Biallelic gain of a permissive chromatin signature precedes productive maternal enhancer-promoter interaction at the *Zim1* imprinted gene during neural commitment

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Genomic imprinting is a key developmental process in which about 150 mammalian genes are expressed on only one allele, depending on their parental origin. Most of these are required for key biological processes, including brain function and behaviour. Allele-specific expression along each imprinted domain is regulated by a key region, the imprinting control region (ICR). In addition to DNA methylation imprints that constitutively mark ICRs on their maternal or paternal alleles, other levels of regulation, including histone modification and chromatin looping, account for the complex and specific spatio-temporal expression patterns of imprinted genes. However, how ICR dynamically orchestrates allele-specific coordination between these regulatory layers along large imprinted domains and fine-tunes the allelic expression of distal genes during lineage commitment remains poorly understood.
To address this question, we are using a multi-level integrative allelic approach to investigate how transcription factors, chromatin signature and 3D conformation interact to regulate imprinted expression within clusters during neural commitment using a hybrid mouse embryonic stem cell-based corticogenesis model that recapitulates the control of imprinted gene expression during neurodevelopment. Here, we used this resource to dissect the regulation at the *Peg3-Zim1* locus, an imprinted domain important for brain function.
Our observation revealed that maternal expression of *Zim1* and paternal expression of *Peg3* are controlled by the same enhancer which is activated upon differentiation and whose allele-specific function is based on the paternal allele-specific insulator function of the ICR (located in the Peg3 promoter). Unexpectedly, we also observed that the gain of maternal *Zim1* expression upon differentiation is a process involving two independent steps: a non-allelic first step leading to the gain of a permissive chromatin structure on both alleles of the promoter, followed by a second step in which only the maternal allele contacted by the enhancer is actually expressed. This observation supports the view that the enhancer plays a role in elongation rather than in transcriptional induction per se at this locus.