



Fam-18:  
 $\alpha$ -*ATM* [c.1896del;p.Glu632AspfsTer17]  
 $\beta$ -*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 ( $\alpha$ ,  $\beta$ ), 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<br>TGGCGCTGGCGGAACGCTATGCCCCGCC<br>AGCCGCGACGAAAGAATTTATGAACTGAT<br>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)       |