Author's response to reviews

**Title:** Exome sequencing circumvents missing clinical data and identifies a BSCL2 mutation in congenital lipodystrophy.

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**Version:** 3  
**Date:** 3 June 2014

**Author's response to reviews:** see over
Author’s response to reviewers

Title: Exome sequencing circumvents missing clinical data and identifies a BSCL2 mutation in congenital lipodystrophy.

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Version: 2 Date: 3 June 2014
Author’s response to reviews: See over. Specific changes are highlighted in the manuscript text.
Reviewer's report

Title: Exome sequencing circumvents missing clinical data and identifies a BSCL2 mutation in congenital lipodystrophy.

Version: 1 Date: 30 April 2014

Reviewer: Sandro Banfi

Major Compulsory Revisions

1. In this paper, the authors report that they identified 34 homozygous mutations after WES. First of all, they should provide a list of them as a Supplementary table.

   A list of the identified homozygous variants is now presented in Supplementary Table 1 (page 7, row 116).

2. Why did they choose the variation in the BSCL2 gene?

   We now state that the BSCL2 variant was considered the most likely candidate due to primarily its compatibility with the available clinical presentation (page 9, row 160-162).

3. Concerning the diagnosis of heterogeneous Mendelian traits, the authors should also indicate that a targeted NGS including a specific subset of genes responsible for a given group of condition, could be a rewarding alternative to WES, as reviewed also by Rhem HL, Nat Rev Genet. 2013, 14:295-300.

   We added a sentence describing targeted NGS with a reference to Rhem HL et al (page 10, row 185-189).

Minor essential revision

5. The authors should provide more details about the average coverage obtained in their WES experiment.

   We added the ‘per base’ coverage obtained in our experiment to the Results section (page 7, row 116-117).

6. More in general, it is essential that the authors tune down their statements and do not imply that a clinical evaluation is not required at all for a correct molecular characterization of patients with Mendelian disorders.

   We have rewritten the manuscript to make it clear that WES is used to complement and accelerate, but not completely replace, a thorough clinical assessment.

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

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
Reviewer’s report

Title: Exome sequencing circumvents missing clinical data and identifies a BSCL2 mutation in congenital lipodystrophy.

Version: 1 Date: 20 May 2014

Reviewer: Massimiliano Rossi

Minor Essential Revisions

1. The authors state that WES can be used to even replace clinical investigations. This is questionable: even if a molecular diagnosis is made, a careful clinical assessment is still essential, in order to characterize the degree of clinical severity especially in conditions characterized by a possible intra/interfamilial variability (such as BSCL2 mutations).
   In general we now state that WES is used to complement and accelerate, but not completely replace, a thorough clinical assessment.

2. Lines 136/137: “increased ALT/GPT ratio (49 U/L)”: please clarify
   The entrance, “increased ALT/GPT ratio (49 U/L)”, is an error by our side; ALT/GPT ratio should have been ALT (GPT), which is the same as ALT. This value (49 U/L) was measured one year prior to the now presented value (64 U/L) (page 8, row 135-137).

3. Figures should be numbered in sequence according to the citations in the text (currently they appear in the text in the following order: 1A; 2; suppl 1A; suppl 1B; 1B; 1C, suppl 1C).
   We removed the first reference to figure 2, as the pictures were retrieved in the clinical re-evaluation of the patients described later in the paper. This should put the Figures more in order according to citations (page 4, row 58-60).

Level of interest: An article of importance in its field

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
EDITORIAL REQUIREMENTS:
*Competing interests: Please include a 'Competing interests' section between the Conclusions and Authors' contributions.
  Added