Reviewer's report

Title: Construction of possible integrated predictive index based on EGFR and ANXA3 polymorphisms for chemotherapy response in fluoropyrimidine-treated Japanese gastric cancer patients using a bioinformatic method

Version: 2

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Reviewer: Hufeng Zhou

Reviewer's report:

This work is impressive and contribute new knowledge to the field of gastric cancer cancer studies.

The author uses a knowledge-based bioinformatic approach to a pharmacogenomics study in which fluoropyrimidine-treated gastric cancer patients were genotyped at 109,365 SNPs using the Illumina Human-1 BeadChip. The author identified the SNP rs2293347 in the human epidermal growth factor receptor (EGFR) gene as a novel genetic factor related to chemotherapeutic response. In the present study, The author reanalyzed these hypothesis-free genomic data using extended knowledge.

The author confirmed that the performance of the rs2867461+rs2293347 model was superior to those of the single factor models. Furthermore, The author propose a novel integrated predictive index (iEA) based on these two polymorphisms in EGFR and ANXA3. The p value for iEA was $1.47 \times 10^{-8}$ by Fisher’s exact test. Recent studies showed that the mutations in EGFR is associated with high expression of dihydropyrimidine dehydrogenase, which is an inactivating and rate-limiting enzyme for fluoropyrimidine, and suggested that the combination of chemotherapy with fluoropyrimidine and EGFR-targeting agents is effective against EGFR-overexpressing gastric tumors, while ANXA3 overexpression confers resistance to tyrosine kinase inhibitors targeting the EGFR pathway. The novel bioinformatics approach used in this work is certainly worth reporting in publication. Overall it is a very high quality work and I strongly suggest for publication.

Minor Essential Revisions

But there are some minor issues that need to be taken care of before it goes to publications.

In the manuscript, the author mentioned “In the previous study, the authors extracted RS numbers (SNP IDs) related to cancer using a combination of National Center for Biotechnology Information (NCBI) dbSNP and NCBI PubMed. In the present study, the authors extracted all SNP numbers linked to PubMed IDs on the basis of dbSNP but excluded SNPs related to cancer.” This manuscript can certain be strengthened if the authors can explain more of the reason behind this change. And Just a little bit more explanation of not using ther
SNP database would also help, say 1000Genome Project, and other SNP databases available.

The authors refereed to Pathway knowledge in this analysis, but here are better and more comprehensive database available (called IntPath database) and most similar studies adopted IntPath instead of KEGG. In this work the author should use IntPath to reference the pathway information, at least should cite the work of IntPath and point out to the reader that effective and systematic analysis by referring to pathway information can be done using IntPath.

There a minor language issues that need to be taken care of before goes to publication.

Level of interest: An article of importance 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:

No conflicts of interest