Reviewer's report

Title: A natural-fertilized 47,XX,+21/46,XY parthenogenetic chimeric fetus with male genitalia

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Reviewer: Ann Nordgren

Reviewer's report:

The manuscript "A natural-fertilized 47,XX,+21/46,XY parthenogenetic chimeric fetus with male genitalia " by K.F. Lee et al describes an unusual case that sheds new light on mechanisms behind chimerism formation. The authors have studied the molecular background and discuss the likely mechanism for the chimerism in an aborted fetus with a 47,XX+21/46,XY karyotype and normal autopsy findings except sandal gap between the 1:st and 2:nd toes. The authors have used karyotyping, and molecular analysis of polymorphic markers from 19 loci in order to define the origin of 47,XX,+21 cells in different tissues. Based on the findings of two paternal alleles and the detection of homozygous maternal alleles without evidence of crossing-over, and the fact that four alleles were never detected, their results indicate that the chimerism in the fetus was the result of dispermic fertilization of a parthenogenetically activated oocyte. It also highlights the difficulties in predicting the clinical outcome in patients with genetic aberrations in chimeric form.

The investigations that have been performed are relevant and the reported results include clinical photographs as well as relevant findings from autopsy and molecular and cytogenetic investigations. The report is accompanied by written and signed informed consent to publish the information and includes a statement to this effect as part of the Consent section in the manuscript.

This case report certainly makes a contribution to medical knowledge and has educational value. I believe that it has the possibility to become suitable for publication after thorough revision.

However I find some serious deficiencies:

1. Major Compulsory Revisions:

The paper is poorly written, sometimes lacks stringency and needs rewriting. Linguistic revision is needed.

Abstract: The abstract is difficult to follow. Especially the parts describing phenotype, ratios of XX,+21/XY and the conclusion need rewriting. The second line starting with Among them .....complement could be omitted.

Case report; Please add information about why the 21 year-old mother asked for amniocentesis? Please clarify acquired mutism in the husband. Was the couple non-consanguinous?
Methods;
Autopsy; Replace the sentence "The lobes of……systems with; Autopsi was performed according to standard procedures. Replace "parts of the tissues with Tissues from heart? Kidneys? and skin were collected for cell culture and DNA was isolated directly from brain, ?? for further genetic analyses.
Preparation of genomic DNA; The descriptions are lengthy and should be replaced by a sentences like; DNA extraction was performed using standard procedures.
Short –tandem-repeat-genotyping; Please shorten this section.

Results;
Morphological examination of the fetus; Please shorten this section.
Karyotypes; It is enough to write that the parents had normal karyotypes. Thus XX… for the mother and 46,XY for the father(karyotypes not shown) could be omitted. Please rewrite the part describing different ratios in different tissues since it is hard to follow. Put placenta and brain together since they have the same ratio.
STR analysis; Add information about the fact that only 5/19 markers were informative (including AMEL) and that they were localized on chromosomes Y, 2, 8 and two markers on chromosome 21.
It would have been informative if you had included a figure with skewed ratios for some markers, with higher maternal peaks compared to the paternal, indicating double, identical, haploid maternal contributions.

Discussion;
The results strongly suggest the causative mechanism in your patient to be that of dispermic fertilization of a parthenogenetically activated oocyte, However, polar body fertilization is unlikely since there are no proofs of crossingover events distinguishing the two maternal haploid genomes. This should be mentioned in the discussion. More markers are needed if the authors want to prove this. Otherwise this part B could be removed from the Figure.
Please discuss the possibility of a postzygotic diploidization and non-disjunction of chr 21 of a triploid as one very possible mechanism.
Please clarify why the death of a twin could not result in the presence of XX and XY cells in the amniotic fluid since reference 10. Hsu LY is difficult to find.
Please explain androgenetic chimera in a better way (isodisomic paternal cell line).

2. Minor Essential Revisions
The word “abortus” should be replaced by the aborted fetus?

Methods; Ethics statement; Replace squares from ?IRB?
3. Discretionary Revisions;
Please consider providing details about the microscopic evaluation of the gonads.

References;

Perhaps add Wiley et al., Am J Med Genet. 2002 Jan 1;107(1):64-6."Dispermic chimerism with two abnormal cell lines, 47,XY, +21 and 47,XX, +12" who reported a 47,XY+21 and 47,XX+12 karyotype in a stillborn male fetus with multiple congenital anomalies


Level of interest: An article of importance in its field

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