

Identification of genetic susceptibility loci for coarctation of the aorta in 205 Swedish families

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Introduction

Coarctation of the aorta (CoA) is a congenital narrowing of the aorta which may present as an isolated condition or in combination with other cardiac anomalies. Males are affected twice as often as females, and it most commonly occurs without associated syndromic features. Even though CoA is typically not inherited in a Mendelian fashion, familial segregation has been described, suggesting underlying genetic influence for development of CoA.

Methods

To identify genetic variants associating with non-syndromic CoA, we collected saliva samples and isolated DNA from 205 Swedish patients with the main diagnosis of an isolated pre- or juxtaductal CoA, requiring surgical correction. This population included patients with an associated bicuspid aortic valve, persistent left superior vena cava, secundum atrial septal defects, patent ductus arteriosus or small muscular ventricular defects. Exclusion criteria were other associated cardiac anomalies, known chromosomal abnormalities, syndromes or extracardiac abnormalities. DNA samples were also collected from the parents, generating in total 205 families whereof 194 complete trios. The samples were genotyped using the Infinium OmniExpressExome chip from Illumina. A total of 564 individuals passed quality control, including 122 affected boys, 69 affected girls and their parents. We then performed transmission disequilibrium testing (TDT) to identify associations between CoA and genetic variants.

Results

The TDT analysis revealed associations with single nucleotide polymorphisms in chromosome regions 4q32.1 (OR 2.15, $p=1.08 \times 10^{-5}$), 6q16.3 (OR 0.45, $p=1.60 \times 10^{-5}$) and 13q33.1 (OR 3.27, $p=2.14 \times 10^{-5}$). In a TDT analysis stratified on sex, associations in the male group were found with variants located in 8q24.23 (OR 3.50, $p=1.04 \times 10^{-5}$), 11q22.3 (OR 0.40, $p=1.13 \times 10^{-5}$) and 8p22 (OR 2.31, $p=1.95 \times 10^{-5}$), while the top associations in the female group were with variants in 6p21.31 (OR 0.24, $p=5.53 \times 10^{-6}$) and 14q22.3 (OR 0.25, $p=1.33 \times 10^{-6}$).

Conclusions

Genome-wide association studies for CoA have not previously been undertaken with a similar number of trios, and this study reveals susceptibility loci that may be involved in the development of the condition. The results also suggest that the genetic associations with CoA differ between the sexes.