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# **EZHIP maintains parental H3K27me3 asymmetric distribution and non-canonical imprinting in mouse embryos**

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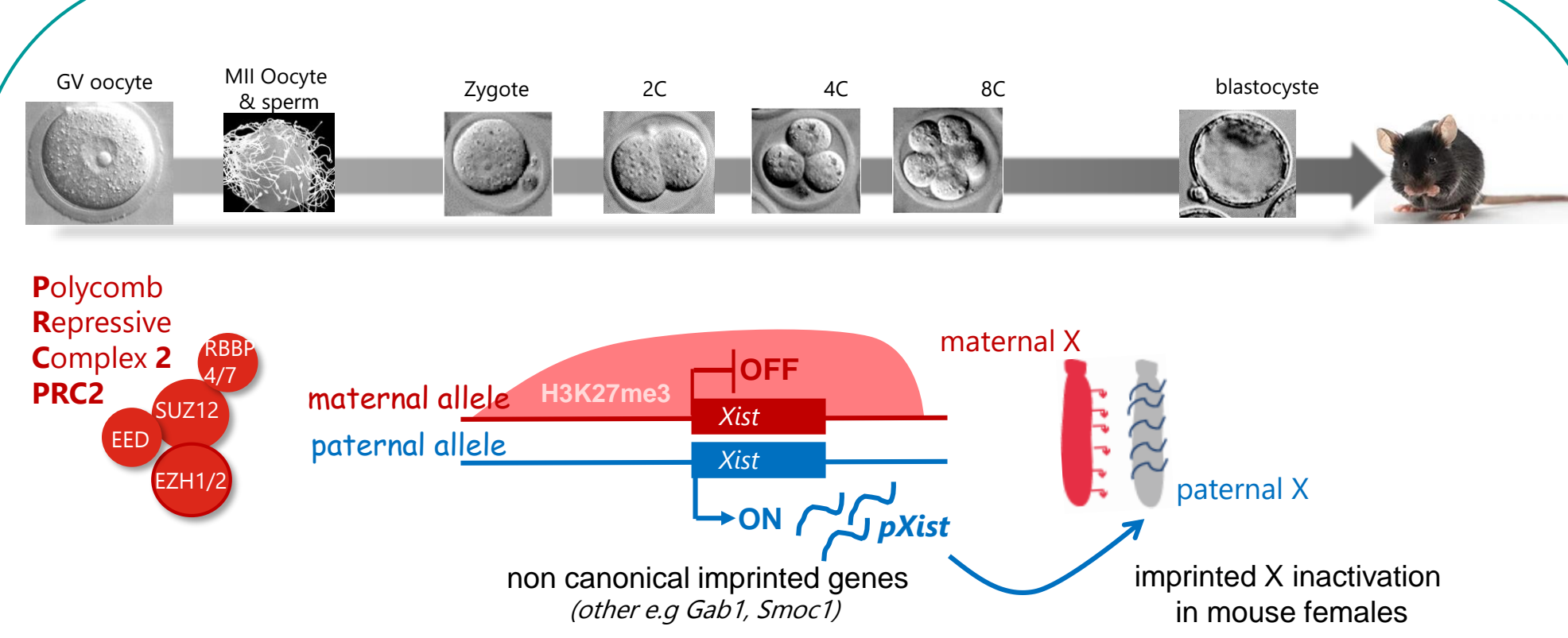


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## Abstract

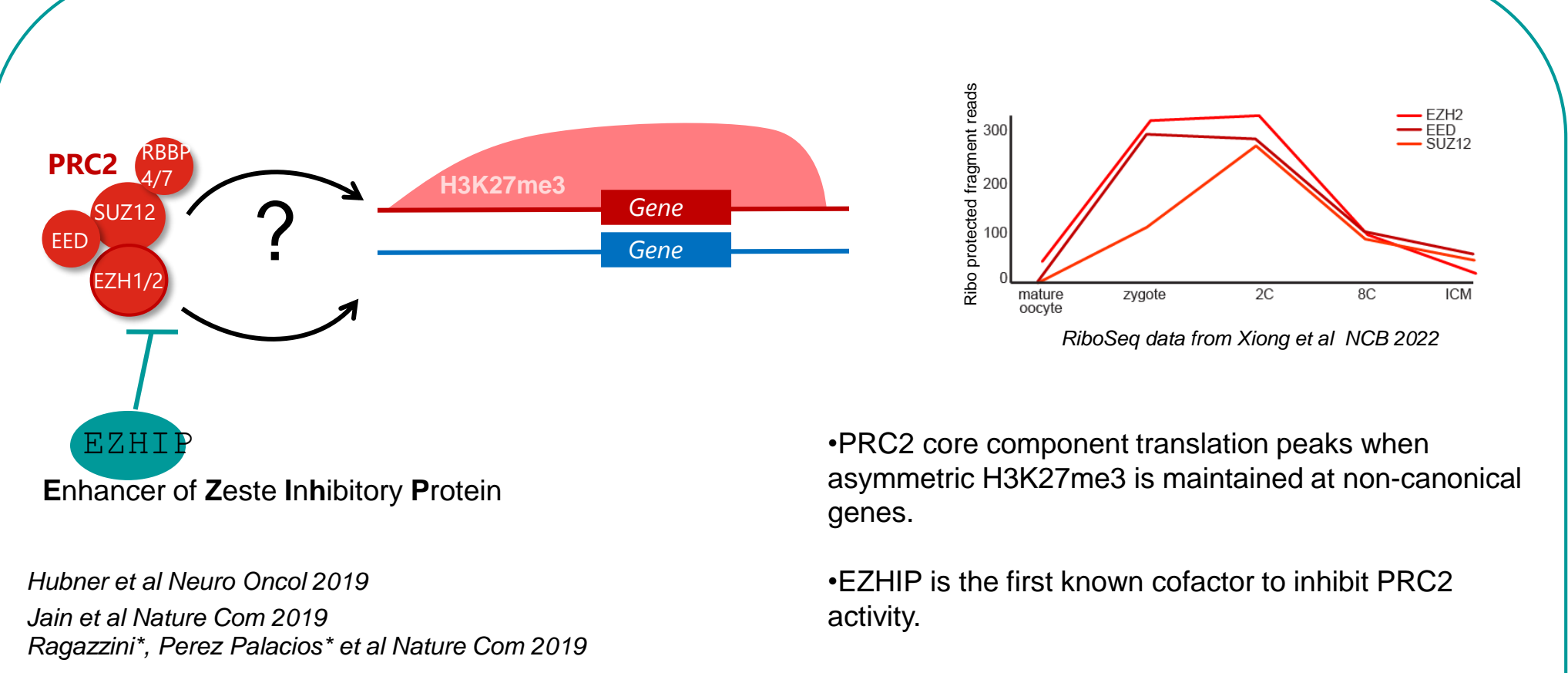
Parental epigenomes are very distinct in early mammalian embryos, and their remodelling is essential for development. A paradigmatic example is the distribution of trimethylation of histone H3 lysine 27 (H3K27me3), the mark deposited by the Polycomb repressive complex 2 (PRC2); at fertilization, it is mostly depleted from the paternal genome, while it is abundant on the maternal genome. Recent studies have revealed that in mouse, maternal H3K27me3 underlies non-canonical (DNA methylation independent) genomic imprinting and is crucial for embryonic viability. Here, we demonstrate that maternal EZHIP, a cofactor of PRC2, is crucial for the maintenance of H3K27me3 parental asymmetry during early development by preventing aberrant gain of H3K27me3 over the paternal genome. Surprisingly, at non-canonical imprinted genes, enrichment of H3K27me3 on both alleles is associated with biallelic transcription at the time of implantation, and this loss of imprinted expression remains for a subset of genes in extraembryonic lineages after implantation. The *Xist* long noncoding gene is amongst the non-canonical imprinted genes that are affected, and we show that its ectopic maternal expression leads to aberrant X chromosome inactivation, and to reduced embryonic viability. Our results not only unveil EZHIP as a new player for the dynamic regulation of H3K27me3 in early embryonic development, but also identify a role for the parental asymmetry of H3K27me3 in non-canonical imprinting mechanisms.

## Polycomb-dependent H3K27me3 participates to a transient gene imprinted expression



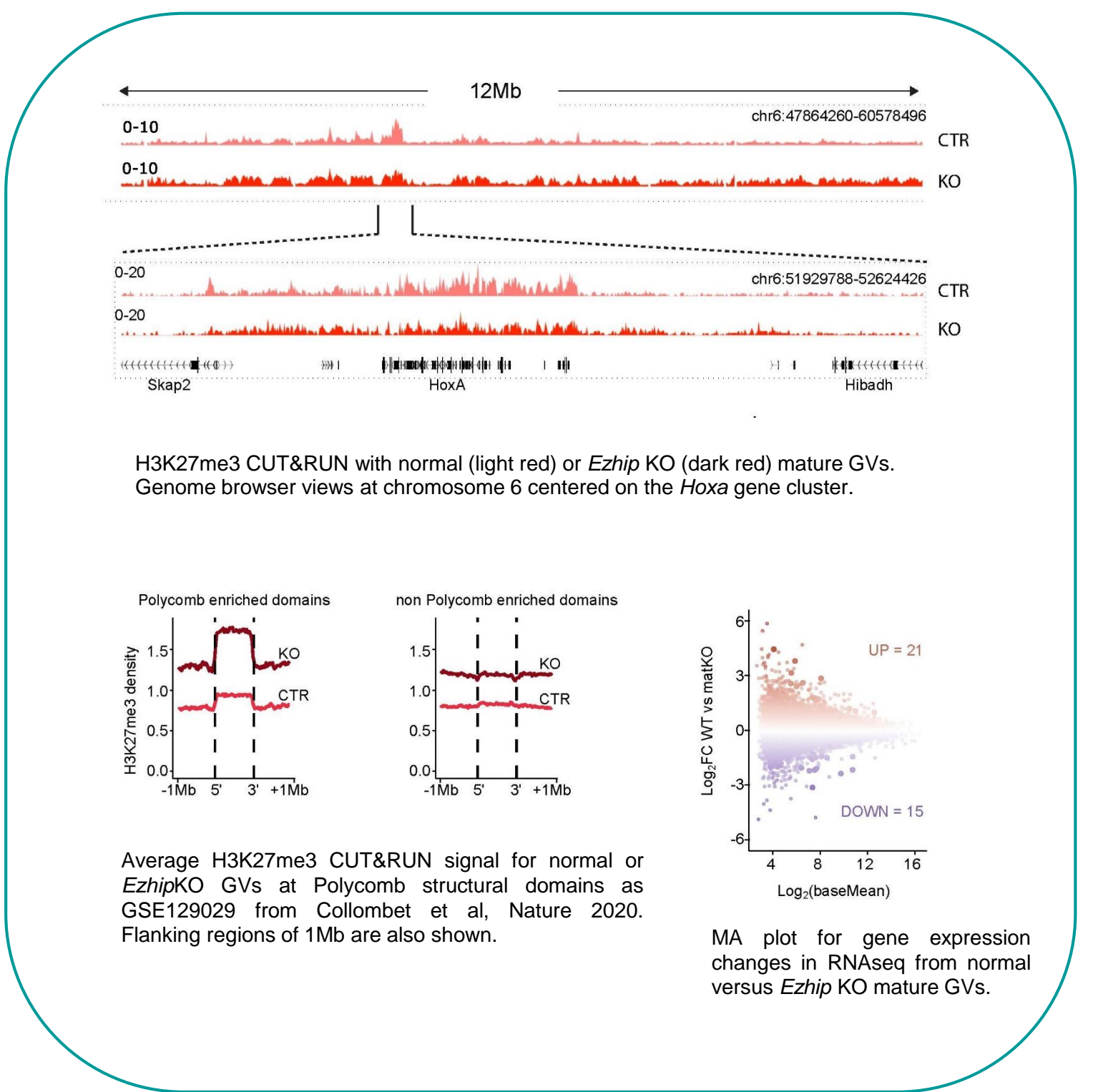
- H3K27me3 is deposited during oocyte maturation by PRC2
- Genome wide H3K27me3 asymmetry between parental genome post fertilization
- Maternal H3K27me3 deposition is necessary non-canonical imprinting

## How is PRC2 activity regulated post-fertilization to maintain parental asymmetric H3K27me3 during few cell cleavages?

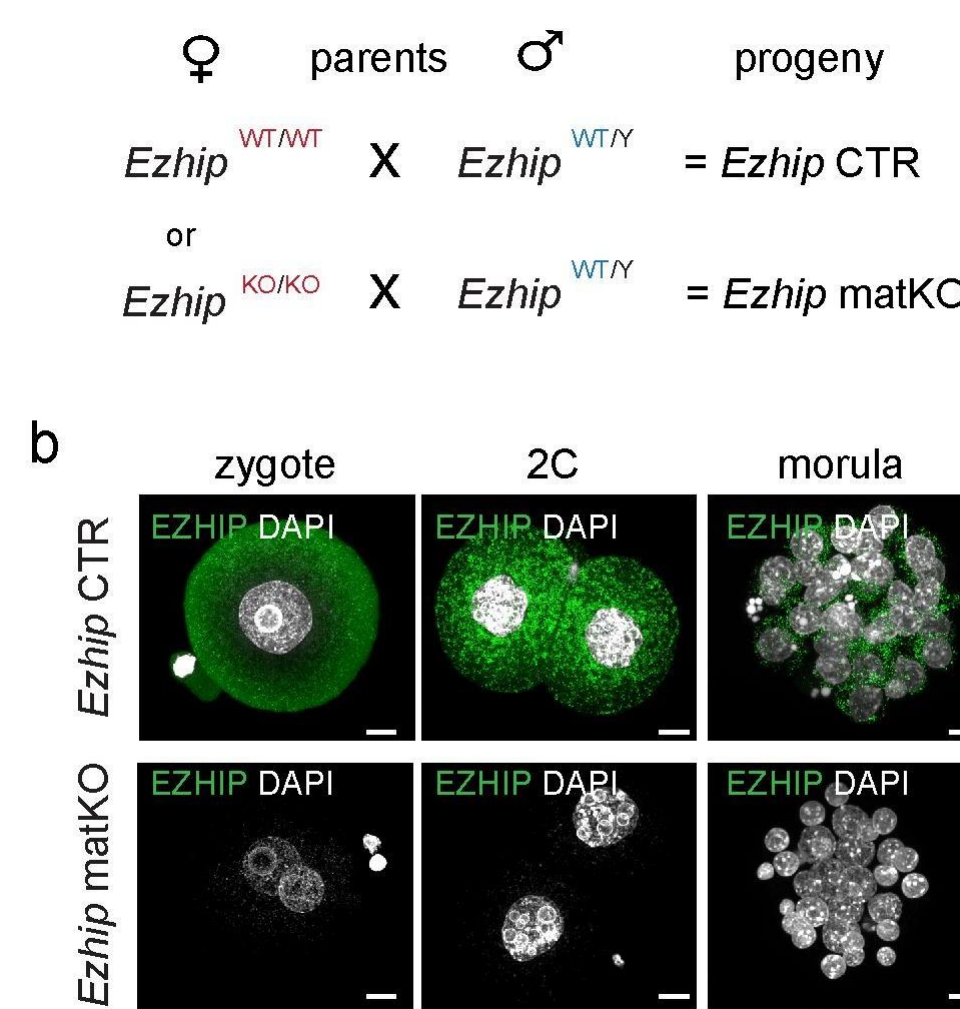


## Is EZHIP a new player in epigenetic regulation in mammalian development?

## H3K27me3 chromatin landscape changes in oocyte upon loss of *Ezhip* but with little impact on the maternal RNA pool



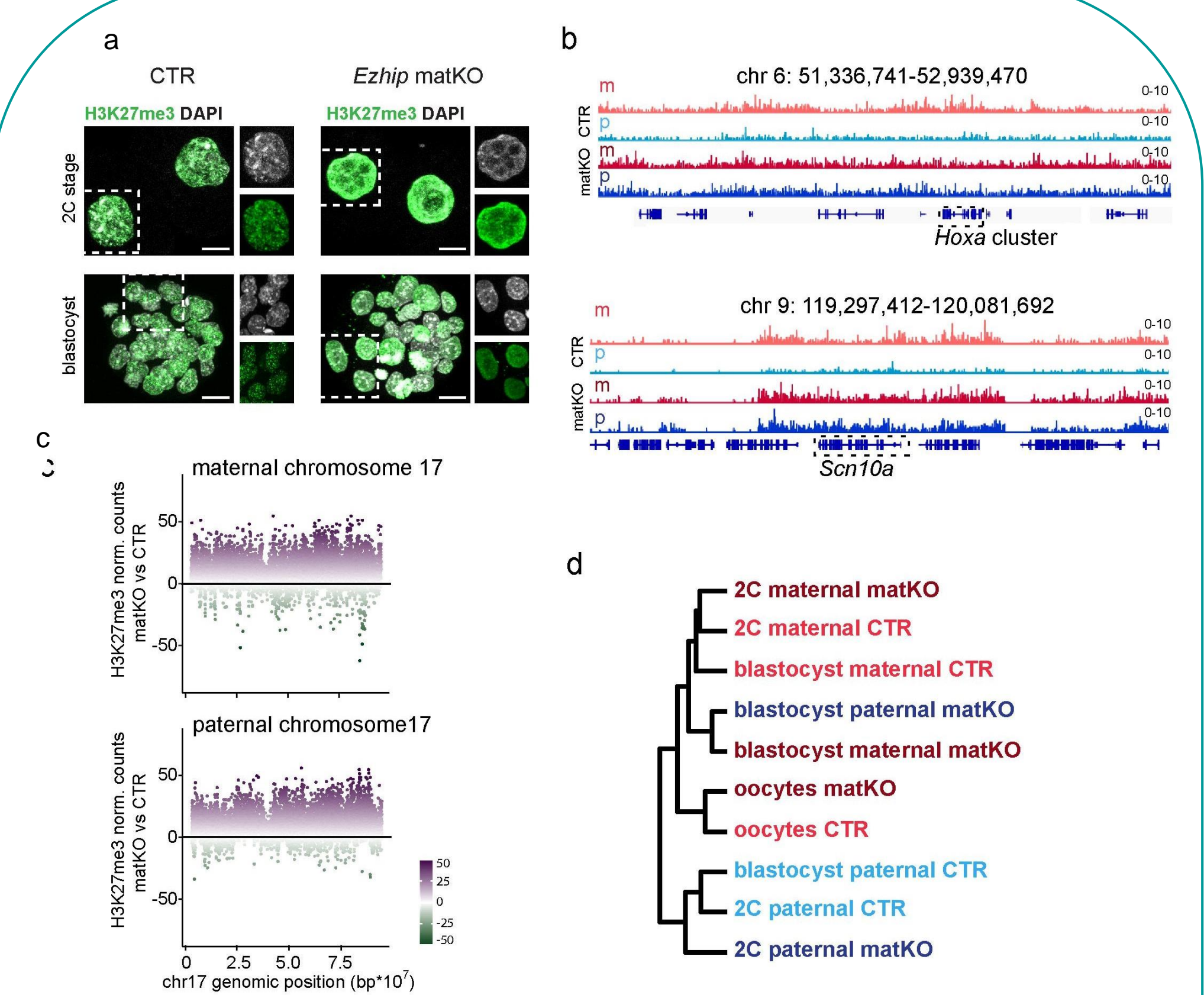
## Exploring EZHIP as a novel regulator of PRC2 activity during preimplantation development



a Mating scheme. b Representative z-stack confocal images of immunofluorescence against EZHIP (in green) for *Ezhip* CTR and matKO embryos at zygote, 2C or morula stages (respective numbers for CTR are n=14, 15 and 9; for matKO n=10; 7 and 4). Control and mutant samples were processed in parallel and acquired using similar settings

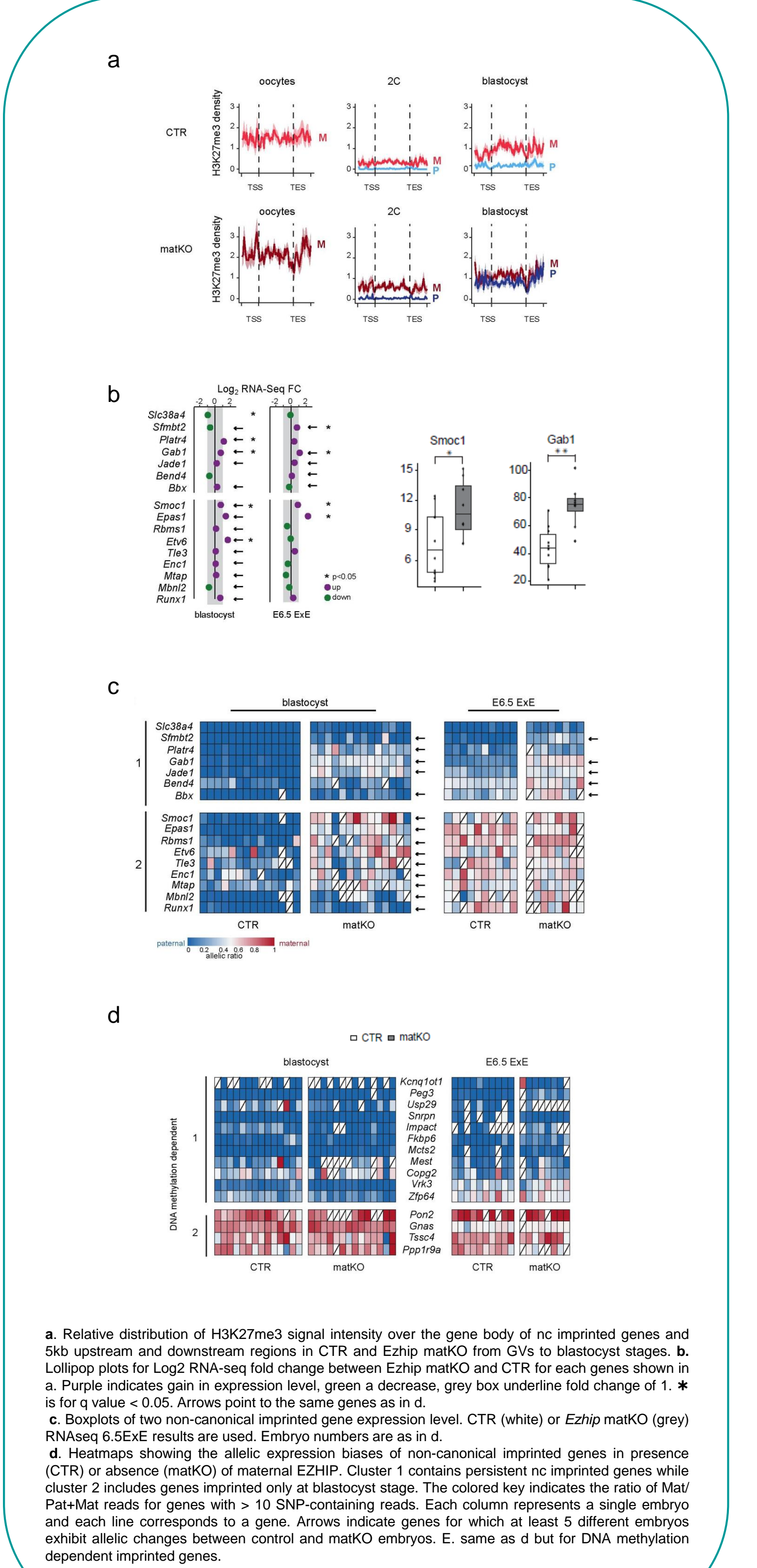
EZHIP is a maternal factor present in preimplantation embryos

## Maternal EZHIP is essential for maintaining asymmetric H3K27me3 distribution

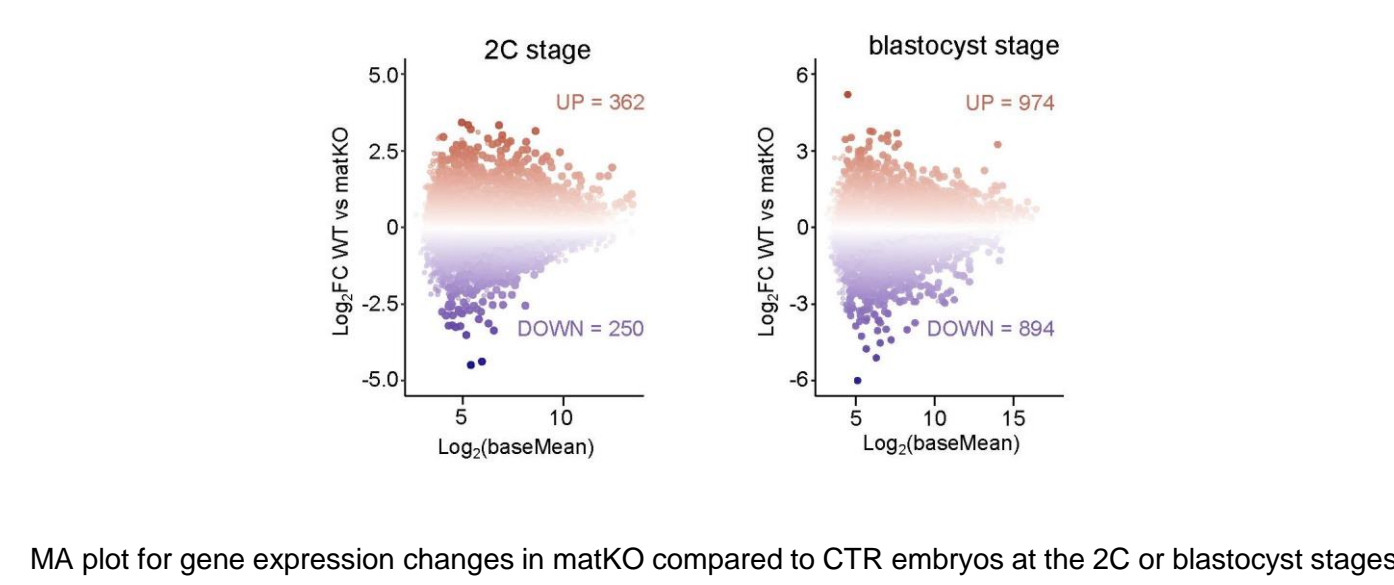


a Representative images of H3K27me3 immunofluorescence signals for control (CTR) and *Ezhip* maternal knockout (matKO) embryos at the 2-cell (2C) and blastocyst stages. The number of embryos analyzed is n = 8 for CTR and 5 for matKO at 2C, and n = 6 for both genotypes at the blastocyst stage. Scale bar = 10 μm. DNA is counterstained with DAPI. b Genome browser views showing H3K27me3 CUT&RUN data for CTR and matKO mature germinal vesicles (GVs) and blastocyst stage embryos at the *Hoxa* cluster and *Scn10a* regions. c Enrichment of H3K27me3 CUT&RUN signals over 10 kb-sized non-overlapping windows along chromosome 17, comparing matKO blastocysts with CTR blastocysts for each parental genome. d Hierarchical clustering analysis of allelic H3K27me3 distribution (10 kb windows) at different developmental stages (from oocyte [GVs] to blastocyst) for CTR and *Ezhip* matKO conditions.

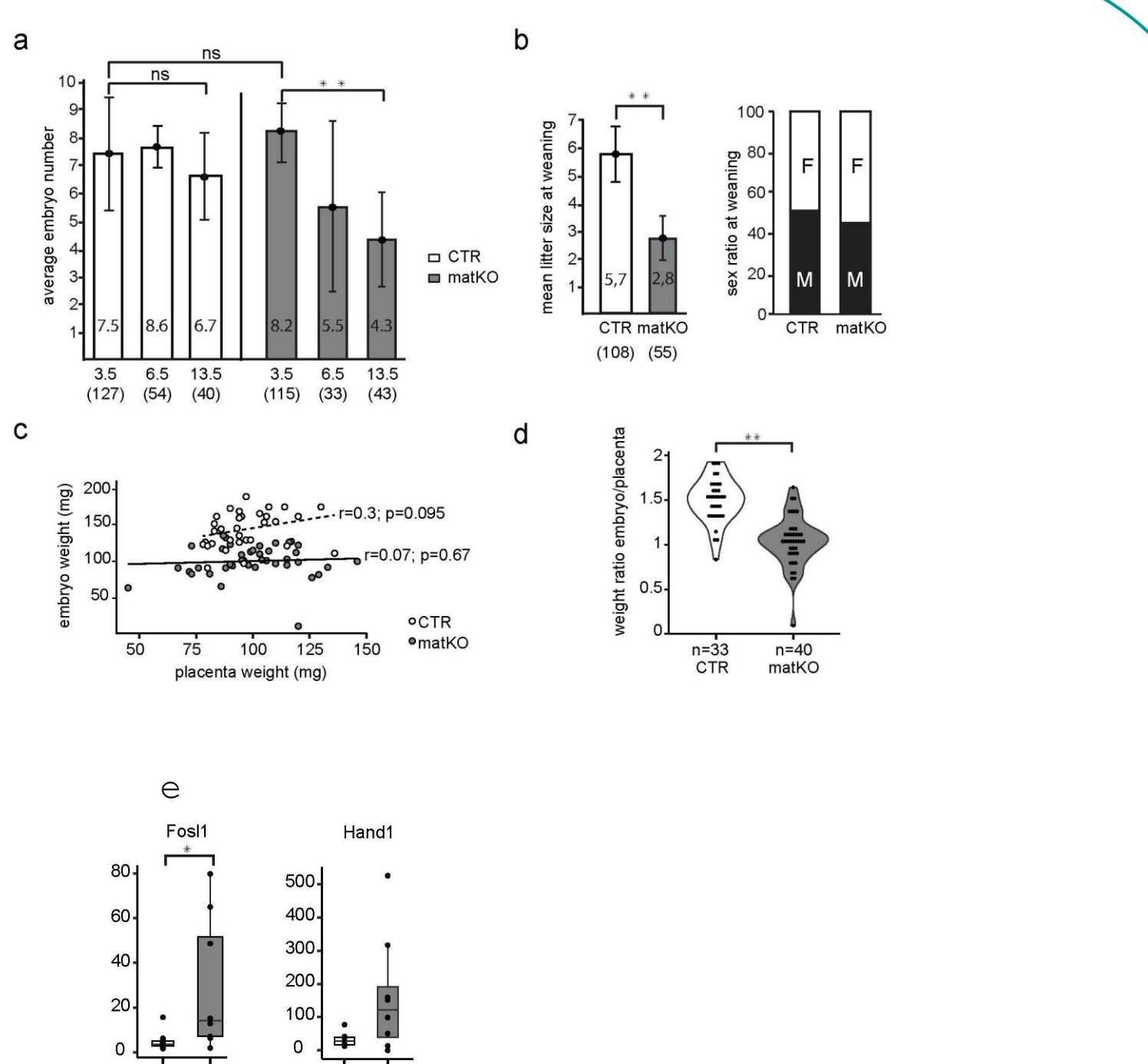
## H3K27me3 equalization between parental genomes causes biallelic expression of non-canonical genes



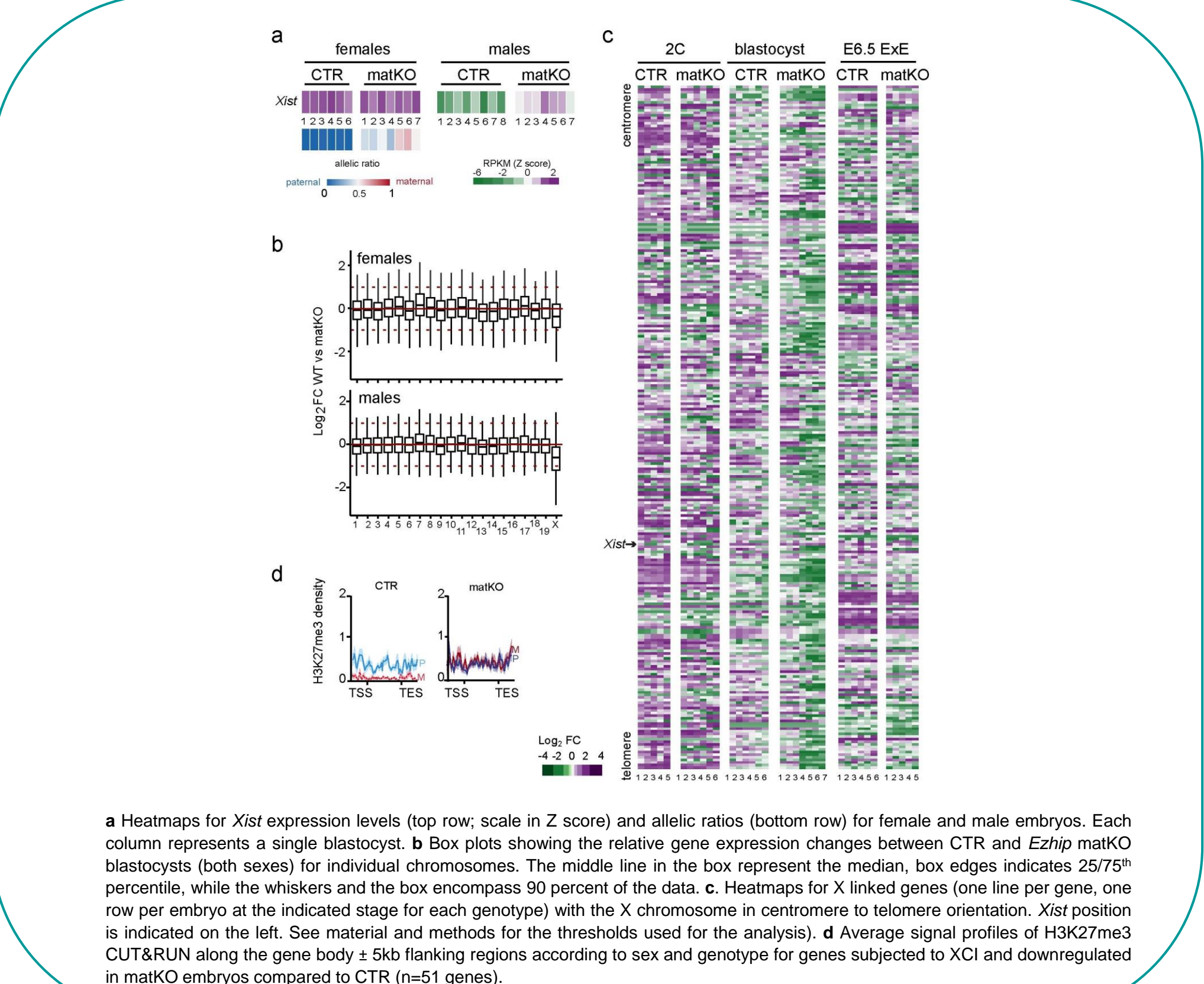
## Dynamic gene expression changes upon loss of EZHIP and accumulation of H3K27me3



## Absence of maternal EZHIP causes long-term effect during gestation



## Absence of maternal EZHIP promotes aberrant X chromosome inactivation in male & female embryos



## Take home message

