Review

AN OUTLINE OF CARDIOGENESIS

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Abstract

The paper presents a description of the development of the human heart based on the present state of knowledge cytogenetics and molecular genetics. Despite the complexity of the genetic mechanisms described, the authors emphasize that it may be just a slice patterns in kardiogenezie. Aberrations and mutations lead to the formation of congenital heart defects in both isolated and components of genetic syndromes.

Key words: *CHD, cardiogenesis, genes, aberrations, mutations*

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INTRODUCTION

Congenital Heart Diseases (CHD) are the most common malformations both as an isolated form and a part of genetic syndromes[1,2,3,4]. Extraordinarily fast development of molecular genetics confirms that almost all CHD are genetically dependent in terms of microaberrations in different regions of a chromosome or single gene mutations [5,6,7]. On the other hand, CHD are an important component of diverse genetic diseases, including monogenic, metabolic and mitochondrial disorders, most often as secondary cardiomyopathies[8,9].

HEART GENETICS OUTLINE

The genes participating in cardiogenesis are located nearly on each chromosome, mainly on pathways, along with ligand genes and co-factors, transcription factors or individually[10,11,12,13,14,15]. Crucial genes controlling and the forming of left and right ventricular outflow (LVOT and RVOT), are primary "homeobox" genes grouped in 4 clusters: HOX1 (7q), HOX2 (17q,21-22), HOX3 (12q,11-21), and HOX4 (2q31-37)[14,16,17,18,19,20,21]. They sequentially control the growth and division of appropriate cell groups and next, their apoptosis. Genes frequently undergo signaling pathways, for example NOTCH1, which participate in the forming of the aorta and mitral valves or constitute gene complexes, e.g. Tbox and Tbx20 for forming heart cavities (Fig.1-3)[16,18,19,20,21].

Moreover, in numerous functional disorders, for example the long Q-T conducting, the reason is also genetic, namely the mutation of ion- channel gene placed in 6 chromosomes: 3p, 4q, 7q, 11p, 17q, and 22q(2x). Presently, over 300 possible mutations are known[22,23,24].

Many genes of cardiogenesis were identified thanks to the investigation of other genetic disorders, for example PTPN11 gene in Noonan syndrome. The gene is also responsible for the development of pulmonary valves or TBX5 gene in Holt-Oram Syndrome, partly involved in the growth of ventricles and the atrial septum[25,26,27].

Heart development is also affected by the phenomenon of imprinting (ref. to about 30

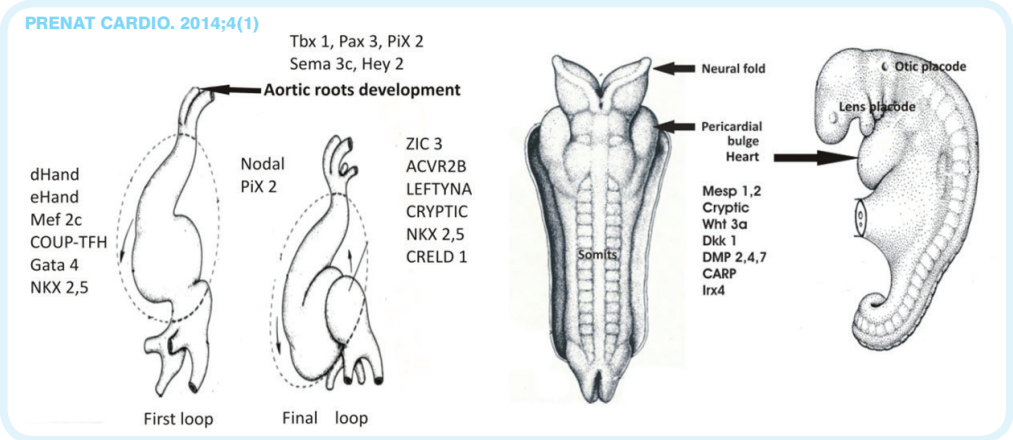

Figure 1. The earliest stage of heart development as studied hitherto

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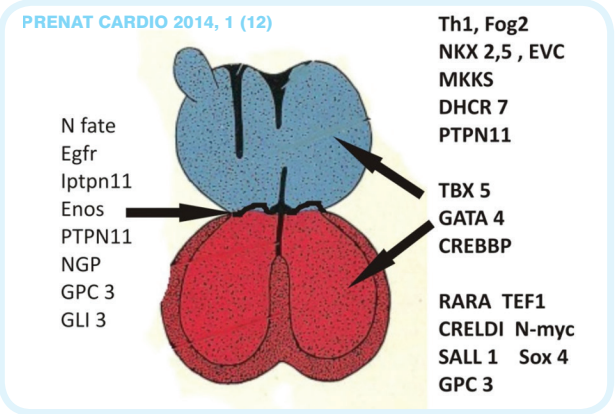

Figure 2. The extraction of septi and valves according to the present state of knowledge

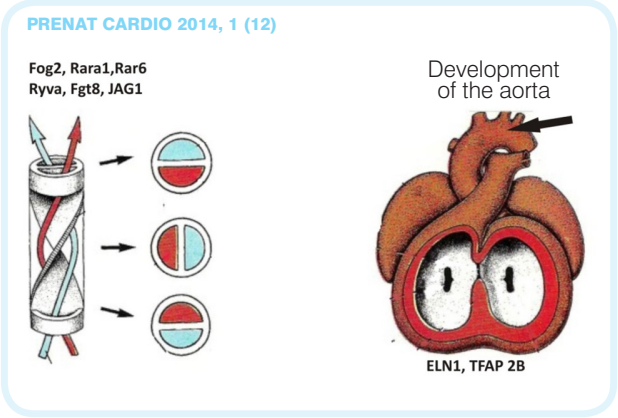

Figure 3. The extraction of septum Ao-TP and the modeling of LVOT and RVOT.

Chromosomal aberrations	
Numerical	Triploidies, Poliploidy X, Trisomies 9, 13, 18, 21, Monosomy X,
Microdeletions (selected)	4p, 4q31, 5p, 9p, 10q, 17p, 18q, 22q,
Microduplications (selected)	3q2, partial 22q
Known mutations in defined genetic syndromes and single genes:	
AD	Noonan, LEOPARD, Holt-Oram, Shprintzen, Townes, Apert, Alagille, Goldenhar, Velo-Cardio-Facial, Ehlers-Danlos tI,II, Marfan, Conotruncal face, Contractural arachnodactyly congenital, Noonan-Ehmke, A-VC congenital, Heterotaxy 6q21, Jacobsen, Pallister-Hall, Rubinstein-Taybi, CdL, ASD + conduction defect,
AR	Ellis-van Creveld, Saldino-Noonan, SRP t I, TAR, Fanconi, Aase, McKusick-Kaufman, Carpenter, Baller-Gerold, Meckel, Lawrence-Moon-Bidel, Cutis laxa,
X-linked	Heterotaxy Xq26.2
Other groups of genetically conditioned disorders	Both dilated and hypertrophic cardiomyopathies in: a) metabolic diseases, b) mitochondrial diseases, c) neuromuscular diseases
Polygenic ground	Hundreds of thousands possible genes

Table 1. CHD in selected monogenic disorders and genetic syndromes

Genetically conditioned CoA	Trisomies 13, 18, 21, Monosomy X, WHS(del 4p), DGS(del22q2), Holt-Oram, Noonan, Velocardiofacial, Ellis-van Creveld, Marfan, WBS, CdL, Allagile and other….
Examples of teratogenic CoA	FAS, Hydantoin, Valproat, Lit, Rubella, mothers PKU
AVC	16 known different genetic syndromes and disorders
PS	11 known different genetic syndromes and disorders
LVOT obstruction	13 known different genetic syndromes and disorders
ASD II	15 known different genetic syndromes and disorders
Isolated VSD	14 known different genetic syndromes and disorders
Pulmonary veins pathologies	4 known different genetic syndromes and disorders
CoA – rupture of the arch	9 known different genetic syndromes and disorders
PDA	24 possible disorders etc.

Table 2. Specific CHD in selected genetic syndromes

genes) and the inactivation of the X chromosome in early (day 21) stage of fetal development. The above mentioned phenomena activate or inactivate specific gene clusters. It is worth emphasizing that mutations can occur in many locations of each gene, hence the number of mutations is not defined.

We propose, e.g. a classification of genetic pathologies connected to CHD (Tab.1).

Yet a more practical classification could refer to specific CHD characteristic of particular disorders, which might prove helpful in daily practice of different specialist and

enables them to focus on identifying the underlying syndromes (Tab.2).

In prenatal diagnosis CHD is often the sole syndrome confirmed by USG scan, which may depend on truly isolated nature or non-specific mild ultrasound co-markers.

It is easily observed how precisely nature manages heart development and as a little bit we know about heart genetics.

To summarize, it should be assumed that the genes and mechanisms described above constitute a mere representation of the complex issue of cardiogenesis. Our aim was to bring recognition to the crucial role played by genetics in the multifaceted process of heart creation. We hope that the outline proves useful in the diagnosis of CHD in daily practice.

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Conflict of interest: The authors declare no conflict of interest

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