Website address:
https://www.gesundheitsindustrie-bw.de/en/article/press-release/spatial-organisation-genetic-material-influences-heart-disease

Spatial organisation of genetic material influences heart disease

In a joint study conducted by the DZHK sites in Heidelberg, Munich and Göttingen, researchers are deciphering how the spatial organisation of the genome in the heart determines genetic disease risks.

Most of the genetic risk variants for heart disease are outside of genes and don't work the same way everywhere in the heart.

A new study published in *Nature Communications* shows why they can contribute specifically to cardiac arrhythmia or heart failure: it is not only the gene itself that is decisive, but also how its regulatory switching elements are organised in the cell nucleus. The study systematically demonstrates for the first time that this gene regulation differs between atrial and ventricular muscle cells, thereby influencing the effect of disease-relevant genetic variants.

An international research team investigated the spatial organisation of genetic material in human heart muscle cells. They analysed isolated cardiomyocytes from the left atrium and left ventricle, as well as from diseased, insufficient hearts. Using high-resolution chromatin contact analyses, the researchers were able to visualise which DNA segments in the cell nucleus are actually in contact with each other and jointly control the activity of individual genes.

Gene regulation differs between the atrium and ventricle

The results show clear chamber-dependent differences: atrial and ventricular heart muscle cells each have their own networks of regulatory DNA segments and target genes. These differences explain why genetic variants outside genes – i.e. in non-coding regions – are preferentially associated with certain heart diseases.

Thus, variants associated with atrial fibrillation are predominantly found in regulatory regions that are active in the atria and connected to disease-relevant genes. In contrast, variants that increase the risk of cardiomyopathies, heart failure, or QT-interval prolongation act mainly through such regulatory interactions in the ventricles.

From genetic risk to measurable heart function

This was particularly evident in the example of the *KCNJ2* gene, which is important for a potassium channel that helps determine the electrical stability of the heart. The study identified several regulatory DNA segments that are spatially linked to *KCNJ2* and carry genetic risk variants. When these segments were specifically silenced, gene activity decreased, electrical currents in the heart muscle cells changed, and the regression of electrical excitation was delayed – a mechanism that corresponds to the clinical picture of a prolonged QT interval.

The study also provides new insights into heart failure. Although the basic three-dimensional organisation of the genetic material in diseased heart muscle cells remains largely intact, individual connections between genes and the DNA segments that control their activity are altered. These targeted switches affect only a few genes, but explain typical disease-related changes in gene activity.

‘Our findings show that genetic risk variants can only be properly understood if we know in which heart chamber and in what spatial context they act,’ says Prof. Ralf Gilsbach from the DZHK site in Heidelberg and last author of the study. ‘The three-dimensional organisation of genetic material is not a minor detail, but a key to understanding heart disease.’

The study thus provides an important basis for assigning genetic findings from large association studies more precisely to individual target genes. In the long term, this knowledge could help to develop new therapeutic approaches that specifically target gene regulation in certain regions of the heart.

Publication:
Haydar, S., Bednarz, R., Laurette, P. et al. Chamber-specific chromatin architecture guides functional interpretation of disease-associated Cis-regulatory elements in human cardiomyocytes. Nat Commun 17, 117 (2026).
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Further information

- German Centre for Cardiovascular Research (DZHK)