Reviewer’s report

Title: ATM variants and cancer risk in breast cancer patients from Southern Finland

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Reviewer: Thilo Doerk

Reviewer’s report:

General

Tomnisika and co-workers investigated the role of ATM gene mutations in Southern Finnish patients with familial breast cancer. They utilized dHPLC to screen the entire coding region of the ATM gene in 47 familial breast cancer patients. Three rare missense alterations were each found in only one patient of over 250 familial patients studied and not among controls. The ivs10-6T>G splicing variant was found in only one patient and no control. Two common ATM variants, 5557G>A and ivs38-8T>C, previously proposed to associate with bilateral breast cancer, were not differentially distributed among 786 familial and 884 unselected breast cancer cases and 708 healthy controls. The authors conclude that there is a very minor effect, if any, of ATM gene variants on familial breast cancer in Southern Finland.

Although several groups have already attempted to elucidate the association of ATM gene mutations with breast cancer, the present manuscript adds some valuable information to this controversially debated issue. The principal limitation here is that the variants found are too rare to be evaluated easily in case-control studies. Another limitation of the present study is that the number of fully screened patients (n=47) is relatively low. Although the study found no evidence for an increased risk, the data probably are still consistent with the epidemiological observations cited in references 5-10. Furthermore, the case series here seems to be biased towards a strong family history of breast cancer (3 or more first and second-degree relatives affected) and towards a family history of leukemia or lymphoma (13/47 families). These are not necessarily features that have been observed for obligate heterozygotes within ataxia-telangiectasia families. On these grounds, any conclusions drawn from the present study should be made with caution.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. The manuscript should include a critical discussion of the study power to detect low, moderate or high risks in the respective sample sizes given the observed allele frequencies and/or the expected AT heterozygote frequency in the general population. One could refer to a previous article by Haber’s group (FitzGerald et al. 1997) and the discussion of these data (Bishop and Hopper 1997). Power estimates might also be informative for the readers in regard of any association of ivs38-8T>C with familial or bilateral disease.

2. The authors report that none of the identified variants segregated with cancer in these families (p.10) but results are not provided. As far as segregation data can contribute to the characterisation of the identified variants, they need to be discussed in more detail, at least the number of diseased carriers and non-carriers per variant should be mentioned.

3. The second most common ATM variant, 735C>T (5/47 families), was not investigated further in the case and control series. This is not clear to me because a previous study from some of the authors had reported this synonymous variant as a splicing mutation that leads to exon 9 skipping in AT patients (Laake et al. 2000. Table 5). If true, the present study appears incomplete, and the authors should either include 735C>T into their screening or comment on whether more recent evidence or exclusion criteria argue against screening for this variant.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct):

Tables 1 and 2 seem to be partly redundant and should be combined.

**What next?:** Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No