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Replication domains are self-interacting structural chromatin units of human chromosomes

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In higher eukaryotes, the absence of specific sequence motifs marking the origins of replication has been a serious hindrance to the understanding of the mechanisms that regulate the initiation and the maintenance of the replication program in different cell types. In silico analysis of nucleotide compositional skew has predicted the existence, in the germline, of replication N-domains bordered by putative replication origins and where the skew decreases rather linearly as the signature of a progressive inversion of the average fork polarity. Here, from the demonstration that the average fork polarity can be directly extracted from the derivative of replication timing profiles, we develop a wavelet-based pattern recognition methodology to delineate replication U-domains where the replication timing profile is shaped as a U and its derivative as a N. Replication U-domains are robustly found in seven cell lines as covering a significant portion (40-50%) of the human genome where the replication timing data actually displays some plasticity between cell lines. The early replication initiation zones at U-domains borders are found to be hypersensitive to DNase I cleavage, to be associated with transcriptional activity and to present a significant enrichment in insular-binding proteins CTCF, the hallmark of an open chromatin structure. A comparative analysis of genome-wide chromatin interaction (HiC) data shows that replication-U domains correspond to self-interacting structural high order chromatin units of megabase characteristic size. Taken together, these findings provide evidence that the epigenetic compartmentalization of the human genome into autonomous replication U-domains comes along with an extensive remodelling of the threedimensional chromosome architecture during development or in specific diseases. The observed cell specific conservation of the replication timing between the human and mouse genomes strongly suggests that this chromosome organization into self-interacting structural and functional units is a general feature of mammalian organisms.