A Study of Birth Defects: Genetic and Epigenetic Determinants

Chapter 2: Review of Literature
Birth defects constitute solitary the largest and leading causes of newborn mortality around the world and account for about 21% of infant deaths across the globe. According to Torfs et al, 2006, birth defects often prove to be lethal. Moreover, for those individuals who survive, these disorders inadvertently lead to a lifetime mental, physical, auditory or visual disability or impairment (Torfs et al., 2006).

According to the March of Dimes Global Report on Birth Defects, 2006, children under the age of five years expire from birth defects every year and millions of those who survive may be disabled for life. Furthermore, although birth defects present a global crisis, their impact is predominantly rigorous upon under developed countries where >94% of the births with severe birth defects and 95% of the deaths of these children take place (A. Christianson et al. 2006). The March of Dimes Global Report on Birth Defects, 2006 further declared that the proportion of infants born with serious birth defects as well as the total number of births are much elevated in poorly developed countries as compared to well developed countries with high economies (A. Christianson et al., 2005).

In developing countries the sharp distinctions in the status of maternal health as well as other major risk factors, including poverty, an elevated percentage of women conceiving an advanced age, a higher frequency of consanguineous marriages and the ickle cell anaemia, thalassemia, and glucose-6-phosphate dehydrogenase (G6PD) deficiency genes complement the condition (A. Christianson et al., 2005).

The report further goes on to state that there are five major birth defects which are of genetic or moderately genetic origin. These include the following

a) Congenital heart defects
b) Down syndrome (trisomy 21)
c) Meiotic non-disjunction
d) Neural tube defects
e) The haemoglobin disorders, thalassemia and sickle cell disease
Taken together, these 5 circumstances constitute about 25% of all the birth defects of genetic or moderately genetic origin. Among them, CHDs and DS are of particular concern as this two pose as serious risk factors in the context of serious birth defects (A. Christianson et al., 2005).

2.1 Congenital Heart Defects

Congenital heart defects are complications within the organization of the heart which are prevalent from the time of birth of the individual. These defects can include:

a) The interior walls of the heart.

b) The valves inside the heart.

c) Congenital heart defects occur during the first eight weeks of fetal development.

d) The arteries and veins that transport blood across the entire body.

e) In majority of cases, no known causes can be detected.

f) More than 50% of children born with CHDs may have one or multiple persistent surgeries in their life span.

g) Congenital heart defects have significant mortality and morbidity rates.

According to the report of Global Burden of Disease Study 2015 authored by Feigin, V et al., 2016 congenital heart defects are the most widespread birth defect across the globe (Mortality & Causes of Death, 2016).

Furthermore, it has been estimated that over the preceding two decades, growth in global population, along with increased average age of the world's population, as well as mostly decreasing age, cause and sex-specific death rates together have driven a wide range shift from contagious, maternal, and nutritional causes towards non-communicable diseases including congenital heart disease (Mortality & Causes of Death, 2016).

According to the same report, India has witnessed a shift from communicable disease towards non-communicable disease in the same period. According to this report, 18% of the world's population resides in India and many states of India have populations which are comparable to those of large nation states and countries. Per capita disease burden has dropped by about a
third in India over the preceding two and half decades. Nevertheless, the enormity and causes of disease burden and the risk factors vary greatly between the individual states. The change to the dominance of non-communicable diseases including congenital heart disease and injuries over communicable, maternal, neonatal, and nutritional causes occurred over the period that spanned a quarter of a century.

Heart defects are most widespread birth defect, and it happens in 1% of new birth. In 2013, 34.3 million people had died of congenital heart defects. In 2010, they resulted in 223,000 deaths which is less that 278,000 deaths occurred 1990 (Global Burden of Disease Study, 2015). For congenital heart defects that begin without a family history, the reappearance risk of CHD in offspring is 3% to 5% (Global Burden of Disease Study, 2015).

Thus, CHD shares a major burden of all known congenital anomalies and should be studied more in terms of its pathogenesis, risk factor, prevention, and management.

### 2.1.1 Mechanism of heart development

According to a review by Srivastava, 2006 the development of a fully functioning heart requires a complex sequence of multifaceted events and a disruption of any portion may result in a serious defect (Srivastava, 2006). Looking deeper into the developmental process of heart it can be found that at about day 15 of maturation, the cells that eventually become the heart, exist as the mesoderm (B. Chen et al., 2000; Srivastava, 2006) and a number of cells migrate from a ectoderm, to the neural crest, which is also the resource of a wide array of cells found right through the body. On 19th day, a pair of vascular elements identified as the endocardial tubes is produced. The tubes undergo fusion and cells from the first heart field, a ring of heart cells (myocytes) around it by day 21. After 22 days, the heart starts to beat and by day 24, it starts blood circulation (Buckingham et al., 2005).

Furthermore, according to Buckingham et al, 2005, at around day 22, the circulatory system becomes bilaterally symmetrical with paired vessels on each side and the heart consists of a simple cylinder placed in the midline of the body plan. Interestingly, the portions that will subsequently become the atria and will thus be located nearest to the head are the most distant from the head at this point. Between days 23 to 28, the heart tube folds and contours, with the
future ventricles moving to the left of centre and the atria starts moving on the way to the head.

On day 28, regions of tissue in the heart tube commence to develop inwards; after approximately two weeks, and as a result of these expansions, the membranous "septum primum" and the muscular endocardial cushions combine to form the four identifiable chambers of the heart. Any failures to merge correctly will invariably lead to a serious defect that may allow the blood to leak between chambers.

![Figure 2.1: Schematic diagram of mammalian cardiac development.](image)

2.1A in the very beginning First Heart Field (FHF) cells form a crescent shape in the anterior embryo with Second Heart Field (SHF) cells media. Fig2.1B day 21 this SHF cells lie dorsal to the straight heart tube and begin to migrate (arrows) into the anterior and posterior ends of the tube to form the right ventricle (RV), conotruncus (CT), and part of the atra. 2.1C Illustrates the rightward looping of the heart tube. Cardiac neural crest (CNC) cells also migrate (arrow) into the outflow tract from the neural folds to septate the outflow tract and pattern the bilaterally symmetric aortic arch arteries (III, IV, and VI). 2.1D Septation of the ventricles, atria, and atrioventricular valves (AVV) results in the four-chambered heart. V, ventricle; LV, left ventricle; LA, left atrium; RA, right atrium; AS, aortic sac; Ao, aorta; PA, pulmonary artery; RSCA, right subclavian artery; LSCA, left subclavian artery; RCA, right carotid artery; LCA, left carotid artery; DA, ductusarteriosus. (Adopted from Srivastava, 2006, Cell. 2006 Sep 22;126(6):1037-48.)
Once this process gets completed, cells which have travelled from the neural apex begin to divide the bulbus cordis, the main outflow region is divided in two by the growth of a spiralling septum. If the separation is not complete, the resulting condition is known as persistent truncus arteriosis (Poaty et al., 2018).

The two parts of the split region must travel into the accurate locations over the correct ventricles. A malfunction may result in some blood flow into the erroneous vessel (e.g. overriding aorta). If the lungs are unexpanded and cannot house the full circulatory volume, two structures exist to shunt blood flow away from the lungs (Friedman & Fahey, 1993).

A small vessel, the ductus arteriosus permits blood from the pulmonary artery to pass to the aorta (Buckingham et al., 2005; Srivastava, 2006). Any perturbation, either genetic or by external factors, to this highly complex but organized process of cardiac development might lead to the cardiac anomaly in the newborn (Akhirome et al., 2017; Fahed et al., 2013).

2.1.2: Potential causes of congenital heart defects

Although in a most of cases the precise reason of congenital heart defects cannot be correctly detected, it is hypothesized that the majority of congenital heart disease may be genetic, or environmental, or a combination of these two factors (Lage et al., 2012).

2.1.3: Genetic causes

According to most of the known causes of CHDs are random genetic changes, which can either be point mutations or deletion or insertion. Large chromosomal deformities such as trisomies 21, 13, and 18 are together responsible for 5–8% of cases of congenital heart defects, where trisomy 21 is one of the major genetic causes (Pont et al., 2006). Small chromosomal anomalies also frequently lead to CHDs, such as micro deletion of the long arm of chromosome 22, 22q11 (Soares et al., 2005).

The genes which are responsible for the regulation of the complex developmental progression are poorly studied. Very few genes are found to be responsible for particular defect however; numerous genes have been associated with cardiac manifestations. Mutations of a protein
associated with the heart muscles, namely α-myosin heavy chain (MYH6) are linked with atrial septal defects.

Furthermore, interactions of many proteins with MYH6 are also having shown to have connection with cardiac defects. Mutations in any one of these proteins are may leads to atrial and VSDs. Additionally, it was also reported that mutation in NKX2-5 is responsible for defects in the electrical conduction of the heart. Whereas, a mutation in the TBX5 is associated with Holt-Oram syndrome. In addition, \( TBX1 \) gene is also associated with velo-cardio-facial syndrome DiGeorge syndrome, the most common deletion which has extensive symptoms including defects of the cardiac outflow tract including TOF.

Furthermore, the Notch signaling pathway plays extensive roles in a number of aspects of cardiac development. For example, Notch signaling is involved in the formation of the endocardial cushions. It is also involved in the maturity of the ventricular wall and the link of the outflow tract to the large vessels (Kumar et al., 2015).

The systematic sequence of cell growth, cell migration, and apoptosis has been studied comprehensively and the genes that regulate the process are being identified in several recent studies. Firulli and Olson, 1997 have identified several complex genetic subprograms in developing cardiac muscle. They identified a cardiac gene called desmin that is expressed in ventricles, not in atria. Mutation of this gene elicits a different response in cardiac development than in skeletal muscles (Firulli & Olson, 1997). Thus, studying this differential and complex nature of genetic regulation in developing heart can give insight into the pathomechanism of developing an atrial or septal defect in growing heart (Firulli & Olson, 1997).

Similarly, Chen et. al., 2000 have found that \( Egfr \), the gene encoding the epidermal growth factor receptor, is essential for semilunar, but not atrioventricular and valve development. From a study of the interaction between egfr and Ptpn11, encoding the protein-tyrosine-phosphatase Shp2, they concluded that Egfr and Shp2 major players in the signaling cascade specifically involved in semilunarvalvulogenesis. This study provides an animal model for aortic valve disease and confirms the role of Shp2 in EGFR signaling in vivo (B. Chen et al.,
2.1.4: Environmental causes

Mills et al., 2010 recognized environmental factors responsible for perpetrating congenital heart defects comprise definite infections during pregnancy such as Rubella, exposure to drugs such as hydantoin, thalidomide, and lithium as well as maternal illness such as diabetes mellitus, phenylketonuria, and systemic lupus erythematosus. Moreover, obesity also increases the risk of congenital heart disease. Furthermore, as maternal obesity may also boost up the risk of heart defects. A distinct physiological mechanism is yet to be identified which can conclusively the link between maternal obesity and congenital heart defects, but both pre-pregnancy deficiency of folate and diabetes have been concerned in some studies (Mills et al., 2010). Lifestyle factors such as smoking and consumption of alcohol have a confounding role in developing CHD in newborns. Lee and Lupo 2013 have shown in their study that the habit of smoking in mothers before conception is strongly associated with the chance of having a child with DS. The occurrence of septal defects, atrial septal defects, and atrioventricular septal defects were found in a dose-responsive behaviour (Lee & Lupo, 2013).

Barua and Junaid, 2015 have extensively reviewed the environmental and maternal lifestyle factors that influence the genetic and epigenetic modulator to consequently develop congenital abnormalities. They have collated the recent evidence that suggests maternal diet, anxiety, diabetes, exposure to tobacco and alcohol at the time of gestation strongly influences the fetal development and these factors can contribute to the etiology of several birth anomalies including neural tube defects, autism spectrum disorder, congenital heart defects, oral clefts, allergies, and cancer (Barua & Junaid, 2015).

They summarized the following influencers of genetic and epigenetic alterations leading to birth defects.
a) **Maternal diet**

Both malnutrition and over-nutrition can cause the alteration in DNA methylation (Epigenetic changes) leading to lifelong susceptibility to different diseases and can affect fetal development.

b) **Maternal obesity & gestational diabetes**

Both of them can induce epigenetic alterations in utero during early fetal development resulting in perturbation of transcriptional and metabolic pathway that controls health status of the fetus.

c) **Maternal stress**

Prenatal stress and anxiety are very common in expecting mothers. These psychological burdens might affect the gene regulation leading to altered developmental status.

d) **Tobacco smoking and consumption of alcohol**

Maternal habit of Smoking and consumption of alcohol can induce detrimental change in the DNA of the fetus which might have both immediate and long-term effect on the offspring.

e) **Environmental epigenome disruptor**

Endocrine disruptors are able to transform epigenetic transforms in the offspring’s genome. Exposure to any such agent during gestation might result in a long-term impairment in social and anxiety-like behaviour, spatial learning, and memory decreased exploratory behaviour of the infant.

In conclusion, the review associates maternal lifestyle during pregnancy with the epigenetic alterations and its role in the pathogenesis of congenital anomalies (Barua & Junaid, 2015).

### 2.2 Down Syndrome

According to a review published by Lana-Elola et al, 2011, DS is caused by trisomy of human chromosome 21 (Hsa21) and results in a large number of phenotypic aberrations which includes distinct facial features, learning disabilities, cardiac defects, as well as leukaemia.
These events are most likely caused by an increased dosage of one or more of the approximately 310 genes that present on Hsa21 (Lana-Elola et al., 2011).

The identification of these dosage-sensitive genes is a key area of focus in the field of DS research as it is essential for a comprehensive understanding of the molecular consequences underlying pathology, and might eventually lead the progression of a more effective therapeutic strategy. The investigation of these dosage-sensitive genes is being carried out by means of both human as well as mouse genetics. Furthermore, according to this review by Lana-Elola et al, 2011, studies of human beings with partial trisomy of Hsa21 have identified several area of this chromosome that contribute towards different phenotypic anomalies (Lana-Elola et al., 2011).

Additionally, the novel genetically modified mouse model are also being used to map the potential sites of dosage-sensitive genes, which, in a small number of cases, has led to the identification of individual genes that are reason behind certain phenotypes. These studies have shown an intricate genetic interplay, demonstrating that the diverse DS phenotypes are probably caused by amplified copies of several genes, with individual genes contributing in dissimilar proportions to the inconsistency in diverse features of the pathology.

2.2.1: Risk factors for DS

As mentioned previously, DS originates, in a majority of the cases (95 %), from a complete trisomy of chromosome 21. According to Fabio et al, 2009, the remainder of the cases are as a consequence of either mosaicism for chromosome 21 or the inheritance of a structural restriction leading to partial trisomy of the majority of its cellular content (Coppede et al., 2009). However, total trisomy 21 and mosaicism are not inherited but are derived from errors during cell divisions at some stage in the development of the egg, sperm or embryo.

2.2.1.1: Parental age

Full trisomy for chromosome 21 is additionally separated into two broad categories i.e. maternal origin, which accounts for the majority of incidences, and cases of paternal origin, which accounts for less than 10 % of incidences. Amongst cases of maternal origin, a further
subdivision should be done into errors that occurred or originated during the first meiotic division in the maternal grandmother’s body and errors in second maternal meiotic division that occurred later in life.

This intricate scenario indicates that the understanding of the threats for trisomy 21 should take into consideration the above classifications as it reproduces diverse individuals and generations wherein the first error was happened. Studies have strongly indicated that advanced maternal age is a strong risk factor for developing DS in offspring. The previous study by Olsen C.L., 1996 has shown that the likelihood of developing Trisomy 21 in the offspring from a woman under 25 and 30 is less than 1 in 1,400 and 1,000 respectively. Furthermore, the risk of having a baby with DS increases to 1 in 350 for women who become pregnant at the age of 35. This risk of having a baby with DS continuously increases in a manner such that a woman of the age 42 and 49 pose a risk of having a DS baby with a probability of 1 in 60 and 1 in 12 respectively (Olsen et al., 1996).

Interestingly, the risk of developing DS in offspring does not restrict to the only advanced age of mother, but the association extends to the age of the grandmother during the birth of the mother. A study by Malini SS and Ramachandra BN, 2006 has shown that increase in the age of the grandmother during conception by 1 year increases the risk of having a DS grandchild by 30%. Moreover, while compared to the effect of the parental age, the age of grandmother was found to be a stronger risk factor for having a DS baby (Malini & Ramachandra, 2006). On the contrary, there are reports that showed the higher percentage of DS babies are born to women younger than 30. James SJ, 1999 showed in their study that almost 80% of the DS baby was born to mother younger than the age of 30 (Mills et al., 2010). A similar result was obtained by Cooley WC, Graham JM in their study (Cooley & Graham JR, 1991). This deviation from well-established risk factor indicates towards some other confounding factors leading to higher risk of DS.

2.2.1.2: Other risk factors

The risk factors which might associated with the birth of a child with DS, including

a) Folate metabolism
b) Dietary
c) Lifestyle
d) Environmental

e) Occupational

f) Genetic and epigenetic factors

In summary, the birth of a DS child is the outcome of multifaceted gene-environment relations and selection method involving diverse generations. Folates are crucial nutrients that are essential for one-carbon biosynthetic and epigenetic processes. Cellular folate deficiency results in aberrant DNA methylation, chromosome breakage, point mutations, defective chromosome recombination and aneuploidy. The impairments in folate/homocysteine metabolism, due to genetic polymorphisms of metabolic enzymes, could raise the risk of having an infant with DS (Coppede et al., 2009).

There are some sparing studies that indicate lifestyle and socio-economic status of a mother as an important risk factor for having DS offspring. Hunter, J.E. et al., 2013 pointed out that factors such as education of parent and maternal grandparents below high school and an annual household income of <$25,000 are significantly associated with the risk of having DS in offspring. Such poor socioeconomic status leads to maternal exposure to hazardous environmental toxicants and malnutrition which can be a contributing factor towards developing DS in the offspring (Hunter et al., 2013).

A few studies have also pointed out that exposure to pesticides and other chemical toxicants have a contributory role in developing birth anomalies. For example, Ray et.al, 2016 have shown that chewing smokeless tobacco results in reduced telomere length which consequently leads to higher risk of Trisomy 21 (Ray et al., 2016). However, more extensive studies are required to establish the association of environmental exposure and occupational hazards to the risk of having offspring with DS.

2.3: Etiologies of Down syndrome

According to Weijerman and Winter, 2006, DS is considered to be one of the largely prevalent chromosome malformation in humans (Weijerman et al., 2010). As per a report published by Disease and Injury Incidence and Prevalence, Collaborators in the Lancet journal in 2016, 5.4 million individuals were suffering from DS and resulted in death of 27,000 individuals, which were less than 43,000 deaths in 1990. As there is no cure for DS,
education and appropriate care are indispensable for improvement of the quality of life for affected individuals (Mortality & Causes of Death, 2016).

The life expectation is around 50 to 60 years in the developed countries if proper health cares taken. As mentioned previously, according to the review by Lana-Elola et al, 2011, DS is occurs in individuals having three copies of the genes on chromosome 21, rather than the normal individual with two. However, it should be noted that the parents of the affected individual may be genetically ordinary (Lana-Elola et al., 2011). Furthermore, according to Nelson, 2011, those individuals who have one child with DS also have the additional risk by 1% of having a second baby with the syndrome, in spite of both parents are normal (Nelson, 1959).

The extra chromosome part may occur via various pathways. However, according to Rubins and Resiner, 2009 the most widespread reason is a complete set of an extra copy of chromosome 21, a condition known as resulting in trisomy 21. As per Rubins and Resiner, 2009, trisomy 21 accounts for about 92–95% of the incidence of DS (Nelson, 1959).

On the other hand, as per Nelson, 2011, in about 1.0 to 2.5% of cases, several cells within the body are ordinary whilst other cells have trisomy 21, a condition described as Mosaic Down syndrome. The additional common mechanisms that may possibly lead to the development of DS include a Robertsonian translocation, isochromosome, or ring chromosome. These have added material from chromosome 21 and account for nearly 2.5% of DS incidence. An isochromosome is formed when the two extended arms of a chromosome divided together rather than the long and short arm separating simultaneously during egg or sperm development (Nelson; Rubin and Reisner, Essentials of Rubin’s Pathology, 2009).

2.3.1: Trisomy 21

Trisomy 21 (also known as the karyotype 47, XX, +21 for female and 47, XY, +21 for male individuals) results from a failure of separation of the 21st chromosome during egg or sperm maturation. Consequently, a sperm or an egg cell is matured with an extra copy of chromosome 21. Thus, this cell has 24 chromosomes instead of 23.
When fused with a typical chromosome containing cell from the different parent, the infant will have 47 chromosomes, where the infant will having three copies of chromosome 21. Approximately 88% of cases of trisomy 21 arise from failure of separation of the chromosomes in the mother, 8% from father, and 3% after the egg and sperm have fused (Rubin and Reisner, *Essentials of Rubin’s Pathology*, 2009).

### 2.3.2: Translocation

Furthermore, according to Rubins and Resiner, 2009 the superfluous chromosome 21 material may also occur due to a Robertsonian translocation, which accounts for nearly 2–4% of DS incidence (Rubin and Reisner, *Essentials of Rubin’s Pathology*, 2009).

According to Cummings 2013, in this scenario, the extended arm of chromosome 21 gets attached to another chromosome, oftentimes chromosome 14. In a male affected with DS, Robertsonian translocation results in a karyotype of 46XY (14q21q). This may be a novel mutation or it may also be a pre-existing condition in one of the parents. More often than not the parent with such a translocation does not exhibit any abnormal phenotype.

Nevertheless, during production of zygotic cells, there remains a higher probability chance of production of reproductive cells with additional chromosome 21 materials. This leads to a 15% and 5% probability of having a child with DS when the mother and father are affected, respectively. The prospect of this type of DS is not associated with the age of the female parent. Some individuals without DS may arbitrarily inherit this translocation and have a higher possibility of giving birth to children with DS. This condition is sometimes referred to as familial DS (Cummings, *Human Heredity: Principles & Issues*, 2003).

### 3.3.3: Morbidities of Down syndrome

According to Lana-Elola et al, 2011, the surplus genetic material present in individuals with DS leads to over expression of a fraction of the 310 genes located on chromosome 21 (Lana-Elola et al., 2011). Bull, MJ in 2011 suggested the DS critical region is located at bands 21q22.1–q22.3, along with other genes. Dementia which is invariably associated with DS results from the excess production of amyloid beta peptide which is produced in the brain and
this condition is similar to Alzheimer's disease. The amyloid beta peptide is derived from an amyloid precursor protein, and the gene for this precursor is situated on chromosome 21.

Senile plaques and neurofibrillary tangles are present in nearly all individuals affected DS by the age of 35 years, although dementia may not be a widely occurring condition. Individuals affected with DS also be deficient of lymphocytes and produce fewer antibodies which consequently contributes towards their increased risk of infection and compromised immunity.

Furthermore, according to Horvath, et al, 2015, DS is widely connected with an augmented threat of several other severe diseases that are otherwise typically associated with advanced age such as Alzheimer's disease. The increased rate of aging also indicates that trisomy 21 advances the biological age of tissues, however, molecular confirmation for this assumption is meager and inconclusive. According to results derived using a biomarker of tissue age known as the epigenetic clock, trisomy 21 increases the age of blood and brain tissue (on average by 6.6 years) (Horvath et al., 2015).

2.4: Epidemiology of DS

The Global Burden of Diseases Study, 2015 has been estimated that as of 2010, DS occurs in about 1 per 1000 births worldwide, and has also led to approximately 17,000 deaths (Wang et al. 1980-2015).

The results of a study conducted by Weijerman and Winter in 2010 also indicate that many children are born with DS in countries where abortion is prohibited as well as in countries where pregnancy more frequently occurs at an advanced age (Weijerman et al., 2010). As per the Global Burden of Diseases Study, 2015 approximately 1.4 per 1000 live births in the United States of America and nearly 1.1 per 1000 live births in Norway are affected by DS. In the 1950s, in the United States, it occurred in 2 per 1000 live births with the decrease since then due to prenatal screening and abortions. It has been estimated that the cause of 8% of all congenital disorders.
Morris et al, 2002 suggests that maternal age is considered to be an important contributing factor towards conceiving an infant with DS. It is estimated that at age 20, the probability of conceiving a child with DS is one in 1441; at age 30, the probability is approximately one in 959; at age 40, it is one in 84; and at age 50 it is one in 44. Even though the probability increases with maternal age, an estimated 70% of offspring affected with DS are born to women who are mostly 35 years of age or younger. The advanced age of the male parent is also considered to be a risk factor (Morris et al., 2002).

According to Hickey et al, 2012, individuals affected with DS are associated with a higher threat of early death than the normal individuals. The cause of death is most often a result of infections or cardiac problem (Hickey et al., 2012).

With the advent of advanced medical concern, especially for gastrointestinal and cardiac defects, the life expectancy has improved significantly. The chances of long-term endurance are partially affected by the occurrence of heart problems (Weijerman & de Winter, 2010). According to Global Burden of Diseases Study, 2015 those individuals with congenital heart defects, 60% survive to an age of 10 years and 50% survive to 30 years of age.

2.4.1: Meiotic non-disjunction

According to Simmons et al., 2012, nondisjunction is a condition caused by the malfunction of homologous sister chromatids or chromosomes to divide appropriately during the process of cell division. There are three variants of nondisjunction: failure of sister chromatids to separate during mitosis, failure of a pair of homologous chromosomes to separate in meiosis I, and failure of sister chromatids to separate during meiosis II. The latter two variants of nondisjunction encompass meiotic nondisjunction. Due to nondisjunction, the cell is produced with abnormal chromosome numbers (aneuploidy) (Snustad and Simmons, Principles of Genetics, 2006).

As per Nagaoka et al., 2012 ovulated eggs turn into arrested in metaphase II pending fertilization, which in turn triggers the second meiotic division of cells. Analogous to the parting events during mitosis, the pair of sister chromatids resultant from the partition of bivalents in meiosis I are further separated in anaphase of meiosis II. In oocytes, one sister
chromatid is segregated into the second polar body, while the other remains inside the egg. During spermatogenesis event, each meiotic division is symmetric in such a manner that each primary spermatocyte gives rise to 2 secondary spermatocytes after meiosis I, and ultimately 4 spermatids after meiosis II. Meiosis II-nondisjunction can also lead to aneuploidy syndromes, but only to a much smaller extent than do segregation failures in meiosis I (Nagaoka et al., 2012).

2.4.2: Sex-specific differences in meiosis

Furthermore, Nagaoka et al., 2012 also states that review of cases of human aneuploidy syndromes have demonstrated that majority of the aneuploidy is received from the female parent (Nagaoka et al., 2012).

According to Nelson Text Book On Pediatrics, the most palpable dissimilarity between female oogenesis and male spermatogenesis is the prolonged arrest of oocytes in late stages of prophase I which can range from several years to many decades. Male gametes on the other hand quickly go through all stages of meiosis I and II. Another important difference between male and female meiosis concerns the frequency of recombination between homologous chromosomes. In male, almost all chromosome pairs are joined by at least one crossover. While in more than 10% of human oocytes have at least one bivalent without any crossover event. Failures of recombination or inappropriately located crossovers have been well documented as contributors to the occurrence of nondisjunction in humans.(Nagaoka et al., 2012).

2.4.3: Consequences of Meiotic non-disjunction

The outcome of this type of error is a cell with the discrepancy of chromosome distribution. As mentioned previously, this type of cell is known as aneuploid. As per Quevedo et al., 2012 monosomy can be defined as the loss of a solitary chromosome (2n-1), where the daughter cell(s) with the anomaly will have one missing chromosome from one of its pairs (Quevedo et al., 2012). On the other hand, trisomy is referred to the condition where daughter cell will have one additional chromosome in adding up its original pairs. In the event where an aneuploidic gamete is fertilized, a number of syndromes might result including DS, Turner Syndrome etc. (Strachan et al. Human Molecular Genetics, 2011).
2.4.3.1: Monosomy

The lone identified survivable condition of monosomy in human beings is Turner syndrome, wherein the patient is monosomic for the X chromosome. All other monosomies are typically detrimental to life during the course of early fetal development. Survival is only possible if not all the cells of the body are affected in case of a mosaicism, or if the usual figure of chromosomes is re-established (Kliegman and Nelson, *Textbook of Pediatrics*, 2011). Moreover, it is also necessary to absolutely characterize the genetic condition carefully using molecular cytogenetic and molecular genetic test (Seth et al., 2018).

2.4.3.2: Karyotype of X monosomy (Turner syndrome)

This situation is associated with the presence of only one X chromosome and absence of Y chromosome. Absolute loss of complete X chromosome is responsible for about 50% of the cases of Turner syndrome. The significance of both X chromosomes during embryonic development is well underscored by the examination that the majority (>99%) of foetuses with only one X chromosome (karyotype 45, X0) are unexpectedly aborted (Kliegman and Nelson, *Textbook of Pediatrics*. 2011).

2.4.3.3: Karyotype of trisomy 21 (Down syndrome)

As mentioned previously, DS, is the most prevalent abnormality of chromosome number in humans. According to Taeusch, 2005, the maximum number of nondisjunction occurs during the maternal meiosis I (MM I). Trisomy occurs in an estimated 0.3% of infants and in nearly 25% of unplanned abortions. It has also been estimated that trisomy 21 is the chief reason of pregnancy wastage and is the known cause of mental retardation (Taeusch et al. *Avery’s Diseases of the Newborn*, 2005).

It has also been well documented by Eichenlaub-Ritter, Ursula, 2012 that higher maternal age is responsible for higher risk of meiotic nondisjunction leading to DS. This may be linked with the long-lasting meiotic arrest of human oocytes potentially lasting for >4 decades (Eichenlaub-Ritter, 2012).
2.4.3.4: Edwards and Patau syndrome

In human apart from trisomy 21, other examples include Edwards and Patau syndrome characterized by an extra 18th and 13th chromosome, respectively. These two are also known as trisomy 18 and trisomy 13 for Edwards and Patau syndrome, correspondingly. This is too a moderately common source of miscarriage in pregnant women. Only in few cases of a mosaicism, the occurrence of a typical cell line, in addition to the trisomic cell line, may maintain the progress of a viable trisomy of the other chromosomes (Snustad and Simmons, 2006; Nagaoka et al. 2012).

2.4.3.5: Sex chromosome aneuploidy

The sex chromosome aneuploidy encompasses the states where an irregular numeral of sex chromosomes, i.e. other than XX (female) or XY (male) occurs. Technically, X chromosome monosomy can also be categorised as a type of sex chromosome aneuploidy (Snustad and Simmons, 2006; Nagaoka et al. 2012).

❖ Klinefelter syndrome (47, XXY)

According to previous literature, Klinefelter syndrome is one the most frequent sex chromosome aneuploidy in humans. It stands for the most frequently occurring cause of hypogonadism as well as infertility in men. The majority cases are occurred through nondisjunction errors in paternal meiosis I. It has been estimated that almost 90% of individuals with this syndrome have one additional X chromosome resulting in the karyotype XXY. The remaining cases have either multiple additional sex chromosomes (48, XXXY; 48, XYY; 49, XXXXY), mosaicism (46, XY/47, XXY), or structural chromosome defects (Taeusch et al. 15, 2005).

❖ XYY Male (47, XYY)

The incidence of the XYY syndrome is around 1 in 800 to 1000 male births. In most of cases it remains undiagnosed because of their regular appearance and fertility, and the absence of acute symptoms. The extra Y chromosome is usually a product of nondisjunction during paternal meiosis II (Snustad and Simmons, 2006).
Trisomy X (47, XXX)

Trisomy X is a variant of X chromosome aneuploidy in females wherein they have erroneously three X chromosomes instead of the normal two. Majority of individual with this condition are only slightly affected by neuropsychological and physical symptoms.

According to Taesuch et al., 2005 and Nagaoka et al., 2012, about 58-63% of cases the origin of the extra X chromosome is caused by nondisjunction in maternal meiosis I, in 16% to 18% cases by nondisjunction in maternal meiosis II, and the other cases by post-zygotic, i.e. mitotic, nondisjunction (Taeusch et al. 2005; Nagaoka et al. 2012).

2.4.3.6: Uniparental disomy

Uniparental disomy represents the condition wherein both chromosomes of a pair have been inherited from the single parent and are thus the same (Engel, 1980). This phenomenon in all likelihood is the product of a pregnancy that started as a trisomy occurred because of nondisjunction (Engel, 1995; Xu et al., 2015).

In view of the fact that most trisomies are fatal, the fetus has chance of survival only when it loses one of the three chromosomes and becomes disomic. Prader-Willi syndrome and Angelman syndrome is characterized by uniparental disomy of chromosome (Nagaoka et al.2012; Taeusch et al.2005).

2.4.3.7: Mosaicism syndromes

Mosaicism syndromes occurs as a result of mitotic nondisjunction during early developmental stage of fetus. In this condition, the person evolves as a combination of cell lines with differing ploidy i.e. a number of chromosomes (L. Devlin & P.J. Morrison, 2004; Papavassiliou et al., 2015). Mosaicism can occur in some tissues. Affected individuals may have a patchy or asymmetric look. Hypomelanosis of Ito and Pallister-Killian syndrome are examples of mosaicism syndromes (Izumi & Krantz, 2014; Kromann et al., 2018). In light of the above discussion, it is evident that an enormous burden of mortality and morbidity is associated with the birth defects such as DS and CHD.
Therefore, understanding the emergent risk factors besides the common ones is utmost important. Moreover, the strong pathophysiological and etiological association between DS and CHD has prompted scientists to study and analyze these two diseases together. An attempt to understand the environmental and occupational risk factors in developing DS and CHD was made in this study. Moreover, the study tries to look into origin of the meiotic nondisjunction and also tries to find out the genetic and epigenetic mechanism of transgenerational inheritance of such disorders.