Supplementary Methods

Data authorization and access. To access TCGA germline sequence data, we obtained approval from the Database of Genotypes and Phenotypes (dbGaP) data access committee and the study conforms to the data usage agreement. Clinical characteristics for individuals with rare germline variants were downloaded from the TCGA website (https://tcga-data.nci.nih.gov/tcga/, November 24, 2014). Somatic mutation burden data were obtained from CBioPortal for Cancer Genomics (www.cbioportal.org, January 20, 2017)[22, 23].

Sequence analysis. At the time of initial access, a total of 842 normal/non-tumor tissue genome and/or exome data were available; they represented 555 unique TCGA identifiers. We downloaded raw BAM alignment files for the eight genes (hg19 coordinates) for samples coded as "blood" or "normal/non-tumor" from the Cancer Genomics Hub (https://cghub.ucsc.edu/) (October 15, 2014). The raw BAM files were processed using GATK realigner (https://www.broadinstitute.org/gatk/index.php) to optimize detection of insertions/deletions (indels). PCR and optical duplicates were identified and filtered with Picard (http://broadinstitute.github.io/picard/). Genomic variant calls were made by converting BAM files into genomic positions with mpileup and using bcftools to make genotype calls. For annotation of mutation positions, we used the following accession numbers: ATM (NM_000051), BRCA2 (NM_000059), CHEK2 (NM_001005735), EGFR (NM_005228), PARK2 (NM_004562), TERT (NM_198253), TP53 (NM_000546) and YAP1 (NM_001282101.1). We annotated and filtered the variant call files (vcf) using PhenoDB[24].

Filtering of variants. We used a filtering algorithm similar to that previously utilized[25]. We first selected variants with minor allele frequency <0.005 in dbSNP build 129, 1000 genomes project, and the Exome Variant Server. Non-synonymous, splice altering and indel variants with at least 20x read depth were then filtered in a second step by frequency in the Exome Aggregation Server (ExAC) (September 30, 2015). Those with a minor allele frequency of $\leq 5 \times 10^{-5}$ were manually verified in raw data files that were downloaded from a second, independently sequenced tumor and/or duplicate normal sample to confirm the germline nature and visualized manually in the Integrated Genomics Viewer (IGV)[26]. Variants not confirmed in a second sample were not analyzed further. Variants that confirmed had to be in 30% to 70% of reads to be considered heterozygous. Each variant call in Table 1 was verified manually and independently by at least two of the authors.

Variant analysis. To determine the significance of the extremely rare variants we identified, we performed a literature search. *ATM* variants were examined in the Ataxia-Telangiectasia syndrome database (http://chromium.lovd.nl/LOVD2). *EGFR*, mutations were considered further if they fell in exons 18-21, as per the standards defined in the literature[27]. To determine the significance of *TP53* mutations, we accessed the Li Fraumeni database at http://p53.iarc.fr/RefsLiFraumeni.aspx[28]. For the remaining tumor suppressor genes, *BRCA2*, *CHEK2* and *PARK2*, rare frameshift variants predicting a null allele were considered deleterious. To characterize the remaining variants, we queried the ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar/) (accessed June, 2015) and other rare variants were classified as variants of unknown significance (VUS) and analyzed using PolyPhen-2

(http://genetics.bwh.harvard.edu/pph2/bgi.shtml), Provean (http://provean.jcvi.org/protein_batch_submit.php?specieshuman) and SIFT (http://sift.bii.a-star.edu.sg/) (October 15, 2015).

Statistics. We used GraphPad Prism v.6.05 software (GraphPad, La Jolla, CA) to generate the pie chart, and to calculate the odds ratio and confidence intervals. The chi-square calculation was two-sided using a Yates' correction.

Supplementary References

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Supplementary Table 1. Ultra-rare variants of unknown significance identified in TCGA adenocarcinoma cases for *ATM, BRCA2, CHEK2, EGFR, PARK2, TP53* (n=52)

Germline Mutation*	Age	M/F	Validation source of DNA	Smoking status	Pack-years	Prior Malignancy	Evidence of pathogenicity		
							POLYPHEN	PROVEAN	SIFT
ATM									
ATM R720H	58	F	Tumor	Former	40		Possibly damaging/Benign	Neutral	Tolerated
ATM R720S	61	M	Tumor	Current	na		Benign/Benign	Neutral	Tolerated
ATM L806F	63	F	Tumor	Never	0		Probably damaging/ Probably damaging	Neutral	Affect protein function
ATM S877T	48	F	Tumor	Current	na		Benign/Benign	Neutral	Tolerated
ATM M1210V	42	M	Tumor	Former	10		Benign/Benign	Neutral	Tolerated
ATM S1383L	65	F	Tumor	Never	0		Possibly damaging/Benign	Deleterious	Affect protein function
ATM C1482Y	75	F	Tumor	Former	42		Benign/Benign	Neutral	Tolerated
ATM R1619K	na	na	Tumor	na	na	na	Benign/Benign	Neutral	Tolerated
ATM D1641H	60	F	Tumor, blood and tissue	Former	45	Lymphoma	Probably damaging/ Possibly damaging	Deleterious	Affect protein function
ATM T1697A	60	F	Tumor	Current	10	Endometrial	Benign/Benign	Neutral	Tolerated
ATM T2333I	41	M	Tumor	Current	11		Benign/Benign	Neutral	Tolerated
ATM N2370D	70	M	Tumor	Never	0		Benign/Benign	Neutral	Tolerated

ATM R2459G	na	na	Tumor	na	na	na	Probably damaging/ Probably damaging	Deleterious	Affect protein function
ATM L2490F	66	M	Tumor, duplicate	Former	12		Probably damaging/ Probably damaging	Deleterious	Affect protein function
ATM G2508R	51	M	Tumor	Former	70		Probably damaging/ Possibly damaging	Neutral	Tolerated
BRCA2									
BRCA2 N235D	74	F	Tumor	Former	25		Benign/Benign	Neutral	Tolerated
BRCA2 D281N	79	F	Tumor	Former	NA		Probably damaging/ Probably damaging	Neutral	Affect protein function
BRCA2 Y296C	58	M	Tumor	Current	60		Benign/Benign	Neutral	Tolerated
BRCA2 D427H	na	na	Tumor	na	na	na	Probably damaging/ Probably damaging	Neutral	Affect protein function
BRCA2 C554W	73	M	Tumor	Former	NA	Colon	Probably damaging/ Possibly damaging	Neutral	Affect protein function
BRCA2 N900D	63	F	Tumor	Former	36	Breast	Possibly damaging/ Benign	Neutral	Tolerated
BRCA2 I1151F	76	F	Tumor	Former	40		Possibly damaging/Benign	Deleterious	Tolerated
BRCA2 K1153R	72	F	Tumor	Former	40		Benign/Benign	Neutral	Tolerated
BRCA2 I1275T	70	F	Tumor	Former	20		Benign/Benign	Neutral	Tolerated
BRCA2 K1474R	55	F	Tumor	Current	na		Probably damaging/ Possibly damaging	Deleterious	Tolerated
BRCA2 S1494R	67	F	Tumor	Current	15	Yes, unknown	Benign/Benign	Deleterious	Tolerated
BRCA2 V1495I	66	F	Tumor	Former	20		Benign/Benign	Neutral	Tolerated

BRCA2 H1640Y	50	F	Tumor	Former	30		Probably damaging/ Possibly damaging	Deleterious	Tolerated
BRCA2 A1689T	56	M	Tumor	Former	na		Probably damaging/ Probably damaging	Deleterious	Affect protein function
BRCA2 N1805S	73	F	Tumor	Former	40		Possibly damaging/Benign	Deleterious	Tolerated
BRCA2 I1851S	70	F	Tumor	Former	28		Benign/Benign	Deleterious	Tolerated
BRCA2 I1957T	75	M	Duplicate Normal	na	NA	Prostate	Benign/Benign	Neutral	Tolerated
BRCA2 H2365Q	NA	F	Tumor	Former	5		Possibly damaging/Benign	Neutral	Affect protein function
BRCA2 P2409L	62	M	Normal Tissue	Never	0		Probably damaging/ Probably damaging	Deleterious	Affect protein function
BRCA2 A2911G	80	F	Tumor	Former	25	Another Lung primary	Possibly damaging/ Possibly damaging	Neutral	Affect protein function
BRCA2 R3052Q	72	M	Tumor	Former	35		Probably damaging/ Probably Damaging	Neutral	Affect protein function
BRCA2 K3083E	na	na	Tumor	na	na	BCC	Probably damaging/ Possibly Damaging	Neutral	Affect protein function
BRCA2 C3198R	62	F	Tumor	Former	75		Possibly damaging/Benign	Neutral	Tolerated
BRCA2 R3302K	na	na	Tumor	na	na	na	Probably damaging/ Probably damaging	Neutral	Affect protein function
BRCA2 E3309K	na	na	Tumor	na	na	na	Probably damaging/ Possibly damaging	Neutral	Tolerated
CHEK2									
CHEK2 R188Q	86	F	Tumor	na	na	Cervical	Probably damaging/ Probably damaging	Deleterious	Affect protein function
CHEK2 I294F	na	na	Tumor	na	na	na	Probably damaging/ Probably damaging	Deleterious	Affect protein function

CHEK2 N384T	48	F	Tumor	Former	33		Probably damaging/ Possibly damaging	Deleterious	Affect protein function
CHEK2 R562Q	61	F	Tumor	Former	7		Possibly damaging/Benign	Neutral	Tolerated
EGFR									
EGFR Q71R	70	F	Tumor	Former	20		Possibly damaging/Benign	Neutral	Tolerated
EGFR H145R	na	na	Tumor	na	na	CLL	Benign/Benign	Neutral	Tolerated
EGFR C231S	na	na	Tumor	na	na	na	Probably damaging/ probably damaging	Deleterious	Affect protein function
EGFR T638A	78	F	Tumor	Former	--		Benign/Benign	Neutral	Tolerated
EGFR G665S	68	M	Tumor	Former	62	Penis	Possibly damaging/Benign	Neutral	Tolerated
EGFR A743T	63	M	Tumor, Duplicate	Former	50		Probably damaging/ Probably damaging	Deleterious	Affect protein function
PARK2									
PARK2 R455H	70	F	Tumor	Former	20		Probably damaging/ probably damaging	Deleterious	Affect protein function
TP53									
TP53 R363G	59	M	Tumor	Current	80		Benign/Benign	Deleterious	Affect protein function

na, not available