

Peer Review

Review of: "Is There a Hereditary Cancer Resistance Genotype?"

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Although limited, variants that decrease the risk of cancer, i.e., cancer resistance, have been reported. This review manuscript aims to summarize these genes and variants. However, details on these variants are not sufficiently described in the main text, and many descriptions in the Discussion section are not related to cancer resistance. Also, the conclusion is confusing. Please see my comments below. Overall, this manuscript requires significant improvement.

1. No reference was cited in the Introduction section. References need to be cited in statements in the Introduction section.
2. Page 3: Which genes are associated with the cancer resistance mechanism in naked mole rats? What is the uniqueness of these genes compared with those of other species, including humans?
3. Similarly, which tumor suppressor genes are associated with the cancer resistance mechanism in bowhead whales? Do they have a larger number of copies than other species, like p53 in elephants?
4. Similarly, more details of associated genes with the cancer-resistant mechanism need to be described for *Mus spretus* and microbats.
5. Which species are long-lived animals? Also, the mutation rates of these species and the other species should be shown.
6. Figures that describe these cancer-resistant genes and their molecular functions would be useful.
7. Page 7: What cancer-resistant variants did Agarwal et al. identify? Which genes had these variants? What is the molecular mechanism of cancer resistance by these variants? Only one example (rs17834140-T non-coding variant) was described. It should be described more broadly.
8. Page 7: Which genes does the rs17834140-T non-coding variant affect? What does it mean by "down-regulating hematopoietic stem cell selective expression," "down regulating function of the

RNA-binding protein MSI2,” and “a higher level of a RNA network that modifies the post-translational expression of the MSI2 gene?” Further details are necessary.

9. Similarly, other known cancer-resistant variants for other cancer types were not sufficiently described. A broader view is necessary, e.g., the number of known variants, the functional category of genes with these variants, and typical molecular mechanisms. Also, more details for each given example are necessary.
10. The discussion is mostly about cancer-associated genes. Since the focus of this paper is on cancer resistance, more discussion on cancer resistance is necessary. And the discussion on cancer-associated genes should be minimized.
11. The conclusion statement is confusing. “Answering the question of the title of this paper, we can say that there is no germline cancer resistance genotype with the possible exception of individuals who suffer from Laron syndrome. However, there are genetic variants with a lower risk for cancer.” Genetic variants that lower cancer risk should be considered a cancer resistance genotype. Also, the description of these variants in the main text does not support the conclusion of “no germline cancer resistance genotype.”

Declarations

Potential competing interests: No potential competing interests to declare.