Journal Club

Spatial genomics enables multi-modal study of clonal heterogeneity in tissues

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Fei Chen, Principal Investigator

Dr. Fei Chen is currently a Core Faculty member at the Broad Institute, and assistant professor at Harvard Stem Cell and Regenerative Biology. He obtained his Ph.D. in biological engineering from the Massachusetts Institute of Technology in 2016. Fei was a Schmidt Fellow at the Broad Institute from 2017-2020.

Fei was an Axline scholar at the California Institute of Technology and graduated with a Bachelor's degree in Electrical Engineering in 2011.

Major achievements of the past

OPTICAL IMAGING

Expansion microscopy

Fei Chen,[1]* Paul W. Tillberg,[2]* Edward S. Boyden[1,3,4,5,6]†

In optical microscopy, fine structural details are resolved by using refraction to magnify images of a specimen. We discovered that by synthesizing a swellable polymer network within a specimen, it can be physically expanded, resulting in physical magnification. By covalently anchoring specific labels located within the specimen directly to the polymer network, labels spaced closer than the optical diffraction limit can be isotropically separated and optically resolved, a process we call expansion microscopy (ExM). Thus, this process can be used to perform scalable superresolution microscopy with diffraction-limited microscopes. We demonstrate ExM with apparent ~70-nanometer lateral resolution in both cultured cells and brain tissue, performing three-color superresolution imaging of ~10^7 cubic micrometers of the mouse hippocampus with a conventional confocal microscope.

nature biotechnology

LETTERS

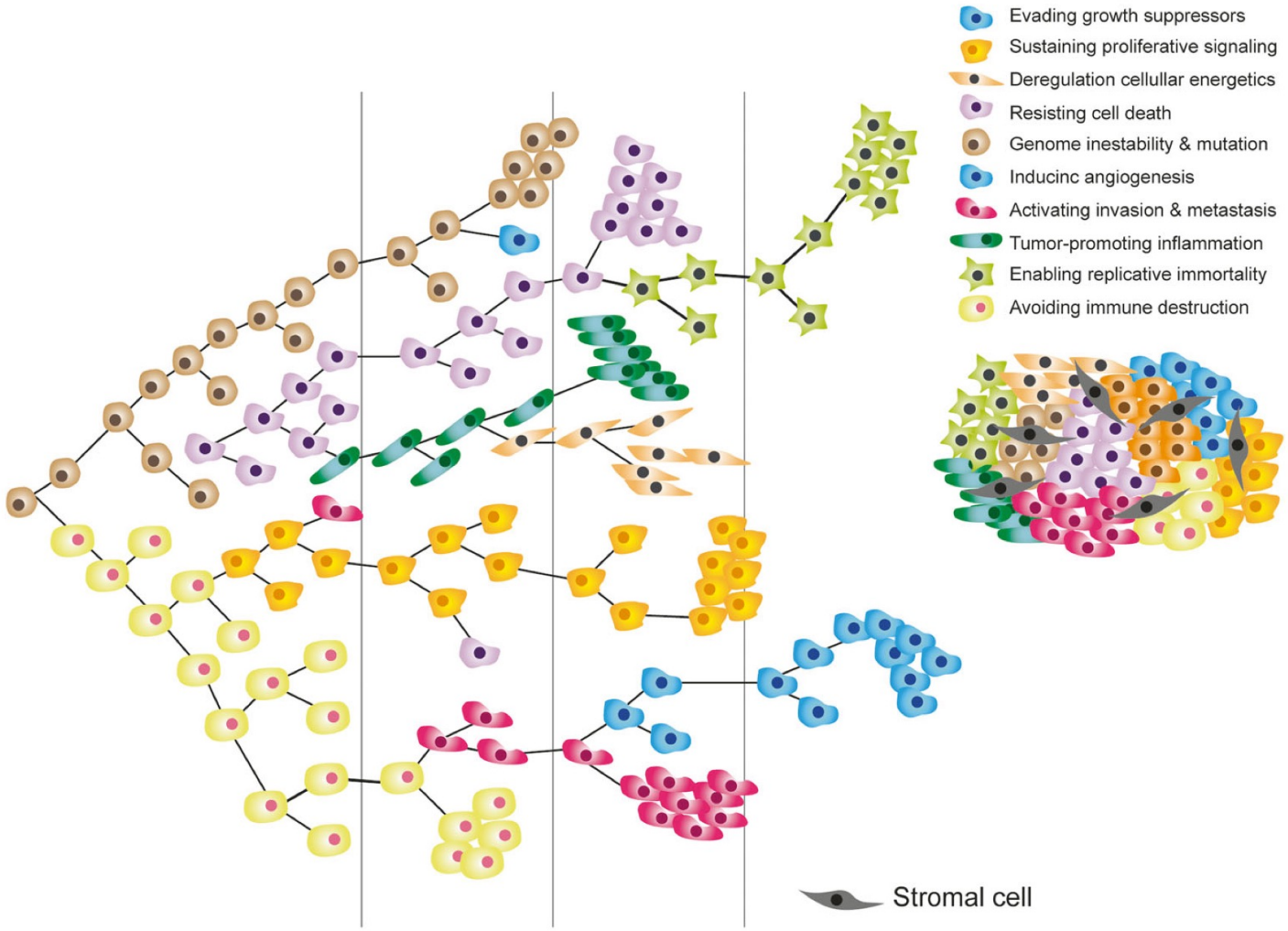
https://doi.org/10.1038/s41587-020-0739-1

Check for updates

Highly sensitive spatial transcriptomics at near-cellular resolution with Slide-seqV2

Robert R. Stickels[1,2,3,6], Evan Murray[1,6], Pawan Kumar[1], Jilong Li[1], Jamie L. Marshall[1], Daniela J. Di Bella[4], Paola Arlotta[5], Evan Z. Macosko[1,5,7] ✉ and Fei Chen[1,4,7] ✉

Detailed tumor heterogeneity study requires a spatial genomic technique



1. Genomic aberration contributes to intra-tumor clonal heterogeneity.
2. Tumor heterogeneity is associated with drug resistance, metastasis and relapse.

Santiago Ramón y Cajal et al., J Mol Med (Berl) (2022).

Detailed tumor heterogeneity study requires a spatial genomic technique

Techniques used to study tumor heterogeneity or spatial genome	Single-cell whole-genome sequencing (scWGS)	Laser-capture microdissection (LCM)	In situ genome sequencing (IGS)
Disadvantage	Missing spatial organization.	Requiring manual selection. De novo discovery is not possible.	Tissue level analysis is not possible.

Article framework

Article

Spatial genomics enables multi-modal study of clonal heterogeneity in tissues

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Tongtong Zhao[1,2,7], Zachary D. Chiang[1,2,3,7], Julia W. Morriss[1,2], Lindsay M. LaFave[2,4,5], Evan M. Murray[1,2], Isabella Del Priore[4,5], Kevin Meli[4,5], Caleb A. Lareau[1,2], Naeem M. Nadaf[1], Jilong Li[1], Andrew S. Earl[1,2,3], Evan Z. Macosko[1,6], Tyler Jacks[1,4,5], Jason D. Buenrostro[1,2,3,8]✉ & Fei Chen[1,2,3,8]✉

1. Slide-DNA-seq enables spatially resolved DNA sequencing.
2. Paired slide-DNA-seq and slide-RNA-seq characterize the genetics and transcriptomes of distinct metastatic clones.
3. De novo identification of spatial tumour clones in primary human colorectal cancer.
4. Decomposition of transcriptional programs driven by genetic aberrations and tumour density.

Schematic of slide-DNA-seq

Analysis on a manually created animal tumor model and de novo analysis on a real human tumor.

Showing the power of the multi-modal study.

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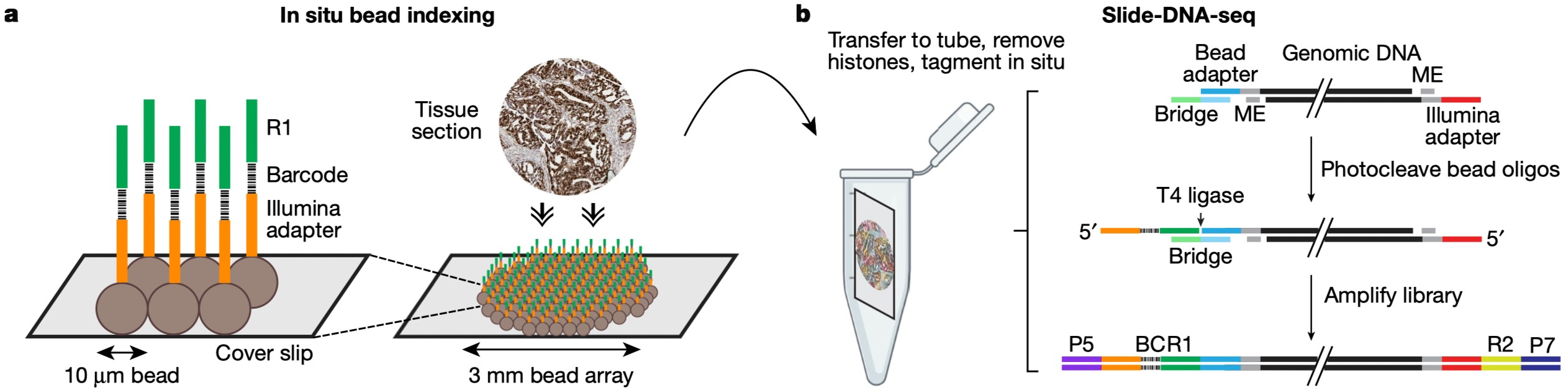
Schematic of slide-DNA-seq

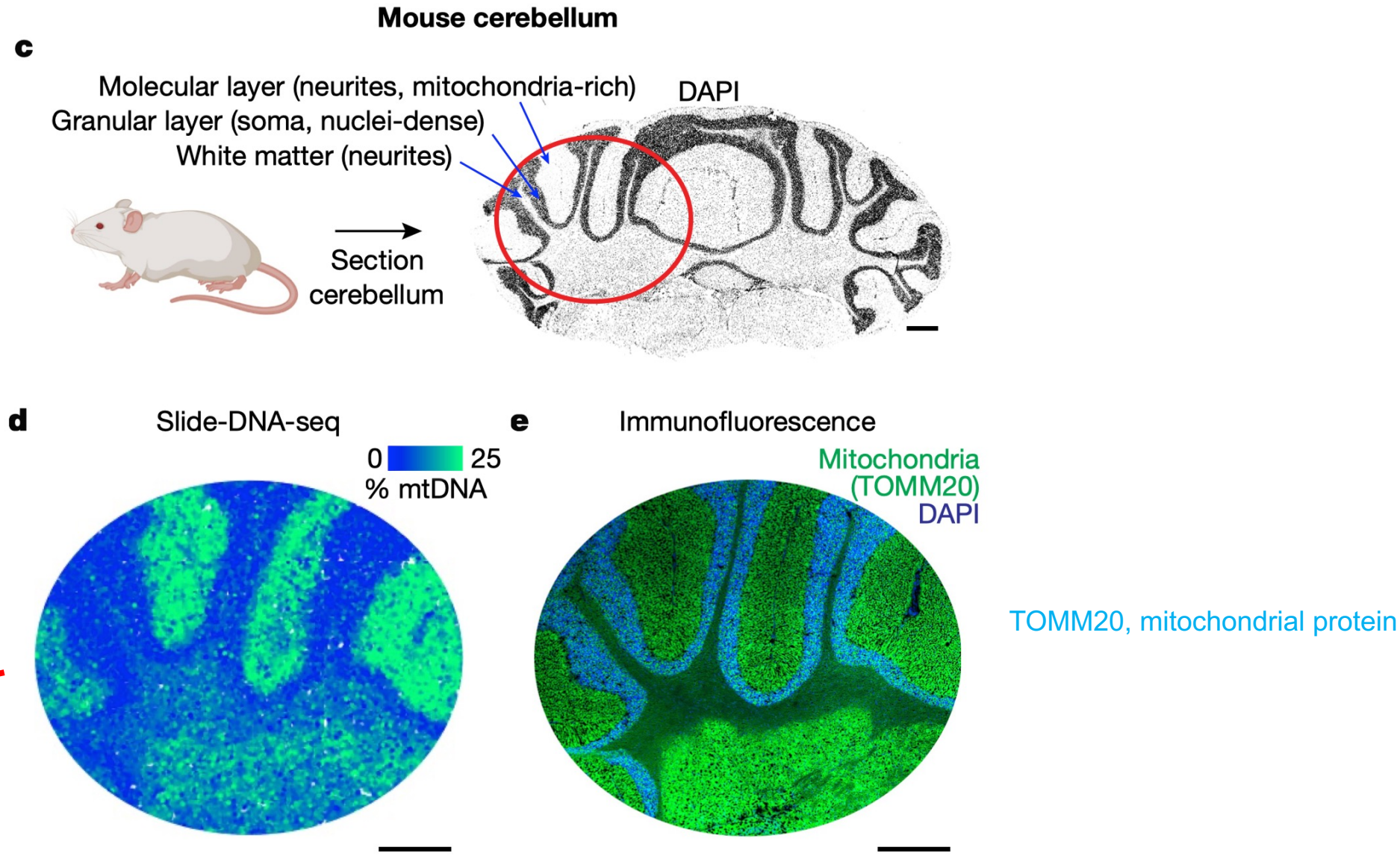


spatially indexed beads
containing a unique DNA barcode

BC, barcode; ME, mosaic ends; P5/P7, Illumina adaptor;
R1, Illumina read 1; R2, Illumina read 2

Rodriques, S. G. et al. Slide-seq: A scalable technology for measuring genome-wide expression at high spatial resolution. Science 363, 1463–1467 (2019).
Stickels, R. R. et al. Highly sensitive spatial transcriptomics at near-cellular resolution with Slide-seqV2. Nat. Biotechnol. 39, 313–319 (2021).

slide-DNA-seq can generate genomic data with good resolution within normal tissues



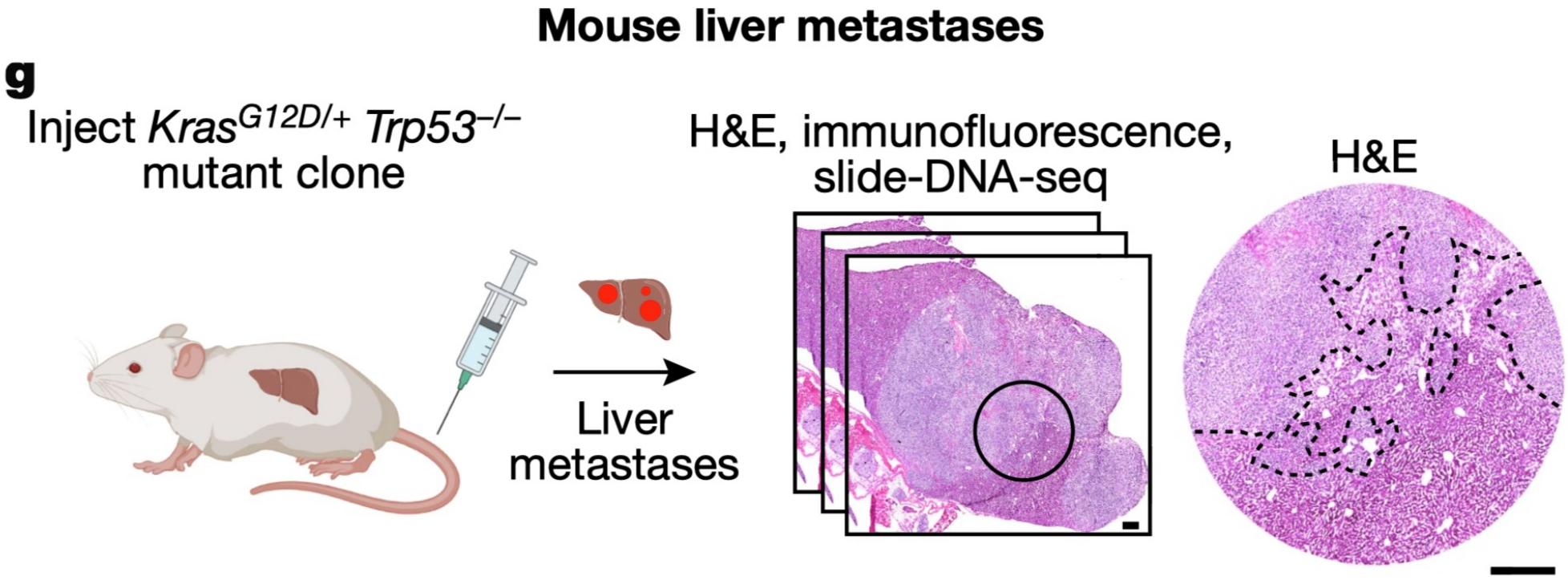
Each point represents one bead

TOMM20, mitochondrial protein

serial sections

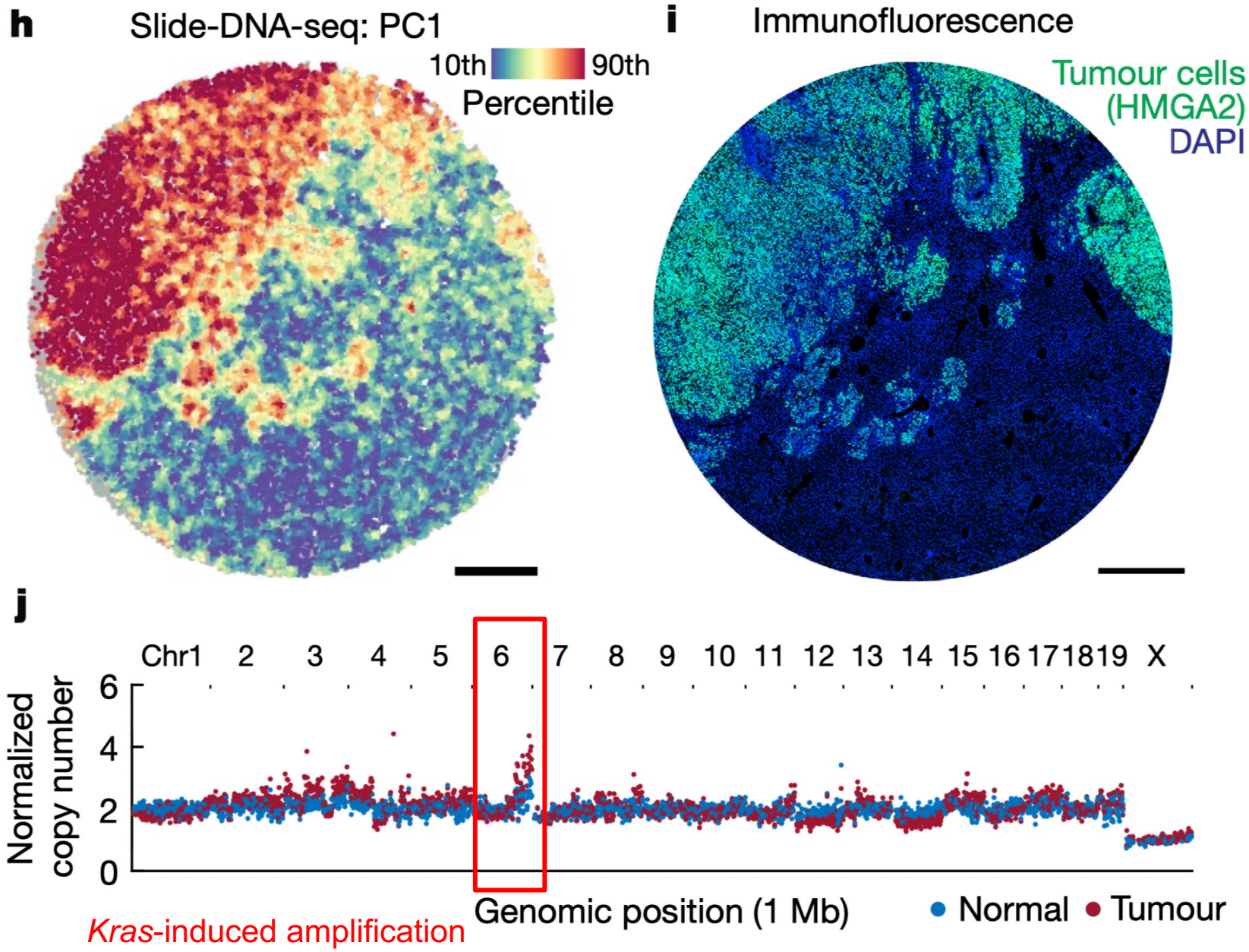
Can slide-DNA-seq detect spatial distribution of copy number alteration (CNA)?

Tissue preparation for tumor heterogeneity analysis using slide-DNA-seq



serial sections

Slide-DNA-seq can identify genomic CNAs in genetically distinct tumour clones



HMGA2,
a late-stage tumour marker

CNA, copy number alterations

(h) and (i) are serial sections

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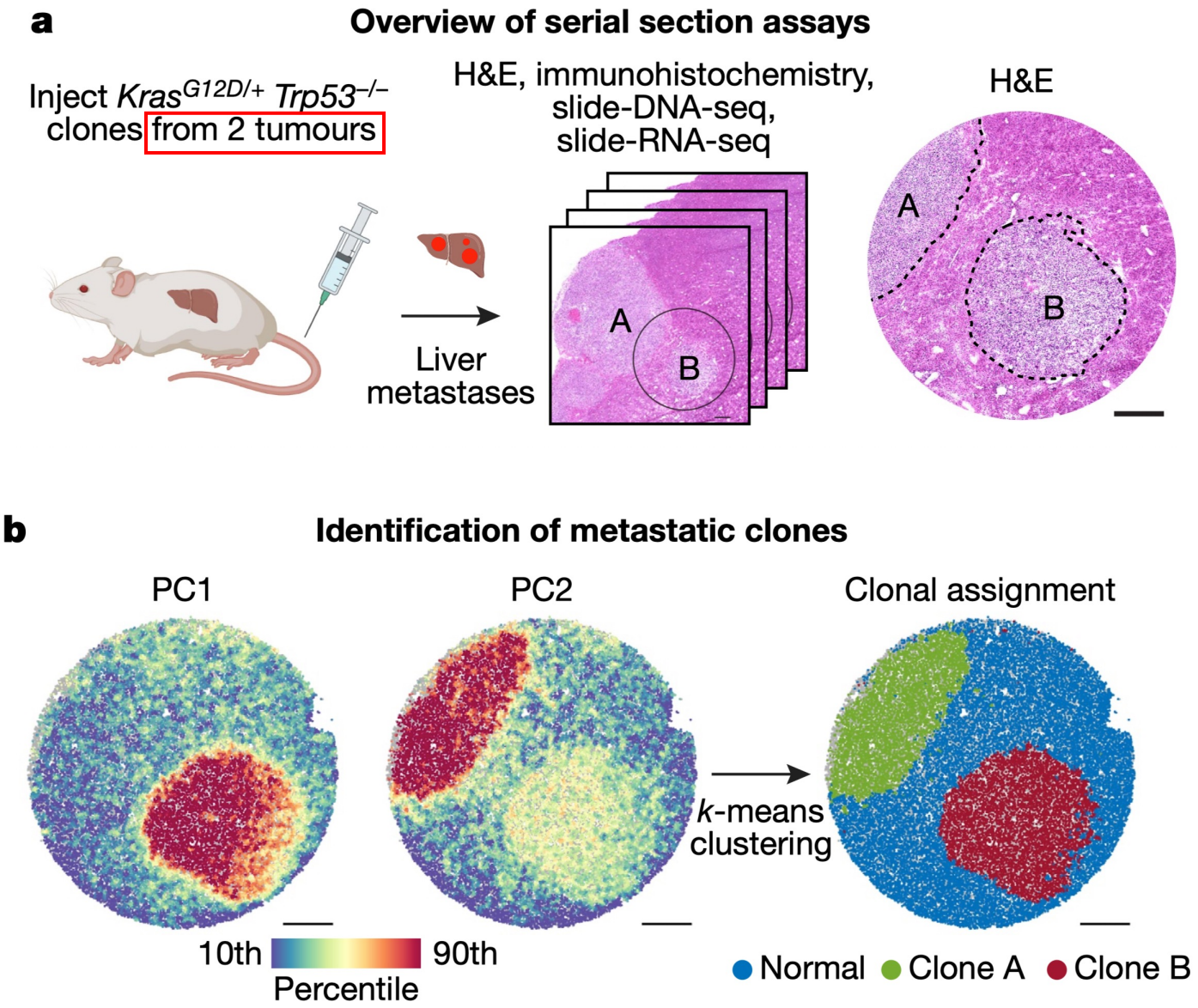
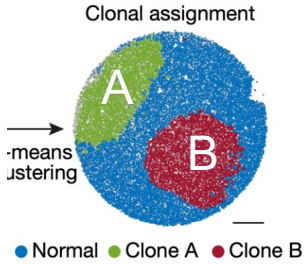
Can slide-DNA-seq distinguish between clones within a tissue?

Schematic of testing multiple-clones-analysis in a tissue using slide-DNA-seq slide-DNA-seq

Technically, the 2 injected tumors will form 2 genetically different clones

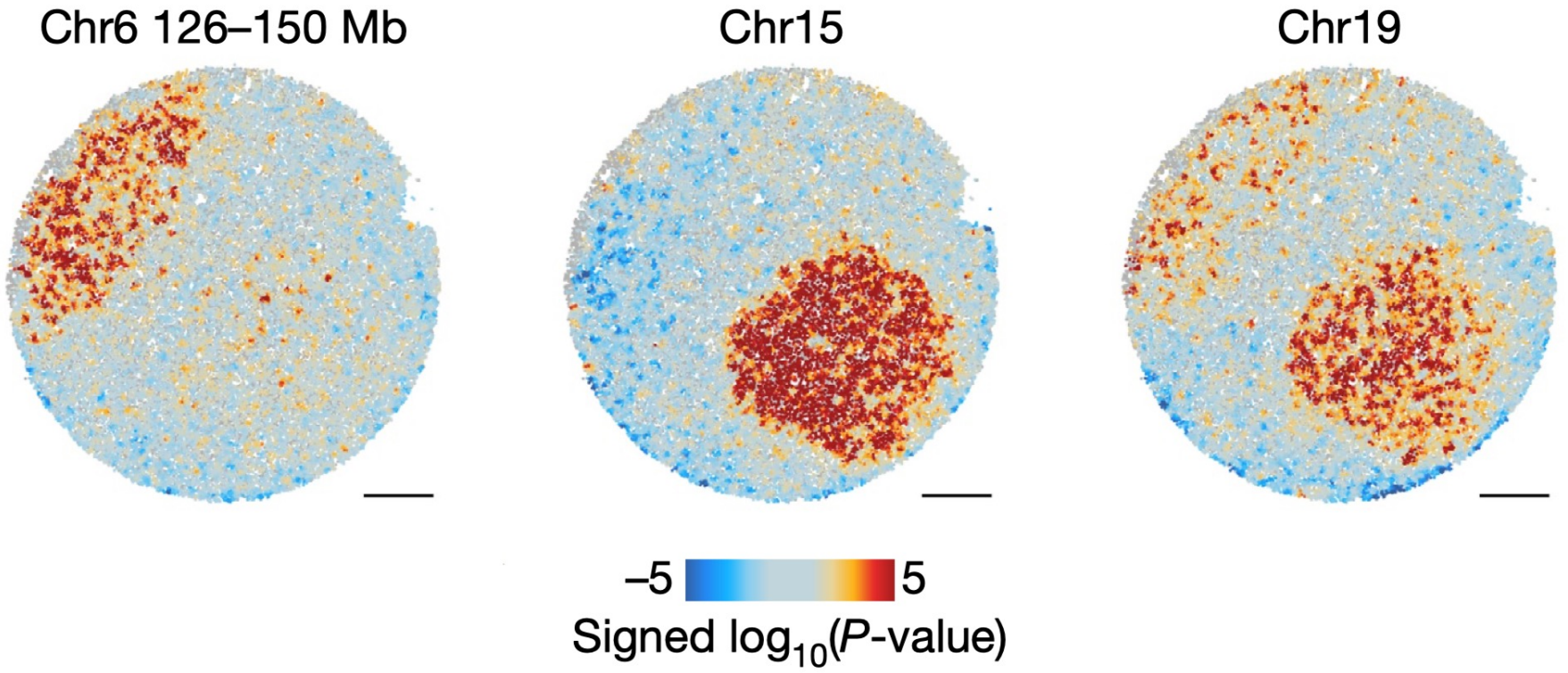




Identification of clone-specific CNAs

slide-DNA-seq

c



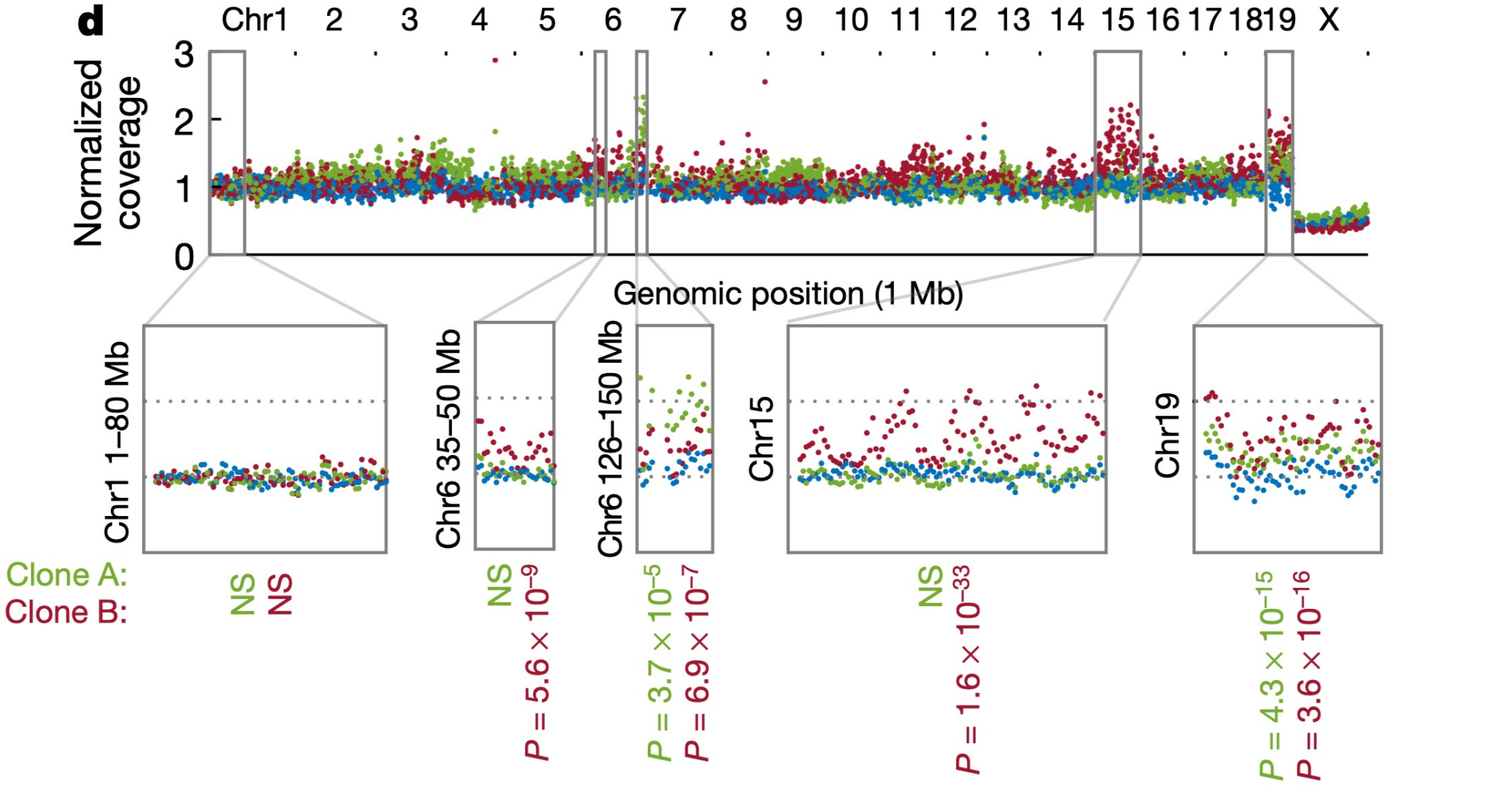
Clone A-specific

Clone B-specific

2 tumor clones-common

Genomic view of clone-specific CNAs

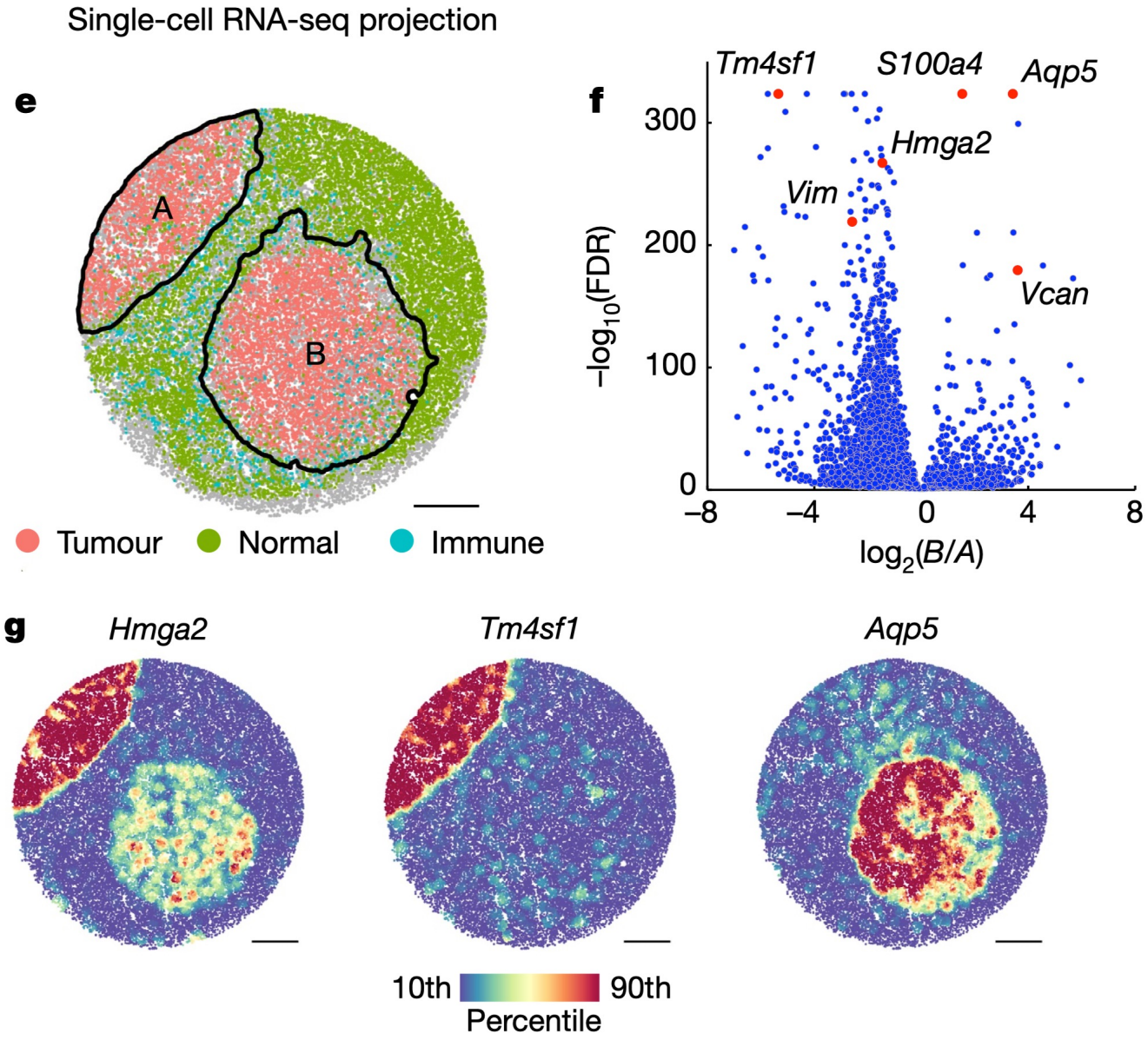
slide-DNA-seq



Clone B-specific Clone A-specific Clone B-specific 2 tumor clones-common

The two genetically different clones are in very different cell state

slide-RNA-seq



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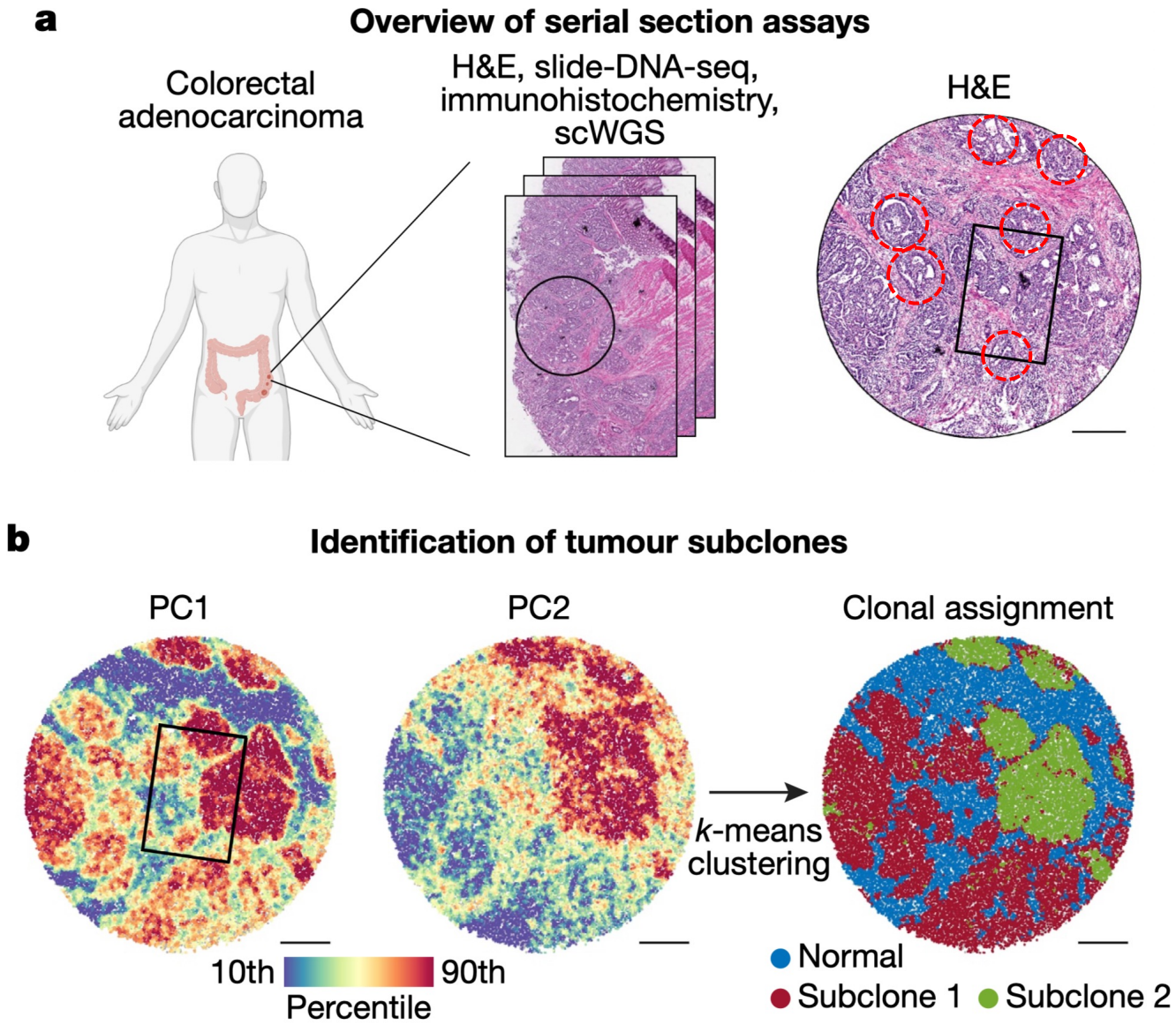
The previous study is based on a manually created animal tumor model.
Can slide-DNA-seq perform de novo analysis in a real human tumor?

Subclone detection in human colon cancer

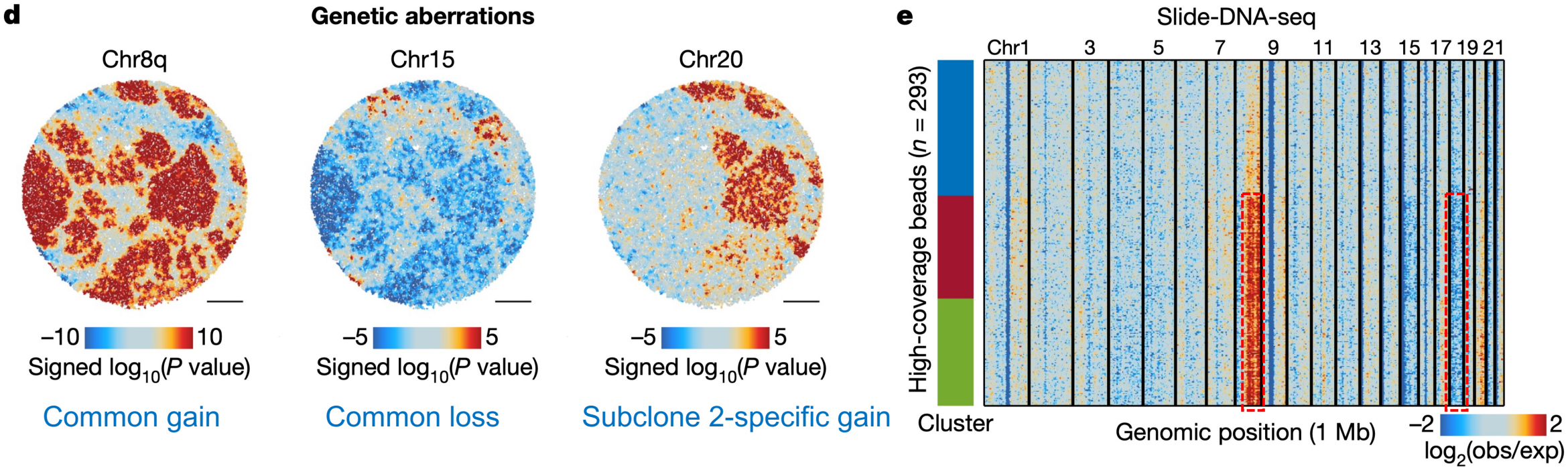


Small aggregates

from a single lineage?
Or from mixed lineages?

Each aggregate originates from a single lineage (subclone 1 or subclone 2), not from mixed lineages

Identification of subclone-specific CNAs for studying the evolution of clonal heterogeneity

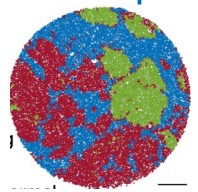


Identified genetic aberrations:
Tumor-common: chr8q, chr15 and chr18 → presumably early tumor marker
Tumor subclone-specific: chr1q, chr7 and chr20 → presumably late tumor marker

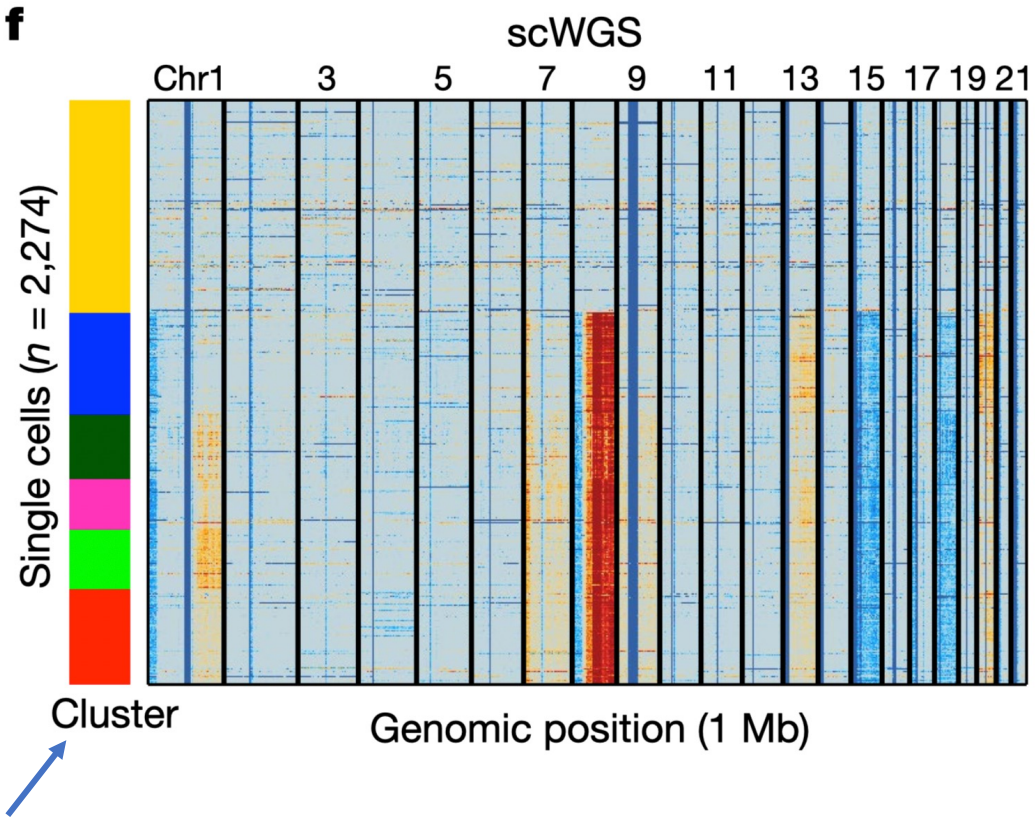
Red: papers supported
Black: papers opposed

Whole-tumor scWGS validates the discovery of slide-DNA-seq and enhances the spatial and genomic resolution

Slide-DNA-seq label

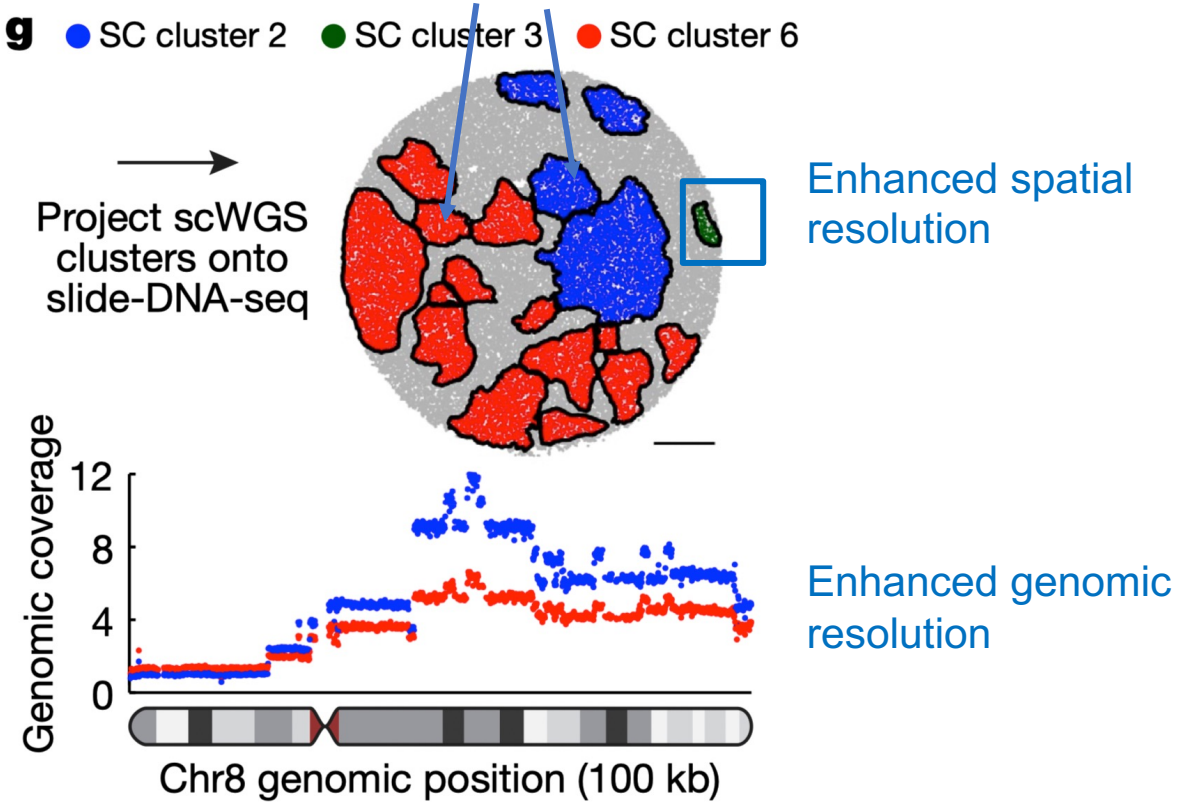


Previous slide-DNA-seq is just for one 10 μm tissue section (it's literally a 2D spatial genome).
So validation by the entire tumor tissue is required.



Much more tissues, more subclones.
It is reasonable.

Subclones validated



Enhanced spatial resolution

Enhanced genomic resolution

Together, these analyses validate that slide-DNA-seq alone is sufficient for de novo discovery and localization of distinct tumour clones within a tissue and show that CNA characterization can be enhanced through integration with scWGS.

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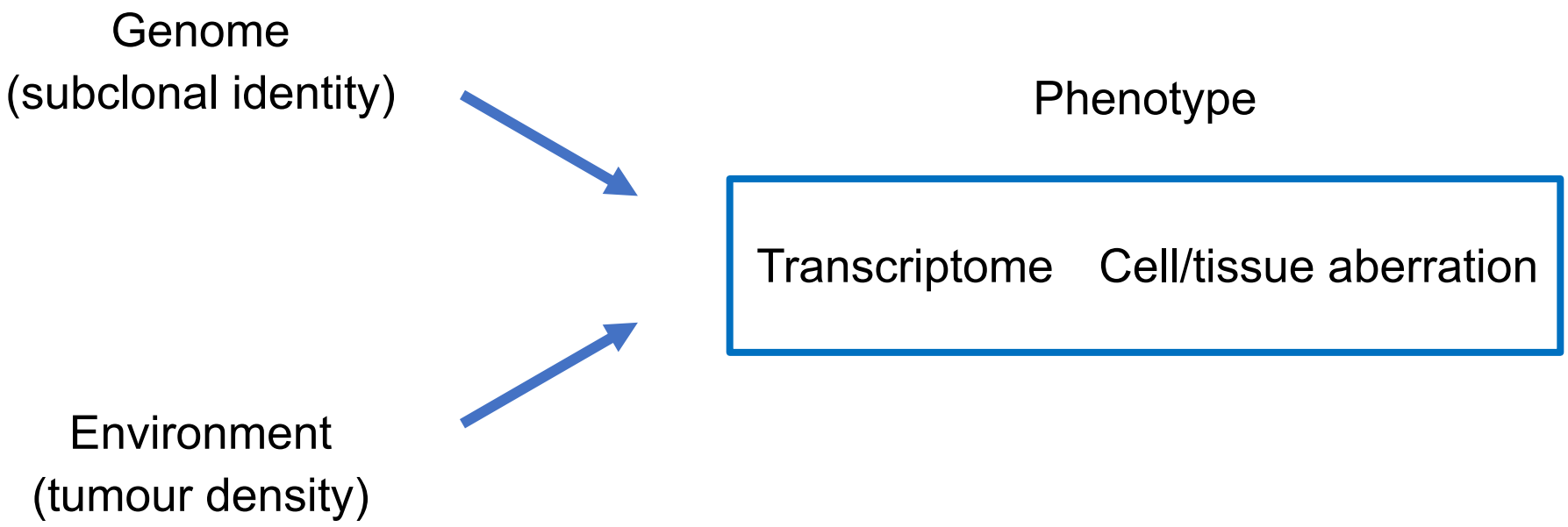
What is the unique capability of a multi-modal spatial sequencing approach?

Phenotype

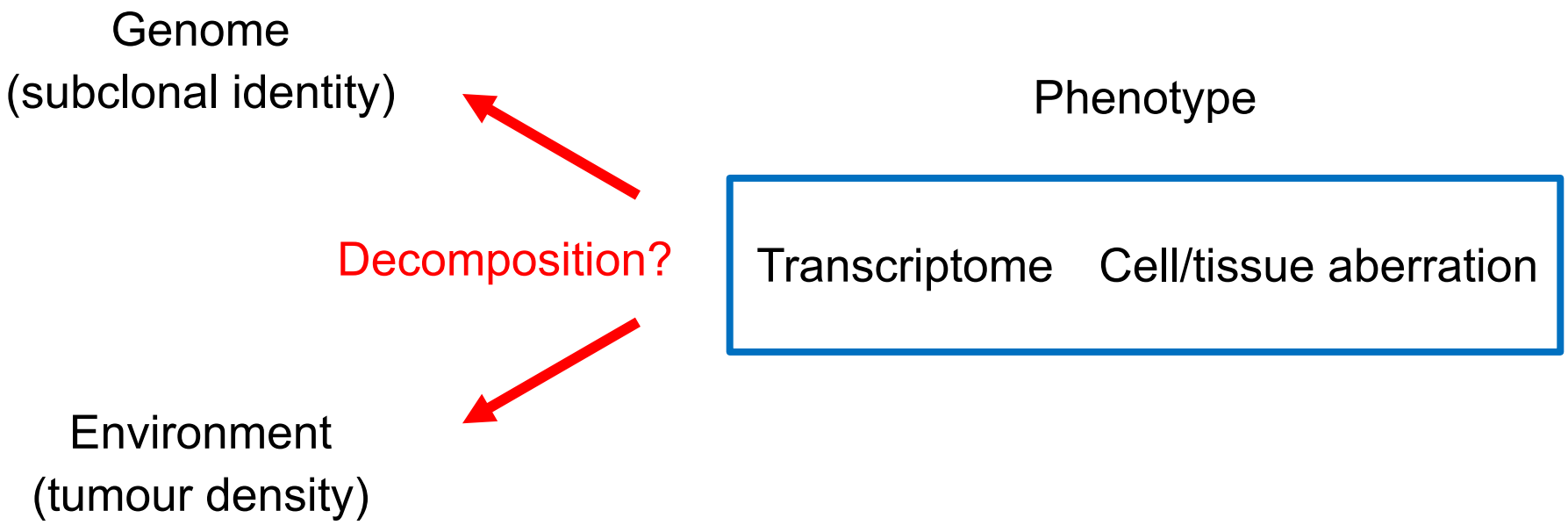
Transcriptome Cell/tissue aberration

What is the unique capability of a multi-modal spatial sequencing approach?

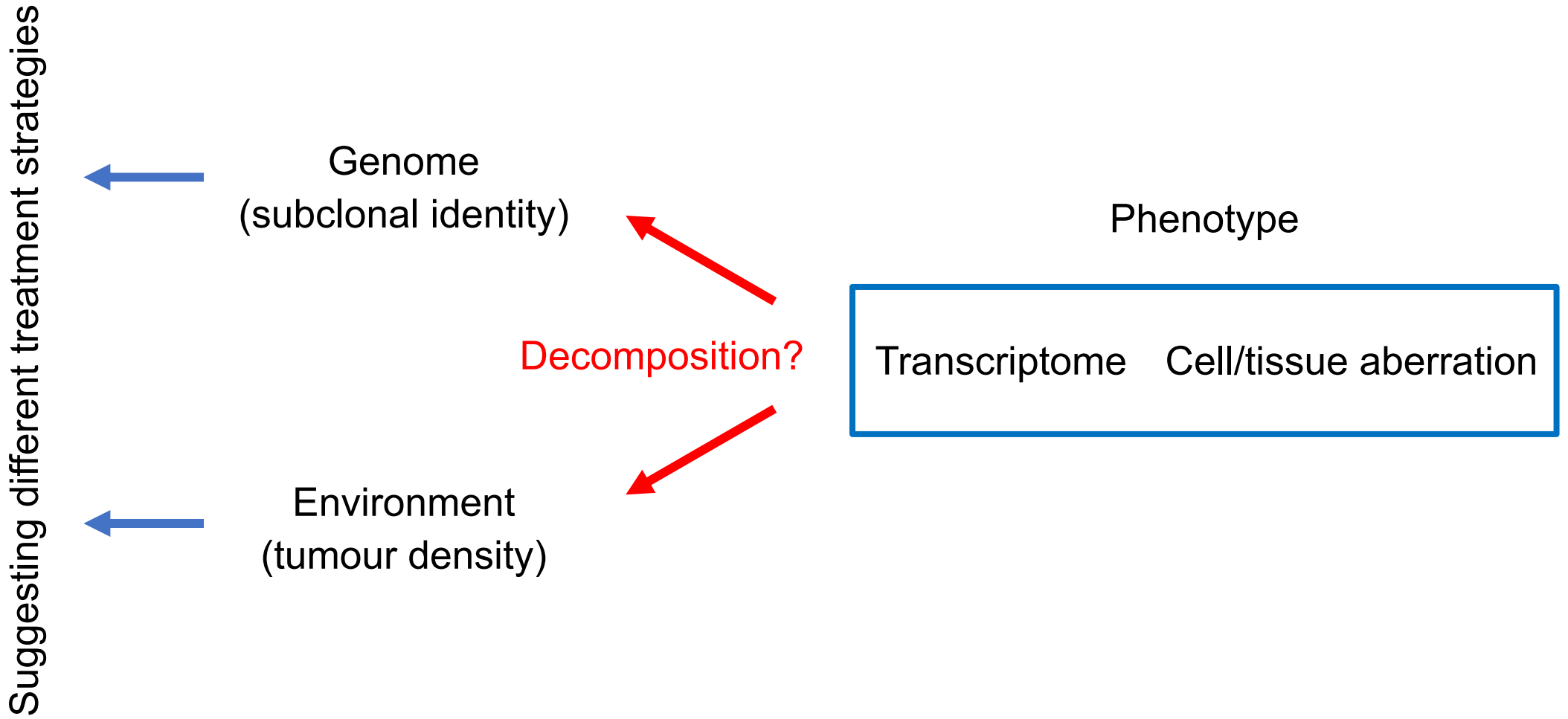


What is the unique capability of a multi-modal spatial sequencing approach?

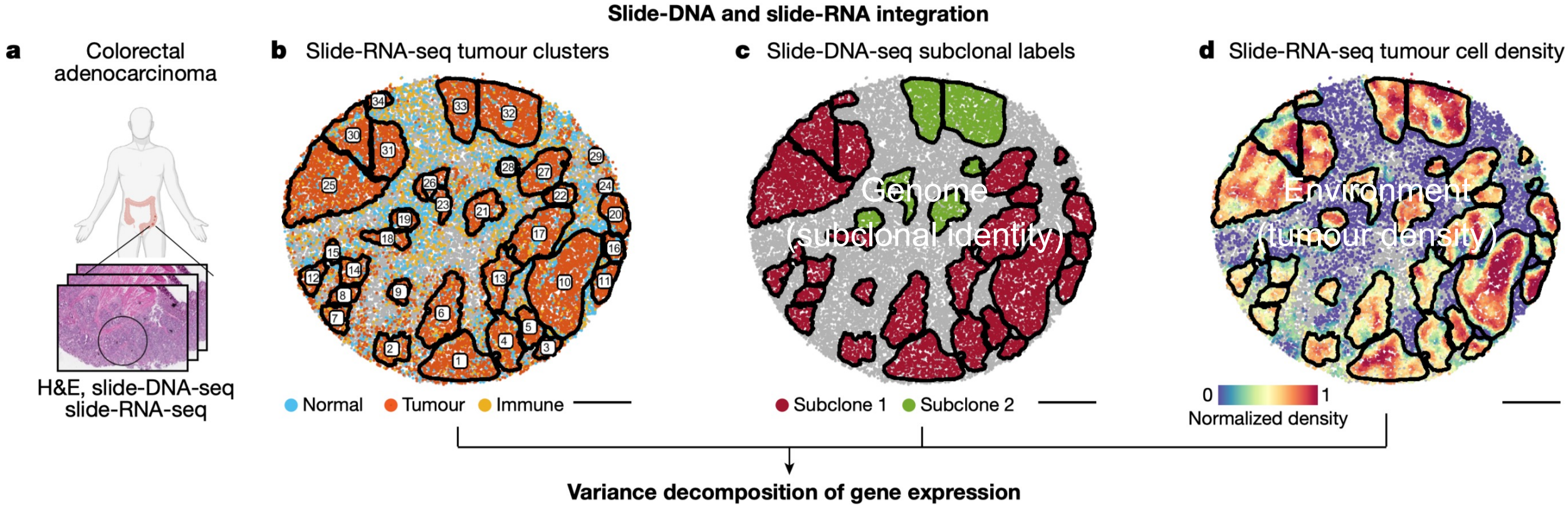
Quantification of genetic and density contributions to transcriptome variance



What is the unique capability of a multi-modal spatial sequencing approach?

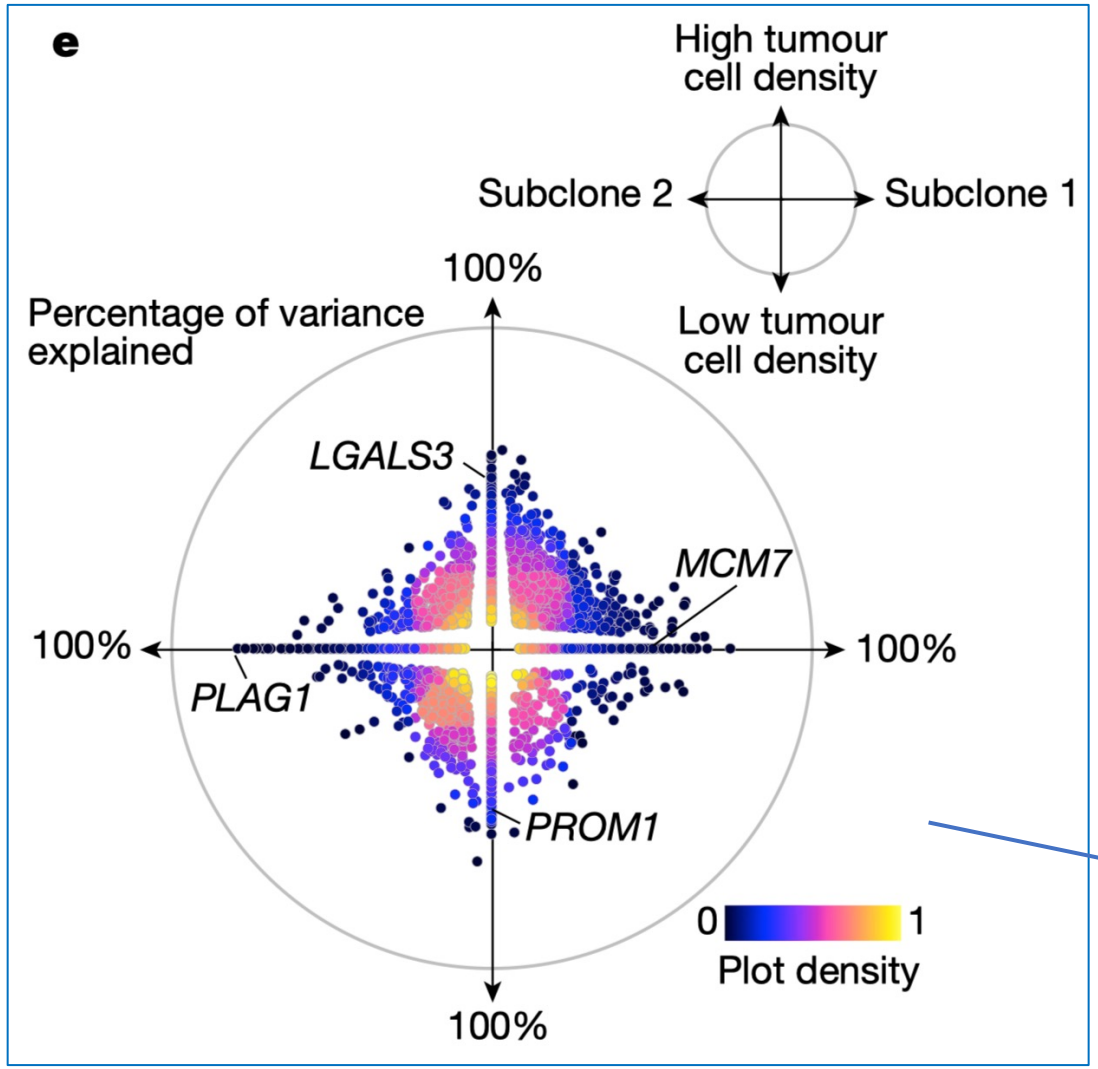


Workflow of multi-modal spatial integration and variance decomposition of gene expression



Variance decomposition of gene expression

Quantification of genetic and density contributions to transcriptome variance

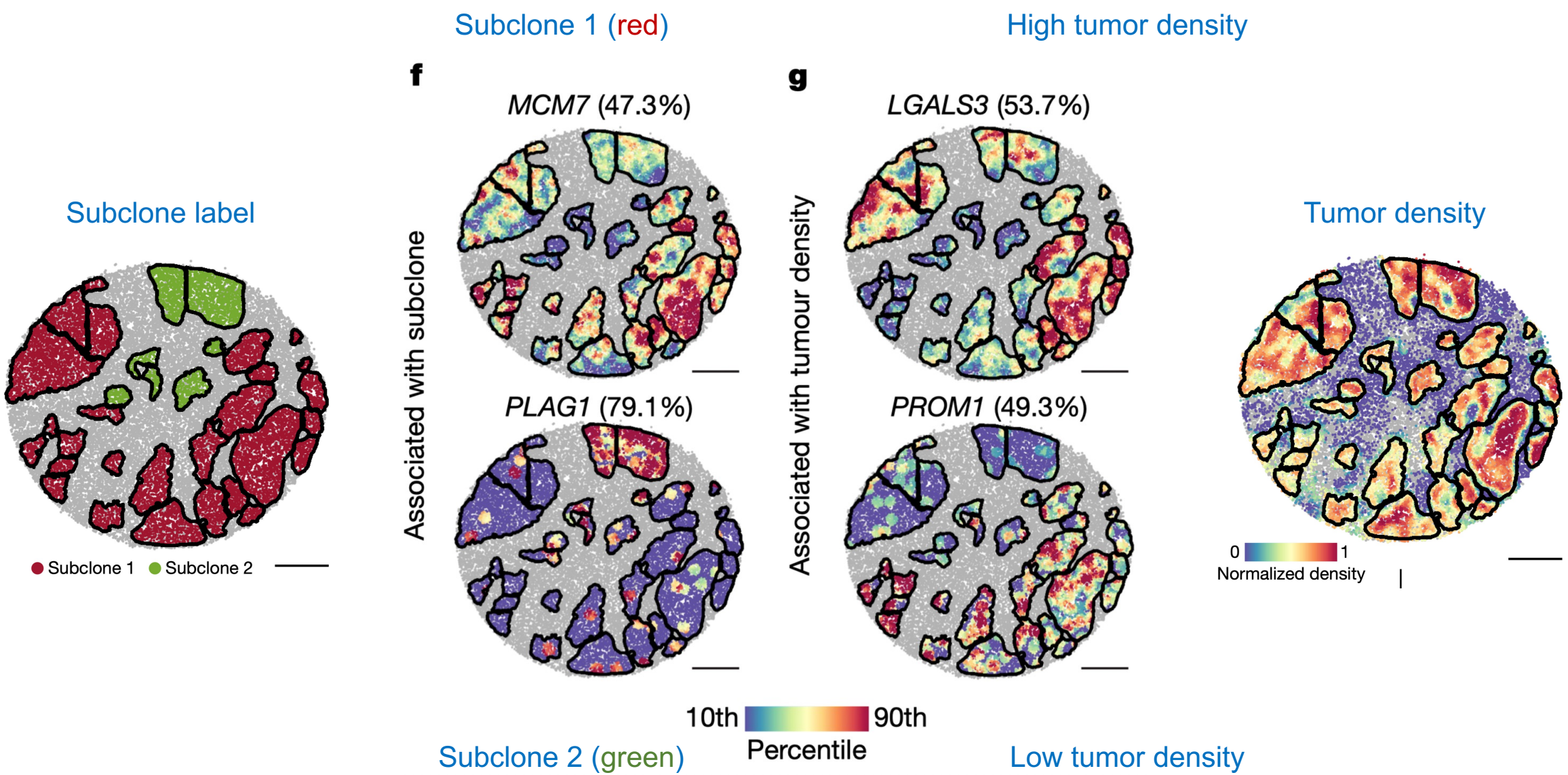


Technically, briefly, a regression model:
gene expression ~ clonal label + tumor density
sum of squares explained (SSE) → percentage of variance explained

Of the 25,074 genes detected by slide-RNA-seq 412 genes were significantly associated with subclonal identity, 638 genes were associated with tumour density, and 1,098 genes were associated with a combination of both.

2,148 genes whose transcriptome can be explained by subclone identity and/or cell density

Visualization of association of gene expression with subclone identity and tumor cell density



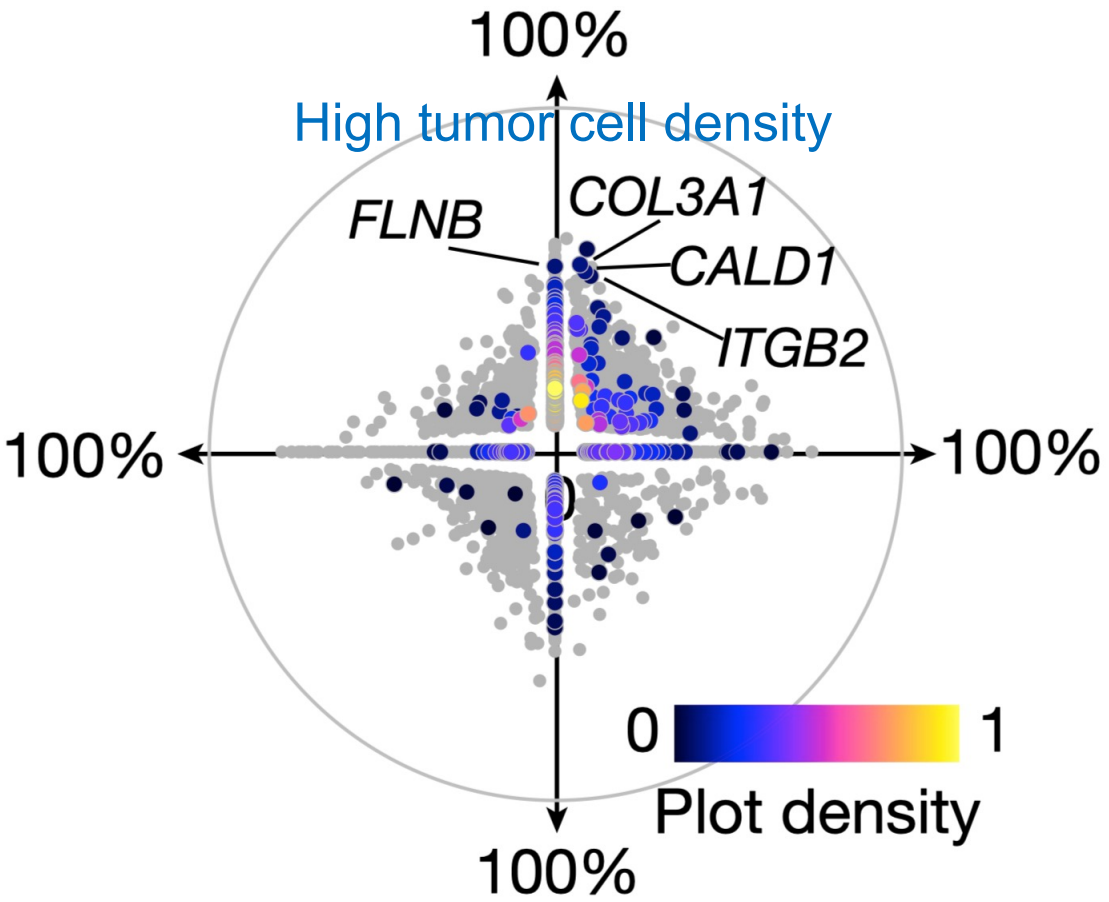
Gene set enrichment analysis for significantly associated genes

h

Subclone-associated gene sets	FDR
MYC targets (V1)	3.0×10^{-13}
E2F targets	1.1×10^{-7}
Oxidative phosphorylation	1.1×10^{-7}

Density-associated gene sets	FDR
Cell adhesion molecule binding	1.7×10^{-6}
Cadherin binding	4.5×10^{-6}
Catalytic activity acting on RNA	1.7×10^{-5}

i Cell adhesion molecule binding



All genes in the gene set, not enriched genes

Discussion --- further direction

1. Extrachromosomal DNA amplifications (integration with scWGS).

2. Tumor evolution atlas.

3. As a complement to current clinical diagnoses such as H&E staining, karyotyping and DNA FISH.

4. Beyond cancer, spatially resolved metagenomics, lineage tracing in healthy tissues…

Thanks for you attention!

Spatial genome data structure