



Robertsonian Translocations t(21q;21q) and t(14q;21q) in Down Syndrome

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ABSTRACT

Mental Retardation (MR), also referred as 'Intellectual Disability', 'Mental Deficit', 'Mental Subnormality' or 'Mental Handicap' means delay in mental development; it means an impairment of the intellectual processes of the mind, making it difficult for the person to cope with environment in which they find themselves. The prevalence rate of mental retardation in the general population is estimated to be approximately 1% to 3%. It has been estimated that environmental factors and genetic factors play equal role. Chromosomal abnormalities (numerical and structural) are responsible for up to 28% in mental retardation with the high prevalence of Down Syndrome (DS). In general, over 95% of Down syndrome individuals possess free trisomy 21. Translocations of chromosome 21 (D or G group) were found in 2-4% while 1-2% are mosaics. The present study was aimed to investigate the chromosomal abnormalities in 100 mentally retarded cases. The frequency of regular trisomy was 18 (18%). The frequency of Robertsonian translocations 46, XY, t (21;21) +21 and 46, XY, t (14;21), +21 were 3 (3%) and 1 (1%) respectively. The frequency of mosaic 46, XY/47, XY, + 21 was 2 (2%). Since the study is already published without detailed case studies, the present paper discusses each case in detail.

Keywords: Mental Retardation, Down Syndrome, Trisomy, Translocations, Mosaics

INTRODUCTION

Mental retardation, also referred as 'Intellectual Disability', 'Mental Deficit', 'Mental Subnormality' or 'Mental Handicap' means delay in mental development; it means an impairment of the intellectual processes of the mind, making it difficult for the person to cope with environment in which they find themselves. In 1992, the American Association on Mental Retardation (AAMR) revised the definition as significantly sub average intellectual functioning (defined as an IQ score below 70) existing concurrently with limitations in two or more of the following adaptive areas like communication, self-care, home living, social skills, self-direction, health and safety, leisure, work and functional academics [1,2].

The prevalence rate of Mental Retardation (MR) in the general population is estimated to be approximately 1% to 3%, with mild MR occurring 7-10 times more frequently than moderate or severe MR [3-5].

The causes of the impairment are extremely heterogeneous and although a cause for mental retardation has been diagnosed in only half of the cases, it has been estimated that half of all cases are due to environmental factors and half to genetic factors. Genetic factors include chromosome abnormalities, monogenetic disorders and polygenic factors.

Chromosomal abnormalities are responsible for up to 28% of all mental retardation cases [6]. Chromosomal abnormalities include numerical chromosome abnormalities and structural chromosome abnormalities. Down Syndrome (DS) is the most common genetic cause of intellectual disability in the population and is due to a gene dosage effect of the presence of an additional chromosome 21 [7]. or a partial trisomy, mainly in the 21q22 region [8]. Out of all autosomal aneuploidies Down Syndrome or Trisomy 21 is the most intermittently found autosomal aneuploidy with an incidence of about 1 in 700 live births. The prevalence of DS in India is 0.88 per 1000 (1 out of 1139) to 1.09 per 1000 (1 out of 916) and 3 DS children are reported to be born every hour [9-11]. In general, over 95% of Down syndrome individuals possess free trisomy 21 resulting from non-disjunctional error of chromosome 21

during gametogenesis in one of the parents. Translocations of chromosome 21 into D or G group chromosomes were found in 2-4% while 1-2% are mosaics showing a normal cell line additionally, due to mosaicism [12]. The present study was aimed at the detailed study of translocation Down Syndrome cases.

The current study comprises 100 mentally retarded cases of above 2 years age from Labenshiff Mentally Handicapped, Visakhapatnam; Asramdham Manovikas Kendram, Anakapalli and Behara Manovikas Kendram, Srikakulam. The study was taken clearance from Institutional Ethical Committee. 100 individuals of same age and sex were taken as controls.

Blood samples of 5 ml were collected into sterile heparinized tubes with prior informed consent and was carried to Department of Human Genetics, Andhra University, Visakhapatnam for Leukocyte blood culture and G banding techniques to evaluate chromosomal abnormalities.

CASE STUDIES

Case 1

A boy of 4 years old was reported with typical features of Down syndrome including mental retardation, low set ears, broad nasal bridge and epicanthic folds. The ages of mother and father were 24 years and 29 years respectively. Cytogenetic studies revealed Robertsonian translocation (21;21) in this boy and the karyotype was 46,XY,rob(21;21),+21 (Figure 1).

Down syndrome with classical trisomy and translocation are phenotypically indistinguishable. However, by considering a review of the literature concerning these G/G translocations, it should be hypothesized that trisomy of a rather delimited segment on chromosome no. 21 is essential for the development of typical features of Down syndrome.

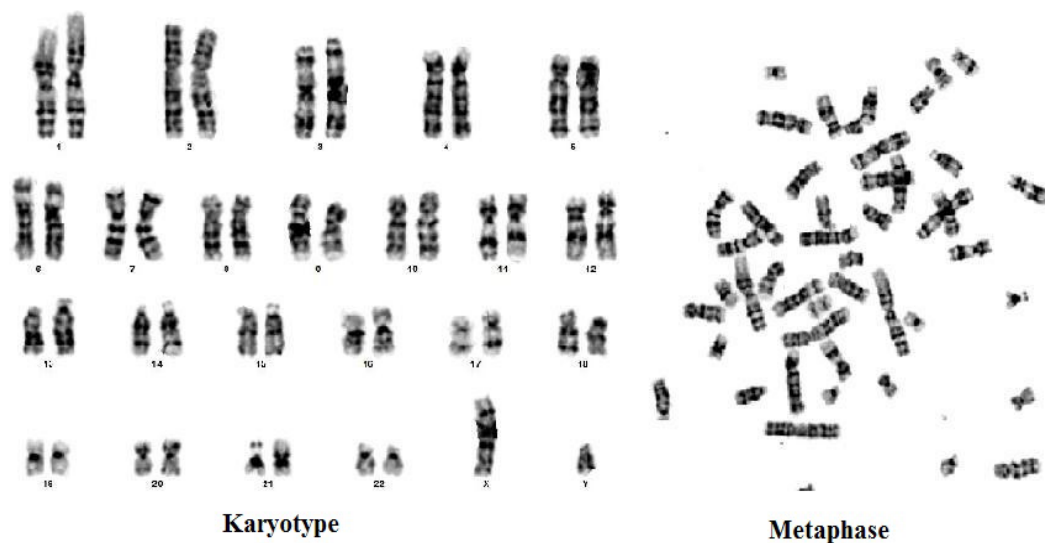


Figure 1 Down syndrome Robertsonian translocation (21; 21); Male 46,XY,rob(21;21),+21

Case 2

The proposita was a third child, born to middle aged parents (mother 33 years, father 38 years). He was a 10 years old boy clinically diagnosed as Down syndrome patient. Though delivery was normal and full term, birth cry was delayed. The child was also found with regular dysmorphic features such as short nose from root to tip, brachycephaly, flat occipital region, slanting palpebral fissure, protruded and creased tongue, epicanthal fold, constantly open mouth, short stature.

In the present case, Robertsonian translocation (21;21) is confirmed cytogenetically. The karyotype was 46,XY,rob(21;21),+21. Two possible events may be theoretically possible to explain the karyotype in this case. They are either non disjunction or formation of T (21;21) during paternal or maternal meiosis (Figure 2).

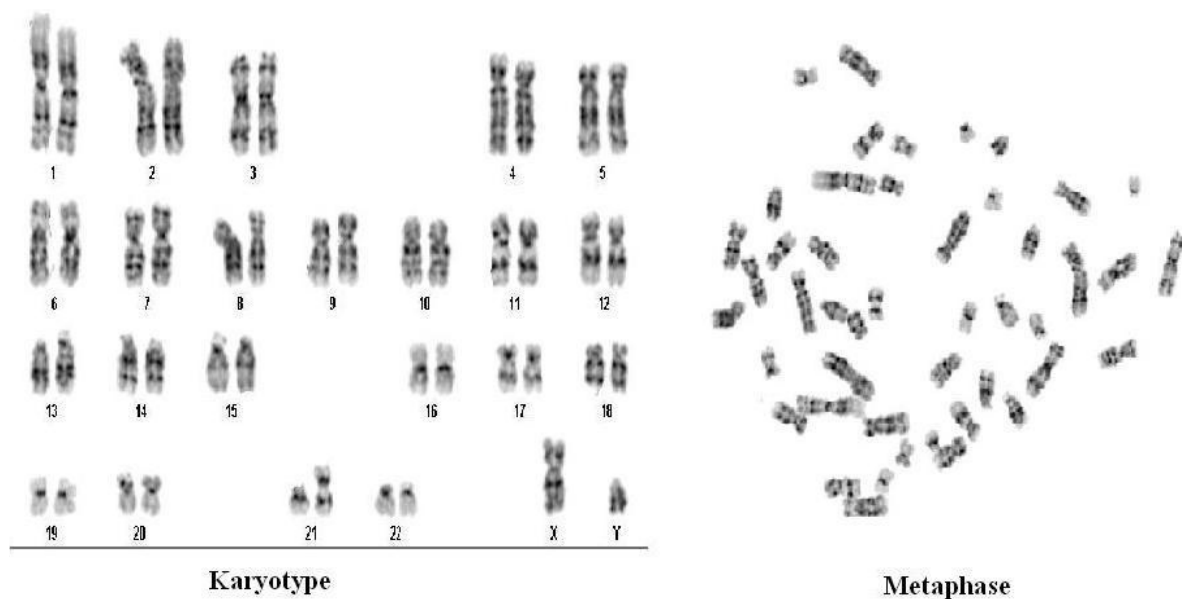


Figure 2 Down syndrome Robertsonian translocation (21;21); Male 46,XY,rob(21;21),+21

Case 3

The Down syndrome frequency in Indian population is roughly estimated at 1 in every 920 live births with an annual incidence of 18,000 cases [16]. Pure trisomy of the 21st chromosome is common in approximately 90% of cases. Mosaic cell lines with varying percentage of normal and trisomy cells were seen in about 6-7% of the Down syndrome cases. A small proportion of 3-5% is due to unbalanced chromosomal translocation involving the acrocentric groups of chromosomes especially chromosomes 14 and 21.

Robertsonian translocations occur during gametogenesis due to non-disjunction at mitosis or meiosis [17]. The occurrence of translocations is either sporadic or secondary if one of the parents is carrier of a balanced translocation. The carrier status of both parents must be established to determine the probability of recurrence of Down syndrome in the next child. Close relatives of translocation Down syndrome cases will have higher chances of carrying the translocation thereby producing affected babies as majority of the translocations are inherited. Thus, close relatives must also be advised to get karyotype done to detect carrier status for balanced translocations before conceiving.

A 6-year-old boy child born to young mother and father aged 22 years and 27 years respectively. The boy has delayed mile stones and mental retardation. The face had dysmorphic features like small chin, slanting eyes and flat nasal bridge. Robertsonian translocation of chromosomes 14 and 21 with trisomy for the long arm of chromosome 21 was detected in karyotype analysis. The cells showed 46,XY,rob(14;21),+21 karyotype in the boy child (Figure 3).

Down syndrome is caused by trisomy of chromosome 21. Though more than 90% of the cases show free trisomy about 5-6% exhibit Robertsonian translocation. While free trisomy is attributed to rising maternal age the Robertsonian translocation is seen in young mothers. It may be sporadic or familial. Most of the familial cases have a carrier of balanced translocation in one of the parents. The recurrence rate of an unbalanced trisomy child is much higher in maternally originated translocations than of paternal origin.

Case 4

A 12-year-old female patient was observed to have mental retardation. The patient was born with flabby muscles, had delayed mile stones, stunted growth for the age, slanting of eyes, flat face and nasal bridge, inelible speech, and had difficulty in carrying out her day-to-day activities. No other family members had any history of mental retardation. The history of the pregnancy during the present case was normal. The maternal and paternal ages were 31 and 36 years respectively.

On cytogenetic evaluation the patient was diagnosed as a case of Down syndrome with Robertsonian translocation

(21; 21) (q10;q10) .One of the most common chromosomal rearrangements in DS is the homologous translocation (21q21q) (Figure 4).

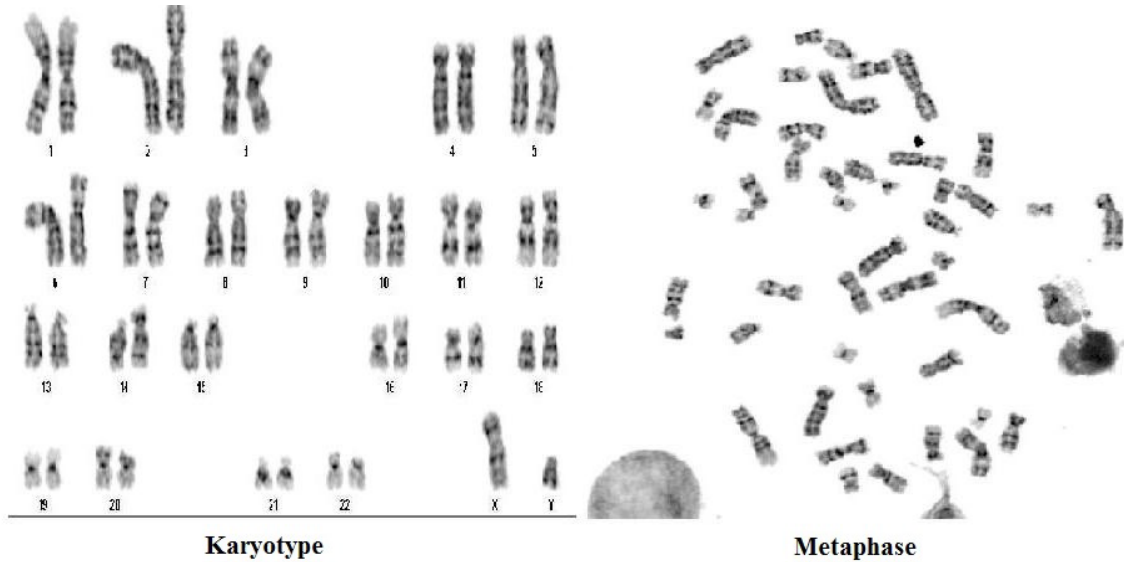


Figure 3 Downs syndrome Robertsonian translocation (14; 21); Male 46,XY,rob(14;21),+21

DS due to translocation may either be de novo or inherited from a balanced carrier parent [18]. A carrier with t (21q;21q) balanced translocation will always have a Down's offspring [19]. In general, carriers of Robertsonian translocations are phenotypically normal. In ~50% of cases of Robertsonian, the rearrangements occur de novo [18] and ~95% of the de novo cases originate during maternal meiosis.

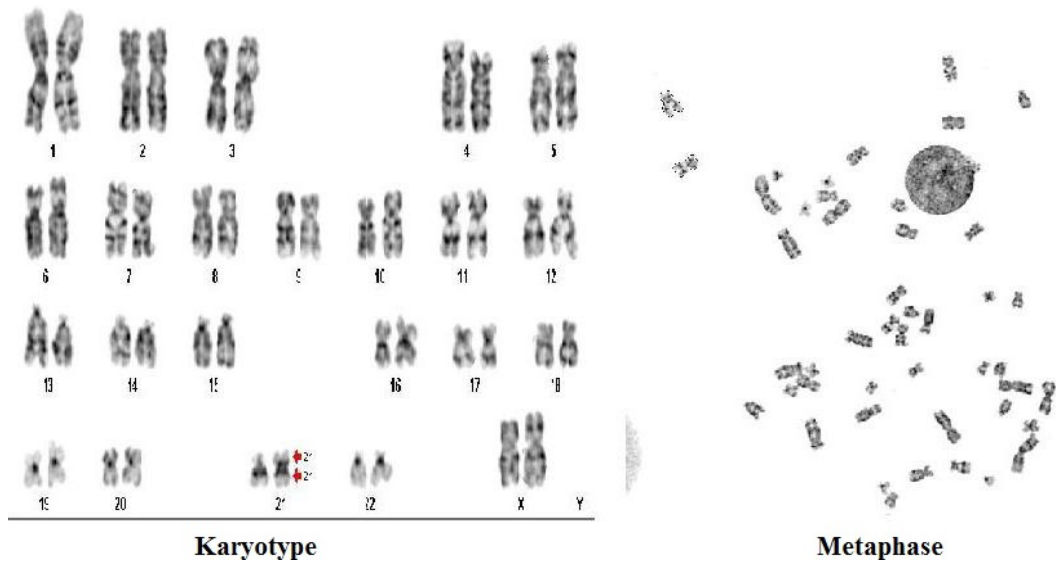


Figure 4 Downs syndrome Robertsonian translocation (21; 21); Female 46,XX,rob(21;21),+21

DISCUSSION

With reference to the previously published paper (ref), Table 1 representing the frequency of chromosomal abnormalities in different studies shows the lower frequency of translocations and mosaicism than the standard regular trisomy. This could be attributed to the high fertility rate and trends towards reproduction even at an advanced maternal age [13].

Table 1 Sex wise distribution of cytogenetic results of mentally retarded people

Chromosomal abnormality	Karyotype	No. of MR people	%	Sex
Down syndrome Trisomy (18 cases)	47,XY,+21	11	11	Male
	47,XX,+21	7	7	Female
Down syndrome	46,XY,rob(21;21),+21	2	2	Male
Robertsonian Translocations (4 cases)	46,XY,rob(14;21), +21	1	1	Male
	46,XX,rob(21;21), +21	1	1	Female
Down syndrome Mosaics (2 cases)	mos 46,XY/47,XY,+21	1	1	Male
	mos 46,XX/47,XX,+21	1	1	Female

Above table describes the sex wise distribution of cytogenetic results of mentally retarded people. The frequency of regular trisomy was 11 (11%) in males and 7 (7%) in females. The frequency of Robertsonian translocation 46,XY,t(21;21),+21 was 2(2%) in males and 1(1%) in females. The frequency of translocation 46, XY,t(14;21),+21 was 1 (1%) in males and it was not seen in females. The frequency of mosaic 46,XY/47,XY,+ 21 was 1 (1%) in both males and females.

In agreement with previous reports [14], there was considerable karyotype variability in individuals with DS, including cases of free trisomy and partial free trisomy of chromosome 21, as well as Robertsonian translocations between chromosomes 14 and 21 and between the two chromosomes 21. These observations emphasize the importance of cytogenetic confirmation in cases of DS.

Familial inheritance in Robertsonian Translocation is seen in one quarter whereas in remaining it arises as *de-novo* [15]. In the present study, the frequency of free T21 is more accounting for 24 (24%) of cases. Robertsonian Translocation was observed in 4 (4%) cases and mosaics in a frequency of 2 (2%). The two most common acrocentric arrangements in Down syndrome are rob (14q;21q) and rob (21q;21q) which occur at approximately equal frequencies.

CONCLUSION

The parents' chromosomes are studied to determine the heredity of a translocation. It is clear the baby inherited the translocation if one parent has the translocation chromosome.

Another important aspect is the parent's relatives (for e.g.: sisters, brothers) may also have inherited the translocation when a parent is found to have a translocation. Thus, the relatives may also have the same risks for problems with a pregnancy. Hence chromosomal studies of the relatives are recommended.

DECLARATIONS

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Authors Contribution

The corresponding author is the one to design the work and research concept. All other authors have contributed substantially to acquisition of data, drafting article and for critical revision.

Conflict of Interest

The authors and planners have disclosed no potential conflicts of interest, financial or otherwise.

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