UNIVERSITY OF UTAH SCHOOL OF MEDICINE | Department of Human Genetics

Analysis of structural variation

Alistair Ward
USTAR Center for Genetic Discovery
University of Utah

USTAR Center for Genetic Discovery

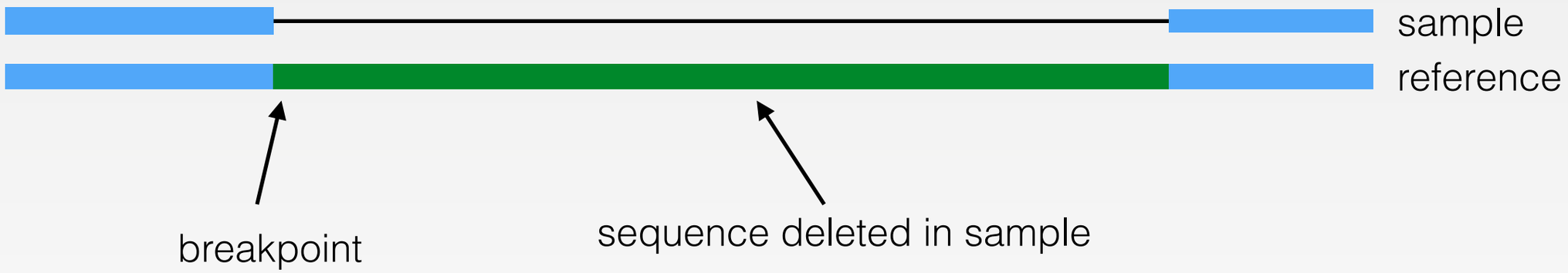
What is structural variation?

- What differentiates SV from short variants?
- What are the major SV types?
- Summary of MEI detection

USTAR Center for Genetic Discovery

What is an SV?

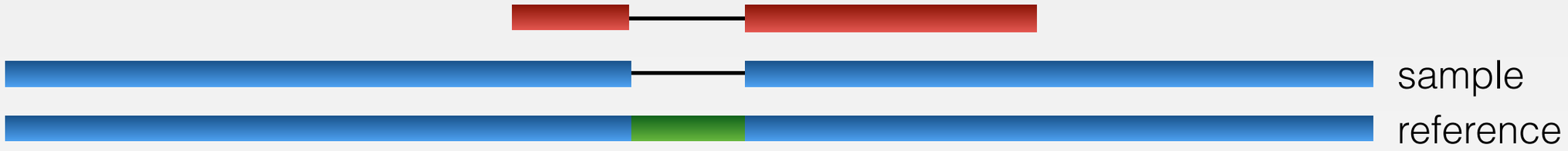
- Often considered to be >1kb or larger
- Practically, often considered >= read length



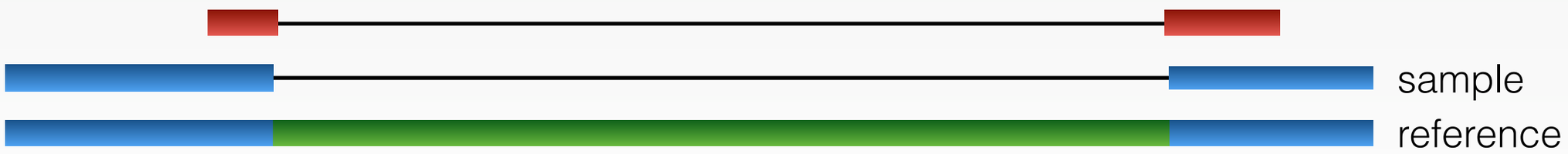
USTAR Center for Genetic Discovery

What is an SV?

- Often considered to be >1kb or larger
- Practically, often considered >= read length



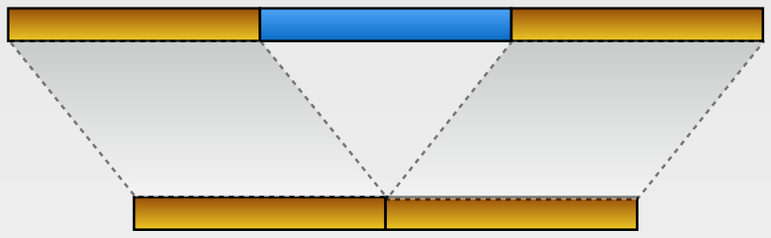
short deletion - mapping can span the gap
can be detected with short variant detectors



structural variation - mapping cannot span the gap
cannot generally be detected with short variant detectors

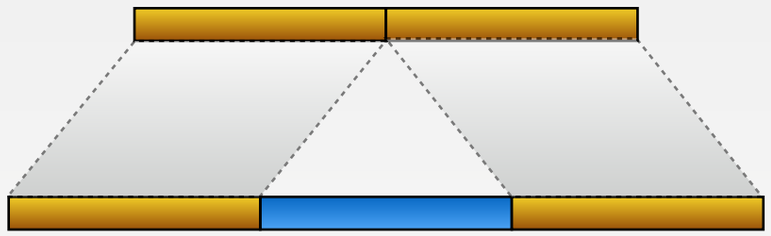
SV types

Deletion



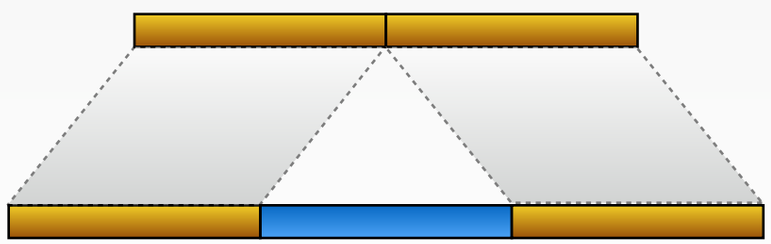
If inserted sequence/deletion ≦ 50bp
-> indel

Novel insertion



sequence ≧ 50bp
-> Copy number variation

Mobile element insertion



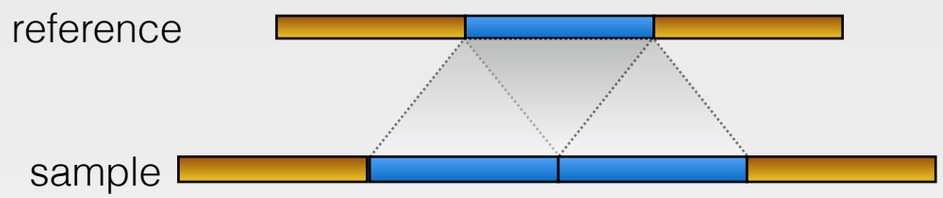
Mobile element sequence is ubiquitous in the genome

USTAR Center for Genetic Discovery

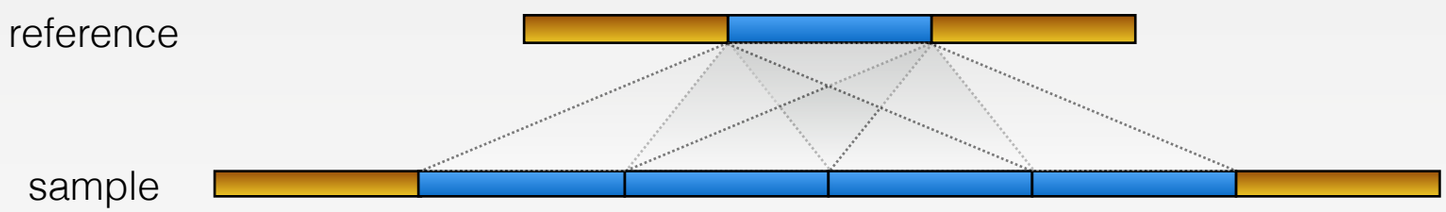
SV types

Duplications cause problems for mappers. From which copy of the duplicated sequence did the read originate?

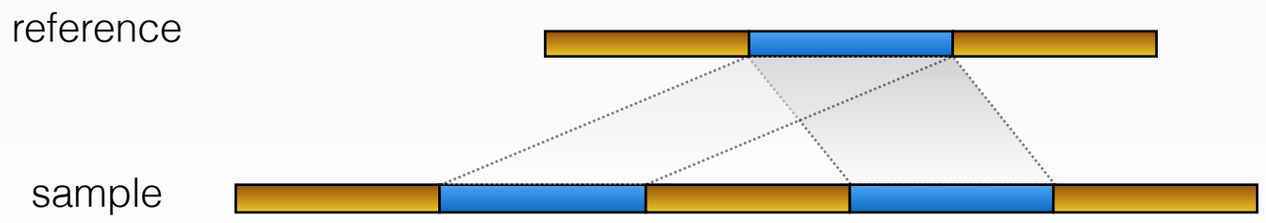
Tandem duplication



Amplification



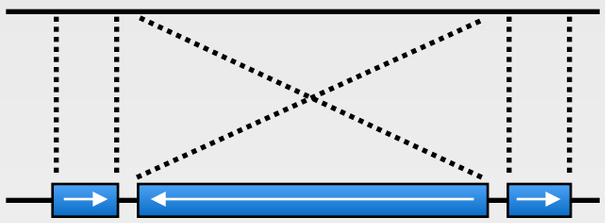
Interspersed duplication



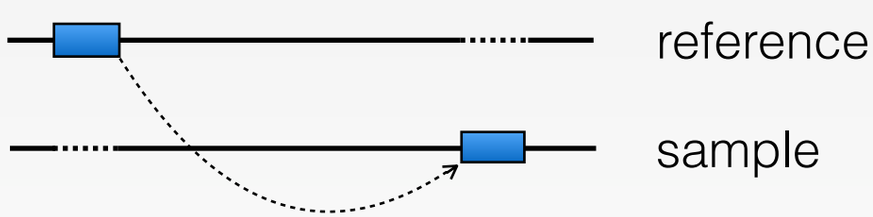
USTAR Center for Genetic Discovery

SV types

Inversion



Mappers will not be able to place reads correctly in the inversion, or across the breakpoints



Mappers will be able to place reads in the translocated sequence, but fail at the breakpoints

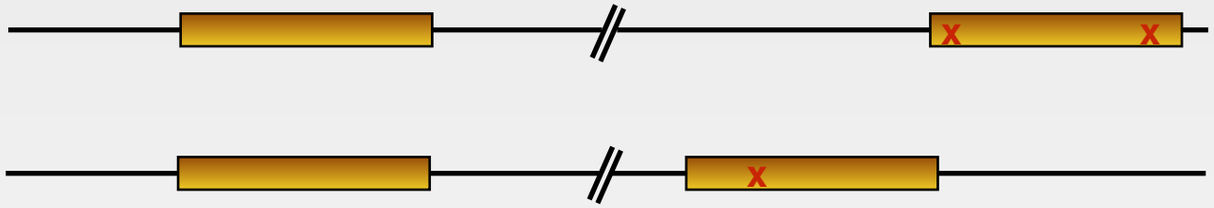
Mobile element insertions (MEIs)

- Retrotransposons comprise nearly 50% of the human genome
- Implicated in a number of diseases, (Crohn's disease, haemophilia, …)
- non-LTR transposons are still active in the human genome
- Why can't we use short variant detectors to find MEIs?

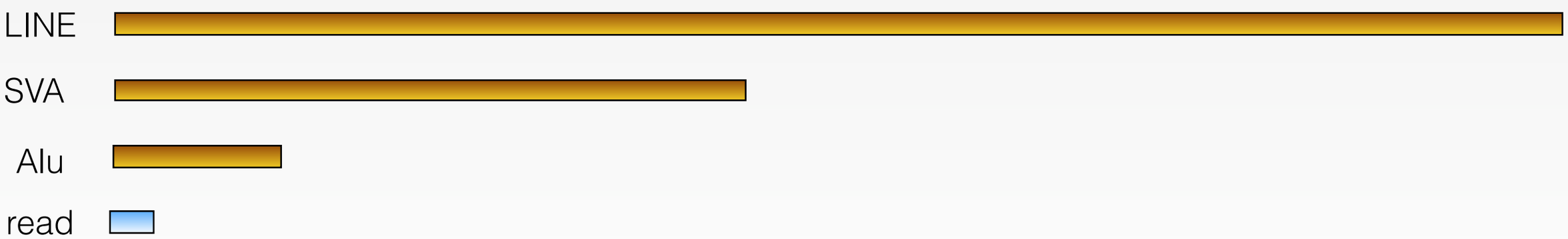
USTAR Center for Genetic Discovery

MEI detection

MEIs are repetitive



MEIs are large with respect to read length*

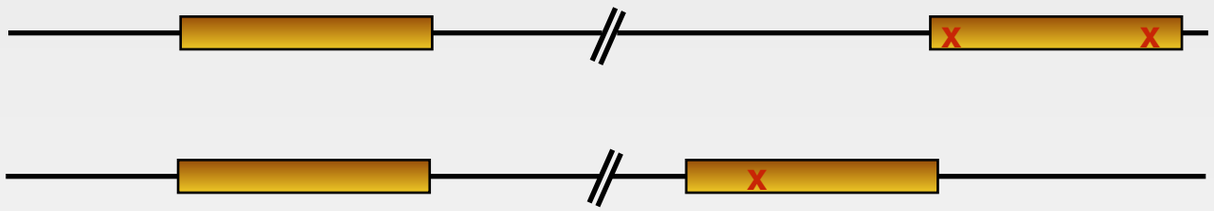


USTAR Center for Genetic Discovery

* sequencing technologies are closing this gap!

Map reads from MEIs

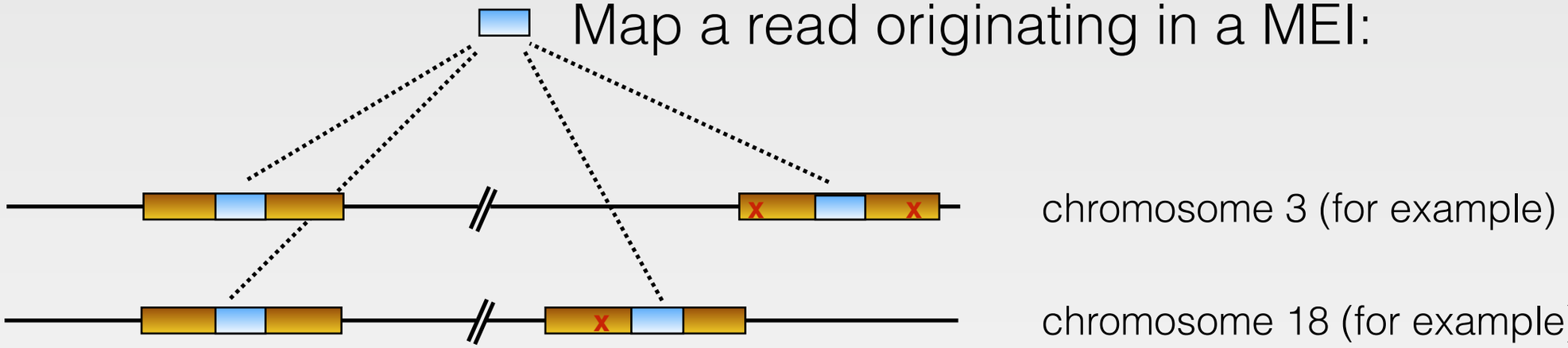
Map a read originating in a MEI: 



USTAR Center for Genetic Discovery

* sequencing technologies are closing this gap!

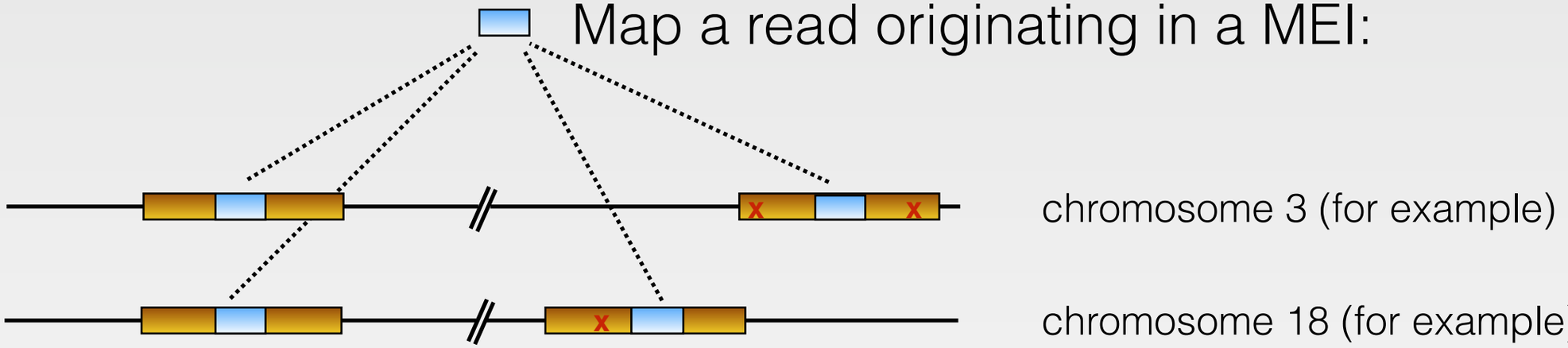
Map reads from MEIs



What did we learn? - Not much

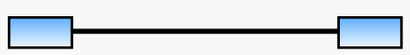
USTAR Center for Genetic Discovery

Map reads from MEIs



What did we learn? - Not much

But remember, we have read pairs!



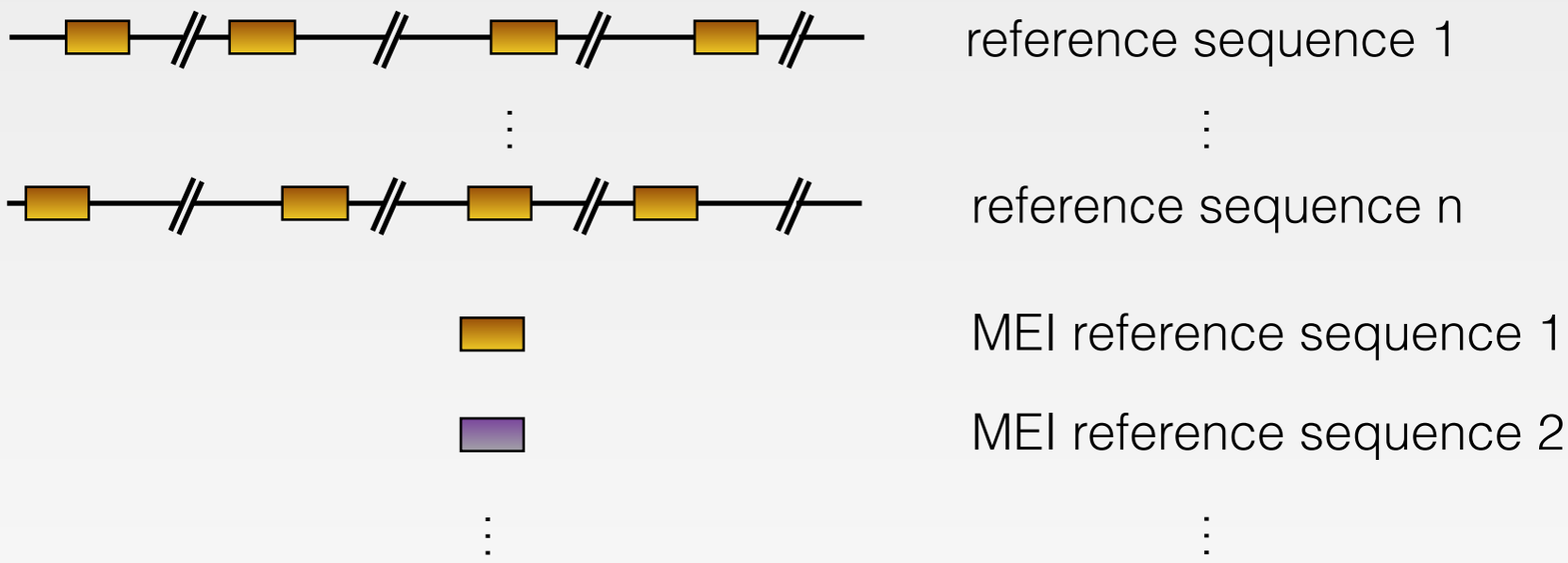
The DNA fragment isn’t so small!

USTAR Center for Genetic Discovery

Update to mapping strategy

There are well over 1,000,000 Alu elements in the human genome

Recall our mapping strategy?



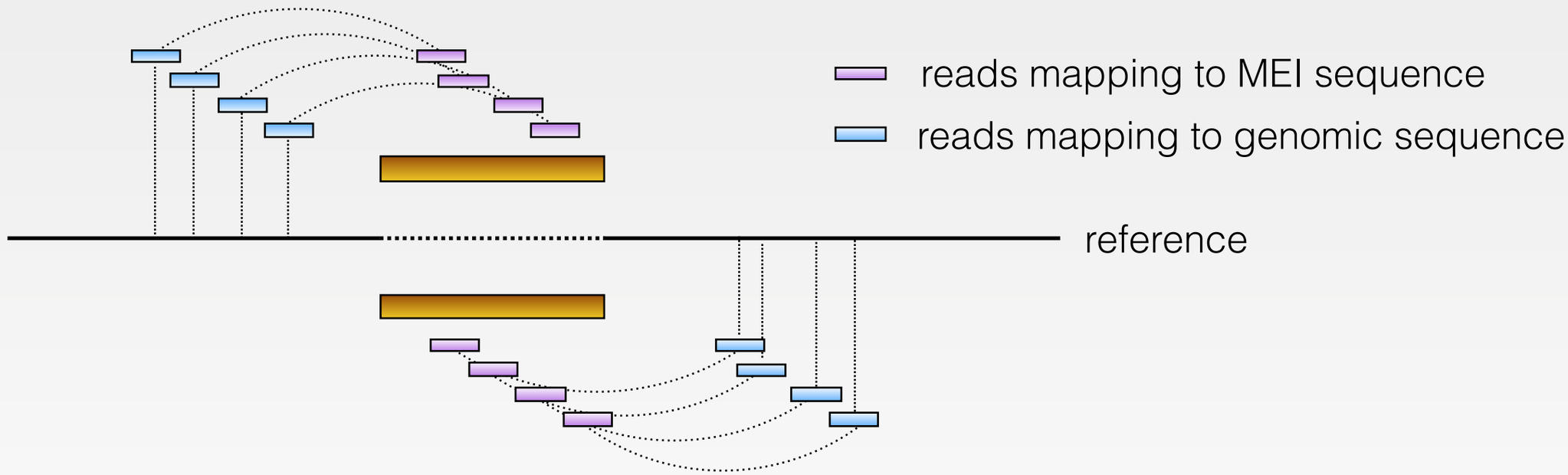
read → Hash read and find clusters in the reference

If clusters in MEI sequence, don't bother looking in the genome

USTAR Center for Genetic Discovery

Evidence for non-reference MEI

Search for fragments with one mate uniquely mapped
and the other falling within an MEI

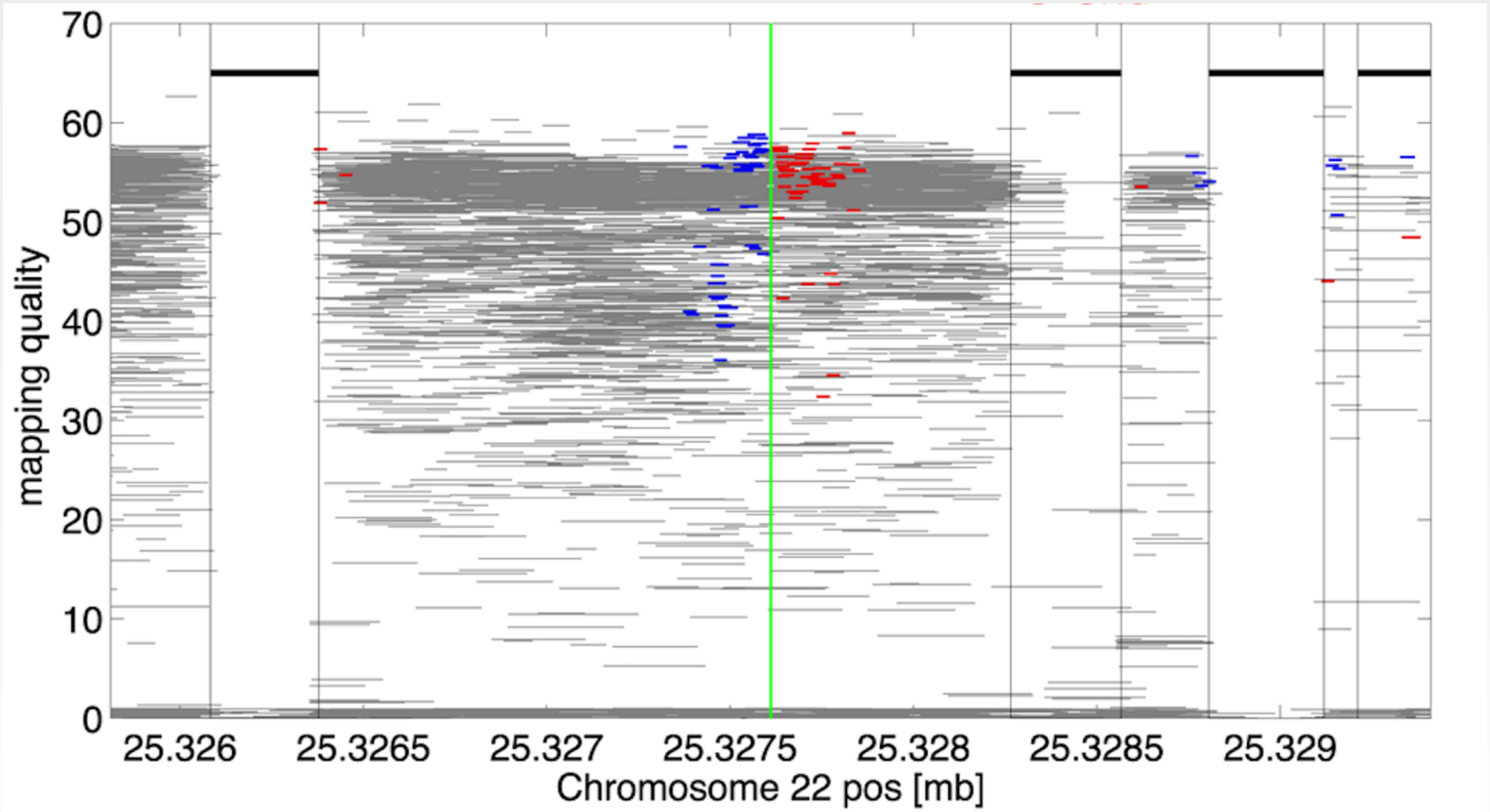


Demand fragments spanning into MEI from both
the 3’ and the 5’ end

USTAR Center for Genetic Discovery

‘Spanning in’ evidence

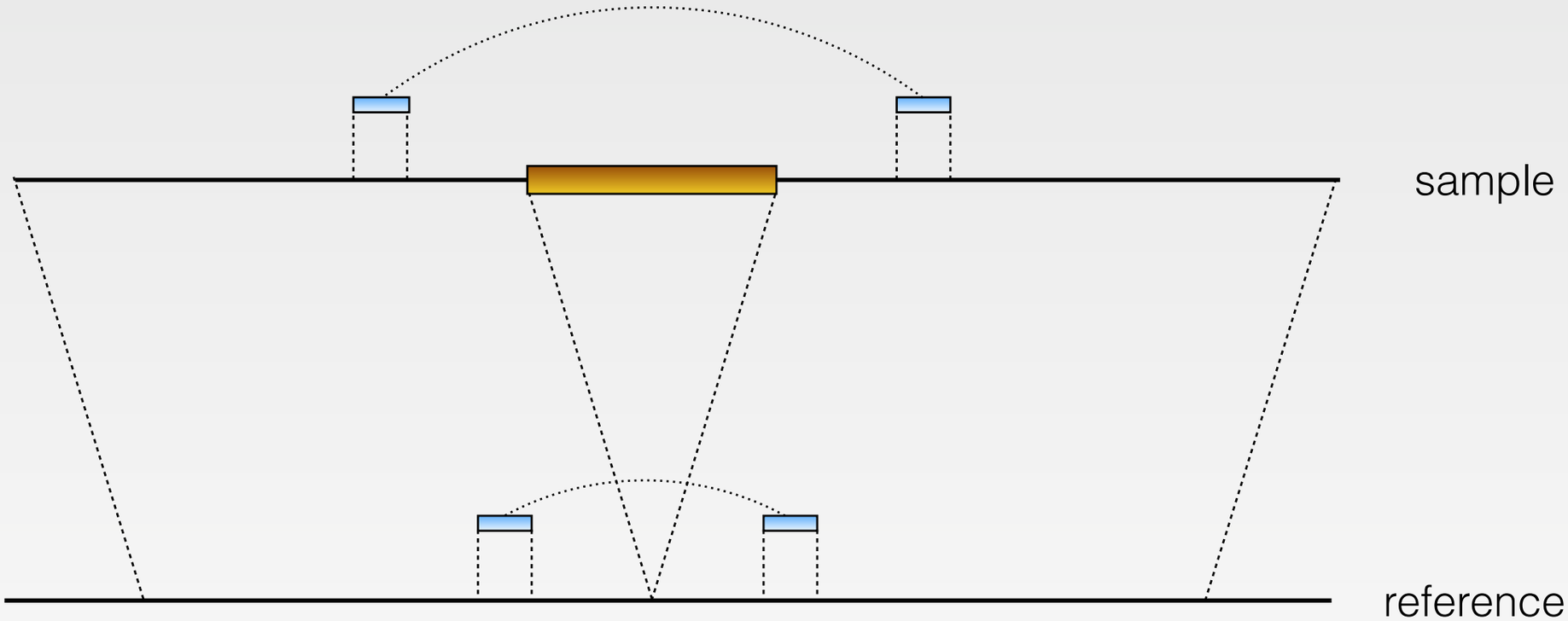
1000 Genomes Pilot Project data



USTAR Center for Genetic Discovery

A Comprehensive Map of Mobile Element Insertion Polymorphisms in Humans, Stewart et. al., (2011)

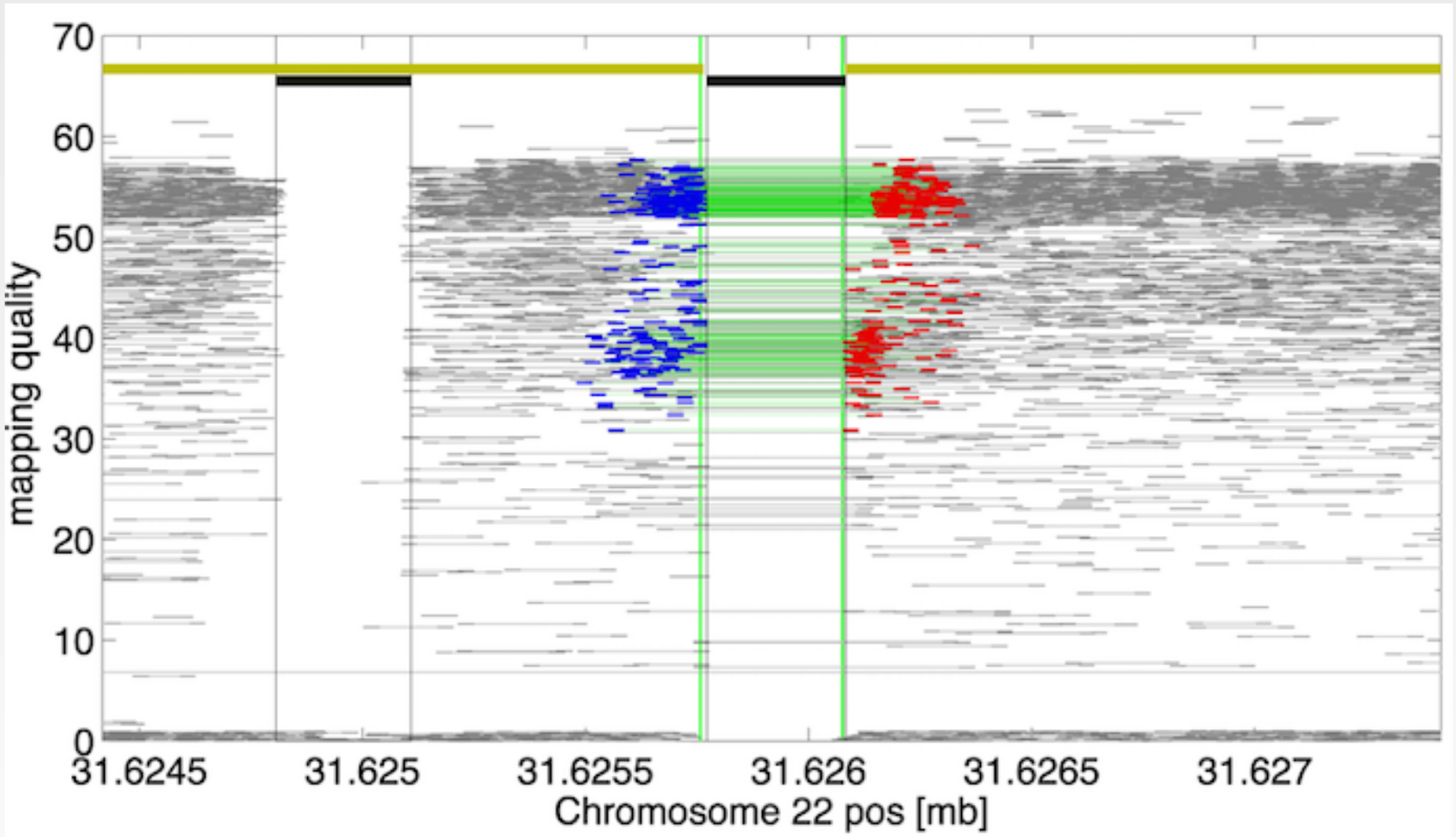
Span across a (non)-reference MEI



Search for mappings with abnormally short or long fragment lengths

USTAR Center for Genetic Discovery

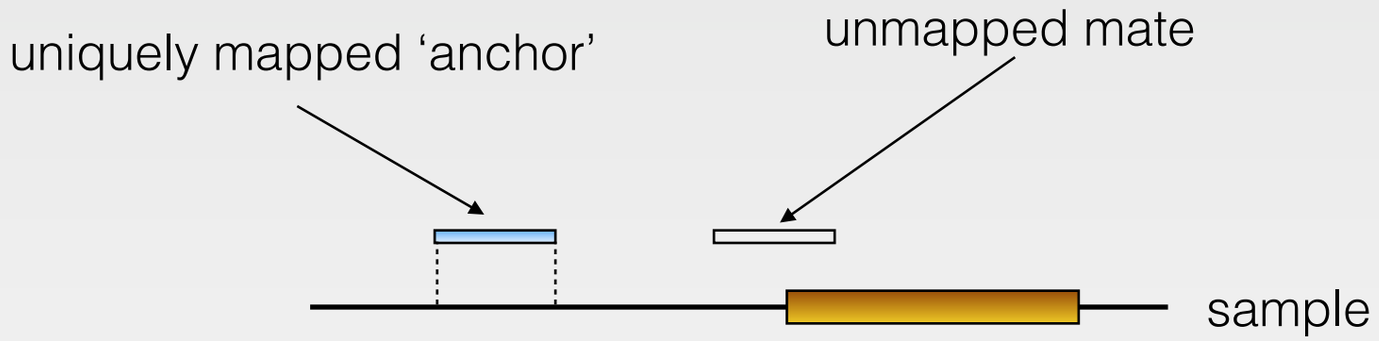
‘Spanning across’ evidence



USTAR Center for Genetic Discovery

A Comprehensive Map of Mobile Element Insertion Polymorphisms in Humans, Stewart et. al., (2011)

Split read evidence



Attempt to:

a) map unmapped mate to reference in a window based on anchor position and fragment length distribution

b) map unmapped mate to known MEI sequences

USTAR Center for Genetic Discovery

Summary

- Modify mapping to explicitly look for MEI mappings (Mosaik is set up to do this)

- Collate evidence from read pair and split read signals

- Leverage population to improve coverage

- Use local graph alignment to aid in genotyping