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# Genetic variation in mitotic regulatory pathway genes is associated with breast tumor grade

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**Mitotic index is an important component of histologic grade and has an etiologic role in breast tumorigenesis. Several small candidate gene studies have reported associations between variation in mitotic genes and breast cancer risk. We measured associations between 2156 single nucleotide polymorphisms (SNPs) from 194 mitotic genes and breast cancer risk, overall and by histologic grade, in the Breast Cancer Association Consortium (BCAC) iCOGS study ($n$ = 39 067 cases; $n$ = 42 106 controls). SNPs in *TACC2* [rs17550038: odds ratio (OR) = 1.24, 95% confidence interval (CI) 1.16–1.33, $P = 4.2 \times 10^{-10}$) and *EIF3H* (rs799890: OR = 1.07, 95% CI 1.04–1.11, $P = 8.7 \times 10^{-6}$) were significantly associated with risk of low-grade breast cancer. The *TACC2* signal was retained (rs17550038: OR = 1.15, 95% CI 1.07–1.23, $P = 7.9 \times 10^{-5}$) after adjustment for breast cancer risk SNPs in the nearby *FGFR2* gene, suggesting that *TACC2* is a novel, independent genome-wide significant genetic risk locus for low-grade breast cancer. While no SNPs were individually associated with high-grade disease, a pathway-level gene set analysis showed that variation across the 194 mitotic genes was associated with high-grade breast cancer risk ($P = 2.1 \times 10^{-3}$). These observations will provide insight into the contribution of mitotic defects to histological grade and the etiology of breast cancer.**

## INTRODUCTION

Inherited variation in genes encoding proteins involved in mitotic regulatory pathways, such as mitotic kinases and centrosome-related genes, has been associated with cancer risk in several small candidate gene studies. Common variants in mitotic genes have been associated with various cancer types such as prostate, lung, uterine, colorectal, and breast cancer (1–7). Specifically for breast cancer, genes involved in centrosome amplification, such as *NIN*, *TACC3*, *GPSM2*, *CDC25C*, *NEK7* and *MCPH1* and variation in mitotic regulators, including *SART1*, *EIF3A*, *RRM2* and *PSCD3* have been associated with breast cancer risk (8,9). SNP by SNP interactions for breast cancer risk have also been observed between *SEPT4* and *TEX14*, both of which participate in the separation into daughter cells during cytokinesis (10). Finally, the mitotic kinases *FYN*, *MAST2* and *MAP2K4*, identified through RNA interference-based functional screening of mitotic kinases in *Drosophila* (11), have been associated with breast cancer risk (12).

Multiple lines of evidence support an etiologic role for disruption of mitotic regulatory pathways in breast tumorigenesis. The disruption of chromosome segregation during mitosis is one mechanism of chromosomal instability, and ultimately aneuploidy, which has been found to occur early in breast tumor development (13,14), is found in ~80% of all breast tumors and is thought to play a direct role in tumor progression (15,16). Further, somatic mutations in spindle assembly checkpoint genes have been identified in human breast tumors, and mutations in orthologous murine genes have been implicated in increased chromosomal instability and tumor development (13,14). Deregulation of mitosis is associated with the pathophysiology of breast cancer through the mitotic index, a component of the histologic grading system of breast tumors. Higher histologic grade is associated with increased aggressiveness and both high mitotic index and high grade are associated with poor prognosis (17). Given the relationship between histologic grade and mitotic index, we hypothesized that genetic variation in mitotic regulatory pathways is associated with high-grade breast cancer risk. Here we report on a comprehensive analysis of variation in mitotic genes in a study of nearly 80 000 subjects ($n$ = 39 067 cases; $n$ = 42 106 controls) with information on histopathologic grade from the Breast Cancer Association Consortium (BCAC). We evaluated 2135 single nucleotide polymorphisms (SNPs) in 194 genes involved in mitosis, encompassing those involved in mitotic entry and progression, the spindle assembly checkpoint and cytokinesis. Utilizing genotype data from a custom Illumina Infinium array (iCOGS) array (18), we investigated whether variation in these 194 mitotic genes influences the risk of breast cancer, both overall and with respect to histologic grade.

## RESULTS

To determine whether variation in genes encoding mitotic regulatory proteins influences invasive breast cancer risk, we evaluated associations between 2156 SNPs in 194 mitotic genes (Supplementary Material, Table S1) and breast cancer risk among women of European ancestry using 39 067 breast cancer cases and 42 106 study-matched controls from BCAC (Supplementary Material, Table S2). Ten SNPs in three loci were significantly associated with overall breast cancer risk after Bonferroni correction ($P < 2.3 \times 10^{-5}$) (Table 1a). Six SNPs in the *ITPR1* locus on chromosome 3, which has been previously reported as a breast cancer susceptibility locus by BCAC (18), were associated with overall breast cancer risk (Table 1a). Four of these SNPs achieved genome-wide significance with invasive breast cancer overall (rs6762644: odds ratio (OR) = 1.06, $P = 1.1 \times 10^{-8}$; rs6774180 OR = 1.06, $P = 1.3 \times 10^{-8}$; rs9867580 OR = 1.06, $P = 4.2 \times 10^{-8}$; rs13313995 OR = 1.06, $P = 4.8 \times 10^{-8}$) (Table 1a). Three SNPs in the *TACC2* locus on chromosome 10 (rs17550038 OR = 1.15, $P = 1.0 \times 10^{-6}$; rs2461211 OR = 1.08, $P = 1.8 \times 10^{-6}$; rs2461210 OR = 1.08, $P = 2.3 \times 10^{-6}$) and one SNP in the *EIF3H* locus on chromosome 8 (rs799890 OR = 1.06, $P = 1.4 \times 10^{-5}$) were also significantly associated with overall breast cancer risk (Table 1a). Of these, the three *TACC2* locus SNPs showed genome-wide significant associations with estrogen receptor (ER)-positive breast cancer but no significant

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**Table 1.** Associations with overall and low-grade breast cancer risk

| SNP | Chr. | Position | Gene | Allele[a] | Controls | Cases | OR | *P*-value |
|---|---|---|---|---|---|---|---|---|
| (a) Overall breast cancer | | | | | | | | |
| rs6762644 | 3 | 4717276 | *ITPR1* | G | 42 100 | 39 055 | 1.06 (1.04–1.08) | $1.1 \times 10^{-8}$ |
| rs6774180 | 3 | 4717779 | *ITPR1* | A | 42 102 | 39 061 | 1.06 (1.04–1.08) | $1.3 \times 10^{-8}$ |
| rs9867580 | 3 | 4722247 | *ITPR1* | C | 42 101 | 39 058 | 1.06 (1.04–1.08) | $4.2 \times 10^{-8}$ |
| rs13313995 | 3 | 4722360 | *ITPR1* | A | 42 097 | 39 048 | 1.06 (1.04–1.08) | $4.8 \times 10^{-8}$ |
| rs17550038 | 10 | 123780679 | *TACC2* | C | 42 101 | 39 058 | 1.15 (1.09–1.22) | $1.0 \times 10^{-6}$ |
| rs2461211 | 10 | 123783865 | *TACC2* | A | 42 101 | 39 064 | 1.08 (1.05–1.12) | $1.8 \times 10^{-6}$ |
| rs2461210 | 10 | 123784538 | *TACC2* | A | 42 105 | 39 065 | 1.08 (1.05–1.12) | $2.3 \times 10^{-6}$ |
| rs9830067 | 3 | 4731814 | *ITPR1* | A | 42 104 | 39 062 | 1.05 (1.03–1.07) | $5.0 \times 10^{-6}$ |
| rs2306881 | 3 | 4728712 | *ITPR1* | G | 42 095 | 39 057 | 1.05 (1.03–1.07) | $6.1 \times 10^{-6}$ |
| rs799890 | 8 | 117318782 | *EIF3H* | C | 42 102 | 39 063 | 1.06 (1.03–1.09) | $1.4 \times 10^{-5}$ |
| (b) Low-grade breast cancer | | | | | | | | |
| rs17550038 | 10 | 123780679 | *TACC2* | C | 42 101 | 16 053 | 1.24 (1.16–1.33) | $4.2 \times 10^{-10}$ |
| rs2461211 | 10 | 123783865 | *TACC2* | A | 42 101 | 16 056 | 1.14 (1.09–1.19) | $4.8 \times 10^{-10}$ |
| rs2461210 | 10 | 123784538 | *TACC2* | A | 42 105 | 16 055 | 1.14 (1.09–1.18) | $7.1 \times 10^{-10}$ |
| rs7898269 | 10 | 123784105 | *TACC2* | A | 42 106 | 16 056 | 1.16 (1.09–1.22) | $2.1 \times 10^{-7}$ |
| rs12146254 | 10 | 123793633 | *TACC2* | A | 42 079 | 16 047 | 1.15 (1.08–1.21) | $1.3 \times 10^{-6}$ |
| rs10887047 | 10 | 123770790 | *TACC2* | A | 42 087 | 16 054 | 1.14 (1.08–1.21) | $2.2 \times 10^{-6}$ |
| rs799890 | 8 | 117318782 | *EIF3H* | C | 42 102 | 16 055 | 1.07 (1.04–1.11) | $8.7 \times 10^{-6}$ |
| rs799889 | 8 | 117320076 | *EIF3H* | C | 42 102 | 16 053 | 1.07 (1.04–1.10) | $1.8 \times 10^{-5}$ |
| rs6762644 | 3 | 4717276 | *ITPR1* | G | 42 100 | 16 052 | 1.06 (1.03–1.08) | $2.3 \times 10^{-5}$ |

[a] Tested allele.

associations with ER-negative breast cancer (Supplementary Material, Table S3a).

The 2156 mitotic SNPs were also assessed for associations with histologic grade of breast cancer, by comparing 19 475 low-grade breast cancers (Grades 1 and 2 combined) and 8780 high-grade (Grade 3) breast cancers to 42 106 controls in a polytomous logistic regression model. Similar to the overall breast cancer analysis, variants in the *TACC2*, *EIF3H* and *ITPR1* loci were significantly associated with low-grade breast cancer risk (Table 1b). Three genotyped SNPs in the *TACC2* locus showed genome-wide significant associations with risk of low-grade breast cancers (rs17550038 OR = 1.24, $P = 4.2 \times 10^{-10}$; rs2461211 OR = 1.14, $P = 4.8 \times 10^{-10}$; rs2461210 OR = 1.14, $P = 7.1 \times 10^{-10}$), and three others retained significance after Bonferroni correction (Table 1b). All six variants were located in intron 2 of *TACC2* (Supplementary Material, Fig. S1). The levels of significance and the effect sizes for the associations with the six *TACC2* SNPs were consistently greater in ER-positive than ER-negative low-grade breast cancers, although this may be due to reduced power for the ER-negative analysis (Supplementary Material, Table S3b). No SNPs in *TACC2* were significantly associated with high-grade breast cancer risk (Supplementary Material, Table S4).

The *TACC2* locus is located ~390 kb downstream of *FGFR2*, a known breast cancer susceptibility locus (18–20), from which *FGFR2* rs2981579 has been strongly associated with overall breast cancer risk in these data (OR = 1.32, $P = 1.23 \times 10^{-102}$) (Table 2a) (18). Although 1000 Genomes Project data showed little evidence of linkage disequilibrium (LD) between SNPs in the *TACC2* and *FGFR2* loci (Supplementary Material, Fig. S2), the proximity of the loci raised the possibility that associations between variants in *TACC2* and low-grade breast cancer were accounted for by variation in the *FGFR2* locus. To explore this in detail we investigated associations between 454 SNPs in the FGFR2 locus and low-grade breast cancer. By adjusting the top *FGFR2* SNP, rs2981579, for each of the 453 remaining *FGFR2* SNPs, rs78985527 was identified as an additional potentially independent *FGFR2* signal for low-grade breast cancer (Table 2b). The analyses of the six significant *TACC2* SNPs were then adjusted simultaneously for rs2981579 and rs78985527 (Table 2c). While the effect sizes and the significance of the findings were reduced, each of the six *TACC2* SNPs remained strongly associated with low-grade breast cancer (Table 2c). In addition, there was no evidence for interaction between *FGFR2* rs2981579, rs78985527, and any of the *TACC2* SNPs (Supplementary Material, Table S5). For completeness, we also adjusted the top *TACC2* SNP rs17550038 for each of the 454 *FGFR2* SNPs, but did not find substantial evidence that *FGFR2* SNPs account for the *TACC2* signal (Supplementary Material, Fig. S3). These findings suggest that the *TACC2* association is independent of previously described genetic associations at the *FGFR2* locus. However, it will be necessary to take into account the potential for long-range transcriptional regulation in this region when exploring the exact functional mechanism underlying this signal.

To identify putative functional SNPs in the *TACC2* locus, we performed a FunciSNP analysis for rs17550038. A total of 27 SNPs in LD with rs17550038 ($R^2 \geq 0.3$), the majority of which were located in introns of *TACC2* ($n = 21$) or *ATE1* ($n = 4$), overlapped with at least one biofeature (Supplementary Material, Table S6, Fig. 1). Of these 27 SNPs, rs11200337 overlapped with biofeatures in three breast cell lines (HMEC, MCF7, T47D). rs11200337 is located 11.5 kb from the *TACC2* index SNP ($R^2 = 0.53$) in a methylated region in each of the cell lines and a DNaseI hypersensitivity (HS) site in HMEC and T47D cells. The SNP is also located in sites of histone modification and open chromatin in HMEC normal mammary epithelial cells. Three additional SNPs located in *TACC2* introns overlapped with biofeatures in at least two of the cell lines (rs4282928, rs4752637, rs11200373).

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**Table 2.** Multivariable analysis of FGFR2 and TACC2 for low-grade breast cancer risk

| Gene | SNP | Adjustments[a] | OR (95% CI) | *P*-value |
|---|---|---|---|---|
| (a) Single SNP analysis | | | | |
| *TACC2* | rs17550038 | | 1.24 (1.16–1.33) | $4.2 \times 10^{-10}$ |
| | rs2461211 | | 1.14 (1.09–1.19) | $4.8 \times 10^{-10}$ |
| | rs2461210 | | 1.14 (1.09–1.18) | $7.1 \times 10^{-10}$ |
| | rs7898269 | | 1.16 (1.09–1.22) | $2.1 \times 10^{-7}$ |
| | rs12146254 | | 1.15 (1.08–1.21) | $1.3 \times 10^{-6}$ |
| | rs10887047 | | 1.14 (1.08–1.21) | $2.2 \times 10^{-6}$ |
| (b) *FGFR2* 2-SNP analysis | | | | |
| | rs2981579 | rs78985527 | 1.33 (1.30–1.37) | $8.3 \times 10^{-106}$ |
| | rs78985527 | rs2981579 | 1.12 (1.06–1.18) | $5.7 \times 10^{-5}$ |
| (c) *TACC2* + *FGFR2* 3-SNP analysis | | | | |
| *TACC2* | rs17550038 | rs2981579, rs78985527 | 1.14 (1.07–1.23) | $1.1 \times 10^{-4}$ |
| | rs2461211 | rs2981579, rs78985527 | 1.08 (1.04–1.13) | $2.1 \times 10^{-4}$ |
| | rs2461210 | rs2981579, rs78985527 | 1.12 (1.04–1.12) | $2.6 \times 10^{-4}$ |
| | rs7898269 | rs2981579, rs78985527 | 1.10 (1.04–1.16) | $1.3 \times 10^{-3}$ |
| | rs12146254 | rs2981579, rs78985527 | 1.09 (1.03–1.15) | $3.2 \times 10^{-3}$ |
| | rs10887047 | rs2981579, rs78985527 | 1.08 (1.03–1.15) | $4.2 \times 10^{-3}$ |
| *FGFR2* | rs2981579 | rs17550038, rs78985527 | 1.32 (1.29–1.36) | $1.3 \times 10^{-100}$ |
| | rs2981579 | rs2461211, rs78985527 | 1.33 (1.29–1.36) | $1.7 \times 10^{-100}$ |
| | rs2981579 | rs2461210, rs78985527 | 1.33 (1.29–1.36) | $1.2 \times 10^{-100}$ |
| | rs2981579 | rs7898269, rs78985527 | 1.33 (1.29–1.36) | $2.8 \times 10^{-102}$ |
| | rs2981579 | rs12146254, rs78985527 | 1.33 (1.30–1.37) | $8.8 \times 10^{-103}$ |
| | rs2981579 | rs10887047, rs78985527 | 1.33 (1.30–1.37) | $7.3 \times 10^{-103}$ |
| *FGFR2* | rs78985527 | rs17550038, rs2981579 | 1.11 (1.05–1.17) | $8.1 \times 10^{-5}$ |
| | rs78985527 | rs2461211, rs2981579 | 1.11 (1.05–1.17) | $1.4 \times 10^{-4}$ |
| | rs78985527 | rs2461210, rs2981579 | 1.11 (1.05–1.17) | $1.5 \times 10^{-4}$ |
| | rs78985527 | rs7898269, rs2981579 | 1.11 (1.05–1.17) | $8.2 \times 10^{-5}$ |
| | rs78985527 | rs12146254, rs2981579 | 1.11 (1.06–1.18) | $5.8 \times 10^{-5}$ |
| | rs78985527 | rs10887047, rs2981579 | 1.11 (1.06–1.17) | $7.4 \times 10^{-5}$ |

[a]In addition to study and principal components.

We also performed an exploratory analysis of correlations between *TACC2* expression and nearby SNPs, utilizing expression quantitative trait locus (eQTL) data available from 484 triple negative (TN) breast tumors from the Triple Negative Breast Cancer Consortium. Seven SNPs around *TACC2* were associated with *TACC2* expression at a 10% false discovery rate (FDR) threshold ($P \leq 5 \times 10^{-5}$), although none of these SNPs were in LD with the risk-associated SNPs (Supplementary Material, Table S7). Similarly, an eQTL analysis using The Cancer Genome Atlas (TCGA) data identified an additional rare SNP, rs3752956 in intron 8 of *TACC2*, as an eQTL for *TACC2* ($P = 4.07 \times 10^{-5}$) in ER-positive breast tumors (21). These data alone do not provide evidence that SNP-mediated deregulation of *TACC2* underlies the breast cancer risk signal at this locus. Further functional analyses in low-grade breast tumors are necessary to understand the mechanistic basis of this association.

In addition to *TACC2*, two SNPs in the *EIF3H* locus (rs799890 OR = 1.07, $P = 8.7 \times 10^{-6}$, rs799889 OR = 1.07, $P = 1.8 \times 10^{-5}$) were associated with low-grade breast cancer risk (Table 1b). A total of 55 SNPs in the *EIF3H* locus were genotyped, with a single peak of association downstream of *EIF3H* (Supplementary Material, Fig. S4). Similar to the overall results, variants in *EIF3H* were associated with ER-positive low-grade breast cancer and marginally with ER-negative low-grade breast cancer, where the effect sizes were slightly larger but the association was less significant due to the small sample size (Supplementary Material, Table S3b). No SNPs in *EIF3H* were significantly associated with high-grade breast cancer risk (Supplementary Material, Table S8). We identified 19 putative functional SNPs correlated with rs799890 in the *EIF3H* locus, all of which were intergenic between the *TRPS1* and *EIF3H* genes (Supplementary Material, Table S9). The only biofeatures associated with these SNPs were open chromatin states and sites of histone modification in HMEC cells.

Similarly, a single SNP in the *ITPR1* locus remained statistically significant among low-grade breast cancers (rs6762644 OR = 1.06, $P = 2.3 \times 10^{-5}$) (Table 1b). As with the *TACC2* SNPs, the *ITPR1* SNP was only associated with ER-positive low-grade breast cancers (Supplementary Material, Table S3b). Several SNPs in *ITPR1*, including rs6762644, were also marginally significantly associated with high-grade breast cancer (Table 1c), suggesting that the *ITPR1* locus is associated with breast cancer risk regardless of histologic grade. SNPs in the *ITPR1* locus that are associated with breast cancer risk have been previously annotated for effects on chromatin using Encyclopedia of DNA Elements (ENCODE) biofeatures identified in HMECs (22). Here we identified 14 SNPs correlated with rs6762644 that also overlap with DNaseI HS sites, Formaldehyde-assisted isolation of regulatory elements (FAIRE) open chromatin signals, and sites of histone modification in T47D and/or MCF7 cells located within introns of *EGOT* (Supplementary Material, Table S10).

No individual SNPs were significantly associated with high-grade breast cancer (Supplementary Material, Table S11). However, considering the original hypothesis that variation in mitotic genes is associated with high-grade breast cancer risk

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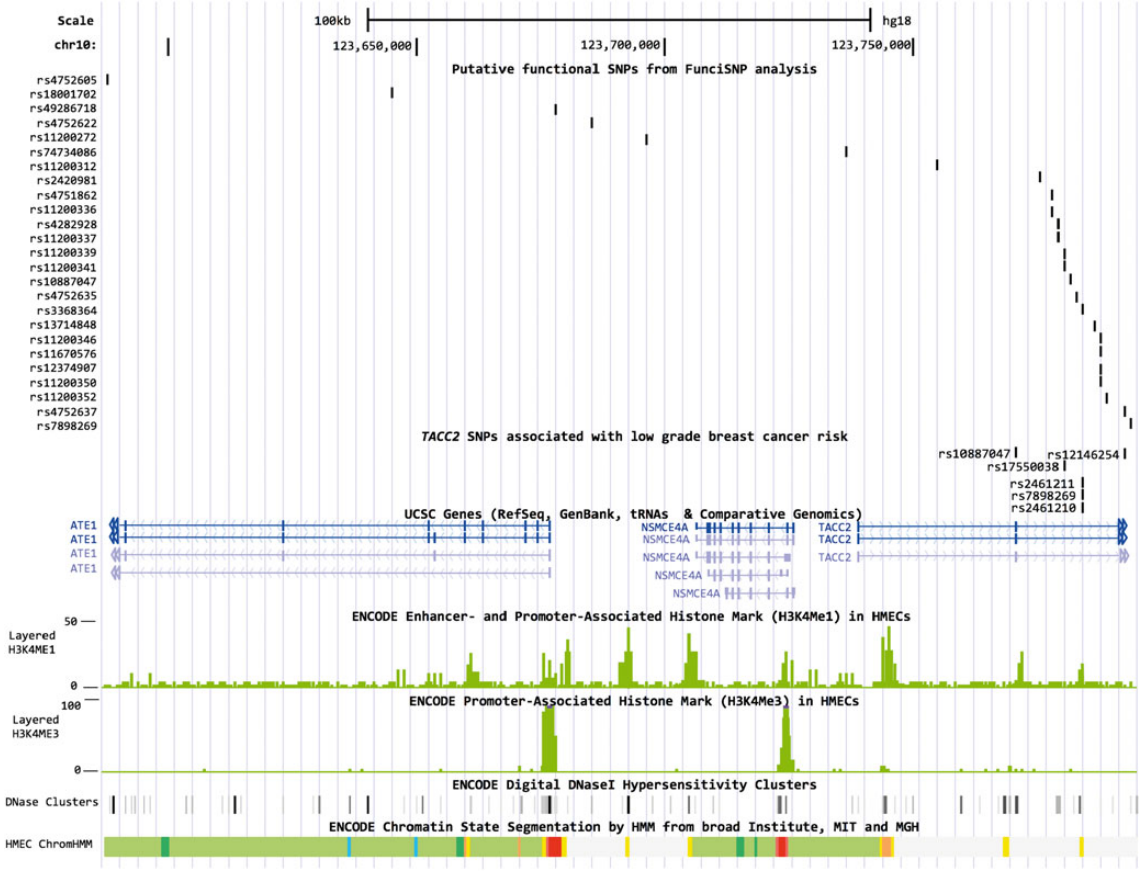



**Figure 1.** Overlap between putative functional SNPs and ENCODE tracks in HMECs. Figures were generated in the UCSC Genome Browser (http://genome.ucsc.edu, last accessed on 19 June 2014) using ENCODE and custom tracks. ChromHMM, Hidden Markov Model predicted chromatin state segmentation; bright red, active promoter; light red, weak promoter; purple, inactive promoter; orange, strong enhancer; yellow, weak enhancer; blue, insulator; dark green, transcriptional elongation; light green, weakly transcribed; dark gray, polycomb-repressed; light gray, repetitive/copy number variation.

and the limited power to detect single SNP associations for high-grade breast cancer, we evaluated whether variation in the 194 mitotic genes influenced high-grade breast cancer risk when analyzed as a pathway. A two-step gene set analysis (PC-GM) was conducted, in which each of the 194 mitotic genes were summarized by principal component analysis and then combined into a single test statistic to evaluate whether the gene set was associated with risk (23). Based on this method, the mitotic pathway was significantly associated with overall breast cancer risk ($P = 2.6 \times 10^{-3}$). This association was maintained even after excluding SNPs in the *TACC2*, *EIF3H* and *ITPR1* loci (filtered $P = 2.5 \times 10^{-3}$). In contrast to the findings with single SNPs, the pathway as a whole was associated with high-grade breast cancer ($P = 2.1 \times 10^{-3}$; filtered $P = 2.6 \times 10^{-3}$) rather than low-grade breast cancer risk ($P = 0.065$; filtered $P = 0.063$). This suggests that variation in mitotic genes is relevant to high-grade breast cancer risk; however these result are preliminary, and it is necessary to replicate this analysis in an independent population and to functionally validate the role of these genetic variants in high-grade breast cancer to confirm these findings.

## DISCUSSION

In this analysis of 194 genes involved in mitotic regulation, we have shown that SNPs in *TACC2*, *EIF3H* and *ITPR1* are associated with risk of low-grade but not high-grade breast cancer, with the greatest effects observed for ER-positive tumors. Several of the *TACC2* SNPs remained associated with low-grade breast cancer risk after adjustment for the nearby *FGFR2* breast cancer risk SNP rs2981579, suggesting that the *TACC2* locus is a new genome-wide significant genetic risk factor for low-grade breast cancer. The association of SNPs in *FGFR2* and *TACC2* with breast cancer suggests a complex relationship between SNPs and genes in this region of chromosome 10. Indeed, it is possible that the underlying functional effect captured by this new signal in the *TACC2* locus is related mechanistically to previously described associations in the *FGFR2* locus, in that variants in the *TACC2* locus may influence *TACC2* and/or long-range transcriptional regulation of *FGFR2*. Analyses of common variants in these loci using ENCODE and eQTL data identified several candidate functional SNPs, which will need to be explored in future *in vitro* and *in vivo* studies to elucidate the underlying biological mechanisms at this locus that influence risk of low-grade breast cancer.

While we generally observed greater effects for ER-positive low-grade tumors, we had limited power to detect significant associations with the modest number of low-grade, ER-negative breast cancers genotyped ($n = 1447$) given the relatively small effect sizes for the *TACC2*, *EIF3H* and

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*ITRP1* SNPs. Future studies by BCAC and other consortia that incorporate large numbers of ER-negative breast cancers with complete histologic grade data will be necessary to completely understand the relationship between these SNPs, grade and ER subtype. In contrast to single SNP effects, variation in the 194 mitotic genes was associated with high-grade breast cancer risk in a pathway-level analysis, although these findings require replication in an independent sample and functional validation. It is important to note that while the total sample size was large, the number of high-grade breast cancers was comparatively small and the statistical power to detect associations with SNPs with small effect sizes was limited. Additionally, due to the design of the iCOGS array, SNP coverage of the genes varied and some known mitotic genes were not represented at all. Nevertheless, we successfully identified biologically interesting genes that appear to influence breast tumor grade, and a series of candidate functional SNPs in these loci that warrant follow-up in future studies.

The *TACC2* gene is a member of the transforming acidic coiled-coil-containing protein family and is located on chromosome 10q26 (24). TACC proteins are an essential component of the centrosome–spindle apparatus during mitosis, and TACC2 is strongly concentrated at centrosomes throughout the cell cycle (25). Interestingly, mutants lacking the *Drosophila melanogaster* TACC gene, *d-tacc*, experience high rates of chromosomal segregation defects (26). In a study of fresh frozen primary human breast cancer tissues, TACC2 expression was increased in high-grade compared with low-grade tumors and in tumors from patients with poor clinical outcomes including metastasis, recurrence, and breast cancer related death, reflected by a shorter disease-free survival for patients with high TACC2 expression (24). However, multiple other studies suggest that TACC2 can be up- or down-regulated in different types of cancer even in the same tissue, including breast (27–29).

Less is known about the exact role of *EIF3H*, located on chromosome 8q23, in cell cycle regulation. The *EIF3H* gene encodes the H subunit of the eukaryotic translation initiation factor 3 (eIF-3) complex, which is required for several steps in the initiation of protein synthesis including mRNA recruitment and disassembly of ribosomal complexes (30). Translational control is a crucial component of cancer development and progression (31), and EIF3H in particular is frequently amplified in breast and prostate cancers (32). Overexpression of eIF3 h in prostate cancers is also associated with increased grade as measured by the Gleason score (33). Two short interfering RNA (siRNA) screens in HeLa cells have identified *EIF3H* as essential for cell division, the disruption of which leads to cell cycle arrest and altered ploidy phenotype (34,35).

In summary, we have reported on a large-scale analysis of the relationship between common variation in mitotic genes and breast cancer grade in a study of ~40 000 invasive breast cancer cases and study-matched controls with extensive histopathologic grade data. While the exact mechanism underlying the association between *TACC2* and *EIF3H* and breast cancer grade are unclear, these results warrant follow-up in functional studies and larger studies of histopathologic subtypes of breast cancer.

## MATERIALS AND METHODS

### iCOGS genotyping

Subjects included in this analysis were a subset of those genotyped on the iCOGS array from the BCAC (18). Women with invasive breast cancer and study-matched controls from 40 studies (Supplementary Material, Table S2) with self-reported European ancestry and >95% subject call rate for genotyping ($n = 39\,067$ cases; $n = 42\,106$ controls) were included. These 40 studies have been described previously (18). The design of the iCOGS array (211 155 SNPs), genotyping methods, and quality control have been previously described (18). Samples were genotyped as part of the Collaborative Oncological Gene-environment Study (COGS) project using the iCOGS array at four genotyping centers. Genotype calling and quality-control analyses were conducted by a single analysis center at the University of Cambridge (18).

### Gene and SNP selection

The iCOGS array included SNPs from 194 genes encoding proteins implicated in normal control of mitotic entry, spindle assembly checkpoint and cytokinesis (GO: http://www.geneontology.org; KEGG http://www.genome.jp/kegg/) (Supplementary Material, Table S1). All 2351 SNPs on the iCOGS array within each of the 194 genes and within a 50 kb window from the beginning and end of the longest transcript were selected. A total of 2156 SNPs had a call rate >95% and were included in the analysis.

### Pathology

The collection of pathology and tumor marker information for BCAC has been described previously (36). Briefly, studies provided information on ER status and grade of differentiation. The most common source of data for ER status was medical records, followed by inmunohistochemistry performed on tumor tissue microarrays or whole section tumor slides. ER-negative status was defined as < 10% of the tumor cells stained for a number of participating studies, where patients were recruited from Europe ($n = 30$), Australia ($n = 3$), Canada ($n = 2$) and the USA ($n = 5$) from 1972–2011 (median recruitment year = 2004). Histologic grade was reported using the Nottingham combined grading system. For the purpose of this analysis, Grades 1 and 2 were jointly considered 'low grade' while Grade 3 was considered 'high grade'.

### Statistical analyses

Single SNP analyses were conducted in PLINK (37), and polytomous logistic regression was implemented in R (http://cran.us.r-project.org/, last accessed on 19 June 2014) when comparing histopathologic subtypes to a common set of controls. SNP associations were tested in a log-additive model and were adjusted for study and European ancestry-specific principal components as described by Michailidou *et al.* (18). Consideration of age, assessed by both the exclusion of studies for which the age of controls was not known and the adjustment for age in 5-year categories and as a continuous covariate, made no substantial difference to the results.

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The two-step gene set pathway analysis (PC-GM) has been previously described (23). Briefly, we first performed principal component (PC) analysis for each of the 194 mitotic genes. The PCs that captured at least 80% of variation in each gene were used to assess the significance of the associations between each gene and breast cancer risk in a logistic regression model. Following determination of these gene-level associations for each of the 194 genes, the *P*-values were summarized using the gamma method (23) to obtain a pathway-level test statistic based on observed data. Empirical gene set association *P*-values and pathway-level test statistics were determined from 1000 permutations, where the response variable (case–control status) was permuted while keeping genotype and covariate data fixed. The final pathway *P*-value was determined as the proportion of permutations in which the empirical pathway-level test statistic was greater than the observed pathway-level test statistic.

### FunciSNP annotation

The FunciSNP package (38) was implemented in R using default parameters with a search window of $\pm$ 500 kb. Analyses were run separately for each of three index SNPs: rs17550038 (*TACC2*), rs799890 (*EIF3H*) and rs6762644 (*ITPR1*). The FunciSNP tool identified all SNPs from the 1000 genomes project (http://www.1000genomes.org/, last accessed on 19 June 2014) within 500 kb of the index SNP that overlapped with at least one biofeature. The biofeatures included in this analysis were (1) built-in consensus promoter regions, ENCODE DNaseI HS and CTCF sites from the getFSNPs function and (2) HS sites, FAIRE signals and histone modification ChIP-seq data (H3K4me1, me2, me3, H3K9Ac and H3K27Ac) downloaded as bed files from ENCODE Build 37 production data (http://genome.ucsc.edu/ENCODE/, last accessed on 19 June 2014) for HMEC normal mammary epithelial cells, and the MCF7 and T47D breast cancer cell lines when available (Supplementary Material, Table S12). Recognizing that observed SNP associations may capture functional SNPs even at relatively low levels of LD, we defined LD with the index SNP at $R^2 \geq 0.3$.

### Triple negative breast cancer expression quantitative trait loci (eQTL) analyses

Expression profiles were generated for 596 triple negative (TN) breast tumors (Supplementary Material, Table S13) using the Illumina Whole Genome cDNA-mediated Annealing, Selection, extension and Ligation (DASL) v4.0 assay. Study sites have been described previously (39,40). Whole formalin fixed paraffin embedded tumor sections were macrodissected for enrichment of tumor cells, guided by a pathologist-read hematoxylin and eosin-stained slide. RNA was extracted using the Roche High Pure RNA Isolation Kit (Indianapolis, USA). DASL expression profiling was performed by the Mayo Clinic Medical Genome Facility Gene Expression Core (Rochester, MN). After $\log_2$-transformation of raw intensity values, a per-sample quality (stress) measure was calculated (41). $\text{Log}_2$-transformed intensity values were median-quantile normalized. Probes with a *P*-value of detection $>0.05$ in all samples were excluded ($n = 713$) yielding 28 664 high-quality probes. Samples were median-centered by 96-well plate to correct for batch effects. Of the 596 TN tumors with high-quality expression data, germline genotype data from the Illumina 660-Quad, HumanHap 500k DUO, CNV370DUO, or iCOGS custom genotyping array (18,40), were available for 516 of the same individuals. *cis*-eQTLs for *TACC2* were defined as associations between ILMN_2315780, ILMN_1686442, ILMN_2363165 probe expression and SNPs within 1 MB of these probes in a robust linear regression model. An FDR was generated using 100 permutations of the genome-wide analysis (*cis* associations between 8 969 066 SNPs and 28 504 probes), and *cis*-eQTLs were excluded at a 10% FDR threshold (equivalent to $P \leq 5.0 \times 10^{-5}$).

## SUPPLEMENTARY MATERIAL

Supplementary Material is available at *HMG* online.

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