SUPPLEMENTAL MATERIAL

Supplemental methods

β-Gal staining and Immunostaining

β-Gal staining was done as previously described [1]. Immunostainings were done on frozen sections of adult heart. Samples were incubated in primary antibody at 4°C overnight. After washing in PBS, sections were incubated in the appropriate fluorescent-labeled secondary antibodies, followed by counterstaining with DAPI (Sigma) then mounted in VECTASHIELD H-1000 mouting medium (Vector Laborataries, Inc.). Primary antibodies used were as follows: Rabbit polyclonal anti-Pitx2 (1:100) (Capra Science) and Rabbit anti- β-catenin (1:100) (Cell Signaling). Secondary antibodies used was as follows: Alexa Fluor® 488 goat anti-rabbit IgG (1:1000) (Molecular Probes). Immunofluorescent images were captured on a Leica TCS SP5 confocal microscope, and all functions were controlled via Leica LAS AF software (Leica Microsystems). All manuscript figures were prepared using Adobe Photoshop CS5 (Adobe Systems Inc.) and Micosoft Powerpoint (Microsoft Inc.).

Realtime RT-PCR and luciferase assay

Total RNA was isolated using the miRNeasy mini Kit (QIAGEN), followed by RT-PCR using qScript™ cDNA SuperMix (Quanta Biosciences). Three biological replicates were collected for control and mutant. Real-time thermal cycling was performed using Stepone Plus thermal cycler (Applied Biosystems) with PerfeCTa™ SYBR Green FASTMix™ (Quanta Biosciences). Comparative Ct method was used to quantitate relative gene expressions. Firstly, Ct value of both mutants and controls was normalized to an endogenous housekeeping gene (*GAPDH*). Secondly, each sample was

calibrated to the mean of control Ct value. Lastly, Ct value was transformed to fold change using exponential transformation. Standard deviation of both control and mutant samples were calculated within the groups. Two-sample Wilcoxon test was performed between control and mutant. Sequences of PCR primers are available upon request.

Luciferase reporters were constructed from PGL3 luciferase reporter vector (Promega) and 1-3 kb DNA fragment amplified from Genomic DNA using primers for ChIP-Seq peak regions. PCR was performed using PrimeSTAR HS DNA Polymerase (Takara Biotechnology Co., LTD.). Clonings were done by using Gateway Vector Conversion System (Invitrogen). Sequences for PCR primers are available upon request. Expression contruct for Pitx2c was obtained from Dr. Brad Amendt. 293FT cells were transfected with the reporter construct and Pitx2c expression construct or control construct.Transfection was done by using Lipofectamine 2000 (Invitrogene) per the manufacturer's protocol. Luciferase activities were measured on Infinite M200 Pro multimode microplate reader (TECAN) using Dual-Glo Luciferase Assay System (Promega) per the instruction of the manufacturer. Average luciferase activity are reported with standard deviation. Two-sample Wilcoxon-test was performed using R.

R-R interval measurement

Telemetry ECG data was collected on DSI Telemetric Physiological Monitor System and processed by Dataquest A.R.T. 3.1 software (Data Sciences International). For each mouse, manually select uninterrupted 1 miniute ECG interval with uniform maximum R-wave voltage; number of heart beats counted accordingly. R-R intervals were measured in the unit of millisecond. Mean and standard deviation of R-R interval from each mouse

were calculated using R software. Two-tailed, unpaired Student's t-test ($n > 400$) was performed for mean and standard deviation values of R-R interval; no significant difference was detected of mean R-R interval value between controls and mutants ($p = 0.54$); standard deviation of R-R interval from mutant mice were significantly greater than that of control mice ($p = 0.003$).

Microarray and ChIP-Seq data processing

The raw data of microarray was generated using Affymetrix Microarray Suite version 5.0 (MAS 5.0) using Affymetrix default analysis settings and global scaling as a normalization method. The trimmed mean target intensity of each array was arbitrarily set to 100. The value distribution of raw intensity from total 18 samples was graphically viewed in box plots. To show reproducibility across three biological replicates within each group, linear correlation coefficient value *r* was measured between each pair of replicates within each groups using R software function *var*.

Differential expressed genes were detected using R bioconductor package 'Limma' version 3.16.8. Briefly, log transformation was performed to the raw intensity values, the normality was checked using histogram and quantile-quantile plot for each condition; Shapiro-Wilk test was performed on randomly selected 300 genes from each array using R shapiro test function, resulted p value > 0.05 for all 18 individual chips. Student's t-test was performed to identify differences of expression level between wild type and mutants for each probe. Benjamini & Hochberg false discovery rate method was used for multiple comparsion correction. Differentially expressed genes were called using cutoffs p-value ≤ 0.05; fold change ≥ 1.5 and FDR ≤ 0.35.

We compared differential expressed genes in 3-, 6- and 12-week of age individually. Total 3,323 genes were collectively called as differentially expressed, and were subjected to R package HOPACH to perform unsupervised clustering based on a cosine angle distance matrix. The first level of the hierarchical tree contains 5 clusters, one of which has 2,697 genes with significant higher expression value compared to the other 4 clusters. Gene ontology analysis showed that genes from this cluster are enriched in heart and atrium. Clusters I-V, shown in Fig.2, were clusters on the third level of the tree derived from this highly expressed, heart-related gene group, with a minimum of 30 genes in each cluster. Raw intensity values from individual samples were used to plot in heat map. Relative expression value was calculated using following formula and illustrated in color:

Relative expression value = (Individual expression density - Mean) / std.deviation

Over-represented gene ontology terms were identified using GO Elite with its default Z score and permutation methods[2-4]. To calculate Z score, the observed number of genes in the input gene list was subtracted from the expected number of genes associated with a particular biological term and divided by the standard deviation of the observed number. To determine the likelihood of observing the calculated Z score by chance, the permutation analysis was performed. The same number of genes as input gene list was randomly selected from background gene list and calculated Z score. This process was repeated 5000 times for each input gene list. False discovery rate was calculated using Benjamini-Hochberg correction. GO terms were plotted using Z score (Fig.3A). Only terms with FDR < 0.10 were reported.

Ion torrent PGM reads were mapped to the mm9 assembly (NCBI Build 37) using Torrent Suite (2.0.1) aligner Tmap (0.2.3) (Life Technologies). The ChIP-Seq signal was normalized to a 10 million reads total and visualized in the UCSC genome browser. ChIP enriched peaks were identified using Homer [4] by the default setting. Briefly, a fixed peak size was calculated automatically, in our case, the peak size was 162 bp. The program then scanned the entire genome for 162 bp clusters with the highest density of reads. After all clusters have been found, the program compared Pitx2 ChIP-Seq reads against input control reads. The cutoffs for calling the peaks were read number enriched at least 4 fold, FDR threshold 0.001, FDR effective Poisson p-value 3.7e-8, and minimum read number 5. This process produced 11,280 enriched peaks. Nearest genes associated to the enriched peaks were annotated using the annotatePeaks function and de novo motif discovery was performed using the findMotifsGenome function in Homer. Genes associated to ChIP-Seq peaks were overlaid with significantly up-regulated genes in 12-week mutants. The overlaid gene list was analyzed with GO Elite for enriched gene ontology terms. Microarray and ChIP-Seq data are available through the NCBI Gene Expression Omnibus (GEO) data repository under accession GSE50401.

Table S1. Abnormal R-R intervals in Pitx2 CKO mice. R-R interval were sampled from unintefrrupted 1 minute ECG tracing of control (*Pitx2 Flox/Flox*) and *Pitx2* CKO (*Pitx2 Flox/Flox MCK-Cre*) mice. Mean and standard deviation of R-R interval from each mouse were listed. Two-sided, unpaired Student's t-test was performed for mean and standard deviation values of R-R interval; no significant difference was detected of mean R-R interval value between controls and mutants (p = 0.543); standard deviation of R-R interval from mutant mice were significantly greater than that of control mice (p = 0.003).

Animals	Age	# of heart beats	R-R interval (ms)	
			Mean (*)	SD (**)
Ctrl 1	2-4 months	554	105	9
Ctrl 2		392	146	10
Ctrl 3		467	123	10
Ctrl 4		447	127	10
Ctrl 5	7 months	420	142	10
CKO 1	2-4 months	488	117	30
CKO 2		408	140	24
CKO 3		420	137	21
CKO 4		485	118	18
CKO 5		505	114	16
CKO 5		585	98	29
CKO 6	7-8 months	513	113	16
CKO 7		420	137	45

ms: millisecond

SD: Standard Deviation

* p = 0.543

** p = 0.003

Table S2. Mice tested by telemetry ECG. The table summarizes genotype, age, number, and phenotype of mice tested by telemetry ECG.

Genotype	Age	Animal number	Phenotype
Pitx2 Flox/Flox	2-4 months	4	Normal sinus rhythm (4/4)
Pitx2 Flox/Flox	7-8 months	1	Normal sinus rhythm (1/1)
Pitx2 Flox/Flox MCK-Cre	2-4 months	5	Sinus node dysfunction with impaired atrial conduction(5/5)
Pitx2 Flox/Flox MCK-Cre	7-8 months	2	Sinus node dysfunction with impaired atrial conduction(2/2)

Table S3. Genes involved in human atrial fibrillation and related arrhythmias identified by GWAS. Gene symbol, gene type and heart function involved are shown.

Gene symbol	Gene type	Heart function involved
Tbx5	T-box Transcription factor	Atrial fibrillation [5]; PR interval [6-10]
Tbx20	T-box Transcription factor	QRS duration[8]
Cav1	Components of the caveolae plasma membranes	Atrial fibrillation [11]; PR interval [6, 7, 9]
Zfhx3	Zinc finger homeobox protein	Atrial fibrillation [11-13]
Cacna1d	Cacium channel voltage dependent	Atrial fibrillation[8, 14]; QRS duration [8]
Kcnq1	potassium voltage-gated channel	Atrial fibrillation [15, 16]; QT interval [16-18]

Table S4. Other gene tested by qRT-PCR. Gene sysmbols and result from the experiments are shown.

Gene symbol	Alternation in expression level in Pitx2 CKO left atrium
Kcnn3	No significant change
Nkx2.5	No significant change
Ctnnb1	No significant change
Tbx5	No significant change
Dlg1	No significant change
Cav2	Decreased

Figure S1. Generation of the Pitx2 conditional knockout mice. (A) Strategy for the generation of the *Pitx2* conditional knockout allele. *Pitx2 Flox* allele has two LoxP sites flanking exon5, which encodes the N terminus of DNA binding homeodomain. Upon the activation of MCK-Cre, recombination between the two *LoxP* sites results in the deletion of exon 5, thus generate the *Pitx2* conditional knockout allele. (B) Expression of MCK-Cre in the heart. *MCK-Cre* mice were mated to *R26R* mice to generate progenies with the genotype *MCK-Cre R26R* which express β-Galactosidase (β-Gal) in the MCK-Cre expression domain. Hearts of embryos and pups from the mating were collected and stained for β-Gal. Images of whole mount E17.5 *MCK-Cre R26R* embryonic heart and P2 heart are shown. In the E17.5 *MCK-Cre R26R* heart, β-Gal staining was detected in the ventricles and was barely detected in the atria (left panel). In P2 heart, β-Gal staining was detected in the whole heart (right panel). (C) Immunofluorescence staining for Pitx2 in the postnatal heart cells show expression of Pitx2 in the nuclei of the control (*Pitx2 Flox/Flox*) heart cells and is nearly lost in *Pitx2 CKO* heart. Nuclei of the heart cells were also labeled by TO-PRO-3 (TOP3). Images show the staining in the left atria of the 3-month-old control (*Pitx2 Flox/Flox*) and *Pitx2* CKO (*Pitx2 Flox/Flox MCK-Cre*) mice. (D) Real time RT-PCR assay using primers spanning exon 5 of *Pitx2* transcripts shows *Pitx2* expression level decreased over 80% in the left atrium of P1 *Pitx2* CKO heart. Values and error bars represent mean and standard deviation (n = 3).

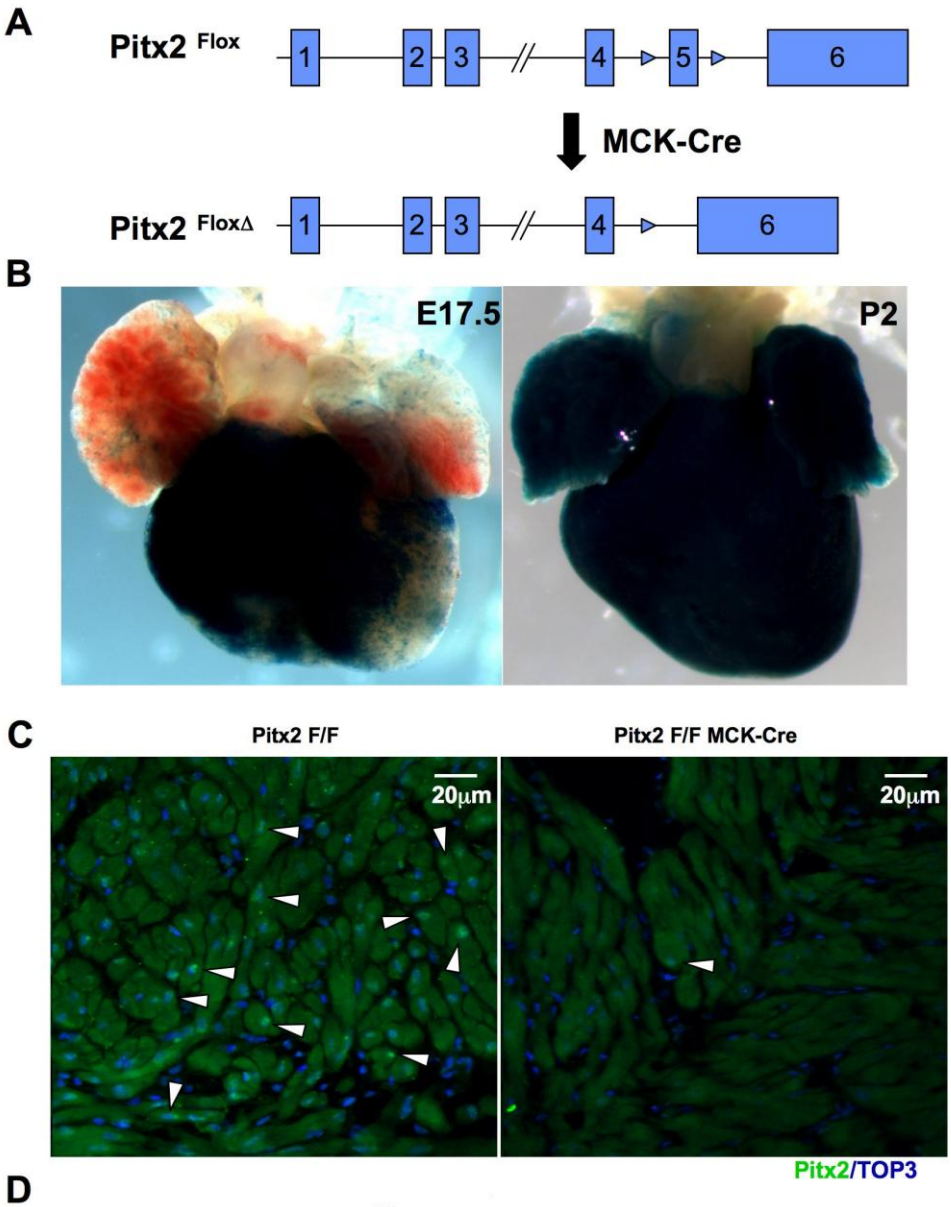

A
Pitx2 Flox
1
2
3
4
5
6
MCK-Cre
Pitx2 FloxΔ
1
2
3
4
6
B
E17.5
P2
C
Pitx2 F/F
Pitx2 F/F MCK-Cre
20μm
20μm
Pitx2/TOP3
D
**
Relative Pitx2 expression level
1.2
1
0.8
0.6
0.4
0.2
0
Pitx2 Flox/Flox
Pitx2 Flox/Flox MCK-Cre
** P ≤ 0.005

Figure S2. Microarray intensity value distribution and reproducibility. (A) Microarray was performed on *Pitx2* control and mutant hearts collected from 3-, 6- and 12-week-old mice. At each time point, three controls and three mutants were collected as biological replicates. Raw signal values were normalized using a logarithmic method. No significant outlier was observed across the samples. (B) Mean of logarithmic raw signal values of biological replicates was used for comparison between groups. No significant outlier was observed across groups. (C) Reproducibility of microarray raw signal across three biological replicates in each group. Each probe was plotted using raw signal value from one biological replicate as x-axis value, and that from another biological replicate as y-axis value. Total 45,101 points were plotted on each diagram. Linear correlation coefficient was measured, as r given in each diagram. The blue lines on each diagram indicate the line of best fit.

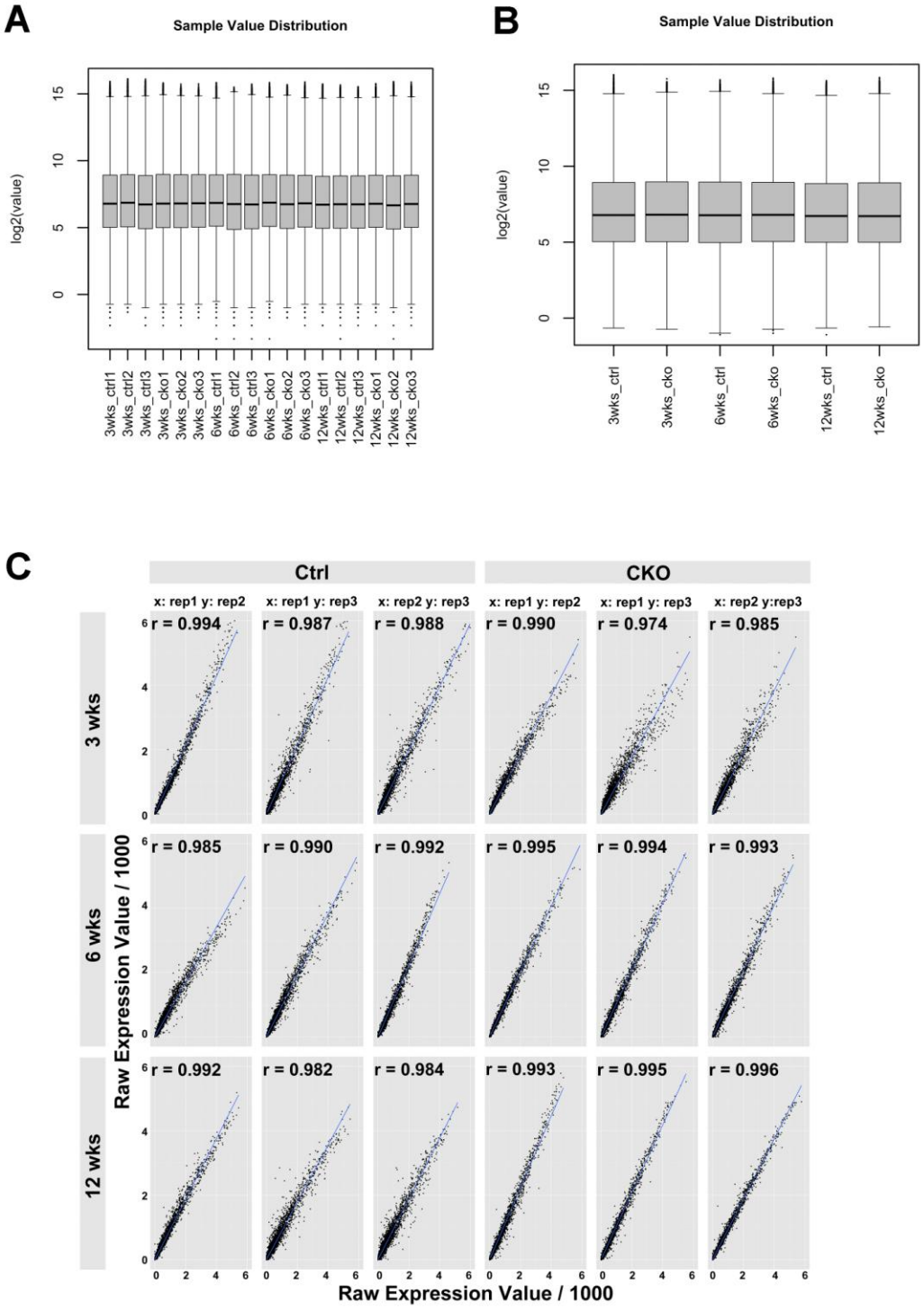

A
Sample Value Distribution
log2(value)
3wks_ctrl1
3wks_ctrl2
3wks_ctrl3
3wks_cko1
3wks_cko2
3wks_cko3
6wks_ctrl1
6wks_ctrl2
6wks_ctrl3
6wks_cko1
6wks_cko2
6wks_cko3
12wks_ctrl1
12wks_ctrl2
12wks_ctrl3
12wks_cko1
12wks_cko2
12wks_cko3
B
Sample Value Distribution
log2(value)
3wks_ctrl
3wks_cko
6wks_ctrl
6wks_cko
12wks_ctrl
12wks_cko
C
Ctrl
CKO
x: rep1 y: rep2
x: rep1 y: rep3
x: rep2 y: rep3
x: rep1 y: rep2
x: rep1 y: rep3
x: rep2 y:rep3
3 wks
6 wks
12 wks
r = 0.994
r = 0.987
r = 0.988
r = 0.990
r = 0.974
r = 0.985
r = 0.985
r = 0.990
r = 0.992
r = 0.995
r = 0.994
r = 0.993
r = 0.992
r = 0.982
r = 0.984
r = 0.993
r = 0.995
r = 0.996
Raw Expression Value / 1000
Raw Expression Value / 1000

Figure S3. Differential expressed genes in each stage. (A-C) *Pitx2* controls and mutants were compared to each other within each stage using linear models. Individual genes were plotted using logarithmic of fold change as x-axis index and -log10 of *p*-value as y-axis index. Total 45,101 points were plotted on each diagram. Differential expressed genes with a fold change of at least 1.5 and *p* value < 0.05 were highlighted in blue. The numbers of genes up-regulated or down-regulated in each stage were shown as *n*.

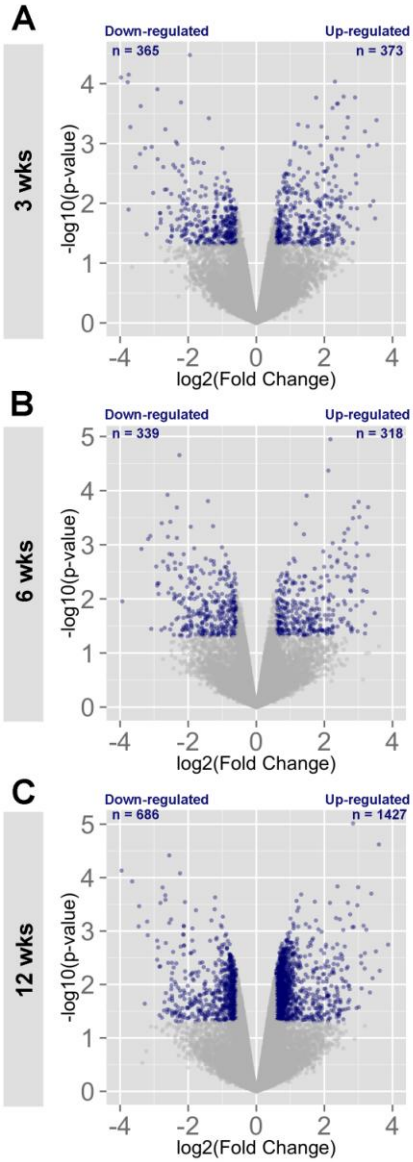


Figure S4. ChIP-Seq peaks overlay with up-regulated genes from microarray. (A) Annotation of Pitx2 ChIP-Seq peaks from 12-week-old heart. Total 11,275 peaks were detected. 18.8% of the Pitx2 ChIP-Seq peaks were located in promoter or transcription start sites (TSS) regions; 12.1% in exons; 35.3% in intron, 32.0% in intergenic regions and 0.1% in transcription terminal sites (TTS). (B) The density of Pitx2 motif (GCTGGGATTACA) within ChIP-Seq peaks was shown. The occurrence of Pitx2 motif was close to the center of the peaks. (C) Total 7,983 unique genes were found by annotating closest gene to the ChIP-Seq peaks. 1,427 genes were up-regulated in 12-week-old Pitx2 mutant hearts. Overlaid 653 genes consist of 8.1% genes having ChIP-Seq peaks and 45.7% up-regulated genes in 12-week-old Pitx2 mutants.

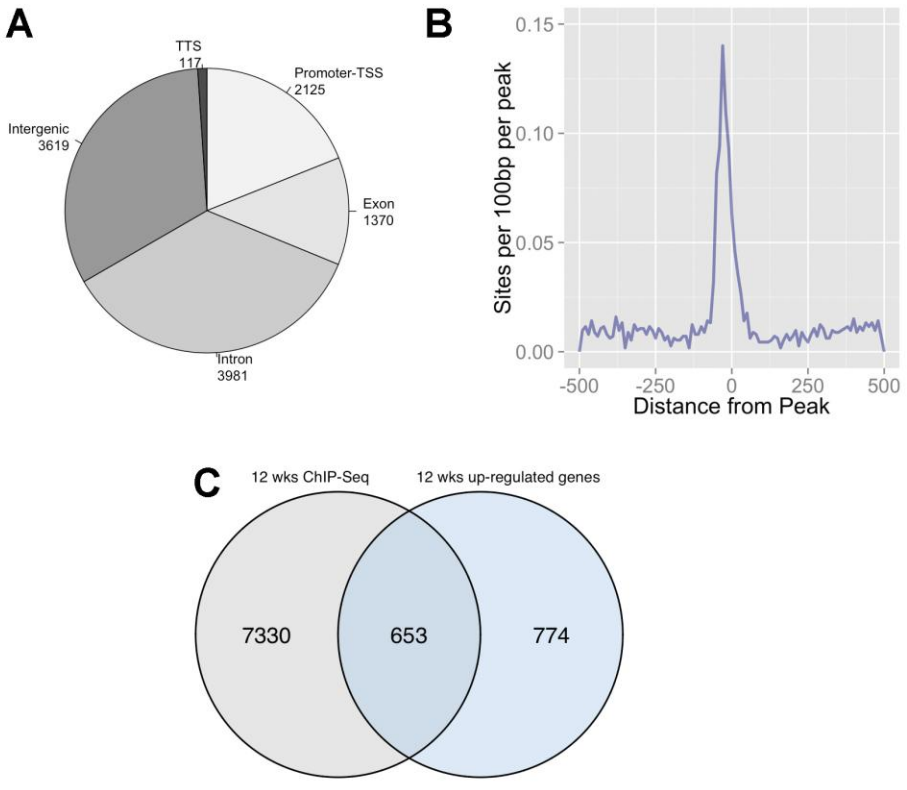
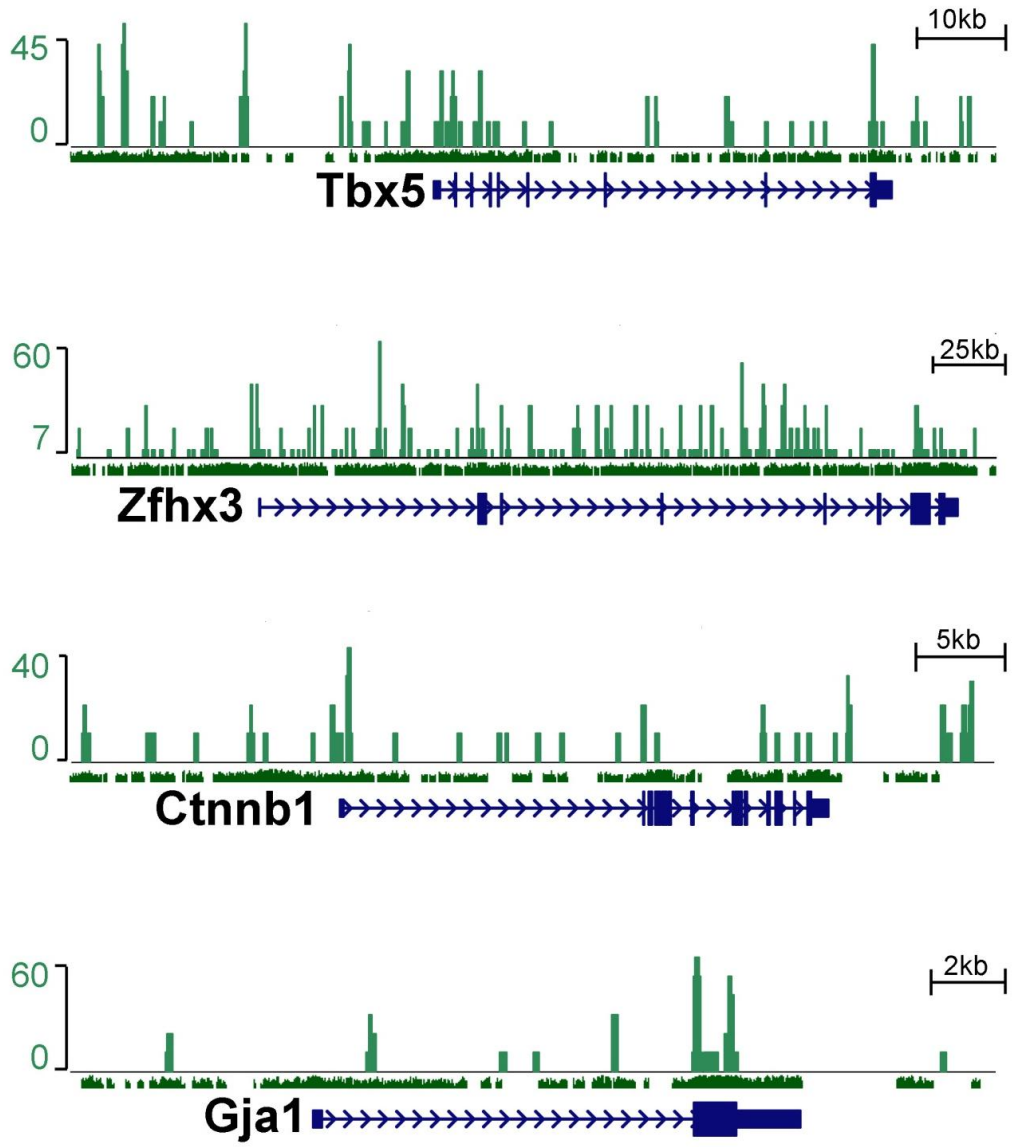


Figure S5. Genome browser tracks for additional potential targets of Pitx2 in adult heart identified by ChIP-Seq. Four potential targets of Pitx2 identified by ChIP-Seq by our studies are shown here: Tbx5, Zfhx3, Ctnnb1 and Gja1. Peaks from ChIP-Seq and conservation with human genome are shown. Normalized ChIP-Seq tag numbers are shown on the Y-axis.



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