Molecular Insights Into Congenital Heart Disease and Implications for Personalized Medicine

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Introduction

A clinician's ability to identify patients with potentially worse outcomes based on genotype can greatly improve personalized tailoring of congenital heart disease (CHD) treatment. The cellular or molecular basis of CHDs can lead to insight into CHD origin as well as the possibility of progressive dynamic complications allowing for risk stratification. Despite advances in the genetic basis of CHD, the etiology for the majority of children who have different CHD defects remains largely unknown. This paper examines the genes reported thus far which have a high degree of association with different CHD defects and implications for future research.

Methods

NCBI Gene Bank, LILACS, PubMed, MEDLINE, SciELO, and ScienceDirect were included to identify1644 relevant papers on genetic variants in CHD published between 1998 and 2022 with the majority (n=839) published in the last seven years. Gene variants were included if genotype-phenotype association found in >=2 studies.

Conclusions

Results

In our analysis of 1644 research publications on CHD defects, we report genes where the genotype-phenotype association was shown in >=2 studies.

Aortic Coarctation	MYH7, del22q11.2, del1p36, del6q25.1, NKX 2.5, NKX2.6, GATA6, TBX1
Aortic Root Dilatation	del22q11.2, del1p36
ASD	GATA4, TBX5, MYHC, ACTC, MYH6, MYH7, TBX20, Trisomy18, del1p36, del6q25.1, CRELD1, TLL1, CITED2, GATA6
AVSD	NKX2.5, CRELD1, GATA4, TBX5, del6q25.1 GJA1, GATA6, NR2F2
Bicuspid Aortic Valve	Notch1, MYH7, TBX20, SMAD6, ROBO4
TGA	CFC1, ZIC3, NKX2.5, PROSIT240
Double-outlet Right Ventricle	CFC1, NKX2.5 , TBX20, CFC1
Ebstein Anamoly	MYH7, GATA4, NKX2.5
Heterotaxy	GATA4, ZIC3, CFC1, ACVR2B, LEFTYA
HLHS	MYH6, Notch1, RBFOX2, NKX2.5, TBX5, del6q25.1, GJA1
Left Ventricular Non Compaction	del22q11.2, del1p36
PDA	TBX5, MYH11, Trisomy18, del1p36, del6q25.1, PRDM6, ACTA2, R187
Polyvalvular disease	Trisomy18, del6q25.1
Premature ventricular contraction	del6q25.1
Pulmonary Artery Hypoplasia	MYH7
TOF	ZFPM2, NKX2.5, JAG1, GATA4, TBX5, TBX20, del22q11.2, del1p36, del6q25.1, GATA6, TBX1
Thoracic Aortic Aneurysms	TBX20
Total Anomalous Pulmonary Venous Return	TBX5
Truncus Arteriosus	TBX5, TBX20, del22q11.2, NKX2.6, GATA6, TBX1, ACTA2, R187
Valvular Dysplasia	NKX2.5, TBX20
VSD	NKX2.5, GATA4, TBX5, MYH7, Trisomy18, del22q11.2, del1p36l, del6q25.1, CITED2, ETS1

Molecular mechanisms are an active area of research in CHD. Further advances will inform personalized medicine in CHD in terms of risk stratification, management, and treatment. The disease prognosis can be affected by changes in mutations; and by growing understanding of associations of the gene variants with static and dynamic progressive phenotype changes, genetic knowledge can be applied to clinical decision-making for more CHD patients.