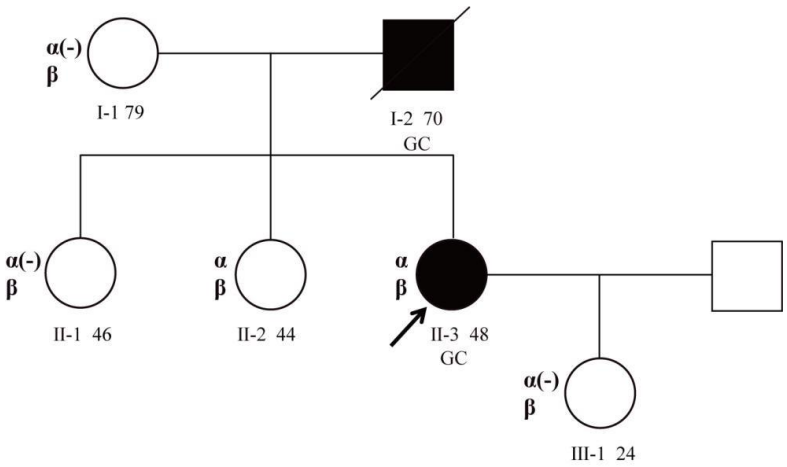

Fam-18:
α-*ATM* [c.1896del;p.Glu632AspfsTer17]
β-*MLH1* [c.1154G>A;p.Arg385His]
↗： prohand

Supplemental Figure 1. **Pedigrees of one HRD+MMR double-muts patient.**

Squares males; circles females. Black filled symbols indicate affected patients. Current age or age at diagnosis, when available, are also detailed. Proband is marked by an arrow, mutation status was studied in available relatives, and those carrying the mutation are shown with the mutation symbol (α, β), and if not patients a (-) is beside the mutation symbol. Abbreviations: GC, gastric cancer; Fam, family.

Supplemental table 1. Prediction results of missense variant, InDel and splice variant in HRD-mut patients

Gene_Name	Variant_Classification	cDNA_Change	Prediction		
			Polyphen-2	PROVEN	FSPLICE
PALB2	missense_variant	c.3296C>T	probably_damaging(0.999)		
FANCL	missense_variant	c.622G>A	probably_damaging(1)		
FANCA	missense_variant	c.209A>G	possibly_damaging(0.782)		
BRCA1	missense_variant	c.2726A>T	probably_damaging(0.953)		
ATM	missense_variant	c.6503C>T	possibly_damaging(0.763)		
MSH3	missense_variant	c.1777C>T	probably_damaging(1)		
APC	missense_variant	c.1984C>A	probably_damaging(0.994)		
ATM	missense_variant	c.107A>G	possibly_damaging(0.511)		
CHEK1	missense_variant	c.184C>G	possibly_damaging(0.764)		
ATM	missense_variant	c.1351C>T	probably_damaging(0.91)		
FANCI	missense_variant	c.2183A>G	possibly_damaging(0.819)		
ERCC2	missense_variant	c.1996C>T	probably_damaging(1)		
PMS2	missense_variant	c.58C>T	probably_damaging(0.924)		
FANCL	missense_variant	c.335C>T	possibly_damaging(0.583)		
FANCC	missense_variant	c.239T>C	possibly_damaging(0.654)		
ATM	missense_variant	c.6671T>C	possibly_damaging(0.762)		
FANCA	missense_variant	c.1840C>T	possibly_damaging(0.641)		
MSH2	missense_variant	c.2649T>G	possibly_damaging(0.729)		
BAP1	missense_variant	c.122G>C	possibly_damaging(0.669)		
BRCA2	missense_variant	c.9538C>T	probably_damaging(1)		
BRIP1	missense_variant	c.748A>G	probably_damaging(0.999)		
PTCH1	missense_variant	c.3784C>T	probably_damaging(0.996)		
BRCA1	missense_variant	c.1819A>G	probably_damaging(0.926)		
PALB2	missense_variant	c.3035C>T	probably_damaging(0.994)		
PTCH1	missense_variant	c.3247G>A	possibly_damaging(0.903)		
ATM	missense_variant	c.2944C>T	probably_damaging(0.977)		
PMS2	missense_variant	c.46A>G	possibly_damaging(0.736)		
FANCD2	missense_variant	c.2867A>G	probably_damaging(0.927)		
MLH1	missense_variant	c.1154G>A	probably_damaging(1)		
NSD1	missense_variant	c.487G>T	possibly_damaging(0.448)		
PDGFRA	missense_variant	c.689C>T	possibly_damaging(0.837)		
FANCA	missense_variant	c.323C>T	probably_damaging(0.976)		
SOS1	missense_variant	c.3257C>T	possibly_damaging(0.67)		
PDGFRA	missense_variant	c.1631T>C	possibly_damaging(0.452)		
SLX4	missense_variant	c.4883C>T	possibly_damaging(0.521)		
BRIP1	missense_variant	c.2301G>C	probably_damaging(0.966)		
CHEK2	missense_variant	c.1438G>A	probably_damaging(0.921)		
PTCH1	missense_variant	c.1558C>T	probably_damaging(0.986)		
MTUS1	missense_variant	c.1825A>C	probably_damaging(0.999)		
ATM	missense_variant	c.8246A>T	possibly_damaging(0.849)		

PDE11A	missense_variant	c.2411G>A	probably_damaging(0.918)
RAD51B	missense_variant	c.728A>G	probably_damaging(1)
BRCA1	missense_variant	c.398G>A	possibly_damaging(0.818)
ATM	missense_variant	c.1481G>A	possibly_damaging(0.462)
FANCA	missense_variant	c.2167C>A	probably_damaging(0.998)
FANCM	missense_variant	c.431A>G	possibly_damaging(0.599)
TP63	missense_variant	c.1244T>G	probably_damaging(0.977)
CDH1	missense_variant	c.2335C>T	probably_damaging(1)
BRCA1	missense_variant	c.3159A>C	probably_damaging(0.994)
BRIP1	missense_variant	c.1954G>A	probably_damaging(1)
USHBP1	missense_variant	c.22C>A	probably_damaging(0.994)
PALB2	missense_variant	c.3146T>C	probably_damaging(0.971)
UROD	missense_variant	c.919C>G	probably_damaging(0.967)
FANCL	missense_variant	c.671C>A	possibly_damaging(0.902)
BRIP1	missense_variant	c.1442G>A	probably_damaging(1)
FANCI	missense_variant	c.1111A>G	probably_damaging(0.958)
NTRK1	missense_variant	c.541G>A	probably_damaging(0.958)
FANCM	missense_variant	c.5387C>G	probably_damaging(0.956)
MLH1	missense_variant	c.1937A>G	probably_damaging(1)
BRCA2	missense_variant	c.7540A>G	probably_damaging(0.967)
ATM	missense_variant	c.7090G>C	probably_damaging(0.979)
SLX4	missense_variant	c.1271C>T	probably_damaging(0.998)
SLX4	missense_variant	c.2449G>C	possibly_damaging(0.903)
ATM	missense_variant	c.7463G>A	possibly_damaging(0.847)
BRCA2	missense_variant	c.8350C>T	probably_damaging(1)
BRIP1	missense_variant	c.2170A>C	probably_damaging(0.998)
POLH	missense_variant	c.1166G>C	possibly_damaging(0.719)
BRCA1	missense_variant	c.5324T>C	possibly_damaging(0.903)
VEGFA	missense_variant	c.1108C>T	probably_damaging(0.992)
BRCA2	missense_variant	c.3372G>C	probably_damaging(0.997)
PALLD	missense_variant	c.2576G>A	probably_damaging(0.999)
ATM	missense_variant	c.7382G>A	possibly_damaging(0.571)
RUNX3	missense_variant	c.58G>A	possibly_damaging(0.821)
BRIP1	missense_variant	c.2291A>G	probably_damaging(0.975)
BRCA2	missense_variant	c.4391C>G	probably_damaging(0.999)
FANCA	missense_variant	c.3163C>T	probably_damaging(0.999)
SDHAF2	missense_variant	c.320G>A	probably_damaging(0.98)
GJB2	missense_variant	c.571T>C	probably_damaging(1)
PALB2	missense_variant	c.2129C>T	probably_damaging(0.973)
FANCA	missense_variant	c.2365G>A	possibly_damaging(0.849)
ATM	missense_variant	c.169T>C	probably_damaging(0.988)
EXT2	missense_variant	c.995G>A	possibly_damaging(0.805)
PDE11A	missense_variant	c.764C>T	probably_damaging(0.925)
FANCA	missense_variant	c.3550C>T	possibly_damaging(0.53)

SMARCA4	missense_variant	c.602A>T	probably_damaging(0.932)		
BUB1B	missense_variant	c.2441G>A	probably_damaging(0.999)		
ELANE	missense_variant	c.100C>T	probably_damaging(0.998)		
FANCA	missense_variant	c.3418A>T	possibly_damaging(0.703)		
MTUS1	missense_variant	c.2732A>C	probably_damaging(0.962)		
MTUS1	missense_variant	c.3313G>C	possibly_damaging(0.867)		
ATM	missense_variant	c.4325A>G	probably_damaging(1)		
EXT2	missense_variant	c.1372G>A	probably_damaging(0.999)		
BRCA2	missense_variant	c.9845C>G	probably_damaging(0.954)		
HMBS	missense_variant	c.674G>A	possibly_damaging(0.857)		
FH	missense_variant	c.929A>G	probably_damaging(0.998)		
BRCA2	missense_variant	c.7109A>C	possibly_damaging(0.775)		
ATM	missense_variant	c.274A>G	probably_damaging(0.979)		
BRIP1	missense_variant	c.2629G>C	probably_damaging(1)		
FANCI	missense_variant	c.284T>A	probably_damaging(0.988)		
BRCA2	missense_variant	c.4405G>C	possibly_damaging(0.77)		
PALB2	missense_variant	c.3296C>G	probably_damaging(1)		
ATM	missense_variant	c.4241C>G	possibly_damaging(0.63)		
ATM	missense_variant	c.993G>C	probably_damaging(0.996)		
POLE	missense_variant	c.1123C>T	probably_damaging(1)		
BRCA1	inframe_deletion	c.3327_3329del		Deleterious(-6.79)	
BRCA2	inframe_deletion	c.5218_5223del		Deleterious(-11.92)	
PALB2	inframe_deletion	c.1206_1208del		Deleterious(-9.47)	
AIP	inframe_insertion	c.703_704insGGGAACTGATCGTGTCATCCC TGGCGCTGGCGGAACGCTATGCCCCCGCC AGCCGCGACGAAAGAATTTATGAACTGAT CCTCGATGAGA		Deleterious(-39.97)	
PTCH1	inframe_deletion	c.3289_3291del		Deleterious(-12.05)	
CHEK2	inframe_deletion	c.885_887del		Deleterious(-6.48)	
BRCA1	splice_donor_variant	c.4484+1G>T			GT site(14.92)
FANCG	splice_acceptor_variant	c.1434-2A>C			AG site(12.35)
CHEK2	splice_donor_variant	c.908+2T>A			GT site(10.58)
PDE11A	splice_acceptor_variant	c.1303-2A>T			AG site(6.9)
ATM	splice_donor_variant	c.3077+1G>A			GT site (9.6)
FANCL	splice_donor_variant	c.216+1G>T			GT site(15.06)

Supplemental Table 2. List of pathogenic/likely pathogenic germline mutations in ClinVar

Gene	Germline Mutation	Condition	ClinVar Classification
ATM	NM_000051.3:c.1402_1403delAA, (p.Lys468Glufs*18)	Hereditary cancer-predisposing syndrome	P/LP
BRCA2	NM_000059.3:c.1298dup, (p.Asn433Lysfs*19)	Breast-ovarian cancer, familial 2	P
BRCA2	NM_000059.3:c.3860del, (p.Asn1287Ilefs*6)	Hereditary cancer-predisposing syndrome/Breast-ovarian cancer, familial 2	P
PALB2	NM_024675.3:c.172_175del, (p.Gln60Argfs*7)	Hereditary breast and ovarian cancer syndrome	P/LP
ATM	NM_000051.3:c.1339C>T, (p.Arg447*)	Hereditary cancer-predisposing syndrome	P/LP
ATM	NC_000011.10(NM_000051.3):c.3077+1G>A	Hereditary cancer-predisposing syndrome	LP
BRCA2	NM_000059.3:c.6486_6489delACAA, (p.Lys2162Asnfs*5)	Hereditary breast and ovarian cancer syndrome	P
PALB2	NM_024675.3:c.1056_1057del, (p.Lys353Ilefs*7)	Hereditary cancer-predisposing syndrome	P
ATM	NM_000051.3:c.3602_3603del, (p.Phe1201Trpfs*3)	Hereditary cancer-predisposing syndrome/Ataxia-telangiectasia syndrome	P
BRCA1	NM_007294.3:c.2796del, (p.Gly933Valfs*67)	Breast-ovarian cancer, familial 1	P
BRCA2	NM_000059.3:c.7409dup, (p.Thr2471Hisfs*4)	Hereditary breast and ovarian cancer syndrome	P
ATM	NM_000051.3:c.7166C>G, (p.Ser2389*)	Ataxia-telangiectasia syndrome	P/LP
FANCA	NM_000135.2:c.3163C>T, (p.Arg1055Trp)	Fanconi anemia	P/LP
BRIP1	NM_032043.2:c.1315C>T, (p.Arg439*)	Hereditary cancer-predisposing syndrome	P
BRCA1	NC_000017.11(NM_007294.3):c.4484+1G>T	Hereditary breast and ovarian cancer syndrome	P
BRCA1	NM_007294.3:c.5335del, (p.Gln1779Asnfs*14)	Hereditary cancer-predisposing syndrome	P

Abbreviations: P, Pathogenic; LP, likely pathogenic

Supplemental Table 3. List of biallelic germline and somatic mutations of core HRD gene

Patient ID	Sex	Germline Mutation	Hom/Het	Somatic Alteration
P18	Female	*ATM* NM_000051.3: c.1896del, (p.Glu632Aspfs*17)	het	*ATM* NM_000051.3:c.6347+1G>T
P21	Male	*ATM* NM_000051.3: c.4995dup, (p.Glu1666Argfs*26)	het	*ATM* NM_000051.3:c.1189A>T, (p.Lys397*)
P24	Male	*BRCA2* NM_000059.3:c.1298dup, (p.Asn433Lysfs*19)	het	*BRCA2* NM_000059.3:c.793+2T>G
P25	Female	*BRCA2* NM_000059.3:c.3860del, (p.Asn1287Ilefs*6)	het	*BRCA2* NM_000059.3:c.3733del, (p.Glu1245Argfs*14)
P27	Male	*PALB2* NM_024675.3:c.172_175del, (p.Gln60Argfs*7)	het	*PALB2* NM_024675.3:c.2462A>G, (p.Asn821Ser)
P44	Male	*BRCA2* NM_000059.3:c.6486_6489delACAA, (p.Lys2162Asnfs*5)	het	*BRCA2* NM_000059.3:c.9521dupA, (p.Asn3174Lysfs*2)
P59	Male	*BRCA2* NM_000059.3:c.7409dup, (p.Thr2471Hisfs*4)	het	*BRCA2* NM_000059.3:c.1580del, (p.Pro527Glnfs*31)
P75	Female	*BRIP1* NM_032043.2:c.1442G>A, (p.Gly481Asp)	het	*BRIP1* NM_032043.2:c.2258A>C, (p.Asp753Ala)