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Ther Maternal-Age Associated Risk of Congenital Heart Disease is Associated with Epigenetic Modification of the Cardiac Genome in the Offspring

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The Maternal-Age Associated Risk of Congenital Heart Disease Is Associated with Epigenetic Modification of the Cardiac Genome in the Offspring

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Older maternal age is a risk factor for congenital heart disease (CHD) in humans and a mouse model caused by a mutation of *Nkx2-5*, a cardiac transcription factor. Our lab has shown that the basis of the age-associated risk relates to an unknown maternal factor that interacts with cardiac development in *Nkx2-5*$^{+/-}$ embryos. Voluntary exercise by mouse mothers reduces the risk. The strain background of the mother affects risk too. We hypothesized that these the effects of age, exercise and strain background on risk would be correlated with epigenetic changes in the cardiac genomes of the offspring. We performed reduced representation bisulfite sequencing on the genomic DNA from the hearts of newborn pups. We then looked for CpG methylation patterns that were correlated with the maternal variables related to the age-associated risk of CHD; they could relate to how the unknown maternal factor affects embryonic cardiac development. In a cross that has a significant maternal-age associated risk, the offspring of old and young mothers have opposite patterns of increased or decreased methylation at a few hundred CpG sites. Voluntary exercise by older mothers causes a shift in the methylation profile to a young mother pattern. However, this shift in methylation due to exercise only occurs with the FVB strain of mice and not the A/J strain. Genomic patterns of methylation in the cardiac genome of newborn mouse pups are associated with variables that influence the maternal-age associated risk of CHD. These results suggest that the unknown maternal factor could affect the risk of CHD through epigenetic modification of cardiac developmental genes in the embryo.