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Commentary

An important resource and analytic platform for human and mouse cardiovascular-related *cis*-regulatory elements

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Cis-regulatory elements (CREs) are a class of *cis*-acting non-coding DNA regions that primarily regulate the expression of neighboring genes. There are several types of CREs including promoters, enhancers, silencers, and insulators.[1] CREs play important roles in complex transcriptional regulation, such as regulating cell-type-specific gene expression, time-specific regulation of gene expression, and inhibitory regulation of gene expressions.[1] Additionally, accumulating evidence has shown that variations in CREs are linked to a wide range of diseases including cardiovascular diseases.[2–4] Thus, it is important to identify and annotate the CREs in the human or animal model (such as mouse) genome to facilitate the investigation and understanding of cardiovascular disease etiology.

In recent years, the rapid development of genomic chromatin profiling technologies (such as chromatin immunoprecipitation sequencing [ChIP-seq], assay for transposase accessible chromatin [ATAC]-seq, DNase-seq, etc.) have offered opportunities to help solve the increasingly severe problem of the high incidence rate of cardiovascular diseases. These high-throughput profiling methods have enabled the rapid accumulation of cardiovascular-related omics data for identifying and annotating genome-wide CREs. However, it remains a challenge for researchers (who have focused mostly on wet-lab experiments and do not have a background in bioinformatics or computer science) to integrate and process such large-scale data. Although some CRE-relevant databases or web servers have been set up at present, they provide limited basic information (*cis*-regulatory regions and basic functions) about CREs or for specific species such as Drosophila and Arabidopsis.[5–9] A comprehensive database that provides upstream and downstream annotations for cardiovascular-specific CREs is still lacking.

In a recent study published in *Molecular Therapy - Nucleic Acids* in 2023, Song et al. curated the first comprehensive cardiovascular-specific CRE web server for human and mouse, named Cis-Cardio.[10] The current release of Cis-Cardio documents a total of 45,382,361 genomic regions from 1,013 cardiovascular-related human and mouse epigenetic datasets. Notably, 1,395,462 non-redundant potential CREs were identified among these genomic regions. To our best knowledge, these represent the most complete collections of cardiovascular-specific CREs in the human and mouse genomes. In addition to providing six functional analysis modules to dissect the candidate CRE-mediated transcription regulation mechanism of cardiovascular diseases, the web interface of Cis-Cardio also allows for quick searching, browsing, and downloading of detailed information about these CREs. These analysis modules allow a user to quickly analyze and obtain detailed regulatory clues from multiple aspects of transcriptional regulation. For instance, users can identify overlapped CREs and identify CRE-mediated transcriptional regulatory axes by genomic region intersection analysis and upstream regulatory/downstream pathway analyses, respectively. Cis-Cardio also provides efficient analysis tools to infer transcription regulators, interpret regulatory effects of variants, and identify synergetic transcription regulators in CREs. Emphatically, Cis-Cardio offers detailed and diverse (epi-)genetic annotations of CREs, including enhancers, super enhancers, transcription factor binding sites (TFBSs), methylation sites, common SNPs, risk SNPs, expression quantitative trait loci (eQTLs), DNase hypersensitive sites (DHSs), motifs, and 3D chromatin interactions, enabling users to deeply understand the regulatory potentials of the CREs. Finally, thanks to the elegant web server Cis-Cardio, researchers lacking an intensive bioinformatics background have an opportunity to comprehend the largely unexplored roles of cardiovascular-specific CREs in the human and mouse.

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AUTHOR CONTRIBUTIONS

L.X., S.W., and X.G. wrote the commentary.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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