

Germline RAD51C mutations confer susceptibility to ovarian cancer

Alfons Meindl, Katharina Eirich, Stefanie Engert, Alexandra Becker, Daniela Endt, Nina Ditsch, Rita K Schmutzler, Detlev Schindler

Angaben zur Veröffentlichung / Publication details:

Meindl, Alfons, Katharina Eirich, Stefanie Engert, Alexandra Becker, Daniela Endt, Nina Ditsch, Rita K Schmutzler, and Detlev Schindler. 2012. "Germline RAD51C mutations confer susceptibility to ovarian cancer." *Nature Genetics* 44 (5): 476. <https://doi.org/10.1038/ng.2223>.

Nutzungsbedingungen / Terms of use:

licgercopyright

Dieses Dokument wird unter folgenden Bedingungen zur Verfügung gestellt: / This document is made available under the following conditions:

Deutsches Urheberrecht

Weitere Informationen finden Sie unter: / For more information see:

<https://www.uni-augsburg.de/de/organisation/bibliothek/publizieren-zitieren-archivieren/publizieren>



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 presented¹ 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 study³, 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 Australia⁶. Although screening of samples of larger size is required, these observations are consistent with population-specific effects.

AUTHOR CONTRIBUTIONS

A.M. wrote the paper and designed the concept. K.E., S.E., A.B., D.E. and N.D. provided experimental or clinical data. R.K.S. designed the concept and collected clinical data. D.S. supervised the experiments.

ACKNOWLEDGMENTS

This work was supported by the German Cancer Aid (Deutsche Krebshilfe) grant 107352.

COMPETING FINANCIAL INTERESTS

The authors declare competing financial interests: details accompany the full-text HTML version of the paper at <http://www.nature.com/naturegenetics/>.

*Alfons Meindl*¹, *Katharina Eirich*², *Stefanie Engert*¹, *Alexandra Becker*³, *Daniela Endt*², *Nina Ditsch*⁴, *Rita K Schmutzler*³ & *Detlev Schindler*²

¹Clinic for Gynecology and Obstetrics, Technische Universität München, Munich, Germany. ²Institute of Human Genetics, Wuerzburg, Germany. ³Center for Familial Breast and Ovarian Cancer, University of Cologne, Cologne, Germany. ⁴Department of Obstetrics and Gynecology, Ludwig Maximilians University, Munich, Germany.
e-mail: alfons.meindl@lrz.tu-muenchen.de

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 cancer³. Indeed, we found that *RAD51C* mutations segregated with breast cancer in two out of the seven families with breast cancer and ovarian cancer we analyzed³. 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).