Reviewer's report

**Title:** Identification of a rare 17p13.3 duplication including the BHLHA9, YWHAE genes in a family with developmental delay and behavioural problems

**Version:** 2  **Date:** 28 June 2012

**Reviewer:** Damien L Bruno

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The authors present a case of a family with several members displaying neurobehavioral phenotypes and alcohol/drug addiction. The proband, an 8 year-old boy, was found to carry a 330Kb duplication in chromosome region 17p13.3, involving seven genes (chiefly CRK, YWHAE and BHLA9). He showed several phenotypic features previously associated with duplications of this genomic region (i.e. class I duplications). The proband’s mother, who was reported as manifesting a milder phenotype, was found to carry the same duplication. I found the manuscript well-prepared, however the manuscript can be improved my making the following changes.

**Major compulsory revisions**

In comparing the duplication reported here with those previously reported in the literature, subjects 1 and 2 from the study by Bi et al are discussed. The duplication in subject 2 is said to be ‘superimposable to that described here’ and the duplication in subject 1 ‘contains only four genes’. However, an assessment of the gene content/breakpoints of these three duplications reveals considerable overlap with the duplications reported in cases 9 and 11 from the study by Bruno et al. The genotype-phenotype assessment would be strengthened by inclusion of these two cases, especially in light of the shared involvement of CRK, YWHAE and BHLA9, each of which has been proposed as a candidate for an aspect of the associated class I duplication phenotype.

In addition, there are a lot of grammatical errors and it is recommended that the authors attempt to get the manuscript reviewed by a native English speaker. The main errors have been addressed below, but there are many others that have not been mentioned.

**Background**

The number of individuals cited with submicroscopic duplications and deletions/duplications in 17p13.3 is somewhat confusing. Please rewrite this section to make clearer how these deletions/duplications differ from one another (i.e. genomic size, gene content, breakpoint clustering etc). Distinguishing between the different ‘classes’ of 17p13.3 duplication would also aid with discussion of the associated phenotypes, which as it stands is also not clear.

**Discussion**
1. The genomic description of MDS is inadequate. Please make mention of the gene(s) that contribute, along with haploinsufficiency of PAFAH1B1, to the development of MDS (see Toyo-oka et al, Nat Genet 2003).

2. The authors should note that the molecular mechanism underpinning TAR syndrome has recently been elucidated (see Albers et al, Nat Genet 2012).

3. The authors conclude that ‘our patient could fit as having a class I duplication’ and go on to say that this case ‘contribute to better define the class 1 microduplications including BHLHA9, YWHAE, and CRK’. A more comprehensive assessment of the minimal region of overlap for class I duplications after inclusion of this additional case would be of value to the diagnostic community.

4. The phenotypic presentation of the carrier mother has not been adequately discussed. It is suggested that the authors discuss the clinical complexities in this family and the implications for genotype-phenotype correlation.

Minor Essential Revisions

Abstract
1. replace ‘…17p13.3 result with…’ with ‘…17p13.3 are associated with…’.
2. replace ‘…PAFAH1B1 gene…’ with ‘…PAFAH1B1…’.
3. replace ‘…including YWHAE gene…’ with ‘…involving both PAFAH1B1 and YWHAE…’.
4. replace ‘Duplications of PAFAH1B1 gene seems to determine…’ with ‘Isolated duplication of PAFAH1B1 has been associated with…’.
5. replace ‘…while YWHAE gene is…’ with ‘while isolated duplication of YWHAE is…’.
6. replace ‘… associated to the group with the PAFAH1B1 or YWHAE gene duplication…’ with ‘…associated with PAFAH1B1 or YWHAE duplication…’.
7. replace ‘…groups according which…’ with ‘…groups according to which…’.
8. replace ‘Kbs’ with ‘kilobases’.
9. replace ‘…the YWHAE gene affected by a mild …’ with ‘…the YWHAE gene, but not PAFAH1B1, affected by a mild …’.
10. replace ‘Genes…’ with ‘We propose that genes…’.
11. replace ‘…she alcohol addicted…’ with ‘…she was alcohol addicted…’.

Background
1. replace ‘Proximal region…’ with ‘The proximal region…’.
2. replace ‘Phenotype…’ with ‘The phenotype…’.

Case Presentation
1. replace ‘Maternal grandmother and his maternal uncle…’ with ‘His maternal grandmother and maternal uncle…’.
2. replace ‘He underwent to physiotherapy treatment…’ with ‘He underwent physiotherapy treatment…’.
3. replace ‘..., he utter the...’ with ‘..., he uttered the...’.
4. replace ‘...Scale resulted was 46.’ with ‘...Scale was 46.’.
5. replace ‘...Fragile-X syndrome resulted negative.' with ‘...Fragile-X syndrome was negative.'.
6. replace ‘FISH analysis,...’ with ‘FISH analyses,...’.
7. replace ‘...array-CGH analysis even if one of them was reported having behavioural problems and aggressiveness, at the moment we cannot exclude that she could carry the same small maternal 17q duplication.' with ‘...array-CGH analysis despite a report that one of them had behavioural problems and aggressiveness; we cannot exclude that she carries the same small maternal 17p13.3 duplication.’.
8. replace ‘...and RP11-100F18 excluded an eventual insertion in other chromosomes.' with ‘...and RP11-100F18 excluded a more complex rearrangement with insertion of the duplicated segment in another chromosome.’.
9. With regard to the coordinates for FISH BAC probes, please provide the reference assembly (e.g. build 37.1, Feb 2009).
10. Remove reference to ‘Database of Genomic Variants...’, which is made after the coordinates for flanking oligomers.

**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