

# Individuals with *FANCM* biallelic mutations do not develop Fanconi anemia, but show risk for breast cancer, chemotherapy toxicity and may display chromosome fragility

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**Purpose:** Monoallelic germ-line mutations in the *BRCA1/FANCS*, *BRCA2/FANCD1* and *PALB2/FANCN* genes confer high risk of breast cancer. Biallelic mutations in these genes cause Fanconi anemia (FA), characterized by malformations, bone marrow failure, chromosome fragility, and cancer predisposition (*BRCA2/FANCD1* and *PALB2/FANCN*), or an FA-like disease presenting a phenotype similar to FA but without bone marrow failure (*BRCA1/FANCS*). *FANCM* monoallelic mutations have been reported as moderate risk factors for breast cancer, but there are no reports of any clinical phenotype observed in carriers of biallelic mutations.

**Methods:** Breast cancer probands were subjected to mutation analysis by sequencing gene panels or testing DNA damage response genes.

**Results:** Five cases homozygous for *FANCM* loss-of-function mutations were identified. They show a heterogeneous phenotype

including cancer predisposition, toxicity to chemotherapy, early menopause, and possibly chromosome fragility. Phenotype severity might correlate with mutation position in the gene.

**Conclusion:** Our data indicate that biallelic *FANCM* mutations do not cause classical FA, providing proof that *FANCM* is not a canonical FA gene. Moreover, our observations support previous findings suggesting that *FANCM* is a breast cancer-predisposing gene. Mutation testing of *FANCM* might be considered for individuals with the above-described clinical features.

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**Key Words:** biallelic *FANCM* mutations; breast cancer risk factors; Fanconi anemia; FA-like disease; genotype/phenotype correlation

## INTRODUCTION

Breast cancer is the most common female oncological disease worldwide. Up to 15% of all cases have family history for the disease, and the risk of developing breast cancer in individuals with an affected relative is twofold higher compared to the general population.<sup>1</sup> *BRCA1*, *BRCA2*, and *PALB2* are major breast cancer-predisposing genes and monoallelic protein-truncating mutations confer risk of developing the disease by

age 70 ranging from 35% to 59%.<sup>2,3</sup> These genes are also designated as *FANCS/BRCA1*, *FANCD1/BRCA2*, and *FANCN/PALB2*, and together with 18 other genes—including the recently identified *FANCV/REV7*<sup>4</sup>—code for proteins involved in a common pathway responsible for DNA interstrand crosslink (ICL) repair, mediated by homologous recombination. Biallelic mutations in genes of this pathway cause the Fanconi anemia (FA) disease characterized by

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congenital defects, bone marrow failure, sensitivity to DNA ICLs, and cancer susceptibility. FA patients often show chemotherapy sensitivity, abnormal inflammatory response, reproductive/endocrine defects, and increased risk of hematological tumors and other solid tumors such as squamous cell carcinoma and breast and ovarian cancer. Biallelic mutations in three of the genes involved in the FA pathway, namely *FANCS/BRCA1*, *FANCO/RAD51C*, and *FANCR/RAD51* cause a FA-like disease that is similar to FA but does not include bone marrow failure (reviewed in ref. 5).

While the *FANCM* gene is a key component of the FA molecular pathway, its role in the etiology of FA disease has been disputed. In 2005, an individual affected with FA was found to carry biallelic mutations in *FAAP250* that were renamed *FANCM* and proposed as a new FA gene.<sup>6</sup> Later, it was discovered that this patient also carried biallelic mutations in the *FANCA* gene.<sup>7</sup> Apart from this case, no other FA patients with *FANCM* biallelic mutations were described to date. Moreover, seven Finnish individuals were found to be homozygous for *FANCM* mutations but had no evidence of blood diseases, increased frequency of cancer events or any other chronic disease.<sup>8</sup> While these observations raised the question of whether *FANCM* was a bona fide FA gene, recent case-control studies indicated that monoallelic truncating mutations located in the C-terminus of the gene might be risk factors for breast cancer. The *FANCM* c.5101C>T mutation (p.Gln1701\*, rs147021911) is relatively frequent in Finland, where it was shown to be statistically associated with breast cancer risk, particularly in familial cases (odds ratio, OR = 2.11) and individuals with triple-negative tumors (OR = 3.56).<sup>9</sup> The *FANCM* c.5791C>T mutation (p.Gly1906Alafs\*12; rs144567652), also known as p.Arg1931\*, was tested in a large series of familial breast cancer cases and controls from different populations, resulting in a statistically significant association with disease risk (OR = 3.93).<sup>10</sup> These observations are supported by a very recent analysis of truncating *FANCM* mutations found by sequencing German familial cases and controls.<sup>11</sup>

In this study, we describe the phenotype of five breast cancer probands incidentally found to carry homozygous *FANCM* loss-of-function mutations. These findings contribute to elucidate the role of this gene in both FA disease and breast cancer predisposition.

## MATERIALS AND METHODS

### Breast cancer probands and mutation testing strategies

The five female individuals included in this study were originally eligible for mutation testing in breast cancer-predisposing genes based on the facts that they were affected with breast cancer, and they had either early onset or family history for the disease, or were affected with hormone receptor-negative cancer. All probands underwent mutation testing through a diagnostic or a research protocol at four different centers in Italy, Germany, Sweden, and Spain. Mutation testing consisted of next-generation sequencing of custom or commercial gene panels including established

and candidate breast cancer genes (**Supplementary Table S1** online). In addition, probands from Italy and Germany were subjected to whole-exome sequencing and of all annotated variants we considered only those located within the genes involved in the DNA damage response (**Supplementary Table S2**). To establish genotype/phenotype correlations, all the variants found in probands' DNA were annotated and prioritized for causality using different pipelines that classified variants considering (i) their effect on the protein product, (ii) their frequency reported in public databases, and (iii) their clinical classification, if available in public databases or literature. All individuals included in this study and herein described signed an informed consent to the use of their biological samples and clinical data for research projects. This study was approved by local ethics committees.

## RESULTS

In this collaborative study, we report the clinical phenotype of five female breast cancer probands who were tested for mutations in breast cancer-related genes and found to be homozygous for loss-of-function mutations in the *FANCM* gene (**Table 1** and **Figure 1**). The presence of homozygous *FANCM* mutations was confirmed in all probands' DNA by Sanger sequencing (**Supplementary Figure S1**). Proband 1 was Italian; she developed early-onset breast cancer at age 29 followed by several other oncological diseases and was found to carry the homozygous mutation *FANCM* c.1972C>T (p.Arg658\*). She was born to first-cousin parents and we speculate they both inherited the same *FANCM* alleles from a common ancestor. Proband 2 was born in Germany. This woman also developed breast cancer at an early age (31) and inherited one *FANCM* c.1972C>T (p.Arg658\*) allele from each of her heterozygous parents. The two probands from Sweden had a family history for breast or ovarian cancer and were homozygous for *FANCM* c.5101C>T (p.Gln1701\*), which is a relatively common mutation in Finland.<sup>9</sup> Finally, the Spanish proband developed a triple-negative breast cancer and was found to be homozygous for the *FANCM* c.5791C>T (p.Arg1931\*) mutation that has been reported as possibly more frequent in southwestern Europe.<sup>10</sup> As we could not specifically test for the presence of single-exon rearrangements, we cannot formally exclude that the homozygosity we observed is due to exonic deletions in the *FANCM* locus.

While these individuals were first diagnosed with breast cancer, the majority of them showed other clinical signs including chemotherapy toxicity and early menopause (**Table 1** and **Supplementary Table S3**). These phenotypes, together with the presence of biallelic mutations in an FA pathway gene, prompted us to measure sensitivity to DNA ICL agents by a chromosome fragility test that was performed as previously described.<sup>12</sup> We could only obtain fresh blood cells from probands 2, 3, and 5, and observed sensitivity to DNA ICLs only in proband 2 (**Supplementary Table S4**).

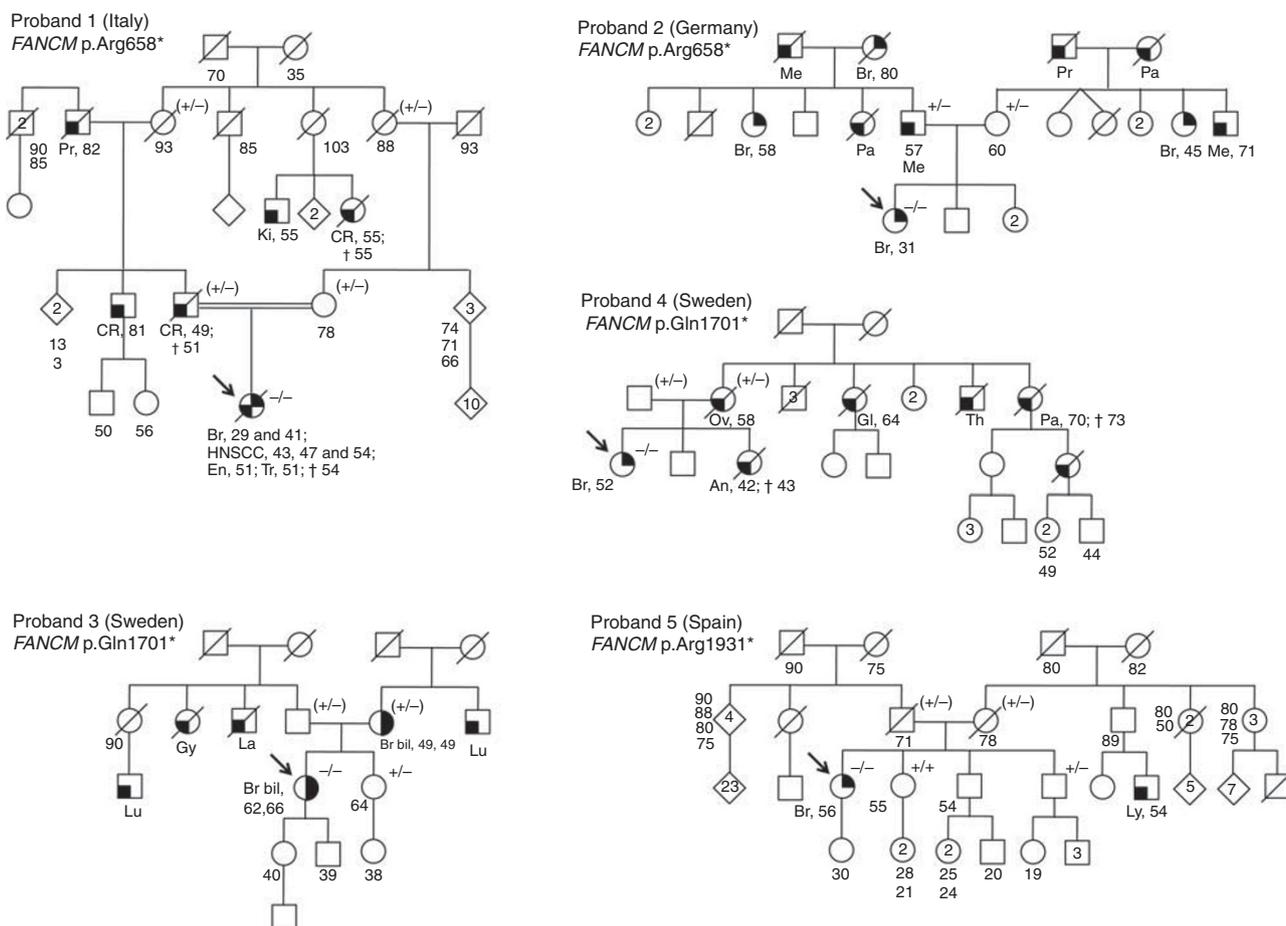
Apart from the *FANCM* homozygous mutations, we only found one other known breast cancer-associated variant, *CHEK2* c.470C>T (p.Ile157Thr), detected in proband 4. As

**Table 1** Description of the five breast cancer probands with *FANCM* homozygous mutations

Proband ID	Nationality	Mutation (frequency) <sup>a</sup>	Breast cancer			Years of follow-up	Clinical and cancer history and cellular phenotype
			Age at diagnosis	Tumor type <sup>b</sup>	ER/PR/HER2 status <sup>b</sup>		
1	Italian	c.1972C > T; p.Arg658*; rs368728266 (0.02%)	29, 41 (ipsilateral)	IDC	– – NA	25	Breast cancer diagnosis followed by quadrantectomy and radiotherapy. Diagnosis of ipsilateral breast cancer followed by mastectomy and chemotherapy that was interrupted for toxicity. Three HNSCCs, treated with surgery, and endometrial carcinoma and trichilemmoma surgically treated. Chromosome fragility test: not performed due to lack of viable cells.
2	German	c.1972C > T; p.Arg658*; rs368728266 (0.02%)	31	IDC	+ + +	5	Low AMH levels suggested reduced ovarian reserve (age 31). Breast cancer diagnosis followed by chemotherapy (neoadjuvant) interrupted due to severe pancytopenia. Quadrantectomy followed by radiotherapy, her2/neu-directed and antihormonal therapy. Chromosome fragility test: sensitivity to DNA ICL agents.
3	Swedish	c.5101C > T; p.Gln1701*; rs147021911 (0.28%)	62, 66 (bilateral)	IDC	+ + +	7	Autoimmune disorder (Sjögren syndrome). Breast cancer diagnosis followed by surgery and chemotherapy that was interrupted for pancytopenia. Chromosome fragility test: lack of sensitivity to DNA ICL agents.
4	Swedish	c.5101C > T; p.Gln1701*; rs147021911 (0.28%)	52	IDC	– – +	3	Early menopause (age 38). Breast cancer diagnosis followed by quadrantectomy (twice, since the first operation was not radical), chemotherapy and radiation. Chromosome fragility test: not performed due to lack of patient cooperation.
5	Spanish	c.5791C > T; p.Arg1931*; rs144567652 (0.19%)	56	IDC	– – –	2	Early menopause (age 30). Breast cancer diagnosis followed by chemotherapy (neoadjuvant) interrupted due to severe pancytopenia. Mastectomy and radiotherapy. Chromosome fragility test: lack of sensitivity to DNA ICL agents (presence of chromosome-type aberrations in not treated cells likely induced by radio/chemotherapy treatments).

AMH, anti-Müllerian hormone; ER, estrogen receptor; HER2, HER2/neu receptor expression; HNSCC, head and neck squamous cell carcinoma; IDC, invasive ductal carcinoma; ICL, interstrand crosslink NA, not available; PR, progesterone receptor.

<sup>a</sup>Frequency of mutation carriers in ExAC database in non-Finnish Europeans. <sup>b</sup>Relative to the first diagnosed tumor.



**Figure 1** Family pedigrees of the five probands homozygous for the *FANCM* c.1972C>T (p.Arg658\*), the c.5101C>T (p.Gln1701\*), and the c.5791C>T (p.Arg1931\*) mutations. Probands are indicated by the arrows. Cancer type, age at diagnosis, and age of death are reported when known. Age of healthy individuals, if known, was at date of genetic counseling. Events occurred after genetic counseling, if known, are annotated. Mutation status is reported as follows: +/+, normal; +/-, heterozygote; -/-, homozygote; (+/-), obligate carrier. Cancer type is reported as follows: An, anal; Br, breast; Br bil, bilateral breast cancer; CR, colorectal; En, endometrial; Gl, glioblastoma; Gy, gynecologic nonspecified cancer; HNSCC, head and neck squamous cells cancer; Ki, kidney; La, larynx; Ly, lymphoma; Lu, lung; Me, melanoma; Ov, ovarian; Pa, pancreas; Pr, prostate; Th, throat; Tr, trichilemmoma.

this variant is reported as a low/moderate risk factor for breast cancer,<sup>13</sup> we cannot exclude that it could have contributed to the phenotype observed in this proband. Nor can we exclude that other mutations possibly influencing the clinical phenotypes might remain undetected. However, since our gene panels included known variants associated with a moderate to high risk for developing breast cancer, with the only exception of *CHEK2* c.470C>T in proband 4, we believe that the homozygous *FANCM* mutations were most likely to be considered the only disease-associated mutations identified in the five probands.

## DISCUSSION

Our data document for the first time the possible association of biallelic *FANCM* mutations with a clinical phenotype. The five probands included in this study were all originally recruited as breast cancer probands, and none was clinically diagnosed with FA or FA-like diseases. While none suffered from congenital abnormalities, bone marrow failure, or

hemato-oncological diseases, some of them showed clinical signs that are included in the FA phenotype spectrum. In particular, four of the five probands showed chemotherapy-related hematological side effects. Moreover, proband 1 developed three head and neck squamous cell carcinomas and another solid cancer. Probands 2, 4, and 5 showed sign of early menopause, and proband 3 suffered from autoimmune disease (Sjögren syndrome). Finally, proband 2 tested positive for chromosome fragility indicating sensitivity to DNA ICLs (Table 1). These clinical observations indicate that *FANCM* is not a bona fide FA gene. The small number of carriers of biallelic *FANCM* mutations that we describe in this study does not allow performing any statistical analysis, or to claim that the *FANCM* genotypes we detected are causative of the observed clinical phenotypes. However, on a less conservative view, we cannot exclude that homozygosity for truncating mutations in *FANCM* may have clinical consequences that are more pronounced than for heterozygous mutation carriers. The phenotypes in our five probands are consistent with

*FANCM* being a gene associated with FA-like cancer susceptibility. This appears to be supported by molecular data from human cell lines and by phenotypic observations from *Fancm*-deficient mice. During the early steps of the physiological repair of DNA ICLs, *FANCM* and the protein products encoded by the seven bona fide FA genes *FANCA*, *-B*, *-C*, *-E*, *-F*, *-G*, and *-L* assemble in the “core complex.” This complex monoubiquitinates the ID2 heterodimer, which mediates the recruitment of “effector proteins” responsible for DNA ICLs repair (reviewed in ref. 5). While biallelic mutations in all the core complex genes abolish monoubiquitination of the ID2 complex, lack of *FANCM* only reduces the efficiency of this mechanism. Moreover, studies in which *FANCM* was depleted in cell lines showed that this loss neither affects the levels of other FA core complex proteins, such as *FANCA* and *FANCG*, nor the ability of *FANCL* to coimmunoprecipitate with them, suggesting that *FANCM* is not essential for FA core complex formation and stabilization (reviewed in ref. 14). With respect to FA mice models, mice deficient for *Fancm* showed increased cancer incidence;<sup>15</sup> an excess of ovarian, mammary, and uterine cancers; and sex-independent gonadal defects.<sup>16</sup>

Monoallelic loss-of-function mutations in *FANCM* have been suggested to be associated with moderate/low risk for breast cancer.<sup>9–11</sup> The identification of breast cancer probands with biallelic *FANCM* mutations corroborates the role of this gene as a breast cancer–predisposing factor. Two of these probands showed early-onset breast cancer and one proband developed bilateral breast cancer, suggesting that *FANCM* biallelic mutations may have a stronger effect on breast cancer risk compared to monoallelic mutations. Such an effect has been previously observed for the moderate breast cancer risk factor *CHEK2* c.1100delC. Homozygote carriers of this variant have been estimated to have a twofold and a fourfold higher risk compared to heterozygotes and women of the general population, respectively.<sup>17</sup> Moreover, of the nine *CHEK2* c.1100delC homozygous familial cases reported to date,<sup>17,18</sup> three developed breast cancer before age 35 and four developed bilateral breast cancer, which is comparable to the clinical phenotypes observed in some of the *FANCM* homozygous probands.

Our data shows that biallelic *FANCM* mutations might be associated with a clinical phenotype including breast cancer predisposition, chemotherapy toxicity, and possibly early menopause and chromosome fragility. In the accompanying manuscript,<sup>19</sup> Bogliolo *et al.* describe additional individuals with *FANCM* homozygous mutations who were affected with different types of early-onset cancer. Altogether, these observations support the hypothesis that biallelic mutations in *FANCM* may cause a heterogeneous cancer susceptibility phenotype. This heterogeneity and the breast cancer severity in terms of age of onset that we observed in our probands, might be influenced by the position of the mutations in the gene (**Supplementary Figure S2**). All three carriers of the p.Gln1701\* and p.Arg1931\* mutations, which are located in the gene C-terminus, developed breast cancer at typical ages and, at least the two who were tested, did not display chromosome

fragility. Both carriers of the p.Arg658\* mutation, which is expected to produce a protein lacking the domains of interaction with the DNA-binding mediators MHF1 and MHF2, and with the Bloom syndrome complex,<sup>20</sup> developed early-onset breast cancer and one showed high chromosome fragility. Similarly, the patients described by Bogliolo *et al.*<sup>19</sup> who suffered from severe early-onset cancers and showed chromosome fragility carried homozygous mutations expected to truncate *FANCM* at amino acid 503 and 863.

In conclusion, our data point out that biallelic mutations in *FANCM* do not cause classical FA, providing evidence that *FANCM* is not a canonical FA gene. Moreover, our observations reinforce the hypothesis that *FANCM* is a breast cancer–predisposing gene with biallelic mutations possibly conferring higher risk. Finally, we suggest that *FANCM* biallelic mutations might be associated with an FA-like cancer susceptibility, characterized by increased risk for breast and other types of cancer, chemotherapy toxicity, and possibly early menopause and chromosome fragility. *FANCM* mutation testing may be offered, in the context of research protocols, to individuals with the above clinical features. Additional genotype/phenotype correlations are necessary to better clarify the clinical impact of *FANCM* biallelic mutations.

#### SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at <http://www.nature.com/gim>

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## DISCLOSURE

The authors declare no conflict of interest.

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