Reviewer’s report

Title: Comparative integromics approach for cryptorchidism evidences joint genomic relations with muscle-contraction pathway and Noonan syndrome

Version: 4 Date: 28 November 2012

Reviewer: julia barthold

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Minor Essential Revisions

The authors have reasonably addressed the majority of points included in the original review and, I believe, have brought some clarification in their discussion regarding the limitations of the data mining and analyses used here. As they note, their goal is to define potential pathways involved in the pathogenesis of cryptorchidism as a baseline for future hypothesis-driven research. However, several corrections are still required to ensure accuracy and further clarify the data being presented:

(1) The Mouse Genome Informatics (MGI) data in Supplementary Table 3 are not completely accurate. While the phenotype associated with the targeted Gli1(-/-)/Gli2(-/+ allele includes cryptorchidism, separate targeting of Gli1 or Gli2 is not associated with cryptorchidism. Similarly, crsp and Rxfp2 are allelic, and Rxfp1(-/-) is only associated with cryptorchidism in Rxfp1/Rxfp2 transgenic mice.

(2) The statement (page 9, line 23) that 112 genes were differentially expressed in the cryptorchid rat model cited (ref. #7) is not correct; the genes included in Supplementary Table 5 reflect a subset (of a total of 3589 differentially expressed genes) that were included in tables within that manuscript based on expression levels, inclusion in specific pathways of interest and/or previous reports showing association with cryptorchidism. As such, it remains important to note that use of this list of genes as the major source of data input for the present analysis likely introduces bias that may in part explain the substantial overlap in pathways identified in the present and previous manuscript, and lead to potential failure to identify other pathways important in the pathogenesis of cryptorchidism.

(3) While a detailed discussion of the large dataset generated by the Hutson lab linking CGRP to cryptorchidism is beyond the scope of the present paper, if included the authors could instead cite a more recent review of work done in multiple species in that laboratory, and include (in Supplementary Table 4) the report showing that analysis of CGRP pathway genes failed to identify mutations in cryptorchid males (Zuccarello D et al, J Endocrinol Invest 27:760, 2004).

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

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.