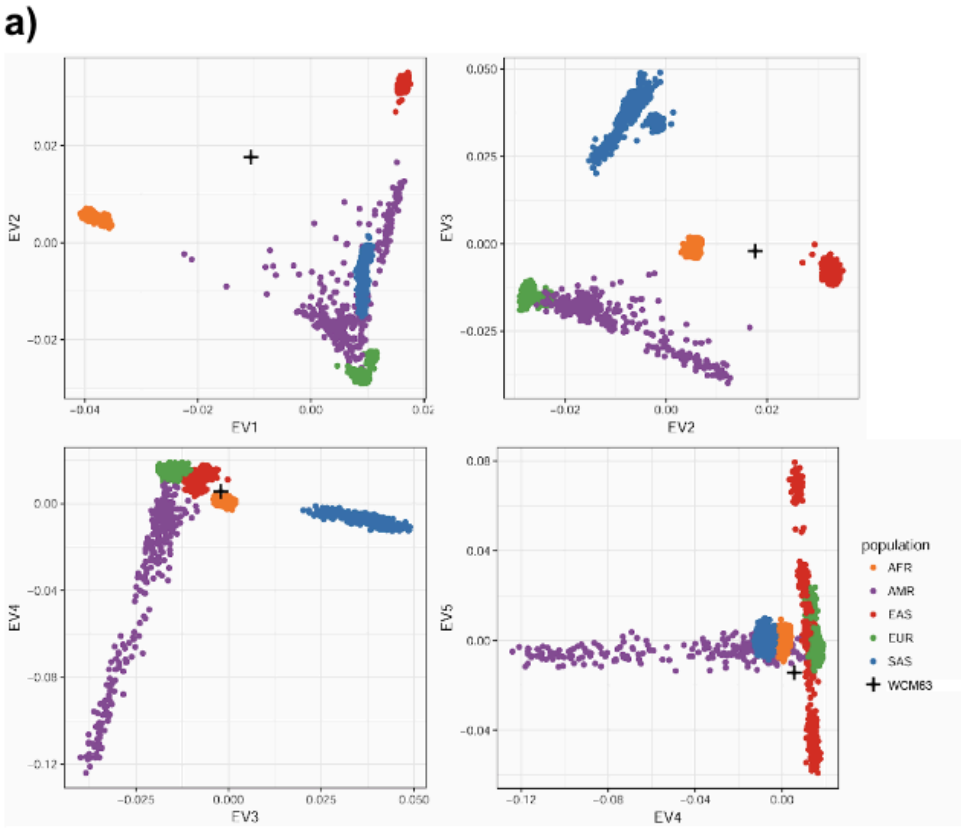
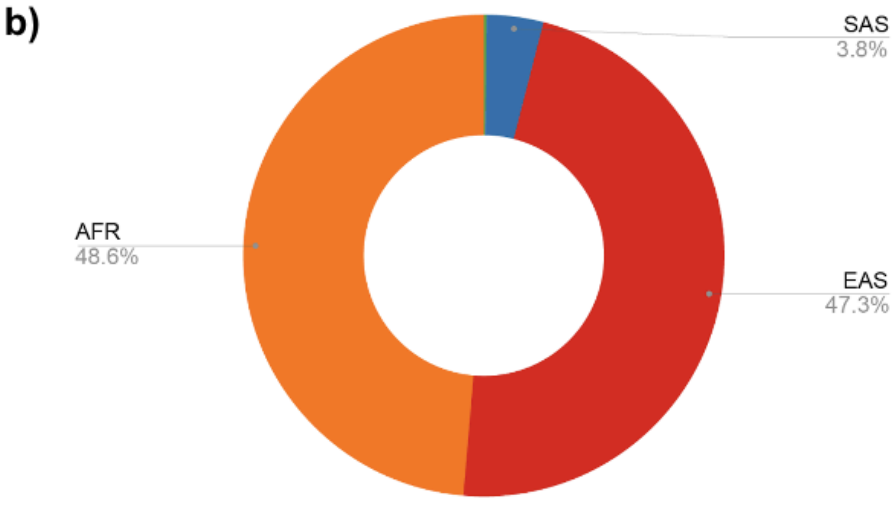
Supplementary Figures

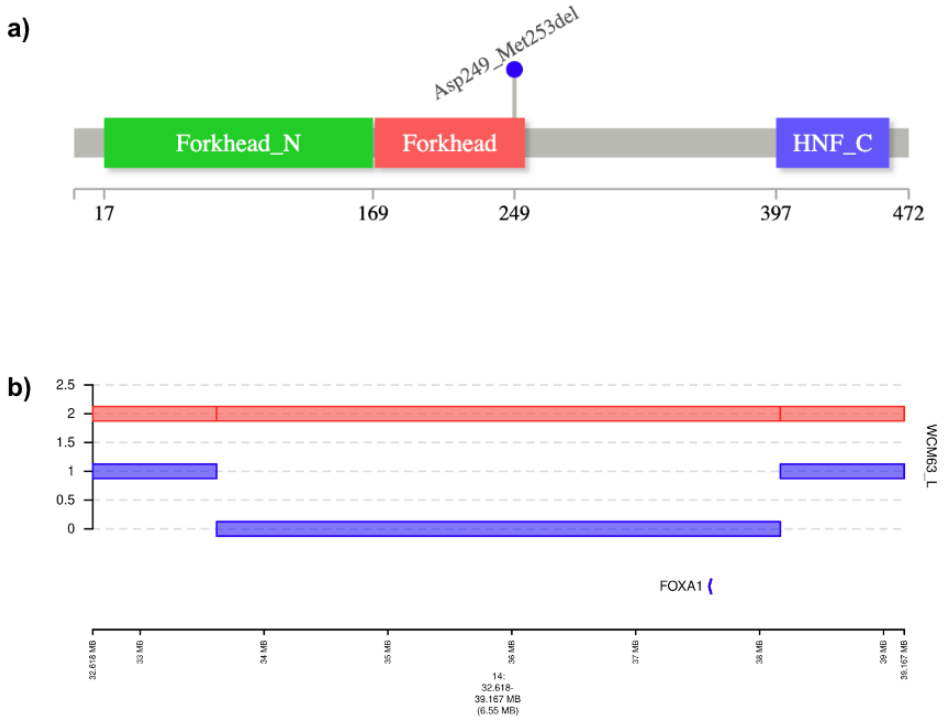




Supplementary Figure 1. Patient's inferred genomic ancestry via ADMIXTURE

a. Plots showing patient (+) mapped on to the reference ancestry panel across principal components 1-5. While estimated to be of admixed East Asian and African ancestry, the plots show that the patient does not group with the reference ancestry clusters.

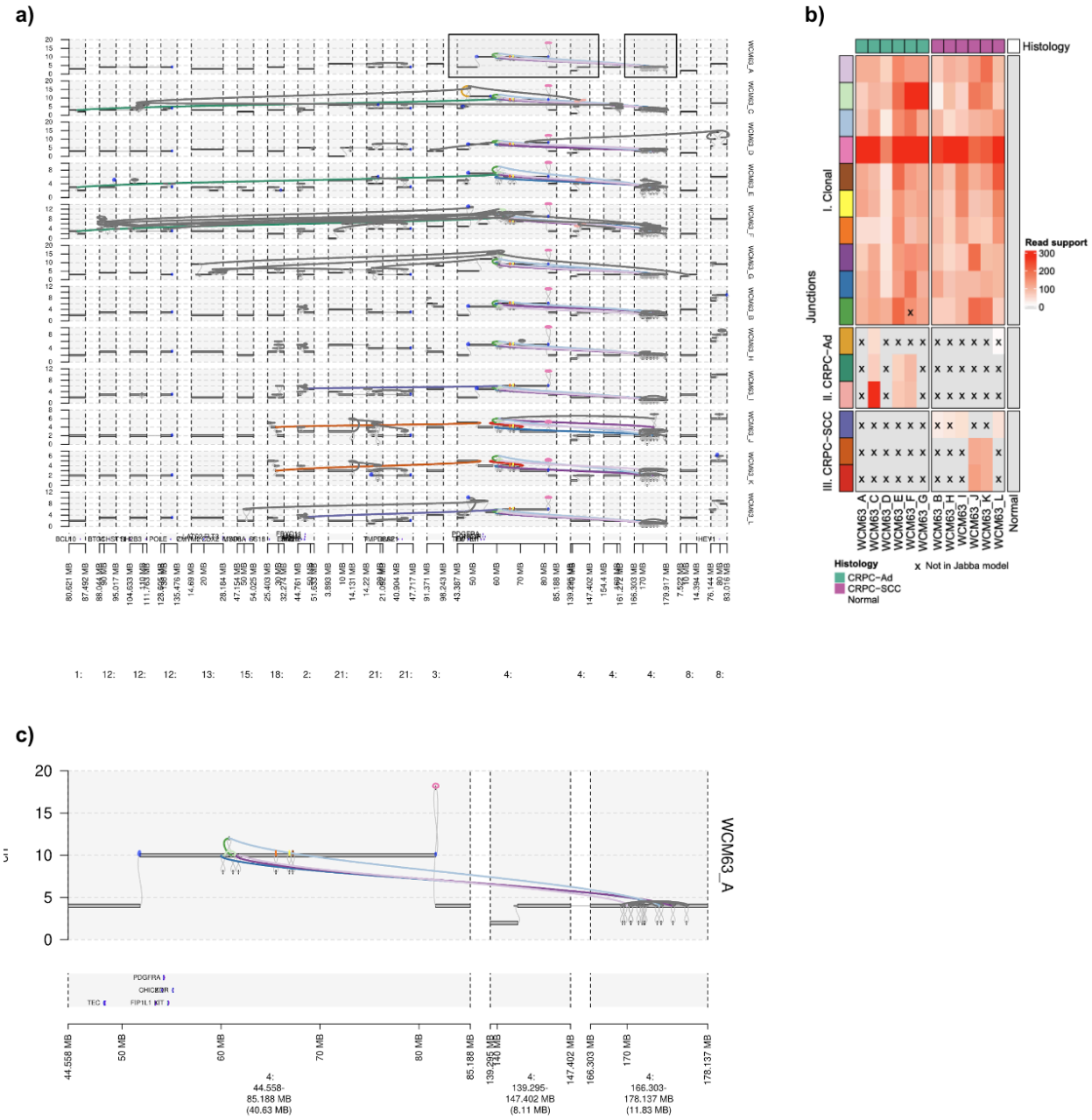
b. Summary proportions of continental genomic ancestry.



Supplementary Figure 2. Loss of truncal FOXA1 mutation via focal deletion in WCM63_L

a. Lollipop plot indicating the position of the truncal mutation within FOXA1.

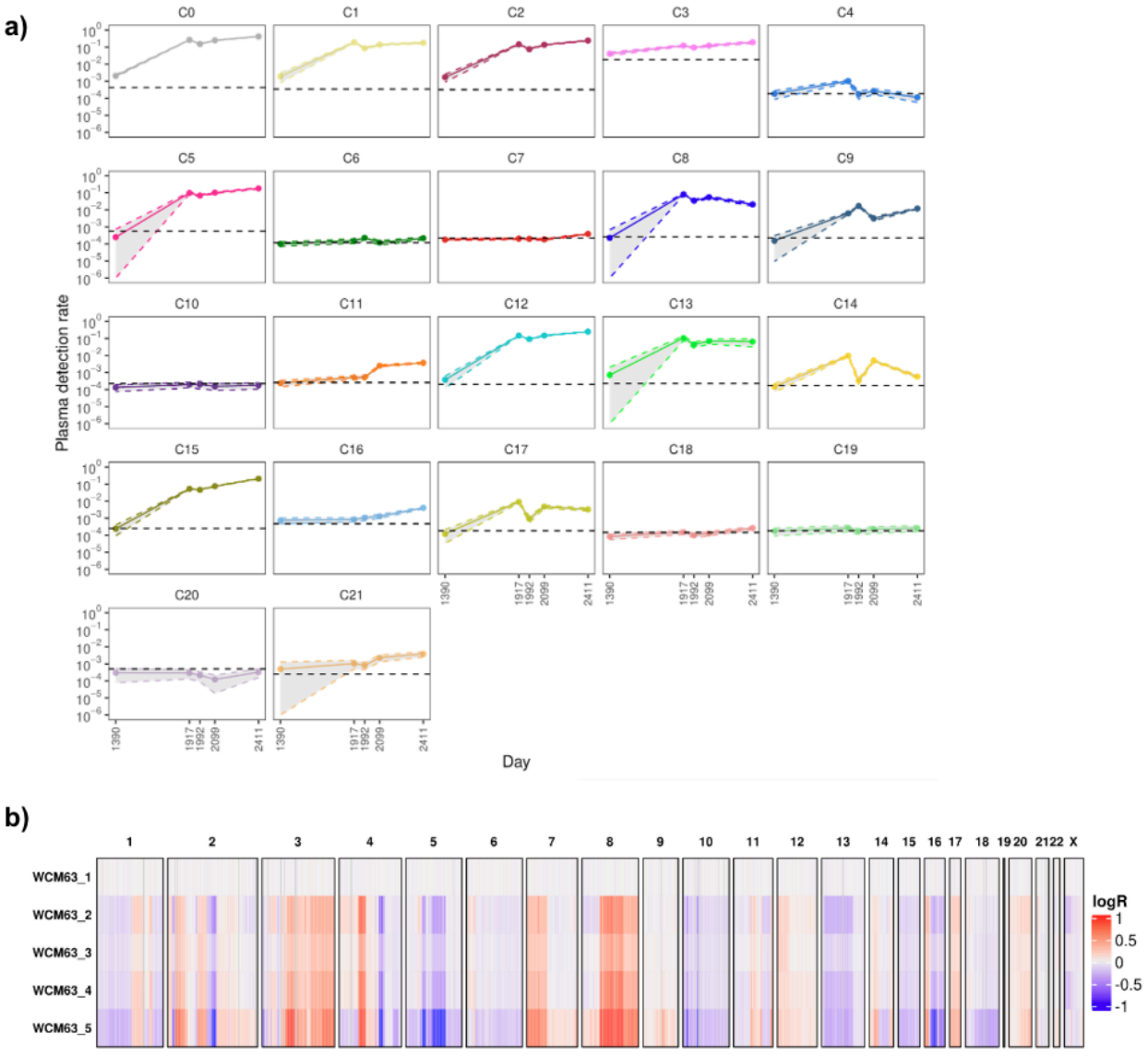
b. Genome-level view of WCM63_L allele-specific copy number for region surrounding FOXA1. Major copy number is indicated by the red bar, and minor copy number by the blue bar. The blue bar shows a 4.5 megabase deletion containing FOXA1, resulting in loss of heterozygosity.



Supplementary Figure 3. **Divergence of a clonal complex structural variant.**

a. Genome-level view of the shared complex structural variant for all samples. The gray bars represent genomic intervals, and the height of the bars indicate their copy number. The gray arcs represent somatic junctions that are private to individual samples, and the multicolored arcs represent junctions shared by at least two samples. These colors align with the heatmap in panel B. Positions of CGC genes are indicated in the bottom track. The gray boxes indicate the scope of panel C.

b. Heatmap showing read support for the shared junctions displayed in panel A. Cells are colored by read support, and are marked with an “x” if that particular junction was not integrated into that sample’s JaBbA model. Samples are grouped by histology, and junctions are grouped by presence across histology, requiring at least 5 supporting reads to be considered present.
c. Genome-level view of the same event shown in panel A, focusing on prostate sample WCM63_A.



Supplementary Figure 4. Tumor-informed SNV/INDEL and CNV-based analysis of cfDNA
a. Plasma detection rate of all clones over time, plotted in $\log_{10}$ scale to show clonal dynamics at low detection rates. The shaded polygon and colored dashed lines represent the 95% bootstrap

confidence intervals of the detection rate, and the black dashed line represents the clone-specific lower limit of detection.

b. Plasma copy number signal as measured by the ichorCNA logR value, in 1 megabase windows. Each sample is represented by a row, and each genomic interval is represented by a column. Genomic windows are grouped by chromosome.

Supplementary Data - Titles and Legends

Supplementary Data 1. Tumor purity/ploidy, sequencing, and alignment quality control.
Metrics of tumor purity, ploidy, and sequencing quality are provided for each tumor and normal tissue from biopsy or collection at autopsy,

Supplementary Data 2. Tumor clone cancer cell fractions (CCFs).
For each clone generated by the clone tree analysis, the number of variants and CCFs represented in each tumor tissue sample are provided.

Supplementary Data 3. Differentially expressed genes between SCC and Adeno tumors.
A complete list of the differentially expressed genes between squamous and adenocarcinoma tumors derived from WCM63.

Supplementary Data 4. The top variable genes between SCC and Adeno tumors.
The differentially expressed genes between squamous and adenocarcinoma tumors derived from WCM63, sorted by the largest standard deviation. Higher standard deviations (column B) correspond to higher expression in adenocarcinoma v SCC.

Supplementary Data 5. List of the differentially expressed genes that have a detectable DNA alteration.
The list of differentially expressed genes, when compared between SCC and adenocarcinoma, was queried within the DNA sequencing to determine which genes harbor DNA alterations that may be contributing to differential expression. Columns B and C lists the number of samples (out of 6) in each histology, respectively, that harbor the DNA alteration listed in columns F-H.

Supplementary Data 6. Plasma tumor fraction, sequencing, and alignment quality control.
Plasma sample tumor fraction, sequencing metrics, and alignment quality control.

Supplementary Data 7. Detection of each clone within each plasma sample.
For each plasma sample (column A), the level of detection of each clone (column B) generated by the clone tree analysis is described. Quality metrics describing detection and the presence or absence of a clone are included (column O).