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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 polygenetic factors. The major high-penetrance breast cancer risk genes include *BRCA1* and *BRCA2*, which are key factors in the DNA double-strand break repair through homologous recombination (HR) and in the inter-strand crosslink (ICL) repair as a part of the Fanconi Anemia (FA) pathway.[1,2] 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.[3] *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.[4] Pathogenic variants in moderate-penetrance genes *ATM* and *CHEK2* are also associated with breast cancer, conferring a 20% average lifetime risk.[5,6] Recently, *BARD1*, *RAD51D*, *BRIP1*, and *RAD51C* have been proposed as risk factors for triple-negative breast cancer (TNBC) with *BARD1* and *RAD51D* conferring high risk, and *BRIP1* and *RAD51C* associated with moderate risk.[7] Thus, the risk associated with pathogenic variants in each gene may vary by breast tumor subtype.

Many of the *BRCA/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 BRCA/FA molecular pathway but has been recently disqualified as a disease-causing factor for FA.[8,9] 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).[10] 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*).[11] 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).[12] 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).[13]

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).[14] 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* variants in 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* or for all mutations combined (Table 1). In the country-restricted analyses, we confirmed the association found for p.Arg658* with risk of ER-negative disease and TNBC (OR = 2.31, 95% CI = 1.05–5.07, $P = 0.047$ and OR = 3.56, 95% CI = 1.46–8.69, $P = 0.011$, respectively). The restricted set also provided evidence for an association between p.Arg1931* and ER-negative subgroup (OR = 1.96, 95% CI = 1.24–3.10, $P = 0.006$), though not for TNBC. No significant association was observed for p.Gln1701* with either subgroups (Table 1).

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.[8] 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	155	66,951	0.232	1.09	0.85–1.38	0.798
ER-positive	97	44,467	0.218	1.02	0.78–1.34	0.893
ER-negative	21	10,748	0.204	0.97	0.61–1.56	0.369
TNBC	10	4794	0.229	1.09	0.57–2.10	0.149
FANCM:p.Arg1931*						
Controls	96	53,633	0.179	NA		
All cases	116	66,968	0.173	1.05	0.80–1.38	0.731
ER-positive	74	44,467	0.166	1.02	0.75–1.38	0.920
ER-negative	27	10,742	0.251	1.52	0.98–2.35	0.070
TNBC	10	4795	0.208	1.29	0.67–2.50	0.461
All variants[a]						
Controls	237	53,455	0.443	NA		
All cases	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					
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
All variants[b]						
Controls	NA					
All cases	NA					
ER-positive	NA					

Table 1 continued

	Country-restricted					
Subgroup	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
[a]The burden analyses were performed by univariate logistic regression
[b]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

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 *Tse*I present in the wt sequence. *Tse*I-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 chromatidic 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/).[15] 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/BRCA 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 Bloom's complexes initiating HR repair[17] (Fig. 2). We studied FANCM:p.Arg658*, p.Gln1701*, and p.Arg1931* in the same genetic *FANCM*$^{-/-}$ background and showed that, after exposure to DEB, the N-terminal *FANCM*:p.Arg658* had a statistically stronger effect on cell survival and chromosome stability (presumably due to less efficient DNA repair activity) than did p.Gln1701* and p.Arg1931*. This also suggests that in human living cells the *FANCM*:p.Arg658* variant might impair DNA repair more severely than p.Gln1701* and p.Arg1931*. We have shown that in vitro both the p.Gln1701*- and the p.Arg1931*-derived FANCM proteins are expressed and that the p.Arg658*-mRNA is transcribed (Fig. 1a, 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 the 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

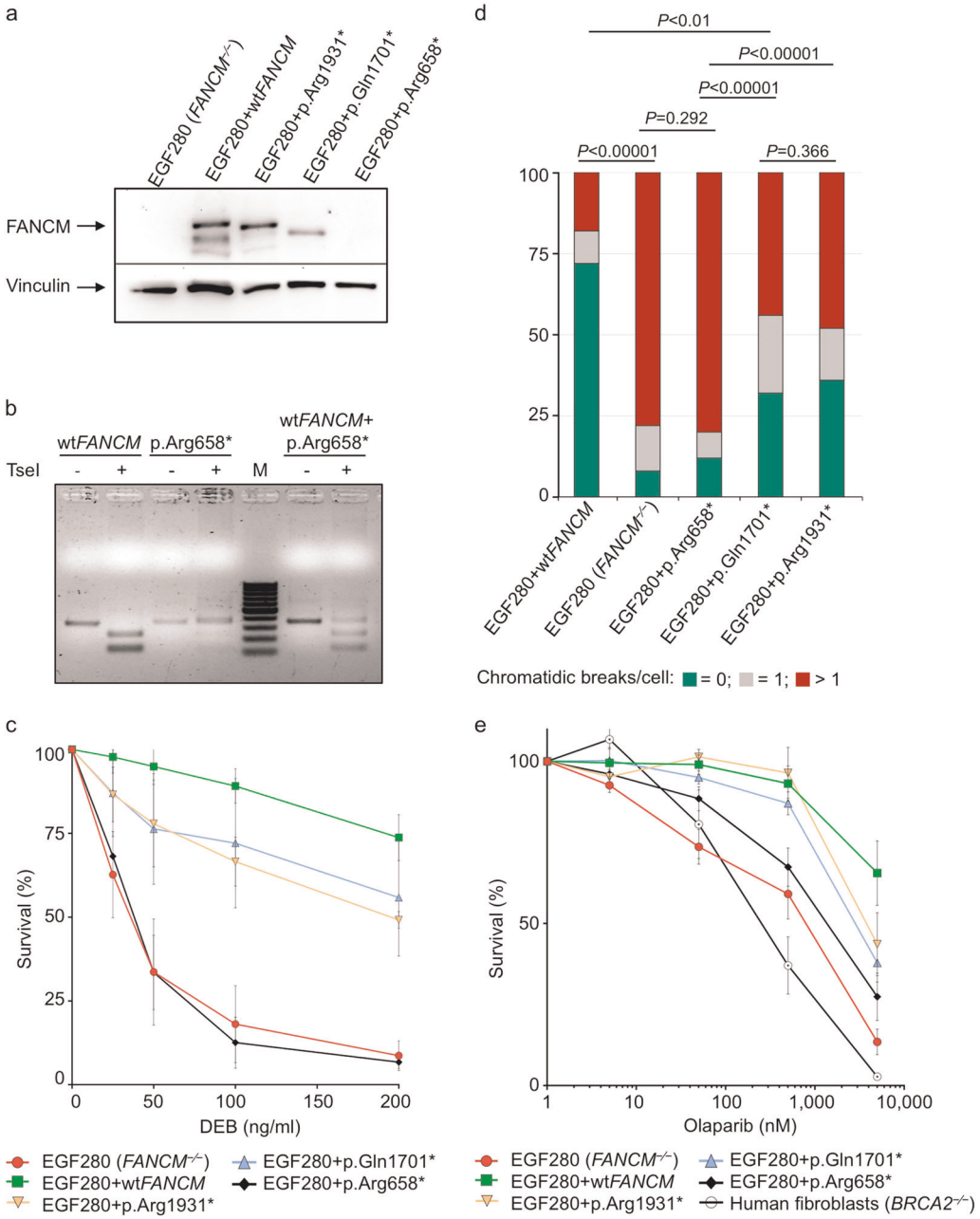

Fig. 1 Functional studies of the *FANCM*:p.Arg658*, p.Gln1701* and p.Arg1931* truncating variants using the patient-derived *FANCM*$^{-/-}$ EGF280 cell line. **a** Western blot showing the FANCM expression in EGF280 cells complemented with lentiviral vectors harboring the three different variants. Bands 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 *Tse*I that is present in the wild-type (wt) cDNA sequence. Total RNA was extracted from EGF280 + wt*FANCM* and from the EGF280 + p.Arg658* and subjected to reverse transcription. PCR-amplified cDNA products were digested with *Tse*I. 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 *Tse*I site. In the two lanes after the molecular weight marker (M) undigested and digested products of the two previous PCR products were mixed 1:1 and loaded as a control. **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** Chromosome fragility induced by DEB treatment (100 ng/ml). Here, the 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

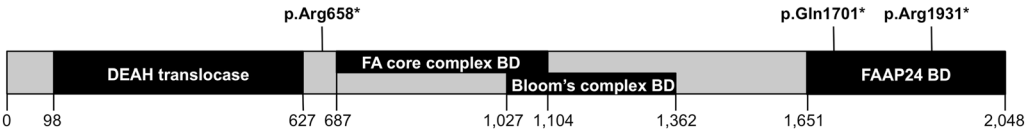

Fig. 2 Schematic diagram of the 2,048 amino acid long FANCM protein. The functional or binding domains (BD) are indicated in black and as reported in Deans and West, 2009. The position of the three *FANCM* truncating variants c.1972C > T (p.Arg658*), c.5101 C > T (p.Gln1701*) and c.5791 C > T (p.Arg1931*) is also shown

probands carrying homozygous *FANCM* truncating variants were recently described.[9] Three of these, two homozygous for p.Gln1701*, and one for p.Arg1931*, developed breast cancer at age 52 years or later and their cells did not demonstrate chromosome fragility. The other two probands were homozygous for p.Arg658* and developed early-onset breast cancer (at age 29 and 32); in addition, one developed several cancers, and the other demonstrated chromosomal fragility.[9]

Due to the rarity of the studied mutations in most populations, estimation of the risks is challenging. Preferably, the cases should be examined in comparison to geographically, ethnically and genetically matched controls. In the Finnish population, p.Gln1701* and p.Arg1931* are reported with carrier frequency of 1.62% and of 0.92%, respectively (https://gnomad.broadinstitute.org/).[15] Case-control studies based on the Finnish population showed a strong statistical evidence of association of p.Gln1701* with ER-negative disease, with OR of 2.37 (95% CI = 1.37–4.12, P = 0.0021), and with TNBC with ORs of 3.56 (95% CI = 1.81–6.98, P = 0.0002),[10] while p.Arg1931* was found associated with TNBC with an OR of 5.14 (95% CI = 1.65–16.0, P = 0.005).[12] However, as our 95% CI of risk estimates for TNBC included odds ratios of 2 for both the latter mutations, the published and our results are not mutually exclusive. Risk estimates associated with rare variants may depend on their frequency and the genetic background of the population studied. Hence, pooling the data from multiple outbred and admixed populations as it was done in the present study, may yield different risk estimates than those derived from geographically, ethnically and genetically matched controls, as in the Finnish studies. Indeed, it would have been interesting to test the *FANCM* variant position effect in the Finnish population, but unfortunately the p.Arg658* is very rare if not absent in this population (https://gnomad.broadinstitute.org/).[15]

Recent attempts to identify novel, high- to moderate-risk breast cancer-predisposing genes have not been particularly fruitful. However, a few genes have emerged as potential risk factors for ER-negative disease and TNBC, with *FANCM*, *BRIP1*, and *RAD51C* being among those suggested to confer moderate risk of these subtypes. Other predisposing genes increasing the risk of ER-negative and TNBC may also exist. Hence, further gene discovery efforts should take into consideration that risk-associated variants may be associated with specific tumor subtypes and/or variation in risk may depend on the variant position. In addition, we provide evidence that lack of FANCM protein and truncating variants identified in breast cancer patients are associated with increased sensitivity to the PARPi olaparib suggesting a therapeutic opportunity to treat FANCM-associated breast tumors that warrants further investigation. The PARPi sensitivity test may also prove useful for preclinical investigation of further truncating or missense *FANCM* variants.

In summary, we have shown that *FANCM*:p.Arg658* is associated with risk of ER-negative breast cancer and TNBC. The outcomes of functional assays testing the DNA repair efficiency in complemented human cells support the hypothesis that breast cancer risk may be greater for N-terminal than C-terminal *FANCM* truncating variants. Further genetic studies and meta-analyses are warranted to derive more precise risk estimates for the different *FANCM* variants.

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 subjects 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 positive 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 *FANCM*:p.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.[14] 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 *FANCM*:p.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.[19] *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.[20] 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[8] was transduced with pLenti CMV rtTA3 Blast, a gift from E. Campeau (Addgene plasmid #26429). The doxycycline-inducible lentiviral vector pLVX-TRE3G-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′-GCCTTCTCGGAACTTGCAGTGAAAGTCATCTATCTTTTCC-3′ and primer 2: 5′-GGAAAAGATAGATGACTTTCACTGCAAGTTCCGAGAAGGC-3′ for the p.Arg658*; *FANCM* c.5101 C > T primer 1: 5′-TTAAACAATGGTCC-TATTGTTTGTTCTTCTTAACAGTGCTTGGGT-3′ and primer 2: 5′-ACCCAAG-CACTGTTAAGAAGAACAAACAATAGGACCATTGTTTAA-3′ for the p.Gln1701*. Generation of the lentiviral vector containing the *FANCM*:c.5791 C > T (p.Arg1931*) and transduction of the EGF280 cells were already described.[11] 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 antibody, clone CV5.1 diluted 1:100 (ref: MABC545, MERCK Millipore), mouse monoclonal anti-Vinculin diluted 1:3000 (ref: ab18058, abcam). Western blotting detection was achieved with Luminata™ Classico (Millipore) (Vinculin) and LuminataForte™ (Millipore) (FANCM). We used RT PCR to test the expression of the mutant *FANCM*:p.Arg658*. Total RNA was extracted (RNeasy Mini Kit Qiagen) from the wt*FANCM* and *FANCM*:p.Arg658* transduced EGF280 cell lines. Reverse transcription was performed using High-Capacity RNA-to-cDNA Kit (Thermofisher); a cDNA region corresponding to the FANCM sequence containing the amino acid (AA) position Arg658 was amplified by PCR using the forward: 5′-AGTAACAGGCAGGTCCTTCA-3′and reverse: 5′-TGATCTTGCCACAGTCTCCA-3′ primers. The 386 bp PCR products were then digested with *TseI* restriction enzyme (New England Biolabs) for two hours at 65 °C and analyzed by standard agarose gel electrophoresis.

Cell survival assay

The effect of the different *FANCM* variants on cell survival was measured with a Sulforhodamine B (SRB) assay.[21] 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™, Tecan Group Ltd. Männedorf, Switzerland). At least three independent experiments were performed for each cell line and in each experiment, 12 wells were measured per concentration point. These results were statistically analyzed using the Prism (GraphPad) software. Two-Way ANOVA test was used for single comparisons between different cell lines and statistical significance was assessed with the Tukey's range test. A *P*-value < 0.05 was considered statistically significant.

Chromosome fragility test

Chromosome fragility test was performed as previously described.[11] Twenty-five metaphases were scored for chromosome breakages using the Metafer Slide Scanning Platform from Metasystems. Results were graphed as distributions of metaphases presenting 0, 1, and >1 chromatid break. Statistical analysis was performed applying chi-squared test.

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary

DATA AVAILABILITY

A subset of the genotype data analysed in this study is publicly available from the dbGaP repository and can be accessed at https://identifiers.org/dbgap:phs001265.v1.p1 (data generated as part of the BCAC studies) and at https://identifiers.org/dbgap:phs001321.v1.p1 (data generated as part of the CIMBA studies). The remaining genotype data analysed in this study (and generated as part of the BCAC and CIMBA studies listed in Supplementary Tables 4 and 5 of the related article, respectively) are not publicly available due to restraints imposed by the ethics committees of individual studies, but can be accessed from the corresponding author on reasonable request as described at https://doi.org/10.6084/m9.figshare.8982296.[22] Additional datasets generated during this study (and supporting Fig. 1 and Supplementary Tables 2 and 3 in the published article) are available on request as described above. The data generated and analyzed during this study are described in the following data record: https://doi.org/10.6084/m9.figshare.8982296.[22]

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COMPETING INTERESTS

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