



## RESEARCH ARTICLE

# Analysis of 11 candidate genes in 849 adult patients with suspected hereditary cancer predisposition

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## Abstract

Hereditary predisposition to cancer concerns between 5% and 10% of cancers. The main genes involved in the most frequent syndromes (hereditary breast and ovarian cancer syndrome, hereditary nonpolyposis colorectal cancer syndrome) were identified in the 1990s. Exploration of their functional pathways then identified novel genes for hereditary predisposition to cancer, and candidate genes whose involvement remains unclear. To determine the contribution of truncating variants in 11 candidate genes (*BARD1*, *FAM175A*, *FANCM*, *MLH3*, *MRE11A*, *PMS1*, *RAD50*, *RAD51*, *RAD51B*, *RINT1*, and *XRCC2*) to cancer predisposition in a population of interest, panel sequencing was performed in 849 patients with a suspected hereditary predisposition to cancer for whom a diagnostic panel of 38 genes identified no causal mutation. Sixteen truncating variants were found in *FANCM* (n = 7), *RINT1* (n = 4), *RAD50* (n = 2), *BARD1*, *PMS1*, and *RAD51B*. *FANCM* (adjusted *P*-value: .03) and *RINT1* (adjusted *P*-value: .04) were significantly associated with hereditary breast and ovarian cancer. However, further studies are required to determine the risk of cancer, including the segregation of the variants in the families of our cases. No mutation was identified in *RAD51*, *MRE11A*, *FAM175A*, *XRCC2*, or *MLH3*. The involvement of these genes in the hereditary predisposition to cancer cannot be ruled out, although if it exists it is rare or does not seem to involve truncating variants.

## KEYWORDS

breast and ovarian cancer syndrome, candidate genes, hereditary colorectal cancer, panel sequencing, predisposition to cancer

## 1 | INTRODUCTION

Hereditary predisposition to cancer concerns between 5% and 10% of cancers.<sup>1</sup> The hereditary predisposition to breast and ovarian cancer (HBOC) is the most frequent of these.<sup>2</sup> The major genes involved in HBOC, *BRCA1*, and *BRCA2*, were identified in the 1990s. The exploration of candidate genes involved in the same biological pathways represented

a logical approach and identified additional predisposition genes involved in this syndrome, including *PALB2*, *RAD51C*, and *RAD51D*.<sup>3</sup> However, the involvement of other homologous recombination genes, such as *FANCM*, *RINT1*, *RAD50*, *RAD51*, *RAD51B*, *BARD1*, *MRE11A*, *FAM175A*, or *XRCC2*,<sup>4</sup> in HBOC predisposition remains uncertain.

Another relatively frequent hereditary predisposition to cancer, hereditary nonpolyposis colorectal cancer (HNPCC) syndrome,

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predisposes mainly to colorectal and endometrial cancer and is caused by heterozygous pathogenic variants in the mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6*, or *PMS2*. However, the involvement of other MMR genes, such as *PMS1* or *MLH3*, is suspected but remains unclear.<sup>5</sup>

Modern high-throughput sequencing allows simultaneous analysis of multiple genes. With the patient's informed consent, candidate genes can thus be examined in parallel with the diagnostic gene panel routinely used for cancer predisposition. The research results are not reported to the patients because of their unknown clinical interest.

Our department explored 11 genes that are candidates for hereditary predisposition to cancer in 849 patients with personal and/or familial indications of hereditary risk and without any causal mutation identified by a diagnostic panel of 38 genes. Our goal was to explore the prevalence of pathogenic variants and their associated phenotypic presentation. The 11 genes included 9 genes involved in homologous recombination and suspected to be involved in HBOC (*FANCM*, *RINT1*, *RAD50*, *RAD51*, *RAD51B*, *BARD1*, *MRE11A*, *FAM175A*, and *XRCC2*) and two genes involved in MMR, and suspected to be implicated in HNPCC syndrome (*PMS1*, *MLH3*).

## 2 | MATERIALS AND METHODS

### 2.1 | Samples

Between 2016 and 2018, 849 patients from our Oncogenetics Department, who did not have a pathogenic or probably pathogenic variant identified by sequencing a 38-gene diagnostic panel (Table 1) (including copy number variations) were analyzed for 11 research genes suspected to be involved in hereditary predisposition to cancer (Table 2). The patients presented HBOC and HNPCC as defined by National Comprehensive Cancer Network (NCCN) guidelines (Figure 1).<sup>6</sup> Cancer-free patients were analyzed in the event of a family history with at least one first-degree relative suggestive of one of these two syndromes but with no affected family member available for study. Each patient signed informed consent for genetic diagnosis of hereditary disease and for research. All genes were analyzed from peripheral blood on EDTA. DNA was extracted from peripheral blood using QIAamp DNA Blood maxikit (Qiagen).

### 2.2 | Panel sequencing

Sonic fragmentation of DNA was performed on a Bioruptor instrument (Diagenode). Kapa HTP library preparation and SeqCap EZ Choice probes and reagents (Roche) were used for library preparation and capture. Quality of fragmentation, library, and capture were controlled using a Bioanalyzer 2100 instrument (Agilent). Sequencing was performed using Miseq v2 kit (300 cycles) on Miseq Instrument (Illumina). All steps were performed following providers' guidelines.

**TABLE 1** Genes in the diagnosis panel

Panel of diagnosis genes sequenced			
APC	(LRG_130t1 & t2)	PALB2	(LRG_308)
ATM	(LRG_135)	PMS2	(LRG_161)
BAP1	(LRG_529)	POLD1	(LRG_785 t1)
BMPR1A	(LRG_298)	POLE	(LRG_789)
BRCA1	(LRG_292)	PTEN	(LRG_311)
BRCA2	(LRG_293)	RAD51C	(LRG_314)
BRIP1	(LRG_300)	RAD51D	(LRG_516)
CDH1	(LRG_301)	RET	(LRG_518 t1)
CDKN2A	(LRG_11t1 & t2)	SDHA	(NM_004168.3)
CHEK2	(NM_007194.3)	SDHAF2	(LRG_519)
EPCAM	(LRG_215)	SDHB	(LRG_316)
FLCN	(LRG_325)	SDHC	(LRG_317)
MAX	(LRG_530)	SDHD	(NM_003002.3)
MEN1	(LRG_509 t2)	SMAD4	(LRG_318)
MLH1	(LRG_216)	STK11	(LRG_319)
MSH2	(LRG_218)	TMEM127	(LRG_528)
MSH6	(LRG_219)	TP53	(LRG_321 t1)
MUTYH	(NM_001048171.1)	VHL	(LRG_322)
NBN	(LRG_158)		
NF2	(LRG_511 t1)		

Note: All patients had a 38 genes diagnosis panel analysis. All of them had no probably pathogenic or pathogenic variants as defined using the American College of Medical Genetic criteria.

**TABLE 2** Genes in the research panel of 11 genes

Panel of research genes sequenced	
BARD1	NM_000465.2
FAM175A	NM_139076.2
FANCM	NM_020937.2
MLH3	NM_001040108.1
Mre11a	NM_05591.3
PMS1	NM_000534.4
RAD50	NM_005732.3
RAD51	NM_002875.4
RAD51B	NM_133509.3
RINT1	NM_021930.4
XRCC2	NM_005431.1

Note: A panel of 11 genes was sequenced in 849 patients, including candidate genes to hereditary breast and ovarian cancer syndrome (*BARD1*, *FAM175A*, *FANCM*, *Mre11a*, *RAD50*, *RAD51*, *RAD51B*, *RINT1* and *XRCC2*) and candidate genes to predisposition colorectal cancer (*MLH1*, *PMS1*).

### 2.3 | Bioinformatic analysis

Demultiplexing was performed using bcl2fastq2 Conversion Software (Illumina). Alignment was performed on University of California Santa

Indications	Number of patients	Number of truncating variants	Genes
HBOC <sup>22</sup>	745	n = 14	FANCM (n = 6) RINT1 (n = 4) RAD50 (n = 2) BARD1 (n = 1) PMS1 (n = 1)
HNPCC <sup>28</sup>	104	n = 2	FANCM (n = 1) RAD51B (n = 1)
Total	849	n = 16	Number of genes : 7

**FIGURE 1** Indications of analyses and detection rates. HBOC, hereditary breast and ovarian cancer, HNPCC, hereditary nonpolyposis colorectal cancer

Cruz human genome reference build 19 using the Burrows-Wheeler Aligner. Genome Analysis Toolkit (GATK) and PICARD tools were used for base quality score recalibration (BaseRecalibrator) and realignment (RealignerTargetCreator, IndelRealigner), as recommended by Eurogentest guidelines (Matthijs et al). Variant calling was performed using GATK HaplotypeCaller and annotated using EnsemblVariantEffectPredictor. Copy number variation analysis was performed using ExomeDef. Variants were filtered for quality score  $\geq 30$ , depth  $\geq 30x$ , and present in  $\geq 20\%$  of reads.

## 2.4 | Variant interpretation

Variants interpretation was aided using ALAMUT (Interactive Bio-Software), which includes splice site analysis tools (SpliceSiteFinder, MaxEntScan), protein-function prediction tools (SIFT, Polyphen 2.0), and links to different databases (ClinVar, LOVD). Only truncating variants were considered in this study: nonsense, frameshift, and canonical splice-site variants that can be considered to be loss-of-function variants. The frequency of truncating variants in the general population was determined using gnomAD, which aggregates whole-exome and whole-genome sequencing data from approximately 140 000 individuals. Missense variants were not included due to unknown impact on function.

## 2.5 | Statistical analyses

For each of the 11 genes, the frequency of variants observed in our dataset was compared to that of the gnomAD population in order to highlight differentially abundant variants. This comparison was made for our entire population, as well as for the HBOC and digestive cases separately. Due to low-expected frequencies, the exact binomial test was preferred to an approximate test for proportions. A modified (for discrete test statistics) Benjamini-Yekutieli multitesting correction (under  $P$ -value dependence) was applied to the raw  $P$ -values obtained from the whole study ( $n = 33$ ). The tests were bilateral, and an adjusted  $P < .05$  was considered statistically significant, indicating evidence against the hypothesis of equality of proportions. Statistical

analysis was performed using R software, v. 3.6.1 (R Core Team, 2019, packages DiscreteFDR and MHTdiscrete).

## 3 | RESULTS

HBOC accounted for 87.75% of cases ( $n = 745$ ), while HNPCC accounted for 12.15% of cases ( $n = 104$ ).

Sixteen truncating variants were identified, corresponding to a detection rate of 1.9%, all in a heterozygous state. The most frequently mutated genes were *FANCM* ( $n = 7$ ), *RINT1* ( $n = 4$ ), and *RAD50* ( $n = 2$ ), followed by *BARD1*, *PMS1*, and *RAD51B* ( $n = 1$ ). No truncating variants were found in *FAM175A*, *MLH3*, *RAD51*, *MRE11A*, or *XRCC2*. Truncating variants were found in 14 HBOC cases (87.5% of variants) and two digestive cases (12.5%) (Figure 2, Table 3).

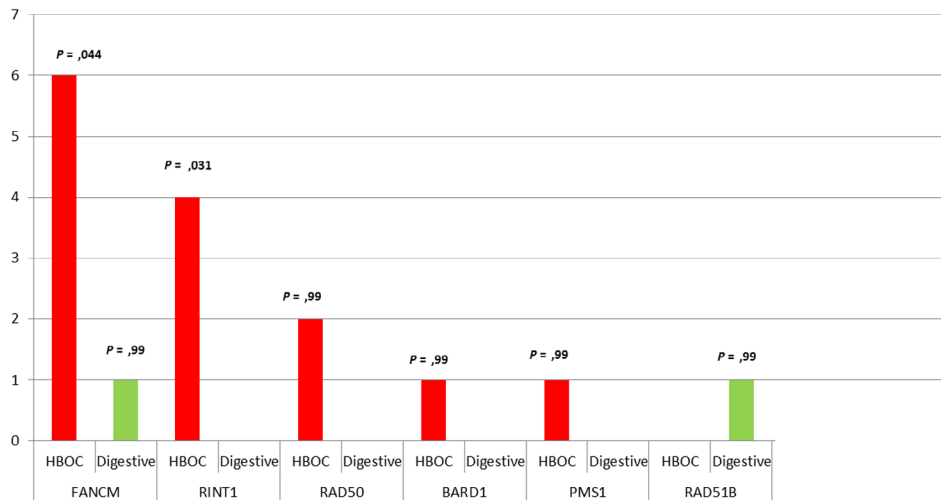
### 3.1.1. | FANCM

Seven truncating variants were identified in our cohort (0.82%, 95% CI 0.33%-1.69%), which is significantly higher than the expected frequency in the general population (0.2%; adjusted  $P = .03$ ), including six variants in HBOC cases (0.81%, 95% CI 0.29-1.74; adjusted  $P = .04$ ) and 1 incidental finding in an HNPCC case (0.96%, 95% CI 0.02%-5.24%). The probands' phenotypes included breast cancer in four cases and ovarian cancer in two cases. One proband presented both breast and ovarian cancer. The median age of onset was 50.5 (STD: 19) for breast cancer and 55 (STD: 9.6) for ovarian cancer. A positive family history of cancer was found in 50% of cases, including only breast cancer, with a median age of onset of 50.5 (STD: 24.14). The variant c.2184del; p.(His729Ilefs\*31) identified in a proband with ovarian cancer at 55 years of age, has not been previously described.

### 3.1.2. | RINT1

Four previously undescribed truncating variants were identified in Rad50 interactor 1 (*RINT1*) in our cohort (0.47%, 95% CI 0.12%-1.2%),

### Number of variants of interest by genes and indications



**FIGURE 2** Number of variants of interest by genes and indications. Sixteen variants of interest were found in our study. *FANCM* and *RINT1* were significantly associated with HBOC indication. No mutation was found in *Mre11a*, *FAM175A*, *MLH3*, *RAD51*, and *XRCC2*. HBOC, hereditary breast and ovarian cancer

**TABLE 3** Variants identified by gene and corresponding individual and familial phenotype

Gene	Variant	Protein effect	Pathology of the proband	Familial history
FANCM	c.-143_5340 + 20del	p.?	TNBC (81) HGSOC (70)	None
	c.1972C > T	p.(Arg658*)	TNBC (59)	None
	c.2184del	p.(His729Ilefs*31)	HGSOC (55)	None
	c.2586_2589del	p.(Lys863Ilefs*12)	Medullary BC (40)	BC: Mother (87); Sister (57)
	c.5101C > T	p.(Gln1701*)	No cancer (Male)	HNPCC
	c.5791C > T	p.(Arg1931*)	Granulosa cell tumor of the ovary (52)	Leukemia: Mother (45), Endometrial cancer: Sister (34); BC: Aunt (29)
RINT1	c.5791C > T	p.(Arg1931*)	BC (45)	BC: Sister (42)
	c.515G > A	p.(Ser172Asn)	No cancer	BC: Mother (67); Sister (34)
RINT1	c.1333 + 1G > A	p.?	BC (50)	BC: Mother (58), Aunt (73)
	c.2303dup	p.(Ile769Asnfs*10)	No cancer	HGSOC: Mother (50) BC: Grandmother and Aunt (50)
	c.2303dup	p.(Ile769Asnfs*10)	BC (43)	None
RAD50	c.130-1G > T	p.?	HGSOC (55)	None
	c.1048C > T	p.(Gln350*)	HGSOC (55)	None
BARD1	c.1935_1954dup20	p.(Glu652Valfs*69)	HGSOC (78)	BC: Aunt (79)
RAD51B	c.139C > T	p.(Arg47*)	CRC (41); MSS	None
PMS1	c.1705C > T	p.(Arg569*)	CRC (50); TNBC (57)	None

Abbreviations: BC, breast cancer; CCR, colorectal cancer; HGSOC, high-grade serous ovarian cancer; HNPCC, hereditary non polyposis colorectal cancer syndrome; MSS, microsatellite stable; TPN, triple negative.

which is significantly higher than the expected frequency in the general population (0.07; adjusted  $P = .04$ ). All four variants were observed in HBOC families (0.54%, 95% CI 0.14%-1.37%; adjusted  $P = .03$ ).

One patient had breast cancer at 43 years of age but no family history of cancer, and one had breast cancer at 50 years of age with a family history of breast cancer. Two probands were unaffected men with a family history of HBOC analysed because all index cases in the family were deceased. Ovarian cancer in an unaffected male proband's mother occurred at 50 years of age; the other male proband's family included only breast cancer. The median age of onset of breast

cancer in relatives was 54 (STD: 13.60). Interestingly, the variant c.2303dup; p.(Ile769Asnfs\*10) was shared by two unrelated patients.

### 3.1.3. | RAD50

Two truncating variants were found in *RAD50* (0.24%, 95% CI 0.02%-0.85%), both found in HBOC patients (0.40%, 95% CI 0.08%-1.17%), who presented an isolated ovarian cancer, occurring in both cases at 55 years of age.

### 3.1.4. | *BARD1*, *RAD51B*, *PMS1*

A previously undescribed truncating variant was found in *BARD1* in a patient with ovarian cancer at 78 years of age, in *RAD51B* in a patient with an early onset colorectal cancer at 41 years old of age and *PMS1* in a patient with rectal cancer at 50 years of age and triple-negative breast cancer at 71 years of age.

## 4 | DISCUSSION

The molecular exploration of 849 patients referred for oncogenetic indications and without any causal mutation identified using a diagnostic panel of 38 genes identified 16 loss-of-function mutations in seven research genes, including two genes significantly associated with HBOC patients (*FANCM* and *RINT1*).

*FANCM* is a regulator of genome maintenance, involved in DNA repair and genome duplication, acting as a tumor suppressor.<sup>7</sup> Bi-allelic loss-of-function mutations are associated with Fanconi Anemia Like phenotype, or azoospermia and primary ovarian insufficiency.<sup>8,9</sup> Mono-allelic mutations have been associated with breast cancer.<sup>10</sup> The two most frequent truncating variants in *FANCM*, c.5101C > T; p.(Gln1701\*) and c.5791C > T; p.(Arg1931\*), both observed in our study, increase breast cancer risk (OR: 2-3.93).<sup>11,12</sup> A particular risk of early onset triple-negative breast cancer has been reported for these variants (OR: 4.13), with a median age of diagnosis at 51 years of age.<sup>13</sup> This is confirmed in our study, with a median age at diagnosis comparable for probands (50.5 years of age), and including all familial breast cancers (49 years of age).

However, the triple-negative sub-type was not associated with the two variants previously described in our study. Moreover, our study describes for the first time an early onset medullary breast cancer at 40 years of age in a patient with a rare variant c.2586\_2589del; p.(Lys863Ilefs\*12) of *FANCM*. Medullary breast cancer is a rare form of cancer, representing less than 2% of breast carcinomas, and presenting triple-negative features in more than 60% of cases and constitutional mutation of *BRCA1* in more than 16% of cases.<sup>14</sup>

*FANCM* has been also associated with ovarian cancer risk.<sup>15,16</sup> However, the penetrance of *FANCM* mutations remains unclear. In our study, the known variant c.5791C > T; p.(Arg1931\*) is reported for the first time in a patient with an ovarian Granulosa cell tumor at 52 years of age, a rare cancer, with a strong familial history of breast cancer. Two patients with isolated high-grade serous ovarian cancers carried previously unknown variants c.2184del; p.(His729Ilefs\*31) and c.-143\_5340 + 20del; p.?. *FANCM* is significantly associated with HBOC patients in our study. The implication of *FANCM* in rare gynecological cancers, such as medullary breast cancer or ovarian Granulosa cell tumors, should be explored.

*RINT1* also presents a significantly higher mutation rate in HBOC patients in our study, in comparison to the general population. *RINT1* acts as a *RAD50* interactor and is involved in cell cycle regulation, telomere elongation, centrosome integrity, and endoplasmic reticulum maintenance.<sup>17</sup> It has been associated with a low to moderate risk of

breast cancer (OR = 2-3.24),<sup>17,18</sup> as well as in Lynch syndrome, but not with ovarian cancer risk. The mechanism suspected in the predisposition to cancer is based on tumor-suppressive or oncogene function.<sup>19</sup>

The four variants found in our study have not been described before. All were identified in HBOC patients, including two breast cancer families and two breast and ovarian cancer families. It is important to note that two variants were present in two cancer-free individuals belonging to HBOC families, in which the mutational status of the index cases was unknown. Thus, the involvement of *RINT1* in the family phenotype can only be suspected.

Overall, *FANCM* and *RINT1* seem to be associated with breast and ovarian cancer syndrome in our study. However, the determination of their impact in hereditary predisposition to cancer and their clinical interest require further investigation, including segregation analysis and more precise risk determination in mutation carriers.

Truncating variants have been identified in other genes, including *RAD50*, *RAD51B*, *BARD1*, *PMS1*, but these mutations were not significant in HBOC or HNPCC indications.

*RAD50* forms a hetero-trimer complex with Mre11a and NBS1, involving in DNA damage response and DNA double-strand break repair.<sup>20</sup> Its biological function makes it a candidate for exploration in HBOC. However, large case-control studies have not confirmed a risk in *RAD50* mutation carriers.<sup>21,22</sup> In our study, truncating variants in *RAD50* were identified in just two ovarian cancer cases that occurred at 55 years of age, and do not seem to be significantly associated with HBOC.

Only one variant was identified in *RAD51B* in our study, in a patient with colorectal cancer at 40 years of age. *RAD51B* is involved in homologous recombination repair. No truncating variants were found in HBOC patients, confirming their extreme rarity.<sup>23</sup> Although the breast cancer risk of truncating *RAD51B* mutations has not been clearly determined at this time, in both breast and ovarian cancer, their rarity induces a limited interest in screening them in HBOC patients. Missense variants in *RAD51B* have been associated with low breast cancer risk (OR 1.15 at 1.24) and were not explored here.<sup>23</sup>

The detection rates of *BARD1* and *PMS1* were also low (0.09%). *PMS1* forms a hetero-trimer with *MLH1* and *PMS2*, products of MMR genes involved in Lynch syndrome.<sup>5</sup> However, like *MLH3* for which no mutation was found in our study, the biological function of *PMS1* is unclear. One variant was identified in a patient with triple-negative breast cancer at 79 years of age, and rectal cancer at 50 years of age. However, microsatellite instability data was not available from the rectal tumor, and the impact of this variant on the MMR system, and so in Lynch syndrome, remains unknown.

*BARD1* interacts with *BRCA1*, known to be a major gene of predisposition to breast and ovarian cancer risk. Mutations in *BARD1* have been associated with breast cancer risk (OR: 2.21 to 5), but not with ovarian cancer.<sup>21,24,25</sup> In our study, one variant has been found in *BARD1* as an incidental finding in a late-onset ovarian cancer patient.

No mutation has been identified in *MRE11A*, *FAM175A*, *MLH3*, *RAD51*, or *XRCC2*. Thus, these genes do not seem to be associated with a hereditary cancer predisposition in our study.

Only the truncating variants were included in our study, because their functional impact is probable, and does not require additional

analyses. Thus, biological filters could have ruled out variants of interest other than truncating variants, in particular missense variants, which are more difficult to interpret. Their exploration would require functional analyses and/or case-control studies of large cohorts.

FANCM and RINT1 have been reported to be associated with a risk of breast and/or ovarian cancer, and are significantly associated with HBOC patients in our study. A complementary segregation study would determinate more precisely the implication of these genes in this predisposition. The other genes analyzed are not significantly associated with a predisposition to cancer, or have no truncating variant in our study. Their involvement in the hereditary predisposition to cancer cannot be ruled out. However, if it exists, it is rare or does not seem to involve truncating variants.

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## ETHICAL STATEMENT

The study has been approved by local ethics committee; reference: 2020/CE54.

## DATA AVAILABILITY STATEMENT

Data are available on request

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