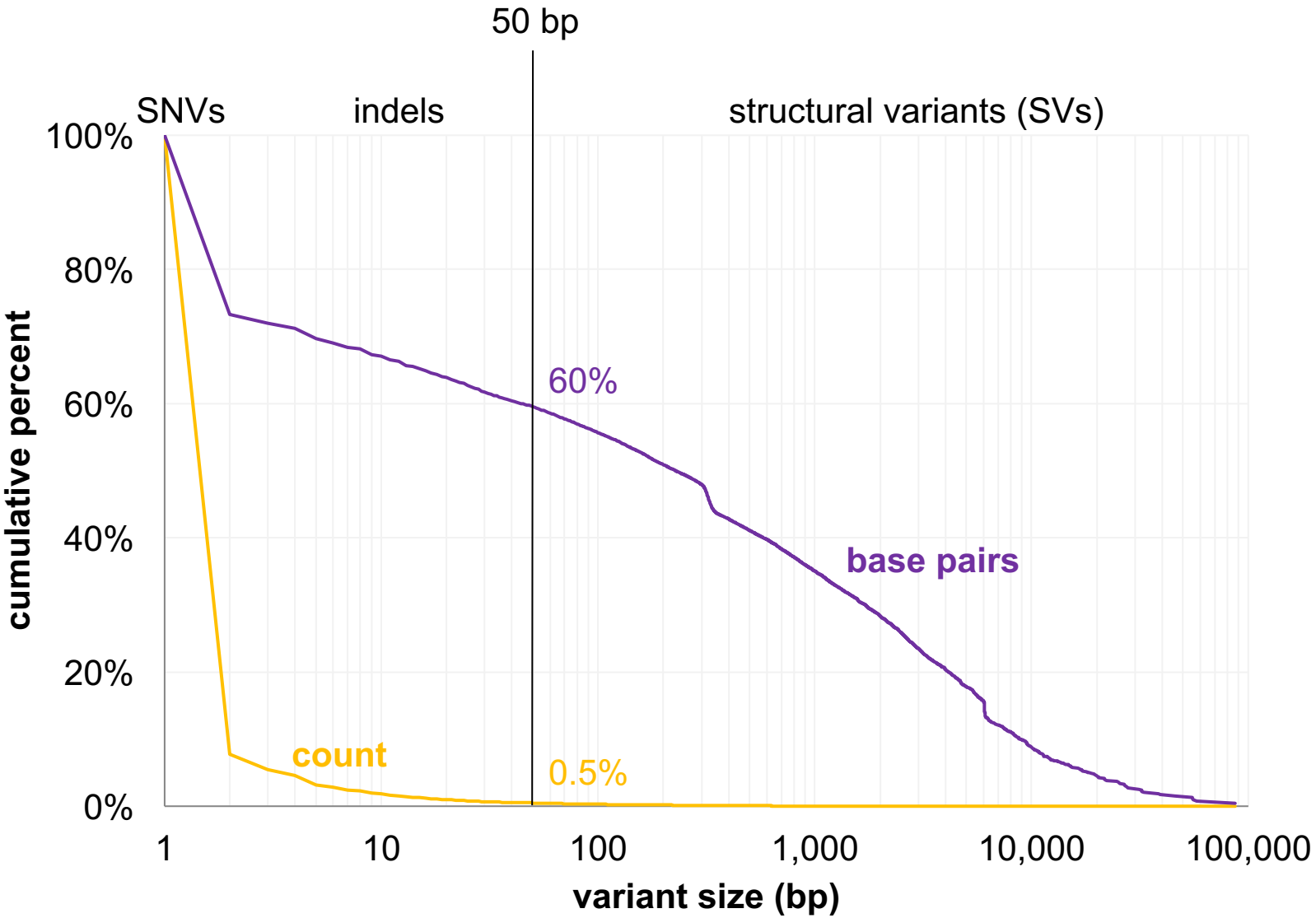
Identifying Structural Variants in Individuals and Populations with PacBio Long Reads

Aaron Wenger

2017-01-17

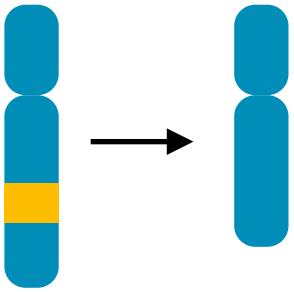
VARIATION IN A HUMAN GENOME – HG00733



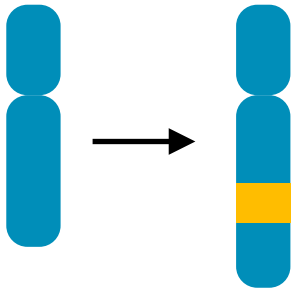
Chaisson et al. (2017) *bioRxiv*. doi:10.1101/193144.

TYPES OF STRUCTURAL VARIATION

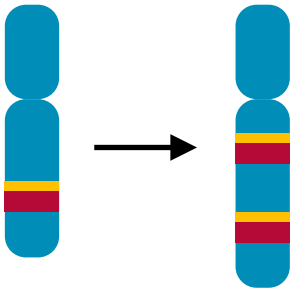
deletion



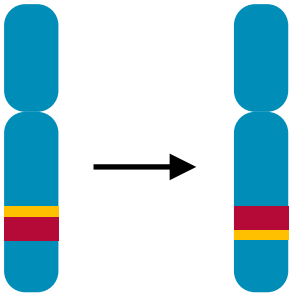
insertion



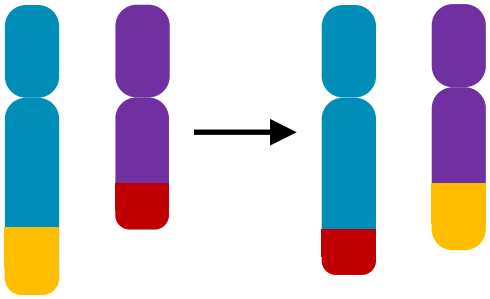
duplication



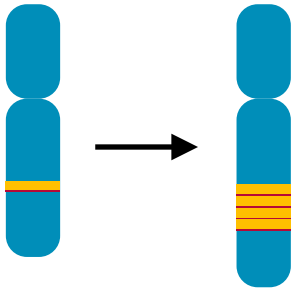
inversion



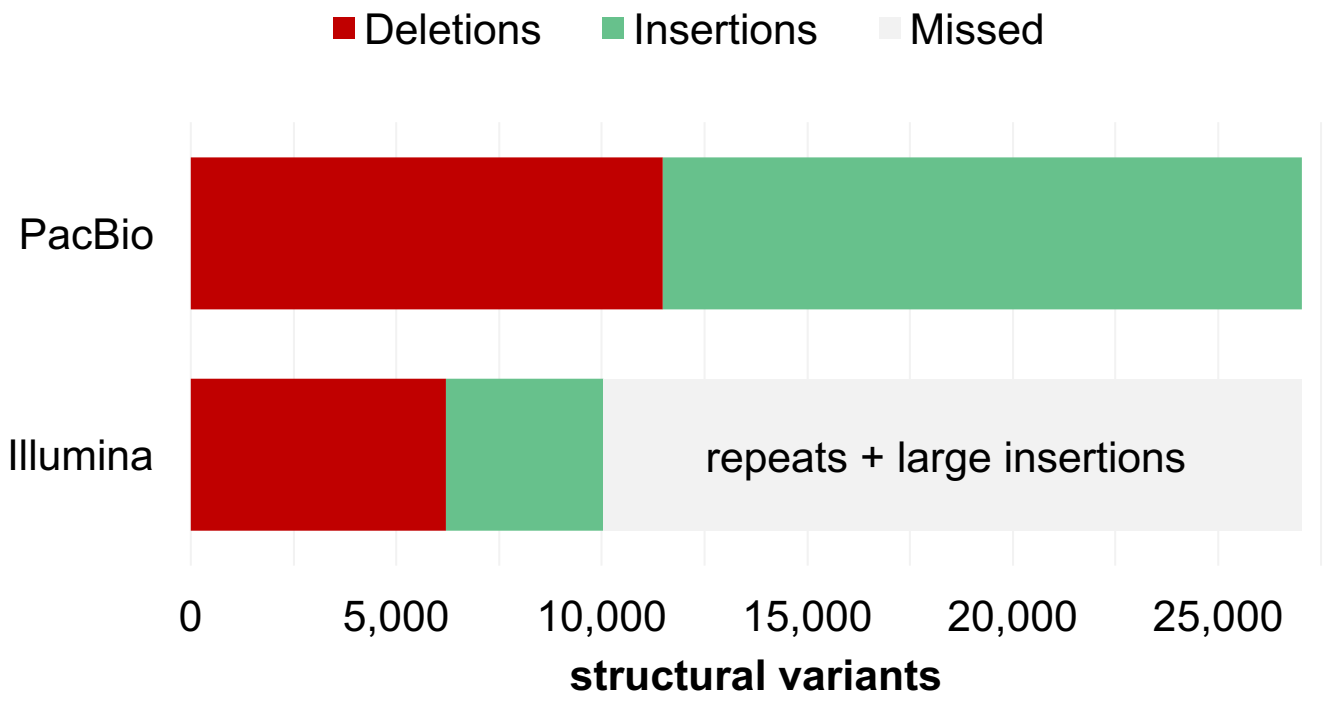
translocation



repeat expansion

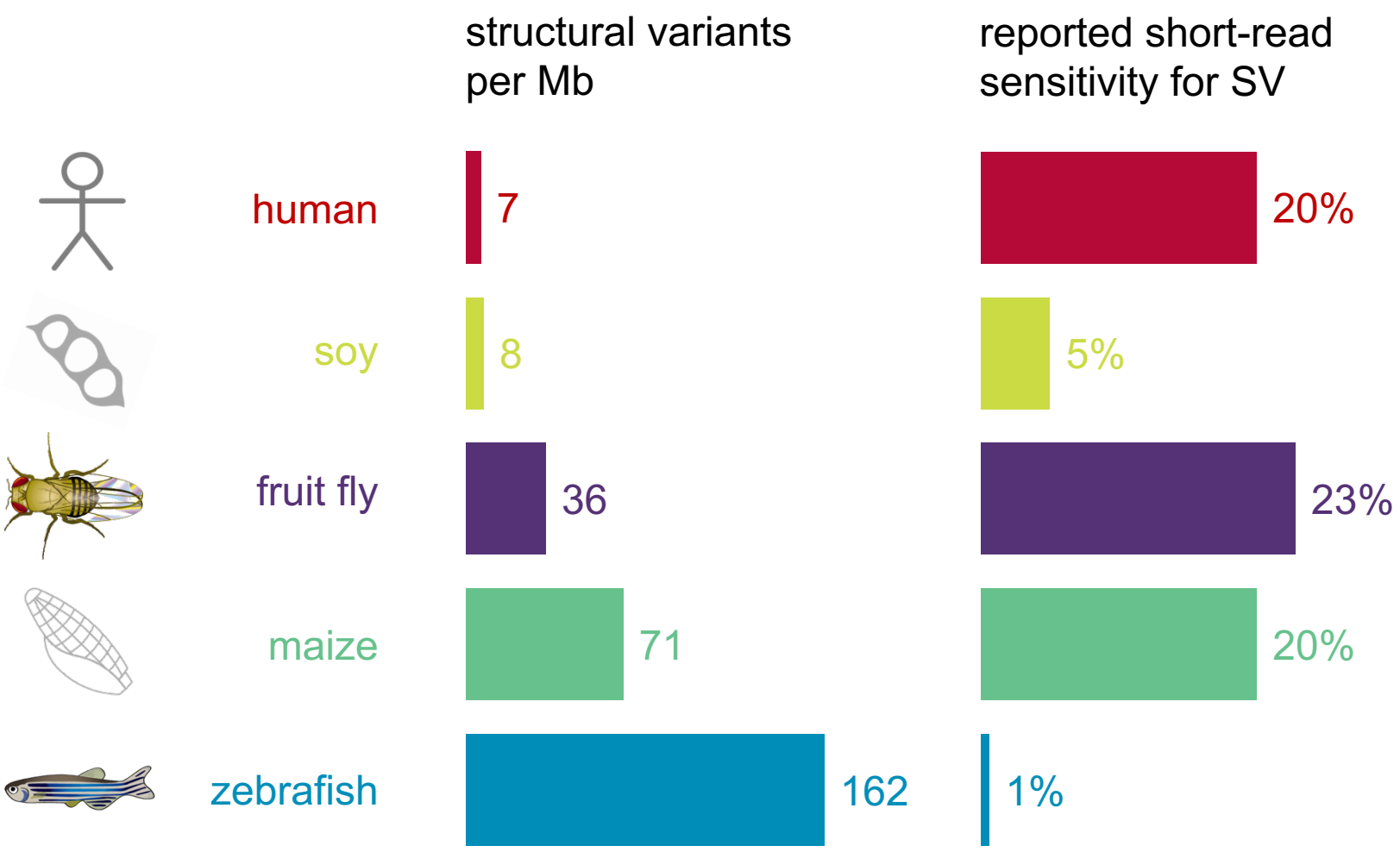


TECHNOLOGY TO DETECT STRUCTURAL VARIANTS



Chaisson et al. (2017) *bioRxiv*. doi:10.1101/193144.

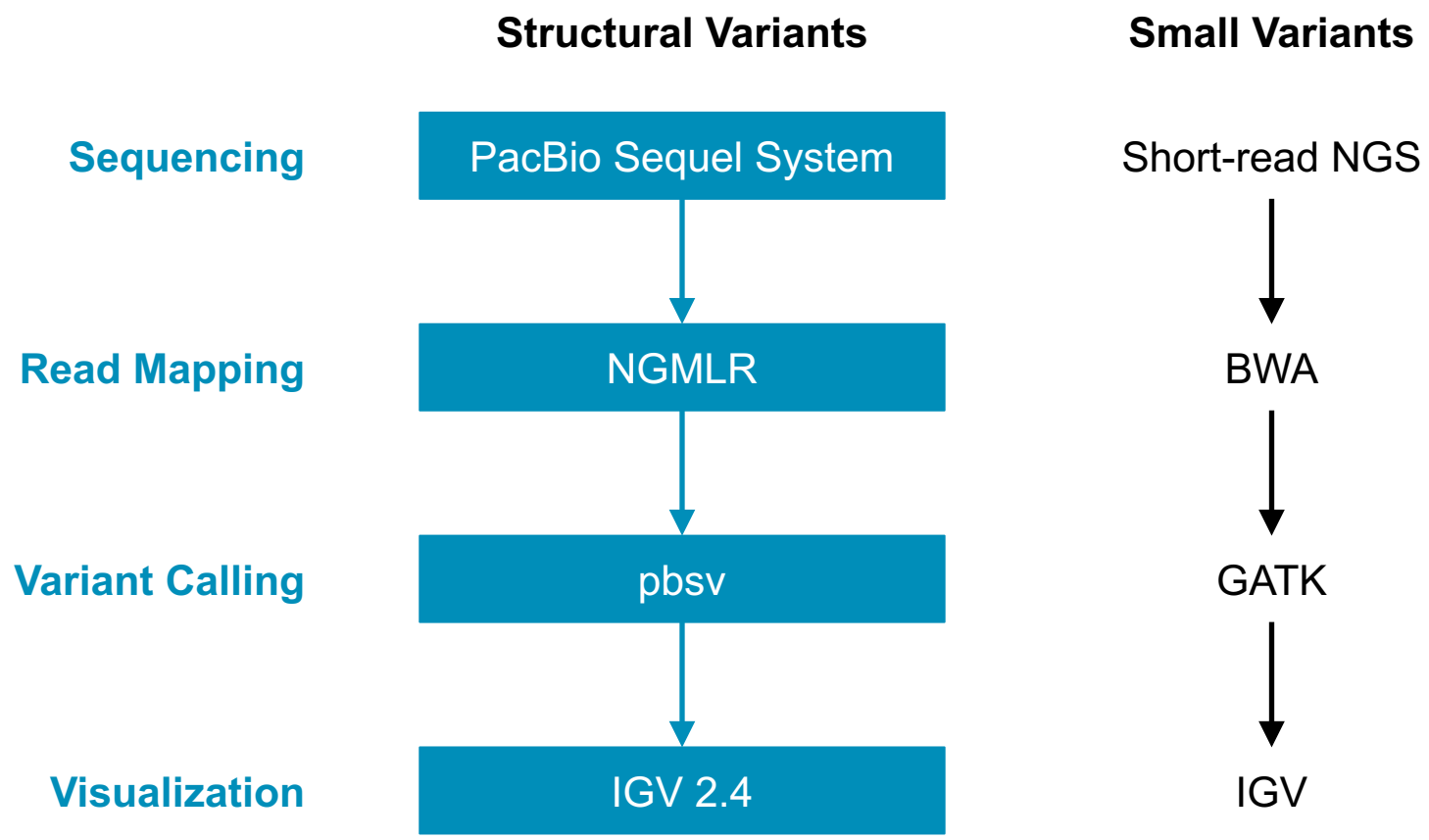
THE HUMAN GENOME IS COMPARATIVELY EASY



Huddleston et al. (2017) *Genome Research* 27(5):677-85.
Zichner et al. (2013) *Genome Research* 23(3):568-79.
Patowary et al. (2013) *Zebrafish* 10(1):15-20.

Concepcion et al. (2018) *PAG.*
Zebrafish image courtesy of Lizzy Griffiths

WGS FOR STRUCTURAL VARIANT DISCOVERY



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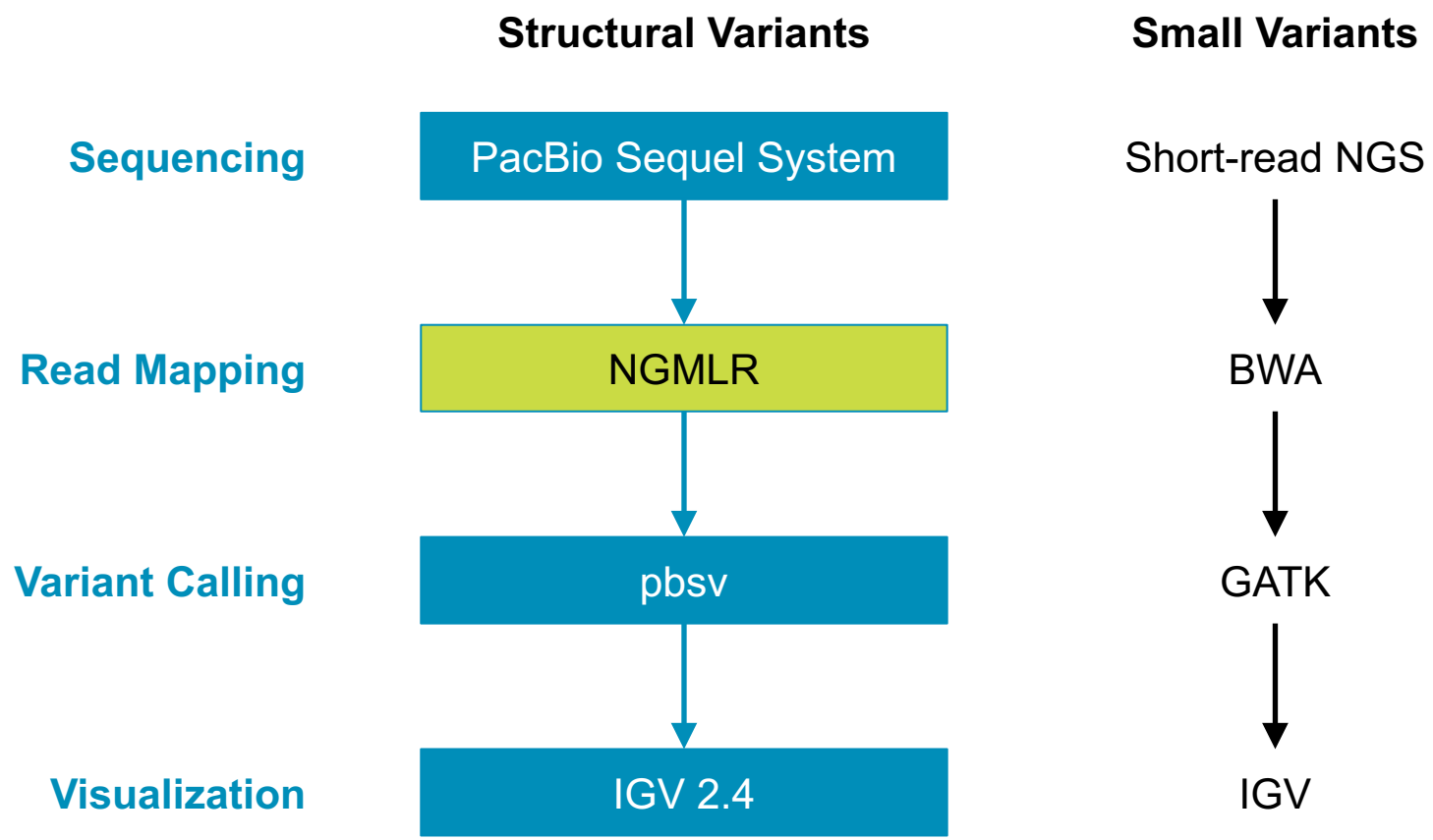
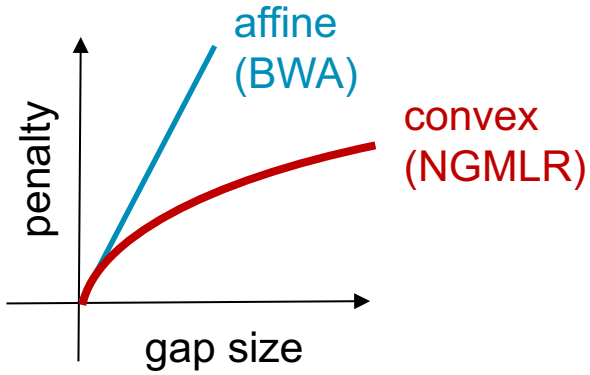
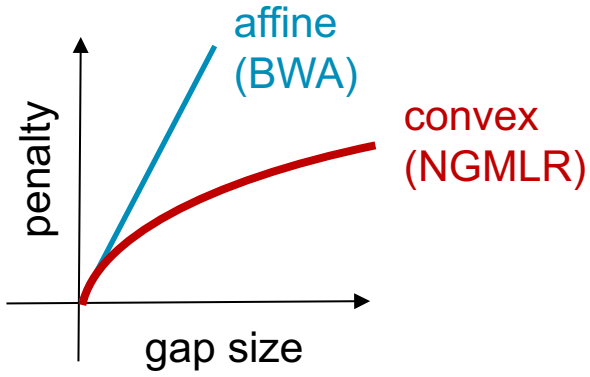


READ MAPPING

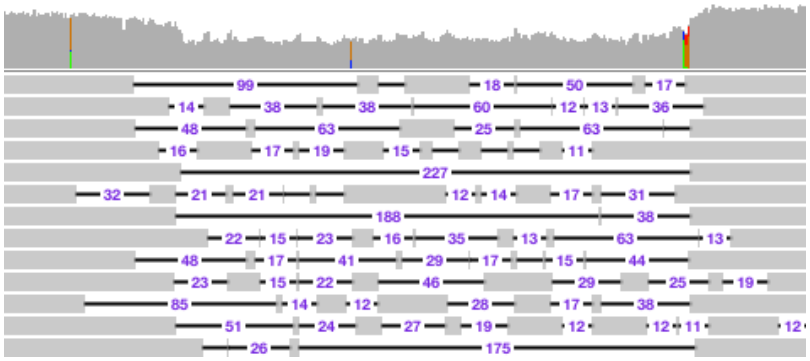


Sedlazeck et al. (2017) *bioRxiv*. doi:10.1101/169557.

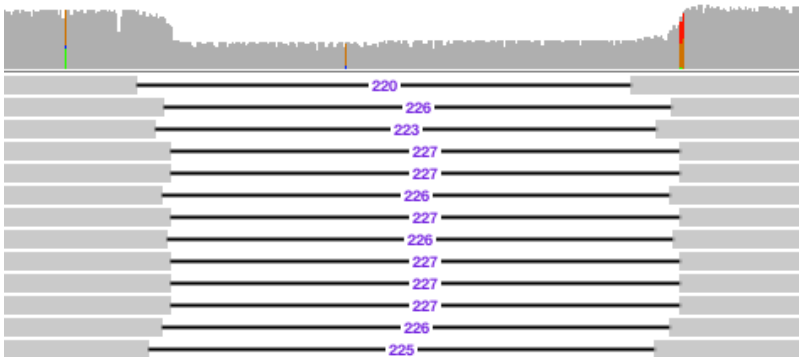
READ MAPPING



BWA



NGMLR



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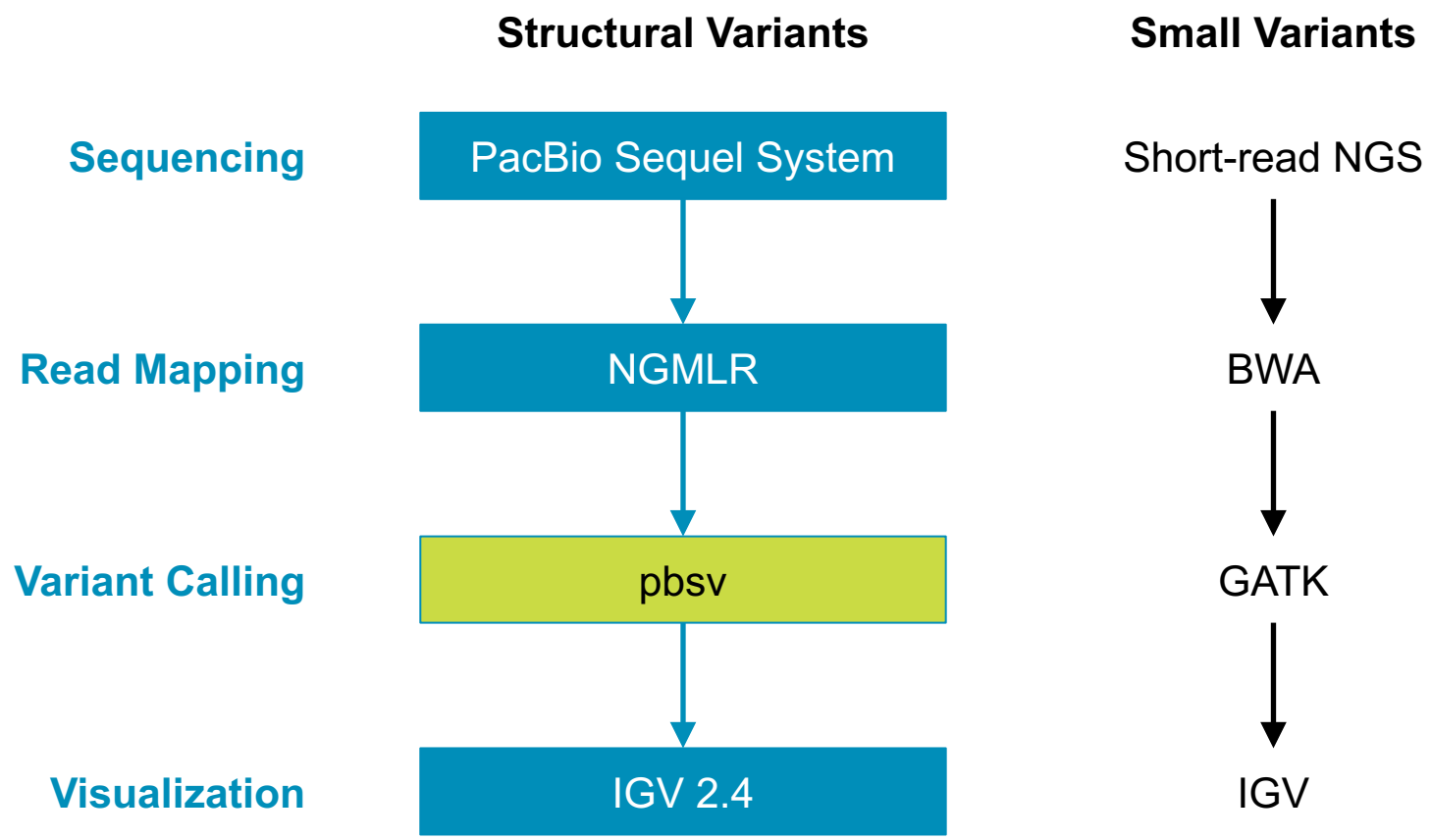


VARIANT CALLING

FIND SV SIGNATURES

CIGAR D & I ≥50 bp

CLUSTER SV SIGNATURES

nearby with similar sequence

FILTER

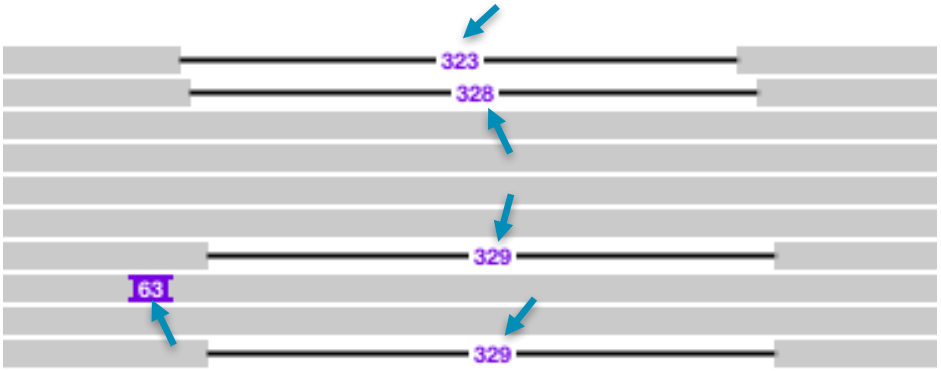
≥2 and ≥20% reads support

SUMMARIZE INTO SV

consensus of supporting reads

GENOTYPE

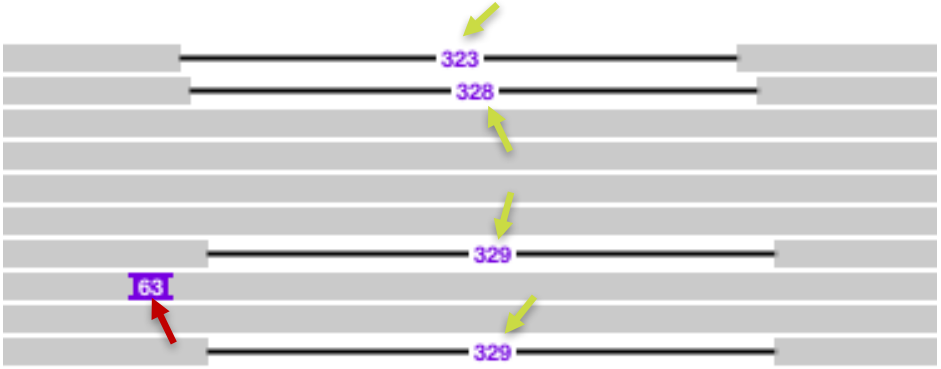
supporting reads / covering reads



http://pacb.com/sv

VARIANT CALLING

FIND SV SIGNATURES	CIGAR D & I ≥50 bp
CLUSTER SV SIGNATURES	nearby with similar sequence
FILTER	≥2 and ≥20% reads support
SUMMARIZE INTO SV	consensus of supporting reads
GENOTYPE	supporting reads / covering reads



VARIANT CALLING

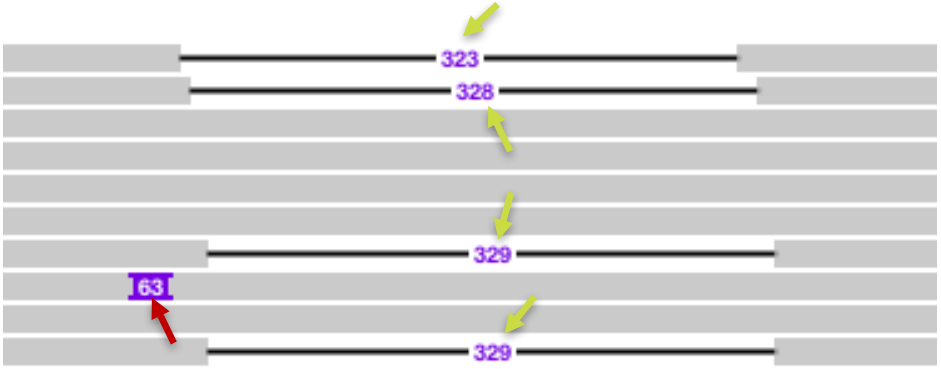
FIND SV SIGNATURES — CIGAR D & I ≥50 bp

CLUSTER SV SIGNATURES — nearby with similar sequence

FILTER — ≥2 and ≥20% reads support

SUMMARIZE INTO SV — consensus of supporting reads

GENOTYPE — supporting reads / covering reads



1 of 10 ✗

4 of 10 ✓

VARIANT CALLING

FIND SV SIGNATURES

CIGAR D & I ≥50 bp

CLUSTER SV SIGNATURES

nearby with similar sequence

FILTER

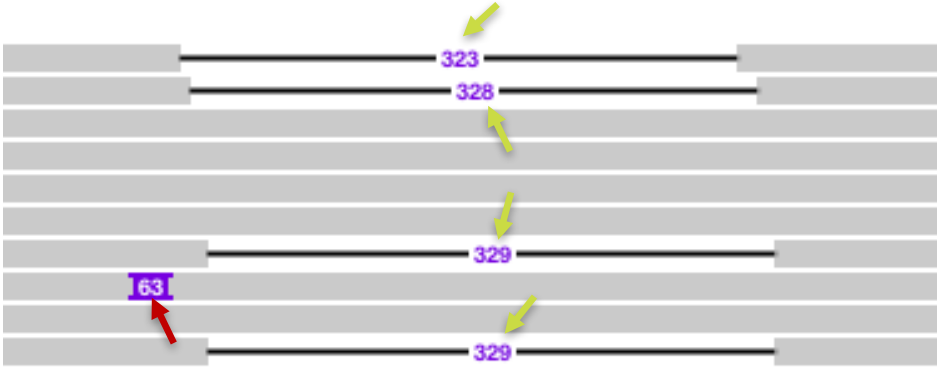
≥2 and ≥20% reads support

SUMMARIZE INTO SV

consensus of supporting reads

GENOTYPE

supporting reads / covering reads



1 of 10

4 of 10

329 bp deletion

http://pacb.com/sv

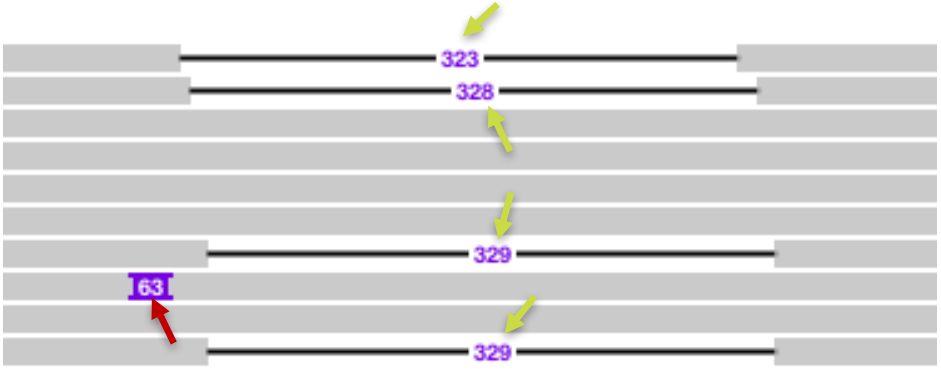
VARIANT CALLING

FIND SV SIGNATURES

CIGAR D & I ≥50 bp

CLUSTER SV SIGNATURES

nearby with similar sequence



FILTER

≥2 and ≥20% reads support

1 of 10

4 of 10

SUMMARIZE INTO SV

consensus of supporting reads

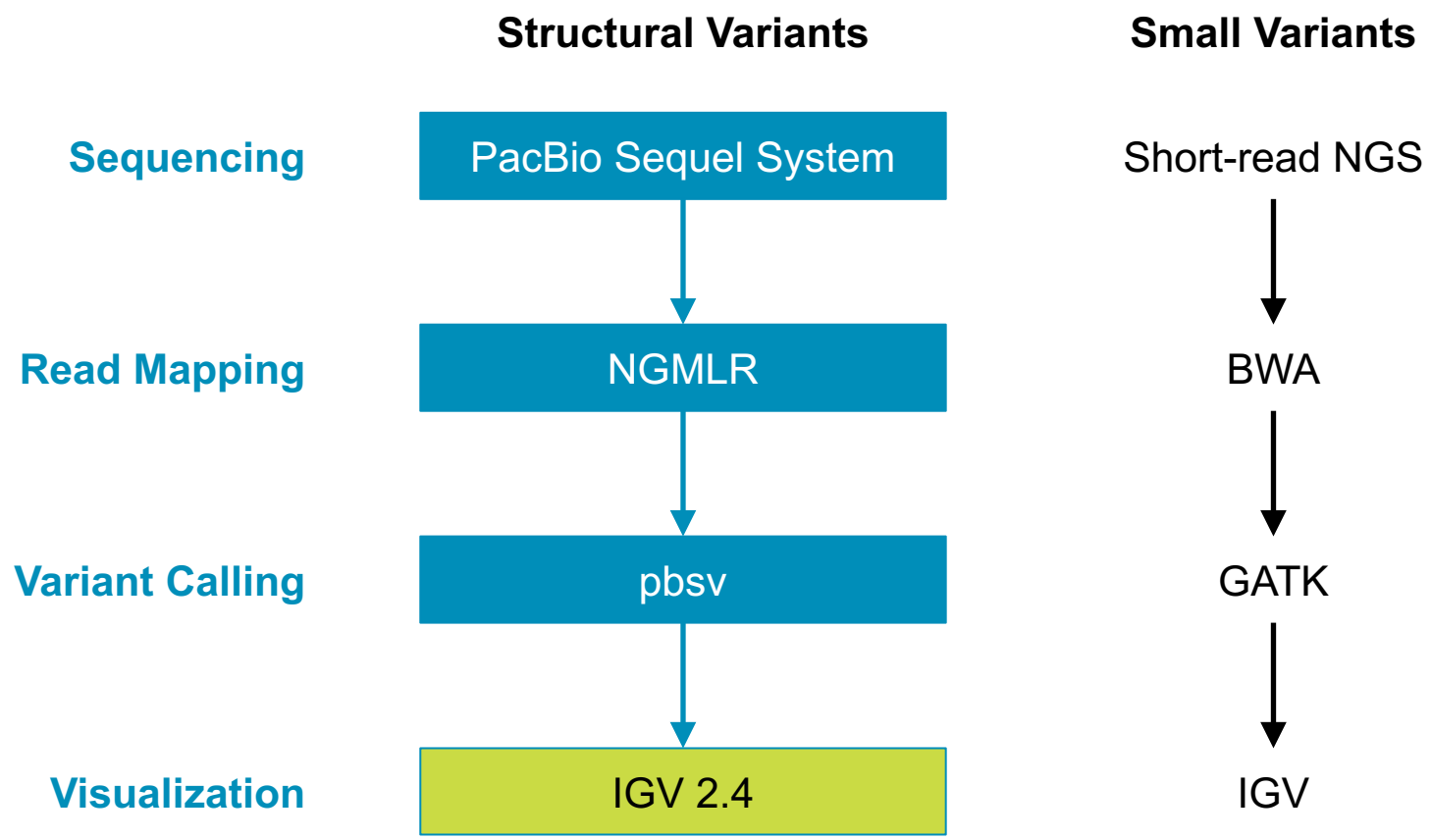
329 bp deletion

GENOTYPE

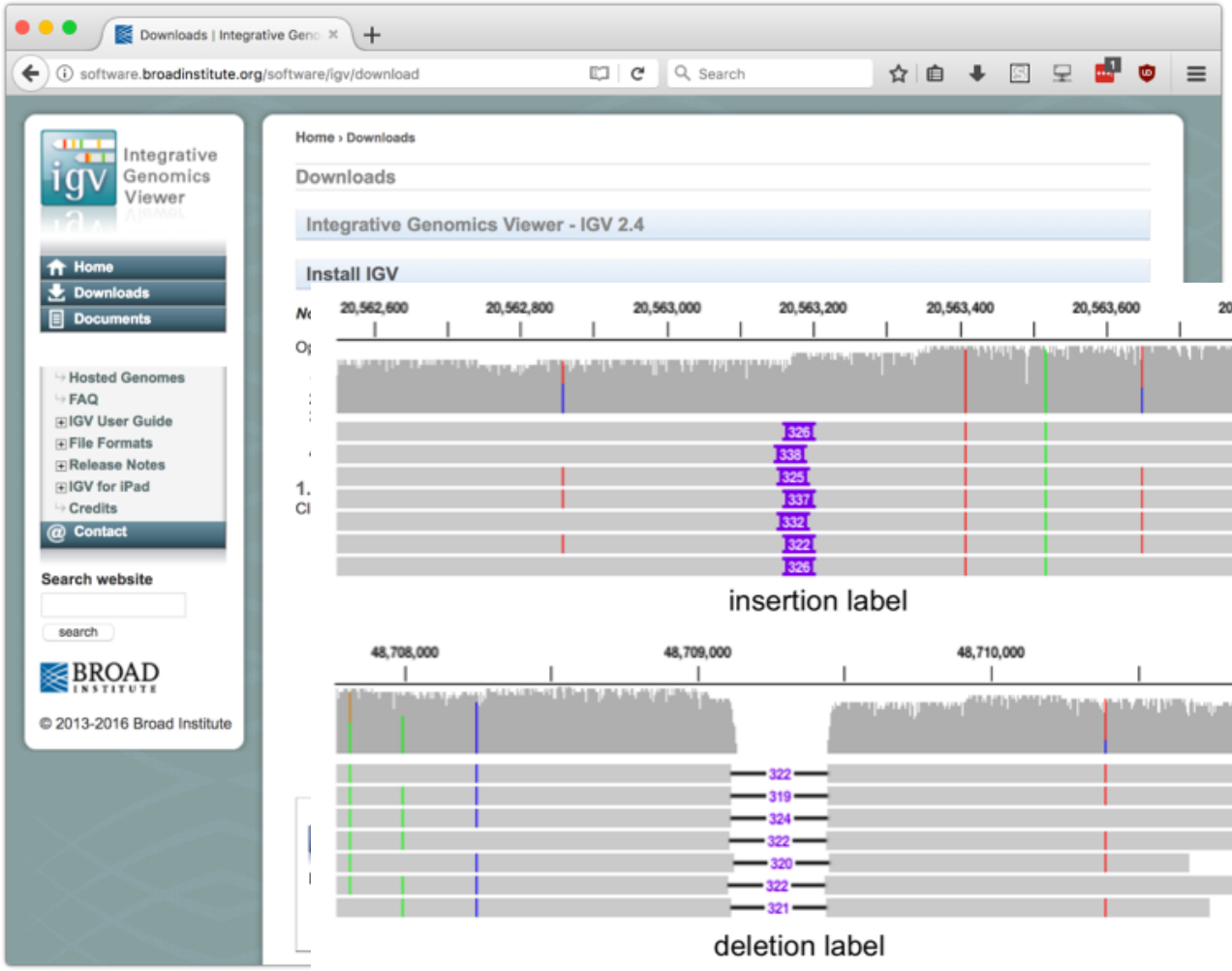
supporting reads / covering reads

heterozygous (4 of 10)

WGS FOR STRUCTURAL VARIANT DISCOVERY



VISUALIZATION – IGV 2.4 (FORMERLY IGV 3 BETA)

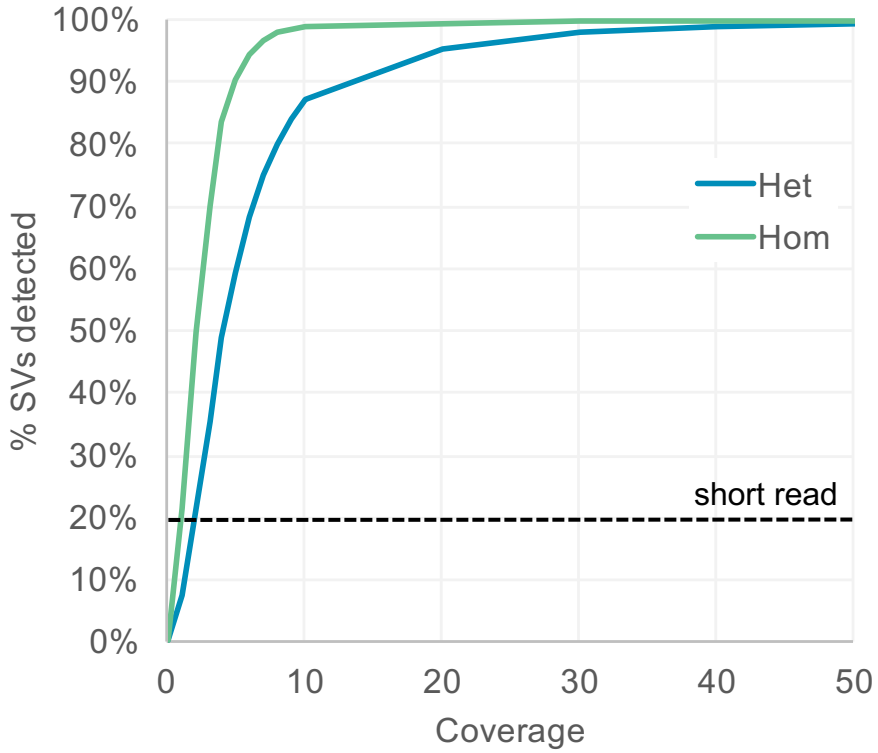


insertion

deletion

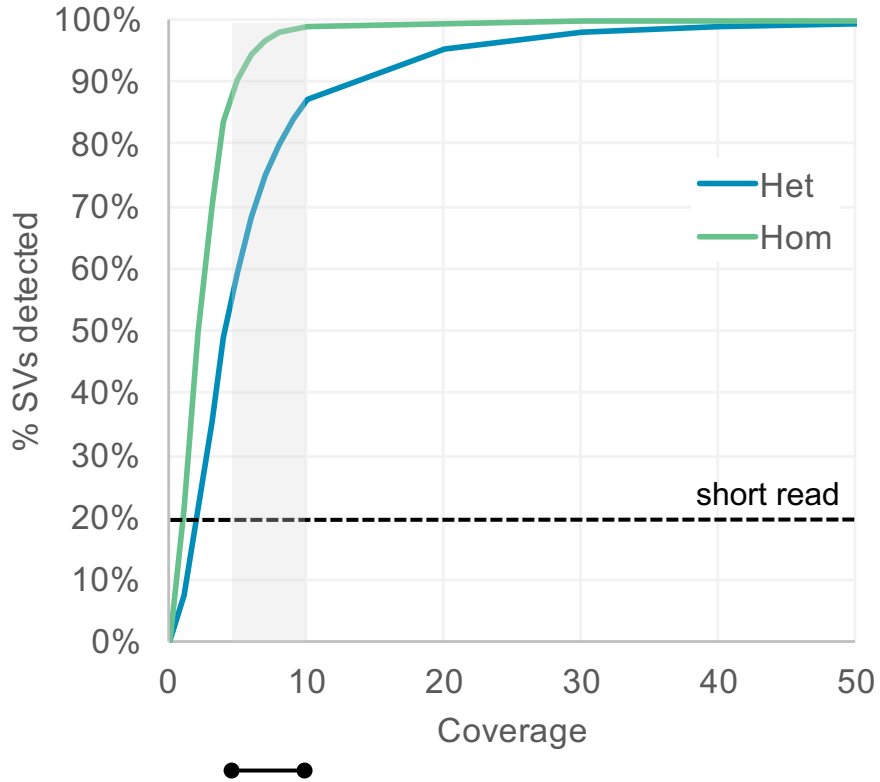
Robinson et al. (2011) *Nature Biotechnology*. doi:10.1038/nbt.1754.

HOW MUCH TO SEQUENCE?



Human HG00733
Sequel System
211 Gb (70-fold)

HOW MUCH TO SEQUENCE?

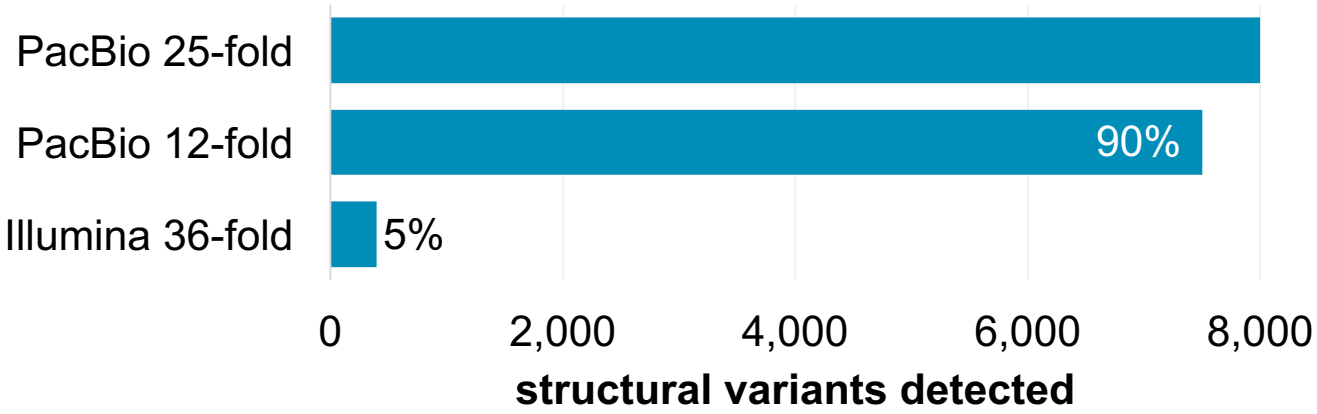


5- to 10-fold
optimal tradeoff of
cost vs. performance

Human HG00733
Sequel System
211 Gb (70-fold)

STRUCTURAL VARIANT SENSITIVITY IN PLANT GENOMES

Soy Wm82
against Wm82a2



STRUCTURAL VARIANT SENSITIVITY IN PLANT GENOMES

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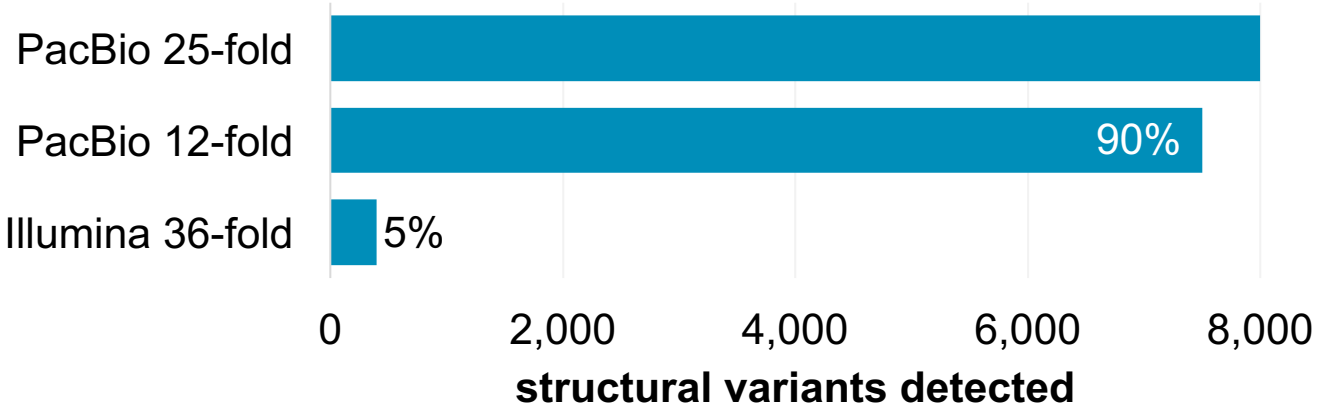
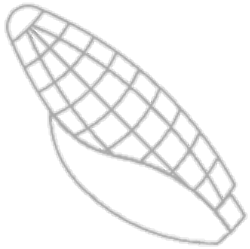
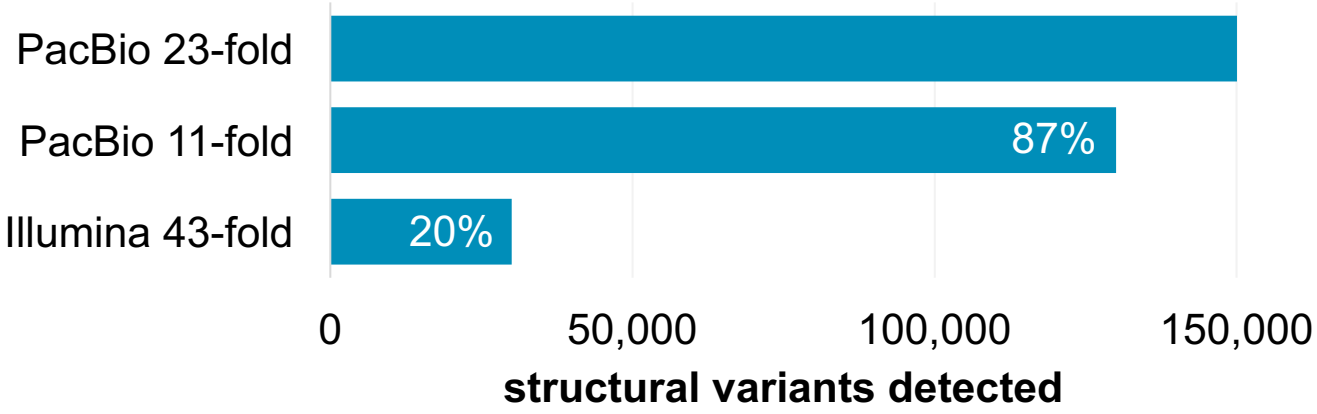




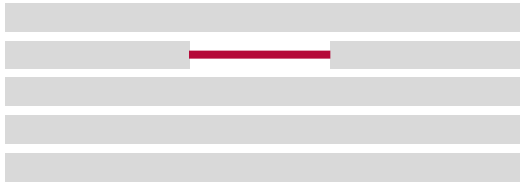
Maize Mo17
against AGPv4



JOINT VARIANT CALLING IN PBSV

Solo Calling

Individual #1

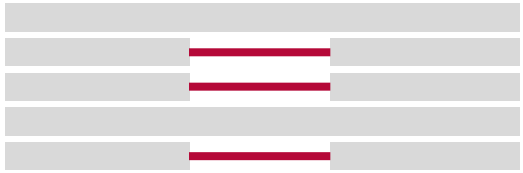


-

Individual #2

-

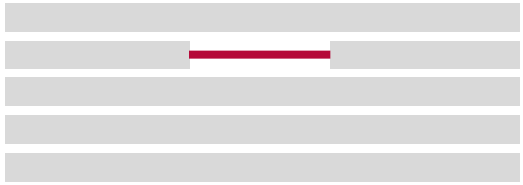
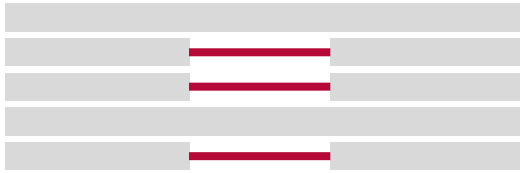
Individual #3



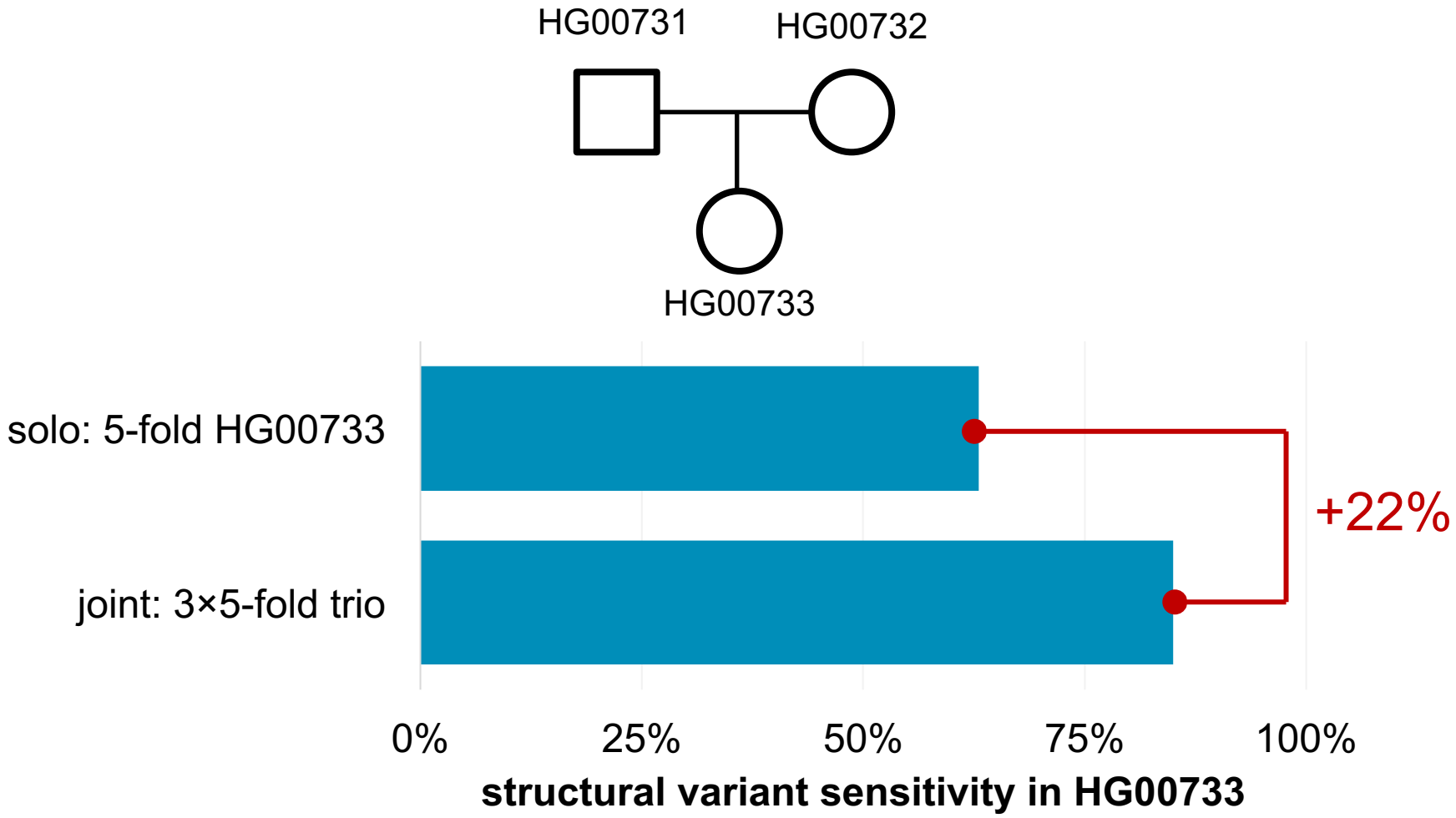
REF/ALT

JOINT VARIANT CALLING IN PBSV

available in next release of SMRT Link

		Solo Calling	Joint Calling
Individual #1		-	REF/ALT
Individual #2		-	REF/REF
Individual #3		REF/ALT	REF/ALT

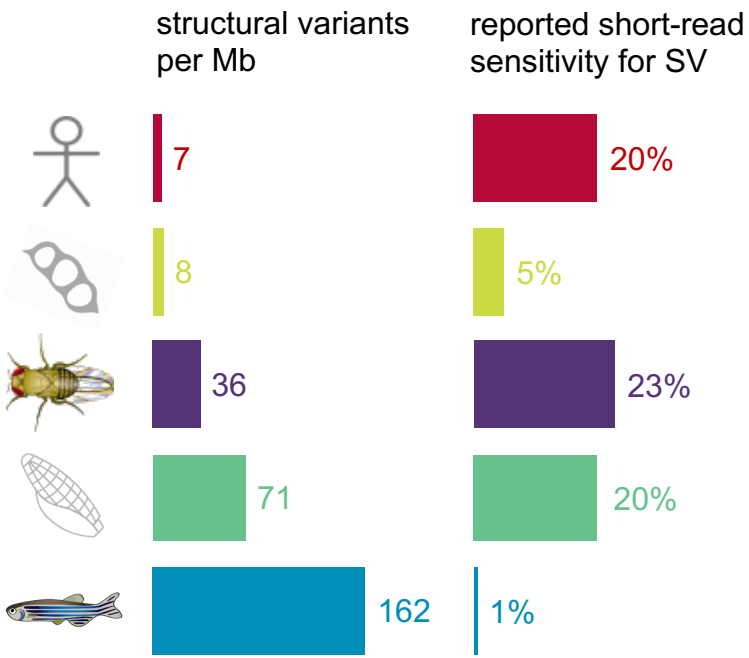
JOINT VARIANT CALLING IN A HUMAN TRIO



SUMMARY

Most base pairs that differ between individuals lie in structural variants.

Most structural variants are missed by short reads.



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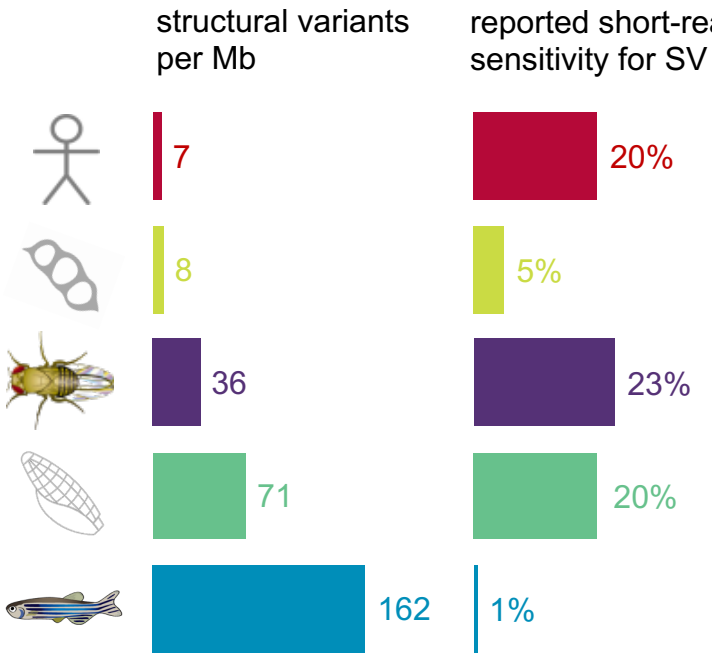
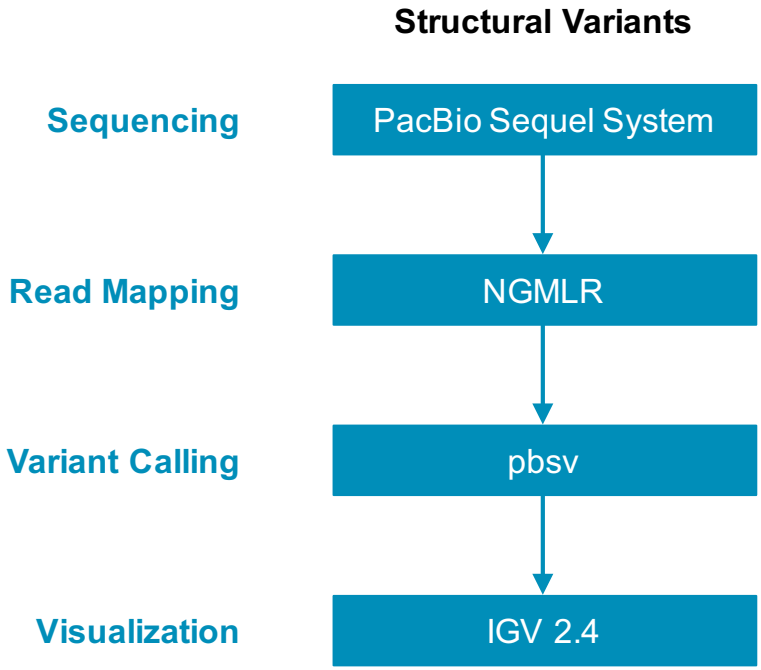


NGMLR and pbsv effectively detect structural variants in diploids.

Joint calling increases sensitivity for shared variants.



ACKNOWLEDGMENTS

Schatz Lab

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PacBio

Mary Budagyan
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Janet Ziegle

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