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The **FANCM**:p.Arg658* truncating variant is associated with risk of triple-negative breast cancer

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Breast cancer is a common disease partially caused by genetic risk factors. Germline pathogenic variants in DNA repair genes **BRCA1**, **BRCA2**, **PALB2**, **ATM**, and **CHEK2** are associated with breast cancer risk. **FANCM**, which encodes for a DNA translocase, has been proposed as a breast cancer predisposition gene, with greater effects for the ER-negative and triple-negative breast cancer (TNBC) subtypes. We tested the three recurrent protein-truncating variants **FANCM**:p.Arg658*, p.Gln1701*, and p.Arg1931* for association with breast cancer risk in 67,112 cases, 53,766 controls, and 26,662 carriers of pathogenic variants of **BRCA1** or **BRCA2**. These three variants were also studied functionally by measuring survival and chromosome fragility in **FANCM**⁻/⁻ patient-derived immortalized fibroblasts treated with diepoxybutane or olaparib. We observed that **FANCM**:p.Arg658* was associated with increased risk of ER-negative disease and TNBC (OR = 2.44, \( P = 0.034 \) and OR = 3.79; \( P = 0.009 \), respectively). In a country-restricted analysis, we confirmed the associations detected for **FANCM**:p.Arg658* and found that also **FANCM**:p.Arg1931* was associated with ER-negative breast cancer risk (OR = 1.96; \( P = 0.006 \)). The functional results indicated that all three variants were deleterious affecting cell survival and chromosome stability with **FANCM**:p.Arg658* causing more severe phenotypes. In conclusion, we confirmed that the two rare **FANCM** deleterious variants p.Arg658* and p.Arg1931* are risk factors for ER-negative and TNBC subtypes. Overall our data suggest that the effect of truncating variants on breast cancer risk may depend on their position in the gene. Cell sensitivity to olaparib exposure, identifies a possible therapeutic option to treat **FANCM**-associated tumors.

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**INTRODUCTION**

The genetic architecture of inherited breast cancer is complex and involves germline pathogenic variants in high and moderate-risk genes and polygenic factors. The major high-penetrance breast cancer risk genes include **BRCA1**, **BRCA2**, **PALB2**, **ATM**, and **CHEK2**. The genetic variants predisposing to different human cancers (e.g., breast, colon, lung, ovary, endometrium and prostate cancers). Recently, based on a prospective cohort of families carrying **BRCA1** or **BRCA2** pathogenic variants, the average cumulative risk by age 80 was estimated to be 72% and 69% for carriers of **BRCA1** and **BRCA2** pathogenic variants, respectively.

**PALB2** has been previously considered a moderate-risk gene, but the latest estimate of about 44% lifetime risk associated with pathogenic variants may raise this gene to the high-risk group. Pathogenic variants in moderate-penetrance genes **ATM** and **CHEK2** are also associated with breast cancer, conferring a 20% average lifetime risk. Recently, **BARD1**, **RADS1D**, **BRI1P1**, and **RADS1C** have been proposed as risk factors for triple-negative breast cancer (TNBC) with **BARD1** and **RADS1D** conferring high risk, and **BRI1P1** and **RADS1C** associated with moderate risk. Thus, the risk associated with pathogenic variants in each gene may vary by breast tumor subtype.

Many of the **BRCA1**/**FA** pathway genes when altered by biallelic mutations cause FA disease. The **FANCM** gene (FA complementation group M, OMIM #609644) encodes for a translocase, which is a member of the **BRCA1**/**FA** molecular pathway but has been recently disqualified as a disease-causing factor for FA. Some protein-truncating variants in the **FANCM** gene were described as moderate breast cancer risk factors with a greater risk of TNBC. In the Finnish population, **FANCM**:c.5101 C > T (p.Gln1701*, rs147021911) is relatively frequent and was reported to be associated with breast cancer with odds ratio (OR) of 1.86 with 95% confidence intervals (CIs) = 1.26–2.75. A larger effect was observed in familial cases (OR = 2.11; 95% CI = 1.43–3.32), for estrogen receptor-negative (ER-negative) breast cancer (OR = 2.37; 95% CI = 1.37–4.12) and for TNBC (OR = 3.56; 95% CI = 1.81–6.98). We showed an increased risk (OR = 3.93; 95% CI = 1.28–12.11) of the **FANCM**:c.5791 C > T (rs144567652) truncating variant using familial cases and controls. In vitro analysis showed that this variant causes the skipping of the **FANCM** exon 22 and the creation of a downstream stop codon (p.Gly1906Alafs12*).

However, in the present study we refer to the **FANCM**:c.5791 C > T base change as to **FANCM**:p.Arg1931*, which is the conventional amino acid annotation (consistent with the stop codon creation according to genetic code). The **FANCM**:p.Arg1931* was also found to be associated with TNBC risk in the Finnish population (OR = 5.14; 95% CI = 1.65–16.0). A burden analysis of truncating variants discovered by a re-sequencing analysis of the entire **FANCM** coding region in German cases and controls confirmed that **FANCM** pathogenic variants had a particularly high risk for TNBC (OR = 3.75; 95% CI = 1.0–12.85).

To study the effect of **FANCM** on breast cancer risk further, we tested three recurrent truncating variants **FANCM**:p.Arg658*, p.Gln1701*, and p.Arg1931*, within the OncoArray Consortium, a collaboration of consortia established to discover germline genetic variants predisposing to different human cancers (e.g., breast, colon, lung, ovary, endometrium and prostate cancers). These three variants were tested for association with breast cancer risk in 67,112 breast cancer cases, 53,766 controls, and 26,662 carriers of pathogenic variants in **BRCA1** or **BRCA2**. We also studied the functional effect of these three variants after their lentiviral transduction into a **FANCM**⁻/⁻ patient-derived cell line in which

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we measured survival and chromosome fragility after exposure to diepoxybutane (DEB) or the poly (ADP-ribose) polymerase inhibitor (PARPi) olaparib.

RESULTS
Case-control analyses
We analyzed the association of three FANCM truncating variants, p.Arg658*, p.Gln1701*, and p.Arg1931*, with breast cancer risk for each variant separately and using a burden analysis. We tested 67,112 invasive breast cancer cases and 53,766 controls collected by the Breast Cancer Association Consortium (BCAC, http://bcac.ccge.medschl.cam.ac.uk/) and 26,662 carriers of BRCA1 or BRCA2 pathogenic variants collected by the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA, http://cimba.ccge.medschl.cam.ac.uk/), of whom 13,497 were affected with breast cancer and 13,165 were unaffected.

In the BCAC dataset we assessed the breast cancer risk associated with the FANCM variation as a primary overall analysis and in a restricted analysis including only countries in which the variant carrier frequencies were higher than the median of the frequencies. In these analyses we tested association with the variants in all available invasive breast cancer cases or in the ER-positive, ER-negative and TNBC subgroups (Table 1). In the overall analysis, no evidence of association was observed, either with the presence of any FANCM variant or with any of the three variants individually. However, FANCM:p.Arg658* showed a higher heterozygote frequency in ER-negative breast cancer cases (0.093%) than in controls (0.035%) with a greater than two-fold increased breast cancer risk (OR = 2.44, 95% CI = 1.12–5.34, P = 0.034). When only TNBC cases were considered, the association was stronger (OR = 3.79, 95% CI = 1.56–9.18, P = 0.009). No association with ER-negative breast cancer or TNBC was seen for p.Gln1701* or p.Arg1931*.

Analyses of carriers of BRCA1 or BRCA2 pathogenic variants
We found no evidence of associations for FANCM:p.Arg658*, p.Gln1701*, and p.Arg1931* truncating variants with breast cancer risk in carriers of BRCA1 or BRCA2 pathogenic variants included in CIMBA (Supplementary Table 1). The p.Arg658* was detected with approximately four-fold higher frequencies in the BRCA1 affected individuals (0.063%) in comparison to the unaffected (0.013%), and in the BRCA2 affected individuals (0.071%) in comparison to the unaffected (0.019%). Consistently, hazard ratios (HRs) above two were estimated for BRCA1 (HR = 2.4, 95% CI = 0.52–11.12) and for BRCA2 (HR = 2.13, 95% CI = 0.41–11.14) pathogenic variant carriers. The frequencies of p.Gln1701* and p.Arg1931* were not increased in affected versus unaffected individuals carrying BRCA1 or BRCA2 pathogenic variants (Supplementary Table 1).

Functional studies
We tested the functional effect of FANCM:p.Arg658*, p.Gln1701*, and p.Arg1931* on DNA repair using genetic complementation assays (Fig. 1). These assays were based on the EGF280 cell line derived from immortalized fibroblasts from a patient who lacked the FANCM protein due to a homozygous c.1506_1507insTA (p. Ile503*, rs764743944) truncating variant. Complemented FANCM–/– cells were tested for sensitivity to DEB and olaparib.

Table 1. Single-variant and burden analyses of FANCM:p.Arg658*, p. Gln1701* and p.Arg1931* truncating variants in overall and country-restricted invasive breast cancer cases and controls

| Overall | Subgroup | Carriers | Non-carriers | Freq % | OR 95% CI | P  |
|---------|----------|----------|--------------|--------|-----------|----|
| FANCM:p.Arg658* | Controls | 19 | 53,717 | 0.035 | NA | |
| All cases | 31 | 67,038 | 0.046 | 1.26 | 0.71–2.25 | 0.430 |
| ER-positive | 19 | 44,516 | 0.043 | 1.15 | 0.61–2.20 | 0.670 |
| ER-negative | 10 | 10,750 | 0.093 | 2.44 | 1.12–5.34 | 0.034 |
| TNBC | 7 | 4794 | 0.146 | 3.79 | 1.56–9.18 | 0.009 |
| FANCM:p.Gln1701* | Controls | 122 | 53,635 | 0.229 | NA | |
| All cases | 116 | 66,968 | 0.232 | 1.09 | 0.85–1.38 | 0.798 |
| ER-positive | 74 | 44,467 | 0.218 | 1.02 | 0.78–1.34 | 0.893 |
| ER-negative | 27 | 10,742 | 0.204 | 0.97 | 0.61–1.56 | 0.369 |
| TNBC | 10 | 4795 | 0.208 | 1.29 | 0.67–2.50 | 0.461 |
| All variants | 237 | 53,455 | 0.443 | NA | |
| Controls | 302 | 66,736 | 0.452 | 1.02 | 0.86–1.21 | 0.823 |
| ER-positive | 190 | 44,323 | 0.427 | 0.96 | 0.79–1.16 | 0.698 |
| ER-negative | 58 | 10,700 | 0.548 | 1.23 | 0.92–1.64 | 0.154 |
| TNBC | 27 | 4773 | 0.583 | 1.32 | 0.89–1.95 | 0.167 |

Country-restricted

| Overall | Subgroup | Carriers | Non-carriers | Freq % | OR 95% CI | P  |
|---------|----------|----------|--------------|--------|-----------|----|
| FANCM:p.Arg658* | Controls | 19 | 48,887 | 0.039 | NA | |
| All cases | 31 | 59,540 | 0.052 | 1.23 | 0.69–2.20 | 0.478 |
| ER-positive | 19 | 39,453 | 0.048 | 1.12 | 0.59–2.15 | 0.722 |
| ER-negative | 10 | 9613 | 0.104 | 2.31 | 1.05–5.07 | 0.047 |
| TNBC | 7 | 4283 | 0.163 | 3.56 | 1.46–8.69 | 0.011 |
| FANCM:p.Gln1701* | Controls | 120 | 48,506 | 0.249 | NA | |
| All cases | 152 | 58,919 | 0.259 | 1.08 | 0.85–1.38 | 0.813 |
| ER-positive | 96 | 38,892 | 0.246 | 1.02 | 0.77–1.34 | 0.895 |
| ER-negative | 21 | 9558 | 0.230 | 0.97 | 0.60–1.56 | 0.368 |
| TNBC | 10 | 4197 | 0.261 | 1.09 | 0.56–2.10 | 0.150 |
| FANCM:p.Arg1931* | Controls | 77 | 34,988 | 0.220 | NA | |
| All cases | 93 | 37,903 | 0.245 | 1.14 | 0.84–1.54 | 0.396 |
| ER-positive | 59 | 25,274 | 0.233 | 1.09 | 0.77–1.53 | 0.632 |
| ER-negative | 25 | 5920 | 0.421 | 1.96 | 1.24–3.10 | 0.006 |
| TNBC | 10 | 2614 | 0.381 | 1.77 | 0.91–3.45 | 0.116 |

Controls NA | All cases NA | ER-positive NA
by measuring cell survival and chromosome fragility. The FANCM protein was not detectable in the EGF280 fibroblasts. The transduction of these cells with lentiviral vectors carrying wild-type (wt) FANCM cDNA and cDNAs harboring FANCM:p.Gln1701* and p.Arg1931* variants produced, as expected, different C-terminal truncated forms of FANCM. In the EGF280 cells transduced with FANCM:p.Arg658* no visible band was observed on western blot (Fig. 1a and Supplementary Fig. 1). As we lack information on the epitope recognized by the antibody, we could not determine whether the p.Arg658*-derived truncated protein was unstable or if the epitope was lost due to the truncation. We therefore analyzed the mRNA expression of FANCM:p.Arg658* by reverse transcription and digestion of the PCR-amplified cDNAs. The c.1972C>T base substitution causing the p.Arg658* variant was expected to abolish a digestion site for the restriction enzyme TseI present in the wt sequence. TseI-digestion of wt and mutated cDNAs clearly indicated the presence of a mutated mRNA product in the EGF280 cells transduced with FANCM:p.Arg658* (Fig. 1b and Supplementary Fig. 1).

In the DEB sensitivity-based assay (Fig. 1c), the EGF280 patient-derived cell line showed a high-sensitivity phenotype, that was rescued by expression of the wt FANCM. EGF280 cells expressing FANCM:p.Arg658* failed to rescue DEB sensitivity and showed survival rates overlapping with those of the native EGF280 cells. In comparison, cells expressing FANCM:p.Gln1701* and p.Arg1931* variants showed an intermediate phenotype with survival rates significantly higher than those of EGF280 cells, though significantly lower than those of the cells expressing wt FANCM (Fig. 1c and Supplementary Table 2). These results were confirmed in the chromosome fragility tests where the number of chromatid breaks in cells harboring p.Gln1701* or p.Arg1931* variants was statistically lower than that of EGF280 cells or cells expressing the p.Arg658* and statistically higher than that of cells expressing wt FANCM (Fig. 1d). In the olaparib sensitivity-based assay, the survival rates of the cell lines transduced with the three FANCM truncating variants were not statistically different. Only at higher olaparib concentrations (>5000 nM) the survival rates of these cell lines were significantly lower than that of the wt FANCM cells and higher than that of the EGF280 cells (Fig. 1e and Supplementary Table 3).

**DISCUSSION**

In this study we investigated the association of the three recurrent FANCM truncating variants p.Arg658*, p.Gln1701*, and p.Arg1931*, with breast cancer risk overall and by tumor subtype. While in non-Finnish Europeans these are the three most common FANCM truncating variants, their carrier frequency is low being 0.033, 0.21 and 0.21%, respectively (https://gnomad.broadinstitute.org/). We conducted large case-control studies in 67,112 unselected breast cancer cases, 53,766 controls, and 26,662 carriers of BRCA1 or BRCA2 pathogenic variants. Furthermore, we performed functional analyses based on a patient-derived FANCM−/− cell line transduced with vectors carrying the three FANCM variants and tested for sensitivity to DEB or olaparib. Our genetic data suggest that FANCM:p.Arg658* is a risk factor for ER-negative and TNBC subtypes with statistically significant ORs of 2.44 and 3.79, respectively. These associations were confirmed when we restricted the analyses to countries with higher carrier frequencies. In these restricted analyses we also found that the p.Arg1931* was associated with breast cancer risk in the ER-negative subtype with statistically significant OR = 1.96. (Table 1). These data, together with previously published genetic studies,10–13 confirm that FANCM truncating variants are risk factors for breast cancer, with a stronger association for the ER-negative and TNBC subtypes. Our functional data, obtained in a background of a FANCM null cell line, support these findings showing that all three truncating variants were deleterious; hence, it is expected that, in the heterozygous state, any of these FANCM variants have partial activity. In the functional tests, we also observed that olaparib had a greater effect on survival of the cells harboring any of the FANCM:p.Arg658*, p.Gln1701*, or p.Arg1931* variants with respect to that on EGF280 cells complemented with wt FANCM (Fig. 1e). As this is consistent with previous results,16 PARP1 inhibition might be a possible therapeutic approach to treat patients with breast tumors associated with germline FANCM pathogenic variants. On the contrary, the DEB sensitivity assays showed that FANCM:p.Arg658*, is associated with a stronger impairment of DNA repair activity, compared to p.Gln1701* and p.Arg1931*, possibly reflecting the position of protein truncation (Fig. 1c, d).

FANCM encodes for a key protein of the upstream FA/BRC-A pathway mediating the assembly of the FA core complex. This protein is 2048 AA long, possesses in its N-terminal region an intrinsic ATP-dependent DNA translocase activity and, with its central region, recognizes the Bloom’s complex, which is also involved in the DNA HR repair. By interacting with its C-terminal binding partner, the FA associated protein 24 (FAAP24), the FANCM protein brings to sites of ICL DNA lesions the FA and the binding partner, the FA associated protein 24 (FAAP24), the central region, recognizes the Bloom’s complex, 17 which is involved in the DNA HR repair. By interacting with its C-terminal binding partner, the FA associated protein 24 (FAAP24), the FANCM protein brings to sites of ICL DNA lesions the FA and the binding partner, the FA associated protein 24 (FAAP24), the central region, recognizes the Bloom’s complex, which is also involved in the DNA HR repair. By interacting with its C-terminal binding partner, the FA associated protein 24 (FAAP24), the FANCM protein brings to sites of ICL DNA lesions the FA and the binding partner, the FA associated protein 24 (FAAP24), the central region, recognizes the Bloom’s complex, which is also involved in the DNA HR repair. The p.Gln1701* and p.Arg1931* forms were expressed and that the p.Arg658*-mRNA is transcribed (Fig. 1b, b). An N-terminus fragment including the first 422 AA of FANCM was shown to be stable when expressed in human cell lines,17 thus supporting the possibility that the FANCM:p.Arg658* derived protein may also be expressed and stable. Hence, we hypothesize that the observed difference in survival and chromosome fragility of cells treated with DEB may be attributable to the diverse residual function of the different truncated forms of FANCM. In fact, the p.Gln1701* and p.Arg1931* derived forms are expected to lose the interaction with FAAP24, but to retain the ability of binding other FANCM interacting proteins. Hence, our data suggest that the lack of interaction between FANCM and FAAP24 has a less severe impact on the DNA damage response than when protein truncation occurs upstream the FANCM domains AA 687–1104 and AA 1027–1362 mediating the interaction with the FA core complex and the Bloom’s complex, respectively.

Previously published genetic and clinical data support our hypothesis of a position effect. FANCM pathogenic variants were shown to be associated with a moderate risk of developing high-grade serous epithelial ovarian cancer, but p.Arg1931* appeared to confer a lower risk.18 Moreover, five female breast cancer

**Table 1 continued**

| Subgroup       | Country-restricted | Carriers | Non-carriers | Freq % OR 95% CI P |
|----------------|-------------------|----------|--------------|--------------------|
| ER-negative    | NA                |          |              |                    |
| TNBC           | NA                |          |              |                    |

In bold are indicated the statistically significant results. Freq frequency, OR odds ratio CI confidence interval, P P-value, TNBC triple-negative breast cancer, NA not applicable.

*The burden analyses were performed by univariate logistic regression.

**These analyses were not possible in the country-restricted cases and controls as different countries were included for each variant. P-values were from Pearson chi-squared test.
Fig. 1 Functional studies of the FANCM:p.Arg658*, p.Gln1701* and p.Arg1931* truncating variants using the patient-derived FANCM−/− EGF280 cell line. 

**a** Western blot showing the FANCM expression in EGF280 cells complemented with lentiviral vectors harboring the three different variants. Bands corresponding to truncated FANCM protein were visible for EGF280+p.Gln1701* and p.Arg1931*, and no bands were present for the EGF280+p.Arg658*.

**b** Study of the expression of the FANCM protein in EGF280+p.Arg658*. The c.1972C > T base substitution, causing the p.Arg658* variant abrogates a digestion site for the restriction enzyme TseI that is present in the wild-type (wt) cDNA sequence. Total RNA was extracted from EGF280+wtFANCM and from the EGF280+p.Arg658* and subjected to reverse transcription. PCR-amplified cDNA products were digested with TseI. Digested and undigested cDNAs were loaded. In the first two lanes are shown bands of 386 bp corresponding to uncut wt cDNA, and bands of 257 and 129 bp corresponding to cut wt cDNA. In next two lanes bands of 386 bp indicate that p.Arg658* cDNA was not cut due to the c.1972C > T base substitution abrogating the TseI site. In the two lanes after the molecular weight marker (M) undigested and digested cDNAs were loaded. In the two lanes after the molecular weight marker (M) undigested and digested cDNAs were loaded. In the two lanes after the molecular weight marker (M) undigested and digested cDNAs were loaded.

**c** Analysis of diepoxybutane (DEB) sensitivity on cell survival. The EGF280 cells expressing p.Arg658* are significantly more sensitive to DEB than the cells expressing p.Gln1701* or p.Arg1931* (P-values from Tukey’s range test are reported in Supplementary Table 4). EGF280 and EGF280+wtFANCM are used as controls (N = 3; error bars: standard deviation).

**d** Chromatidic break patterns of the cells expressing wt FANCM, of the cells harboring p.Gln1701* or p.Arg1931* variants, and of the native EGF280 cells or the cells expressing p.Arg658* were statistically different. (P-values from chi-squared test; N = 2).

**e** Analysis of cellular sensitivity to olaparib. Contrarily to what we observed in the DEB sensitivity assays, survival rates of the different complemented cell lines were apparently not different. Human fibroblasts (BRCA2−/−) were homozygous for the c.469 A > T (p.Lys157*) truncating variant and were used as a positive control. (P-values from Tukey’s range test are reported in Supplementary Table 5; N = 3; error bars: standard deviation). All blots derive from the same experiment and were processed in parallel.
METHODS

Study participants

The individuals included in this study were women of genetically confirmed European ancestry who were originally ascertained in 73 case-control studies from 19 countries participating in the BCAC or in 59 studies enrolling BRCA1 or BRCA2 pathogenic variants carrier from 30 countries participating in the CIMBA.

Ethics

All participating studies, listed in Supplementary Table 4 and Supplementary Table 5, were approved by their ethics review boards and followed national guidelines for informed consent. However, due to the retrospective nature of the majority of the studies, not all participant individuals have provided written informed consent to take part in the present analysis. The Milan Breast Cancer Study Group (MBCSG) was approved by ethics committee from Istituto Nazionale dei Tumori di Milano and Istituto Europeo di Oncologia, in Milan.

The BCAC studies contributed 67,112 invasive breast cancer cases and 53,766 controls. The majority of these studies were population-based, hospital-based or case-control studies nested within population-based cohorts (86%); few were family-clinic-based studies (14%; Supplementary Table 4). For each study subject, information on the disease status and the age at diagnosis or at interview were provided. Data on lifestyle risk factors were available for most studies and clinical and pathological data were available for most cases. All these data were incorporated in the BCAC dataset (version 10). A total of 44,565 (66%) cases were ER-positive, 10,770 (16%) were ER-negative, and 4,805 (7%) were TNBC; 13,743 (20%) had a first-degree family history of breast cancer.

The CIMBA studies contributed 15,679 carriers of a pathogenic BRCA1 variant and 10,983 carriers of a pathogenic BRCA2 variant to this analysis (Supplementary Table 5). Nearly all (98%) of these carriers were ascertained through cancer genetic clinics; few carriers were recruited by population-based sampling of cases or by community recruitment. In some instances, multiple members of the same family were included. For each pathogenic variant carrier, the information on the type of the BRCA1 or BRCA2 variant, disease status, and censoring variables (see below, Statistical analyses) were collected and included in the CIMBA database.

Genotyping

Genotyping of FANCMp.Arg658*, p.Gln1701*, and p.Arg1931* truncating variants was conducted using a custom-designed Illumina genotyping array (the “OncoArray”), Illumina, Inc. San Diego, CA, USA at six independent laboratories. To ensure consistency of the genotype data, all laboratories used the same genotype-clustering file and genotyped the same set of reference-samples selected from the HapMap project. Samples with a call rate <95% and those with heterozygosity <5% or >40% were excluded. Further details of the genotype-calling and quality control have been described previously. The cluster plots of the three FANCM truncating variants were curated manually to confirm the automatic calls (Supplementary Fig. 2).

Statistical analyses

The BCAC data were analyzed to test the association between FANCMp.Arg658*, p.Gln1701*, and p.Arg1931* and breast cancer risk. Logistic regression analyses were performed to estimate ORs with 95% CIs for variant carriers versus non-carriers, adjusting for country and the first ten principal components, as previously described. P-values were calculated by applying the likelihood ratio test (LRT) comparing the model containing the variant carrier status as a covariate to a model without the variant carrier status. The primary analyses were performed including all invasive breast cancer cases and controls and subgrouping cases based on tumor hormonal status. We then performed a country-restricted analysis.
including the 50% of the countries with the higher variant carrier frequencies. Specifically, we included only countries in which the carrier frequencies in cases and controls combined were higher than the median of the carrier frequencies observed in all countries. Median frequencies were 0.007, 0.114 and 0.163 for p.Arg658*, p.Gln1701* and p.Arg1931* carriers, respectively.

The CIMBA data were analyzed to evaluate the association between each FANCM truncating variant and breast cancer risk in carriers of BRCA1 or BRCA2 pathogenic variant. A survival analyses framework was applied. Briefly, each variant carrier was followed from the age of 18 years until the first breast cancer diagnosis, or censored as unaffected at ovarian cancer diagnosis, bilateral prophylactic mastectomy, or age at last follow-up. The analyses were performed by modelling the retrospective likelihood of the observed genotypes conditional on the disease phenotype as detailed previously. All analyses were stratified for country. The per-allele hazard ratio (HR), 95% CIs were estimated separately for each variant. A score test was used to derive P-values for the associations. The analyses of the BCAC data were performed using STATA version 15 (StataCorp LLC, College Station, Texas, USA). The analyses of the CIMBA data were carried out using custom-written code in Python and Fortran. All statistical tests were two-sided and P-values <0.05 were considered statistically significant.

Cell lines, plasmids, and lentiviral particles production and transduction

The immortalized patient-derived FANCM−/− cell line EGF280 was transduced with pLenti CMV rtTA3 Blast, a gift from E. Campeau (Addgene plasmid #26429). The doxyxycycline-inducible lentiviral vector pLVX-3TRE3-G-FANCM, a gift from N. Ameziane (Vrije Universiteit Medical Center, Amsterdam) was mutated by site-directed mutagenesis using the QuickChange II XL Site-Directed Mutagenesis Kit (Agilent Technologies) and the following PAGE purified mutagenic primers. FANCM c.1972C>T primer 1: 5′-GCTTCTCGGAACTTGAGAAGTCTCATCTTCTCC-3′ and primer 2: 5′-GGGAAATGATGACCTTCACTGGAAGTCCAGAACG-3′ for the p.Arg658*; FANCM c.5101C>T primer 1: 5′-TAAACATGTCGC-TATGTGCTTCCTTTAAGCGTCTCTGTTG-3′ and primer 2: 5′-ACCCAAAGCAGTTGAAAGAACCAACAGGACCACCTGTTAAA-3′ for the p.Gln1701*.

Generation of the lentiviral vector containing the FANCMc.5791C>T (p.Arg1931*) and transduction of the EGF280 cells were already described. Expression of exogenous FANCM protein was achieved supplementing cell culture medium with doxycycline (1 μg/ml, final concentration). All the cell lines used in this study were routinely checked for mycoplasma contamination using the MycoAlert™ Mycoplasma Detection Kit (Lonza).

Western blot and mRNA expression studies

Cell lysis and western blot assays were performed as previously described.8 The following primary antibodies were used: mouse monoclonal anti-FANCM primary antibody, clone C2V1 diluted 1:100 (ref. MABC45, MERCK Millipore), mouse monoclonal anti-Vinculin diluted 1:3000 (ref: ab18058, abcam). Western blotting detection was achieved with LuminataTM (Millipore), mouse monoclonal anti-Vinculin (clone CV5.1 diluted 1:100 (ref: MABC545, MERCK Millipore), mouse monoclonal anti-Vinculin diluted 1:3000 (ref: ab18058, abcam). Western blot and mRNA expression studies

Cell survival assay

The effect of the different FANCM variants on cell survival was measured with a Sulforhodamine B (SRB) assay.5 One-thousand cells were seeded in 96-well plates and treated constantly with DEB or PARPi olaparib at the indicated concentrations until untreated cells reached confluency. Cell monolayers were fixed overnight at 4 °C with 75 μl of 20% trichloroacetic acid (TCA). TCA was aspirated, and cells washed with tap water. Once dried, 50 μl of SRB was added to the wells and plates were incubated on a shaker at room temperature for 30 min. The excess of SRB dye was removed by washing repeatedly with 1% acetic acid, the plates were dried for 20 min, and the protein-bound dye was dissolved in 10 mM Tris for OD determination at 492 nm using a microplate reader (Tecan Sunrise™).
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G. Figlioli et al.

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G. F. and M. B. contributed equally to this work as first author. J. S. and P. P. contributed equally to this work as last author. Conceived the study: G. F., M. B., I. C., P. R., H. N., J. S., P. P. Wrote the manuscript: G. F., P. P. Contributed to manuscript writing: M. B., T. A., A. J., M. H. G., W. C. K., R. L. M., G. C. T., D. T., M. K. S., D. F. E., P. R., H. N. Conceived, designed, or obtained financial support for the OncoArray: P. K., J. S., D. F. E. A. Data management: D. J., J. D., K. M., M. K. B. G., A. L. M. D. L., Q. L. W., L. M., T. M. P. P., D. P. P., A. C. Statistical analyses: G. F., J. J. K., H. N. P. P. Functional analyses: M. B., L. C., S. V. L., J. P., P. J., J. D. T., M. A. T., T. T., N. T., M. U., C. M., J. S. C., K. B. M., C. C., A. C., T. A. C., D. G. C., C. C., K. M. B., D. M. B., D. M. D., P. D., V. C. D. G. S., D. N., S. M. D., C. M. D., I. D. S. S., K. D., M. D., D. M., A. B. E., A. H. E., C. E., M. E., D. G. E., P. A. F., J. F., J. F. W., D. F. F., T. M. F., E. M. F., G. M. O., M. G. D., C. M. G., S. M. G., J. M. G., J. A. S., M. M. G., S. A. G. G., G. G., A. K. G., M. D. G. E., P. G., G. U., A. G. B., L. H., C. A. H., N. H., P. H., U. A., H. P., A. H., J. H., P. H., A. H., J. L. H., H. D. H. I. I. H., A. H. O., C. H., P. J. H., D. H., E. N. I., J. N., C. W., A. W., X. R. Y., W. Z., A. Z., K. K. Z., A. M. O. A., S. M. O., J. E. O., H. O., A. O., L. O., B. P., A. P., J. P., D. P.-K., T. P., N. P., M. A. P., K. B., J. R., M. U. R., R. R. M., G. H. S., A. R., A. R., E. M., R. R., V. R., M. U., E. S., K. S., M. S., M. T. S., R. K. S., M. C. S., C. S. L., M. S. H., P. S., X. O.-S., J. S., C. F. S., C. S. O., P. S., M. C. S., J. S. L., D. S. L., W. J. T., M. R. T., M. B. T., M. T., J. T., D. L. T., M. T., R. A. E. M. T., D. T. M. A. T. T., N. T., M. U., C. M. V., E. J. V. R., E. M. V., A. V., A. V., B. W., J. N. W., C. W., G. W., A. W., X. R. Y., W. Z., A. K., K. Z., A. M. D., M. L., Q. L. W., L. M., T. M. P. P. P., P. F., A. E. T., L. A. I., S. J. R., A. J. S., M. H. G., W. C. K., R. L. M., G. C. T., D. T., M. K. S. D. E. F., P. R., E. H., A. C. A., F. J. H., N. H., P. P. All authors read and approved the final version of the manuscript.

Competing Interests
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