CORRESPONDENCE

Re: Association of a Common Variant of the CASP8 Gene With Reduced Risk of Breast Cancer

Recently, MacPherson et al. *(1)* reported an association between the common caspase-8 (CASP8) gene variant D302H and reduced breast cancer risk. They studied two independent U.K. cohorts from Sheffield and East Anglia and observed statistically significant lower frequencies of the CASP8 DH and HH genotypes in both case patient populations compared with the respective control subjects, considering D302H as causative variant in a dose-dependent manner.

We investigated the influence of the D302H variant on familial breast cancer risk using a German study cohort. Detailed information regarding the design and methods of this case–control study has been described elsewhere *(2)*. In brief, we recruited a study population of 355 breast cancer case patients and 1098 control individuals. The case patients were unrelated German women (mean age = 44.7 years, range = 21–80 years) without BRCA1/2 mutations. The control subjects were healthy, unrelated female blood donors (mean age = 41.0 years, range = 18–68 years) with the same ethnic background as the breast cancer case patients. The study was approved by the Ethics Committee of the University of Heidelberg, Germany.

Genotype-specific odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using unconditional logistic regression and adjusted for age. A one-sided Cochran–Armitage trend test was used to assess the change of breast cancer risk with the number of carried alleles. The computations were performed using SAS, version 8.2.

We observed lower frequencies of the DH and HH CASP8 D302H genotypes in case patients compared with control subjects (21.4% versus 23.7% and 1.1% versus 2.1%, respectively; Table 1). Genotype frequencies in case patients and in control subjects were consistent with Hardy–Weinberg equilibrium. The adjusted odds ratios were 0.87 (95% CI = 0.65 to 1.17; $P = .35$) for the DH heterozygotes versus the DD homozygotes and 0.49 (95% CI = 0.17 to 1.44; $P = .20$) for the HH homozygotes versus the DD homozygotes. The Cochran–Armitage test for trend also suggested a dose-dependent association between allele type and breast cancer risk ($P_{trend} = .077$). These data are widely comparable to those of the Sheffield and East Anglia studies *(1)*, although our results did not reach statistical significance.

Table 1. Genotype frequencies of CASP8 D302H in unrelated German BRCA1/2 mutation negative breast cancer patients and healthy, unrelated female control subjects

CASP D302H genotype	Case patients N (%)	Control subjects N (%)
DD	275 (77.5)	815 (74.2)
DH	76 (21.4)	260 (23.7)
HH	4 (1.1)	23 (2.1)
Total	355 (100)	1098 (100)

Multiple reasons exist that might account for the slight differences found between the study by MacPherson et al. and our study. The sample size of our study was smaller than that of the MacPherson et al. study. We had 90% power to detect an odds ratio of 0.54 or less *(3)*. In contrast to standard case–control association studies, this study comprised case patients selected for family history of breast cancer *(4)*, thus likely improving the above-mentioned power *(5)*. In addition, unrecognized environmental factors may exist that modify the genetic association of caspase-8 and breast cancer risk, and they may vary between populations.

In conclusion, our case–control study supports results recently published by the Journal *(1)*. Our data point to a dose-dependent association between carrying the CASP8 D302H allele and a reduced risk of breast cancer, although it lacks statistical significance.

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Notes

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RESPONSE

We read with interest the letter from Frank et al., which describes an analysis of the caspase-8 (CASP8) D302H gene variant in 355 familial breast cancer case patients and 1098 control subjects from Germany. Their results, although not statistically significant, suggest a dose-dependent association of the H allele with a reduced risk of breast cancer. This is consistent with the results we obtained from Sheffield and East Anglian study samples in the United Kingdom *(1)*.

To evaluate the overall evidence for the CASP8 D302H association, we used logistic regression adjusting for study sample. The resulting odds ratios were 0.84 (95% confidence interval [CI] = 0.75 to 0.94, $P = .003$), for the DH heterozygote and 0.58 (95% CI = 0.39 to 0.84, $P = .004$) for the HH homozygote genotypes. The odds ratios from the German study are consistent with the original estimates, and there was no evidence of heterogeneity between study samples (Mantel–Haenszel test for homogeneity of odds ratios, $P = .75$ and $P = .98$, respectively). The point estimate of the homozygote odds ratio is slightly (but not statistically significantly) lower for the German study than for the Sheffield and East Anglian studies (0.49 versus 0.58). This difference may reflect the fact that associations between genetic traits and disease risk are more extreme in those with a family history of the disease *(2)*—the German study population comprised women with a family history of breast cancer, in contrast to the women in the U.K. study population, who were not selected for family history.

The combined data are consistent with a multiplicative model for the effect of the H allele, with the overall evidence being very strongly statistically significant ($P_{trend} = 7.4 \times 10^{-5}$). In our original report *(1)*, we discussed the false-positive report probability (FPRP) of our observations as described by Wacholder et al. *(3)*. Given that D302H is a nonsynonymous single nucleotide polymorphism, we assumed a prior probability of .001 for its association with breast cancer *(3)*. Using this assumption, and after adding the data from Frank et al., the FPRP is reduced from .27 to .10. Thus, the available data so far yield strong evidence that the D302H single nucleotide polymorphism is associated with breast cancer susceptibility. However, to thoroughly evaluate the effect of this variant, it should be investigated in other large case–control data sets around the world. Functional studies are also required to determine whether the CASP8 D302H variant has a direct role in the apoptotic response and tumorigenesis.

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NOTES

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