Reviewer’s report

Title: Genetic Association of Human Corticotropin-Releasing Hormone Receptor 1 (CRHR1) with Internet Gaming Addiction in Korean Male Adolescents

Version: 0 Date: 26 Aug 2018

Reviewer: Markku Lahteenvuo

Reviewer’s report:

Dear authors,

Thank you for participating in an important field of research. Internet use and Internet gaming is getting more and more prominent and Internet addiction can grow to become a major problem in society.

I’m unable to give a full review of the manuscript as some important information, especially the participant demographics, is missing.

However, even with this information I do not think the manuscript is suitable for publication in it's current form. The language needs major revision. Even the conclusions chapter has flawed sentences.

My concerns with the manuscript:

- 5 genes were tested for correlation, but no corrections for multiple comparisons were made. If corrections would be made using the Bonferroni method, no results would remain statistically significant. Therefore it is unclear whether this manuscript has any significant results.

- The abstract states that CRHR1 polymorphism plays an important role in IGA susceptibility. However, this is a genetic study that tries to discover correlation not causation. Also, the CRHR1 AA-genotype was present in 92.2% of the "IGAs" and 82 % of the "non-IGAs". Therefore it would not seem to be of vital importance, as almost everyone carries it and only a small proportion of the carriers get affected. Maybe the AG-genotype is protective? Of course, from a genotype correlation study no-one could say.

- Some might have concerns on deciding that 15-18 year old children can already be classified as addicts, since their personality development is still not finished. Also, the study used cut-off scores of > 38 in the KADO-scale as IGA, although the authors themselves state that scores of 38 - 49 usually comprise only overuse and potential risk of IGA. How would the results look, if higher cut-off points would be used (say > 49).

- The manuscript states that subjects were recruited from a sports center. If this is not a center for e-sports, one might think that participants recruited from a sports center might not include the
worst cases for IGA (who are likely playing at home, not doing sports). It also seems like quite a coincidence that roughly 50% of the participants had IGA. The recruitment/sampling methods need more description to explain for this.

- I could not access the demographic information that was said to be in reference 29. I could only access the abstract for that publication, which states that it had 68 participants? It would seem unlikely to contain information for the over 200 participants described here? This information would be important since, as the authors state, CRHR has been associated with alcohol dependency and no data is shown for this demographic (although it is stated that there are no differences). One might think that there could be differences in other addictive behaviours with IGA and non-IGA subjects. Either that IGA subjects have tendency for other addictions as well, or that IGA subjects do not have the time to get into other addictions, as their time is spent gaming.

- I think it has not been well shown that Internet gaming is a stress event, as is said on line 301. Internet gaming can have a lot of different forms, some more stressful than others. Also the fact that being away from gaming COULD cause withdrawal symptoms does not for a fact mean that these withdrawal symptoms cause significant stress (or happen to all with IGA or overly use of the Internet).

- Line 307 states that excessive immersion causes stress but does not give any references.

- line 328 states that behavioural treatments could be tailored for certain genotypes in the future. I don't think we have any implications of this yet?

- line 347 states that early intervention is needed to prevent adverse GENETIC consequences. What would these genetic consequences be?

All in all, although the subject is interesting and the results are in line with previous findings, I think this manuscript needs quite a lot of more work and rethinking.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

No

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No
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I am able to assess the statistics

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