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14. ABSTRACT The AURORA-A/BTAK/STK15 gene encodes a centrosome-associated kinase that causes centrosome amplification, failure of cytokinesis, and aneuploidy when amplified and/or overexpressed in breast tumors. A number of gene association studies using matching breast cancer cases and controls have shown that the F31I polymorphism in STK15 increases risk of breast. We hypothesized that the F31I polymorphism is associated with increased risk of breast cancer in BRCA1 and BRCA2 mutation carriers. Using over 7,000 carriers of BRCA1 and BRCA2 deleterious mutations we showed that F31I has no influence on breast cancer risk. In parallel, we completed an association study of 2400 polymorphisms in other cell division regulatory genes in 800 breast cancer cases and 800 controls collected at the Mayo Clinic. A total of 52 of these polymorphisms along with 332 other polymorphisms displaying associations with breast cancer risk were evaluated for associations with breast cancer risk in approximately 5,400 BRCA1 and BRCA2 mutation carriers. Several polymorphisms displaying significant associations ($p < 10^{-4}$) with risk of breast cancer in BRCA2 mutation carriers were observed.					
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Introduction

Studies have shown that the age of onset of breast cancers in BRCA2 mutation carriers is significantly later than for BRCA1 mutation carriers (Fodor et al., 1998). However, while the age specific penetrance may differ the cumulative lifetime risk appears to be similar. In addition, there is substantial variation in the age of onset and the site of cancer amongst BRCA1 and BRCA2 mutation carriers, even in the same family (Goldgar et al., 1994). This strongly suggests that genetic and/or environmental modifiers of breast cancer risk in BRCA1/2 mutation carriers exist (Rebbeck 2002). Certainly, some component of this effect is due to differential risks associated with different mutations in the genes (Gayther et al. 1995, 1997). However, there are likely to be multiple low-penetrance genes that also increase the susceptibility to breast cancer. Mutated forms of these genes probably confer only a small to moderate increase in the lifetime breast cancer risk, but because variations in these low penetrance genes are present in a large number of people, the population risk for breast cancer caused by these genes could be substantial (Rebbeck 1999). These observations raise the question of whether genes associated with other functions of BRCA1 and BRCA2 might also be modifiers of breast cancer risk in carriers. Both BRCA1 and BRCA2 proteins are components of the centrosome, which mediates chromosomal division. Both proteins interact with Aurora-A a centrosome-associated kinase that causes centrosome amplification, failure of cytokinesis, and aneuploidy when amplified and/or overexpressed in breast tumors. The F31I polymorphism in STK15 was originally identified as a candidate lung tumor risk modifier locus in a mouse model (Ewart-Toland et al., 2003). F31I altered the activity of the Aurora box-1 of the STK15 protein, resulting in disruption of p53 binding and a decreased rate of degradation of STK15. The stabilized STK15 was associated with centrosome amplification and failure of cytokinesis, increased chromosomal instability and aneuploidy, suggesting a direct effect on the F31I variant on promotion of tumor formation (Ewart-Toland et al., 2003). In a study of incident breast cancer cases (n = 941) and age-matched population controls (n=830), Egan et al. (Egan et al., 2004) found that the breast cancer risk for Ile/Ile homozygotes were at increased risk for breast cancer (OR = 1.54; 95% CI: 0.96-2.47), although this finding was not significant. Sun et al. observed that the Ile encoding allele is the common allele in the Chinese population whereas the Phe encoding allele is more common in Caucasian populations (Sun et al., 2004). In addition, an association between Ile/Ile homozygotes and ER negative breast carcinomas (OR = 2.56; 95% CI: 1.24-5.26) was detected. Lo et al. reported a significant association between *AURKA* haplotypes and breast cancer risk (Lo et al., 2005). Ewart-Toland et al. also found an increase in cancer risk for the *Ile/Ile* homozygotes (OR = 1.35, 95% CI: 1.12–1.64; $p = 0.002$) in a meta-analysis of data from four case-control breast cancer populations (Ewart-Toland et al., 2005). Based on these data, we hypothesized that the F31I polymorphism is associated with increased risk of breast cancer in BRCA1 and BRCA2 mutation carriers.

Since then additional studies of STK15 F31I have been completed. Post-menopausal women homozygous for the F31I and I57V alleles of *AURKA* in a case-control study nested within the Nurses' Health Study prospective cohort had an increased risk of invasive breast cancer (OR 1.63, 95% CI 1.08–2.45) (Cox et al., 2006). In contrast, Dai et al. did not observe a significant association with breast cancer risk for Ile/Ile homozygotes (OR = 1.2; 95% CI, 0.9-1.6) in a population based case-control series of Han Chinese (Dai et al., 2004), and Fletcher et al. (Fletcher et al., 2006) found no association between Ile/Ile homozygotes and risk of bilateral breast cancer (OR = 0.63, 95% CI 0.34-1.13).

Body

Aim 1. To validate the association between Val57Ile in STK15 and increased risk of breast cancer in a large cohort of BRCA1/2 mutation carriers.

Task 1. In an effort to verify the association of F31I with breast cancer risk in *BRCA1* and *BRCA2* carriers we established a large consortium of investigators from the U.S.A. and Europe. A total of 4935 female *BRCA1*, 2241 female *BRCA2* deleterious mutation carriers and 11 individuals carrying both *BRCA1* and *BRCA2* mutations from 16 participating groups were included in this study. Of these 7187 mutation carriers, 3884 had a diagnosis of breast cancer at the end of follow up and 3303 were censored as unaffected at a mean age of 43.4 years.

Task 2. To avoid overlap between studies we compared carriers by country of origin, year of birth, mutation and reported ages. The frequency of the recessive Ile/Ile encoding genotype in the 16 groups varied between 3% and 8%, which is similar to estimates from other populations. There was no difference in the frequency of the Ile/Ile recessive genotype across genotyping platforms ($p=0.33$). Similarly, the study sites with the highest Ile/Ile frequencies did not have ethnic mixtures significantly different to the other study sites. The F31I polymorphism did not deviate significantly from Hardy-Weinberg equilibrium ($p=0.07$) among all 7187 affected and unaffected carriers.

The estimated risk of breast cancer associated with the recessive genotype for F31I in *BRCA1* and *BRCA2* carriers was calculated using a weighted Cox proportional hazards model. While there was a suggestion of a protective effect (HR = 0.91; 95%CI 0.77-1.06) overall, the result was not statistically significant. Similarly, no association with risk was observed for individual participating centers, other than for two centers that contributed small numbers of carriers to the study. A test for heterogeneity across study site was not significant ($p=0.06$). We also evaluated whether the Ile/Ile genotype was associated with risk of breast cancer in *BRCA1* carriers alone or *BRCA2* carriers alone. No significant association with risk was detected for either *BRCA1* (HR = 0.90; 95%CI 0.75-1.08) or *BRCA2* carriers (HR = 0.93; 95%CI 0.67-1.29) (Couch et al., 2007). As other studies have reported an association between the recessive Ile/Ile encoding genotype and postmenopausal status in non-carriers (Egan et al., 2003; Cox et al., 2006), we considered the influence of menopausal status of carriers on breast cancer risk. At the end of follow-up, 4201 carriers were pre-menopausal and 2986 were post-menopausal. No significant association with risk was detected (Couch et al., 2007). Because prophylactic oophorectomy substantially reduces the risk of breast cancer in *BRCA1* and *BRCA2* mutation carriers (Rebbeck et al., 2002), we also evaluated the influence of prophylactic oophorectomy status. A total of 707 individuals reported undergoing prophylactic oophorectomy, 4298 reported no history of oophorectomy, while 2182 (30%) provided no data at last follow up. Associations with breast cancer risk by category of prophylactic oophorectomy did not differ markedly from the overall results. Secondary analyses using a two degree-of-freedom general model also failed to detect a significant association for either a single copy ($p=0.97$) or two copies ($p=0.24$) of the F31I polymorphism compared to no copies (Couch et al., 2007).

In an effort to account for possible survival bias and the inclusion of prevalent cases in the collection of *BRCA1* and *BRCA2* carriers, we repeated our analysis after excluding cases diagnosed more than three years prior to the date of ascertainment. For this analysis we excluded records where an age at interview was not provided. Overall, the mean difference between age of diagnosis and age at interview for the 3422 cases with available data was 8.7 years. Of these 1,322 (38.6%) cases had been diagnosed less than three years prior to the date of ascertainment. When excluding prevalent cases no association between the Ile/Ile genotype and breast cancer risk was observed, and the risk estimates were similar to those obtained when using both prevalent and incident cases (Couch et al., 2007). Thus, STK15 F31I does not appear to be associated with breast cancer risk modification in *BRCA1* or *BRCA2* mutation carriers.

In parallel, we worked with a separate consortium of investigators to assess the influence of STK15 F31I on breast cancer risk in sporadic breast cancer cases. This consortium, named Breast Cancer Association Consortium (BCAC) is comprised of 18 groups from the USA and Europe who are pooling genotyping data on various polymorphisms in order to generate sufficient sample sizes for clarifying genetic risks associated with these polymorphisms. We genotyped the F31I polymorphism on 724 breast cancer cases and 767 controls. Cases were collected through the Mayo Clinic oncology clinic from 2002 to 2005 and were restricted to Caucasians from a 6-state region surrounding the Mayo Clinic. Controls were recruited from Internal Medicine Clinics at Mayo Clinic, had no previous history of breast cancer and were matched to cases by age and residence. In the Mayo Clinic case-control study the F31I polymorphism was not associated with altered risk of breast cancer (OR = 1.00 (0.80-1.24)) for heterozygotes and (OR = 0.95 (0.59-1.52)) for homozygotes. Similarly when pooled with data from five other centers no association with risk was observed (OR = 0.98 (0.92-1.04)) for homozygotes. Stratifying by age in order to consider postmenopausal women only also failed to identify any association with risk. This report completes all effort associated with Tasks 1-2.

Task 3 and 4. In Aim #1 we also stated that we would evaluate single nucleotide polymorphisms (SNPs) in other mitotic regulators for effects on breast cancer risk in *BRCA1* and *BRCA2* mutation carriers. We have now completed a large-scale genotyping study of 798 breast cancer cases and 840 controls from the Mayo Clinic for polymorphisms in genes encoding regulators of mitosis. The Mayo Clinic Breast Cancer study is an on-going clinic-based case-control study initiated in February 2001 at Mayo Clinic, Rochester, MN. Details of the study design and data collection procedures have been previously described (14) wrong reference. Briefly, cases were women over age 20 years with histologically confirmed primary invasive breast carcinoma who were enrolled within six months of date of diagnosis. Controls without prior history of cancer (other than non-melanoma skin cancer) were matched on age (± 5 years) and region of residence to cases. Controls were selected from the outpatient clinic in the Department of Internal Medicine at Mayo Clinic where they were seen for general medical examinations. Written informed consent was obtained from all participants. Case participation was 69% and control participation was 71%. The present analysis genotyped Caucasian women (99% of study participants) enrolled through June 30, 2005, representing 798 cases and 843 controls. Both the cases and controls completed a self-administered risk factor questionnaire. Cases and controls provided blood samples from which genomic DNA was isolated using standard protocols. The samples were bar coded to ensure accurate and reliable sample processing and storage. A total of 2,400 SNPs from the 273 genes were selected and genotyped on the cases and controls along with 5% duplicate samples. Genotyping was highly successful. Only 165 SNPs failed genotyping. Of the remainder, call rates for genotypes were greater than 98%. Duplicates demonstrated 100% concordance. Only two SNPs were not in Hardy Weinberg Equilibrium (HWE) ($p < 0.05$).

Individual SNP associations for breast cancer risk were assessed using unconditional logistic regression to estimate ORs and 95% CIs. Primary tests for associations were carried out assuming an ordinal (log-additive or additive) genotypic relationship using simple tests for trend within the logistic and linear regression models. All analyses were adjusted for the design variables of age and region of residence. We also examined the influence of demographic or clinical variables and excluded those variables that were not statistically significant at $p > 0.10$ using a backward elimination selection approach, performed separately for risk and density analyses. A total of 144 SNPs displayed significant association with breast cancer risk ($p < 0.05$). Thus, several SNPs in regulators of cell division may influence the risk of breast cancer in the population.

We subsequently proposed to extend these findings into the *BRCA1* and *BRCA2* carrier population. Specifically, we initiated a study aimed at evaluating the 144 SNPs from genes involved in regulation of cell division as modifiers of breast cancer risk in mutation carriers. We selected the Illumina 384-SNP goldengate array as the most cost-effective, high-quality genotyping platform for this study. This system is available in the genotyping core of the Mayo Clinic. To make full use of the 384 SNP array we selected the 52 SNPs ($p < 0.01$) and also selected 332 SNPs from genes that commonly displayed associations with breast cancer risk in two breast cancer genome wide association studies conducted by Douglas Easton from Cambridge University (Easton et al., 2007) and from David Hunter from the Nurses Health Study representing the CGEMS group at NCI (Hunter et al., 2007). Through our collaboration with Dr. Easton, we had access to genotyping data, odds ratios and p-values for all 12,026 SNPs that were evaluated in stage 2 of the genome wide study (Easton et al., 2007). In terms of CGEMS, Dr. Hunter provided the top 100 SNPs after the completion of CGEMS Stage 2. The 100 CGEMS SNPs, the cell division SNPs and 234 SNPs from Dr. Easton were combined on a 384-SNP goldengate array (Illumina Inc.). A total of 6048 of these arrays were used to genotype 5520 DNA samples from *BRCA1* and *BRCA2* carriers, 252 controls, and 276 duplicates in the Genotype Shared Resource at Mayo Clinic. These DNA samples were provided by nine collaborating groups. Epidemiological risk factor data matching all of these specimens were obtained through the CIMBA consortium database (Couch et al., 2007; Chenevix-Trench et al., 2007). Quality control of genotype data resulted in exclusion of 23 SNPs leaving a total of 361 for analyses. In addition, 5461 of the 5520 samples remained after exclusion of samples with low call rates or for significant differences from Hardy-Weinberg equilibrium ($p < 0.0001$).

In the primary analysis, Hazard Ratios (HR) and 95% CIs were estimated using weighted Cox proportional hazards regression models. Each subject was followed from birth to the earliest of breast cancer, mastectomy, ovarian cancer, last follow-up, or age 80. Weights were calculated for each individual based upon mutation status as well as the affected/unaffected status and age at event/censoring. Analyses were stratified by

categorized year of birth (based on quartiles of unaffected), ethnicity, country of residence, study site, and mutation status. Clustering by family ID was performed by robust variance estimation. Each of the 361 SNPs was examined assuming a log-additive (trend or ordinal) relationship between the number of minor alleles carried by each individual. Three SNPs exhibited a strong association with breast cancer risk in *BRCA2* carriers ($p < 0.001$) and another nine exhibited moderate significance ($p < 0.01$). In particular rs9393597 in an undefined locus increased breast cancer risk (HR, 1.55; 95%CI: 1.25-1.92; $p = 6.0 \times 10^{-5}$). Likewise, two SNPs displayed strongly significant ($p < 0.001$) associations with breast cancer in *BRCA1* mutations carriers and another six showed moderate significance ($p < 0.01$). In particular rs6138178 from SNRPB reduced the risk of breast cancer in *BRCA1* carriers (HR, 0.78; 95%CI: 0.69-0.90; $p = 0.0004$). Adjusting for survival bias by restricting to carriers clinically diagnosed with disease within five years of genetic diagnosis did not influence the significance of these associations. Similarly adjusted for prophylactic oophorectomy as a time dependent variable had no effect. At the conclusion of the study we have identified five strong candidate genetic modifiers of breast cancer risk in *BRCA1* and *BRCA2* mutations carriers. These variants will be further investigated in other populations in studies that are outside the scope of this grant.

Aim 2. To demonstrate that Val57Ile alters STK15 function and co-operates with *BRCA1/2* mutations to disrupt mitotic regulation.

Task 5 and 6. When we began this study, the F31I variant had already been shown to alter the activity of the Aurora box-1 of STK15 protein, resulting in disruption of p53 binding and a decreased rate of degradation of STK15 (Ewart-Toland et al., 2003). It had also been shown by others that stabilized STK15 was associated with centrosome amplification and failure of cytokinesis, increased chromosomal instability and aneuploidy, suggesting a direct effect of the F31I variant on promotion of tumor formation (Ewart-Toland et al., 2003). As a result, Tasks 5 and 6 were deemed to be complete. Our subsequent finding that F31I does not influence breast cancer risk in *BRCA1* and *BRCA2* carriers suggests that these effects of STK15 stability make no contribution to cancer risk.

Aim 3. To establish the involvement of STK15 in breast tumor formation using Val57 and Ile57-STK15 transgenic mice and to evaluate synergism with *BRCA1/2* by intercrossing with conditional *brca1* and *brca2* mutant mouse models.

Tasks 7-9. As noted above, neither STK15 F31I or V57I are associated with increased risk of breast cancer. On the basis of this finding we felt that it was inappropriate to continue with the proposed generation of transgenic animals expressing these mutant forms of STK15 in order to assess their influence on breast cancer development *in vivo*. Instead, we focused our efforts on Task 3 and 4 in an effort to identify variants in other mitotic regulators that modify the risk of breast cancer in *BRCA1* and *BRCA2* carriers.

Key Research Accomplishments

- The F31I and V57I polymorphisms in STK15 are not associated with modification of breast cancer risk in *BRCA1* and *BRCA2* carriers.
- The F31I polymorphism in STK15 is not associated with breast cancer risk in a series of case-control studies.
- Common genetic variants in genes encoding mitotic regulators are associated with altered risk of breast cancer in a breast cancer case-control study.
- Common genetic variants in genes encoding mitotic regulators are associated with altered risk of breast cancer in *BRCA1* and *BRCA2* mutation carriers.

Reportable Outcomes

1. The Breast Cancer Association Consortium. Commonly studied single nucleotide polymorphisms and breast cancer: results from the Breast Cancer Association Consortium. JNCI. 98:1382-1396, 2006.
2. Chenevix-Trench G, Milne RL, Antoniou AC, **Couch FJ**, Easton DF, Goldgar DE; CIMBA. An international initiative to identify genetic modifiers of cancer risk in *BRCA1* and *BRCA2* mutation carriers:

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Conclusions

We have used very large datasets to demonstrate that the F31I polymorphism in STK15 does not increase the risk of breast cancer in carriers of *BRCA1* and *BRCA2* mutations. A similar lack of effect was seen in another very large pooled dataset from sporadic breast cancer case-control studies. However, it is likely that polymorphisms in other mitotic regulators alter breast cancer risk in sporadic and familial breast cancer patients. We have evaluated a number of such variants in a breast cancer case-control study and identified a small number of variants in mitotic regulators that may influence risk of breast cancer. Similarly, by gathering a large set of DNA samples from *BRCA1* and *BRCA2* mutation carriers we have shown that variants in mitotic regulators modify the risk of breast cancer in *BRCA1* and *BRCA2* mutation carriers.

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