Reviewer's report

Title: Mechanisms of ring chromosome formation, ring instability and clinical consequences.

Version: 1 Date: 6 September 2011

Reviewer: Karoly Szuhai

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In the manuscript by Guilherme et al.: “Mechanisms of ring chromosome formation, ring instability and clinical consequences” the authors present a comprehensive study on molecular characterization of ring chromosomes with various chromosomal origin derived from 14 patients. Next to conventional cytogenetic approaches the authors used molecular tools (FISH, MLPA and various forms of SNP arrays). Based on the results authors correlated their findings with cellular and clinical features. The study has been well-performed and is of interest on the field.

Some modification will be needed before publications;

Minor Essential Revisions

1. Although, authors state in the title the clinical consequences of the ring formation, the overall clinical of the cases is presented at all. In line with this, table 1 should be incorporated into the manuscript and should have at least a short description of clinical features that would allow correlation of the clinical sings with other cases. (A short style used in Decipher database as an example can be used here.)

2. In table one, the breakpoint positions are given in ISCN format but it lacks the annotation providing information regarding the sequence (for example: GRCh37/hg19), the lack of this information may point to very different genomic regions depending on the used annotation and annotation tools. (In some instances the position of a reporter SNP or other reporters may easily be 1 Mb different between the different versions of the databases). In fact, already in ISCN this annotation should be compulsory, or it should be related to the name of the reporters.

3. Authors categorized their cases based on the type of rearrangements they observed, but the use of these high resolution array tools must allow precise estimation of the breakpoints, which in turn might be correlated to the presence or absence of repeat cassettes (LCRs, chained self alignments). To match the statements from the title these issues should be addressed.

4. The annotation of Figure 2C should be changed from “C) FISH with centromeric probe showing the r(3) and its homologue” to “C) FISH with centromeric probe showing the r(13) and its homologue”.
5. For chromosome 13, most likely, they used a pericentromeric LSU probe as chromosome 13 specific centromeric probe does not exist. This should be corrected accordingly and listed in the Materials and Methods section.

6. The resolution of Figure 2A could be increased.

**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