New Results

Follow this preprint

Haplotype-Resolved Genomics Reveals Conserved Chromatin Architecture and Epigenetic Constraints of Human Neocentromeres

Savannah J. Hoyt, Gabrielle A. Hartley, Mariah C. Antopia, Thomas W. Tullius, Dylan J. Taylor, Nicole M. Tillquist, Shane Neph, Nicole Pauloski, Katherine M. Munson, Kendra Hoekzema, Evan E. Eichler, Andrew B. Stergachis, Glennis A. Logsdon, Rachel J. O'Neill

doi: https://doi.org/10.64898/2025.12.23.696241

Abstract | Full Text | Info/History | Metrics | Preview PDF

Abstract

Human neocentromeres are functional centromeres demarcated by CENP-A nucleosomes that form ectopically at alpha satellite-free loci. How neocentromeres reshape local chromatin and which features of native centromeric chromatin are preserved are unknown. We generated gapless, haplotype-resolved assemblies of native and neocentromeres from three patient-derived cell lines. Integrating CpG methylation, CENP-A profiling, and single-molecule chromatin fiber sequencing, we reveal chromatin features that define the essential centromeric architecture reconstituted during neocentromere establishment. We find that a deletion within the satellite array encompassing the hypo-CpG methylation centromere dip regions (CDRs) led to native centromere inactivation, that neocentromeres harbor CDRs and a dichromatin architecture, recapitulating features of alpha-satellite centromeres, and that LINEs demarcate neocentromere boundaries, implicating transposable elements in restricting CENP-A domain spreading. Moreover, neocentromeric chromatin is incompatible with promoter-like chromatin states, redefining the regulatory landscape within genic regions. Finally, using haplotype-specific chromatin footprinting, we resolve CENP-A nucleosome chromatin architecture of active centromeres.

Andrew B. Stergachis, M.D., Ph.D., FACMG

Associate Professor, Division of Medical Genetics, Department of Medicine, University of Washington
Associate Professor, Department of Genome Sciences, University of Washington
Member, Brotman Baty Institute, Seattle, Washington

M.D., University of Washington, 2015
Ph.D. in Genome Sciences, University of Washington, 2013
B.S. in Biochemistry and B.A. in Chemistry, University of Chicago, 2007
Residency in Internal Medicine, Brigham and Women's Hospital, 2020
Residency in Medical Genetics and Genomics, Harvard Medical School, 2020

Google Scholar | absterga [at] uw [dot] edu

Glennis Logsdon, Ph.D.

Assistant Professor of Genetics

Core Member, Penn Epigenetics Institute

Member, Penn Center for Global Genomics and Health Equity

Department: Genetics

Rachel O'Neill

Board of Trustees Distinguished Professor
Molecular and Cell Biology / Genetics and Genomics

Education: PhD La Trobe University

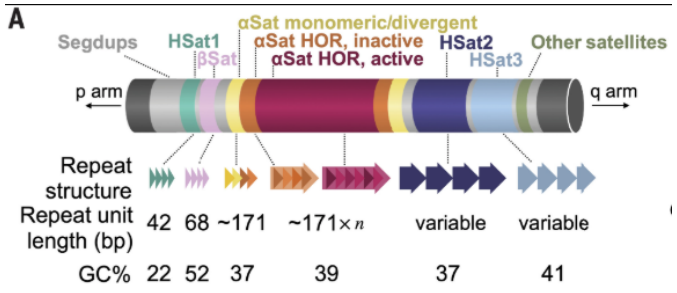
Research Interests: My research programs employ molecular genetics, cytogenetics, genomics and computational approaches to study the mechanisms that maintain, and disrupt, genome stability and foster genome innovation. Projects include studying: retroelement transcription and centromere function; global chromosome and genome changes during instability; chromosome and genome evolution; species-specific genomic features linked to unique adaptations; and, methods of genome assembly and annotation. We use a diverse set of rapidly evolving next generation sequencing (NGS) technologies and novel library preparation and computational methodologies for generating telomere-to-telomere (T2T) genome assemblies and characterizing genome sequences and epigenomic features in efforts to establish broad eukaryotic species as models for studying genome biology. Projects include generating genome assemblies and comparative analyses for our own lab work including species from all three mammalian lineages (eutherian, marsupial, monotreme), major vertebrate lineages such as birds, marine species, plants, and insects. Our work is part of larger efforts, including : Human T2T Consortium, Primate T2T Consortium, Gibbon T2T Consortium, Earth Biogenomes Project, Ruminant T2T Consortium, Fly T2T Consortium, Deep Ocean Genomes Project, Antarctic Genomes Consortium, the Colossal Foundation, and UConn's Biodiversity and Conservation Genomics program.

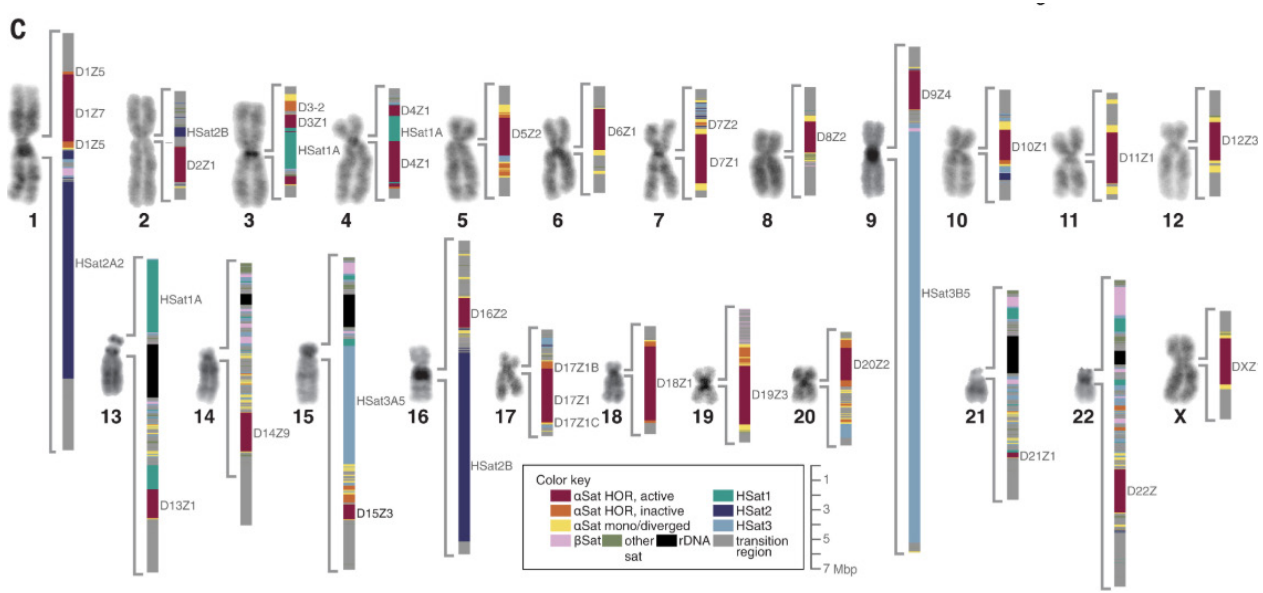
Select Recent Publications – see: https://roneill.lab.uconn.edu/publications/ for full list

Email	rachel.oneill@uconn.edu
Phone	860-486-6031
Fax	860-486-4331
Mailing Address	67 North Eagleville Road, Unit 3197 Engineering Science Building 306B Storrs, CT 06269 -3197
Office Location	Engineering Science Building 305A

Genetic and epigenetic feature of human centromere

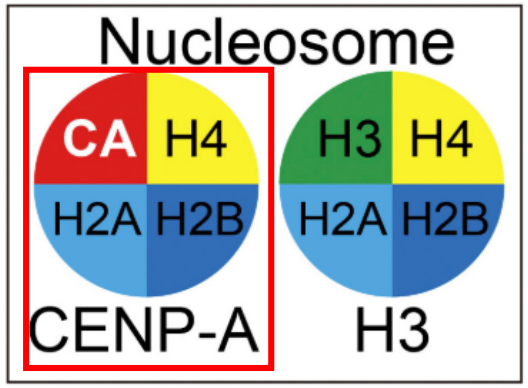
Genetic feature of centromere



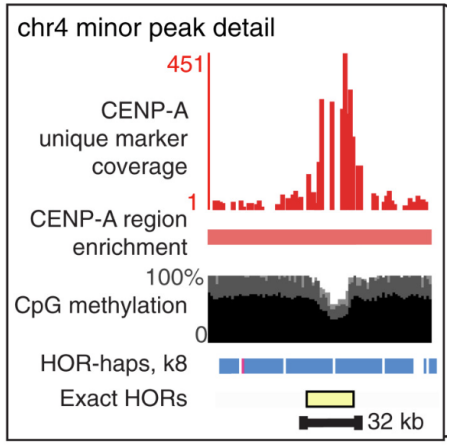


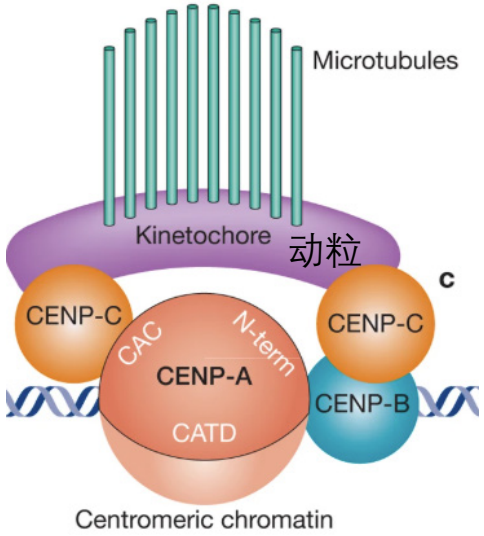
- In most human, centromere is formed on alpha satellite array

epigenetic feature of centromere



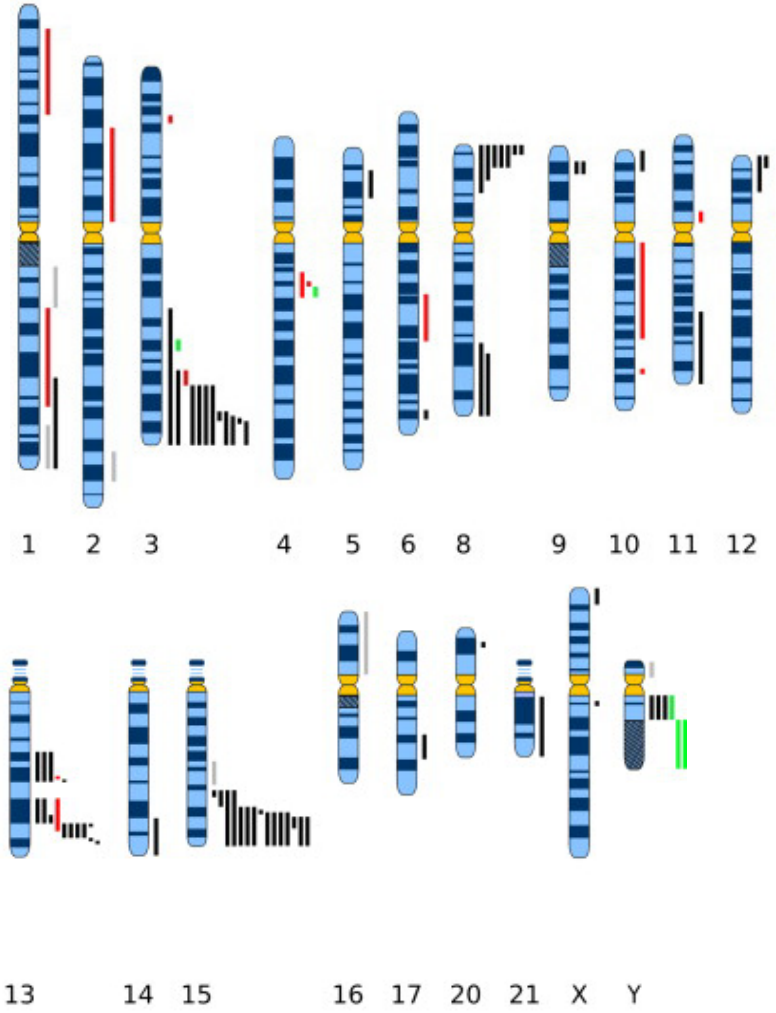
Centromere enriched

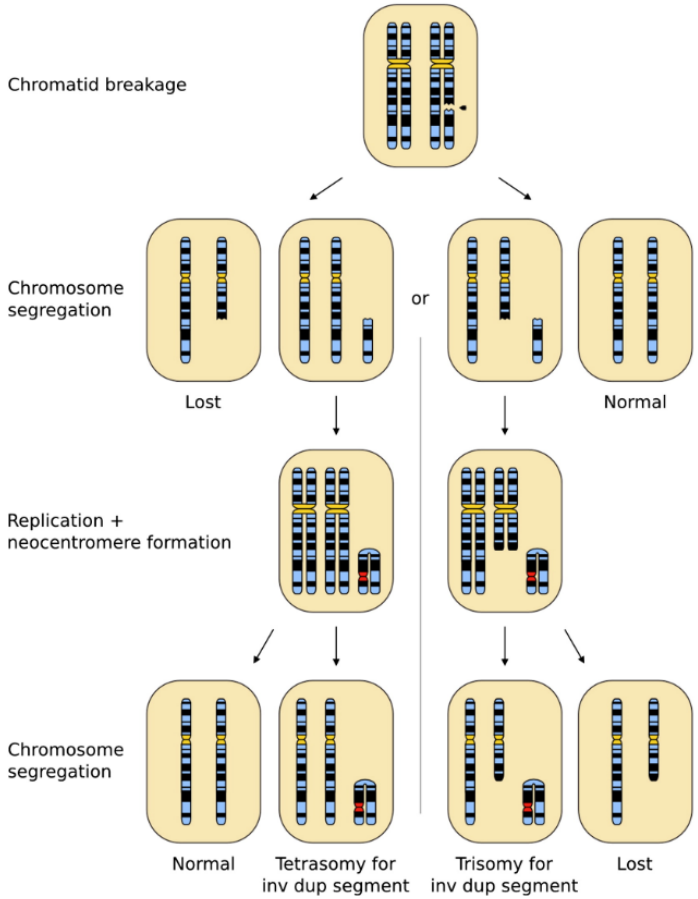




- CENP-A is always associated with functional centromere region
- Centromere dip region(CDR) always coincide with functional centromere region

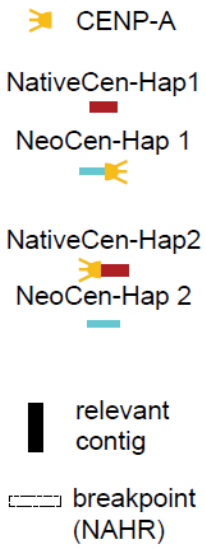
Neocentromere landscape in human genome



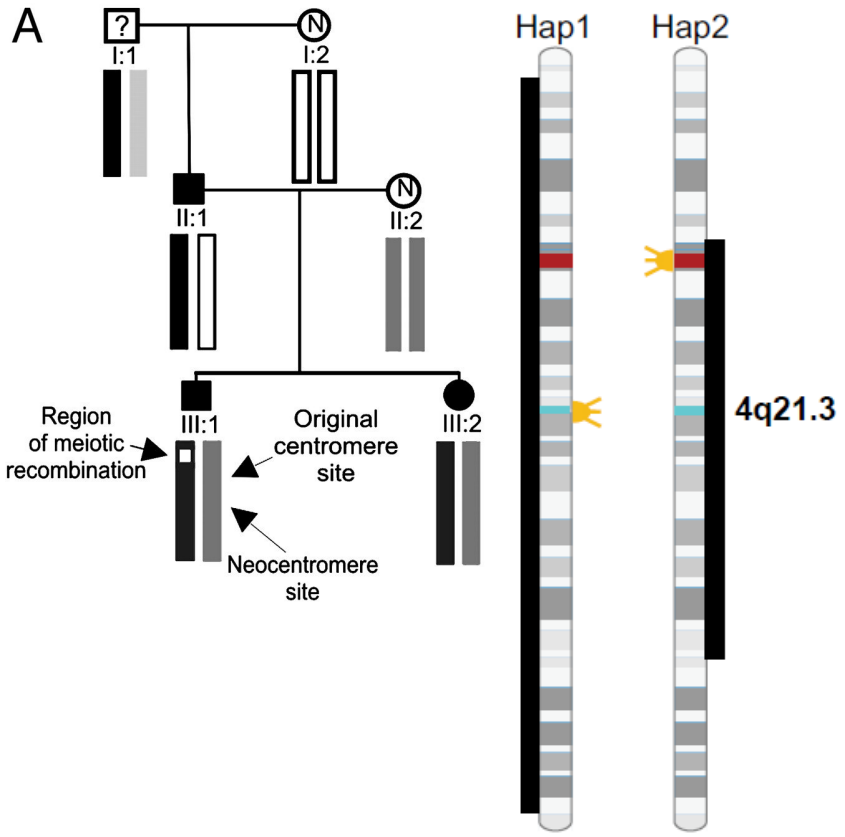


- 1 people out of every 100,000 contains a neocentromere chromosome;
- Most neo-centromeres are associated with chromosome variant;
- Centromere repositioning can occasionally happen without any accompanying chromosome variants.

3 cell lines choice for this study



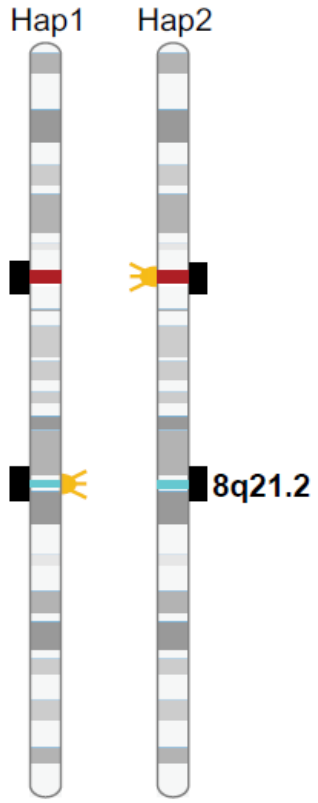
Chromosome 4



7-year-old girl with cognitive impairment

The neocentromere homolog is inherited from the paternal grandfather

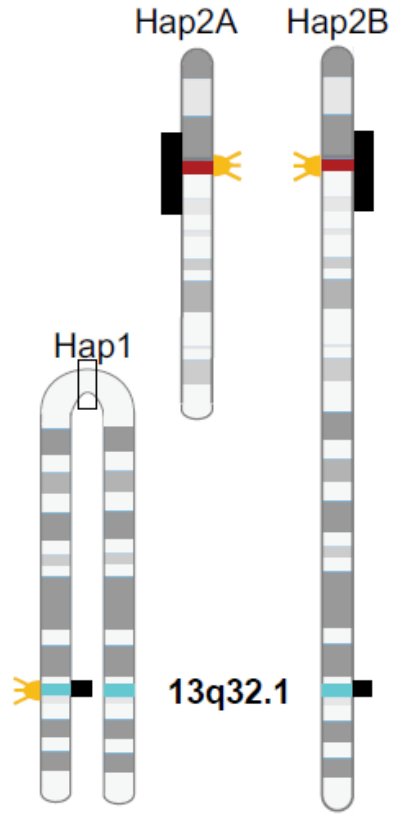
Chromosome 8



A male with no phenotypic abnormalities

His aborted fetus also carry a neocentromere homolog

Chromosome 13

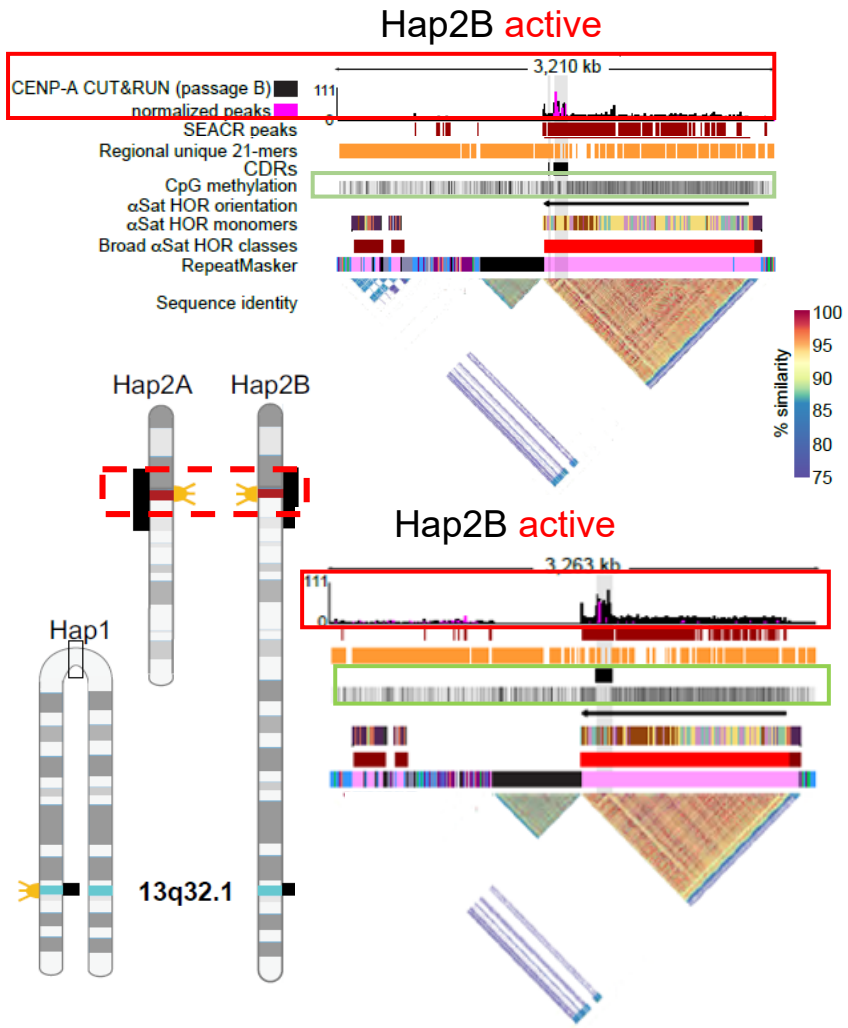


10-month-old girl with developmental delay

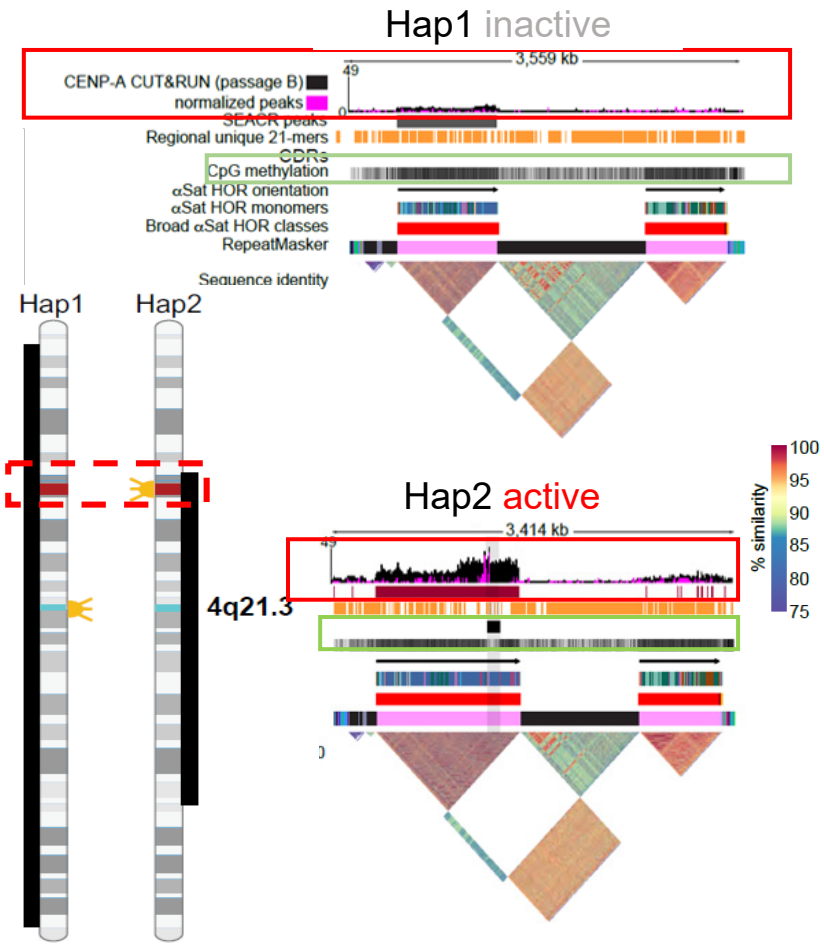
Neocentromere from due to chromosome variation

The comparison of initial centromere region between the two hap

Chromosome 13



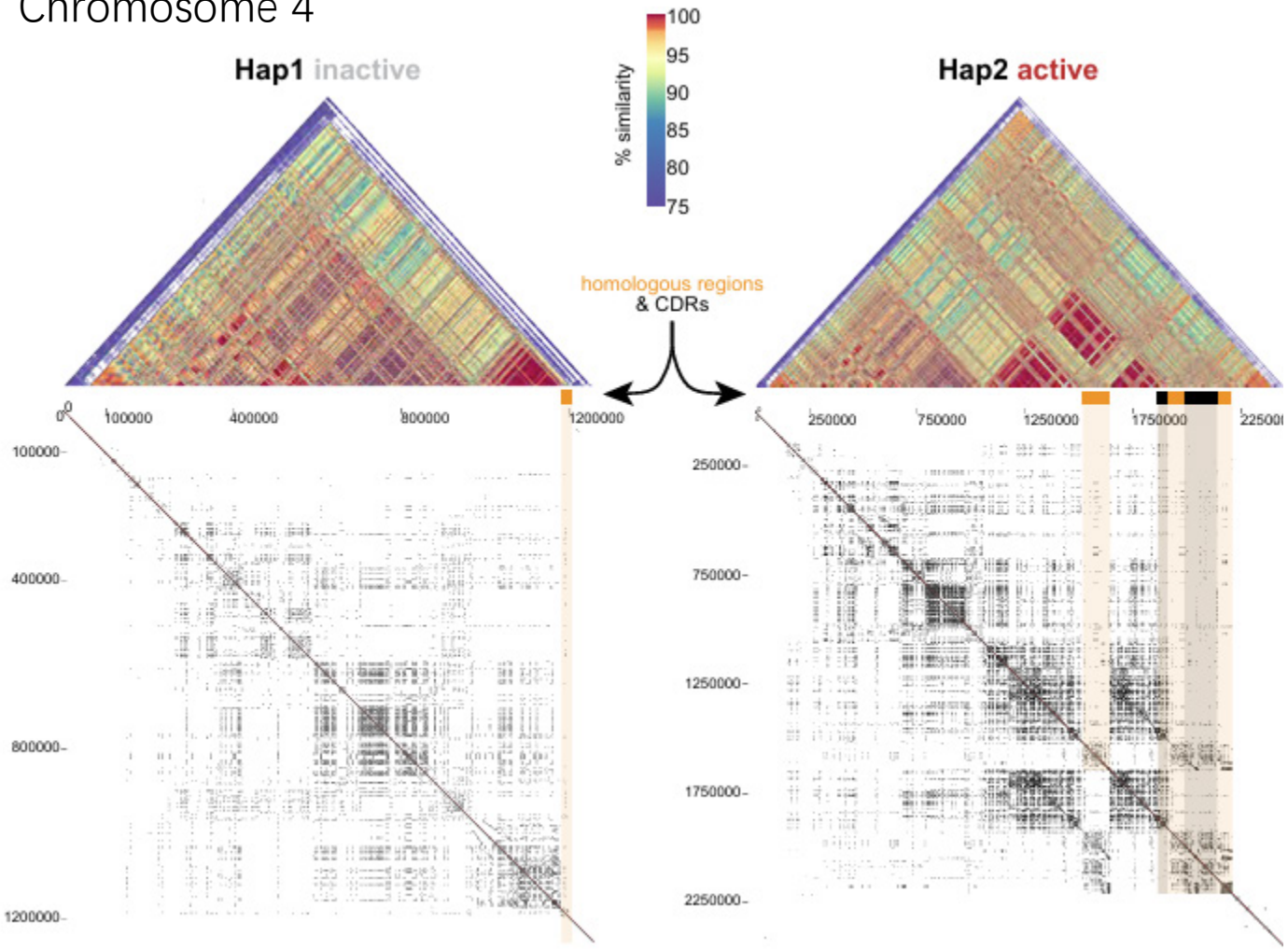
Chromosome 4

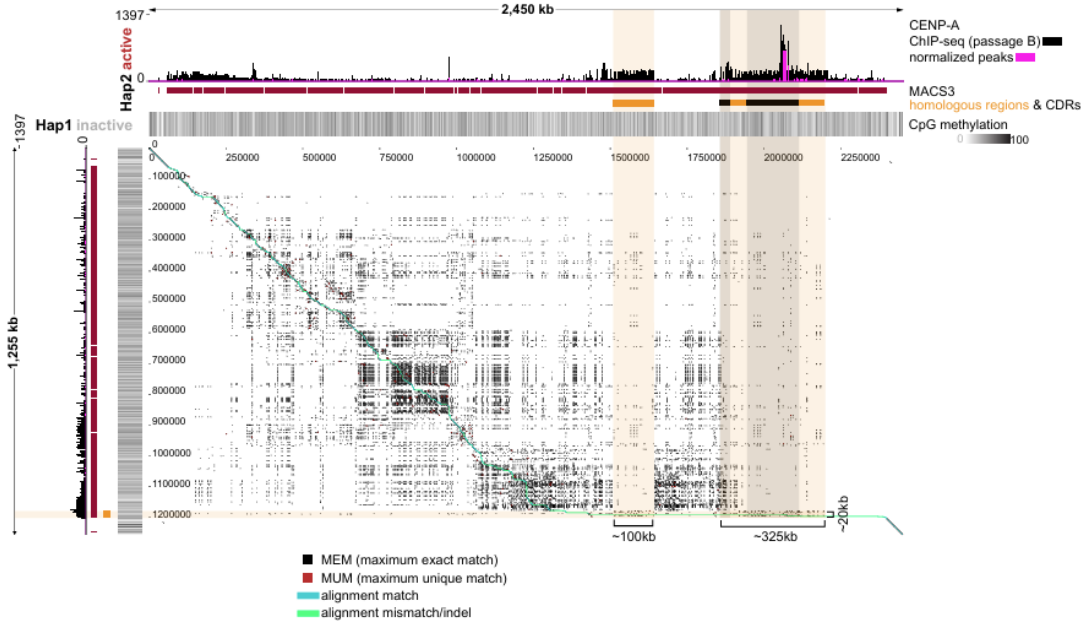


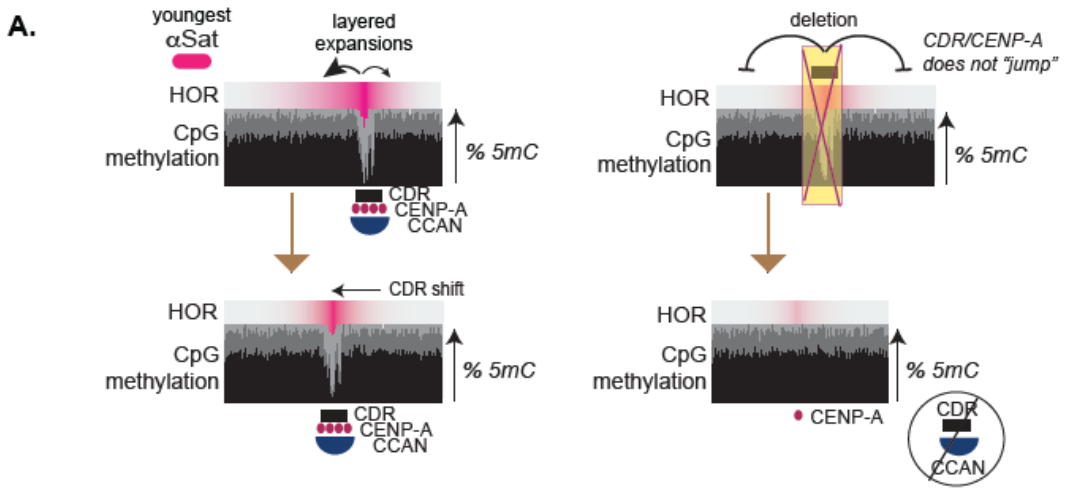
The epigenetic marker of centromere is almost last at the neocentromere homolog

Large deletion induce the lose of function in original centromere loci

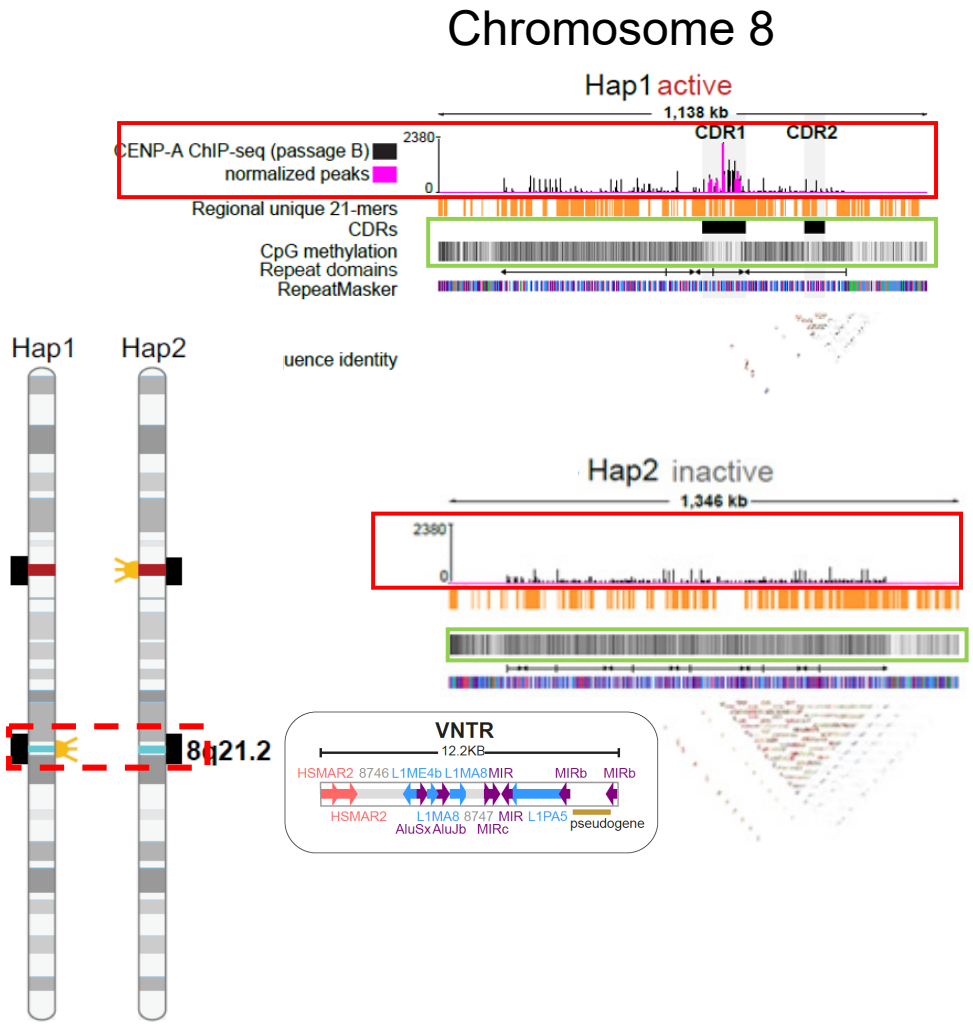
Chromosome 4

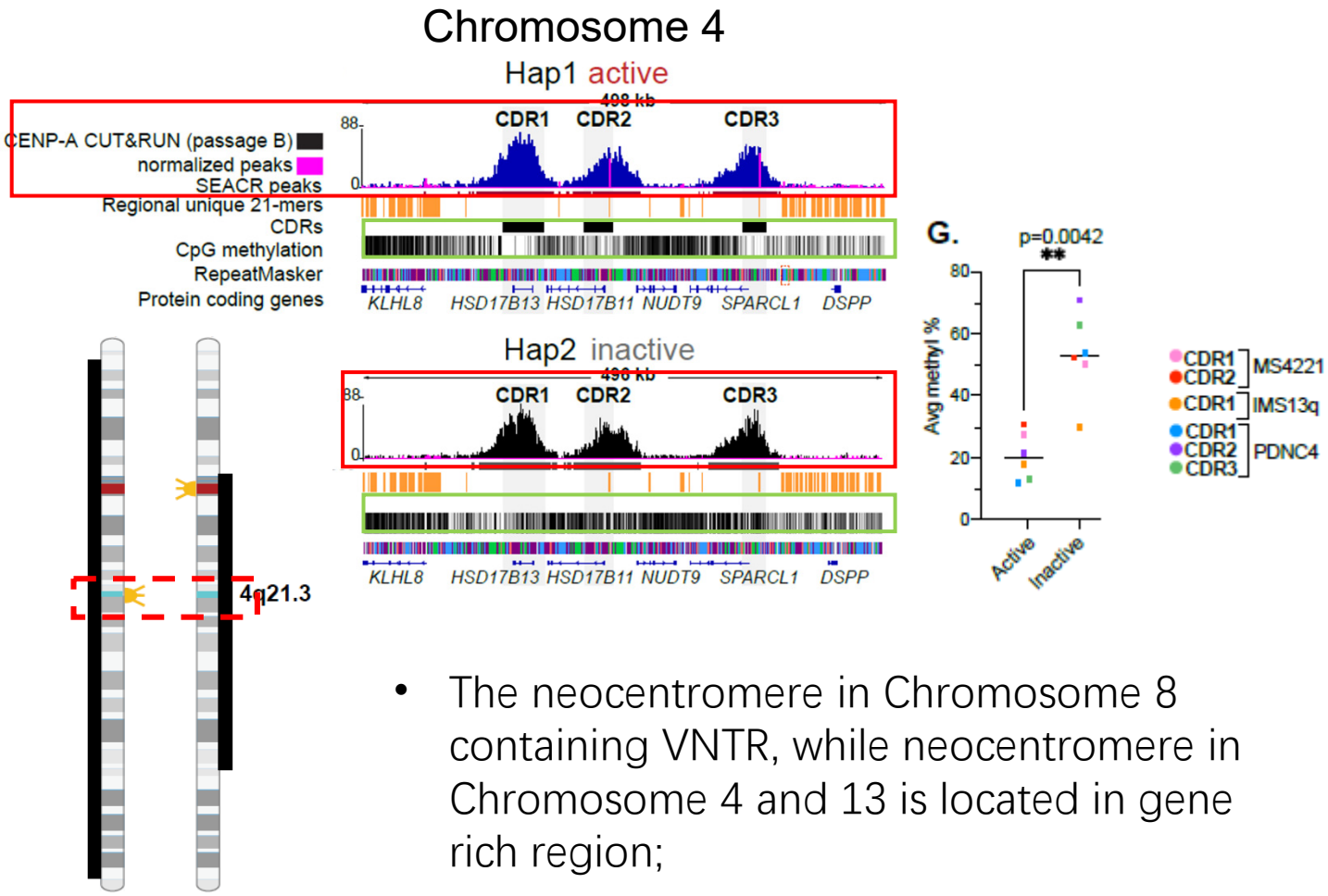






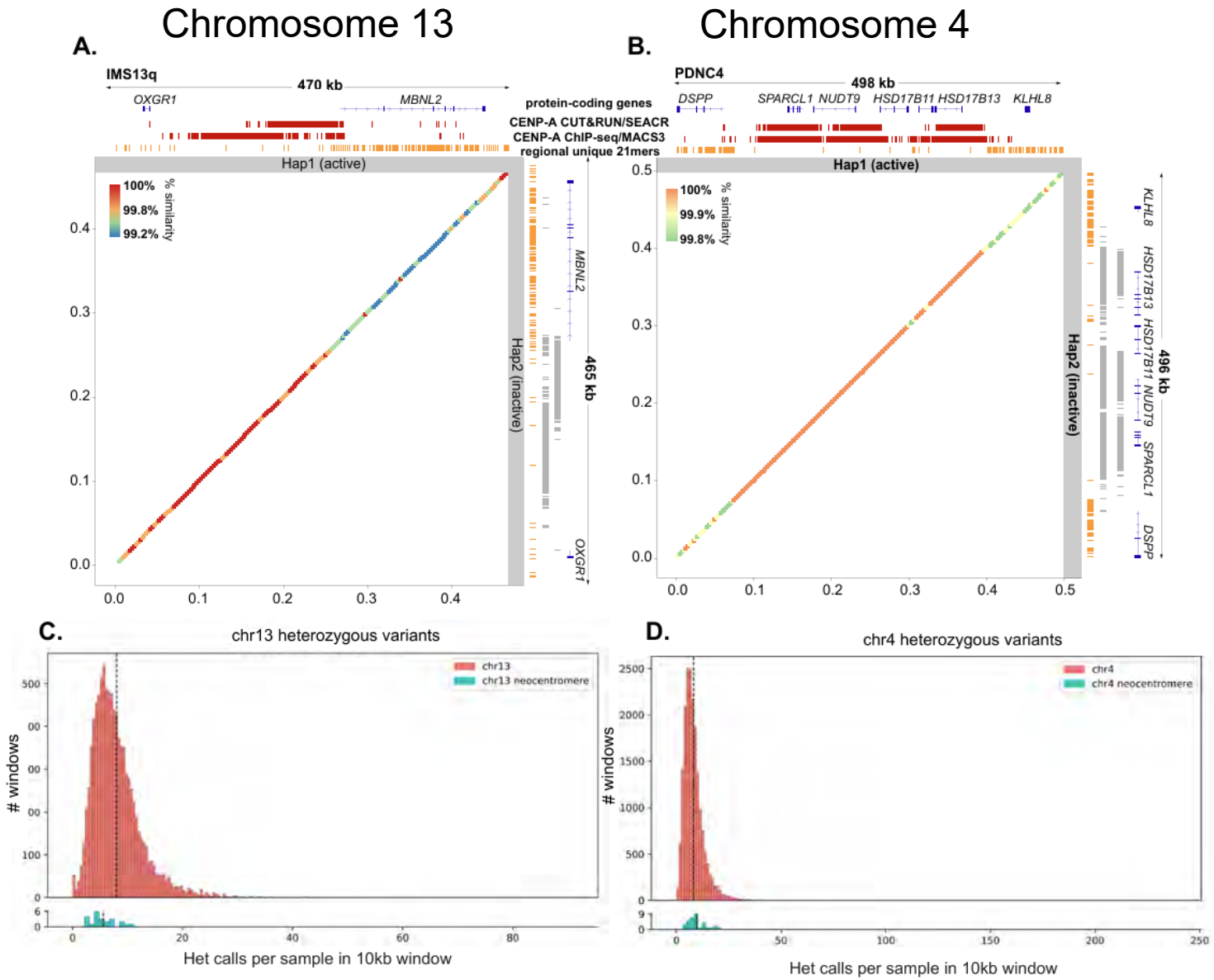
The comparison of neo-centromere region between the two hap





- The neocentromere in Chromosome 8 containing VNTR, while neocentromere in Chromosome 4 and 13 is located in gene rich region;
- Centromere epigenetic marker also exist in the neocentromere region

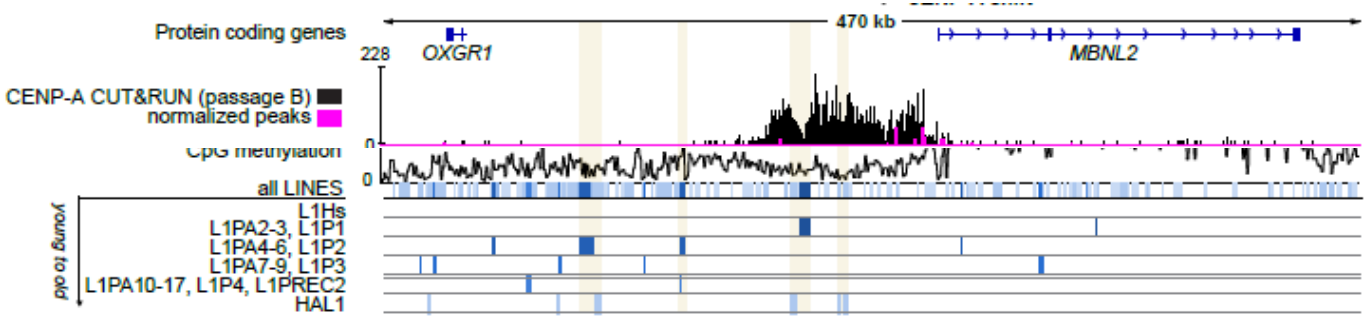
Where the neocentromere may form



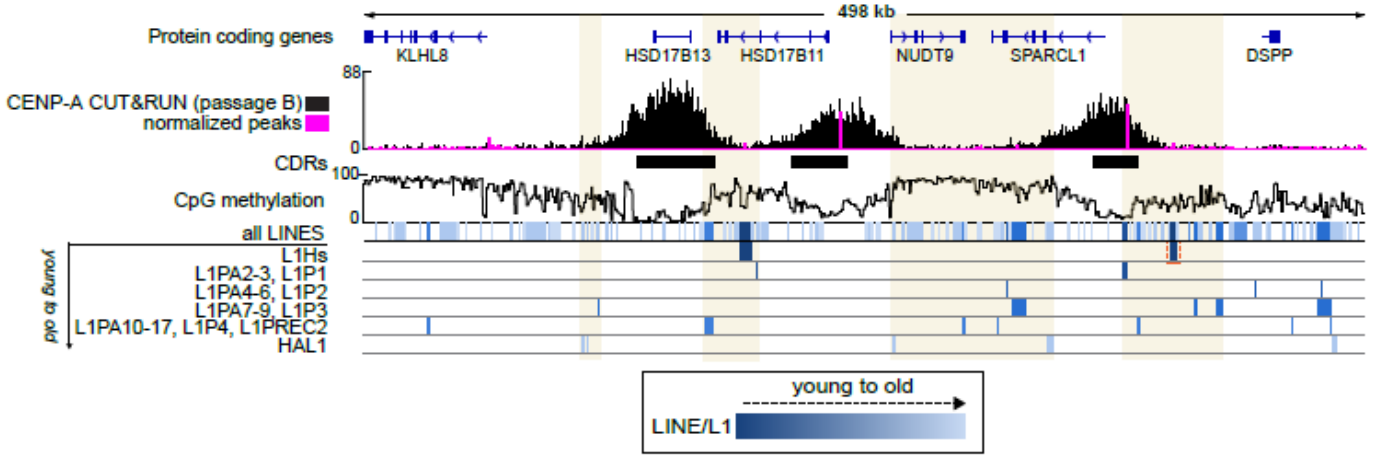
- The low heterozygous region may be preferred via neo-centromere

Where the neocentromere may form

Chromosome 13



Chromosome 4

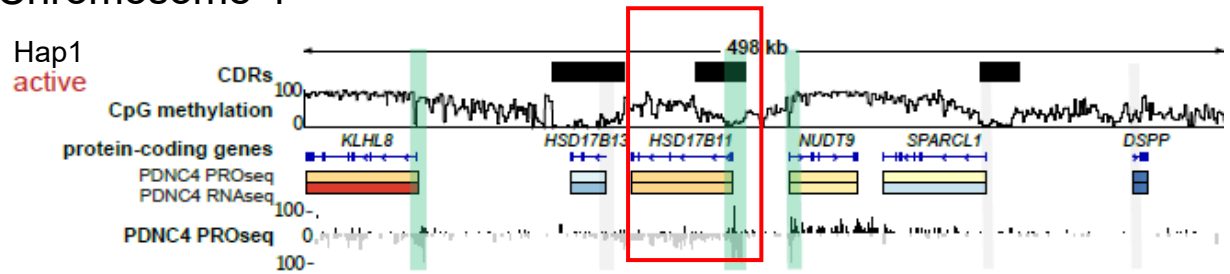


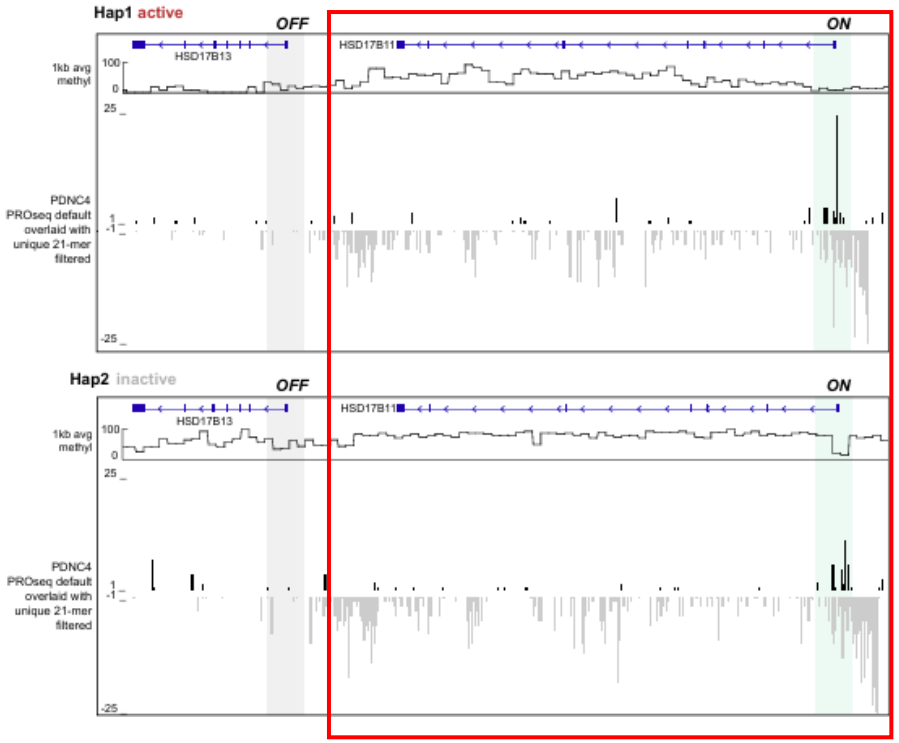
Centromere is shifted within a 500Kb region

No matter how the centromere is shifted, the boundary is always corresponding to a LINE element

What is the consequence of neocentromere

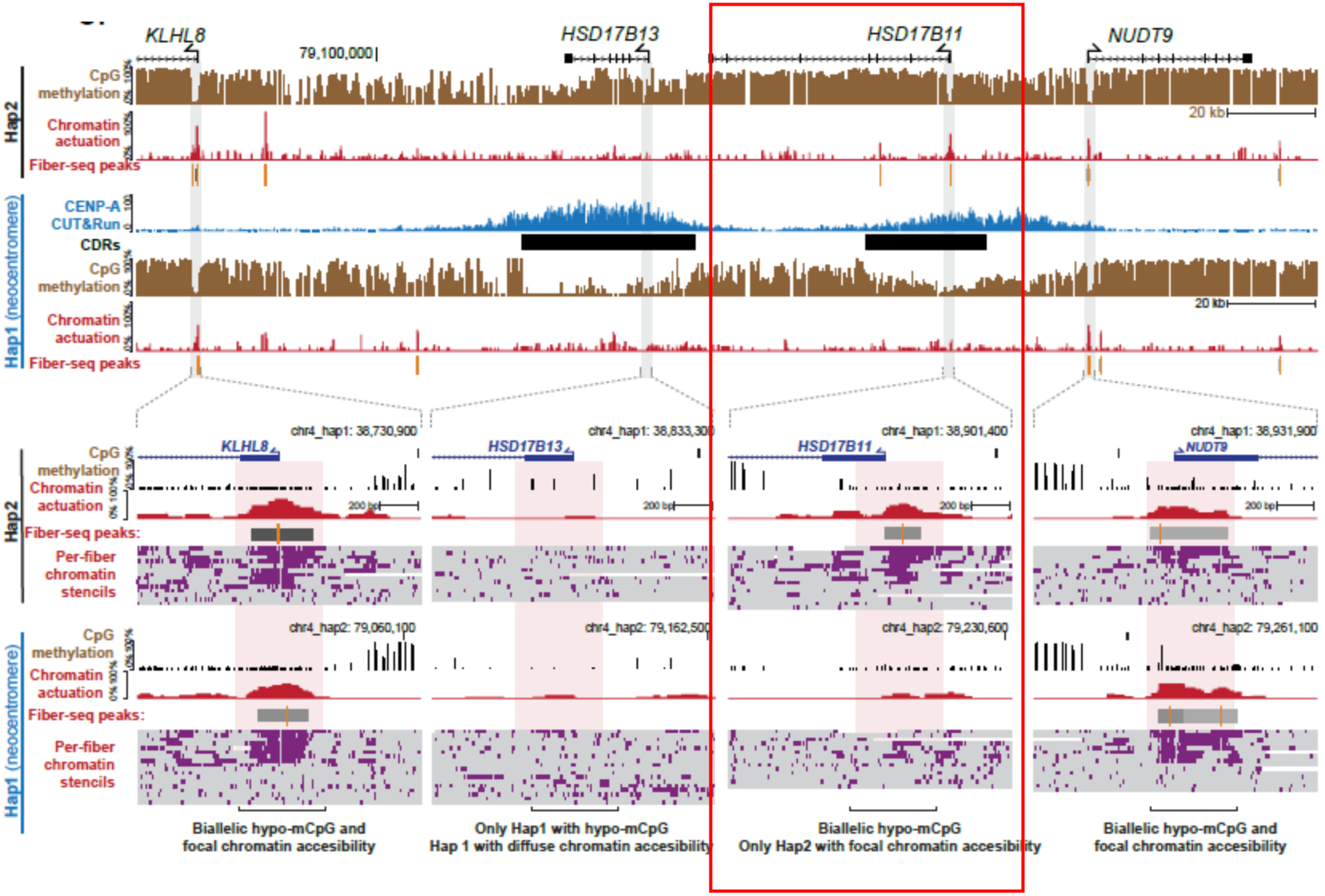
Chromosome 4

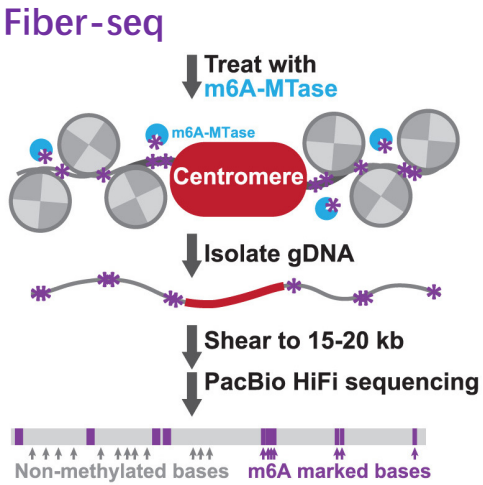




- HSD17B11 is associated with androgen metabolism
- The PROseq cannot determine which homolog the is transcriptionally active

What is the consequence of neocentromere: underlying gene may be silenced

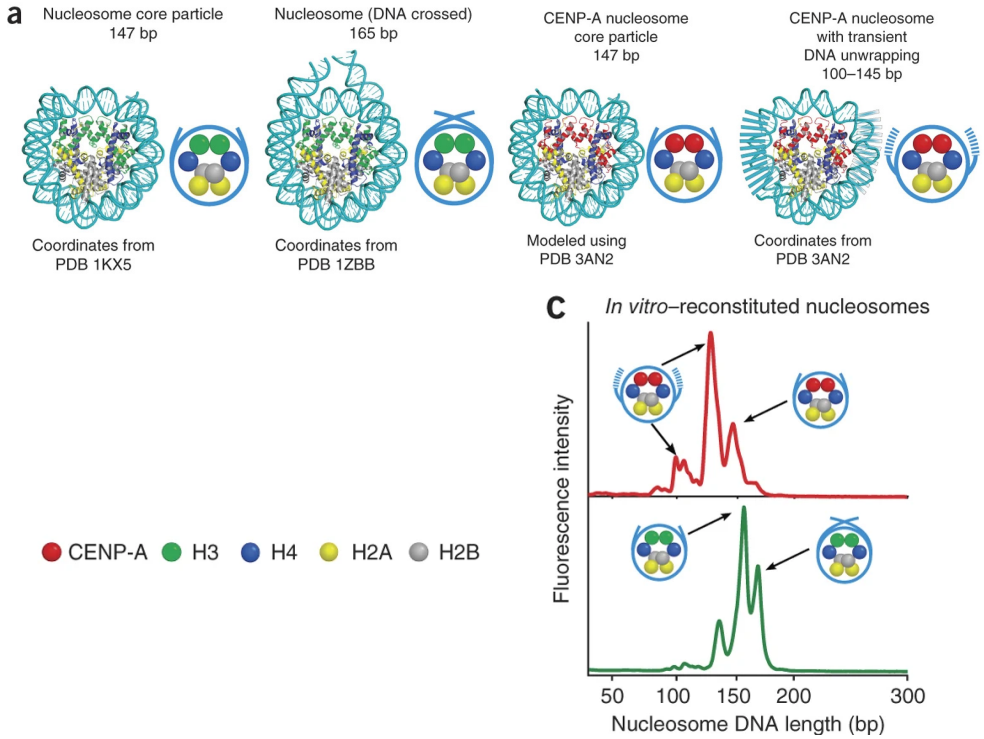




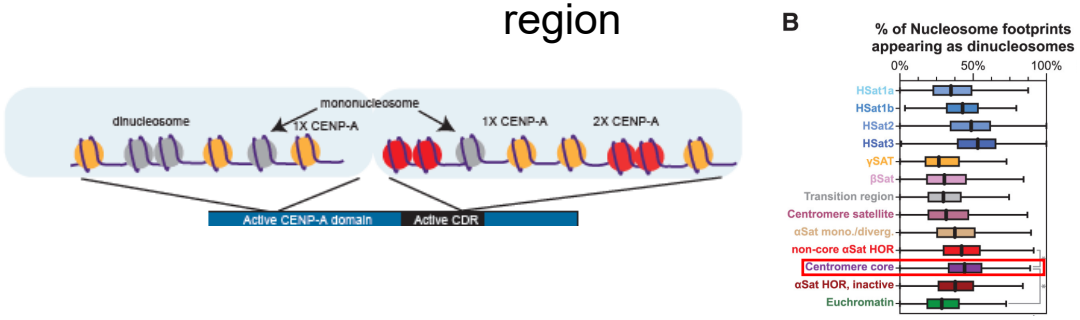
Chromatin state imply that HSD17B11 is transcriptionally inactive in the neocentromere homolog

Chromatin pattern in neocentromere region

CENP-A nucleosome warp less DNA than H3 nucleosome

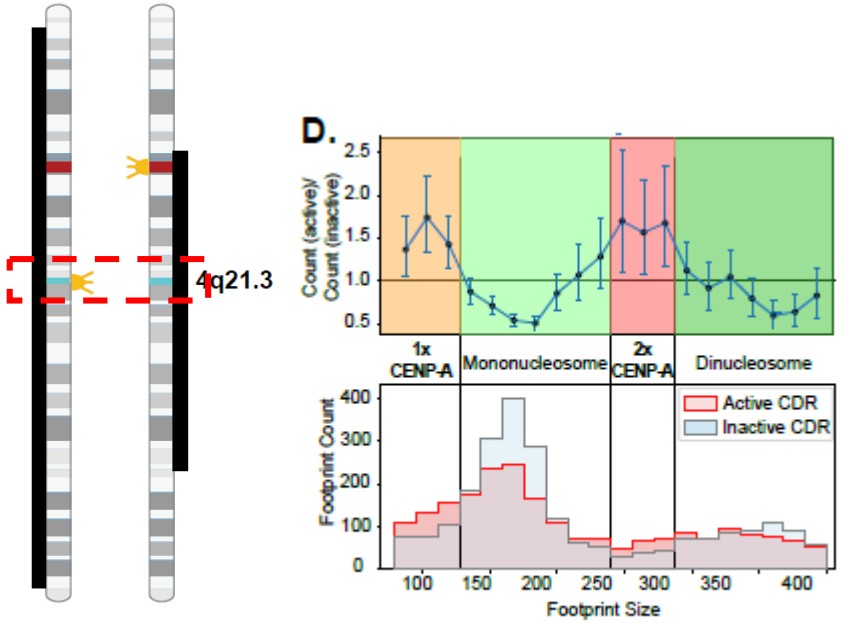


Dichromotin is abundant in functional centromere region



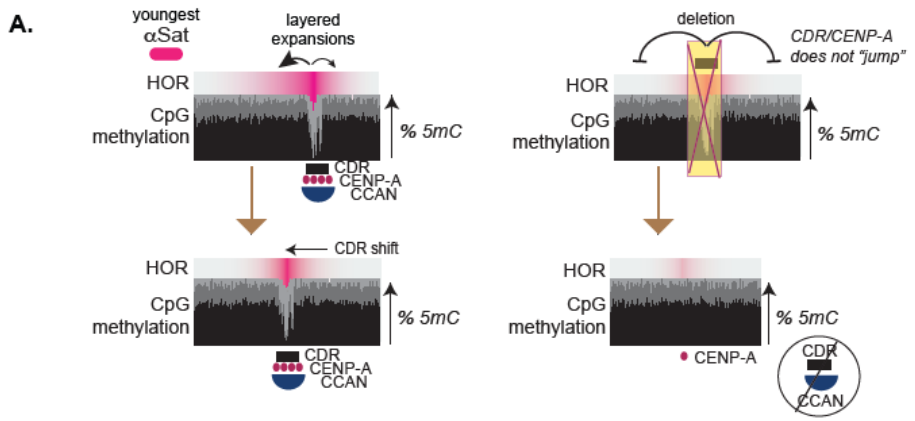
Nucleosome footprints

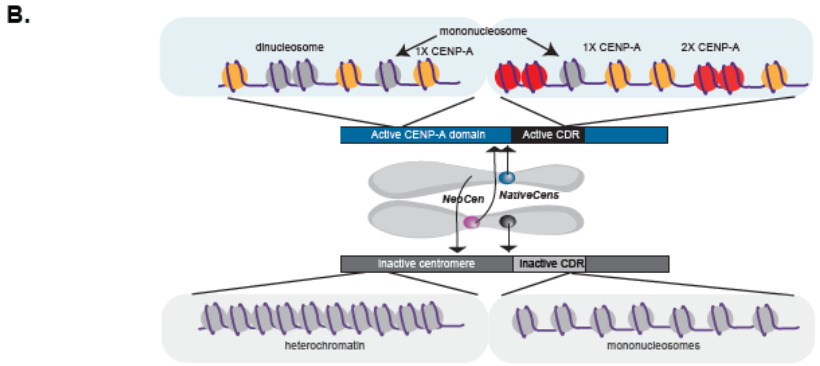
MTase-Sensitive Patches (MSP)



- Nucleosome footprint is maintained in neocentromere region.

Conclusion





- Large deletion induce the centromere lost in alpha satellite region
- Neocentromere form on low heterozygous region and keep the centromere epigenetic pattern
- Underlying gene may be silenced due to the chromatin pattern in centromere

Remanent Question:

- What SV can induce lost of centromere function in alpha satellite region?
- Does all neocentromere form on heterozygous region and what feature determine it