NOTCH 1 variants in children with aortic coarctation

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Objectives: To investigate the contribution of the genetic component in the COA development by analyzing the family histories and searching mutations in NOTCH1.

Methods: We collected 68 unrelated children with COA, diagnosed by echocardiography, cardiac catheterization, and/or surgical observation. Echocardiographic data were obtained for the relatives when available. The genetic study included 51 patients with CAO. We applied a strategy of targeted mutation screening for 10 out of 34 exons of the NOTCH1 gene by direct sequencing. Control DNA was obtained from 200 healthy donors.

Results: The age of patients at the time of the study was 11.2±1.2. The sex distribution was 47 males and 21 females. The mean pressure gradient in the ascending aorta was 45.7 ± 2.6 mm Hg. COA was combined with BAV in 55.9% cases, with hypoplasia of the aortic arch 32.4% or descending aorta 13.2%; 2.9% patients had complete interruption of the aortic arch and 2.9% had subaortic stenosis. Mitral valve pathology was observed in 13.2% cases. Combinations of COA with other forms of CHD were identified in 26.5% of the cases (12 PDA, 9 VSD, 6 ASD, 1 TGA). Echocardiography data was available for 82.4% mothers and 30.9% fathers. CHD were noted in 13 parents (7 BAV, 1 VSD, 4 ASD, 1 PVS).

29 variants of the NOTCH1 gene were identified. Four of them led to amino acid exchange, but only R1279H was observed in patients 7/51 and controls 4/200 (p=0.00026). Exon substitutions were more representative for children with COA. For example, at least one variant in exons 12 (g.30469C/T, g.30445C/T), 23 (g.39006G/A), 34 (g.48696G/A, g.48901G/A, g.48930G/A) was identified in 25.5% of patients and 4.0% of the controls. Intron substitutions, on the contrary, frequently observed in the controls: variant intron 29 (g.43831T/C) in the control and study groups was identified in 75.5% and 21.6% (p=6×10^-13), intron 12 (g.30591C/T) - in 70.0% and 15.7% (p=1×10^-12).

Conclusions: Statistical analysis showed, that the weighted combination of substitutions gene NOTCH1 will concern this observation as favorable in 82.5% of cases in healthy donors and in 96% of patients will indicate a risk of COA.