ANSWERING REVIEWERS

Title: Biomarkers in schizophrenia: A focus on blood based diagnostics and theranostics

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ESPS Manuscript NO: 21827

The manuscript has been improved according to the suggestions of reviewers:

Note: all the changes in text are in red color.

Reviewer 1

1. RE: The term "theranostics" in the title is relatively new, you should explain it in detail in the introduction section.

Reply: To address this concern, we have added more description in Abstract and INTRODUCTION as follows:

a) In Abstract:
(p3, paragraph 1)
Identifying biomarkers that can be used as diagnostics or predictors of treatment response (theranostics) in people with schizophrenia (Sz) will be an important step towards being able to provide personalized treatment.

b) In INTRODUCTION:
(p5, paragraph 1)
Identifying biomarkers that can be used as diagnostics or predictors of treatment response (theranostics) in people with schizophrenia (Sz) will be an important step towards being able to provide personalized treatment and would support efforts to develop new drug treatments[1-3].

2. RE: Abstract: Neuroimaging techniques are not only expensive but also their scientific results related to possible schizophrenia biomarkers are inconclusive. The same idea is valid for Introduction.

Reply: We have adopted the suggestion and added the description in Abstract and INTRODUCTION as follows:

a) In Abstract:
(p3, paragraph 1)
…because brain biopsies are not acceptable and neuroimaging techniques are expensive and the results are inconclusive

b) In INTRODUCTION:
(p5, paragraph 1)

…because brain biopsies are not acceptable and neuroimaging techniques are expensive[5] and the results are inconclusive

3. RE: In my opinion, the language needs some corrections, for example: page 2, Core tip: "using biological based"; page 3, Core tip: "standardize blood collection conditions"
Reply: We have corrected the sentence in Core Tip and CONCLUSION as follows:

a) In Core Tip:

(p4, paragraph 1)

… dissected into subtype using biomarkers…. We suggest that a prediction model-based, Sz specific, blood oriented study design as well as standard blood collection procedures would be useful for development of Sz biomarkers.

b) In CONCLUSION:

(p26, paragraph 1)

…should develop standardized blood collection procedures…

4. RE: page 15: The sentence "Oxidative stress markers, such as pentosidine... was found to be lower in people with Sz" (in my opinion, some subject is missing at the end of the sentence)
Reply: We have added the subject that is missing in section of OXIDATIVE STRESS RESPONSE AND METABOLISM as follows:

(p18, paragraph 1)

Oxidative stress markers…were found to be higher among people with Sz and carbonyl stress was found to be lower in people with the disorder [104, 105, 107]

5. RE: Page 16: A point is missing at the end of the sentence "...suggesting it to be a promising biomarker"
Reply: We have made the revision for this in section of OXIDATIVE STRESS RESPONSE AND METABOLISM as follows:

(p18, paragraph 2 to p19, paragraph 1)

It has also been reported that the activity of platelet mitochondrial complex I is associated with positive symptoms and clinical disease course in people with Sz [108]. Significantly, the activity of platelet mitochondrial complex I is not altered in people with bipolar disorder[106] and mRNA levels for platelet mitochondrial complex I is not altered in white blood cells from people with autism spectrum disorder[113]. These latter findings are an indicator that the activity of platelet mitochondrial complex I is associated with positive symptoms and clinical disease course may be specific to schizophrenia and a potentially useful biomarker for those features of the disorder.

6. RE: Page 17: "...with most of the istes located..." (it should be sites); Page 18: "...with changes miRNA levels" (changes of miRNA levels).
Reply: We have corrected this in section of EPIGENETICS AND MICRORNA (MIRNA) as follows:

(p19, paragraph 3)
…with most of the sites located

(p20, paragraph 1)
…with changes of miRNA levels

7. RE: Page 18: You should explain what "Omics studies" are. On the other hand, I appreciate the scientific content of your article; Page 20: The sentence "...identified a set of 35 transcripts can discriminate..." ("which" is probably missing); Page 21: "...between people with Sz people and..." (people is written twice)

Reply: We have changed the title of OMICS STUDIES to THE HUMAN TRANSCRIPTOME AND HUMAN PROTEOME STUDIES and added the description and corrected the typo in this section, Abstract and GENERAL DESCRIPTION OF THE INCLUDED STUDIES as follows:

a) In **THE HUMAN TRANSCRIPTOME AND HUMAN PROTEOME STUDIES**

(p21, paragraph 3 to paragraph 4)

Modern technologies allow the investigation of levels of thousands of mRNAs and proteins at the same time. The studies at the levels of mRNA are known as studies of the transcriptome whereas studies at the levels of proteins are known as studies of the proteome.

Most studies of the transcriptome have involved measuring levels of mRNA is gene expression microarrays. In psychiatry, such studies have involved the use of whole blood[129-131], lymphocytes[132] or PBMC samples[133-135] to identify potential biomarkers for Sz. Other studies examined proteomics information in RBC[109], T cells[136], and serum[61, 109, 137, 138] in attempts to answer the same question. This approach has typically led to a large set of mRNAs or proteins being proposed as possible biomarkers in Sz but most findings await replication.

(p23, paragraph 1)
…identified a set of 35 transcripts which can discriminate…

(p24, paragraph 2)
..between people with Sz ~~people~~ and…

b) In **Abstract**

(p3, paragraph 1)
…and vi) transcriptome and proteome studies.

c) In **GENERAL DESCRIPTION OF THE INCLUDED STUDIES**

(p3, paragraph 1)
…and vi) transcriptome and proteome studies.

8. Page 22: "...should be initially simply be viewed..." ("be" is twice)

Reply: We have corrected this in section of **CONCLUSION** as follows:

(p26, paragraph 1)
…should be initially simply ~~be~~ viewed as…

Reviewer 2

1. Line 5, page 17, "istes" may be type error of "sites".

Reply: We have corrected this in section of **EPIGENETICS AND MICRORNA (MIRNA)** as follows:

(p19, paragraph 3)

…with most of the sites located in promoter regions of genes.

2. Regarding abbreviation of dopamine receptor subtypes, DRD2, 3 or 4, the numbers should be subscripted.

Reply: We have adopted the suggestion and corrected in the following sections:

a) **Monoamine pathways**

(p13, paragraph 1 and 2)

Both mRNA expression and receptor binding of DRD_2 were increased in lymphocytes from people with Sz who were drug-naive[71, 72], however the up-regulation of DRD_2 mRNA was not replicated[73, 74]. The levels of lymphocyte DRD_3 mRNA was reported…It's noteworthy that higher DRD_3 mRNA has been reported in people with heroin addiction, whilst lower DRD_4 mRNA has…

There is evidence to suggest that lymphocyte DRD_2 mRNA levels.... In addition, the changes of lymphocyte DRD_3 and DRD_5 mRNA were associated with …

(p14, paragraph 1)

…a critical downstream target of DRD_1 and DRD_5- mediated signaling,…

(p15, paragraph 1)

…a single study found that lymphocyte DRD_2 and platelet 5-HT_{2A} receptor binding…In addition, lymphocyte DRD_3 and DRD_5 mRNA was reported to show dynamic,…

b) **FIGURE LEGENDS**

(p28, figure 3 legend)

… DRD_2: dopamine receptors D_2;…

3. If illustration of figures is not original, authors should cite references.

Reply: We have added the description for this in the section of **FIGURE LEGENDS** as follows:

In Figure 1:

(p27, paragraph 1)

The figure is an extension of figure 1 in Marques-Deak *et al* [23].