The heart in Down syndrome
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CHAPTER 1

General introduction

Cardiovascular Disorders among persons with Down Syndrome

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Health issues among persons with Down syndrome, 2010

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ABSTRACT

Down syndrome is the most common chromosomal abnormality among liveborn infants and is the most frequent chromosomal cause of intellectual disability.\(^1\) It is a multisystem disorder, characterized by various congenital defects, organic disorders, dysmorphic features and other health-related problems.\(^2\) The heart is affected frequently and the association between Down syndrome and congenital heart disease was already recognized by Garrod in 1894.\(^3\) Although a critical region on chromosome 21 as well as several candidate genes has been proposed, the genetic basis and pathogenesis of congenital heart defects in Down syndrome remain largely unknown. Cardiovascular disorders related to Down syndrome are numerous. Here, we review prenatal screening, intrauterine interventions and management of congenital heart defects in early childhood. Moreover, we discuss cardiovascular manifestations in adulthood, in particular pulmonary arterial hypertension and cardiac surgery in adults with Down syndrome.

**Key words**: Down syndrome; congenital heart defects; pulmonary hypertension, cardiac surgery; genetics
THE UNBORN CHILD WITH DOWN SYNDROME

The fetal blood circulation

In order to address the cardiovascular problems related to Down syndrome, it is important to understand the basic knowledge of the normal anatomy of the heart and blood circulation and fetal circulation. The development of the heart and blood vessels before birth is a complex and interesting happening. At an early stage in pregnancy, after 12 weeks of gestation, the development has already been fully completed. The remaining time before birth will be spent for growth. However, after birth the blood circulation will change dramatically, due to the expansion of the lungs after breathing; pulmonary pressure drops rapidly and blood flows through the lungs. The ductus arteriosus closes, left atrial pressure rises above right atrial pressure leading to closure of the foramen ovale, the opening between both atria. (See figure 1)

![Diagram of fetal blood circulation](image)

Figure 1 Normal fetal blood circulation. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.
Dotted line represents fetal blood circulation disappearing after birth
Continuous line represents remaining blood circulation after birth
1: Foramen ovale, 2: Ductus arteriosus, 3: Ductus venosus
Prenatal diagnosis and management of cardiovascular disorders in Down syndrome

In most western countries prenatal screening programs for Down syndrome and structural anomalies are currently available. Since the introduction of first trimester screening in most countries the combined test is the screening test of choice for Down syndrome. The combined test includes nuchal translucency (NT) measurement and first trimester biochemistry (Papp-A and free Beta-HCG). NT refers to the nuchal fluid accumulation visible in first trimester fetuses and measurable at ultrasound examination. An enlarged NT entails an increased risk for Down syndrome, but also for congenital heart defects (CHDs). Therefore the test preferentially identifies Down syndrome fetuses with a CHD. Mothers of fetuses with an enlarged NT are therefore offered karyotyping and detailed ultrasound examinations for the detection of congenital anomalies already from the late first trimester of pregnancy. Out of 967 fetuses referred to our Fetal Medicine Unit for fetal echocardiography in view of an enlarged NT, 68 (7%) had a CHD. In 13 cases (19%) the cardiac defect (9 atrioventricular septal defects (AVSD), 2 inlet ventricular septal defect, 1 Tetralogy of Fallot, 1 other) was associated with Down syndrome. Next to first trimester screening, routine ultrasound screening at 20 weeks is part of standard pregnancy care in most western countries and contributes to the detection of the majority of CHD in the fetus. Diagnostic accuracy and sensitivity of this ultrasound technique varies according to gestational age at diagnosis, characteristics of the used equipment and experience of the ultrasonographer. Every time a cardiac defect is seen at ultrasound examination mothers are offered karyotyping. Down syndrome is diagnosed in 4-9% of fetuses with cardiac defects. In prenatal series more than 50% of Down syndrome fetuses undergoing echocardiography have recognizable cardiac defects. All major cardiovascular defects in Down syndrome fetuses are amenable to prenatal diagnosis by fetal echocardiography. The spectrum of CHD is similar to what is seen after birth, AVSD being the most common of the severe defects (44%). Conversely, of all the AVSD diagnosed prenatally by echocardiography, 43% are associated with Down syndrome. In prenatal life the frequency of CHD in Down syndrome fetuses is higher and severe defects are more frequently observed. This is due to the fact that fetuses with severe cardiac defects are more likely to die in utero and mothers may be more inclined to terminate the pregnancy when a severe cardiac defect is seen. Moreover, milder defects such as small ventricular septal
defects or subtle variants of endocardial cushion defects may be more frequently missed at fetal echocardiography. Also the prenatal diagnosis of aortic coarctation remains a challenge as the only obvious detectable prenatal feature in this anomaly is ventricular chambers disproportion in the second or third trimester of pregnancy. One may expect that in view of the increasing availability of prenatal screening the total number of Down syndrome live births and of related CHD should decrease. Interestingly, over the decade 1989-2008 the number of Down syndrome cases diagnosed before or after birth in England and Wales increased by 71%, since mothers are having babies at an older age. However, owing to the effect of prenatal screening and consequent terminations of pregnancy the number of live births with Down syndrome has fallen by 1%. Overall about 92% of mothers confronted with the diagnosis Down syndrome in England and Wales terminate pregnancy. In other counties termination rates vary considerably, reflecting prenatal screening participation and women attitudes towards Down syndrome. When a CHD is diagnosed in a Down syndrome fetus couples are counselled about the prognosis of the cardiac defect in a baby with a chromosomal anomaly. If they choose for continuation of pregnancy, pregnancy care is organized at a Perinatal Centre with a neonatal intensive care unit and experience in the management of delivery and immediate postnatal care of a fetus/neonate with a CHD.

During pregnancy, fetal echocardiography is repeated at regular interval until birth to check for signs of impending cardiac failure or deterioration of the anomaly (ascites, pericardial effusion, abnormal cardiac rhythm, cardiac chambers dilatation) that may be an indication for earlier delivery.

CARDIOVASCULAR DISORDERS IN CHILDHOOD

3.1. Congenital heart defects in Down syndrome

Down syndrome is associated with multiple malformations and there is an increased risk of leukemia (<1%); hearing loss (75%), gastrointestinal malformations (14%), celiac disease (17%), eye disease (60%), thyroid disease (15%) and CHDs. In the general population CHDs occur in approximately 8 per 1000 newborns, whereas almost 50 percent of the neonates with Down syndrome have a CHD. Down syndrome also shows a fixed pattern of CHD, with overrepresentation of septal defects. In patients with a CHD, an AVSD is the most common defect, with a
prevalence of 45 percent, followed by a ventricular septal defect in 35 percent and an isolated atrial septal defect in 8 percent of the cases (see Table 1). Tetralogy of Fallot and a patent arterial duct account for 10 percent of the cardiac defects in Down syndrome, while other defects are rare. Recent findings suggest that sex and ethnic differences exist in the incidence of AVSDs in Down syndrome, with twice as many females and blacks affected. Hispanics are affected less frequently compared to Caucasians.

<table>
<thead>
<tr>
<th>Table 1. Congenital heart defects</th>
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<tr>
<td>Frid et al. 1999</td>
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<td>n = 219</td>
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<tr>
<td>Percentage with congenital heart defects</td>
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<tr>
<td>Type of defect¹</td>
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<tr>
<td>Atrioventricular septal defect</td>
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<tr>
<td>complete</td>
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<tr>
<td>partial</td>
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<tr>
<td>Ventricular septal defect</td>
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<td>Atrial septal defect, type ²</td>
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<td>Patent arterial duct</td>
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<tr>
<td>Aortic coarctation</td>
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<tr>
<td>Tetralogy of Fallot</td>
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<tr>
<td>Other</td>
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Septal defects can be classified into three major subgroups based on location of the defect. An atrial septal defect is an opening between the two atria (the upper chambers of the heart). Type of atrial septal defect is classified by the location of the defect in the atrial septum (see figure 2). A ventricular septal defect is an opening between the two ventricles (the main chambers of the heart). Ventricular septal defects are muscular or membranous and they are located on various locations of the ventricular septum (see figure 3). Approximately 24% of the small ventricular septal defects close spontaneously by 18 months. Up to 75% are closed by the age of 10. Moderate to large ventricular septal defects often become smaller but remain patent and allow shunting of blood from one side of the circulation to the other. Because the left (systemic) blood pressure is higher than the right (pulmonary), the shunt is left to right and increased blood is circulated through the lungs. Eventually,
the increased flow rates through the pulmonary circulation lead to obliteration of the lung tissue and pulmonary hypertension. An atrioventricular septal defect, also known as atrioventricular canal defect or endocardial cushion defect, is an opening between the atrial component of the septum which continues down between the ventricular component of the septum. The primary defect is the failure of formation of the part of the heart that arises from an embryonic structure called the endocardial cushions. The endocardial cushions are responsible for separating the central parts of the heart near the tricuspid and mitral valves (atrioventricular valves), which separate the atria from the ventricles. Two different types can be classified; complete and partial AVSD (see figure 4). A complete AVSD is one in which there are defects in all structures formed by the endocardial cushions and the atrioventricular valves remains undivided or "common." A partial or incomplete AVSD is one in which the bridging leaflets of the atrioventricular valves are fixed to the ventricular septum, leaving only a (type 1) atrial septal defect, and the atrioventricular valves are divided into two distinct valves. Usually, a ventricular septal defect is absent, but there may be a small, hemodynamically unimportant interventricular communication.14

Figure 2 Atrial septal defect. RA, right atrium; LV, left ventricle; AO, aorta; VCI, vena cava inferior; VCS; vena cava superior. 1: atrial septal defect type 1, 2: atrial septal defect type 2, 3: sinus venosus defect, 4: sinus coronarius defect
Figure 3 Ventricular septal defect. RV, right ventricle; RA, right atrium
1: perimembranous (inlet) ventricular septal defect, 2: muscular (trabecular) ventricular septal defect, 3: subarterial (outlet) ventricular septal defect

Figure 4 Atrioventricular septal defect. RV, right ventricle; RA, right atrium, LA, left atrium; LV, left ventricle T; tricuspid valve, M; mitral valve, a; aorta, p; pulmonary artery

Presenting symptoms and development
Newborns with a CHD are at risk to develop congestive heart failure. Symptoms are rapid breathing, sweating and failure to thrive. Frequently, they develop low airway infections and grow slowly or sometimes they even have loss of weight. These symptoms usually develop gradually over the first 1 to 2 months of life. The
turbulence of the increased amount of blood being pushed towards the lungs and blood leaking through the pulmonary valve can be heard as a heart murmur.

Down syndrome patients with AVSD are also exposed to persistent left-to-right shunts. The magnitude of the shunt depends on the size of the ventricular septal defect and the ratio of pulmonary to systemic flow. In the healthy newborn without CHDs, pulmonary vascular resistance normalizes from a high fetal value in 7 to 10 days. However in case of a shunt this mechanism may be delayed for three to six weeks, so the onset of pulmonary vascular remodelling causing dyspnea is usually delayed. Particularly in children with Down syndrome the delay in fall of pulmonary vascular resistance may be prolonged or remains high and symptoms of cyanosis and right-to-left shunting occur. Over time, the exposure to increased pulmonary blood flow results in increased shear stress on endothelial cells. Production of nitric oxide, a potent vasodilator is impaired and pulmonary arterial hypertension develops.

**Diagnostic procedures**

*Physical examination*

As described above, CHDs are common in Down syndrome. Physical examination alone is insufficient in detection of CHDs. Therefore, echocardiographic evaluation, shortly after birth, is recommended by the American Academy of Paediatrics. Tubman et al. reported that physical examination alone can miss 40 to 50% of the CHDs. The newborn may be asymptomatic and clinical signs such as murmurs may not be evident, due to high pulmonary vascular resistance. Nonetheless, physical examination could provide important signs for the presence of a CHD, irrespective of patients with and without Down syndrome. When focused on septal defects the following diagnostic signs should be considered specifically. The pulse, respiratory rate, oxygen saturation, and blood pressure yield important information in a cyanotic infant. Infants with cyanotic CHDs commonly present with cyanosis with mild or absent tachypnea.

*Chest radiography*

Chest radiography alone as examination method is insensitive for detecting CHDs in neonates with Down syndrome. However four features of the chest radiograph could provide important information in the evaluation of CHDs: 1) heart size, 2) heart
shape, 3) pulmonary vascular markings, and 4) the course of the aortic arch. Patients with left-sided obstructive lesions may have cardiomegaly due to heart failure. Extreme cardiomegaly suggests lesions associated with a dilated right atrium. Characteristic abnormalities of heart shape are associated with specific lesions. Examples are the boot-shape and egg-on-a-string shape in patients with a Tetralogy of Fallot and transposition of the great arteries, respectively. Pulmonary vascular markings are decreased in most cyanotic CHDs and increased in patients with common AVSD as pulmonary vascular resistance falls. An abnormal right descending aortic arch is present in approximately 20 percent of patients with Tetralogy of Fallot and 30 percent with truncus arteriosus.

**Electrocardiography**

In the fetus, the right ventricle has a larger volume load than the left ventricle since there is limited pulmonary flow and thus reduced blood volume in the left heart (see figure 1). As a result, the normal neonatal electrocardiogram has a right axis and a precordial pattern of right ventricular hypertrophy. In many cyanotic heart lesions, the electrocardiogram is normal in the neonatal period. However specific markings can indicate that CHDs are present. First-degree heart block is common in AVSD and a superior mean frontal QRS axis (left axis deviation) is the most common finding on the electrocardiogram. The mechanism responsible for the superior axis is the congenital displacement of the conduction pathways in the ventricles, and thus the superior axis is seen in at least 97% of complete atroventricular canals at birth.

**Cardiac echocardiography**

Because of its noninvasive nature and widespread availability, echocardiography has become the method of choice in the diagnosis of a CHD in neonates with Down syndrome. Two-dimensional echocardiography allows visualization of structural CHDs and valvular abnormalities. Echocardiography, including two-dimensional imaging and pulsed and colour flow Doppler interrogation of flow patterns, provides a complete determination of cardiac anatomy and function (see figure 5). By routine echocardiographic evaluation in the newborn with Down syndrome, definite imaging of AVSDs can be made. An echocardiogram also provides additional information about 1) level and direction of shunting 2) function of the common or divided
atrioventricular valve(s) 3) ventricular function and size 4) presence of outflow tract obstructions or existence of other anomalies. Echocardiographic images of an adult with Down syndrome and an AVSD are showed in figure 6. Figure 7 highlights the level and direction of shunting by colour flow Doppler imaging in a patient with a ventricular septal defect.

Figure 5 Echocardiogram of a normal heart. LA, left atrium; LV, left ventricle; RV, right ventricle
a) On the left panel a two-chamber parasternal long-axis view of a normal heart
b) On the right panel an apical four-chamber view of a normal heart;

Figure 6 Echocardiogram of an adult with Down syndrome and AVSD. AVSD, atrioventricular septal defect; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. The asterisk sign shows the defect with interruption of the septum.

a) On the left panel a two-chamber parasternal long-axis view of a patient with an atrioventricular septal defect and pulmonary arterial hypertension. Note the extremely hypertrophied right ventricle and septum.
b) On the right panel an apical four-chamber view of a patient with an atrioventricular septal defect and pulmonary arterial hypertension.
Figure 7. Echocardiogram of an adult with Down syndrome and VSD. VSD, ventricular septal defect; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. The asterisk sign shows the defect with interruption of the septum.

a) On the left panel an apical four-chamber view of a patient with a ventricular septal defect.

b) On the right panel the same apical four-chamber view with Doppler echocardiography. Colors are used to represent the velocity and direction of blood flow. This image shows a left-to-right shunt from left- to right ventricle.

Cardiac catheterization
Diagnostic cardiac catheterization in CHD patients have been for the most part replaced by non-invasive imaging techniques such as echocardiography and cardiac Magnetic Resonance Imaging (MRI). However, cardiac catheterization and angiography still remains important to make an anatomic and physiological diagnosis in CHD patients with complex or unusual cardiac anatomy. Meaningful and accurate hemodynamic and anatomical data must be obtained for the preoperative evaluation of CHD patients to guide clinical decision-making. For this reason, the majority of patients with univentricular physiology still undergo diagnostic catheterization before bidirectional Glenn and Fontan surgeries. Also patients with complex pulmonary atresia and ventricular septal defect usually require catheterization and angiography for optimal visualization of the anatomy of the pulmonary arteries. In older children and adults with large left to right shunts, in particular in patients with Down syndrome,
precise calculation of pulmonary vascular resistance by catheterization can be necessary to assess operability.

**Treatment of congenital heart disease**

*Catheter interventions*

The progress in pediatric interventional cardiology has changed the therapeutic approach for many CHD patients. The balloon atrial septostomy, introduced by Rashkind in 1966, was the first pediatric catheter intervention and is still widely used to create an interatrial communication in cyanotic newborns with transposition of the great arteries. Balloon dilatations and stent placements have become the procedures of choice for pulmonary and aortic valvular stenosis, recoarctation, and branch pulmonary artery stenosis. Lesions with left to right shunts, including atrial septal defects, ventricular septal defects and persistent ductus arteriosus, can now be closed safely and effectively by transcatheter techniques using different devices. These procedures are now considered good alternatives to surgical closure and are the most common transcatheter interventions in patients with Down syndrome. Recently, percutaneous pulmonary valve replacement has become an attractive therapy in CHD patients with pulmonary regurgitation or stenosis delaying the need for open-heart surgery. A heart valve attached to a stent functions as an artificial pulmonary valve for CHD patients, mostly with Tetralogy of Fallot.

*Cardiac surgery in childhood*

Twenty years ago corrective cardiac surgery was often not attempted in children with Down syndrome due to high surgical mortality of up to 60% and short life expectancy. Since then, techniques of corrective cardiac surgery have been dramatically improved outcomes. Recent papers have shown that the presence of Down syndrome did not increase operative mortality in children with Down syndrome with ventricular septal defect or Tetralogy of Fallot. Interestingly, in patients with AVSD, patients with Down syndrome had significantly lower perioperative mortality than patients without Down syndrome. Patients with complete AVSDs are operatively corrected usually in the first 6 months of life. Moderate ventricular septal defects are generally repaired at age 1 year if there is associated failure to thrive or recurrent...
lower respiratory infections. If a moderate ventricular septal defect appears to be getting smaller, one can wait several years (up to age 5 years) to provide an opportunity to avoid surgery. Atrial septal defects that need surgery are typically operated on after 2 years of age.24

There is paucity of information on surgical outcome in patients with Down syndrome and a single ventricle, due to the low incidence of ventricular hypoplasia or unbalanced ventricles in trisomy 21. The study of Wada et al. in which six children with Down syndrome and single ventricle underwent surgical palliation, showed that single ventricle repair has difficulties due to associated problems in Down syndrome, such as rapidly progressing pulmonary vascular changes and airway obstruction.25 The study by Gupta-Malhotra et al., showed that mortality after cavopulmonary shunt operations for univentricular hearts was significantly increased in patients with Down syndrome compared to those without (35% vs 10%).26 Down syndrome appeared to be an independent predictor for mortality. Corrective cardiac surgery is not contraindicated in patients with Down syndrome, however specific surgical procedures are associated with higher mortality rates and patient selection should be done carefully.

**Survival of Down syndrome patients and congenital heart defects**

Average life expectancy of all patients with Down syndrome, with and without CHDs, has increased from a mere 12 years in the 1940s to 60 years in present-day populations.27 In spite of this, neonatal and infant mortality are respectively 5 and 8 times higher in patients with Down syndrome compared to the general population, mostly due to the presence of CHDs.28 In an extensive study of Yang et al. about mortality in patients with Down syndrome, almost 18,000 death certificates of persons with Down syndrome in the USA from 1983 to 1997 were analyzed.29 CHDs and respiratory infections were the most frequently reported medical disorders on death certificates of people with Down's syndrome. A sharply increased median age at death in persons with Down syndrome and additional CHDs was found after 1992, from 0 year of age in 1992 to 18 years of age in 1994. As 50% of the children with Down syndrome have a CHD, this indicates that survival of children with Down syndrome substantially and rapidly improved in the early 1990s.29
CARDIOVASCULAR DISORDERS IN ADULTHOOD

Introduction
Acquired cardiovascular disease is common in the general population, affecting the majority of adults past the age of 60 years. Acquired cardiovascular disorders include coronary heart disease (myocardial infarction and heart failure), cerebrovascular disease (stroke, transient ischemic attack), peripheral arterial disease and atherosclerosis. Life expectancy has increased last decades; however the number of cardiovascular deaths in the general population remains high. For persons aged 40 years, the lifetime risk of developing coronary heart disease is 49 percent in men and 32 percent in women. Many important risk factors have been identified. These included smoking, dyslipidemia, hypertension, diabetes, abdominal obesity. Beneficial factors are daily consumption of fruits and vegetables, regular alcohol consumption, and regular physical activity.

Atherosclerosis in Down syndrome
Adults with intellectual disabilities have increased cardiovascular risk factors. A sedentary lifestyle and an unhealthy diet are common, especially in individuals with Down syndrome living in community settings. In patients with Down syndrome, prevalence of overweight and obesity is significantly higher, compared to other patients with intellectual disabilities and to the general population. With a reported prevalence of obesity in adults with Down syndrome between 31 and 47 percent. Although abnormalities in lipid metabolism, which are associated with high risk of premature atherosclerosis in the general population, are frequently seen in patients with Down syndrome, coronary artery disease related mortality is surprisingly low. Histopathological investigations showed no increase in atherosclerosis, or even a total lack of atherosclerotic changes. Duffels et al. found a decreased carotid intima media thickness, an accepted valid marker for atherosclerosis, in adult patients with cyanotic congenital heart disease compared to healthy controls. Of the cyanotic patients 35% had Down syndrome. The concept of Down syndrome as an atherosclerosis-free model has even been proposed. Both environmental and genetic factors have been suggested to contribute to the low levels of atherosclerosis. Prevalence of smoking and hypertension is low in patients with Down syndrome. Another explanation could be the overexpression, due to triplication of chromosome...
21, of atherosclerotic protective factors.\textsuperscript{43-45} Suggested overexpressed protective factors are cystathionine-beta-synthase, leading to decreased level of homocysteine\textsuperscript{46-49} and brain-derived neurotrophic factor.\textsuperscript{50} The hypothesis mentioned above is based on the assumption of an overexpression of genes on chromosome 21. However, the assumption of a 50 percent increase of all genes on chromosome 21 is too simplistic, as some gene products are more sensitive to gene dosage effects than others, caused by negative feedback mechanisms and gene-expression variation among individuals.\textsuperscript{46, 51}

**Thyroid-related cardiac impairment in Down syndrome**

**Hypothyroidism**

Down syndrome has long been associated with a variety of autoimmune conditions, with the thyroid gland being most frequently affected. Prevalence of thyroid disease in Down syndrome varies between 7 to 50 percent, depending on the selected population and the diagnostic criteria.\textsuperscript{52, 52, 53} Therefore the American Academy of Paediatrics recommends routine thyroid screening early in life.\textsuperscript{5} Thyroid disease has an effect on the cardiovascular system and may lead to impairment of ventricular function.\textsuperscript{54} Even subclinical hypothyroidism, with a slight elevation of serum thyrotopin concentrations and normal thyroxin concentrations, is suggested to decrease myocardial contractility and cardiac output.\textsuperscript{55-57} However, these findings were not confirmed by Toscano et al., who found no increased risk of thyroid-related cardiac impairment in children with Down syndrome and subclinical hypothyroidism, compared to matched euthyroid subjects with Down syndrome.\textsuperscript{58}

**Hyperthyroidism**

Hyperthyroidism occurs less frequently in patients with Down syndrome. Although the reported prevalence varies between 0.8 and 2.5 percent,\textsuperscript{52, 59-61} this could be an underestimation. Firstly, there is low awareness of the association between hyperthyroidism and Down syndrome among physicians. Secondly, symptoms of hyperthyroidism can easily be overshadowed by the intellectual disability. Physicians should be suspicious on thyreotoxicosis, associated tachyarrhythmias, thromboembolism, and heart failure. Moreover, previous reports suggest an association between hyperthyroidism and mild or transient pulmonary hypertension.\textsuperscript{62}
caused by an increased cardiac output (up to 300 percent). Hyperthyroidism-related pulmonary hypertension is largely asymptomatic and has good prognosis after restoration of euthyroid state. Thus, hyperthyroidism can cause potentially serious complications that need prompt recognition and effective management, highlighting the need for routine evaluation of thyroid function in individuals with Down syndrome.

**Pulmonary hypertension**

Pulmonary arterial hypertension is rare syndrome characterized by symptoms of dyspnea, fatigue, chest pain and syncope. Underlying mechanism is a progressive increase of pulmonary vascular resistance and a sustained elevation of pulmonary arterial pressure. Pulmonary arterial hypertension associated with congenital heart disease is caused by intra-cardiac shunting (most frequently uncorrected AVSD in patients with Down syndrome) and pulmonary blood volume overload. Patients with Down syndrome and CHDs are at higher risk of developing pulmonary arterial hypertension compared to patients without Down syndrome. Several predisposing factors are recognized to play a role e.g. a diminished number of alveoli, a thinner media of pulmonary arterioles and an impaired endothelial function in these patients. Most commonly symptoms do not develop until the twenties when evidence of pulmonary vascular disease becomes apparent. Therefore, early corrective cardiac surgery is warranted to prevent irreversible pulmonary vascular lung damage.

Recent successes have been achieved with the use of therapies targeted against the pathophysiological pathways that underlie pulmonary arterial hypertension. Three main pathways have been detected: prostacyclin (e.g. epoprostenol, iloprost, trepostinil), phosphodiesterase-5-inhibitor (e.g. sildenafil) and endothelin receptor antagonists (e.g. sitaxentan, ambrisentan, bosentan). These advanced therapies have been demonstrated to improve clinical status and life expectancy of patients with pulmonary arterial hypertension. A recent study showed that the positive effects of these treatment strategies are similar in Eisenmenger patients with Down syndrome, compared to Eisenmenger patients without Down syndrome. Exercise capacity initially improved, and stabilized thereafter.
Cardiac surgery in adulthood

Nowadays, cardiac surgery at young age is no longer refrained in patients with Down syndrome and CHDs. Thus, the group of adult patients with unrepaired CHDs is declining. However, residual lesions, like residual shunting or residual atrioventricular valve regurgitation require additional reoperations in a substantial group of adult patients. In their single centre retrospective study (40 years follow-up), Majdalany et al. showed that 27% (4 out of 15) of adult patients with Down syndrome that had been operated in childhood required reoperations. Patients with Down syndrome and uncorrected cardiac defects are also potential candidates for heart-lung transplantation. However, no reports are published on heart-lung transplantation in Down syndrome. Physicians may worry that transplantation is a ‘bridge too far’ for patients with Down syndrome, because of coexisting medical problems, the intellectual disability, and the concerns of immunological abnormalities. Therefore outcome predictions are hard to make in these patients.

GENETICS IN CONGENITAL HEART DISEASE IN DOWN SYNDROME

Chromosome 21 is among the smallest of human chromosomes, and was originally estimated to contain 225 genes but up till now more than 420 genes have been identified. The function of only a minority of these genes is currently known (http://chr21.egr.vcu.edu:8888/).

Although the phenotypic features of Down syndrome must ultimately be due to the third copy of chromosome 21, the genetic mechanisms by which the phenotype arises are not understood. Two hypotheses exist; one assumes the phenotype is caused by the increased dosage and hence overexpression of one or more genes on chromosome 21, the other states that phenotypic instability due to the extra genetic information leads to the phenotype. The genes on chromosome 21 involved in the phenotypic features of Down syndrome have been tried to be identified for many years, but no single gene has been linked to a specific feature yet. Even so, the genes responsible for the CHDs in Down syndrome are unknown. Several genes are currently known to be implied in human CHDs, such as NKX2.5, GATA4, GATA5 and NOTCH1, but mutations in these genes have been found in only a small proportion of CHD patients, and none of these genes maps to chromosome 21. As the heart defects in Down syndrome typically involve the atrioventricular valve septum, genes
expressed in these tissues during heart development may be candidates for the heart defects in Down syndrome. Many of these genes are not located on chromosome 21, however. Although in the past years various candidate genes located on chromosome 21 have been proposed for CHDs in Down syndrome (see below), no gene has been definitively established to be involved in CHDs in Down syndrome.

**Down syndrome-CHD critical region**

The existence of rare Down syndrome patients who are trisomic for only a part of chromosome 21 has lead to the assumption that only a small region of chromosome 21 may be involved in producing most features of Down syndrome, i.e. that only a small part of chromosome 21 actually needs to be triplicated to cause the Down syndrome phenotype. This chromosomal region was referred to as the so-called ‘Down syndrome critical region’ (DSCR). A relatively large number of patients with partial trisomies has been characterized clinically, cytogenetically and molecularly to identify the genomic regions responsible for the Down syndrome phenotype. Investigation of additional cases suggested that no DSCR exists which can be said to be totally responsible for the clinical findings in Down syndrome, but that there are multiple critical regions for certain phenotypic features. It has also been tried to identify a specific critical region for the CHDs in Down syndrome (Down syndrome-CHD critical region), as the identification of such a critical region may guide the search for genes involved in CHDs. Initially, the minimal region believed to be needed to be triplicated to produce CHDs in Down syndrome was 10.5 Mb long and mapped to the chromosomal marker D21S55 region on distal 21q22.2 to q22.3 (the telomeric end of chromosome 21q). In the following years, that critical region was narrowed further by analyses of subsequent patients with partial trisomies. Barlow et al. (2001) mapped the Down syndrome-CHD critical region to a 5.5 Mb region between marker D21S3 and PFKL. Korbel et al. narrowed this segment to a 2.82 Mb critical region likely involved in defects of the atrioventricular septum. By integrating their data with several other lines of evidence, in particular information from partial trisomic mouse models, the authors proposed a 1.77 Mb Down syndrome-CHD critical region (see figure 8) containing 10 genes, the Down syndrome cell adhesion molecule (DSCAM) gene defining the centromeric border. The authors suggested DSCAM as a candidate for CHD. Several other genes
previously proposed as having a role in Down syndrome CHD were located outside the mapped region (see below).

Nevertheless, a high degree of phenotypic variability exists in trisomy 21, with more than half of patients with full trisomy not having CHDs. This suggests that factors other than overexpression of genes on (the critical region of) chromosome 21 must be involved in CHDs and that a possible critical region thus may be described as a susceptibility region. The genes on chromosome 21 act together and interact with genes elsewhere in the genome, as well as with environmental and stochastic factors, to produce CHDs and other features of the Down syndrome phenotype. This makes the CHDs and other features of Down syndrome multifactorial conditions.

Figure 8 Chromosome 21. DSCHD-region: Down Syndrome Congenital Heart Defect-region. Figure based on published data of Korbel et al 2009.

Mouse models and expression studies
Additional approaches for identifying genes and other functional genomic elements contributing to the features of Down syndrome have been the construction of partial trisomic mouse models and gene and protein expression studies. A number of trisomy 21 mouse models exhibit heart defects similar to those observed in Down syndrome, suggesting that trisomy of one or more of the genes in these models have a role in heart development. As the orthologous genes of human chromosome 21 are distributed among 3 different chromosomes (chromosomes 10, 16 and 17) in the mouse, the development of mouse models of human trisomy 21 has not been easy: the different mouse models are trisomic for genes not located on human chromosome 21, while disomic for genes that would be triplicated in human trisomy.
This makes translation of results from mouse models to the human situation difficult. More recently, mice trisomic for more precise regions of human chromosome 21 have been produced, which may aid in identification of genes responsible for CHDs and other features of Down syndrome.

Studies on the spatial and temporal pattern of expression of genes on chromosome 21 also contribute to prioritizing candidate genes. Studies focusing on the level of gene expression found that only part of the genes on chromosome 21 are actually overexpressed in trisomy 21, also in the heart. It was therefore hypothesized that genes showing minimal overlap in expression between Down syndrome and euploid individuals have a primary role in the phenotype of Down syndrome, while the genes having a variable expression might play a role in the phenotypic variability in Down syndrome.

Candidate genes
The study of mouse models and expression studies have lead to several genes being proposed as candidates to play a role in CHDs in Down syndrome. Many of these proposed genes are located outside the latest mapped ‘critical region’. A subset of the candidate genes will be discussed here.

Korbel et al. proposed Down syndrome cell adhesion molecule (DSCAM) as a candidate gene, because of its properties and its location within the critical region that had been identified by the authors. DSCAM encodes a cell adhesion molecule involved in the development of the nervous system, but which is also highly expressed in the heart during cardiac development. Located outside their critical region but also suggested as a candidate gene for CHDs, is the Down syndrome critical region 1 gene (DSCR1, also named Regulator of Calcineurin 1, RCAN1). DSCR1 encodes an inhibitor of calcineurin/NFAT signalling and is expressed in many tissues including the heart. The NFAT signalling pathway is known to be a critical regulator of vertebrate development and organogenesis and was suggested to be critical for CHDs in Down syndrome. Arron et al. suggested DSCR1 to act synergistically with another chromosome 21 gene, dual-specificity tyrosine-(Y)-phosphorylation-regulated kinase 1A (DYRK1A), to inhibit the nuclear occupancy of NFAT transcription factors. DYRK1A encodes a nuclear kinase that regulates several transcription factors. Increased dosage of these two genes was
suggested to produce many of the features of Down syndrome, including heart defects.

The genes for the α1 and α2 chains of collagen VI are located on the subtelomeric end of the long arm of chromosome 21. Collagen VI is a microfibrillar component of many extracellular matrices, acting as a bridge between cell surfaces and the surrounding extracellular matrix. Collagen VI has been suggested to play a role in the pathogenesis of atrioventricular canal defects in Down syndrome. Altered expression of collagen VI was found in endocardial cushions of fetuses with trisomy 21 as compared to normal fetuses. The genes for collagen VI α1 and α2 chains were excluded from the latest Down syndrome-CHD critical region, because patients with Tetralogy of Fallot or atrial septal defects were observed without a triplication of the collagen VI gene. However, all patients in these studies with defects resulting from abnormal atrioventricular cushion differentiation, did have three copies of the collagen VI gene, not excluding a role for collagen VI in these types of CHDs. The gene encoding collagen XVIII is also located on chromosome 21, and collagen XVIII was found to be highly expressed throughout the connective tissue core of the endocardial cushions and forming atrioventricular valve leaflets in mice, suggesting a role in cardiac valve morphogenesis and possibly underlying the CHDs in Down syndrome.

The SH3 binding glutamic acid-rich (SH3BGR) gene, encoding a protein containing a highly conserved SH3 binding motif and a glutamic acid-rich domain at the COOH terminal, was also suggested to be involved in CHD in Down syndrome, since it is expressed early in the mouse heart. However, overexpression of SH3BGR was not found to affect heart morphogenesis in mice.

In contrast to the abovementioned genes proposed to have a role in the generation of CHDs, it has also been suggested that overexpression of some chromosome 21 genes may be a protective factor against some types of CHDs, as transposition of the great arteries and atresia of the atrioventricular-valves, among others, are virtually absent in patients with Down syndrome.

Although many more candidate genes have been proposed, no gene has definitively been connected to CHD in Down syndrome. Further studies will be required to identify the function of chromosome 21 genes and identify those genes implicated in CHD in Down syndrome.
Genetics of the atrioventricular septal defect

As AVSD occurs most frequently in the context of Down syndrome, chromosome 21 must harbour at least one gene that increases susceptibility for AVSD. However, AVSD also occurs in other syndromes and chromosomal abnormalities as well as in a non-syndromic fashion, implying genetic heterogeneity. Currently, two loci for non-syndromic AVSD have been identified. The AVSD1 locus is located on chromosome 1p31-p21, but the AVSD1 gene itself is unknown.117 The AVSD2 locus is on chromosome 3p25 and cysteine rich with EGF domains 1 (CRELD1) was identified as the responsible gene.118, 119 CRELD1 encodes a cell surface protein, that likely functions as a cell adhesion molecule. Missense mutations in CRELD1 are found in a small proportion of patients with non-syndromic AVSD.119, 120 These mutations act in a dominant manner with incomplete penetrance, and therefore CRELD1 is an AVSD susceptibility gene. Maslen et al. found missense mutations in CRELD1 in two of 39 patients with Down syndrome and complete AVSD, suggesting that defects in CRELD1 may contribute to the pathogenesis of AVSD in the context of trisomy 21.121

Mutations in GATA4, a transcription factor essential for cardiac development, have also been described in a patient with AVSD, although the main phenotype of GATA4 mutations are secundum atrial septal defects. Other genes that have been suggested to play a role in non-syndromic AVSD are CRELD2, BMP4, ALK2, and CFC1.124

Conclusion

Although a critical region as well as several candidate genes has been proposed, the genetic basis and pathogenesis of CHDs in Down syndrome remain largely unknown. The recent recognition that epigenetic factors such as DNA methylation, and micro-RNAs may also be involved in Down syndrome (reviewed in Patterson, 2009), adds to the complexity of the pathogenesis of Down syndrome. A critical aspect of understanding the pathogenesis of CHDs in Down syndrome remains the determination of the function of chromosome 21 genes. Further studies, including continuation of specific mouse model production, expression studies and studies of additional human subjects who are carefully phenotyped, are required to identify genes and other genetically active elements contributing to CHDs. Integration of the many different types of analyses will be required to enlarge our understanding of the pathogenesis underlying the CHDs in Down syndrome.
COMMENT

Down syndrome is a multi-organ disorder, affecting the heart and vascular system in both a structural and a functional way. The fixed pattern of congenital heart defects is intriguing, with the atrioventricular septal defect as the most common defect in persons with Down syndrome. Recent papers have shown that operative mortality was not increased in children with Down syndrome and repaired septal defects. This has resulted in a substantially and rapidly improved survival of children with Down syndrome. Although a critical region on chromosome 21 as well as several candidate genes has been proposed, the genetic basis and pathogenesis of congenital heart defects in Down syndrome remain largely unknown. Future molecular studies might give us more insight into cardiac development. Prevalence of thyroid disorders is high and might influence cardiac function. Therefore, routine screening on thyroid dysfunction is warranted in persons with Down syndrome.

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