Clin Epigenetics. 2021 Jan 6;13(1):3. doi: 10.1186/s13148-020-00996-1.

Integrated analysis reveals the alterations that LMNA interacts with euchromatin in LMNA mutation-associated dilated cardiomyopathy

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PMID: 33407844 PMCID: PMC7788725 DOI: 10.1186/s13148-020-00996-1

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Abstract

Background: Dilated cardiomyopathy (DCM) is a serious cardiac heterogeneous pathological disease, which may be caused by mutations in the LMNA gene. Lamins interact with not only lamina-associated domains (LADs) but also euchromatin by alone or associates with the lamina-associated polypeptide 2 alpha (LAP2α). Numerous studies have documented that LMNA regulates gene expression by interacting with LADs in heterochromatin. However, the role of LMNA in regulating euchromatin in DCM is poorly understood. Here, we determine the differential binding genes on euchromatin in DCM induced by LMNA mutation by performing an integrated analysis of bioinformatics and explore the possible molecular pathogenesis mechanism.

Results: Six hundred twenty-three and 4484 differential binding genes were identified by ChIP-seq technology. The ChIP-seq analysis results and matched RNA-Seq transcriptome data were integrated to further validate the differential binding genes of ChIP-seq. Five and 60 candidate genes involved in a series of downstream analysis were identified. Finally, 4 key genes (CREBBP, PPP2R2B, BMP4, and BMP7) were harvested, and these genes may regulate LMNA mutation-induced DCM through WNT/β-catenin or TGFβ-BMP pathways.

Conclusions: We identified four key genes that may serve as potential biomarkers and novel therapeutic targets. Our study also illuminates the possible molecular pathogenesis mechanism that the abnormal binding between LMNA or LAP2α-lamin A/C complexes and euchromatin DNA in LMNA mutations, which may cause DCM through the changes of CREBBP, PPP2R2B, BMP4, BMP7 expressions, and the dysregulation of WNT/β-catenin or TGFβ-BMP pathways, providing valuable insights to improve the occurrence and development of DCM.

Keywords: Dilated cardiomyopathy; LMNA; Mutation; TGFβ-BMP signaling; WNT signaling.

Figures

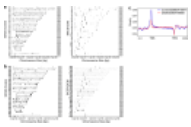

Fig. 1 Visualization of the chromosomal binding...

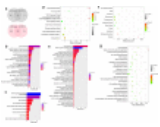

Fig. 2 Identification of ChIP-seq differential binding...

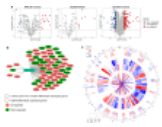

Fig. 3 Identification and visualization of the...

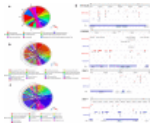

Fig. 4 Functional enrichment analysis of candidate...

Fig. 5 TFBS motif enrichment analysis. **a...**

Fig. 6 Possible mechanism diagram of key...

All figures (7)

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