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Molecular cytogenetic study of Down syndrome and it's health care experience

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Abstract

Down syndrome (DS) is a genetic complex condition which is collection of physical, mental and functional abnormalities that result from trisomy 21, the presence in genome of three rather than the normal two chromosome. Mouse model of DS have shown the involvement of trisomy of all or part of human chromosome 21 or orthologous mouse genomic regions and also provide valuable information into contribution of triplicated gene related to many clinical manifestations in DS. Medical advances, special educational programs, and increasing social acceptance of disabled people in the community have resulted in current trends of normalization and deinstitutionalization of these patients. In this study we performed the detailed literature searches to ameliorate molecular cytogenetic study of Down syndrome and its care.

Keywords: Trisomy-21; Molecular Diagnostic; Karyotyping; Cytogenetics; Down Syndrome

1. Introduction

A trisomy is a chromosomal anomaly characterized by presence of three copies of chromosome instead of normal two and leads to malformation of various part of the body. Although they have an elevated risk (80%) in mortality, Fetuses with trisomy of some chromosomes survive at least up to certain period of embryonic development reaching the full term for example chromosome 21, 18 and 13. Down syndrome (Down,1866) is one of the most congenital anomalies in humans (Chen H),cause of mental disability among 1 in 750 live birth with world-wide incident (Newberger DS,200) and millions of patients face different types of chronic health issues including leukaemia, cancer, Alzheimer disease, congenital heart disease etc. Down syndrome is also common in India and it affects approximately 23,000-29,000 children born in India every year. In 1959, two scientist team (Lejeune et al. 1959, Jacobs et a l. 1959) independently determined that DS is caused by trisomy 21. Several studies have revealed that large frequency of free trisomy 21 and less frequency of mosaicism and unbalanced translocation can lead to Down syndrome (Bornstein et al., 2010; Ringman et al., 2008). In all studies in different countries, it was reported that the excess of males appears to be universal. In developed countries the average life span for individuals with DS has increased from 25 years in 1983 to over 60 years at present (Covelli et al. 2000, De Grafe et al. 2017). Down syndrome has genetic complexity with its phenotype variability. Down syndrome occurs in people of all races and economic levels, though older women have an increased chance of having a child with Down syndrome. Several hypotheses have been formulated to show a corelation between the effect of maternal age on Down syndrome patients and finally advanced maternal age is confirmed as important determinant of nondisjunction trisomy 21 (Penrose 1933). Birth Prevalence of Down Syndrome with maternal age show a "J"-Curved for example DS baby every 1 in 1400 (pregnant women under 25yrs), to 1 in 350 (women under 35 yrs), to 1 in 12 (women > 45 yrs). Although the DS risk increases with the maternal age, 80% of DS babies are born to young women of less than 35 yrs but the exact mechanism responsible for nondisjunction of chromosome 21 in younger mother has not been explored. Several molecular techniques have shown that 90-95% cases from maternal nondisjunction errors and 3-4% cases from paternal meiotic errors. Trisomic fetuses are at elevated risk of miscarriages

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and DS people have increased incidence of developing several medical conditions (Moris et al. 1999). Advanced maternal age and selective terminations by prenatal testing, increase in birth control measures and decrease in family sizes also play a role in the prevalence rates in more recent times. But with improved medical and surgical care, the survival of children born with DS has significantly improved over recent decades (Kucik et al. 2013).

2. Clinical observation of Down syndrome

The gold parameter for diagnosis of down syndrome is karyotyping demonstration of an extra copy of the long arm of chromosome 21. But another conventional method for discrimination of the Down Syndrome is clinical diagnosis based on characteristic appearance and behaviour of affected individuals. Clinical features are important for early diagnosis to reduce morbidity and mortality. The clinical description may be more challenging in some cases for example premature infants, some older adults, with those individuals whose features are changed by significant mosaicism and structural modification of chromosome leads to partial duplication of long arm of chromosome. Down syndrome patients have a most characteristic facial pattern (rounded face, epicanthic folds, protruding tongue, drooping neck) right from the birth that facilitates their recognition. But Children born at home show a significant delay in diagnosis.

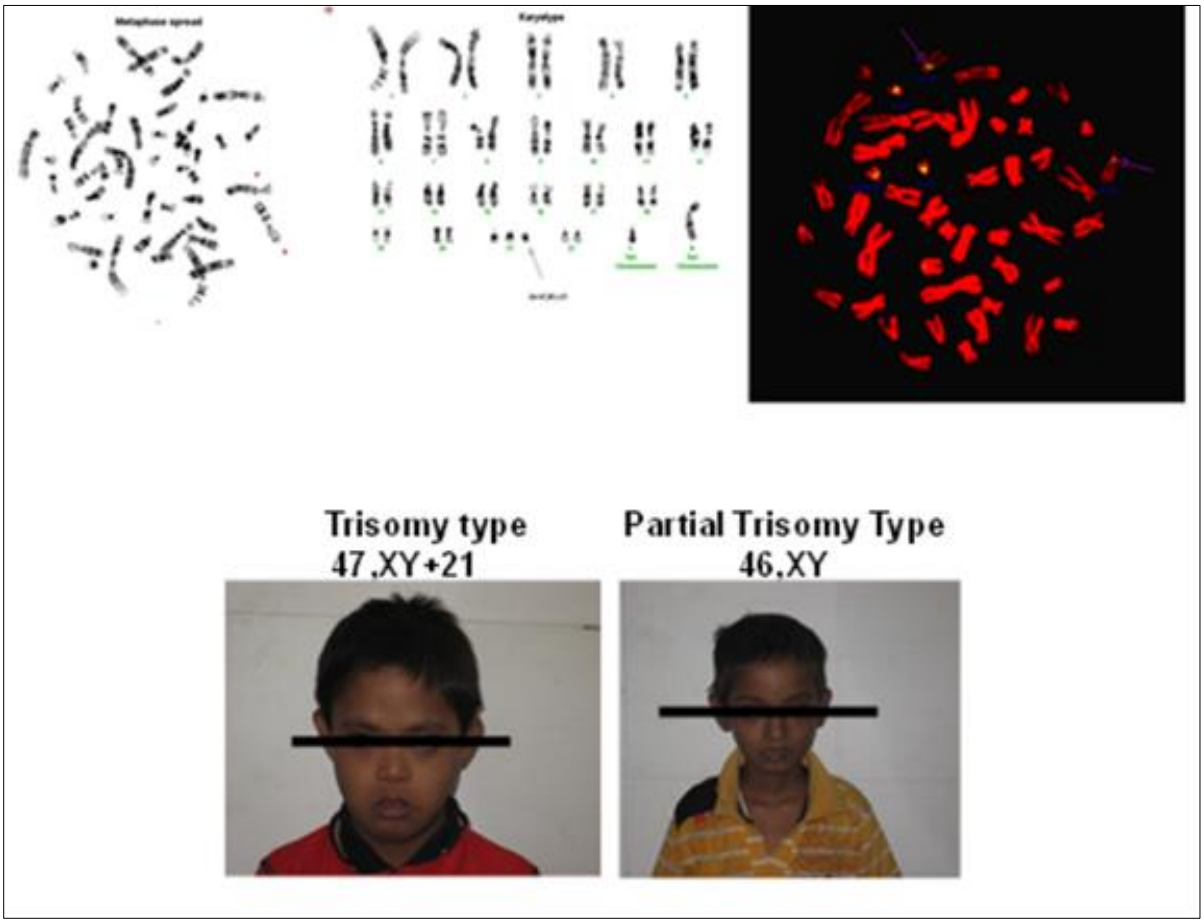

Figure 1 Upper left metaphase spread, middle karyotype, right FISH on chromosome with alphoid probe. Lower panal shows phenotypic similarities of different DS children

However, nearly 80 different features have been identified in DS, not all of them occurring in a case (Epstein et al. 1991, 2002). Neonates with Down syndrome show some typical features including hyper extensibility, hypotonia, poor behaviour responses, open mouth, serrated mouth corner, serrated tongue, nyst agmus, dental caries, digestive tract abnormality, weak immunity are observed most frequently. Skull becomes slightly microcephalic and brachycephalic with a flattened occupit, fontanels tend to be large and may be palpable. The face is round in shape in neonate and infants of Down syndrome but with age become more oval in shape. Due to underdevelopment the upper facial length and depth of maxillary arc asymmetrically decreased with flattened appearance of mid face. Some of the more common morphological features (Figure 1) include single simian crease, short nose with flattened nasal root, midfacial hypoplasia, wide gap between 1st and 2nd toe (sandal toe), abnormal dermatoglyphics, dysmorphic nails etc (Epstein et

al. 1986). Peripherally placed Brushfield Spot, rosy coloured optic disk with increased number of retinal vessels, down turned mouth with small oral contributes to tendency to protrude along tongue to breath, prognathism, small cupped or square shaped ear by overfolded upper helix, nuchal skin and wider neck with age are most common features of Down syndrome patients. Other characteristics of Down Syndrome include short hands with a high frequency of single palmar creases, presence of short and/or triangular middle phalanx of the fifth finger results in a single flexion crease or clinodactyly, respectively, larger frequency of arches and ulnar loops on thumb, index middle finger. In addition to these, there are more severe pathological features. Mild to severe mental retardation is common to 100% DS patients, the IQ ranging from 20 to 80 and asthmatic symptoms occur in around 30% of them (Carr 1995). Neurodevelopmental problems, relating limited social awareness, decreased motor coordination, an increased incidence of autism spectrum disorder, psychiatric problems have been recognized (Bull, 2011). Early onset of Alzheimer's disease, which is usually a late age short-term memory loss disorder, is common in DS (Tolmie 2002) after the age of 40 years. However, such person remains asymptomatic, with cognitive decline decades later. An unusual neurodevelopment disorder in person has been termed as “disintrigative disorder” manifested as autistic like regression and dementia. Behaviour management is often a challenge for parents and caregivers of children with DS. Counselling and behavioural support have been shown to be useful for families addressing these disease (Capone et al. 2006).

Down syndrome is cause for congenital heart disease and most early deaths in DS occur due to this defect, mostly presented with septal defects, such as Atrioventricular septal Defects (AVSD 45%) Ventricular Septal Defects (VSD 35%), Atrial Septal Defects (ASD 8%) and tetralogy of fallot (4%) (Hosokawa et al. 2018; Nasser et al. 2018). It is also documented that patients with DS are at risk of thyroid hormone abnormalities, with 24% (Paediatric et al. 2017). Children with DS can have pulmonary complications, such as pulmonary hypertension, sleep-disordered breathing and air way anomalies, as well as respiratory infections (McDowell & Craven, 2011). In some cases, haematologic abnormalities are common and developing Acute Myeloid Leukemia at latter stage (Poddar G et al.2012). People have 20fold higher risk of Acute Lymphoblastic Leukemia (ALL) with the children of Down Syndrome than in those who do not (Lange B,2000, Taub et al. 2017). Epidemiologic studies suggest that DS patients may have protection against the solid tumour but testicular cancer occur more frequent in these patients than age matched populations (Hasle, 2016). Autoimmune conditions, including Hashimoto’s disease, type 1 diabeties, alopecia, celiac disease, juvenile idiopathic arthritis and vitiligo occur in disproportionate number among the persons with Down Syndrome. Moyamoya disease an uncommon vascular abnormality named with an increased incidence among patients with DS (Kainth et al. 2013) due to stenosis of supraclinoid portion of internal carotid arteries. A systematic clinical observation protocol published by Epstein et al. 1991 helps for an accurate diagnosis of the case. Despite knowing countless number of clinical features, there are some limitations in the timely diagnosis of individuals with Down syndrome in many countries. Two main reasons are phenotypic variations in different ethnicities and the lack of antenatal screening facilities in developing countries.

3. Cytogenetic study of Down syndrome

Cytogenetic technique is the study of chromosomal structure, properties and behavior during the cell division in growth and development. By the cytogenetic analysis the confirmation of Trisomy Syndrome is done. The chromosomal constitution of a typical Down syndrome was first published by Lejeune et al. (1959), which showed 47 chromosomes with an additional group G chromosome and D group Chromosome. Nondisjunction occurs when chromosomes fail to segregate during meiosis and is the major cause of pregnancy wastage and mental retardation in humans. The nondisjunction error is more frequent in first meiotic division (80%) rather than second meiotic division (20%) (Hassold, 2001). Chromosomal data show that more than 95% cases, DS are caused by free trisomy of chromosome 21 (Fryns 1987). The polymorphic microsatellites have revealed that vast majority of defects leading to free trisomy 21 occur due to error in eggs nearly as 90% of maternal meiotic error, approximately 10% of paternal meiotic error (Ghosh, 2003) and a small proportion (1.8%) are attributable to post-zygotic mitotic nondisjunction. Maternal meiosis is more complicated and error prone process compared to parental meiosis, as a result about 20% of oocytes are aneuploid.

However nearly 5% of DS become familial because of translocation of chromosome 21 to another chromosome. The extra chromosome 21 is translocate to G group (chromosome 21, 22) and D group (chromosome 13, 14, 15). Such type of translocation known as Robertsonian translocation with two different forms of Down syndrome: familiar and de novo. In case of Familial form, translocation Down Syndrome can be inherited from carrier parents (Han JY 1994). For the de novo cases, parents with normal karyotype and the abnormal chromosome due to a spontaneous event in maternal meiosis I from a chromatid translocation (Petersen MB, 1991). Non homologous Robertsonian translocation between chromosome 14 and 21 [rob (14q; 21q)] is more common than homologous Robertsonian translocation between chromosome 21 and 21 [rob(21q;21q)] (Earle E et al. 1992). There is a significant increased risk of giving birth to a child with Trisomy 21 when one parent is a Robertsonian translocation carrier or of reciprocal translocations as they may produce balanced and unbalanced gametes during gametogenesis (kolgeci et al. 2013, Munne et al.2000).

Another rarest category of Ds is caused by the Mosaicism for chromosome 21 trisomy. Mosaicism is a condition in which an individual has two or more genetically distinct cell lines that originated from a single zygote [Nussbaum et al., 2001]. Mosaicism for trisomy 21 was first reported in 1961 by Clarke et al. and in case of mosaicism trisomy individual have both trisomic (47, XX or XY+21) and euploid (46, XX or XY) cell line. On the basis of several studies, the frequency of mosaicism for trisomy 21 has been estimated to range from every 1 in 16670 to 1 in 41670 or approximately 1.3-5% of all people having some form of Down syndrome (Jackson-Cook, 2011). Prenatally ascertained fetuses with mosaicism showed a significantly lower frequency of ultrasound aberrations and screening test anomalies when compared to fetuses with non-mosaic trisomy 21 (Bornstein et al., 2009). However, there is no striking difference in the etiology of the DS arising out of trisomy or as mosaics.

Apart from these, Partial duplication within the specific region of chromosome itself 21q22(qter) is responsible for common phenotype of Down Syndrome. However, there is no estimate available regarding prevalence of the partial duplication cases. The region around 21q22 was suspected to the Down syndrome critical region (Nadal et al. 2001). The length of 21q is 33.5 Mb (Lyle et al. 2009) and 21 p is 5–15 Mb (Emark et al. 2006). This region was defined by different boundaries include proximal one between markers D21S17 (35 892 kb) and D21S55 (38 012 kb) and a distal one at MX1 (41720 kb). Results from dosage imbalance of genes located on human chromosome 21(Hsa 21) leads to DS complex Phenotypes. The genetic nature of DS together with the relatively small size of Hsa 21 encouraged scientist to concentrate efforts towards the complete characterization of this chromosome in the past few years. During last decades, considerable progress has been made towards the gene content of chromosome 21, approximately 225 genes were estimated when initial sequence of 21q was published. Hsa 21 contain 40.06% repeat content out of which the repeat content of SINE's, LINE's, and LTR are 10.84%, 15.15%, 9.21% respectively. But function of most genes and their specific contribution to final Ds phenotype still unknown. However, recent evidence suggests that genes outside this region may also contribute to the DS phenotype (Korenberg JR et al, 1994).

3.1. Risk factor

Despite years of intensive studies, we still know relatively little about the factors that influence the frequency of trisomy 21 of humans. Advanced maternal age has been considered as important determinant for DS Child birth (lamb et a. 1996, Morris et al. 2002), as it is possible for all human autosomal trisomies. The risk is associated with nondisjunction homologues chromosome as well as chromatid during meiosis at the time of oocyte formation. But the proper mechanism for nondisjunction due to advanced maternal age still remain unknown. Improper segregation of chromosome HSA21 in both maternal meiosis I and meiosis II by degradation of meiotic machinery occurs due to accumulation of unfavorable factors during long arrest phase in meiosis I of oogenesis and gradual loss of cohesion at the stage of advance maternal age. Apart from this, altered recombination have been shown as second risk factor to be associated with increased susceptibility for mal-segregation of chromosome (Lamb et al.1996). It has been suggested that advanced grand maternal age has been supposed to be crucial for proper chromosomal segregation during gamete formation (Malini and Ramchandra, 2006). However, some of recent studies did not support this hypothesis (Allen et al. 2009; kovaleva et al.2010). High incidence of DS cases in younger mother suggested that besides advanced maternal age, interaction of environmental factors and genetic factors could be responsible for abnormal segregation of chromosome 21. Several studies, conducted worldwide, have reported the association of MTHFR677C>T polymorphism and other polymorphism of folate related with risk of DS child birth (James et al. 1996; Hobbs et al. 2000; O'Leary et al. 2002).

3.2. Health care guidelines

Down Syndrome is associated with a broad variety of age-related medical problems, ranging from congenital heart disease to dementia to recurrent respiratory infections. The medical chain around the Down syndrome is complex with many multidisciplinary challenges, involving numerous professionals (Weijerman et al.,2010). "Health Care Guidelines for Individuals with Down Syndrome" is the most widely published health care guidelines that include adults. Most of the studies have been focused on descriptions of the higher prevalence of a condition in persons with Down syndrome but health care screening in persons with Down syndrome has not been well elecuited. As usual health maintenance, adult person with Down syndrome represents a unique population who are in need of clinical guidelines to address their medical care including health screening and prevention. In addition to regular screening should be done for hypothyroidism, obesity, behavioural, psychiatric or intellectual changes, the development of cardiac valve, vision, dental, or hearing abnormalities, and musculoskeletal changes. Initiatives arise to improve the DS care but the current quality of care is still unknown. Skotko et al. (2013) explained how a *DS* specialty clinic can address many healthcare needs of children and adolescents with DS beyond the provision of primary care. Some review also demonstrated the importance to early induced down syndrome patients into preventive programs and periodontal therapy because oral hygiene is important for prevention to control the periodontal disease (Ferreira R et al. 2016). There is a high prevalence of congenital heart disease (CHD) during infancy. So in clinical practice the need for regular follow-up of repaired

congenital heart disease (CHD) throughout adulthood is well accepted. Adults with should be screened as the incidence of undiagnosed CHD and valve regurgitation are both high (Baraona et al., 2013). Some report stated that clinical trials also focused on weight reduction, long-term management and prevention of obesity in adolescents and adults with DS are needed in conjunction with exploration of predisposing physiologic factors (Bertapelli, Pitetti, Agiovlasitis, & Guerra-Junior, 2016; Fleming et al., 2008).

Family physician can help the patients with Down syndrome develop good communication and social skills that will enhance their ability to live independently and get a better life. Although the initiative for these skills is started from childhood, there are still ways to help adult Down syndrome patients more effectively. Speech therapy may improve the intelligibility of language as well as vocational training are also helpful for this type of person. Local guardian support group can obtain from National organizations, such as National Down Syndrome Society plays important role. It provides valuable information about the relationship, sexual training, abuse prevention and estate planning for the family.

4. Discussion

In this present study, cases were diagnosed with clinical test and cytogenetic tests and discussed about its heath care. Peripheral blood samples taken from the propositus and the parents were used for chromosome analysis (Henegariu 2001) and DNA extraction. Genomic DNA extraction was carried out by Salting out method (Millers et al. 1988). Routinely, Giemsa (GTG) banding technique was performed to identify the chromosomes. Additional banding techniques like Centromeric (CGB) and NOR were used to confirm the structurally alerted chromosomes. The results of the present study could be summarized as follows, clinical and molecular cytogenetic analysis of Down syndrome patients allowed the identification of band, responsible for many features of Down syndrome, including mental retardation.

Despite the high detection rate of Down syndrome by various antenatal screening programmes, it is still the common genetic cause for mental retardation with an incident of every 0.88 to 1.09 per 1000 live births in India (Verma, 2000). Though it is not fatal in the developed countries but in India it continues to be fatal, but there is very little open dialogue on this topic in India. Nondisjunction, translocation, and mosaicism are the classical anomalies of DS. In the past decades, nonclassical types of chromosomal anomalies (whether numerical or structural) have been reported in many DS studies, with frequency ranging from 0.3 to 1.2%;(Verma et al. 1991, Chandra et al. 2010) only one study reported a higher frequency (2.4%) of nonclassical DS (Sheth et al., 2007). Although during the last decade considerable progress has been made towards discovering the gene content of chromosome 21, but the functions of most of these genes and their specific contribution to the final DS phenotype is still unknown.

In brief, we had focussed on certain of genetic aspects of Down syndrome in BHU, Varanasi. Overall frequencies of free trisomy, translocation and mosaic appear to be as with the global data (Jyothy et al., 2001). Our preliminary data on young DS mothers are particularly encouraging, and need to be extended on different populations in this country. It was diagnosed that after karyotyping, each of genetic disorders are of several sub-types, like in we have now 125 DS cases, subtypes are free trisomy 21, isochromosome 21, translocation involving chromosome 21, duplication of some or all portion of chromosome 21 in our present study. Cytogenetic analysis of DS cases from India reported different frequency of trisomy ranging from 83.65%-97.8%, frequency of translocation ranged from 2.2%-13.7% and mosaic karyotype range from 0-11.6%. Slight differences among different reports might be due to differences in size of sample and time period analysis and population studied.

The association between increasing maternal age and trisomy is probably the most important etiological factor in human genetics disease. The maternal age effect may be due to differential selection and accumulation of trisomy 21 oocytes in the ovarian reserve of older women (Hultemn MA et al. 2008). Several studies have related the maternal risk factor for DS with genetic polymorphism involved in folate mechanism. Due to abnormal folate metabolism hypomethylation of centromeric DNA occurs which may lead to abnormal chromosomal segregation. But many other studies had shown increased number of DS babies born to Young Mother. In case of younger mothers, the mechanism behind the nondisjunction is not well understood. One of the reasons could be that the ovaries of young women are biologically older than their chronological age, which may lead to increased incidence of nondisjunction (Schupf N et al. 1994). The role of the environmental factors for mal segregation of chromosome 21 has been suggested as another reason of high incident of DS cases in Younger mother. Cytogenetic and epidemiological studies have identified many candidates for extrinsic risk factors, including smoking, alcohol, maternal irradiation, fertility drugs, oral contraceptives, and spermicides. However, unequivocal proof is still lacking for these and other intrinsic and extrinsic factors. Among environmental factors, nutrition associated with folate homocysteine metabolism due to polymorphism has been considered to play a key role in chromosome disjunction, as mechanism involved in hypomethylation and nucleic acid

biosynthesis both are required for proper functioning of cell division machinery. However, the effect of paternal age has not been extensively studied.

Maternal age is also related to type of chromosomal abnormality. Some authors reported high presence of Robertsonian translocation 14q; 21q in children with translocation trisomy 21 (62.34%) (Jayalakshamma , 2000). It has been reported that in 75% of all translocation cases it may occur *de novo*, while in 25% of cases, can be inherited from one carrier parent, but more frequently by the mother side (Schaffer et al. 1992). Gender biasness in case of Down Syndrome leading to a male preponderance has been reported from various populations world-wide with ratio ranging from 1.1:1 to 2.3:1, Kovaleva, 2002 explained genetic basis of male preponderance stating that trisomy and translocation are predominantly associated with male. It has been hypothesized that there is joint segregation of 21 and Y chromosome in spermatogenesis. Moreover, chromosome non disjunction during second meiotic division of oogenesis caused by Y Chromosome bearing spermatozoa has also been hypothesized to be responsible for the most genetic basis of trisomy which constitutes of 95% of Ds (Kovaleva, 2002).

DS Children are presented with large heterogeneity in clinical features, of which frequency and manifestation is also variable. Craniofacial features are most conspicuous for diagnosis. Children with DS have been shown to have deficits in verbal processing in addition to more behavioural and social problems also. The knowledge of clinical manifestation of DS is most important to make an early postnatal diagnosis. It has been considered that differences in clinical features may reflect cytogenetic profile such as proportion of free trisomy, mosaicism, translocation. Several other factor may contribute to phenotype heterogeneity in Ds patient include allelic heterogeneity for chromosomal 21 gene presented in three copies, individual's genetic makeup and the environmental factors (Reeves, 2001). Gene dosage imbalance hypothesis states that DS patients have an increased dosage or copy number of genes on Hsa 21 that may lead to an increase in gene expression (Sinet et al. 1994, Antonarakis, 2004) and this hypothesis has been extended to include the possibility that specific genes or subsets of genes may control specific DS phenotypes (Pritchard, 1997).

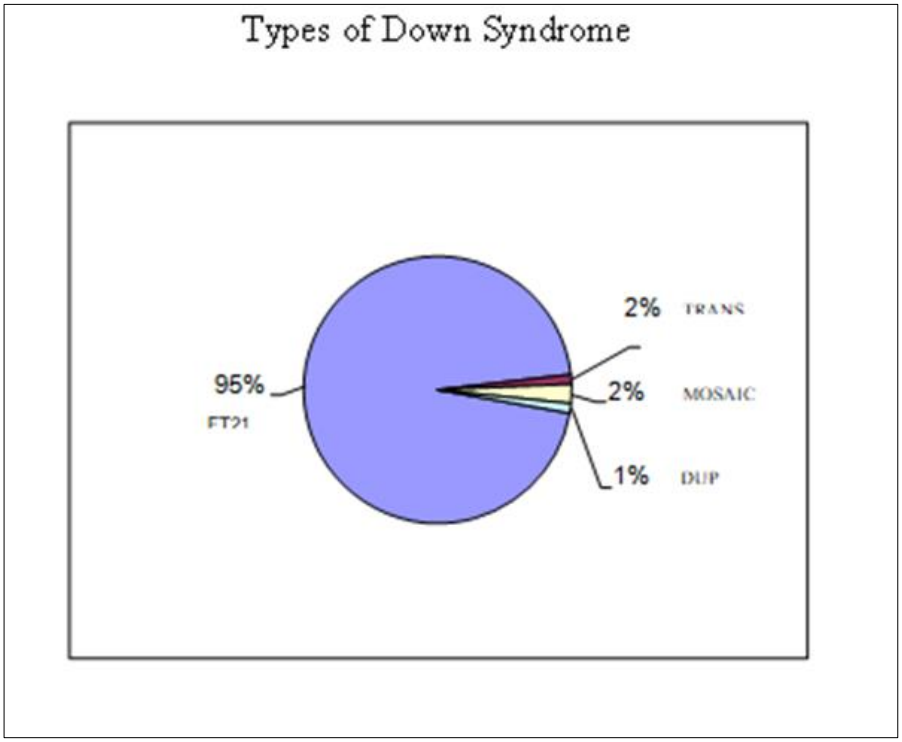

Figure 2 Incidence various types of DS

The findings of longitudinal studies illustrate the complex, varied, and changing relationships between persons, their contexts, and the effects of experience across the life span (Hyes et al. 1991). There is no proper cure for Down Syndrome (Steinbock, Bonnie, 2011). Early case detection is important for early intervention to the patients and their families by genetic counselling and helping in planning care to these children to improve their life's quality. Late diagnosis may result in to delayed preliminary intervention of appropriate preventive measure for some risks conditions such as physical, mental and psychological development. A relatively simple way to control birth incidence of Down syndrome is the limitation or reduction of the number of pregnant women older than 35 years and the frequency of birth of

children with Down syndrome is expected to be reduced up to 20-45% with these process (Owens et al. 1983). It is important to educate women at high risk of recurrence (e.g., advanced maternal age) to go for screening during pregnancy. Prenatal preventive diagnostic tests in modern medicine can be used and some other preventive strategies are considered to prevent the birth of child with Down syndrome recently, such as: pre-implantation genetic diagnosis (PGD) and folic acid supplementation (Cuckle, 2005).

Research is needed on potentially modifiable factors contributing to competence and other aspects of personal development. The purpose of primary care is to identify conditions for which prevention, early identification, and treatment can decrease an individual's morbidity and mortality (Robertson et al. 2011). Advances in medical science, improved educational systems, greater social acceptance of people with disabilities in the community and relentless efforts of the National Down Syndrome Society is working toward the normalization of this population. In addition to screening for Down syndrome specific comorbidities, it is important to ensure both age- and gender-appropriate screening. This includes typical primary care domains such as reproductive health screening, diet, exercise, and primary prevention of general adult conditions, such as cardiovascular disease (Bittles et al. 2007). Through which we can estimate the size of the problem and the future needs of these physically challenged children through a large-scale national community-based survey. In light of such findings, it is important to remember that improved screening has the potential to identify issues that can be readily treated and lead to decreased morbidity and mortality (Jenson et al. 2013). Persons with Down Syndrome and their families have to be kept a positive attitude to express their desire for a best quality of life that builds on strength and skills of affected person.

5. Conclusion

The heath issues and life trajectory of persons with Down syndrome are complex and the condition is associated with many medical, psychological, and social issues from infancy to through adulthood. In this study, cytogenetical analysis by karyotyping are encountered for all cases that have clinical features of DS to confirm the clinical diagnosis and to determine the frequency of different types of DS. Our results suggest that the vast majority belongs to the free trisomy of chromosome 21 category than translocation and mosaic karyotypes. And even though partial trisomy has also shown DS phenotypes, a critical region has not been precisely mapped. The results were comparable to several international studies in the world to confirm the precise diagnosis by providing basis of genetic counselling. Further studies are needed to assess the implications of preventive screening recommendations and more timely identification of comorbidities on clinical outcomes.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no conflict of interest in this study.

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