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## **Extra Cardiac Anomalies (ECA) in 2020 Subjects with Congenital Cardiovascular Malformation (CCVM) and Control: Etiological Perspective**

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The main objective of this research was to analyze the spectrum of Congenital Cardiovascular Mal-formations (CCVM), Congenital Cardiovascular Malformation (ECA), the frequency of extra-cardiac malformations, extra cardiac anomalies and the proportion of chromosome aberrations among live born infants in order to generate hypothetical theories of congenital cardiovascular malformation etiology. It was found that out of 1010 congenital cardiovascular malformation, 288 were affected by extra cardiac anomalies (28.5%). Among the most common congenital cardiovascular malformations, Atrioventricular Septal Defect was associated up to 72% with extra cardiac anomalies while Dextro-transposition of Great Arteries was related only up to 8.7%. The syndromes were the common extra cardiac anomalies (37%) with congenital cardiovascular malformation. Overall, in live born infants, the congenital cardiovascular malformations were quite common and these were often associated with other cardiovascular and extra-cardiac malformations, as well as with chromosome anomalies. However, the complex heart defects such as hypoplastic left heart syndrome and double outlet right ventricle were infrequent in live born infants.

**Key words:** Congenital cardiovascular malformation, extra cardiac anomalies, heart syndrome, right and left ventricles, live born, infants

## INTRODUCTION

Various epidemiological studies have shown that in live born infants the incidence of congenital heart defects is between four and eight per 1000 (Ferencz *et al.*, 1993, 1985; Hoffman and Christianson, 1978; Mitchell *et al.*, 1971). We confirmed, higher incidence of congenital cardiac malformations in Saudi population, than most of all incidence figures in medical literature, up to 10.67 per 1000 live birth (Alabdulgader, 2001). Samanek *et al.* (1985) stated that in stillborn infants, the incidence of congenital heart defects was 10 times higher than that of live births (Samanek *et al.*, 1985). The etiology of most Congenital Heart Defects (CHD) is unknown; only around 15% of them can be attributed to a known cause (Botto and Correa, 2003). Approximately 5-10% are associated with a chromosome abnormality, 35% can be linked to defects in single genes and about 2% are attributed to known environmental factors (Clark, 2001).

According to Ferencz *et al.* (1993), in Baltimore-Washington infant study during 1981-1989, the frequency of associated congenital cardiovascular malformation with extra cardiac anomalies in live births was quite variable in different studies. e.g., from autopsy series, it ranged from 13-37%, while from clinical series the range was 9-42%. Overall, these were 27.71% in the study cases vs. 3.4% in controls (Ferencz *et al.*, 1989a), respectively.

In fact extra cardiac anomalies incidence is defect specific. Ferencz *et al.* (1993) revealed that extra cardiac anomalies is associated with 9% of cases with dextro-transposition of great arteries, compared to 51% with atrioventricular septal defect. Congenital cardiovascular malformation may occur at similar vulnerable time with other systems.

Syndromes such as Noonan, Cornelia De Lange, Holt oarm, Seckle, Vacterl, William and Marfan are the most common extra cardiac anomalies in congenital cardiovascular malformation cases: For example down-syndrome is frequent in 9% of the cases, the most dominant chromosomal group (Ferencz *et al.*, 1993). The specificity of down syndrome is well associated with certain congenital cardiovascular malformation (Rowe and Uchida, 1961). On the other hand, it has been revealed that 75% of the cases are left ventricular outflow track obstruction (turner syndrome) (Ferencz *et al.*, 1989b). While it is also being mentioned that 50% of cases affected with pulmonary stenosis are associated with Noonan syndrome (Van der Hauwaert *et al.*, 1978). Frequency involvement of congenital cardiovascular malformation with different body systems (Greenwood *et al.*, 1975) is presented in descending order as Musculo-skeletal (8.8%), syndrome (Noonan, Cornelia

De Lange, Holt oarm, Seckle, Vacterl, William and Marfan) (8.5%), central nervous system (6.9%), renal-urinary (5.3%), gastro-intestinal tract (4.2%), respiratory (3.8%) and hematological (<1%). In general there is a paucity of extra cardiac anomalies association with Dextro-Transposition of great artery which amount only to 9% (Losekoot and Becker, 1987).

The present study attempts to investigate associations of congenital cardiovascular malformations, frequency of extra cardiac malformations and the proportion of chromosome aberrations among Saudi live born infants contributing to unravel some of the congenital heart defects mysteries.

## MATERIALS AND METHODS

During a period of 52 months, congenital cardiovascular malformation clinical findings were performed at Prince Sultan Cardiac Center (PSCC). A total of 1010 live born infants aged between 0-13 years were categorized in 10 groups.

Investigations were carried out using CXR, Echo Cardiograph, Echocardiography w/o Cathartic and surgery, Others procedures include, CT-Scan and Skeletal survey Muscle.

Biopsy, Barium studies, chromosomal analysis and electrophoresis etc, were performed for cytogenetic analysis and determination of chromosomal aberrations. Metabolic screening was also performed. Congenital cardiovascular malformation were defined as gross structural abnormality of the heart or intra-thoracic great vessels that is actually or potentially of functional significance.

Minor extra cardiac anomalies with no potential increase of morbidity and mortality were excluded. Extra cardiac anomalies were categorized into 9 major groups including chromosomal and non chromosomal syndromes.

**Statistical analysis:** Data management and statistical analysis were conducted using Statistical Analysis System (SAS/STAT Software, 2004) 2004 version 9.1 computer software package applying conditional logistic regression and specialized macros for fine matching and stratification (SAS/STAT Software, 2004).

For the case-control design, every effort was ensured to match controls to cases based on certain factors in order to minimize inherent variation within these factors. So, for a valid analysis, a modeling technique that correctly incorporates the matched nature of the data was performed. Strength of association was measured by odds ratio and tested statistically (p value of significance less than 0.05).

**RESULTS AND DISCUSSION**

The congenital cardiovascular malformation spectrums, diagnosed clinically, were ventricular septal defect (35%), atrial septal defect (12%), pulmonary stenosis (10%), patent ductus arteriosus (08%), tetralogy of fallot (05%), atrioventricular septal defect (04%), aortic stenosis (04%), coarctation of the aorta (03%), dextro-transposition of great arteries (02%) and others (18%) as shown in Fig. 1.

Frequency of extra cardiac anomalies, with and without chromosome syndromes, associated with different cardiac lesions are presented in Table 1. In terms of extra cardiac anomalies and congenital cardiovascular malformation association, overall 288 cases (28.5%) were associated with extra cardiac anomalies as compared to 10.6% extra cardiac anomalies incidence in the control (Fig. 2). The odd ratio for this association was highly significant ( $p < 0.05$ ) which amounted to almost 3.0.

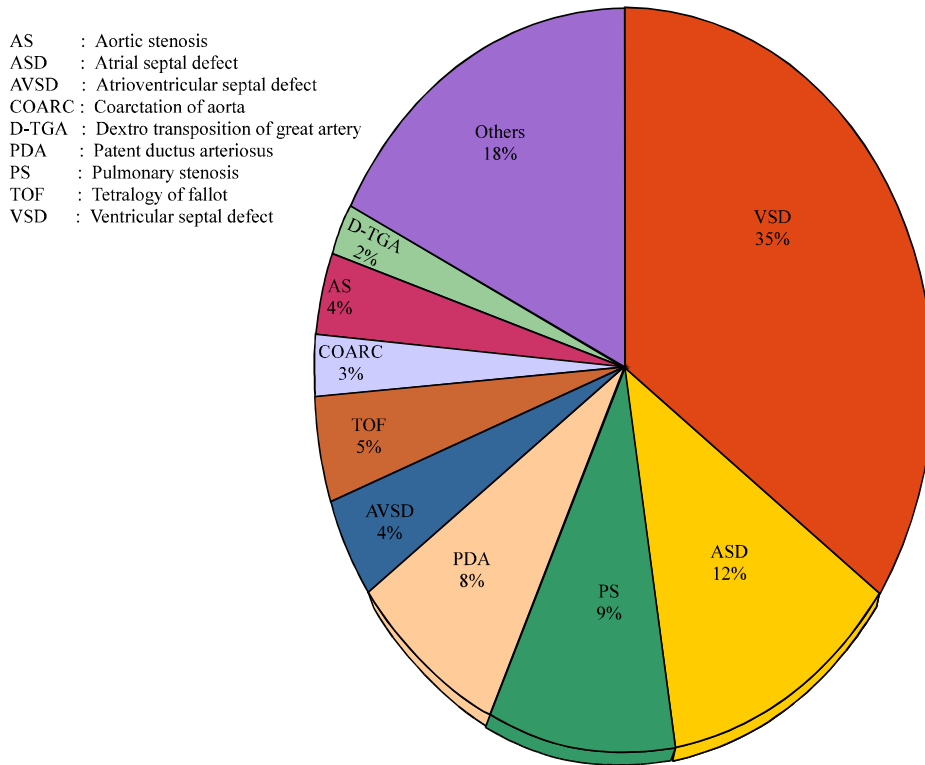


Fig. 1: Distribution of various CCVM lesions in 1010 subjects

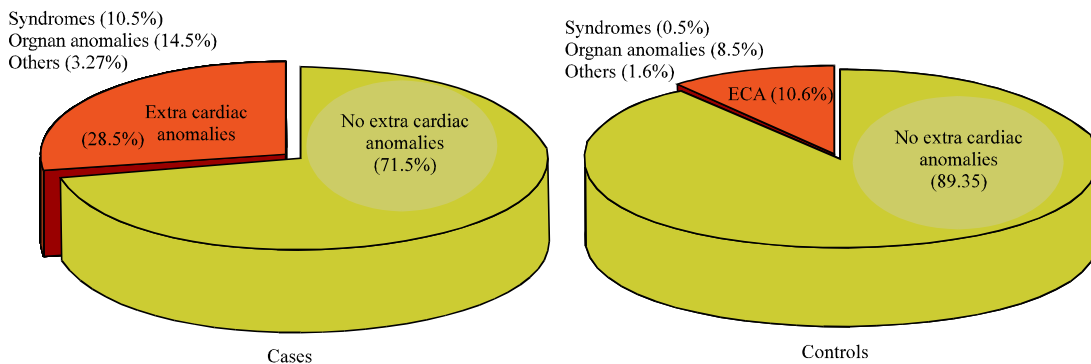


Fig. 2: CCVM and ECA association for cases as compared to control, ECA: Extra cardiac anomalies

**Table 1: Frequency of extra cardiac anomalies, chromosomally and non-chromosomally syndromes associated with different cardiac lesions (congenital cardiovascular malformation)**

Cardiac malformation	No. of anomalies in different body systems syndrome											
	Total No.	ECAs No.	%	MK	RS	CNS	GU	GI	HE	Others	NCH	CH
V. Septal defect	355	93	26.200	9	1	14	3	13	16	6	6	25 (7)
Atrial septal defect	124	43	34.680	2	0	8	3	3	4	10	2	11 (9)
Pulmonary stenosis	96	27	28.125	2	1	4	3	3	6	3	5	0 (0)
Patent ductus arteriosus	81	23	28.395	0	1	4	1	2	0	4	2	9 (11)
Atrioventricular septal defect	43	31	72.100	3	0	0	0	0	0	2	0	26 (61)
Tetralogy of fallot	46	14	30.440	0	0	4	1	0	1	2	1	5 (11)
Coarctation of the aorta	27	14	51.850	1	0	2	1	2	3	2	0	3 (11)
Aortic stenosis	36	9	25.000	0	0	1	3	0	3	0	1	1 (3)
Dextro-transposition of great arteries	23	2	8.700	0	0	0	1	0	0	1	0	0 (0)
Others	179	32	17.877	4	0	7	2	3	3	3	2	8 (5)
<b>Total</b>	<b>1010</b>	<b>288</b>	<b>28.500</b>	<b>21</b>	<b>3</b>	<b>44</b>	<b>18</b>	<b>26</b>	<b>36</b>	<b>33</b>	<b>19</b>	<b>88 (9)</b>

MK: Musculo-skeletal, RS: Respiratory system, CNS: Central nervous system, GU: Genito-urinary, GI: Gastro-intestinal, HE: Hematological, NCH: Non-chromosomal, CH: Chromosomal (Figures in braces show the% for each)

In order of the most frequent extra cardiac anomalies with various congenital cardiovascular malformation categories, these were: Atrioventricular septal defect (72.10%), coarctation of the aorta (51.85%), atrial septal defect (34.68%), tetralogy of fallot (30.44%), pulmonary stenosis (28.125%), patent ductus arteriosus (28.395%), ventricular septal defect (26.2%), aortic stenosis (25.0%), dextro-transposition of great arteries (8.70%) and others (17.877%) as presented in Table 1.

The most frequent of these anomalies involved were the Syndromes (such as Noonan, Cornelia De Lange, Holt oarm, Seckle, Vacterl, William and Marfan) (37.15%), central nervous (15.27%), hematological (12.50%), gastro-intestinal tract (9.02%), musculo skeletal (7.29%), genito urinary (6.25%), others (3.27%) and respiratory (1.04%) as shown in Table 2 and Fig. 3.

Congenital cardiovascular malformation frequencies found in various chromosomally abnormal groups were 26 out of 43 cases of atrioventricular septal defect, 25 of the 355 cases of ventricular septal defect, 5 of the 46 cases of tetralogy of Fallot, 9 out of 81 cases of patent ductus arteriosus, three of the 27 cases of coarctation of the aorta, 11 of 124 of atrial septal defect, a single case of 36 cases of Aortic stenosis and 0 cases of pulmonary stenosis and transposition of great artery (Table 1).

Percentage-wise these were: Atrioventricular septal defect (61%), patent ductus arteriosus (11%), tetralogy of fallot (11%), coarctation of the aorta (11%), atrial septal defect (9%), ventricular septal defect (7%), aortic stenosis (3%), pulmonary stenosis (0%) dextro-transposition of great arteries (0%), others (5%) and total (9%) are presented in Table 1.

Significant statistical associations between specific cardiac lesions and specific body systems are presented in Table 3.

Overall, 81 chromosomally abnormal cases out of 88 were linked with down syndrome. None of all these cases

**Table 2: Frequency of extra cardiac anomalies in CCMV according to affected system**

System	No.	Percent
<b>Syndromes</b>	<b>107</b>	<b>37.15</b>
Central nervous	44	15.27
Hematological	36	12.50
Gastro-intestinal tract	26	9.02
Musculo skeletal	21	7.29
Genito urinary	18	6.25
Respiratory	3	1.04
Others	33	11.45
<b>Total</b>	<b>288</b>	<b>28.50</b>

**Table 3: Specific cardiac lesion to specific systems statistical associations**

Congenital cardiovascular Malformation	System	Odds Ratio	Significance
Malformation aortic stenosis	Genitor urinary	5.80	**
Dextro-transposition of great artery	Genitor urinary	4.18	**
Pulmonary stenosis	Non chromosomal	3.50	**
Atrioventricular septal defect	Chromosomal Syndromes	14.50	***

Significant: \*\*p value<0.05, Highly significant: \*\*\*p value<0.001

**Table 4: Chromosomal syndromes associated with 1010 patients with congenital cardiovascular malformation**

Syndrome	No. of Patients
Down syndrome	81
Turner syndrome	3
Edward syndrome	2
4P Trisomy	1
Unbalanced translocation 4P syndrome	1
<b>Total</b>	<b>88</b>

had an isolated congenital cardiovascular malformation (Table 4). These were all either accompanied by other congenital cardiovascular malformation or extra cardiac anomalies. Distributions of congenital cardiovascular malformation (Ventricular Septical Defect (VSP), Atrial Septical Defect (ASD), Atrioventricular Septical Defect (AVSP), Tetralogy of fallot (TOA), Patent Ductus Arteriosus (PDA) and Others) in these 81 cases was presented in Fig. 4.

In contrast, cases with Dextro-transposition of the great arteries, pulmonary valve stenosis/pulmonary valve atresia, had a normal karyotype. Atrioventricular septal

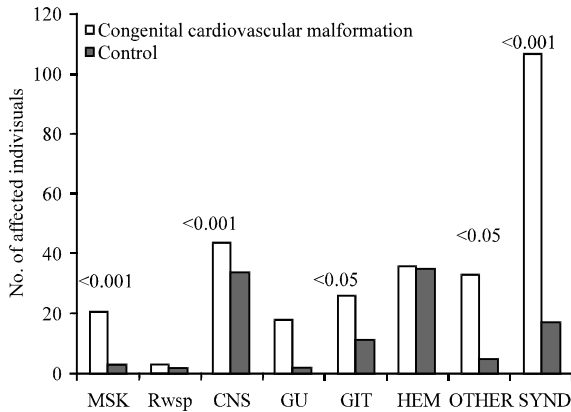


Fig. 3: Bar diagram comparing cases and controls for the different systems with corresponding p-value, MK: Musculo-skeletal, Rwspl: Respiratory system, CNS: Central nervous system, GU: Genito-urinary, GIT: Gastro-intestinal tract, HEM: Hematological, SYND: Syndrome

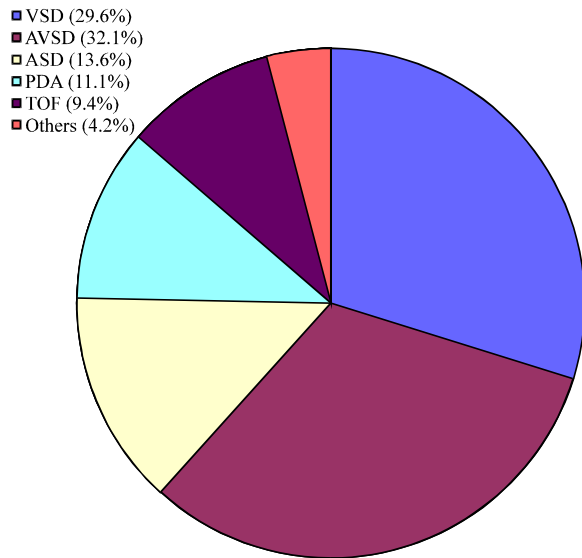


Fig. 4: Distributions of various cardiac lesions in 81 mongoloid individuals

defect was the commonest type of congenital heart defect in cases of chromosome anomaly. This is in agreement with the Baltimore infant study where trisomy 21 and trisomy 18 were more often associated with atrioventricular septal defect or ventricular septal defect than with coarctation of the aorta or tetralogy of Fallot. In the Baltimore study (Ferencz *et al.*, 1993), 9 of the cases were associated with trisomy 21, 3 with trisomy 18 and 1 with trisomy 22.

The non-chromosomal syndromes diagnosed in congenital cardiovascular malformation population were presented in Table 5.

Table 5: Non-chromosomal syndromes in 1010 patients with congenital cardiovascular malformation

Syndrome	No. of Patients
Noonan syndrome	5
Cornelia de lange syndrome	5
Pierre robin	2
Holt oram syndrome	2
Seckle syndrome	1
Vacterl association	1
William syndrome	1
Marfan syndrome	1
Ehler dablos	1
Total	19

## DISCUSSION

**Association with extracardiac anomalies:** In the present population, 288 cases (28.5%) with congenital cardiovascular malformation also had extra cardiac anomalies. This high proportion of extra cardiac anomalies reflects the detailed ultrasonic and comprehensive investigations which took into account all the presented cases. This is in agreement with the Baltimore infant study where 27% of the congenital heart defects were associated with extra cardiac anomalies (Ferencz *et al.*, 1987). Interestingly, these results were at variance with higher findings of (66%) (Tennstedt *et al.*, 1999). However, it is worth to mention that their findings were necropsy-based while the present results were clinically founded.

The most frequent extra cardiac anomalies were found in the central nervous system, the kidneys, the urinary tract and the genital system and the gastrointestinal system; malformations of the respiratory system and the skeletal system were less common. Similar findings were reported by Ferencz *et al.* (1993) in the Baltimore infant study where the most frequent extra cardiac anomalies were in the central nervous system, the eyes, the gastrointestinal system and the kidneys, urinary tract and genital system, as well as of the abdominal wall (Ferencz *et al.*, 1987).

It was noted in the Baltimore study (Ferencz *et al.*, 1993) that majority of cases of transposition of the great arteries and right and left sided obstructive defects were not associated with extra-cardiac anomalies, whereas in the present study only two cases of transposition of the great arteries were associated with an extra cardiac malformation. For malformations of the outflow tract, a combined ratio of isolated extra cardiac anomalies were given, 1:2.5 (Lurie *et al.*, 1995).

**Chromosome abnormalities:** In the present study, overall association between chromosome abnormalities and cardiac defects was observed in 9% of all congenital cardiovascular malformation cases. The highest incidence was observed in atrioventricular septal defect (61%) group followed by patent ductus arteriosus (11%),

tetralogy of fallot (11%), coarctation of the aorta (11%), atrial septal defect (9%), ventricular septal defect (7%), aortic stenosis (3%), while pulmonary stenosis (0%), dextro-transposition of great arteries (0%), cases lack any association. Most of these associations were associated with down syndrome. In the Baltimore infant study (Ferencz *et al.*, 1987), trisomy 21 was the most frequent abnormality associated with congenital heart defects, followed by trisomy 18, trisomy 13 and monosomy X (45, X).

In a comparative study (Tennstedt *et al.*, 1999), ventricular septal defect, atrioventricular septal defect, hypoplastic left heart and double outlet right ventricle were associated with the highest rates of chromosome abnormalities, in contrast to cases with simple vascular obstruction or malformations such as pulmonary valve stenosis/pulmonary valve atresia, tricuspid atresia and transposition of the great arteries, where there was a low prevalence of chromosome anomalies.

Prenatal investigations Chaoui *et al.* (1996) showed a higher rate of chromosomal abnormalities in fetuses with congenital heart defects (22%) than among live births. In an analysis of fetuses with heart defects (Gembruch *et al.*, 1991), the authors found chromosome abnormalities in 28%. The incidence of congenital heart defects and chromosome abnormalities in fetuses is higher than in live born infants or stillbirths as the fetuses often do not survive until birth and are therefore, not included in statistical data collected by pediatric cardiologists (Allan *et al.*, 1991, 1994; Copel *et al.*, 1988). Up to now aborted fetuses have not been included in investigations of the genetic basis of heart defects (Debrus *et al.*, 1996).

The molecular/genetic basis of many congenital cardiac defects has been elucidated in recent years as a result of new insights into the molecular control of developmental events. The discovery of cardiac regulatory gene networks has allowed for genetic testing for cardiac disease genes. Progress in molecular techniques has allowed the discovery of several genetic factors associated with congenital cardiovascular malformation. For example, conotruncal heart defects such as tetralogy of Fallot, truncus arteriosus communis, double outlet right ventricle and transposition of the great arteries, together with various types of ventricular septal defects, are associated with a micro-deletion on chromosome 22. (Goldmuntz *et al.*, 1998; Momma *et al.*, 1997, 1995, 1996; Johnson *et al.*, 1995; Merscher *et al.*, 2001; McElhinney *et al.*, 2003; Frohn-Mulder *et al.*, 1999; Lewin *et al.*, 1997; Takahashi *et al.*, 1995).

Alagille syndrome and Holt-Oram syndrome as single-gene disorders reflect genes responsible for congenital heart defects and for multiple other clinical features.

Mutations in Nkx2-5 cause a spectrum of congenital heart defects (Basson *et al.*, 1997) including cardiac conduction abnormalities, Ventricular-septal Defects (VSDs) and Atrial-septal Defects (ASDs). Mutations in Tbx5 are responsible for Holt-Oram syndrome (Lindsay *et al.*, 2001). An autosomal dominant disorder associated with structural and functional cardiac defects and deletion of Tbx1 results in malformations of the cardiac outflow tract and ventricular-septal defects due to failure in the migration of neural crest cells to the heart (Merscher *et al.*, 2001). Mutations in GATA4, some of which disrupt its interaction with Tbx5, cause atrial-septal defects and ventricular-septal defects (Garg *et al.*, 2003) and Alagille syndrome (Li *et al.*, 1997). Deletions in the jagged1 gene which encodes a signaling molecule in the Notch pathway, have been identified in patients with this syndrome.

In summary congenital cardiovascular malformation and extra cardiac anomalies associations and incidence of frequent chromosomal aberrations in Saudi population reflect importance of underlying genetic factors which may have pleiotropic effects and shared common pathways. In this context molecular and bioinformatic approaches uncovering regulatory gene-networks may provide insights needed to understand cardiogenesis and congenital cardiovascular malformation etiology.

## CONCLUSIONS

Association of congenital cardiovascular malformation with extra cardiac anomalies is well documented. Out of 1010 congenital cardiovascular malformation, 288 are extra cardiac anomalies affected (28.5%). Atrioventricular septal defect is the most common congenital cardiovascular malformation associated with extra cardiac anomalies (72%) while dextro-transposition of great arteries is the lowest (8.7%). Syndromes such as Noonan, Cornelia De Lange, Holt oarm, Seckle, Vacterl, William and Marfan were the most common extra cardiac anomalies associated with congenital cardiovascular malformation to the level of 37%. Statistically significant association has been proven between some congenital cardiovascular malformation and certain systems. This is an important evidence to the multiple types of genetic factors in the etiology of congenital cardiovascular malformation. Better knowledge of congenital cardiovascular malformation with extra cardiac anomalies and establishment of congenital cardiovascular malformation nationwide registry (which is at its terminal stage now) should solve some of the mysteries of cardiac dysmorphogenesis in human.

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