Supplemental Figures and Figure Legends

Figure S1

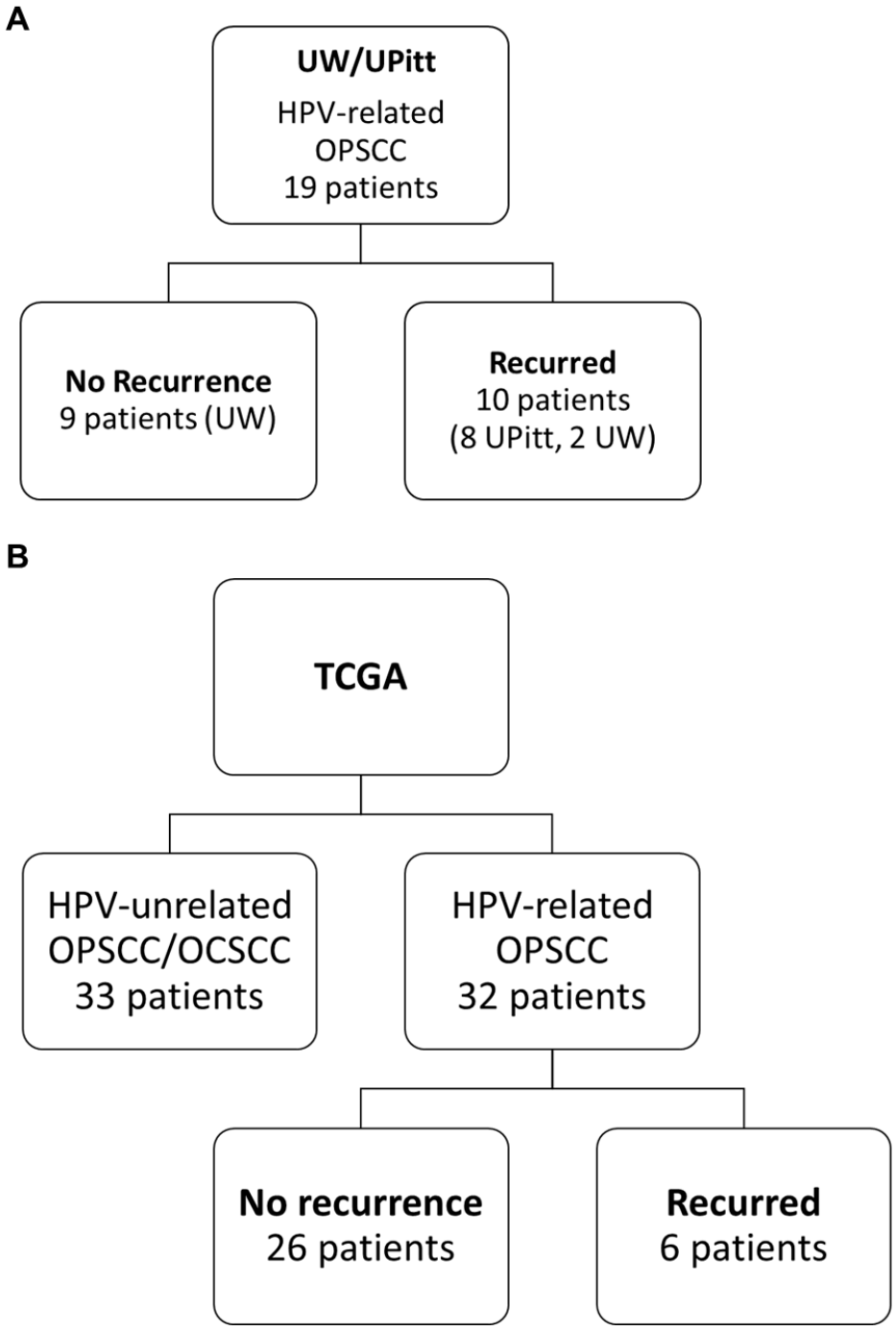

Figure S1 Legend

Figure S1. Study subjects. *A*, UW and UPitt primary HPV-related OPSCC tumors that did or did not recur. *B*, TCGA dataset primary HPV-related OPSCC tumors that did or did not recur.

Figure S2

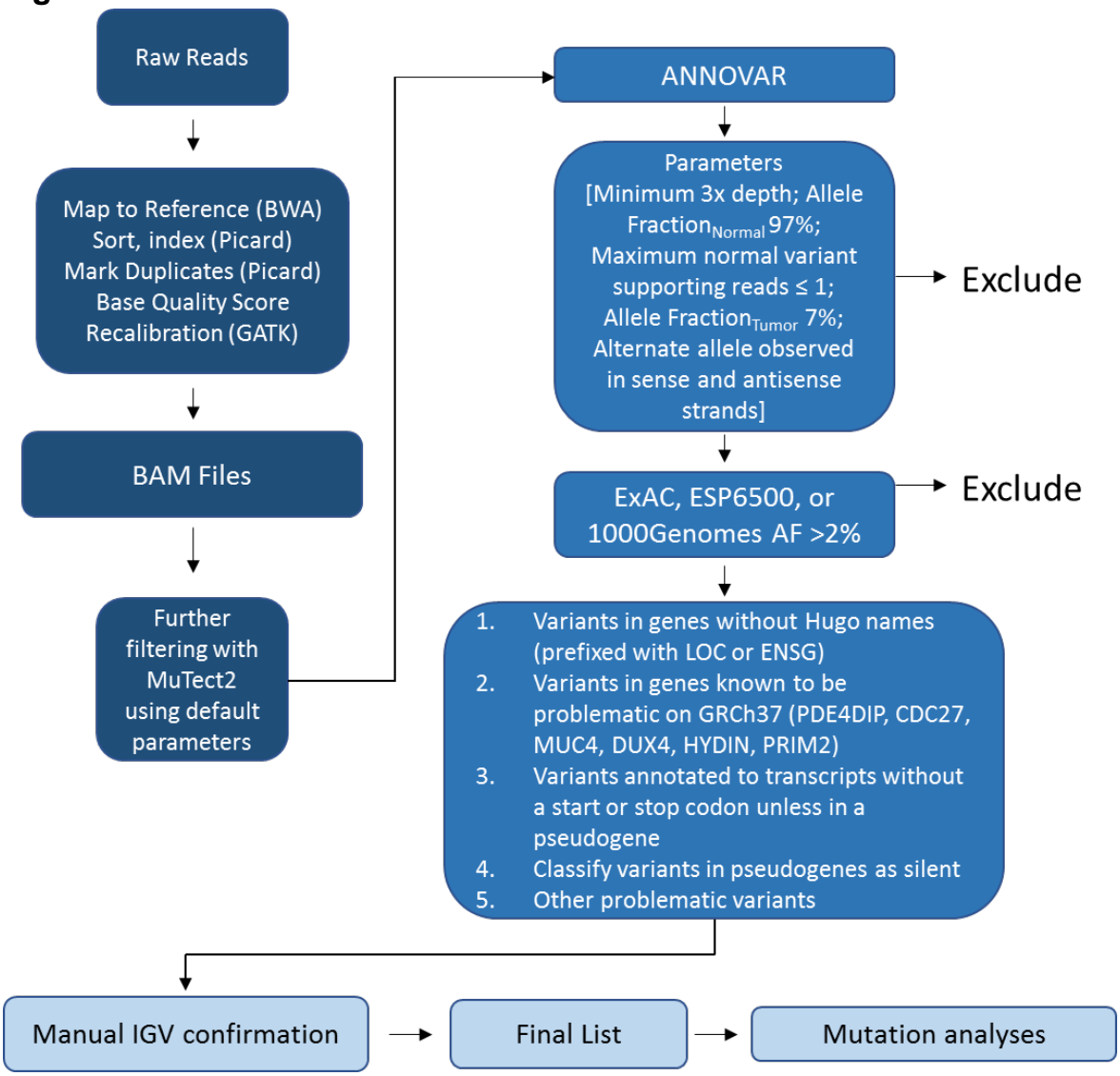

Figure S2 Legend

Figure S2. Mutation data curation methodology. Raw whole exome sequencing reads were generated and filtered to reduce false positive variants. A final list of variants was curated for statistical analyses.

Figure S3

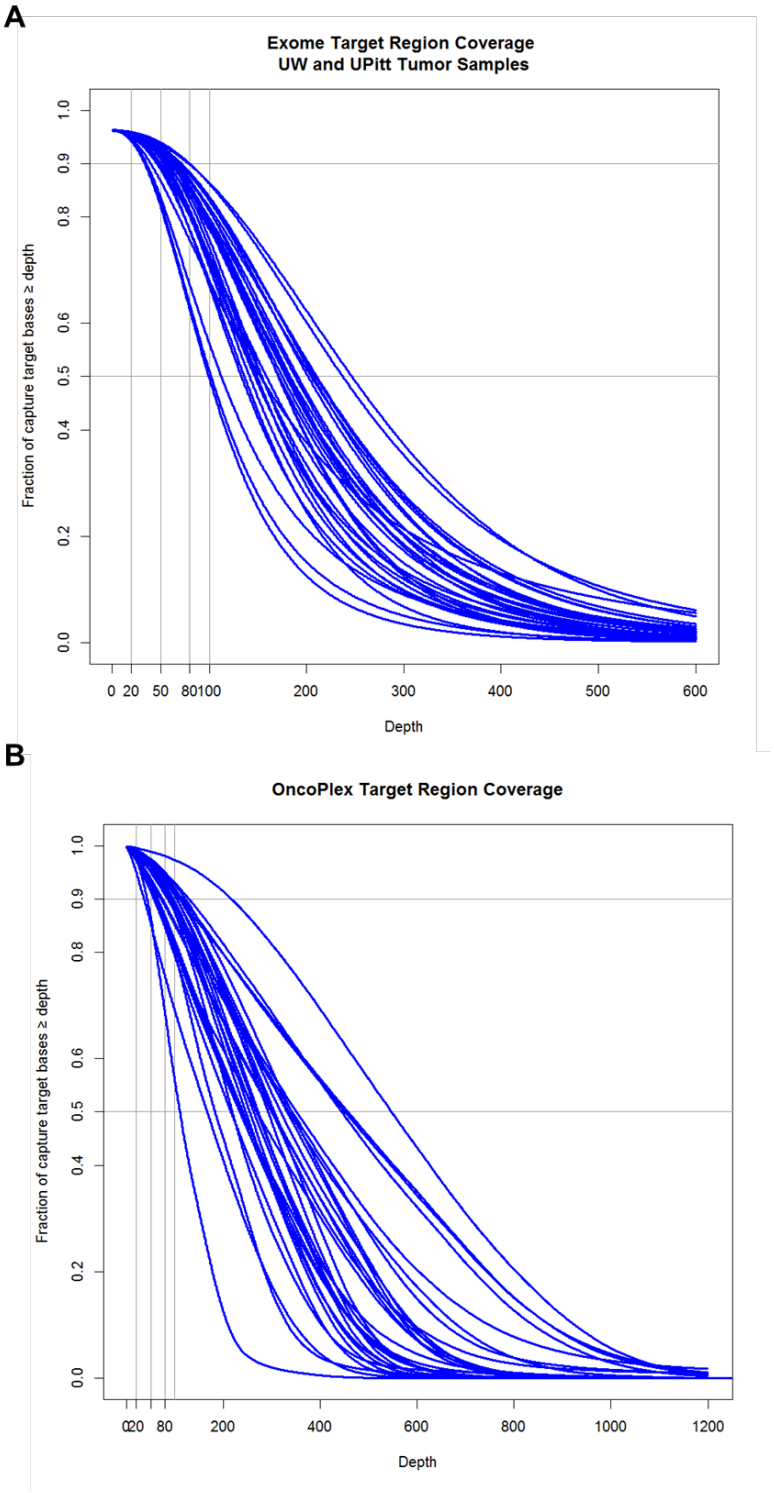

Figure S3 Legend

Figure S3. Whole exome and OncoPlex target region coverage for UW and UPitt samples. *A*, Whole exome sequencing target region coverage. *B*, OncoPlex multiplexed sequencing assay target region coverage.

Figure S4

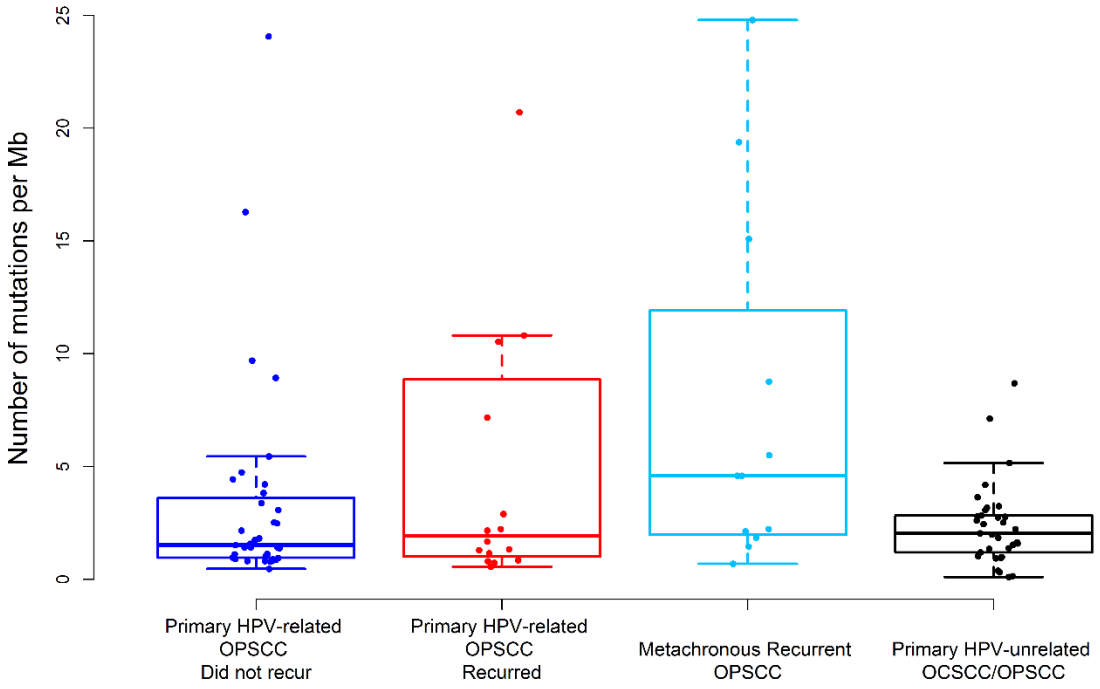

Figure S4 Legend

Figure S4. Mutational burden among primary HPV-related and unrelated and metachronous recurrent tumors. The median (IQR) mutations per Mb was 1.52 (2.65) and 1.91 (6.94) among the primary HPV-related OPSCCs that did not recur (n = 35, *blue boxes and points*) or did recur (n = 16, *red boxes and points*), respectively. Mutations per Mb was 4.59 (8.29) for metachronous recurrent OPSCCs (n = 12, *green boxes and points*) and 2.03 (1.64) for primary HPV-unrelated OCSCCs and OPSCCs (n = 33, *black boxes and points*). Mutations per Mb were greater among metachronous recurrent tumors compared to HPV-unrelated tumors (*FDR q-value* = 0.10, Dunn test) or primary HPV-related OPSCCs that did not recur (*FDR q-value* = 0.13, Dunn test). *OPSCC*, oropharyngeal squamous cell carcinoma. *OCSCC*, oral cavity squamous cell carcinoma.

Figure S5

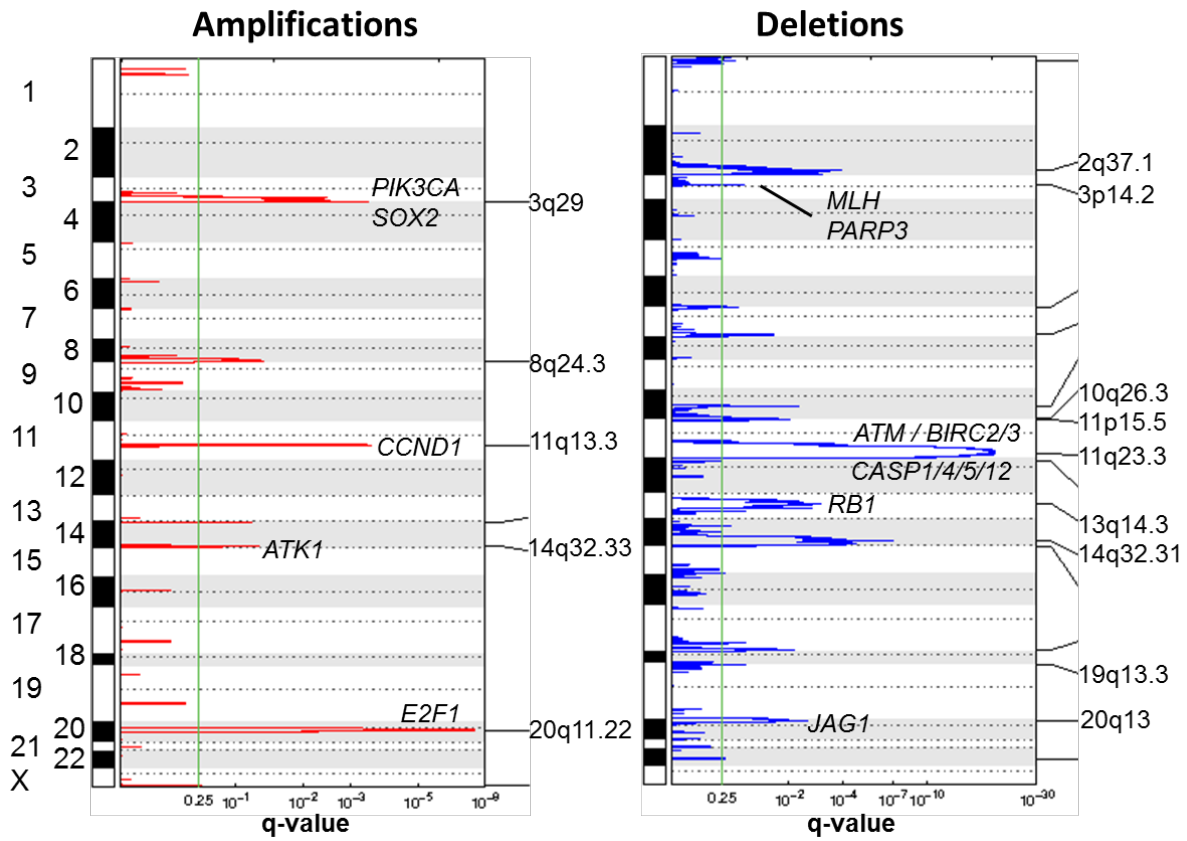

Figure S5 Legend

Figure S5. GISTIC2.0 significant amplifications or deletions across all primary HPV-related OPSCs. Significant amplifications or deletions are depicted on the left or right, respectively. Selected genes are annotated on respective cytobands. *Green line*, significance threshold (*FDR q-value* = 0.25).

Figure S6

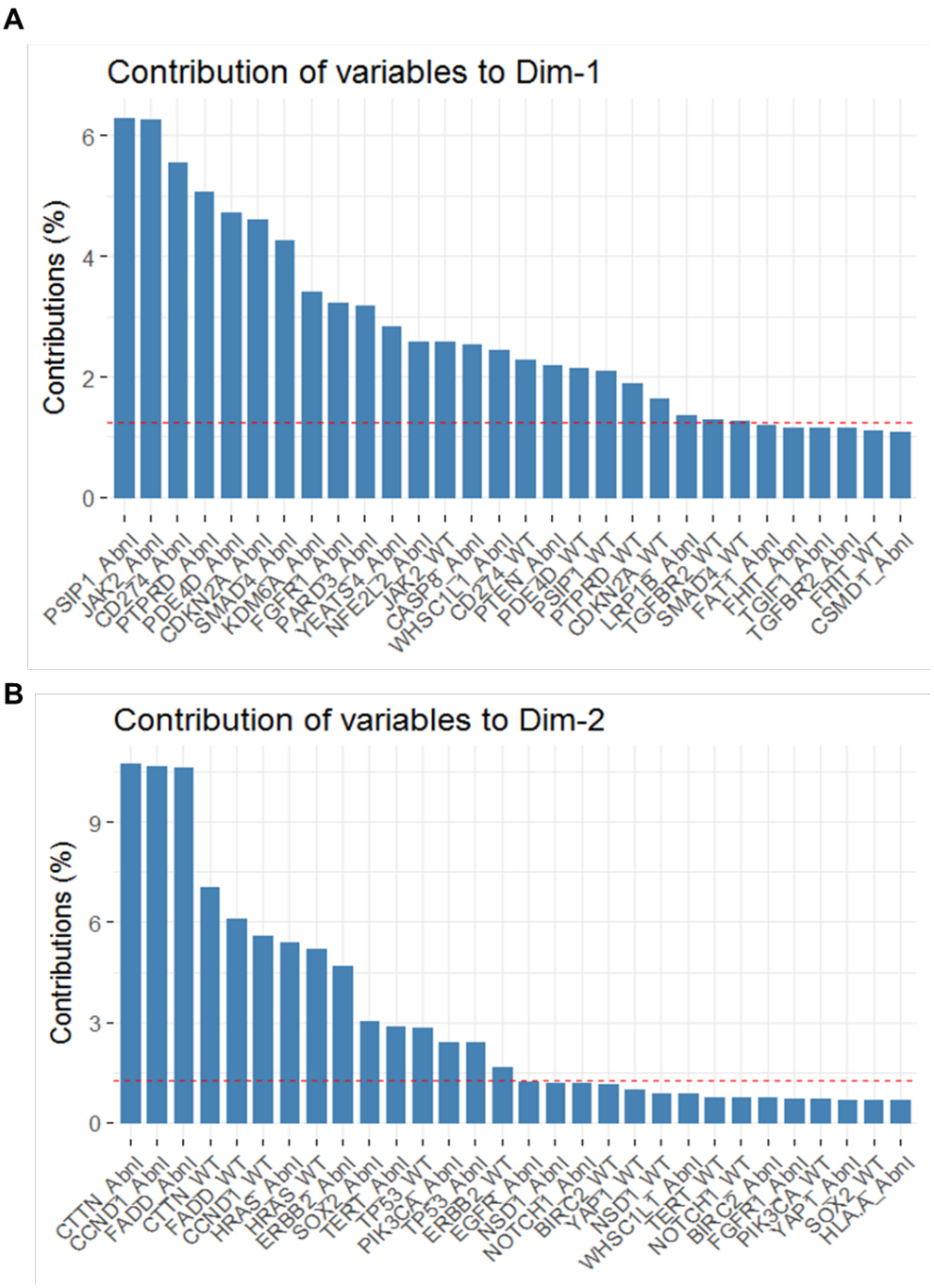

Figure S6 Legend

Figure S6. Contribution of variance to first and second dimensions of multiple correspondence analysis (MCA). Percent contribution to the overall variance encompassed by the first (*A*) and second (*B*) dimensions of the MCA plot analyzing genomic aberrations between primary HPV-related OPSCCs that did or did not recur, metachronous recurrent OPSCCs and HPV-unrelated OCSCC and OPSCCs. Dashed red line at 1.25% represents the expected average contribution

if the variable categories were uniform (1/number of categories = 1/80 = 1.25%). Gene with (*Abnl*) or without (*WT*) somatic mutation and/or copy number variant.

Figure S7

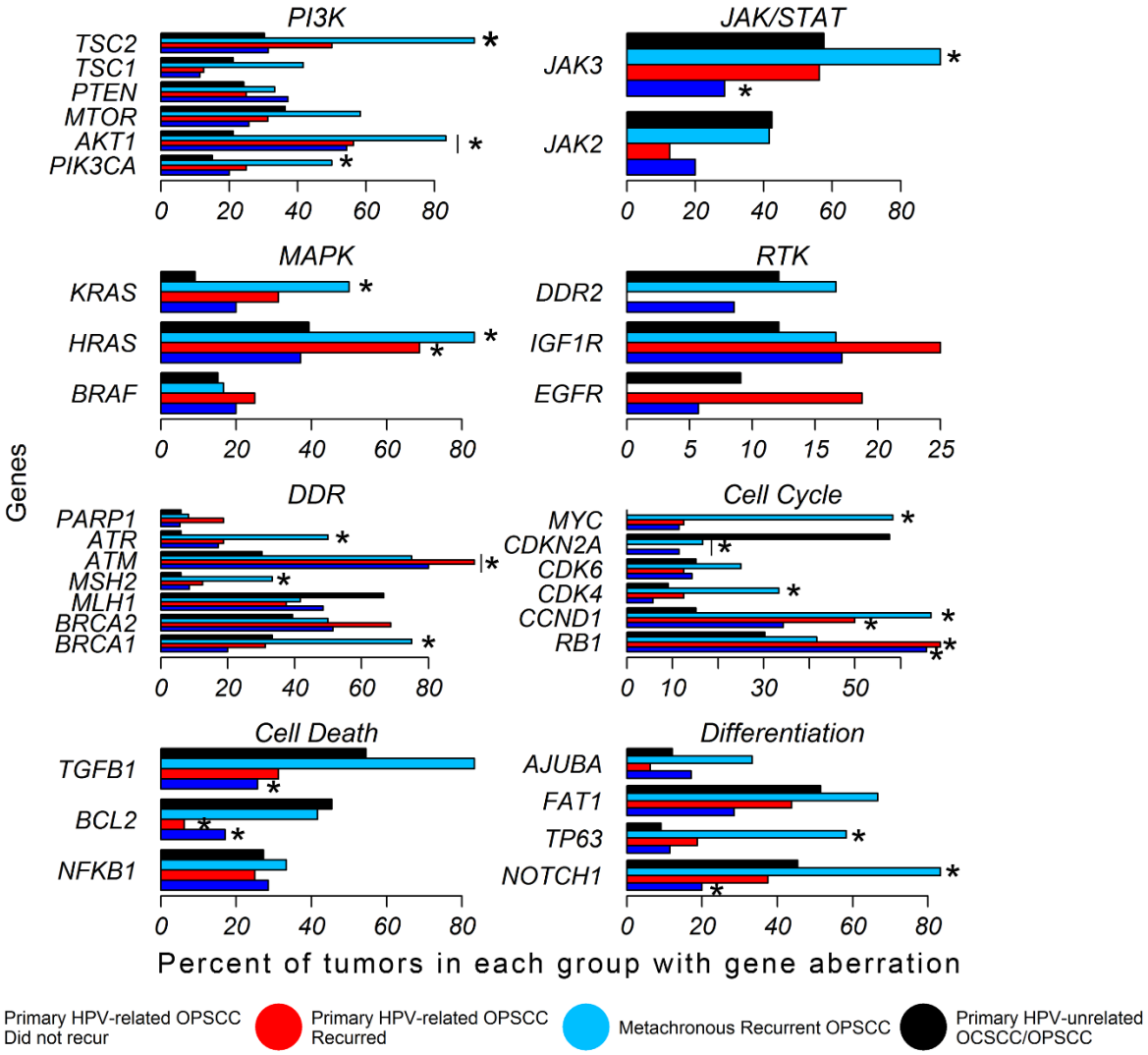

Figure S7 Legend

Figure S7. Selection of potentially actionable genes for a given pathway. Blue boxes and points represent primary HPV-related OPSCCs that did not recur, and red boxes and points represent primary HPV-related OPSCCs that did recur. Metachronous recurrent OPSCCs are illustrated in green. TCGA HPV-unrelated OCSCC and OPSCCs are represented in black. *RTK*, receptor tyrosine kinase. *DDR*, DNA damage repair. Percent of tumors with genomic aberration for the given gene illustrated on x-axis. Genes are on the y-axis. Asterisks,*, illustrate statistically significant differences comparing the HPV-related OPSCC groups against the HPV-unrelated OCSCC / OPSCCs (*FDR q-value* < 0.1, Fisher exact test)

Figure S8

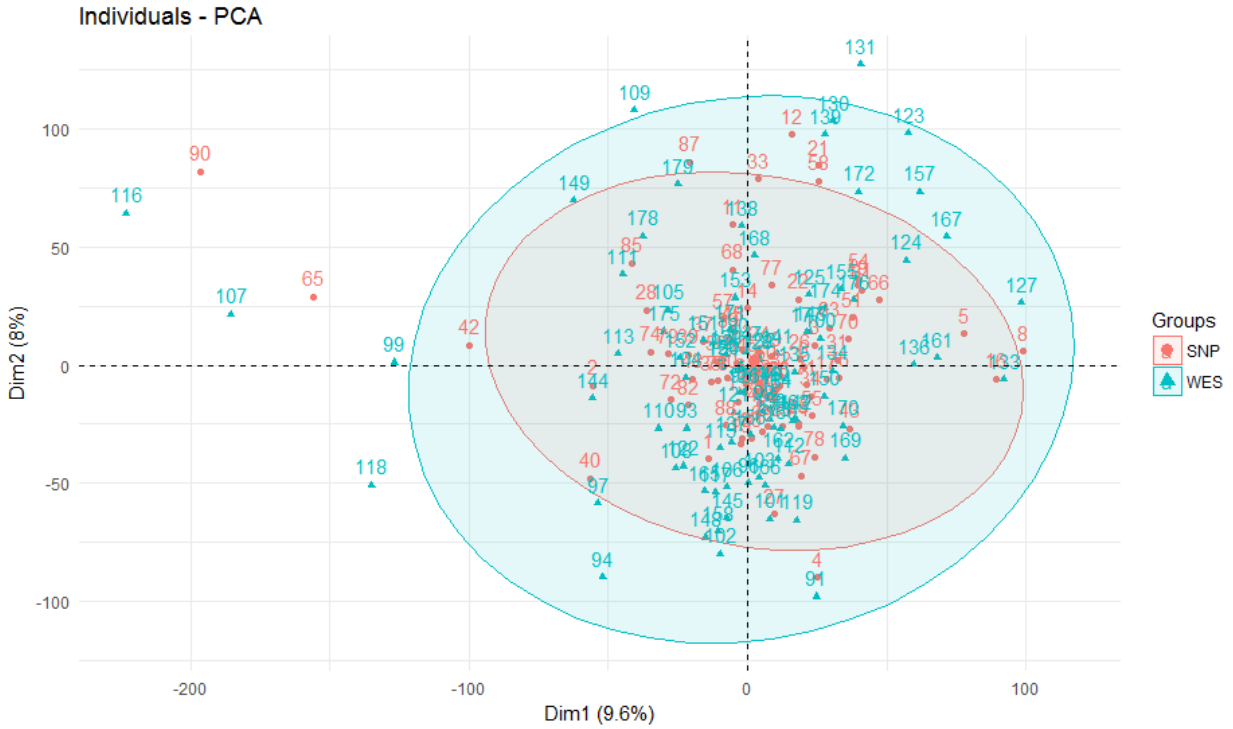

Figure S8 Legend

Figure S8. Principal component analysis (PCA) plot of TCGA copy number data inferred via SNP array or whole exome sequencing data among primary HPV-unrelated OCSCC and OPSCCs and HPV-related OPSCCs. 95% confidence ellipses presented. *SNP*, TCGA copy number data generated using data from a SNP array. *WES*, TCGA copy number data generated using data from whole exome sequencing results.

Figure S9

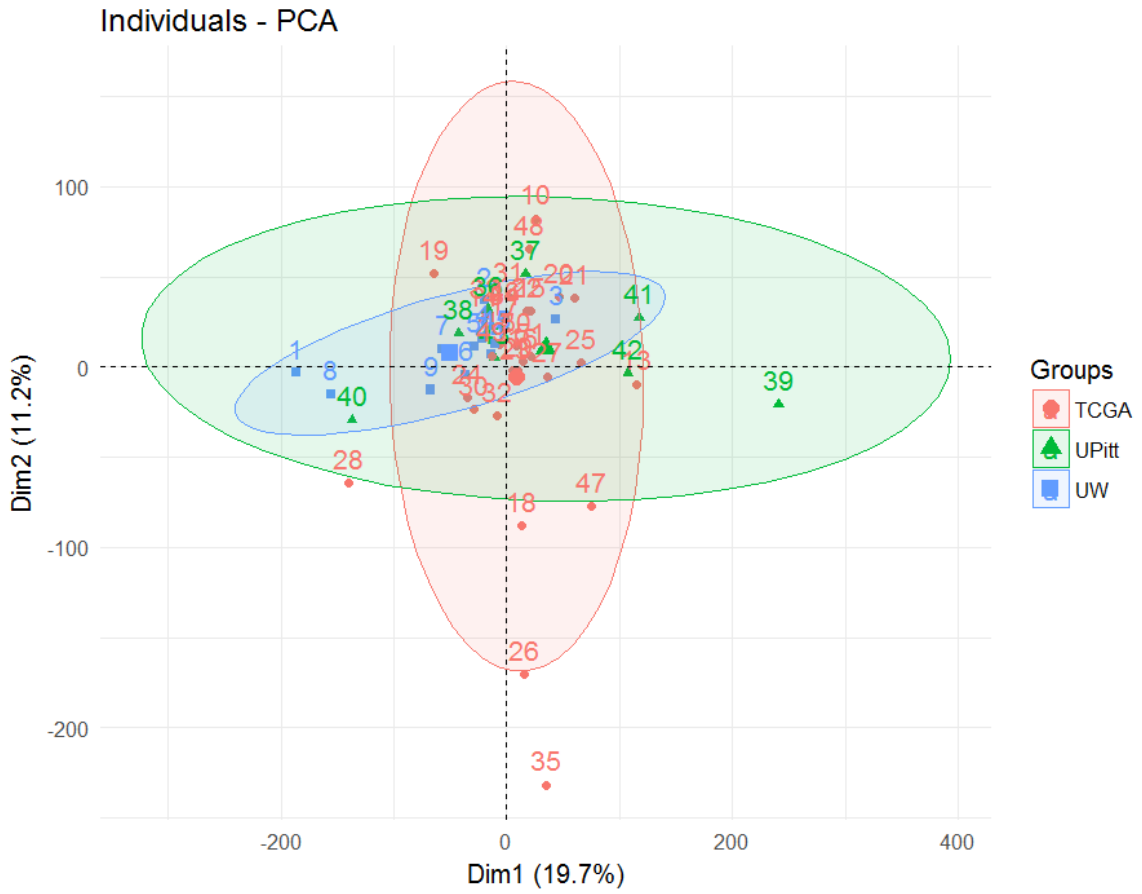

Figure S9 Legend

Figure S9. Principal component analysis (PCA) plot of whole exome-derived copy number data among primary HPV-related OPSCCs by data origin. 95% confidence ellipses presented. *TCGA*, TCGA head and neck copy number data. *UPitt*, UPitt head and neck copy number data. *UW*, UW head and neck copy number data.