Two truncating variants in FANCC and breast cancer risk

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Fanconi anemia (FA) is a genetically heterogeneous disorder with 22 disease-causing genes reported to date. In some FA genes, monoallelic mutations have been found to be associated with breast cancer risk, while the risk associations of others remain unknown. The gene for FA type C, FANCc, has been proposed as a breast cancer susceptibility gene based on epidemiological and sequencing studies. We used the Oncoarray project to genotype two truncating FANCC variants (p.R185X and p.R548X) in 64,760 breast cancer cases and 69,793 controls of European descent. FANCC mutations were observed in 25 cases (14 with p.R185X, 11 with p.R548X) and 26 controls (18 with p.R185X, 8 with p.R548X). There was no evidence of an association with the risk of breast cancer, neither overall (odds ratio 0.77, 95%CI 0.44–1.33, p = 0.4) nor by histology, hormone receptor status, age or family history. We conclude that the breast cancer risk association of these two FANCC variants, if any, is much smaller than for BRCA1, BRCA2 or PALB2 mutations. If this applies to all truncating variants in FANCC it would suggest there are differences between FA genes in their roles on breast cancer risk and demonstrates the merit of large consortia for clarifying risk associations of rare variants.

Fanconi Anemia (FA) is a rare recessively inherited disorder characterized by congenital malformations, progressive bone marrow failure and predisposition to cancer. Twenty-two different FA causative genes have now been identified whose products act in concert to mediate DNA interstrand crosslink repair. At least seven of them (BRCA2/FANCD2, PALB2/FANCl, RAD51C/FANCO, RAD51/FANCl, BRCA1/FANCS, XRCC2/FANCU, and RFWD3/FANCR) are involved in different stages of homology-directed recombinational DNA repair (HRR), a pathway for error-free maintenance of the genome during replication and after DNA damage. A number of FA genes (including BRCA1/FANCS, BRCA2/FANCD1 and PALB2/FANCl) have been shown to be breast cancer susceptibility genes. The products of BRCA1, BRCA2, and PALB2 are central to early stages of HRR. Further interactors in this pathway, in particular BRIP1/FANCl, mainly have been linked to ovarian cancer risk. It is less known to what extent other FA gene products may play a role in the inherited component of breast cancer susceptibility. Few of these other FA genes have been tested for mutations in relatively small breast cancer case-control studies, thus far.

Early studies suggested that blood relatives of FA patients show an increased risk of breast cancer, although these findings have not been corroborated in a replication study and could not assess distinct FA complementation groups due to lack of genetic information at that time. After FA was stratified into subsets defined by complementation assays, an increased risk of breast cancer was attributed to heterozygous carriers of FANCC mutations. This was the first of the FA genes to be identified and accounts for 8–15% of FA cases. More recently, FANCC has been suggested as a candidate breast cancer susceptibility gene in an exome sequencing study of 33 familial breast cancer cases and extension to another 438 cases. However, the evidence for an association between FANCC and breast cancer risk is limited by the low prevalence of mutations and, much larger numbers of individuals are needed to provide sufficient power to detect associations of plausible magnitude.
In the present study, we genotyped two truncating variants of FANCC (p.R185X and p.R548X) using the Oncoarray (see Methods) in 64,760 female breast cancer cases and 49,793 female population controls of European descent. Both mutations are disease-causing in European FA patients and are recurrent in the FA mutation database23.

Results
We identified the truncating FANCC variants p.R185X (rs121917783) and p.R548X (rs104886457) in 40 of 153,899 individuals and 20 of 153,904 individuals, respectively. All mutation carriers were heterozygotes. Carrier distributions per study and intensity cluster plots for Europeans (which included the majority of mutation carriers) are shown in Supplementary Table 1 and Supplementary Fig. 1, respectively. Since the majority of carriers were women of European ancestry, we restricted the subsequent case-control association analysis to participants from this population. Logistic regression analyses were adjusted for study and 15 principal components.

In Europeans, the two FANCC variants were observed in 25/64,760 cases (14 with p.R185X, 11 with p.R548X) and in 26/49,793 controls (18 with p.R185X, 8 with p.R548X). There was no evidence of association between the FANCC variants and breast cancer risk, either for carriers of both variants combined (OR 0.77, 95%CI 0.44–1.33, p = 0.35), or for either variant individually (Table 1). Similarly, we found no evidence for an association with estrogen receptor (ER)-negative (OR 0.91, 0.35–2.37) or ER-positive (OR 0.67, 0.37–1.28) disease, nor for subsets of disease defined by age at diagnosis (<50 years), bilaterality, family history, histological morphology, grade or nodal status (Table 2).

For comparison, we also analysed the PALB2/FANCN*p.R414X truncating variant that was genotyped in parallel on the same array. This variant was detected in 22/64,780 cases and 3/49,816 controls and was significantly associated with risk of breast cancer (OR 5.89, 95%CI 1.76–19.74, p = 0.004). The variant carriers were markedly enriched among cases with ER-negative tumours (p = 9.4 × 10⁻⁶; padj = 0.0006 in a log-likelihood ratio test) and specifically triple-negative breast tumours (p = 3.8 × 10⁻²; padj = 0.0001). The p.R414X truncating variant was also associated with ducal morphology, a positive first-degree family history of breast cancer, early age at diagnosis (<50 years), and low-differentiated tumours (grade 3) (Suppl. Table 1). Hence, by contrast with the two tested FANCC variants, p.R185X and p.R548X, the FANCN/PALB2 variant p.R414X was strongly associated with overall and with ER-negative disease under the same genotyping and analysis conditions.

Discussion
Functional defects of DNA repair are a hallmark of genomic instability syndromes as well as of carcinogenesis. FA is a genome instability and cancer prone disorder that has been investigated for breast cancer predisposition in homozygotes and heterozygotes for more than three decades11,12. Monoallelic mutations in five FA genes (BRCA1, BRCA2, RAD51C, BRIP1) have now been confirmed to predispose to breast or ovarian cancer while biallelic mutations in these genes cause FA1. However, the role of the FA genes most commonly mutated, FANCA and FANCC, in the risk of developing breast cancer has remained uncertain. Epidemiological and segregation studies have provided some evidence of an increased breast cancer risk for grandmothers of FA patients, particularly those who carry the FANCC mutation13.

A previous sequencing study of Australian multiple-case breast cancer families had identified truncating variants in FANCC in 3 of 438 multiple-case breast cancer families but in none of 464 healthy controls, suggestive of a predisposing role for FANCC variants in breast cancer14. One of these variants, p.R185X, was also screened in our study. p.R185X was first reported shortly after the identification of the FANCC gene, and thus is one of the earliest recognized FA-causing mutations. Although representing an apparent nonsense mutation in exon 6, it also results in exon 6 being spliced out of a proportion of transcripts, suggesting this variant may alter splice site selection, with the aberrant transcript retaining the reading frame22. p.R548X, also an early-detected FANCC truncating variant23, is an authentic stop mutation in exon 14, and although in the last exon, it proved to be clearly pathogenic for FA23.

The fact that these two disease-causing variants have been frequently observed in European patients with FA23 prompted us to investigate their association with breast cancer in a large case-control study. However, we did not observe a significant difference between their frequency among breast cancer cases and controls. The upper 95% confidence limit was 1.33, thus excluding a two-fold or greater increase in risk found for moderate- or high-penetrance alleles in predisposition genes such as CHEK2 and ATM. Moreover, we found no evidence of association in subgroups defined by earlier age at onset, a positive family history of breast cancer, bilateral occurrence, or defined tumor parameters (histology, grade or hormone receptor status). However, confidence intervals for those estimates for subsets were wider as numbers were small – in particular we could not rule out a 2-fold increased risk for ER-negative or triple-negative breast cancer.

In contrast, we observed a clear association between the PALB2/FANCN variant p.R414X and breast cancer risk. PALB2 is an established breast cancer susceptibility gene, and the investigated mutation p.R414X25 occurred

| Mutation | Cases | Controls | Odds Ratio (95% CI) | p |
|----------|-------|----------|---------------------|---|
| p.R185X  | 14/64,778 | 18/49,810 | 0.64 (0.32; 1.29) | 0.215 |
| p.R548X | 11/64,788 | 8/49,816 | 1.03 (0.41; 2.56) | 0.942 |
| All FANCC | 25/64,760 | 26/49,793 | 0.77 (0.44; 1.33) | 0.345 |

Table 1. Overall analysis of FANCC variants p.R185X and p.R548X. Association analyses of FANCC variants p.R185X and p.R548X with overall breast cancer risk. Results are given as odds ratios (OR) with 95% confidence interval (CI) and p-value (p).
After many nuclease and translesion polymerase steps, a DNA double stranded intermediate is formed and its repair requires proteins from the homology-directed repair pathway, including FANCD1/BRCA2 and FANCN/PALB2. While truncating variants in BRCA2 and PALB2 confer a substantial risk of breast cancer, our study suggests that truncating FANCC variants do not confer a comparable risk. It is possible that members of the FA core complex that act upstream of HRR are less relevant for breast cancer due to their more specialized function in the repair of interstrand crosslink while BRCA1, BRCA2, and PALB2 function more globally at DNA double-strand breaks. On the other hand, there is some evidence that truncating mutations in another gene involved in the early detection and repair of DNA damage, FANCC, is a component of the FA core complex which is thought to recognize an inter-strand crosslink. FANCL, an E3 ubiquitin ligase in the core complex, ubiquinates FANCI and FANCD2. Although PALB2 and FANCC are both FA genes, their products exert different roles in the recognition and repair of DNA damage. FANCC is a component of the FA core complex which is thought to recognize an inter-strand crosslink.

### Table 2. Analysis of FANCC variants (p.R158X and p.R548X combined) by tumour subtype. Association analyses of FANCC variants p.R158X and p.R548X with breast cancer risk for subgroups. Results are given as odds ratios (OR) with 95% confidence interval (CI) and p-value (p). Cases in subgroups were compared to the frequency 26/ 49,793 for all controls (derived from Table 1). Familial cases were defined as those with a first-degree family history of breast cancer; premenopausal cases were those with age at diagnosis < 50 years. ER, estrogen-receptor; TNBC, triple-negative breast cancer.

| Stratum       | Cases | Odds Ratio (95% CI) | p   |
|---------------|-------|--------------------|-----|
| ER-negative   | 5/10,124 | 0.91 (0.35; 2.37) | 0.845 |
| ER-positive   | 14/40,855 | 0.67 (0.37; 1.28) | 0.223 |
| TNBC          | 2/4,126   | 0.89 (0.21; 3.77) | 0.877 |
| Ductal        | 6/36,695  | 0.33 (0.13; 0.80) | 0.014 |
| Lobular       | 4/6,842   | 1.27 (0.43; 3.69) | 0.665 |
| High grade    | 3/14,582  | 0.39 (0.12; 1.31) | 0.129 |
| Node-positive | 1/15,937  | 0.14 (0.02; 1.00) | 0.050 |
| Familial      | 7/9,720   | 1.01 (0.43; 2.35) | 0.988 |
| Premenopausal | 12/22,232 | 1.09 (0.55; 2.16) | 0.814 |
| Bilateral     | 0/2,741   | —                  | 0.645 |

at a similar frequency to the tested FANCC mutations. The observed six-fold enrichment of p.R414X in breast cancer patients is in line with previous findings for other PALB2 founder mutations and in the upper range of the overall mutational effect size in PALB2 case-control sequencing studies. We confirmed stronger associations with ER-negative breast cancer, with familial breast cancer and with a high tumor grade. While genotyping arrays such as the Oncoarray are primarily used for evaluating common variants, these data confirm that the array provides a robust platform for evaluating even very rare alleles.

Although PALB2 and FANCC are both FA genes, their products exert different roles in the recognition and repair of DNA damage. FANCC is a component of the FA core complex which is thought to recognize an inter-strand crosslink. FANCL, an E3 ubiquitin ligase in the core complex, ubiquinates FANCI and FANCD2. After many nuclease and translesion polymerase steps, a DNA double stranded intermediate is formed and its repair requires proteins from the homology-directed repair pathway, including FANCD1/BRCA2 and FANCN/PALB2. While truncating variants in BRCA2 and PALB2 confer a substantial risk of breast cancer, our study suggests that truncating FANCC variants do not confer a comparable risk. It is possible that members of the FA core complex that act upstream of HRR are less relevant for breast cancer due to their more specialized function in the repair of interstrand crosslinks while BRCA1, BRCA2, and PALB2 function more globally at DNA double-strand breaks. On the other hand, there is some evidence that truncating mutations in another gene involved in the early detection of intra-strand crosslinks, FANCM, are associated with both breast and ovarian cancer risk, though FANCM is part of an anchor complex rather than the FA core complex and is not considered a classical FA gene. It is also possible that the two prototype FANCC truncating variants analysed here, despite being FA-causing, have reduced penetrance for breast cancer due to some residual function, and other particular FANCC variants may confer a more substantial risk. More work will be required to clarify the role of each FA core complex member for breast cancer susceptibility.

In conclusion, our study findings suggest important differences between FA genes, indicating that truncating variants in FANCC do not confer a high overall risk of breast cancer unlike PALB2, BRCA1 and BRCA2. Our study does not exclude a role of monoallelic FANCC variants as low-penetrance alleles for breast cancer or as a genetic risk factor for certain breast cancer subgroups. Very large datasets, such as those generated through the BCAC, are critical to evaluate such rare mutations.

### Methods

#### Patients.
A total of 87 studies from the Breast Cancer Association Consortium (BCAC), of which 78 were case-control studies (some nested within prospective cohort studies) and 9 were case-only studies, contributed data as summarized in Supplementary Table 1. All studies provided data on disease status and age at diagnosis/observation, and the majority provided information on clinico-pathological and epidemiological factors, which have been curated and incorporated into the BCAC database (version 6). All participating studies were approved by their appropriate ethics review boards and all subjects provided informed consent. A list of the ethics review boards by study is provided in Supplementary Table 3.

#### Genotyping.

The Illumina OncoArray design and genotyping procedure have been described previously. In brief, approximately 72,000 variants were selected, among others, for inclusion on the array specifically for their potential relevance to breast cancer, based on prior evidence of association with overall or subtype-specific disease, with breast density or with breast tissue specific gene expression. After genotype calling and quality control of the cluster file, variants with a call rate <95% in any consortium, not in Hardy-Weinberg equilibrium ($P < 10^{-7}$ in controls or $P < 10^{-12}$ in cases) or with concordance <98% among 5,280 duplicate pairs were excluded. We also excluded samples with extreme heterozygosity ($>4.89$ standard deviations [SD] from the mean for the respective ethnicity). The final dataset, before restriction based on ethnicity, consisted of 153,673 samples of which 89,733 were cases and 63,940 were controls.
Statistical analyses. Per-allele odds ratios and 95% confidence intervals were generated using logistic regression with adjustment for principal components and study. Principal component analysis was performed using data for 33,661 uncorrelated SNPs (which included 2,318 markers of continental ancestry) with a MAPE = 0.05 and maximum correlation of 0.1, using purpose-written PCcalc software (written by Jonathan Tyrer and available at http://ccgpe.medschl.cam.ac.uk/software/pccalc/).

We also estimated subtype-specific per-allele ORs after restricting the cases by hormone receptor and/or HER2/neu status, by tumor grade, by ductal or lobular morphology, by nodal status, by bilateral occurrence of the tumor, by early diagnosis (<50 years), and by first-degree family history of breast cancer, using available BCAC data for the cases. Since we analysed 3 variants across 10 subgroups, a two-sided p-value < 0.016 for the overall analyses and a two-sided p-value < 0.0016 for the subgroup analyses were considered nominally significant.

Ethical approval. All experimental protocols were approved by the respective ethical institutions of participating BCAC centers. The study was carried out in accordance with the Declaration of Helsinki, and informed consent was obtained from all study participants.

Data Availability

The genotyping results from the Oncoarray are available in the dbGAP repository. The FANCC variants analysed in the current study are deposited in the NCBI SNP database as rs121917783 and rs104886457. The datasets analysed during the current study are available from the corresponding author upon reasonable request and with permission of the Data Access Committee of the Breast Cancer Association Consortium.

References

1. Cecchaldi, R., Sarangi, P. & D’Andrea, A. D. The Fanconi anaemia pathway: new players and new functions. Nat. Rev. Mol. Cell Biol. 17, 337–349 (2016).
2. Knies, K. et al. Biallelic mutations in the ubiquitin ligase RNF135 cause Fanconi anemia. J. Clin. Invest. 127, 3013–3027 (2017).
3. Nalepa, G. & Clapp, D. W. Fanconi anemia and cancer: an intricate relationship. Nat. Rev. Cancer 18, 168–185 (2018).
4. Ramus, S. J. et al. Germline Mutations in the BRIP1, BARD1, PALB2, and NBN Genes in Women With Ovarian Cancer. J. Natl. Cancer Inst. 107, 11 (2015).
5. Easton, D. F. et al. No evidence that protein truncating variants in BRIP1 are associated with breast cancer risk: implications for gene panel testing. J. Med. Genet. 53, 298–309 (2016).
6. García, M. J. et al. Mutational analysis of FANCI, FANCM and the recently identified FANCI suggests that among the 13 known Fanconi Anemia genes, only FANCD1/BRC2 plays a major role in high-risk breast cancer predisposition. Carcinogenesis 30, 1899–1902 (2009).
7. Bakker, J. L. et al. Analysis of the novel Fanconi anemia gene SLX4/FANCN in familial breast cancer cases. Hum. Mutat. 34, 70–73 (2013).
8. Osorio, A. et al. Evaluation of rare variants in the new fanconi anemia gene ERCC4 (FANCQ) as familial breast/ovarian cancer susceptibility alleles. Hum. Mutat. 34, 1615–1618 (2013).
9. Lhota, F. et al. Hereditary truncating mutations of DNA repair and other genes in BRCA1/BRC2/PALB2-negatively tested breast cancer patients. Clin. Genet. 90, 324–333 (2016).
10. Swift, M. Fanconi’s anemia in the genetics of neoplasia. Nature 230, 370–373 (1971).
11. Swift, M., Caldwell, R. J. & Chase, C. Reassessment of cancer predisposition of Fanconi anemia heterozygotes. J. Natl. Cancer Inst. 65, 863–867 (1980).
12. Jacobs, P. & Karabus, C. Fanconi’s anemia. A family study with 20-year follow-up including associated breast pathology. Cancer 54, 1850–1853 (1984).
13. Berwick, M. et al. Genetic heterogeneity among Fanconi anemia heterozygotes and risk of cancer. Cancer Res. 67, 9591–9596 (2007).
14. Strathdee, C. A. et al. Cloning of cDNAs for Fanconi’s anemia by functional complementation. Nature 356, 763–767 (1992).
15. Gibson, R. A. et al. Genetic mapping of the FACC gene and linkage analysis in Fanconi anemia families. J. Med. Genet. 31, 868–871 (1994).
16. Verlander, P. C. et al. Mutation analysis of the Fanconi anemia gene FACC. Am. J. Hum. Genet. 54, 595–601 (1994).
17. Thompson, E. R. et al. Exome sequencing identifies rare deleterious mutations in DNA repair genes FANCC and BLM as potential breast cancer susceptibility alleles. PLoS Genet. 8, e1002894 (2012).
18. Seal, S. et al. Evaluation of Fanconi Anemia genes in familial breast cancer predisposition. Cancer Res. 63, 8596–8599 (2003).
19. Ellis, N. A. & Offit, K. Heterozygous mutations in DNA repair genes and hereditary breast cancer: a question of power. PLoS Genet. 8, e1003008 (2012).
20. Fanconi anemia mutation database, http://www2.rockefeller.edu/fanconi/.
21. Michaloudi, K. et al. Association analysis identifies 65 new breast cancer risk loci. Nature 551, 92–94 (2017).
22. Gibson, R. A. et al. A nonsense mutation and exon skipping in the Fanconi anemia group C gene. Hum Mol Genet. 2, 797–799 (1993).
23. Murer-Orlando, M., Llerena, J. C. Jr. & Birjandi, F. FACC gene mutations and early prenatal diagnosis of Fanconi’s anemia. Lancet. p. 866 (1993).
24. Lo ten Foe, J. R. et al. Sequence variations in the Fanconi anemia gene, FACC: pathogenicity of 1806insA and R548X and recognition of D195V as a polymorphic variant. Hum. Genet. 98, 522–523 (1996).
25. Bogdanova, N. et al. PALB2 mutations in German and Russian patients with bilateral breast cancer. Breast Cancer Res. Treat. 126, 545–550 (2011).
26. Erkko, H. et al. A recurrent mutation in PALB2 in Finnish cancer families. Nature 446, 316–319 (2007).
27. Southey, M. C. et al. A PALB2 mutation associated with high risk of breast cancer. Breast Cancer Res. 12, R109 (2010).
28. Noskowicz, M. et al. Prevalence of PALB2 mutation c.509_510delGA in unselected breast cancer patients from Central and Eastern Europe. Fam. Cancer 13, 137–142 (2014).
29. Rahman, N. et al. PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene. Nat. Genet. 39, 165–167 (2007).
30. Tsichkowitz, M. et al. Rare germline mutations in PALB2 and breast cancer risk: a population-based study. Hum. Mutat. 33, 674–680 (2012).
31. Heikkinen, T. et al. The breast cancer susceptibility mutation PALB2 1592delT is associated with an aggressive tumor phenotype. Clin. Cancer Res. 15, 3214–3222 (2009).
32. Kükki, J. I. et al. Exome sequencing identifies FANCM as a susceptibility gene for triple-negative breast cancer. Proc. Natl. Acad. Sci. USA 111, 15172–15177 (2014).
33. PETERLONGO, P. et al. FANCM c.5791C>T nonsense mutation (rs144567652) induces exon skipping, affects DNA repair activity and is a familial breast cancer risk factor. Hum. Mol. Genet. 24, 5345–5355 (2015).
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