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Title: Epigenetics in psychiatry: beyond DNA methylation

Authors: Katarina Kouter, Iris Šalamon Arčan and Alja Videtič Paska

Subject: Revision Letter

Date: January 30, 2023

Dear Professor Tampi,

below we have listed our responses to the Reviewers' comments on our manuscript entitled, "Epigenetics in psychiatry: beyond DNA methylation".

At this point we would like to thank the Reviewers for their constructive comments and helpful suggestions. We are grateful for your suggestions, as they have been helpful in our efforts to revise and improve the quality of our manuscript. We have addressed all of the comments and marked the changes in yellow throughout the manuscript. Any text deletion was done using MS Word "track changes" function.

We hope that our fully revised manuscript will now be of suitable quality and reader interest for publication in World Journal of Psychiatry.

Sincerely,

Alja Videtič Paska

Reviewer #1: Contemporary research on DNA hydroxymethylation and psychiatric disorders is particularly significant, especially in the field of suicide, schizophrenia, bipolar disorder, depression, and obsessive-compulsive disorder, as it contributes to elucidating our understanding of the molecular background of psychiatric disorders. In your manuscript, you provided an overview of all studies on this topic and explained the etiology of psychiatric disorders at the molecular level.

We would like to thank Reviewer 1 for the encouraging words and useful comment. Below we have answered the comment more specifically. In the revised version of the manuscript, we highlighted the changes in yellow. Any text deletion was done using MS Word "track changes" function.

As a limitation I think that from the aspect of epigenetics, it would be important to investigate personality disorders and addictive diseases that also carry a high risk for suicidal behavior.

We thank reviewer 1 for the suggestions. However, to our knowledge, there are no studies investigating DNA hydroxymethylation on personality disorders, but there are studies investigating DNA methylation. Our aim is to present studies investigating DNA hydroxymethylation therefore this topic cannot be included in this article. On the other hand, there are few studies investigating DNA hydroxymethylation on substanceuse use disorder (addiction to different substances). We included this topic in the article. It can be found under a new subtitle 'DNA hydroxymethylation and substance use disorder'.

Reviewer #2: Dear authors, I have a few comments on your manuscript: - You are rather courageous when you submit a manuscript to the World Journal in Psychiatry not having any psychiatrist in your authors´ team at all. I do not doubt your high expertise in molecular genetics, but your knowledge of psychiatry is below-average. On the other hand, I appreciate the topic of your manuscript, which is important and innovative in etiology of mental disorders.

We thank Reviewer 2 for the useful suggestions, which we have taken into consideration when revising and improving our manuscript. Our more specific answers are given below, along with the comments of the Reviewer. In the revised version of the manuscript, we highlighted the changes in yellow. Any text deletion was done using MS Word "track changes" function.

- Introduction: Biomarkers and psychiatric disorders - the lines 3 and 4 from above: In psychiatry, diagnoses are made based on psychiatric examnation, not on "physical" examination. Not only the Diagnostic and Statistical Manual of Mental Disorders (in America, created by the American Psychiatric Association), but also the International Classification of Mental Disorders ICD-11 (in the rest of the world, created by the WHO) are applied in psychiatric diagnostics.

We thank Reviewer 2 for noticing this error. We corrected this part according to the comment. We added 'In the field of psychiatry, diagnoses are made based on psychiatric examination using the Diagnostic and Statistical Manual or Mental Disorders (DSM-V) or International Classification of Diseases (ICD-11).'

- The readers of the journal are mostly clinical psychiatrists. So the part of your manuscript "Methods for DNA hydroxymethylation detection" will be too uninteresting and unsuitable for them. I suggest you to shorten this part of your manuscript by about a half.

Thank you for the suggestion and direction. We have added the "Methods for DNA hydroxymethylation detection" part of the paper precisely for this reason; because a large part of the readers are clinical psychiatrists, it is all the more important for them to familiarize themselves with the basics of the methods used for the study. Nevertheless, we have made alterations as proposed; this part of the paper was further shortened and simplified as much as possible.

- Current overview of DNA hydroxymethylation studies...: Psychiatric disorders (their etiology) are influenced not only by genetic and epigenetic factors, but also by microbiome, environmental factors and last but not least by their wide interactions, labeled e.g. as GxGxGxExE...

Thank you for the proposed text. We tried to include it in the manuscript, but it does not really fit, as the manuscript in whole is oriented on hydroxymethylation. In the text throughout the manuscript, however, we do add that the psychiatric disorders are influenced by several factors, such as genetic, neurobiological, environmental etc. and their interactions.

- DNA hydroxymethylation and depression: "Depression" is a very broad term usually not used in psychiatric professional articles because of its vagueness. If you use the term "depression", you should always specify it more, e.g. "major depresssion", "organic depressive disorders", "depression within an adjustment disorder" etc.

Thank you for the comment. We have corrected the term depression to MDD, as also in the papers cited in the manuscript the data are for MDD.

- Conclusion: I do not agree with the first sentence "In treatment of psychiatric disorders there are currently no validated biomarkers in use". You should know that biomarkers can be not only molecular/genetic ones, but we also have e.g. electrophysiological biomarkers (EEG), neuropsychological biomarkers, brain imaging biomarkers, blood biomarkers etc. For example, in Alzheimer´s dementia, brain imaging or the examination of cerebrospinal fluid have already been applied

and useful in finding proper biomarkers for the diagnostics and treatment (brain atrophy, tau-protein, beta-amyloid etc.).

As proposed we have improved the first sentence of the introduction, specifying more particularly the status of biomarkers in psychiatry.

- Conclusion: You mention that "psychiatric disorders are polygenic". You should also mention that in addition to single nucleotide polymorphisms (SNPs), copy number variations (CNVs), genetic pleiotropy, epistasis etc. play an important role in the genetics of mental disorders.

Thank you for the comment. We have added also other genetic components/effects to the text.