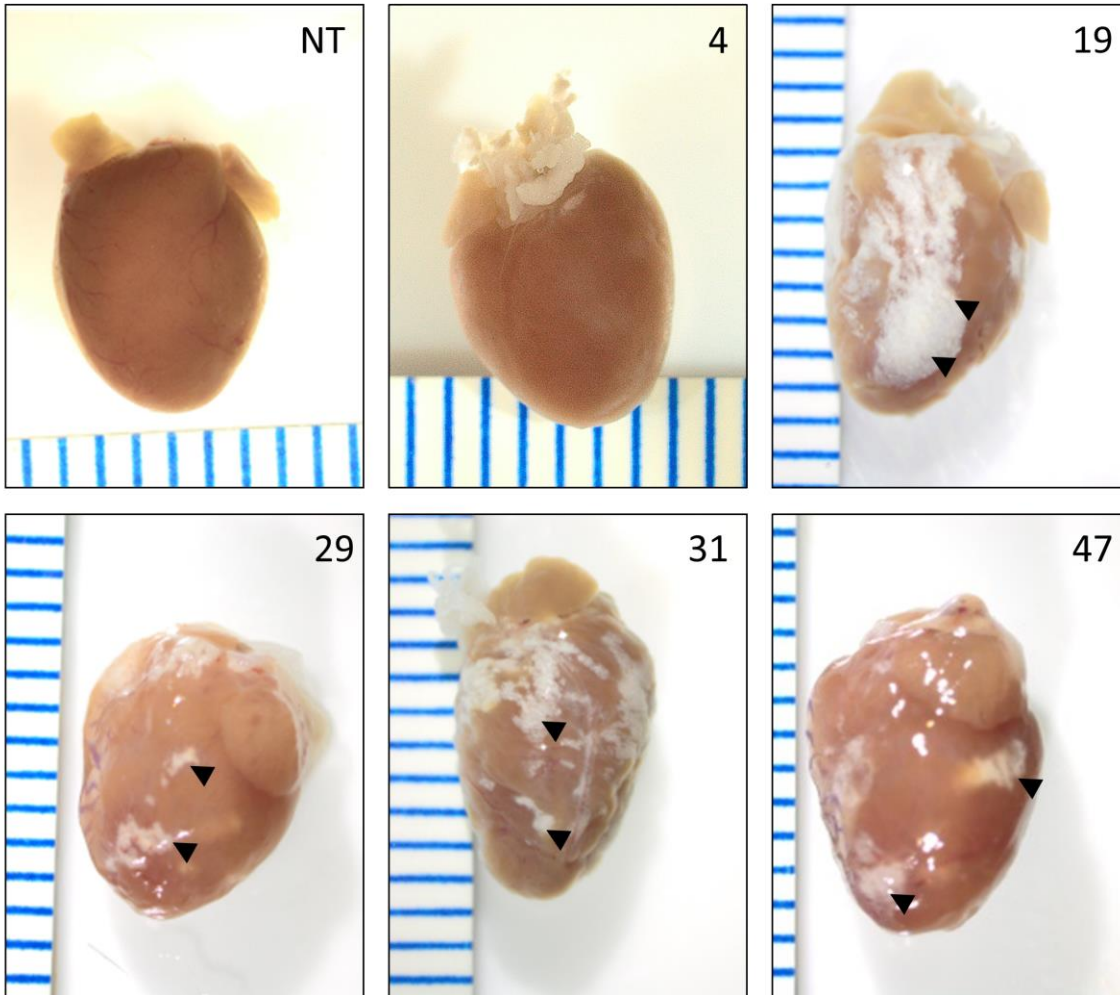


## S1 Dataset

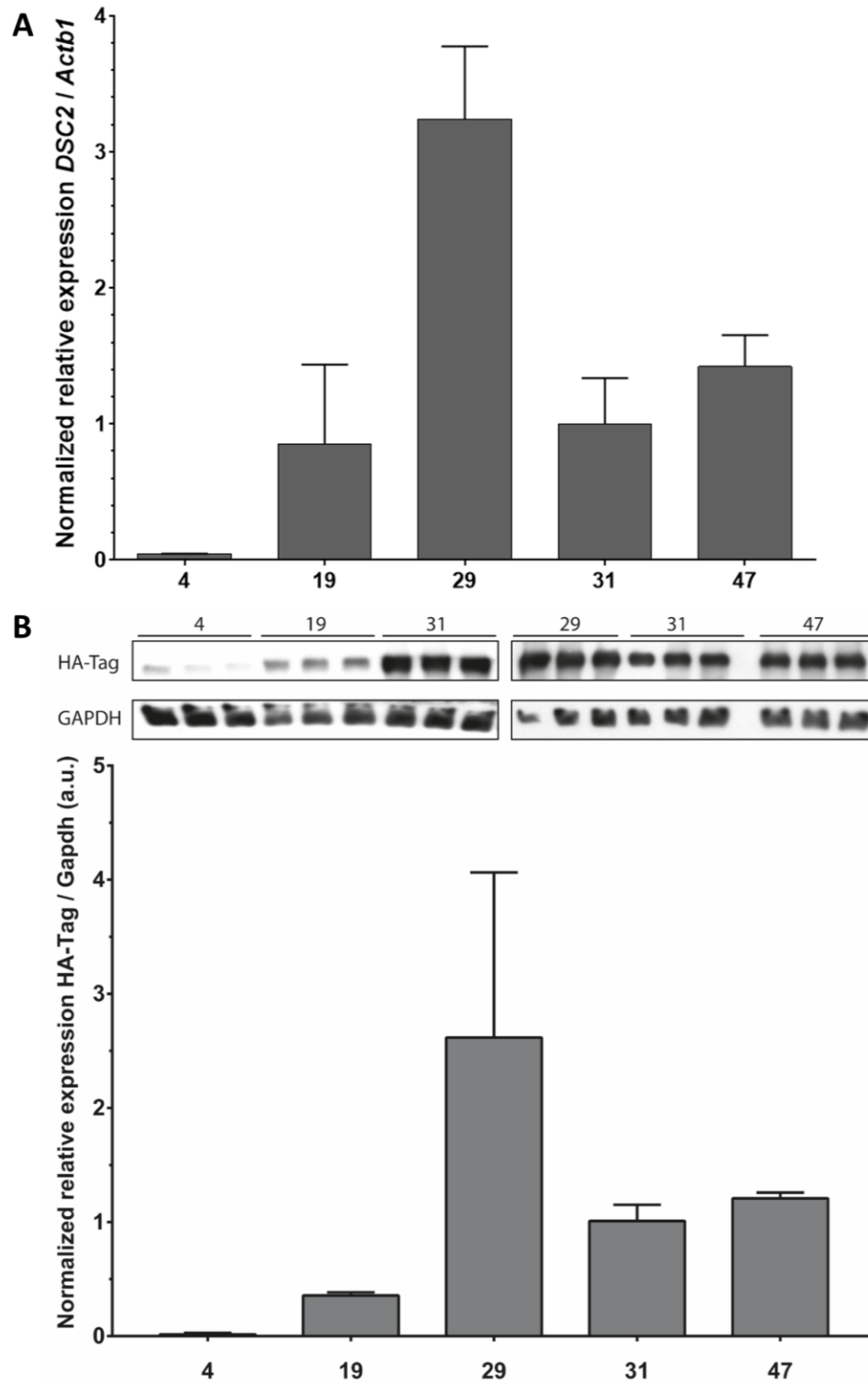
### Figures A-N



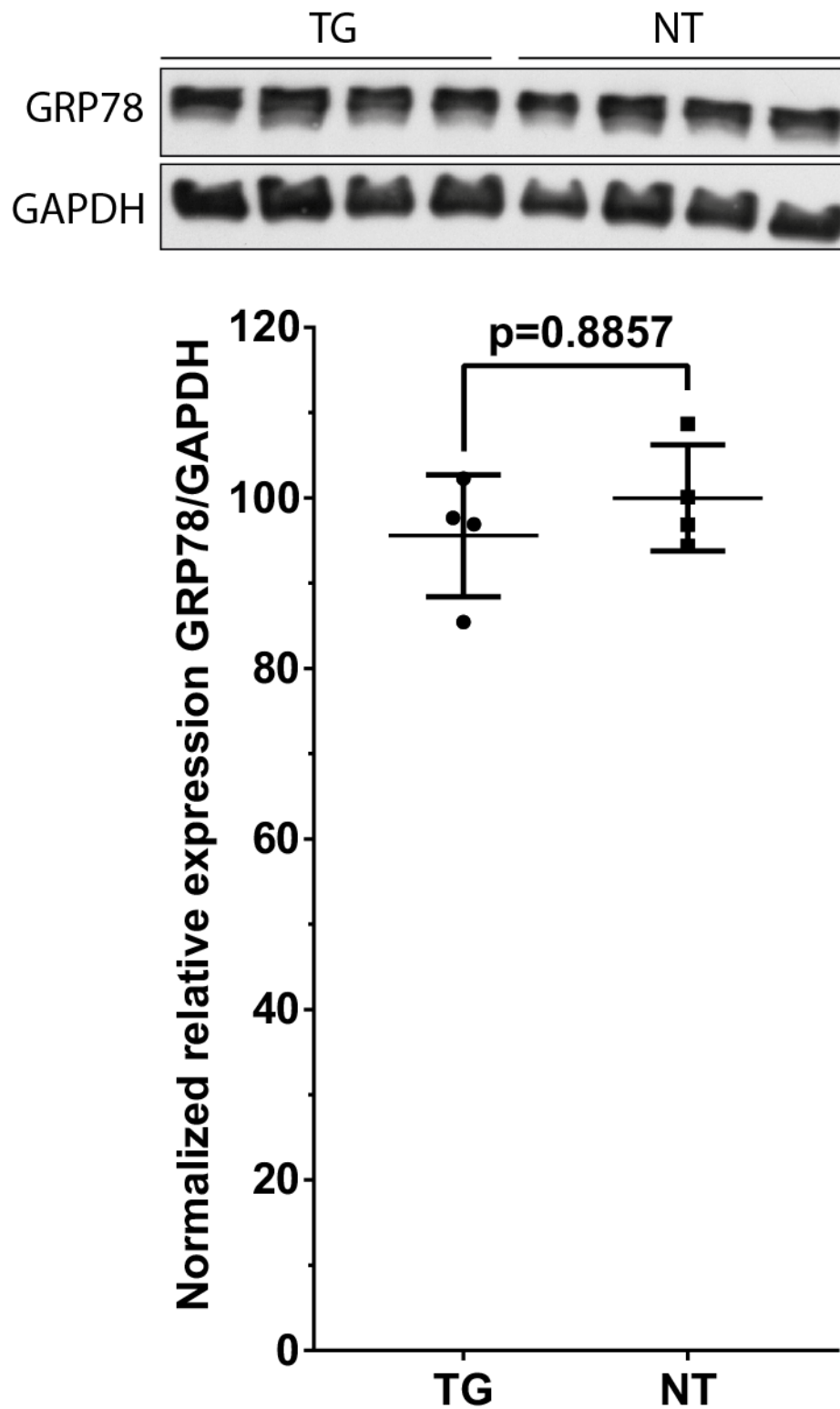
**Figure A:** DNA agarose gel of genotyping PCRs of transgenic founder mice.



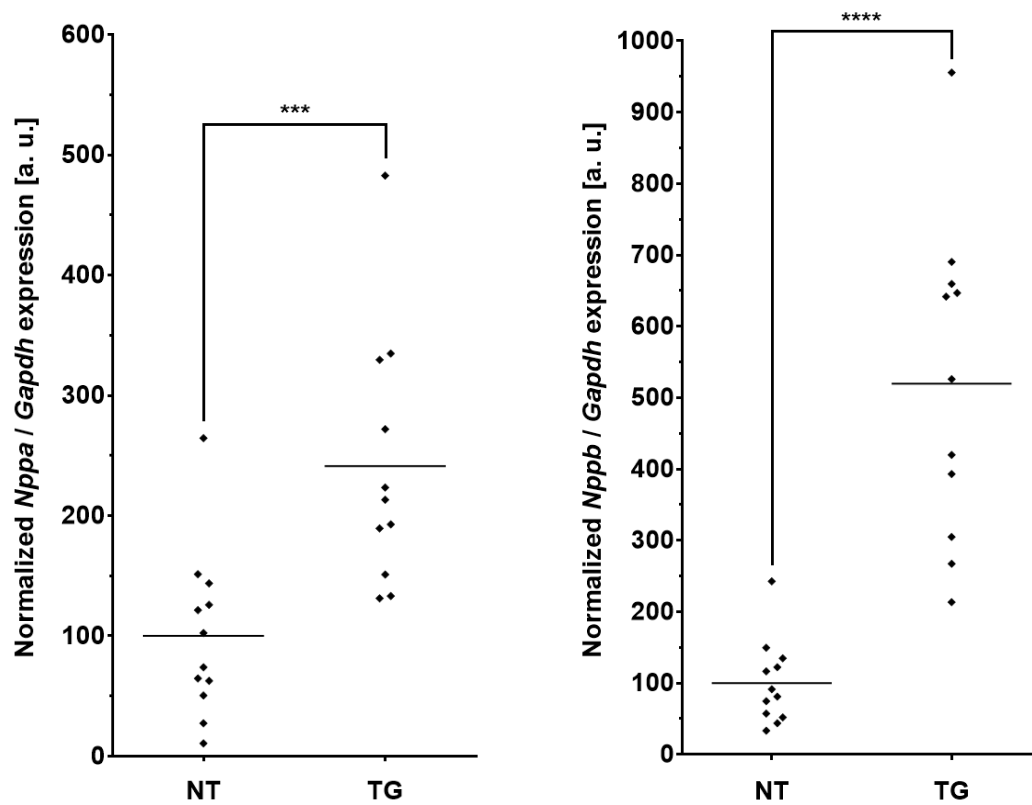
**Figure B:** Morphological analysis of dissected hearts (9 weeks) from a non-transgenic mouse and from different founder lines (4; 19; 29; 31; 47). Of note, fibrous areas (black arrows) were present in four of the founder lines (19; 29; 31; 47). Scale bars represent 1 mm.



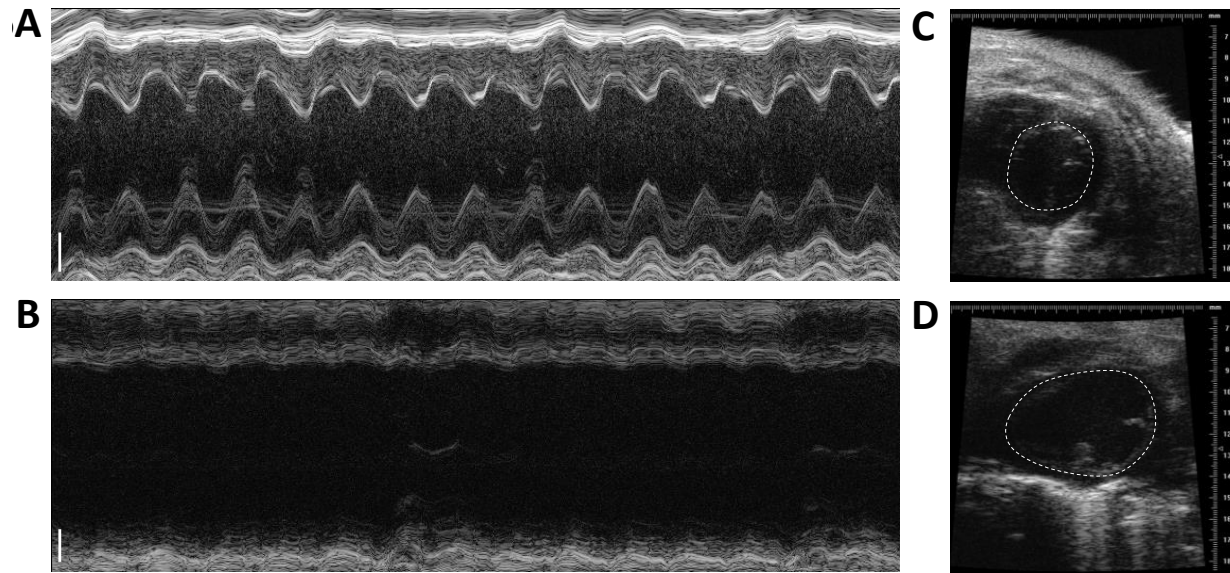
**Figure C:** DSC2 expression analysis using qRT-PCR (**A**) and Western blot analysis using HA-tag antibodies (**B**). Data represent mean  $\pm$  SD.



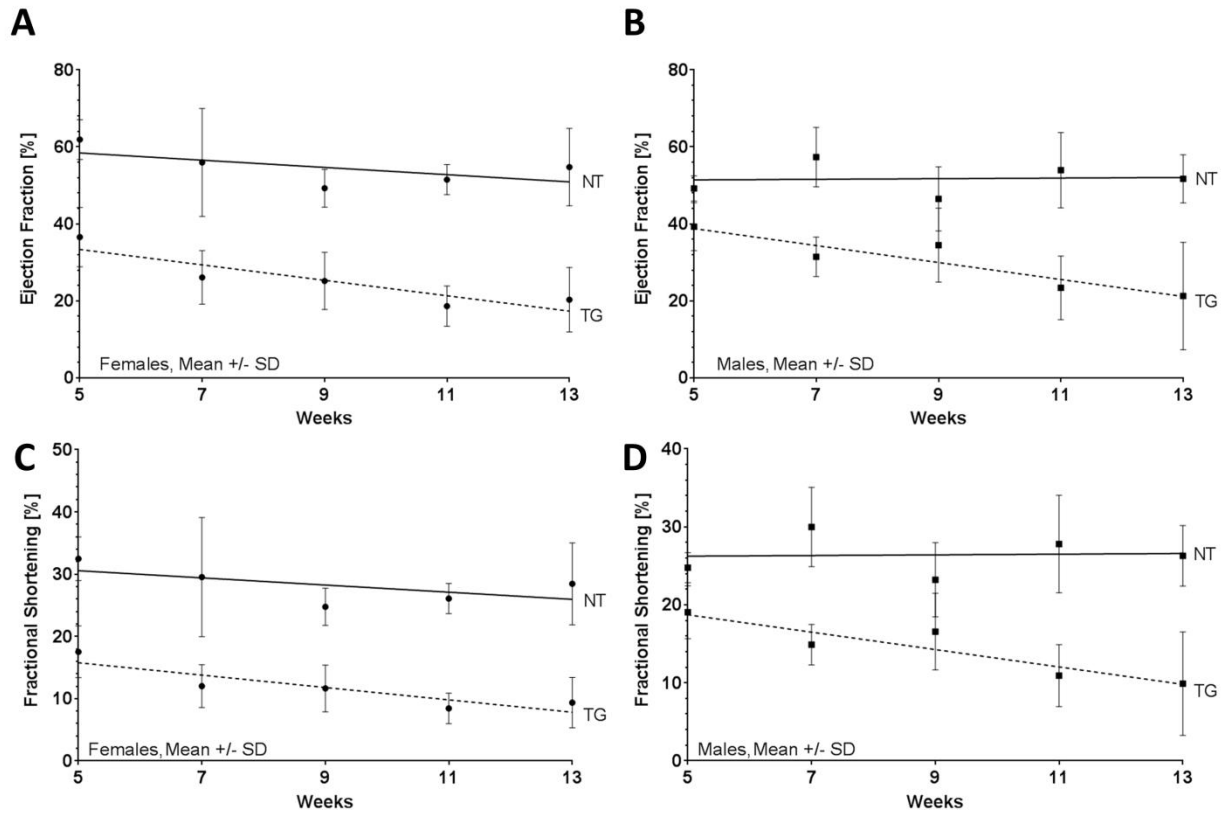
**Figure D:** Myocardial GRP78 protein expression in transgenic (TG) and non transgenic mice. Data represent mean  $\pm$  SD.



**Figure E:** *Nppa* (ANP) and *Nppb* (BNP) mRNA myocardial expression in transgenic and non-transgenic mice (13 weeks). Data represent mean  $\pm$  SD.



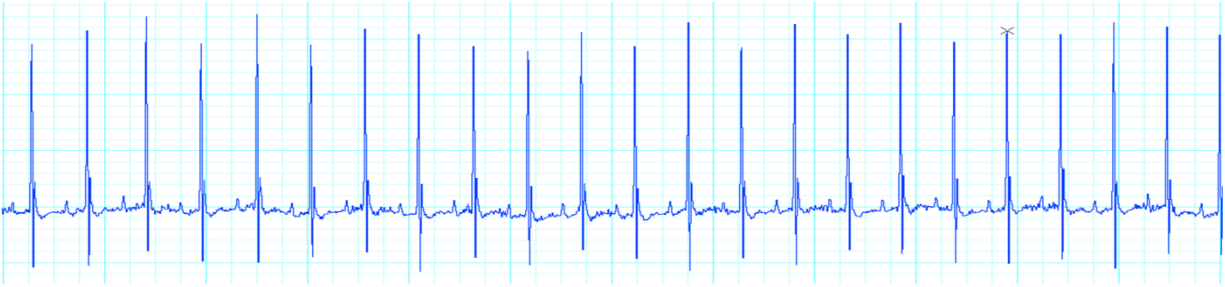
**Figure F:** Representative images of M-mode (**A-B**) and B-mode (**C-D**) echocardiography heart analysis of non-transgenic (**A, C**) and DSC2 transgenic animals (**B, D**).



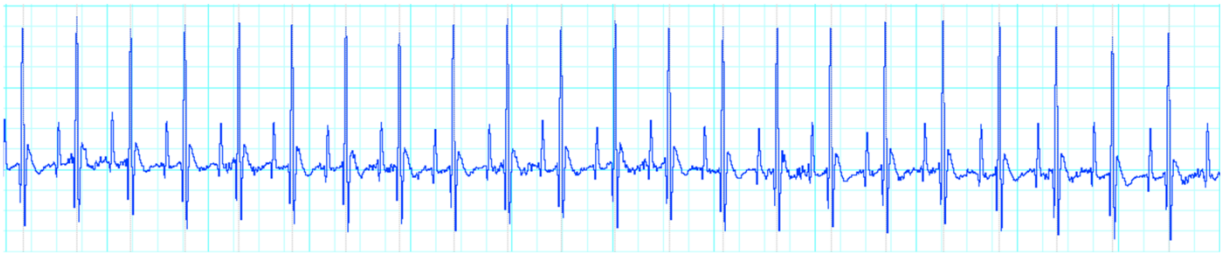
**Figure G:** Time dependent analysis of **(A-B)** ejection fraction and **(C-D)** fractional shortening of females **(A-C)** and males **(B-D)** between 5-13 weeks. The solid lines represent data of non-transgenic animals and the dotted line represents data of the transgenic animals. Data are presented as mean  $\pm$  SD. One DSC2 transgenic male died at the age of 12 weeks.

**F**

**A**

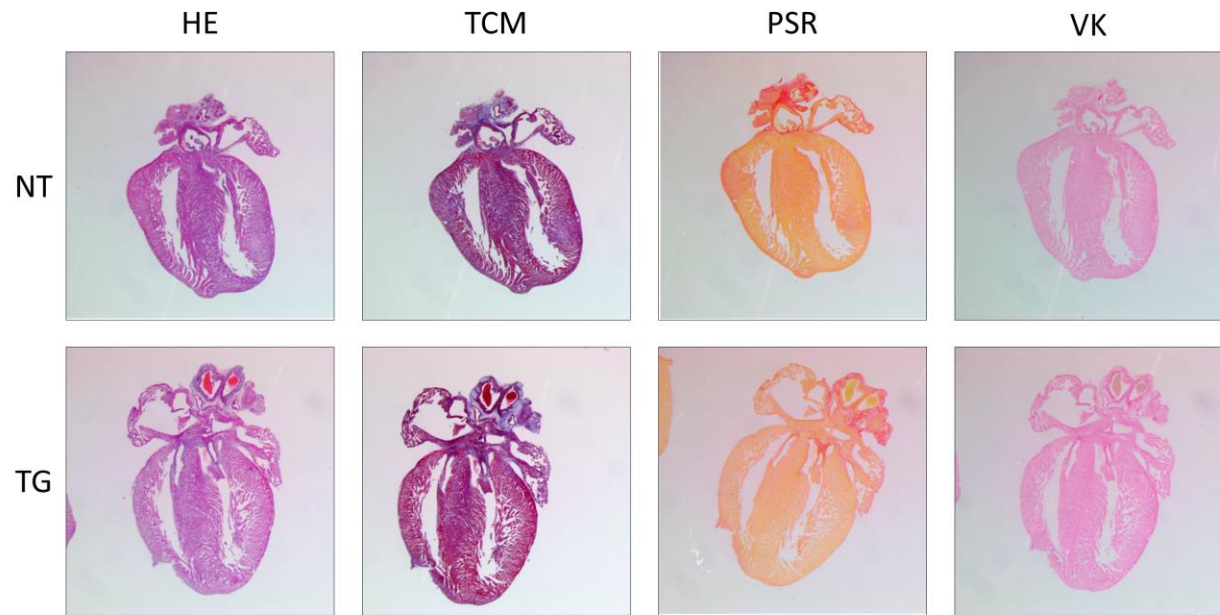


**B**

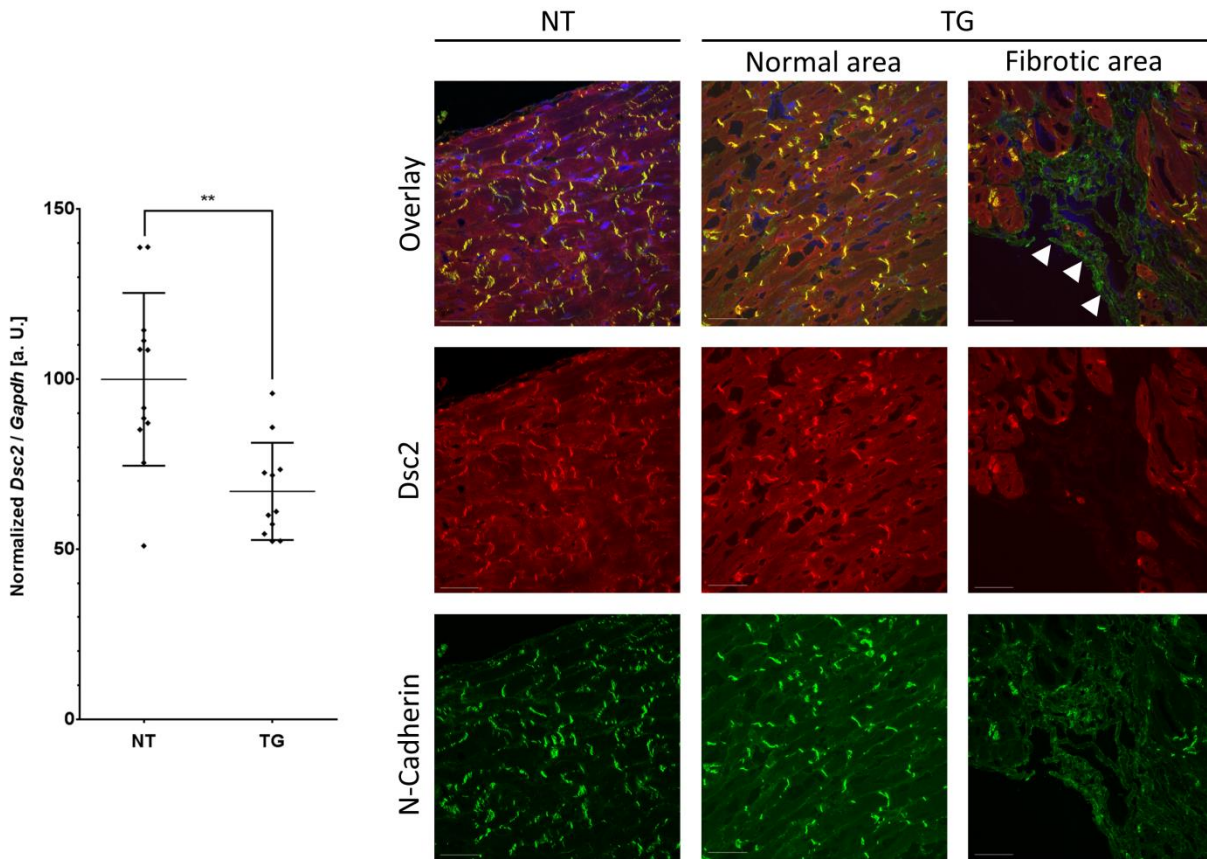


**Figure H:** Representative electrophysiological analysis of non-transgenic control mouse **(A)** and a transgenic DSC2 mouse **(B)** by using telemetry.

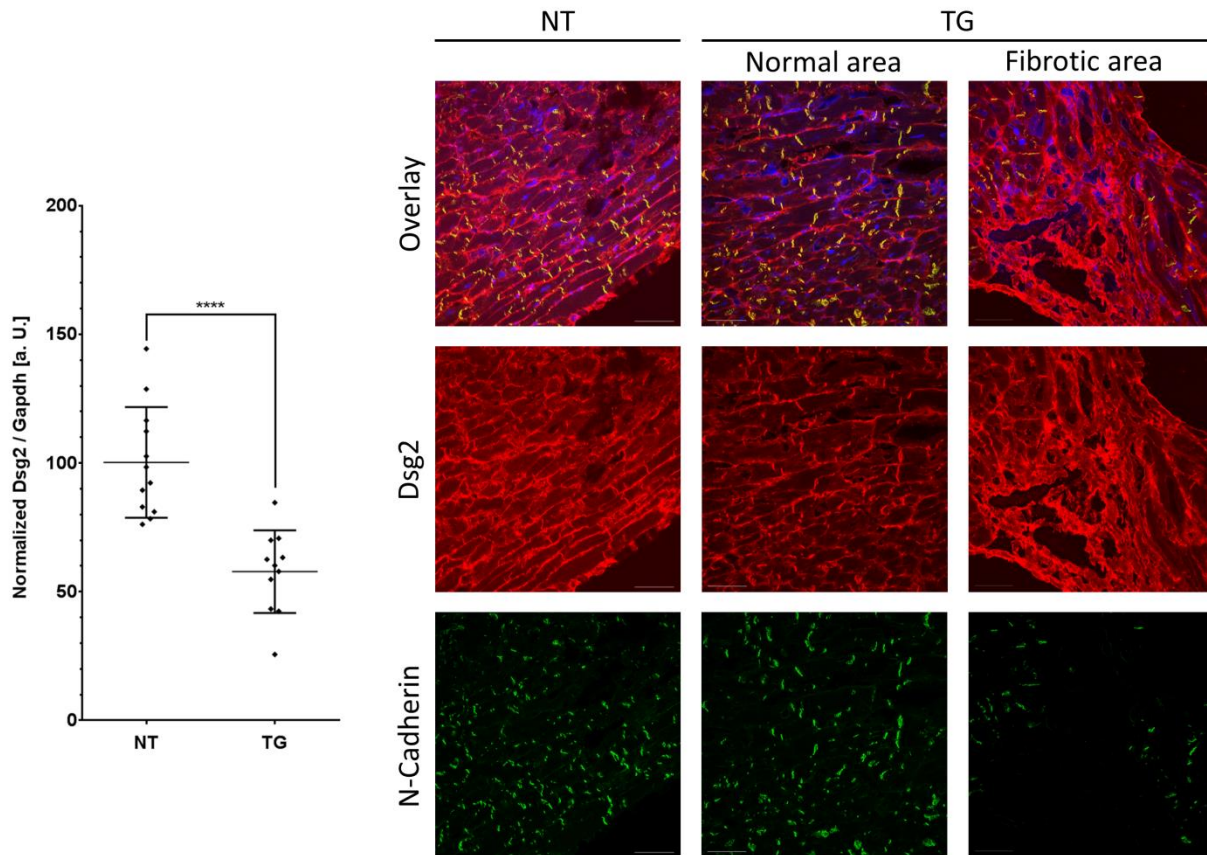




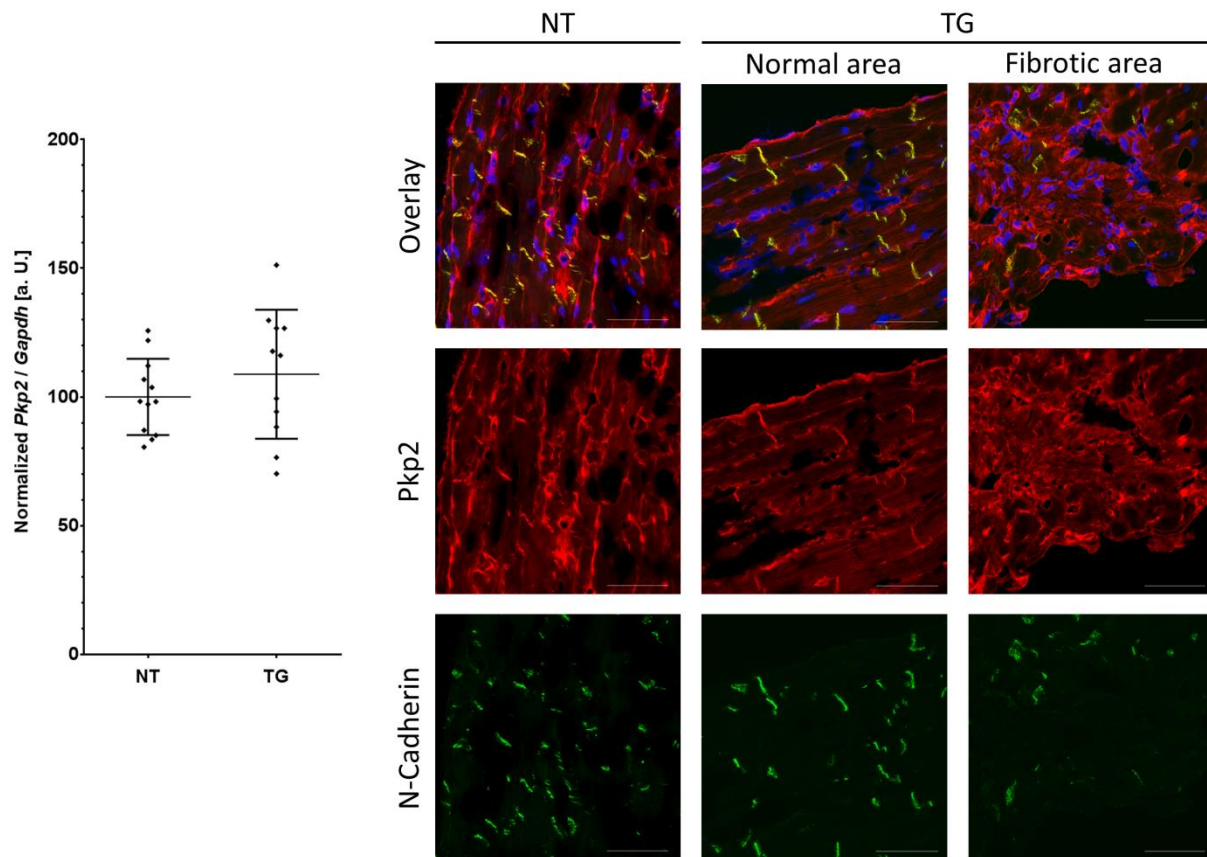
**Figure I:** Histology non-transgenic and transgenic new born animals. HE = Haematoxilin and Eosin staining. TCM = Trichrome staining after Masson. PCR = Picro Sirius Red staining. VK = Von-Kossa staining.



**Figure J:** Structural and expression analysis of Dsc2 using quantitative real-time polymerase chain reaction and immunohistochemistry. Normalized mRNA expression of endogenous Dsc2 (13 w; 12 NT; 11 TG). Statistical analysis was performed by non-parametric Kruskal-Wallis test (\*\* $p < 0.01$ ). Immunohistochemistry analysis of Dsc2 (red) and N-cadherin (green). Of note, the cells within the fibrotic area are positive for N-Cadherin but negative for Dsc2 (white arrows). The nuclei were stained with 4',6-Diamidin-2-phenylindol (DAPI, blue). Scale bars represent 50  $\mu\text{m}$ .

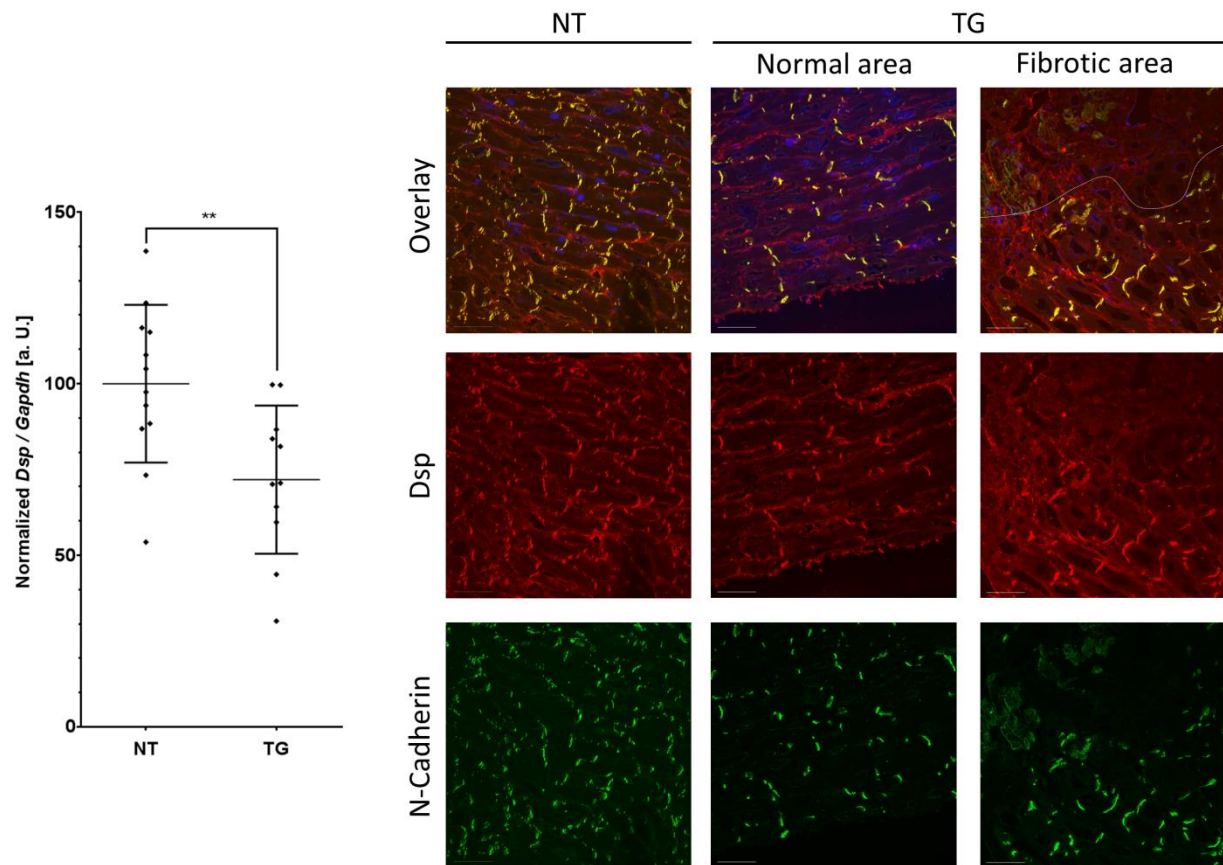


**Figure K:** Structural and expression analysis of Dsg2 using quantitative real-time polymerase chain reaction and immunohistochemistry. Normalized mRNA expression of endogenous Dsg2 (13 w; 12 NT; 11 TG). Statistical analysis was performed by non-parametric Kruskal-Wallis test (\*\*\*\* $p < 0.0001$ ). Immunohistochemistry analysis of Dsg2 (red) and N-cadherin (green). The nuclei were stained with 4',6-Diamidin-2-phenylindol (DAPI, blue). Scale bars represent 50  $\mu$ m.

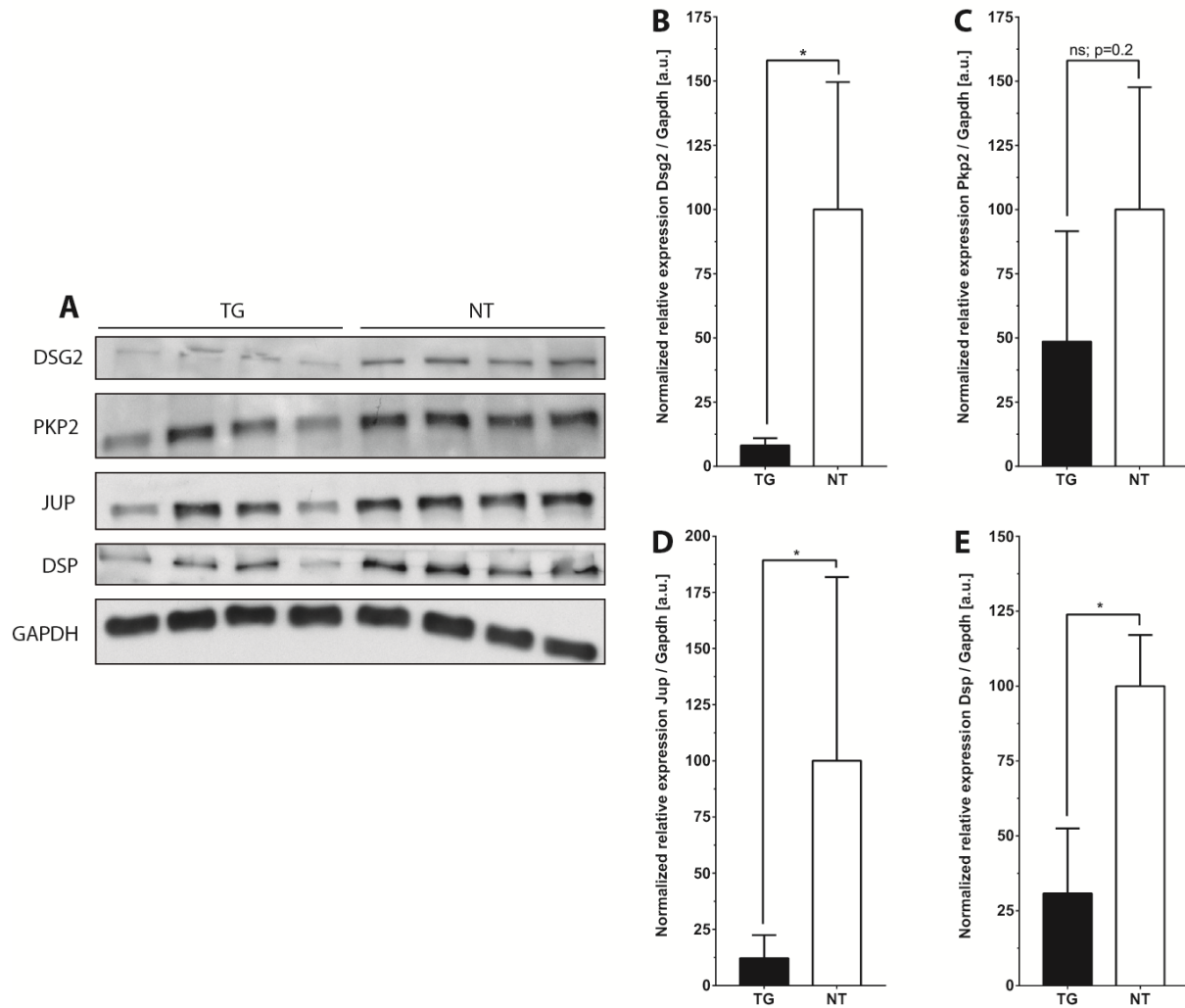


**Figure L:** Structural and expression analysis of Pkp2 using quantitative real-time polymerase chain reaction and immunohistochemistry. Normalized mRNA expression of endogenous Pkp2 (13 w; 12 NT; 11 TG). Statistical analysis was performed by non-parametric Kruskal-Wallis test (no significant differences). Immunohistochemistry analysis of Pkp2 (red) and N-cadherin (green). The nuclei were stained with 4',6-Diamidin-2-phenylindol (DAPI, blue). Scale bars represent 50  $\mu\text{m}$ .





**Figure M:** Structural and expression analysis of Dsp using quantitative real-time polymerase chain reaction and immunohistochemistry. Normalized mRNA expression of endogenous Dsp (13 w; 12 NT; 11 TG). Statistical analysis was performed by non-parametric Kruskal-Wallis test (\*\* $p < 0.01$ ). Immunohistochemistry analysis of Dsp (red) and N-cadherin (green). The dashed line indicates the border between the fibrotic and normal areas. The nuclei were stained with 4',6-Diamidin-2-phenylindol (DAPI, blue). Scale bars represent 50  $\mu\text{m}$ .



**Figure N:** Myocardial expression analysis of endogenous desmosomal proteins in DSC2-transgenic (TG) and non-transgenic animals using Western blot analysis (**A**). Normalized relative protein expression of endogenous Dsg2 (**B**), Pkp2 (**C**), Jup (**D**) and Dsp (**E**) in DSC2-transgenic and non-transgenic animals (N=4). Statistical analysis was performed by non-parametric Kruskal-Wallis test; \*p<0.05.