- **Title and abstract**
o Does the title clearly reflect the content of the article? [] Yes, [x] No (please explain), [] I don't know

The end of the title, "supports a toxic Y effect on human longevity" is, I think, too ambitious considering the results presented. I would advise the authors to change it, for example: "The impact of variations in sex chromosome number on transposable element expression in humans", and mention the toxic Y hypothesis in the abstract.

o Does the abstract present the main findings of the study? [x] Yes, [] No (please explain), [] I don't know

Yes, but I have the same remark than above. In the sentence "These findings support the existence of a toxic Y effect on men's longevity", "support" is a strong word when the direct effect on longevity was not actually tested. I would say "are consistent with".

- **Introduction**
o Are the research questions/hypotheses/predictions clearly presented? [x] Yes, [] No (please explain), [ ] I don't know
o Does the introduction build on relevant research in the field? [x] Yes, [ ] No (please explain), [ ] I don't know
- **Materials and methods**
o Are the methods and analyses sufficiently detailed to allow replication by other researchers? [x] Yes, [ ] No (please explain), [ ] I don't know
o Are the methods and statistical analyses appropriate and well described? [x] Yes, [ ] No (please explain), [ ] I don't know
- **Results**
o In the case of negative results, is there a statistical power analysis (or an adequate Bayesian analysis or equivalence testing)? [x] Yes, [ ] No (please explain), [ ] I don't know
o Are the results described and interpreted correctly? [ ] Yes, [x] No (please explain), [ ] I don't know

Some of the figures are of poor quality (especially Figure 1 and Figure S8). The figure axis names are sometimes unclear and not defined in the legends. Figure 1 and 2 have different Y axis scales, but it's not clear as both are defined as "normalized counts" (in the legend for Figure 1 and on the axis name for Figure 2). If I understood correctly, one of the axes represents the proportion and the other the counts. The authors should clarify the legends and axis names accordingly. Finally, it is not clear why different metrics (counts vs proportions) are used and how it affects the results.

In Figure 1, the term "normalized" is used without being defined. The term "count" in "TE count" is misleading, as it can be interpreted as the TE counts in the genomes, instead of the transcript counts.

When the authors compare TE proportions between groups, they use a lot of Wilcoxon tests and, as far as I can tell, the p-values are not corrected for multiple testing. The statistical results support the conclusion but not **strongly.** Indeed, the sample size being small, the p-values are not strongly significant, but show interesting tendencies.

- **Discussion**

o Have the authors appropriately emphasized the strengths and limitations of their study/theory/methods/argument? [ ] Yes, [x] No (please explain), [ ] I don't know

I advise the authors to emphasize that, although their results are very promising and exciting, they are based on a very small sample size (6 females XX, 6 males XY, 8 males XXY, 4 males XYY). They say really well that "their findings **open a new window** to study the toxic effect of the Y chromosome in human". I strongly agree with this, and I think it is the strength of this study. They showed that this question is worth putting more efforts into.

Parts of the discussion need clarifying, with introducing sentences for each aspect of the results that are being discussed. The authors should consider merging the discussion on the article Bogu et al. 2019 that is divided in two parts: beginning with L401 "In humans, differential TE expression according to sex has already been studied using the GTEx dataset" and the latter part l414 "In humans, differential TE expression with respect to age was investigated in the GTEx dataset".

o Are the conclusions adequately supported by the results (without overstating the implications of the findings)? [x] Yes, [ ] No (please explain), [ ] I don't know

General comments:

The article is well written. It is clear why the study is important as a first step for understanding the impact of the toxic Y on human longevity. The present study is a proof-of-concept study with very promising results. The sample sizes are small, I however recognize the difficulty in acquiring samples from individuals with sex chromosome aneuploidies, and I find the idea behind this study design clever and innovative. The bioinformatics tools and the statistical testing are adequate to answer the questions.

However, the author should carefully revise some of their conclusions, as the direct link between the results and longevity is not demonstrated. The only link is that individuals with XYY have a lower longevity than individuals with XXY in general, but the design of the study does not allow for testing directly the influence of the Y chromosome counts on longevity. What the study does show is that there is a link between TE expression and the number of Y chromosomes, which in itself is interesting.

Minor comments:

Figure S3, S11: "MA plots", is MA an acronym? If yes, it needs to be defined.

Figure S12: "normalized counts", normalized for what? The figures should be understandable without reading the main text.

Figure S10: the axis is named "Proportions of TE counts among all counts (TEs and Genes)" but in the legend it is written "Boxplots of normalized counts combining all TE subfamilies after removing batch effect" so the genes are not mentioned.

L439: SGL? define the acronym.