Reviewer's report

Title: The utility of exome sequencing for genetic diagnosis in a familial microcephaly epilepsy syndrome

Version: 1 Date: 10 December 2013

Reviewer: Bobby Koeleman

Reviewer's report:

This is an interesting paper describing the use of Exome sequencing in the setting of clinical genetic counseling of a single family suffering from microcephaly epilepsy syndrome. The paper describes the procedure through which the most likely causal mutation has been detected, which turns out to be a homozygous mutation in WDR62, a gene known to be associated to microcephaly. The paper is straightforward and touches upon the cost-effectiveness and speed with which a genetic diagnosis can be made. This is certainly an interesting topic. However, I miss some details that would clarify the process and give more insight in the decisions made and ambiguities that are inherent to the process of prioritizing rare variants.

Major Compulsory Revisions:

1- The description of method 1 and method 2 is very brief and should be extended. It is hard to believe that the WDR mutation is the only homozygous rare variant in the homozygous regions in this family. The authors now just state that in the largest homozygous region one homozygous variant was detected. Similar for method two, it is of interest to see how and which filter settings leads to prioritizing the WDR mutation. If indeed more rare homozygous or compound heterozygous mutations are present in the family in either the homozygous regions and in the MCPH genes, it is of interest to see why they are excluded as the cause for this phenotype. Furthermore, although it is clear that this family is recessive, can a dominant mutation be excluded?

2. Similarly, figure 2 has to be adapted to give insight in the number of variants filtered and passed on to the next level filtering. The numbers before and after filtering should be given. I would like to see: total number of variants mapped and annotated after exome sequencing, number after filtering for MAF <1% for 1000genomes and in-house db separately. Then for method 1 and 2 number of variants in homozygous region / in MCPH genes, number of missense, nonsense, predicted damaging, homozygous variants, and compound heterozygous variants.

3. Figure 2. The current numbers of variants filtered for method 1 and 2 are identical. This is probably not correct.

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.

Declaration of competing interests:

I declare that I have no competing interests