Received: 12 August 2021 | Revised: 16 September 2021 | Accepted: 27 September 2021

DOI: 10.1111/cge.14068

ORIGINAL ARTICLE

CLINICAL GENETICS WILEY

Dominant-negative pathogenic variant BRIP1 c.1045G>C is a high-risk allele for non-mucinous epithelial ovarian cancer: A case-control study

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Funding information
Cancer Research UK Manchester Centre, Grant/Award Numbers: C147/A18083, C147/A25254; National Institute for Health Research, Grant/Award Number: NIHR300650; National Institute for Health Research (NIHR) Manchester Biomedical Research Centre, Grant/Award Number: IS-BRC-1215-20007; Prevent Breast Cancer, Grant/Award Numbers: GA 15-002, GA19-002

Abstract

BRIP1 is a moderate susceptibility epithelial ovarian cancer (EOC) gene. Having identified the *BRIP1* c.1045G>C missense variant in a number of families with EOC, we aimed to investigate the frequency of this and *BRIP1*.2392C>T pathogenic variant in patients with breast cancer (BC) and/or EOC. A case-control study of 3767 cases and 2043 controls was undertaken investigating the presence of these variants using Sanger sequencing and gene panel data. Individuals with BC and/or EOC were grouped by family history. *BRIP1* c.1045G>C was associated with increased risk of BC/EOC (OR = 37.7; 95% CI 5.3–444.2; $P = 0.0001$). The risk was highest for women with EOC (OR = 140.8; 95% CI 23.5–1723.0; $P < 0.0001$) and lower for BC (OR = 11.1; 95% CI 1.2–106.5; $P = 0.1588$). *BRIP1* c.2392C>T was associated with smaller risks for BC/EOC (OR = 5.4; 95%CI 2.4–12.7; $P = 0.0003$), EOC (OR = 5.9; 95% CI 1.3–23.0; $p = 0.0550$) and BC (OR = 5.3; 95%CI 2.3–12.9; $P = 0.0009$). Our study highlights the importance of *BRIP1* as an EOC susceptibility gene, especially in familial EOC. The variant *BRIP1* c.1045G>C, rs149364097, is of particular interest as its dominant-negative effect may confer a higher risk of EOC than that of the previously reported *BRIP1* c.2392C>T nonsense variant. Dominant-negative missense variants may confer higher risks than their loss-of-function counterparts.

Nicola Flaum and Elke M. van Veen have contributed equally.

KEYWORDS
breast cancer, *BRIP1*, epithelial ovarian cancer, familial cancer predisposition, genetics

1 | INTRODUCTION

Epithelial ovarian cancer (EOC) is a highly heritable cancer, with a three-fold increase in risk for first-degree relatives of affected women.[1] Approximately 10–15% of EOC is considered to be hereditary. This is somewhat higher in the most common high grade serous (HGSOC) subtype, although the precise figure is unknown.[1–4] For many years BC and EOC have been noted to affect multiple individuals in some families,[5] leading to the identification of hereditary breast and ovarian cancer syndrome (HBOC). Pathogenic variants (PVs) in *BRCA1* and *BRCA2* explain approximately 25% of HBOC, and PVs in other genes in homologous recombination, mismatch repair and cell cycle checkpoint pathways account for additional significant contributions to risk.[6,7] However, the cause of approximately 35% of familial EOC remains unexplained.

The gene *BRCA1 interacting protein 1 (BRIP1)* encodes the protein BRIP1, which interacts with BRCA1 through BRCT repeats at the c-terminal end of BRCA1 and is required for normal repair of double-strand DNA breaks.[8] PVs have been found in the first two-thirds of the gene, between nucleotides 68–2508, predicted to truncate the protein before the BRCA1 binding domain.[9] The gene is part of the Fanconi anaemia complement group family of proteins and is also known as *FANCJ* and *BACH1*.[10]

BRIP1 was originally considered to be a BC susceptibility gene in 2006 by Seal et al.[11] with identification of truncating PVs in *BRIP1* in nine of 1212 women with BC, but in only two of 2081 controls ($p = 0.003$), conferring an estimated relative risk (RR) of 2.0. All women with breast cancer had a family history of BC and/or EOC. The most common PV found was the truncating variant *BRIP1* c.2392C>T; p.(Arg798Ter) in exon 17, occurring in five affected women and one of the controls.[11] *BRIP1* PVs were further reported in subsequent studies,[12–14] including one[15] that genotyped the *BRIP1* c.2392C>T; p.(Arg798Ter) variant and 10 missense variants in >48 000 affected individuals and 43 000 controls from the Breast Cancer Association Consortium (BCAC). The coding regions in >16 000 affected individuals and >8000 controls were also sequenced and there was some weak evidence of an association between *BRIP1* c.2392C>T; (p.Arg798Ter) and ER-negative and triple-negative disease. However, overall there was no significant association between *BRIP1* and BC risk.[15] Conflicting or no significant evidence of *BRIP1* as a BC risk gene was confirmed in further studies,[16,17] but the most definitive evidence from over 60 000 women with BC suggests there is no association.[18]

BRIP1 is now considered more significant in conferring risk for EOC. An Icelandic study found a frameshift variant, *BRIP1* c.2040_2041insTT increased EOC risk with an odds ratio (OR) of 8.13, and carriers of the variant with an average 3.6 years shorter life expectancy than non-carriers.[19] A study of germline variants in genes associated with EOC from 1915 women with EOC compared PV frequencies with women from the NHLBI GO Exome Sequencing Project (ESP) and the Exome Aggregation Consortium (ExAC) and found ORs of 9.1 compared to ESP controls and 6.4 compared to ExAC controls.[20] In a 2017 study, standardised RR for *BRIP1* and EOC of 4.99 was calculated from 7768 EOC patients of European ancestry.[21] In a 2018 case-control study *BRIP1* loss of function PVs were described to confer a high risk of OC in women with a strong family history of OC (OR = 20.97; OR for late-onset OC = 29.91).[16] Overall, *BRIP1* PV carriers seem to develop EOC at the same age as in the general population, and have an estimated 5.8% cumulative lifetime risk.[9,22] A recent meta-analysis by Suszynska et al. including 22 494 EOC cases found *BRIP1* to have an OR of 4.94 (95% 4.07–6.00; $P < 0.0001$).[23]

In 2019 three unrelated women with familial non-mucinous EOC ascertained through the Manchester Centre of Genomic Medicine (MCGM) were found to carry the missense variant *BRIP1* c.1045G>C; p.(Ala349Pro), (rs149364097). This variant is described as pathogenic/likely pathogenic in ClinVar.[24] We hypothesised that this variant may be enriched in our patient population as an EOC and/or BC PV. We aimed to investigate the frequency of this variant as well as the established *BRIP1* c.2392C>T variant through a case-control study.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

Women were recruited through the 'Investigation of genetic modifiers in *BRCA1/2* breast cancer and non *BRCA1/2* high risk families' study for whole exome sequencing and Sanger sequencing at MCGM, the Predicting Risk of Cancer at Screening (PROCAS) study and FH-Risk.[25] Five hundred and twenty-one women from our centre had been included in the study by Seal et al.[11] and as such had had DNA analysed for variant *BRIP1* c.2392C>T; p.(Arg798Ter). The primary source of participants included in our study is summarised in Table 1.

The PROCAS study recruited women aged 46–73 years attending BC screening in Greater Manchester, who were not affected with either BC or EOC at study entry. Women who developed BC after entry were included as cases.[25] Their samples underwent panel testing as part of the Breast Cancer Risk after Diagnostic Gene Sequencing (BRIDGES) study.[18] Women who were recruited to the Predicting Risk of Cancer at Screening (PROCAS) study with no BC diagnosis were included as controls; this meant that the controls would be from the same geographical region as the cases and similarly known to MCGM.

Cases comprised all women with non-mucinous EOC or BC, aged 18 years or over known to MCGM. They were recruited 1990–2020, but the ovarian cancer cases predominantly from 2016. Controls were women with no history of EOC or BC and no prior known PVs. They were recruited through PROCAS 2009–2013, and cancer-free as of 2020. Controls (group 1) were compared with cases in five groups: women with BC and no family history of EOC (group 2), women with BC

TABLE 1 Table of sources of study participants genotyped for *BRIP1* c.1045G>C and *BRIP1* c.2392C>T pathogenic variants

Primary[a] source of BRIP1 variant data	Participants included (*n*)	Number tested for *BRIP1* c.1045G>C	Number tested for *BRIP1* c.2392C>T
PROCAS/BRIDGES studies (controls)	2566	2566	2566
Sanger sequencing at MCGM (cases)	2172	2172	2162
BC cases	1551	1551	1550
EOC cases	698	698	688
Cancer panels (cases)	365	365	365
BC cases	350	350	350
EOC cases	17	17	17
FH-risk (cases)	207	197	207
BC cases	206	196	206
EOC cases	2	2	2
Seal et al. study (cases)	500	0	500
BC cases	500	N/A	500
EOC cases	0	N/A	0
Total	5810	5300	5800
Cases	3244	2734	3234
Controls	2566	2566	2566

[a]Where participants were included in multiple categories (for example cancer panels and the Seal et al. study) the source with the most genetic information has been listed as the primary source.

and a family history of EOC (group 3), women with EOC and no BC/EOC family history (group 4), women with EOC and family history of BC only (group 5), and women with familial EOC (≥2 family members) (group 6).

2.2 | Data extraction

Relevant clinical information (histology of EOC and BC diagnoses, age at diagnosis, family history of BC and/or EOC) was obtained from local clinical record systems. Data for PROCAS patients was obtained from a questionnaire completed at study entry. Prospective cancer diagnoses were updated through the cancer registry.

2.3 | DNA extraction

DNA was extracted from peripheral blood lymphocytes from women who attended MCGM with EOC and ≥2 affected relatives with EOC. DNA from the women in PROCAS was extracted from saliva using an Oragene kit (DNA Genotek) according to the manufacturer's protocols.

2.4 | Sanger sequencing

Amplification of exon 8 of *BRIP1* to genotype c.1045G>C was done by using the following forward and reverse primers: 5′-GTGG CTTTAATGATGTTCCTC-3′ and 5′-CTCACACTTTCCCTTATTT GTG-3′, respectively. Similarly, amplification of a 702 bp region was used to screen exon 17 of *BRIP1* for the truncation PV c.2392C>T; p.(Arg798Ter). Sequences for the forward and reverse primers were: 5′-GTAATTTAAGGAATGTGAAGC-3′ and 5′-GAGC ATCTTTGTGTGCTATTC-3′. The amplified fragments were then visualised using gel electrophoresis, purified, and sequencing reactions were prepared using the BigDye™ Terminator v3.1 Cycle Sequencing kit (Thermo Fisher Scientific Inc., Waltham, MA). Sequencing reactions were analysed using an ABI3730xl DNA Analyser (Life Technologies, Paisley, UK).

2.5 | Statistical methods

Data was combined from the patients included in the panel screening, the patients included in the Seal et al.[11] patients included in PROCAS-BRIDGES, those who had undergone exome sequencing and those on whom we performed Sanger sequencing for these two variants. Duplicates, cases who had undergone panel screening which did not include *BRIP1*, and cases with inappropriate histology/diagnosis or absent cancer information were removed.

We examined the ORs for the case–control study grouped in five ways[1]: all cases (groups 2–6)[2]; all EOC cases (groups 4–6)[3]; BC cases (groups 2 and 3)[4]; family history of EOC (groups 4 and 6); and[5] women with BC only. In all OR estimations data from gnomAD v.2.1.1 for each variant (controls, European non-Finnish population[26]) was used for the control value as no PVs were detected in our control group.

Odds ratios were calculated using GraphPad Prism 8.4.3 and 95% confidence intervals and two-sided *p*-values using the Baptista-Pike method and Fisher's exact test. *P*-value was considered significant at 0.05.

The STROBE case-control checklist was used to present the data.[27]

TABLE 2 Table of genotyped study participant demographics

Total participants	
Cases (*n*)	3767
Controls (*n*)	2043
Total genotyped for *BRIP1* c.1045G>C; p.(Ala349Pro)	
Cases (*n*)	3210
Controls (*n*)	2043
EOC (*n*)	690
BC (*n*)	2592
EOC and BC (*n*)	73
Total genotyped for *BRIP1* c.2392C>T; p.(Arg798Ter)	
Cases (*n*)	3700
Controls (*n*)	2043
EOC (*n*)	682
BC (*n*)	3091
EOC and BC (*n*)	74
Epithelial ovarian cancer	
Total with EOC diagnosis (*n*)	717
Mean age at diagnosis (range)	57 (20–83)
HGSOC (%)	556 (77.5)
Breast cancer	
Total with BC diagnosis (*n*)	3129
Mean age at diagnosis (range)	46 (15–90)
ER positive[a] (%)	1133/2062 (54.9)
HER2 positive[a] (%)	178/1124 (15.8)
TNBC[a] (%)	348/1120 (31.0)
MBC (%)	34 (1.1)

Abbreviations: EOC, epithelial ovarian cancer; BC, breast cancer; HGSOC, high grade serous ovarian cancer; ER, Estrogen receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple negative breast cancer; MBC, male breast cancer.
[a]Where data available.

3 | RESULTS

3.1 | Patient demographics

A total of 3767 individuals with BC and/or EOC and 2043 controls were tested for the two variants. These are described further in Table 2.

3.2 | *BRIP1* c.1045G>C frequency

Cases and controls were categorised by diagnosis and relevant family history, as shown in Table 3. Four out of six individuals with this variant had EOC. Three of these were in group 6 and had HGSOC, and one patient was in group 5 and was diagnosed with poorly differentiated ovarian adenocarcinoma at 60 years and ER-positive HER2-negative ductal BC at 63 years. They were all white British; the mean age at EOC diagnosis 62.5 (range 51–71) years. Two women with BC in group 2 recruited from PROCAS had this PV; one woman also had a *BRCA2* PV and was subsequently removed from analysis as this was presumed to be the disease associated PV in this case. The remaining woman was diagnosed with intermediate grade, ER-positive, HER2-negative ductal carcinoma in-situ at 61 years.

The variant was not detected in the control group. Therefore, ORs for the missense PV *BRIP1* c.1045G>C were calculated using control frequencies from the gnomAD v2.1.1 control data using the European non-Finnish population to be as representative of our study population as possible[26] (allele frequency 1/48286 = 0.00002071; 1/24143 women).

The PV *BRIP1* c.1045G>C was associated with increased risk of BC/EOC in groups 2–6 (OR = 37.7; 95% CI 5.3–444.2; $P = 0.0001$). The risk was especially strong for women with EOC (groups 4–6) (OR = 140.8; 95% CI 23.5–1723.0; $P < 0.0001$) and maintained in women with a diagnosis and family history exclusively of EOC (groups 4 and 6) (OR = 139.3; 95% CI 20.7–1809.0; $P < 0.0001$).

TABLE 3 Table of results for *BRIP1* c.1045G>C and *BRIP1* c.2392C>T genotyping in affected individuals and controls

Group	Total number tested for *BRIP1* c.1045G>C	*BRIP1* c.1045G>C positive	*BRIP1* c.1045G>C positive (%)	Total number tested for *BRIP1* c.2392C>T	*BRIP1* c.2392C>T positive	*BRIP1* c.2392C>T positive (%)
1 (controls)	2043	0	0.00	2043	0	0.00
2	2180	1	0.05	2655	6	0.23
3	339	0	0.00	363	2	0.55
4	430	0	0.00	423	1	0.24
5	167	1	0.60	174	1	0.57
6	93	3	3.23	85	0	0.00
All cases (2–6)	3209	5	0.16	3700	10	0.27
gnomAD[a]	24 143	1	0.00	23 901	12	0.00

Note: Group 1 – Controls; Group 2 – Breast cancer diagnosis only, no family history of ovarian cancer. Group 3 – Breast cancer diagnosis only, positive family history of ovarian cancer. Group 4 – Ovarian cancer diagnosis, no family history of breast cancer. Group 5 – Ovarian cancer diagnosis, positive family history of breast cancer only. Group 6 – Ovarian cancer diagnosis, strong family history of ovarian cancer (≥2 family members).
[a]Controls, European, non-Finnish population.

The risk was not significant for BC (groups 2 and 3) (OR = 9.6; 95% CI 0.5–182.2; $P = 0.18$) or in individuals with BC only and no family history of EOC (group 2) (OR = 11.1; 95% CI 1.2–106.5; $P = 0.1588$).

3.3 | *BRIP1* c.2392C>T frequency

A breakdown of results by group is shown in Table 3. Of the 10 individuals carrying this variant, eight had BC, one had EOC and one had BC and EOC. All white British, of the individuals with BC the mean age at diagnosis was 44 (range 30–74) years, eight had infiltrating ductal carcinoma and two had lobular carcinoma. Three women had ER-positive disease, four ER-negative and in two the ER status was unknown. Six had HER2-negative disease and in the other three HER2 status was unknown; four women had triple negative disease. The two women with an EOC diagnosis had HGSOC and were diagnosed at 59 and 60 years.

As there was no frequency for stop-gain PV *BRIP1* c.2392C>T in local controls, ORs were calculated using control frequencies from the European non-Finnish gnomAD v2.1.1 population (allele frequency for: 12/47 802 alleles = 0.0002510, 12/23 901 women). The PV *BRIP1* c.2392C>T was associated with a significant, but much weaker risk of BC /EOC in groups 2–6 (OR = 5.4; 95%CI 2.4–12.7; $P = 0.0003$). This risk was close to signficance in all women with EOC (groups 4–6) (OR = 5.9; 95% CI 1.3–23.0; $p = 0.0550$) and not significant for women with a diagnosis and family history exclusively of EOC (groups 4 and 6) (OR = 3.9; 95% CI 0.4–24.6; $P = 0.2393$).

The variant was associated with significant risk of BC in all BC groups 2 and 3 (OR = 5.3; 95%CI 2.3–12.9; $P = 0.0009$) and in individuals with BC and no family history of EOC (group 2) (OR = 4.5; 95%CI 1.8–11.3; $p = 0.0064$).

4 | DISCUSSION

Our study highlights the importance of *BRIP1* as an EOC susceptibility gene, in particular in familial EOC cases. The *BRIP1* c.1045G>C PV was present in 3.23% of our cases with familial EOC. The finding of this variant in this population is of particular interest and it may be that this variant is more common in North-West of England as it has not been described as significantly in other studies. Although to the best of our knowledge our *BRIP1* c.1045G>C PV carriers are unrelated, it is possible that they could link several generations before. As the majority of the data were generated through Sanger sequencing for these specific variants, insufficient data were available for haplotype analysis. No samples were available from other affected family members to perform segregation analysis.

This variant seems extremely relevant to EOC risk, and not significantly for BC. The meta-analysis by Suszynska et al. found the *BRIP1* c.2392C>T present in 14/22 494 (0.06%) cases, compared to 37/131 983 (0.03%) controls with an associated OR of 2.22 (95% CI 1.20–4.11; $P = 0.011$). There was one *BRIP1* c.1045G>C (1/22 494; 0.0044%) variant in the affected individuals and 4 out of 134 094 controls (0.003%).[23] The affected individual was reported in an American study of 4439 women with EOC (74.8% Caucasian origin).[28] The *BRIP1* c.1045G>C variant has been reported in individuals with Fanconi anaemia in three studies[10,29,30] as well as in individuals with EOC[31] and BC.[15] However the frequency of this variant in individuals with BC /EOC is scarce and multiple affected individuals have not been reported before.

In a previous study, the variant was noted to be immediately adjacent to a highly conserved cysteine of the iron-sulphur domain. This Fe-S domain is important in DNA repair proteins from structural and functional studies.[29] The p.Arg349Pro BRIP1 differed from wild-type BRIP1 by possessing only one iron atom per polypeptide compared to three for wild-type; had no DNA helicase activity; disrupted protein-DNA interactions, and exerted a dominant-negative effect on cell survival or DNA damage accumulation following cisplatin or telomestatin treatment.[29]

Overall these biochemical and cellular function studies provide supporting evidence for the theory this variant affects DNA damage repair and therefore could be an EOC susceptibility PV, similar to those in other homologous recombination genes. This would have potential treatment implications in terms of patients with this variant being likely to respond to PARP inhibitors.[32]

Of clinical significance, PVs in *BRIP1* have been demonstrated to make cells very sensitive to cisplatin, a DNA-crosslinking agent.[33] It follows that patients with pathogenic *BRIP1* variants may be more likely to have platinum-sensitive EOC and treatment could be planned accordingly. As a gene involved in homologous recombination it may also be the case that patients with *BRIP1* PVs would be highly sensitive to treatment with poly-ADP ribose polymerase (PARP) inhibitors, as is the situation for women carrying *BRCA1/2* PVs.

The dominant-negative nature of some missense variants has been shown to increase the risk of associated cancer with some other genes. Notably the *ATM* missense variant c.7271T>G (p.Val2424Gly) has been shown to confer a high risk of BC (>50% lifetime risk) compared to the more moderate 2–3 fold relative risk (lifetime risk 20–30%) associated with *ATM* loss of function variants [28]. The same genotype–phenotype effect has been reported for dominant-negative *TP53* missense variants in Li Fraumeni syndrome.[29] The nature of these dominant-negative variants is that the abnormal protein interferes with function of wild type by dimerization or tetramerization thus reducing the availability of wild type protein even below the 50% associated with loss of function variants. In the case of *BRIP1* c.1045G>C, this is associated with a far higher risk of EOC than the loss of function *BRIP1* c.2392C>T variant.

This is demonstrated particularly by the presence of such a high frequency in the women with familial EOC. The situation with missense variants in *ATM*, *TP53* and now *BRIP1* is different to the weaker effects of missense variants in genes like *CHEK2*, where loss of function variants confer a higher risk, than missense variants.[30]

The *BRIP1* c.2392C>T PV showed a significant increase of risk for BC and a significant but smaller risk for the combined group in our study. We had a detection rate for this variant of 10/3700 (0.27%),

five times higher assuming the same OR than the detection rate of 0.047% in the Easton et al study.[15] As we found an OR of 5 for BC and this was not found in the Easton study there may be another factor such as a potential founder effect contributing, or our ORs are incorrect and a more accurate OR for this variant would be a fifth of what we found. We did nonetheless not find this variant in over 2000 controls meaning a local population rate below 0.05%. It is possible therefore the truth lies in between.

There are some limitations to the present study. Both *BRIP1* variants may be local founders and the true odds ratios of their effects may be lower. Nevertheless, we did not find either variant in over 2000 control samples and the larger gnomAD control dataset, restricted to the European non-Finnish population, was the best alternative. Even still the EOC conferred by the nonsense variant *BRIP1* c.2392C>T is similar to previous estimates.

While this needs further validation, the dominant-negative effect of the *BRIP1* c.1045G>C variant is likely to mean a more significant EOC risk than that of the well-known stop-gain *BRIP1* c.2392C>T variant. Although rarer, due to the dominant-negative effect it has, it appears to confer a higher risk of EOC and should be considered in investigation of women with familial EOC. Finally, clinicians should not assume that a missense variant that is classified as pathogenic or likely pathogenic confers the same risk as loss of function variants. In particular, an assessment of whether the variant may be associated with a dominant-negative effect is important.

ACKNOWLEDGEMENTS

DGE, WGN, MJS and EJC are supported by the National Institute for Health Research (NIHR) Manchester Biomedical Research Centre (IS-BRC-1215-20007). EJC is an NIHR Advanced Fellow (NIHR300650). NF is supported by CRUK via the funding to Cancer Research UK Manchester Centre: [C147/A18083] and [C147/A25254]. EVV is supported by Prevent breast cancer (GA 15-002 and GA19-002).

CONFLICT OF INTEREST

The authors have not conflicting interests to declare.

ETHICS DECLARATION

The FH-Risk study was approved by the NHS North Manchester Research Ethics Committee (08/H1006/77) and the University of Manchester ethics committee (08229) and a later Substantial Amendment to incorporate the study 'Investigation of genetic modifiers in *BRCA1/2* breast cancer and non *BRCA1/2* high risk families' study (Reference 08/H1006/77) was approved by Greater Manchester West (GM West) Research Ethics Committee. The PROCAS study was approved by the North Manchester Research Ethics Committee (ref. 09/H1008/81) and participants agreed for their samples to be used in other ethically approved studies. Informed consent was obtained from all participants. Clinical data was anonymised for analysis.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/cge.14068.

DATA AVAILABILITY STATEMENT

Anonymised data is available on request to the Corresponding Author.

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How to cite this article: Flaum N, van Veen EM, Smith O, et al. Dominant-negative pathogenic variant BRIP1 c.1045G>C is a high-risk allele for non-mucinous epithelial ovarian cancer: A case-control study. *Clinical Genetics*. 2021;1-7. doi: 10.1111/cge.14068