Reviewer's report

**Title:** Array-CGH in patients with Kabuki-like phenotype: Identification of two patients with complex rearrangements including 2q37 deletions and no other recurrent aberration

**Version:** 1  **Date:** 10 December 2007

**Reviewer:** Jeff M Milunsky

**Reviewer's report:**

Cusco et al describe 16 patients with an initial clinical diagnosis of Kabuki syndrome, 10 of whom had enough DNA to perform several different analyses including array CGH. There have already been several articles published using different microarray technology examining individuals who meet the cardinal diagnostic criteria of Kabuki syndrome. None of these findings have been replicated by other groups. Cusco et al take a slightly different approach combining both classic Kabuki patients with those who on an initial examination have several features of Kabuki syndrome but do not meet cardinal diagnostic criteria. The methods they have used are appropriate and well described. The two patients that they highlight not only do not meet the cardinal clinical criteria suggested for a diagnosis of Kabuki syndrome, but more closely resemble patients with the 2q37 deletion syndrome. Their first patient (KS2) has a de novo 11 Mb inversion duplication of chromosome 2 and a 4.5 Mb terminal deletion of 2q. This patient specifically does not have long palpebral fissures, lower eyelid palpebral eversion or short stature. The facies are not typical of classic Kabuki syndrome. Their second patient (KS 14) has a de novo 7.2 Mb terminal 2q deletion and a de novo 1.5 Mb chromosome 16 deletion. This patient also does not have classic Kabuki facies. Interestingly, both KS 2 and KS 14 share rib anomalies (less common in KS) and both have VSDs which are described in the 2q37 deletion syndrome. The title of their manuscript implies that 2q37 may contribute to Kabuki syndrome. This is not adequately supported by their data. Rather, their conclusion that the 2q37 deletion syndrome be considered in the differential diagnosis of patients with several features of Kabuki syndrome is appropriate and reasonable.

Major compulsory revisions:

1. I would recommend that the title and the focus of the manuscript be changed to reporting their 2 individuals with the 2q37 deletions and comparing them to the more than 60 already described. This can be reported in addition to the negative data from chromosome 8 and 20 as reported by others in the literature.
2. In Table 1 they should report the findings of their patients in comparison with those with the 2q37 deletion syndrome as well.
3. The chromosome 8 findings previously reported were from American patients, not Japanese. This should be reflected in their discussion.
4. In order to report de novo copy number changes, paternity testing is necessary and should be reported.

5. More discussion about the de novo 16p11.2 deletion in KS 14 is necessary.

Minor essential revisions
1. A specific comment is necessary indicating that there is no deletion or duplication at the chromosome 15/17 breakpoints in KS 14.
2. The Figure 1 legend needs to be changed as they are not all "KS patients."
3. The Table 2 title needs to be changed as not all of the rearrangements found are pathogenic (ie loss of 17q12 in KS 9).
4. Table 2: correct spelling of origin.
5. In the background section: correct the spelling of microrearrangements.

Discretionary revisions
1. In the array CGH section, the authors consider a potential rearrangement when only 3 out of 3-5 consecutive probes gave M values outside. They should consider mentioning the approximate segment size (ie 100 Kb).
2. In the MLPA section consider clarifying sentence: "in each MLPA signal was normalized and compared to the corresponding peak height obtained in a control DNA sample." The reader needs to know how many controls were used.

I believe that this is a valuable manuscript that should be accepted after the authors have responded to the major compulsory revisions.

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 financial interests, but am an active Kabuki syndrome researcher.