> the benefits of exercise training are mediated by an oligosaccharide present in breast milk

exercised-trained *St3gal4*$^{-/-}$ dams did not confer benefits to wild-type offspring of sedentary dams. Finally, the offspring of sedentary, wild-type mice that were supplemented with 3′-SL during lactation had improved metabolism and cardiac function as adults.

"To our knowledge, this is the first study to identify a role for exercise to induce adaptations to the composition of breast milk and also the first study to identify a role for 3′-SL to mediate improvements in metabolic health and cardiac function in offspring," concludes Stanford. "In the future, we would like to determine the mechanism through which 3′-SL improves metabolic and cardiac function."

Shimona Starling, Senior Editor,
Nature Reviews Endocrinology

This article is modified from the original in *Nat. Rev. Endocrinol.* (https://doi.org/10.1038/s41574-020-0393-1)

ORIGINAL ARTICLE Harris, J. E. et al. Exercise-induced 3′-sialyllactose in breast milk is a critical mediator to improve metabolic health and cardiac function in mouse offspring. *Nat. Metab.* https://doi.org/10.1038/s42255-020-0223-8 (2020)

> the cardioprotection mediated by SS-31 and mCAT has overlapping mechanisms

mitochondrial ROS production, protein oxidation and cellular senescence in the hearts of old mice and normalized the age-induced increase in mitochondrial proton leak.

Adeno-associated virus-mediated expression of mCAT in old mice similarly reversed age-related diastolic dysfunction and mitochondrial ROS accumulation. However, SS-31 treatment did not further improve diastolic function in old transgenic mCAT mice, indicating that the cardioprotection mediated by SS-31 and mCAT has overlapping mechanisms.

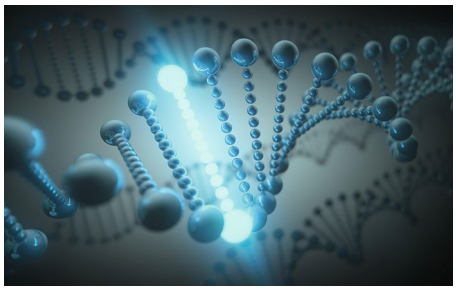
"This study demonstrates the potential of SS-31 as an intervention to improve diastolic function in elderly people," comments Chiao. "The findings also provide a mechanistic understanding of the age-related changes in the mitochondria that underlie cardiac dysfunction."

Karina Huynh

ORIGINAL ARTICLE Chiao, Y. A. et al. Late-life restoration of mitochondrial function reverses cardiac dysfunction in old mice. *eLife* **9**, e55513 (2020)
RELATED ARTICLE Picca, A. et al. Mitochondrial quality control mechanisms as molecular targets in cardiac ageing. *Nat. Rev. Cardiol.* **15**, 543–554 (2018)

CONGENITAL HEART CONDITIONS

De novo variants in gene regulatory regions contribute to CHD



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Non-coding de novo variants (DNVs) contribute to congenital heart disease (CHD) through transcriptional and post-transcriptional regulatory effects during cardiac development, according to a new study. Moreover, the proportion of individuals with CHD ascribed to non-coding DNVs might be at least as high as that with CHD attributed to coding DNVs.

CHD is the most common congenital disorder in humans, occurring in 1% of live births. A genetic cause is identified in 33% of patients with CHD but only 8% are attributed to coding DNVs. Thus, Felix Richter and colleagues hypothesized that additional variants causing CHD might be located in non-coding elements that are active during cardiac development. To examine this hypothesis, the research team compared genome sequences from 749 probands with CHD without identified probable causal genetic variants and their unaffected parents with those from 1,611 child–parent trios without CHD. The researchers used three strategies: two transcription-based approaches centred on cardiac gene regulatory elements and an analysis of post-transcriptional regulation. "We ensured cardiac relevance with a large corpus of publicly available and newly generated cardiac epigenomic data," explains Richter.

One strategy involved a neural network algorithm that could predict functional effect differences with variant-level resolution. A second approach involved the analysis of non-coding DNVs on enhancer regions that had been implicated in human cardiac development gene expression regulation in experimental studies. The neural network identified a significant enrichment of non-coding DNVs in patients with CHD compared with controls. The enhancer analysis showed that 27 genes were marginally enriched for DNVs among patients with CHD, whereas no gene was enriched for DNVs in controls. Both approaches showed a significant overlap between results. Of note, of the CHD-associated genes identified by both approaches, only *COL1A2* had been previously implicated in heart development. Functional validation assays showed that five of 31 DNVs analysed significantly altered transcription levels in the associated genes, which included *JPH2* (encoding a membrane protein necessary for transverse-tubule formation) and *SEMA4B* (which is in the top quartile for gene expression in the developing heart).

The third approach focused on RNA processing and showed DNV enrichment in RNA-binding-protein regulatory sites in individuals with CHD compared with controls. Finally, Richter and colleagues assessed whether the non-coding DNVs were associated with phenotypic CHD subgroups. The analysis revealed potentially contributory non-coding DNVs in probands with isolated CHD and in those with neurodevelopmental delays or extracardiac anomalies, suggesting varying degrees of cardiac specificity of the DNVs.

Taken together, these analyses indicate that cardiac regulatory non-coding DNVs contribute to CHD pathogenesis at the transcriptional and post-transcriptional regulatory levels. "This work highlights a continued need to perform whole-genome sequencing in larger cohorts, obtain more robust and diverse cardiac epigenomic data, and develop algorithms to understand non-coding genetics," says Richter.

Irene Fernández-Ruiz

ORIGINAL ARTICLE Richter, F. et al. Genomic analyses implicate noncoding de novo variants in congenital heart disease. *Nat. Genet.* https://doi.org/10.1038/s41588-020-0652-z (2020)