PURSUIT OF ZΩH — THE WEEKLY

This Week in

Genetics & Molecular Biology

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THIS WEEK

Genes in context, from BRCA1 to flies

BRCA1 variants that read differently by cell type, embryo nuclei that soften to wake their genes, cells that ride out polymerase shortfalls, and flies that defy genomic forecasts.

IN THIS ISSUE

01 VARIANT INTERPRETATION
A BRCA1 variant's verdict depends on the cell type

02 EMBRYO BIOPHYSICS
Mouse embryos soften their nuclei to wake their genes

03 TRANSCRIPTION
Cells keep transcribing when polymerase runs short

04 EVOLUTIONARY GENETICS
Flies reveal evolution's direction, not its genes

01

VARIANT INTERPRETATION

A BRCA1 variant's verdict depends on the cell type

Over half of reported single-nucleotide variants in BRCA1, a breast and ovarian cancer risk gene, lack a firm clinical interpretation.[1] A Francis Crick Institute team used saturation genome editing to score 4,113 untested variants in HAP1 cells, then built a matching assay in breast epithelial cells.[1] HAP1 scores sorted known harmful from harmless variants almost perfectly.[1] Yet nearly half of HAP1 loss-of-function variants looked neutral in the breast cells.[1]

WHY IT MATTERS

Those variants proved to be partly working (hypomorphic) alleles with intermediate cancer risk, so testing several cell types sharpens variant reading.[1]

CAVEAT *Scores come from two cultured cell models.*[1]

[1] doi:10.1038/s41588-026-02832-3

4,113

previously unassayed BRCA1 variants scored by saturation genome editing in HAP1 cells

SOURCE 1

ON THE ROAD?

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02

EMBRYO BIOPHYSICS

Mouse embryos soften their nuclei to wake their genes

A mouse embryo must soon start using its own genes, a step called zygotic gene activation.[2] A National Institute of Genetics and Kyushu University team found nuclei unusually soft at the two-cell stage, stiff again by the four-cell stage.[2,3] The cause: the autophagy protein LC3 rapidly clears lamin B1 from the nuclear envelope.[2] Retaining or adding lamin B1, or tethering nuclei stiff, left key zygotic genes underactive and impaired development.[2]

WHY IT MATTERS

It adds a mechanical ingredient, the stiffness of the nucleus itself, to a transition usually described in terms of chromatin.[2]

CAVEAT *The experiments were done in mouse embryos.*[2]

[2] doi:10.1038/s41586-026-11240-w · [3] phys.org

MECHANISM

Two-cell stage: LC3 clears lamin B1

↓

Nuclear envelope turns soft and pliable

↓

Active Pol II and key loci gather at rim

↓

Zygotic genes switch on; embryo develops

03

TRANSCRIPTION

Cells keep transcribing when polymerase runs short

Two Molecular Cell papers ask how much RNA polymerase II, the enzyme that copies genes into messenger RNA, human cells need.[4,5] A University of New South Wales team saw steady transcription across 70%-160% of normal levels, backed by a nuclear reserve pool and a constantly overproduced subunit.[5] In Copenhagen, modest depletion altered initiation, pausing, elongation and splicing, but strongly paused genes were largely resistant.[4]

WHY IT MATTERS

Pausing near the start of genes, long seen as a control point, may also absorb shocks in polymerase supply, as the Copenhagen authors propose.[4]

CAVEAT *The studies differ in emphasis: one reports steady output over a wide range, the other changes even at modest depletion.*[4,5]

[4] doi:10.1016/j.molcel.2026.10.020 · [5] doi:10.1016/j.molcel.2026.10.025

70%-160%

range of normal RNA Pol II levels over which transcription stayed stable in human cells

SOURCE 5

04

EVOLUTIONARY GENETICS

Flies reveal evolution's direction, not its genes

Stanford and University of Pennsylvania researchers asked in Science whether genomic data can forecast adaptation, using diverse Drosophila melanogaster evolving outdoors and in the lab.[6] Tracking pigmentation and genome-wide allele frequencies, they built a genotype-phenotype map that stayed remarkably stable across independent populations.[6] It correctly predicted the direction pigmentation evolved in both settings.[6] Which loci actually responded to selection, though, was largely unpredictable.[6]

WHY IT MATTERS

It marks a limit of genomic prediction: a good gene-to-trait map can say where a trait is heading without saying which genes will take it there.[6]

CAVEAT *The study follows one trait, pigmentation, in one fly species.*[6]

[6] doi:10.1126/science.aee0342

MECHANISM

Diverse fly populations evolve

↓

Pigment and allele frequencies tracked

↓

Genotype-phenotype map stays stable

↓

Direction predicted; responding loci not

WORDS THIS WEEK

Saturation genome editing
Using CRISPR to write every possible single-letter change into part of a gene in its natural place in the genome, then measuring how each change affects cell fitness.

Hypomorphic variant
A gene version that works, but less well than normal: a partial loss of function rather than a complete break.

Zygotic gene activation
The point in early development when an embryo starts transcribing its own genes instead of relying on molecules supplied by the egg.

Lamin B1
A protein of the nuclear lamina, a meshwork lining the inside of the nuclear envelope that helps set the nucleus's shape and stiffness.

Promoter-proximal pausing
A halt by RNA polymerase II a short way into a gene, after it starts copying; release from the pause is a key step in controlling gene output.

Genotype-phenotype map
A description of which genetic variants are linked to which values of a trait, and how strongly, in a given population.

SOURCES

1. PAPER P. Dace et al., “Saturation genome editing of BRCA1 across cell types improves interpretation of variant pathogenicity,” Nature Genetics (11 Nov 2026). doi:10.1038/s41588-026-02832-3
2. PAPER M. Tanaka et al., “Transient nuclear softening for zygotic gene activation in mice,” Nature (11 Nov 2026). doi:10.1038/s41586-026-11240-w
3. NEWS “Nuclear softening at an embryo's two-cell stage may be vital for further embryonic development,” Phys.org, provided by Kyushu University (11 Nov 2026). https://phys.org/news/2026-11-nuclear-softening-embryo-cell-stage.html
4. PAPER A. M. Olthof et al., “Promoter-proximal pausing enables transcriptional buffering of RNA polymerase II availability,” Molecular Cell (online 9 Nov 2026). doi:10.1016/j.molcel.2026.10.020
5. PAPER A. Gillis et al., “Hierarchical buffering of cellular RNA polymerase II pools maintains transcriptional homeostasis,” Molecular Cell (online 9 Nov 2026). doi:10.1016/j.molcel.2026.10.025
6. PAPER J. A. Smiley-Rhodes et al., “Limited genomic predictability of complex trait evolution despite genotype-phenotype stability,” Science (12 Nov 2026). doi:10.1126/science.aee0342

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