

MINTIE is a catch-all cryptic variant finder for cancer RNA-seq data

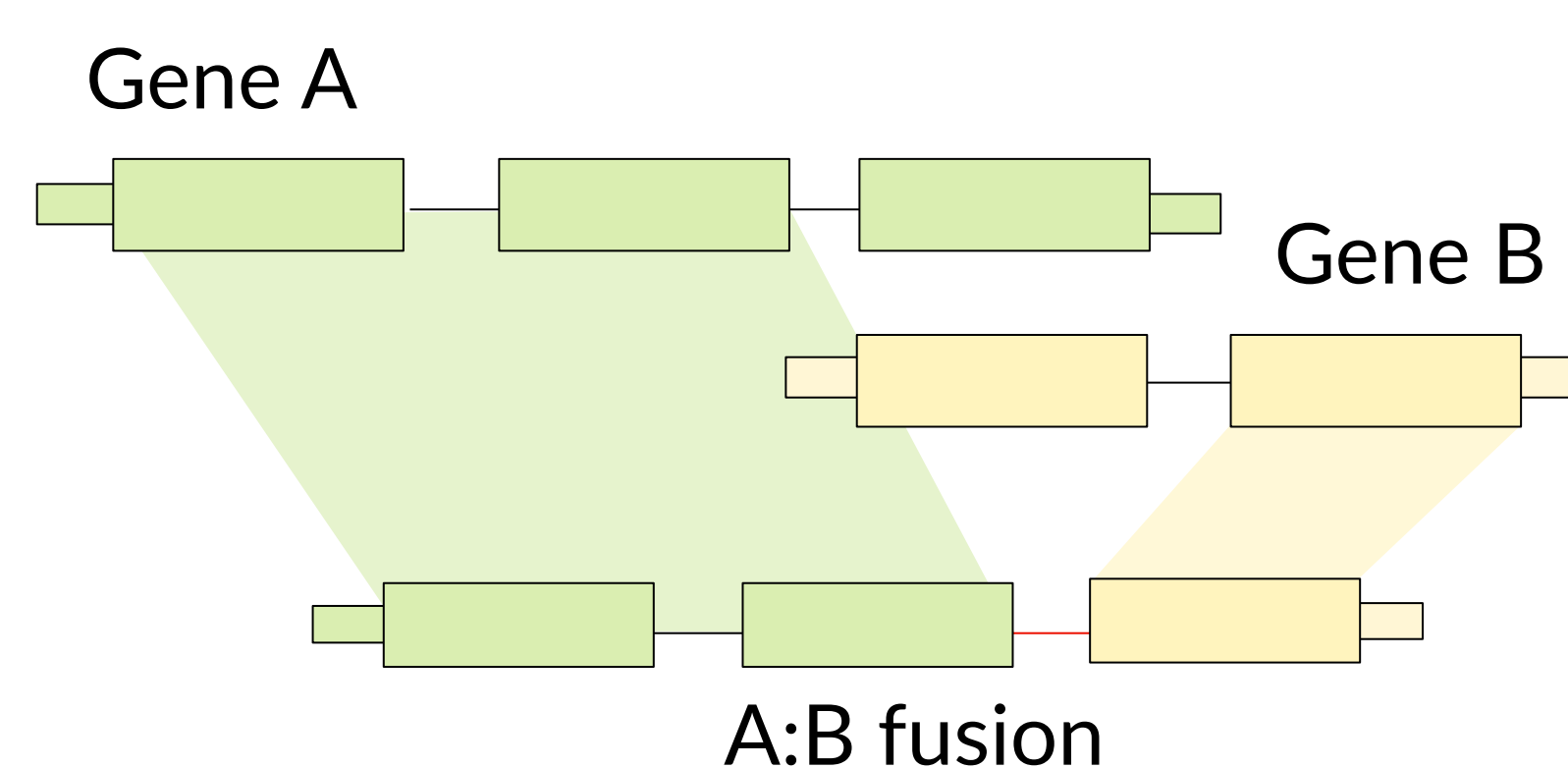
Marek Cmero, Breon Schmidt, Ian Majewski, Paul Ekert, Alicia Oshlack, Nadia Davidson

Motivation

- **Cryptic variants** are observed in **cancers**, and can create gain-of-function **driver** variants or disrupt **tumour suppressor** genes.
- Cryptic variants are difficult to detect in RNA-seq with current tools.

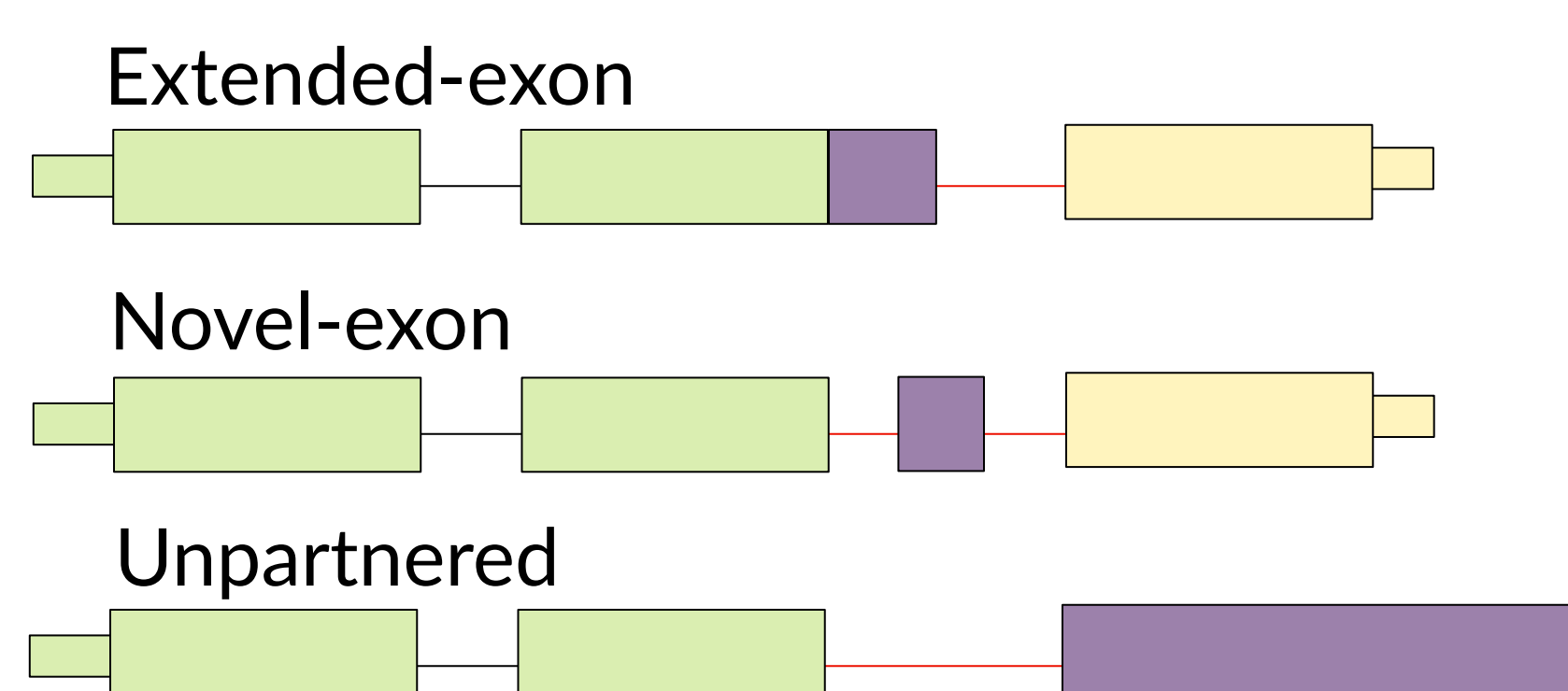
What are cryptic variants?

Let's consider the **canonical fusion** as a single gene product formed by two genes joined at an **exon-exon boundary**:



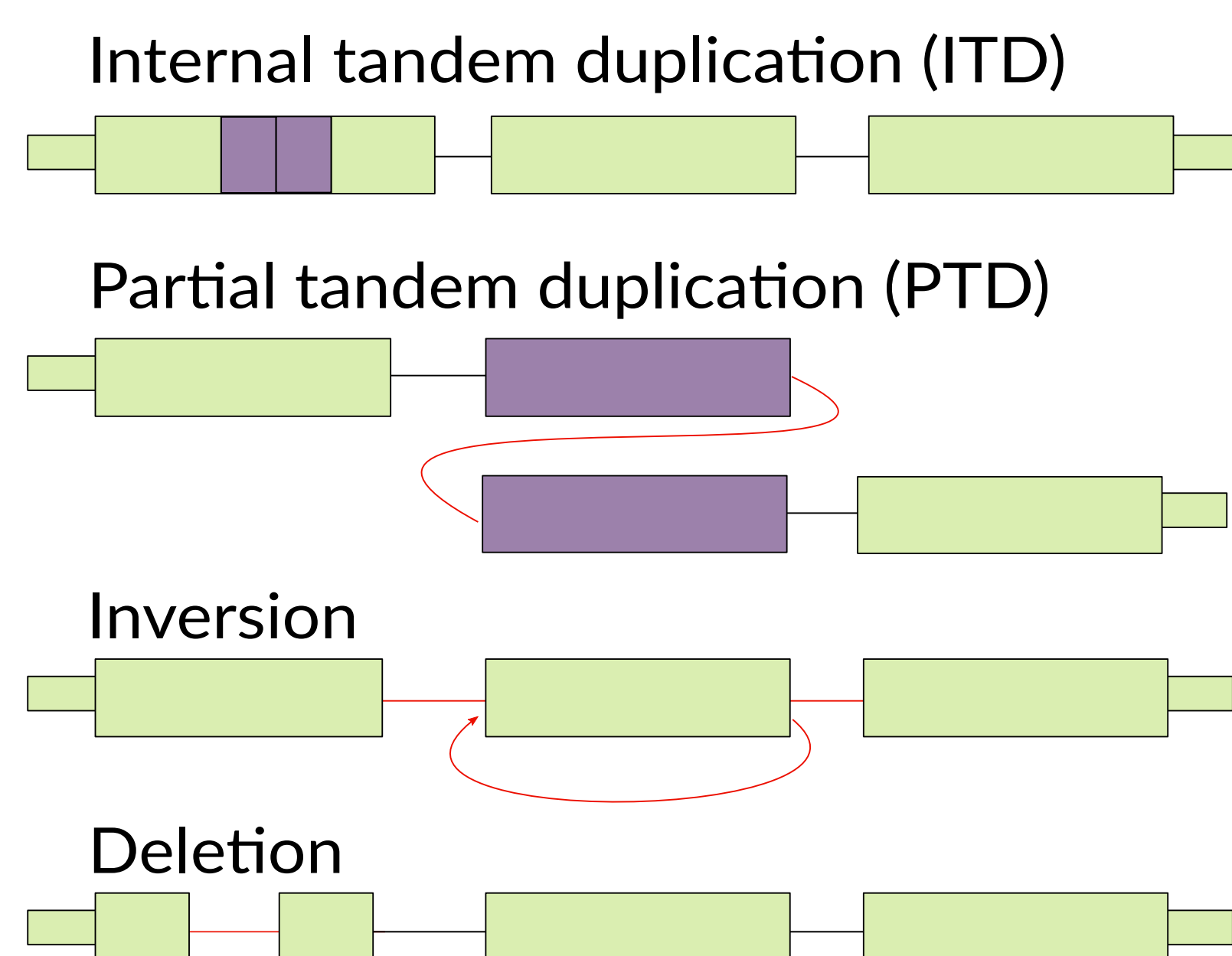
Fusion finders use very strict filters and do not consider non-standard fusions, such as:

Cryptic fusions

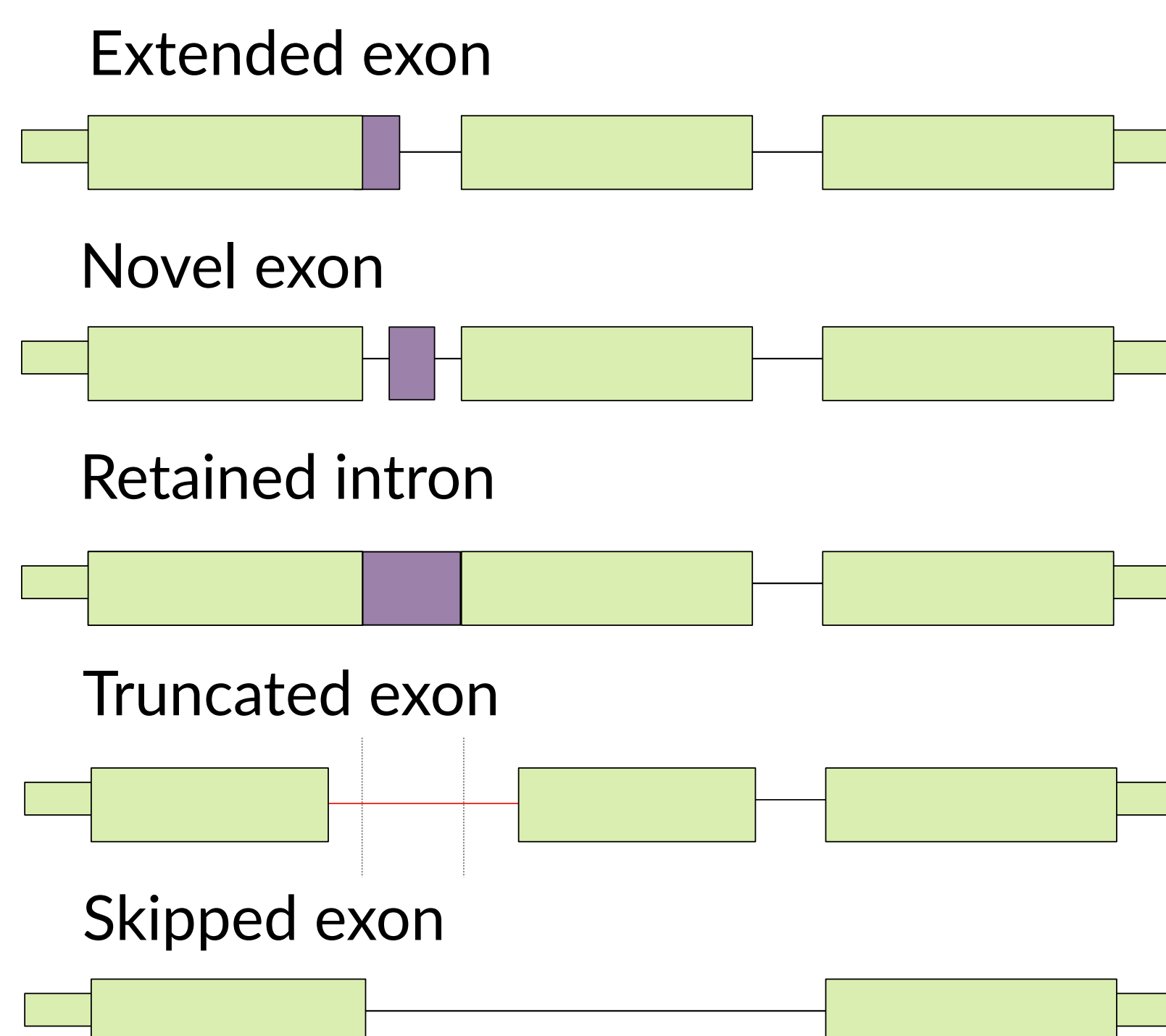


We also consider **cryptic variants** in single-genes:

Transcribed structural variants

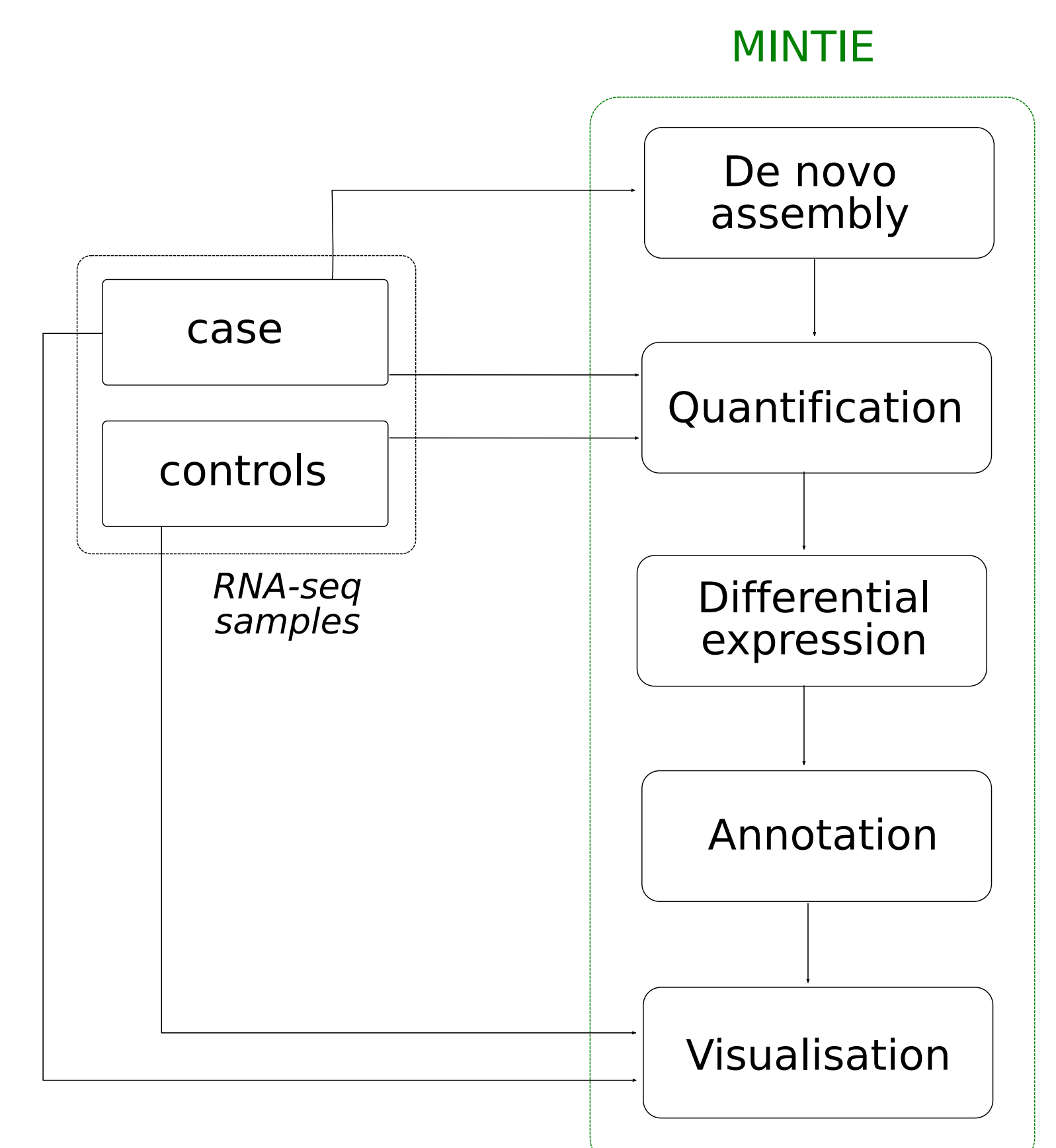


Novel splice variants



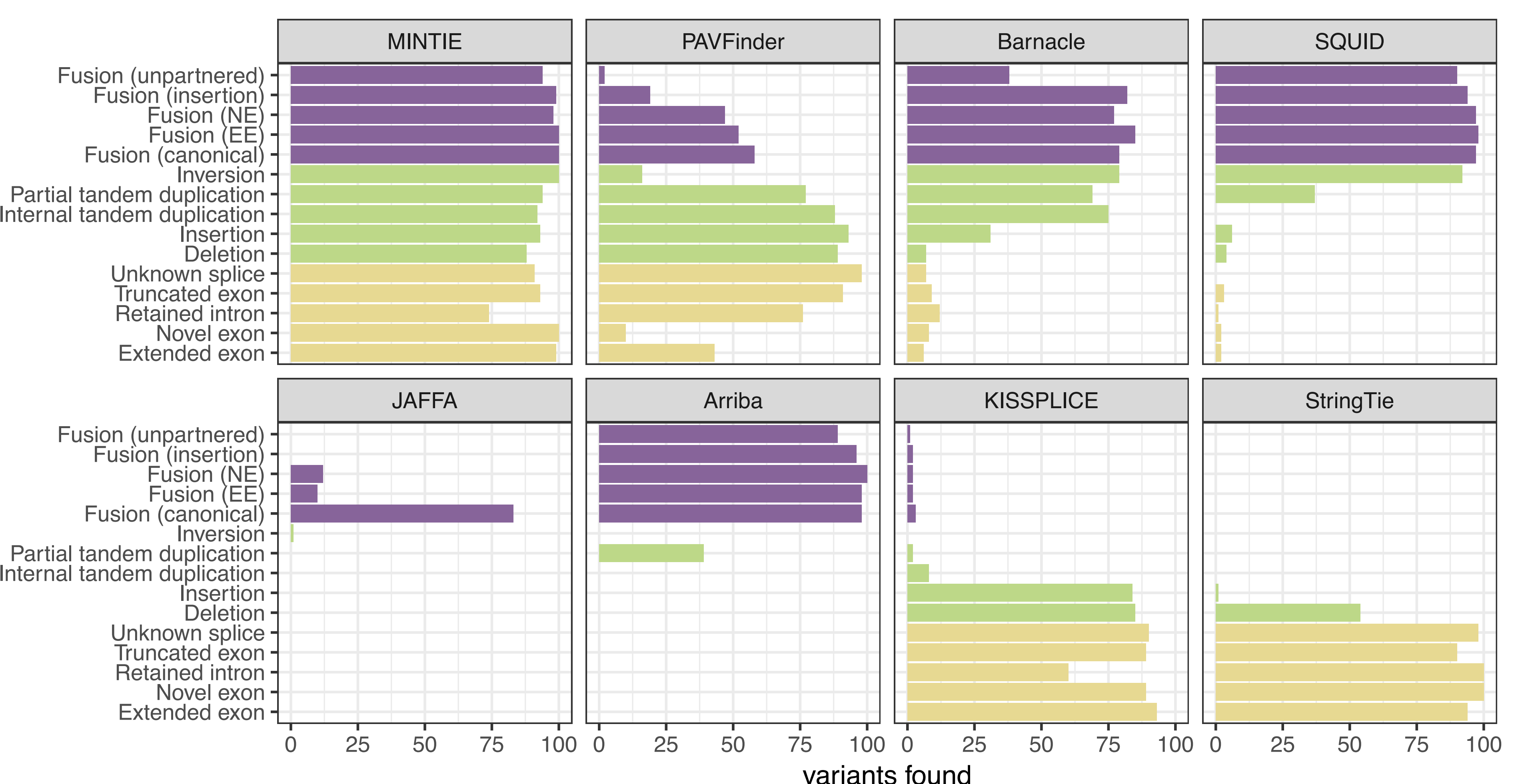
The MINTIE method

1. **De novo assemble** all transcripts in the case (cancer) sample.
2. **Quantify** all assembled transcripts in cancer and a set of controls (may be other cancer samples).
3. Perform **differential expression** on assembled transcripts (case vs. controls).
4. **Align** significant transcripts and **identify novel regions**.
5. Output IGV tracks for **visualisation**.



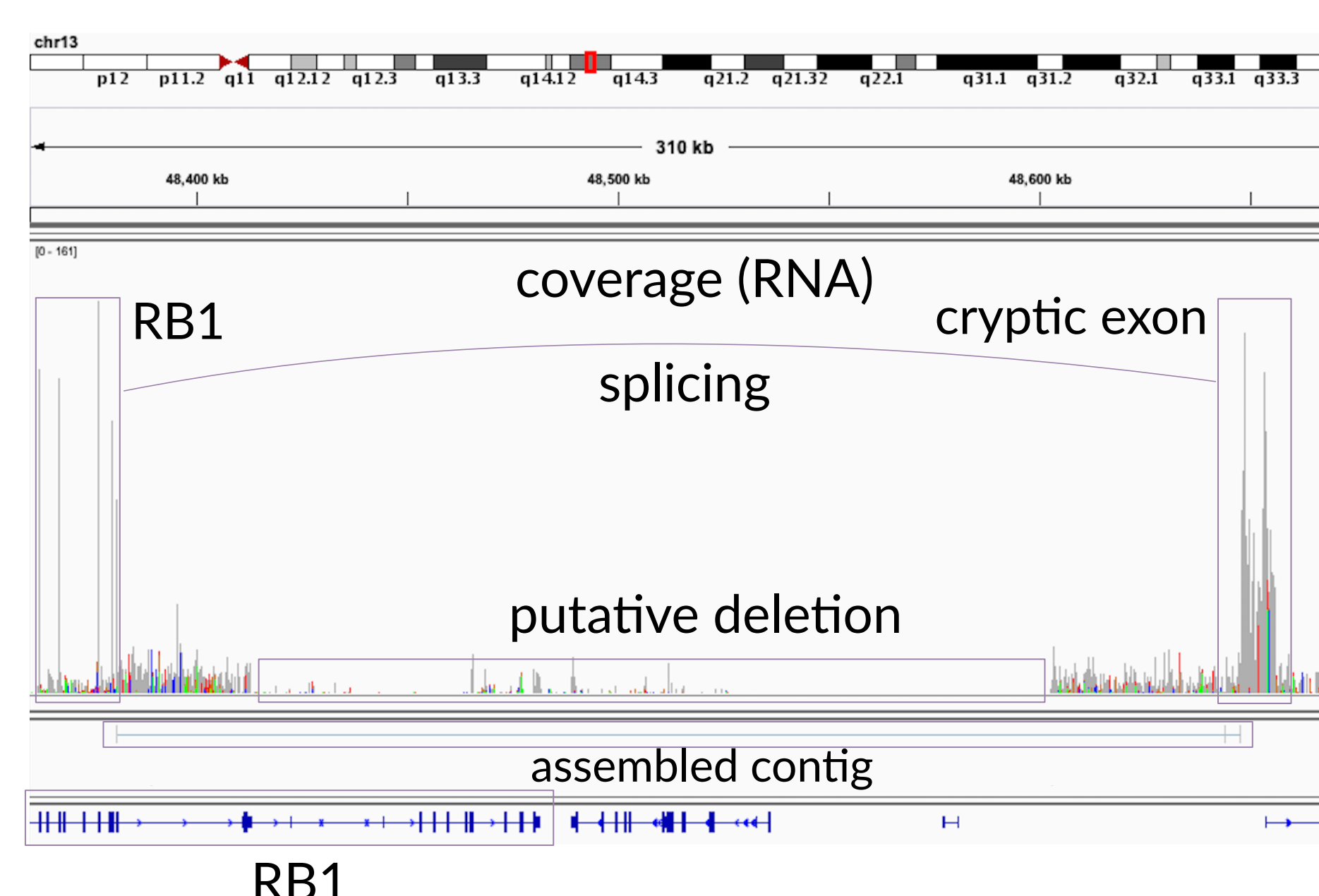
Simulation results

- We simulated **1500 variants** across **15 types**.
- **MINTIE** successfully found **>93%** of variants.
- We ran these simulations on 7 other tools and found that **MINTIE** could find and annotate **more variants than any other method**.

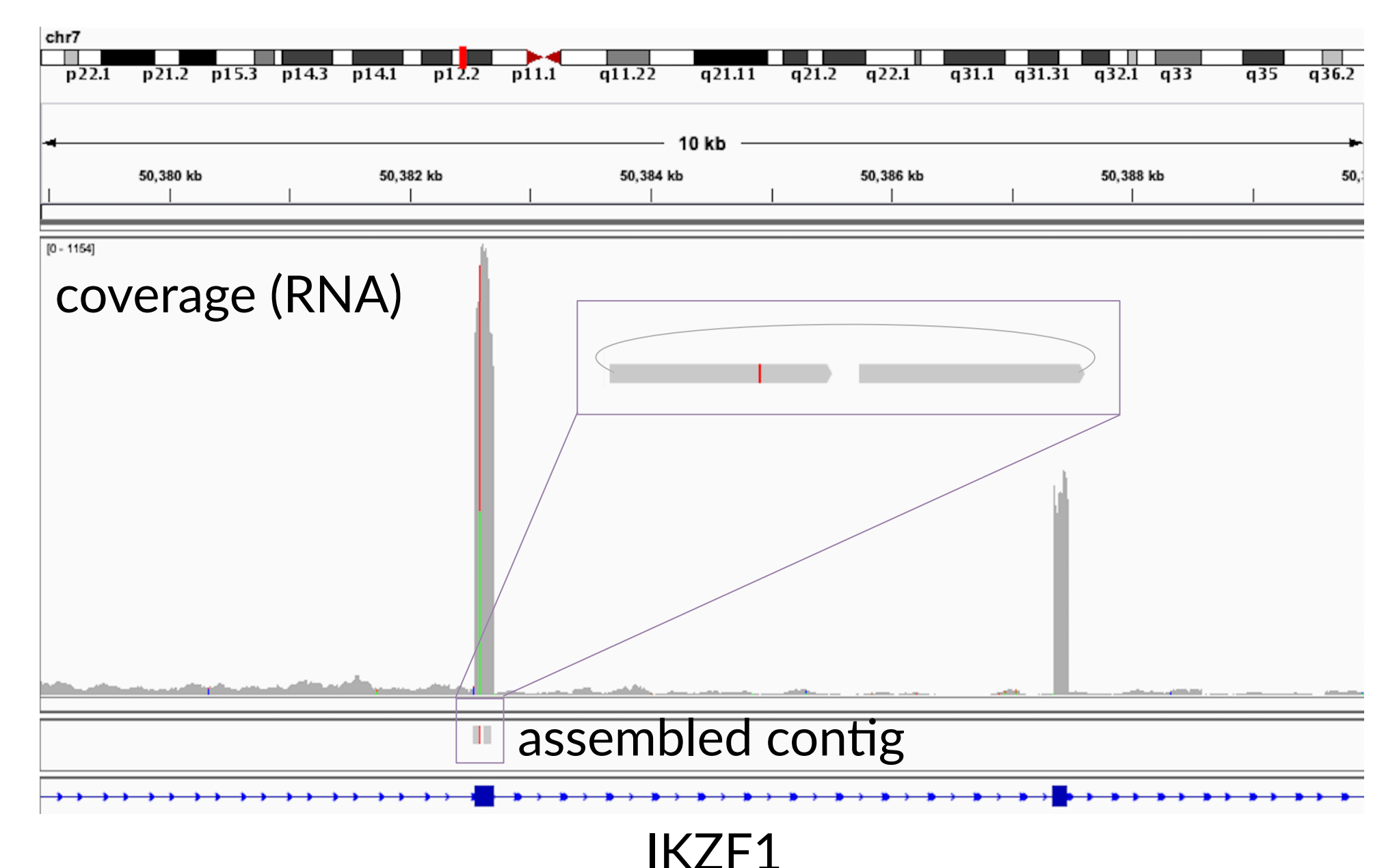


Candidate cryptic variants in paediatric leukaemia

We ran **MINTIE** on 97 B-ALLs from the Royal Children's Hospital, and found several clinically relevant cryptic variants, including the following in two patients with high risk disease and no previously detected relevant alterations.



Novel downstream exon reveals likely **loss-of-function** deletion in tumour suppressor **RB1**.



PTD found in **IKZF1**, known gene associated with B-cell acute lymphoblastic leukaemia and regulator of lymphocyte differentiation.

