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From Gene to Function: Exploring the Effects of *ACTA2* Gene Variants on Cardiac Development

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The journal *Nature* published a paper titled "Cardiac Manifestations of Human ACTA2 Variants Recapitated in a Zebrafish Model" on February 5, 2024, authored by Wulan Apridita Sebastian, Masanori Inoue, Nobuyuki Shimizu and others, from the Department of Cell Biology, Oita University, Faculty of Medicine, Oita, Japan. This study explored the cardiac performance caused by human *ACTA2* gene mutations by using a zebrafish model, revealing the effects of *ACTA2* G148R and R179H mutations on left ventricular non compression and abnormal cardiac morphology development. The *ACTA2* gene encodes vascular smooth muscle cells α-actin β2. It is the main protein in vascular smooth muscle. The missense mutation of *ACTA2* gene may lead to hereditary thoracic aortic disease. This study reported a patient with an abnormal mutation in the *ACTA2* gene Gly148Arg (G148R), exhibiting rare left ventricular non compression. The pathogenicity of this rare variant in cardiac development and function was validated through live zebrafish models.

1 Experimental Data Analysis

The key findings of this study include: zebrafish carrying harmful mutations have significantly reduced heart shortening scores, thinner myocardial walls than wild-type, and significantly reduced total number of cells in the myocardium. These results demonstrate that the *ACTA2* G148R and R179H variants have an impact on the development of left ventricular non compression and cardiac morphological abnormalities, emphasizing the unknown importance of the *ACTA2* gene in multiple aspects of cardiovascular development.

Figure 1 shows the cardiac ultrasound image and MRCP of a patient carrying the *ACTA2* G148R variant. Part A shows the long axis view (diastole) of the left ventricle in echocardiography. The ventricular wall of the left ventricle is composed of an outer dense layer (C) and an inner non dense trabecular layer (NC), with a ratio of 2.0 between NC and C. The deep depression formed by the trabecular layer has blood infiltration (indicated by the white arrow). The MRCP in section B shows that the main pancreatic duct in the head area of the pancreas presents a reverse Z-shape (indicated by a black arrow). The chest magnetic resonance imaging of parts C and D showed a shift in the descending part of the aorta. In these imaging findings, it can be noted that the atypical trabecular layer of the left ventricle may be associated with mutations in the *ACTA2* gene, while the abnormal orientation of the pancreatic duct and the abnormal appearance of the aorta may also be related to the phenotype of this genetic variation. These findings contribute to understanding how the *ACTA2* G148R variant affects the anatomical structure of cardiovascular and pancreatic systems.

Figure 2 shows the expression of endogenous *ACTA2* in the cardiac region of transgenic zebrafish larvae (labeled as Tg[cmlc2:EGFP]) at 4 days after fertilization. Part A shows the brain region and *ACTA2* was not detected, while part B shows a high expression of endogenous *ACTA2* in the heart region, with EGFP green fluorescence, red signal stained with anti ACTA2 antibodies, and blue signal stained with DAPI in the nucleus. The high magnification in the image shows a detailed image of immunostaining, with a lack of red signal in the brain, indicating that *ACTA2* is not expressed or the expression level is extremely low in this region; The overlapping red

and green signals in the heart indicate that *ACTA2* co localizes with the cardiac muscle protein EGFP, which may indicate that *ACTA2* plays a crucial role in the development of the heart.

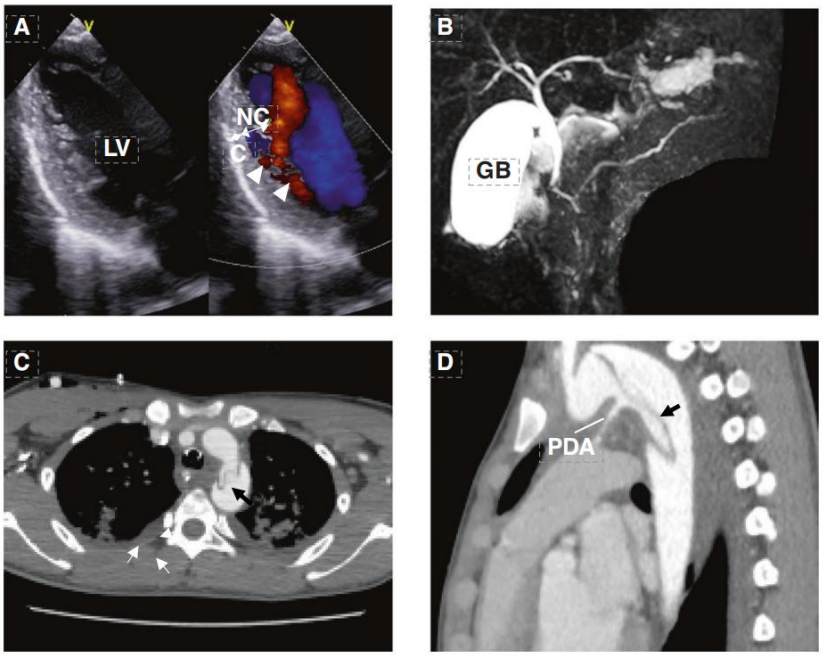

Figure 1 Echocardiography and magnetic resonance cholangio-pancreatography (MCRP) of the patient with the ACTA2 G148R variant

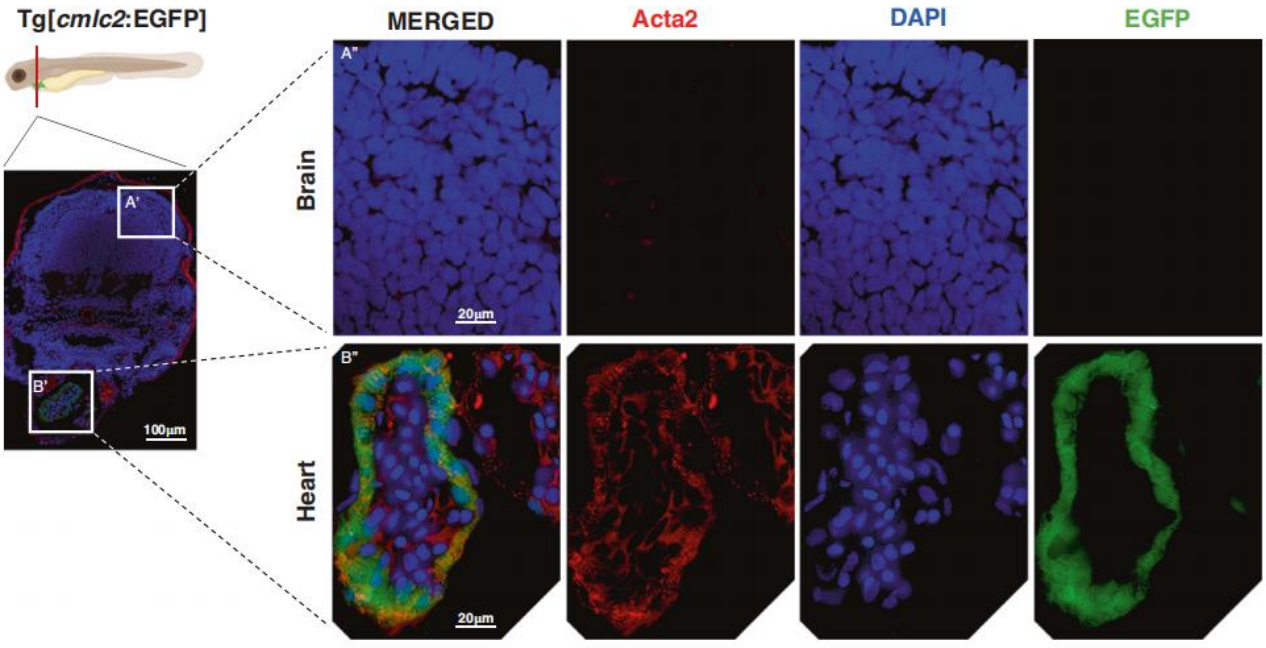

Figure 2 Endogenous ACTA2 expression in the heart

Figure 3 shows the effect of *ACTA2* gene mutations on cardiac contractile function in zebrafish larvae. Part A shows that zebrafish with *ACTA2* p.G148R and *ACTA2* p.R179H exhibit an increase in heart rate (measured in beats per minute). Compared with the wild-type (WT), this increase is not significant for the G148R variant (ns indicates no significance), while the R179H variant has a significant increase (** indicates $P<0.01$). Part B shows that the shortening fraction is significantly reduced in zebrafish carrying G148R and R179H mutations (*** indicates $P<0.001$). These results indicate that mutations in *ACTA2* G148R and R179H may lead to impaired cardiac contractile function.

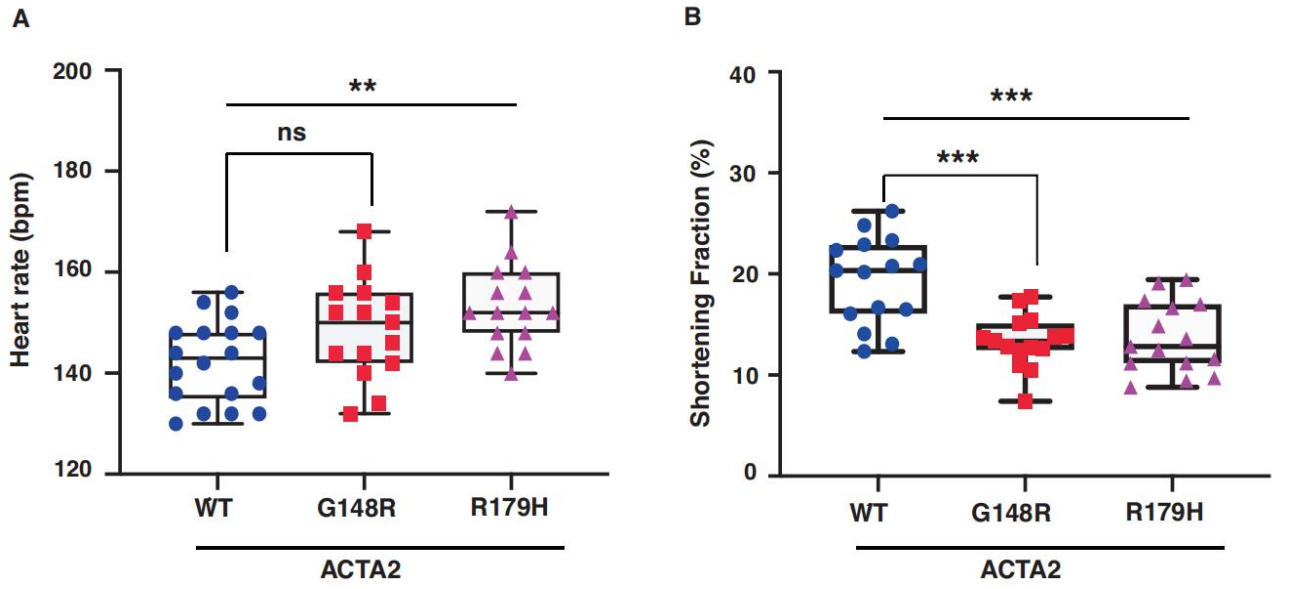

Figure 3 Heart contraction impairs in the ACTA2 G148R variant

Figure 4 shows the decrease of cell proliferation in the heart of zebrafish with *ACTA2* G148R variant on the the fourth day after fertilization. Compared with the wild-type (WT), zebrafish with *ACTA2* p.G148R and *ACTA2* p.R179H showed a decrease in the number of proliferative cells (indicated by the white arrow) in the myocardial wall region by using immunostaining techniques with proliferative cell labeling PCNA (red) and DAPI co staining (blue). In the endothelial region, all pathogenic variants of endothelial cells (indicated by yellow arrows) also showed decreased proliferation. The data from part B and C show that the *ACTA2* G148R and R179H variants significantly reduced the proliferation of myocardial and endothelial cells. These results may suggest that these specific mutations in the *ACTA2* gene have adverse effects on heart development and repair ability.

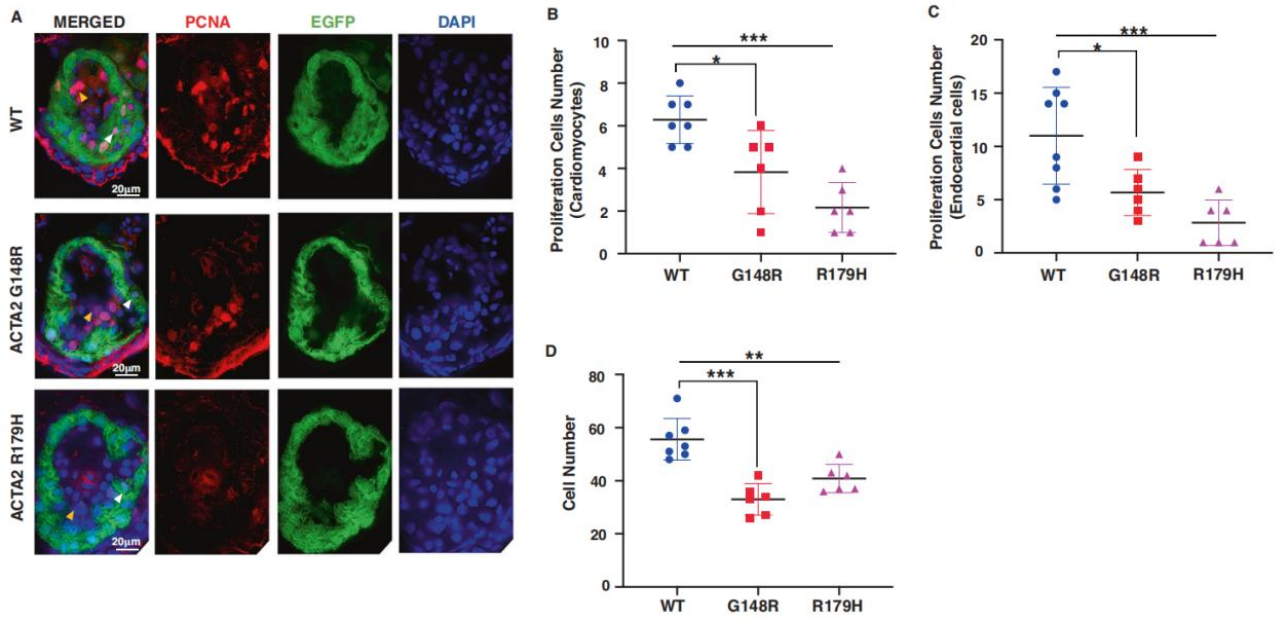

Figure 4 Proliferating cells were reduced in the ACTA2 G148R variant

2 Analysis of Research Findings

This study demonstrates the effects of *ACTA2* G148R and R179H variants on left ventricular non compression and abnormal cardiac morphology, particularly in terms of increased heart rate and decreased cardiac contractility, as well as decreased cell proliferation ability within the heart. The study emphasizes the previously unknown importance of the *ACTA2* gene in multiple aspects of cardiovascular development, revealing the molecular

mechanisms of cardiac dysplasia and providing new insights into how mutations in the *ACTA2* gene affect cardiac function.

3 Evaluation of the Research

This study effectively reproduced the cardiac manifestations of human *ACTA2* gene mutations by using a zebrafish model, providing a new method for studying cardiac dysplasia and cardiac morphological abnormalities. This not only deepens our understanding of the role of *ACTA2* gene in cardiovascular development, but also provides potential new targets for future research on the treatment of heart diseases.

4 Conclusions

The mutations in the *ACTA2* gene significantly affect cardiac development and function, and the zebrafish model used in this study further confirms the pathogenic role of these mutations in cardiac morphological abnormalities and dysfunction.

5 Access the Full Text

Sebastian, W.A., Inoue, M., Shimizu, N. et al. Cardiac manifestations of human ACTA2 variants recapitulated in a zebrafish model. Nature (2024). https://doi.org/10.1038/s10038-024-01221-0.

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