Reviewer's report

Title: Submicroscopic aberrations on 1q21.1 in patients with congenital heart defects and velocardiofacial-like features

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Reviewer: Stefania Gimelli

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Concerning article 1544534040248275:
Submicroscopic aberrations on 1q21.1 in patients with congenital heart defects and velocardiofacial-like features

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Comments from Dr. Stefania Gimelli (stefania.gimelli@gmail.com):

The manuscript deals with a CNV analysis of 18 VCFS-like patients, not presenting the typical 22q11 microdeletion, using a whole genome and a chromosome 22-specific BAC array. Various CNVs have been detected; among them the authors focused especially on a complex 1q21.1 rearrangement, consisting of a microduplication reciprocal to the TAR syndrome and a 1.15Mb deletion previously reported as associated with CHD and schizophrenia. This case, previously published by Mefford and Sharp., 2008, is here studied more in details, in relation to his hypothetical association with CHD. Moreover the same “TAR-duplication” was found in one out of 73 unrelated CHD cases that have been screened to determine whether rearrangements within the 1q21.1 region could be associated with CHD. Furthermore, the authors describe some selected inherited CNVs identified in other loci throughout the genome.

The applied methods as the idea to use a sandwich-like hybridization and a dye-swap approach are appropriated, innovative and well described. The patient carrying the complex 1q21.1 rearrangement has been already previously published and the hypothetical correlation between the 1q21.1 microdeletion and CHD has been already described. However, the results and the discussion of the manuscript, with the additional screening of 73 CHD cases, looks enough interesting and exhaustive.

Therefore I have some comments:

1) Major Compulsory Revisions:

In results and discussion: the section concerning the CNVs detection throughout the genome (excluding the 1q21.1 rearrangements), and their hypothetical pathological relevance, doesn’t fit completely with the title and it should be better
explained or revisited.

The results chapter should be more exhaustive especially with regard to the basis for the selection of the “interesting” loci to be validated: why some CNVs have been excluded and not others? Why the validation has been done only for few of them? Four out of five of the validated CNVs are inherited and present in the Database of genomic variants, however they have been considered potentially pathological. While the others, that overlap with benign CNVs present in the same Database, have been previously eliminated?

Page 10 line 10. Among the eleven selected loci, it is not clear which ones were not present in control, not previously described or previously reported. Could be useful to describe this point more in detail; perhaps this could be summarized in a table.

Supplementary table 1 needs a more detailed legend, and the eleven selected cases have to be better highlighted (in bold?). (For example it is not clear what do the numbers inside the columns “GAIN/LOSSES” mean).

The unbalances’ extension and BAC content should be indicated in the results chapter (from which position/BAC to which position/BAC they extent)

Page 13 line 14/15. By doing a dye-swap experiment, the authors should have seen twice the positive calls. Although, when confirming the result with the MLPA approach, they could not confirm them. This doesn’t necessarily mean that they are false positive. This point should be better discussed or revisited.

2) Minor Essential Revisions

Page 5 line 20 and 21. I suggest to use: BOTH in children with mental retardation associated with dysmorphic features AND in patients with CHD

Page 12 lines 7 and 8. Maybe should be better to give this information before

Page 10 line 6. Perhaps is better to indicate the Human genome Build version instead to “variants as in December 2008”

Page 11 line 5. Patient V5 instead of patients V5

Page 11 lines 16/17. “To screen the 1q21.1 region, on 73 additional cases with congenital heart defects have been screened using, we used the same MLPA mix designed for the validation of case V5.”

Page 12 line 1. The samples of cases V5 and 112

Page 12 line 1. Is this a whole-genome array? Which is the coverage resolution within the 1q21.1 region? Is it a BAC or oligo-array?

Supplementary tables 2 and 3. The authors should use a smaller type dimension in the “oligos sequences” cells

3) Discretionary Revisions
Considering that this is a paper concerning the finding of a complex rearrangement 1q21.1 and his hypothetical association with CHD, the authors might consider the option to modify the “inherited CNVs” section and just summarize all the CNVs findings (without making a selection of the most/less interesting) in a exhaustive table (perhaps using the one already done with some minor revisions). This means the paper could be more focus on the 1q21.1 region and on its possible correlation with the CHD as the title conveys. Moreover, the CNVs described in this section are found in single individuals, inherited from an unaffected parent and present in the Database of genomic variants, meaning that their pathogenicity is hard to discuss. In addition, none of them have been discussed in details regarding their gene contents and potentially pathological role.

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

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