

Object Title	Page #
Supplementary Figure 1: Electropherogram	2
Supplementary Figure 2: Ramachandran plot	3
Supplementary Figure 3: Modeling <i>ERCC3</i> R109X via CRISPR/Cas9 genome editing.	4
Supplementary Figure 4: Haplotype analyses from the TAGC heterozygote carriers	5
Supplementary Figure 5: <i>ERCC3</i> mutations present in the cBioPortal (MSKCC) datasets.	6
Supplementary Figure 6: <i>ERCC3</i> transcript levels in patient derived whole blood.	7
Supplementary Table 1: Family history and pathology information on R109X carriers	8
Supplementary Table 2: Identity of mutations in HMLE cell lines generated by CRISPR/Cas9. ...	9

Supplementary Figure 1: Electropherogram showing heterozygous nonsense mutation c.325C>T in 3 siblings affected with breast cancer from the kindred shown in Figure 1.

Supplementary Figure 2: Ramachandran plot of the first 300 amino acids of ERCC3 shows the Arg109 residue within the left lower quadrant corresponding to the right handed alpha-helix as predicted by the *ab-initio* modeling server EVfold. Lack of high resolution template structure limits any further modeling of this domain.

Supplementary Figure 3: Modeling *ERCC3* R109X via CRISPR/Cas9 genome editing. Sanger sequencing performed on genomic DNA extracted from CRISPR/Cas9 edited HMLE cell lines harboring frameshift or point mutation at the *ERCC3* R109 locus. The star indicates the nucleotide position c.325C within the chromatogram. The arrow indicates the position at which the CRISPR/Cas9 mediated change occurs.

Supplementary Figure 4: Haplotype analyses from the TAGC heterozygote carriers. Carriers of the R109X mutation show a mean haplotype length of 3.4 cM which was significantly longer than non-carriers ($p < 10^{-14}$), suggesting a founder mutation.

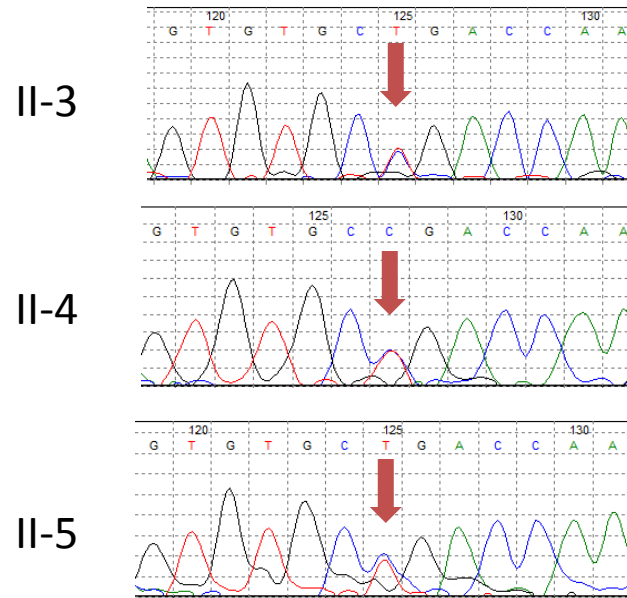
Supplementary Figure 5: *ERCC3* mutations present in the cBioPortal (MSKCC) datasets. (A) Lollipop plot indicating positions of mutations within the ERCC3 protein. Colour of diagram circles indicates missense mutations (green), truncating mutations (red) and different mutation types (purple). The red arrow marks the R109X mutation. (B) Mutation frequencies of *ERCC3* across different cancer types. Filter was applied to display only cancer types that show 1% or higher mutation frequency.

Supplementary Figure 6: *ERCC3* transcript levels in patient derived whole blood. (A) Real time quantitative PCR of *ERCC3* transcript (spanning exons 9 & 10). The relative transcript levels are reduced in the mutation carrier derived cDNA relative to a non-carrier sibling. (B) Electropherogram of genomic DNA and cDNA showing the reduced peaks of the mutant allele.

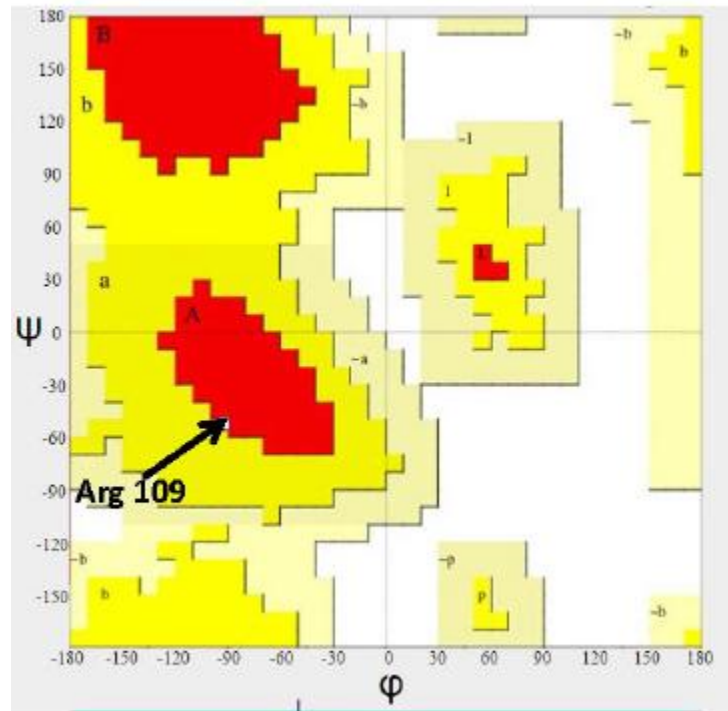
Supplementary Table 1: Family history and pathology information on R109X carriers

Supplementary Table 2: Identity of mutations in HMLE cell lines generated by CRISPR/Cas9.

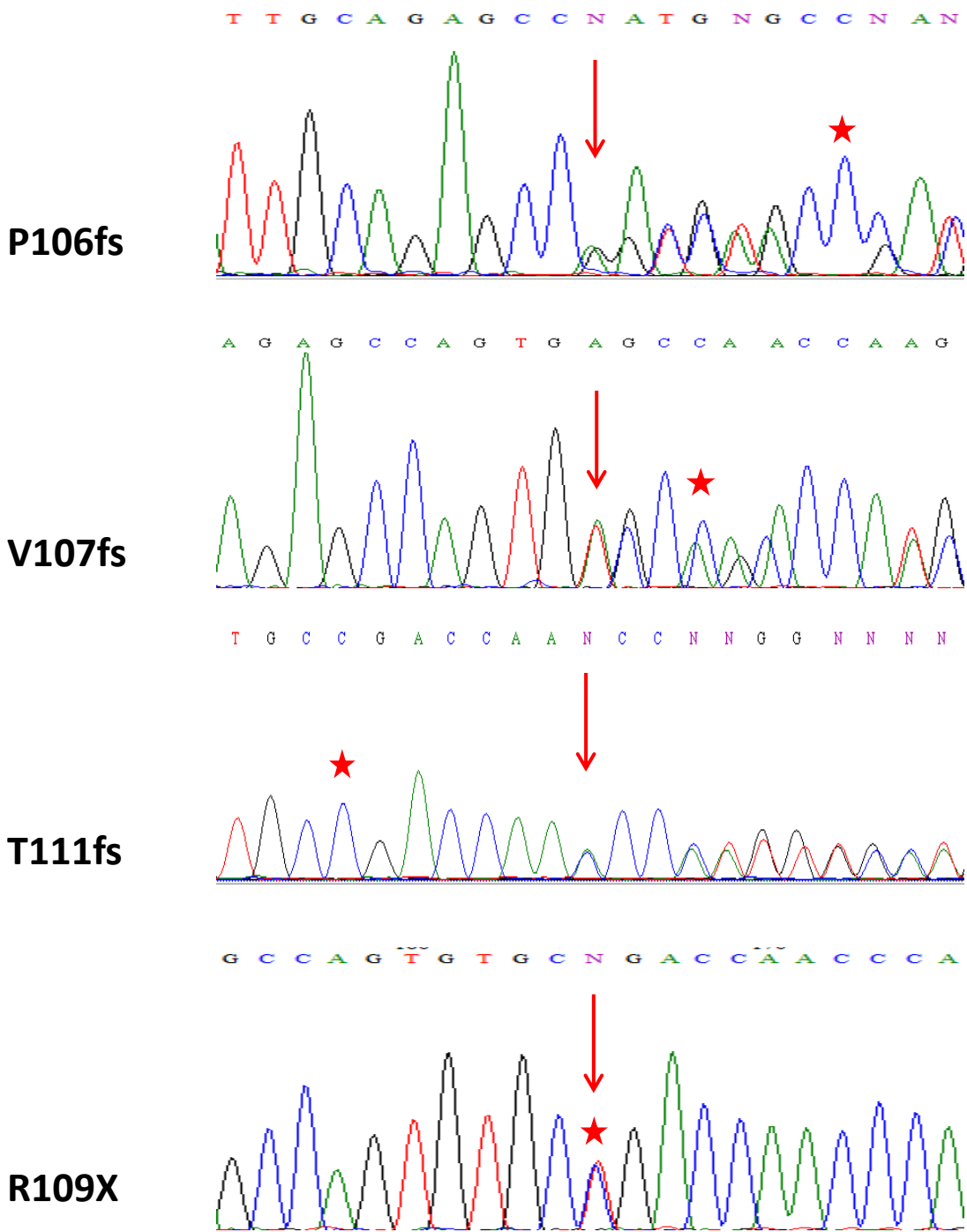
Supplementary Figure 1



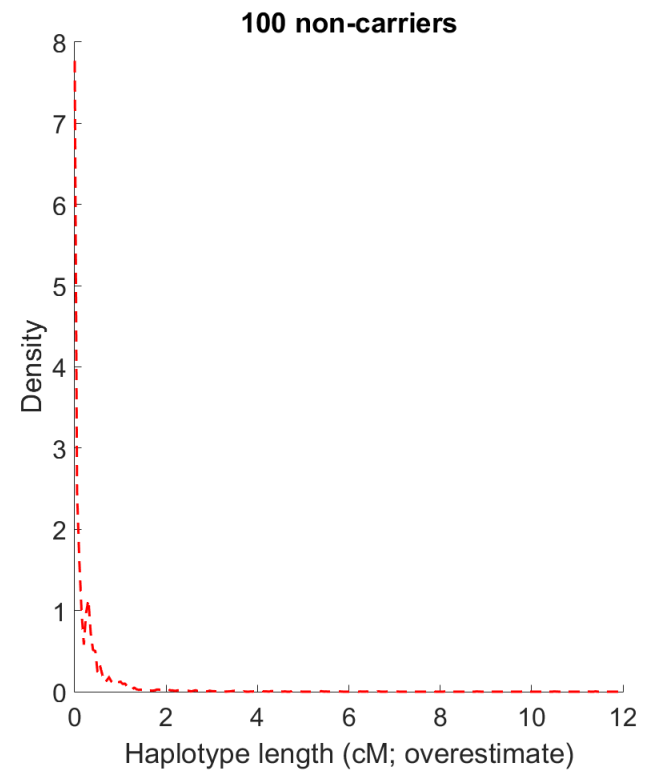
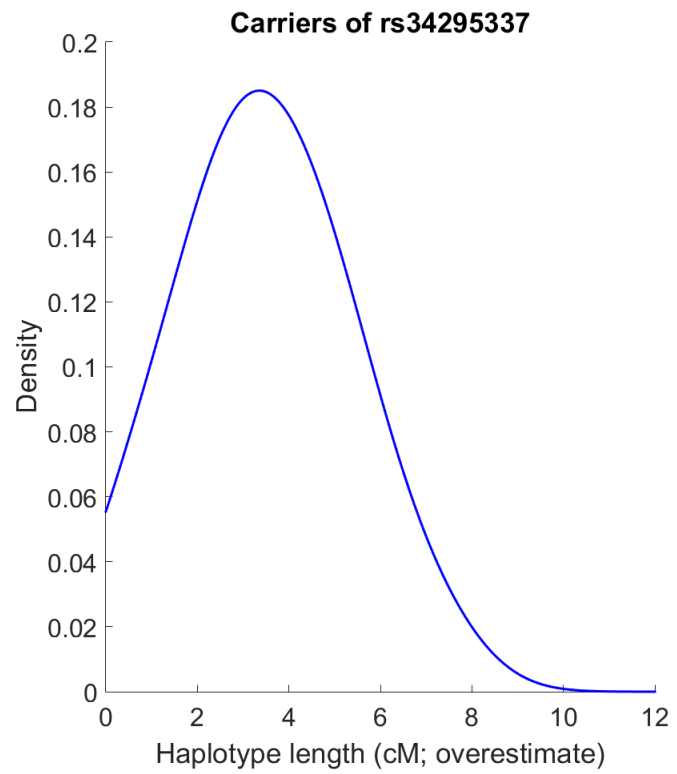
Supplementary Figure 2



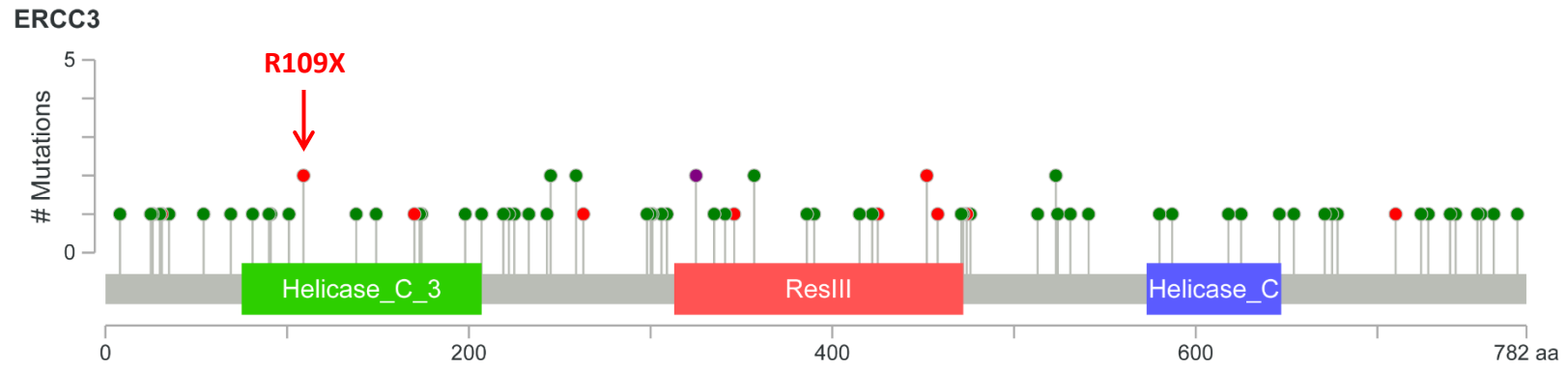
Supplementary Figure 3



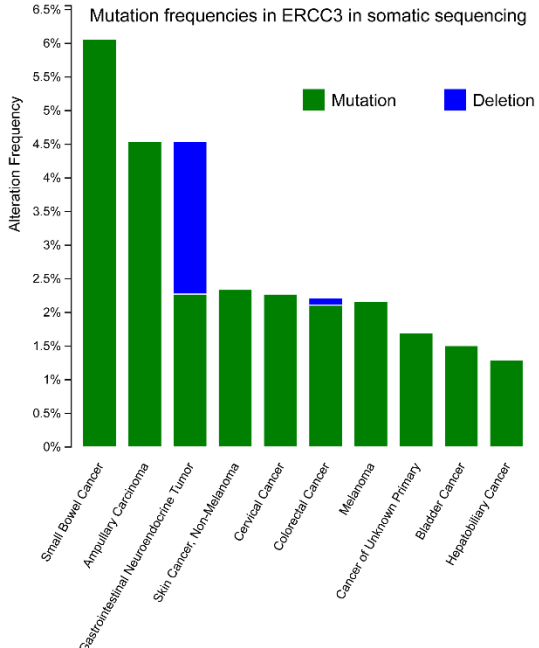
Supplementary Figure 4



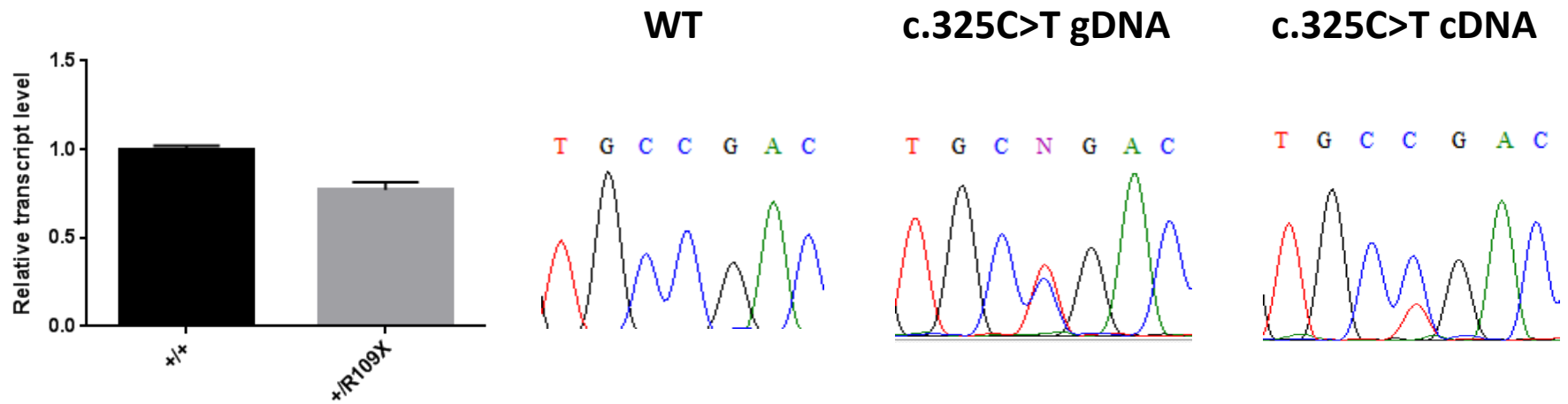
Supplementary Figure 5A



Supplementary Figure 5B



Supplementary Figure 6



Supplementary Table 1

Family ID	Cancer Diagnosis	Histology	Age of Onset	Ancestry / Religion	Family History	ER Status	PR Status	HER-2 Status	Gender
48732	Breast	Lobular and Ductal	52	Ashkenazi Jewish	Mother: Colorectal at 61; Maternal Aunt: Breast at 74	Positive	Negative	Negative	Unknown
48346	Breast	Lobular	64	Ashkenazi Jewish	Mother Melanoma at 53; Maternal Aunt: Colorectal at 70; Paternal Mother: Early-onset Breast	Positive	Negative	Negative	Unknown
47704	Breast	Ductal	54	Ashkenazi Jewish	Mother: Breast at 82; Maternal cousin: Breast at 52; Father: Colorectal at 80; Paternal Uncle: Lung at 50; Paternal Aunt: "Blood Cancer" at 71	Positive	Positive	Negative	Unknown
47473	Breast	Ductal	52	Ashkenazi Jewish	Mother: Breast at 41, Colorectal and Melanoma age UNK; Maternal cousin: Breast at 30	Positive	Negative	Positive	Unknown
42836	Breast	Lobular and Ductal	52	Ashkenazi Jewish	Mother: Breast at 68; Maternal Uncle: Prostate at 65	Unknown	Unknown	Unknown	Unknown
44371	Breast	Ductal	57	Ashkenazi Jewish	Mother: Breast at 45; Father: Pancreas at 85	Positive	Positive	Negative	Unknown
44965	Breast	Ductal	72	Ashkenazi Jewish	Mother: Breast at 78; Sister: Stomach at 69; Maternal Aunt: Breast at 60	Unknown	Unknown	Unknown	Unknown
44997	Breast	Ductal	70	Ashkenazi Jewish	Brother: Prostate at 70; Paternal Aunt: *CSU; Paternal Aunt: *CSU; Niece: Breast at 37; Niece: Lymphoma age UNK; Niece: *CSU	Positive	Positive	Positive	Unknown
44618	Breast (Bilateral)	Ductal	>80	Ashkenazi Jewish	Mother: Breast at 75, Bladder at 85; Brother: Lung at 83; Maternal Grandmother: *CSU at 76	Positive	Positive	Positive	Unknown
45678	Breast, Colorectal	Lobular	60	Ashkenazi Jewish	Maternal Aunt: Colorectal; Niece: Breast <60	Unknown	Unknown	Unknown	Unknown
45759	Breast	DCIS	59	Ashkenazi Jewish	Sister: Breast at 65; Sister: Lymphoma age UNK; Brother: Liver at 55	Positive	Positive	Unknown	Unknown
57546	Control	N/A	N/A	Unknown	Maternal Sister: Esophagus at 78	N/A	N/A	N/A	Unknown
53103	Control	N/A	N/A	Muslim	No significant family history	N/A	N/A	N/A	Unknown
53158	Control	N/A	N/A	Unknown	Mother: Breast at 52, Eye at 31; Paternal Grandmother: Breast at 70; Paternal Aunt: Bone at 51	N/A	N/A	N/A	Unknown

*"CSU": Cancer Site Unspecified

Supplementary Table 2

Clone	Mutation type	Mutation position	AA change	Stop codon AA
P106fs	delTGCCG	c.318	P106fs	112
V107fs	delAGTGTGCC	c.321	V107fs	113
T111fs	insA	c.331	T111fs	115
R109X	C>T	c.325	R109X	109