Reviewer's report

Title: De novo frameshift mutation in ASXL3 in a patient with global developmental delay, microcephaly, and craniofacial anomalies

Version: 1 Date: 10 August 2013

Reviewer: Yong-hui Jiang

Reviewer’s report:

Dinwiddie et al. report a de novo frameshift mutation of ASXL3 gene in a patient with global developmental delay, microcephaly, and craniofacial anomalies by whole exome sequencing of trio. This finding is consistent with the recent other reports of mutations in ASXL3 and other ASXL family gene with similar or overlapping clinical phenotypes. Authors has done excellent work to describe the clinical features of proband in manuscript.

A few specific suggestions for the revision

1) Although I agree that the case is reasonable strong to make that this is a causal mutation, it is valuable for readers if authors can describe or discuss how this conclusion is reached. In the case that the clinical phenotypes are not characteristic and there is only a single case report, this may even have more value.

2) For example, how many de novo mutations were found in the proband? Is this only one or there are additional? If there is additional de novo. Was the model of recessive inheritance analyzed?

3) Author mentioned ABCC8 variant, did WES also confirm this variant?

4) Could authors show the Sanger sequence result for 2 bp deletion of the trio in Figure? I noted that this has been confirmed in clinical lab. Because it is heterozygous change, this will be helpful information to show reader, particular no concern for space.

5) I understand the rationale that authors want to analyze and discuss other SNVs of ASXL3 gene. However, I am confused about the statement in conclusion, as stated “----provide evidence that rare, nonsynonymous, damaging mutations are not associated with developmental delay or microcephaly”. If this statement is valid, why should readers be convinced that ASXL3 is the cause for this patient.

Minor point:

1) Not sure that need underlies for the OMIM ID.

2) Are additional SNVs present in other exomes in public databases?

Level of interest: An article of importance in its field

Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.