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Is Hypoplastic Left Heart Syndrome a Disease of Aortic Valve? A Genetic Perspective

Federici D.(1), Iascone M. (2), Marcora S.(1) , Pak V (1), Marchetti D.(2), Seddio F.(1), Lincesso AR.(2), Pezzoli L.(2), Galletti L.(1) and Ferrazzi P(1).
Cardiovascular Department, "Ospedali Riuniti", Bergamo, Italy(1)
Laboratory of Medical Genetics, "Ospedali Riuniti", Bergamo, Italy (2)

Objective Hypoplastic left heart syndrome (HLHS) is one of the most severe congenital heart malformations, characterized by a large spectrum of underdevelopment of the structures in the left heart-aorta complex. One of the challenges in the management of these patients is the decision to proceed with a 1- versus 2-ventricle repair. Several observations suggest that in some patients the ventricle is still capable of growth when the primary defect is in valve development, while in others HLHS may be due to a primary defect in left ventricular development and growth. The aim of this study was the identification of the specific genetic causes of HLHS that may lead to a stratification scheme facilitating the selection of surgical strategies.
Methods We have analyzed 53 well-characterized patients, using an integrated genomic approach combining DNA sequencing of five candidate genes and a genome-wide survey by high-resolution array CGH.
Results We have identified in 30 patients two de novo mutations in NOTCH1, 8 rare inherited gene variants in NOTCH1, FOXC2 and FOXL1 and 33 mostly inherited copy numbers variants. Some of these variants coexist in the same patient.
Conclusions Our findings predict that HLHS is characterized by a complex and heterogeneous pattern of inheritance with rare de novo highly penetrant mutation or multiple interacting low penetrant alterations contributing to the etiology of the disorder. Moreover, in-silico analysis of the identified anomalies shows a functional association between seven genes involved in cardiac valve development indicating that HLHS is at least in part a "valve" disease.