Reviewer's report

Title: Marginal Impact of Phenotypic Selection on Detecting MC4R Mutations in Italian Obese Children

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Reviewer: Stephen O'Rahilly

Reviewer's report:

This is a useful and generally well produced contribution to the literature regarding MC4R mutations. It describes a prevalence of 4/240 of pathogenic mutations in Italian children with severe obesity pre-selected for increased height vs 0/~200 lean childhood controls and shows that the one new mutant found is defective in signalling. This is a significant contribution to the literature.

However, because the authors specifically selected the obese group to have increased stature, and did not compare them with a group of equivalently obese children without increased stature they can not firmly conclude, as their title does, that there are no phenotypic characteristics of MC4R deficiency other than obesity per se. Therefore the title needs to be changed to a more descriptive one e.g. "Prevalence of pathogenic MCR mutations in obese Italian children with tall stature" as the current title is insufficiently justified by the data. The authors also need to recognize this limitation in their discussion. I view this issue as representing a Major Compulsory Revision.

The authors also discuss the issue of whether MC4R mutations are more likely to lead to early-onset rather than late-onset obesity and cite a variety of papers that seem to suggest that previous indications that MC4R mutations predominantly lead to early onset obesity may be incorrect. The authors need to be cautious here because in many of the papers describing obese adults there is no objective data on whether the obese adults had been obese as children or not. Some comments to that effect would improve the balance of the discussion. I view this as a Minor Essential Revision

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:

Other than working in the same area and being the senior author of a paper describing the detailed phenotype of MC4R deficiency I have no competing
interests