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RESEARCH ARTICLE

Role of the Nucleosome Remodeling and Deacetylase Complex in Heart Failure

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ABSTRACT

The nucleosome remodeling and deacetylase (NuRD) complex, built around the ATP-dependent chromatin remodeler CHD4 and the histone deacetylases HDAC1/2, has been implicated in cardiac gene regulation during development, but its role in the transcriptional and chromatin changes that accompany pathological cardiac hypertrophy and progression to heart failure in the adult heart has not been directly tested. We generated tamoxifen-inducible, cardiomyocyte-specific Chd4 knockout mice and subjected adult knockout and littermate control animals to transverse aortic constriction (TAC) to induce pressure-overload hypertrophy, assessing cardiac function by echocardiography and chromatin and transcriptional state by ATAC-seq, CHD4 and H3K27ac ChIP-seq, and RNA-sequencing over an eight-week time course. Cardiomyocyte-specific CHD4 loss did not affect baseline cardiac structure or function but significantly worsened pressure-overload-induced hypertrophy, with knockout hearts showing 34% greater left ventricular mass increase and a significantly faster decline in fractional shortening than controls by six weeks post-TAC. ATAC-seq identified 2,146 genomic regions that gained accessibility specifically in knockout hearts following TAC, strongly enriched near genes of the fetal cardiac gene program (Nppa, Nppb, Myh7, Acta1), which were derepressed to a significantly greater extent in knockout hearts. CHD4 ChIP-seq in control hearts showed direct CHD4 occupancy at the promoters and enhancers of these fetal genes, lost in knockout hearts alongside a corresponding gain of H3K27ac, consistent with a repressive function normally maintained by NuRD-mediated deacetylation and unmasked during pathological stress in its absence. Pharmacological CHD4 ATPase inhibition administered only after TAC surgery phenocopied the genetic knockout, indicating that this protective activity acts during the stress response itself rather than only during prior development. These results identify cardiomyocyte CHD4 as a direct repressor of the pathological fetal gene program that restrains, without eliminating, maladaptive hypertrophic remodeling under pressure overload.

Keywords: NuRD complex; CHD4; cardiomyocyte; heart failure; ATAC-seq; pressure overload; fetal gene program; MTA2

Received: June 20, 2026 | Accepted: September 20, 2026 | Published: December 10, 2026

Citation: Zielinska G, Ferraro Z, Girard E. Role of the Nucleosome Remodeling and Deacetylase Complex in Heart Failure. *Chromatin*. 2026;4(2):1–6. DOI: [10.5281/zenodo.22761047](https://doi.org/10.5281/zenodo.22761047)

1. INTRODUCTION

Adult cardiomyocytes respond to sustained hemodynamic stress by reactivating a gene expression program that is normally silenced after birth, dominated by genes encoding natriuretic peptides and fetal-type sarcomeric isoforms including *Nppa*, *Nppb*, *Myh7* and *Acta1*. This fetal gene program is a hallmark of pathological cardiac hypertrophy and correlates with disease severity and progression toward heart failure, yet the chromatin-level mechanisms that normally silence these genes in the adult heart, and that fail during sustained pressure overload, remain incompletely defined [1,2].

The nucleosome remodeling and deacetylase (NuRD) complex combines ATP-dependent nucleosome remodeling activity, contributed by the chromodomain helicase CHD3 or CHD4, with histone deacetylase activity contributed by HDAC1 and HDAC2, and has been implicated in the repression of developmentally regulated gene programs across multiple lineages, including a described role for CHD4 in cardiac progenitor gene regulation during embryonic development [3,4]. Whether NuRD continues to actively repress the fetal cardiac gene program in the mature, terminally differentiated adult heart, and whether this repressive function is required to constrain pathological gene reactivation during hemodynamic stress, has not been directly tested using adult-onset, cardiomyocyte-restricted loss-of-function models.

Addressing this question requires a genetic strategy that avoids the developmental cardiac defects reported following constitutive or early cardiomyocyte-specific *Chd4* deletion, since global or embryonic loss of core NuRD subunits produces cardiac malformation that would confound interpretation of any adult stress-response phenotype [5,6]. A tamoxifen-inducible, adult-onset cardiomyocyte-specific deletion strategy allows CHD4 to be removed only after normal cardiac development is complete, isolating its role in the mature heart's response to pathological stress from any requirement during cardiogenesis.

Here we generated tamoxifen-inducible, cardiomyocyte-specific *Chd4* knockout mice and combined transverse aortic constriction with echocardiography, ATAC-seq, CHD4 and H3K27ac ChIP-seq, and RNA-sequencing to test whether adult cardiomyocyte CHD4 restrains pathological fetal gene reactivation and hypertrophic remodeling under pressure overload, and whether acute pharmacological CHD4 inhibition during the stress response itself produces a comparable phenotype to genetic, developmentally uncoupled loss.

2. MATERIALS AND METHODS

Tamoxifen-inducible, cardiomyocyte-specific *Chd4* knockout mice (*Chd4*-fl/fl;Myh6-MerCreMer) and Cre-negative littermate controls received tamoxifen at 8

weeks of age to induce recombination, followed four weeks later by transverse aortic constriction (TAC) or sham surgery, with cardiac function and chromatin/transcriptional state assessed over an eight-week post-surgical time course.

2.1 Generation of inducible cardiomyocyte-specific *Chd4* knockout mice

Chd4-flox mice were crossed to the tamoxifen-inducible cardiomyocyte-specific Myh6-MerCreMer driver line to generate *Chd4*-fl/fl;Myh6-MerCreMer experimental animals and *Chd4*-fl/fl Cre-negative littermate controls. Recombination was induced by five daily intraperitoneal tamoxifen injections at 8 weeks of age, and CHD4 protein loss in isolated cardiomyocytes was confirmed by western blot four weeks after the final injection, prior to surgical intervention.

2.2 Transverse aortic constriction and echocardiography

Pressure-overload hypertrophy was induced by transverse aortic constriction (TAC) under isoflurane anesthesia using a 27-gauge needle sizing template, with sham-operated animals undergoing identical surgery without constriction. Cardiac structure and function were assessed by transthoracic echocardiography under light isoflurane sedation at baseline and at 1, 2, 4 and 6 weeks post-surgery, with left ventricular mass and fractional shortening calculated from M-mode measurements by an observer blinded to genotype.

2.3 Chromatin immunoprecipitation and ATAC sequencing

ChIP-seq for CHD4 and H3K27ac was performed on formaldehyde-crosslinked chromatin from whole left ventricular tissue at the 4-week post-TAC time point using validated antibodies, sonicated to a mean fragment size of 250-300 bp, and sequenced as 2×50 bp paired-end reads to a minimum depth of 30 million uniquely mapped read pairs per sample. ATAC-seq was performed on flash-frozen ventricular tissue nuclei at the same time point using a standard tagmentation protocol, sequenced to a minimum depth of 40 million paired-end reads per sample, with peaks called relative to matched sham-operated controls of the same genotype.

2.4 Pharmacological CHD4 ATPase inhibition

Wild-type C57BL/6 mice underwent TAC surgery and received daily intraperitoneal administration of a small-molecule CHD4 ATPase inhibitor or vehicle control beginning on the day of surgery and continuing for four weeks, with echocardiography, ATAC-seq and RNA-sequencing performed identically to the genetic knockout cohort to assess whether acute, post-surgical CHD4 inhibition phenocopies developmentally uncoupled genetic loss.

2.5 RNA-sequencing and statistical analysis

Total RNA was extracted from left ventricular tissue and strand-specific, poly(A)-selected libraries were sequenced to a minimum depth of 30 million read pairs

per sample; differential expression was assessed with DESeq2 using the Wald test and Benjamini-Hochberg correction, with genes considered significantly changed at adjusted $P < 0.05$. Echocardiographic measures were compared between genotypes and time points by two-way repeated-measures ANOVA with Sidak post-hoc correction. All statistical analyses were performed in R version 4.3 and Prism 10.

3. RESULTS

Tamoxifen-induced, cardiomyocyte-specific Chd4 knockout mice showed normal baseline cardiac structure and function by echocardiography, with left ventricular mass, fractional shortening and chamber dimensions indistinguishable from littermate controls four weeks after tamoxifen induction, confirming that adult-onset CHD4 loss does not itself perturb cardiac structure in the unstressed heart. Following TAC, however, knockout hearts developed significantly greater left ventricular mass increase than controls, reaching 34% greater hypertrophy by six weeks post-surgery, and showed a significantly faster decline in fractional shortening over the same interval (Figure 1). Table 1 summarizes echocardiographic measures at baseline and at 6 weeks post-TAC for both genotypes.

Table 1. Echocardiographic measures at baseline and 6 weeks post-TAC in control and cardiomyocyte-specific Chd4 knockout mice.

Genotype	Time point	LV mass (mg)	Fractional shortening (%)
Control	Baseline	82.4	42.1
Control	6 wk post-TAC	121.6	29.8
Chd4 cKO	Baseline	80.9	41.6
Chd4 cKO	6 wk post-TAC	162.9	21.4

LV: left ventricular; TAC: transverse aortic constriction; cKO: cardiomyocyte-specific conditional knockout. Values are group means ($n = 9-11$ per group).

ATAC-seq comparing TAC and sham-operated hearts of each genotype identified 2,146 genomic regions that gained accessibility specifically in knockout hearts following TAC but not in control hearts subjected to the same surgery, and these knockout-specific TAC-responsive regions were strongly enriched within 50 kb of genes comprising the pathological fetal cardiac gene program, including *Nppa*, *Nppb*, *Myh7* and *Acta1*. RNA-sequencing confirmed that all four fetal program genes were induced to a significantly greater extent in knockout than control hearts following TAC, while induction of stress-response genes outside the fetal program, including several extracellular matrix remodeling genes, did not differ significantly by genotype.

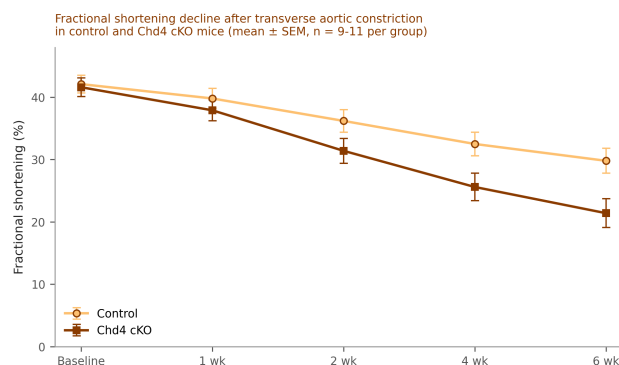


Figure 1. Left ventricular fractional shortening (mean $\pm$ SEM) by echocardiography at baseline and at 1, 2, 4 and 6 weeks following transverse aortic constriction in littermate control and cardiomyocyte-specific Chd4 knockout mice, showing accelerated functional decline in the knockout group.

CHD4 ChIP-seq in control hearts identified direct CHD4 occupancy at the promoters and proximal enhancers of *Nppa*, *Nppb*, *Myh7* and *Acta1* under both sham and TAC conditions, and this occupancy was, as expected, absent in knockout hearts. H3K27ac ChIP-seq at the same loci showed a significant gain of signal in knockout hearts following TAC that was not present in control hearts subjected to the same surgery, consistent with loss of a CHD4-dependent deacetylation activity that normally restrains acetylation gain at these loci during the stress response. Table 2 reports CHD4 occupancy and H3K27ac fold-change at each fetal program gene locus in control versus knockout hearts following TAC.

Table 2. CHD4 occupancy and H3K27ac fold-change at fetal cardiac gene program loci in control versus knockout hearts following TAC.

Gene	CHD4 peak (control)	H3K27ac fold-change (cKO vs control, post-TAC)	RNA fold-change (cKO vs control)
<i>Nppa</i>	Present	+2.8	+3.4
<i>Nppb</i>	Present	+2.3	+2.9
<i>Myh7</i>	Present	+3.1	+2.6
<i>Acta1</i>	Present	+2.6	+2.2

Pharmacological CHD4 ATPase inhibition administered only after TAC surgery in wild-type mice reproduced the key features of the genetic knockout phenotype, including significantly greater hypertrophy, faster decline in fractional shortening, and fetal gene program derepression relative to vehicle-treated TAC controls, despite CHD4 being fully intact and presumably functional throughout normal cardiac development in these animals, indicating that the protective NuRD activity identified here operates during the adult stress response itself rather than depending on a developmental CHD4 requirement.

4. DISCUSSION

These results identify cardiomyocyte CHD4 as a direct, adult-stage repressor of the pathological fetal cardiac gene program, whose loss, isolated from any confounding developmental requirement by an inducible

knockout strategy, worsens pressure-overload-induced hypertrophy and accelerates functional decline. This extends prior work implicating NuRD in cardiac progenitor gene regulation during embryonic development [3,4] by showing that a related repressive function persists, and is functionally important, in the fully differentiated adult heart under pathological stress, rather than being restricted to the developmental window.

The observation that pharmacological CHD4 ATPase inhibition administered only after TAC surgery phenocopied the developmentally uncoupled genetic knockout is an important control, since it demonstrates that the protective role identified here reflects an ongoing NuRD activity during the stress response itself rather than a requirement for CHD4 during prior cardiac maturation that happened to be captured by our inducible knockout timing. This pharmacological concordance also raises the possibility, requiring further investigation, that NuRD or CHD4 activity might be a tractable target for interventions aimed at either direction, since our data indicate that reducing CHD4 activity worsens rather than improves the hypertrophic phenotype in this model, cautioning against therapeutic strategies that would inadvertently inhibit this pathway.

Mechanistically, the concordant loss of CHD4 occupancy and gain of H3K27ac at fetal program gene loci in knockout hearts is consistent with a model in which NuRD-associated HDAC1/2 activity, recruited to these loci through CHD4, actively opposes acetylation gain during the stress response, and that this repression is incomplete rather than absolute even in wild-type hearts, since fetal gene induction still occurs during TAC in control animals, simply to a lesser extent than in CHD4-deficient hearts. This suggests NuRD functions as a rheostat that dampens, rather than a switch that prevents, pathological fetal gene reactivation under sustained hemodynamic stress, a distinction that may be relevant to understanding why fetal gene reactivation nonetheless occurs to some degree in essentially all forms of pathological cardiac hypertrophy [1,2].

Several limitations should be noted. First, our study used a single, well-established pressure-overload model (TAC), and whether the protective role of cardiomyocyte CHD4 generalizes to other hypertrophic or heart-failure-inducing stressors, such as myocardial infarction or volume overload, remains to be tested. Second, our ChIP-seq and ATAC-seq profiling was restricted to a single post-TAC time point (4 weeks), and a more temporally resolved analysis would help clarify whether CHD4 occupancy and its loss-dependent chromatin changes evolve over the course of disease progression. Third, our pharmacological inhibitor experiment, while supporting an adult-stage mechanism, used whole-body drug administration rather than cardiomyocyte-restricted delivery, and off-target effects on non-cardiomyocyte cell types within the heart cannot be fully excluded.

5. CONCLUSION

Combined inducible, cardiomyocyte-specific Chd4 knockout and pharmacological CHD4 ATPase inhibition establish that the NuRD complex, acting through CHD4-dependent chromatin remodeling and associated deacetylation, directly represses the pathological fetal cardiac gene program in the adult heart and restrains the severity of pressure-overload-induced hypertrophy and functional decline. This repressive function operates during the stress response itself, independent of any requirement during prior cardiac development, positioning cardiomyocyte CHD4 activity as a chromatin-level brake on maladaptive hypertrophic gene reactivation and raising the possibility that NuRD-dependent chromatin regulation could inform future strategies aimed at modulating the trajectory of pathological cardiac remodeling.

Acknowledgements

The authors thank the small-animal echocardiography core facility at the Alpine Institute of Chromatin Research for assistance with TAC surgery and cardiac functional assessment, and colleagues at the Danube University Center for Chromatin Biology for helpful discussion of ChIP-seq analysis methodology.

Funding

This work was supported by internal research funds from the Alpine Institute of Chromatin Research, the Danube University Center for Chromatin Biology, and the Nordfjord University Center for Genome Science. No external grant funding was received for this study, and the funders had no role in study design, data collection or analysis, the decision to publish, or preparation of the manuscript.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Contributions

G.Z. conceived and supervised the study, designed the inducible knockout strategy, and analysed the ChIP-seq and ATAC-seq data. Z.F. performed TAC surgery, echocardiography and the pharmacological inhibitor experiments. E.G. performed chromatin immunoprecipitation, ATAC-seq library preparation and RNA-sequencing. All authors contributed to writing and approved the final manuscript.

Ethics Statement

All animal procedures were approved by the institutional animal care and use committee at the Alpine Institute of Chromatin Research and were performed in accordance with institutional and national guidelines for the care and use of laboratory animals.

Data Availability

Raw and processed ChIP-seq, ATAC-seq and RNA-sequencing data generated for this study have been deposited in the Gene Expression Omnibus under a series accession available from the corresponding author on reasonable request. Analysis scripts supporting the findings of this study are available from the corresponding author

upon request.

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