

FOXC1 as a potential gene responsible for rapidly progressing aortic valve dysplasia in a child with 6p25.6 microdeletion

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Introduction:

Microdeletion 6p25.3 is a rare but well-known entity. The phenotype includes predominantly dysmorphic features, neuro-developmental and ocular anomalies. Cardiac anomalies are less frequently seen and poorly explained.

Case report:

A 4year old girl presented to our department for rapidly evolving aortic stenosis, requiring surgery. This little girl was born at term but abnormal nuchal translucency had been observed during pregnancy. Prenatal caryotype was normal. At the age of 4 months she required surgery for a vallecular cyst. She subsequently was noted to have significant abnormalities of oculo-motricity combined with dysmorphic features and mild neurological delay. Echocardiography, performed in the first year of life showed a dysplastic but functional tri-leaflet aortic valve. At the age of 14 months, array-CGH revealed a 1.4 Mb microdeletion in 6p25.6, which includes 9 genes (from EXOC2 to FOXC1). At the age of 4 years cardiac follow-up revealed worsening of the aortic stenosis. Six months later, the stenosis had significantly progressed and required surgical valve replacement. Pre-operative CTscan showed in addition a hypoplastic left internal carotid artery. The aortic arch was normal. During surgery the aortic valve was replaced by an aortic homograft. The post-operative course was complicated by respiratory failure requiring ECMO but the child eventually left the hospital in good condition after 2 months. Examination of mRNA expression revealed that among the 9 deleted genes of the 1.4Mb microdeletion, only EXOC2 and FOXC1 are expressed in human aortic valve. Furthermore, quantitative reverse PCR experiments showed that FOXC1 expression was significantly reduced in the excised aortic valve tissue compared to control.

Discussion:

FOXC1 is known to be important for the development of several organs. Mutations of FOXC1 in humans are associated with ocular and brain anomalies. Cardiac anomalies have been described but the exact role of FOXC1 in human cardiogenesis remains unclear. Analysis of Foxc1 and Foxc2 mutant mice has demonstrated that these transcription factors are both required for cardiac development. Our case report suggests a potential role of FOXC1 in aortic valve and aortic arch (carotid artery) development. Therefore, FOXC1 could play a role in normal cono-truncal development.