Reviewer's report

Title: Identification of the first intragenic deletion of PITX2 gene causing an Axenfeld-Rieger-Syndrome: Case report

Version: 5  Date: 13 September 2006

Reviewer: Tord Hjalt

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General

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This is a well written report on a novel medium-sized deletion in PITX2 causing ARS. This report highlights the need to perform gene analyses of pedigrees with this type of medium deletions in mind. Some ARS pedigrees might warrant re-examination?

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

1) In the text, the authors mention a 3kb band present in normals, whereas a smaller represents the intron deletion in these patients. But in fig 4D, no 3kb band is visible for the normals I-I and II-2. In fact, for control I-I, there are weak bands at 350 and 700 bp. What are these?

2) The authors overstate the importance of use of quantitative genomic PCR and a specific commercial enzyme for detection of mutations such as in this manuscript. These statements (page 12 and elsewhere) should be modulated accordingly. The mutation described (3 kb deletion of intron 6 with small deletions of end of exon 5 and start of exon 6) could have been detected with normal genomic PCR using intron-spanning primers, and an enzyme such as e.g. Advantage2 by BRL/Clontech.

3) The authors should list all primer sequences used for mutation detection in a table. Did the authors study splice site mutations? The entire length of all exons?

4) The authors should also list primer sequences used for RTPCR of 'PITX2', as well as clarify which of the at least four mRNA isoforms of PITX2 were amplified, or if several isoforms would have been detected with one primer set.

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) As much of the text in the background seems to be adapted from a recent review (ref 18), it is perhaps fitting to move up this reference to number 4 or something on page 3, rather than only the last.

2) Comparing page 7, bottom to p 8 top, with p11-12, the authors should clarify on p12 if it was the aberrant form that was undetectable.

Discretionary Revisions (which the author can choose to ignore)

1) It would perhaps be interesting to study the extended pedigree mentioned at p 12, to see if there are any pre-symptomatic genomic changes leading to this deletion?

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

Level of interest: An article of importance in its field
Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

'I declare that I have no competing interests'