HGGA, Volume *5*

Supplemental information

Targeted sequencing for hereditary breast and ovarian cancer in BRCA1/2-negative families reveals complex genetic architecture and phenocopies

Jocelyn N. Plowman, Evanjalina J. Matoy, Lavanya V. Uppala, Samantha B. Draves, Cynthia J. Watson, Bridget A. Sefranek, Mark L. Stacey, Samuel P. Anderson, Michael A. Belshan, Elizabeth E. Blue, Chad D. Huff, Yusi Fu, and Holly A.F. Stessman

SUPPLEMENTAL INFORMATION

Supplemental Figures

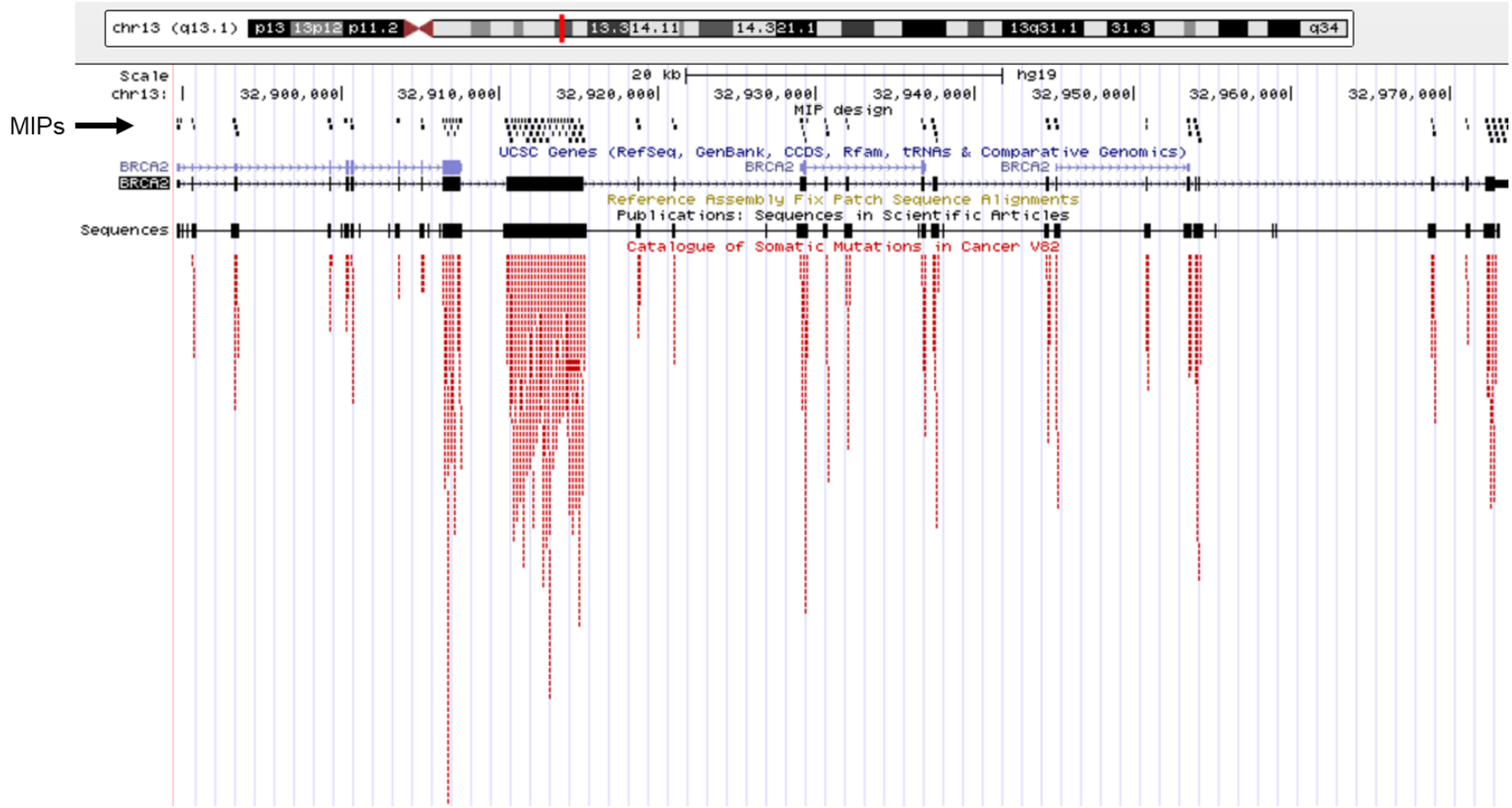


Figure S1. Example of MIP coverage across *BRCA2*. Individual MIPs (track indicated by the black arrow) tile across all coding exons of the target gene, *BRCA2*. MIP design shown on the UCSC genome browser (hg19).

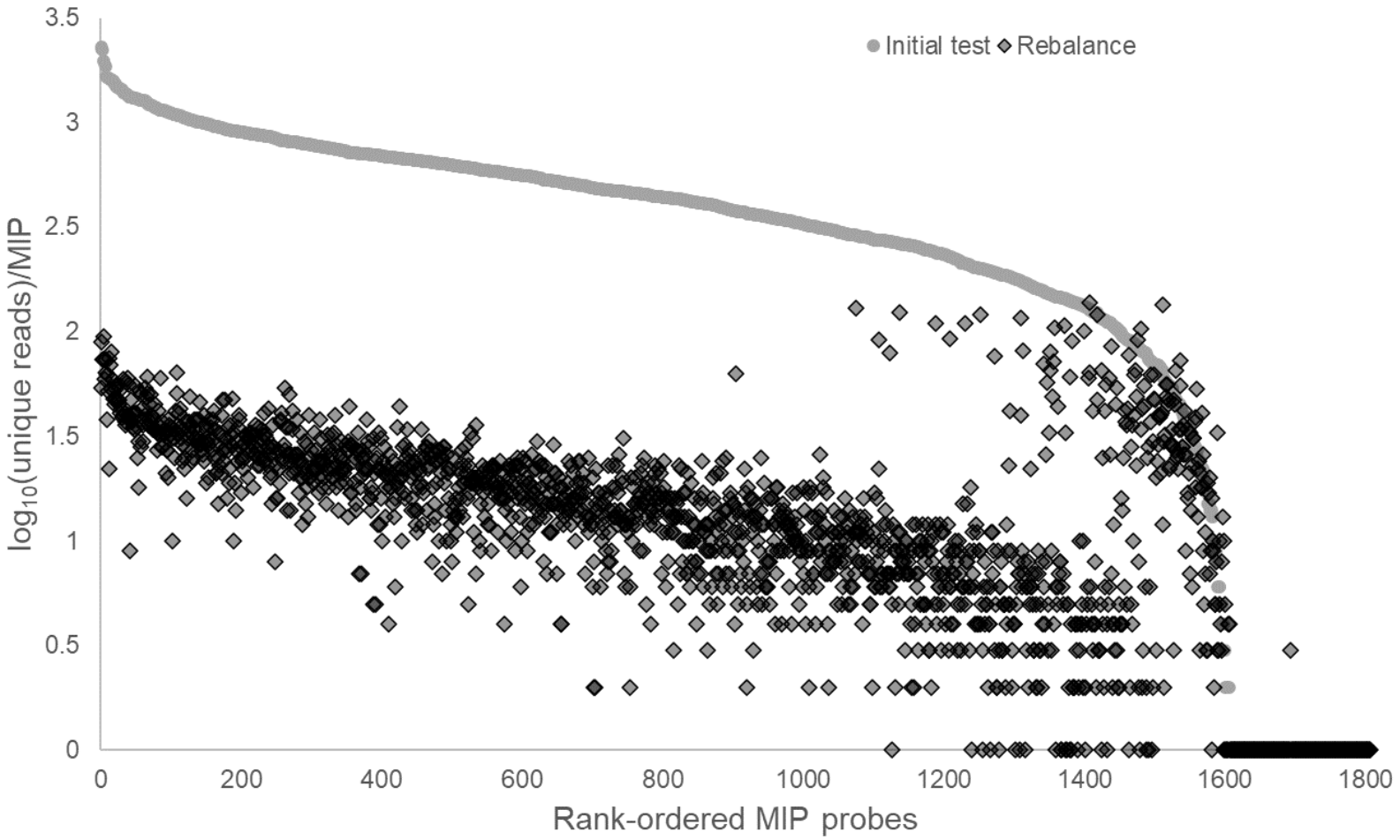


Figure S2. Capture pool rebalancing improves coverage uniformity of poor performing MIPs. Performance of all MIPs rank ordered best to worst at equimolar (1X) concentration for target capture shown in grey ("initial test). For the "rebalance" run, poor performing MIPs from the initial run were spiked into the capture pool at 30:1 to all other MIPs. MIPs were plotted in the same order as in the initial run showing improved sequencing uniformity of initially poor performing MIPs.

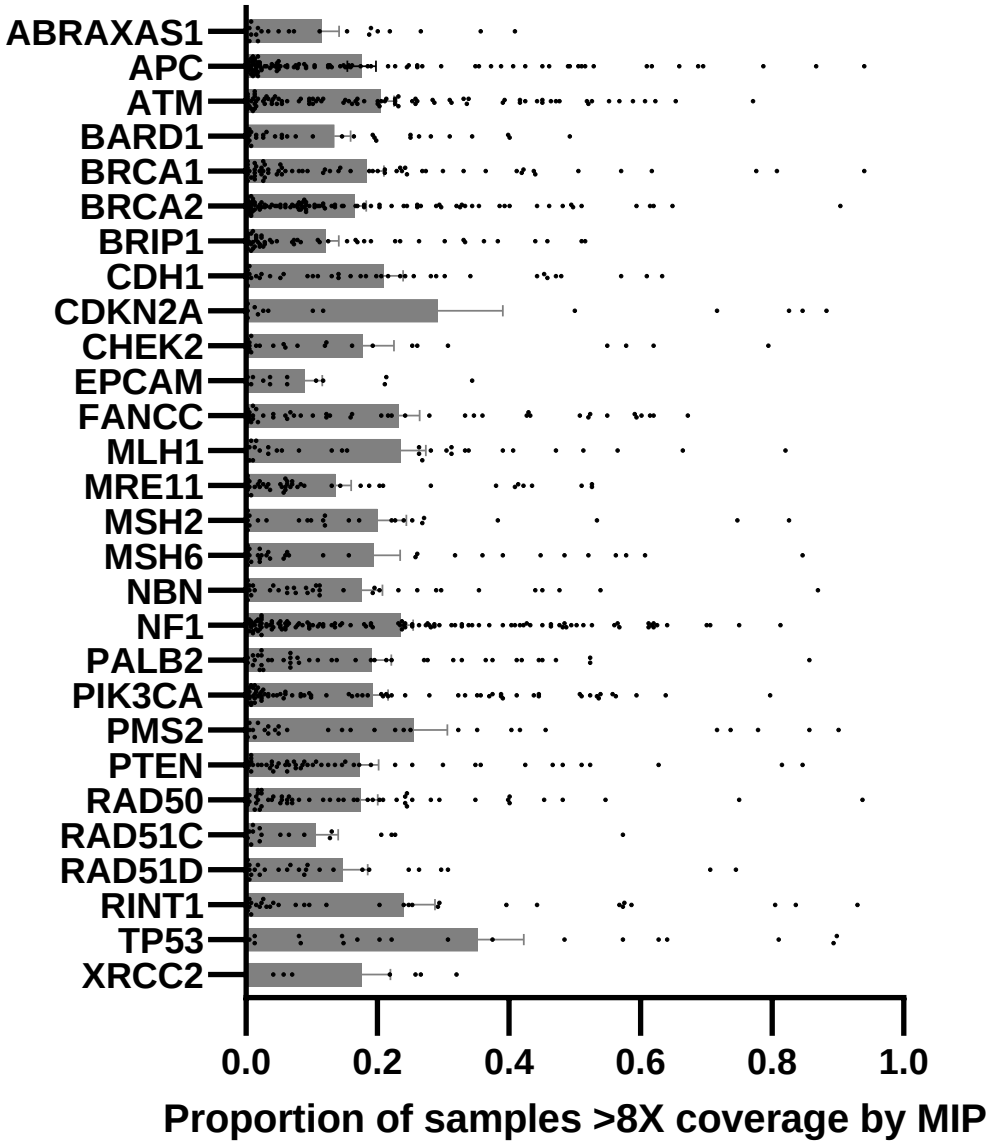


Figure S3. MIP performance across all samples. Bar graph of the proportion of samples with greater than 8X coverage per MIP/gene. Each dot represents an independent MIP from the final capture design (Table S1). Bars show mean + SEM.

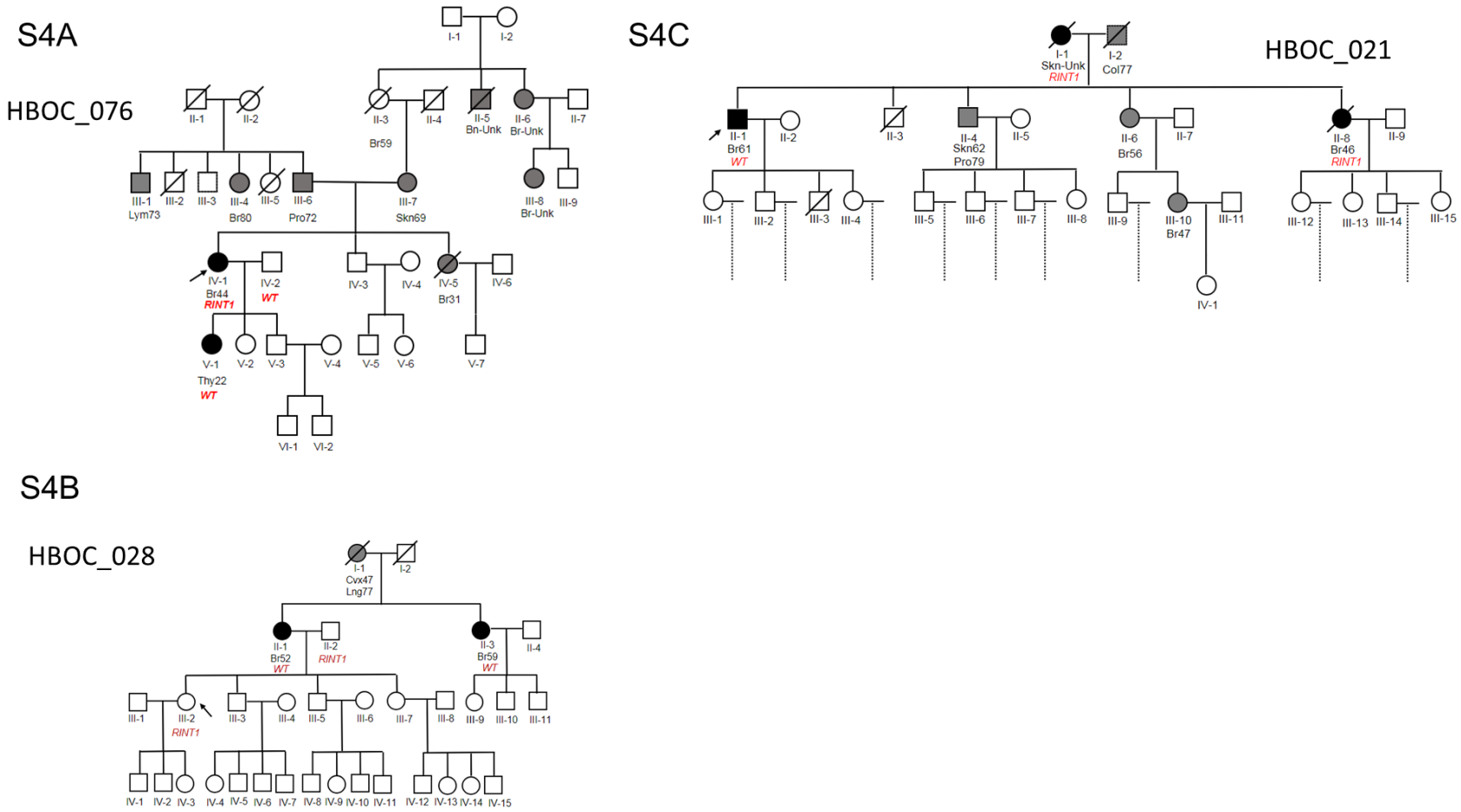
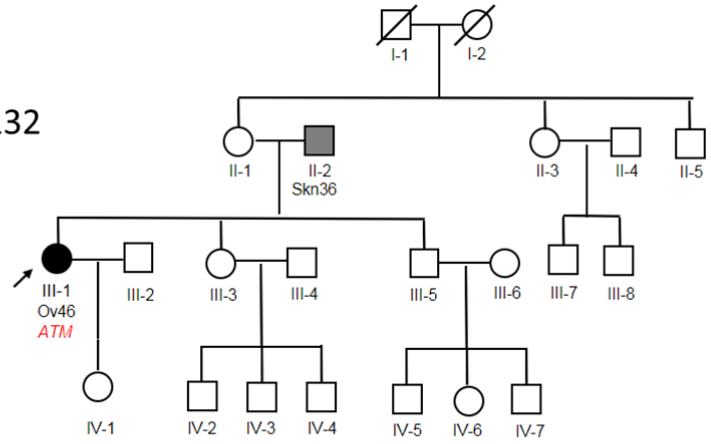


Figure S4. Families identified with *RINT1* VOUS(s). (**A**) Family 076 carried a single *RINT1* VOUS c.2361G>A . Absence of this variant in cancer-affected family members suggest additional risk variants may be present. (**B**) Family 028 carried a single *RINT1* VOUS c.376C>T. All carriers were unaffected suggesting this variant is likely-benign. (**C**) Family 021 carried a single *RINT1* VOUS c.41C>T. The proband is an affected non-carrier. This VOUS did not contribute to the proband's cancer risk. WT= wildtype for corresponding gene. Cancer types: Br=breast, Bn=brain, Skn=skin, Lym=lymphoma, Thy=thyroid, Lng=lung, Pro=prostate, Col=colorectal, Cvx=cervical.

S5A

HBOC_132



S5B

HBOC_065

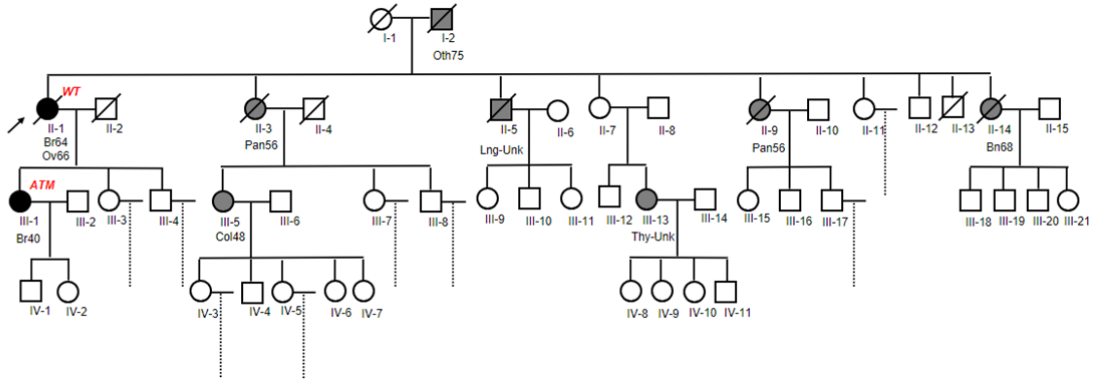


Figure S5. Families identified with *ATM* VOUSs. (**A**) Family 132 carried an *ATM* variant c.8734A>G. Due to a limited number of samples and clinical history, risk for this variant cannot be determined. (**B**) Family 065 carried an *ATM* variant c.6293T>C. The proband is an affected non-carrier. III-1 is an affected carrier. Due to a limited number of samples and clinical history, risk for this variant cannot be determined. WT= wildtype for corresponding gene. Cancer types: Br=breast, Skn=skin, Ov=ovarian, Pan=pancreatic, Col=colorectal, Thy=thyroid, Lng=lung, Bn=brain, Oth=unknown source.

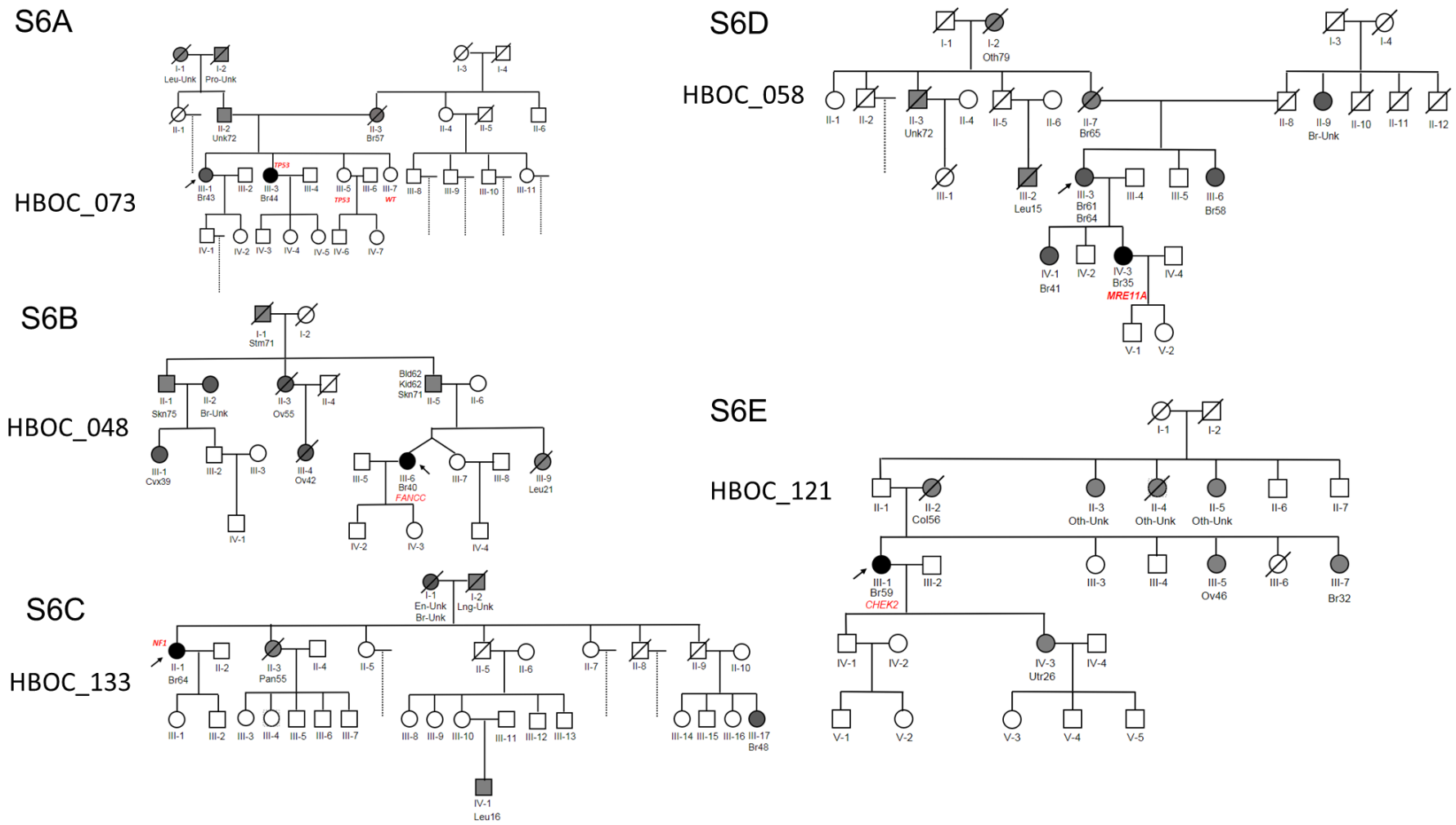


Figure S6. Families identified with other hereditary cancer syndrome gene VOUSs. (**A**) Family 073 carried a *TP53* VOUS c.1175A>C. (**B**) Family 048 carried a *FANCC* VOUS c.1483T>C. (**C**) Family 133 carried a *NF1* VOUS c.7396A>G. (**D**) Family 058 carried a *MRE11A* VOUS c.1475C>A. (**E**) Family 121 carried a *CHEK2* VOUS c.1465A>G. WT=wildtype for corresponding gene. Cancer types: Br=breast, Leu=leukemia, Skn=skin, Ov=ovarian, Kid=kidney, Bld=bladder, Stm=stomach, En=endometrial, Lng=lung, Pan=pancreatic, Utr=uterine, Col=colorectal, Pro=prostate, Cvx=cervical,Utr=uterine, Oth/Unk=unknown source.

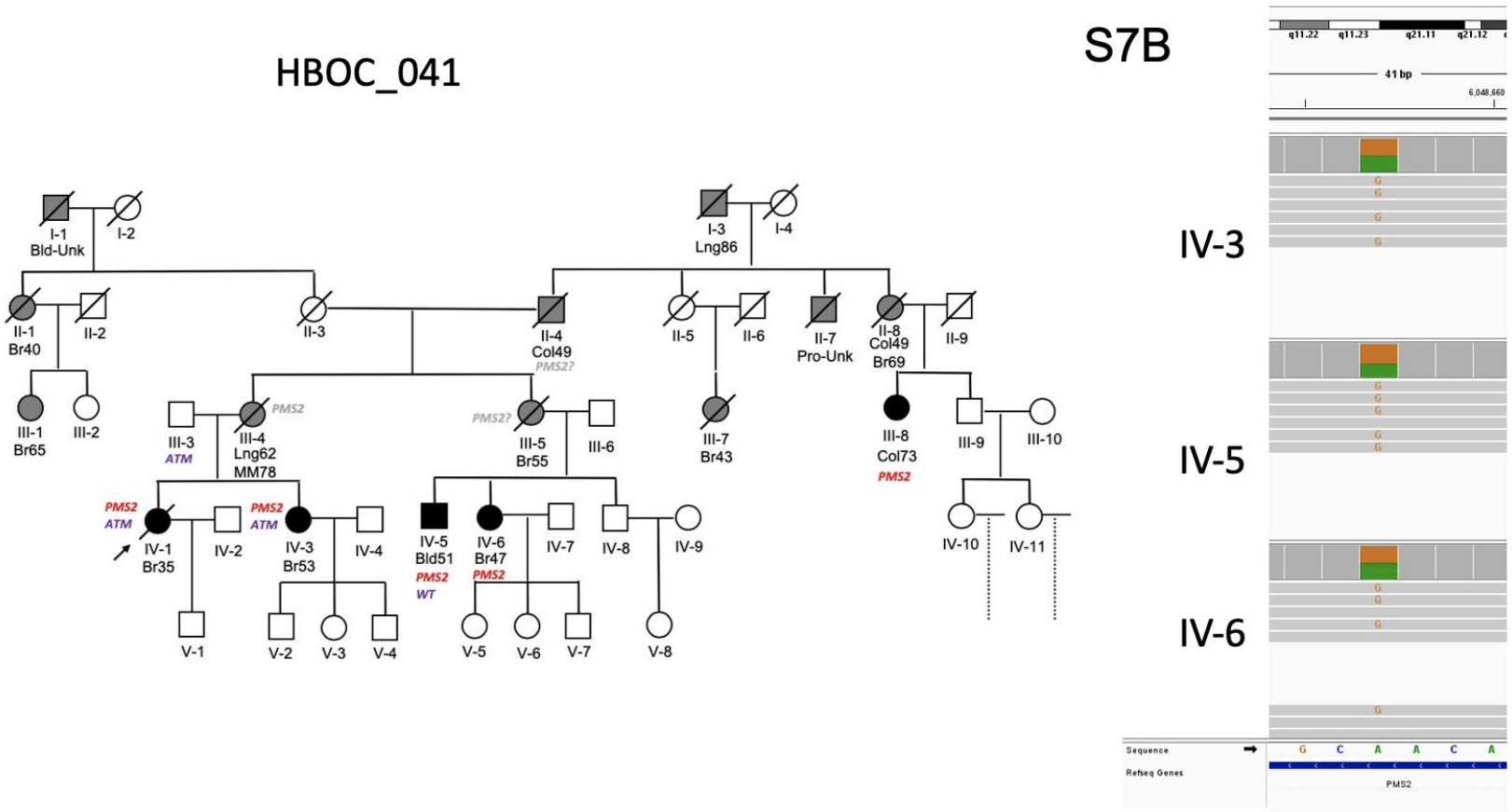


Figure S7. Family 041 identified with multiple VOUSs. (**A**) Pedigree for Family 041 carried an *ATM VOUS* c.1703G>T and a *PMS2* VOUS c.-7T>C. The proband is an affected carrier of both variants. The *PMS2* variants could not be Sanger validated, but likely transmitted through the maternal lineage and is benign. (**B**) IGV data from Family 041 showing high probability of the PMS2 c.-7T>C variant being a true positive in this family. WT= wildtype for gene. If more than one variant existed, gene names were colored with WT written in the corresponding color. Cancer types: Br=breast, Bld=bladder, Col=colorectal, Lng=lung, Pro=prostate, Lng=lung, MM=multiple myeloma.

Supplemental Tables

Supplemental Tables 1-8 provided in separate Excel document.