# Supplementary Information

## *Genomic alterations associated with mutational signatures, DNA damage repair and chromatin remodeling pathways in cervical carcinoma*

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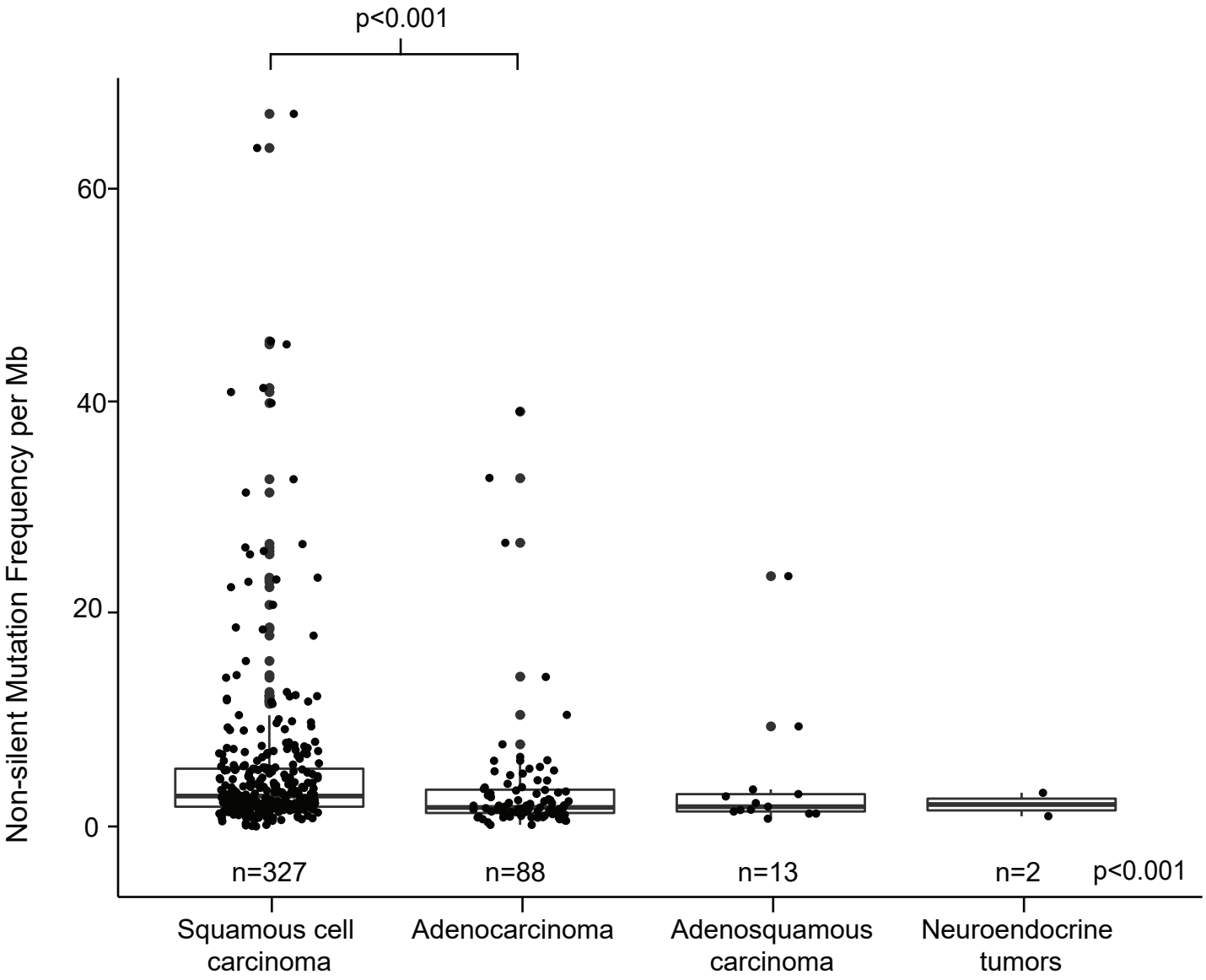
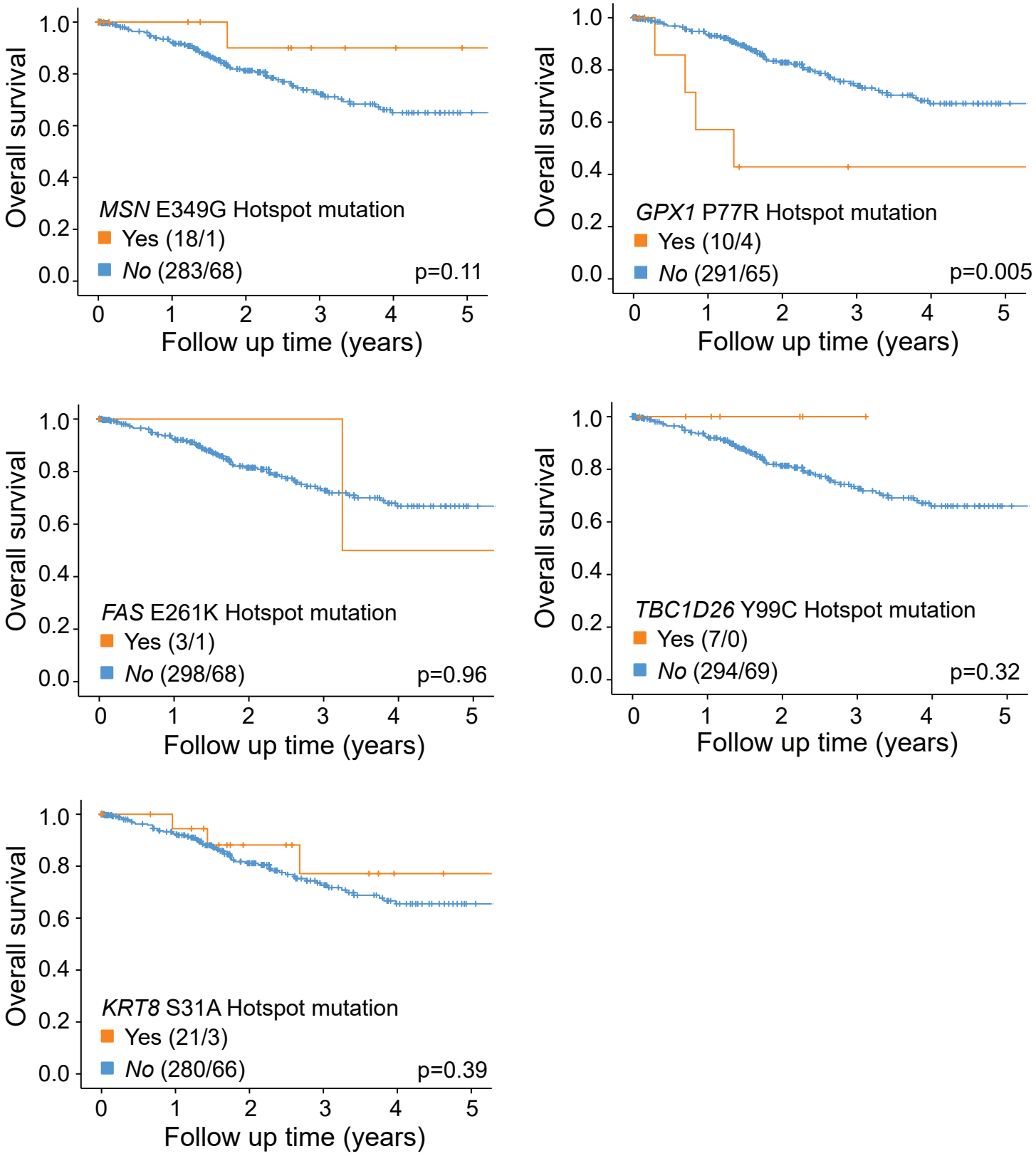
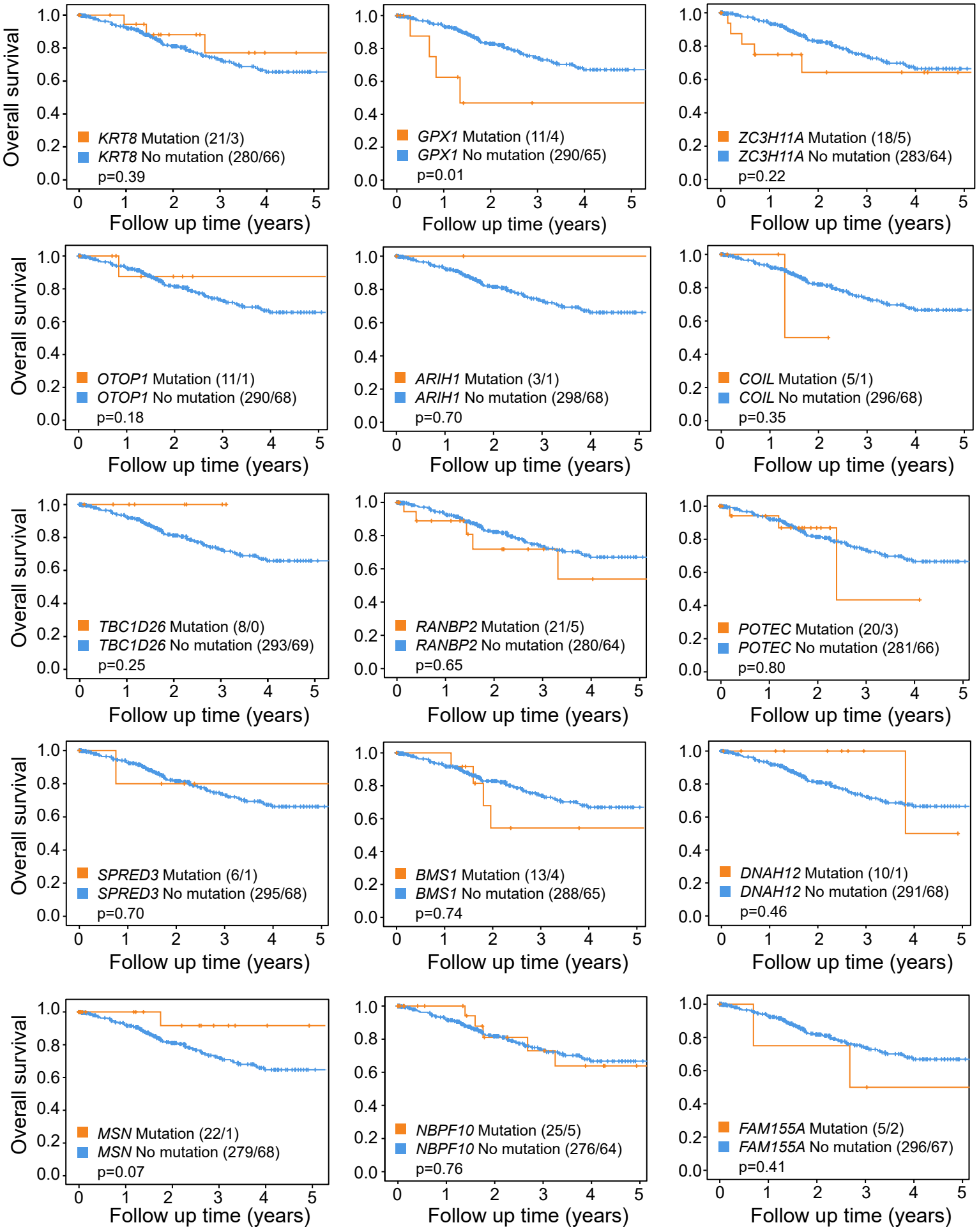


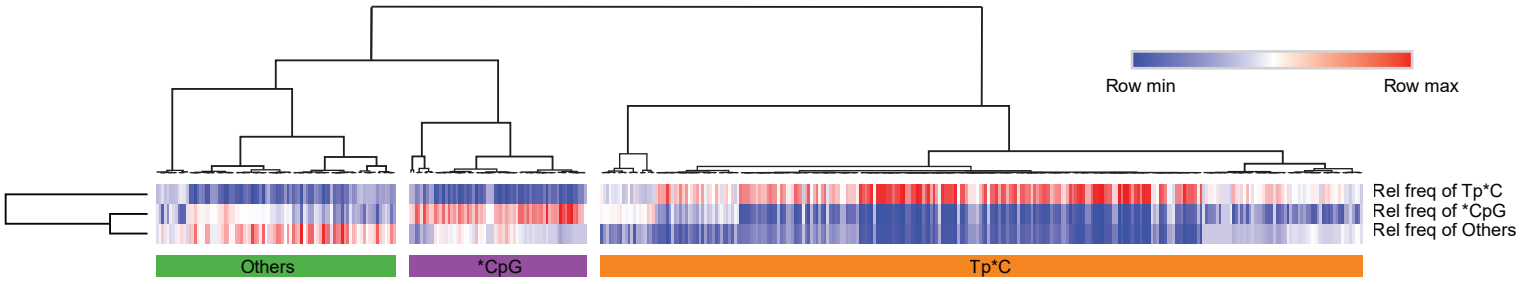

**Supplementary Figure 1. Non silent mutation rate related to histologic types.** Abbreviations: MB: Megabase.



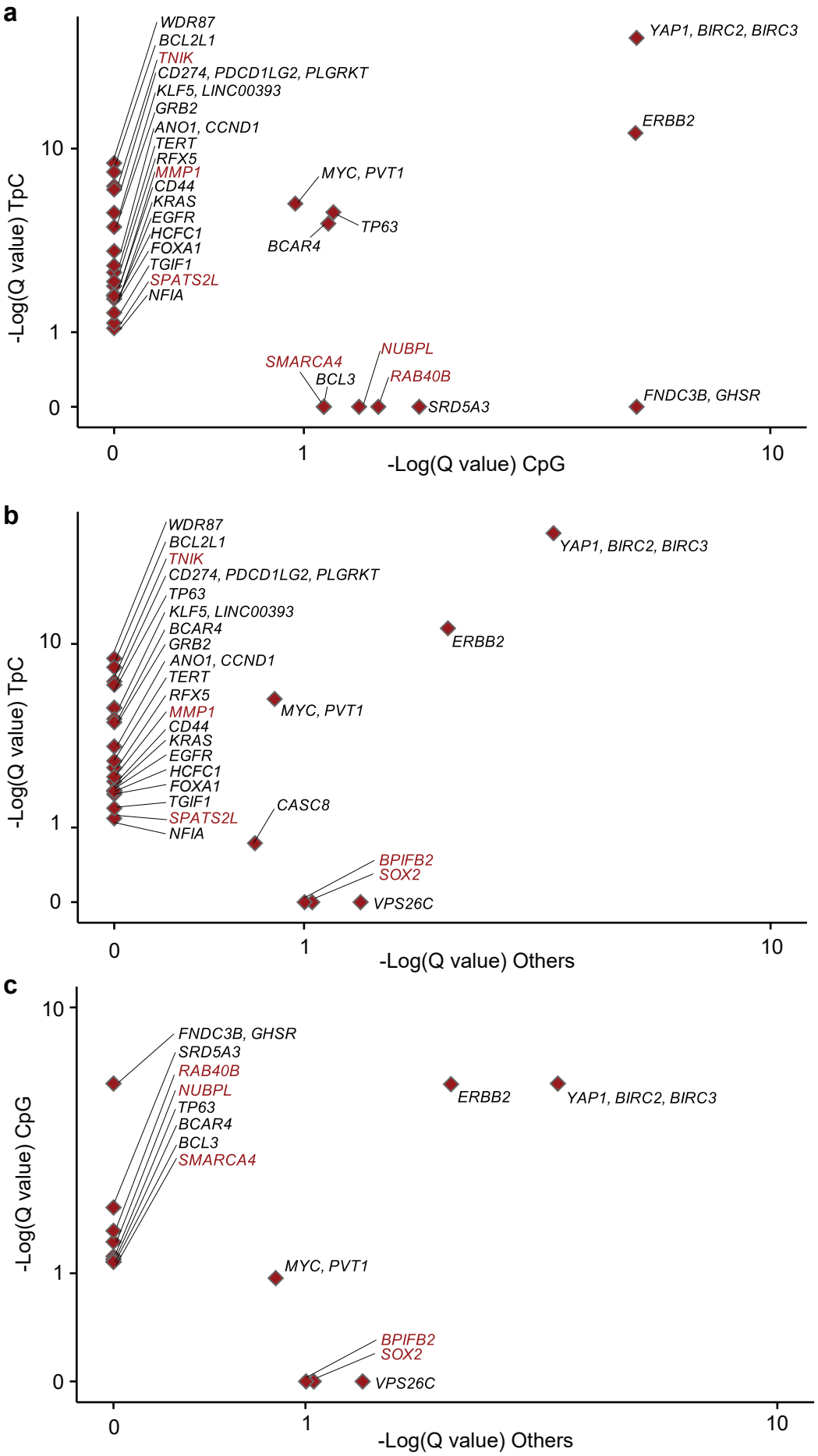

**Supplementary Figure 2. Selected recurrent hotspot mutations in relation to survival.** Overall survival for cervical cancer patients in relation to hotspot mutation status represented by Kaplan-Meier curves with probability values for Mantel-Cox log rank test that compares categories. The number of patients and events are given in parentheses (patients/events).



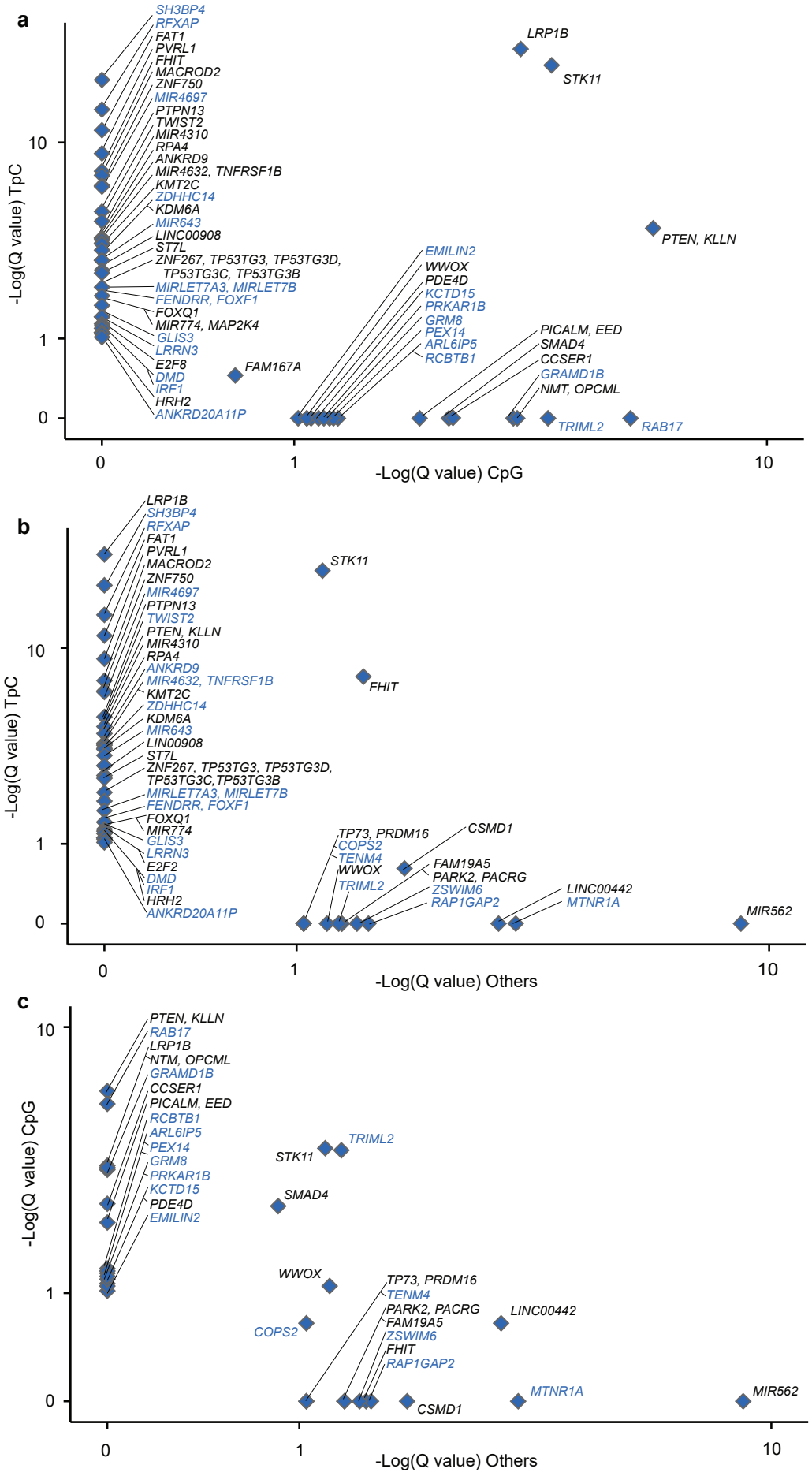

**Supplementary Figure 3. Mutated previously unreported significantly mutated genes in relation to survival.** Overall survival for cervical cancer patients in relation to mutation status of all novel significantly mutated genes discovered within this study. Kaplan-Meier curves are presented with probability values for Mantel-Cox log rank tests that compare categories. The number of patients and events are given in parenthesis (patients/events).




**Supplementary Figure 4. Hierarchical clustering of the relative frequencies of the trinucleotide mutational contexts in each tumor.**
Abbreviations: Rel freq: Relative frequencies




**Supplementary Figure 5. Focal amplification events within 371 cervical carcinomas with predominantly TpC (n=245), CpG (n=87) and other (n=39) mutational profiles.** Somatic copy number alterations were analyzed by GISTIC. 2D scatterplots showing the association between focal amplifications in tumors with predominantly different mutational signatures. Negative equivalents of log transformed Q values of each focal amplification event and the cancer-related gene(s) within that chromosomal peak/region for TpC tumors (*y-axis*) vs CpG tumors (*x-axis*) (**a**), TpC tumors (*y-axis*) vs tumors with other mutational profiles (x-axis) (**b**) and CpG tumors vs tumors with other mutational profiles (*x-axis*) (**c**). Cancer related genes in peaks unique to the specific subgroup/not found in the full dataset are outlined in red. Chromosomal position of the listed genes has been documented in the Cancer Gene Census.




**Supplementary Figure 6. Focal deletion events within 371 cervical carcinomas with predominantly TpC (n=245), CpG (n=87) and other (n=39) mutational profiles.** Somatic copy number alterations were analyzed by GISTIC. Scatterplots showing the association between focal deletions in tumors with predominantly different mutational signatures. Negative equivalents of log transformed Q values of each focal deletion event and the cancer-related gene(s) within that chromosomal peak/region for TpC tumors (*y-axis*) vs CpG (*x-axis*) (**a**), TpC (*y-axis*) vs other mutational profiles (*x-axis*) (**b**) and CpG vs other mutational profiles (*x-axis*) (**c**). Cancer related genes in peaks unique to the specific subgroup/not found in the full dataset are outlined in blue. Chromosomal position of the listed genes has been documented in the Cancer Gene Census.


**Supplementary Figure 7. Single nucleotide mutation and homozygous deletion frequencies in other DNA damage repair (DDR) genes.** The ten genes with highest frequency of mutation (left) and mutation plus homozygous deletion (right) within base excision repair, damage sensor, mismatch repair, translesion synthesis and other DDR modulators. **a**) and **b**, left) Total mutation frequencies were calculated across 430 cervical carcinomas and includes missense (blue), stop codon (orange), splice site (grey) and indels (yellow). **b** and **c**, right) Frequencies of DDR aberrations including mutation (green) and homozygous deletion (blue) were calculated across 372 cervical carcinomas with overlapping GISTIC and MutSig data.

**Supplementary Table 1** *Clinicopathological Characteristics across the three included patient cohorts.*

| **Cohorts** | **TCGA n=301** | **Ojesina *et al* n=114** | **Chung *et al* n=15** | **Total n=430** |
|---|---|---|---|---|
| **Clinicopathological characteristics** | n (%) | n (%) | n (%) | n (%) |
| ***Median age at diagnosis*** | 46 | 47 | 54 | 46.5 |
| ***Histological type*** | | | | |
| Squamous cell carcinoma | 249 (83) | 78 (68) | 0 (0) | 327 (76) |
| Adenocarcinoma | 47 (15) | 26 (24) | 15 (100) | 88 (20.5) |
| Adenosquamous carcinoma | 5 (2) | 8 (7) | 0 (0) | 13 (3) |
| Neuroendocrine carcinoma | 0 (0) | 2 (2) | 0 (0) | 2 (0.5) |
| ***FIGO stage*** | | | | |
| I | 159 (54) | 78 (78) | 7 (47) | 244 (60) |
| II | 69 (23) | 18 (18) | 8 (53) | 95 (23) |
| III | 46 (16) | 2 (2) | 0 (0) | 48 (12) |
| IV | 20 (7) | 2 (2) | 0 (0) | 22 (5) |
| ***Grade*** | | | | |
| Grade 1 | 18 (7) | 6 (6) | | 24 (7) |
| Grade 2 | 134 (50) | 54 (57) | | 188 (51) |
| Grade 3 | 118 (43) | 35 (37) | | 153 (42) |
| ***Race*** | | | | |
| Caucasian | 205 (77) | 114 (100) | 0 (0) | 319 (81) |
| Asian/Mongolian | 30 (11.5) | 0 (0) | 15 (100) | 45 (11) |
| Black | 30 (11.5) | 0 (0) | 0 (0) | 30 (8) |

[a]Missing data for the TCGA cohort: Age at diagnosis: n=2, FIGO stage: n=7, Grade: n=31, Race: n= 36

[b]Missing data for the Ojesina et al cohort: Age at diagnosis and FIGO stage: n=14, Grade: n=19

[c]Missing data for the Chung et al cohort: Grade: n=15

Abbreviations: c: cohort

**Supplementary Table 2** *Mutation counts and frequencies across 430 cervical carcinomas.*

| **Type of mutation** | **Count** | **Frequency (%)** |
|---|---|---|
| Frame Shift Deletion | 1787 | 1.6 |
| Frame Shift Insertion | 728 | 0.7 |
| In Frame Deletion | 613 | 0.5 |
| In Frame Insertion | 129 | 0.1 |
| Missense Mutation | 70060 | 62.6 |
| Nonsense Mutation | 6044 | 5.4 |
| Nonstop Mutation | 147 | 0.1 |
| Silent Mutation | 29491 | 26.4 |
| Splice Site | 2494 | 2.2 |
| Translation Start Site | 399 | 0.4 |
| ***Total*** | ***111892*** | ***100*** |

**Supplementary Table 3** *Top 50 significantly mutated genes across 430 cervical carcinomas called by the MutSig2CV analysis*.*

| Rank | Gene | Coding Nucleotides | Silent mutations | Mis-sense mutations | Non-sense mutations | Splice-site mutations | Indels | Non-silent mutations | Patients | Unique sites | MutFreq (% pat) | p | q |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | *EP300* | 7365 | 4 | 36 | 20 | 3 | 5 | 64 | 52 | 53 | 12.1 | 1.00E-16 | 6.29E-13 |
| 2 | *FBXW7* | 2580 | 0 | 39 | 13 | 0 | 1 | 53 | 50 | 29 | 11.6 | 1.00E-16 | 6.29E-13 |
| 3 | *KRAS* | 709 | 0 | 20 | 0 | 0 | 0 | 20 | 20 | 6 | 4.7 | 1.00E-16 | 6.29E-13 |
| 4 | *PTEN* | 1244 | 1 | 17 | 13 | 3 | 7 | 40 | 33 | 31 | 7.7 | 4.77E-15 | 2.25E-11 |
| 5 | *HLA-B* | 1119 | 3 | 6 | 7 | 4 | 7 | 24 | 21 | 20 | 4.9 | 2.42E-13 | 9.11E-10 |
| 6 | *HLA-A* | 1128 | 2 | 8 | 6 | 7 | 3 | 24 | 24 | 19 | 5.6 | 9.16E-13 | 2.88E-09 |
| 7 | *MLL3* | 14968 | 11 | 47 | 43 | 4 | 13 | 107 | 83 | 99 | 19.3 | 9.51E-12 | 2.56E-08 |
| 8 | *KRT8* | 1481 | 1 | 26 | 0 | 0 | 0 | 26 | 25 | 3 | 5.8 | 2.59E-09 | 6.10E-06 |
| 9 | *NFE2L2* | 1834 | 1 | 22 | 1 | 0 | 1 | 24 | 20 | 16 | 4.7 | 3.72E-09 | 7.80E-06 |
| 10 | *RB1* | 3716 | 2 | 8 | 11 | 5 | 6 | 30 | 25 | 29 | 5.8 | 5.24E-09 | 9.89E-06 |
| 11 | *MLL2* | 16826 | 14 | 37 | 30 | 3 | 5 | 75 | 55 | 71 | 12.8 | 2.51E-08 | 4.31E-05 |
| 12 | *MAPK1* | 1115 | 1 | 18 | 0 | 0 | 0 | 18 | 18 | 5 | 4.2 | 4.13E-08 | 6.49E-05 |
| 13 | *ARID1A* | 6934 | 5 | 14 | 18 | 1 | 8 | 41 | 29 | 37 | 6.7 | 8.53E-08 | 1.24E-04 |
| 14 | *ZNF750* | 2176 | 3 | 5 | 4 | 0 | 7 | 16 | 15 | 16 | 3.5 | 1.75E-07 | 2.36E-04 |
| 15 | *GPX1* | 725 | 1 | 11 | 1 | 0 | 0 | 12 | 11 | 3 | 2.6 | 2.04E-07 | 2.57E-04 |
| 16 | *ZC3H11A* | 2493 | 3 | 10 | 9 | 0 | 1 | 20 | 19 | 9 | 4.4 | 3.17E-07 | 3.73E-04 |
| 17 | *SMAD4* | 1699 | 0 | 9 | 4 | 0 | 0 | 13 | 13 | 12 | 3 | 7.71E-07 | 8.56E-04 |
| 18 | *DDX3X* | 2053 | 0 | 13 | 3 | 0 | 2 | 18 | 18 | 18 | 4.2 | 1.78E-06 | 1.86E-03 |
| 19 | *TGFBR2* | 1807 | 0 | 6 | 1 | 2 | 2 | 11 | 11 | 10 | 2.6 | 1.99E-06 | 1.98E-03 |
| 20 | *CASP8* | 1749 | 3 | 10 | 9 | 2 | 2 | 23 | 21 | 21 | 4.9 | 2.10E-06 | 1.98E-03 |
| 21 | *PIK3CA* | 3287 | 0 | 129 | 0 | 2 | 2 | 133 | 118 | 32 | 27.4 | 2.65E-06 | 2.38E-03 |
| 22 | *TP63* | 2258 | 2 | 10 | 1 | 1 | 0 | 12 | 12 | 10 | 2.8 | 4.98E-06 | 4.27E-03 |
| 23 | *ERBB2* | 3896 | 4 | 25 | 0 | 0 | 1 | 26 | 21 | 17 | 4.9 | 5.65E-06 | 4.64E-03 |
| 24 | *B2M* | 374 | 0 | 3 | 3 | 0 | 2 | 8 | 8 | 8 | 1.9 | 8.03E-06 | 6.31E-03 |
| 25 | *OTOP1* | 1861 | 0 | 4 | 0 | 0 | 7 | 11 | 11 | 5 | 2.6 | 1.31E-05 | 9.88E-03 |
| 26 | *ARIH1* | 1726 | 0 | 0 | 0 | 0 | 3 | 3 | 3 | 1 | 0.7 | 1.49E-05 | 1.05E-02 |
| 27 | *COIL* | 1757 | 0 | 5 | 1 | 0 | 4 | 10 | 9 | 7 | 2.1 | 1.50E-05 | 1.05E-02 |
| 28 | *NF2* | 1894 | 2 | 5 | 5 | 3 | 1 | 14 | 14 | 13 | 3.3 | 1.67E-05 | 1.13E-02 |
| 29 | *TBC1D26* | 792 | 1 | 9 | 0 | 0 | 0 | 9 | 8 | 3 | 1.9 | 2.58E-05 | 1.68E-02 |
| 30 | *RANBP2* | 9787 | 5 | 24 | 2 | 1 | 2 | 29 | 26 | 23 | 6 | 3.41E-05 | 2.15E-02 |
| 31 | *POTEC* | 1669 | 3 | 23 | 1 | 1 | 1 | 26 | 24 | 13 | 5.6 | 4.14E-05 | 2.52E-02 |
| 33 | *OR5H1* | 940 | 2 | 13 | 0 | 0 | 0 | 13 | 8 | 5 | 1.9 | 6.04E-05 | 3.45E-02 |
| 32 | *SPRED3* | 1293 | 0 | 0 | 0 | 0 | 7 | 7 | 7 | 1 | 1.6 | 5.90E-05 | 3.45E-02 |
| 34 | *FAS* | 1044 | 1 | 7 | 0 | 0 | 1 | 8 | 8 | 6 | 1.9 | 6.25E-05 | 3.45E-02 |
| 35 | *OR2J2* | 940 | 0 | 1 | 2 | 0 | 2 | 5 | 5 | 3 | 1.2 | 6.40E-05 | 3.45E-02 |
| 36 | *AKT1* | 1495 | 0 | 9 | 0 | 0 | 0 | 9 | 9 | 5 | 2.1 | 7.04E-05 | 3.69E-02 |
| 37 | *KLF5* | 1386 | 2 | 10 | 1 | 0 | 1 | 12 | 10 | 7 | 2.3 | 7.42E-05 | 3.78E-02 |
| 38 | *TRAF3* | 1747 | 0 | 4 | 2 | 1 | 0 | 7 | 7 | 5 | 1.6 | 7.61E-05 | 3.78E-02 |
| 39 | *CTNNB1* | 2406 | 0 | 9 | 0 | 0 | 0 | 9 | 7 | 7 | 1.6 | 9.89E-05 | 4.78E-02 |
| 40 | *BMS1* | 3937 | 4 | 14 | 1 | 0 | 0 | 15 | 15 | 10 | 3.5 | 1.12E-04 | 5.29E-02 |
| 42 | *DNAH12* | 9554 | 2 | 5 | 2 | 1 | 2 | 10 | 10 | 9 | 2.3 | 1.25E-04 | 5.49E-02 |
| 41 | *MSN* | 1782 | 16 | 25 | 0 | 0 | 1 | 26 | 26 | 8 | 6 | 1.24E-04 | 5.49E-02 |
| 43 | *NBPF10* | 10994 | 23 | 29 | 4 | 0 | 2 | 35 | 33 | 26 | 7.7 | 1.25E-04 | 5.49E-02 |
| 44 | *CREBBP* | 7449 | 7 | 20 | 6 | 3 | 3 | 32 | 29 | 30 | 6.7 | 1.29E-04 | 5.53E-02 |
| 45 | *ERBB3* | 4266 | 5 | 19 | 0 | 0 | 1 | 20 | 18 | 16 | 4.2 | 1.50E-04 | 6.27E-02 |
| 46 | *FAM155A* | 1385 | 0 | 2 | 1 | 0 | 4 | 7 | 7 | 4 | 1.6 | 1.87E-04 | 7.68E-02 |
| 47 | *TP53* | 1890 | 5 | 23 | 8 | 0 | 1 | 32 | 29 | 28 | 6.7 | 2.02E-04 | 8.10E-02 |
| 48 | *FAT1* | 13871 | 11 | 16 | 15 | 1 | 8 | 40 | 35 | 40 | 8.1 | 2.54E-04 | 9.98E-02 |
| 49 | *TNFRSF10C* | 796 | 0 | 4 | 0 | 0 | 0 | 4 | 4 | 2 | 0.9 | 2.84E-04 | 1.09E-01 |
| 50 | *SLC4A9* | 2966 | 0 | 2 | 1 | 0 | 1 | 4 | 4 | 3 | 0.9 | 3.29E-04 | 1.24E-01 |

*Categories are extensively explained in under Supplementary Table 5.

**Supplementary Table 4** *Top 50 significantly mutated genes 327 squamous cell carcinomas called by the MutSig2CV analysis*.*

| Rank | Gene | Coding Nucleotides | Silent mutations | Mis-sense mutations | Non-sense mutations | Splice-site mutations | Indels | Non-silent mutations | Patients | Unique sites | MutFreq (% pat) | p | q |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | *EP300* | 7365 | 3 | 32 | 17 | 2 | 5 | 56 | 45 | 47 | 13.8 | 1.00E-16 | 1.89E-12 |
| 2 | *FBXW7* | 2580 | 0 | 31 | 12 | 0 | 1 | 44 | 41 | 26 | 12.5 | 3.33E-16 | 3.14E-12 |
| 3 | *HLA-A* | 1128 | 2 | 6 | 6 | 7 | 3 | 22 | 22 | 18 | 6.7 | 7.77E-16 | 4.89E-12 |
| 4 | *PTEN* | 1244 | 0 | 11 | 12 | 3 | 3 | 29 | 24 | 24 | 7.3 | 2.26E-14 | 1.07E-10 |
| 5 | *HLA-B* | 1119 | 2 | 5 | 7 | 3 | 6 | 21 | 19 | 18 | 5.8 | 3.86E-13 | 1.46E-09 |
| 6 | *MAPK1* | 1115 | 1 | 17 | 0 | 0 | 0 | 17 | 17 | 5 | 5.2 | 5.84E-12 | 1.84E-08 |
| 7 | *MLL3* | 14968 | 8 | 35 | 37 | 4 | 9 | 85 | 64 | 78 | 19.6 | 1.96E-10 | 5.29E-07 |
| 8 | *RB1* | 3716 | 2 | 7 | 11 | 5 | 5 | 28 | 23 | 27 | 7 | 3.08E-10 | 7.25E-07 |
| 9 | *NFE2L2* | 1834 | 1 | 21 | 1 | 0 | 1 | 23 | 19 | 16 | 5.8 | 2.03E-09 | 4.25E-06 |
| 10 | *MLL2* | 16826 | 13 | 32 | 29 | 2 | 5 | 68 | 48 | 64 | 14.7 | 2.76E-09 | 5.20E-06 |
| 11 | *CASP8* | 1749 | 2 | 8 | 9 | 2 | 2 | 21 | 19 | 19 | 5.8 | 7.85E-08 | 1.35E-04 |
| 12 | *KRT8* | 1481 | 1 | 17 | 0 | 0 | 0 | 17 | 17 | 1 | 5.2 | 2.13E-07 | 3.35E-04 |
| 13 | *KRAS* | 709 | 0 | 8 | 0 | 0 | 0 | 8 | 8 | 5 | 2.4 | 2.49E-07 | 3.61E-04 |
| 14 | *ZNF750* | 2176 | 3 | 5 | 3 | 0 | 7 | 15 | 14 | 15 | 4.3 | 1.48E-06 | 2.00E-03 |
| 15 | *TP63* | 2258 | 1 | 10 | 1 | 1 | 0 | 12 | 12 | 10 | 3.7 | 1.85E-06 | 2.33E-03 |
| 16 | *TGFBR2* | 1807 | 0 | 6 | 1 | 1 | 2 | 10 | 10 | 9 | 3.1 | 7.73E-06 | 9.11E-03 |
| 17 | *PIK3CA* | 3287 | 0 | 95 | 0 | 0 | 2 | 97 | 87 | 23 | 26.6 | 8.50E-06 | 9.16E-03 |
| 18 | *SMAD4* | 1699 | 0 | 6 | 4 | 0 | 0 | 10 | 10 | 9 | 3.1 | 8.75E-06 | 9.16E-03 |
| 19 | *OTOP1* | 1861 | 0 | 3 | 0 | 0 | 6 | 9 | 9 | 4 | 2.8 | 1.04E-05 | 1.03E-02 |
| 20 | *RANBP2* | 9787 | 4 | 21 | 1 | 1 | 2 | 25 | 22 | 20 | 6.7 | 1.53E-05 | 1.44E-02 |
| 21 | *TP53* | 1890 | 2 | 13 | 6 | 0 | 0 | 19 | 17 | 15 | 5.2 | 1.86E-05 | 1.67E-02 |
| 22 | *COIL* | 1757 | 0 | 5 | 0 | 0 | 4 | 9 | 8 | 6 | 2.4 | 2.32E-05 | 1.99E-02 |
| 23 | *KLF5* | 1386 | 2 | 9 | 0 | 0 | 1 | 10 | 8 | 5 | 2.4 | 2.90E-05 | 2.37E-02 |
| 24 | *ZC3H11A* | 2493 | 2 | 7 | 6 | 0 | 1 | 14 | 14 | 8 | 4.3 | 3.55E-05 | 2.74E-02 |
| 25 | *OR2J2* | 940 | 0 | 1 | 2 | 0 | 2 | 5 | 5 | 3 | 1.5 | 3.64E-05 | 2.74E-02 |
| 26 | *SPRED3* | 1293 | 0 | 0 | 0 | 0 | 6 | 6 | 6 | 1 | 1.8 | 3.92E-05 | 2.84E-02 |
| 27 | *GPX1* | 725 | 1 | 9 | 1 | 0 | 0 | 10 | 9 | 3 | 2.8 | 4.41E-05 | 2.99E-02 |
| 28 | *POTEC* | 1669 | 2 | 18 | 1 | 1 | 1 | 21 | 20 | 10 | 6.1 | 4.44E-05 | 2.99E-02 |
| 29 | *FAS* | 1044 | 1 | 7 | 0 | 0 | 1 | 8 | 8 | 6 | 2.4 | 5.80E-05 | 3.78E-02 |
| 30 | *DDX3X* | 2053 | 0 | 8 | 3 | 0 | 2 | 13 | 13 | 13 | 4 | 6.53E-05 | 4.11E-02 |
| 31 | *ERBB3* | 4266 | 5 | 10 | 0 | 0 | 1 | 11 | 10 | 8 | 3.1 | 6.87E-05 | 4.18E-02 |
| 32 | *B2M* | 374 | 0 | 3 | 3 | 0 | 2 | 8 | 8 | 8 | 2.4 | 7.11E-05 | 4.19E-02 |
| 33 | *SLC4A9* | 2966 | 0 | 2 | 1 | 0 | 1 | 4 | 4 | 3 | 1.2 | 8.63E-05 | 4.93E-02 |
| 34 | *C12orf43* | 811 | 0 | 5 | 0 | 0 | 0 | 5 | 5 | 2 | 1.5 | 9.48E-05 | 5.26E-02 |
| 35 | *FAT1* | 13871 | 7 | 14 | 12 | 1 | 8 | 35 | 30 | 35 | 9.2 | 1.07E-04 | 5.78E-02 |
| 36 | *BMS1* | 3937 | 3 | 12 | 1 | 0 | 0 | 13 | 13 | 9 | 4 | 1.10E-04 | 5.79E-02 |
| 37 | *MSN* | 1782 | 14 | 21 | 0 | 0 | 0 | 21 | 21 | 5 | 6.4 | 1.25E-04 | 6.38E-02 |
| 38 | *NF2* | 1894 | 2 | 5 | 4 | 2 | 1 | 12 | 12 | 11 | 3.7 | 1.35E-04 | 6.72E-02 |
| 39 | *C3orf27* | 450 | 1 | 3 | 0 | 0 | 2 | 5 | 5 | 4 | 1.5 | 1.65E-04 | 7.92E-02 |
| 40 | *BAP1* | 2254 | 0 | 3 | 7 | 0 | 1 | 11 | 11 | 9 | 3.4 | 1.74E-04 | 7.92E-02 |
| 41 | *TRIM41* | 2009 | 0 | 3 | 1 | 0 | 3 | 7 | 7 | 6 | 2.1 | 1.75E-04 | 7.92E-02 |
| 42 | *IFNGR1* | 1495 | 0 | 3 | 7 | 0 | 0 | 10 | 9 | 9 | 2.8 | 1.76E-04 | 7.92E-02 |
| 43 | *SIRPB1* | 2358 | 0 | 8 | 0 | 0 | 0 | 8 | 8 | 4 | 2.4 | 2.06E-04 | 9.03E-02 |
| 44 | *TRAF3* | 1747 | 0 | 4 | 2 | 1 | 0 | 7 | 7 | 5 | 2.1 | 2.54E-04 | 1.09E-01 |
| 45 | *MEF2A* | 1696 | 1 | 7 | 0 | 0 | 2 | 9 | 9 | 8 | 2.8 | 3.13E-04 | 1.31E-01 |
| 46 | *CGB7* | 508 | 0 | 3 | 0 | 2 | 0 | 5 | 5 | 4 | 1.5 | 3.26E-04 | 1.34E-01 |
| 47 | *USP28* | 3332 | 1 | 6 | 1 | 3 | 0 | 10 | 10 | 9 | 3.1 | 4.00E-04 | 1.61E-01 |
| 48 | *MUC17* | 13532 | 8 | 37 | 5 | 0 | 3 | 45 | 39 | 42 | 11.9 | 4.78E-04 | 1.88E-01 |
| 49 | *C6orf223* | 786 | 0 | 1 | 0 | 0 | 2 | 3 | 3 | 1 | 0.9 | 5.06E-04 | 1.90E-01 |
| 50 | *TNFRSF10C* | 796 | 0 | 4 | 0 | 0 | 0 | 4 | 4 | 2 | 1.2 | 5.11E-04 | 1.90E-01 |

*Categories are extensively explained in under Supplementary Table 5.

**Supplementary Table 5** *Top 30 mutated genes across 86 non-squamous cell carcinomas called by the MutSig2CV analysis*.*

| Rank | Gene | Coding Nucleotides | Silent mutations | Missense mutations | Non-sense mutations | Splice-site mutations | Indels | Non-silent mutations | Patients | Unique sites | MutFreq (% pat) | p | q |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | *KRAS* | 709 | 0 | 12 | 0 | 0 | 0 | 12 | 12 | 4 | 14.0 | 2.87E-13 | 5.42E-09 |
| 2 | *ARID1A* | 6934 | 0 | 3 | 6 | 0 | 3 | 12 | 11 | 11 | 12.8 | 1.53E-08 | 1.44E-04 |
| 3 | *IL28A* | 627 | 0 | 2 | 1 | 1 | 0 | 4 | 4 | 4 | 4.7 | 2.63E-06 | 1.65E-02 |
| 4 | *TP53* | 1890 | 1 | 7 | 1 | 0 | 1 | 9 | 8 | 9 | 9.3 | 4.33E-06 | 1.66E-02 |
| 5 | *FBXW7* | 2580 | 0 | 6 | 1 | 0 | 0 | 7 | 7 | 7 | 8.1 | 4.40E-06 | 1.66E-02 |
| 6 | *MLL3* | 14968 | 2 | 9 | 5 | 0 | 4 | 18 | 16 | 18 | 18.6 | 9.20E-06 | 2.89E-02 |
| 7 | *PIK3CA* | 3287 | 0 | 25 | 0 | 2 | 0 | 27 | 22 | 12 | 25.6 | 1.35E-05 | 3.64E-02 |
| 8 | *PTEN* | 1244 | 1 | 3 | 0 | 0 | 4 | 7 | 6 | 7 | 7.0 | 2.77E-05 | 6.53E-02 |
| 9 | *AKT1* | 1495 | 0 | 4 | 0 | 0 | 0 | 4 | 4 | 3 | 4.7 | 4.64E-05 | 9.67E-02 |
| 10 | *ZC3H11A* | 2493 | 0 | 3 | 3 | 0 | 0 | 6 | 5 | 3 | 5.8 | 5.13E-05 | 9.67E-02 |
| 11 | *ERBB2* | 3896 | 0 | 9 | 0 | 0 | 0 | 9 | 8 | 7 | 9.3 | 9.73E-05 | 1.67E-01 |
| 12 | *EP300* | 7365 | 1 | 1 | 3 | 1 | 0 | 5 | 4 | 5 | 4.7 | 1.53E-04 | 2.40E-01 |
| 13 | *KRT8* | 1481 | 0 | 3 | 0 | 0 | 0 | 3 | 3 | 1 | 3.5 | 4.87E-04 | 7.07E-01 |
| 14 | *CBFB* | 615 | 0 | 1 | 0 | 0 | 1 | 2 | 2 | 2 | 2.3 | 9.65E-04 | 1 |
| 15 | *SOX17* | 1249 | 0 | 1 | 0 | 0 | 1 | 2 | 2 | 2 | 2.3 | 1.14E-03 | 1 |
| 16 | *TGM4* | 2109 | 0 | 0 | 1 | 1 | 0 | 2 | 2 | 2 | 2.3 | 1.22E-03 | 1 |
| 17 | *ATXN3* | 1128 | 0 | 0 | 0 | 0 | 3 | 3 | 2 | 2 | 2.3 | 1.37E-03 | 1 |
| 18 | *ELF3* | 1148 | 1 | 2 | 1 | 0 | 3 | 6 | 6 | 6 | 7.0 | 1.54E-03 | 1 |
| 19 | *POLM* | 1527 | 0 | 2 | 0 | 1 | 1 | 4 | 3 | 4 | 3.5 | 1.65E-03 | 1 |
| 20 | *PODXL* | 1709 | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 2 | 2.3 | 2.57E-03 | 1 |
| 21 | *HSH2D* | 1082 | 0 | 2 | 1 | 0 | 0 | 3 | 2 | 3 | 2.3 | 2.80E-03 | 1 |
| 22 | *C21orf58* | 1005 | 0 | 1 | 0 | 0 | 2 | 3 | 3 | 2 | 3.5 | 3.02E-03 | 1 |
| 23 | *CCDC33* | 2603 | 0 | 3 | 0 | 0 | 0 | 3 | 3 | 3 | 3.5 | 3.13E-03 | 1 |
| 24 | *DNAH12* | 9554 | 0 | 0 | 1 | 1 | 1 | 3 | 3 | 3 | 3.5 | 3.57E-03 | 1 |
| 25 | *ABHD4* | 1055 | 0 | 0 | 2 | 0 | 0 | 2 | 2 | 1 | 2.3 | 3.95E-03 | 1 |
| 26 | *GPR110* | 2837 | 0 | 1 | 1 | 0 | 0 | 2 | 2 | 1 | 2.3 | 4.16E-03 | 1 |
| 27 | *ZFP36L1* | 1198 | 0 | 1 | 1 | 0 | 0 | 2 | 2 | 2 | 2.3 | 4.20E-03 | 1 |
| 28 | *LAMTOR4* | 314 | 0 | 0 | 0 | 1 | 1 | 2 | 2 | 2 | 2.3 | 4.40E-03 | 1 |
| 29 | *MBNL1* | 1685 | 0 | 1 | 2 | 0 | 0 | 3 | 2 | 3 | 2.3 | 4.58E-03 | 1 |
| 30 | *DNASE1L1* | 1226 | 0 | 2 | 0 | 0 | 0 | 2 | 2 | 1 | 2.3 | 4.91E-03 | 1 |

*Extended category explanation:

Coding nucleotides: number of coding nucleotides within this gene covered by sequencing
Silent mutations: number of silent mutations in this gene across the individual set
Missense mutation: number of missense mutations in this gene across the individual set
Non-sense mutations: number of nonsense mutations in this gene across the individual set
Splice site mutations: number of splice site mutations in this gene across the individual set
Indel: number of indel mutations in this gene across the individual set
Non-silent mutations: number of (non-silent) mutations in this gene across the individual set
Patients: number of patients (individuals) with at least one non-silent mutation
Unique sites: number of unique sites having a non-silent mutation
p: p-value (overall)
q: q-value, False Discovery Rate (Benjamini-Hochberg procedure)

**Supplementary Table 6** *Mutations in chromatin remodeling families or genes.*

| *Gene/Family* | *Family members mutated* | *# patients with mutation* | *Frequency (%)* |
|---|---|---|---|
| MLL family | *MLL, MLL2, MLL3* | 119 | 27.7 |
| KDM Family | *KDM1A, KDM1B, KDM2A, KDM2B, KDM3A, KDM3B, KDM4A, KDM4B, KDM4C, KDM4D, KDM4DL, KDM5A, KDM5B, KDM5C, KDM5D, KDM6A, KDM6B* | 94 | 21.9 |
| ARID Family | *ARID1A, ARID1B, ARID2, ARID3A, ARID3B, ARID3C, ARID4A, ARID4B ARID5A, ARID5B* | 59 | 13.7 |
| EP300 | | 52 | 12.1 |
| SMARC Family | *SMARCA1, SMARCA2, SMARCAD1, SMARCC2, SMARCD1, SMARCD3, SMARCE1* | 35 | 8.1 |
| DNMT Family | *DNMT1, DNMT3A, DNMT3B, DNMT3L* | 22 | 5.1 |
| HIST Family | *HIST1H1A, HIST1H1B, HIST1H1C, HIST1H1D, HIST1H1E, HIST1H1T* | 16 | 3.7 |
| PBRM1 | | 9 | 2.1 |
| **# samples with mutated chromatin modifiers** | | **228** | **53.0** |
| **Total samples** | | **430** | **100.0** |

**Supplementary Table 7** *Novel focal amplifications (**a**) and deletions (**b**) across 430 cervical carcinomas.*

| ***Supplementary Table 7a Focal copy number amplifications*** | | | | |
|---|---|---|---|---|
| ***Cytoband*** | ***Genomic region*** | ***Putative driver gene(s)*** | ***Comment*** | ***Reference(s)*** |
| **1p31.1** | chr1:61831890 - 61932604 | *NFIA* | | (1) |
| **1q21.3** | chr1:151300377 - 151331927 | *RFX5* | Transcriptional activator in hepatocellular carcinoma | (2, 3) |
| **4q12** | chr4:56093585 - 56222716 | *SRD5A3* | Overexpressed in prostate cancer. | (4) |
| **6p21.33** | chr6:30526845 - 30526845 | *GNL1* | GNL1 is a nucleolar GTPase, which promotes cell cycle and proliferation by inducing hyperphosphorylation of retinoblastoma protein. | (5) |
| **18p11.31** | chr18:3155700 - 3254846 | *TGIF1* | | (6, 7) |
| **19q13.13** | chr19:38373478 - 38390659 | *WDR87* | *Manuscript in preparation.* | |
| **19q13.2** | chr19:3383496 - 3401817 | *NFIC* | | (8) |
| **Xq28** | chrX:153212816 - 153254952 | *HCFC1, TMEM187* | HCFC1 is overexpressed in multiple tumors | (9) |
| ***Supplementary Table 7b Focal copy number deletions*** | | | | |
| ***Cytoband*** | ***Genomic region*** | ***Putative driver gene(s)*** | ***Comment*** | ***References(s)*** |
| **2q37.1** | chr2:233034495 - 233048132 | *MIR562* | The putative role of miR-562 as the tumor suppressor in the 2q37.1 deletion peak has been previously proposed in the context of Wilms' tumors. | (10) |
| | | *DIS3L2* | DISA3L2 loss fosters susceptibility to Wilms tumor and its overexpression is associated with decreased cellular proliferation. Tumor suppressive in colon cancer, inversely proportional to cell cycle inhibitors p27 and p21, and knockdown promotes cellular proliferation. | (11, 12) |
| **4q22.1** | chr4:91039783 - 92523213 | *CCSER1* | Patel et al demonstrated that CCSER1 (aka FAM190A) deficient is associated with a cell division defect. | (13) |
| **5q12.1** | chr5:58261529- 59818040 | *PDE4D* | Although thought to have pro-cancer properties, PDE4D deletions have been observed in multiple tumor types | (14, 15) |
| **6p25.3** | chr6:1309918 - 1315309 | *FOXQ1* | Possibly paradoxical; FOXQ1 has oncogenic properties in several cancer types | (16) |
| **6q26** | chr6:163145416 - 163736814 | *PACRG, PARK2* | | (17, 18) |
| **8p23.2** | chr8:2792739 - 4852925 | *CSMD1* | | (19, 20) |
| **11q14.2** | chr11:85803238 - 85805593 | *EED* | EED is a context-dependent tumor-suppressor gene in KRAS-driven lung cancer. | (21) |
| | | *PICALM* | PICALM deficiency increases cholesterol biosynthesis. | (22) |
| **11q23.3** | chr11:85803238 - 85805593 | *PVRL1* | PVRL1 is a metastasis suppressor gene in melanoma. | (23) |
| **11q25** | chr11:131239804 - 132208428 | *NTM* | NTM belongs to the IgLON family of GPI-anchored cell adhesion molecules, which is part of the immunoglobulin (Ig) domain-containing superfamily. The IgLON family gets its name from the 3 members LSAMP, OPCML, and neurotrimin (NTM). | (24) |
| **14q32.2** | chr14:100148237 - 100195717 | *CYP46A1* | CYP46A1 is a cholesterol-regulatory gene with putative tumor suppressor function in glioblastoma. | (25) |
| **15q15.1** | chr15:42138456 - 42186351 | *MIR4310* | Negative transcriptional regulator of MMP-10, which promotes cervical cancer progression. | (26, 27) |
| **16q11.2** | chr16:31850299 - 46615362 | *ZNF267, TP53TG3, TP53TG3B TP53TG3C TP53TG3D* | Induced by TP53. | (28) |
| **Xp11.3** | chrX:44729855 - 44975013 | *KDM6A* | Inactivated in multiple cancers. | (29-31) |

**Supplementary Table 8** *Significantly enriched MSigDB Curated (c2), Gene Ontology (c5) and Hallmarks (H) gene sets within amplified and mutated oncogenes in the whole cohort.*

| ***Significantly enriched Curated gene sets (c2)*** | ***P-value*** | ***FDR q-value*** |
|---|---|---|
| KEGG_PATHWAYS_IN_CANCER | 1.05E-20 | 5.83E-17 |
| KEGG_ENDOMETRIAL_CANCER | 2.30E-19 | 6.37E-16 |
| KEGG_ERBB_SIGNALING_PATHWAY | 5.61E-17 | 9.84E-14 |
| KEGG_PROSTATE_CANCER | 7.12E-17 | 9.84E-14 |
| BIOCARTA_TFF_PATHWAY | 2.82E-15 | 3.12E-12 |
| REACTOME_SIGNALING_BY_ERBB2 | 5.33E-15 | 4.24E-12 |
| KEGG_FOCAL_ADHESION | 5.37E-15 | 4.24E-12 |
| KEGG_NON_SMALL_CELL_LUNG_CANCER | 1.03E-14 | 7.10E-12 |
| REACTOME_CYTOKINE_SIGNALING_IN_IMMUNE_SYSTEM | 4.43E-14 | 2.66E-11 |
| KEGG_GLIOMA | 4.93E-14 | 2.66E-11 |
| REACTOME_NEGATIVE_REGULATION_OF_THE_PI3K_AKT_NETWORK | 5.29E-14 | 2.66E-11 |
| BIOCARTA_TEL_PATHWAY | 7.96E-14 | 3.67E-11 |
| KEGG_PANCREATIC_CANCER | 9.16E-14 | 3.90E-11 |
| KEGG_CHRONIC_MYELOID_LEUKEMIA | 1.30E-13 | 5.14E-11 |
| PID_ERBB2_ERBB3_PATHWAY | 3.06E-13 | 1.13E-10 |
| KEGG_SMALL_CELL_LUNG_CANCER | 4.17E-13 | 1.44E-10 |
| BIOCARTA_HER2_PATHWAY | 6.45E-13 | 2.10E-10 |
| REACTOME_SIGNALING_BY_ERBB2_IN_CANCER | 1.47E-12 | 4.50E-10 |
| KEGG_ACUTE_MYELOID_LEUKEMIA | 2.08E-12 | 6.05E-10 |
| KEGG_COLORECTAL_CANCER | 3.85E-12 | 1.06E-09 |
| ***Significantly enriched Gene Ontology gene sets (c5)*** | ***P-value*** | ***FDR q-value*** |
| GO_POSITIVE_REGULATION_OF_CELL_POPULATION_PROLIFERATION | 1.04E-15 | 1.06E-11 |
| GO_NEGATIVE_REGULATION_OF_CELL_DEATH | 6.45E-14 | 2.32E-10 |
| GO_REGULATION_OF_CELL_POPULATION_PROLIFERATION | 6.82E-14 | 2.32E-10 |
| GO_REGULATION_OF_CELL_DEATH | 9.48E-14 | 2.41E-10 |
| GO_POSITIVE_REGULATION_OF_MULTICELLULAR_ORGANISMAL_PROCESS | 2.04E-13 | 4.04E-10 |
| GO_TUBE_DEVELOPMENT | 2.38E-13 | 4.04E-10 |
| GO_REGULATION_OF_IMMUNE_SYSTEM_PROCESS | 5.95E-13 | 8.66E-10 |
| GO_POSITIVE_REGULATION_OF_RNA_METABOLIC_PROCESS | 8.85E-13 | 1.13E-09 |
| GO_REGULATION_OF_INTRACELLULAR_SIGNAL_TRANSDUCTION | 3.70E-12 | 3.65E-09 |
| GO_POSITIVE_REGULATION_OF_SIGNALING | 3.91E-12 | 3.65E-09 |
| GO_POSITIVE_REGULATION_OF_NUCLEOBASE_CONTAINING_COMPOUND_METABOLIC_PROCESS | 3.94E-12 | 3.65E-09 |
| GO_TUBE_MORPHOGENESIS | 4.73E-12 | 4.01E-09 |
| GO_POSITIVE_REGULATION_OF_CELLULAR_BIOSYNTHETIC_PROCESS | 1.09E-11 | 8.53E-09 |
| GO_TRANSCRIPTION_FACTOR_BINDING | 2.64E-11 | 1.92E-08 |
| GO_POSITIVE_REGULATION_OF_DEVELOPMENTAL_PROCESS | 1.15E-10 | 7.82E-08 |
| GO_POSITIVE_REGULATION_OF_TRANSCRIPTION_BY_RNA_POLYMERASE_II | 1.37E-10 | 8.75E-08 |
| GO_APOPTOTIC_SIGNALING_PATHWAY | 1.74E-10 | 1.05E-07 |
| GO_RESPONSE_TO_ABIOTIC_STIMULUS | 2.04E-10 | 1.16E-07 |
| GO_POSITIVE_REGULATION_OF_INTRACELLULAR_SIGNAL_TRANSDUCTION | 2.66E-10 | 1.43E-07 |
| GO_CELLULAR_RESPONSE_TO_DNA_DAMAGE_STIMULUS | 4.65E-10 | 2.37E-07 |
| ***Significantly enriched Hallmark gene sets (H)*** | ***P-value*** | ***FDR q-value*** |
| HALLMARK_APOPTOSIS | 3.42E-09 | 1.71E-07 |
| HALLMARK_TNFA_SIGNALING_VIA_NFKB | 1.54E-08 | 3.84E-07 |
| HALLMARK_PI3K_AKT_MTOR_SIGNALING | 1.62E-05 | 2.69E-04 |
| HALLMARK_UV_RESPONSE_DN | 5.57E-05 | 6.97E-04 |
| HALLMARK_IL2_STAT5_SIGNALING | 1.94E-04 | 1.41E-03 |
| HALLMARK_APICAL_JUNCTION | 1.98E-04 | 1.41E-03 |
| HALLMARK_ESTROGEN_RESPONSE_EARLY | 1.98E-04 | 1.41E-03 |
| HALLMARK_WNT_BETA_CATENIN_SIGNALING | 1.67E-03 | 1.04E-02 |
| HALLMARK_TGF_BETA_SIGNALING | 2.75E-03 | 1.15E-02 |
| HALLMARK_ALLOGRAFT_REJECTION | 2.99E-03 | 1.15E-02 |
| HALLMARK_G2M_CHECKPOINT | 2.99E-03 | 1.15E-02 |
| HALLMARK_GLYCOLYSIS | 2.99E-03 | 1.15E-02 |
| HALLMARK_KRAS_SIGNALING_UP | 2.99E-03 | 1.15E-02 |
| HALLMARK_IL6_JAK_STAT3_SIGNALING | 6.97E-03 | 2.49E-02 |
| HALLMARK_PROTEIN_SECRETION | 8.42E-03 | 2.81E-02 |
| HALLMARK_ANDROGEN_RESPONSE | 9.11E-03 | 2.85E-02 |

**Supplementary Table 9** *Significantly enriched MSigDB Curated (c2), Gene Ontology (c5) and Hallmarks (H) gene sets within deleted and mutated tumor suppressors within the whole cohort.*

| ***Significantly enriched Curated gene sets (c2)*** | **P-value** | **FDR q-value** |
|---|---|---|
| GRESHOCK_CANCER_COPY_NUMBER_UP | 2.10E-14 | 1.16E-10 |
| REACTOME_RNA_POLYMERASE_II_TRANSCRIPTION | 2.50E-12 | 6.90E-09 |
| KEGG_PATHWAYS_IN_CANCER | 3.59E-10 | 6.61E-07 |
| TAKADA_GASTRIC_CANCER_COPY_NUMBER_DN | 1.54E-09 | 2.12E-06 |
| BIOCARTA_FAS_PATHWAY | 2.22E-09 | 2.46E-06 |
| PID_P53_DOWNSTREAM_PATHWAY | 5.65E-09 | 5.21E-06 |
| LIN_MELANOMA_COPY_NUMBER_DN | 1.15E-08 | 9.09E-06 |
| BIOCARTA_PML_PATHWAY | 2.23E-08 | 1.54E-05 |
| REACTOME_CHROMATIN_MODIFYING_ENZYMES | 3.48E-08 | 1.93E-05 |
| BIOCARTA_TGFB_PATHWAY | 3.62E-08 | 1.93E-05 |
| DACOSTA_UV_RESPONSE_VIA_ERCC3_DN | 3.83E-08 | 1.93E-05 |
| BIOCARTA_NTHI_PATHWAY | 8.23E-08 | 3.79E-05 |
| REACTOME_ACTIVATION_OF_ANTERIOR_HOX_GENES_IN_HINDBRAIN_DEVELOPMENT_DURING_EARLY_EMBRYOGENESIS | 9.24E-08 | 3.90E-05 |
| BIOCARTA_CTCF_PATHWAY | 9.87E-08 | 3.90E-05 |
| KUROKAWA_LIVER_CANCER_EARLY_RECURRENCE_DN | 1.11E-07 | 4.08E-05 |
| DING_LUNG_CANCER_MUTATED_SIGNIFICANTLY | 1.38E-07 | 4.78E-05 |
| KEGG_ADHERENS_JUNCTION | 2.21E-07 | 7.18E-05 |
| DER_IFN_ALPHA_RESPONSE_UP | 2.36E-07 | 7.26E-05 |
| REACTOME_DISEASE | 2.93E-07 | 8.19E-05 |
| TCGA_GLIOBLASTOMA_MUTATED | 3.09E-07 | 8.19E-05 |
| ***Significantly enriched Gene Ontology gene sets (c5)*** | ***P-value*** | ***FDR q-value*** |
| GO_PEPTIDYL_AMINO_ACID_MODIFICATION | 6.18E-11 | 5.38E-07 |
| GO_INTRINSIC_APOPTOTIC_SIGNALING_PATHWAY_BY_P53_CLASS_MEDIATOR | 1.06E-10 | 5.38E-07 |
| GO_NEGATIVE_REGULATION_OF_SIGNALING | 4.28E-10 | 1.45E-06 |
| GO_APOPTOTIC_SIGNALING_PATHWAY | 7.87E-10 | 2.00E-06 |
| GO_SIGNAL_TRANSDUCTION_BY_P53_CLASS_MEDIATOR | 1.31E-09 | 2.66E-06 |
| GO_GROWTH | 2.17E-09 | 3.46E-06 |
| GO_REGULATION_OF_CELLULAR_RESPONSE_TO_TRANSFORMING_GROWTH_FACTOR_BETA_STIMULUS | 2.37E-09 | 3.46E-06 |
| GO_DEVELOPMENTAL_GROWTH | 2.88E-09 | 3.67E-06 |
| GO_REGULATION_OF_PROTEIN_MODIFICATION_PROCESS | 3.80E-09 | 3.67E-06 |
| GO_REGULATION_OF_CELL_DIFFERENTIATION | 3.83E-09 | 3.67E-06 |
| GO_NEGATIVE_REGULATION_OF_TRANSCRIPTION_BY_RNA_POLYMERASE_II | 3.96E-09 | 3.67E-06 |
| GO_CELLULAR_RESPONSE_TO_ENDOGENOUS_STIMULUS | 4.73E-09 | 4.01E-06 |
| GO_TRANSCRIPTION_COREGULATOR_ACTIVITY | 5.66E-09 | 4.03E-06 |
| GO_NEGATIVE_REGULATION_OF_RESPONSE_TO_STIMULUS | 6.09E-09 | 4.03E-06 |
| GO_POSITIVE_REGULATION_OF_RNA_METABOLIC_PROCESS | 6.47E-09 | 4.03E-06 |
| GO_TRANSCRIPTION_COACTIVATOR_ACTIVITY | 6.86E-09 | 4.03E-06 |
| GO_TRANSCRIPTION_REGULATOR_ACTIVITY | 6.94E-09 | 4.03E-06 |
| GO_RESPONSE_TO_ENDOGENOUS_STIMULUS | 7.12E-09 | 4.03E-06 |
| GO_HEART_DEVELOPMENT | 8.22E-09 | 4.40E-06 |
| GO_REGULATION_OF_CELL_DEATH | 8.96E-09 | 4.40E-06 |
| ***Significantly enriched Hallmark gene sets (H)*** | ***P-value*** | ***FDR q-value*** |
| HALLMARK_INTERFERON_GAMMA_RESPONSE | 3.12E-05 | 7.81E-04 |
| HALLMARK_P53_PATHWAY | 3.12E-05 | 7.81E-04 |
| HALLMARK_WNT_BETA_CATENIN_SIGNALING | 2.61E-03 | 3.87E-02 |
| HALLMARK_APOPTOSIS | 3.09E-03 | 3.87E-02 |
| HALLMARK_ALLOGRAFT_REJECTION | 5.66E-03 | 4.05E-02 |
| HALLMARK_APICAL_JUNCTION | 5.66E-03 | 4.05E-02 |
| HALLMARK_E2F_TARGETS | 5.66E-03 | 4.05E-02 |

**Supplementary Table 10** *Focal copy number amplifications across 290 squamous cell carcinoma (**a**) and 69 non-squamous cell carcinomas (**b**).*

| ***Supplementary Table 10a Squamous cell carcinoma*** | | | | |
|---|---|---|---|---|
| ***Cytoband*** | ***Genomic region*** | ***Putative driver gene(s)*** | ***Comment*** | ***Reference(s)*** |
| **1q44** | chr1:244167131-244243575 | *AKT3* | | (32) |
| **3q28** | chr3:189647767-189660321 | *TP63* | | (33) |
| **4q12** | chr4:56093585-56222716 | *SRD5A3* | Overexpressed in prostate cancer. | (4) |
| **7p11.2** | chr7:55054805-55094029 | *EGFR* | | (34, 35) |
| **9p24.1** | chr9:5341593-5423103 | *CD274, PLGRKT, PDCD1LG2* | | (36, 37) |
| **11p12** | chr11:36320780-36962794 | *TRAF6* | | (38) |
| **11q13.3** | chr11:70189517-70370188 | *CTTN, PPFIA1* | CTTN is an amplification core in oral SCC correlated with PPFIA1. | (39) |
| **11q22.1** | chr11:101894838-101984747 | *YAP1, BIRC2, BIRC3* | | (40) |
| **12p12.1** | chr12:25240140-25784001 | *KRAS* | | (41, 42) |
| **13q22.1** | chr13:73953432-73954914 | *LINC00393, KLF5* | | (43, 44) |
| **17q25.1** | chr17:73270906-73289296 | *GRB2* | | (45) |
| **18p11.31** | chr18:3155700-3254846 | *TGIF1* | | (6, 7) |
| **19q13.13** | chr19:38373478-38390659 | *WDR87* | *Manuscript in preparation.* | |
| **19q13.32** | chr19:45253104-45256035 | *BCL3* | | (46) |
| **21q22.13** | chr21:38470347-38682147 | *VPS26C/DSCR3* | VPS26C/DSCR3 is a member of the Retriever complex for endosomal cargo cycling, required for HPV viral DNA to reach the nucleus. | (47) |
| ***Supplementary Table 10b Non-squamous cell carcinoma*** | | | | |
| ***Cytoband*** | ***Genomic Region*** | ***Putative driver gene(s)*** | ***Comment*** | ***Reference(s)*** |
| **3q26.2** | chr3:191370766-191372559 | *PYDC2* | Regulates inflammasome activation. | (48) |
| **7q36.3** | chr7:157696405-157700614 | *PTPRN2* | Tyrosine phosphatase receptor that promotes metastasis in breast cancer through actin remodeling. | (49) |
| **19q12** | chr19:29309499-30307451 | *CCNE1, PLEKHF1, POP4* | Inhibition of POP4, PLEKHF1, CCNE1 and TSZH3 lowers cell viability in cancer cells harboring their amplification. | (50) |
| | | | POP4 represses H3.3 chromatin assembly and promotes H3K9me3 and H3K27me3. | (51) |

**Supplementary Table 11** *Significantly enriched MSigDB Curated (c2), Gene Ontology (c5) and Hallmarks (H) gene sets within amplified and mutated SCC oncogenes.*

| ***Significantly enriched Curated gene sets (c2)*** | **P-value** | **FDR q-value** |
|---|---|---|
| KEGG_ERBB_SIGNALING_PATHWAY | 1.75E-13 | 6.36E-10 |
| KEGG_PATHWAYS_IN_CANCER | 2.30E-13 | 6.36E-10 |
| KEGG_ENDOMETRIAL_CANCER | 3.87E-13 | 7.12E-10 |
| SNIJDERS_AMPLIFIED_IN_HEAD_AND_NECK_TUMORS | 6.22E-12 | 8.60E-09 |
| REACTOME_SIGNALING_BY_ERBB2 | 4.20E-11 | 4.65E-08 |
| REACTOME_SHC1_EVENTS_IN_ERBB2_SIGNALING | 6.38E-11 | 5.35E-08 |
| KEGG_NON_SMALL_CELL_LUNG_CANCER | 6.80E-11 | 5.35E-08 |
| BIOCARTA_HER2_PATHWAY | 8.14E-11 | 5.35E-08 |
| REACTOME_NEGATIVE_REGULATION_OF_THE_PI3K_AKT_NETWORK | 8.71E-11 | 5.35E-08 |
| KEGG_DORSO_VENTRAL_AXIS_FORMATION | 1.03E-10 | 5.68E-08 |
| REACTOME_SIGNALING_BY_ERBB2_IN_CANCER | 1.59E-10 | 7.98E-08 |
| CHARAFE_BREAST_CANCER_LUMINAL_VS_BASAL_DN | 2.12E-10 | 9.75E-08 |
| KEGG_PANCREATIC_CANCER | 3.40E-10 | 1.45E-07 |
| DUTTA_APOPTOSIS_VIA_NFKB | 4.08E-10 | 1.50E-07 |
| PID_CD40_PATHWAY | 4.08E-10 | 1.50E-07 |
| KEGG_CHRONIC_MYELOID_LEUKEMIA | 4.40E-10 | 1.52E-07 |
| REACTOME_CYTOKINE_SIGNALING_IN_IMMUNE_SYSTEM | 4.77E-10 | 1.55E-07 |
| KEGG_SMALL_CELL_LUNG_CANCER | 1.04E-09 | 3.20E-07 |
| KEGG_PROSTATE_CANCER | 1.48E-09 | 4.31E-07 |
| KEGG_BLADDER_CANCER | 2.02E-09 | 5.40E-07 |
| ***Significantly enriched Gene Ontology gene sets (c5)*** | **P-value** | **FDR q-value** |
| GO_POSITIVE_REGULATION_OF_CELL_POPULATION_PROLIFERATION | 1.04E-15 | 1.06E-11 |
| GO_NEGATIVE_REGULATION_OF_CELL_DEATH | 6.45E-14 | 2.32E-10 |
| GO_REGULATION_OF_CELL_POPULATION_PROLIFERATION | 6.82E-14 | 2.32E-10 |
| GO_REGULATION_OF_CELL_DEATH | 9.48E-14 | 2.41E-10 |
| GO_POSITIVE_REGULATION_OF_MULTICELLULAR_ORGANISMAL_PROCESS | 2.04E-13 | 4.04E-10 |
| GO_TUBE_DEVELOPMENT | 2.38E-13 | 4.04E-10 |
| GO_REGULATION_OF_IMMUNE_SYSTEM_PROCESS | 5.95E-13 | 8.66E-10 |
| GO_POSITIVE_REGULATION_OF_RNA_METABOLIC_PROCESS | 8.85E-13 | 1.13E-09 |
| GO_REGULATION_OF_INTRACELLULAR_SIGNAL_TRANSDUCTION | 3.70E-12 | 3.65E-09 |
| GO_POSITIVE_REGULATION_OF_SIGNALING | 3.91E-12 | 3.65E-09 |
| GO_POSITIVE_REGULATION_OF_NUCLEOBASE_CONTAINING_COMPOUND_METABOLIC_PROCESS | 3.94E-12 | 3.65E-09 |
| GO_TUBE_MORPHOGENESIS | 4.73E-12 | 4.01E-09 |
| GO_POSITIVE_REGULATION_OF_CELLULAR_BIOSYNTHETIC_PROCESS | 1.09E-11 | 8.53E-09 |
| GO_TRANSCRIPTION_FACTOR_BINDING | 2.64E-11 | 1.92E-08 |
| GO_POSITIVE_REGULATION_OF_DEVELOPMENTAL_PROCESS | 1.15E-10 | 7.82E-08 |
| GO_POSITIVE_REGULATION_OF_TRANSCRIPTION_BY_RNA_POLYMERASE_II | 1.37E-10 | 8.75E-08 |
| GO_APOPTOTIC_SIGNALING_PATHWAY | 1.74E-10 | 1.05E-07 |
| GO_RESPONSE_TO_ABIOTIC_STIMULUS | 2.04E-10 | 1.16E-07 |
| GO_POSITIVE_REGULATION_OF_INTRACELLULAR_SIGNAL_TRANSDUCTION | 2.66E-10 | 1.43E-07 |
| GO_CELLULAR_RESPONSE_TO_DNA_DAMAGE_STIMULUS | 4.65E-10 | 2.37E-07 |
| ***Significantly enriched Hallmark gene sets (H)*** | **P-value** | **FDR q-value** |
| HALLMARK_TNFA_SIGNALING_VIA_NFKB | 1.89E-07 | 9.46E-06 |
| HALLMARK_APOPTOSIS | 1.80E-06 | 4.50E-05 |
| HALLMARK_UV_RESPONSE_DN | 3.24E-05 | 5.41E-04 |
| HALLMARK_APICAL_JUNCTION | 1.16E-04 | 1.16E-03 |
| HALLMARK_G2M_CHECKPOINT | 1.16E-04 | 1.16E-03 |
| HALLMARK_PI3K_AKT_MTOR_SIGNALING | 3.14E-04 | 2.62E-03 |
| HALLMARK_PROTEIN_SECRETION | 6.47E-03 | 4.62E-02 |

**Supplementary Table 12** *Significantly enriched MSigDB Curated (c2), Gene Ontology (c5) and Hallmarks (H) gene sets within amplified and mutated non-SCC oncogenes.*

| ***Significantly enriched Curated gene sets (c2)*** | **P-value** | **FDR q-value** |
|---|---|---|
| KEGG_PATHWAYS_IN_CANCER | 2.06E-10 | 7.85E-07 |
| LIN_MELANOMA_COPY_NUMBER_UP | 2.84E-10 | 7.85E-07 |
| CLIMENT_BREAST_CANCER_COPY_NUMBER_UP | 4.70E-10 | 8.67E-07 |
| CHIN_BREAST_CANCER_COPY_NUMBER_UP | 9.31E-10 | 1.29E-06 |
| REACTOME_INTERLEUKIN_4_AND_INTERLEUKIN_13_SIGNALING | 2.76E-09 | 3.05E-06 |
| REACTOME_CYTOKINE_SIGNALING_IN_IMMUNE_SYSTEM | 5.97E-09 | 5.50E-06 |
| KEGG_ENDOMETRIAL_CANCER | 1.42E-08 | 1.13E-05 |
| KEGG_PANCREATIC_CANCER | 4.80E-08 | 3.12E-05 |
| KEGG_MELANOMA | 5.08E-08 | 3.12E-05 |
| KEGG_CHRONIC_MYELOID_LEUKEMIA | 5.69E-08 | 3.14E-05 |
| KEGG_SMALL_CELL_LUNG_CANCER | 1.00E-07 | 5.05E-05 |
| REACTOME_PI3K_AKT_SIGNALING_IN_CANCER | 2.20E-07 | 1.01E-04 |
| REACTOME_NEGATIVE_REGULATION_OF_THE_PI3K_AKT_NETWORK | 2.98E-07 | 1.27E-04 |
| PID_CD40_PATHWAY | 5.38E-07 | 2.12E-04 |
| PID_IL2_PI3K_PATHWAY | 7.15E-07 | 2.64E-04 |
| REACTOME_DISEASES_OF_SIGNAL_TRANSDUCTION_BY_GROWTH_FACTOR_RECEPTORS_AND_SECOND_MESSENGERS | 1.17E-06 | 3.82E-04 |
| KEGG_JAK_STAT_SIGNALING_PATHWAY | 1.18E-06 | 3.82E-04 |
| NIKOLSKY_BREAST_CANCER_11Q12_Q14_AMPLICON | 1.27E-06 | 3.90E-04 |
| KEGG_BLADDER_CANCER | 1.37E-06 | 3.98E-04 |
| PID_IL6_7_PATHWAY | 1.93E-06 | 5.25E-04 |
| ***Significantly enriched Gene Ontology gene sets (c5)*** | **P-value** | **FDR q-value** |
| GO_POSITIVE_REGULATION_OF_CELL_POPULATION_PROLIFERATION | 1.43E-08 | 1.46E-04 |
| GO_POSITIVE_REGULATION_OF_EPITHELIAL_CELL_PROLIFERATION | 6.44E-08 | 3.19E-04 |
| GO_CYTOKINE_MEDIATED_SIGNALING_PATHWAY | 9.40E-08 | 3.19E-04 |
| GO_REGULATION_OF_CELL_POPULATION_PROLIFERATION | 1.22E-06 | 3.10E-03 |
| GO_RESPONSE_TO_CYTOKINE | 1.64E-06 | 3.34E-03 |
| GO_REGULATION_OF_INTRACELLULAR_SIGNAL_TRANSDUCTION | 2.25E-06 | 3.34E-03 |
| GO_POSITIVE_REGULATION_OF_SIGNALING | 2.31E-06 | 3.34E-03 |
| GO_EPITHELIAL_CELL_PROLIFERATION | 2.63E-06 | 3.34E-03 |
| GO_RESPONSE_TO_UV_A | 3.86E-06 | 4.37E-03 |
| GO_POSITIVE_REGULATION_OF_TRANSPORT | 7.94E-06 | 8.08E-03 |
| GO_REGULATION_OF_RESPONSE_TO_STRESS | 8.72E-06 | 8.08E-03 |
| GO_POSITIVE_REGULATION_OF_INTRACELLULAR_SIGNAL_TRANSDUCTION | 1.01E-05 | 8.17E-03 |
| GO_REGULATION_OF_PROTEIN_LOCALIZATION | 1.07E-05 | 8.17E-03 |
| GO_PROTEIN_KINASE_B_SIGNALING | 1.12E-05 | 8.17E-03 |
| GO_RESPONSE_TO_OXYGEN_CONTAINING_COMPOUND | 1.52E-05 | 1.03E-02 |
| GO_RESPONSE_TO_ABIOTIC_STIMULUS | 2.87E-05 | 1.77E-02 |
| GO_RESPONSE_TO_GROWTH_FACTOR | 3.03E-05 | 1.77E-02 |
| GO_POSITIVE_REGULATION_OF_CELL_DEATH | 3.13E-05 | 1.77E-02 |
| GO_REGULATION_OF_CELLULAR_RESPONSE_TO_STRESS | 3.43E-05 | 1.84E-02 |
| GO_NEGATIVE_REGULATION_OF_RELEASE_OF_CYTOCHROME_C_FROM_MITOCHONDRIA | 4.38E-05 | 2.23E-02 |
| ***Significantly enriched Hallmark gene sets (H)*** | **P-value** | **FDR q-value** |
| HALLMARK_APOPTOSIS | 7.82E-05 | 3.91E-03 |
| HALLMARK_ANDROGEN_RESPONSE | 1.24E-03 | 3.09E-02 |
| HALLMARK_UV_RESPONSE_DN | 2.54E-03 | 3.44E-02 |
| HALLMARK_IL2_STAT5_SIGNALING | 4.77E-03 | 3.44E-02 |
| HALLMARK_ESTROGEN_RESPONSE_EARLY | 4.82E-03 | 3.44E-02 |
| HALLMARK_G2M_CHECKPOINT | 4.82E-03 | 3.44E-02 |
| HALLMARK_TNFA_SIGNALING_VIA_NFKB | 4.82E-03 | 3.44E-02 |

**Supplementary Table 13** *Focal copy number deletions in 290 squamous cell carcinomas (**a**) and 69 non-squamous cell carcinomas (**b**).*

| ***Supplementary Table 13a Squamous cell carcinoma*** | | | | |
|---|---|---|---|---|
| ***Cytoband*** | ***Genomic region*** | ***Putative driver gene(s)*** | ***Comment*** | ***Reference(s)*** |
| **1p36.22** | chr1:10531619-10694040 | *PEX14* | | (52) |
| **1p13.2** | chr1:112912722-113195407 | *ST7L* | | (53) |
| **2q37.1** | chr2:233514309-233654381 | *EFHD1, GIGYF2* | EFHD1 has putative tumor suppressive properties in renal cell carcinoma. GIGYF2 is a translational repressor. | (54, 55) |
| **3p14.2** | chr3:59702821-61237398 | *FHIT* | | (56) |
| **4q21.3** | chr4:87511571-87737413 | *PTPN13* | Loss is associated with HPV-induced oncogenic cervical transformation, and expression is restored by curcumin treatment of cervical cancer cells. | (57, 58) |
| **4q22.1** | chr4:91039783-92523213 | *CCSER1* | Patel et al demonstrated that CCSER1 (aka FAM190A) deficient is associated with a cell division defect. | (13) |
| **5q11.2** | chr5:52391230-52416203 | *MOCS2, ITGA2* | Silencing of ITGA2 stimulates breast cancer cell migration | (59) |
| **6p24** | chr6:11077198-11084637 | *ELOVL2* | Tumor suppressive in breast cancer and neuroblastoma. | (60, 61) |
| **6q27** | chr6:168331594-168862574 | *KIF25, FRMD1, DACT2* | DACT2 is a tumor suppressor in colorectal cancer. | (62) |
| **8p23.1** | chr8:11278600-11332602 | *FAM167A* | | |
| **8p23.2** | chr8:2792739-4852925 | *CSMD1* | | (19) |
| **9p24.2** | chr9:2720219-2847114 | *KIAA0020, KCNV2* | | (63) |
| **11q25** | chr11:133766301-133768886 | *MIR4697* | | |
| **13q12.11** | chr13:19581842-19586754 | *LINC00442* | | |
| **13q14.11** | chr13:41482177-42387731 | *ELF1, KBTBD6, KBTBD7* | ELF1 is downregulated in prostate cancer. Decreased in metastasis and inhibits EMT. *KBTBD6/KBTBD7 d*epletion is associated with increased invasive potential. | (64, 65) |
| **13q14.2** | chr13:50105055-50160945 | *RCBTB1* | Deletion is associated with sarcoma metastasis and docetaxel resistance. | (66) |
| **16q12.1** | chr16:50903329-50904271 | *CYLD* | CYLD loss of function mutations are common in HPV-positive cylindroma-like basaloid carcinomas of the anus. | (67) |
| **16p13.3** | chr16:762953-797786 | *NARFL* | Cellular defense against hyperoxia-induced loss of sister chromatid cohesion. | (68) |
| **17q25.3** | chr17:80917016-80917016 | *METRNL* | METRNL regulates immune-adipose interactions and insulin resistance. | (69) |
| | | *FOXK2, ZNF750* | FOXK2 is a transcriptional repressor, which inhibits hypoxic response and suppresses breast cancer proliferation and invasion. | (70, 71) |
| **18q23** | chr18:74240503-74326105 | *LINC00908* | | (72) |
| **19q13.43** | chr19:56296582-56348438 | *NLRP11* | Targets TRAF6 for ubiquitination. | (73) |
| **Xp11.3** | chrX:44729855-44975013 | *KDM6A* | Inactivated in multiple cancers. | (29-31) |
| **Xq21.33** | chrX:95939469-96860054 | *RPA4* | Replication factor essential for DNA repair. RPA4 expression is decreased in cancerous tissues. | (74, 75) |

| ***Supplementary Table 13b Non-squamous carcinoma*** | | | | |
|---|---|---|---|---|
| ***Cytoband*** | ***Genomic Region*** | ***Putative driver gene(s)*** | ***Comment*** | ***Reference(s)*** |
| **1p36.32** | chr1:3218610-3400790 | *TP73, PRDM16* | Suppresses lung adenocarcinoma metastasis. | (76) |
| **2q37.3** | chr2:238534955-238724424 | *LRRFIP1* | Paradoxical; suggested to have oncogenic properties | (77) |
| **4q21.3** | chr4:87460995-87466631 | *MIR4452* | | |

| | | | | |
|---|---|---|---|---|
| **11q23.3** | chr11:117947433-119604854 | *PVRL1* | PVRL1 is a metastasis suppressor gene in melanoma. | (23) |
| **14q32.31** | chr14:102225526-102395370 | *PPP2R5C* | Dephosphorylates and activates p53. | (78) |
| **15q21.1** | chr15:45694421-45720715 | *SPATA5L1* | | |
| **16q12.2** | chr16:54952032-54978787 | *IRX5* | IRX5 deficiency facilitates growth of Wilms' tumors. | (79) |
| **18q21.2** | chr18:48492168-48616656 | *SMAD4* | Smad4/DPC4-mediated tumor suppression through suppression of angiogenesis. | (80) |
| **Xp22.31** | chrX:9101276-9103093 | *MIR4707, MIR4767* | Depletion through lncRNA sponging leads to suppression of apoptosis and promotion of cell migration in vascular endothelial cells. | (81, 82) |

**Supplementary Table 14** *Significantly enriched MSigDB Curated (c2), Gene Ontology (c5) and Hallmarks (H) gene sets within deleted and mutated SCC tumor suppressors.*

| **Significantly enriched Curated gene sets (c2)** | **P-value** | **FDR q-value** |
|---|---|---|
| TAKADA_GASTRIC_CANCER_COPY_NUMBER_DN | 9.64E-10 | 3.17E-06 |
| DACOSTA_UV_RESPONSE_VIA_ERCC3_DN | 1.15E-09 | 3.17E-06 |
| DER_IFN_BETA_RESPONSE_UP | 1.93E-08 | 3.55E-05 |
| GRESHOCK_CANCER_COPY_NUMBER_UP | 5.95E-08 | 8.22E-05 |
| KUROKAWA_LIVER_CANCER_EARLY_RECURRENCE_DN | 8.38E-08 | 9.27E-05 |
| DER_IFN_ALPHA_RESPONSE_UP | 1.49E-07 | 1.37E-04 |
| BIOCARTA_FAS_PATHWAY | 1.74E-07 | 1.38E-04 |
| LIN_MELANOMA_COPY_NUMBER_DN | 6.36E-07 | 3.80E-04 |
| REACTOME_ENDOSOMAL_VACUOLAR_PATHWAY | 6.88E-07 | 3.80E-04 |
| WUNDER_INFLAMMATORY_RESPONSE_AND_CHOLESTEROL_DN | 6.88E-07 | 3.80E-04 |
| KEGG_PATHWAYS_IN_CANCER | 1.07E-06 | 5.40E-04 |
| BIOCARTA_CTL_PATHWAY | 1.19E-06 | 5.48E-04 |
| BROWNE_HCMV_INFECTION_24HR_DN | 4.22E-06 | 1.79E-03 |
| DER_IFN_GAMMA_RESPONSE_UP | 5.88E-06 | 2.32E-03 |
| BIOCARTA_CTCF_PATHWAY | 8.31E-06 | 3.06E-03 |
| PID_P73PATHWAY | 9.01E-06 | 3.07E-03 |
| REACTOME_ANTIGEN_PRESENTATION_FOLDING_ASSEMBLY_AND_PEPTIDE_LOADING_OF_CLASS_I_MHC | 9.43E-06 | 3.07E-03 |
| DACOSTA_UV_RESPONSE_VIA_ERCC3_COMMON_DN | 1.01E-05 | 3.09E-03 |
| DING_LUNG_CANCER_MUTATED_SIGNIFICANTLY | 1.06E-05 | 3.10E-03 |
| KEGG_SMALL_CELL_LUNG_CANCER | 1.15E-05 | 3.15E-03 |
| ***Significantly enriched Gene Ontology gene sets (c5)*** | **P-value** | **FDR q-value** |
| GO_NEGATIVE_REGULATION_OF_RESPONSE_TO_STIMULUS | 1.33E-09 | 1.36E-05 |
| GO_NEGATIVE_REGULATION_OF_SIGNALING | 7.54E-09 | 3.84E-05 |
| GO_REGULATION_OF_RESPONSE_TO_STRESS | 2.44E-08 | 8.29E-05 |
| GO_GLAND_DEVELOPMENT | 4.05E-08 | 8.61E-05 |
| GO_REGULATION_OF_CELL_DIFFERENTIATION | 4.23E-08 | 8.61E-05 |
| GO_APOPTOTIC_SIGNALING_PATHWAY | 5.12E-08 | 8.70E-05 |
| GO_RESPONSE_TO_ABIOTIC_STIMULUS | 8.69E-08 | 1.19E-04 |
| GO_MESODERM_DEVELOPMENT | 9.30E-08 | 1.19E-04 |
| GO_EPITHELIUM_DEVELOPMENT | 1.51E-07 | 1.58E-04 |
| GO_DIGESTIVE_SYSTEM_DEVELOPMENT | 1.55E-07 | 1.58E-04 |
| GO_REGULATION_OF_PHOSPHORUS_METABOLIC_PROCESS | 1.87E-07 | 1.73E-04 |
| GO_REGULATION_OF_PHOSPHORYLATION | 2.97E-07 | 2.53E-04 |
| GO_REGULATION_OF_APOPTOTIC_SIGNALING_PATHWAY | 3.52E-07 | 2.68E-04 |
| GO_REGULATORY_REGION_NUCLEIC_ACID_BINDING | 4.23E-07 | 2.68E-04 |
| GO_POSITIVE_REGULATION_OF_DEVELOPMENTAL_PROCESS | 4.56E-07 | 2.68E-04 |
| GO_EMBRYONIC_MORPHOGENESIS | 5.22E-07 | 2.68E-04 |
| GO_POSITIVE_REGULATION_OF_APOPTOTIC_SIGNALING_PATHWAY | 5.31E-07 | 2.68E-04 |
| GO_POSITIVE_REGULATION_OF_RNA_METABOLIC_PROCESS | 5.49E-07 | 2.68E-04 |
| GO_CELLULAR_RESPONSE_TO_ENDOGENOUS_STIMULUS | 5.58E-07 | 2.68E-04 |
| GO_IMMUNE_SYSTEM_DEVELOPMENT | 5.72E-07 | 2.68E-04 |
| **Significantly enriched Hallmark gene sets (H)** | **P-value** | **FDR q-value** |
| HALLMARK_INTERFERON_GAMMA_RESPONSE | 2.00E-05 | 1.00E-03 |
| HALLMARK_INTERFERON_ALPHA_RESPONSE | 5.56E-04 | 1.39E-02 |
| HALLMARK_UV_RESPONSE_DN | 1.74E-03 | 2.90E-02 |
| HALLMARK_APOPTOSIS | 2.39E-03 | 2.99E-02 |
| HALLMARK_ALLOGRAFT_REJECTION | 4.39E-03 | 3.14E-02 |
| HALLMARK_APICAL_JUNCTION | 4.39E-03 | 3.14E-02 |
| HALLMARK_P53_PATHWAY | 4.39E-03 | 3.14E-02 |

**Supplementary Table 15** *Significantly mutated gene sets within deleted and mutated non-SCC tumor suppressors.*

| **Significantly enriched Curated gene sets (c2)** | **P-value** | **FDR q-value** |
|---|---|---|
| REACTOME_RNA_POLYMERASE_II_TRANSCRIPTION | 3.51E-07 | 1.94E-03 |
| DING_LUNG_CANCER_MUTATED_SIGNIFICANTLY | 8.92E-07 | 2.47E-03 |
| TCGA_GLIOBLASTOMA_COPY_NUMBER_DN | 1.54E-06 | 2.84E-03 |
| LIN_MELANOMA_COPY_NUMBER_DN | 3.63E-06 | 5.02E-03 |
| TCGA_GLIOBLASTOMA_MUTATED | 1.43E-05 | 1.58E-02 |
| HELLEBREKERS_SILENCED_DURING_TUMOR_ANGIOGENESIS | 2.45E-05 | 2.26E-02 |
| DING_LUNG_CANCER_MUTATED_FREQUENTLY | 3.37E-05 | 2.66E-02 |
| FLECHNER_BIOPSY_KIDNEY_TRANSPLANT_REJECTED_VS_OK_DN | 4.54E-05 | 3.14E-02 |
| ***Significantly enriched Gene Ontology gene sets (c5)*** | **P-value** | **FDR q-value** |
| GO_CELL_MORPHOGENESIS_INVOLVED_IN_DIFFERENTIATION | 8.57E-07 | 3.19E-03 |
| GO_NEURON_DEVELOPMENT | 9.06E-07 | 3.19E-03 |
| GO_CELLULAR_COMPONENT_MORPHOGENESIS | 1.08E-06 | 3.19E-03 |
| GO_POSITIVE_REGULATION_OF_CELLULAR_RESPONSE_TO_TRANSFORMING_GROWTH_FACTOR_BETA_STIMULUS | 1.25E-06 | 3.19E-03 |
| GO_CAMERA_TYPE_EYE_MORPHOGENESIS | 1.69E-06 | 3.45E-03 |
| GO_CELL_MORPHOGENESIS_INVOLVED_IN_NEURON_DIFFERENTIATION | 3.69E-06 | 5.28E-03 |
| GO_NEURON_DIFFERENTIATION | 4.11E-06 | 5.28E-03 |
| GO_EYE_MORPHOGENESIS | 4.14E-06 | 5.28E-03 |
| GO_CELLULAR_RESPONSE_TO_ENDOGENOUS_STIMULUS | 6.54E-06 | 7.21E-03 |
| GO_NEGATIVE_REGULATION_OF_CELL_DEATH | 7.07E-06 | 7.21E-03 |
| GO_CELL_PART_MORPHOGENESIS | 8.93E-06 | 8.27E-03 |
| GO_NEUROGENESIS | 1.47E-05 | 1.18E-02 |
| GO_REPRODUCTIVE_SYSTEM_DEVELOPMENT | 1.51E-05 | 1.18E-02 |
| GO_CIRCULATORY_SYSTEM_DEVELOPMENT | 1.66E-05 | 1.21E-02 |
| GO_NEGATIVE_REGULATION_OF_PROTEIN_METABOLIC_PROCESS | 1.79E-05 | 1.22E-02 |
| GO_NEGATIVE_REGULATION_OF_RESPONSE_TO_STIMULUS | 2.06E-05 | 1.31E-02 |
| GO_RESPONSE_TO_ENDOGENOUS_STIMULUS | 2.22E-05 | 1.33E-02 |
| GO_CELL_GROWTH | 2.39E-05 | 1.35E-02 |
| GO_AXON_DEVELOPMENT | 3.49E-05 | 1.83E-02 |
| GO_SENSORY_ORGAN_MORPHOGENESIS | 3.59E-05 | 1.83E-02 |

**Supplementary Table 16 a-c** *Focal copy number amplifications across tumors with "TpC-predominant" (n=245) (**a**), "CpG-predominant" (n=87) (**b**) and "Other" (n=39) (**c**) mutations signatures.*

***Supplementary Table 16a TpC-predominant tumors***

| Cytoband | Genomic region | Putative driver gene(s) | Comment | Reference(s) |
|---|---|---|---|---|
| **1q21.3** | chr1:151300377 - 151331927 | *RFX5* | Transcriptional activator in hepatocellular carcinoma. | (2, 3) |
| **1p31.3** | chr1:61831890 - 61932604 | *NFIA* | | (1) |
| **2q33.1** | chr2:201314735 - 201352739 | *SPATS2L* | | (83) |
| **3q26.2** | chr3:170766695 - 170820725 | *TNIK* | TNIK inhibition abrogates colorectal cancer stemness. | (84) |
| **5p15.33** | chr5:914233 - 1020354 | *TERT* | | (85) |
| **9p24.1** | chr9:5341593 - 5423103 | *CD274, PLGRKT, PDCD1LG2* | | (42, 86) |
| **11q22.2** | chr11:102666106 - 102676891 | *MMP1* | Prognostic in cervical cancer. | (87) |
| **11p13** | chr11:35244643 - 35257677 | *CD44* | | (42, 88) |
| **11q13.3** | chr11:69873977 - 69989793 | *ANO1, CCND1* | | (89, 90) |
| **12p12.1** | chr12:25939146 - 26114034 | *KRAS* | | (41, 42) |
| **13q22.1** | chr13:73953432 - 73954914 | *LINC00393, KLF5* | | (42, 43) |
| **16p13.13** | chr16:11901466 - 11913383 | *BCAR4* | | (42) |
| **17q25.1** | chr17:73270906 - 73296953 | *GRB2* | | (45) |
| **18p11.31** | chr18:3155700 - 3254846 | *TGIF1* | | (6, 7) |
| **19q13.13** | chr19:38373478 - 38390659 | *WDR87* | *Manuscript in preparation.* | |

***Supplementary Table 16b CpG-predominant tumors***

| Cytoband | Genomic region | Putative driver gene(s) | Comment | Reference(s) |
|---|---|---|---|---|
| **3q26.31** | chr3:172093535 - 172160428 | *FNDC3B, GHSR* | Induces EMT; upregulated in cervical cancer. | (91, 92) |
| **4q12** | chr4:56003117 - 56400995 | *SRD5A3* | Overexpressed in prostate cancer. | (4) |
| **17q25.3** | chr17:80648318 - 80648857 | *RAB40B* | GTPase that facilitates breast cancer cell invasion. | (93) |
| **14q12** | chr14:31364669 - 32080009 | *NUBPL* | Induces ENT in colorectal cancer. | (94) |
| **19p13.2** | chr19:11080491 - 11101731 | *SMARCA4* | | (95) |

***Supplementary Table 16c 'Other'-subset tumors***

| Cytoband | Genomic region | Putative driver gene(s) | Comment | Reference(s) |
|---|---|---|---|---|
| **3q26.33** | chr3:181377182 - 181479964 | *SOX2* | | (96) |
| **20q11.21** | chr20:31558283 - 31680334 | *BPIFB2* | Has higher expression in gastric carcinomas with high stromal score and is associated with resistance to PD1/PDL1 immunotherapy. | (97) |
| **21q22.13** | chr21:38450795 - 38682147 | *VPS26C* | VPS26C is a member of the Retriever complex for endosomal cargo cycling, required for HPV viral DNA to reach the nucleus, suggesting it can facilitate HPV-driven oncogenesis. | (47) |

**Supplementary Table 17** *Significantly enriched MSigDB Curated (c2), Gene Ontology (c5) and Hallmarks (H) gene sets within amplified genes found in TpC-, but not CpC-predominant tumors.*

| ***Significantly enriched Curated gene sets (c2)*** | **P-value** | **FDR q-value** |
|---|---|---|
| BIOCARTA_TEL_PATHWAY | 8.20E-10 | 3.59E-06 |
| PROVENZANI_METASTASIS_DN | 1.50E-09 | 3.59E-06 |
| KEGG_GLIOMA | 1.95E-09 | 3.59E-06 |
| KEGG_DORSO_VENTRAL_AXIS_FORMATION | 3.65E-09 | 5.04E-06 |
| NOJIMA_SFRP2_TARGETS_DN | 5.13E-09 | 5.67E-06 |
| KEGG_PATHWAYS_IN_CANCER | 6.44E-09 | 5.93E-06 |
| KEGG_PROSTATE_CANCER | 9.66E-09 | 7.63E-06 |
| KEGG_BLADDER_CANCER | 3.80E-08 | 2.10E-05 |
| REACTOME_EGFR_TRANSACTIVATION_BY_GASTRIN | 3.99E-08 | 2.10E-05 |
| REACTOME_SHC_RELATED_EVENTS_TRIGGERED_BY_IGF1R | 3.99E-08 | 2.10E-05 |
| ZHU_CMV_ALL_DN | 4.18E-08 | 2.10E-05 |
| KEGG_ENDOMETRIAL_CANCER | 9.15E-08 | 4.22E-05 |
| KEGG_NON_SMALL_CELL_LUNG_CANCER | 1.07E-07 | 4.54E-05 |
| PID_SHP2_PATHWAY | 1.33E-07 | 5.26E-05 |
| BARIS_THYROID_CANCER_DN | 1.53E-07 | 5.60E-05 |
| OZANNE_AP1_TARGETS_UP | 1.72E-07 | 5.60E-05 |
| REACTOME_SHC1_EVENTS_IN_EGFR_SIGNALING | 1.72E-07 | 5.60E-05 |
| REACTOME_CONSTITUTIVE_SIGNALING_BY_EGFRVIII | 2.15E-07 | 6.61E-05 |
| REACTOME_GRB2_EVENTS_IN_ERBB2_SIGNALING | 2.65E-07 | 6.97E-05 |
| REACTOME_SIGNALING_BY_ERBB2_ECD_MUTANTS | 2.65E-07 | 6.97E-05 |
| ***Significantly enriched Gene Ontology gene sets (c5)*** | **P-value** | **FDR q-value** |
| GO_POSITIVE_REGULATION_OF_CELL_POPULATION_PROLIFERATION | 1.21E-10 | 1.23E-06 |
| GO_NEGATIVE_REGULATION_OF_TRANSCRIPTION_BY_RNA_POLYMERASE_II | 1.76E-08 | 8.97E-05 |
| GO_RESPONSE_TO_OXYGEN_CONTAINING_COMPOUND | 4.56E-08 | 1.29E-04 |
| GO_REGULATION_OF_CELL_POPULATION_PROLIFERATION | 5.08E-08 | 1.29E-04 |
| GO_POSITIVE_REGULATION_OF_SIGNALING | 1.21E-07 | 2.36E-04 |
| GO_NEGATIVE_REGULATION_OF_NUCLEOBASE_CONTAINING_COMPOUND_METABOLIC_PROCESS | 1.39E-07 | 2.36E-04 |
| GO_POSITIVE_REGULATION_OF_MITOTIC_CELL_CYCLE | 2.07E-07 | 3.02E-04 |
| GO_CELLULAR_RESPONSE_TO_DNA_DAMAGE_STIMULUS | 2.95E-07 | 3.26E-04 |
| GO_CELLULAR_RESPONSE_TO_OXYGEN_CONTAINING_COMPOUND | 3.16E-07 | 3.26E-04 |
| GO_RESPONSE_TO_CYTOKINE | 3.20E-07 | 3.26E-04 |
| GO_REGULATION_OF_CELL_CYCLE | 3.53E-07 | 3.27E-04 |
| GO_CELL_CELL_SIGNALING | 4.39E-07 | 3.73E-04 |
| GO_NEGATIVE_REGULATION_OF_RNA_BIOSYNTHETIC_PROCESS | 5.13E-07 | 4.02E-04 |
| GO_EPITHELIUM_DEVELOPMENT | 5.69E-07 | 4.04E-04 |
| GO_RESPONSE_TO_ENDOGENOUS_STIMULUS | 5.95E-07 | 4.04E-04 |
| GO_POSITIVE_REGULATION_OF_CELL_CYCLE | 6.36E-07 | 4.05E-04 |
| GO_REGULATION_OF_MITOTIC_CELL_CYCLE | 8.20E-07 | 4.49E-04 |
| GO_DOUBLE_STRANDED_DNA_BINDING | 8.25E-07 | 4.49E-04 |
| GO_TRANSCRIPTION_FACTOR_BINDING | 8.37E-07 | 4.49E-04 |
| GO_POSITIVE_REGULATION_OF_INTRACELLULAR_SIGNAL_TRANSDUCTION | 1.15E-06 | 5.88E-04 |
| ***Significantly enriched Hallmark gene sets (H)*** | **P-value** | **FDR q-value** |
| HALLMARK_APOPTOSIS | 2.98E-04 | 4.68E-03 |
| HALLMARK_NOTCH_SIGNALING | 3.08E-04 | 4.68E-03 |
| HALLMARK_IL2_STAT5_SIGNALING | 5.54E-04 | 4.68E-03 |
| HALLMARK_EPITHELIAL_MESENCHYMAL_TRANSITION | 5.62E-04 | 4.68E-03 |
| HALLMARK_ESTROGEN_RESPONSE_EARLY | 5.62E-04 | 4.68E-03 |
| HALLMARK_TNFA_SIGNALING_VIA_NFKB | 5.62E-04 | 4.68E-03 |
| HALLMARK_IL6_JAK_STAT3_SIGNALING | 2.26E-03 | 1.61E-02 |
| HALLMARK_PI3K_AKT_MTOR_SIGNALING | 3.27E-03 | 2.04E-02 |
| HALLMARK_UV_RESPONSE_DN | 6.05E-03 | 3.36E-02 |
| HALLMARK_APICAL_JUNCTION | 1.14E-02 | 4.06E-02 |
| HALLMARK_ESTROGEN_RESPONSE_LATE | 1.14E-02 | 4.06E-02 |
| HALLMARK_G2M_CHECKPOINT | 1.14E-02 | 4.06E-02 |
| HALLMARK_GLYCOLYSIS | 1.14E-02 | 4.06E-02 |
| HALLMARK_KRAS_SIGNALING_UP | 1.14E-02 | 4.06E-02 |

**Supplementary Table 18** *Significantly enriched MSigDB Curated (c2), Gene Ontology (c5) and Hallmarks (H) gene sets within amplified genes found in TpC-predominant, but not in the 'Other'-subset tumors.*

| ***Significantly enriched Curated gene sets (c2)*** | **P-value** | **FDR q-value** |
|---|---|---|
| BIOCARTA_TEL_PATHWAY | 9.37E-10 | 4.25E-06 |
| PROVENZANI_METASTASIS_DN | 1.84E-09 | 4.25E-06 |
| KEGG_GLIOMA | 2.31E-09 | 4.25E-06 |
| KEGG_DORSO_VENTRAL_AXIS_FORMATION | 4.17E-09 | 5.76E-06 |
| NOJIMA_SFRP2_TARGETS_DN | 5.86E-09 | 6.48E-06 |
| KEGG_PATHWAYS_IN_CANCER | 8.18E-09 | 7.54E-06 |
| KEGG_PROSTATE_CANCER | 1.14E-08 | 9.03E-06 |
| KEGG_BLADDER_CANCER | 4.34E-08 | 2.43E-05 |
| REACTOME_EGFR_TRANSACTIVATION_BY_GASTRIN | 4.40E-08 | 2.43E-05 |
| REACTOME_SHC_RELATED_EVENTS_TRIGGERED_BY_IGF1R | 4.40E-08 | 2.43E-05 |
| ZHU_CMV_ALL_DN | 4.94E-08 | 2.48E-05 |
| KEGG_ENDOMETRIAL_CANCER | 1.04E-07 | 4.81E-05 |
| KEGG_NON_SMALL_CELL_LUNG_CANCER | 1.22E-07 | 5.18E-05 |
| PID_SHP2_PATHWAY | 1.52E-07 | 6.00E-05 |
| BARIS_THYROID_CANCER_DN | 1.75E-07 | 6.18E-05 |
| OZANNE_AP1_TARGETS_UP | 1.90E-07 | 6.18E-05 |
| REACTOME_SHC1_EVENTS_IN_EGFR_SIGNALING | 1.90E-07 | 6.18E-05 |
| REACTOME_CONSTITUTIVE_SIGNALING_BY_EGFRVIII | 2.37E-07 | 7.29E-05 |
| REACTOME_GRB2_EVENTS_IN_ERBB2_SIGNALING | 2.92E-07 | 7.69E-05 |
| REACTOME_SIGNALING_BY_ERBB2_ECD_MUTANTS | 2.92E-07 | 7.69E-05 |
| ***Significantly enriched Gene Ontology gene sets (c5)*** | **P-value** | **FDR q-value** |
| GO_POSITIVE_REGULATION_OF_CELL_POPULATION_PROLIFERATION | 7.93E-12 | 8.08E-08 |
| GO_NEGATIVE_REGULATION_OF_TRANSCRIPTION_BY_RNA_POLYMERASE_II | 1.24E-09 | 6.34E-06 |
| GO_REGULATION_OF_CELL_POPULATION_PROLIFERATION | 5.98E-09 | 2.03E-05 |
| GO_NEGATIVE_REGULATION_OF_NUCLEOBASE_CONTAINING_COMPOUND_METABOLIC_PROCESS | 1.53E-08 | 3.16E-05 |
| GO_POSITIVE_REGULATION_OF_SIGNALING | 1.55E-08 | 3.16E-05 |
| GO_CELLULAR_RESPONSE_TO_DNA_DAMAGE_STIMULUS | 2.31E-08 | 3.92E-05 |
| GO_NEGATIVE_REGULATION_OF_RNA_BIOSYNTHETIC_PROCESS | 5.40E-08 | 6.00E-05 |
| GO_CELL_CELL_SIGNALING | 5.47E-08 | 6.00E-05 |
| GO_EPITHELIUM_DEVELOPMENT | 6.06E-08 | 6.00E-05 |
| GO_REPRODUCTIVE_SYSTEM_DEVELOPMENT | 6.39E-08 | 6.00E-05 |
| GO_RESPONSE_TO_OXYGEN_CONTAINING_COMPOUND | 6.68E-08 | 6.00E-05 |
| GO_DOUBLE_STRANDED_DNA_BINDING | 7.38E-08 | 6.00E-05 |
| GO_RESPONSE_TO_ENDOGENOUS_STIMULUS | 7.65E-08 | 6.00E-05 |
| GO_REPRODUCTION | 1.80E-07 | 1.31E-04 |
| GO_POSITIVE_REGULATION_OF_MITOTIC_CELL_CYCLE | 2.45E-07 | 1.66E-04 |
| GO_MORPHOGENESIS_OF_AN_EPITHELIUM | 2.73E-07 | 1.74E-04 |
| GO_SEQUENCE_SPECIFIC_DNA_BINDING | 3.74E-07 | 2.24E-04 |
| GO_CELLULAR_RESPONSE_TO_OXYGEN_CONTAINING_COMPOUND | 4.27E-07 | 2.32E-04 |
| GO_RESPONSE_TO_CYTOKINE | 4.33E-07 | 2.32E-04 |
| GO_REGULATION_OF_CELL_CYCLE | 4.77E-07 | 2.43E-04 |
| ***Significantly enriched Hallmark gene sets (H)*** | **P-value** | **FDR q-value** |
| HALLMARK_APOPTOSIS | 3.28E-04 | 5.14E-03 |
| HALLMARK_NOTCH_SIGNALING | 3.28E-04 | 5.14E-03 |
| HALLMARK_IL2_STAT5_SIGNALING | 6.08E-04 | 5.14E-03 |
| HALLMARK_EPITHELIAL_MESENCHYMAL_TRANSITION | 6.17E-04 | 5.14E-03 |
| HALLMARK_ESTROGEN_RESPONSE_EARLY | 6.17E-04 | 5.14E-03 |
| HALLMARK_TNFA_SIGNALING_VIA_NFKB | 6.17E-04 | 5.14E-03 |
| HALLMARK_IL6_JAK_STAT3_SIGNALING | 2.41E-03 | 1.72E-02 |
| HALLMARK_PI3K_AKT_MTOR_SIGNALING | 3.48E-03 | 2.18E-02 |
| HALLMARK_UV_RESPONSE_DN | 6.43E-03 | 3.57E-02 |
| HALLMARK_APICAL_JUNCTION | 1.21E-02 | 4.31E-02 |
| HALLMARK_ESTROGEN_RESPONSE_LATE | 1.21E-02 | 4.31E-02 |
| HALLMARK_G2M_CHECKPOINT | 1.21E-02 | 4.31E-02 |
| HALLMARK_GLYCOLYSIS | 1.21E-02 | 4.31E-02 |
| HALLMARK_KRAS_SIGNALING_UP | 1.21E-02 | 4.31E-02 |

**Supplementary Table 19 a-*c*** *Focal copy number deletions across tumors with "TpC-predominant" (n=245) (**a**), "CpG-predominant" (n=87) (**b**) and "Other" (n=39) (**c**) mutations signatures.*

| ***Supplementary Table 19a Tp*C-predominant tumors*** | | | | |
|---|---|---|---|---|
| ***Cytoband*** | ***Genomic region*** | ***Putative driver gene(s)*** | ***Comment*** | ***Reference(s)*** |
| **1p13.2** | chr1:112912722 - 113195407 | *ST7L* | | (53) |
| **1p36.22** | chr1:12225351 - 12269707 | *MIR4632, TNFRSF1B* | Possibly paradoxical; TNFRSF1B has oncogenic properties in several cancer types | (98) |
| **2q37.1** | chr2:234825559 - 234929559 | *SH3BP4* | Negative regulator of mTORC1 signaling and inhibits beta-catenin nuclear localization | (99, 100) |
| **2q37.3** | chr2:239748320 - 240337482 | *TWIST2* | Tumor suppressor in murine osteosarcoma. Activates p21 in AML. | (101, 102) |
| **4q21.3** | chr4:87511571 - 87737413 | *PTPN13* | Loss is associated with HPV-induced oncogenic cervical transformation. Expression can by restored by curcumin treatment of cervical cancer cells. | (57, 58) |
| **4q35.2** | chr4:187508513 - 187652260 | *FAT1* | | (42) |
| **5q31.1** | chr5:131817027 - 131827191 | *IRF1* | | (103) |
| **5q35.2** | chr5:175082112 - 175113539 | *HRH2* | | (104) |
| **6p25.3** | chr6:1309918 - 1315309 | *FOXQ1* | Possibly paradoxical; FOXQ1 has oncogenic properties in several cancer types | (18) |
| **6q25.3** | chr6:157775999 - 158099269 | *ZDHHC14* | | (105) |
| **7q31.1** | chr7:110239721 - 111353361 | *LRRN3* | | |
| **7q36.1** | chr7:151830319 - 152135594 | *KMT2C* | | (106) |
| **11p15.1** | chr11:19371907 - 20143721 | *E2F8* | | (107, 108) |
| **11q23.3** | chr11:119492338 - 119604854 | *PVRL1* | PVRL1 is a metastasis suppressor gene in melanoma. | (23) |
| **11q25** | chr11:133708065 - 133768886 | *MIR4697* | | |
| **13q13.3** | chr13:37389687 - 37404660 | *RFXAP* | | (109) |
| **14q32.31** | chr14:102972764 - 103011886 | *ANKRD9* | | (110) |
| **15q15.1** | chr15:42138456 - 42186351 | *MIR4310* | Negative transcriptional regulator of MMP-10 which promotes cervical cancer progression. | (26, 27) |
| **16q11.2** | chr16:31850299 - 46615362 | *ZNF267, TP53TG3, TP53TG3D, TP53TG3C, TP53TG3B* | Induced by TP53. | (28) |
| **16q24.1** | chr16:86506106 - 86555873 | *FENDRR, FOXF1* | lncRNA FENDRR inhibits progression of lung cancer, colon cancer, and cholangiocarcinoma. | (111-115) |
| **17p12** | chr17:11921944 - 12047931 | *MIR744, MAP2K4* | Possibly paradoxical; MAP2K4 in an oncogene in breast cancer. | (116) |
| **17q25.3** | chr17:80917016 - 80917016 | *METRNL FOXK2, ZNF750* | METRNL regulates immune-adipose interactions and insulin resistance. FOXK2 is a transcriptional repressor, which inhibits hypoxic response and suppresses breast cancer proliferation and invasion. | (69, 71) |
| **18q23** | chr18:74240503 - 74326105 | *LINC00908* | | (72) |
| **19q13.41** | chr19:52766328 - 52795985 | *MIR643* | | (117) |
| **20p12.1** | chr20:13974549 - 16036115 | *MACROD2, FLRT3* | | (118) |
| **21q11.2** | chr21:15347621 - 15372509 | *ANKRD20A11P* | | |
| **22q13.31** | chr22:46505806 - 46511645 | *MIRLET7A3, MIRLET7B* | | (119, 120) |

| | | | | |
|---|---|---|---|---|
| **Xp11.3** | chrX:44729855 - 44975013 | *KDM6A* | Inactivated in multiple cancers. | (29-31) |
| **Xp21.1** | chrX:30873422 - 34033463 | *DMD* | | (121) |
| **Xq21.33** | chrX:95939469 - 96860054 | *RPA4* | Replication factor essential for DNA repair; RPA4 expression is decreased in cancerous tissues. | (74, 75) |

***Supplementary Table 19b *CpG-predominant tumors***

| ***Cytoband*** | ***Genomic region*** | ***Putative driver gene(s)*** | ***Comment*** | ***Reference(s)*** |
|---|---|---|---|---|
| **1p36.22** | chr1:10531619 - 10694040 | *PEX14* | | (52) |
| **2q37.3** | chr2:23839114 3 - 238466356 | *RAB17* | | (122) |
| **3p14.1** | chr3:69152593 - 69186319 | *ARL6IP5* | | (123) |
| **4q22.1** | chr4:91039783 - 92523213 | *CCSER1* | Patel et al demonstrated that CCSER1 (aka FAM190A) deficient is associated with a cell division defect. | (18) |
| **4q35.2** | chr4:18876224 0 - 188762240 | *TRIML2* | | (124) |
| **5q12.1** | chr5:58261529-59818040 | *PDE4D* | | |
| **5q12.1** | chr5:58261529-59818040 | *PDE4D* | Although thought to have pro-cancer properties, PDE4D deletions have been observed in multiple tumor types. | (14, 15) |
| **7q31.33** | chr7:12605852 2 - 126898623 | *GRM8* | | (125) |
| **7p22.3** | chr7:762577 - 832985 | *PRKAR1B* | | (126) |
| **11q24.1** | chr11:1233957 13 - 123502821 | *GRAMD1B* | | (127) |
| **11q25** | chr11:1312398 04 - 132208428 | *NTM, OPCML* | NTM belongs to the IgLON family of GPI-anchored cell adhesion molecules, which is part of the immunoglobulin (Ig) domain-containing superfamily. | (24) |
| **11q14.2** | chr11:8580323 8 - 85805593 | *PICALM, EED* | EED is a context-dependent tumor-suppressor in KRAS-driven lung cancer. | (21, 22) |
| **13q14.2** | chr13:5010505 5 - 50160945 | *RCBTB1* | Deletion is associated with sarcoma metastasis and docetaxel resistance. | (66) |
| **18p11.32** | chr18:2846246 - 2916005 | *EMILIN2* | | (128) |
| *18q21.2* | *chr18:4849216 8 - 48616656* | *SMAD4* | *Smad4/DPC4-mediated tumor suppression through suppression of angiogenesis.* | *(80)* |
| **19q13.11** | chr19:3428334 0 - 34308164 | *KCTD15* | | (129) |

***Supplementary Table 19c 'Other'-subset tumors***

| **Cytoband** | **Genomic region** | **Putative driver gene(s)** | **Comment** | **Reference(s)** |
|---|---|---|---|---|
| **1p36.32** | chr1:3218610 - 3819336 | *TP73, PRDM16* | PRDM16 suppresses lung adenocarcinoma metastasis. | (76) |
| **2q37.1** | chr2:233034495 - 233048132 | *MIR562* | A putative role of miR-562 as the tumor suppressor in the 2q37.1 deletion peak in Wilms' tumors. | (10) |
| **4q35.2** | chr4:187383890 - 187479257 | *MTNR1A* | Paradoxical; oncogene in gastric adenocarcinoma. | (130) |
| **5q12.1** | chr5:60621045 - 60842284 | *ZSWIM6* | | |
| **7p22.3** | chr7:762577 - 832985 | *PRKAR1B* | | (126) |
| **8p23.3** | chr8:42933372 - 47460945 | *CSMD1* | | (19) |
| **11q14.1** | chr11:78363072 - 79153837 | *TENM4* | | (131) |
| **13q12.11** | chr13:19520887 - 19643178 | *LINC00442* | | |
| **15q21.1** | chr15:47474882 - 48066582 | *COPS2, SEMA6D* | | (132) |
| **17p13.3** | chr17:3118733 - 3119871 | *RAP1GAP2* | | (133) |

**Supplementary Table 20** *DNA repair pathway genes*

| **Supplementary Table 20a.** *276 curated DNA repair pathway genes from Knijnenburg et al 2018* **.** | | | |
|---|---|---|---|
| *AEN* | *FANCF* | *PARPBP* | *RNMT* |
| *ALKBH1* | *FANCG* | *PAXIP1* | *RPA1* |
| *ALKBH2* | *FANCI* | *PCNA* | *RPA2* |
| *ALKBH3* | *FANCL* | *PER1* | *RPA3* |
| *APEX1* | *FANCM* | *PLK3* | *RPA4* |
| *APEX2* | *FEN1* | *PLRG1* | *RRM1* |
| *APITD1* | *GADD45A* | *PMS1* | *RRM2* |
| *APLF* | *GADD45G* | *PMS2* | *RRM2B* |
| *APTX* | *GEN1* | *PNKP* | *RTEL1* |
| *ASCC3* | *GTF2H1* | *POLA1* | *SETMAR* |
| *ATM* | *GTF2H2* | *POLB* | *SHFM1* |
| *ATR* | *GTF2H3* | *POLD1* | *SHPRH* |
| *ATRIP* | *GTF2H4* | *POLD2* | *SLX1A* |
| *ATRX* | *GTF2H5* | *POLD3* | *SLX1B* |
| *BABAM1* | *H2AFX* | *POLD4* | *SLX4* |
| *BARD1* | *HELQ* | *POLE* | *SMARCA4* |
| *BCAS2* | *HERC2* | *POLE2* | *SMARCAD1* |
| *BLM* | *HES1* | *POLE3* | *SMARCC1* |
| *BRCA1* | *HFM1* | *POLE4* | *SMC5* |
| *BRCA2* | *HLTF* | *POLG* | *SMC6* |
| *BRCC3* | *HMGB1* | *POLH* | *SMUG1* |
| *BRE* | *HMGB2* | *POLI* | *SOX4* |
| *BRIP1* | *HUS1* | *POLK* | *SPO11* |
| *CCNH* | *IDH1* | *POLL* | *SPRTN* |
| *CDC25A* | *INO80* | *POLM* | *STRA13* |
| *CDC25B* | *KAT5* | *POLN* | *SWI5* |
| *CDC25C* | *LIG1* | *POLQ* | *SWSAP1* |
| *CDC5L* | *LIG3* | *PPP4C* | *TCEA1* |
| *CDK7* | *LIG4* | *PPP4R1* | *TCEB1* |
| *CETN2* | *MAD2L2* | *PPP4R2* | *TCEB2* |
| *CHAF1A* | *MBD4* | *PPP4R4* | *TCEB3* |
| *CHEK1* | *MDC1* | *PRKDC* | *TDG* |
| *CHEK2* | *MGMT* | *PRPF19* | *TDP1* |
| *CLK2* | *MLH1* | *PTEN* | *TDP2* |
| *CUL3* | *MLH3* | *RAD1* | *TELO2* |
| *CUL4A* | *MMS19* | *RAD17* | *TOP3A* |
| *CUL5* | *MNAT1* | *RAD18* | *TOP3B* |
| *DCLRE1A* | *MORF4L1* | *RAD23A* | *TOPBP1* |
| *DCLRE1B* | *MPG* | *RAD23B* | *TP53* |
| *DCLRE1C* | *MPLKIP* | *RAD50* | *TP53BP1* |
| *DDB1* | *MRE11A* | *RAD51* | *TREX1* |
| *DDB2* | *MRPL40* | *RAD51B* | *TREX2* |
| *DMC1* | *MSH2* | *RAD51C* | *TTK* |
| *DNA2* | *MSH3* | *RAD51D* | *TYMS* |
| *DNTT* | *MSH6* | *RAD52* | *UBE2A* |
| *DUT* | *MUS81* | *RAD54B* | *UBE2B* |
| *EID3* | *MUTYH* | *RAD54L* | *UBE2N* |
| *EME1* | *NABP2* | *RAD9A* | *UBE2T* |
| *EME2* | *NBN* | *RAD9B* | *UBE2V2* |
| *ENDOV* | *NEIL1* | *RBBP8* | *UIMC1* |
| *ERCC1* | *NEIL2* | *RBX1* | *UNG* |
| *ERCC2* | *NEIL3* | *RDM1* | *USP1* |
| *ERCC3* | *NFATC2IP* | *RECQL* | *UVSSA* |
| *ERCC4* | *NHEJ1* | *RECQL4* | *WDR48* |
| *ERCC5* | *NSMCE1* | *RECQL5* | *WEE1* |
| *ERCC6* | *NSMCE2* | *REV1* | *WRN* |
| *ERCC8* | *NSMCE3* | *REV3L* | *XAB2* |
| *EXO1* | *NSMCE4A* | *RFC1* | *XPA* |
| *EXO5* | *NTHL1* | *RFC2* | *XPC* |
| *FAAP100* | *NUDT1* | *RFC3* | *XRCC1* |
| *FAAP20* | *NUDT15* | *RFC4* | *XRCC2* |
| *FAAP24* | *NUDT18* | *RFC5* | *XRCC3* |
| *FAM175A* | *OGG1* | *RIF1* | *XRCC4* |
| *FAN1* | *PALB2* | *RMI1* | *XRCC5* |
| *FANCA* | *PARG* | *RMI2* | *XRCC6* |
| *FANCB* | *PARP1* | *RNF168* | *YWHAB* |
| *FANCC* | *PARP2* | *RNF169* | *YWHAE* |
| *FANCD2* | *PARP3* | *RNF4* | *YWHAG* |
| *FANCE* | *PARP4* | *RNF8* | *ZSWIM7* |

| **Supplementary Table 20b.** *255 DNA repair pathway overlapping with the Mutational allelic frequency (MAF) file* **.** | | | |
|---|---|---|---|
| *AEN* | *GADD45G* | *POLD1* | *SMARCC1* |
| *ALKBH1* | *GEN1* | *POLD2* | *SMC5* |
| *ALKBH2* | *GTF2H1* | *POLD3* | *SMC6* |
| *ALKBH3* | *GTF2H2* | *POLD4* | *SMUG1* |
| *APEX1* | *GTF2H3* | *POLE* | *SOX4* |
| *APEX2* | *GTF2H4* | *POLE2* | *SPO11* |
| *APITD1* | *GTF2H5* | *POLE3* | *STRA13* |
| *APLF* | *H2AFX* | *POLE4* | *TCEA1* |
| *APTX* | *HELQ* | *POLG* | *TCEB1* |
| *ASCC3* | *HERC2* | *POLH* | *TCEB2* |
| *ATM* | *HES1* | *POLI* | *TCEB3* |
| *ATR* | *HFM1* | *POLK* | *TDG* |
| *ATRIP* | *HLTF* | *POLL* | *TDP1* |
| *ATRX* | *HMGB1* | *POLM* | *TDP2* |
| *BARD1* | *HMGB2* | *POLN* | *TELO2* |
| *BCAS2* | *HUS1* | *POLQ* | *TOP3A* |
| *BLM* | *IDH1* | *PPP4C* | *TOP3B* |
| *BRCA1* | *INO80* | *PPP4R1* | *TOPBP1* |
| *BRCA2* | *KAT5* | *PPP4R2* | *TP53* |
| *BRCC3* | *LIG1* | *PPP4R4* | *TP53BP1* |
| *BRE* | *LIG3* | *PRKDC* | *TREX1* |
| *BRIP1* | *LIG4* | *PRPF19* | *TREX2* |
| *CCNH* | *MAD2L2* | *PTEN* | *TTK* |
| *CDC25A* | *MBD4* | *RAD1* | *TYMS* |
| *CDC25B* | *MDC1* | *RAD17* | *UBE2A* |
| *CDC25C* | *MGMT* | *RAD18* | *UBE2B* |
| *CDC5L* | *MLH1* | *RAD23A* | *UBE2N* |
| *CDK7* | *MLH3* | *RAD23B* | *UBE2T* |
| *CETN2* | *MMS19* | *RAD50* | *UBE2V2* |
| *CHAF1A* | *MNAT1* | *RAD51* | *UIMC1* |
| *CHEK1* | *MORF4L1* | *RAD51C* | *UNG* |
| *CHEK2* | *MPG* | *RAD52* | *USP1* |
| *CLK2* | *MRE11A* | *RAD54B* | *WDR48* |
| *CUL3* | *MRPL40* | *RAD54L* | *WEE1* |
| *CUL4A* | *MSH2* | *RAD9A* | *WRN* |
| *CUL5* | *MSH3* | *RAD9B* | *XAB2* |
| *DCLRE1A* | *MSH6* | *RBBP8* | *XPA* |
| *DCLRE1B* | *MUS81* | *RBX1* | *XPC* |
| *DCLRE1C* | *MUTYH* | *RDM1* | *XRCC1* |
| *DDB1* | *NBN* | *RECQL* | *XRCC2* |
| *DDB2* | *NEIL1* | *RECQL4* | *XRCC3* |
| *DMC1* | *NEIL2* | *RECQL5* | *XRCC4* |
| *DNA2* | *NEIL3* | *REV1* | *XRCC5* |
| *DNTT* | *NFATC2IP* | *REV3L* | *XRCC6* |
| *DUT* | *NHEJ1* | *RFC1* | *YWHAB* |
| *EID3* | *NSMCE1* | *RFC2* | *YWHAE* |
| *EME1* | *NSMCE2* | *RFC3* | *YWHAG* |
| *EME2* | *NSMCE4A* | *RFC4* | *ZSWIM7* |
| *ERCC1* | *NTHL1* | *RFC5* | |
| *ERCC2* | *NUDT1* | *RIF1* | |
| *ERCC3* | *NUDT15* | *RMI1* | |
| *ERCC4* | *NUDT18* | *RNF168* | |
| *ERCC5* | *OGG1* | *RNF169* | |
| *ERCC6* | *PALB2* | *RNF4* | |
| *ERCC8* | *PARG* | *RNF8* | |
| *EXO1* | *PARP1* | *RNMT* | |
| *FAM175A* | *PARP2* | *RPA1* | |
| *FANCA* | *PARP3* | *RPA2* | |
| *FANCB* | *PARP4* | *RPA3* | |
| *FANCC* | *PAXIP1* | *RPA4* | |
| *FANCD2* | *PCNA* | *RRM1* | |
| *FANCE* | *PER1* | *RRM2* | |
| *FANCF* | *PLK3* | *RRM2B* | |
| *FANCG* | *PLRG1* | *RTEL1* | |
| *FANCI* | *PMS1* | *SETMAR* | |
| *FANCL* | *PMS2* | *SHFM1* | |
| *FANCM* | *PNKP* | *SHPRH* | |
| *FEN1* | *POLA1* | *SMARCA4* | |
| *GADD45A* | *POLB* | *SMARCAD1* | |

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