Author's response to reviews

Title: Array-CGH analysis in Rwandan patients presenting Development Delay/Intellectual Disability with Multiple Congenital Anomalies

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Version: 2 Date: 26 May 2014

Author's response to reviews: see over
To Dr Tim Sands
Executive Editor
BMC-series Journals
BioMed Central
Floor 6, 236 Gray's Inn Road
London, WC1X 8HL

Dear Sir,

Re: Cover letter of Revisions made to the Reviewers’ Comments

Please find below all revisions made to the reviewers’ critics regarding our manuscript entitled “Array-CGH analysis in Rwandan patients presenting Development Delay/ Intellectual Disability with Multiple Congenital Anomalies”. All revisions, as mentioned below and in the manuscript, have been highlighted in yellow and unnecessary changes have been deleted as indicated.

#Reviewer 1: Yuri Yurov

1. Publication of images (photos of patients) needs confirmation that “written informed consent was obtained from the patient for publication of this report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal”.
   # A copy of written consents are sent to the Editor-in-Chief.
2. Please, use the term “array-CGH” or “arrCGH”, not a-CGH or aCGH.
   # The term aCGH or a-CGH were changed to array-CGH.
3. The list of citations should be corrected ( Lourov and al ?)
   # The list of citation has been corrected Lourov changed into Iourov and al. (reference n°15) in the manuscript.
4. Multiplex ligation-dependent probe amplification (MLPA) and Fluorescence in situ hybridization (FISH) data are not present, there are no possibility to evaluate this data.
   # File with MLPA and FISH data have been added as supplementary materials.
5. The list of citations should be corrected ( Lourov and al ?)
   # The list of citation has been corrected Lourov changed to Iourov and al (reference n°15). The bibliography is in correct order.
6. Figures A-G are not readable.
   # Figure A-G have been revised with high resolution.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Needs some language corrections before being published. Done

Statistical review: No, the manuscript does not need to be seen by a statistician. Done

#Reviewer 2: Santhosh Girirajan

**Major Compulsory Revisions** (which the author must respond to before a decision on publication can be reached)

1. It would be appropriate to only use the term “intellectual disability” and delete the term “mental retardation” throughout the manuscript.
   
   #The term “mental retardation “ has been deleted and replaced by “intellectual disability”.

2. The References are not cited at appropriate locations throughout the manuscript (probably due to bug in the reference management software). Some sections need relevant citations – for example Lourov and colleagues (Page paragraph 1) is not found in the bibliography.
   
   # The list of citation has been corrected Lourov changed into Iourov and al. , this reference has been added in the bibliography (reference n°15) in the manuscript.

   a. Please cite Roper HH (Annual Rev of Genomics and Human Genet, 2010). Roper HH (Annual Rev of Genomics and Human Genet, 2010) has been cited, by adding the following sentence:

   Line 68: In low-income countries, environmental factors such as malnutrition, infections, birth asphyxia, cultural deprivation, poor health and parental consanguinity play a key-leading role in the occurrence of ID and DD.

   b. Citations for sections describing the role of array CGH in ID phenotypes and those for 7q11.23 and 22q11.2 CNVs should include original work.
   
   #Following citations for sections describing the role of array CGH in ID phenotypes and those for 7q11.23 and 22q11.2 CNVs have been replaced by original work:

   Reference n° 18: Metcalfe K and al.
   Reference n° 19: Van der Aa N and al
   Reference n° 20: Tordjman S and al
   Reference n° 21: Porter MA and al
   Reference n° 22: Monteiro FP and al.

   Original work included in the bibliography are:

   Reference n° 17: Ewart AK and al.
   Reference n° 18: Frangiskakis JM and al.
   Reference n° 19: Tassabehji M and al
   Reference n° 20: Somerville MJ and al
   Reference n° 21: Chieffo C and al
3. It would be useful if the authors could add a sentence or two in the discussion about the genomic architecture surrounding 17q21.31 deletion. The H1 and H2 haplotypes are stratified in the European and African population (Steinberg, Nature Genetics, 2012). Could the authors comment on the ethnic background of the patient with the deletion in relevance to the genomic architecture (segmental duplications) at 17q21.31?

Following paragraph has been included in the discussion about the genomic architecture surrounding 17q21.31 deletion.

Line 265 to line 278: Most case of 17q21.31 deletions reported map to large clusters of flanking low copy repeats (LCRs), suggesting that the deletions are stimulated by non-allelic homologous recombination (NAHR). The 17q21.31 genomic interval contains a common 900 kb inversion polymorphism, resulting in a haplotype block with two highly divergent haplotypes designated H1 and H2. The H2 haplotype is enriched in Europeans, and carriers are predisposed to the 17q21.31 microdeletion syndrome as a result of NAHR between directly oriented segmental duplications mapping on the inverted chromosome. An ancestral H2 haplotype (H2') lacking these duplications was identified and Steinberg and al suggested that it arose in Eastern or Central Africa [27]. Our patient is the second known African American reported with 17q21.31 microdeletion.[28]. Moreover, the breakpoints of our patient's deletion do not map inside the recurrent minimal 424 kb critical region deleted found in patients reported by Koolen and al [26].

Following citations have been included:
- Steinberg KM and al. Nature genetics 2012,
- Cooper GM and al., Nature genetics 2011

Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore): None
#Appreciated

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct):

1. Typo page 11, last paragraph: change from "cor pulmonare" to "cor pulmonale"
#"cor pulmonare" changed to "cor pulmonale"

2. Please follow one abbreviation: array-CGH or aCGH or a-CGH.
The term aCGH or a-CGH were changed to array-CGH.

Level of interest: An article of importance in its field
#Appreciated

Quality of written English: Needs some language corrections before being published
Done

Statistical review: No, the manuscript does not need to be seen by a statistician.
#Reviewer 3: Jean-Paul Misson

Level of interest: An article whose findings are important to those with closely related research interests

#Appreciated

Quality of written English: Acceptable

#Appreciated

Statistical review: No, the manuscript does not need to be seen by a statistician.

#Appreciated

Yours sincerely,

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