Reviewer’s report

Title: Genetic and protein characterization in symptomatic female DMD carriers: lack of correlation between X-inactivation, transcriptional DMD allele balancing and phenotype

Version: 1 Date: 15 June 2012

Reviewer: Hendrika Ginjaar

Reviewer’s report:

The manuscript describes an interesting study about symptomatic and asymptomatic DMD carriers and the possible correlation between clinical data and various molecular analyzes that may influence progression of this disease in female carriers. The fact that the correlation between X-inactivation and phenotype is lacking has already been stated before in different articles in the past as stated by the authors. The same accounts for the expression pattern of dystrophin in muscle tissue and phenotype. Interesting is their observation that there is no relationship between X-inactivation pattern and transcriptional behaviour and dystrophic phenotype in females although the number of females investigated in the study is limited. As is the number of females studied for SPP1 polymorphism genotyping to make a clear statement about the role of this polymorphism with respect to an increase in muscle weakness and progression of the disease as has been found in a DMD patient cohort. However, the statement that their data seem to support the possible relationship between dystrophin protein levels and phenotype is based on quantitative Western blot analysis of two females only. Moreover one of the symptomatic females selected for this analysis is a possible female DMD patient and not a carrier.

Compulsory revisions:

1. Carrier 1 in the study is a female with a balanced translocation indicating a female DMD patient. Immunohistochemical analysis of dystrophin in her muscle tissue is not very clear (figure 1A): some fibers do express dystrophin as is also observed in DMD boys. C1 has the highest CK levels of all ‘carriers’ in this study. No further data are available about her phenotype. It is possible that she is still too young for further information about her phenotype. Not clear is whether she has a balanced translocation in all her cells. If not, this might explain the presence of the full size dystrophin band on blot. If she is a female DMD patient she should be removed from this study. So more information is needed to clarify this issue.

2. Although muscle tissue was available for RNA studies of all carriers, Western blot analysis has been carried out for two of them only: one symptomatic and one asymptomatic carrier. However, the authors state that their data seem to support the possible relationship between dystrophin protein levels and phenotype. Further Western blot analysis of the carriers of this study is recommended to
substantiate this proposition.

**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