



**PEER-REVIEW REPORT**

**Name of journal:** World Journal of Diabetes

**Manuscript NO:** 53262

**Title:** Shared (epi)genomic background connecting neurodegenerative diseases and Type 2 Diabetes.

**Reviewer’s code:** 02904354

**Position:** Editorial Board

**Academic degree:** MD, PhD

**Professional title:** Associate Professor, Postdoc

**Reviewer’s country:** China

**Author’s country:** Italy

**Reviewer chosen by:** Jin-Zhou Tang

**Reviewer accepted review:** 2020-01-03 03:49

**Reviewer performed review:** 2020-01-04 03:05

**Review time:** 23 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer’s expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input type="checkbox"/> No

**SPECIFIC COMMENTS TO AUTHORS**



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The paper is clearly written. I recommend its potential publication in this journal. There are several comments. 1. The authors collected and described the evidence in this topic, but they seemed to be scattered. How to avoid the bias in reporting the evidence is important. So I suggest to do a systematic review of literature. 2. The table is interesting. Give a reference for each biological function. 3. From my side, the figure 1a is not clear. Lots of lines are difficult to be seen or understood.

#### **INITIAL REVIEW OF THE MANUSCRIPT**

##### ***Google Search:***

- The same title
- Duplicate publication
- Plagiarism
- No

##### ***BPG Search:***

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- No



**PEER-REVIEW REPORT**

**Name of journal:** World Journal of Diabetes

**Manuscript NO:** 53262

**Title:** Shared (epi)genomic background connecting neurodegenerative diseases and Type 2 Diabetes.

**Reviewer's code:** 02950171

**Position:** Peer Reviewer

**Academic degree:** PhD

**Professional title:** Postdoctoral Fellow

**Reviewer's country:** Denmark

**Author's country:** Italy

**Reviewer chosen by:** Jin-Zhou Tang

**Reviewer accepted review:** 2020-01-06 09:47

**Reviewer performed review:** 2020-01-12 13:58

**Review time:** 6 Days and 4 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

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The authors review studies showing common (epi)genomic (with a focus on genomic) background for the strongly age-related diseases T2D and neurodegenerative diseases. The reviewer finds the review rather speculative and without any strong, well-established common molecular factors to T2D and AD/PD. This points to that the focus of the review, which is indeed interesting, is at its infancy and that no strong relationships yet exists. If the authors agrees that this is the case, this should be emphasized throughout the review.

**Title** Because the authors do not present any epigenetic data that are shared between T2D, AD and PD, I suggest that “(epi)” is removed from the title. Alternatively, the authors should add more data on epigenetic alterations that are shared between T2D and neurodegenerative diseases (if they exists), and introduce the focus on epigenetics in the abstract and introduction.

**Abstract** Please specify/summarize the content of the review at the end of the abstract so that the reader gets an idea of where we are today: how well-established is the shared genetic background, that is not related to age per se, between T2D and neurodegenerative diseases?

**Manuscript Introduction, page 3:** Brain insulin resistance is unknown to many. What is it, and how does it link T2D with AD/PD? Are insulin levels, the insulin receptors, the transport across the blood-brain barrier increased or decreased? Please explain the mechanisms behind it, and how it is related to neuroinflammation, which is mentioned frequently in this review.

When introducing beta amyloid and Tau protein in the text, please explain the importance of these molecules for the development of AD, and include add a reference.

**Page 4:** Please remove the sentence “As previously mentioned, insulin resistance dramatically affects brain functions and neuronal activity.” This is neither well-explained in the review nor well-established in the scientific community.

What is the difference in 927 and 395 risk variants? Are these findings from the same study? Please reformulate the sentence “These SNPs are involved in immunity/inflammation-related pathways, cell-cell communication and neuronal



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plasticity, and their dysregulation may lead to increase in the neuroinflammation typically occurring in T2D and AD." SNPs can not be "dysregulated" and include reference(s) with information of how common neuroinflammation is in T2D and AD.

Page 5: Add a reference and specify the epigenetic modification of chromatin to the following sentence: "KANSL1 has been found to be associated with AD, suggesting that the encoded protein, that is mainly involved in the epigenetic regulation of chromatin, may also take part in neuronal development." "Therefore, the knowledge of shared genetic factors and gene expression profiles may help to further dissect the molecular network characterizing and linking T2D, AD and PD (Figure 1)." How does this sentence relate to the figure? What do you mean by "dissect the molecular network"?

Epigenetics section, page 5-6: This section is very speculative and can be shortened. The scientific studies presented are either related to T2D or AD/PD. If there currently are no studies showing epigenetic data that is related to both T2D and AD or PD, this should be explained. Also, please reformulate the text about epigenetic modifications from "...epigenetic modifications, including DNA methylation and histones' modification (by direct modulation at the transcription level), and noncoding (nc)RNAs (which mediate the gene expression at the post-transcriptional level)[55]." to e.g. "...epigenetic modifications, including DNA methylation and histone modifications (which might affect gene transcription), and noncoding (nc)RNAs (which might change gene expression at the post-transcriptional level)[55]".

Conclusion: The conclusion would improve by being less speculative and more humble in regards to what we know today and what is not yet known. Also, references should be added to all biological findings in this section.

Section 2: "On this subject, the enhancement of social and cognitive activities in the high-income countries". Why only in "high-income countries"?

Section 3: What do you mean by "treat these conditions through a network medicine approach"? Please specify or reformulate.

Figure The figure is not very informative;



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it is not specified if the genes presented are based on SNP, epigenetic or transcriptional data and to what specific disease(s) they have been linked. Moreover, it is not indicated how the genes have been selected. Please add information to this figure or remove it from the review. Table How have the genes included in Table 1 been selected? Please include information in e.g. the footnote of the table. Why are information on “Potential associated disease” not included for all SNPs? Potential association to T2D and PD and/or AD should be a criteria for all SNPs in the table? If possible, please include references to studies where these SNPs have been found associated with T2D, AD and PD, to the table.

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