



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

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

<i>SMARCA4</i>	missense_variant	c.602A>T	probably_damaging(0.932)	
<i>BUB1B</i>	missense_variant	c.2441G>A	probably_damaging(0.999)	
<i>ELANE</i>	missense_variant	c.100C>T	probably_damaging(0.998)	
<i>FANCA</i>	missense_variant	c.3418A>T	possibly_damaging(0.703)	
<i>MTUS1</i>	missense_variant	c.2732A>C	probably_damaging(0.962)	
<i>MTUS1</i>	missense_variant	c.3313G>C	possibly_damaging(0.867)	
<i>ATM</i>	missense_variant	c.4325A>G	probably_damaging(1)	
<i>EXT2</i>	missense_variant	c.1372G>A	probably_damaging(0.999)	
<i>BRCA2</i>	missense_variant	c.9845C>G	probably_damaging(0.954)	
<i>HMBS</i>	missense_variant	c.674G>A	possibly_damaging(0.857)	
<i>FH</i>	missense_variant	c.929A>G	probably_damaging(0.998)	
<i>BRCA2</i>	missense_variant	c.7109A>C	possibly_damaging(0.775)	
<i>ATM</i>	missense_variant	c.274A>G	probably_damaging(0.979)	
<i>BRIP1</i>	missense_variant	c.2629G>C	probably_damaging(1)	
<i>FANCI</i>	missense_variant	c.284T>A	probably_damaging(0.988)	
<i>BRCA2</i>	missense_variant	c.4405G>C	possibly_damaging(0.77)	
<i>PALB2</i>	missense_variant	c.3296C>G	probably_damaging(1)	
<i>ATM</i>	missense_variant	c.4241C>G	possibly_damaging(0.63)	
<i>ATM</i>	missense_variant	c.993G>C	probably_damaging(0.996)	
<i>POLE</i>	missense_variant	c.1123C>T	probably_damaging(1)	
<i>BRCA1</i>	inframe_deletion	c.3327_3329del		Deleterious(-6.79)
<i>BRCA2</i>	inframe_deletion	c.5218_5223del		Deleterious(-11.92)
<i>PALB2</i>	inframe_deletion	c.1206_1208del		Deleterious(-9.47)
<i>AIP</i>	inframe_insertion	c.703_704insGGGAAGTATCGTGCATCCC TGGCGCTGGCGGAACGCTATGCCCCGCC AGCCGCGACGAAAGAATTTATGAACTGAT CCTCGATGAGA		Deleterious(-39.97)
<i>PTCH1</i>	inframe_deletion	c.3289_3291del		Deleterious(-12.05)
<i>CHEK2</i>	inframe_deletion	c.885_887del		Deleterious(-6.48)
<i>BRCA1</i>	splice_donor_variant	c.4484+1G>T		GT site(14.92)
<i>FANCG</i>	splice_acceptor_variant	c.1434-2A>C		AG site(12.35)
<i>CHEK2</i>	splice_donor_variant	c.908+2T>A		GT site(10.58)
<i>PDE11A</i>	splice_acceptor_variant	c.1303-2A>T		AG site(6.9)
<i>ATM</i>	splice_donor_variant	c.3077+1G>A		GT site(9.6)
<i>FANCL</i>	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
<i>ATM</i>	NM_000051.3:c.1402_1403delAA, (p.Lys468Glufs*18)	Hereditary cancer-predisposing syndrome	P/LP
<i>BRCA2</i>	NM_000059.3:c.1298dup, (p.Asn433Lysfs*19)	Breast-ovarian cancer, familial 2	P
<i>BRCA2</i>	NM_000059.3:c.3860del, (p.Asn1287Ilefs*6)	Hereditary cancer-predisposing syndrome/Breast-ovarian cancer, familial 2	P
<i>PALB2</i>	NM_024675.3:c.172_175del, (p.Gln60Argfs*7)	Hereditary breast and ovarian cancer syndrome	P/LP
<i>ATM</i>	NM_000051.3:c.1339C>T, (p.Arg447*)	Hereditary cancer-predisposing syndrome	P/LP
<i>ATM</i>	NC_000011.10(NM_000051.3):c.3077+1G>A	Hereditary cancer-predisposing syndrome	LP
<i>BRCA2</i>	NM_000059.3:c.6486_6489delACAA, (p.Lys2162Asnfs*5)	Hereditary breast and ovarian cancer syndrome	P
<i>PALB2</i>	NM_024675.3:c.1056_1057del, (p.Lys353Ilefs*7)	Hereditary cancer-predisposing syndrome	P
<i>ATM</i>	NM_000051.3:c.3602_3603del, (p.Phe1201Trpfs*3)	Hereditary cancer-predisposing syndrome/Ataxia-telangiectasia syndrome	P
<i>BRCA1</i>	NM_007294.3:c.2796del, (p.Gly933Valfs*67)	Breast-ovarian cancer, familial 1	P
<i>BRCA2</i>	NM_000059.3:c.7409dup, (p.Thr2471Hisfs*4)	Hereditary breast and ovarian cancer syndrome	P
<i>ATM</i>	NM_000051.3:c.7166C>G, (p.Ser2389*)	Ataxia-telangiectasia syndrome	P/LP
<i>FANCA</i>	NM_000135.2:c.3163C>T, (p.Arg1055Trp)	Fanconi anemia	P/LP
<i>BRIP1</i>	NM_032043.2:c.1315C>T, (p.Arg439*)	Hereditary cancer-predisposing syndrome	P
<i>BRCA1</i>	NC_000017.11(NM_007294.3):c.4484+1G>T	Hereditary breast and ovarian cancer syndrome	P
<i>BRCA1</i>	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	Hon/Het	Somatic Alteration
P18	Female	<i>ATM</i> NM_000051.3:c.1896del, (p.Glu632Aspfs*17)	het	<i>ATM</i> NM_000051.3:c.6347+1G>T
P21	Male	<i>ATM</i> NM_000051.3:c.4995dup, (p.Glu1666Argfs*26)	het	<i>ATM</i> NM_000051.3:c.1189A>T, (p.Lys397*)
P24	Male	<i>BRCA2</i> NM_000059.3:c.1298dup, (p.Asn433Lysfs*19)	het	<i>BRCA2</i> NM_000059.3:c.793+2T>G
P25	Female	<i>BRCA2</i> NM_000059.3:c.3860del, (p.Asn1287Ilefs*6)	het	<i>BRCA2</i> NM_000059.3:c.3733del, (p.Glu1245Argfs*14)
P27	Male	<i>PALB2</i> NM_024675.3:c.172_175del, (p.Gln60Argfs*7)	het	<i>PALB2</i> NM_024675.3:c.246A>G, (p.Asn821Ser)
P44	Male	<i>BRCA2</i> NM_000059.3:c.6486_6489delACAA, (p.Lys2162Asnfs*5)	het	<i>BRCA2</i> NM_000059.3:c.9521dupA, (p.Asn3174Lysfs*2)
P59	Male	<i>BRCA2</i> NM_000059.3:c.7409dup, (p.Thr2471Hisfs*4)	het	<i>BRCA2</i> NM_000059.3:c.1580del, (p.Pro527Glnfs*31)
P75	Female	<i>BRIP1</i> NM_032043.2:c.1442G>A, (p.Gly481Asp)	het	<i>BRIP1</i> NM_032043.2:c.2258A>C, (p.Asp753Ala)