Reviewer’s report

Title: WRN polymorphisms affect expression levels of plasminogen activator inhibitor type 1 in cultured fibroblasts

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Reviewer: Junko Oshima

Reviewer’s report:

General

The authors describe the increased expression of PAI-1 in plasma and fibroblasts with WRN polymorphisms associated with increased risk of cardiovascular disorders (CVD). This suggests that increased risk of CVD associated with WRN polymorphisms may be mediated by the PAI-1 expression level.

There have been a number of association studies between WRN polymorphisms and CVD. To my knowledge, this is the first report describing a mechanistic link between them. It is a unique study in the sense that gene product outside of the DNA repair system was investigated as a downstream effector of WRN protein.

Though the sample numbers are not extremely large for a population study, results are convincing enough to conclude that WRN polymorphism modulate on PAI-1 levels, as it was examined in various ways, namely in serum, fibroblast mRNA, and WRN knockdown cells.

The manuscript, however, has numerous English problems, which make this important finding hard to follow. Some wording is very unusual. Noticeable points are listed under Minor Essential Revisions below.

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

The major problem is in the overall quality of English. I suggest to that authors have the manuscript be edited senior scientists or, if possible, professionals.

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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)

1. In Abstract, all the necessary information are presented but writing is rather rough. For example, in Background “in order to” was repeated, and “Beside” does not fit here. Results of serum level should be added to the abstract. 1367R and 1074L being protective allele for CVD can be mentioned here.
2. The title of the first subsection of the Results is not grammatically correct, and it is not clear what “inflammation” exactly means without further explanation. It can be changed to “Demography of the study population”. The author may start off with one sentence on the study population and clearly state why markers of inflammation were measured (“We measured the serum markers of inflammation because…”).

3. I suggest that table 2 is presented before Fig 1, as it is followed by the cell biological experiments.

4. On page 5, the method of Western analysis should be moved to Materials and Methods section. This subsection (“WRN was not detected…” can be combined with the following section.

5. In Discussion, avoid using “etc”. This section is relatively well written and very informative.

Discretionary Revisions (which the author can choose to ignore)

**What next?:** Accept after minor essential revisions

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Needs some language corrections before being published

**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