Reviewer's report

Title: Constitutional CHEK2 Mutations are Infrequent in Early-Onset and Familial Breast/Ovarian Cancer Patients from Pakistan

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Reviewer: Thilo Dork

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Rashid and colleagues report on an extensive DHPLC scanning of the whole CHEK2 coding sequence in a combined series of 145 familial breast or ovarian cancer patients from Pakistan. Although BRCA1 and BRCA2 mutations had already been excluded, there was an exceptionally early median age at onset in this patient group. Apart from known polymorphisms, two unclassified CHEK2 missense mutations, p.P92R and p.R406C, were identified in single patients.

The novel Pro92Arg substitution, which flanks the FHA domain, was predicted to be potentially damaging in some but not all in silico tools and only partially segregated with breast cancer in this family, thus its role remains unclear. The Arg406Cys change, which resides in the kinase domain, was seen in a patient with serous ovarian cancer but is a previously reported breast-cancer associated variant, thus the presented data contribute to its characterisation as a potentially harmful substitution. A subsequent screen in additional patients and controls did not reveal further carriers.

Overall, this study identifies a novel missense mutation and helps to better define the CHEK2 mutational distribution in a hitherto underdescribed population. The manuscript is well written and should find the interest of those working in the field of breast cancer and CHEK2.

Minor essential revisions:

1. The index cases included 111 female breast cancer patients, 11 male breast cancer patients, and 27 ovarian cancer patients. As this does not sum up to 145, some 6 index patients appear to have both breast and ovarian cancer but this should be specified and is not immediately obvious from Table 1.

2. It might be appropriate to provide a figure for the novel p.P92R mutation as a supplemental file.

3. It is stated for p.P92R that “the mutation was predicted to be likely pathogenic in two of the four tools”, this result should be specified.

4. It is discussed that “CHEK2-linked breast tumors (c.1100delC, c.IVS2+1G>A, del5395) were predominantly ER-positive and of non-lobular type”. But the authors report missense variants. While the ER-positive phenotype is clear, the predominance of non-lobular breast cancer is under debate for such a mutation.
type (e.g. Huzarski 2005, Domagala 2012) and the authors may argue more cautiously in this regard

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests