Evolution and funtion of non-B DNA elements

Sheng Qian
Yanqing Sun
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Article

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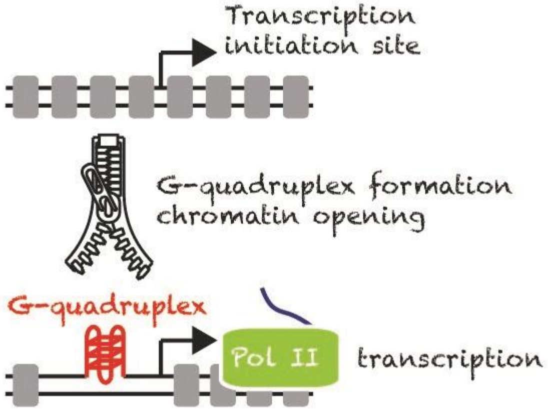
G-quadruplexes are promoter elements controlling nucleosome exclusion and RNA polymerase II pausing



Team leader

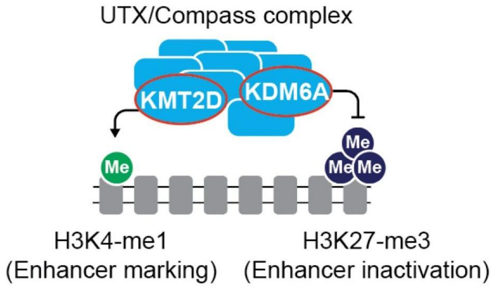
Jean-Christophe ANDRAU

Chercheur DR2

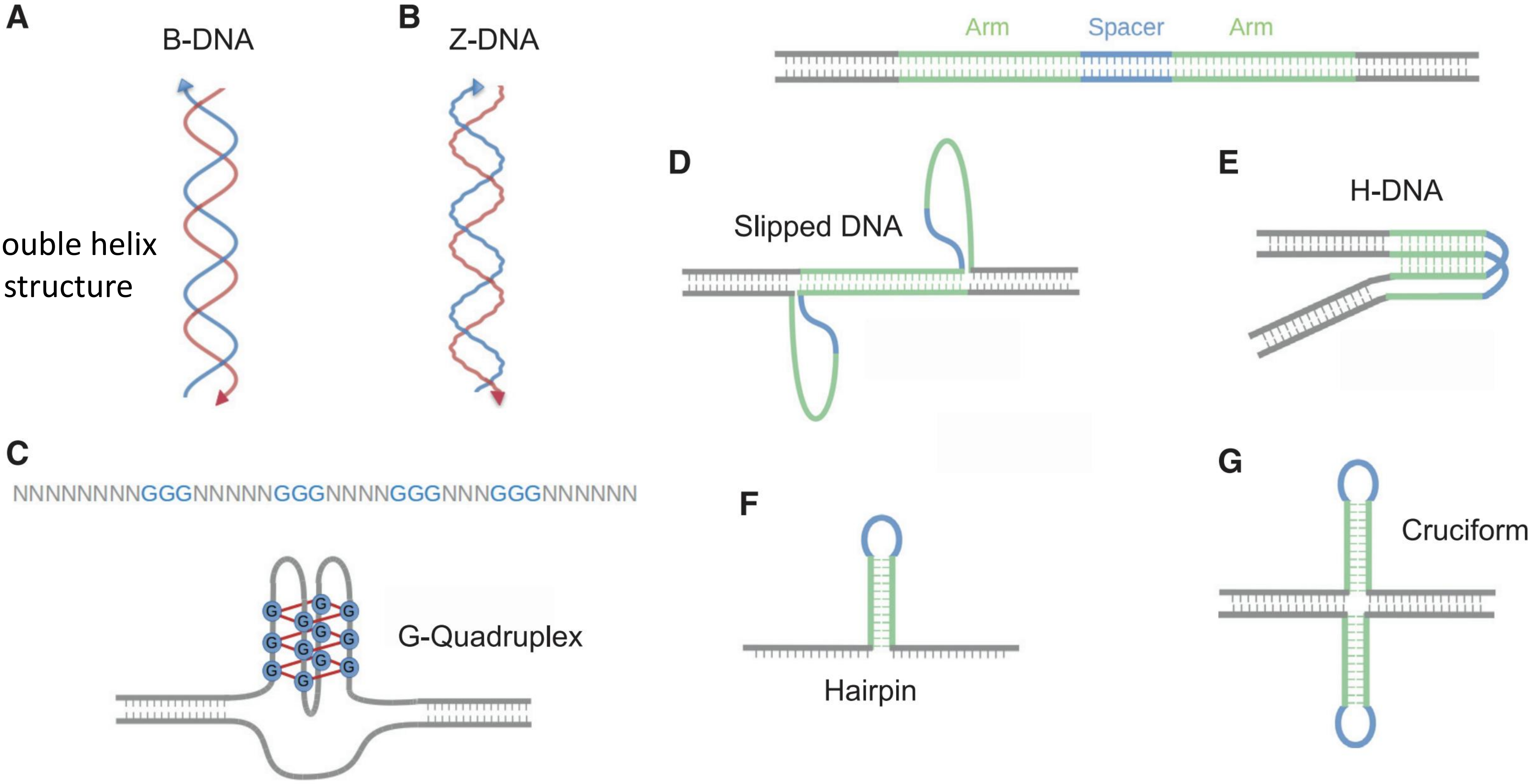
University of Montpellier

Kabuki syndrome

- Mental retardation
- Distinctive facial features
- Bone abnormalities
- Poor muscle tone
- Congenital heart defects
- high prevalence of immunopathological



Non-B DNA constitutes 13% of the human genome

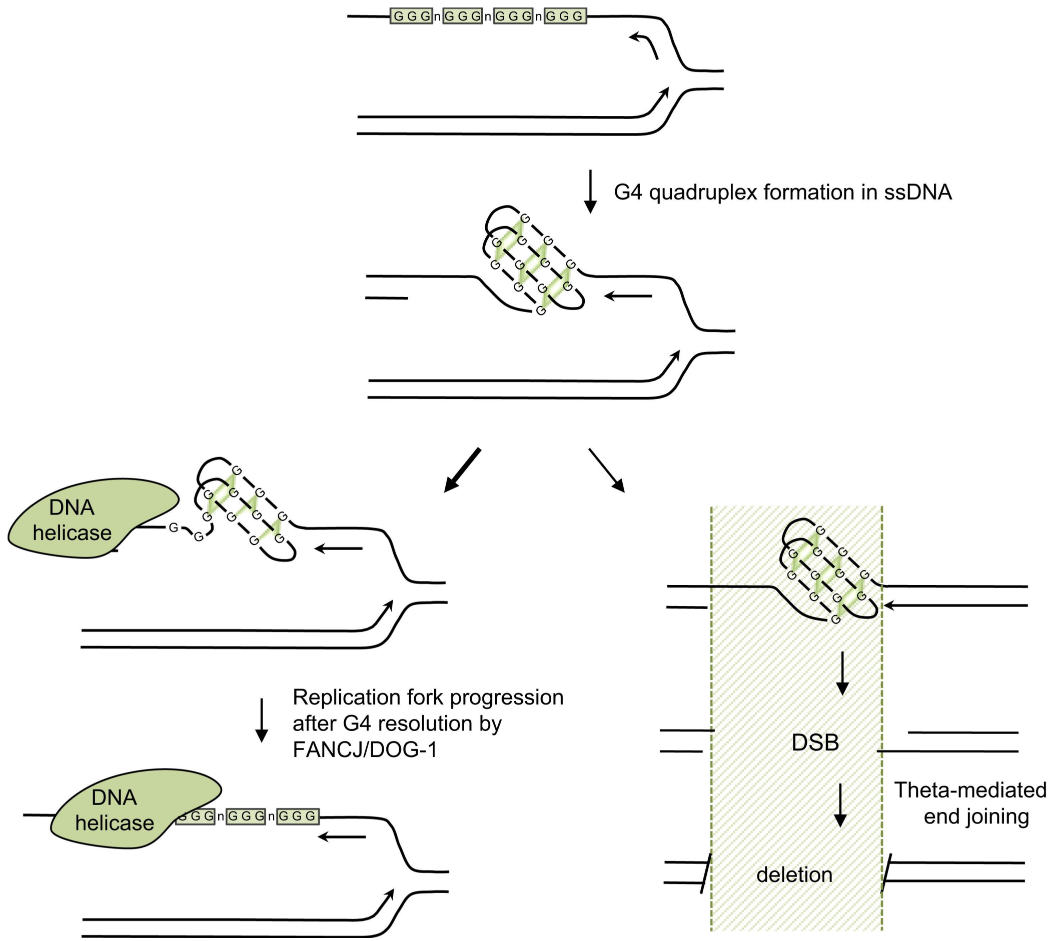


Double helix structure

Georgakopoulos-Soares et al. *Cell Genom.* 2022
Wang et al. *Nat Rev Genet.* 2023

G-quadruplex (G4) as a double-edged sword in the genome

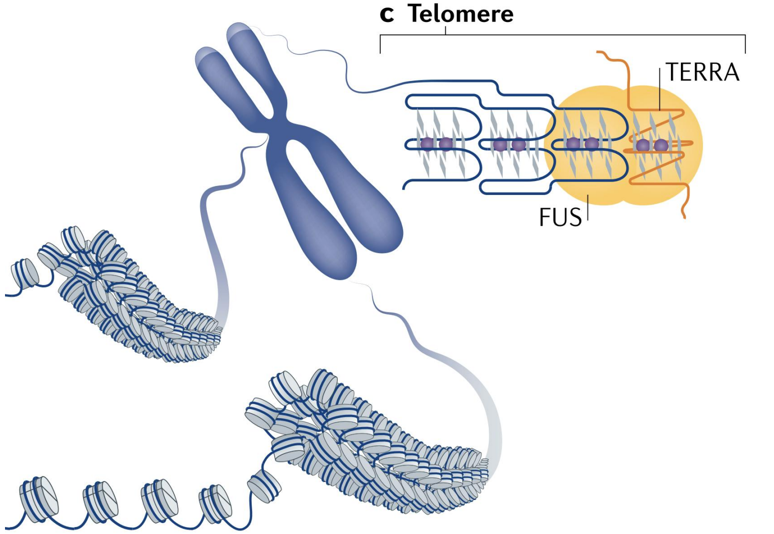
1) Increase mutation burden

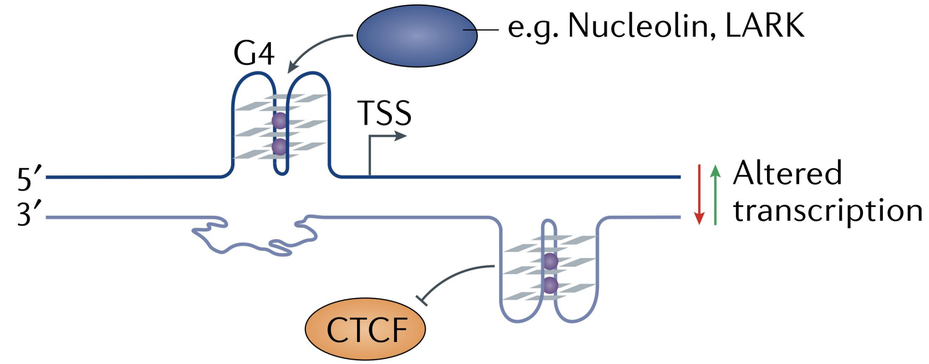


Van et al. *Exp Cell Res*. 2014
Wang et al. *Nat Rev Genet*. 2023

VS

2) Involved in transcription regulation





Varshney et al. *Nat Rev Mol Cell Biol*. 2020
Esnault et al. *Nat Genet*. 2023

Background

- Eukaryotic transcription requires open chromatin at promoters
- Nucleosome (核小体) exclusion is essential for open chromatin

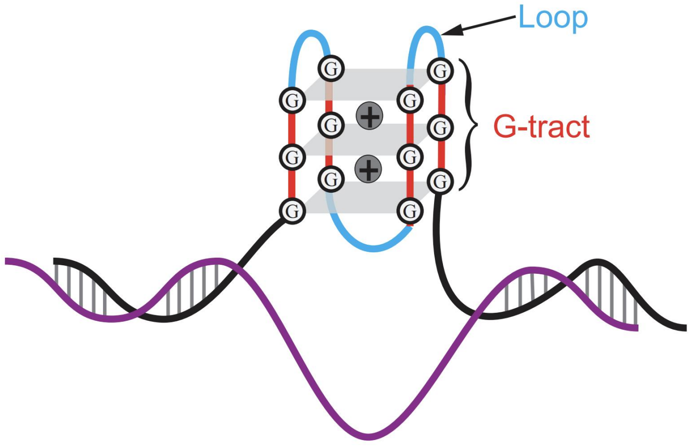
However:

- No universal promoter element has been identified that directly explains how chromatin opening is established

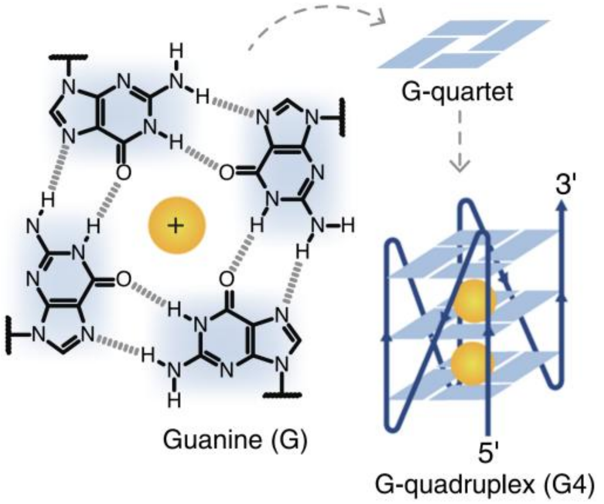
Hypothesis

- Key idea
  - DNA secondary structures may act as promoter elements

- Focus on:
  - G-quadruplexes (G4s)



$G_{\geq3}N_{1\text{-}12}G_{\geq3}N_{1\text{-}12}G_{\geq3}N_{1\text{-}12}G_{\geq3}$



Outline

- G4 in promoter
- G4 in nucleosome
- G4 in intergenic region
- G4 in transcription (TATA box and RNA pol II)

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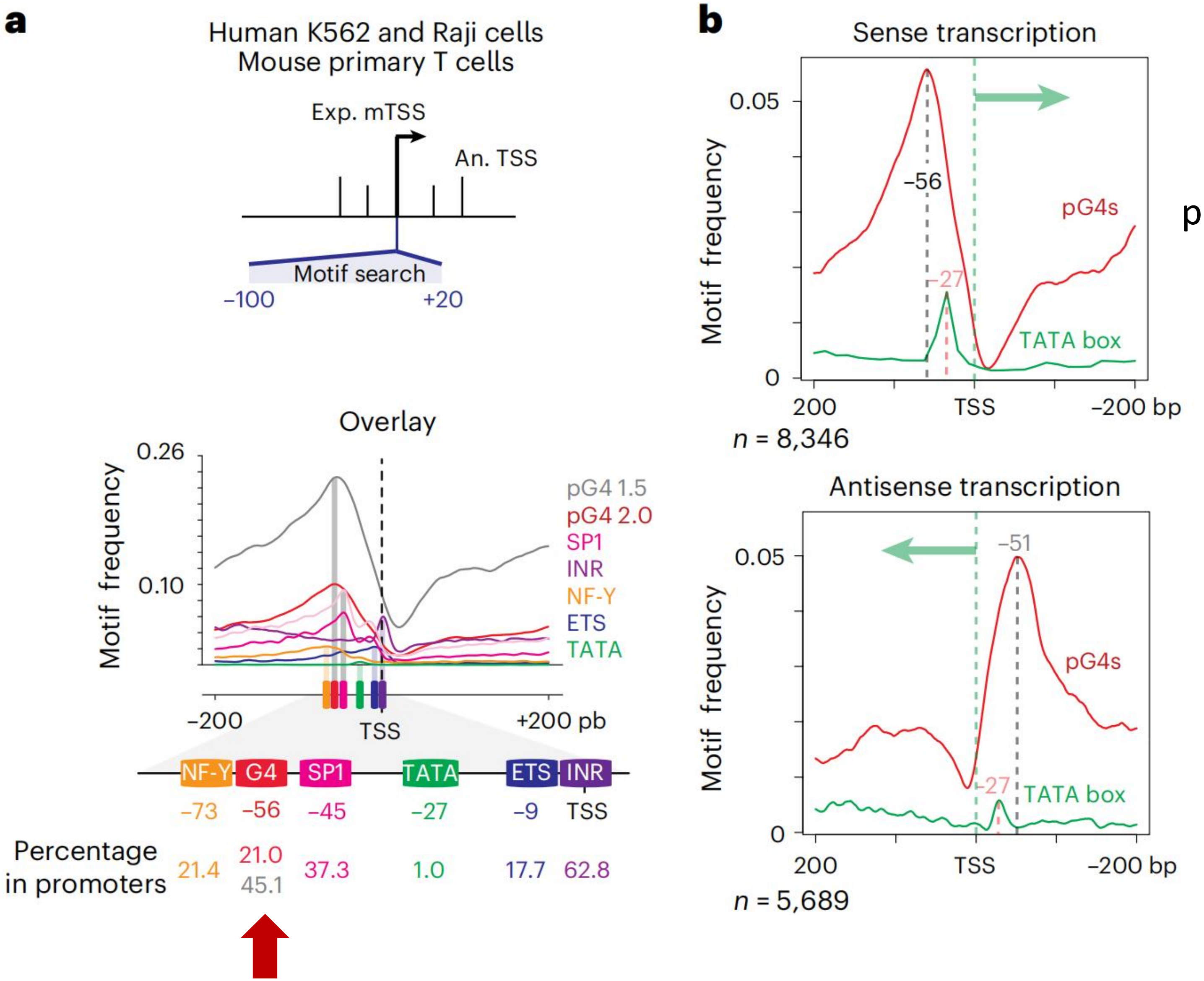
R1. G4s are enriched at promoters and correlate with activity

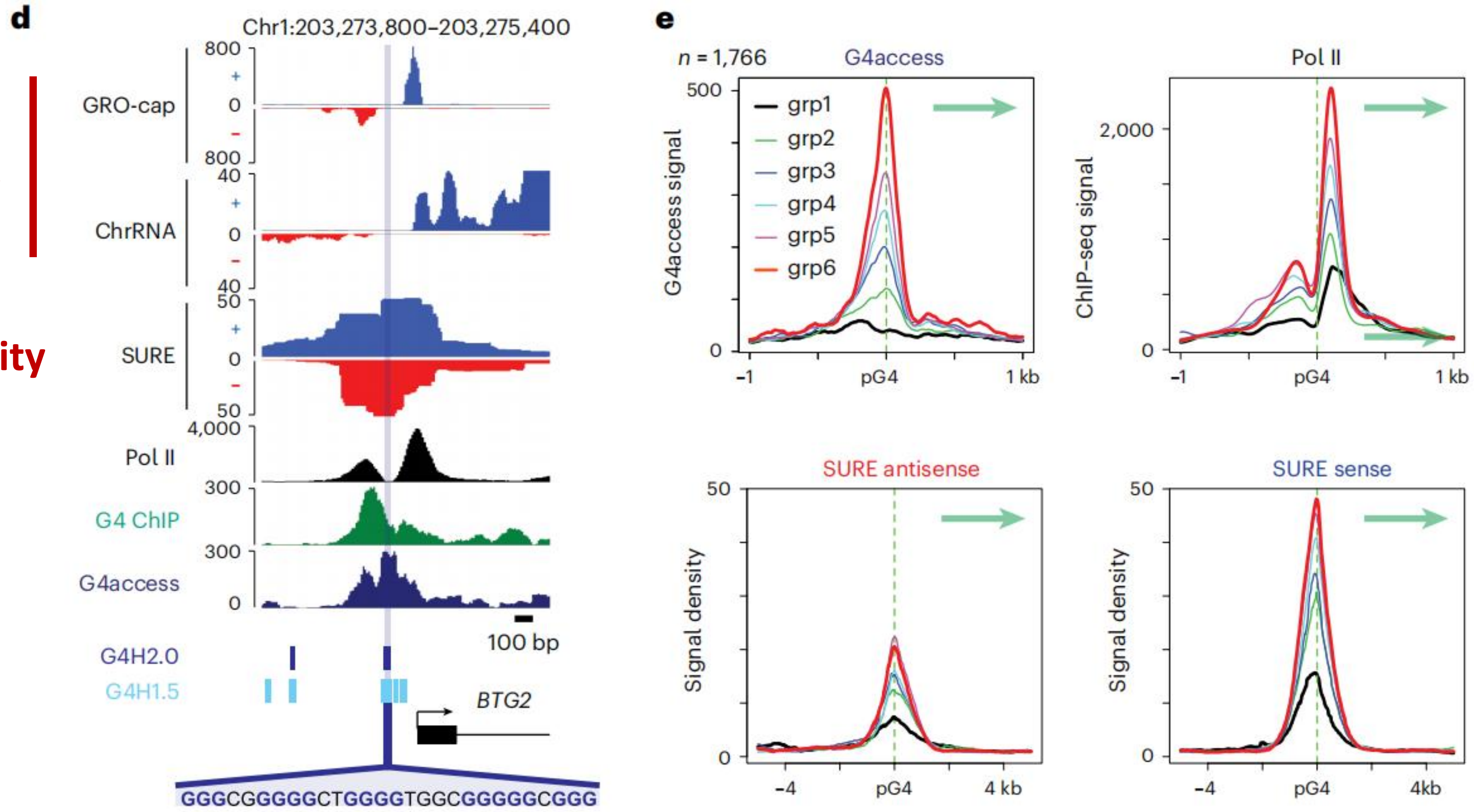


pG4s, predicted G4s

R1. G4s are enriched at promoters and correlate with activity

nascent RNA

promoter activity



nascent RNA

GRO-cap (Global run-on associated to CAP sequencing)
chrRNA (chromatin-associated RNA sequencing)

promoter activity

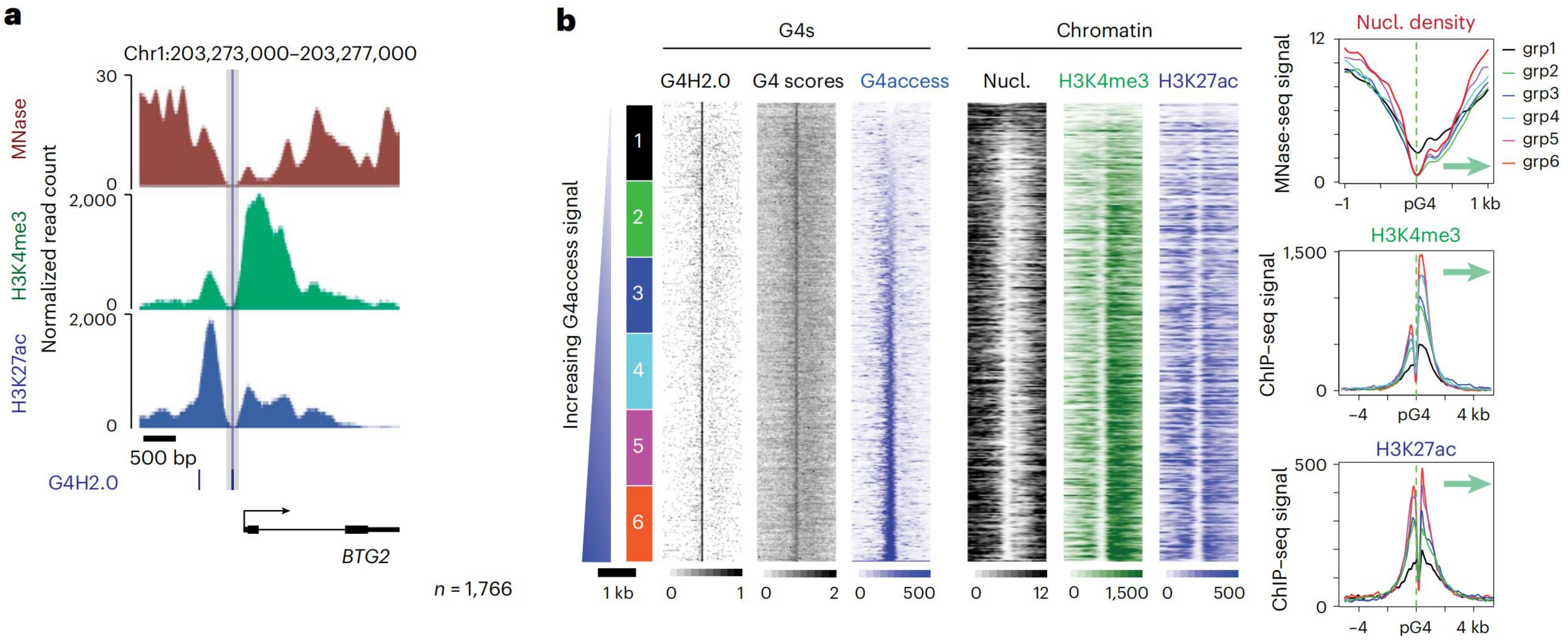
SURE (Survey of Regulatory Elements)

Outline

- G4 in promoter
- G4 in nucleosome
- G4 in intergenic region
- G4 in transcription (TATA box and RNA pol II)

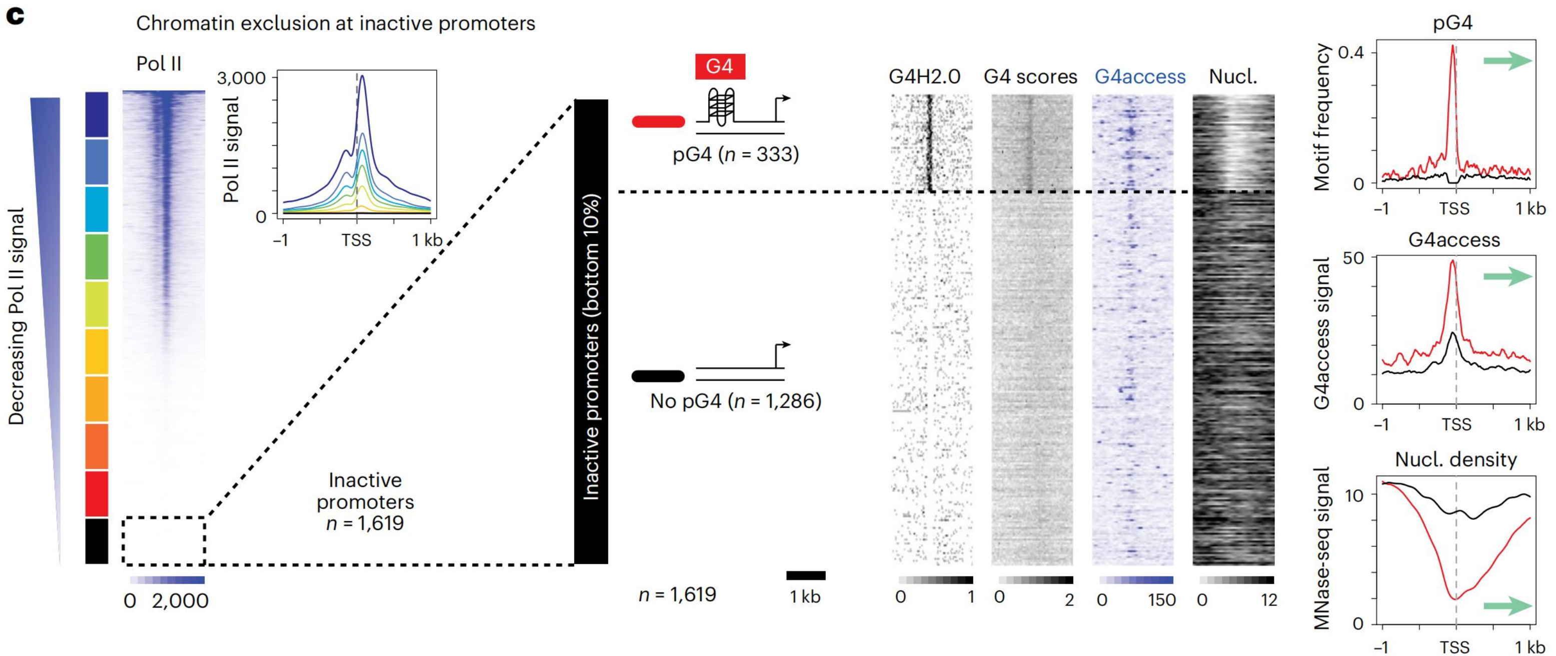
Does G4 actively shape chromatin architecture, particularly nucleosome exclusion?

R2. G4s localize at nucleosome-depleted regions (NDRs)

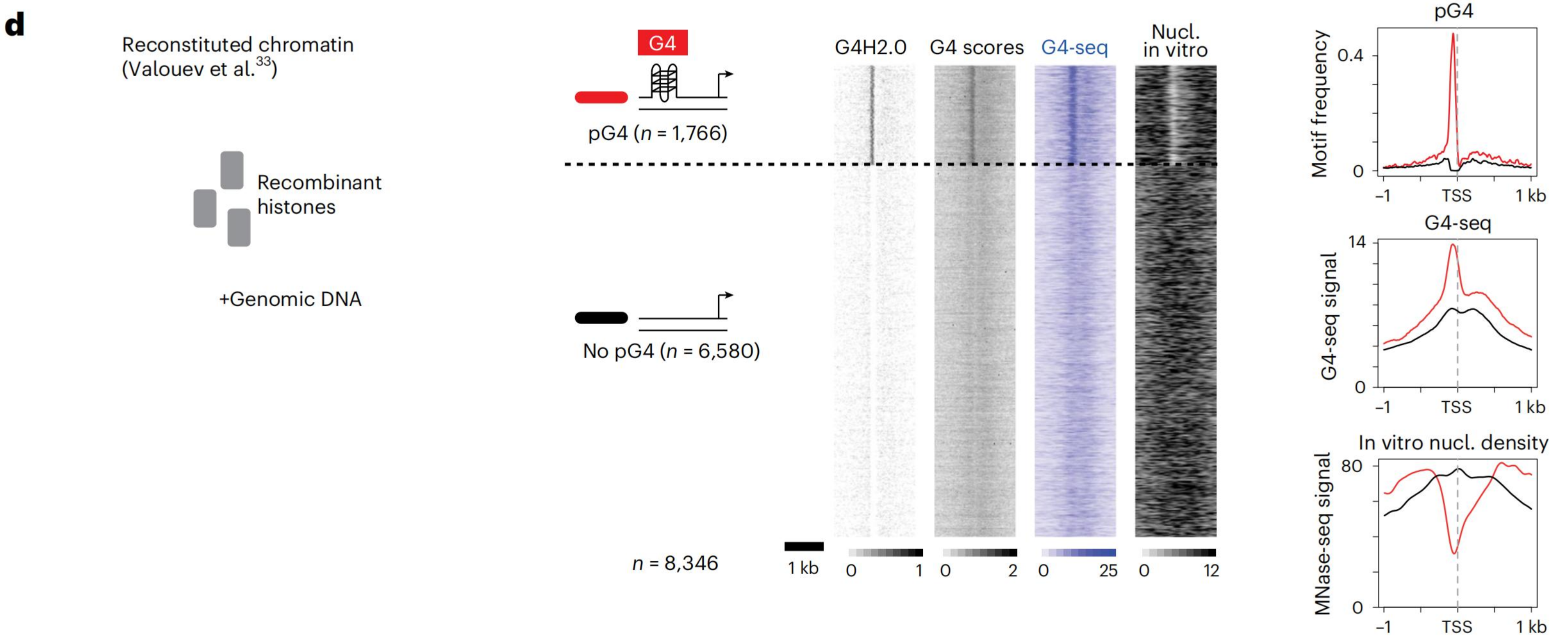


MNase, nucleosome density
H3K4me3/H3K27ac, active gene promoters

R2. G4-mediated nucleosome exclusion is independent of other regulators



In vivio



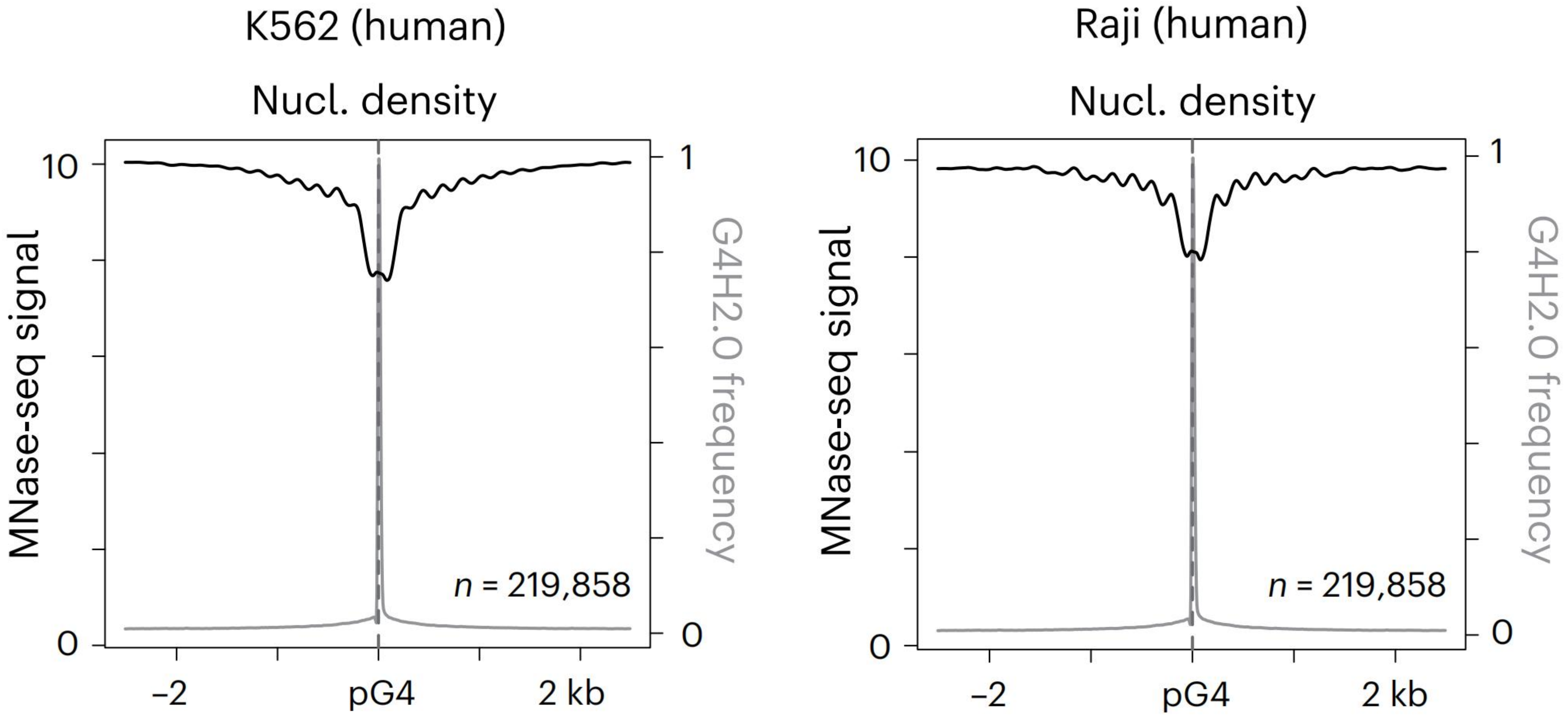
In vitro

Outline

- G4 in promoter
- G4 in nucleosome
- G4 in intergenic region
- G4 in transcription (TATA box and RNA pol II)

Is this property restricted to promoters, or does it represent a general principle across the genome?

R3. G4s exclude nucleosomes genome-wide

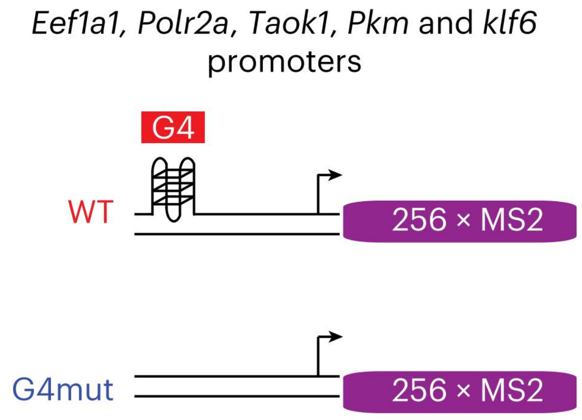


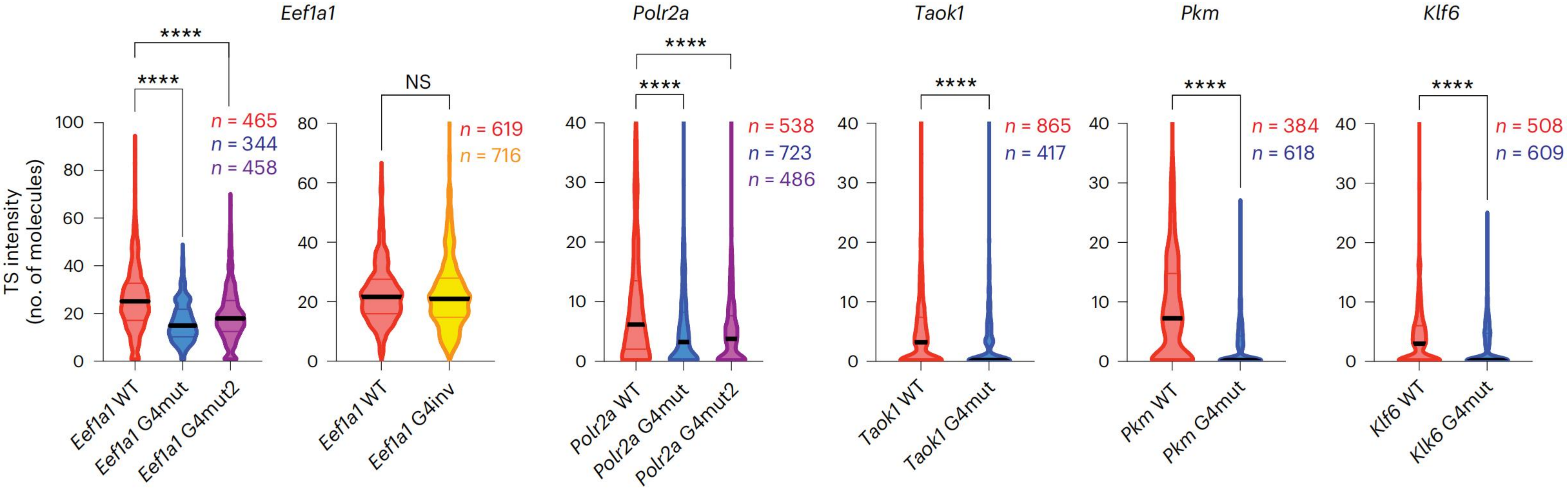
Outline

- G4 in promoter
- G4 in nucleosome
- G4 in intergenic region
- G4 in transcription (TATA box and RNA pol II)

Does G4 causally contribute to transcription?

R4. G4 promoter mutations decrease transcription



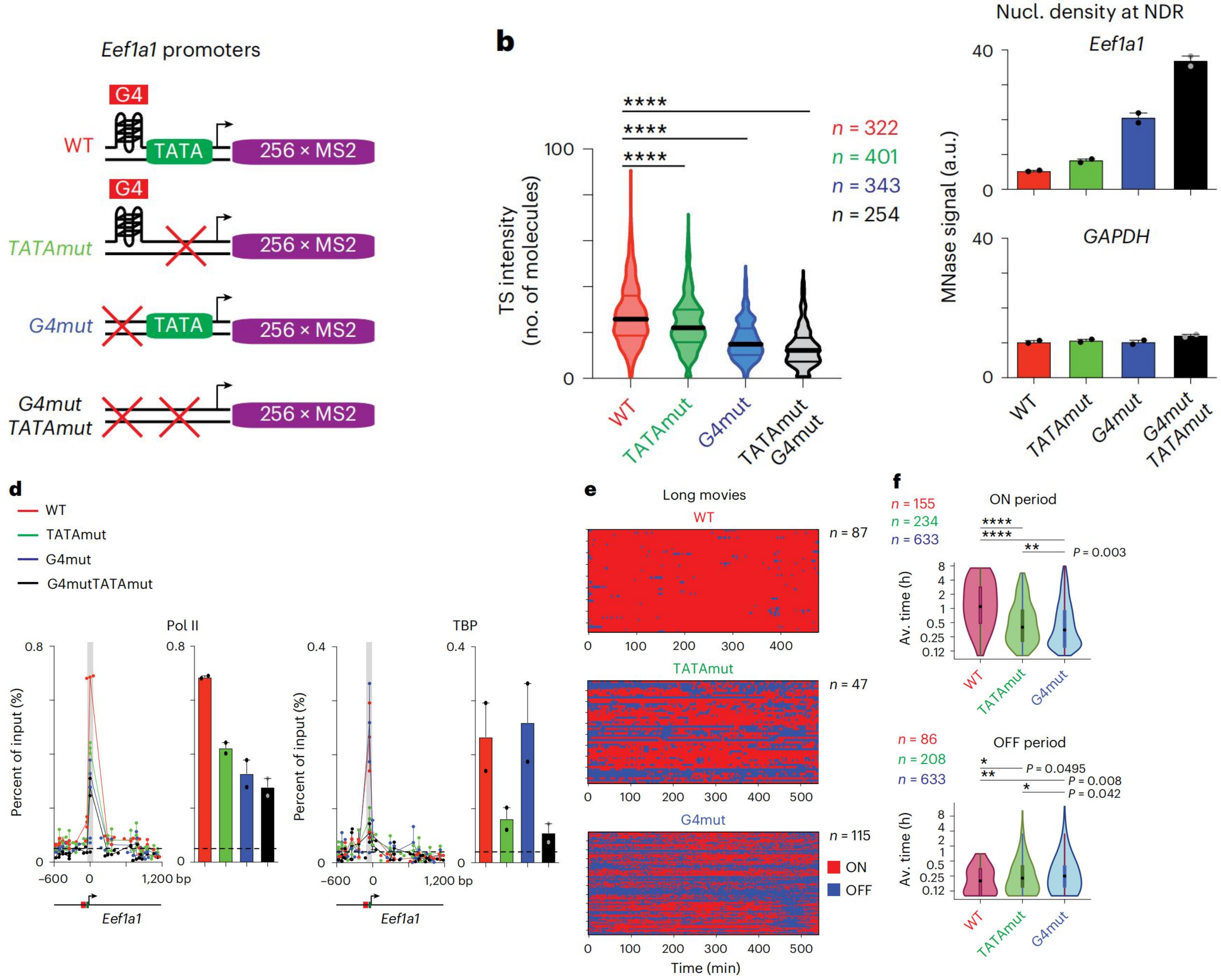


Outline

- G4 in promoter
- G4 in nucleosome
- G4 in intergenic region
- G4 in CpG island
- G4 in transcription (TATA box and RNA pol II)

How do G4s mechanistically compare with classical promoter elements such as the TATA box?

R5. G4s are enriched at promoters and correlate with activity

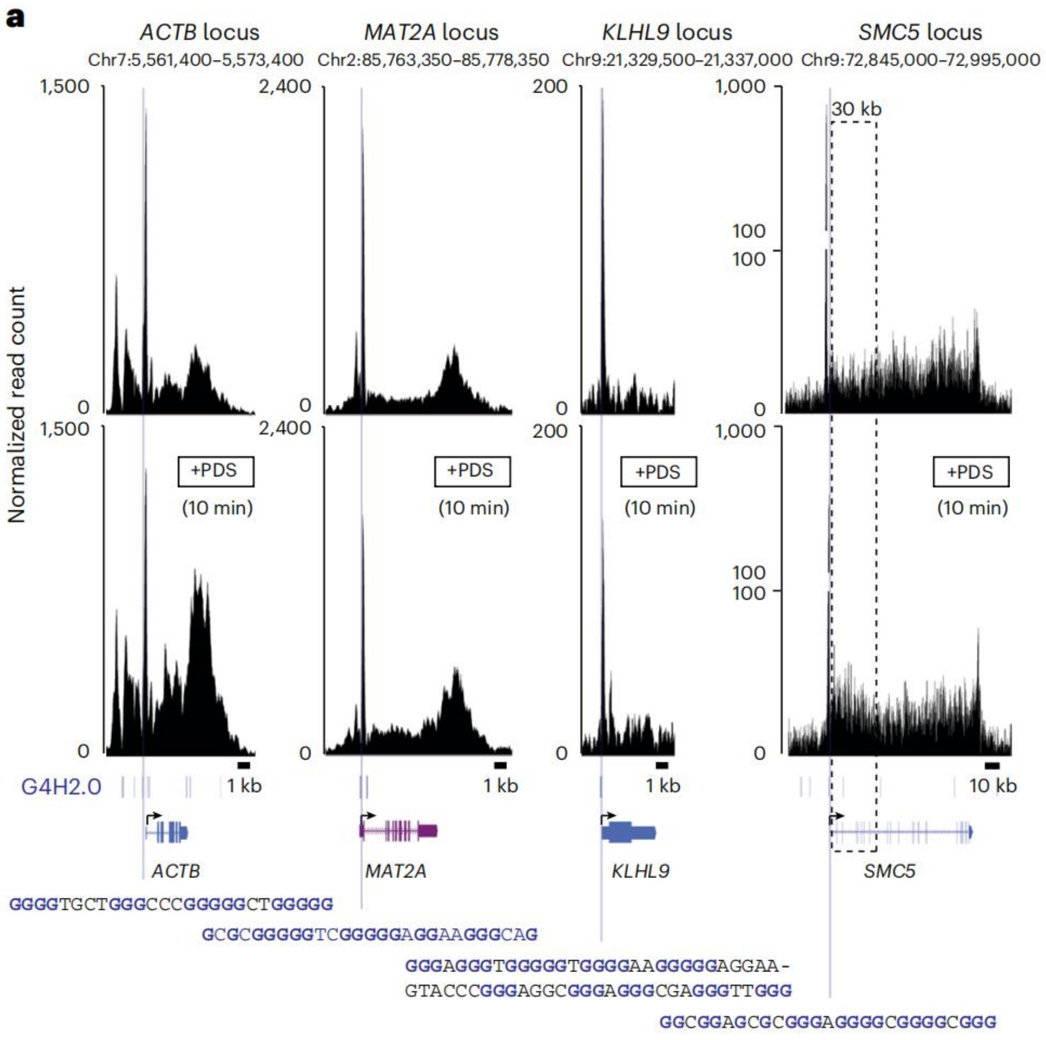


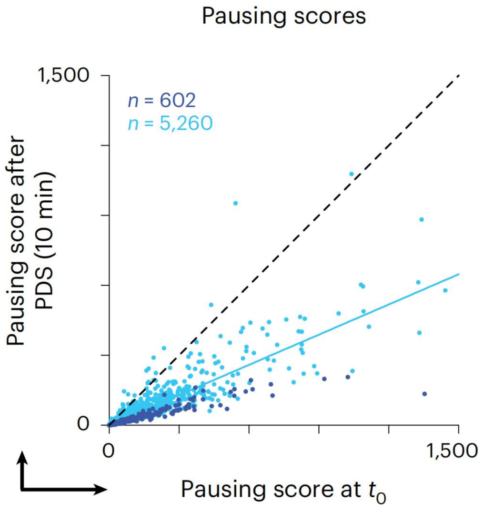
Outline

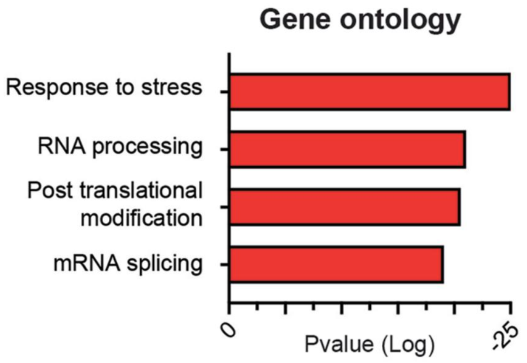
- G4 in promoter
- G4 in nucleosome
- G4 in intergenic region
- G4 in CpG island
- G4 in transcription (TATA box and RNA pol II)

Do G4 structures also directly influence RNA polymerase II dynamics?

R6. G4 stabilization results in Pol II promoter pause–release







转录大致可以分三步：

1. **Initiation（起始）**
    - RNA Pol II 招募到 promoter
    - 形成 pre-initiation complex（PIC）
    - 合成 20–60 nt 的 RNA
2. **Promoter-proximal pausing（启动子附近停顿）**
    - Pol II 在起始后不久被 DSIF/NELF 阻止继续延伸
    - RNA 已经开始合成，但 Pol II 暂停
    - 此阶段**不算真正的 productive elongation**
3. **Pause-release（暂停释放）**
    - P-TEFb 磷酸化 Pol II CTD、DSIF、NELF
    - NELF 脱离，DSIF 转为正向延伸因子
    - Pol II 进入**productive elongation**
    - RNA 开始被有效延伸，生成完整转录本

Summarized by ChatGPT

Take home message

Collectively, this study establishes G4s as structural promoter elements that function at multiple levels:

1. Gene activity

facilitating gene transcription

2. Chromatin architecture

excluding nucleosomes and creating open promoters

3. Transcription kinetics

promoting pol II pause–release

Thank you

Welcome any questions