A-to-I RNA editing in *D. melanogaster* — alternative RNA structure expression and its role in alternative splicing

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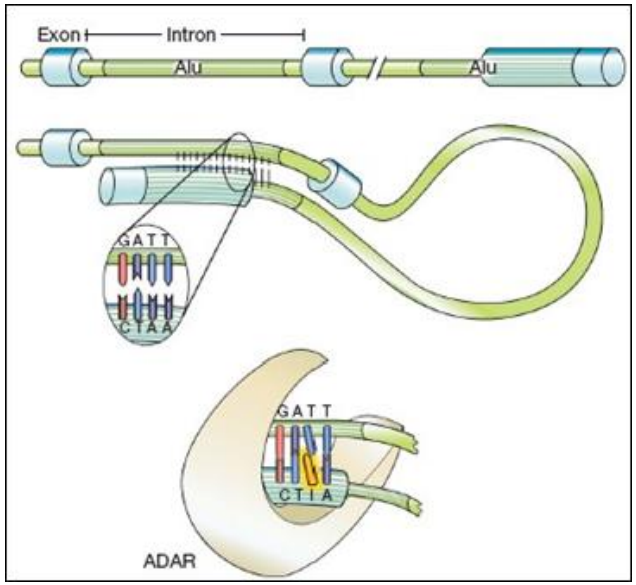
A-to-I RNA editing in *D. melanogaster*:

- abundant in mammals, but also fruit fly
- carried out by ADAR proteins (ADARs)
- requires double-stranded RNA (dsRNA)
- seemingly done in a sequence-unspecific way
- one dsRNA can have multiple editing sites

! different copies of same transcript in the same cell can be edited differently

! editing can turn dsRNA into ssRNA



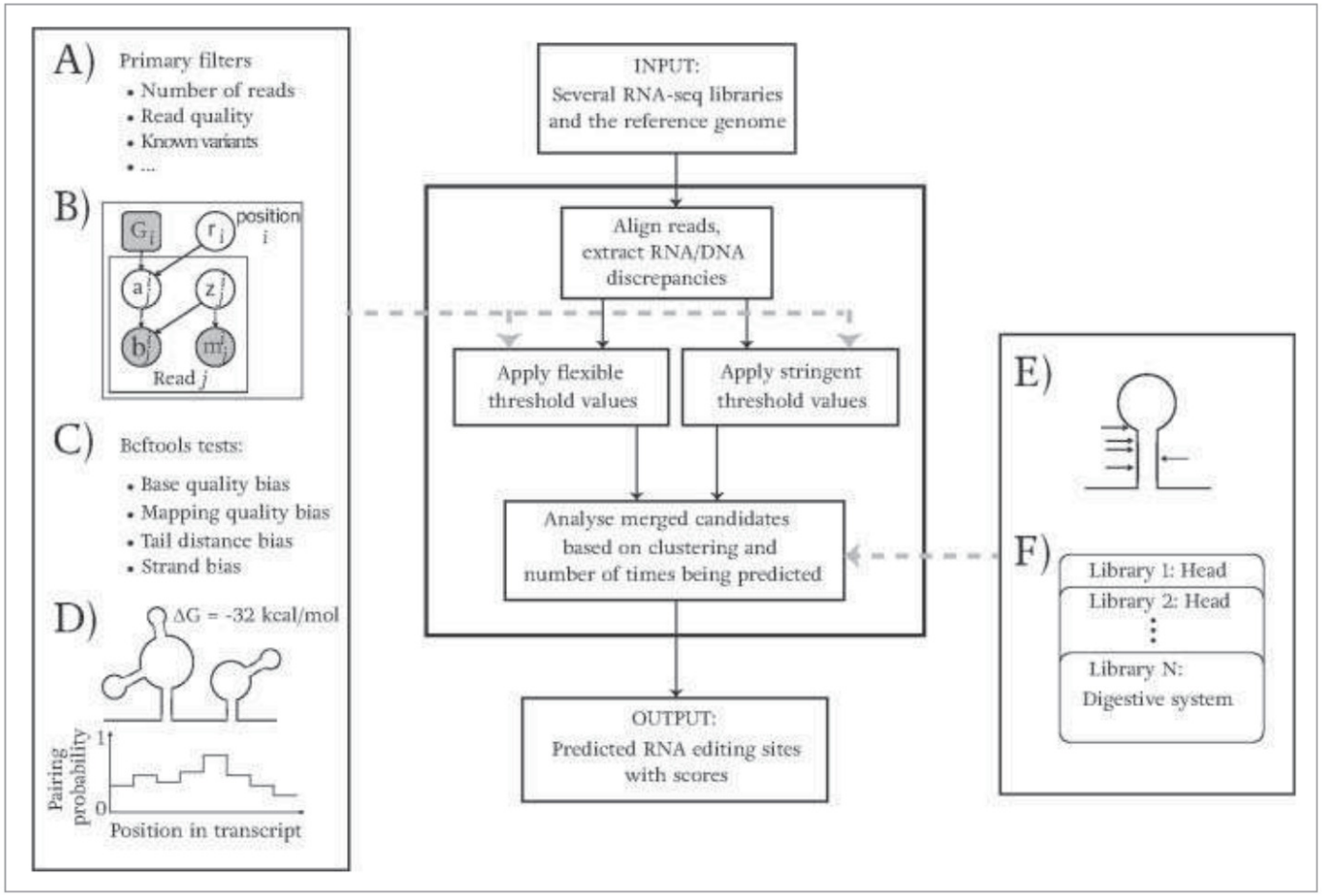
Hypothesis: Can alternative splicing be regulated by A-to-I editing via RNA structure changes ?

Result #1: analysis pipeline for detecting A-to-I editing sites

Key features:

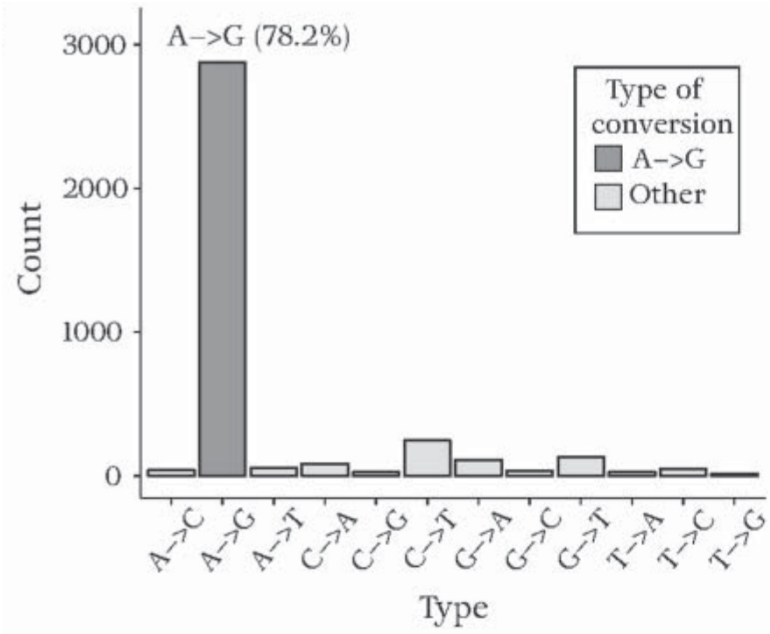
- (1) filter against artifacts due to mapping and sequencing errors
- (2) explicitly capture ADAR-specific features such as requirement for dsRNA and that editing sites tend to occur in clusters
- (3) leverage the statistical power derived from the size and number of our input data sets
- (4) devise probabilistic pipeline whose parameters can be trained and whose predictions can be ranked

Result #1: analysis pipeline for detecting A-to-I editing sites



Results #2: analysis of detected RNA-editing sites

- **data:** stranded, paired-end RNA-seq data (29 libraries, 10 tissue types)
- **results:**
- $\approx$ 2000 new editing sites
- A-to-I editing especially in head and CNS
- majority of editing cites in non-coding regions
- editing sites mostly tissue-specific
- alternatively spliced genes higher chance of being edited (p-value $< 2 \cdot 10^{-15}$)
- editing 3 x more likely in altern. spliced exons (p-value $< 2 \cdot 10^{-15}$)



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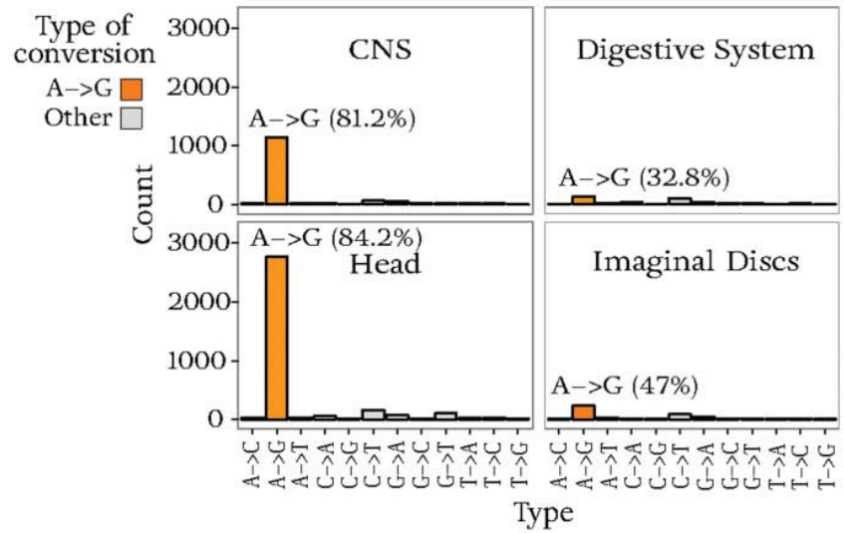

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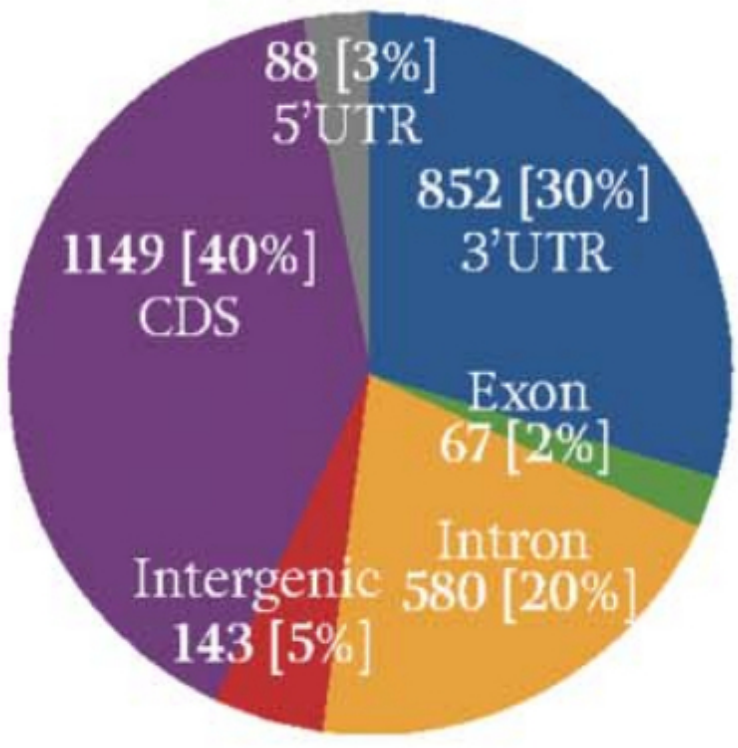

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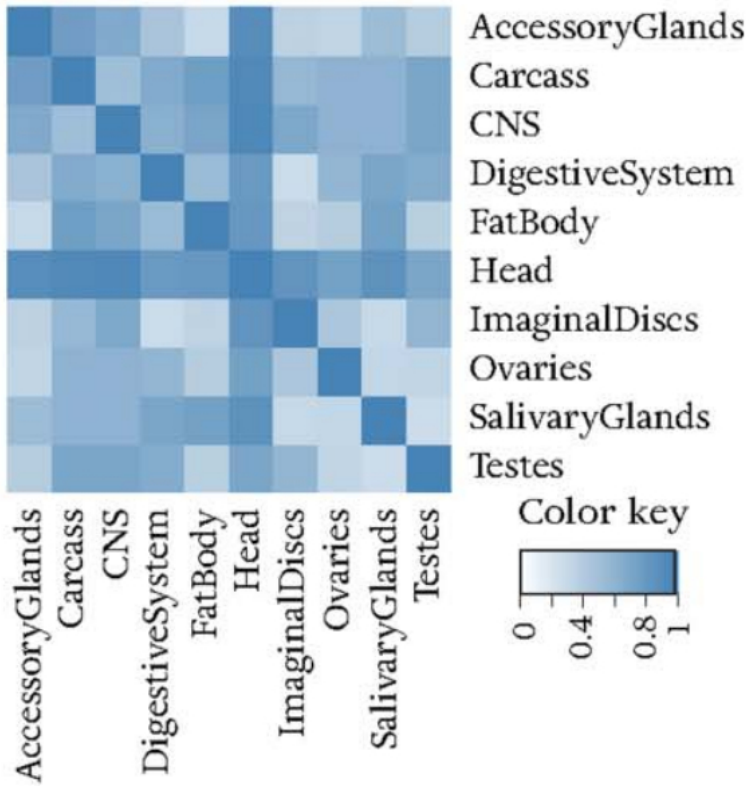

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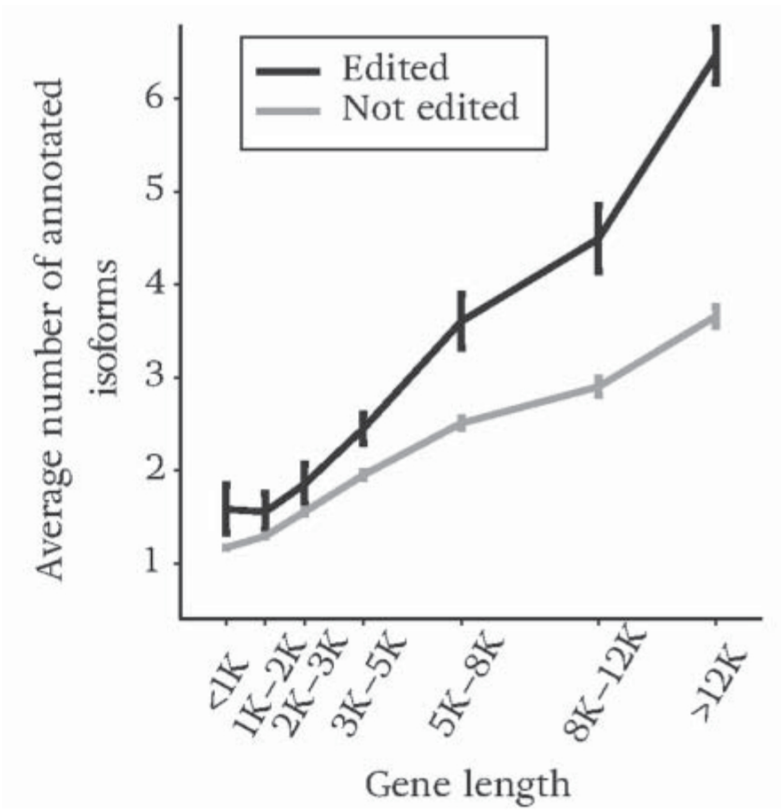
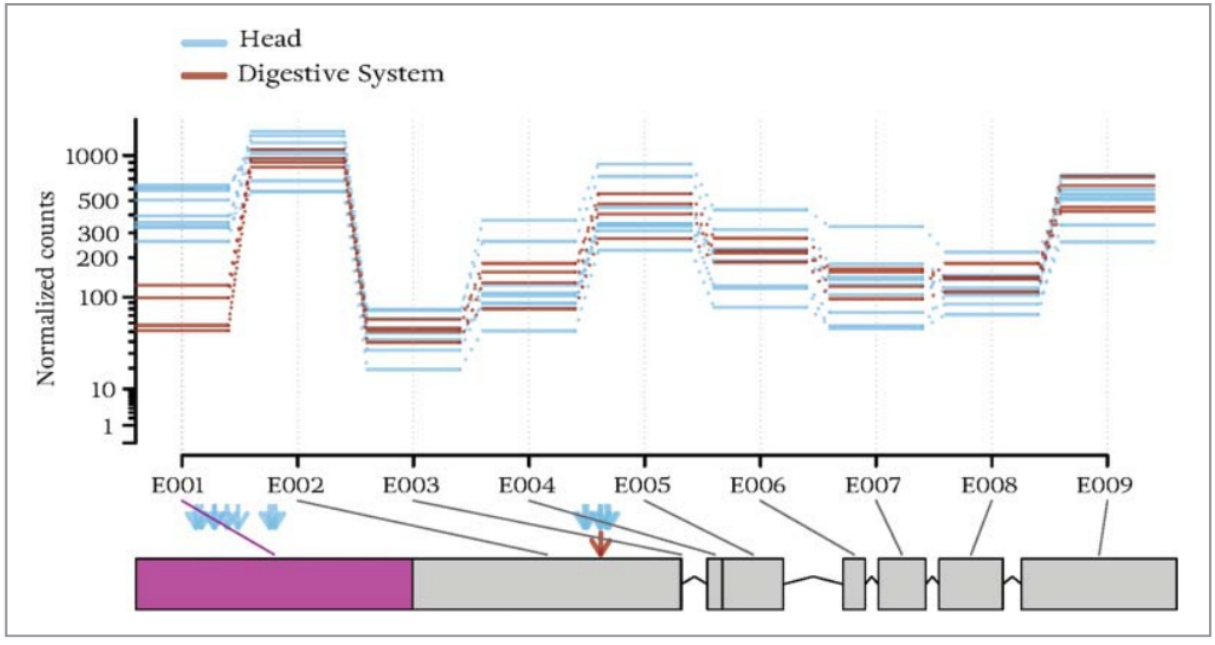


Result # 3: link between splicing and A-to-I editing



- identify 244 edited regions: editing and change in splicing
- 96 of 244 regions contain evolutionarily conserved RNA structure

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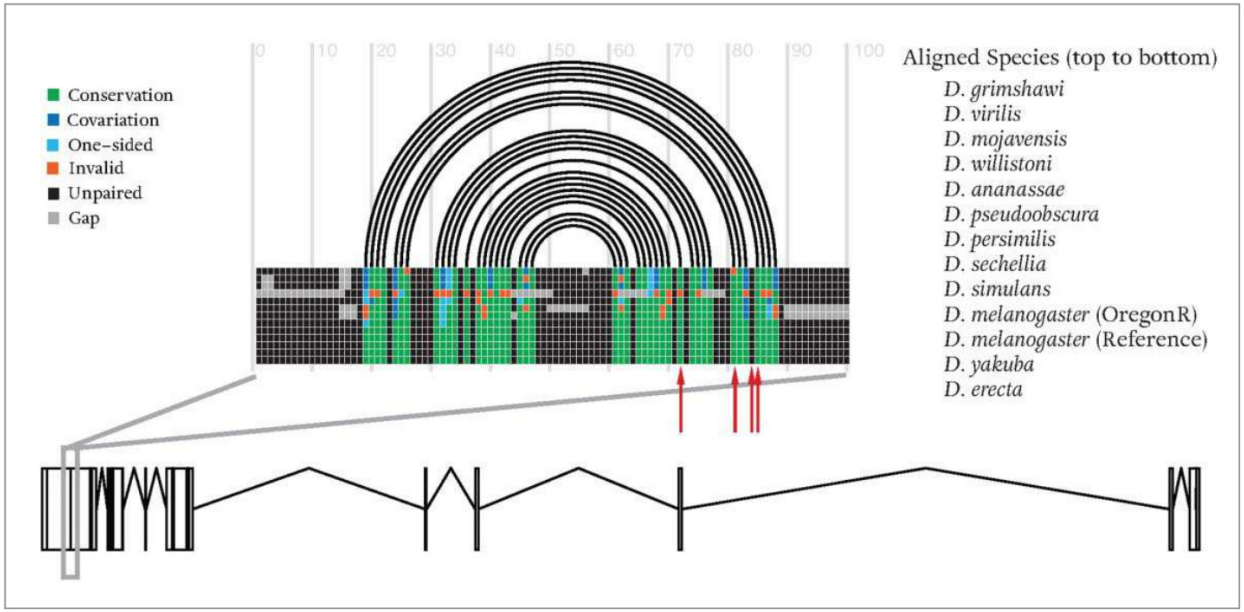

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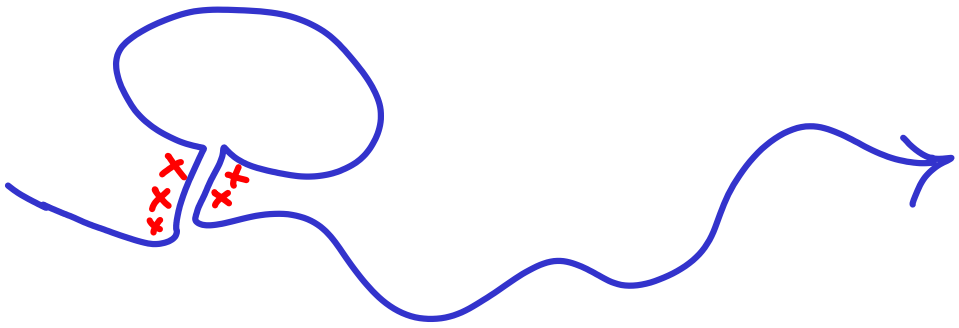

tissue-specific RNA editing of dsRNAs near splice sites

$\Rightarrow$ induced changes in local RNA structure

$\Rightarrow$ induced changes in splicing pattern

[Brugiolo *et al.*, F1000Prime Rep. (2013) 5:9; Mazloomian & Meyer, RNA Biology (2015) 12(12):1391-401; Herzel *et al.*, Nat. Rev. Mol. Cell Biol. (2017) 18(10):637-650; Meyer, Methods (2017) 120:3-16.]

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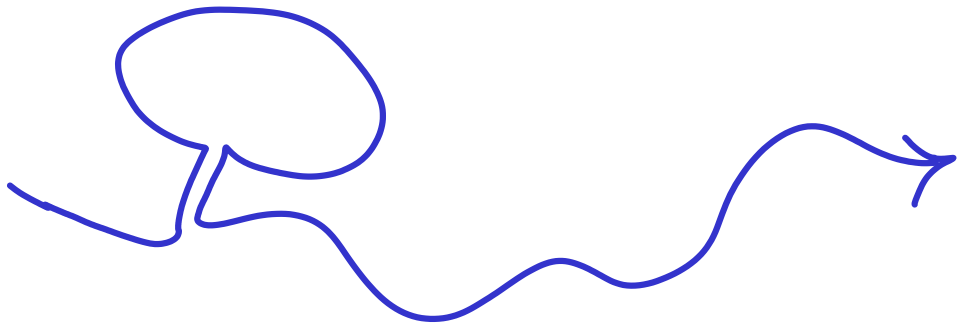

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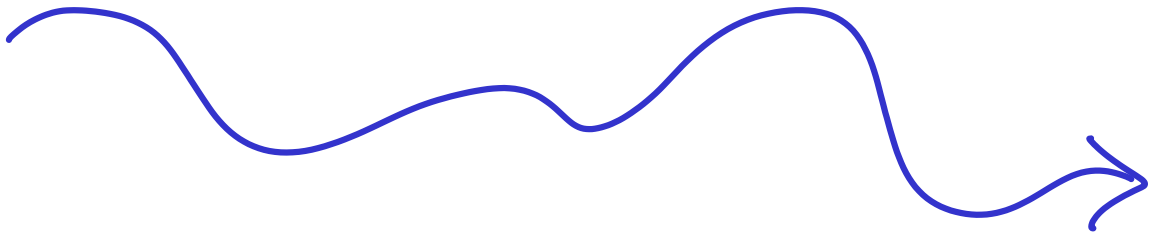

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Summary & Acknowledgements:

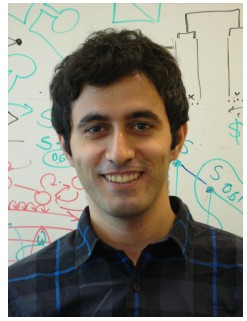
Key points:

- local RNA structure can be involved in regulating splicing via RNA structure changes

  Concept of *alternative RNA structure expression*.

- repeats may play a functional role in regulating splicing

  N.B.: 10% of human genome are Alu-repeats. These could constitute potential A-to-I editing sites.



A. Mazloomian

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