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Functional mechanisms underlying pleiotropic risk alleles at the 19p13.1 breast-ovarian cancer susceptibility locus

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A locus at 19p13 is associated with breast cancer (BC) and ovarian cancer (OC) risk. Here we analyse 438 SNPs in this region in 46,451 BC and 15,438 OC cases, 15,252 *BRCA1* mutation carriers and 73,444 controls and identify 13 candidate causal SNPs associated with serous OC ($P=9.2 \times 10^{-20}$), ER-negative BC ($P=1.1 \times 10^{-13}$), *BRCA1*-associated BC ($P=7.7 \times 10^{-16}$) and triple negative BC ($P\text{-diff}=2 \times 10^{-5}$). Genotype-gene expression associations are identified for candidate target genes *ANKLE1* ($P=2 \times 10^{-3}$) and *ABHD8* ($P<2 \times 10^{-3}$). Chromosome conformation capture identifies interactions between four candidate SNPs and *ABHD8*, and luciferase assays indicate six risk alleles increased transactivation of the *ADHD8* promoter. Targeted deletion of a region containing risk SNP rs56069439 in a putative enhancer induces *ANKLE1* downregulation; and mRNA stability assays indicate functional effects for an *ANKLE1* 3'-UTR SNP. Altogether, these data suggest that multiple SNPs at 19p13 regulate *ABHD8* and perhaps *ANKLE1* expression, and indicate common mechanisms underlying breast and ovarian cancer risk.

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Genome-wide association studies (GWAS) have identified more than 100 different genetic susceptibility regions for breast cancer (BC)^{1–6} and 20 regions for epithelial ovarian cancer (EOC)^{7–13}. A few of these regions, and in some cases the same genetic variants, are associated with risks of both cancers (pleiotropy), suggesting there may be underlying functional mechanisms and biological pathways common to different cancers. The *TERT-CLPTMIL* locus (5p15) is one such example in which the same variants are associated with risks of oestrogen receptor (ER)-negative BC, BC in *BRCA1* mutation carriers and serous invasive OC¹⁰.

Few studies have comprehensively described the functional mechanisms underlying common variant susceptibility loci^{10,14–18}. More than 90% of risk alleles lie in non-protein-coding DNA and there is now unequivocal evidence that susceptibility regions are enriched for risk-associated single-nucleotide polymorphisms (SNPs) intersecting regulatory elements, such as transcriptional enhancers, predicted to control the expression of target genes *in cis*^{19–21}. Establishing causality for risk SNPs is very challenging; of the thousands of risk associations identified by GWAS, functional validation of causal variants using genome editing has only been experimentally performed for two SNPs, one for prostate cancer²² using the CAUSEL pipeline and the other for obesity²³. Thus, there is a critical need to identify the causal risk SNP(s) and the overlapping regulatory element(s) and the target gene(s) regulated in an allele-specific manner.

Breast and high-grade serous OC share common genetic and non-genetic risk factors, with mutations in *BRCA1* and *BRCA2* the most significant risk factors for both cancers, suggesting similar biological mechanisms drive breast and OC development. A region on chromosome 19p13.1 has previously been associated with susceptibility to BC and OC in the general population, and to modify the risks of *BRCA1*-related BC and *BRCA2*-related OC^{9,24–27}. Initial studies indicated that the association signal was centred around the SNP rs8170 located in the *BRCA1*-interacting gene *BABAM1* (ref. 9), and subsequent studies have refined the subtype specific BC risks associated with these SNPs^{24–26,28}.

In the current study, we hypothesized that the same functional mechanism underlies the 19p13.1 risk association in both BC and OC. To evaluate this hypothesis we performed genetic fine mapping in BC and OC patients and in *BRCA1* mutation carriers,

and performed a wide range of functional assays in breast and ovarian tissues and *in vitro* models to identify the likely causal alleles, and target regulatory elements and susceptibility gene(s). Our data indicate that multiple SNPs are involved in the regulation of *ABHD8* and perhaps *ANKLE1* at this locus.

Results

Genetic association analyses with breast and OC risks. A total of 438 SNPs spanning 420 kb at the chromosome 19p13 locus (nucleotides 17,130,000–17,550,000 (NCBI build 37)) were genotyped successfully in the following populations: 46,451 BC cases (of which 7,435 cases had ER-negative tumours) and 42,599 controls from the Breast Cancer Association Consortium (BCAC); 15,438 cases of EOC (of which 9,630 were of serous histology) and 30,845 controls from the Ovarian Cancer Association Consortium (OCAC); and 15,252 *BRCA1* mutation carriers from the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA; 7,797 with BC and 7,455 unaffected; Supplementary Table 1). Genotypes for variants identified through the 1,000 genomes project (minor allele frequency (MAF) > 0.1%) were imputed for all participants of European ancestry. A total of 2,269 genotyped and imputed SNPs were analysed for their associations with ER-negative BC risk in the general population, 2,311 SNPs with BC/OC risk for *BRCA1* mutation carriers, and 2,565 SNPs with risk of serous OC. Results for all SNPs associated with these phenotypes at $P < 10^{-4}$ are illustrated in Fig. 1 and Supplementary Fig. 1. Two perfectly correlated SNPs rs61494113 and rs67397200 located between the *ANKLE1* and *ABHD8* genes demonstrated the strongest association with BC risk among *BRCA1* mutation carriers (χ^2 -test $P = 7.8 \times 10^{-16}$) and ER-negative BC in BCAC (χ^2 -test $P = 1.3 \times 10^{-13}$, P -meta-analysis = 7.3×10^{-28}). There was no association for ER-positive BC (χ^2 -test $P = 0.21$ for rs61494113). The strongest association with invasive and serous OC was for rs4808075 (correlated with rs61494113 with $r^2 = 0.99$) located in the *BABAM1* gene (χ^2 -test $P = 9.2 \times 10^{-20}$). We observed no associations with risk of other histological subtypes of invasive OC (Supplementary Table 2). The correlations between the SNP exhibiting the strongest risk association (rs67397200) in the meta-analysis of BC risk for *BRCA1* mutation carriers and ER-negative BC, with the previously reported risk-associated SNPs

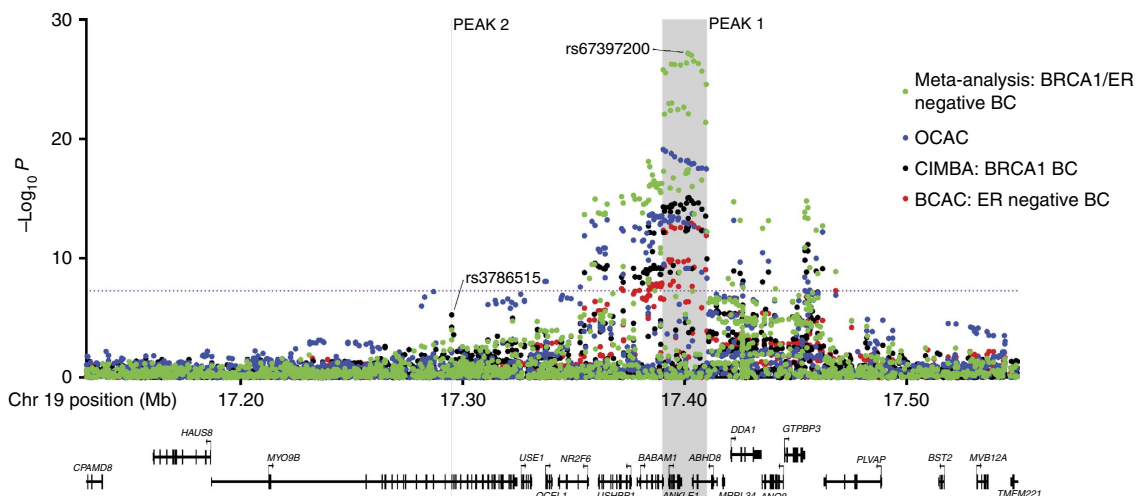


Figure 1 | Regional association plot disease-specific risk associations. Results for ER negative breast cancer from BCAC, for ovarian cancer from OCAC and for *BRCA1* mutation carriers with breast cancer from CIMBA are shown. Also shown are the results of a meta-analysis for *BRCA1* and general population ER negative breast cancer cases. The grey bars indicate the boundaries of the two association peaks, and the dotted horizontal line indicates the cutoff for genome-wide significance (χ^2 -test $P = 5 \times 10^{-8}$). Previously identified GWAS SNPs are indicated with italic font. Genes in the region are displayed beneath the association results.

for breast, OC and *BRCA1*-associated BCs can be found in Supplementary Table 3.

All SNPs with an association *P* value < 0.001 with each phenotype were included in forward stepwise Cox regression models for risks of *BRCA1* BC, and logistic regression models for ER-negative BC and serous OC. The most parsimonious models for ER-negative BC and serous OC each included one SNP, rs67397200 for ER-negative BC and rs4808075 for serous OC (referred to as Peak 1). The most parsimonious model in the analysis of BC risk for *BRCA1* mutation carriers included two virtually uncorrelated SNPs (pairwise correlation $r^2 = 0.018$) rs61494113 (*P* value = 4.4×10^{-16} in conditional regression analysis), and rs3786515 (Peak 2, conditional regression *P* value = 9.6×10^{-5} , pairwise correlation $r^2 = 0.018$; Fig. 1). No other SNP was retained in the model at the *P* value threshold of 0.0001.

Candidate causal variants. Peak 1 includes SNPs that encompass the *BABAM1*, *ABHD8* and *ANKLE1* gene and are associated with serous OC, ER-negative BC and BC risk for *BRCA1* mutation carriers (Fig. 1 and Supplementary Fig. 1); Peak 2 includes SNPs located in the *MYO9B* gene associated only with BC risk in *BRCA1* mutation carriers. SNPs in Peaks 1 and 2 are virtually uncorrelated.

To identify the strongest candidate causal SNPs, we computed likelihood ratios of each SNP relative to the SNP with the strongest association in each peak for risks of each phenotype.

Due to the similarities in associations between ER-negative BC and *BRCA1*-associated BC in Peak 1, we computed the likelihood ratios on the basis of the meta-analysis results. Table 1 includes the SNPs that cannot be excluded at a likelihood ratio of > 1:100 fold. In Peak 1, all but 12 SNPs can be excluded from being causal for ER-negative BC and *BRCA1*-associated BC. An additional SNP (rs10424198) cannot be excluded from being causal for serous OC. All 13 SNPs were highly correlated ($r^2 > 0.95$) and spanned a region of 19.4 kb. In Peak 2, the likelihood ratios of each SNP were calculated on the basis of the *BRCA1* association analysis conditional on the top SNP rs61494113. All but seven SNPs correlated with rs3786515 ($r^2 > 0.10$) cannot be excluded from being the causal SNP for *BRCA1*-associated BC risk. With the exception of rs3786514 (pairwise r^2 with rs3786515 = 0.87) all other SNPs had r^2 with rs3786515 between 0.13 and 0.20.

Associations for *BRCA1* and *BRCA2* mutation carriers. SNPs in Peak 1 were only associated with risk of ER-negative BC for *BRCA1* mutation carriers and provided no evidence of association with ER-positive BC for *BRCA1*. SNPs in Peak 1 were also associated with OC risk for *BRCA1* mutation carriers. SNPs in Peak 2 were also primarily associated with *BRCA1*-related ER-negative BC but there was no evidence of association with OC risk (Supplementary Table 4). SNPs in peak 1 were not associated with overall risk of BC in *BRCA2* carriers (for example, rs67397200 HR for BC = 1.00 (95% confidence interval (CI): 0.93–0.89)); however, SNP rs67397200 showed evidence of

Table 1 | SNPs associated with risk ovarian cancer, ER-negative breast cancer or breast cancer in *BRCA1* carriers at the 19p13 locus.

SNP*	Nucleotide position (build 37)	Allele freq.	BRCA1 breast cancer		ER-negative breast cancer		BRCA1/ER-negative breast cancer meta-analysis (<i>P</i> value)	Serous ovarian cancer	
			HR (95% confidence intervals)	<i>P</i> value	OR (95% confidence intervals)	<i>P</i> value		OR (95% confidence intervals)	<i>P</i> value
Peak 1									
rs4808075 (I)	17390291	0.30	1.19 (1.14–1.24)	4.77×10^{-15}	1.16 (1.11–1.21)	4.42×10^{-13}	1.55×10^{-26}	1.19 (1.14–1.23)	9.17×10^{-20}
rs10419397 (I)	17391328	0.30	1.19 (1.14–1.24)	5.55×10^{-15}	1.16 (1.11–1.21)	6.57×10^{-13}	2.7×10^{-26}	1.19 (1.14–1.23)	1.29×10^{-19}
rs56069439 (I)	17393925	0.30	1.19 (1.14–1.24)	3.33×10^{-15}	1.16 (1.12–1.21)	2.22×10^{-13}	5.26×10^{-27}	1.19 (1.14–1.23)	1.94×10^{-19}
rs4808076 (I)	17395401	0.30	1.19 (1.14–1.24)	2.55×10^{-15}	1.16 (1.12–1.21)	2.9×10^{-13}	5.59×10^{-27}	1.18 (1.14–1.23)	3.72×10^{-19}
rs111961716 (I)	17398085	0.30	1.19 (1.14–1.24)	3.22×10^{-15}	1.16 (1.12–1.21)	2.63×10^{-13}	6.07×10^{-27}	1.18 (1.14–1.23)	6.97×10^{-19}
rs113299211 (I)	17400765	0.30	1.19 (1.14–1.24)	2.33×10^{-15}	1.16 (1.12–1.21)	2.4×10^{-13}	4.22×10^{-27}	1.18 (1.14–1.23)	8.13×10^{-19}
rs67397200 (G)	17401404	0.30	1.19 (1.14–1.24)	8.88×10^{-16}	1.16 (1.12–1.21)	1.10×10^{-13}	6.18×10^{-28}	1.18 (1.14–1.23)	7.75×10^{-19}
rs61494113 (G)	17401859	0.30	1.19 (1.14–1.25)	7.77×10^{-16}	1.16 (1.12–1.21)	1.27×10^{-13}	7.31×10^{-28}	1.18 (1.14–1.23)	1.14×10^{-18}
rs4808616 (G)	17403033	0.31	1.19 (1.14–1.24)	1.44×10^{-15}	1.16 (1.12–1.21)	1.10×10^{-13}	9.37×10^{-28}	1.18 (1.14–1.23)	1.51×10^{-18}
rs55924783 (I)	17404072	0.30	1.19 (1.14–1.24)	2.44×10^{-15}	1.16 (1.12–1.21)	1.61×10^{-13}	2.81×10^{-27}	1.18 (1.14–1.23)	1.35×10^{-18}
rs28473003 (I)	17406167	0.30	1.19 (1.14–1.24)	2.11×10^{-15}	1.16 (1.12–1.21)	2.8×10^{-13}	4.55×10^{-27}	1.18 (1.14–1.22)	3.43×10^{-18}
rs13343778 (I)	17407695	0.30	1.19 (1.14–1.24)	7.44×10^{-15}	1.16 (1.12–1.21)	3.92×10^{-13}	2.06×10^{-26}	1.18 (1.14–1.22)	3.18×10^{-18}
rs10424198 (I)	17409671	0.30	1.18 (1.13–1.24)	3.13×10^{-14}	1.16 (1.12–1.20)	1.18×10^{-12}	2.56×10^{-25}	1.18 (1.14–1.22)	3.85×10^{-18}
Peak 2									
rs3786514 (G)	17294954	0.48	1.08 (1.04–1.13)	5.85×10^{-05}	1.02 (0.98–1.06)	0.364	6.52×10^{-04}	1.05 (1.01–1.08)	8.01×10^{-03}
rs3786515 (G)	17295023	0.45	1.10 (1.05–1.14)	5.42×10^{-06}	1.02 (0.98–1.06)	0.281	9.94×10^{-05}	1.05 (1.01–1.09)	5.62×10^{-03}
rs891205 (G)	17354586	0.61	1.09 (1.05–1.13)	4.16×10^{-05}	1.05 (1.01–1.09)	0.0164	5.39×10^{-06}	1.07 (1.04–1.11)	1.26×10^{-04}
rs7247493 (G)	17362941	0.60	1.09 (1.04–1.13)	5.85×10^{-05}	1.05 (1.01–1.09)	0.014	5.73×10^{-06}	1.07 (1.04–1.11)	9.68×10^{-05}
rs7246243 (I)	17363068	0.60	1.09 (1.04–1.13)	5.28×10^{-05}	1.05 (1.01–1.09)	0.0149	5.74×10^{-06}	1.08 (1.04–1.11)	3.73×10^{-05}
rs4464206 (G)	17367585	0.62	1.10 (1.05–1.14)	7.28×10^{-05}	1.06 (1.02–1.10)	0.0172	8.87×10^{-06}	1.08 (1.04–1.12)	2.54×10^{-05}
C19pos17261271 (G)	17400271	0.50	0.92 (0.88–0.96)	2.41×10^{-05}	0.96 (0.92–0.99)	0.020	4.76×10^{-06}	0.92 (0.89–0.96)	9.26×10^{-06}
Peak 2 (conditional <i>P</i> values on top SNP from Peak 1)									
rs3786514	17294954			1.40×10^{-03}					
rs3786515	17295023			9.13×10^{-05}					
rs891205	17354586			0.0107					
rs7247493	17362941			0.0131					
rs7246243	17363068			0.0122					
rs4464206	17367585			115					
c19_pos17261271	17400271			6.31×10^{-03}					

EOC, epithelial ovarian cancer; ER, oestrogen receptor; freq., frequency; HR, hazards ratio; OR, odds ratio; SNP, single-nucleotide polymorphism. SNPs in Peak 1 and Peak 2 that cannot be excluded at a likelihood ratio of > 1:100 fold relative to the most significant SNP for the meta-analysis and serous EOC (Peak 1) and *BRCA1* association breast cancer for Peak 2. *Imputed (I) or genotyped (G) SNPs.

association with OC for *BRCA2* mutation carriers (hazards ratio (HR) = 1.18, 95% CI: 1.06–1.36, χ^2 -test $P = 0.0056$). SNPs in peak 2 did not show any evidence of association with breast or OC risk for *BRCA2* mutation carriers.

Associations with risk among BC subtypes. None of the Peak 1 SNPs were associated with risk of ER-positive BC. When analyses were restricted to triple negative BC, the odds ratio (OR) estimates for SNPs in Peak 1 were larger than the corresponding OR estimates for ER-negative disease (Supplementary Table 4). There was no evidence of association with ER-negative and HER2-positive BC risk, with the association restricted only to triple-negative BC (test of difference between triple-negative versus ER-negative/HER2+, P -diff = 2.2×10^{-5} for SNP rs61494113).

Analysis in Asian and African ancestry studies. None of the SNPs in the fine-mapping region were associated with ER-negative BC in samples of Asian ancestry after adjusting for multiple testing (P values ≥ 0.0018). However, the risk alleles of the 13 candidate causal SNPs in Peak 1 are uncommon in the Asian population (MAF = 0.0079–0.011); hence, the power to detect an association was limited and, due to the wide CIs for the estimated ORs for these SNPs, we cannot rule out that the minor allele of these SNPs in Asian subjects is associated with similar level of risk as in Europeans. In samples of African ancestry only rs4808616 (MAF = 0.22) showed evidence of association with risk for overall BC or ER-negative disease (OR for BC = 1.19, 95% CI: 1.02–1.39, χ^2 -test $P = 0.03$; OR for ER-negative BC = 1.59, 95% CI: 1.02–2.49, χ^2 -test $P = 0.04$).

Functional characterization of the 19p13.1 region. Functional characterization focused on the 13 candidate causal SNPs for ER-negative and *BRCA1*-associated BC and serous OC in Peak 1, based on the hypothesis that the functional mechanisms mediated by one or more of these SNPs were the same for these phenotypes.

Genotype-gene expression associations. We used expression quantitative trait locus (eQTL) analyses to evaluate associations between risk SNPs and the expression of genes in a 1 Mb region spanning rs4808075 in: 135 normal breast tissues²⁹, 60 normal ovarian and fallopian tube epithelial cell cultures, 391 ER positive BCs³⁰, 59 ER-negative BCs²⁹ and 340 high-grade serous OCs³⁰. We identified significant eQTL associations for *ABHD8* expression (linear regression P value range 2×10^{-3} – 7×10^{-3}) in normal breast tissues and between rs480816 and *ABHD8*

expression in OCs (linear regression $P = 3 \times 10^{-5}$). In both instances the risk allele was associated with higher *ABHD8* expression (Fig. 2a, Supplementary Data 1 and 2 and Supplementary Table 5). We examined whether risk SNPs were the top eQTL SNPs in this region. rs4808616 was the strongest predictor of *ABHD8* expression in OCs. However, in normal breast tissues the top eQTL SNP for *ABHD8* was rs11666308 (linear regression $P = 3.3 \times 10^{-4}$), a marginally better predictor than rs4808616 (linear regression $P = 2.8 \times 10^{-3}$). The two SNPs were correlated ($r^2 = 0.79$) and regressing out effects of either SNP from the expression levels of *ABHD8* and repeating eQTL analysis abolished the eQTL signal for the other SNP, confirming their statistical inseparability. In addition we found significant associations between rs4808616 and *NXNLI* expression in OCs (linear regression $P = 4 \times 10^{-3}$) and with *ANKLE1* expression ($P = 0.002$) in normal ovarian surface epithelial cells (OSECs). There were no eQTL associations for any other genes in the region.

We also performed allele-specific expression analysis in BC using RNA sequencing data³¹ for coding SNPs in *ABHD8* (rs56069439) and *BABAMI* (rs10424198). Both SNPs were correlated with rs4808616 ($r^2 = 0.91$). There was a significant association between rs56069439 and the allelic ratio of *ABHD8* transcripts (F-test $P = 0.016$) with greater expression associated the risk allele (Supplementary Fig. 2; Supplementary Data 3).

Chromosome conformation capture. Chromosome conformation capture (3C) analysis was used to investigate DNA–DNA interactions between *ABHD8* and 5 of 13 candidate causal SNPs in Peak 1. Eight SNPs close to the *ABHD8* promoter were too near to be resolved, and the close proximity of candidate causal SNPs to *ANKLE1* precluded 3C analysis for this gene. The *ABHD8* promoter showed an interaction with a 6.3 kb region ~ 20 kb telomeric to the gene in both normal breast (Bre80) and ovarian (IOSE11) epithelial cells, and in breast (MCF7) and ovarian (A2780) cancer cell lines (Fig. 3). This region spans the *ANKLE1* promoter and includes four candidate causal SNPs: rs4808075, rs10419397, rs56069439 and rs4808076. There was no evidence of interaction for any candidate causal SNP with *BABAMI* (Supplementary Fig. 3).

Annotation of candidate causal SNPs. All 13 candidate causal SNPs were located in non-protein coding DNA. We annotated putative functional regulatory elements that coincided with the candidate causal SNPs in normal human mammary epithelial cells (HMECs), and normal fallopian tube and ovarian epithelial cells¹⁹, and in OC cell lines. Five of the 13 SNPs coincide with

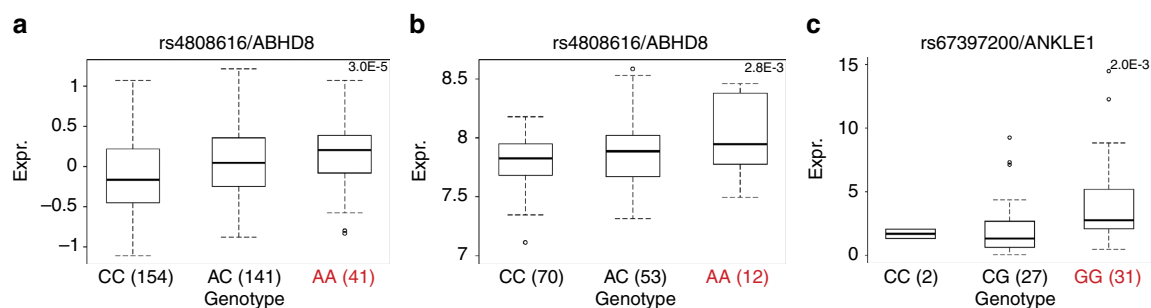


Figure 2 | Expression quantitative trait locus analyses. Significant eQTL associations identified between rs4808616 and *ABHD8* expression in (a) ovarian cancer tissues and (b) in normal breast tissues. (c) A significant association was also identified between rs4808616 and *ANKLE1* expression in primary normal ovarian/fallopian tube epithelial cell cultures. The horizontal line indicates the median expression, the limits of the boxes denote the first and third quartiles, and the whiskers represent 1.5 times the interquartile range of the data. Outliers are indicated with circles.

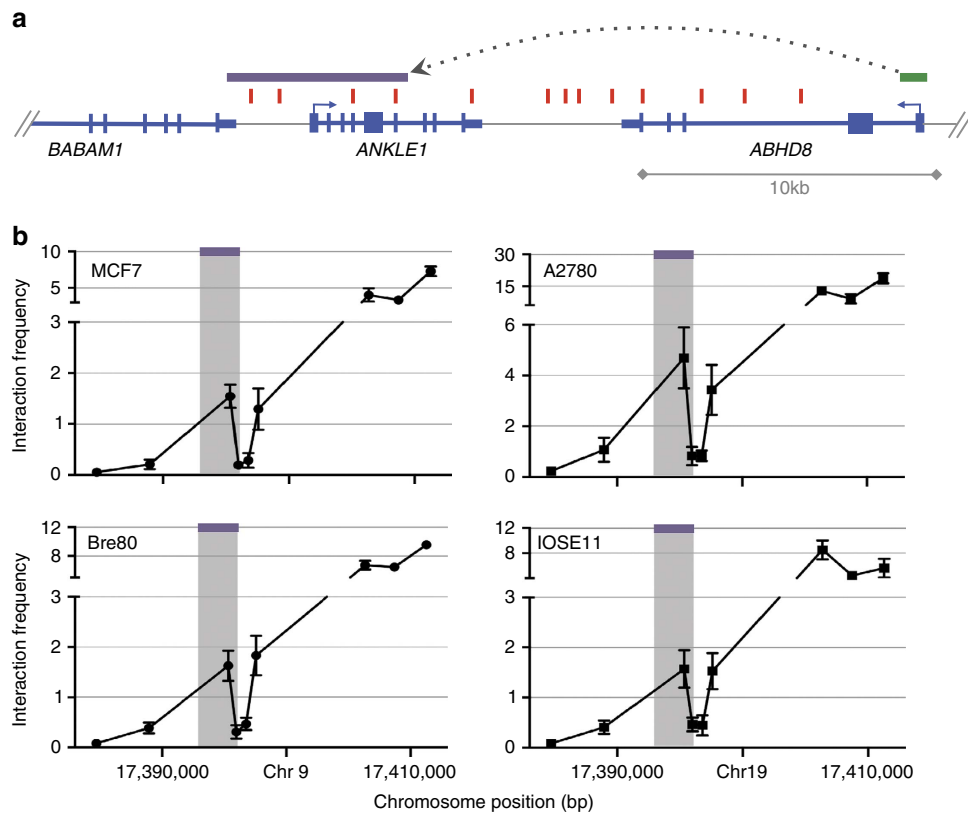


Figure 3 | Chromosome conformation capture analysis of long-range interactions at the 19p13 region. 3C interaction profiles in breast and ovarian cell lines. 3C libraries were generated with *NcoI*, with the anchor point set at the *ABHD8* promoter region. (a) A physical map of the region interrogated by 3C is shown, with annotated genes shown in blue, the 13 risk-associated SNPs shown in red, the *ABHD8* promoter fragment shown in green and the position of the interacting *NcoI* fragment represented by the purple bar (not to scale). (b) Relative interaction frequencies between the *ABHD8* promoter and regions spanning risk associated SNPs in normal breast (Bre80) and ovarian (IOSE11) epithelial cell lines, and in breast (MCF7) and ovarian (A2780) cancer cell lines. A peak of interaction with the *ABHD8* was observed for one region (purple bar) in all four cell lines. There were no interactions detected between the purple region and the *BABAM1* or *USHBP1* promoters. The interacting region contains four candidate causal SNPs (from left to right) rs4808075, rs10419397, rs56069439 and rs4808076. Error bars represent s.d. ($N=3$).

regulatory elements that were reproducible in two biological replicate samples (Fig. 4). Three SNPs were located in epigenetic marks in breast and/or ovarian cells: rs55924783 coincided with insulator marks in HMECs and enhancer marks in ovarian cells; rs113299211 coincided with enhancer marks in ovarian cells and is predicted to alter transcription factor binding sites for ELF1, ELK4 and GABP; and rs56069439 coincided with experimentally derived ChIP-seq footprints (for CTCF, ATF2 and ZNF263), enhancer marks in ovarian cells and both enhancer (H3K4me1) and insulator (CTCF) marks in breast cells. Two SNPs were located in 3'-untranslated regions (UTRs) of protein coding genes: rs111961716 in *ANKLE1* and rs4808616 in *ABHD8*. rs4808616 also coincided with enhancer marks in ovarian and breast cells. Finally, rs10419397 lay within the putative promoter of *ANKLE1*, ~1,200 bp from the transcription start site.

Functional analysis of candidate causal SNPs in UTRs. We evaluated the effects on mRNA stability of the SNPs located in 3' UTRs of *ANKLE1* (rs111961716) and *ABHD8* (rs4808616, Figs 4 and 5a) in normal primary ovarian epithelial cell lines carrying different SNP genotypes. RNA transcript abundance was measured after blocking mRNA transcription by treating cells with actinomycin D. For rs111961716, *ANKLE1* transcript expression was significantly more stable in cell lines homozygous for the A (risk) allele of rs111961716 compared with

heterozygous cells or cells homozygous for the C allele ($P=0.006$, analysis of variance; Fig. 5b). There was no association between *ABHD8* mRNA stability and genotypes of rs4808616 (Fig. 5b).

Functional analysis of promoter and enhancer SNPs. Seven of the 13 candidate causal SNPs in Peak 1 resided either in the *ANKLE1* promoter or in putative regulatory elements (PREs-A-C) in breast and ovarian normal and cancer cell lines (Figs 4 and 5a). SNP rs10419397 fell within the *ANKLE1* promoter region, but had no effect on promoter activity (Fig. 5c). PRE-A contained SNP rs56069439, PRE-B contained SNPs rs113299211, rs67397200, rs61494113 and PRE-C contained SNPs rs4808616 and rs55924783. We examined the effect of these PREs, and of the risk alleles of each SNP cloned into luciferase constructs containing the *ABHD8* or *ANKLE1* promoters. Inclusion of the reference allele of PREs A, B and C significantly increased *ABHD8* promoter activity in both OC (A2780) and normal breast (Bre80) cell lines (Fig. 5). Constructs containing the risk alleles further enhanced *ABHD8* promoter activity compared with the reference allele for PREs A, B and C in Bre80 cells (P values = 0.0027, 0.0308 and 0.0342, respectively, two-way analysis of variance (ANOVA)) and for PREs A, B and C in A2780 cells (P values = 0.0193, 0.0115 and <0.0001, respectively, two-way ANOVA; Fig. 5d,e). Constructs containing the reference allele of PRE-A showed a silencing effect on the *ANKLE1* promoter in both cell types with the risk allele further silencing the activity of the

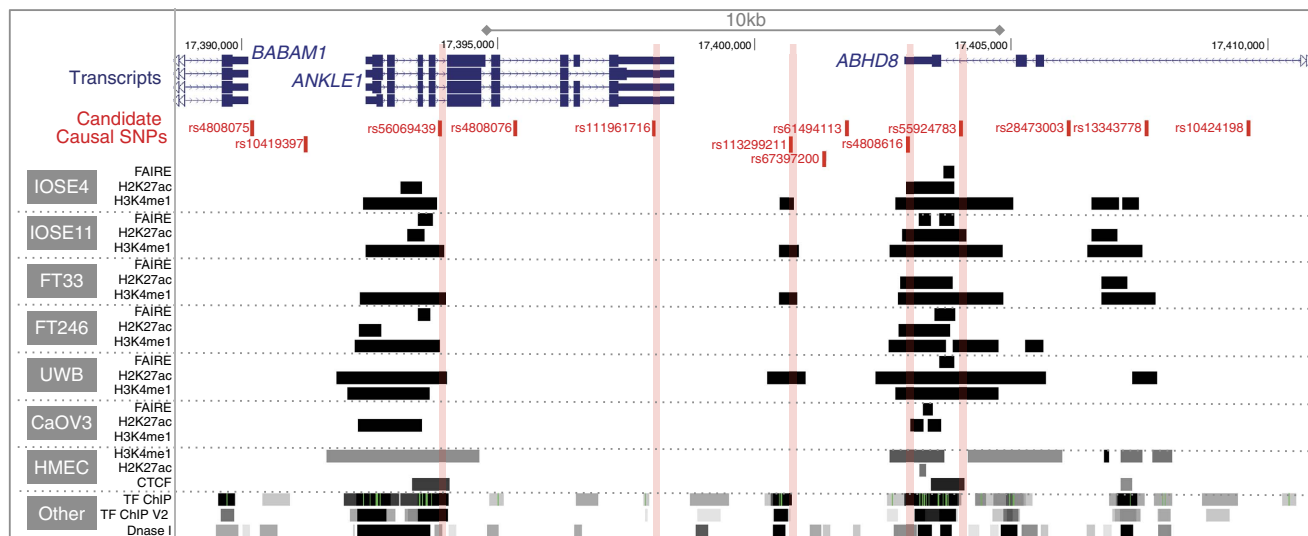


Figure 4 | Epigenetic marks intersecting candidate causal SNPs in the 19p13 susceptibility region and analyses of UTR SNPs. The thirteen candidate SNPs were aligned with open chromatin and enhancer marks (H3K27ac and H3K4me1) in high-grade serous ovarian cancer cells (UWB1.289 and CaOV3) and ovarian cancer precursor cells (ovarian epithelial cells, IOSE and fallopian epithelial cells, FT). Enhancer and insulator (CTCF) data for human mammary epithelial cells (HMECs) were obtained from ENCODE. Five SNPs coincide with biofeatures in breast and/or ovarian cells (indicated in red).

reference allele in A2780 cells ($P=0.0049$, two-way ANOVA). The reference allele of PRE-B had no effect on *ANKLE1* promoter activity, while the risk allele significantly increased activity compared with the reference allele in A2780 cells ($P=0.0034$, two-way ANOVA). Constructs containing the reference allele of PRE-C significantly increased *ANKLE1* promoter activity in both ovarian ($P=0.0004$, two-way ANOVA) and breast cell lines ($P=0.0067$, two-way ANOVA). However the risk allele showed a silencing effect on the reference allele in only Br80 cells ($P=0.0289$, two-way ANOVA; Fig. 5d,e).

Functional effects of rs56069439 deletion. Collectively, the data above suggested that rs56069439 may regulate the expression of *ANKLE1* and/or *ABHD8*. We used Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/Cas9-mediated genome editing to delete a 57 bp region containing the regulatory region that includes rs56069439 in breast (MCF10A) and ovarian (IOSE19) epithelial cells (Fig. 6a). Analysis of multiple clones containing confirmed homozygous deletions (Fig. 6b,c) indicated a significant reduction in *ANKLE1* expression compared with parental cells ($P=0.025$, two-tailed paired *T*-test) and a trend towards reduced *ANKLE1* expression in IOSE19 cells ($P=0.29$, two-tailed paired *T*-test; Fig. 6d). Expression of *ABHD8* and *BABAM1* was unchanged following deletion of the region containing rs56069439.

In vitro functional analysis of candidate genes. We analysed the effects of perturbing *ABHD8*, *ANKLE1* and *BABAM1* expression in *in vitro* models of ‘normal’ breast (MCF10A) and ovarian (IOSE19 (ref. 32)) epithelial cells. For each gene, we overexpressed full length, green fluorescent protein-tagged constructs, because genes at 19p13 were frequently overexpressed in ovarian and BCs⁹ and because eQTL analyses indicated that risk alleles were associated with increased expression of *ABHD8* and *ANKLE1*. After confirming gene overexpression (Supplementary Fig. 3a) we evaluated cell growth, migration and invasion, and anchorage-independent growth (Fig. 7 and Supplementary Fig. 3b). Overexpression of *ABHD8* caused a significant reduction in cell migration ($P=0.007$ in

MCF10A; $P=0.047$ in IOSE19, two-tailed paired *T*-test) and a decrease in invasion ($P=0.018$ in MCF10A; $P=0.063$ in IOSE19, two-tailed paired *T*-test; Fig. 7). *BABAM1* and *ANKLE1* overexpression had no effect on these cellular phenotypes for either cell type.

RNA sequencing was used to profile transcriptomic changes caused by overexpression of *ABHD8*, *ANKLE1* and *BABAM1* and pathway analyses performed using Ingenuity Pathway Analysis. We found no indication of significant changes in relevant pathways after overexpressing *BABAM1* in breast or ovarian epithelial cells. Cells overexpressing *ANKLE1* showed a significant enrichment for cancer-associated and cell growth/proliferation pathways in both breast ($P=3.36 \times 10^{-6}$) and ovarian ($P=2.43 \times 10^{-27}$) epithelial cells. Cells overexpressing *ABHD8* were enriched for expression changes in cancer related pathways ($P<5.52 \times 10^{-8}$) and fibrosis pathways ($P<1.23 \times 10^{-2}$, all right-tailed Fisher’s exact tests; Supplementary Tables 6-8).

Discussion

Through fine-scale mapping of the 19p13.1 region we have found evidence of two independent regions of genetic association with BC and/or OC risk among women of European ancestry. The minor alleles of all candidate causal variants in Peak 1 conferred increased risks of ER-negative BC and serous OC and increased risks of both cancers for *BRCA1* mutation carriers. We were able to rule out associations with ER-positive BC and risks for other OC histotypes. There was weaker evidence that SNPs in Peak 2 were independently associated with BC risk among *BRCA1* mutation carriers only. When analyses in BCAC were restricted to triple-negative BC, the strength of association was greater and there was no evidence of association with ER-negative/HER2-positive BC. Thus, our results suggested that these variants are primarily associated with triple-negative BC, the predominant tumour subtype in *BRCA1* mutation carriers³³. These results are in line with previous findings for the initial SNPs identified through GWAS²⁶.

The increased sample size resulting from combining data from BCAC, OCAC and CIMBA for variants in Peak 1 have enabled us to restrict the likely functional variants at 19p13.1 to 13 SNPs.

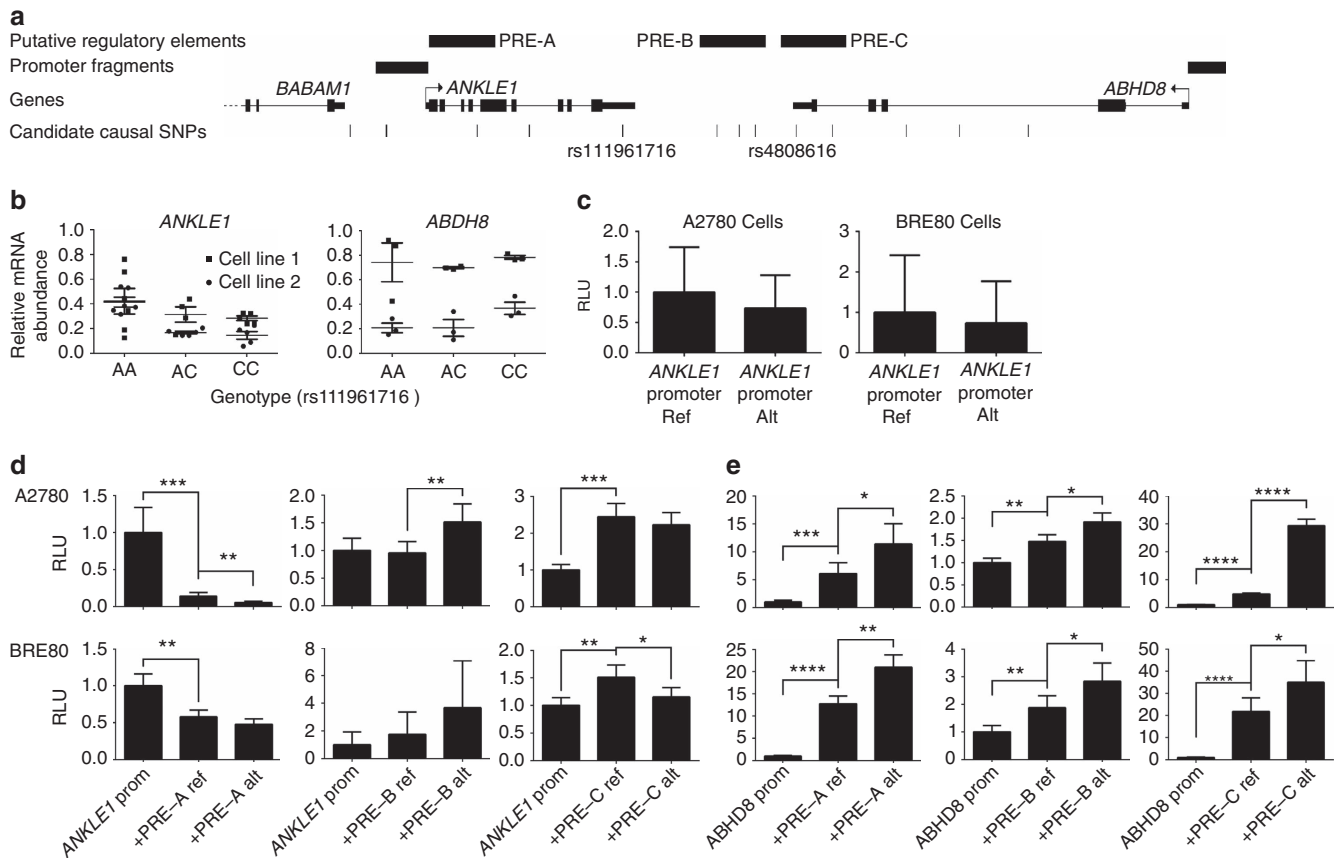


Figure 5 | Allele specific analysis of susceptibility SNPs. (a) Location of SNPs in putative regulatory elements (PREs) and 5' untranslated regions. (b) RNA stability assays in primary ovarian epithelial cell lines for risk-associated UTR SNPs in *ABHD8* and *ANKLE1*. Normal ovarian epithelial cell lines carrying different genotypes of the risk SNP rs4808616, located in the 3' UTR of *ABHD8*. Rs4808616 is tightly correlated with rs111961716 ($R^2 = 0.98$) located in the 3' UTR of *ANKLE1*. The risk allele of rs111961716 was associated with decreased mRNA stability of *ANKLE1* compared with the protective allele ($P = 0.006$, ANOVA). Different genotypes of rs4808616 are not associated with the stability of the *ABHD8* transcript. (c–e) Luciferase assays to evaluate SNP-dependent promoter and enhancer activity. (c) The *ANKLE1* promoter SNP did not affect *ANKLE1* expression in ovarian cancer cells (A2780) and normal breast cells (Bre80). (d) Allele-specific activity of PRE-A, PRE-B and PRE-C on the *ANKLE1* promoter. (e) Allele-specific activity of PRE-A, PRE-B and PRE-C on *ABHD8* promoter activity. * $P > 0.05$, ** $P > 0.01$, *** $P > 0.001$, **** $P > 0.0001$, two-way ANOVA. RLU, relative light units.

The 13 candidate causal risk SNPs in this region were the same for both BC and OC leading us to hypothesize that the underlying functional mechanisms are the same in both cancers and the overlap between these SNPs and functional elements provided multiple testable hypotheses, necessitating a range of different functional assays to evaluate their possible causality. Multiple assays were performed in breast and ovarian tissues and cell lines to establish if there is true evidence of pleiotropy. The candidate causal SNPs in Peak 1 clustered around two candidate genes, *ANKLE1* and *ABHD8*, neither of which have been previously implicated in BC or OC. Proximal to these SNPs is *BABAM1*, a gene involved in recruiting *BRCA1* to sites of DNA damage^{34,35} and therefore a compelling candidate gene at this locus. While gene regulation can be mediated across long genomic distances, the majority of interactions occur over a distance of 1 Mb) or less^{36,37}. We, therefore, evaluated all candidate genes within a 1 Mb region centred on the Peak 1 risk SNPs for eQTL associations. We found significant eQTL associations for *ABHD8* in OCs and normal breast tissues, plus allele-specific expression of *ABHD8* in BCs, but no compelling evidence for any other gene at this locus. Nonetheless, the identification of *ABHD8* as the most likely target susceptibility gene must be treated with some caution as it is plausible that more distant *cis*-eQTL or even *trans*-eQTL associations exist for these risk SNPs. Unfortunately, the limited power of eQTL analysis based on the current sample

size precluded us from performing genome-wide eQTL analysis to address these hypotheses.

The weight of our functional data, in particular the eQTL associations, indicates that *ABHD8* is a target of functional SNPs at this locus, and therefore a novel breast and OC susceptibility gene. 3C identified an interaction between a region containing four candidate causal SNPs and the *ABHD8* promoter in both breast and OC and normal epithelial cell lines. The luciferase assays of three PREs (including one encompassing rs56069439 in the interacting region) consistently showed that they acted as enhancers, and furthermore the risk-associated alleles of rs56069439, rs113299211, rs67397200, rs61494113, rs4808616 and rs55924783 (within PREs A-C) further increase *ABHD8* promoter activity in both breast and ovarian cells. These results were consistent with our eQTL studies and support the hypothesis that increased *ABHD8* expression is associated with an increased cancer risk. *ABHD8* is a poorly studied lipase³⁸. The Achilles heel project identified *ABHD8* as a lineage-specific cancer cell vulnerability in OC cell lines³⁹ and a recent study identified *ABHD8* as a potential OC susceptibility gene though its participation in a homeobox transcription factor-centred gene network associated with serous OC risk⁴⁰. Overexpression of *ABHD8* led to significant reductions in the invasive and migratory potential of breast and ovarian cells and enriched for genes involved in cellular movement (IOSE19) and mTOR

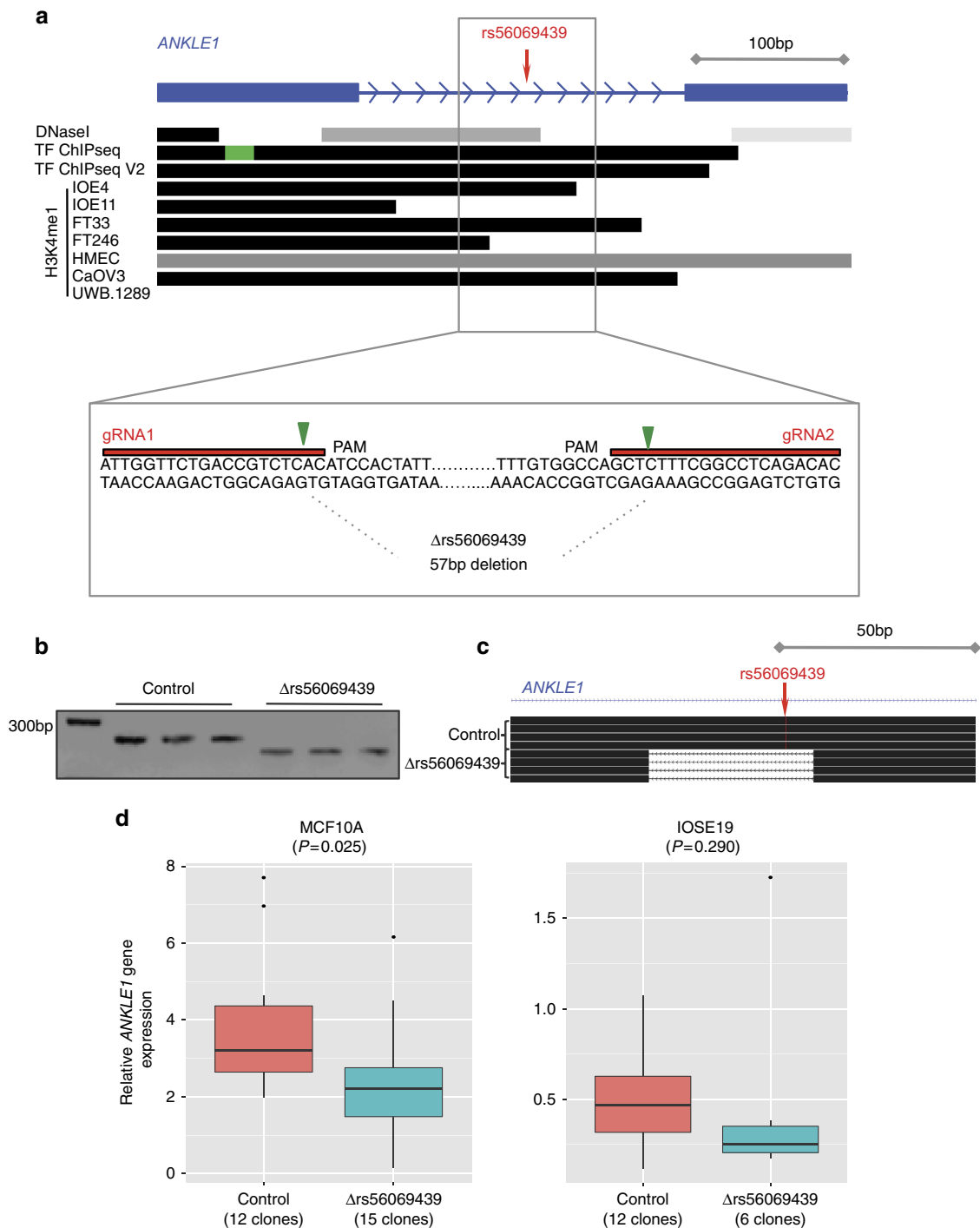


Figure 6 | Effects of deletion of the putative enhancer containing the rs56069439 risk SNP in breast and ovarian epithelial cells. (a) Illustration of the 57 bp region in an intron of *ANKLE1* containing rs56069439; H3K4me1 marks overlapped rs56069439 in ovarian, fallopian and breast cells. Location of the two guide RNAs (gRNAs) used to create the stable Δ rs56069439 deletion by CRISPR/Cas9 genome editing, cutting sites are indicated with the green arrow. PAM, protospacer adjacent motif. **(b)** PCR analysis of targeted region in representative MCF10A (breast) epithelial cell clones. Control clones were transfected with the vector backbone only. **(c)** Verification of deletions by Sanger sequencing, and alignment to the genome using BLAT. **(d)** Gene expression analysis using TaqMan probes showing downregulation of *ANKLE1* was associated with deletion of a region containing rs56069439.

signalling (MCF10A), consistent with the observed changes in invasion and migration. The direction of the effect was opposite to what we might expect from the eQTL data, which might reflect different functions of *ABHD8* in different contexts, similar to the observations for another BC susceptibility gene, *TOX3* (ref. 41). For example, under specific microenvironmental cues or in a tumour cell (rather than the normal cells used in these

experiments) increased *ABHD8* may promote rather than inhibit migration and invasion.

Nonetheless, we cannot unequivocally exclude other genes as the targets of candidate causal variants at this locus, in particular *ANKLE1*. The close proximity of the candidate causal SNPs to the *ANKLE1* gene precluded 3C analysis; but in the luciferase assays, these same PREs and SNPs had variable, context-dependent

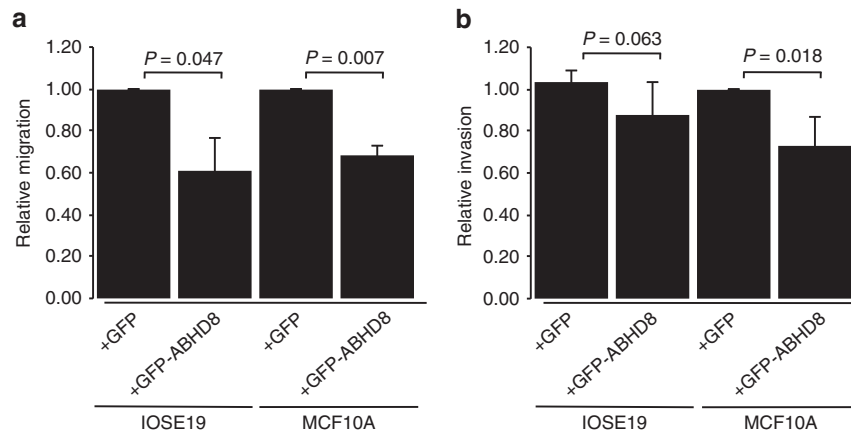


Figure 7 | Phenotypic effects of overexpressing full length *ABHD8GFP* fusion transcript in normal breast and ovarian epithelial cells. (a) *ABHD8* overexpression induced a significant decrease in migration in both breast (MCF10A) and ovarian (IOSE19) cells; **(b)** *ABHD8* overexpression induced a significant decrease in invasion in breast epithelial cells and a similar trend of decreased invasion in ovarian epithelial cells.

effects on *ANKLE1* promoter activity. This raises the possibility that the SNPs were cooperatively acting to alter *ANKLE1* expression although it was difficult to predict the overall direction of their effects from this assay. We were able to rule out the SNP rs10419397 in the promoter of *ANKLE1* as a likely causal variant. The SNP rs111961716 in the 3'-UTR of *ANKLE1* was associated with allele-specific *ANKLE1* mRNA stability; but stable overexpression of *ANKLE1* had no influence on the phenotype of normal breast and ovarian epithelial cells even though pathway after overexpression of *ANKLE1* found a significant enrichment for cancer and cell death/proliferation associated pathways in both breast and ovarian epithelial cells. More recently, *ANKLE1* has been implicated in DNA damage responses, while other, better-characterized endonucleases (for example, ERCC1) are involved in nucleotide excision repair, which are important for the repair of bulky adducts⁴².

This study has highlighted the challenges in establishing causality for both candidate causal SNPs at common variant susceptibility loci and the susceptibility genes targets. The multitude of functional assays that can be used to test allele specific functional activity rarely provide unequivocal evidence of one SNP over another. Genome editing, which allows the creation of isogenic experimental models carrying the different alleles of candidate causal SNP, is emerging as a single assay approach that can evaluate the function of common variants. However, until now the technical challenges of genome editing have restricted its application to two non-coding risk SNPs identified by GWAS at susceptibility loci for prostate cancer and obesity, respectively^{22,23}. It was beyond the scope of the current study to utilize genome editing to test all 13 candidate causal SNPs in Peak 1 at 19p13 in BC and OC and normal cell line models. Instead, we used CRISPR-Cas9 genome editing to evaluate the effects of a putative enhancer containing most plausible functional SNP (rs56069439) identified from 3C analysis and mapping of putative regulatory elements. This revealed strong functional evidence for a breast/ovarian epithelial cell enhancer, within an intron of *ANKLE1*. When this enhancer containing rs56069439 was deleted *ANKLE1* expression was significantly reduced, without any reduction in *BABAM1* or *ABHD8* expression. Further experiments using homology-directed repair will be required to determine if there is allele-specific activity of the rs56069439 SNP in regulating *ANKLE1* expression, and to determine whether shadow enhancers are employed to maintain *ABHD8* expression⁴³.

In conclusion, we have performed detailed functional analysis of SNPs and candidate target genes at the 19p13 locus in breast

and ovarian normal and cancer cells. *ABHD8* is the most likely target gene although we cannot rule out a role for *ANKLE1* in the development of breast and OC or the possibility that both genes, acting independently or in synergy may be functional targets of candidate causal SNPs. Using a combination of genetic fine mapping, and a spectrum of *in silico* and functional assays, seven of thirteen showed evidence of functionality.

These data suggest that the underlying functional mechanism(s) at the 19p13 locus may be mediated by many SNPs rather than by a single causal allele. This hypothesis is supported by studies showing tissue-specific enrichment of correlated risk-associated SNPs at susceptibility loci within regulatory biofeatures, including enhancers and transcription factor binding sites^{19,20}. Such enrichments would not be detected if a single causal SNP at a locus was driving disease development. Taken together these data suggest that common molecular mechanisms are likely to underlie this pleiotropic risk locus.

Methods

Study populations. All specimens used in this study were collected with informed consent and under the approval of local Institutional Review Boards. We used epidemiological and genotype data from studies participating in the BCAC⁴⁴, the OCAC¹² and the CIMBA⁴⁵ that have been genotyped using the iCOGS array that included ~200,000 SNPs.

BC association consortium. Data were available from 52 BC case-control studies, 41 studies of European ancestry, 9 studies of Asian ancestry and 2 studies of African-American ancestry. Details of all studies, the genotyping process and the quality control process have been described elsewhere^{6,44}, standard sample and genotyping QC criteria were applied. After the quality control process, data on 46,451 cases and 42,599 controls of European ancestry, 6,269 cases and 6,624 controls of Asian ancestry and 1,117 cases and 932 controls of African-American ancestry were available for analysis. Data on the BC ER status were available for 34,509 cases of European ancestry, 7,435 (22%) of whom had ER-negative tumours.

OC association consortium. Data were available from 41 case-control studies of EOC from OCAC that were genotyped using the iCOGS array¹². In addition to the OCAC iCOGS data, genotype data were available for stage 1 of three population-based OC genome-wide association studies. The final data set comprised genotype data for 11,069 cases and 21,722 controls from COGS ('OCAC-iCOGS'), 2,165 cases and 2,564 controls from a GWAS from North America ('US GWAS')⁴⁶, 1,762 cases and 6,118 controls from a UK-based GWAS ('UK GWAS')⁷, and 441 cases and 441 controls from the Mayo Clinic. All subjects included in this analysis provided written informed consent as well as data and blood samples under ethically approved protocols. Overall, 43 studies from 11 countries provided data on 15,437 women diagnosed with invasive EOC, 9,627 of whom were diagnosed with serous EOC and 30,845 controls from the general population.

Consortium of investigators of modifiers of BRCA1/2. Data on *BRCA1* mutation carriers were obtained through CIMBA. Eligibility in CIMBA is restricted to females 18 years or older with pathogenic mutations in *BRCA1* or *BRCA2*. The majority of the participants were sampled through cancer genetics clinics⁴⁷, including some related participants. Fifty-one studies from 25 countries contributed data on *BRCA1* mutation carriers who were genotyped using the iCOGS array⁴⁵. After quality control of the phenotypes and genotypes, data were available on 15,252 *BRCA1* mutation carriers of whom 7,455 had been diagnosed with BC, 2,639 with ER-negative BC and 1,724 with OC, all of European ancestry. Analyses in *BRCA1* mutation carriers focused on assessing associations with BC risk, following the evidence from the original GWAS in *BRCA1* mutation carriers⁴⁸.

URLs: 1000 Genomes Project, <http://www.1000genomes.org/>; BCAC, <http://ccge.medschl.cam.ac.uk/consortia/bcac/index.html>; CIMBA, <http://ccge.medschl.cam.ac.uk/consortia/cimba/index.html>; COGS, <http://www.cogseu.org/>; iCOGS, <http://ccge.medschl.cam.ac.uk/research/consortia/icogs/>; SNAP <https://www.broadinstitute.org/mpg/snap/>; TCGA, <https://tcga-data.nci.nih.gov/>; CGHub, <https://cghub.ucsc.edu/>

iCOGS SNP selection for fine mapping and imputation. The fine mapping region was defined as Chromosome 19 positions: 17,130,000–17,550,000 (NCBI build 37). To identify the set of variants potentially responsible for the original GWAS reports, we considered all variants with minor allele frequencies of >0.02 from the 1,000 Genomes Project (March 2010 version) and selected all SNPs correlated ($r^2 > 0.1$) with either of the two SNPs that had been identified through the *BRCA1* and EOC GWAS studies (rs8170 and rs2363956)^{12,45}, plus an additional set of SNPs that tagged all remaining SNPs in the region with $r^2 > 0.9$. A total of 438 SNPs that were included on iCOGS in the 19p13 region passed QC and were available for the analyses. Data on these SNPs were used to impute the genotypes of all known variants from the 1,000 genomes project (V3, April 2012 release49) using the IMPUTE (version 2) software. After excluding SNPs with MAF < 0.001 and SNPs with imputation r^2 accuracy score of ≤ 0.3 , there were 2,269 imputed SNPs in BCAC, 2,565 in OCAC and 2,311 in *BRCA1* mutation.

BCAC and OCAC association analysis and logistic regression. To evaluate the association of each SNP with breast and EOC risk in BCAC and OCAC we used a Wald test statistic based on logistic regression, by estimating the per-allele OR and its s.e. Analyses restricted to specific tumour subtypes (ER-negative BC or high-grade serous EOC) were assessed separately using all available controls. All analyses were adjusted for principal components, described in more detail elsewhere^{12,44}. Conditional logistic regression was used to assess the evidence that there are multiple independent association signals in the region, by evaluating the associations of genetic variants in the region while adjusting for the SNP with the smallest P value. We considered only SNPs with P values of association of $< 10^{-3}$ and MAF $> 0.1\%$ and the most parsimonious model was identified using step-wise forward logistic regression and a threshold of $P < 10^{-4}$ for retaining SNPs in the model.

CIMBA retrospective cohort analysis. All associations between genotypes and BC risk in *BRCA1* mutation carriers were evaluated using a 1 df per allele trend-test (P -trend), based on modelling the retrospective likelihood of the observed genotypes conditional on BC phenotypes⁴⁹. To allow for the non-independence among related individuals, an adjusted test statistic was used which took into account the correlation in genotypes⁴⁸. Per allele HR estimates were obtained by maximizing the retrospective likelihood. All analyses were stratified by country of residence. To identify the most parsimonious model that includes multiple SNPs, forward-selection Cox-regression analysis was performed, using the same P value thresholds as in the BCAC and OCAC analysis. This approach provides valid tests of association, although the parameter estimates can be biased^{49,50}. Parameter estimates for the most parsimonious model were obtained using the retrospective likelihood approach.

Meta-analysis. It is well established that the majority of BCs in *BRCA1* mutation carriers are ER-negative^{51,52}. To increase the statistical power for identifying the most likely causal variants, we also performed a meta-analysis of the associations of BC risk for *BRCA1* mutation carriers and ER-negative BC in the general population (in BCAC) for both genotyped and imputed SNPs. We used an inverse variance approach assuming mixed effects, by combining the logarithm of the per-allele HR for the association with BC risk for *BRCA1* mutation carriers and the logarithm of the OR estimate for the association with ER-negative BC in BCAC.

eQTL and allele-specific expression analyses. Germline genotype data were obtained from the Affymetrix SNP 6.0 (METABRIC) and Illumina 1M-Duo (TCGA HGSOC). No SNPs from Peak 1 and 2 were present on the Affymetrix platform so these genotypes were imputed into the 1000 Genomes European reference panel (March 2012, version 3) using IMPUTE version 2 (ref. 53). All analyses were restricted to patients of $>90\%$ European ancestry as per LAMP estimates⁵⁴ and SNPs with info score > 0.3 . For METABRIC, gene expression data consisted of probe-level measurements from the Illumina HT-12 v3 microarray

platform for a total of 135 samples obtained from normal breast tissue adjacent to tumour and 59 samples obtained from ER-negative breast tumours were analysed. For TCGA HGSOC, gene expression data consisted of measurements from the Agilent 244 K microarray for 340 HGSOC tumours downloaded from the cBioportal. Only genes and probes < 1 Mb from the top Peak 1 SNP were analysed. Tumour gene expression data was first adjusted for copy number (TCGA and METBRIC, Affymetrix SNP 6.0 calls) and methylation (TCGA only, Illumina 27 K beta values) using the method of Li *et al.*⁵¹. Expression QTL analysis was conducted by linear regression with genotypes as predictors, as implemented in the R package Matrix eQTL⁵⁵.

Sixty early passage primary normal OSECs and fallopian tube epithelial cells were collected and cultured as previously described^{27,56}. Briefly, OSECs were harvested from ovaries using a sterile cytobrush and cultured in Medium 199 and MCDB105, mixed in a 1:1 ratio and supplemented with 15% fetal bovine serum (FBS, Hyclone), 10 ng ml⁻¹ epidermal growth factor, 0.5 mg ml⁻¹ hydrocortisone, 5 mg ml⁻¹ insulin (all Sigma, St Louis, MO, USA) and 34 mg protein per ml bovine pituitary extract (Life Technologies). Fresh fallopian specimens were subjected to 48–72 h Pronase (Roche) and DNase I digests to release the epithelial cells. Epithelial cells were pelleted and cultured on collagen in DMEM/F12 supplemented with 10% FBS (Seradigm). RNA was isolated from cell cultures harvested at $\sim 80\%$ confluency using the QIAgen miRNAeasy kit with on-column DNase 1 digestion. 500 ng of RNA was reverse transcribed using SuperScript III First-Strand Synthesis System (Invitrogen). The cDNA was diluted to 10 ng μ l⁻¹ and 12.5 ng was used in target specific amplification before real-time PCR using TaqMan PreAmp Master Mix Kit (Applied Biosystems) following Fluidigm's Specific Target Amplification Protocol. 1.25 μ l of the 25 μ l pre-amplified cDNA was added to each chip. Each sample was run in triplicate and each experiment included no template controls and no template controls from the cDNA reactions. 96.96 Dynamic Array Integrated Fluidic Circuits (Fluidigm) were loaded with 96 pre-amplified cDNA samples and 96 TaqMan gene expression probes (Applied Biosystems) using the BioMark HD System (Fluidigm). Expression levels for each gene were normalized to the average expression of control genes (*GAPDH* and *ACTB*). Relative expression levels were calculated using the $\Delta\Delta C_t$ method. Correlations between genotype and gene expression were calculated in R 2.14.1. Genotype specific gene expression was compared using the Jonckheere-Terpstra test. Genes with significant eQTL results were validated by individual Taqman (Applied Biosystems, Warrington UK) reactions run on ABI 7900HT Sequence Detection System equipment and analysed with SDS software according to the manufacturer's instructions. Normal cell line DNAs were analysed on iCOGS arrays to obtain genotype information. We analysed all protein-coding genes within a 1 Mb region of the risk association. The method for allele specific expression analysis has been described previously³¹.

Breast and ovarian normal and cancer cell lines. Breast and OC cell lines MCF7 (ER+, breast; ATCC #HTB-22) and A2780 (ER+, ovarian; kindly provided by Thomas Hamilton, NCI, Maryland) were grown in RPMI medium with 10% FBS and antibiotics. The normal breast epithelial cell lines Bre-80 (kindly provided by Roger Reddel, CMRI, Sydney) and MCF10A (ATCC #CRL-10317) were grown in DMEM/F12 medium with 5% horse serum, 10 mg ml⁻¹ insulin, 0.5 mg ml⁻¹ hydrocortisone, 20 ng ml⁻¹ epidermal growth factor, 100 ng ml⁻¹ cholera toxin and antibiotics. The phenotypically normal TERT immortalized ovarian epithelial cell lines IOSE11 and IOSE19 (ref. 32) were grown in NOSE-CM. All cell lines were maintained under standard conditions, were routinely tested for *Mycoplasma* and were profiled with short tandem repeats to confirm their identity.

Functional annotation of risk SNPs. FAIRE-seq and ChIP-seq for H3K27ac and H3K4me1 marks in normal ovarian (IOSE4, IOSE11) and fallopian epithelial cell lines (FT33, FT246) and OC cell lines (CaOV3, UWB1.289) were generated in-house using standard protocols and have been previously described^{19,27}. Epigenetic marks in HMECs were downloaded from ENCODE (genome.ucsc.edu).

Chromosome conformation capture. 3C libraries were generated using *NcoI* as described previously¹⁴. To quantify interactions by real-time quantitative PCR (qPCR) was performed using primers listed in Supplementary Table 9. All qPCRs were performed on a RotorGene 6,000 using MyTaq HS DNA polymerase with the addition of 5 mM of Syto9, annealing temperature of 66 °C and extension of 30 s. Each experiment was performed three times in duplicate. The BAC clone (CTD-2278110) covering the 19p13 region was used to normalize for PCR efficiency and a by reference region within *GAPDH* used to calculate relative interaction frequencies. All qPCR products were resolved on 2% agarose gels, gel purified and sequenced to verify the 3C product.

RNA stability assays. For each genotype (two homozygotes and the heterozygote) two early passage primary normal ovarian epithelial cell lines were incubated with actinomycin D for 20 h. RNA was extracted using the QIAgen RNeasy extraction kit and reverse transcribed using MMLV RT enzyme and random hexamers (Promega). Quantitative PCR was performed using TaqMan gene expression probes for *ABHD8* (Hs00225984_m1) and *ANKLE1* (Hs01094673_g1). Signal for each gene of interest was normalized to signal for *ACTB* (Hs01060665_g1) and

GAPDH (Hs02758991_g1) and relative gene expression calculated using the $\Delta\Delta Ct$ method, relative to untreated cells. 18s rRNA (Hs99999901_s1) and *MYC* (Hs00153408_m1) mRNA levels were included as internal controls.

Promoter and allele specific enhancer assays. A 1119 bp fragment containing the *ABHD8* promoter was cloned into the pGL3 basic luciferase reporter. Reference and risk associated *ANKLE1* promoter fragments were synthesized by GenScript and cloned into pGL3 basic. We generated PCR fragments corresponding to PRE A and PRE B and had PRE C haplotype fragments synthesized by GenScript and these were also sub-cloned into *ABHD8* and *ANKLE1* promoter constructs. PCR primers are listed in Supplementary Table 10. Bre80 and A2780 cells were transiently transfected with equimolar amounts of luciferase reporter constructs using *Renilla* luciferase as an internal control reporter. Luciferase was measured 24 h after transfection using Dual-Glo Luciferase (Promega). To correct for any differences in transfection efficiency or cell lysate preparation, *Firefly* luciferase activity was normalized to *Renilla* luciferase, and the activity of each construct was measured relative to the promoter alone construct, which had a defined activity of 1. Association was assessed by log transforming the data and performing two-way ANOVA, followed by Dunnett's multiple comparisons test; for ease of interpretation, values were back transformed to the original scale for the graphs.

Genome editing. Guide RNAs targeting the region flanking rs56069439 (5'-GTGAGACGGTCAGAACCAAT-3' and 5'-GTGTCTGAGGCCGAAAGAGC-3') were designed using the CRISPR design tool from the Zhang lab (www.crispr.mit.edu)⁵⁷. The gRNAs were cloned into the lentiCRISPR (Addgene Plasmid 49535) vector by using the *BsmBI* restriction enzyme site and lentiviral supernatants made by cotransfection of HEK293T cells. IOSE19 and MCF10A cells were transduced with viral supernatants and infected cells selected using 400 ng ml⁻¹ and 500 ng ml⁻¹ puromycin (Sigma Aldrich) respectively. Selected cells were sorted into single cells using flow cytometry and expanded *in vitro*. Screening for clones containing the deletion was performed using the following primers: Forwards: 5'-CCCTGACATC CAGGGTCTTC-3' and Reverse: 5'-AGTCCAGCGTCTCATCGGTA-3'. For sequence verification of the deletion the following primers were used: Forwards: 5'-TCTGTGACACAGTCCCTGACA-3' and Reverse: 5'-CAGCGTCTCATCGGT AGGTC-3'. RNA was isolated from positive clones using the Zymo Quick-RNA kit and reverse transcribed using Superscript III (Life Technologies). Real time gene expression analysis was performed using TaqMan probes, as described above.

In vitro analysis of candidate genes. The three candidate genes were overexpressed as green fluorescent protein fusion proteins. The *BABAM1* overexpression construct was a kind gift from Dr S Elledge⁵⁸. *ANKLE1* and *ABHD8* constructs were purchased from Genecopoeia. Virus was made in-house by cotransfection of HEK293Ts and used to transduce MCF10A and IOSE19 cells. Positive cells were selected using 400 ng ml⁻¹ (for IOSE19 cells) or 500 ng ml⁻¹ (for MCF10A cells) puromycin. Anchorage dependent and independent growth assays were performed as previously described^{32,59}. For invasion and migration assays Millipore luminescent transwell assays (24 well plate format) were used, following the manufacturer's protocol.

Data availability. The relevant SNP genotype data underpinning these analyses can be accessed by applying to the OCAC, BCAC and CIMBA consortia (see URLs). EQTL data are available in supplementary information. All other data are available on request.

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Additional information

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