

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.

For more information visit www.intechopen.com



Heart Diseases in Down Syndrome

A. K. M. Mamunur Rashid

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/46009>

1. Introduction

Down syndrome (trisomy 21) is the common disorder among chromosomal anomalies. Trisomy 21 remains the commonest with its incidence 1:650 – 1: 1000 live births (Hassold TA and Sherman S 2000). The clinical manifestations of Down syndrome (DS) are numerous and can present in any body system. The most significant include intellectual impairment, short stature, heart disease, digestive disorders and orthopedic abnormalities (Ramakrishnan V, 2011).

Cardiac malformations present at birth are an important component of pediatric cardiovascular disease and contribute a major percentage of clinically significant birth defects with an estimated prevalence of 4 to 5 per 1000 live births. It is estimated that 4 to 10 live born infants per 1000 have cardiac malformation, 40% of which are diagnosed in the first year of life.(Hoffman J I, 1990 ; Moller J H et al, 1993). Congenital heart defect are the most common of all birth defects, which is found to affect nearly 1% of newborns, and their frequency in spontaneously aborted pregnancies is estimated to be tenfold higher (Behrman RE et al., 2000). In the year 2000, prevalence of CHD in the pediatric population was estimated at approximately 623000 (320000 with single lesion, 165000 with moderately complex disease, and 138000 with highly complex CHD). (Hoffman J I et al, 2004) Among the CHD the incidence of ventricular septal defect (VSD) has been demonstrated to be high as 5% in 2 independent cohorts of 5000 serial newborns, 5000 serial premature infants. (Roguin N et al., 1995; Du Z D et al., 1996)

The causes for CHD can be categorized in to three major groups such as chromosomal, single gene disorder (10-15%) and multiple factors (85-90%). (Payne M et al., 1995)

Its association of congenital heart disease is well known. Among all cases of congenital heart diseases, 4%-10% are associated with Down syndrome, and 40%-60% of Down syndrome patients present congenital heart disease. Cardiac malformation in DS is the principal cause

of mortality in the first two years of life. (Rodriguez LH, 1984; Stoll C, et al., 1998) This congenital heart disease contributes significantly to the morbidity and mortality of children with Down syndrome, who may develop congestive heart failure, pulmonary vascular disease, pneumonia, or failure to thrive. In the first few days life symptoms or signs may be absent or minimal despite the presence of significant congenital heart disease. The characteristic heart defects seen in Down syndrome derives from the abnormal development of endocardial cushions and results in a spectrum of defects involving the atrioventricular septum and valves. Accounting for approximately 63% of all DS-CHD, their lesion varies in severity from persistent of the common atrioventricular canal and membranous ventricular septal defects to ostium primum patency with valvular anomalies. (Cooney T P et al., 1982; Anderson R H, 1991) The specificity of atrioventricular septal defects for trisomy 21 is emphasized by the observation that individuals with Down syndrome account for 70% of all atrioventricular septal defects. (Ferencz C et al., 1997) This is followed by patent ductus arteriosus and atrial septal defects. Other forms of complex heart disease can occur including overriding aorta and Tetralogy of fallot. (Berr C and Borghi E, 1990) The hypothesis suggests the existence of a gene or gene clusters on chromosome 21 which is involved in cell adhesion and likely plays an important role in valvuloseptal morphogenesis, but when over expressed, result in the defects of Down syndrome – congenital heart disease. (Barlow G M et al., 2001)

2. Etiology and genetics

Down syndrome which is normally caused by trisomy 21 is a major cause of congenital heart disease and provides an important model with which to link individual to the pathways controlling heart development. The characteristic heart defect seen in Down syndrome derives from the abnormal development of the endocardial cushions and results in a spectrum of defects involving atrioventricular septum and valves. Accounting for approximately 63% of all DS-CHD, (Van PR et al., 1996) these lesions vary in severity from persistence of the common atrioventricular canal and membranous ventricular septal defects to Ostium primum patency with valvular anomalies. (Cooney TP et al., 1982; Anderson RH, 1991) Independent and intersecting approaches to identifying the gene(s) for DS-CHD have included mapping genes known to be involved in cardiac development (none of which localized to chromosome 21) and studying rare individuals with CHD and partial duplications of chromosome 21. There are number of genetic tests that can assist the clinician in diagnosing genetic alterations in the child with CHD. These include cytogenetic technique, fluorescence in situ hybridization (FISH), and DNA mutation analysis. (Pierpont ME et al., 2007) The studies initially suggested that subsets of the DS phenotype were associated with three copies of chromosome band 21q22.2-22.3 (Rahmani Z et al., 1989; McCormick MK et al., 1989; Korenberg JR et al., 1990) and later, that DS-CHD was caused by the over expression of genes in the region including D21S55 through the telomere. (Korenberg JR et al., 1992; Delabar JM et al., 1993; Korenberg JR et al., 1994) Another work focused on the identification of a transcriptional map of DS-CHD region using a 3.5 Mb contiguous clone array covering the interval from D21S55 through

MX1/2.(Hubert RS et al., 1997) Recent study speculate that the over expression of Down syndrome cell adhesion molecule may have the potential to perturb epithelial-mesenchymal transformation and/or the migration and proliferation of mesenchymal cells, and possibly thus contribute to the increased intercellular adhesion seen in DS cushion fibroblasts and abnormal cushion development seen in DS-CHD. The DSCAM gene constitutes a large part of the DS-CHD region, spanning more than 840Kb of the region between D21S3 and (PFKL) as determined from BAC contigs (Yamakawa K et al., 1998) and genomic sequence analysis.(Hattori M et al., 2000) The study for DS-CHD suggests that the candidate region for DS-CHD may be narrowed to D21S3 (Defined by VSD), through PFKL (defined by TOF), comprising 5.5 Mb. This represents significant reduction of the previously described candidate region, which spanned 10.5 Mb from D21S55 to the telomere. (Korenberg JR et al., 1992; Korenberg JR et al., 1994) This study supports the hypothesis that trisomy for a gene in the DS-CHD candidate region is essential for the production of DS-CHD including TOF and VSD, trisomy for additional genes located in the telomere and other regions likely contributes the phenotypic variability of DS-CHD. (Barlow GM et al., 2001)

3. Type of heart defects in children with Down syndrome

- Atrioventricular septal defects (AVSDs)- These are the most common in children with Down syndrome.
- Atrial Septal Defects (ASDs)
- Patent Ductus arteriosus (PDA)
- Tetralogy of Fallot (TOF)

In a study by TRJ Tubman & et al. among 34 babies of Down syndrome had congenital heart disease detected by echocardiography (13 had atrioventricularseptal defects, seven secundum atrial septal defects, six solitary patent ductusarteriosus, five isolated ventricular septal defects, and three combinations of heart defects.)(Tubman TRJ et al., 1991)

Another study showed the association between CHD and DS in atrioventricularseptal defect 56 (35%), ventricular septal defect 48 (30%),ASD 14 (8.7%), TOF 8(5%), PDA 18 (11.2%) and other heart defects 20(12.5%). (Ramakrishnan, V. 2011)

4. Presentations

4.1. Atrioventricular Septal Defects (AVSDs)

These heart defects are marked by a hole in the wall between the top chambers (atria) and bottom chambers (ventricles) and one common valve between the two atria. In some cases,

there might not be a hole between the bottom chambers. Or the valves may be joined together, but either or both might leak.

Because of the high pressure in the left ventricle which is needed to pump the blood around the body, blood is forced through the holes in the central heart wall (septum) when the ventricles contract. This increases the pressure in the right ventricles. This increased pressure (pulmonary hypertension) results in excess blood flow to the lung.

Some of the early symptoms seen are difficulty in eating, weight gain, fast irregular breathing and a degree of cyanosis (blueness) particularly noticeable around the mouth, fingers and toes. Clinical examination may show an enlarged heart and liver, and a diagnosis of heart failure may be given. This term, not all children will exhibit symptoms early in life, and those that do will not always show all of these features.

4.2. Ventricular Septal Defects (VSDs)

In this defect there is a hole between the bottom chambers (pumping chambers or ventricles). Because of the higher pressure in the left side of the heart this allows oxygenated blood to flow through the hole from the left to the right side of the heart and back to the lungs in addition to the normal flow. The amount of blood flow from the left to right ventricle depends on the size of the hole and on the pressure between the ventricles. In other words, the higher the rate of flow means more strain on the heart. The abnormal blood flow is responsible for the murmur that may be heard.

Generally patients with a small VSD will not exhibit symptoms (they are asymptomatic) and the problem may only be found when a murmur is detected upon routine examination. Patients with a moderate VSD may breathe quickly, exhibit poor weight gain and be slower at eating. These children are also much more prone to chest infection. This tends to be more pronounced when the hole is large.

4.3. Atrial Septal Defects (ASDs)

In this defect there is a hole between the top chambers (receiving chambers or atria). Because of the higher pressure in the left side of the heart, oxygenated blood flows through the hole from the left to the right side, and back to the lungs, in addition to the normal flow.

There are three types of atrial septal defects; the most common is when there is a hole in the middle of the central heart wall. Holes in the lower part of the septum, called primum defect (partial atrioventricular septal defect), are often associated with a problem of the mitral valve that often results in a leak. Less common are sinus venosus defects or holes in the top of the septum. These are associated with an abnormality of the right upper lung vein.

Generally patients with an ASD defect will exhibit no symptoms and the problem is only found when a routine clinical examination detects a heart murmur. Occasionally children with this problem will exhibit poor weight gain and a failure to thrive, and if there is mitral valve leakage there may be early symptoms of breathlessness.

4.4. Patent Ductus Arteriosus (PDA)

This defect is the continuance of a direct connection between the aorta and the lung (pulmonary) artery, which normally closes shortly after birth. A baby in the womb is supplied oxygen by the placenta via the umbilical cord. The baby's lungs are not expanded and require only a small amount of blood for them to grow. The ductus is a blood vessel that allows blood to bypass the baby's lungs.

If the ductus has partially closed and only a narrow connection remains, the baby won't show symptoms. If the connection is larger, the baby may be breathless and tired and show poor weight gain.

4.5. Tetralogy of fallot

A small percentage of babies with Down syndrome have this complex heart condition which combines the most common defect associated with Down syndrome, AVSD, with Tetralogy of fallot.

This anomaly includes four different heart problems:

- A hole between the top chambers and a hole between the bottom chambers
- Combined mitral and tricuspid valves (common atrioventricular valve)
- Narrowed pulmonary artery (from heart to lungs) or the area under or above the valve, or all three
- Thickening of the right bottom chamber (ventricle)

The combination of these defects early in life almost seems to balance out such that the child may be rather blue, but not too breathless. There can, of course, be too much blueness or too much breathlessness, depending on the severity of the different conditions.

In Tetralogy of fallot (TOF), often cyanosis is not present at birth but increasing hypertrophy of the right ventricular infundibulum and cyanosis occur usually in the later part of infancy. But cyanosis is present since birth if Tetralogy of Fallot is accompanied with Down Syndrome. This may be due to increased hypertrophy of the right ventricular infundibulum in patient of TOF with DS at birth. (AKMM Rashid et al., 2009)

5. Case

A case of eleven months boy was admitted in a hospital with the complaints of bluish discoloration of lip and finger since birth and low grade fever, cough for seven days. Bluish discoloration aggravates during crying. He was born to an elderly mother and was completely immunized. There was no such illness in the family. On examination the child was cyanosed, heart rate 130/m, weight 7.5 kg. He had got mongoloid face with flat occiput, depressed nasal bridge, upward slanting of eyes, medial epicanthic fold. There was gap be-

tween the first and second toes with clinodactyly. On examination of the precordium there was left parasternal heave, pansystolic murmur was present in the lower sternal border. There was motor developmental delay. The boy was clinically diagnosed with congenital cyanotic heart disease with Down syndrome. On investigation his hemoglobin was 78%, Total leucocyte count 14700/cum, Neutrophil 82%, X – Ray chest had the feature of boot shaped cardiac shadow. ECG showed right ventricular hypertrophy. Karyotyping showed trisomy 21. Tetralogy of fallot was detected by Echocardiogram. Finally the child was diagnosed as Down Syndrome with Tetralogy of Fallot. (AKMM Rashid et al., 2009)



Figure 1. Patient with Down syndrome.

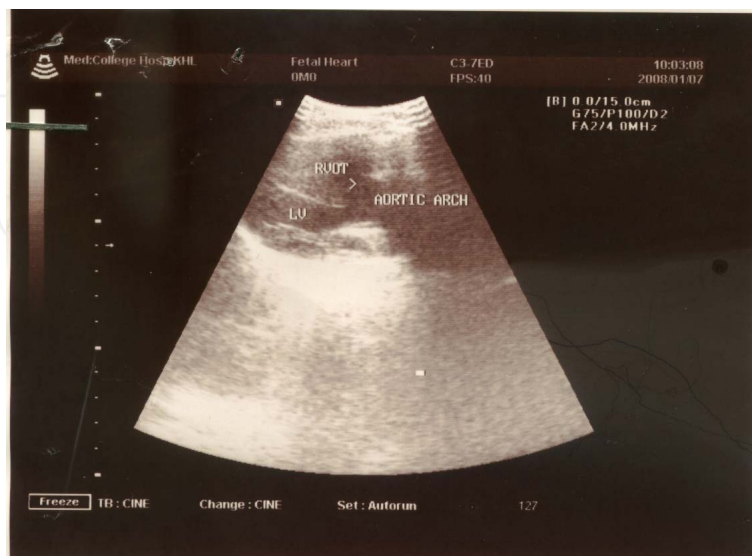


Figure 2. Echocardiogram showing Tetralogy of Fallot.

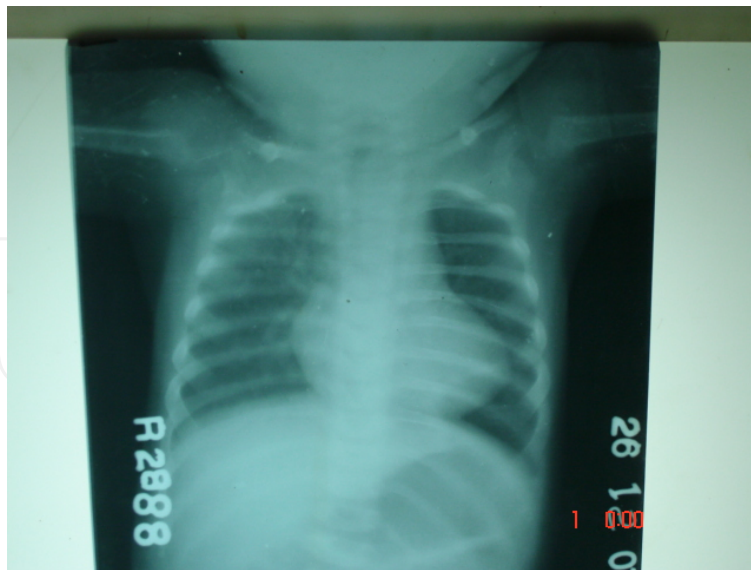


Figure 3. X-ray chest showing : boot shaped heart.

6. Other heart related problems in Down syndrome

In addition to the heart defects associated with Down syndrome, high blood pressure in the lungs (pulmonary hypertension) is more common in people with Down syndrome. This high blood pressure may be a result of malformation of the lung tissue, but the exact cause is not known. High blood pressure may limit the amount of blood flow to the lungs and therefore decrease the likelihood of symptoms of congestive heart failure seen in babies with complete AV canals or large ventricular septal defects.

7. Diagnosis

All babies that have been diagnosed with Down syndrome should have a cardiology evaluation because of the high incidence of associated congenital heart defects. A good history and physical examination should be performed in all Down syndrome children to rule out any obvious heart defect. Early diagnosis of congenital heart disease particularly of large left to right shunts, could enable a paediatrician to follow the baby carefully, to start medical treatment with diuretics and digoxin at an earlier stage and possibly to plan for earlier surgical intervention should this be indicated. Babies should be seen as early in life as possible, preferably in the first six months of life before pulmonary vascular disease can develop.

Electrocardiogram can be very helpful in making the diagnosis of AV canal defect, even in the absence of physical findings.(Shashi V et al., 2002)

Echocardiography has to be performed routinely early in life in Down syndrome can detect congenital heart disease that might otherwise be missed. Early detection may help prevent

complications such as pulmonary vascular disease that may adversely affect the outcome of cardiac surgery.

Occasionally a repeat electrocardiogram, chest x-ray, or echocardiogram is performed to further evaluate clinical changes. These tests are likely to be repeated before surgical repair is recommended.

Rarely, a cardiac catheterization is required for complete evaluation prior to corrective surgery especially in patients where elevated pressures in the lungs are a concern.

8. Treatment

Children with Down syndrome and symptoms of congestive heart failure can be initially managed medically with the use of diuretics, blood pressure medications to allow the heart to eject more blood out to the body rather than out to the lungs; and/or digoxin, a medication and to improve the pumping ability of the heart.

If the baby is having difficulty with feeding and weight gain, nasogastric tube feeding with calorie formula or fortified breast milk can be used to help with growth.

These are all temporary solutions to allow the baby to grow while deciding if and when surgery is indicated. If the baby has no signs of heart failure or is controlled well with medications, the decisions for surgical closure can be delayed. The decision must be individualized to each child's physical state as well as the family's concerns. The majority of cases of AVSD usually require surgical intervention; this generally takes place within the first six months of life.

Many VSD, will close spontaneously or get much smaller, so, it is normal practice to leave a child with a small or moderate VSD and monitor their progress before deciding to operate. Surgery may be needed if there is failure to thrive despite medication, or concern about pulmonary hypertension. If a large VSD is present, surgery is almost always recommended.

Small holes in ASD which allows little blood flow from left to right generally causes no problems. If they are located in the middle portion of the central heart wall, they may even close on their own. However, moderate and large holes do not close, and the extra work over the years places a strain of the right side of the heart causing an enlargement of both pumping chambers. Therefore, Surgery is recommended in the first few years of life or larger holes, before excessive strain has been placed on the heart.

If the ductus open for more than three months, it is unlikely to close on its own and surgical closure is imperative.

The types of surgery in TOF depend on the severity of the AVSD or the Fallots. Usually the children are quite blue and require a BT shunt to increase the amount of blue going to the lungs. Then another operation is performed later- usually at 1-2 years of age- so, that the holes can be closed, the valves repaired and the way out to the lung artery widened. (Cincinnati Children's hospital medical Center, 2006)

9. Long-term outlook

Over all, survival beyond one year of age is 85 percent in all children with Down syndrome. Over 50 percent of individuals with Down syndrome live to be greater than 50 years of age.

Congenital heart disease is the most common causes of death in early childhood. However, as of the late 1980s, 70 percent of children with Down syndrome and congenital heart disease lived beyond their first birth day with improved medical and surgical care, these numbers continue to improve. (Cincinnati Children's hospital medical Center, 2009)

Abbreviation

ASD – Atrial Septal Defect

AVSD- Atrioventricular Septal Defect

BAC- Beta-site APP –Cleaving

CHD- Congenital Heart Disease

DSCAM- Down syndrome cell adhesion molecule

DS- Down syndrome

MX- Myxovirus resistance

PDA- Patent Ductus Arteriosus

PFKL- Phosphofructo-kinase liver types

TOF- Tetralogy of fallot

VSD-Ventricular Septal defect

BT- Blalock Taussig

Author details

A. K. M. Mamunur Rashid

Dept. of Pediatrics, Khulna Medical College, Khulna, Bangladesh

References

- [1] AKM Mamunur Rashid, Biswajit Basu, Md. Mizanur Rahman. Tetralogy of Fallot in Down syndrome (Trisomy 21)- An uncommon association. *Pak J Med Sci*, 2009 vol. 25, no.4, 698-700.
- [2] Anderson RH. Simplifying the understanding of congenital malformations of the heart. *Int J Cardiol* 1991; 32: 131-42.
- [3] Barlow G M., Xiao-Ning Chen, Zheng Y. Shi, Gary E Lyons, David M. Kurnit, Livija Celle, Nancy B. Spinner, Elaine Zackai, Mark J. Pettenati, Alexander J. Van Riper, Michael J. Vekemans, Corey H. Mjaatvedt, Julie R Korenberg. *Genetics in Medicine* March/April 2001-Vol.3, No.2, 91-101.
- [4] Behrman RE, Kliegman RM and Jenson HB. From congenital heart disease. Philadelphia: Harcourt Asia Pvt. Ltd. Nelson Textbook of Pediatrics. 2000; 16 1362-63.
- [5] Berr C and Borghi E. Risk of Down syndrome in relatives of trisomy 21 children. A case-control study. *Ann Genet* 1990;33:137-40.
- [6] Cooney TP, Thurlbeck WM. Pulmonary hypoplasia in Down's syndrome. *N Engl J Med* 1982; 307: 1170-73.
- [7] Cincinnati Children's hospital medical Center. Heart- Related Syndrome (Trisomy 21). 2006 :1-4. www.cincinnatichildrens.org/health/heart-encyclopedia/anomalies/pda
- [8] Cincinnati Children's hospital medical Center. Down Syndrome (Trisomy 21). 2009:1-4. www.cincinnatichildrens.org/health/d/down
- [9] Delabar JM, Theophile D, Rahmani Z, Chettouh Z, Blouin JL, Preiur M, Noel B, Sinet PM. Molecular mapping of 24 features of Down syndrome on chromosome 21. *Eur J Hum Genet* 1993; 1: 114-24.
- [10] Du ZD, Roguin N, Barak M, Bihari SG, Ben-Elisha M. High prevalence of muscular ventricular septal defect in preterm neonates. *Am J Cardiol*. 1996; 78: 1183-85.
- [11] Ferencz C, Loffredo CA, Correa-Villasenor A, Wilson PD, , editors. *Perspective in pediatric cardiology*. Vol 5. Armonk NY: The Baltimore-Washington infant study, 1997.
- [12] Francis F, Lehrach H, Reinhardt R, Yaspo MI. The DNA sequence of human chromosome 21. *Nature* 2000; 405: 311-19.
- [13] Hubert RS, Mitchell S, Chen X-N, Ekmekji K, Gadomski C, Sun Z, Noya D, Kim U-J, Chen C, Shizuya H, Simon M, de jong PJ, Korenberg JR. BAC and PAC contigs covering 3.5 Mb of the down syndrome congenital heart disease region between D21S55 and MX1 on chromosome 21. *Genomics* 1997; 41: 218-26.
- [14] Hattori M, Fujiyama A, Taylor TD, Watanabe H, Yada T, Park HS, Toyoda A, Ishii K, Totoki Y, Choi DK, Soeda E, Ohki M, Takagi T, Sakaki T, Taudien S, Blechschmidt K,

- Polley A, Menzel U, Delabar J, Kumpf K, Lehmann R, Patterson D, Reichwald K, Rump A, Schillhabel M, Schudy A, Zimmermann W, Rosenthal A, Kudoh J, Shibuya K, Kawasaki K, Asakawa S, Shintani A, Sasaki T, Nagamine K, Mitsuyama S, Antonarakis SE, Minoshima S, Shimizu N, Nordsick G, Hornischer K, Bendt P, Scharfe M, Schn O, Desario A, Reichelt J, Kaur G, Blocker H, Ramser J, Beck A, Klages S, Hennig S, Rielssenmann I, Dagand F, Haaf T, wehrmeyer S, Borzym K, Gardiner k, Nizetic D, Francis F, Lehrach H, Reirhardt R, Yas Po MI. The DNA sequence of human chromosome 21. *Nature* 2000;405:311-19.
- [15] Hassold TA, and Sherman S. Down syndrome; Genetic recombination and origin of the extra chromosome 21. *Clin Genet*, 2000; 57: 95-100.
- [16] Hoffman JI. Congenital heart disease: incidence and inheritance. *Pediatr Clin North Am.* 1990; 37: 25-43.
- [17] Hoffman JI, Kaplan S, Liberthson RR. Prevalence of congenital heart disease. *Am Heart J.* 2004; 147: 425-39.
- [18] Korenberg JR, Kawashima H, Pulst SM, Ikeuchi T, Ogasawara SA, Yamatoto K, Schonberg SA. Molecular definition of a region of chromosome 21 that causes features of the Down syndrome phenotype. *Am J Hum Genet* 1990; 47: 236-46.
- [19] Korenberg JR, Bradley C, Disteche C. Down syndrome: molecular mapping of the congenital heart disease and duodenal stenosis. *Am J Hum Genet* 1992; 50: 294-302.
- [20] Korenberg JR, Chen X-N, Schipper R, Sun Z, Gonsky R, Gerwehr S, Carpenter N, Daumer C, Dignan P, Disteche C, Graham JM, Hudgins L, McGillivray B, Miyazaki K, Ogasawara N, Park JP, Pagon R, Puschel S, Sack G, Say B, Schuffenhaur S, Soukup S, Yamanaka T. Down syndrome phenotypes: the consequences of chromosomal imbalance. *Proc Natl Acad Sci U S A* 1994;91:4997-5001.
- [21] Moller JH, Allen HD, Clerk EB, Dajani AS, Golden A, Hayman LL, Lauer RM, Marmar EL, McAnulty JH, Oparil S. Report of the task force on children and youth: American heart association. *Circulation.* 1993; 88: 2479-86.
- [22] McCormick MK, Schinzel A, Petersen MB, Stetten G, Driscoll DJ, Cantu ES, Tranebjaerg L, Mikkelsen M, Watkins PC, Antonarakis SE. Molecular genetic approach to the characterization of the "Down syndrome region" of chromosome 21. *Genomics* 1989; 5: 325-31.
- [23] Payne M, Johnson MC, Grant JW, and Strauss AW. 1995. Towards a molecular understanding of congenital heart disease . *Circulation.* 91: 494-504.
- [24] Piperpont ME, Craig T, Basson D, Benson W, Jr. Bruce DG, Giglia TM, Goldmuntz E, McGee G, Craig A Sable, Srivastava D, and Catherine L. Webb. Genetic Basis for Congenital Heart Defects: Current Knowledge: *Circulation* 2007; 115: 3015-3038.
- [25] Rahmani Z, Blouin JI, Creau-Goldberg N, Watkins PC, Mattei JF, Poissonnier M, Prieur M, Chettouh Z, Nicole A, Aurias A, Sinet P, Delabar J. Critical role of the

D21S55 region on chromosome 21 in the pathogenesis of Down syndrome. *Proc Natl Acad Sci U S A* 1989; 86: 5958-62.

- [26] Ramakrishnan V. Research Article: Genetic aspects of congenital heart disease in Down syndrome. *Inter J Cur Res* 2011; 3(6): 165-70.
- [27] Roguin N, Du ZD, Barak M, Nasser N, hershkowitz S, Milgram E. High prevalence of muscular ventricular septal defect in neonates. *J Am Coll Cardiol.* 1995; 26: 1545-48.
- [28] Rodriguez LH, and Reyes JN. Cardiopatias en el syndrome de Down. *Bol Med Hosp Infant Mex.* 1984; 41: 622-25.
- [29] Shashi V, Berry MN, Covitz W. A combination of physical examination and ECG detects the majority of hemodynamically significant heart defects in neonates with Down syndrome. *Am J Med Genet* 2002 Mar 15;108(3):205-8.
- [30] Stoll C, Alembik Y, Dott B, Roth MP. 1998. Study of Down syndrome in 238,942 consecutive births. *Ann Genet.* 41: 44-51.
- [31] T R J Tubman, M D Shields, B G Craig, H C Mulholland, N c Nevin. Congenital Heart Disease in Down syndrome; two year prospective early screening study. *B M J*, Volume 302, 15 June, 1991, 1425-27.
- [32] Van Praagh R, Papagiannis J, Bar-EI YI, Schwint OA. The heart in Down syndrome: Pathologic anatomy. In: Marino B, Puschel SM, editors. *Heart disease in persons with Down syndrome.* Baltimore, MD: Paul H Brookers Publishing Co. 1996: 69-110.
- [33] Yamakawa K, Huo YK, Haendelt MA, Hubert R, Chen X-N, Lyones GE, Korenberg JR. DSCAM: a novel member of the immunoglobulin super family maps in a Down syndrome region and is involved in the development of the nervous system. *Hum Mol Genet* 1998; 7: 227-37.

IntechOpen