Reviewer’s report

Title: Fragile X protein in newborn dried blood spots: implications for newborn screening

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Reviewer: Montserrat Mila

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Major Compulsory Revisions

The authors present a study about the variability of FMRP expression in 2000 samples as well as 76 retrospective samples, showing the usefulness of this method as screening method for FXS in dry blood spots.

They conclude that this method is feasible, economical and can be readily adapted to high-throughput application.

There is a previous work from the same group (LaFauci et al., 2013) where they clearly demonstrated the utility of the method in males, and with some limitations in females. It is well known that FMRP expression study is different for females and males, since FMR1 is an X-linked gene. Based on these and previous results, the application of this methodology for a newborn screening can be questionable.

One major problem of this work is the sample size. Taking into account the prevalence of full mutation in the general population, it could be expected not to find any full mutation.

Why are the 76 newborn retrospective DBS included in the study? They could just have included FXS samples as positive controls. The data presented in table 2 show 6 full mutation samples plus 3 “nl” from Australian newborns. Which is the meaning of “nl”?

The fact that they include the Australian population, that is older than the 2000 samples from New York, implicates that they are working with two groups of samples with different technical characteristics. These samples should not be used as control group.

Finally, in the last paragraph of the discussion they state that is better for a newborn screening not to detect premutations. We agree with the authors although when a FXS is diagnosed, a cascade screening will be necessary for the rest of the family, which will implicate to detect premutations.

Level of interest: An article of limited interest

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