Reviewer's report

Title: Autism Spectrum Disorder in Microphthalmia with Linear Skin Defects Syndrome

Version: 2 Date: 8 December 2013

Reviewer: Marwan Shinawi

Reviewer's report:

The authors describe a 15-year-old-female with MLS syndrome and autism spectrum disorder (ASD). The patient was found having a 12.9-Mb deletion on Xp22.32-p22.2. The deletion encompasses the HCCS gene and other autism X-linked genes. The authors conclude that patients with large deletions at Xp22 can display MLS with ASD and that this contiguous deletion syndrome is subjected to highly variable phenotype due to skewed X-inactivation and somatic mosaicism.

Major Points:

1. The coexistence of MLS with ASD in this patient does not prove causality. Therefore, the title as well as parts of the discussion are misleading since they imply causal relationship.

2. The emphasis of this manuscript should be on the Xp22.32-p22.2 deletion and the associated contiguous gene syndrome. To this end, the authors should better define the breakpoints of the deletion and compare it to previously reported cases. Which platform was used for aCGH? How the deletion was detected in the mother (FISH or aCGH)?

3. The authors rightly indicated that the ASD in this patient is most likely related to autism related genes but unfortunately they did not elaborate on these genes.

4. The authors briefly discuss potential mechanisms for phenotypic variability including skewed X-inactivation and somatic mosaicism. I am wondering if these mechanisms were studied in the proband and her mother.

5. The mother was found to have the same deletion but a detailed phenotypic characterization of the mother was not provided.

6. The first paragraph of Discussion is not needed. This information can be found in any textbook.

Minor Points:

1. The official name of HCCS is holocytochrome c-type synthase

2. Please use intellectual disability instead of mental retardation (MR)

3. Reword “Noting that cytochrome c is the final product of HCCS activity,…”

4. Provide details on anxiety disorders and epilepsy in the family history.

5. IUGR is difficult to diagnose before 18-20 weeks of gestation. I am wondering
how the diagnosis was made during 1st trimester in this patient.
6. Reword: “resulted negative at genetic analyse.”
7. Is the micromelia part of the Xp22.32-p22.2 deletion?
8. Did brain MRI show brain atrophy and or microcephaly, which observed by PE?

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

**Quality of written English:** Not suitable for publication unless extensively edited

**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