Peer Review File

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Comment 1: This study requires some grammatical correction overall. Some examples- In line 107, it should be “selected”. Line 140- “unluckily”- there is no luck involved. Please change to “We are not able to replicate…”

Reply1: We have modified our text as advised (see Page 6, line 99). We have modified our text as advised (see Page 7, line 129).

Comment 2: In line 69 reference for RET SNPs is incorrect. Please cite the following PMID: 27693352, PMID: 27693352, PMID: 25839327.

Reply2: We have modified our text as advised (see Page 4, line 65).

Comment 3: Please correct genetic terminologies- Line 81, not correlation but association. Line 83, not Hong Kong Population but Chinese population.

Reply3: We have modified our text as advised (see Page 5, line 76). We have modified our text as advised (see Page 5, line 77).

Comment 4: It’s unclear why did the authors choose these 2 particular SNPs among the 6 that were associated with HSCR in the Tang et al study. Please justify.

Reply4: We randomly selected three SNPs rs10979597rs2230793 and rs2275630 from six SNPs The three SNPs of rs10979596, rs10979597 and rs10979607 in Tang et.al are highly linked, but there is no polymorphism. Therefore, we chose rs2230793 and rs2275630 for the next study.

Comment 5: In the Tang et.al study the association of the SNPs at the ELP1 locus was with individuals who had RET coding variants. The authors should sequence the RET gene in the cases to see their mutation status. This might improve the association if they look at only individuals with RET coding mutations.

Reply5: In our study, we only measured rs2230793 and rs2275630, not RET coding variables, which will be considered later. Tang et.al conducted the research based on the background of RET coding variants. We do not have RET coding variants, so our results are not completely consistent.

Comment 6: For rs2275630 since it’s a non-coding SNP please check ENCODE and NIH epigenomics roadmap data to see if there are known enhancer marks like

H3K27Ac and H3K4me1 in the human fetal gut present over the region. Also check if the polymorphism disrupts a putative transcription factor (TF) motif. This will allow the authors to demonstrate that the non-coding intronic region can be putative enhancer and the associated SNP disrupts a TF binding to affect gene expression. That allows them to speculate on a mechanism of action.

Reply6: For rs2275630, there are known enhancer marks in the human fetal gut present over the region in NCBI (Figure1). The polymorphism disrupts putative transcription factor (TF) motif (Table5). Like SRF, it mediates developmental neuronal migration, MEIS1 is one of the decisive factors involved in differentiation during striatal development, BCL6is an adverse biological risk factor for lymphoma. This point itself does not affect the expression on GTEx.