

## Supplemental Data

### Common genetic variant in *SCN10A* modulates cardiac *SCN5A* expression

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**Supplementary Figure 1**

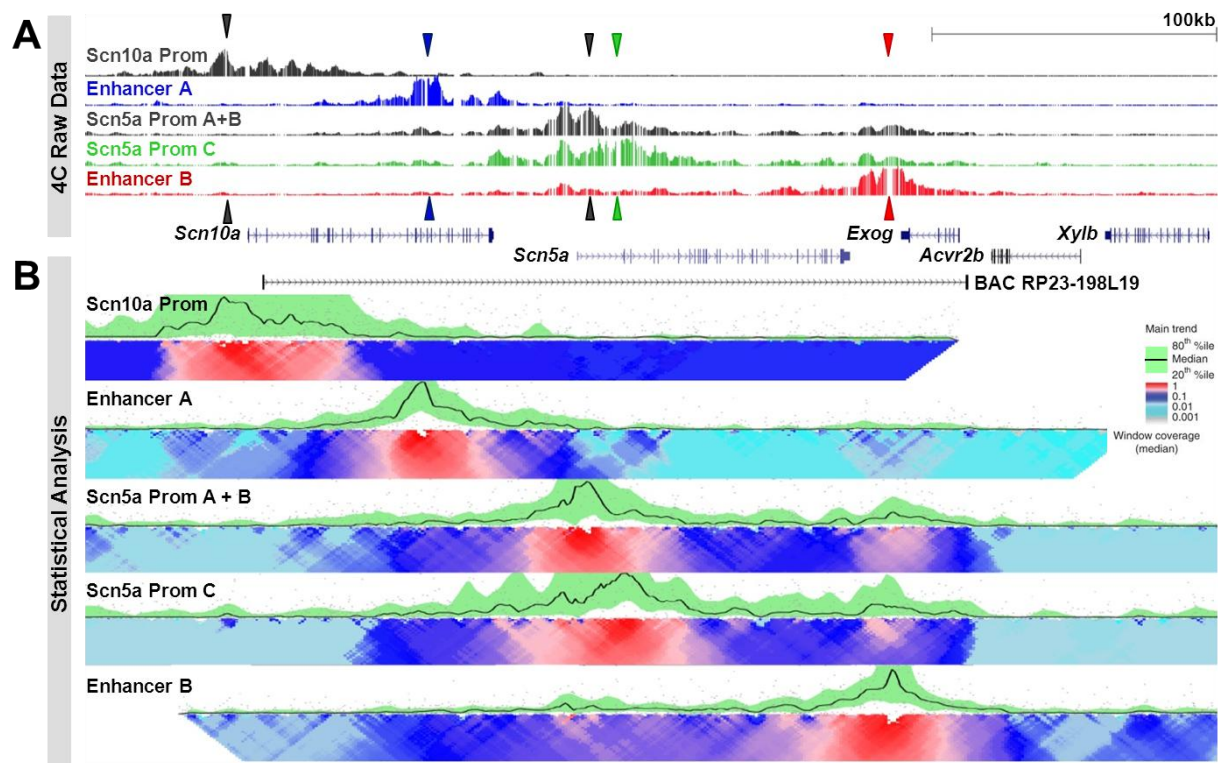
**Supplementary Figure 2**

**Supplementary Figure 3**

**Supplementary Figure 4**

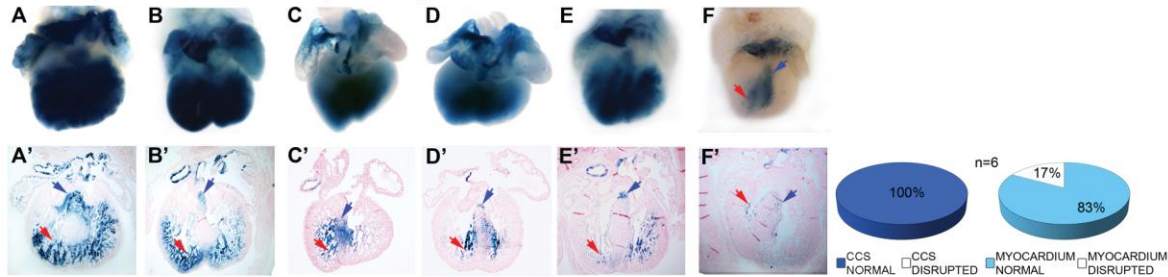
**Supplementary Figure 5**

**Supplementary Table 1**

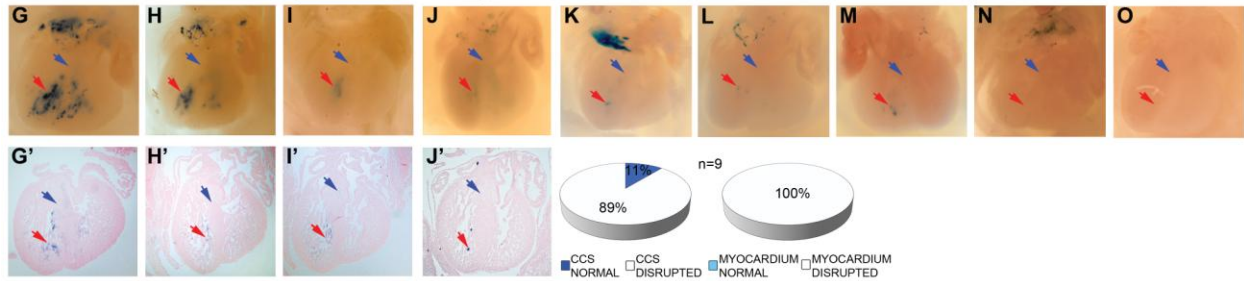


**Supplementary Figure 1: Contact profiles of enhancers and promoters of the *Scn5a-Scn10a* locus.** (A) UCSC genome browser traces are shown for viewpoints of the *Scn10a* promoter (grey, first lane), enhancer A (blue, second lane), *Scn5a* promoter A+B (grey, third lane), *Scn5a* promoter C (green) and enhancer B (red). (B) In this figure, normalized contact intensities (gray dots) and their running median trends (black line) are depicted for all viewpoints in and around *Scn10a* and *Scn5a*. Medians are computed for 4 kb windows and the green band displays the 20–80% percentiles for these windows. Below the profile, statistical enrichment across differently scaled window sizes (from 2 kb (top row) to 50 kb (bottom)) is depicted of the observed number of sequenced ligation products over the expected total coverage of captured products, with the latter being estimated based on a probabilistic background model (26). Local changes in color codes indicate regions statistically enriched for captured sequences, which correspond to the promoter-enhancer contacts described. Note that the green 80% percentile band and color codes in the Enhancer A viewpoint tract indicates contacts between Enhancer A, B and the *Scn5a* promoter regions. From the *Scn5a* Prom A+B and Prom C viewpoints, contacts with enhancer A and B and weakly with the *Scn10a* promoter region can be observed. From Enhancer B contacts with the *Scn5a* promoter region and, weakly, with Enhancer A can be seen. The *Scn10a* promoter viewpoint (top tract) does not reveal contacts between the enhancer regions and promoter of *Scn5a*.

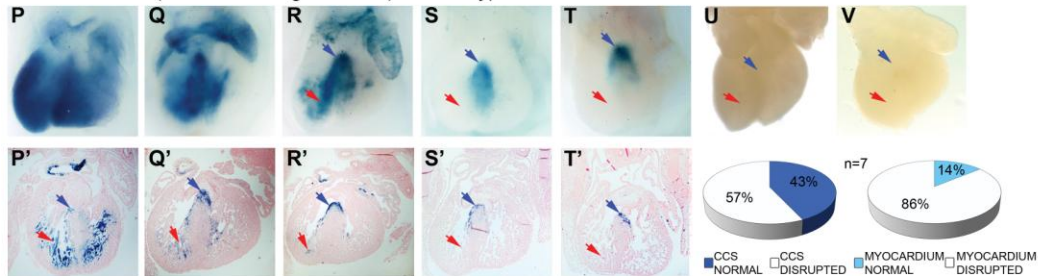
WT BAC (transient transgenic lines): 6 Genotype Positive



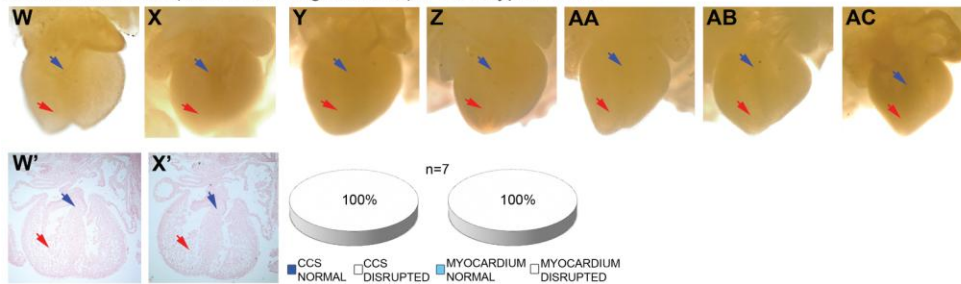
EnhA DEL BAC (transient transgenic lines): 9 Genotype Positive



EnhB DEL BAC (transient transgenic lines): 7 Genotype Positive

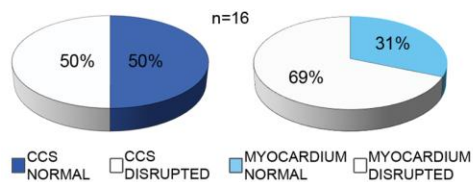
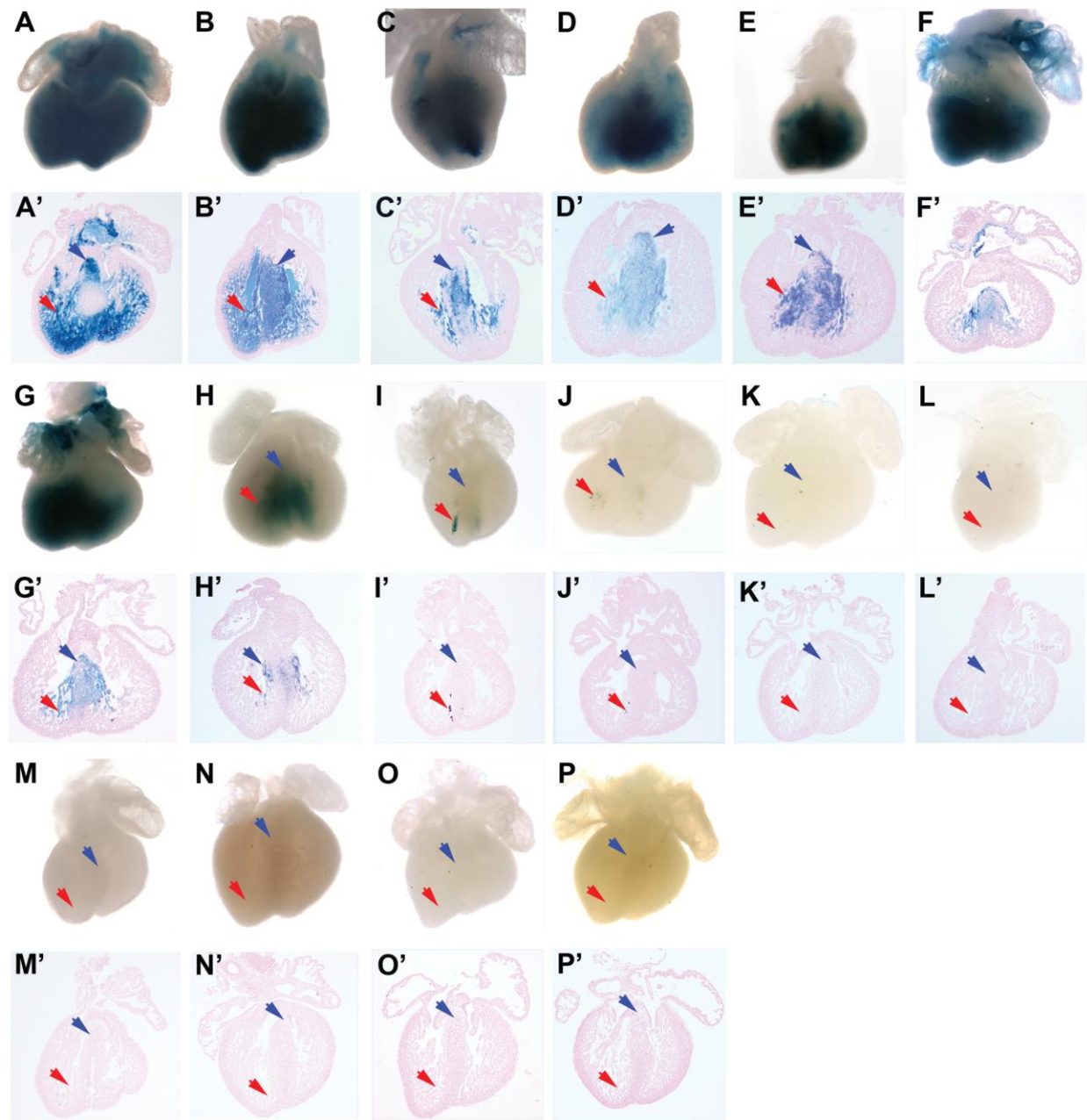


EnhA/B DEL BAC (transient transgenic lines): 7 Genotype Positive

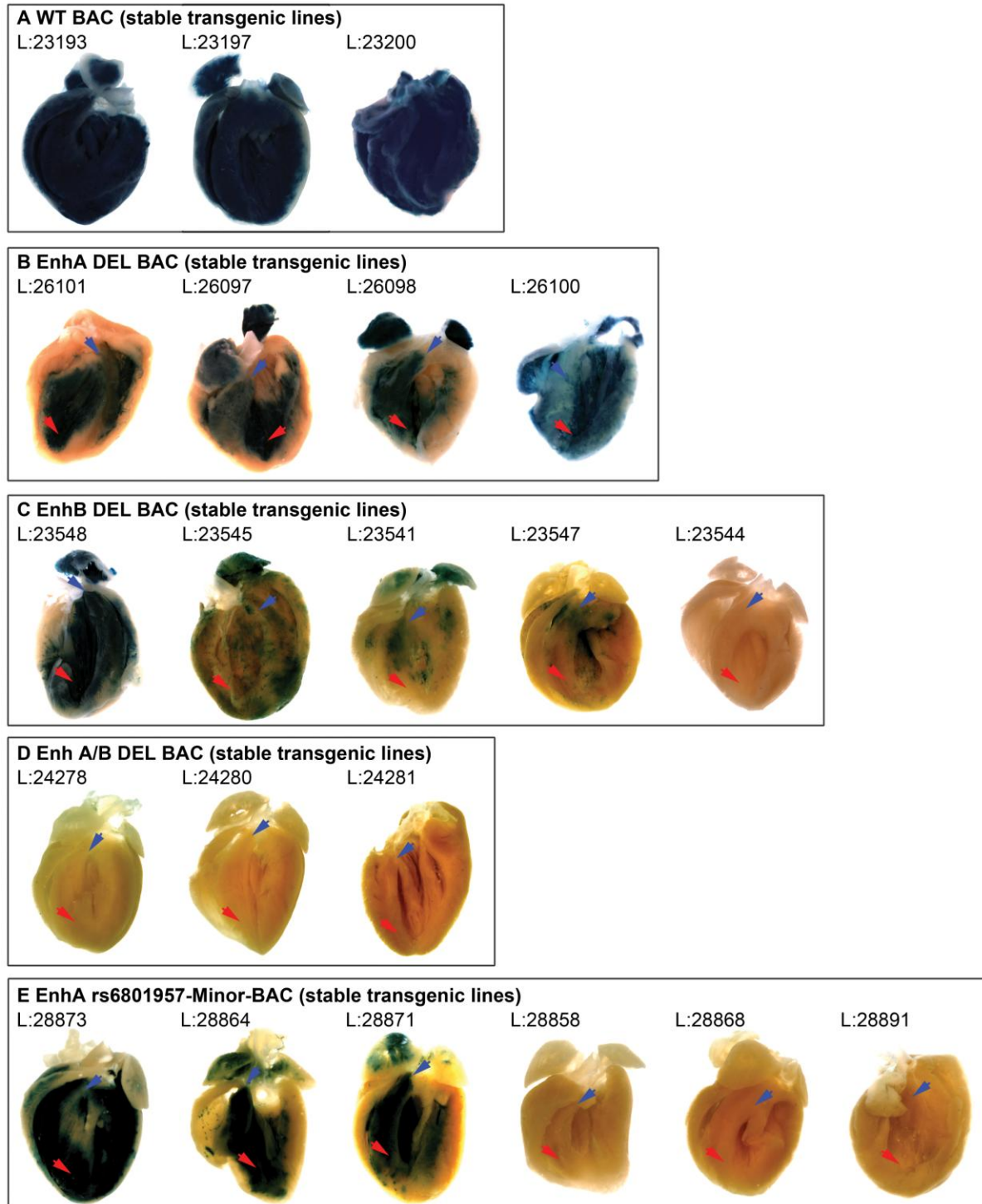


**Supplementary Figure 2: Evaluation of all BAC transgenic embryos at E13.5.** All wild-type (n=6), enhancer A deleted (n=9), enhancer B deleted (n=7), and enhancer A and B deleted (n=7) BAC transgenic embryos are shown. Embryos are arranged in descending order of staining intensity for each construct. Sections embryos are shown at 10x original magnification.

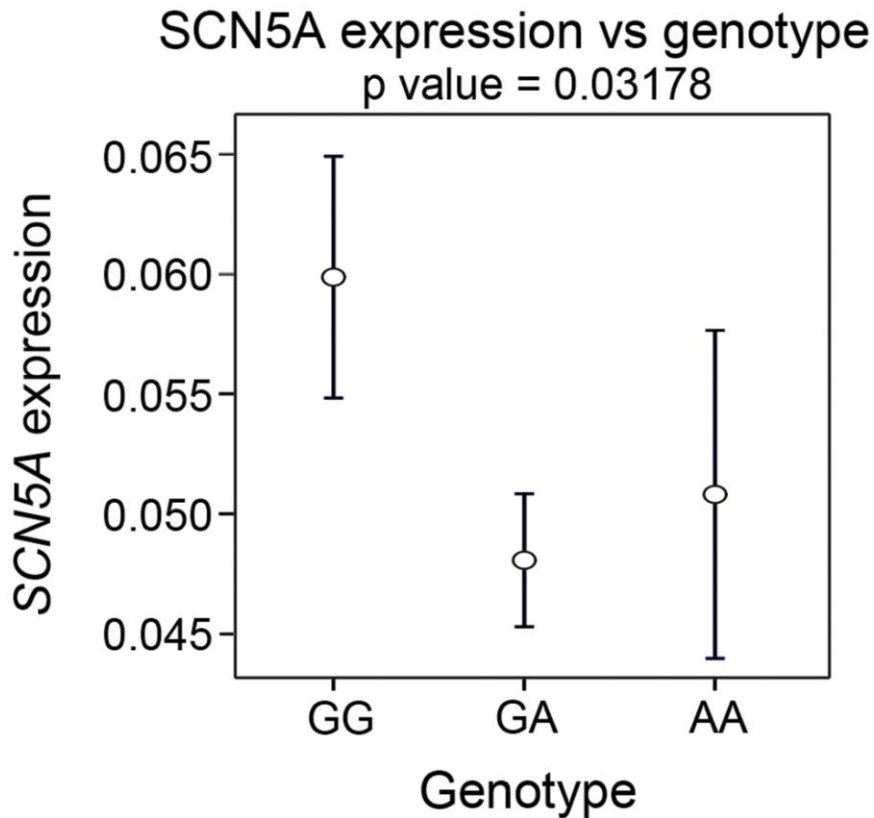
EnhA rs6801957-Minor-BAC (transient transgenic lines): 16 Genotype Positive



**Supplementary Figure 3: Evaluation of enhancer A SNP rs6801957 BAC transgenic embryos.** All enhancer A SNP rs6801957 BAC transgenic embryos (n=16) with the minor allele are shown at E13.5. Embryos are arranged in descending order of staining intensity for each construct. Sections embryos are shown at 10x original magnification.



**Supplementary Figure 4: Evaluation of all BAC stable transgenic lines.** Adult hearts from 12-week-old wild-type (n=3 independent transgenic lines), enhancer A deleted (n=4 independent transgenic lines), enhancer B deleted (n=5 independent transgenic lines), enhancer A and B deleted (n=3 independent transgenic lines), and enhancer A SNP rs6801957 (n=6 independent transgenic lines) BAC stable transgenic lines are shown. Lines are arranged in descending order of staining intensity for each construct. At least 3 adult hearts of each stable line were evaluated.



**Supplementary Figure 5: Correlation of *SCN5A* mRNA expression with SNP rs6801957 genotype in a set consisting of non-disease human donor hearts.** *SCN5A* expression was assessed by qRT-PCR in 87 human cardiac tissue samples. Samples homozygous at rs6801957 for the G allele expressed significantly more *SCN5A* RNA ( $0.060 \pm 0.029$  normalized expression,  $n=33$ ) than GA tissue samples ( $0.048 \pm 0.017$  normalized expression,  $n=37$ ) or AA tissue samples ( $0.050 \pm 0.028$  normalized expression  $n=17$ ) (additive genetic model,  $p=0.11$ ; dominant genetic model,  $p=0.03$ ). Expression was normalized for mRNA levels of *TNNI3* and *HPRT1*. Middle points represent median value, boxes represent 25% - 75% percentiles range, and the whiskers represent 5% - 95% percentiles range.

## Supplementary Table 1: Primers used for 4C-seq studies

Scn10a promoter F	AATGATACGGCGACCACCGAACACTCTTTCCCTACACGACGCTCTTCCGATCTGATAGGGTCACCTTCACAGATC
Scn10a promoter R	CAAGCAGAAGACGGCATAACGATGAGTGCGTTATCTTAGCTT
EnhancerA-1 F	AATGATACGGCGACCACCGAACACTCTTTCCCTACACGACGCTCTTCCGATCTGAGAGACCCACACGTTAGGATC
EnhancerA-1 R	CAAGCAGAAGACGGCATAACGACGGTGAGGACAACATAGAC
EnhancerA-2 F	AATGATACGGCGACCACCGAACACTCTTTCCCTACACGACGCTCTTCCGATCTGACAGAGTTAGTGAACCTGATC
EnhancerA-2 R	CAAGCAGAAGACGGCATAACGAGATACCAGCCCCACCAGATA
Scn5a promoter A-B F	AATGATACGGCGACCACCGAACACTCTTTCCCTACACGACGCTCTTCCGATCTGTGCCAAGGGCACACTGATC
Scn5a promoter A-B R	CAAGCAGAAGACGGCATAACGACCTCTAGAGAGCCTAGTCCC
Scn5a promoter C F	AATGATACGGCGACCACCGAACACTCTTTCCCTACACGACGCTCTTCCGATCTGAAAAATAGTGTCTCTGGATC
Scn5a promoter C R	CAAGCAGAAGACGGCATAACGAGGAAAGGGAATCTCTGTCTT
EnhancerB F	AATGATACGGCGACCACCGAACACTCTTTCCCTACACGACGCTCTTCCGATCTGAGACAGGCACATGCTGGGATC
EnhancerB R	CAAGCAGAAGACGGCATAACGAAAGGAACTACACAGTCCCAA