are predicted to affect amino-acid residues conserved in at least three of the five RAD51 paralogs, and the effects of the variants have been characterized by functional approaches. It is, of course, easier to classify a truncating mutation as pathogenic. We note that Clague et al.[5] recently reported a missense variant in RAD51C, which seems to compromise the interaction between the RAD51C protein and its interacting partners RAD51B and XRCC3.

The statistical arguments presented[1] might be valid only for a subgroup of families or populations. Here we agree with Rahman and colleagues that RAD51C, as well as RAD51D, have to be validated in larger cohorts to generate reasonable clinical proposals or conclusions. Rahman et al., as in our study[3], found the p.Gly264Ser alteration in RAD51C (encoded by a c.790G>A mutation) overrepresented in families with breast cancer and ovarian cancer compared to controls. However, there was also a statistically significant overrepresentation of this variant in individuals with ovarian cancer from Australia[6]. Although screening of samples of larger size is required, these observations are consistent with population-specific effects.

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Meindl et al. reply:
Loveday et al.[1] claim, as do Pelttari et al.[2], that RAD51C is a predisposing gene for ovarian cancer. However, their screening results do not falsify or disprove our assertion that RAD51C is a predisposing gene for breast cancer and ovarian cancer[3]. Indeed, we found that RAD51C mutations segregated with breast cancer in two out of the seven families with breast cancer and ovarian cancer we analyzed[3]. Furthermore, Vuorela et al.[4] found an in-frame deletion in one individual with breast cancer from a family with four cases of breast cancer and four cases of ovarian cancer. However, they were unable to establish segregation in this pedigree.

The skepticism of Loveday et al. toward a pathogenic role for missense mutations is unwarranted. In general, these authors refuse to accept the causality of missense mutations in RAD51C in breast cancer. In fact, most of the variants discussed here

1. Loveday, C. et al. Nat. Genet. 44, 475–476 (2012).
2. Pelttari, L.M. et al. Hum. Mol. Genet. 20, 3278–3288 (2011).
3. Meindl, A. et al. Nat. Genet. 42, 410–414 (2010).
4. Vuorela, M. et al. Breast Cancer Res. Treat. 130, 1003–1010 (2011).
5. Clague, J. et al. PLoS ONE 6, e25632 (2011).
6. Thompson, E.R. et al. Hum. Mutat. 33, 95–99 (2012).