Cardiomyopathies and epigenetic inheritance

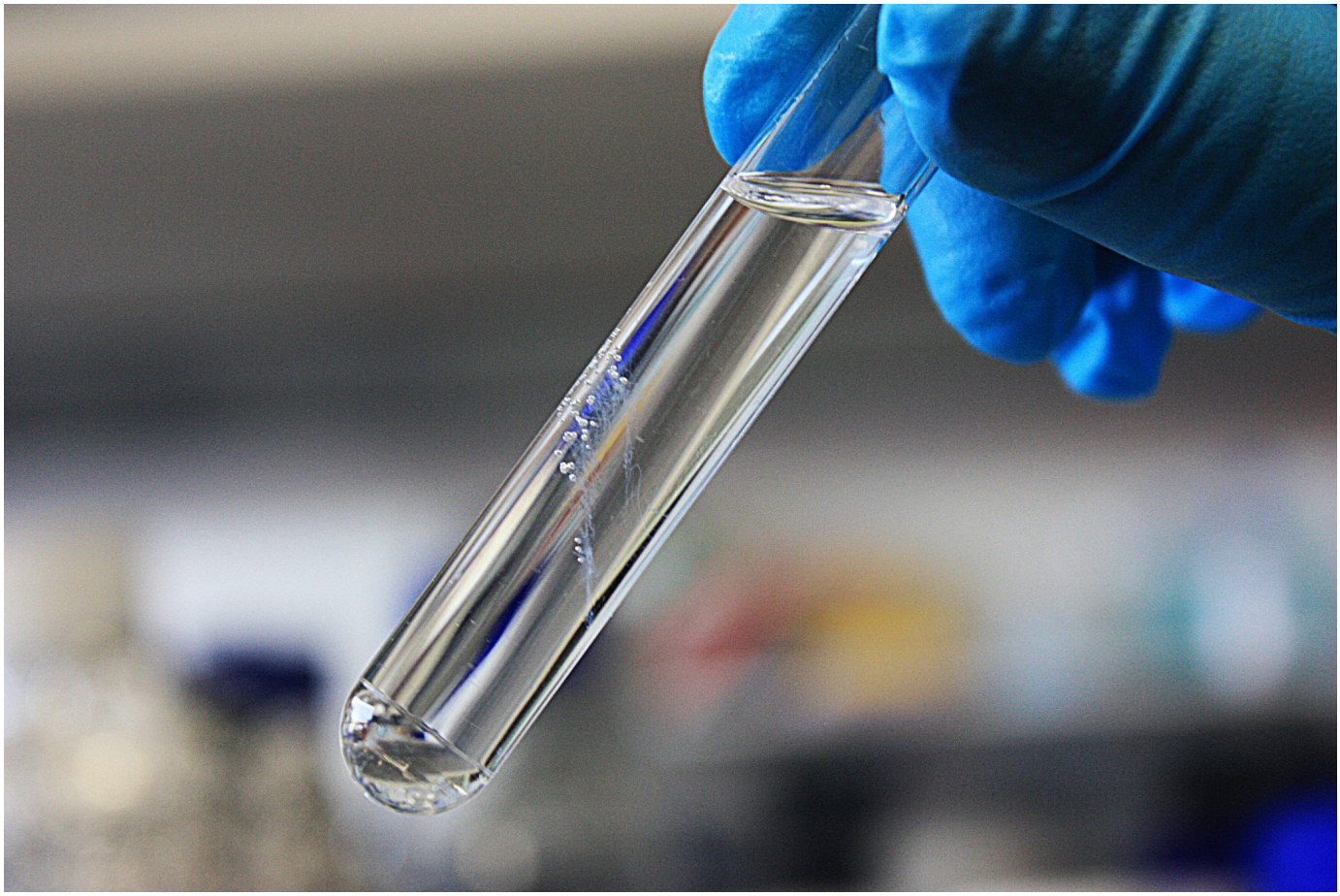
Epigenetic mechanisms, along with gene mutations, have been shown to play important roles in the development of heart diseases. Researchers from Heidelberg have discovered that the methylation of two specific genes has an impact on the development of dilated cardiomyopathy. These epigenetic modifications have the potential to be used as molecular markers and improve the diagnosis and therapy of these particular heart diseases.

The Annual Meeting of the German Cardiac Society, which is traditionally held in the Rosengarten Congress Center in Mannheim, specifically focussed on cardiomyopathies. On 3rd April 2013, Professor Dr. Hugo Katus, medical director of the Department of Cardiology, Angiology and Pneumology at the Heidelberg University Hospital and president of the 79th Annual Meeting, discussed the issue in a press conference held at the meeting which attracted upwards of 8,000 people and is the largest cardiology conference in Europe. The Department of Cardiology at Heidelberg University Hospital is one of the major centres in Germany focussed on research into cardiomyopathies.

Katus reported that substantial progress has been made in recent years in the field of cardiomyopathies, especially with regard to the impact of genetic factors on the development of these heart muscle disorders. Cardiomyopathy literally means heart muscle disease, which indicates that the disease is not an indirect cause of damage resulting from cardiac infarction or cardiac valve defects. The course of the disease and its symptoms vary from individual to individual, which makes therapy and prognosis rather difficult. Genetic factors play an important role in the development and progression of the disease in around 80 percent of the 250,000 or so cardiomyopathy patients in Germany.

Around 50 genes that have some kind of association with cardiomyopathy have been identified, and these findings have had an impact on disease therapy. Katus came with the recommendation that all close relatives of anyone suffering from cardiomyopathy should undergo an ultrasound examination, a pain-free and harmless procedure, in order to detect potential disease signs that require immediate treatment. If the disease is detected at an early stage before it has led to clinical symptoms, currently available therapies are able to reduce the risk of death from the deterioration of heart muscle function by 50%.

However, the genetic basis of inheritable cardiomyopathies is fairly complex and far from being understood in detail. The disease can even vary considerably between patients in the same family. It is therefore assumed that there are mechanisms other than changes in the underlying DNA sequence that have a considerable effect on the progression and outcome of the disease.



Test tube with DNA of cardiac cells derived from patients with cardiac insufficiency.

Call for molecular markers

At the 78th Annual Meeting of the German Cardiac Society in 2012, numerous speakers called on participants to focus on finding reliable biomarkers for early disease stages in order to be able to diagnose and start treating the disease at a point when its further progression can be stopped and sudden heart failure can be avoided (see link on right-hand side: "German Cardiac Society meeting 2012 - Medicine for sick hearts"). Researchers in Germany and abroad are working on the development of molecular diagnostic procedures that enable a distinction to be made between the different forms and progression of this relatively heterogeneous disease. However, no reliable criteria to enable the risk of sudden cardiac death to be determined are yet available. Some patients have no or very little response to treatments involving ACE inhibitors, beta blockers, and other drugs. Molecular markers that enable a patient's response to therapy to be predicted could potentially enable treatment to be adapted to individual patient requirements.

Epigenetic modifications

Researchers from Heidelberg have now solved the puzzle as to why cardiomyopathies can follow a different course despite similar genetic disposition. Their study, published in the renowned journal "EMBO Molecular Medicine", shows that DNA methylation plays an important role in the progression of the disease. The project was led by Dr. Benjamin Meder and involved scientists and doctors from Heidelberg University Hospital, the German Cancer Research Center and other institutes and was part of the programme "Inflammatory and hereditary cardiomyopathies" of the German Centre for Cardiovascular Research (DZHK). The methylation of the DNA base cytosine is an important mechanism for inactivating genes. The methylation pattern differs between different cells and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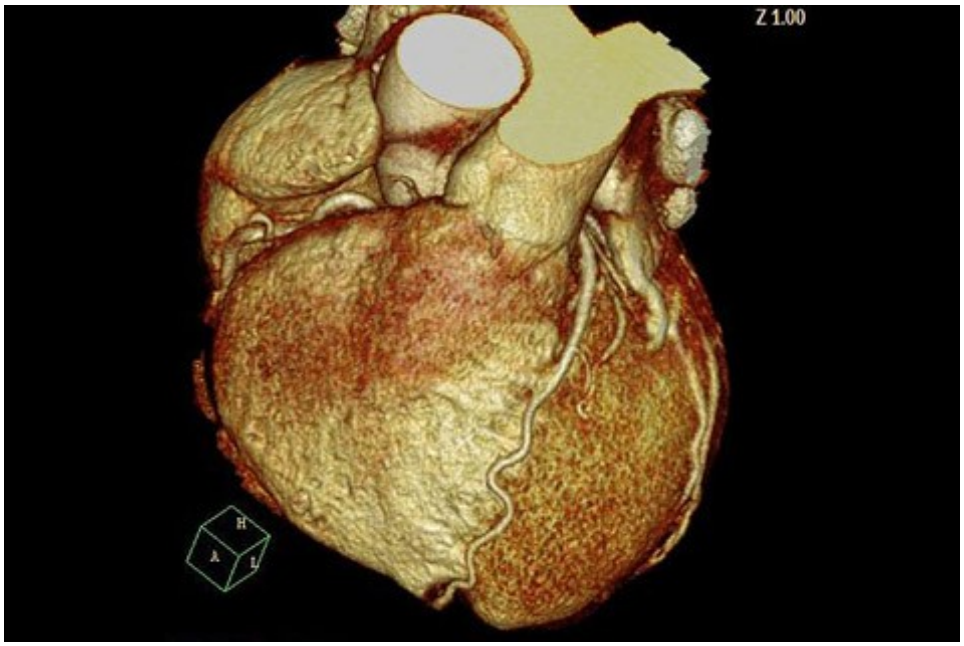
differentiation states; DNA methylation patterns are also known to be modified by environmental factors.

In addition to other chemical modifications of the DNA and the histone proteins, DNA methylation is an epigenetic mechanism that regulates gene expression without altering the underlying DNA sequence. The phenomenon of epigenetic modification has been studied intensively with regard to its role in the pathogenesis of cancer. The researchers from Heidelberg have used tiny tissue samples from 39 patients suffering from what is known as "dilated cardiomyopathy" (DCM) and compared the methylation pattern of their genome with that of healthy people. The samples were withdrawn from the heart muscle during routine investigations. The researchers found that in comparison with control tissue, the diseased hearts contained numerous methylated genes.

Improvements in diagnosis and therapy



Computer tomogramme of a human heart.
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It was already known that many of these genes are involved in metabolic pathways that play a role in the development of cardiac diseases. The researchers also found differences in the methylation pattern of four genes ("lymphocyte antigen 75" (LY75), "tyrosine kinase-type cell surface receptor HER3" (ERBB3), "homeobox B13" (HOXB13) and "adenosine receptor A2A" (ADORA2A) whose function in DCM or heart failure was not previously known. Mass spectrometric analyses and bisulphite sequencing were used to identify and confirm alterations in the DNA methylation pattern in different patient cohorts. In the DCM patients, methylation led to the almost complete inhibition of the transcription of the genes LY75 and ADORA2A into mRNA. These genes were subsequently studied in greater detail using zebrafish as animal models. Each of the two respective zebrafish genes was blocked, with the result that the animals developed hearts whose pumping efficiency was considerably reduced. This is evidence that the methylation of the genes LY75 and ADORA2A does have an impact on the development of cardiac diseases.

"We have entered unchartered territory with the analysis of the methylation pattern and identified

disease mechanisms in cardiac patients that can in future be studied in greater detail," said Meder. The disease-specific changes of the methylation pattern, in particular of the LY75 and ADORA2A genes, could be the sought-after biomarkers that might in future facilitate the diagnosis of cardiomyopathies and potentially also allow predictions to be made on the course of the disease. Additional studies will have to be carried out in order to identify the signalling pathways by which the genes impact the heart muscle and to find out whether they can be used as targets for new therapies.

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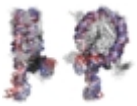

Epigenetics – heritable traits without changing the DNA sequence