Reviewer’s report

Title: LINE-1 methylation is inherited in familial testicular cancer kindreds

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Reviewer: Joe Nadeau

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Manuscript review:
Mirabello et al. (M. Greene, corresponding author)
LINE-1 methylation is inherited in familial testicular cancer kindreds

This manuscript reports evidence for a strong correlation across generations for LINE-1 methylation status, with a significant correlation between father and daughter and mother and daughter – gender-specific inheritance, as well as between father and affected son pairs.

Increasing evidence suggests inheritance of epigenetic effects, including for TGCTs at least in mouse models. Although relatively modest in scope, the work reported in this manuscript provides evidence for a molecular basis for these unusual effects.

Several concerns are evident however:
1. The range of variation in LINE-1 methylation is remarkably narrow (see Table 1), making the results vulnerable to epidemiological artifacts.

2. Was multiple testing taken into account (see page 5 and also Fig. 1)? Several of the tests are only modestly significant at what appears to be the nominal P-0.05 level.

3. The first paragraph of the Results section (page 5) should be revised; it is rambling with arguments and evidence going back and forth between methylation and epidemiological evidence.

4. The Discussion is too long (3 pages) given the amount of evidence that is presented (2 pages).

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.