Algorithms for studying the structure and function of genomes

Michael Schatz

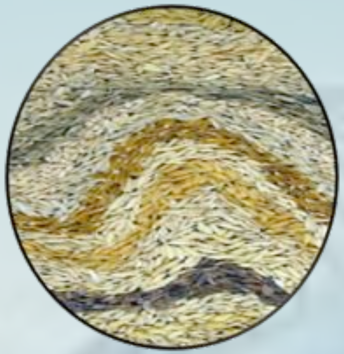
April 7, 2015
LIIGH UNAM

Schatzlab Overview

Human Genetics

Role of mutations in disease

Narzisi *et al.* (2014)
Iossifov *et al.* (2014)



Plant Biology

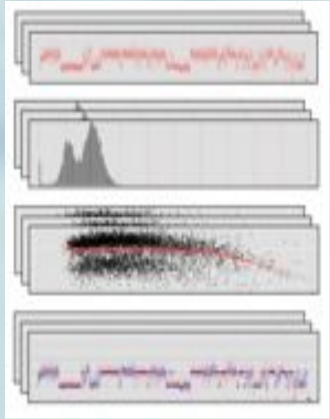
Genomes & Transcriptomes

Schatz *et al.* (2014)
Ming *et al.* (2013)

Algorithmics & Systems Research

Ultra-large scale biocomputing

Blood *et al.* (2014)
Schatz *et al.* (2013)



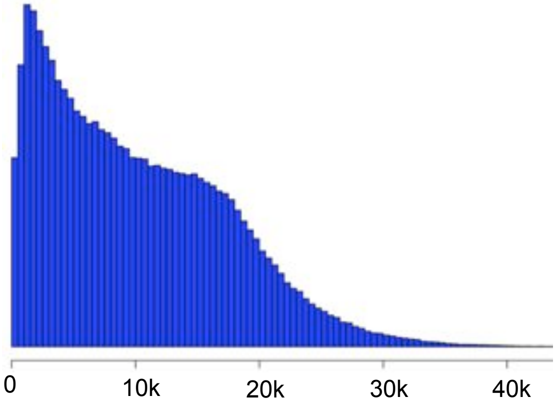
Single Cell & Single Molecule

CNVs, SVs, & Cell Phylogenetics

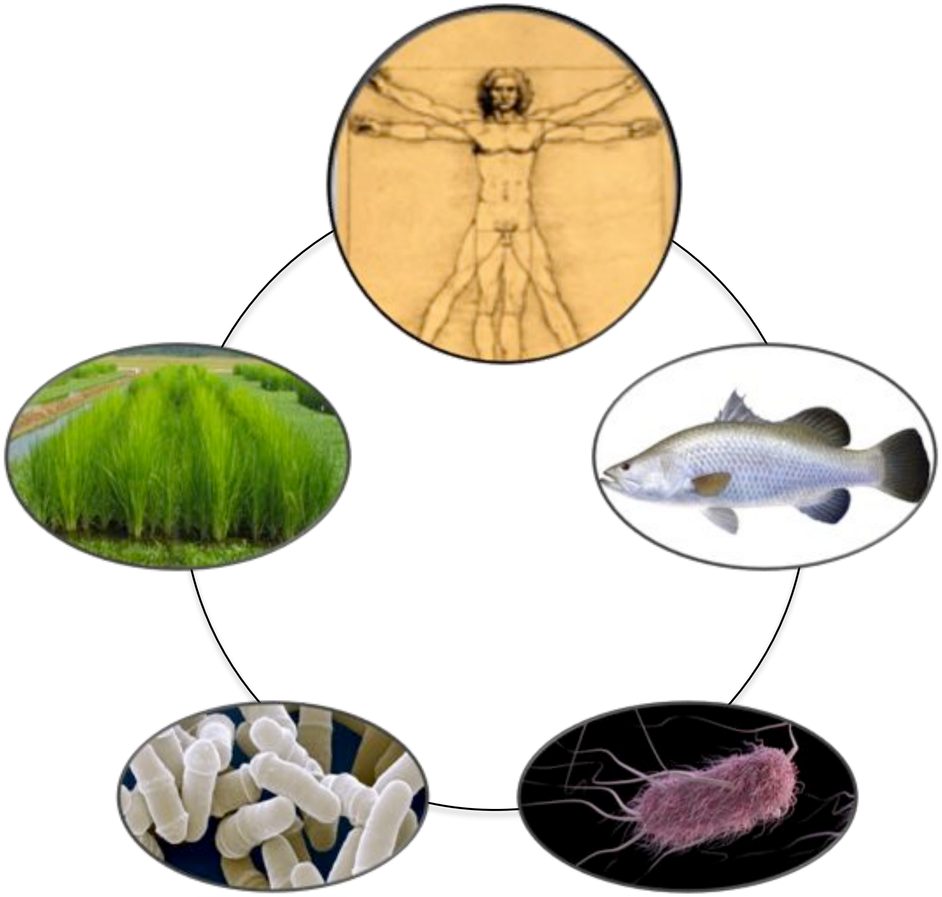
Garvin *et al.* (2014)
Roberts *et al.* (2013)

3rd Gen Long Read Sequencing

PacBio RS II

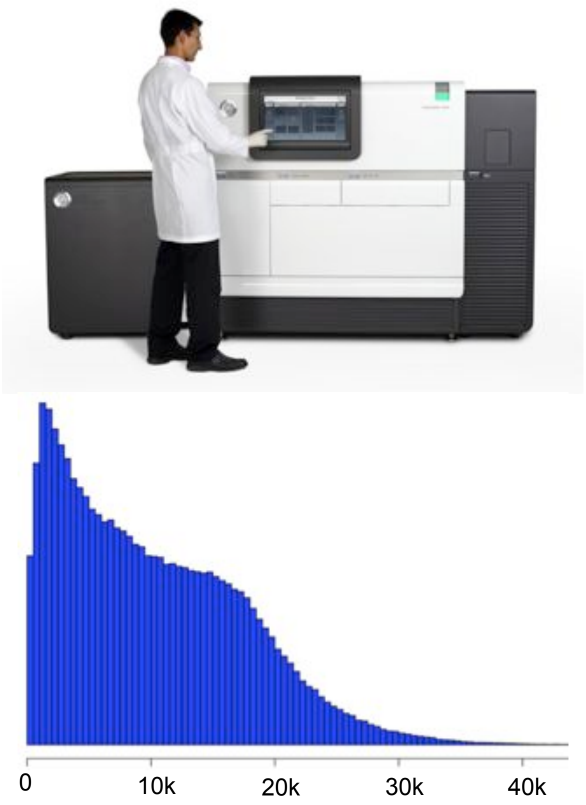


CSHL/PacBio

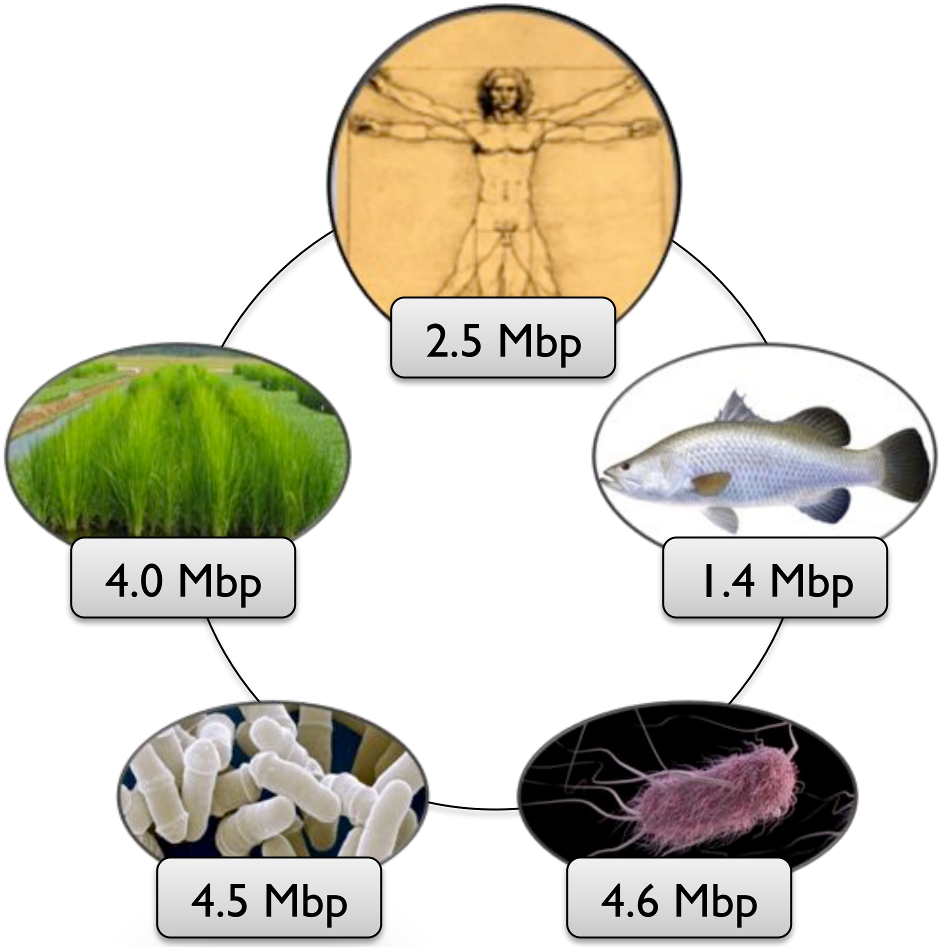


3rd Gen Long Read Sequencing

PacBio RS II



CSHL/PacBio



2.5 Mbp

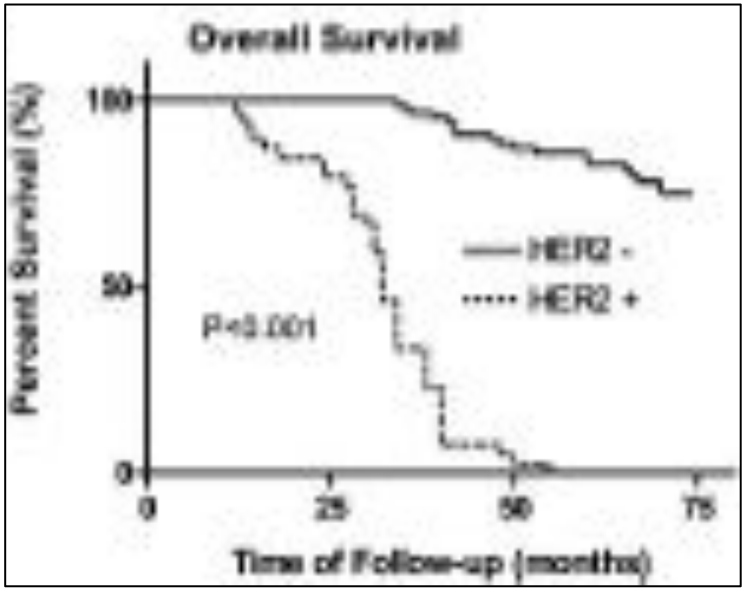
4.0 Mbp

1.4 Mbp

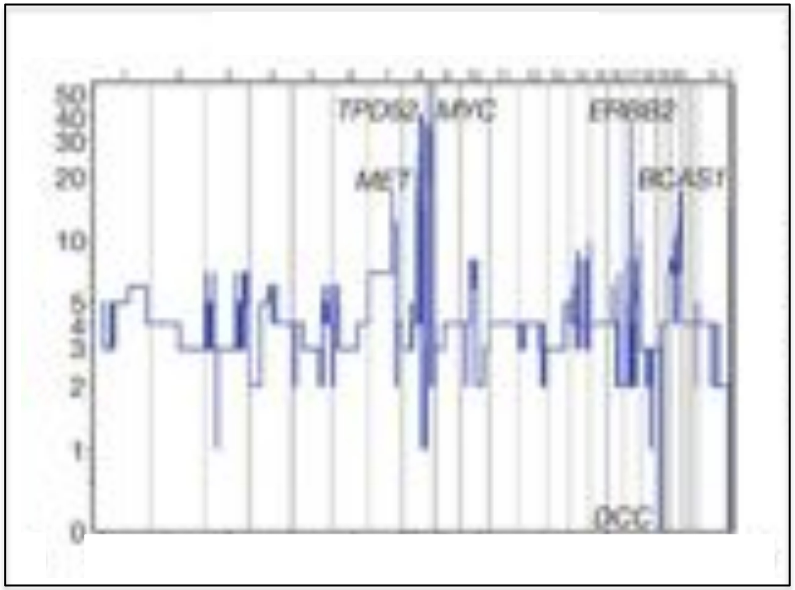
4.5 Mbp

4.6 Mbp

Long Read Sequencing of SK-BR-3



(Wen-Sheng et al, 2009)



(Navin et al, 2011)

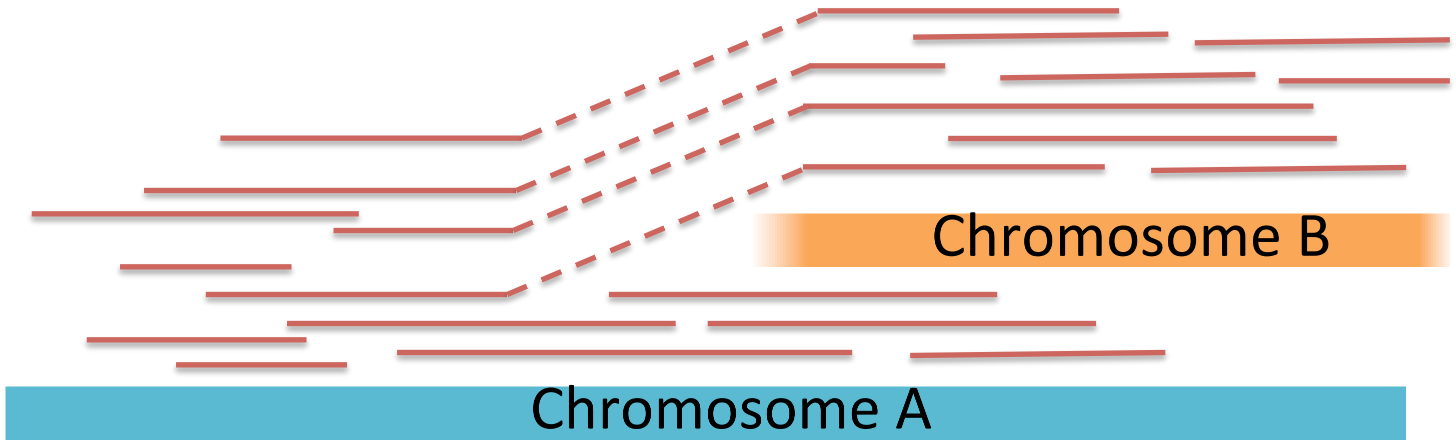
Long read PacBio sequencing of SK-BR-3 breast cancer cell line

- Her2+ breast cancer is one of the most deadly forms of the disease
- SK-BR-3 is one of the most important models, known to have widespread CNVs

- Currently have 72x coverage with long read PacBio sequencing (mean: ~10kbp)
- Analyzing breakpoints in an attempt to infer the mutation history, especially around HER2

In collaboration with McCombie (CSHL) and McPherson (OICR) labs

Structural variant discovery with long reads



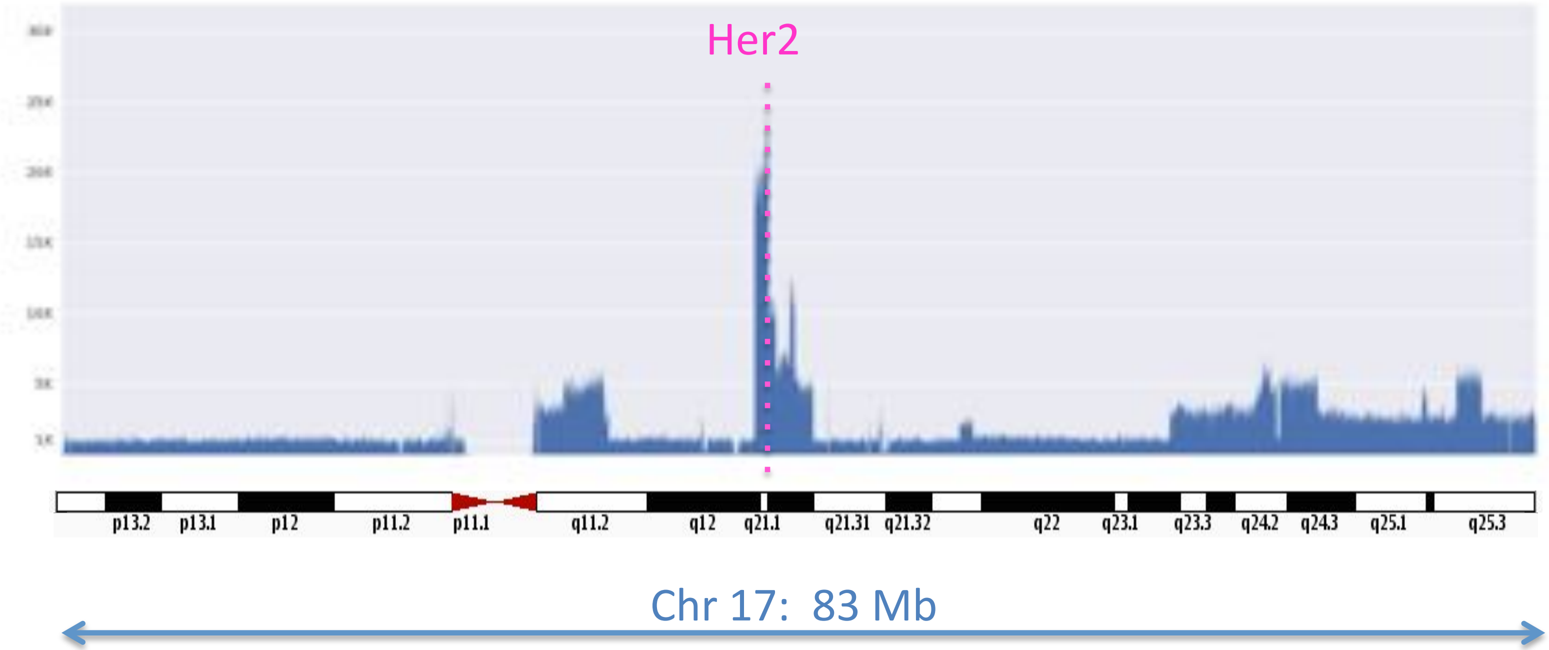
1. Alignment-based split read analysis: Efficient capture of most events
BWA-MEM + Lumpy

2. Local assembly of regions of interest: In-depth analysis with *base-pair precision*
Localized HGAP + Celera Assembler + MUMmer

3. Whole genome assembly: In-depth analysis including *novel sequences*
DNAnexus-enabled version of Falcon

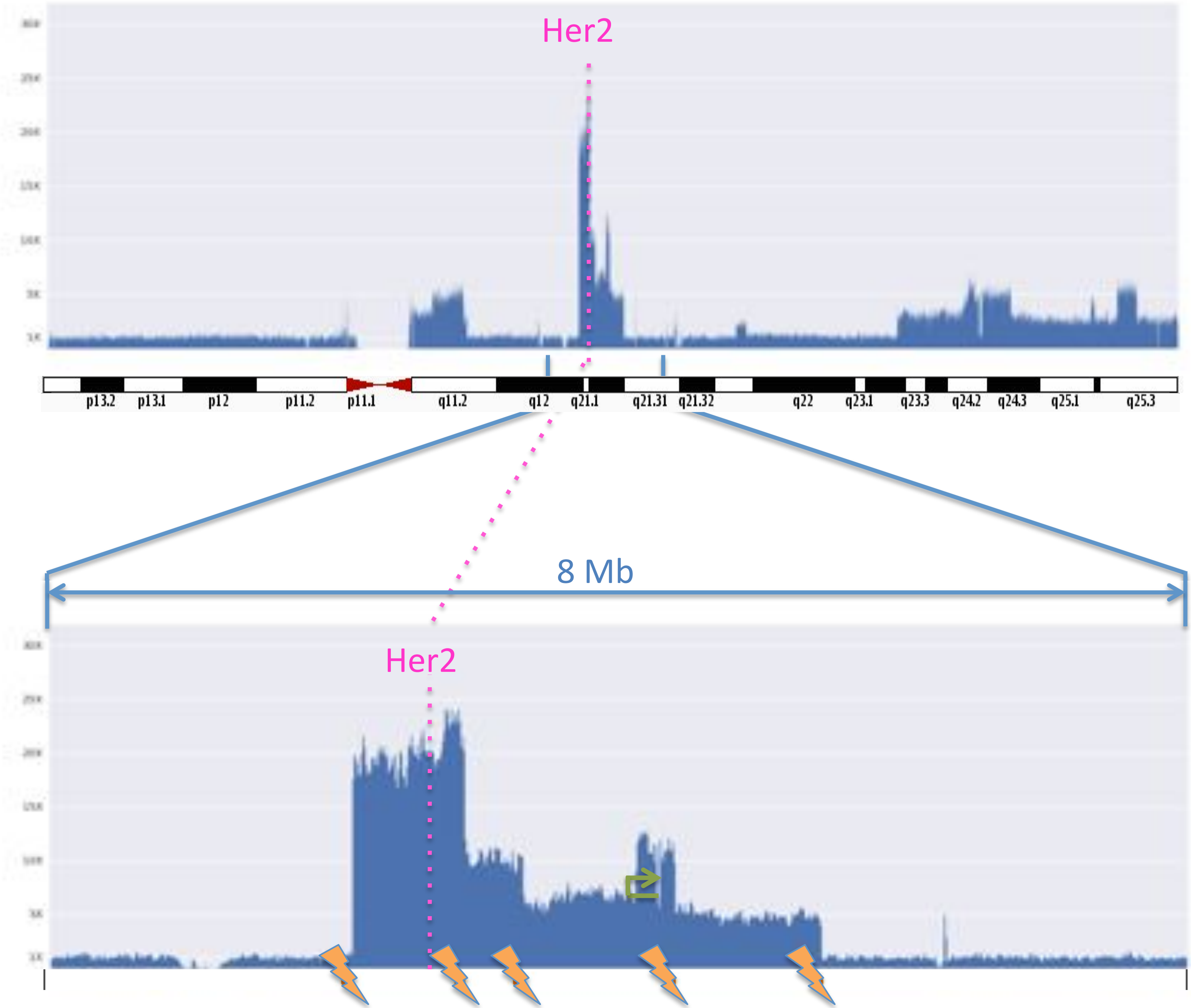
Total Assembly: 2.64Gbp **Contig N50: 2.56 Mbp** **Max Contig: 23.5Mbp**

PacBio

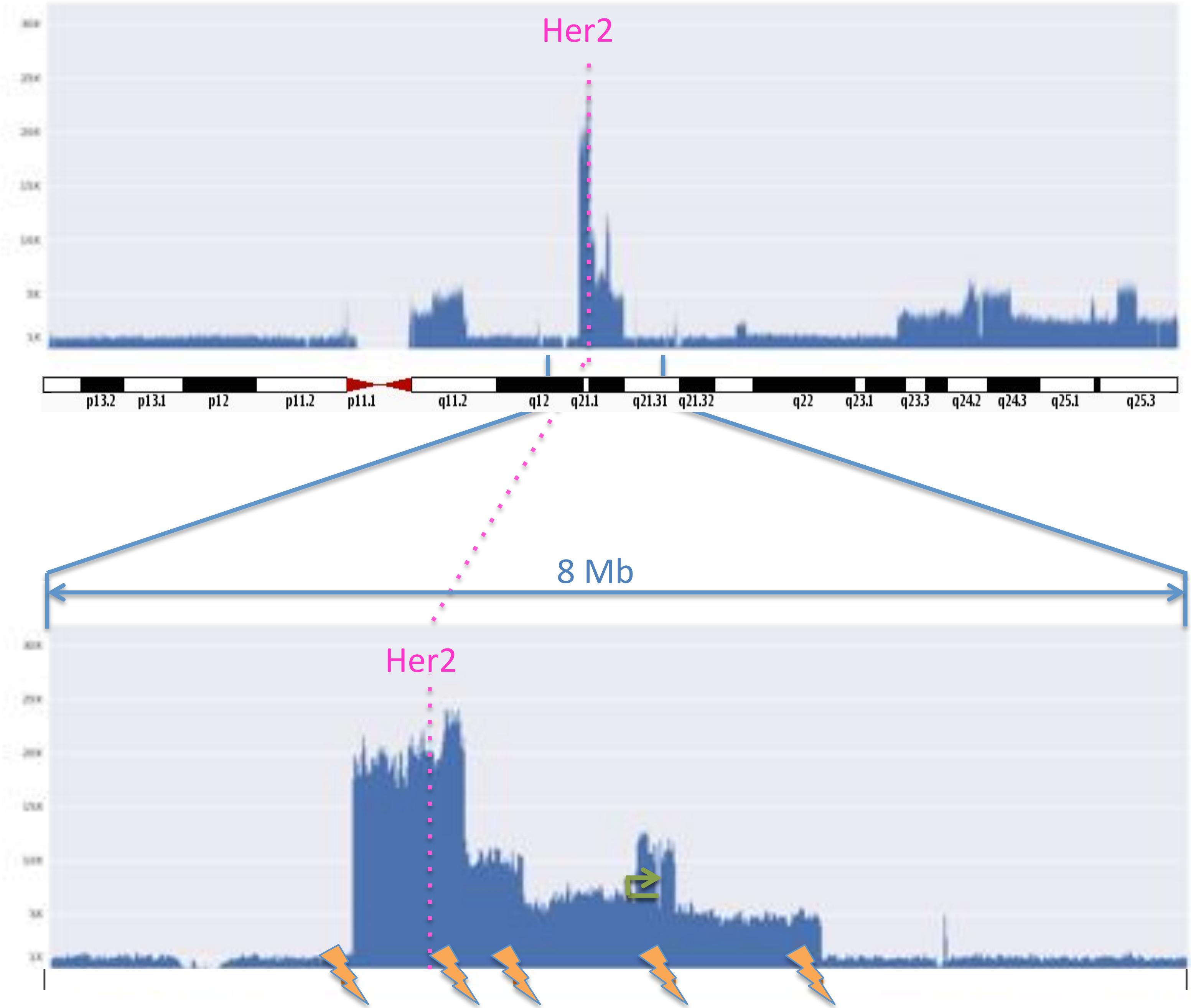

Her2
30K
25K
20K
15K
10K
5K
1K
p13.2
p13.1
p12
p11.2
p11.1
q11.2
q12
q21.1
q21.31
q21.32
q22
q23.1
q23.3
q24.2
q24.3
q25.1
q25.3
Chr 17: 83 Mb

PacBio

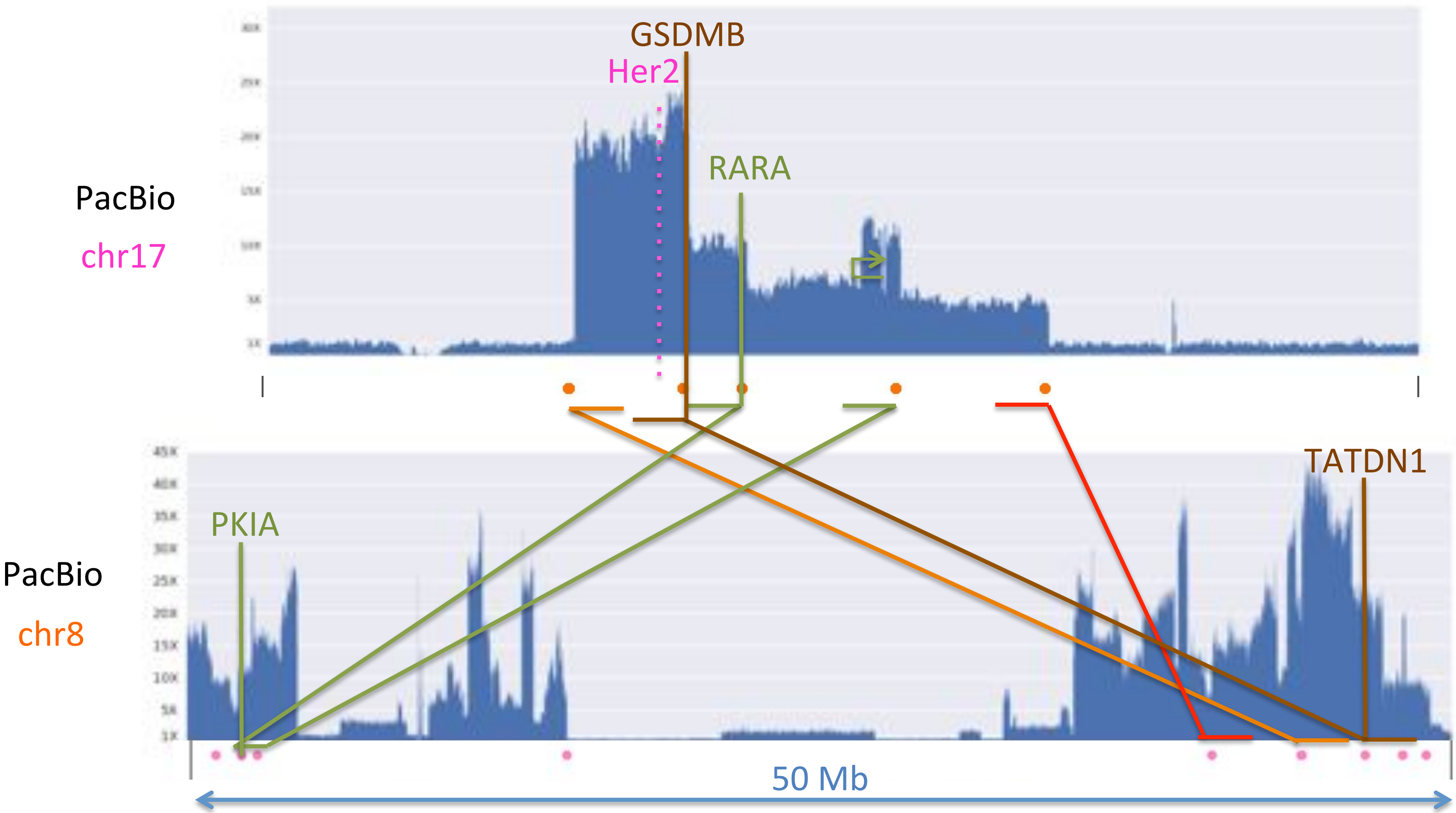
PacBio
chr17



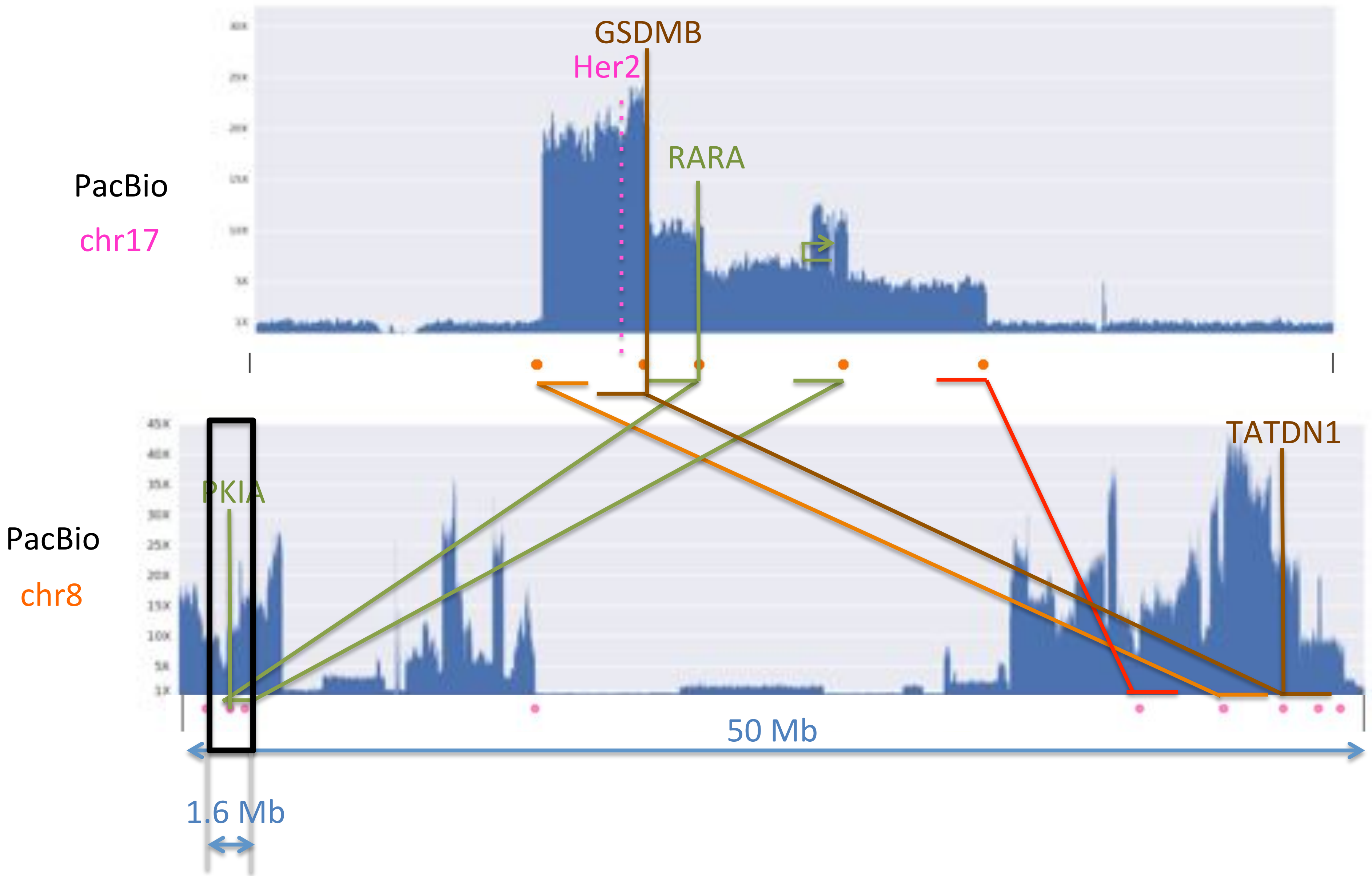
PacBio



PacBio
chr17



Confirmed both known gene fusions in this region



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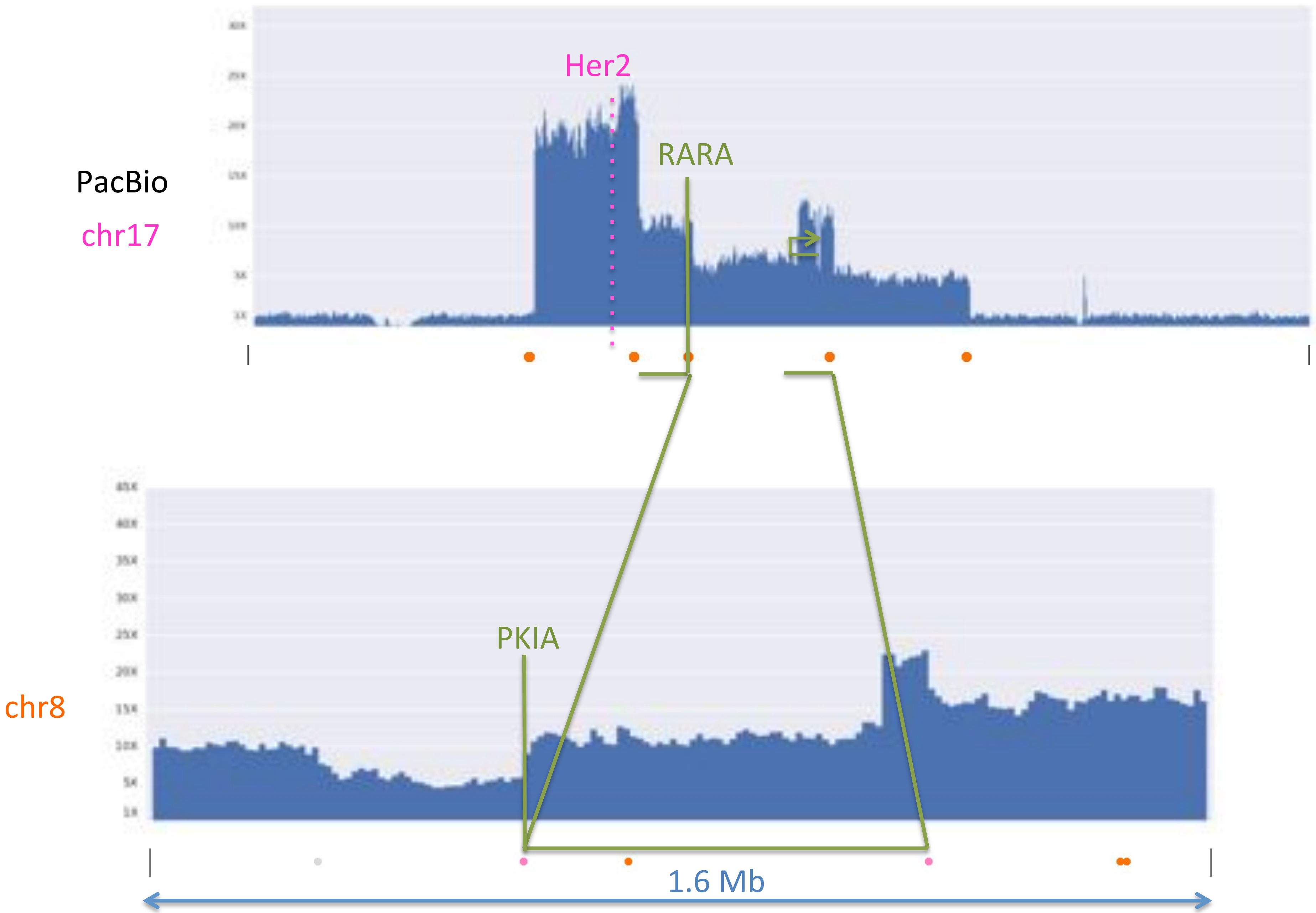
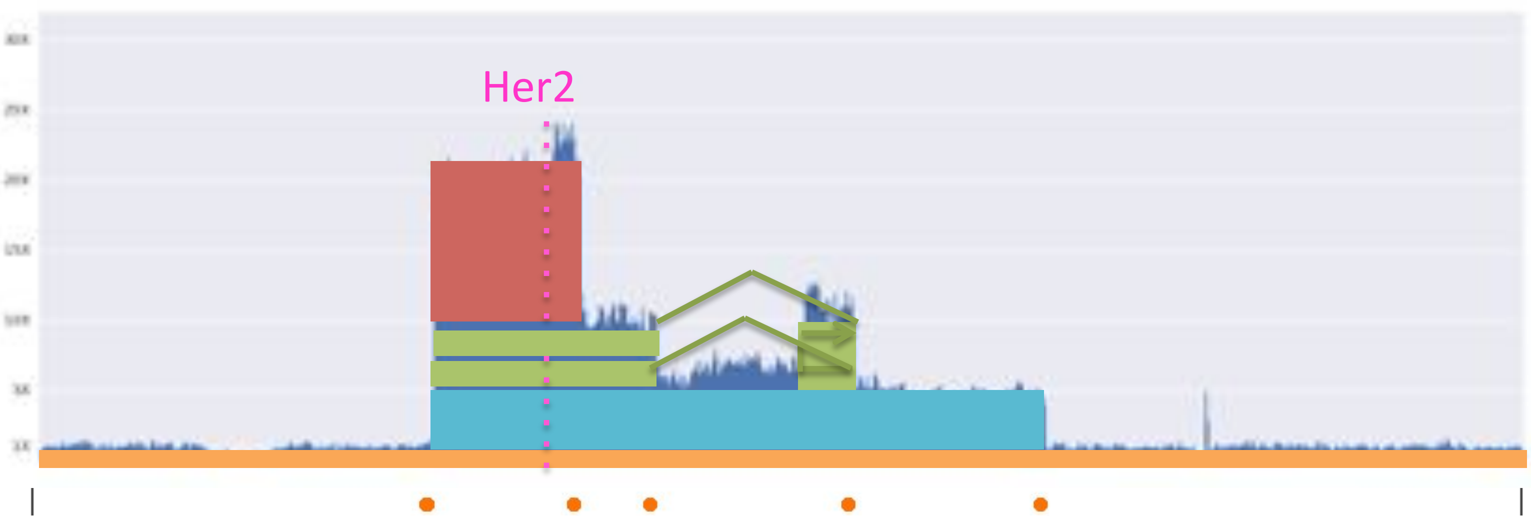


Joint coverage and breakpoint analysis to discover underlying events

Cancer lesion Reconstruction

PacBio

chr17



By comparing the proportion of reads that are spanning or split at breakpoints we can begin to infer the history of the genetic lesions.

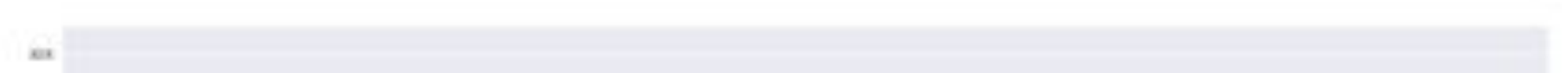
1. Healthy diploid genome

2. Original translocation into chromosome 8

3. Duplication, inversion, and inverted duplication within chromosome 8

4. Final duplication from within chromosome 8

Cancer lesion Reconstruction



Available *today* under the Toronto Agreement:

- Fastq & BAM files of aligned reads
- Interactive Coverage Analysis with BAM.IOBIO
- Whole genome assembly

Available soon

- Whole genome methylation analysis
- Full length cDNA transciptome analysis
- Comparison to single cell analysis of >100 individual cells

http://schatzlab.cshl.edu

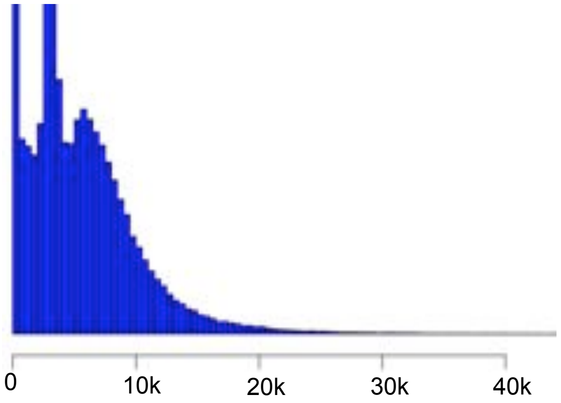
3. Duplication, inversion, and inverted duplication within chromosome 8

4. Final duplication from within chromosome 8

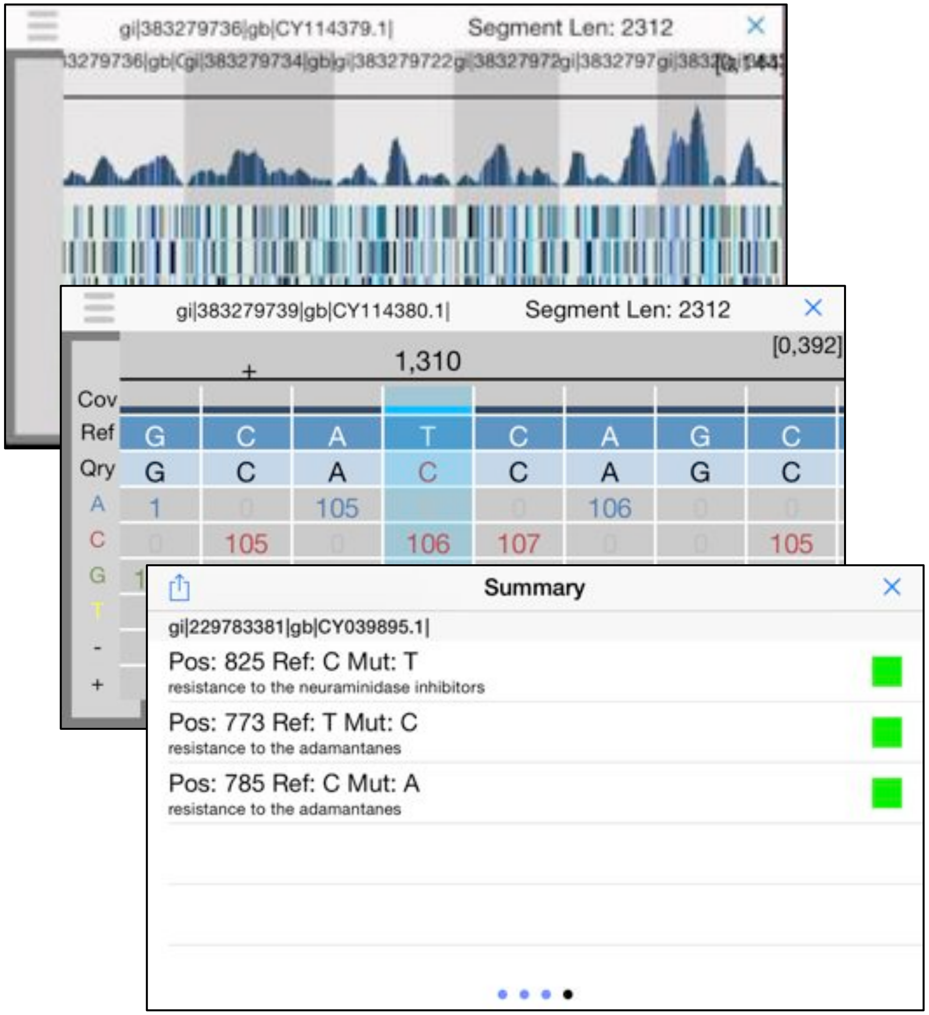
Genomic Futures?

Mobile Sequencing

Oxford Nanopore



CSHL/ONT



gi|383279736|gb|CY114379.1| Segment Len: 2312

gi|383279739|gb|CY114380.1| Segment Len: 2312

[0,392]

1,310

Cov								
Ref	G	C	A	T	C	A	G	C
Qry	G	C	A	C	C	A	G	C
A	1	0	105	0	0	106	0	0
C	0	105	0	106	107	0	0	105

Summary

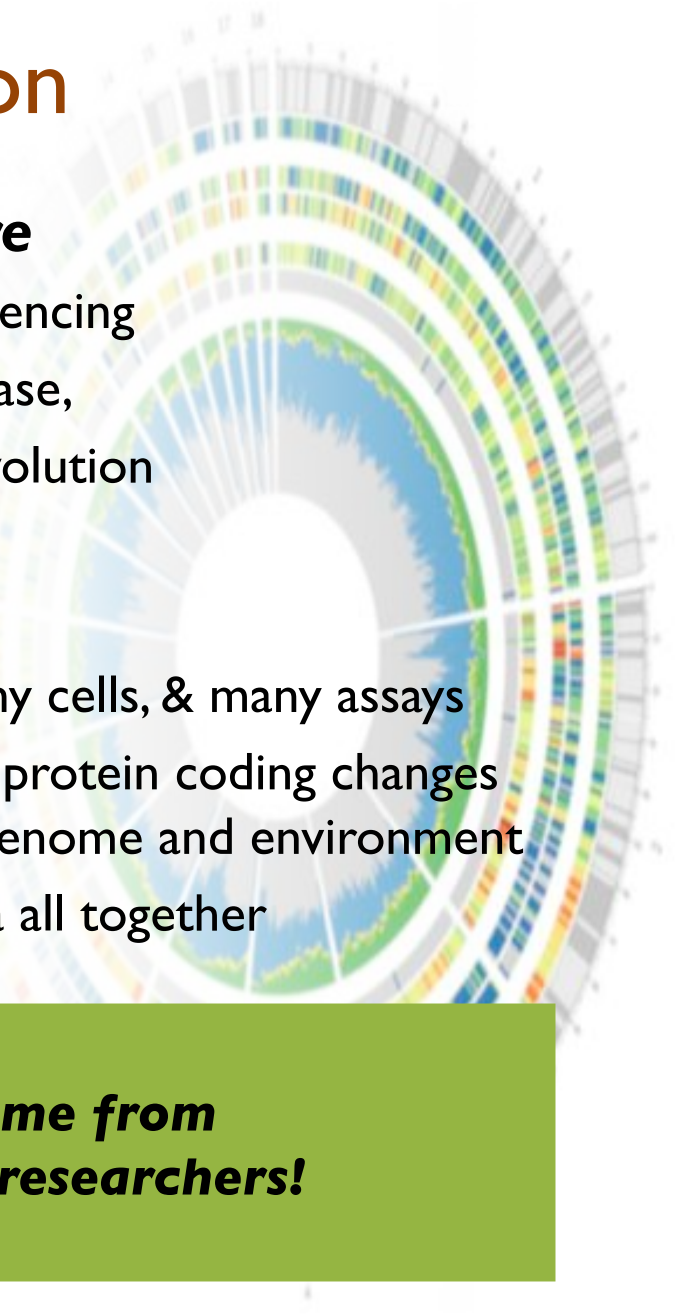
gi|229783381|gb|CY039895.1|

Pos: 825 Ref: C Mut: T 🟩
resistance to the neuraminidase inhibitors

Pos: 773 Ref: T Mut: C 🟩
resistance to the adamantanes

Pos: 785 Ref: C Mut: A 🟩
resistance to the adamantanes

Understanding Genome Structure & Function



Reference quality genome assembly is here

- Driven by new technologies for long read sequencing
- Provide us new insights into the origins of disease, the stages of development, and the forces of evolution

Focus on population analysis

- Large scale sequencing of many individuals, many cells, & many assays
- Shift from relatively straightforward analysis of protein coding changes into more and more subtle signals across the genome and environment
- Informatics is the key for integrating these data all together

Ultimately the discoveries will come from the next generation of students and researchers!

Acknowledgements

Schatz Lab

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Gingeras Lab
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Hicks Lab
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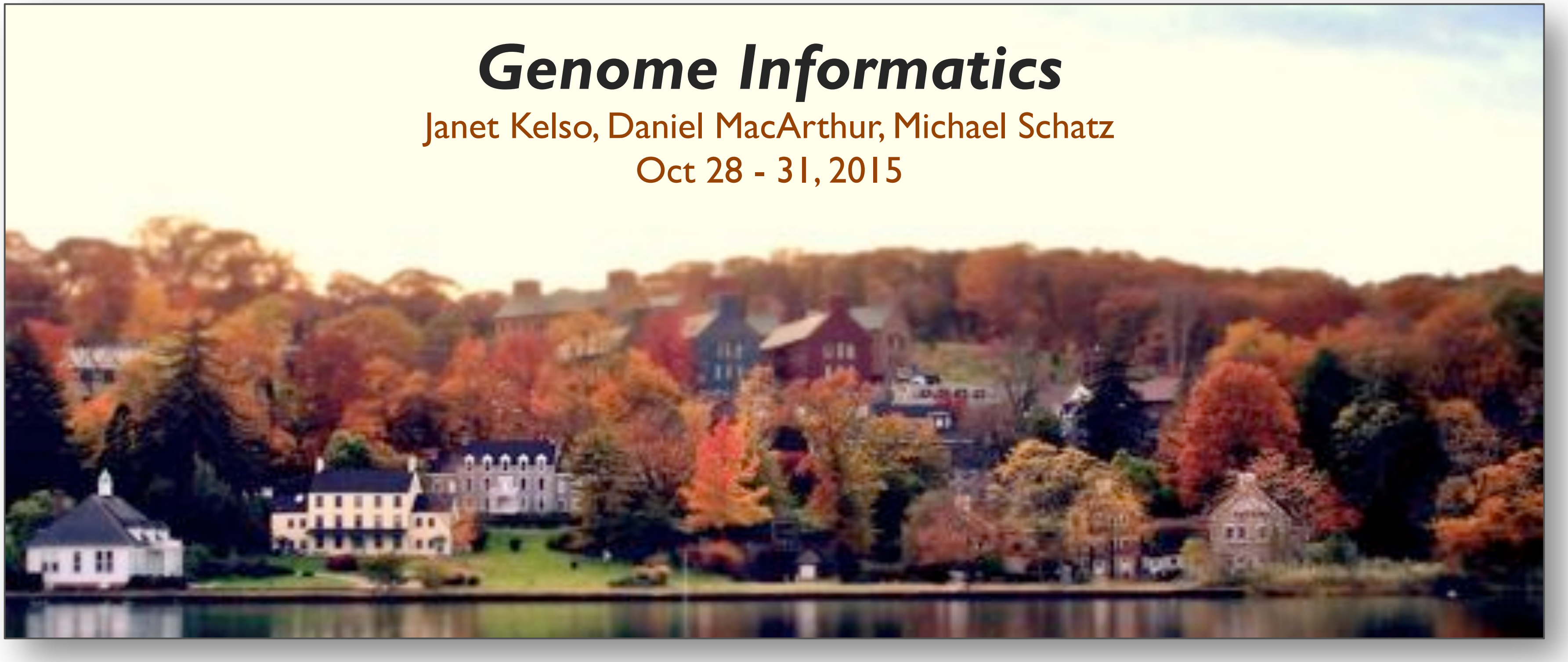

Genome Informatics

Janet Kelso, Daniel MacArthur, Michael Schatz

Oct 28 - 31, 2015

Thank you

http://schatzlab.cshl.edu

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