Reviewer's report

Title: Mutations in the 3'-untranslated region of GATA4 as molecular hotspots for congenital heart disease (CHD)

Version: 1 Date: 26 March 2007

Reviewer: Giuseppe Novelli

Reviewer's report:

General
This paper describes the sequence analysis of the 3'UTR of GATA4 gene in 68 formalin-fixed explanted hearts with congenital heart defects, in the blood samples of 12 patients and of 100 unrelated healthy individuals.

The authors identified 9 sequence variations and 6 SNPs in the 3'UTR of GATA4 and moreover determine that 7/9 sequence variations affect RNA folding. The 9 sequence variations have not been identified in the tissue distal to the septation defects of the formalin-fixed hearts suggesting a somatic origin for these mutations.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

The paper is interesting and offers new important suggestions for a molecular pathogenetic mechanism for CHD. Nevertheless I find the paper confused. In fact the authors have conducted on the same 68 formalin-fixed hearts, mutation analysis of other cardiac transcription factors (see references 6, 17, 18, 40) but is not clear if mutations in these other transcription factors are present even if in the presence of GATA4 mutations. Moreover is not clear if, in the 68 malformed hearts, are present at the same time both nonsynonimous mutations in the coding region of GATA 4 (reference 19) and sequence variations of the 3'UTR.

1. Table 2 must be changed with a patient-code to identify if a malformed heart carries different somatic mutations in the coding and 3'UTR region of GATA4
2. In the discussion section the authors must specify better if they have found malformed heart carrying somatic mutations in different genes.
3. At page 7 line 20 the authors affirm they amplify the first 609 bp of the 3'UTR; why they don't analyse the entire 3'UTR (1,525 bp)?

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. At page 8 line 12 the nucleotide position of the polyadenylation signals (c.+1505-1507) doesn’t correspond to the length of the signal (6 bases).
2. At page 8 line 16 is reported that 17/68 malformed heart don’t carry nucleotide changes in the 3'UTR. By summing the mutated malformed heart from table 2 (column Total) the number of mutated heart is 47; 47+17=64! Is this analysis failed in 4/68 formalin-fixed malformed heart?
3. At page 8 lines 17-19 are mentioned fragments 7-1, 7-3, 7-4. They have not described these fragments before. What is their location?
4. Figure 3B must report the haplotype described in the text (page 9 lines 11-13).

Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

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