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A common coding variant in *CASP8* is associated with breast cancer risk

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The Breast Cancer Association Consortium (BCAC) has been established to conduct combined case-control analyses with augmented statistical power to try to confirm putative genetic associations with breast cancer. We genotyped nine SNPs for which there was some prior evidence of an association with breast cancer: *CASP8* D302H (rs1045485), *IGFBP3* –202 C→A (rs2854744), *SOD2* V16A (rs1799725), *TGFB1* L10P (rs1982073), *ATM* S49C (rs1800054), *ADH1B* 3′ UTR A→G (rs1042026), *CDKN1A* S31R (rs1801270), *ICAM5* V301I (rs1056538) and *NUMA1* A794G (rs3750913). We included data from 9–15 studies, comprising 11,391–18,290 cases and 14,753–22,670 controls. We found evidence of an association with breast cancer for *CASP8* D302H (with odds ratios (OR) of 0.89 (95% confidence interval (c.i.): 0.85–0.94) and 0.74 (95% c.i.: 0.62–0.87) for heterozygotes and rare homozygotes, respectively, compared with common homozygotes; $P_{trend} = 1.1 \times 10^{-7}$) and weaker evidence for *TGFB1* L10P (OR = 1.07 (95% c.i.: 1.02–1.13) and 1.16 (95% c.i.: 1.08–1.25), respectively; $P_{trend} = 2.8 \times 10^{-5}$). These results demonstrate that common breast cancer susceptibility alleles with small effects on risk can be identified, given sufficiently powerful studies.

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Rare, high-penetrance germline mutations in genes such as *BRCA1* or *BRCA2* account for less than 25% of the familial risk of breast cancer, and much of the remaining variation in genetic risk is likely to be explained by combinations of more common, lower-penetrance variants[1]. To date, case-control studies have generally focused on the investigation of putative functional candidate gene variants to attempt to identify low-penetrance susceptibility variants. However, individual studies often have only enough statistical power to detect effects of the order of 1.5 or more, depending on the frequency of the variant[2], and thus collaborative studies are needed in order to achieve the sample sizes necessary to detect more modest effects. The Breast Cancer Association Consortium (BCAC) was established in 2005 to facilitate such collaborative studies in breast cancer. The consortium currently comprises over 20 international collaborating research groups, with a potential combined sample size of up to 30,000 cases and 30,000 controls. The first combined data analysis carried out by the consortium involved 16 SNPs that had been investigated in at least three independent studies with at least 10,000 genotyped subjects in total[3]. Members of the consortium then carried out further genotyping for four of these SNPs that showed borderline evidence of associations with risk: caspase-8 (*CASP8*) D302H (rs1045485), insulin-like growth factor binding protein 3 (*IGFBP3*) –202 C→A (rs2854744), manganese superoxide dismutase (*SOD2* or *MnSOD*) V16A (rs1799725) and transforming growth factor beta (*TGFB1*) L10P (rs1982073), in order to confirm or refute these results. In addition, the BCAC examined five other SNPs for which there was published or unpublished evidence of an association: ataxia telangiectasia mutated (*ATM*) S49C (rs1800054)[4,5], class I alcohol dehydrogenase 1B (*ADH1B*, formerly called *ADH2*) 3′UTR A→G (rs1042026) (P.D.P.P. *et al.*, unpublished data), cyclin-dependent kinase inhibitor 1A (*CDKN1A*) S31R (rs1801270) (P.D.P.P. *et al.* and A.C. *et al.*, unpublished data), intercellular adhesion molecule 5 (*ICAM5*) V301I (rs1056538)[6] and nuclear mitotic apparatus protein (*NUMA1*) A794G (rs3750913)[7].

Details of the 20 studies contributing data to this report are shown in **Supplementary Table 1** online. Apart from two studies in Asian populations, cases and controls were selected from populations of predominantly European ancestry, all with high breast cancer incidence rates (age-standardized rates ranging from 42.6 per 100,000 to 99.4 per 100,000 (ref. 8)).

Two of the nine SNPs evaluated showed significant associations with invasive breast cancer: *CASP8* D302H and *TGFB1* L10P. Caspase-8 is an important initiator of apoptosis (programmed cell death) and is activated by external death signals and in response to DNA damage[9]. Two previous studies suggested that the D302H polymorphism in *CASP8* (rs1045485), which results in an aspartic acid to histidine substitution, could reduce breast cancer risk[10,11].

Our analysis of 16,423 cases and 17,109 controls from 14 studies showed convincing evidence for a protective effect in an allele dose–dependent manner ($P_{trend} = 1.1 \times 10^{-7}$, per allele odds ratio (OR) = 0.88 (with 95% confidence interval (c.i.) of 0.84–0.92); **Table 1** and **Fig. 1a**). The result remained significant after excluding the initial positive result from the Sheffield Breast Cancer Study[10] ($P_{trend} = 1 \times 10^{-6}$), and there was no evidence of between-study heterogeneity ($P = 0.97$). We found no evidence that the ORs varied

Table 1 Summary odds ratios and 95% confidence intervals for nine polymorphisms and breast cancer risk

SNP	No. of studies	No. of controls	No. of cases	MAF	Between-study heterogeneity[a]	Test for association[a]	Trend test[a]	Analysis model	Per-allele OR (95% c.i.)[b]	Heterozygote OR (95% c.i.)[b]	Rare homozygote OR (95% c.i.)[b]
ADH1B 3′ UTR A→G rs1042026	9	15,570	11,391	0.29	0.35	0.044	0.54	Fixed effects	0.99 (0.95, 1.03)	0.94 (0.89, 1.00)	1.04 (0.95, 1.14)
								Random effects	0.99 (0.95, 1.04)	0.99 (0.90, 1.10)	1.04 (0.95, 1.14)
CASP8 D302H rs1045485	14	17,109	16,423	0.13	0.97	5.7×10^{-7}	1.1×10^{-7}	Fixed effects	0.88 (0.84, 0.92)	0.89 (0.85, 0.94)	0.74 (0.62, 0.87)
								Random effects	0.88 (0.84, 0.92)	0.89 (0.85, 0.94)	0.73 (0.60, 0.90)
CDKN1A S31R rs1801270	15	22,670	18,290	0.072	0.009	0.55	0.28	Fixed effects	1.03 (0.98, 1.09)[c]	1.03 (0.97, 1.10)	1.07 (0.86, 1.33)[c]
								Random effects	1.02 (0.93, 1.11)[c]	1.04 (0.93, 1.09)	1.20 (0.82, 1.76)[c]
ICAM5 V301I rs1056538	15	22,229	17,687	0.39	0.57	0.54	0.98	Fixed effects	1.00 (0.97, 1.03)	1.02 (0.98, 1.07)	1.00 (0.94, 1.06)
								Random effects	1.00 (0.97, 1.03)	1.02 (0.97, 1.08)	0.99 (0.93, 1.06)
IGFBP3 –202C→A rs2854744	10	17,926	13,101	0.45	0.72	0.051	0.046	Fixed effects	0.97 (0.94, 1.00)	1.00 (0.94, 1.05)	0.93 (0.87, 0.99)
								Random effects	0.97 (0.93, 1.00)	1.00 (0.94, 1.05)	0.92 (0.86, 0.99)
SOD2 V16A rs1799725	13	21,349	16, 273	0.50	0.016	0.13	0.31	Fixed effects	0.98 (0.96, 1.01)	1.02 (0.97, 1.08)	0.97 (0.91, 1.03)
								Random effects	0.98 (0.94, 1.03)	1.02 (0.97, 1.08)	0.96 (0.88, 1.06)
TGFB1 L10P rs1982073	11	15,109	12,946	0.38	0.68	1.5×10^{-4}	2.8×10^{-5}	Fixed effects	1.08 (1.04, 1.11)	1.07 (1.02, 1.13)	1.16 (1.08, 1.25)
								Random effects	1.08 (1.04, 1.11)	1.07 (1.02, 1.13)	1.16 (1.08, 1.25)
ATM S49C rs1800054	12	19,488	15,905	0.012	0.27	0.08[d]		Fixed effects		1.13[d] (0.99, 1.30)	
								Random effects		1.13[d] (0.96, 1.32)	
NUMA1 A794G rs3750913	13	18,320	14,642	0.028	0.029	0.52[d]		Fixed effects		1.03[d] (0.94, 1.14)	
								Random effects		1.03[d] (0.90, 1.19)	

MAF: Minor allele frequency in the control sample.
[a]*P* values. The test of association and trend test are 2 d.f. and 1 d.f. LRT, respectively. [b]Reference group: common homozygotes. [c]Analyses excluded three studies (Helsinki Breast Cancer Study, Mayo Clinic Breast Cancer Study and USRT) because no homozygous variants were observed among cases or controls. [d]Heterozygote and homozygote variant genotypes were combined because of small number of women with the homozygote variant genotype.

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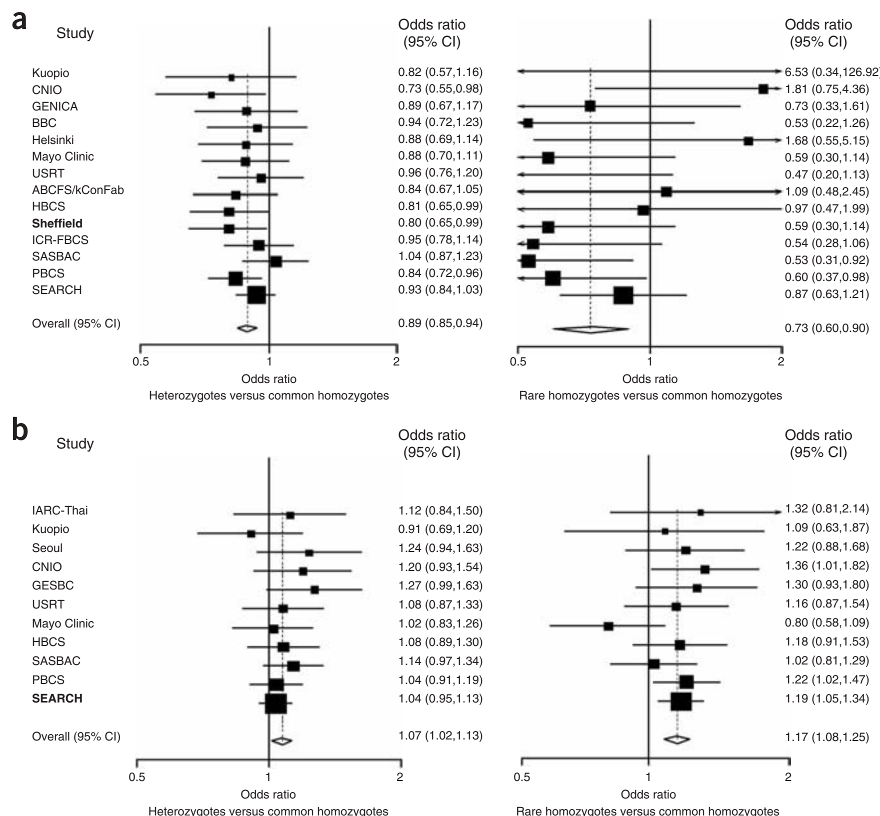

Figure 1 Genotype-specific OR and 95% c.i. by study. (**a**) *CASP8* D302H (rs1045485). (**b**) *TGFB1* L10P (rs1982073). Common homozygotes are the reference group. The initial study is indicated in bold. Studies are weighted and ranked according to the inverse of the variance of the log OR estimate for the heterozygotes.

with age, estrogen receptor or progesterone receptor status, grade, stage or histopathological subtype (**Table 2**). The ORs for ductal carcinoma *in situ* (DCIS) tumors were similar to that for invasive breast cancer. We saw no evidence of a stronger association in women with a history of breast cancer in first-degree female relatives, such as has been observed for other susceptibility alleles in *ATM* and *CHEK2* (refs. 12,13) (per-allele OR for *CASP8* D302H = 0.87 (95% c.i.: 0.82–0.91), 0.98 (95% c.i.: 0.89–1.07) and 0.90 (95% c.i.: 0.79–1.01) for zero, one and two or more first-degree relatives, respectively). An association with family history would be expected under a polygenic model with multiplicative effects at different loci, and this result may therefore suggest a different pattern of interaction with other susceptibility alleles. Of note, this site was not polymorphic in Korean, Han Chinese or Japanese women (D.K. *et al.*, unpublished data, http://www.hapmap.org/). The functional consequences of the aspartic acid-to-histidine substitution are not yet known, and further experiments are required to establish whether D302H itself, or another variant in strong linkage disequilibrium with it, is causative. Although this SNP was identified through a candidate gene approach, the association achieved a significance level close to that required for genome-wide studies[14].

Transforming growth factor-β (TGF-β) is a polypeptide cytokine that, *inter alia*, regulates normal mammary gland development and function by activating the TGF-β signaling pathway (reviewed in ref. 15). There is a dual-role model for the action of TGF-β in which it is thought to inhibit the development of early benign tumors, but once somatic oncogenic mutations have destroyed the normal tumor suppressor action of TGF-β, it then promotes tumor invasion and metastasis[15,16]. Our analysis of the L10P variant (rs1982073) in the *TGFB1* signal peptide showed a significant dose-dependent association of the proline-encoding allele with increased risk of invasive breast cancer based on analyses of data from 11 studies comprising 12,946 cases and 15,109 controls ($P_{trend} = 2.8 \times 10^{-5}$, per-allele OR = 1.08, (95% c.i.: 1.04–1.11); **Table 1** and **Fig. 1b**). This result remained significant after exclusion of the initial result from the Studies of Epidemiology and Risk Factors in Cancer Heredity (SEARCH)[17] ($P_{trend} = 8.0 \times 10^{-4}$), with no evidence of between-study heterogeneity ($P = 0.68$).

The proline variant of *TGFB1* has been associated with higher circulating levels of acid-activatable TGF-β[18] and increased rates of TGF-β secretion in *in vitro* transfection experiments[17]. From the dual-role model, it has been suggested that the proline (rapid TGF-β secretion) variant should be associated with a reduced risk of *in situ* tumors but an increased risk of invasive cancer. This study had insufficient cases with ductal carcinoma *in situ* (DCIS) to detect a significant differential risk ($n = 328$), but the estimated ORs for DCIS were consistent with a protective effect (**Table 3**). As might be predicted by a polygenic model, the ORs were greatest in those under 40 and closer to unity in older age groups, although this trend was not significant at the $P = 0.05$ level (**Table 3**). The ORs did not vary substantially by stage, grade or estrogen receptor status of the tumor. However, the significant association of the proline variant was confined to individuals with progesterone receptor–negative (rather than progesterone receptor–positive) tumors ($P = 0.017$; **Table 3**).

The findings of previously published studies, which have not subsequently been subsumed into the BCAC, have been contradictory or null[19–24]. A meta-analysis of the BCAC data together with the published studies (the latter totaling 4,021 cases and 8,253 controls) showed much weaker evidence for an increase in risk of the rare allele (per-allele OR = 1.04 (95% c.i.: 1.01–1.07), $P_{trend} = 0.012$). Differences in case selection or characteristics between studies could contribute to the discrepancy with the published results. The BCAC data may be more reliable, as it should be less susceptible to any publication bias. However, despite the size of our study and the relatively high level of significance, we cannot rule out the possibility that the *TGFB1* L10P association we found is a false positive result.

We observed borderline evidence of associations for two additional SNPs. The data suggest a recessive association for a promoter SNP in *IGFBP3* (–202C→A, rs2854744), (OR = 0.93 (95% c.i.: 0.87–0.99), $P_{trend} = 0.046$, **Table 1**). Two of the three previously published studies are included in the current analysis[25,26]; one previous null report is not included[27]. IGFBP3 is the principal binding protein regulating the activity of insulin-like growth factor 1 (IGF1), a circulating peptide hormone and growth factor for breast and other tissues. The A allele of the 202C→A SNP has been repeatedly shown to be associated with

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Table 2 Subgroup analysis for *CASP8* D302H and breast cancer risk

	Category	No. of cases	Test for association[b]	Heterozygotes[c] OR	Heterozygotes[c] 95% c.i.	Rare homozygotes[c] OR	Rare homozygotes[c] 95% c.i.	Heterogeneity test[d]
Age group, years[a]	<40	1,737	0.038	0.75	(0.60, 0.94)	1.16	(0.56, 2.40)	0.61
	40–49	3,962	0.0024	0.86	(0.76, 0.98)	0.55	(0.36, 0.85)	
	50–59	5,309	0.26	0.93	(0.84, 1.02)	0.91	(0.67, 1.23)	
	≥60	5,065	0.0058	0.89	(0.81, 0.98)	0.70	(0.51, 0.95)	
ER status	+	5,846	0.0042	0.89	(0.82, 0.96)	0.83	(0.65, 1.06)	0.24
	–	1,776	0.46	0.95	(0.84, 1.07)	0.82	(0.55, 1.24)	
PR status	+	3,416	0.024	0.90	(0.81, 0.99)	0.74	(0.53, 1.04)	0.82
	–	1,838	0.087	0.87	(0.76, 0.99)	0.94	(0.64, 1.40)	
Stage	I	3,591	0.31	0.95	(0.87, 1.05)	0.82	(0.59, 1.13)	0.32
	II	2,952	0.063	0.88	(0.79, 0.98)	0.93	(0.67, 1.31)	
	III/IV	288	0.82	0.91	(0.68, 1.23)	0.88	(0.32, 2.40)	
Grade	1	1,924	0.41	0.93	(0.83, 1.05)	0.86	(0.58, 1.28)	0.44
	2	4,229	0.026	0.90	(0.83, 0.98)	0.80	(0.61, 1.07)	
	3	2,731	0.017	0.88	(0.80, 0.98)	0.74	(0.52, 1.04)	
Histopathology	Ductal	7,629	0.0002	0.87	(0.81, 0.93)	0.85	(0.68, 1.07)	0.93
	Lobular	1,504	0.047	0.92	(0.80, 1.05)	0.59	(0.35, 0.98)	
DCIS		456	0.42	0.86	(0.68, 1.09)	0.86	(0.40, 1.84)	

ER, estrogen receptor; PR, progesterone receptor.
[a]Age in years at diagnosis (cases) or interview (controls). [b]LRT, 2 d.f. [c]Reference group: common homozygotes. [d]*P* value for case-only LRT of between-subgroup heterogeneity.

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increased circulating IGFBP3 levels[27,28]. However, the role of plasma IGFBP3 levels in breast cancer risk remains uncertain. Our data are consistent with the hypothesis that higher circulating levels of IGFBP3 are protective, but even the current large investigation has insufficient power to detect a recessive association with this allele at more than borderline levels of significance. *ADH1B* 3′ UTR A→G (rs1042026) also yielded a borderline significant association ($P = 0.044$). However, the heterozygote and homozygote genotypic associations were in opposite directions (**Table 1**), they were not consistent across studies and they were not seen under the random effects model (**Table 1**, **Supplementary Tables 2** and **3** online). Given that there is no biological rationale for such an observation, it is highly likely that the heterozygote association is due to chance.

ATM S49C (rs1800054) was not significantly associated with overall breast cancer risk. However, the c.i. did not exclude a modest association, and this SNP increased the risk of progesterone receptor–positive breast cancer (OR = 1.48 (95% c.i.: 1.08–2.04) under a dominant model (**Supplementary Table 4** online). For the remaining four SNPs (*CDKN1A* S31R, *ICAM5* V301I, *SOD2* V16A and *NUMA1* A794G), there was no evidence of an association with breast cancer (**Table 1** and **Supplementary Fig. 1** online). There was some evidence for heterogeneity between studies for *CDKN1A* S31R ($P = 0.009$), *NUMA1* A794G ($P = 0.029$) and *SOD2* V16A ($P = 0.016$), but all ORs and 95% confidence intervals were virtually unchanged using a random effects model to allow for heterogeneity (**Table 1**). When we removed the only study of *CDKN1A* S31R in Asian women (International Agency for Research on Cancer-Thailand Study (IARC-Thai)), summary estimates from the remaining 14 studies in women of predominately European ancestry suggested a recessive association for this SNP (OR = 1.37 (95% c.i.: 1.04–1.81) comparing rare homozygotes with common homozygotes; $P = 0.051$). OR estimates for the other two SNPs were similar in the two studies in Asian countries, and we found no clear explanation for the observed heterogeneity. Confidence intervals for summary ORs, particularly from random effects models, did not exclude modest associations for these SNPs (**Table 1**). We did not observe any additional modification of genotype associations with breast cancer risk by age, estrogen receptor or progesterone receptor tumor status and did not find any significant associations for DCIS tumors (**Supplementary Tables 4–7** online).

We estimate that the *CASP8* D302H and *TGFB1* L10P variants may account for approximately 0.3% and 0.2% of the excess familial risk of breast cancer, respectively, in populations of European ancestry. These data are the strongest evidence to date for common breast cancer susceptibility alleles, and they demonstrate the value of large consortia in identifying these variants.

METHODS

Subjects. Twenty breast cancer case-control studies contributed data to these analyses. A summary of the individual studies is given in **Supplementary Table 1**. All but two comprise subjects of predominantly European descent. Seven of the studies used population-based case ascertainment, nine ascertained cases from hospital-based series and one from a cohort. Five studies specifically included cases with a strong family history and/or bilateral cases. All studies were approved by the appropriate local Institutional Review Board or Research Ethics Committee, and informed consent was obtained from all

Table 3 Subgroup analysis for *TGFB1* L10P and breast cancer risk

	Category	No. of cases	Test for association[b]	Heterozygotes[c] OR	Heterozygotes[c] 95% c.i.	Rare homozygotes[c] OR	Rare homozygotes[c] 95% c.i.	Heterogeneity test[d]
Age group, years[a]	<40	1,123	0.09	1.27	(1.01, 1.60)	1.29	(0.94, 1.76)	0.32
	40–49	3,502	0.15	1.05	(0.93, 1.19)	1.19	(1.00, 1.41)	
	50–59	4,145	0.07	1.08	(0.98, 1.18)	1.16	(1.02, 1.32)	
	≥60	3,808	0.52	1.06	(0.96, 1.16)	1.03	(0.90, 1.18)	
ER status	+	4,571	0.04	1.01	(0.94, 1.09)	1.14	(1.03, 1.27)	0.59
	–	1,398	0.09	1.11	(0.98, 1.25)	1.19	(1.00, 1.42)	
PR status	+	2,473	0.87	0.98	(0.89, 1.09)	1.01	(0.88, 1.17)	0.017
	–	1,318	0.01	1.15	(1.01, 1.31)	1.31	(1.09, 1.57)	
Stage	I	3,175	0.15	1.05	(0.96, 1.14)	1.13	(1.00, 1.28)	0.42
	II	2,762	0.041	1.04	(0.95, 1.14)	1.19	(1.04, 1.35)	
	III/IV	222	0.21	1.15	(0.86, 1.55)	1.43	(0.97, 2.13)	
Grade	1	1,527	0.21	1.02	(0.91, 1.15)	1.16	(0.98, 1.36)	0.35
	2	3,374	0.0096	1.02	(0.93, 1.11)	1.19	(1.06, 1.34)	
	3	2,092	0.0051	1.14	(1.03, 1.26)	1.24	(1.08, 1.43)	
Histopathology	Ductal	6,643	0.0001	1.03	(0.96, 1.10)	1.22	(1.11, 1.33)	0.30
	Lobular	1,236	0.42	1.09	(0.96, 1.24)	1.03	(0.85, 1.24)	
DCIS		328	0.61	0.89	(0.70, 1.13)	0.90	(0.63, 1.27)	

ER, estrogen receptor; PR, progesterone receptor.
[a]Age in years at diagnosis (cases) or interview (controls). [b]LRT, 2 d.f. [c]Reference group: common homozygotes. [d]*P* value for case-only LRT of between-subgroup heterogeneity.

subjects (for the Netherlands Cancer Institute Study, an approved coding procedure was used; see ref. 17 in **Supplementary Table 1**).

Genotyping. Primers and probes used for TaqMan assays are listed in **Supplementary Table 8** online; alternative assay methods were used by some studies (**Supplementary Table 1**). Genotyping quality control was tested using duplicate DNA samples within studies and SNP assays. For all SNPs, $>99\%$ concordant results were obtained. Studies using DNA from lymphocytes on the TaqMan and MALDI-TOF MS platforms obtained genotype calls in $>96\%$ of samples tested. A minority of studies that used DNA from paraffin blocks or buccal cells or other genotyping platforms had lower completion rates. Quality control data for each SNP are shown in **Supplementary Table 9** online.

Statistical methods. Deviation of the genotype frequencies in the controls from those expected under Hardy-Weinberg Equilibrium (HWE) was assessed by χ^2 tests (1 degree of freedom (d.f.)), for each study separately. The main test of the null hypothesis of no association (with invasive breast cancer; that is, excluding DCIS) was a likelihood ratio test (LRT) (2 d.f.) comparing a model that included terms for genotype and study with a model including only a term for study, and a trend test (1d.f.) that included a single parameter for allele dose. Genotype-specific risks for each SNP were estimated as ORs for the heterozygote and rare homozygote genotypes with the common homozygote as the baseline category using unconditional logistic regression. We also estimated a per-allele risk under a multiplicative codominant genetic model by fitting the number of rare alleles carried as an ordinal covariate.

Genotype counts from individual studies are given in **Supplementary Table 2** online, and study-specific ORs are given in **Supplementary Table 3** online. We tested for heterogeneity between study strata by comparing logistic regression models with and without a genotype × study interaction term using a likelihood ratio test. Data were also analyzed using a random-effects model to allow for heterogeneity.

We estimated category-specific risks by comparing the genotype distribution of cases and controls within each category (for age) or between each case category and all controls (for other variables) (**Tables 2** and **3** and **Supplementary Tables 4–7**). To investigate the effects of age, subjects were separated into four categories (under 40, 40–49, 50–59 and 60+) according to age at diagnosis (cases) or interview (controls). Family history categories were (i) no family history of breast cancer, (ii) one first-degree relative with breast cancer and (iii) two or more first-degree relatives with breast cancers or bilateral breast cancer cases. Estrogen receptor and progesterone receptor status were categorized as positive or negative; tumor grade as 1, 2 or 3; and stage as I, II or III/IV. Histopathology categories were ductal and lobular. Individuals with DCIS were defined as not having had invasive breast cancer up to and including the time of diagnosis of DCIS. Category-specific data were not available for all subjects; the number of cases with data available for the relevant variables is indicated in **Tables 2** and **3** and **Supplementary Tables 4–7**.

We tested for interaction between genotype and other variables (age at diagnosis, family history, estrogen receptor status, progesterone receptor status, grade, stage and histopathological subtype) using a cases-only design. This approach is more powerful than standard case-control methods for detecting interaction[29]. Polytomous logistic regression was used to compare genotype frequencies in the different subgroups of each category stratified by study (**Tables 2** and **3** and **Supplementary Tables 4–7**). The other variables and the number of rare alleles carried were fitted as ordinal covariates and a LRT (1 d.f.) then used to compare a model that included terms for genotype and study with a model including only a term for study.

The relative risk to daughters of an affected individual attributable to a given SNP was calculated using the formula

$$\lambda^* = \frac{p(pr_2+qr_1)^2+q(pr_1+q)^2}{[p^2r_2+2pqr_1+q^2]^2}$$

where p is the population frequency of the minor allele, $q = 1 - p$, and r_1 and r_2 are the relative risks (estimated as OR) for heterozygotes and rare homozygotes, relative to common homozygotes. The proportion of the familial risk attributable to the SNP was then calculated as $\log(\lambda^*)/\log(\lambda_0)$, where λ_0 is the overall familial relative risk to offspring estimated from epidemiological studies (this formula assumes a multiplicative interaction between the SNP of interest and the other susceptibility alleles). λ_0 was assumed to be 1.8 (ref. 30).

Note: Supplementary information is available on the Nature Genetics website.

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AUTHOR CONTRIBUTIONS

A.C., A.M.D. and M.G.-C. contributed equally to the writing of this manuscript. Data analysis was carried out by P.D.P.P. and M.G.-C. and the project was coordinated by D.F.E. The Sheffield Breast Cancer Study was designed and initiated by M.W.R.R., and genotyping and data management were coordinated by A.C. S.B. was responsible for patient recruitment, collection and validation of clinicopathological data and assisted in revising the manuscript. The SEARCH study was initiated by B.A.J.P. and is managed by P.D.P.P., D.F.E. and B.A.J.P. Genotyping was coordinated by A.M.D., K.A.P. and C. Baynes carried out genotyping within SEARCH and provided reagents, protocols and technical advice to BCAC members. S. Scollen carried out genotyping and assisted in drafting the manuscript. M.G.-C., L.B., J. Lissowska and B.P. initiated the Polish Breast Cancer Study and participated in the study design as well as in data and biological specimen collection. M.G.-C. was responsible for the overall supervision of the study, quality control, and genotyping. S.C. contributed to genotyping. J.L.H., M.R.E.McC., G.G.G and M.C.S. devised and designed the ABCFS study, were responsible for the recruitment of subjects and collection of samples and critically reviewed the manuscript. A.B.S. participated in the study design, genotyping design, supervision and quality control, data management and critical review of the manuscript for the kConFab study. J. Beesley was involved in genotyping design, implementation, quality control and critical review of the manuscript. G.C.-T. was involved in the study design, funding, project supervision and critical review of manuscript. O.F., N.J., L.G. and I.d.S.S. all participated in the design of the British Breast Cancer Study and collection of the samples. N.J. was responsible for the genotyping and O.F. and L.G. were responsible for coding and cleaning of data. S.E.B., B.G.N. and C.K.A. all initiated the Copenhagen Breast Cancer Study and designed the concept. B.G.N. secured funding and provided administrative support. B.G.N. provided controls, and C.K.A. provided patients. S.E.B. directed the molecular analyses and collected and assembled the data. S.E.B., B.G.N. and C.K.A. all revised the manuscript. U.H. initiated the GENICA study, designed the concept and secured funding. She was responsible for molecular analyses and was involved in revising the manuscript. H.B. initiated and coordinated the GENICA study, designed concepts and secured funding. She is responsible for the conduct of molecular analyses and participated in the revision of the manuscript. C.J. participated in the GENICA study, particularly in the molecular design and analyses, and was involved in revising the manuscript. D.T. participated in the GENICA study, particularly in the molecular design and analyses. J.C.-C. initiated and designed the Genetic Epidemiology Study of Breast Cancer by Age 50, secured funding and participated in revising the manuscript. S.K. was responsible for data collection and analysis and participated in revising the manuscript. A. Risch was responsible for the molecular analyses of IGFBP3 and participated in revising the manuscript. S.W.-G. initiated and conducted the molecular analyses for *SOD2* and participated in revising the manuscript. N.B. and P.S. contributed to the molecular design of the Hannover Breast Cancer Study, performed TaqMan assays and ARMS analyses of the HBCS samples and participated in revising the manuscript. T.D. coordinated the Hannover Breast Cancer Study and took part in the project design, experimental work, data evaluation and critical review of the manuscript. R.F. and K.A. coordinated the genotyping, data collection and management, C. Blomquist was responsible for the recruitment of the patients and H.N. initiated and coordinated the Helsinki Breast Cancer Study. M.R.S. and N.R. were responsible for the design of the ICR_FBCS study. S. Seal and A. Renwick undertook the genotyping. The IARC-Thai study was jointly designed by S. Sangrajrang and P.B. S. Sangrajrang coordinated the recruitment of participants and collection of biological samples. The genotyping was coordinated by D.H. and F.O. A.M., V.K. and V.-M.K. participated in the study design for the Kuopio Breast Cancer Project. V.K. coordinated the data collection and clinical data update and contributed to the funding. V.-M.K. was responsible for the histological analyses, revised the manuscript and contributed to the funding. A.M. was responsible for the molecular analyses and was involved in the revision of the manuscript. J.H. contributed to the genotyping and participated in the revision of the manuscript. F.J.C. participated in the Mayo Clinic Breast Cancer Study design, was responsible for the genotyping and was involved in revising the manuscript. J.E.O. oversaw biological sample and data collection and assisted in revising the manuscript, E.L.G. assisted in manuscript revision. A.B., M.K.S., F. B.L.H. and L.J.V.V. were responsible for and/or contributed to project initiation and data collection, performance and interpretation of SNP array test and data cleaning and formatting for Dutch patients (contribution of the Netherlands Cancer Institute) and were involved in revision of the manuscript. P.H., S.W., Y.-L.L. and J. Liu contributed in the securing of funding, study design, genotyping and revision of the manuscript for the SASBAC study. D.K. designed the Seoul Breast Cancer Study. K.-Y.Y. participated in risk factor analysis. D.-Y.N. and S.-H.A. provided biological samples. R.L.M. participated in the CNIO study design, was responsible for data cleaning and formatting and participated in revising the manuscript. G.R. and A.G.-N. were responsible for genotyping and participated in the revision of the manuscript. J. Benitez was responsible for the design of the CNIO study and the securing of funding (Genome Spain grant) and was involved in revising the manuscript. A.J.S. participated in the US Radiologic Technologist (USRT) study design, oversaw biologic sample and data collection and assisted in revising the manuscript. D.L.S. performed the genotyping and participated in the revision of the manuscript. B.H.A. participated in USRT study design, oversaw sample and data collection and assisted in revising the manuscript. J.P.S. participated in the USRT study design, was responsible for the genotyping and was involved in revising the manuscript.

COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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Corrigendum: Differential translation efficiency of orthologous genes is involved in phenotypic divergence of yeast species

Orna Man & Yitzhak Pilpel

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In **Figure 2** of the original version of this paper, panels **c** and **d** were accidentally transposed, resulting in incorrect information in the legend. **Figure 2c** shows genes of the tricarboxylic acid (TCA) cycle, and **Figure 2d** shows glycolysis genes. The error has been corrected in the HTML and PDF versions of the article.

Corrigendum: A common coding variant in *CASP8* is associated with breast cancer risk

Angela Cox, Alison M Dunning, Montserrat Garcia-Closas, Sabapathy Balasubramanian, Malcolm W R Reed, Karen A Pooley, Serena Scollen, Caroline Baynes, Bruce A J Ponder, Stephen Chanock, Jolanta Lissowska, Louise Brinton, Beata Peplonska, Melissa C Southey, John L Hopper, Margaret R E McCredie, Graham G Giles, Olivia Fletcher, Nichola Johnson, Isabel dos Santos Silva, Lorna Gibson, Stig E Bojesen, Børge G Nordestgaard, Christen K Axelsson, Diana Torres, Ute Hamann, Christina Justenhoven, Hiltrud Brauch, Jenny Chang-Claude, Silke Kropp, Angela Risch, Shan Wang-Gohrke, Peter Schürmann, Natalia Bogdanova, Thilo Dörk, Rainer Fagerholm, Kirsimari Aaltonen, Carl Blomqvist, Heli Nevanlinna, Sheila Seal, Anthony Renwick, Michael R Stratton, Nazneen Rahman, Suleeporn Sangrajrang, David Hughes, Fabrice Odefrey, Paul Brennan, Amanda B Spurdle, Georgia Chenevix-Trench, The Kathleen Cunningham Foundation Consortium for Research into Familial Breast Cancer, Jonathan Beesley, Arto Mannermaa, Jaana Hartikainen, Vesa Kataja, Veli-Matti Kosma, Fergus J Couch, Janet E Olson, Ellen L Goode, Annegien Broeks, Marjanka K Schmidt, Frans B L Hogervorst, Laura J Van't Veer, Daehee Kang, Keun-Young Yoo, Dong-Young Noh, Sei-Hyun Ahn, Sara Wedrén, Per Hall, Yen-Ling Low, Jianjun Liu, Roger L Milne, Gloria Ribas, Anna Gonzalez-Neira, Javier Benitez, Alice J Sigurdson, Denise L Stredrick, Bruce H Alexander, Jeffery P Struewing, Paul D P Pharoah & Douglas F Easton, on behalf of the Breast Cancer Association Consortium

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In the version of this article initially published, there was an error that affected the calculations of the odds ratios, confidence intervals, between-study heterogeneity, trend test and test for association for SNP *ICAM5* V301I in **Table 1** (*ICAM5* V301I); genotype counts in **Supplementary Table 2** (*ICAM5*; ICR_FBCS and Kuopio studies) and minor allele frequencies, trend test and odds ratios for heterozygotes and rare homozygotes in **Supplementary Table 3** (*ICAM5*; ICR_FBCS and Kuopio studies). The corrected rows from each table are reproduced below.

The errors in **Table 1** have been corrected in the PDF version of the article. The errors in supplementary information have been corrected online.

Table 1 Summary odds ratios and 95% confidence intervals for nine polymorphisms and breast cancer risk

SNP	Between-study heterogeneity	Test for association	Trend test	Analysis model	Heterozygote OR (95% c.i.)	Rare homozygote OR (95% c.i.)
ICAM5 V301I	0.57	0.54	0.98	Fixed effects	1.02 (0.97, 1.07)	0.99 (0.93, 1.05)
rs1056538				Random effects	1.02 (0.97, 1.07)	0.99 (0.93, 1.05)

Supplementary Table 2 Genotype counts among cases and controls by study

			Controls				Cases			
Gene	SNP	Study	AA	Aa	aa	Total	AA	Aa	aa	Total
ICAM5	rs1056538	ICR_FBCS	207	243	71	521	212	239	68	519
		Kuopio	178	209	46	433	193	206	48	447

Supplementary Table 3 Association between nine polymorphisms and breast cancer risk by study

					Heterozygotes			Rare homozygotes		
Gene	SNP	Study	MAF	Trend test	OR	95% c.i.		OR	95% c.i.	
ICAM5	rs1056538	ICR_FBCS	0.369	0.698	0.960	0.739	1.248	0.935	0.637	1.373
		Kuopio	0.348	0.658	0.909	0.687	1.203	0.962	0.612	1.513

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