

## STUDY OF THE FREQUENCY OF DOWN SYNDROME IN A NORTH EAST INDIAN POPULATION

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### ARTICLE INFO

Received: 16<sup>th</sup> Jun 2015

Revised: 12<sup>th</sup> Sep 2015

Accepted: 24<sup>th</sup> Sep 2015

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**Keywords:** Down syndrome, Trisomy 21, Free trisomy 21, Translocation trisomy 21, Mosaic, North East India

### INTRODUCTION

Down Syndrome (DS) or Trisomy 21 is the commonest autosomal chromosomal abnormality in the newborns<sup>[1]</sup>. Incidence of Down Syndrome varies from 1 in 600 to 1 in 1000 in live born infants<sup>[1,2]</sup>. In India, the reported incidence of Down syndrome is 1 in 1250<sup>[1]</sup>.

Down syndrome is recognizable at birth. Dr. Langdon Down (1828 – 1896) was the first to describe the clinical features of Down Syndrome children precisely<sup>[3]</sup>. Patients present with characteristic phenotypic features of the face, eyelids, tongue, etc., with retarded physical and mental growth<sup>[4]</sup>. However, the diagnosis may be difficult with the diagnostic accuracy ranging from 100% in non disjunction and translocation to as low as 37% in mosaicism<sup>[5]</sup>. Therefore confirmation of diagnosis by chromosomal analysis is needed. This in turn helps to determine the risk of recurrence and guides genetic counseling<sup>[2]</sup>.

Down Syndrome patients may present in three varied cytogenetic types: Free Trisomy 21, translocation trisomy 21 and mosaic trisomy 21<sup>[6]</sup>. Free trisomy 21 is the most common variety, seen in 95% cases and occurs due to paternal meiotic non disjunction<sup>[1]</sup>.

### ABSTRACT

**Context:** Down Syndrome or Trisomy 21, with three sets of chromosome number 21 is the commonest chromosomal abnormality in newborn. There are three types of Trisomy 21: Free Trisomy 21, Translocation Trisomy 21 and Mosaic Trisomy 21. **Aims:** The study aimed at finding the frequency of Down syndrome and its various cytogenetic types in a population from North East India. **Methods and Materials:** Karyotyping from G-Banded peripheral lymphocyte of patients with suspected chromosomal abnormality was done from peripheral blood and stained with Giemsa stain as per the Standard Operating Protocol of the Diagnostic Genetic Laboratory (CFDMGD). One to three ml of blood was withdrawn aseptically from each patient. 20-30 spreads were analyzed for each case. For mosaics, 30-50 spreads were studied. The slides were analysed for detection of various chromosomal abnormalities including Down syndrome (Trisomy 21). For the translocation Down Syndrome cases, parents were investigated to determine the parental carrier status. **Results:** 38 cases of Trisomy 21 were detected. Free Trisomy 21 was found in 92.11% cases, translocation trisomy 21 was seen in 2.63% case and Mosaic Trisomy 21 was seen in 5.26% cases. Male: female ratio was 1.38:1. **Conclusions:** Knowledge of the cytogenetic types has important clinical implications as it helps clinician/geneticist determine the recurrence risk in subsequent pregnancies and helps couples take an informed decision. This in turn would help in decreasing the load of the disease in society.

Translocation Down Syndrome is seen in 4% cases of Down Syndrome<sup>[1]</sup>. The extra chromosome 21 is translocated to the acrocentric chromosome of D group (Chromosome 13,14,15) or G group (Chromosome 21,22). Such translocations are usually Robertsonian in type<sup>[1]</sup>. Non homologous Robertsonian translocation between chromosome 14 and 21 [rob(14q;21q)] is the most common type while homologous Robertsonian translocation between chromosome 21 and 21 [rob(21q;21q)] is the second most common type<sup>[1]</sup>. Translocation Down Syndrome can be inherited from carrier parents<sup>[6]</sup>. It can also be created spontaneously de novo during the process of gametogenesis in one of the parents<sup>[6]</sup>. In a sporadically created translocation Down Syndrome, the risk to the second offspring is small. But in case of a 21q21q Robertsonian translocation in one the parent, all the gametes shall be unbalanced and the risk to the second offspring is 100%<sup>[6]</sup>. Hence karyotype of the parents is needed to locate the source of translocation and to estimate the risk of recurrence.

The third variant of Down Syndrome is mosaicism for chromosome 21, reported at 1%<sup>[1]</sup>. The patient has two

cell lines, one with 46 chromosomes and the other with 47, +21. The typical features of Down Syndrome may be less marked depending on the percentage of normal to trisomy 21 cell lines<sup>[1]</sup>. As diagnostic accuracy in such cases is less<sup>[5]</sup>, confirmation by cytogenetic tests is necessary. However the incidences in Down syndrome show wide variations among different populations. North East India has a unique ethnic population different from the rest of India. As no such study on Down syndrome have been done so far in this region to the best of our knowledge, this study may throw some light on the ethnic variations in the frequency of Down syndrome.

## MATERIALS AND METHODS

**Study design:** This was observational study

**Ethical approval:** The study was ethically approved with prior Institutional Ethical clearance obtained; proper informed consent was taken from the participants

**Inclusion criteria:** Included children with congenital malformations or suspected chromosomal abnormalities.

**Exclusion criteria:** Subjects suspected with other genetic diseases like single gene disorders, inborn errors of metabolism and multi factorial genetic diseases were excluded from the study.

**Sample size:** 38 cases of Down syndrome were analyzed cytogenetically.

**Study duration and place:** Children with congenital malformations or suspected chromosomal abnormalities were studied in the Cytogenetic Unit, DBT-sponsored Diagnostic Genetic Lab, Comprehensive Facility for Diagnosis and Management of Genetic Diseases (CFDMGD) and the Cytogenetic Viability Lab, Department of Anatomy, Assam Medical College, Dibrugarh, Assam. The study was done from August 2011 to March 2015.

**Methodology:** Karyotyping was carried out for peripheral lymphocytes, cultured from peripheral blood and stained with Giemsa stain as per the Standard Operating Protocol of the Diagnostic Genetic Laboratory (CFDMGD). Leica Cytogenetic Workstation (Manufacturer name: Leica Microsystems, Kolkota, India; model:Leica DM6000B and Leica CTR6000) was also used during the study.

One to three ml of blood was withdrawn aseptically from each patient. 20-30 spreads were analyzed for each case. For mosaics, 30-50 spreads were studied. The slides were analysed for detection of various chromosomal abnormalities including Down syndrome (Trisomy 21). For the translocation Down syndrome cases, parents were investigated to determine the parental carrier status.

**Statistical analysis:** The data found in this study were compared with similar findings of other authors in other country or in a different part of India and statistically analysed manually using two proportional Z-Test.

## RESULTS

Of the 38 cases of DS studied, Free trisomy 21 (Fig: 1) was noted in 92.11% cases; translocation DS (Fig: 2) was

noted in 2.63% cases while mosaics were seen in 5.26% cases (Table 1). One case of translocation DS (21q; 21q) was detected. On cytogenetic analysis of both parents, *de novo* translocation was seen, with both the parents having normal karyotypes. Male: Female Sex ratio observed in this study was 1.38:1.

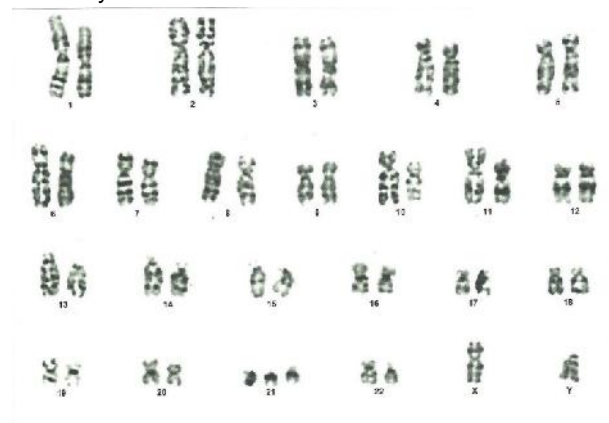


Fig.1.Karyotype showing Free Trisomy 21

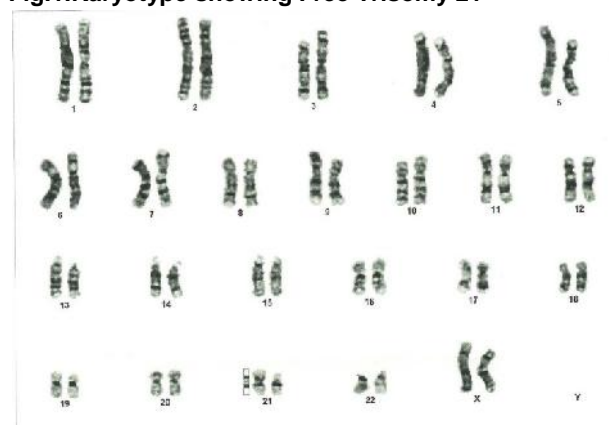


Fig.2.Karyotype showing Translocation Trisomy 21

Table 1: Frequency of various types of Trisomy 21

| Type                     |                            | Male      | Female    | %          |      |
|--------------------------|----------------------------|-----------|-----------|------------|------|
| Free Trisomy 21          |                            | 22        | 13        | 92.11      |      |
| Translocation trisomy 21 | Robertsonian translocation | 13q;21q   | -         | -          | -    |
|                          |                            | 14q;21q   | -         | -          | -    |
|                          |                            | 15q;21q   | -         | -          | -    |
|                          |                            | 21q;21q   | -         | 1          | 2.63 |
|                          |                            | 21q;22q   | -         | -          | -    |
|                          | Others                     | -         | -         | -          |      |
| Reciprocal translocation |                            | -         | -         | -          |      |
| Mosaic trisomy 21        |                            | -         | 2         | 5.26       |      |
| <b>Total</b>             |                            | <b>22</b> | <b>16</b> | <b>100</b> |      |

## DISCUSSION

The percentages of various types of trisomies were compared with those found by other authors (Table 2). Among the cases of Robertsonian translocation, Jyothy *et al.*<sup>[9]</sup> and Jayalakshmma *et al.*<sup>[1]</sup> reported higher percentage of t(14q;21q) (47.47% and 62.34% respectively).

**Table 2: Comparison of the frequency of various types of trisomy 21 among different authors**

| Author  | Source/Population/Study group | Total No. | Free trisomy 21 | Translocation trisomy 21 | Mosaic trisomy 21 | Non classic |
|---|-------------------------------|-----------|-----------------|--------------------------|-------------------|-------------|
| Mokhtar <i>et al.</i> <sup>7</sup> (2003)       | Egypt                         | 673       | 642(95.4%)      | 18(2.7%)                 | 5(0.7%)           | 8(1.2%)     |
| Devlin <i>et al.</i> <sup>5</sup> (2004)        | Ireland                       | 208       | 197(94.7%)      | 3(1.45%)                 | 8(3.85%)          | 0           |
| Azman <i>et al.</i> <sup>8</sup> (2007)         | Malaysia                      | 149       | 141(94.6%)      | 1(0.7%)                  | 7(4.7%)           | 0           |
| Amayreh <i>et al.</i> <sup>2</sup> (2009)       | Jordan                        | 80        | 74(92.5%)       | 2(2.5%)                  | 3(3.8%)           | 1(1.3%)     |
| Jayalakshamma <i>et al.</i> <sup>1</sup> (2010) | Karnataka, India              | 874       | 759(86.9%)      | 77(8.8%)                 | 38(4.3%)          | -           |
| Podder <i>et al.</i> <sup>3</sup> (2012)        | West Bengal, India            | 85        | 78(91.8%)       | 2(2.4%)                  | 5(5.9%)           | -           |
| Kolgechi <i>et al.</i> <sup>6</sup> (2013)      | Kosova Albanian Population    | 305       | 285(93.4%)      | 17(5.6%)                 | 3(1%)             | -           |
| Present study (Das <i>et al.</i> )              | Dibrugarh, Assam              | 32        | 29(90.63%)      | 1(3.13%)                 | 2(6.25%)          | 0           |

However, Kolgechi *et al.*<sup>[6]</sup> found t(21q;21q) translocation to be the most common (58.8%) type. The only translocation found in this study was t(21q;21q), which therefore formed the most common type. This matches the results of Kolgechi *et al.*<sup>[6]</sup>.

Most de novo rearrangement of 21q;21q are isochromosomes derived from a single parent #21 and only a small proportion are true Robertsonian translocation<sup>[10,11]</sup>. Translocation can also be reciprocal. Kolgechi *et al.*<sup>[6]</sup> found 0.3% cases with reciprocal translocation between chromosome 21 and 8.

The results of this study were compared with one Indian study<sup>[1]</sup> and one study abroad<sup>[7]</sup> and statistically analyzed by manual method using two proportional Z-test. Although Free trisomy 21 and translocation trisomy 21 did not show significant difference when compared with both the authors, mosaic trisomy 21 showed a significant difference with the Egyptian population<sup>[7]</sup>.

The Sex ratio of 1.38:1 showed a male preponderance. This was in conformity with the findings of other authors as well. Higher male sex ratio may be due to the inherent tendency of Y chromosome belonging to the G group (acrocentric chromosomes) which also includes the chromosomes 21 and 22<sup>[1]</sup>.

Recurrence risk is <1% in a *de novo* translocation Down Syndrome. In familial Robertsonian translocation, the recurrence risk is about 10%, which increases to 15% at amniocentesis. For male carrier, the recurrence risk is about 1%<sup>[12]</sup>. In families with a *de novo* translocation Down Syndrome and parents with normal karyotype, the risk of a second child with Down Syndrome is small (1-2%). For couples who are carriers of silent Robertsonian translocation t(21q; 21q), the risk of having a second child with Down Syndrome is 100% and they shall be unable to have healthy baby<sup>[6]</sup>. In t(21q; 21q), if one parent is a carrier, the recurrence risk is 100% while in t(21q; 22q) if one parent is a carrier, the recurrence risk is <5%. If mother is a carrier, the recurrence risk is 10% but if father is the carrier, the recurrence risk is <5% in case of a D/G translocation<sup>[9]</sup>.

Parental karyotype is therefore essential for all patients with translocation Down Syndrome. Prenatal diagnosis must be offered if any of the parents shows an abnormal

karyotype<sup>[9]</sup>. Earlier clinical diagnosis helps parents to make crucial medical decisions.

## CONCLUSION

The study showed interesting variations in the frequency of Down Syndrome in a North East Indian population. Knowing the type of translocation and status of the parent is important to estimate the risk of recurrence in future pregnancies. This information, assisted with advances in prenatal diagnosis can help parents in decision making and reduce the burden of Down syndrome births in the society.

**Limitation of the study:** The relatively small sample size. This is because, the disease is relatively rare and the awareness of the need for genetic test among the public in this area is still in its infancy. Further study with more number of participants with the developing awareness shall bring out more information from this region.

**Conflict of interest:** Nil

**Acknowledgments:** The authors acknowledge the Department of Biotechnology, Government of India for providing the entire financial support (including manpower, equipments and consumables) to carry out the present study under the CFDMGD project, Assam Medical College, Dibrugarh, Assam. We appreciate the technical support provided by our laboratory technicians Mr. Rupjyoti Lahon, Mrs. Mitali Barman, Miss. Pompei Saikia and Miss. Arunima Borah. We are also thankful to Miss. Debashri Boruah for her help in statistical analysis. We thank the Genetics Unit, Department of Paediatrics, All India Institute of Medical Sciences, New Delhi for assisting us in quality control. We are grateful to Prof. A.K. Adhikari, The Principal-cum-Chief Superintendent and Dr. J. Lahon, Professor and Head of Anatomy, Assam Medical College for their support and encouragement. We thank all the referring doctors who have made this study possible.

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