Reviewer's report

Title: Circadian gene expression and impact of iduronate-2-sulfatase treatment in human fibroblasts from Hunter syndrome

Version: 1 Date: 1 July 2013

Reviewer: Gigliola Grassi Zucconi

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The study is aimed at verifying an involvement of clock genes in mucopolysaccharidosis Type II (Hunter syndrome), a lysosomal storage disease caused by deficiency of the enzyme iduronate-2-sulfatase (I2S).

The study, pursued on fibroblasts of patients affected by Hunter syndrome, shows altered levels of clock gene expression during the disease. In addition, the findings indicate that treatment with idursulfase (the recombinant form of the enzyme) results in transient changes in the expression of these genes.

The addressed questions are clearly presented, the methods are adequate and properly described, and the conclusions seem supported by the data (but see point 3 of “discretionary revisions”).

The article therefore reports data of interest also in relation to knowledge on a disease that is at present incurable.

The following issues should, however, be taken into account to improve the manuscript

Minor Essential Revisions
1. for the ARNTL and NR1D, also the alternative titles BMAL and REV-ERB should be reported
2. BACKGROUND line 9, “lysosomal” should be corrected
3. FOCUS line 4, “syndrome” should be corrected

Discretionary Revisions
1. The Discussion should be shortened and should be more stringent, also with a more rigorous selection of quoted references (the deletion of non essential references would make the text easier to read)
2. Table 1 should be reorganized, presenting only the expression of the genes discussed in the text. The other data should be presented as supplemental material.
3. At the end of the Discussion, the limitations of the study should be adequately emphasized, and in particular the limited number of patients investigated here, who anyhow suffer from a disease that is clinically heterogeneous in terms of onset, severity and progression.
**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests