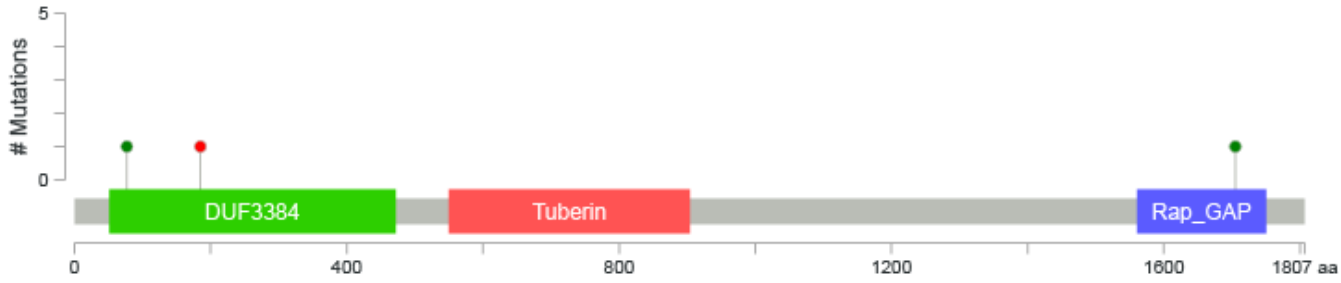

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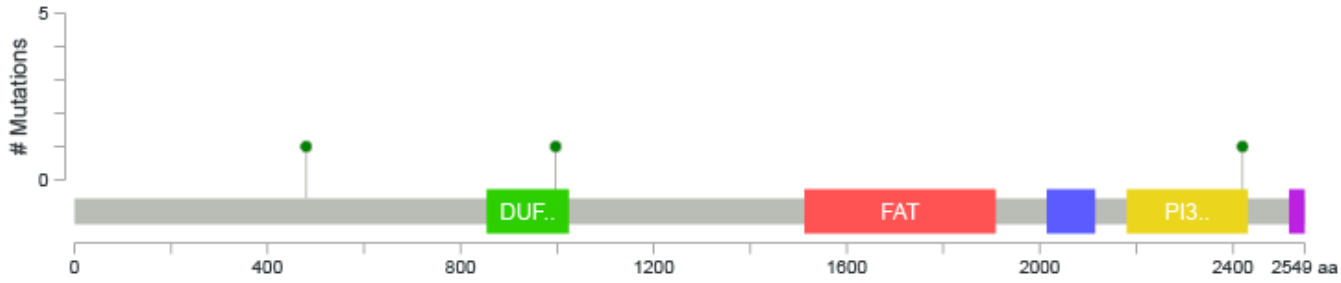

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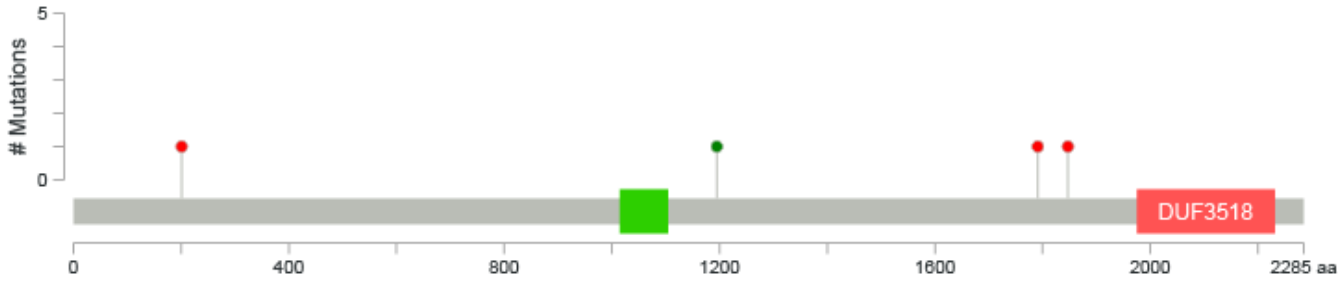

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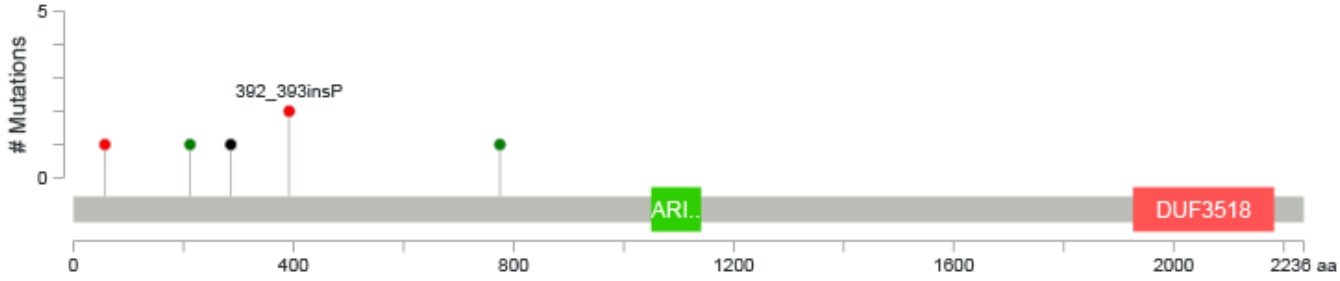

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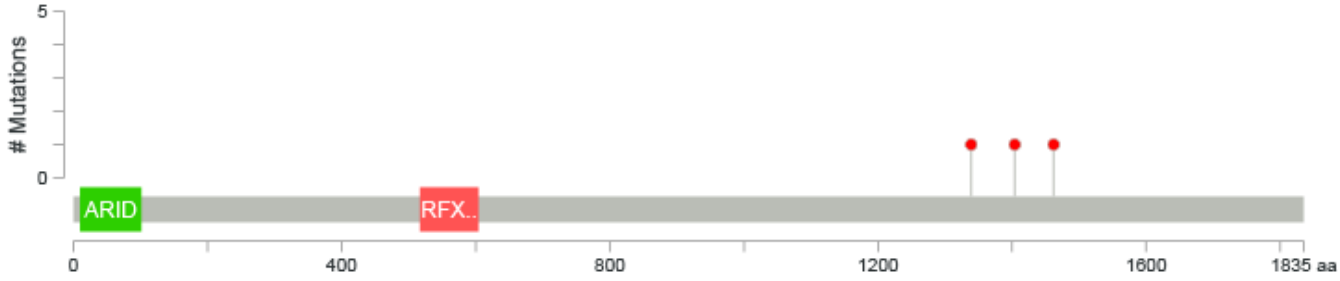

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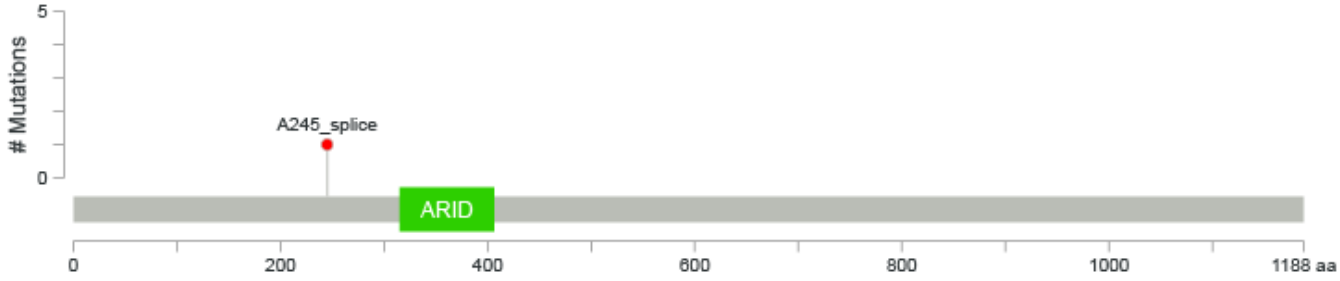

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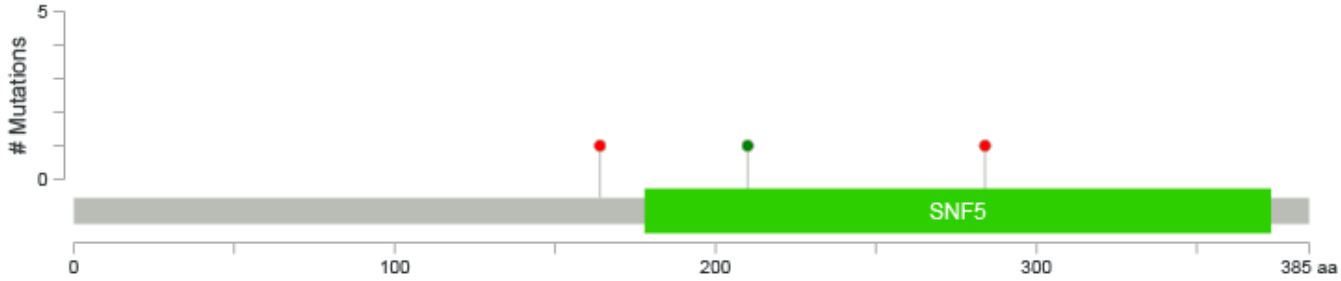

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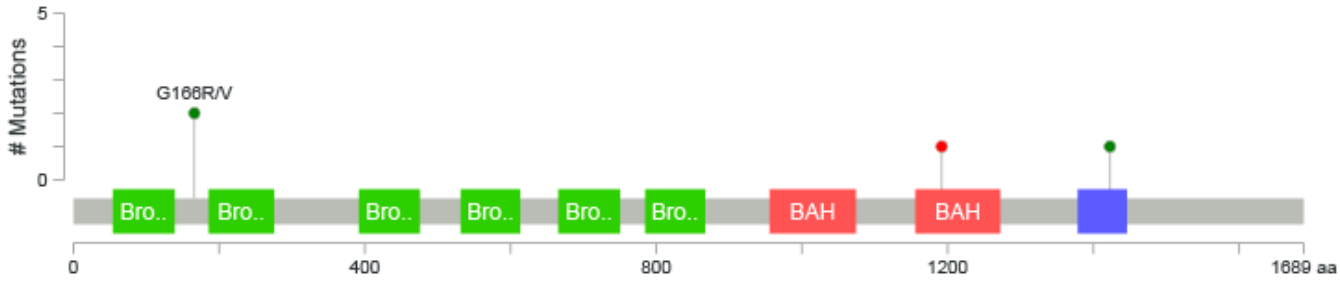

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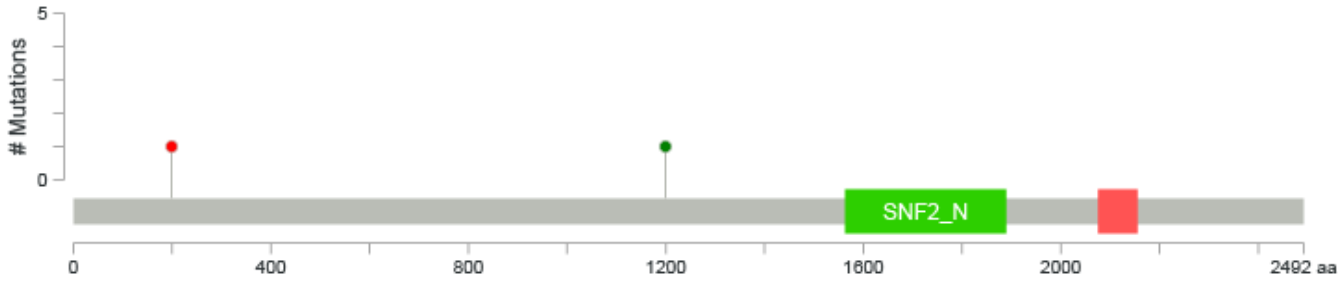

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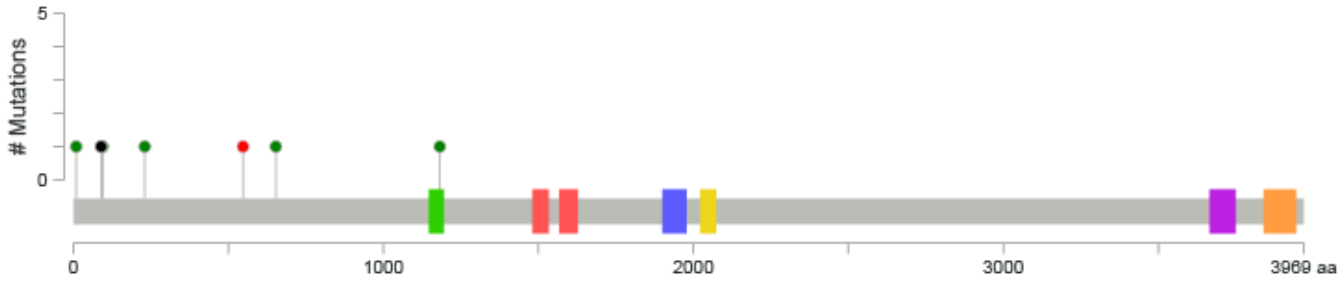

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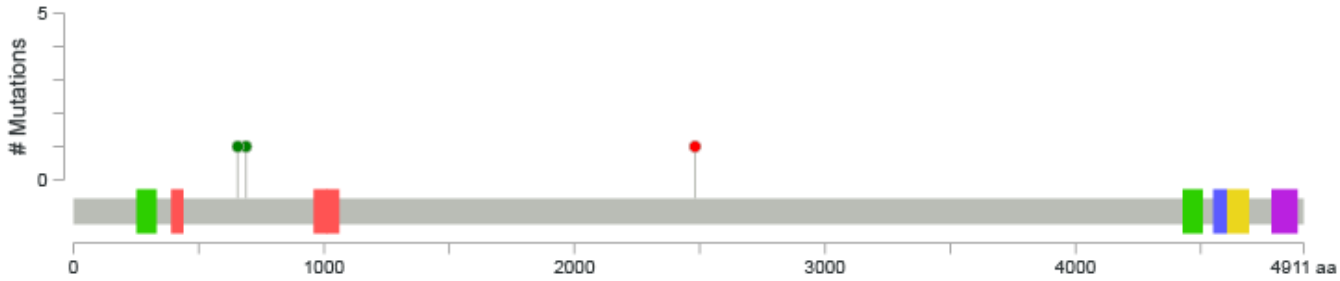

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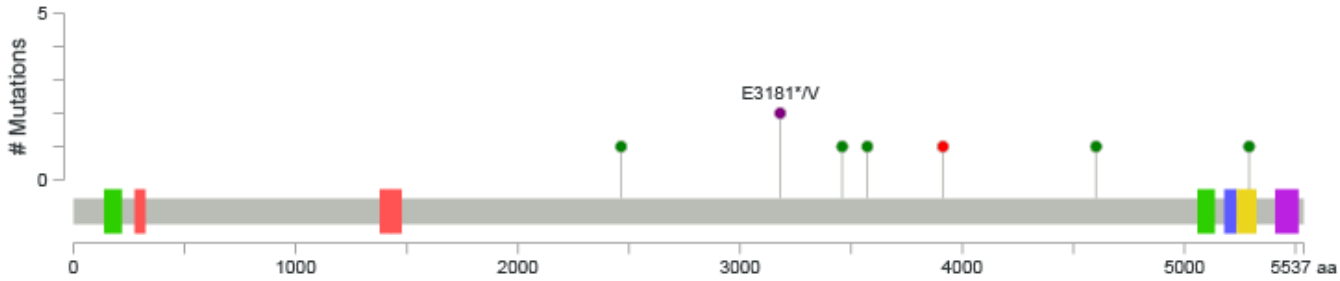

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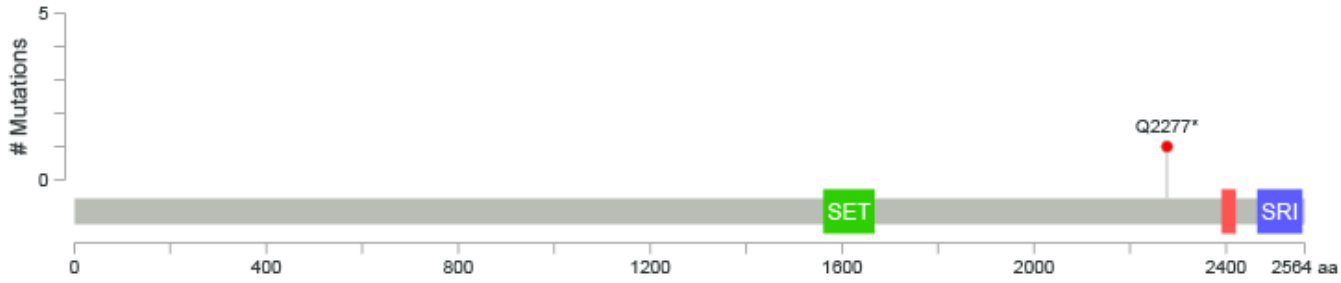

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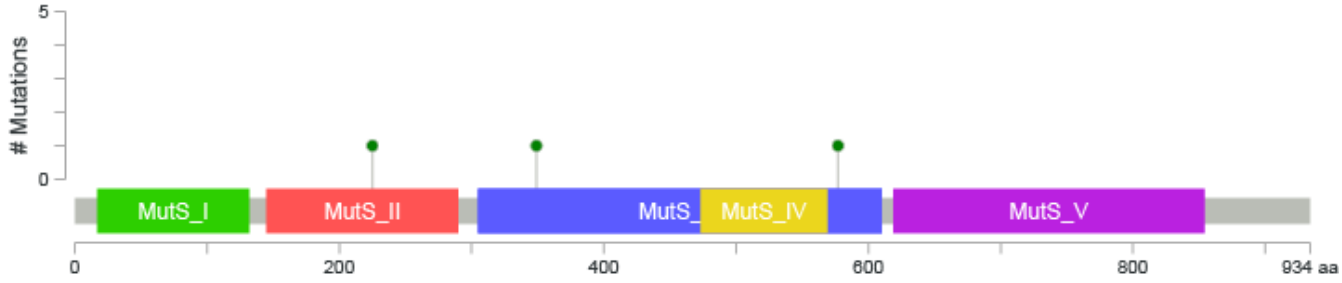

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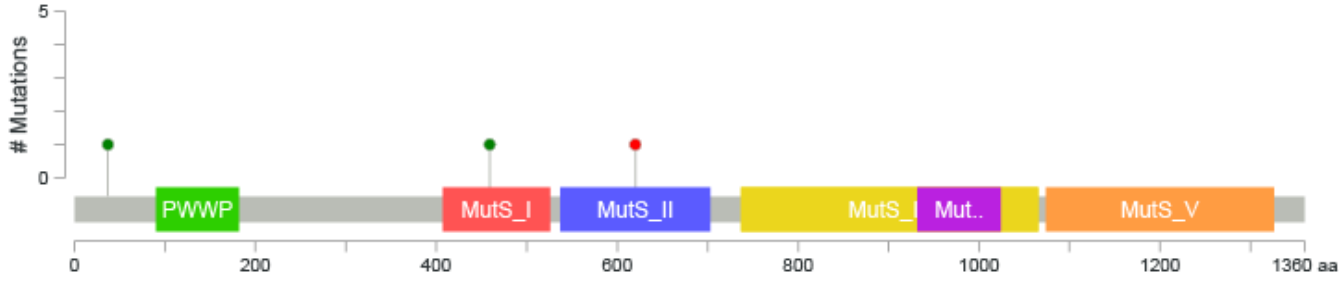

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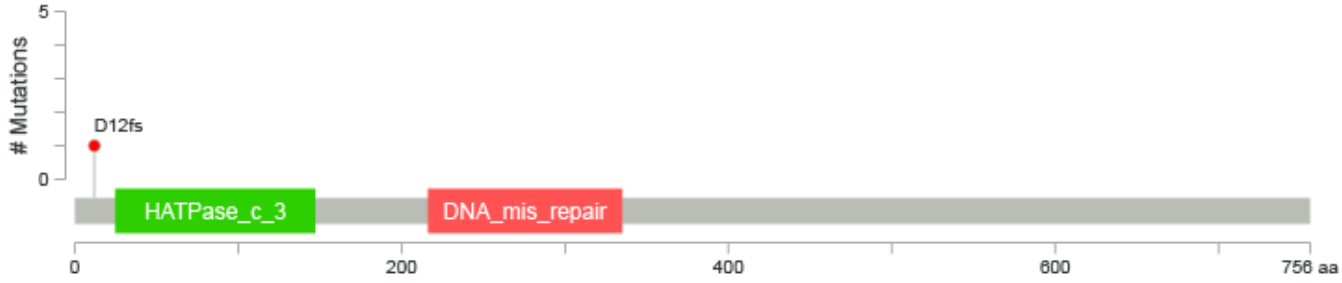

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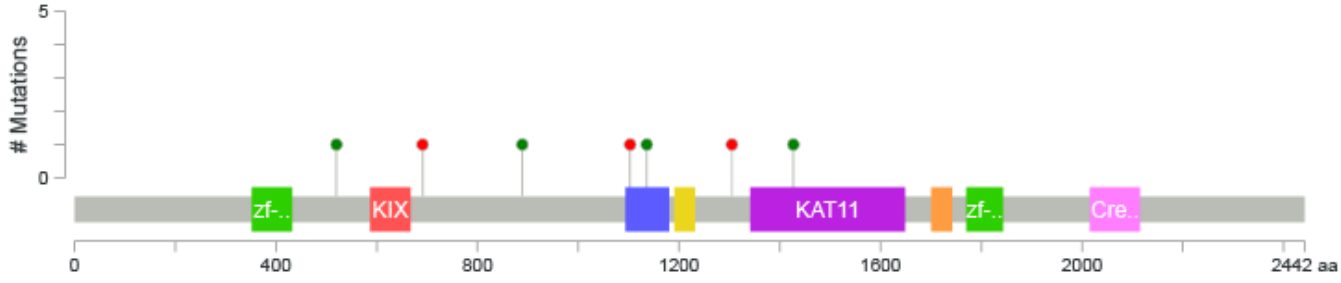

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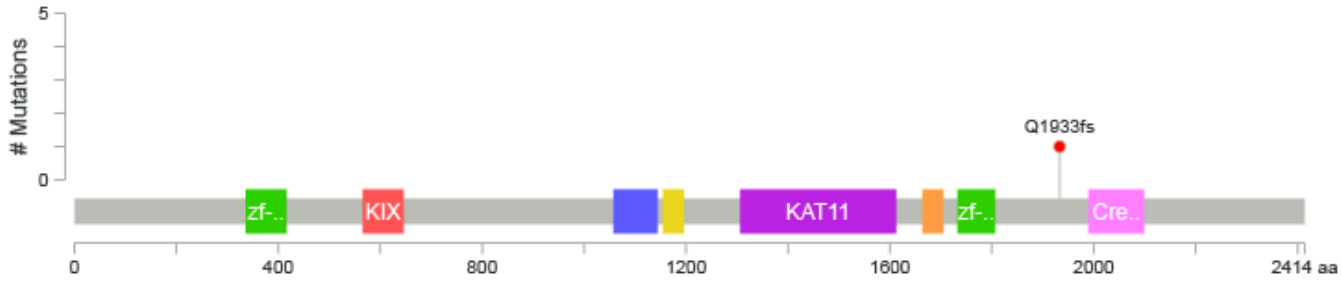
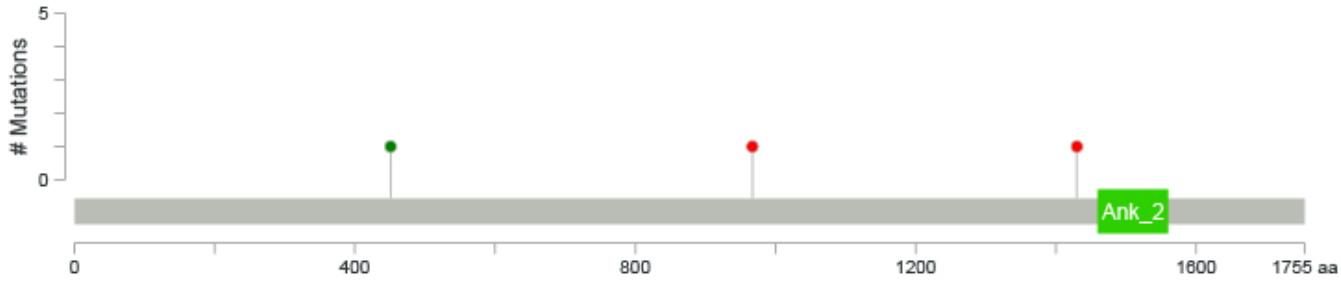


AP. BCOR



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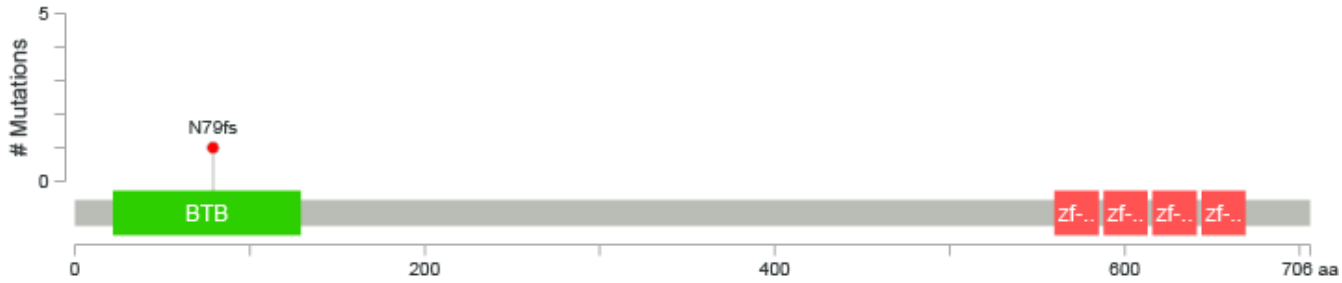
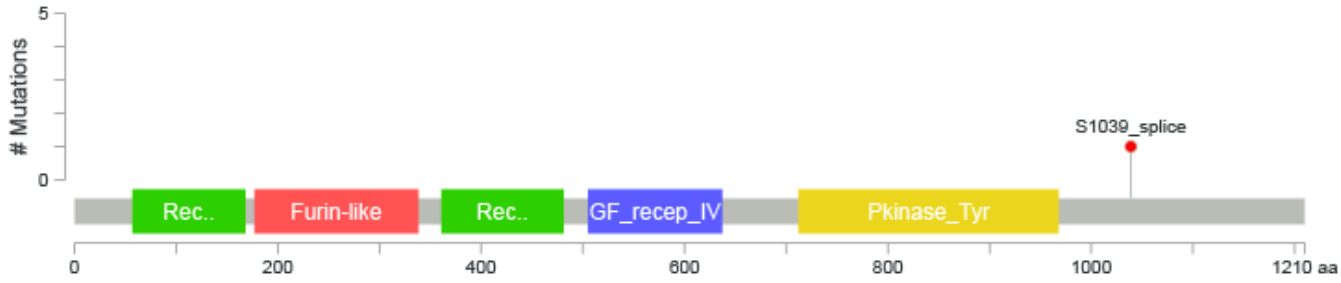


AR. EGFR



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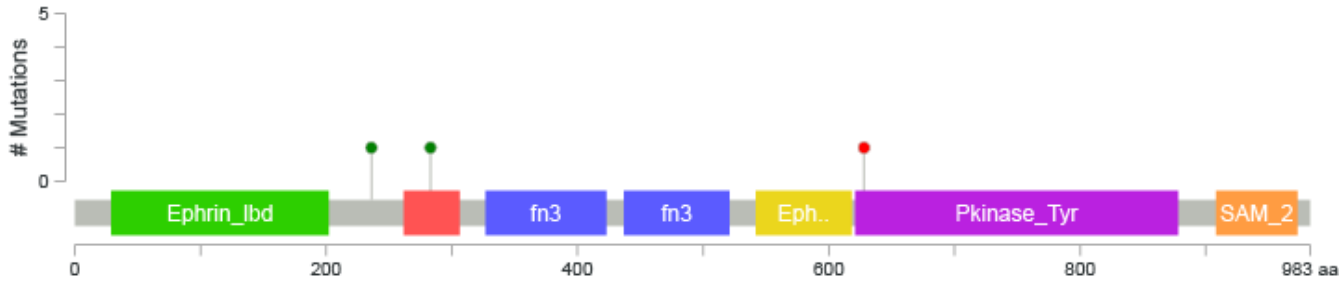

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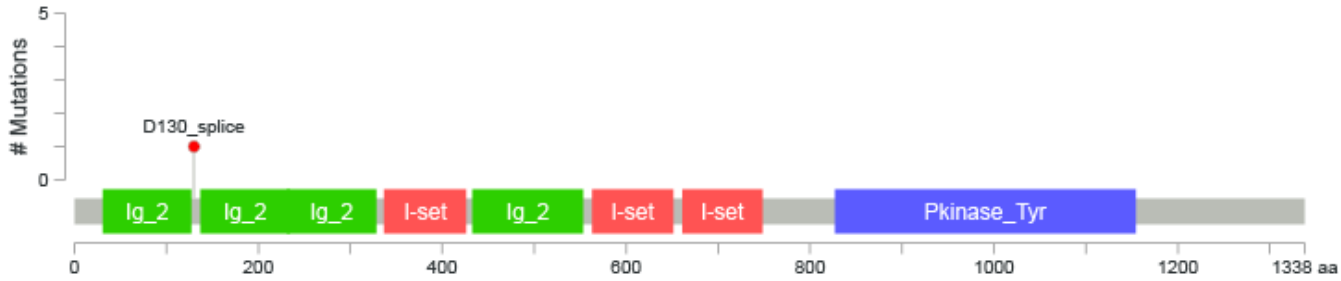
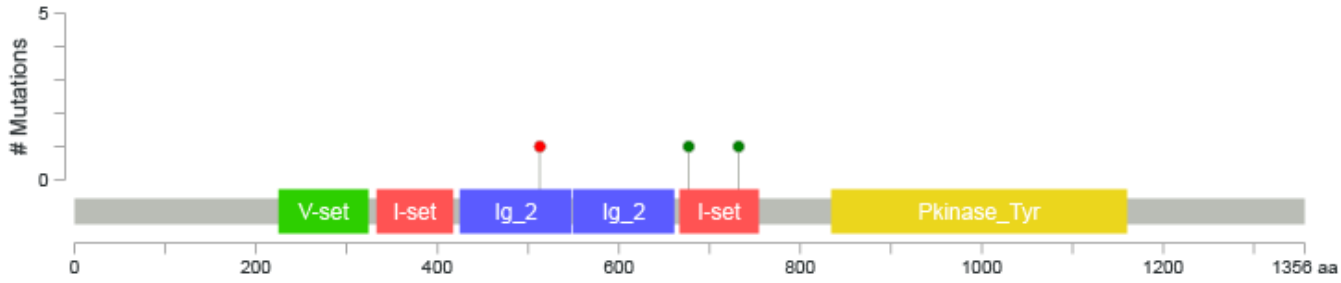


AU. FLT4

AV. KDR



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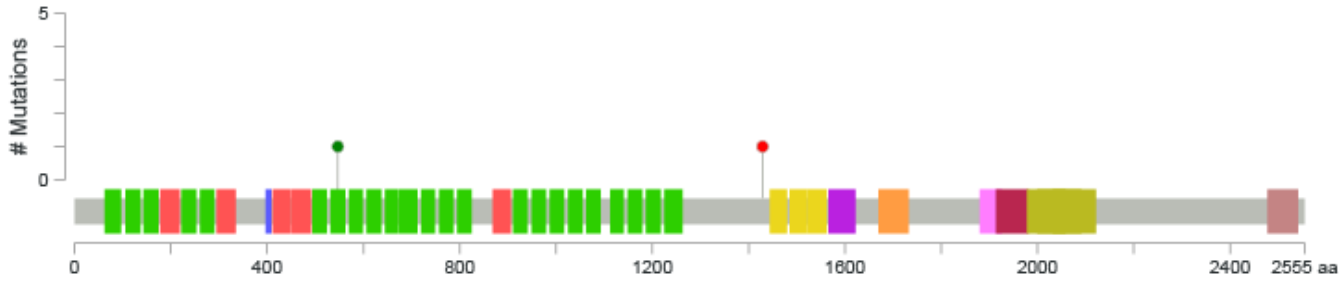

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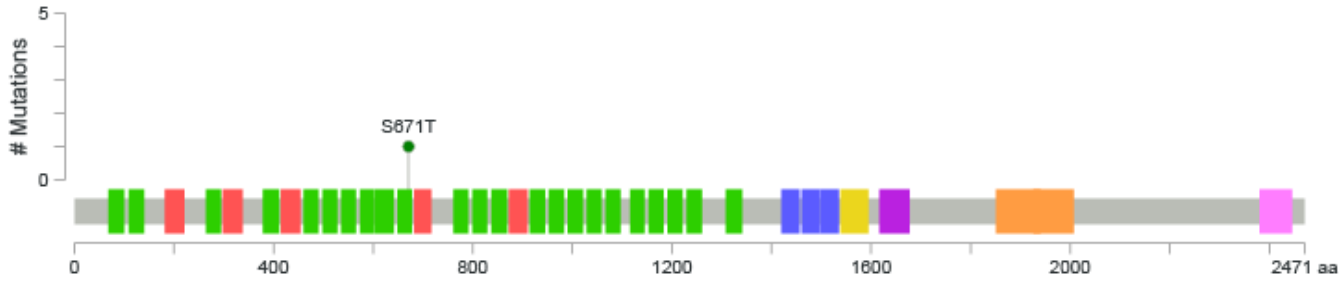

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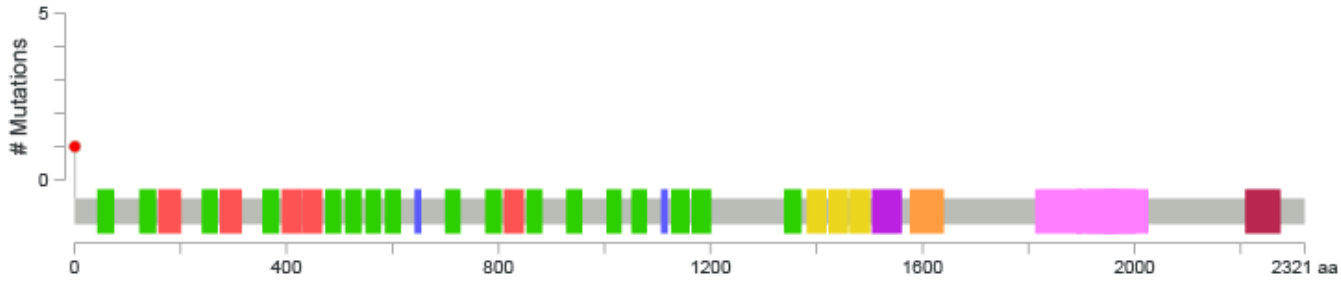

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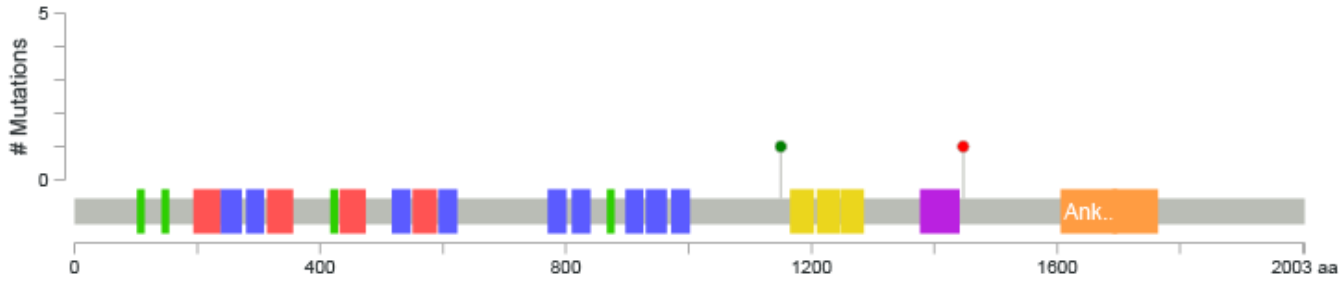

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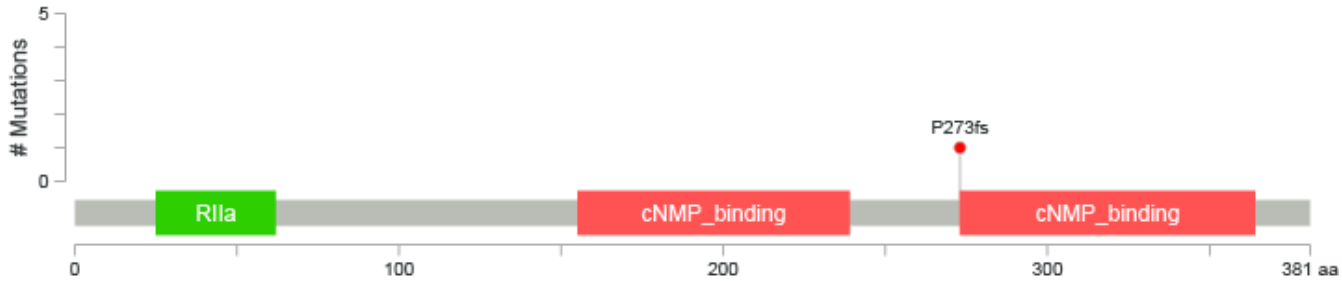

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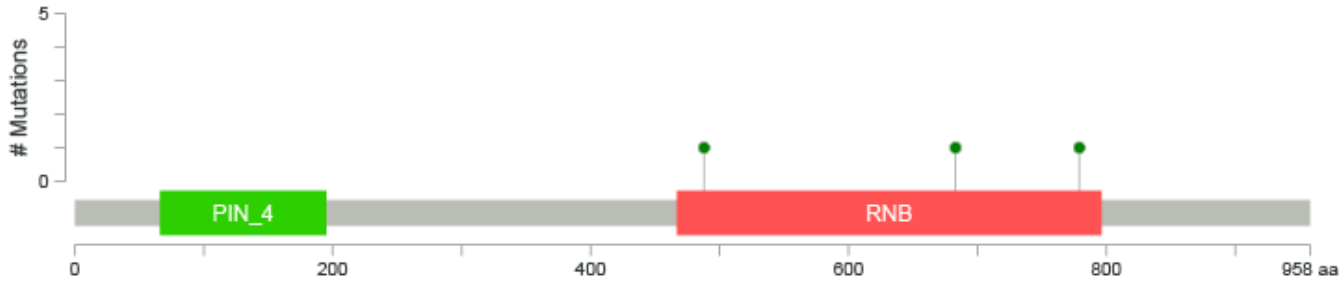
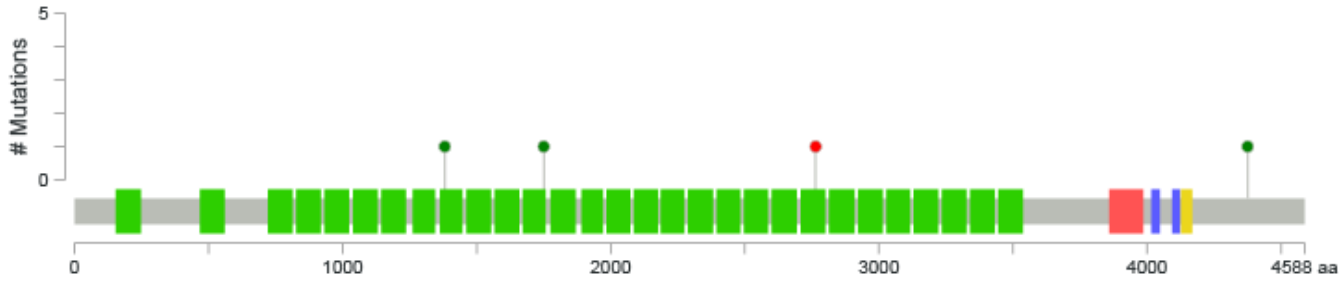


BC. FAT1



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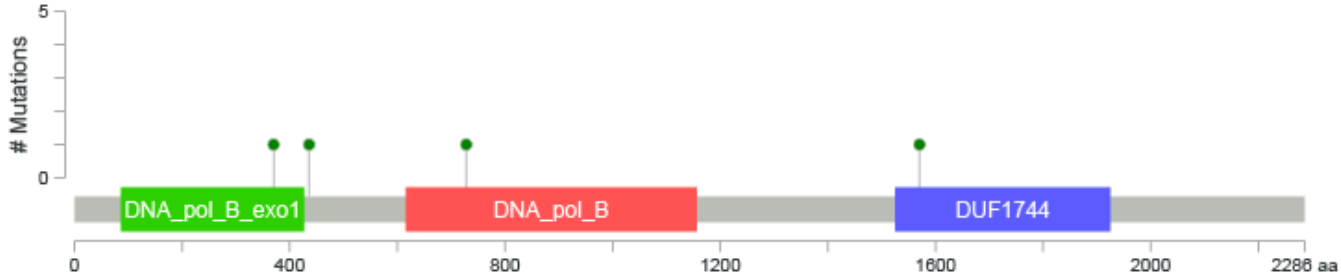

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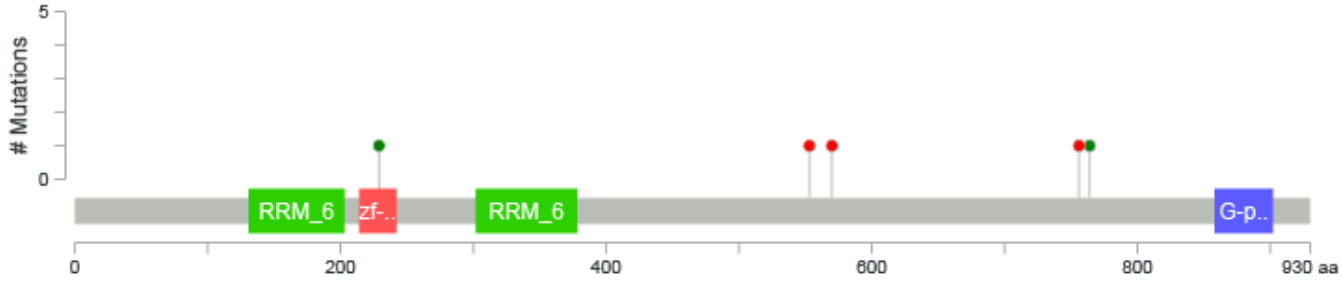

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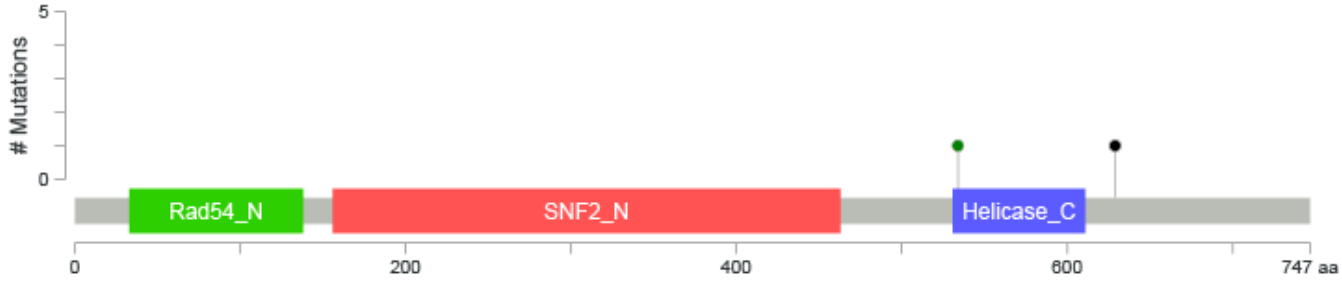

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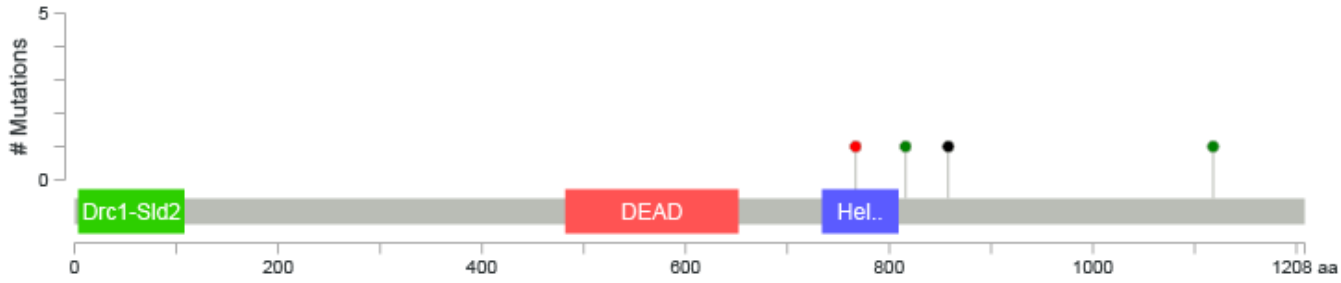

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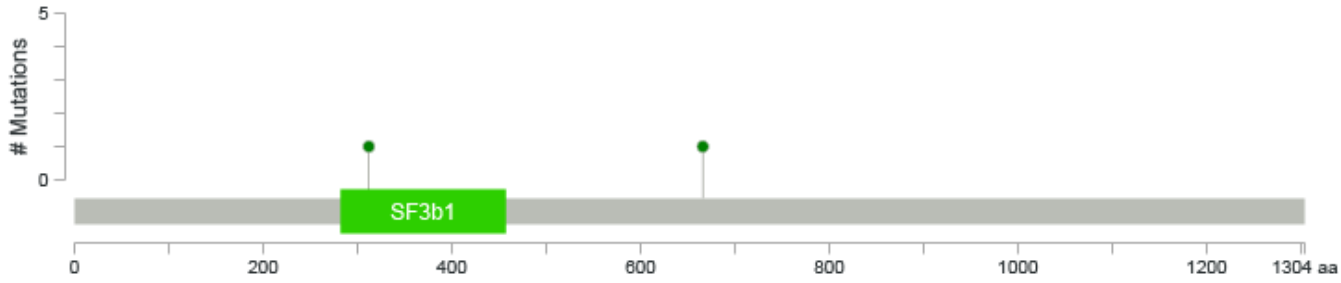
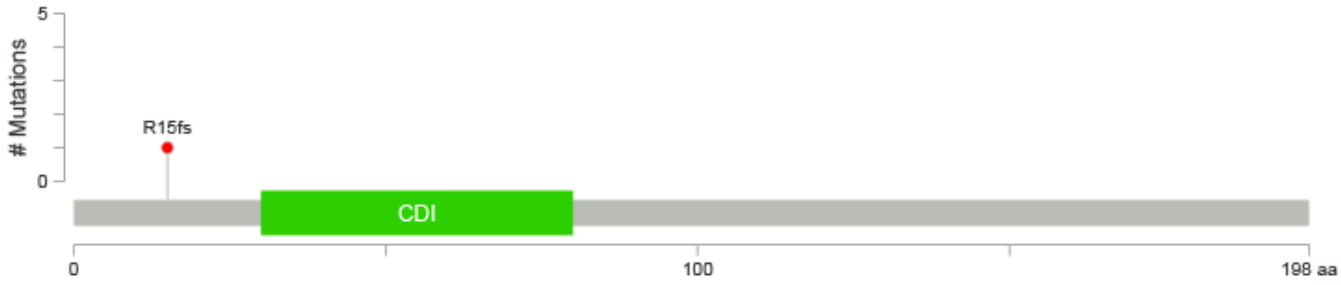
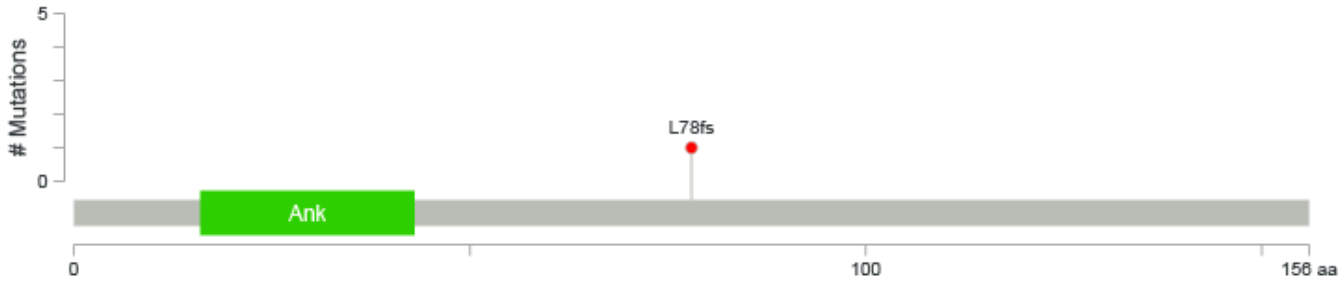


BI. CDKN1B



BJ. CDKN2A



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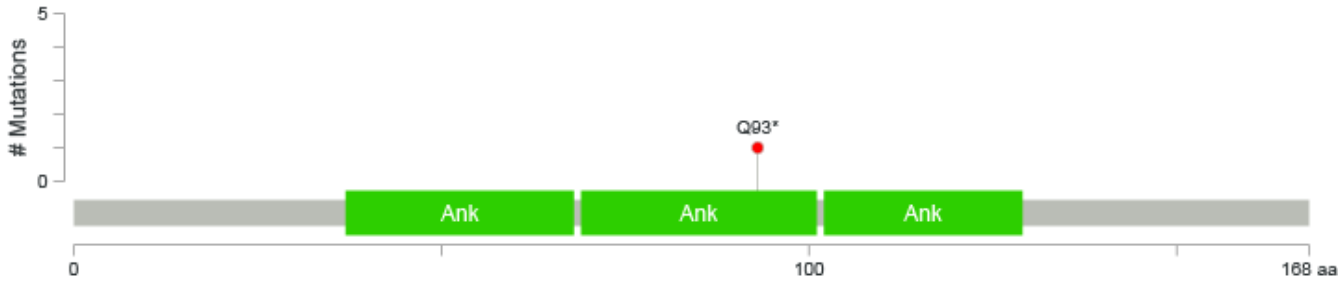
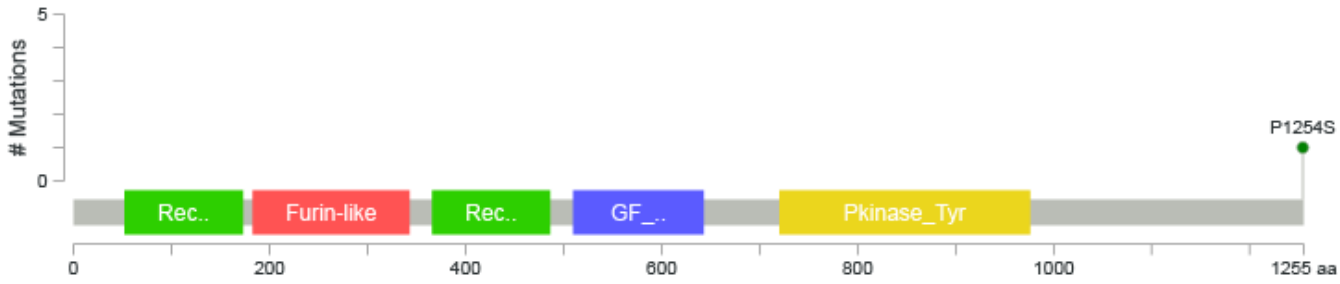
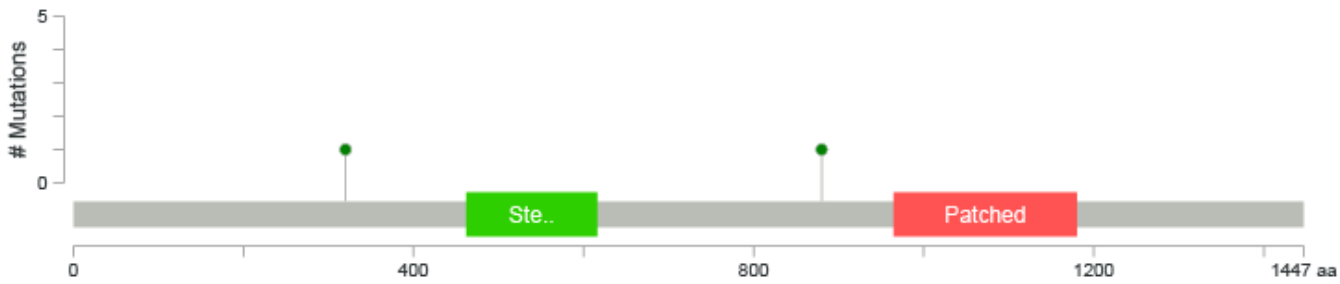


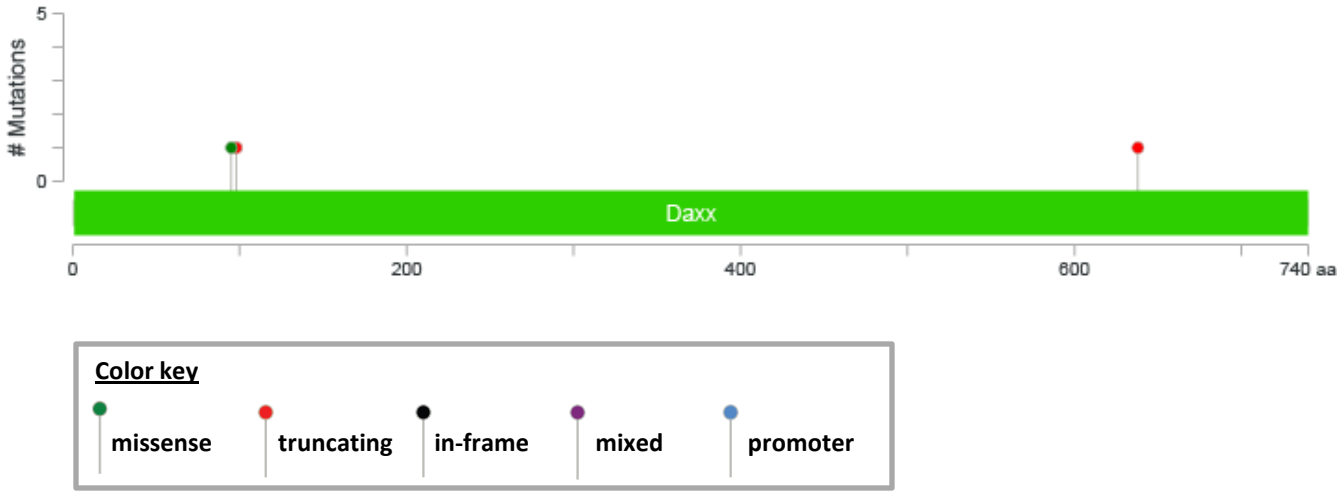
BL. ERBB2

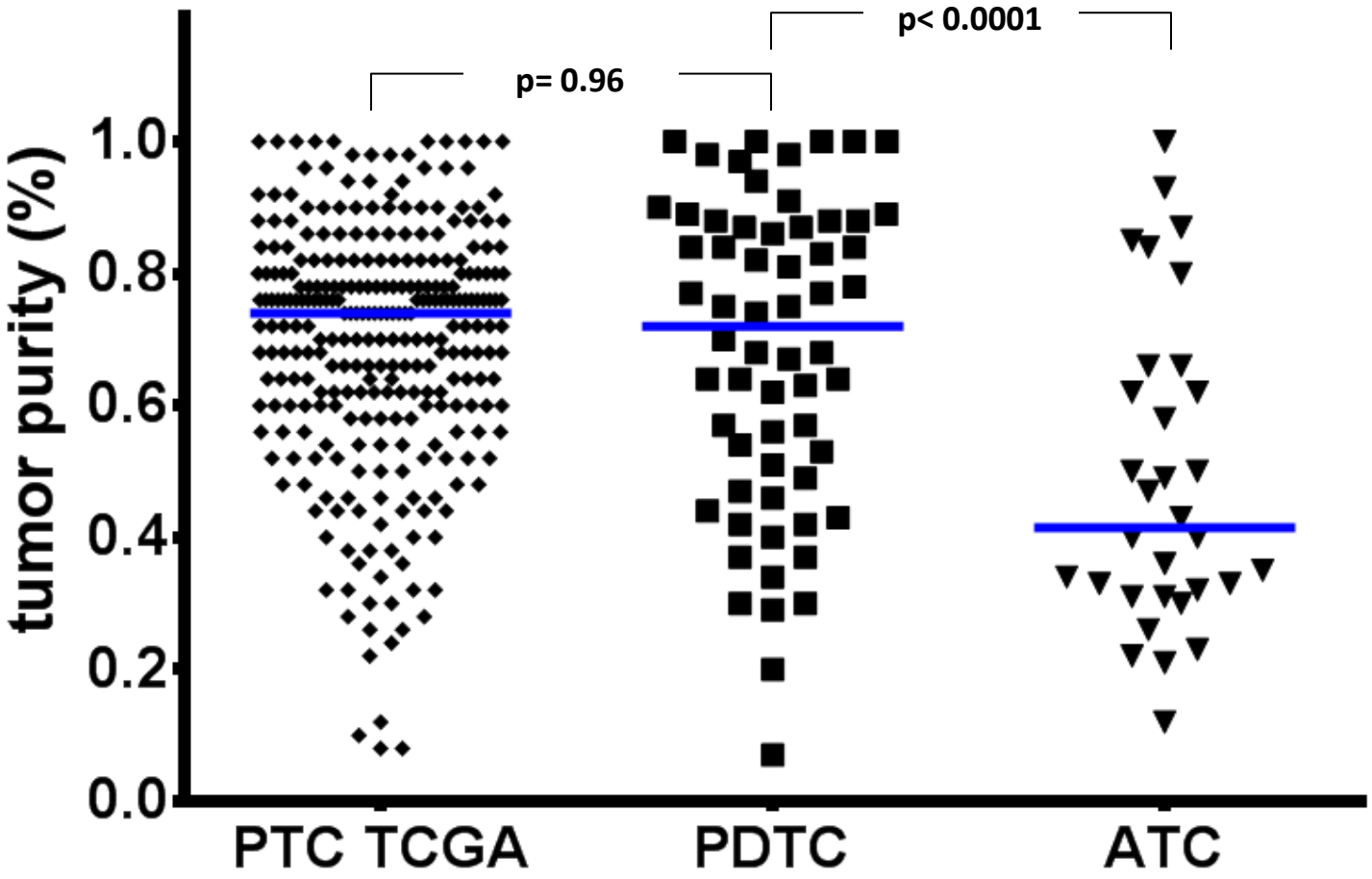


BM. PTCH1



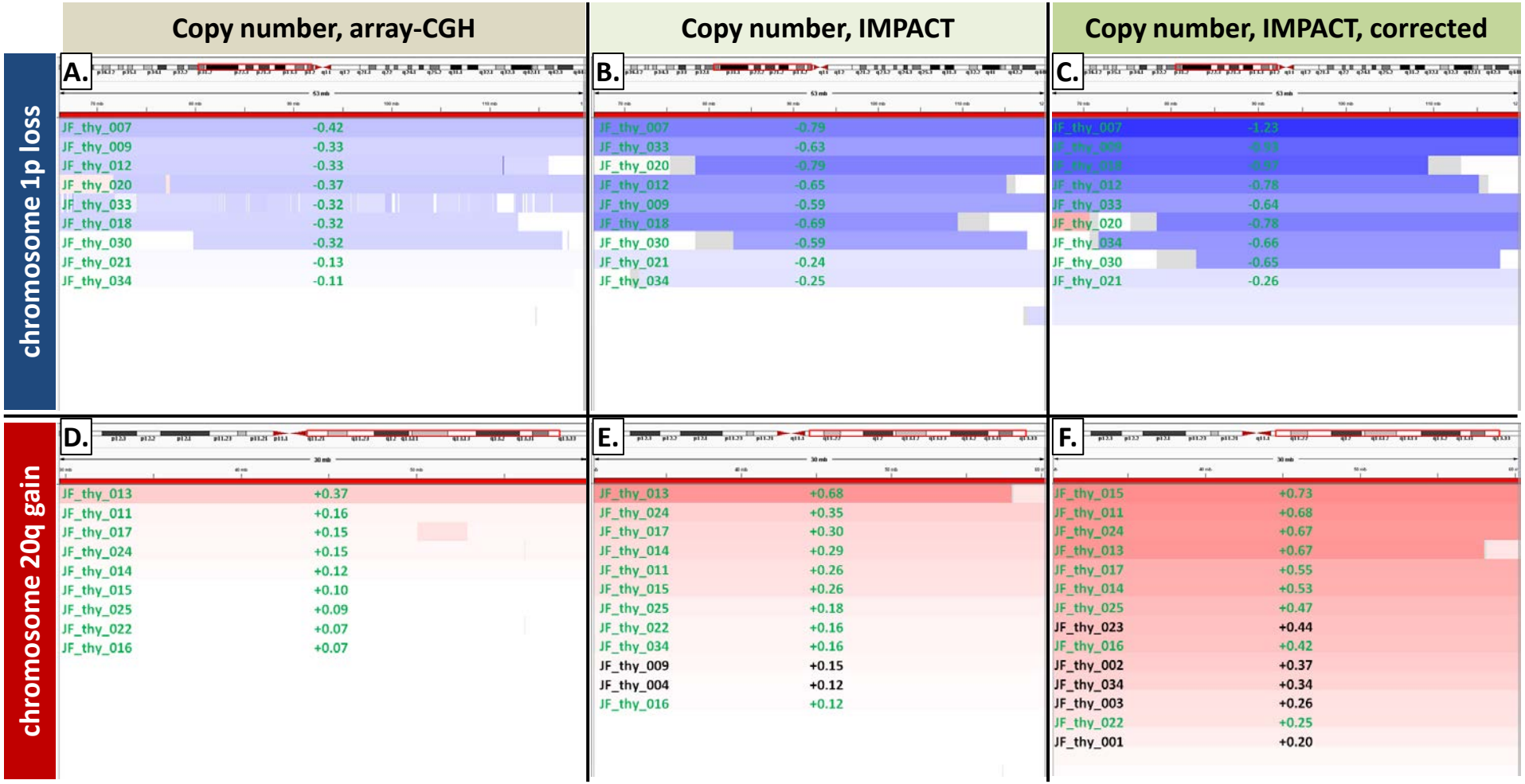
BN. DAXX


Mutations
5
0
Daxx
0
200
400
600
740 aa
Color key
missense
truncating
in-frame
mixed
promoter



	PTC TCGA	PDTC	ATC
Number of tumors	286	62	32
Median purity	0.74	0.72	0.42

Suppl Fig S2

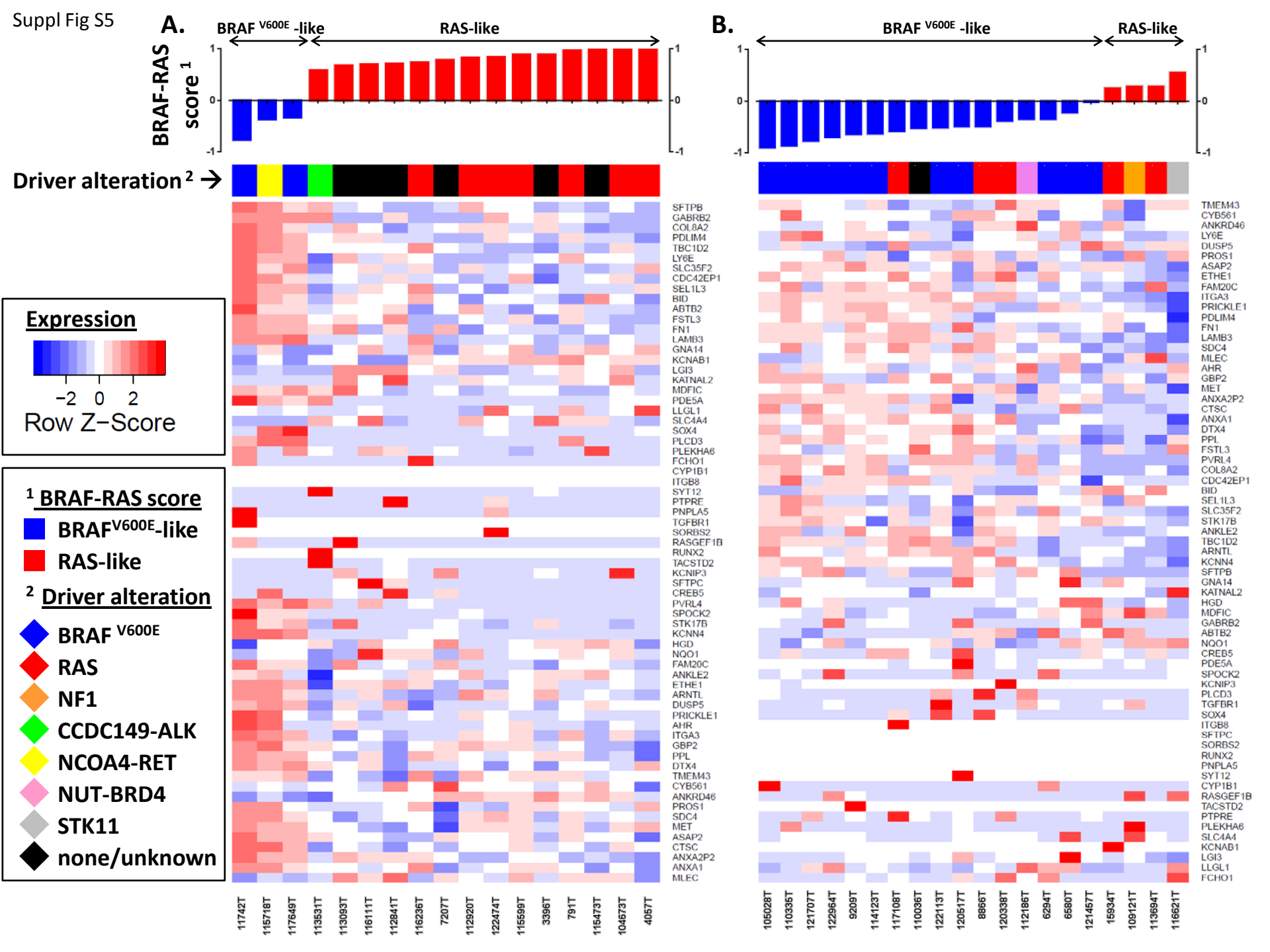

Copy number, array-CGH
Copy number, IMPACT
Copy number, IMPACT, corrected
chromosome 1p loss
chromosome 20q gain
A.
B.
C.
D.
E.
F.
JF_thy_007 -0.42
JF_thy_009 -0.33
JF_thy_012 -0.33
JF_thy_020 -0.37
JF_thy_033 -0.32
JF_thy_018 -0.32
JF_thy_030 -0.32
JF_thy_021 -0.13
JF_thy_034 -0.11
JF_thy_007 -0.79
JF_thy_033 -0.63
JF_thy_020 -0.79
JF_thy_012 -0.65
JF_thy_009 -0.59
JF_thy_018 -0.69
JF_thy_030 -0.59
JF_thy_021 -0.24
JF_thy_034 -0.25
JF_thy_007 -1.23
JF_thy_012 -0.78
JF_thy_033 -0.64
JF_thy_020 -0.78
JF_thy_034 -0.66
JF_thy_030 -0.65
JF_thy_021 -0.26
JF_thy_013 +0.37
JF_thy_011 +0.16
JF_thy_017 +0.15
JF_thy_024 +0.15
JF_thy_014 +0.12
JF_thy_015 +0.10
JF_thy_025 +0.09
JF_thy_022 +0.07
JF_thy_016 +0.07
JF_thy_013 +0.68
JF_thy_024 +0.35
JF_thy_017 +0.30
JF_thy_014 +0.29
JF_thy_011 +0.26
JF_thy_015 +0.26
JF_thy_025 +0.18
JF_thy_022 +0.16
JF_thy_034 +0.16
JF_thy_009 +0.15
JF_thy_004 +0.12
JF_thy_016 +0.12
JF_thy_015 +0.73
JF_thy_011 +0.68
JF_thy_024 +0.67
JF_thy_013 +0.67
JF_thy_017 +0.55
JF_thy_014 +0.53
JF_thy_025 +0.47
JF_thy_023 +0.44
JF_thy_016 +0.42
JF_thy_002 +0.37
JF_thy_034 +0.34
JF_thy_003 +0.26
JF_thy_022 +0.25
JF_thy_001 +0.20

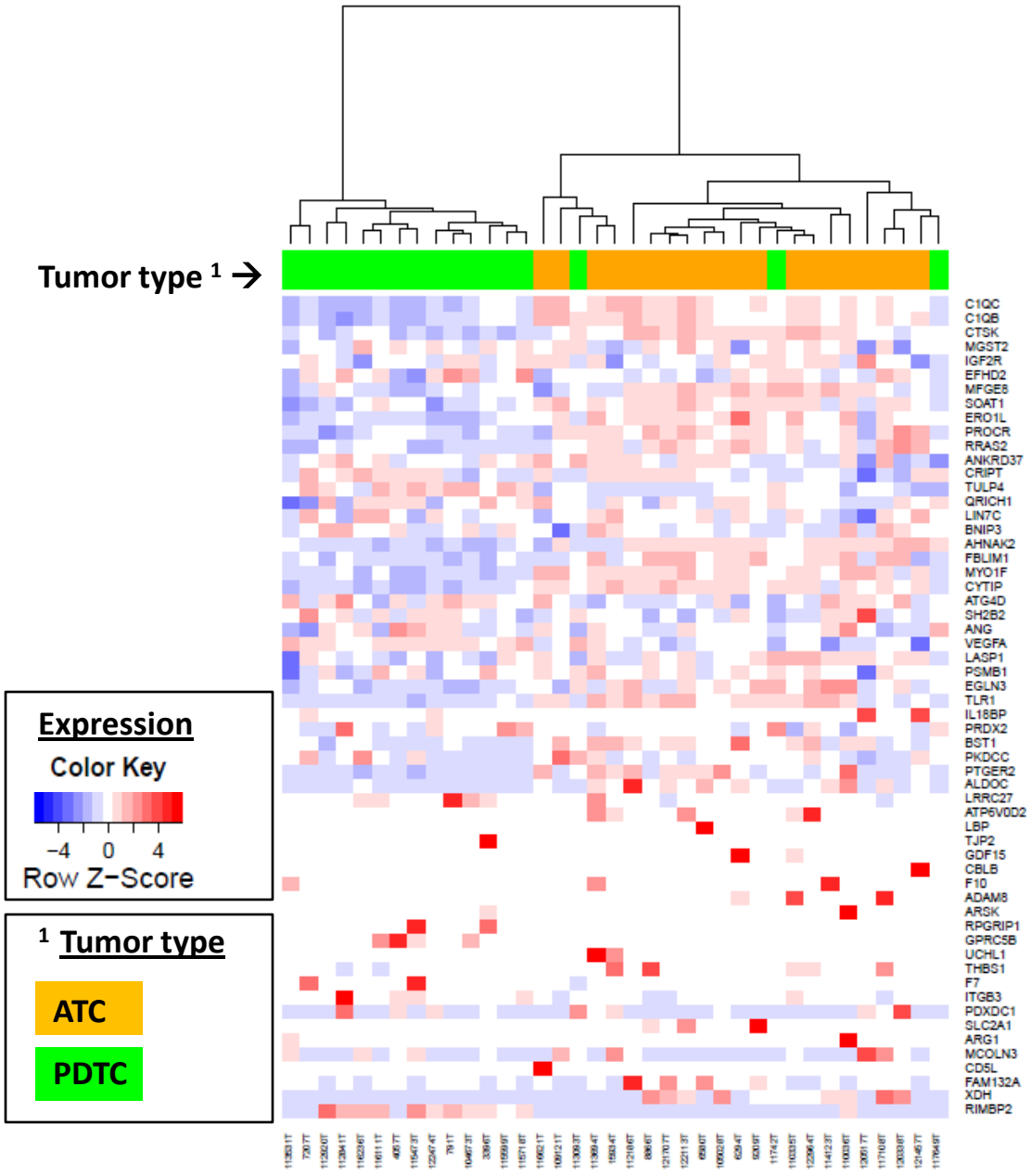
Suppl Fig S3


Tumor type
Genetic driver
Tumor purity
1p loss
1q gain
8p loss
13q loss
15q loss
17p loss
20q gain
22q loss
Copy number (log-ratios)
+1.5
+0.9
+0.3
- 0.3
- 0.9
- 1.5
Tumor type
PDTC
ATC
Genetic driver
BRAF
RAS
Fusion
Tumor purity
100%
75%
25%
N/A
Poorly-differentiated thyroid cancers
BRAF
RAS
Fusion
Anaplastic
BRAF
RAS

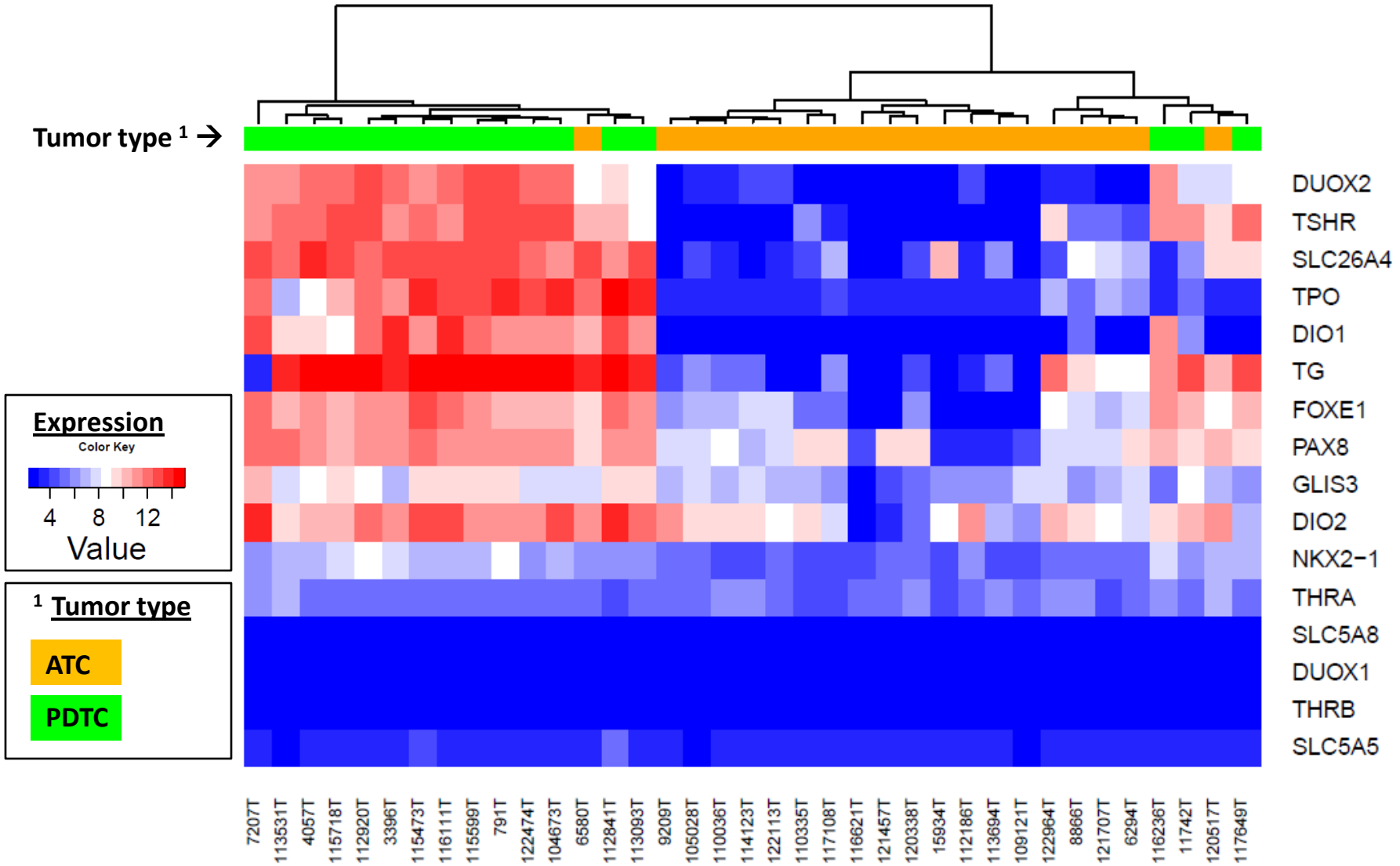
Suppl Fig S4

Suppl Fig S5


A.
B.
BRAF V600E -like
RAS-like
BRAF-RAS score 1
Driver alteration 2
Expression
−2 0 2
Row Z−Score
1 BRAF-RAS score
BRAFV600E-like
RAS-like
2 Driver alteration
BRAF V600E
RAS
NF1
CCDC149-ALK
NCOA4-RET
NUT-BRD4
STK11
none/unknown
SFTPB GABRB2 COL8A2 PDLIM4 TBC1D2 LY6E SLC35F2 CDC42EP1 SEL1L3 BID ABTB2 FSTL3 FN1 LAMB3 GNA14 KCNAB1 LGI3 KATNAL2 MDFIC PDE5A LLGL1 SLC4A4 SOX4 PLCD3 PLEKHA6 FCHO1 CYP1B1 ITGB8 SYT12 PTPRE PNPLA5 TGFBR1 SORBS2 RASGEF1B RUNX2 TACSTD2 KCNIP3 SFTPC CREB5 PVRL4 SPOCK2 STK17B KCNN4 HGD NQO1 FAM20C ANKLE2 ETHE1 ARNTL DUSP5 PRICKLE1 AHR ITGA3 GBP2 PPL DTX4 TMEM43 CYB561 ANKRD46 PROS1 SDC4 MET ASAP2 CTSC ANXA2P2 ANXA1 MLEC
117742T 115718T 117649T 113531T 113093T 116111T 112841T 116236T 7207T 112920T 122474T 115599T 3396T 791T 115473T 104673T 4057T
TMEM43 CYB561 ANKRD46 LY6E DUSP5 PROS1 ASAP2 ETHE1 FAM20C ITGA3 PRICKLE1 PDLIM4 FN1 LAMB3 SDC4 MLEC AHR GBP2 MET ANXA2P2 CTSC ANXA1 DTX4 PPL FSTL3 PVRL4 COL8A2 CDC42EP1 BID SEL1L3 SLC35F2 STK17B ANKLE2 TBC1D2 ARNTL KCNN4 SFTPB GNA14 KATNAL2 HGD MDFIC GABRB2 ABTB2 NQO1 CREB5 PDE5A SPOCK2 KCNIP3 PLCD3 TGFBR1 SOX4 ITGB8 SFTPC SORBS2 RUNX2 PNPLA5 SYT12 CYP1B1 RASGEF1B TACSTD2 PTPRE PLEKHA6 SLC4A4 KCNAB1 LGI3 LLGL1 FCHO1
105028T 110335T 121707T 122964T 9209T 114123T 117108T 110036T 122113T 120517T 8866T 120338T 112186T 6294T 6580T 121457T 15934T 109121T 113694T 116621T


Tumor type [1] →
C1QC
C1QB
CTSK
MGST2
IGF2R
EFHD2
MFGE8
SOAT1
ERO1L
PROCR
RRAS2
ANKRD37
CRIPT
TULP4
QRICH1
LIN7C
BNIP3
AHNAK2
FBLIM1
MYO1F
CYTIP
ATG4D
SH2B2
ANG
VEGFA
LASP1
PSMB1
EGLN3
TLR1
IL18BP
PRDX2
BST1
PKDCC
PTGER2
ALDOC
LRRC27
ATP6V0D2
LBP
TJP2
GDF15
CBLB
F10
ADAM8
ARSK
RPGRIP1
GPRC5B
UCHL1
THBS1
F7
ITGB3
PDXDC1
SLC2A1
ARG1
MCOLN3
CD5L
FAM132A
XDH
RIMBP2
Expression
Color Key
−4
0
4
Row Z−Score
[1] Tumor type
ATC
PDTC

Suppl Fig S6


Tumor type [1] →
Expression
Color Key
4
8
12
Value
[1] Tumor type
ATC
PDTC
DUOX2
TSHR
SLC26A4
TPO
DIO1
TG
FOXE1
PAX8
GLIS3
DIO2
NKX2−1
THRA
SLC5A8
DUOX1
THRB
SLC5A5
7207T
113531T
4057T
115718T
112920T
3396T
115473T
116111T
115599T
791T
122474T
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6580T
112841T
113093T
9209T
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114123T
122113T
110335T
117108T
116621T
121457T
120338T
15934T
112186T
113694T
109121T
122964T
8866T
121707T
6294T
116236T
11742T
120517T
117649T

Suppl Fig S7

Supplementary Table S2. Impact of mutation burden on clinicopathological features of advanced thyroid tumors.

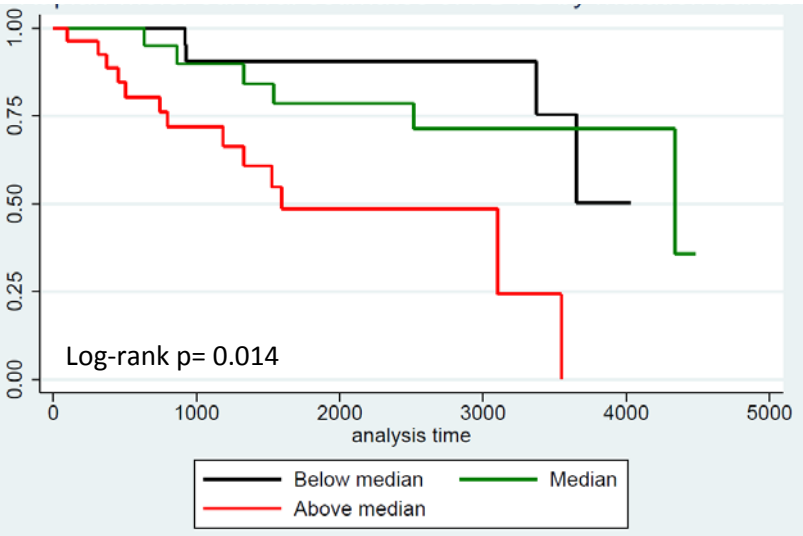
A. Anaplastic thyroid cancers (ATC)

Total ATC = 28	**Below median(13)**	**Median(6)**	**Above median (9)**	**p value**
Age (y)	67±13	67±9	64±8	0.402
Gender (%F)	54%	33%	67%	0.483
Tobacco (%yes)	31%	33%	25%	1
Tumor size	5.8±2.4	7.2±2	5.6±1	0.051
Pathology staging				
T2	1	0	0	
T3	0	0	2	
T4	9	4	4	
T4b	1	1	1	0.743
N0	1	0	0	
N1a	0	1	2	
N1b	6	4	3	
Nx	4	0	2	0.566
M0	0	0	0	
M1	5	2	4	
Mx	7	3	3	0.876
Mitotic activity				0.895
Mild	0	0	1	
Moderate	1	1	1	
Marked	6	3	4	
Necrosis				0.922
None	2	0	1	
Present	1	0	1	
Extensive	5	4	4	
Vascular invasion				0.089
No	3	0	0	
Yes	5	5	6	
Extrathyroidal extension				0.805
No	1	0	1	
Minimal	3	3	3	
Gross	6	3	2	
Overall survival (died)	54%	100%	37.5%	0.053
Overall survival time (days±SD)	410±968	166±112	233±92	0.21
Survival analysis: HR (95%CI)			HR: 0.76 (0.43-1.35)	0.352

B. Poorly differentiated thyroid cancers (PDTC)

PDTC = 78	Below median (26)	Median (24)	Above median(28)	p value
Age (y)	47±15	58±15	64±15	**<0.001**
Gender (%F)	73%	58%	54%	0.314
Family history TC(%yes)	12%	0%	7%	0.452
Tumor size				
≤ 4	64%	57%	29%	
>4	36%	43%	71%	**0.038**
Pathology staging				
T1/T2	17%	15%	4%	
T3/T4	83%	85%	96%	0.405
Nx/N0	54%	45%	52%	
N1a/N1b	46%	55%	48%	0.822
M0	73%	54%	32%	
M1	8%	29%	57%	
Mx	19%	17%	11%	**0.002**
RAI				0.874
No	19%	29%	18%	
Yes	73%	63%	75%	
RAI Uptake				
No uptake	8%	4%	0%	
Thyroid bed	38%	29%	21%	
Outside thyroid bed	27%	29%	50%	0.391
Overall survival (died)	19%	25%	46%	0.07
Overall survival time (days±SD)	2242±1332	2181±1406	1469±1158	**0.05**
Survival analysis: HR (95%CI)			HR:2.03 (1.19-3.47)	**0.01**
Log rank				**0.014**

Kaplan-Meier. Mutation burden in PDTCs



Supplementary Table S3. Contingency analysis of the main genetic alterations in PDTCs and ATCs.

Gene status / Tumor type	Number of tumors		Fisher's exact test p-value [3]
	PDTC	ATC	
***BRAF* wildtype**	56	18	0.29
***BRAF* mutant**	28	15	
***NRAS* wildtype**	66	27	0.80
***NRAS* mutant**	18	6	
***HRAS* wildtype**	80	31	1
***HRAS* mutant**	4	2	
***KRAS* wildtype**	82	33	1
***KRAS* mutant**	2	0	
***RAS* wildtype** [1]	60	25	0.82
***RAS* mutant** [1]	24	8	
***NF1* wildtype**	84	30	**0.02**
***NF1* mutant**	0	3	
***TSHR* wildtype**	82	31	0.32
***TSHR* mutant**	2	2	
***STK11* wildtype**	83	31	0.19
***STK11* mutant**	1	2	
***EIF1AX* wildtype**	75	30	1
***EIF1AX* mutant**	9	3	
***PIK3CA* wildtype**	82	27	**0.006**
***PIK3CA* mutant**	2	6	
***PTEN* wildtype**	81	28	**0.04**
***PTEN* mutant**	3	5	
***RET* wildtype**	79	33	0.32
***RET* rearranged**	5	0	
PAX8-PPARG wildtype	81	33	0.56
PAX8-PPARG rearranged	3	0	
***ALK* wildtype**	81	33	0.56
***ALK* rearranged**	3	0	
Thyroid fusions not present [2]	73	33	**0.03**
Thyroid fusions present [2]	11	0	
NUT-BRD4 wildtype	84	32	0.28
NUT-BRD4 rearranged	0	1	
***TERT* promoter wildtype**	50	9	**0.002**
***TERT* promoter mutant**	34	24	
***TP53* wildtype**	77	9	**< 0.0001**
***TP53* mutant**	7	24	

Supplementary Table S3. (continued)

Gene status / Tumor type	Number of tumors		Fisher's exact test p-value [3]
	PDTC	ATC	
***ATM* wildtype**	78	30	0.71
***ATM* mutant**	6	3	
***RB1* wildtype**	83	30	0.07
***RB1* mutant**	1	3	
***NF2* wildtype**	84	31	0.08
***NF2* mutant**	0	2	
***MEN1* wildtype**	83	32	0.49
***MEN1* mutant**	1	1	
PI3K/AKT pathway wildtype	75	20	**0.001**
PI3K/AKT pathway mutant	9	13	
SWI/SNF complex wildtype	79	21	**0.0001**
SWI/SNF complex mutant	5	12	
HMTs group wildtype	78	25	**0.02**
HMTs group mutant	6	8	
MMR pathway wildtype	82	29	0.05
MMR pathway mutant	2	4	

[1] "RAS" category includes NRAS, HRAS and KRAS.

[2] "Thyroid fusions" include rearrangements of genes previously reported in thyroid tumors.

[3] Significant p-values are highlighted in yellow; marginally significant are highlighted in grey.

Abbreviations: HMT =histone methyltransferase, MMR= mismatch excision repair.

Supplementary Table S5. Clinicopathological characteristics of ATCs and PDTCs according to *BRAF* and *RAS* mutation status and gene fusions.

A. Anaplastic thyroid cancers (ATC)

Total ATC = 33	BRAF wt (18)	BRAF + (15)	p value
Age (y)	62±12	69±7	0.055
Gender (%F)	44%	67%	0.202
Tobacco (%yes)	35%	20%	0.337
Tumor size	7±2	5.1±2	**0.012**
Pathology staging			
T2	0	1	
T3	1	1	
T4	11	10	
T4b	3	0	0.518
N0	1	0	
N1a	2	1	
N1b	7	8	
Nx	3	3	0.974
M0	0	0	
M1	9	6	
Mx	5	8	0.296
Mitotic activity			0.232
Mild	0	1	
Moderate	1	2	
Marked	10	4	
Necrosis			0.177
None	3	0	
Present	0	2	
Extensive	8	6	
Vascular invasion			0.566
No	1	2	
Yes	10	7	
Extrathyroidal extension			0.840
No	1	1	
Minimal	4	6	
Gross	6	6	
Positive LN (mean num ± SD)	4±3.5	4.75±3.4	0.615
Largest LN (mean ± SD, cm)	1.6±1.2	2.4±1.2	0.356
Extranodal extension	5/6	3/5	0.545
Overall survival (died)	56%	73%	0.458
Overall survival time (days±SD)	387±866	165±125	0.334
Survival analysis: HR (95%CI)		HR:1.3 (0.54-3.27)	0.528

Total ATC = 33	RAS wt (25)	RAS + (8)	p value
Age (y)	64±10	67±12	0.558
Gender (%F)	60%	37.5%	0.266
Tobacco (%yes)	25%	37.5%	0.496
Tumor size	5.8±2	7.4±2	0.07
Pathology staging			
T2	1	0	
T3	2	0	
T4	14	7	
T4b	2	1	0.464
N0	1	0	
N1a	2	1	
N1b	10	5	
Nx	5	1	0.730
M0	0	0	
M1	9	6	
Mx	11	2	0.210
Mitotic activity			1
Mild	1	0	
Moderate	2	1	
Marked	10	4	
Necrosis			0.210
None	1	2	
Present	2	0	
Extensive	11	3	
Vascular invasion			1
No	2	1	
Yes	13	4	
Extrathyroidal extension			0.441
No	2	0	
Minimal	9	1	
Gross	8	4	
Positive LN (mean num ± SD)	4.2±3	4.6±4	0.818
Largest LN (mean ± SD, cm)	2±1.3	1.7±1	0.581
Extranodal extension	4/6	4/5	1
Overall survival (died)	57%	87.5%	0.203
Overall survival time (days±SD)	318±727	170±118	0.575
Survival analysis: HR (95%CI)		HR: 1.76 (0.68-4.56)	0.247

Total ATC = 33	BRAF/RAS/Fusion – (9)	BRAF/RAS/Fusion + (24)	p value
Age (y)	60±8	67±11	0.115
Gender (%F)	44%	58%	0.475
Tobacco (%yes)	37.5%	25%	0.496
Tumor size	7±1.6	6±2.2	0.237
Pathology staging			
T2	0	1	
T3	1	1	
T4	3	18	
T4b	2	1	0.077
N0	0	1	
N1a	1	2	
N1b	2	13	
Nx	2	4	0.324
M0	0	0	
M1	3	12	
Mx	2	11	**0.024**
Mitotic activity			0.650
Mild	0	1	
Moderate	0	3	
Marked	5	9	
Necrosis			1
None	1	2	
Present	0	2	
Extensive	4	10	
Vascular invasion			0.539
No	0	3	
Yes	5	12	
Extrathyroidal extension			0.221
No	1	1	
Minimal	3	7	
Gross	1	11	
Positive LN (mean num ± SD)	4±2.6	4.4±3.6	0.874
Largest LN (mean ± SD, cm)	1.5±2	2±1	0.675
Extranodal extension	1/1	7/10	1
Overall survival (died)	**29%**	**75%**	**0.024**
Overall survival time (days±SD)	175±82	310±713	0.624
Survival analysis : HR (95%CI)		HR:2.1 (0.48-9.37)	0.323

B. Poorly differentiated thyroid cancers (PDTC)

Total PDTC = 84	BRAF wt (56)	BRAF + (28)	p value
Age (y)	58±16	53±18	0.179
Gender (%F)	50%	82%	**0.004**
Family history TC(%yes)	9%	4%	0.686
Tumor size			
≤ 4	40%	70%	
>4	60%	30%	**0.01**
Pathology staging			
T1/T2	11%	15%	
T3/T4	89%	85%	0.720
Nx/N0	61%	37%	
N1a/N1b	39%	63%	**0.049**
M0	38%	79%	
M1	45%	14%	
Mx	17%	7%	**0.009**
Encapsulation			0.121 (missing)
No	29%	46%	
Partial	18%	18%	
Complete	34%	11%	
Capsular invasion			0.039 (missing)
No	9%	4%	
Yes	38%	14%	
Vascular invasion			**0.001**
No	11%	48%	
Yes	89%	52%	
Extrathyroidal extension			**0.049**
No	37%	15%	
Minimal	30%	26%	
Gross	33%	59%	
Multicentricity			0.074
No	48%	43%	
Yes	29%	50%	
Margins compromised			**0.001**
No	54%	18%	
Yes	30%	71%	
RAI			0.585
No	21%	18%	
Yes	70%	79%	
RAI Uptake			**0.005**
No uptake	2%	11%	
Thyroid bed	20%	46%	
Outside thyroid bed	46%	18%	
Overall survival (died)	30%	36%	0.62
Overall survival time (days±SD)	1942±1420	2206±1386	0.42
Survival analysis: HR (95%CI)		HR:0.95 (0.43-2.13)	0.91

Total PDTC = 84	RAS wt (60)	RAS + (24)	p value
Age (y)	54±17	64±12	**0.015**
Gender (%F)	66%	46%	0.077
Family history TC(%yes)	5%	12.5%	0.52
Tumor size			**0.001**
≤ 4	63%	19%	
>4	37%	81%	
Pathology staging			
T1/T2	16%	5%	
T3/T4	84%	95%	0.259
Nx/N0	37%	86%	
N1a/N1b	63%	14%	**<0.001**
M0	62%	25%	
M1	22%	67%	
Mx	16%	8	**0.003**
Encapsulation			**0.003**
No	38%	25%	
Partial	20%	13%	
Complete	15%	54%	
Capsular invasion			**0.024**
No	7%	8%	
Yes	22%	50%	
Vascular invasion			**0.001**
No	35%	0%	
Yes	65%	100%	
Extrathyroidal extension			0.220
No	22%	43%	
Minimal	33%	19%	
Gross	45%	38%	
Multicentricity			0.949
No	45%	50%	
Yes	37%	33%	
Margins compromised			0.137
No	35%	58%	
Yes	50%	30%	
RAI			0.150
No	25%	8%	
Yes	67%	88%	
RAI Uptake			**<0.001**
No uptake	5%	4%	
Thyroid bed	37%	8%	
Outside thyroid bed	23%	71%	
Overall survival (died)	30%	37.5%	0.506
Overall survival time (days±SD)	1889±1331	2381±1551	0.148
Survival analysis: HR (95%CI)		HR: 0.87 (0.38-2.02)	0.754

PDTC = 84	No fusions (73)	Fusions (11)	p value
Age (y)	58±16	49±17	0.04
Gender (%F)	64%	42%	0.203
Family history TC(%yes)	7%	8%	0.476
Tumor size			0.189
≤ 4	48%	70%	
>4	52%	30%	
Pathology staging			
T1/T2	12%	22%	
T3/T4	88%	78%	0.6
Nx/N0	55%	40%	
N1a/N1b	45%	60%	0.5
M0	49%	67%	
M1	36%	25%	
Mx	15%	8%	0.622
RAI			0.558
No	19%	25%	
Yes	72%	75%	
RAI Uptake			1
No uptake	6%	0%	
Thyroid bed	28%	33%	
Outside thyroid bed	38%	42%	
Overall survival (died)	34%	18%	0.49
Overall survival time (days±SD)	2092±1444	1620±1080	0.30

Total PDTC = 84	None(20)	BRAF +(28)	RAS+ (24)	Fusion + (11)	p value
Age (y)	58±16	53±18	64±12	49±17	**0.04**
Gender (%F)	60%	82%	46%	42%	**0.02**
Tobacco (%yes)	59%	82%	52%	42%	0.05
Tumor size			0.201	5	0.007
≤ 4	47%	68%	23%	70%	
>4	53%	32%	77%	30%	
Pathology staging					
T1/T2	14%	14%	9%	22%	
T3/T4	86%	86%	91%	78%	0.757
Nx/N0	36%	39%	87%	40%	
N1a/N1b	64%	**61%**	**13%**	60%	**0.002**
M0	35%	79%	25%	67%	
M1	30%	14%	67%	25%	
Mx	35%	7%	8%	8%	**<0.001**
RAI					0.043
No	35%	18%	8%	25%	
Yes	45%	79%	88%	75%	
RAI Uptake					**0.001**
No uptake	0%	11%	4%	0%	
Thyroid bed	25%	46%	8%	33%	
Outside thyroid bed	20%	21%	71%	42%	
Overall survival (died)	30%	36%	38%	17%	0.644
Overall survival time (days±SD)	1674±1335	2206±1386	2381±1551	1509±1099	0.182
Survival analysis: HR (95%CI)				HR:0.85(0.55-1.1.34)	0.493

Supplementary Table S6. Clinicopathological characteristics of ATCs and PDTCs according to *EIF1AX* mutation status.

A. Anaplastic thyroid cancers (ATC)

Total ATC = 33	**EIF1AXwt (30)**	**EIF1AX+ (3)**	**p value**
Age (y)	65.5±11	59±5.7	0.351
Gender (%F)	57%	33%	0.579
Tobacco (%yes)	28%	33%	1
Tumor size	6.1±2	7.6±1.9	0.252
Pathology staging			
T2	1	0	
T3	2	0	
T4	19	2	
T4b	2	1	0.525
N0	1	0	
N1a	2	1	
N1b	13	2	
Nx	6	0	0.372
M0	0	0	
M1	13	2	
Mx	12	1	1
Mitotic activity			1
Mild	1	0	
Moderate	3	0	
Marked	11	3	
Necrosis			1
None	3	0	
Present	2	0	
Extensive	11	3	
Vascular invasion			
No	3	0	
Yes	14	3	
Extrathyroidal extension			1
No	2	0	
Minimal	9	1	
Gross	10	2	
Positive LN (mean num ± SD)	4±3	5.7±5	0.455
Largest LN (mean ± SD, cm)	2±1.2	1.6±1.3	0.604
Extranodal extension	6/8	2/3	1
Overall survival (died)	61%	100%	0.535
Overall survival time (days±SD)	283±662	250±75	0.934
Survival analysis: HR (95%CI)		HR: 1.10(0.32-3.85)	0.877

B. Poorly differentiated thyroid cancers (PDTC)

Total PDTC = 84	EIF1AXwt (75)	EIF1AX+ (9)	p value
Age (y)	56±17	67±8	**0.04**
Gender (%F)	61%	55%	0.737
Family history TC(%yes)	7%	11%	0.268
Tumor size			**0.001**
≤ 4	57%	0%	
>4	43%	100%	
Pathology staging			
T1/T2	15%	0%	
T3/T4	85%	100%	0.347
Nx/N0	47%	100%	
N1a/N1b	53%	0%	**0.003**
M0	53%	33%	
M1	31%	67%	
Mx	16%	0%	0.279
RAI			0.839
No	21%	11%	
Yes	71%	89%	
RAI Uptake			0.404
No uptake	5%	0%	
Thyroid bed	29%	22%	
Outside thyroid bed	35%	67%	
Overall survival (died)	29%	56%	0.139
Overall survival time (days ±SD)	2073±1443	1667±1040	0.416
Survival analysis: HR (95% CI)		**HR:2.6** (0.97-7.14)	**0.05**
Logrank			**0.048**

Supplementary Table S7. Clinicopathological characteristics of ATCs and PDTCs according to *TERT* promoter mutation status.

A. Anaplastic thyroid cancers (ATC)

Total ATC = 33	TERT wt (9)	TERT + (24)	p value
Age (y)	60±12	67±10	0.08
Gender (%F)	44%	58%	0.476
Tobacco (%yes)	22%	30%	0.642
Tumor size	6.5±1.7	6.1±2.3	0.657
Pathology staging			
T2	0	1	
T3	1	1	
T4	4	17	
T4b	2	1	0.288
N0	1	0	
N1a	2	1	
N1b	4	11	
Nx	0	6	0.108
M0	0	0	
M1	3	12	
Mx	5	8	0.577
Mitotic activity			0.339
Mild	0	1	
Moderate	0	3	
Marked	7	7	
Necrosis			0.225
None	0	3	
Present	0	2	
Extensive	7	7	
Vascular invasion			0.242
No	0	3	
Yes	8	9	
Extrathyroidal extension			1
No	1	1	
Minimal	3	7	
Gross	4	8	
Positive LN (mean num ± SD)	3.6±3.6	4.8±3.3	0.477
Largest LN (mean ± SD, cm)	1.2±1.3	2.3±1	0.150
Extranodal extension	2/3	6/8	1
Overall survival (died)	57%	67%	0.676
Overall survival time (days±SD)	732±1271	147±112	**0.027**
Survival analysis: HR (95%CI)		HR:2.2 (0.73-6.71)	**0.164**

Total ATC = 33	None(5)	BRAF/RAS+(4)	TERT + (5)	RAF/RAS+TERT(19)	p value
Age (y)	56±13	64.3±11	59±10	69±8.5	0.651
Gender (%F)	40%	50%	60%	58%	0.947
Tobacco (%yes)	20%	25%	50%	26%	0.856
Tumor size	6±1.5	6.9±2	7.5±1.7	5.8±2.3	0.748
Pathology staging					
T2	0	0	0	1	
T3	1	0	0	1	
T4	1	3	3	14	
T4b	1	1	1	0	0.185
N0	1	0	0	0	
N1a	1	1	0	1	
N1b	1	3	1	10	
Nx	0	0	2	4	0.194
M0	0	0	0	0	
M1	1	2	2	10	
Mx	3	2	0	8	0.071
Mitotic activity					0.738
Mild	0	0	0	1	
Moderate	0	0	0	3	
Marked	4	3	2	5	
Necrosis					0.644
None	0	0	1	2	
Present	0	0	0	2	
Extensive	4	3	1	6	
Vascular invasion					0.544
No	0	0	0	3	
Yes	4	4	2	7	
Extrathyroidal extension					0.841
No	1	0	0	1	
Minimal	2	1	1	6	
Gross	1	3	1	7	
Positive LN (mean num ± SD)	1.7±1.5	5±4.3	7±0	4.5±3.4	0.416
Largest LN (mean ± SD, cm)	0.1±0	1.6±1.3	3±0	2.2±1	0.730
Extranodal extension	.	2/3	1/1	5/7	1
Overall survival (died)	0	100%	40%	74%	**0.020**
Overall survival time (days ±SD)	1382±50	245±62	138±58	150±124	**<0.001**
Survival analysis: HR (95%CI)				HR: 1.5 (0.95-2.46)	**0.08**

B. Poorly differentiated thyroid cancers (PDTC)

Total PDTC = 84	TERT wt (50)	TERT + (34)	p value
Age (y)	53±17	62±14	**0.01**
Gender (%F)	64%	56%	0.455
Family history TC(%yes)	8%	6%	1
Tumor size			0.201
≤ 4	57%	41%	
>4	43%	59%	
Pathology staging			
T1/T2	16%	7%	
T3/T4	84%	93%	0.468
Nx/N0	56%	46%	
N1a/N1b	44%	54%	0.448
M0	64%	32%	
M1	20%	56%	
Mx	16%	12%	**0.013**
Encapsulation			0.484
No	38%	29%	
Partial	20%	15%	
Complete	26%	26%	
Capsular invasion			**0.05**
No	12%	0%	
Yes	24%	38%	
Vascular invasion			0.401
No	27%	19%	
Yes	73%	81%	
Extrathyroidal extension			0.235
No	32%	22%	
Minimal	33%	22%	
Gross	35%	56%	
Multicentricity			0.597
No	44%	50%	
Yes	40%	29%	
Margins compromised			0.953
No	40%	44%	
Yes	46%	41%	
RAI			0.599
No	24%	15%	
Yes	68%	79%	
RAI Uptake			**0.07**
No uptake	6%	3%	
Thyroid bed	36%	18%	
Outside thyroid bed	26%	53%	
Overall survival (died)	26%	41%	0.144
Overall survival time (days±SD)	2152±1263	1850±1595	0.337
Survival analysis: HR (95%CI)		HR: 1.7 (0.79-3.7)	0.175

Total PDTC = 52	BRAF/RAS alone (26)	BRAF/RAS+TERT (26)	p value
Age (y)	52±16	64±14	**0.007**
Tumor size			0.171
≤ 4	58%	38%	
>4	42%	62%	
Pathology staging			
T1/T2	15%	8%	
T3/T4	85%	92%	0.668
Nx/N0	65%	56%	
N1a/N1b	35%	44%	0.493
M0	69%	38%	
M1	23%	54%	
Mx	8%	8%	**0.05**
RAI			0.703
No	19%	8%	
Yes	77%	88%	
RAI Uptake			0.309
No uptake	12%	9%	
Thyroid bed	35%	23%	
Outside thyroid bed	31%	58%	
OS (died)	23%	50%	0.08
OS time (days±SD)	2413±1266	2161±1633	0.536
Survival analysis HR (95%CI)		HR: 1.5(0.94-2.49)	0.09

Supplementary Table S8. Prevalence of common gene mutations in advanced thyroid cancers reported in the literature. Summary of published studies reporting genetic alterations in PDTCs and/or ATCs for *BRAF*, *RAS*, RET/PTC, *TP53*, *PIK3CA*, *PTEN*, *AKT1*, *CTNNB1*, *AXIN1*, *APC*, *TERT* promoter and *EIF1AX*.

		ATC		PDTC	
Gene	**Study (reference)**	**N**	**%**	**N**	**%**
BRAF	**Nikiforova *et al*, 2003 (1)**	3/29	10.3	2/16	12.5
	Soares *et al*, 2004 [1] (2)	6/17	35.3	0/19	0.0
	Garcia Rostan *et al*, 2005 (3)	19/69	27.5	N/A	N/A
	Santarpia *et al*, 2008 (4)	2/18	11.1	N/A	N/A
	Liu *et al*, 2008 [#] (5)	14/50	28.0	N/A	N/A
	Costa *et al*, 2008 (6)	9/36	25.0	4/24	16.7
	Ricarte-Filho *et al*, 2009 (7)	8/18	44.4	4/34	11.8
	Pita *et al*, 2014 (8)	2/26	7.7	1/22	4.5
	Kuntsman *et al*, 2015 (9)	6/22	27.3	N/A	N/A
	Current series	15/33	45.5	28/84	33.3
RAS	**Manenti *et al*, 1994 (10)**	1/5	20.0	3/11	27.3
	Capella *et al*, 1996 (11)	8/13	61.5	N/A	N/A
	Pilotti *et al*, 1997 [1] (12)	N/A	N/A	5/8	62.5
	Garcia Rostan *et al*, 2003 (13)	15/29	51.7	16/29	55.2
	Hou *et al*, 2007 [#] (14)	4/50	8.0	N/A	N/A
	Santarpia *et al*, 2008 (4)	2/18	11.1	N/A	N/A
	Liu *et al*, 2008 [#] (5)	4/51	7.8	N/A	N/A
	Costa *et al*, 2008 (6)	13/36	36.1	11/24	45.8
	Ricarte-Filho *et al*, 2009 (7)	4/18	22.2	15/34	44.1
	Pita *et al*, 2014 (8)	8/26	30.8	4/22	18.2
	Kuntsman *et al*, 2015 (9)	4/22	18.2	N/A	N/A
	Current series	8/33	24.2	24/84	28.6
RET/PTC	**Santoro *et al*, 1992 (15)**	0/15	0.0	N/A	N/A
	Santoro *et al*, 2002 (16)	N/A	N/A	8/62	12.9
	Ricarte-Filho *et al*, 2009 (7)	0/18	0.0	6/34	17.6
	Kuntsman *et al*, 2015 (9)	N/A	N/A	N/A	N/A
	Current series	0/33	0.0	5/84	6.0

Supplementary Table S8. (continued)

		ATC		PDTC	
Gene	**Study (reference)**	**N**	**%**	**N**	**%**
TP53	**Ito *et al*, 1992 (17)**	6/7	85.7	N/A	N/A
	Nakamura *et al*, 1992 (18)	2/9	22.2	N/A	N/A
	Fagin *et al*, 1993 (19)	5/6	83.3	N/A	N/A
	Donghi *et al*, 1993 (20)	5/7	71.4	2/8	25.0
	Dobashi *et al*, 1994 [2] (21)	4/6	66.7	2/6	33.3
	Ho *et al*, 1996 (22)	0/4	0.0	5/29	17.2
	Takeuchi *et al*, 1999 [1] (23)	N/A	N/A	14/46	30.4
	Pita *et al*, 2014 (8)	11/26	42.3	6/22	27.3
	Kuntsman *et al*, 2015 (9)	6/22	27.3	N/A	N/A
	Current series	24/33	72.7	7/84	8.3
PIK3CA	**Garcia Rostan *et al*, 2005 [3] (3)**	16/70	22.9	N/A	N/A
	Hou *et al*, 2007 [4, #] (14)	6/50	12.0	N/A	N/A
	Santarpia…Sherman, 2008 (4)	4/18	22.2	N/A	N/A
	Ricarte-Filho *et al*, 2009 (7)	1/18	5.6	2/34	5.9
	Pita *et al*, 2014 (8)	1/26	3.8	3/22	13.6
	Kuntsman *et al*, 2015 (9)	2/22	9.1	N/A	N/A
	Current series	6/33	18.2	2/84	2.4
PTEN	**Hou *et al*, 2007 [4, #] (14)**	8/50	16.0	N/A	N/A
	Santarpia *et al*, 2008 (4)	2/18	11.1	N/A	N/A
	Pita *et al*, 2014 (8)	2/20	10.0	3/15	20.0
	Kuntsman *et al*, 2015 (9)	0/22	0.0	N/A	N/A
	Current series	5/33	15.2	3/84	3.6
AKT1	**Liu *et al*, 2008 [#] (5)**	0/47	0.0	N/A	N/A
	Ricarte-Filho *et al*, [5] (7)	0/18	0.0	0/34, 6/32	0.0, 18.8
	Kuntsman *et al*, 2015 (9)	0/22	0.0	N/A	N/A
	Current series	0/33	0.0	0/84	0.0
CTNNB1	**Garcia Rostan *et al*, 1999 [6, *] (24)**	19/31	61.3	N/A	N/A
	Garcia Rostan *et al*, 2001 * (25)	19/29	65.5	7/28	25.0
	Kurihara *et al*, 2004 [7] (26)	1/22	4.5	N/A	N/A
	Pita *et al*, 2014 [8] (8)	0/26	0.0	1/22	4.5
	Kuntsman *et al*, 2015 (9)	1/22	4.5	N/A	N/A
	Current series [9]	0/33	0.0	1/84	1.2
AXIN1	**Kurihara *et al*, 2004 [7] (26)**	18/22	81.8	N/A	N/A
	Kuntsman *et al*, 2015 (9)	0/22	0.0	N/A	N/A
	Current series [10]	1/33	3.0	1/84	1.2

Supplementary Table S8. (continued)

		ATC		PDTC	
Gene	**Study (reference)**	**N**	**%**	**N**	**%**
APC	**Kurihara *et al*, 2004 [7] (26)**	2/22	9.1	N/A	N/A
	Kuntsman *et al*, 2015 (9)	0/22	0.0	N/A	N/A
	Current series	1/33	3.0	0/84	0.0
TERT	**Liu *et al*, 2013 [$] (27)**	25/54	46.3	3/8	37.5
promoter	**Landa *et al*, 2013 [11] (28)**	10/20	50.0	30/58	51.7
	Vinagre *et al*, 2013 [&] (29)	2/16	12.5	3/14	21.4
	Liu *et al*, 2013 (30)	10/20	50.0	N/A	N/A
	Melo *et al*, 2014 [&] (31)	12/36	33.3	9/31	29.0
	Shi *et al*, 2015 [$] (32)	41/106	38.7	N/A	N/A
	Kuntsman *et al*, 2015 (9)	N/A	N/A	N/A	N/A
	Current series [11]	24/33	72.7	34/84	40.5
EIF1AX	**Kuntsman *et al*, 2015 (9)**	3/22	13.6	N/A	N/A
	Current series	3/33	9.1	9/84	10.7

[1] Only "insular and insular-like" PDTCs were studied.

[2] Cases with negative p53 immunostaining were not sequenced for *TP53* mutations.

[3] Among *PIK3CA* mutations there are some canonical (E542K found in one tumor and H1047R in three) and some non-canonical events. Paired normals were available for 22/70 ATCs.

[4] It is unclear whether paired normals were available. Reported *PIK3CA* mutations are non-canonical; PTEN mutations are all missense

[5] *AKT1* mutations found exclusively on metastatic/recurrent PDTC but not on primary tumors

[6] No paired normals available; all *CTNNB1* mutations cluster on exon 3

[7] Paired normals available at least for some tumors, unclear if for all

[8] Only seven paired normals available

[9] *CTNNB1* mutation not in COSMIC and different from those reported.

[10] *AXIN1* mutations not confirmed somatic.

[11] 20/33 ATCs and 17/84 PDTCs were evaluated for *TERT* mutations in both studies

[#] These two papers used overlapping series of ATCs (n=50 *vs*. 51)

* These two papers used overlapping series of ATCs (n=31 *vs.* 29)

[$] 49 ATCs from Shi, 2015 already reported in Liu, 2013

[&] Probably partially overlapping series

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