Replication timing is regulated by the number of MCMs loaded at origins

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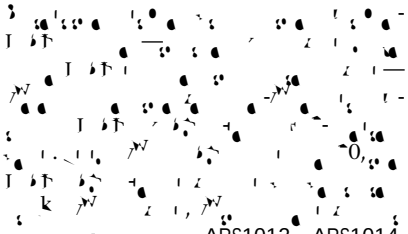
[1] [illegible]

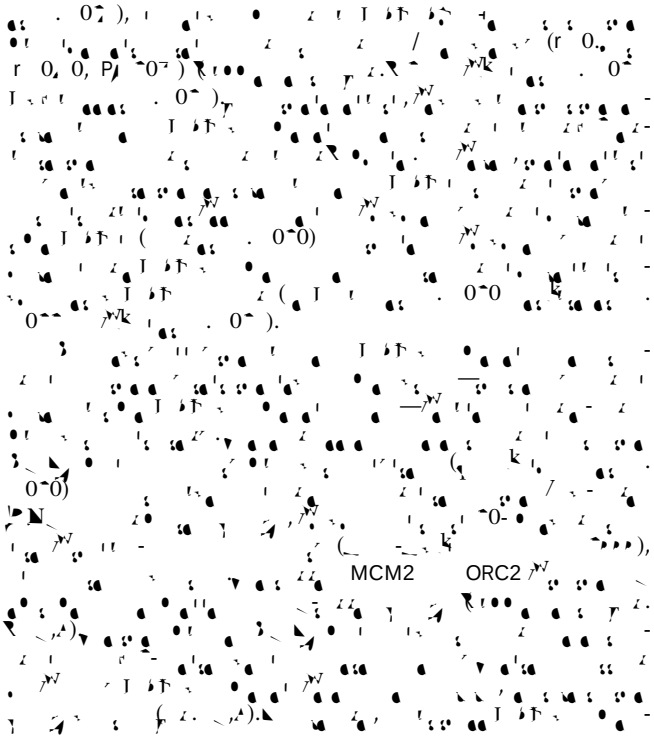
Replication timing is a crucial aspect of genome regulation that is strongly correlated with chromatin structure, gene expression, DNA repair, and genome evolution. Replication timing is determined by the timing of replication origin firing, which involves activation of MCM helicase complexes loaded at replication origins. Nonetheless, how the timing of such origin firing is regulated remains mysterious. Here, we show that the number of MCMs loaded at origins regulates replication timing. We show for the first time in vivo that multiple MCMs are loaded at origins. Because early origins have more MCMs loaded, they are, on average, more likely to fire early in S phase. Our results provide a mechanistic explanation for the observed heterogeneity in origin firing and help to explain how defined replication timing profiles emerge from stochastic origin firing. These results establish a framework in which further mechanistic studies on replication timing, such as the strong effect of heterochromatin, can be pursued.

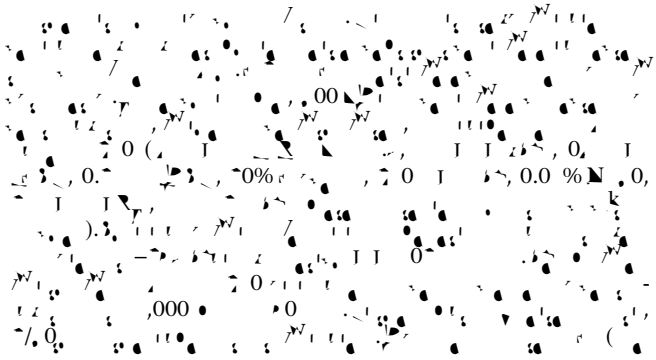
[Supplemental material is available for this article.]

Results



ARS1012, ARS1014, ARS1018, ARS1019, ARS1008, ARS1009, ARS1010, ARS1016


MCM2
ORC2



. Genes Dev **28:**
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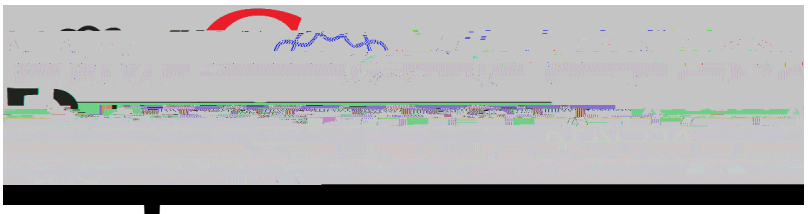
Saccharomyces cerevisiae. Genes Dev **23:** 0 0 0.
S. cerevisiae. Cell **148:** .
. Genome Res **20:** 0.



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