Format for ANSWERING REVIEWERS

January 31, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6923 Minireview revised 10.2.14).

Title: Osteopathia striata with cranial sclerosis, Wilms tumor, and the *WTX* gene

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Name of Journal: *World Journal of Medical Genetics*

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The manuscript has been improved according to the suggestions of reviewer:

Reviewer's comment 1- *Details regarding position of mutations reported in OSCS and WT might be reviewed and presented in a form of table or picture.*

> **Reply:** As suggested, a picture detailing the position of *WTX* mutations in OSCS and WTs has been inserted (Figure 1)

Reviewer's comment 2–*The point is importance because the work aims to raise a question why there was no association between the two entities that have the same genetic background. The author may suggest way(s) to answer their question. For example, certain data that can explain the phenotype disparity. The majority of mutations of WTX in WT are somatic, which is consistent with the fact that WTX-associated WTs are sporadic cases when WT1-associated WTs are mostly found syndromic. In addition, more than 75% WT1 mutations in WT are found together with abnormality in CTNNB1 when WTX abnormalities tends to be mutually exclusive with CTNNB1 mutation. These difference may partly explain the difference between the case of WT1 and WTX.*

Reply:

- As suggested, we have implemented the discussion about the lack of association between OSCS and WT.
- as for *WTX* and *CTNNB1* mutations, the scenario is controversial. Some reported that *WTX* mutations were negatively associated with *CTNNB1* exon 3 mutations (affecting phosphorilatable residues involved in protein stability) (reviewed in Huff V., *Nat Rev Cancer*

2011; **11**:111-121 [PMID: 21248786 DOI: 10.1038/nrc3002]), contrariwise, the investigation of more than 400 WT cases found a comparable frequency of *CTNNB1* exon 3 mutations in WTs with and without *WTX* anomalies.

Reviewer's comment 3 - *There were some typing errors, i.e. Page 7 Line 13 'NRs are found in ca. (?) 1% of infant autopsies' and Line 15 WTX-knockout mouse ?.*

Reply: "Ca." has been corrected in "approximately", "Wtx-mouse knockouts" has been corrected in "Wtx-knockout mice".

Senior Authors (Paolo Radice, Luigi Tarani, Angelo Selicorni, Daniela Perotti) carefully re-edited the manuscript and believe that the language of the manuscript has reached Grade A.

Thank you again for publishing our manuscript in the *World Journal of Medical Genetics*

Sincerely yours,

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