



Review article

## Congenital heart disease associated with the most prevalent chromosomal syndromes: a literature review

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### ABSTRACT

The most frequent chromosomal syndromes like Down, Patau, Edwards, Turner, and Williams affect the pediatric population in various ways, and congenital heart disease contributes to the poor quality of life they experience. There is a lack of studies reviewing the cardiac anomalies in these syndromes, and the ones that exist are publications from past decades. We reviewed databases such as MEDLINE, LILACS, SCIELO, and Google Scholar, selecting the best possible evidence, and each chromosomal syndrome was investigated in relation to congenital heart disease, constituting five search groups. This article shows the characteristics of each heart disease described in the reviewed studies, the author, date of publication, country, and population, as well as a brief description of the frequency of the disease and its mortality. The results described in this review were contrasted with previous existing literature to verify if there was concordance between the reported frequencies. The most frequent congenital heart diseases were atrioventricular septal defect (AVSD), ventricular septal defect (VSD), atrial septal defect (ASD), and persistent ductus arteriosus (PDA) in Down syndrome patients, PDA, ASD, and VSD in Patau syndrome patients, AVSD, PDA and valvular defects in Edwards syndrome, bicuspid aortic valve, aortic coarctation and aortic stenosis in Turner syndrome, and supravalvular aortic stenosis and pulmonary stenosis in Williams syndrome.

**Keywords:** Heart defects congenital; Down syndrome; Trisomy 13 syndrome; Trisomy 18 syndrome; Turner Syndrome; Williams Syndrome (source: MeSH NLM).

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## Introduction

Chromosomal syndromes refer to any alteration in the normal number or structure of chromosomes, including aneuploidies, characterized by the loss or gain of genetic material resulting in an abnormal number of chromosomes, and deletions, which are structural defects resulting from the loss of a varying number of genes. These chromosomal alterations predispose those who have them to congenital diseases, the most common being congenital heart disease<sup>(1)</sup>.

Cardiac malformations, a term used to define abnormalities in the heart and its great vessels as a consequence of an embryogenesis defect, are detected in 3-5% of newborns and 1 in 33 has a severe anomaly<sup>(1,2)</sup>. Technological advances in genetics have made it possible to better clarify the role of chromosomal alterations in the genesis of congenital heart disease and their association with any syndrome.

This review will focus on the current evidence of congenital heart disease associated with frequent chromosomal syndromes, due to the transcendent role that the natural evolution of this type of pathology has in the development of children. Our intention is to provide health professionals with relevant information that supports the diagnostic suspicion in patients with cardiac symptomatology and who present a certain type of syndrome, so that the most appropriate treatment -clinical or surgical- can be determined, and thus improve the quality of life of the affected person. The aim of this review is to describe the frequency and analyze the characteristics of the main congenital heart diseases associated with the most prevalent chromosomal syndromes in pediatric patients.

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## Methodology

Electronic databases such as MEDLINE, LILACS, SCIELO, and Google Scholar were searched. In the case of MEDLINE, we used MeSH terms and free terms, while for the other databases, we used keywords and connectors in order to reduce the results to the most relevant ones. The results of the final search were limited to articles in English and Spanish published between 2000 and 2021 and that were conducted in humans; the initial searches were made without limitations to analyze whether there were any articles in different languages that were important.

The selection of articles to be evaluated was made by identifying titles and abstracts describing the frequency

of congenital heart disease in patients with chromosomal abnormalities, for which an individualized search was made for each of the chromosomal abnormalities to be addressed in this review (Down syndrome, trisomy 13 syndrome, trisomy 18 syndrome, Turner syndrome and Williams syndrome), for example: "Congenital heart disease associated with Down syndrome" (Figure 1).

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## Results

### Down syndrome

It is the most frequent chromosomal anomaly, occurring mainly due to three mechanisms: trisomy 21 (95%), Robertsonian translocation (3-4%) and trisomy 21 mosaicism (1-2%)<sup>(3)</sup>; in almost 90% of trisomy 21 cases, the extra chromosome 21 comes from the mother, which is why the risk increases with advanced maternal age. According to WHO, the global prevalence is estimated to be 10 per 10,000 live newborns, but it is important to note that the figures depend on sociocultural variations such as the legalization of abortion and early prenatal diagnosis<sup>(4)</sup>.

Down syndrome can affect practically all systems and organs, but some of the most prevalent conditions are learning disabilities, hypothyroidism, congenital heart disease, gastrointestinal disorders and leukemias. Diagnosis is guided by Hall's criteria, which are evaluated in all live newborns and confirmed by cytogenetics<sup>(4)</sup>. This syndrome is the trisomy with the best survival rate; in fact, a retrospective cohort study evaluated 16,506 live births between 1982-2003, and found that the survival rates at 1 month, 1, 5 and 20 years were 98%, 93%, 91% and 88%, respectively<sup>(5)</sup>.

Associated morbidities such as adenoid hypertrophy, asthma, umbilical hernia, and hypothyroidism have been reported<sup>(6)</sup>. The most frequent complication was pulmonary hypertension, almost 50% suffer from it and it occurs mostly in association with atrioventricular septal defect; however, literature emphasizes that babies not initially affected with pulmonary hypertension may become symptomatic in infancy or later; likewise, mitral insufficiency, respiratory infections and pulmonary edema have also been reported<sup>(7)</sup>.

Approximately 50% of children with Down syndrome suffer from some type of congenital heart disease and the highest mortality rates have been found during the first two years<sup>(8)</sup>. In a

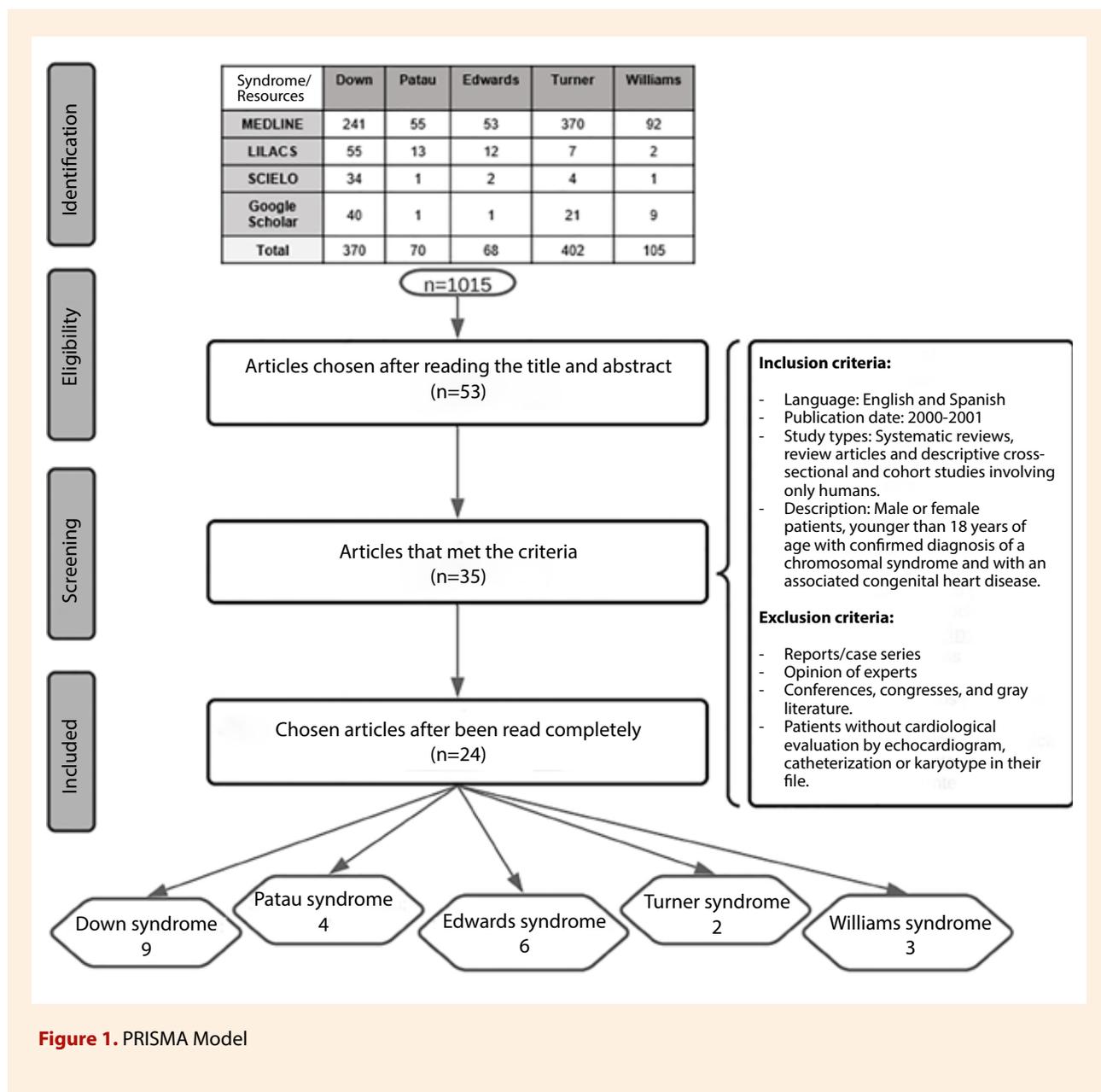


Figure 1. PRISMA Model

retrospective study conducted in Morocco, the mortality rate was found to be 14.1%<sup>(8)</sup>, this shows a great contrast with Sweden, where the mortality rate has decreased from 41 to 4% in a period of 50 years from 1973 to 2003<sup>(9)</sup>; in Latin America, Panama reports a mortality rate of 3.45%<sup>(6)</sup>. In addition, a large population-based study in England found that mortality decreased from 30 to 5% after early surgical intervention<sup>(10)</sup>. The main causes of mortality are septic and cardiogenic shock<sup>(11,12)</sup>, so it is reasonable that patients with Down syndrome should be evaluated during the neonatal and postnatal period, in order to reduce morbidity and mortality in relation to complications<sup>(13,14)</sup>. **Table 1** describes the main congenital heart diseases frequently associated with Down syndrome.

### Patau syndrome

This syndrome has three pathogenic mechanisms: trisomy 13, Robertsonian translocation and mosaicism. The characteristic clinical triad is constituted by micro/anophthalmia, cleft palate and postaxial polydactyly<sup>(15)</sup>. Patients with this syndrome generally suffer from multiple alterations, whether anatomical or functional, with a risk of fetal death of 80%; this syndrome is associated with craniofacial, ocular, cerebral, hematological, abdominal and cardiopathic malformations, due to which the prognosis is not very good, with survival being less than 1 year in most cases, and exceeding 10 years is exceptional<sup>(16)</sup>. Prevalence varies between 1 in 10,000 live births or 1 in 30,000 live births.

**Table 1.** Frequencies of congenital heart disease in Down syndrome.

Author (date)	De Rubens et al. (2003)	Freeman et al. (2008)	Irving et al. (2012)	Bermúdez et al. (2015)	Benhaourech et al. (2016)	Bergstrom et al. (2016)	Ruz et al. (2017)	Yaqoob et al. (2019)	Sotillo et al. (2020)
Location of the study	Mexico (Mexico)	Multicentric (USA)	Newcastle (England)	Parana (Brazil)	Casablanca (Morocco)	Multicentric (Sweden)	Medellín (Colombia)	Multicentric (Pakistan)	Panama
Study period	1994-1998	2000-2004	1985-2006	2005-2013	2008-2014	1992-2012	2010-2013	2010-2016	2011-2018
Population	270 (160)	1,673 (1,469)	821 (342)	1,207 (604)	128	2,588 (1,387)	99	350 (117)	67 (53)
AVSD	9%*	17.2%*	43%*	42.1%*	29%*	42%*	31.31%	12%*	13,79%*
VSD	30%*	19.2%*	31%*	12.7%*	21.5%*	22.1%*	61.62%	41%*	31,03%*
ASD	38%*	18.6%*	15%*	14.6%*	19.9%*	16.2%*	46.46%	8.5%*	6,9%*
TOF	1%*	2.7%*	5%*	2%*	5.4%*	2.6%*	17.17%	5.1%*	3,45%*
PDA	21%*	< 1.3%*	4%*	6.6%*	16.7%*	5%*	38.38%	15.4%*	20,69%*

**AVSD:** Atrioventricular septal defect. **VSD:** Ventricular septal defect. **ASD:** Atrial septal defect. **TOF:** Tetralogy of Fallot. **PDA:** Persistent ductus arteriosus. (\*) Main diagnosis.

It is the third most common trisomy after trisomy 21 and 18, depending on sociocultural factors <sup>(16)</sup>.

Heart defects associated with trisomy 13 are often multiple; it is rare to find these congenital defects isolated in pediatric patients. Diagnosis is suspected with an ultrasound during the first trimester of pregnancy plus the use of chromosomal markers, and a morphological study is used during the second trimester; karyotyping confirms the diagnosis <sup>(16)</sup>. Congenital heart disease occurs in 80% of cases, the median survival time is 7 days and most die during the first month of life <sup>(17)</sup>. One study found that the lower frequency of cardiac anomalies contributes to longer survival <sup>(18)</sup>.

The main cause of death is cardiopulmonary complications, 50% die in the first month after birth and 70% at 6 months; however, in-hospital mortality decreases by 45% in patients who undergo surgery <sup>(19)</sup>. Therefore, although most patients die in the first weeks after birth, some may survive beyond the first year <sup>(20,21)</sup>. In the reviewed literature, several congenital heart diseases frequently associated with Patau syndrome were found (**Table 2**).

**Edwards syndrome**

The Edwards syndrome is a genetic disorder caused by the presence, either total or partial, of an extra chromosome 18,

**Table 2.** Frequency of congenital heart disease in Patau syndrome

Author (date)	Lin et al. (2007)	Maeda et al. (2011)	Polli et al. (2013)	Kosiv et al. (2017)
Location of the study	Taipei (China)	Multicentric (Japan)	Porto Alegre (Brasil)	Multicentric (USA)
Study period	1985-2004	2005-2008	2000-2004	2004-2015
Population	22	23	15	555
Pulmonary atresia-stenosis	18%	-	16%	11%
Double outlet RV	< 15%	11%*	-	12%
PDA	68%	-	37%	52%
ASD	50%	19%*	53%	45%
VSD	50%	15%*	26%	40%

PDA: Persistent ductus arteriosus. ASD: Atrial septal defect. VSD: Ventricular septal defect. CoA: Coarctation of the aorta. TOF: Tetralogy of Fallot. (\*) Main diagnosis.

**Table 3.** Frequency of congenital heart disease in Edwards syndrome.

Author (date)	Lin et al. (2006)	Kosho et al. (2006)	Kaneko et al. (2008)	Peterson et al. (2017)	Kosiv et al. (2017)	Cooper et al. (2019)
Location of the study	Taipei (Taiwan)	Nagano (Japan)	Tokio (Japan)	Multicentric (USA/Canada)	Multicentric (USA)	Multicentric (USA)
Study period	1988-2004	1994-2003	2000-2005	1982 - 2008	2004-2015	2010-2017
Population	39 (31)	24 (24)	22 (22)	121 (69)	1020 (925)	270 (270)
VSD	94%	75%	77.2%	48%*	60%	54.1% *
PDA	77%	75%	68.1%	5% *	57%	7.4% *
ASD	68%	21%	-	-	43%	3.3% *
CoA	< 6%	8.3%	27.2%	9% *	13%	3% *
TOF	< 6%	8.3 %	4.5%	14.8% *	6%	5.9% *
Aortic stenosis	10%	-	-	-	16%	-
Aortic insufficiency		-	-	-		-
AoV atresia	< 6%	-	-	-		-

**VSD:** Ventricular septal defect. **PDA:** Persistent *ductus arteriosus*. **ASD:** Atrial septal defect. **CoA:** Coarctation of the aorta. **TOF:** Tetralogy of Fallot. **AoV atresia:** Aortic valve atresia. (\*) Main diagnosis.

this syndrome is the second most frequent trisomy after Down syndrome. Its overall prevalence is between 1 in 7,000 live births, which increases with increasing maternal age. The mortality rate after birth is high, with 50% surviving beyond the first week and 5-10% surviving beyond one year of age (22). Diagnosis of these patients is mostly made prenatally by detecting anatomical malformations on ultrasound (nuchal translucency, growth retardation) or by karyotyping after amniocentesis or cordocentesis (22).

The clinical manifestations of this syndrome include: alterations in growth, psychomotor retardation, congenital heart disease, facial anomalies, malformations of the skull, thorax, abdomen and genitalia (23). Congenital heart defects are the most frequent clinical manifestations (90% of cases), besides being the main cause of death (24). Some of the most frequent congenital heart defects are: septal defects, patent ductus arteriosus and valvular defects (19) (Table 3).

**Turner syndrome**

Also called Ullrich-Turner syndrome or monosomy X; as its name suggests, it is caused by the partial or total absence of the second X chromosome and is the only monosomy compatible with life. The great majority of “45, X” pregnancies end in spontaneous

abortions, mainly because of cardiac abnormalities (25,26). It is estimated that Turner syndrome is present in 3% of female fetuses, of which 10% survive; it also has a prevalence of 1 in 2,500 live births. No data on postnatal mortality were found, except for a prospective study carried out with 156 women in 1986, followed for 17 years, with 15 of them dying during this period (3.6%) (27).

Diagnosis is made by identification of recognizable clinical features and karyotyping (26). This syndrome is characterized by short stature, intellectual delay, premature ovulatory failure, facial anomalies, winged neck, lymphedema and congenital heart defects. The phenotype of these patients is highly variable.

The percentage of women with congenital heart disease varies according to different literature (25-50%), the most frequent are those that affect the left heart: bicuspid aortic valve, coarctation of the aorta and aortic valve stenosis (26,27). Table 4 details the reviewed literature with the main congenital heart diseases associated with Turner syndrome.

**Williams syndrome**

This syndrome, also known as Williams-Beuren syndrome, is caused by the loss of 26 to 28 genes due to deletion of chromosome 7, specifically 7q11.23. The prevalence of this

**Table 4.** Frequency of congenital heart disease in Turner syndrome

Author (date)	Volki et al. (2005)	Kim et al. (2010)
Location of the study	Erlangen (Germany)	Cincinnati (USA)
Study period	1980-2003	2007 - 2009
Population	117 (35)	51 (51)
CoA	15.4%	15.7%
Bicuspid aortic valve	12.8%	39.2%
Aortic stenosis	8.5%	-
VSD	4.3%	-
PAPVD	3.4%	15.7%
ASD	1.7%	-

**CoA:** Coarctation of the aorta. **VSD:** Ventricular septal defect. **PAPVD:** Partial anomalous pulmonary venous drainage. **ASD:** Atrial septal defect.

condition is 1 in 10,000 live births. As a result of this genetic abnormality there are alterations that involve different systems, among them: nervous, hematological, connective tissue, osteoarticular, cardiovascular, and others (28). Cardiovascular involvement is caused by the affectation of the gene that encodes elastin (ELN), which leads to an abnormal or deficient deposit of this protein during the embryonic period, which is very important for the formation of blood vessels. Congenital malformations involving the cardiovascular system are present in about 75-80% of patients (29).

In the reviewed literature, vascular alterations such as pulmonary artery stenosis and supravalvular aortic stenosis were the most frequent defects compared to intracardiac alterations, which were mostly classified as atypical findings (28-30). In the reviewed literature, several congenital heart defects were found to be associated with Williams syndrome (Table 5).

In summary, and according to the literature, the most frequent congenital heart diseases associated with chromosomal syndromes are described in Table 6.

**Table 5.** Frequency of congenital heart disease in Williams syndrome.

Author (date)	Bruno et al. (2003)	Del Pasqua et al. (2009)	Collins et al. (2007)
Location of the study	Cordoba (Argentina)	Rome (Italy)	Philadelphia (USA)
Study period	1980-2002	1981-2006	1980-2007
Population	53 (85)	150 (113)	129 (129)
Supravalvular aortic stenosis	71%	64.6%	57%
Peripheral pulmonary stenosis			62%
Supravalvular pulmonary stenosis	38%	45.1%	20%
Valvular pulmonary stenosis	11%		16%
Mitral valve prolapse	27%	6.2%	15%
CoA	4%	6.2%	18%
VSD	4%	7.9%	21%

**CoA:** Coarctation of the aorta. **VSD:** Ventricular septal defect

**Table 6.** Most common congenital heart diseases by syndrome

Down syndrome	Patau syndrome	Edwards syndrome	Turner syndrome	Williams syndrome
DSAV (9-43%)	PDA (37-68%)	VSD (48-94%)	Bicuspid aortic valve (21.8-39.2%)	Supravalvular aortic stenosis (57-71%)
VSD (12.7-41%)	ASD (19-53%)	PDA (57-77%)	CoA (15.4-15.7%)	Pulmonary stenosis (38-62%)
ASD (6.9-38%)	VSD (15-50%)	ASD (21-68%)	Aortic stenosis (8.5%)	Mitral valve prolapse (6.2-27%)
PDA (1.3-21%)	TOF (5-23%)	CoA (3-27.2%)	PAPVD (3.4-15.7%)	VSD (4-21%)
TOF (1-5.4%)	Pulmonary Stenosis (11-18%)	Aortic stenosis (10-16%)	VSD (4.3%)	ASD (4-18%)

**AVSD:** Atrioventricular septal defect. **VSD:** Ventricular septal defect. **ASD:** Atrial septal defect. **TOF:** Tetralogy of Fallot. **PDA:** Patent ductus arteriosus. **CoA:** Coarctation of the aorta. **PAPVD:** Partial anomalous pulmonary venous drainage.

## Discussion

### Down syndrome

Although the congenital heart disease mostly associated with Down syndrome was the atrioventricular septal defect, there was great variability in the size of the samples and the percentage obtained. The highest percentages were observed in England, Brazil and Sweden, in contrast to Panama, Pakistan and Mexico, in which, according to the population studied, only 6% of the sample had the defect.

Ventricular septal defect was more frequent in Colombia and Pakistan, where 62% and 41% of their samples had this type of congenital heart disease; in the other study populations no major variation was found, and the frequency ranged between 13-31%. Colombia also had the highest rates of atrial septal defect.

Tetralogy of Fallot was found to be a fairly infrequent heart disease; the studies reported a frequency variation in the range of 1-5.5%, with the exception of Colombia, where it reached 17.17%. On the other hand, persistent *ductus arteriosus* was more frequent in Colombia, Mexico, Panama, Morocco and Pakistan; other descriptive studies from countries such as the United States, England, Sweden and Brazil had a frequency of between 1-7%.

The large variability of the data expressed as percentages is due to sociocultural variation and the increasing diagnostic capacity of congenital heart disease over the years; likewise, the large proportion found in the Colombian study may be partially explained by the fact that its percentages did not exclude data

on multiple heart diseases, unlike the other studies, which considered only isolated heart diseases.

Although congenital heart defects are diagnosed in up to 50% of patients with Down syndrome, the frequency is lower in those with trisomy 21 mosaicism <sup>(1)</sup>. The fact is that congenital heart defects have become less common in infants diagnosed with Down syndrome, probably because of improvements in prenatal diagnosis and selective abortion <sup>(9)</sup>.

### Patau syndrome

Despite the few studies obtained and the small sample size, the most frequently associated heart disease in China and the United States was persistent *ductus arteriosus*, in contrast to Brazil and Japan, where the first places were occupied by atrial septal defects and interventricular septal defects. Pulmonary atresia-stenosis ranged between 11-18%, but in the Japanese study the frequency was nil.

Tetralogy of Fallot was more frequent in China when compared to the descriptive studies from other countries; on the other hand, double outlet right ventricle and coarctation of the aorta showed similar frequencies in China, Japan and the United States; it should be noted that no data on these heart diseases were obtained from Brazil.

The prior explanation given for Down syndrome regarding data variability also applies to data about the Patau syndrome. It is also important to note that the Japanese study only considered percentages of isolated or single congenital heart defects and not multiple, as is the case of the studies from China, Brazil and the United States.

## Edwards syndrome

Ventricular septal defect was found to be the most frequent congenital heart disease (48-94%) in all the studies reviewed, and was also the one most frequently reported in the reviewed literature<sup>(2)</sup> where it is showed a frequency of more than 90%, followed by PDA, with many more variations between each of the studies.

We reviewed studies that statistically considered only the main diagnoses of each case, which would explain the reason for very pronounced variations in the percentages, in addition to underestimating the frequency of other pathologies that could be present concomitantly in each of the evaluated patients. Thus, it is difficult to compare the data and to know the absolute values of each one of them.

There were studies that did not report the presence of some heart diseases, like aortic stenosis, aortic insufficiency and aortic valve atresia, which may be explained by the difference in the number of the evaluated populations, since some studies included 22 cases compared to another with 1020 patients.

## Turner syndrome

The two most frequent congenital heart diseases related to the Turner syndrome that were reported in the two reviewed studies were those involving the aortic artery and valve: coarctation of the aorta and bicuspid aortic valve. This correlates with what was described by Bondy<sup>(27)</sup>, who reviewed five studies with more than 100 patients, published prior to our search, in which bicuspid aortic valve (12-30%) and coarctation of the aorta (7-18%) were found to be the most frequent presentations, followed by septal defects and partial anomalous pulmonary venous circulation. However, Lin<sup>(2)</sup> describes other anomalies with a similar frequency to those mentioned: transverse aortic elongation (25-50%), aortic dilatation (25-40%) and congenital coronary anomalies (5-25%).

The frequency of coarctation of the aorta is similar in the analyzed studies<sup>(26,27)</sup>, but there was no concordance in the percentages of the other heart diseases and even the presence of other conditions such as aortic valve stenosis or intercavity communications was not reported. The small number of studies found and the difference in the size of the populations do not allow a proper comparison between the results. This added to the fact that other congenital heart diseases that were considered in Volk's study were not reported<sup>(25)</sup>.

## Williams syndrome

The three reviewed studies on Williams syndrome point to supra-aortic stenosis as the most frequent anomalous

cardiac condition. The scientific literature also reports supra-aortic stenosis as the main condition, with frequencies ranging from 45 to 75%<sup>(28)</sup>. The same happens with pulmonary stenosis in its different presentations (peripheral, supra-aortic, valvular) with frequencies that place it in a range of 37-75%, with most studies reporting a frequency of 40%<sup>(29)</sup>.

Mitral valve prolapse is found in 27% of cases in Argentina, a slightly higher frequency compared to the United States of America (USA) (15%) and Italy (6.2%). Coarctation of the aorta and ventricular septal defect had a similar frequency in Argentina and Italy, but the percentage increased in the USA. Based on the aforementioned, it can be concluded that the populations of Argentina and Italy are similar in terms of congenital heart disease associated with Williams syndrome, and the percentages are mostly higher in the USA, where peripheral pulmonary stenosis is more frequent.

## Limitations

Most of the reviewed studies were published during the past decade, which makes it difficult to know the current status of these heart diseases. There is a limited number of studies dealing with heart disease associated with chromosomal syndromes other than Down syndrome; in addition, the small population size does not allow an accurate estimation of the real frequency of these pathologies. The nationality, study types (some multicenter), methodology, the ways of presenting the information and results vary greatly between the studies, which makes it difficult to compare and analyze them. Finally, the lack of Peruvian articles on this subject does not allow us to know relevant information on the current situation in the country, hence the need to carry out scientific research on these topics.

## Conclusions

The frequency of congenital heart disease in children with chromosomal syndromes is high, but highly variable. For this reason, the importance of research during the neonatal period is emphasized in order to reduce morbidity and mortality rates and ensure a better quality of life during the development of these children.

## Authors' contribution

JECL and OEEA: Participated in the study design, data extraction and analysis, and drafting of the manuscript. GPHB: Participated in the study design, review of the manuscript and approval of the final version of the manuscript.

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