

Dear Dr. Narasimhan,

Thank you for considering our manuscript as a potential paper on cell. We especially appreciate the time you and the external experts took to read and to assess the manuscript. While we agree that the manuscript still needs to be worked regarding its presentation, to our understanding, it was a consensus between you and the potential reviewers that this manuscript presents a valuable resource for the community. That is particularly evident when expert one says “discriminating autonomous L1 transcription from pervasive transcription is thoughtful and will be very valuable for the field”. That said, we are wondering if it is possible for you to reconsider your decision and perhaps send it to reviewers so we can publish it as a resource paper.

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Overall, the experts seem to be mostly concerned about the confusion between LINE-1 activity and LINE-1 transcriptional activity. We carefully make this distinction through the manuscript. The method we developed relies on RNA-seq to gauge the transcriptional activity of LINE-1 elements and therefore, it is agnostic to the protein levels or retrotransposition levels of LINE-1. On the other hand, it is a clear consensus across the community that gene transcription level is a proxy for gene activity, hence the vast amount of RNA-seq experiments available to date. Moreover, other methods to gauge LINE-1 activity (WGS, MS) are expensive and laborious, precluding the analysis of thousands of samples as we did here. Even though we do not have protein or genomic data, we took an extra step and showed that LINE-1 transcripts are poly-adenylated and most of the signal derives from the cytoplasm. Therefore, we believe is reasonable to assume that these could be translated into LINE-1 proteins.

Experts seem to be mostly concerned about the theory that LINE-1 create small insertions and deletions (INDELs). We agree that this is a preliminary result, but this is the exact reason we submitted it as a theory paper. The proposed mechanism, as we describe in the manuscript, is reasonable: LINE-1 was previously shown to create double strand breaks in the genomic DNA and there is independent evidence that double strand breaks are fixed by NHEJ creating small insertions and deletions.

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Our intention is to show that our approach is powerful and can be used shed light on LINE-1 biology.

Furthermore, it is important to stress that our method is the first to be able to gauge LINE-1 transcriptional activity from regular RNA-seq experiments, this opens an enormous opportunity for the LINE-1 community to explore this approach for other transposable element families and also investigate the transcription of LINE-1 in other organisms. We will be looking forward to hearing from you soon.

Yours Sincerely,

Mark Gerstein