Reviewer's report

**Title:** Dystonia, facial dysmorphism, intellectual disability and breast cancer associated with a chromosome 13q34 duplication and overexpression of TFDP1: Case report

**Version:** 1 Date: 20 October 2012

**Reviewer:** Lorenzo Melchor

**Reviewer’s report:**

The manuscript by Moscovich and colleagues reports a clinical case of a 36-year-old female with global developmental delay, facial dysmorphism, tall stature, breast cancer and dystonia. Molecular cytogenetic analyses allowed the authors to identify not only a 218,345 bp duplication in 13q34, including genes such as ADPRHL1, DCUN1D2, and TMCO3; but also a 69 bp fragment from a long terminal repeat (LTR) located within intron 3 of TFDP1. The authors carried out a genetic analysis of the family to also find the duplications in the proband’s father. Gene expression levels were assessed and all three genes located within the duplication resulted overexpressed in both subjects in comparison with her mother and neurologically normal controls. Furthermore, the patient, but not her father, also showed overexpression of TFDP1. This leads the authors to subject that TFDP1 may be involved with dystonia, tall stature and breast cancer seen in the patient.

Overall, the study carried out by Moscovich and colleagues is a well-conducted analysis relatively important in its field, as it is the first report to describe a potential connection between chromosomal region 13q34, TFDP1, and dystonia. The report firstly describes the patient clinical symptoms, to further show the finding of the genomic duplication and the definition of its boundaries using very appropriate techniques for such purposes. The discussion is also well structured with an emphasis on the mechanism of TFDP1 upregulation as well as its gender specificity.

Having said this, some minor and discretionary changes need to be addressed to improve the quality of this interesting manuscript, and thus to ensure acceptance. The authors need not only to improve the genomic definition of the 13q34 duplication by adding chromosome 13 SNP array profiles to the Figure 2, but also to carry out statistical analysis in the comparative analysis of copy number values and gene expression levels. A list of discretionary changes is also provided, with suggestions for additional information or a new figure/table to show the clinical evolution of the patient at a quick glance.

**MINOR ESSENTIAL REVISIONS**

1) Genomic characterisation of 13q34 duplication

The genomic characterisation of 13q34 duplication seems well explained in the
text, but remains scarce in Figure 2. This referee would suggest additional sections in Figure 2 to show the genomic aberration definition as follows:

Figure 2A: First, in the manuscript section Case Presentation page 5, the authors mention “(...) Karyotype analysis exposed a chromosome 13q34 duplication (...)” If picture of the conventional karyotype is available for the authors and the segment duplication can be noted, which may be difficult as is only 218Kb, it would be beneficial to show the abnormal and the normal chromosomes 13 with arrows pointing out the duplicated segment. However, if the sentence refers to results given by the SNP Array analysis, it should be changed to “(...) Molecular cytogenetic analysis exposed a chromosome 13q34 duplication” to prevent misunderstandings.

Figure 2B: The authors identified a copy number aberration in 13q34 using Affymetrix Genome-Wide Human SNP Array 6.0. It is common in clinical reports identifying small genomic imbalances to show such aberrations with an array CGH profile picture (See for instance Capra et al BMC Med Gen 2012 or Carrascosa Romero et al. Am J Med Genet 2012). An image of the SNP Array profile of the chromosome 13 will add value and accuracy to the genomic definition.

Figure 2C: Current Figure 2 could comprise the third section of a modified Figure 2. References to each of these sections should thus be included across the text when convenient.

2) Statistical analyses

Table 2 and Table 3 show the results of the quantitative PCR of genomic DNA and the relative gene expression level analyses in leukocytes from peripheral blood of normal controls, patient, her father (carrier) and her mother. Although there are differences in copy number values and gene expression levels between subjects, statistical tests should be carried out to ensure significance.

The U-Mann Whitney Test could be used for pair wise comparisons (patient versus control, patient versus father, patient versus mother, father versus control, father versus mother, mother versus control) or the Kruskal-Wallis Analysis for multiple group comparisons. These statistical tests should be performed for each assay and their p-values shown in the tables.

DISCRETIONARY REVISIONS

1) Minor typos can be found throughout the text:

Page 6. Identification of the duplication 1st paragraph: “Four genes were involved in the genomic alternation” Substitute alternation for alteration.

Page 8. “(...) allowed us to identify the 5’ and 3’ breakpoints (Chr13:114,020,670 and Chr:114,239,014) (...)” Substitute last coordinate for Chr13:114,239,014.
2) Follow the Guidelines for Gene nomenclature when citing gene/protein names.

Page 10. “(...) Neddylation is the process by which Nedd8 is conjugated to target proteins. Nedd8 is an ubiquitin-like modifier of protein function (...)” Unless it is referred to a non-human study, use capital letters for NEDD8 and in italics, if referred to the gene.

3) Further description of the family

The authors may choose to expand the information of the family, if consent is provided, to find out whether more cases of breast cancer and/or dystonia were seen in the paternal side of the family. The patient was very young at the time of diagnosis (35 years old) of a mucinous carcinoma, usually reported in older patients, which thus may suggest an inherited germ line predisposition. More breast cancer cases in the family would support the findings of this manuscript. Nevertheless, this may have already been explored but no additional patients with breast cancer and/or dystonia may have been found.

4) A table or figure to sum up the chronology and the patient’s clinical symptoms would be useful for a quick glance of the patient evolution.

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.