ORIGINAL RESEARCH PAPER

Paediatrics

KEY WORDS:

# MICROARRAY BASED COMPARATIVE GENOMIC HYBRIDISATION IN IDIOPATHIC MENTAL RETARDATION
SUBJECT: PAEDIATRICS

**Dr Dhanna Ram Bajiya** Junior specialist(pediatrics SDH Deedwana Nagaur

**Dr Naresh Kumar*** medical officer paediatrics janana hospital government medical college bharatpur *Corresponding Author

ABSTRACT

Intellectual disability (ID),also known as general learning disability, and mental retardation (MR) is a generalized neuro developmental disorder characterized by significantly impaired intellectual and adaptive functioning. It is defined by an IQ score under 70 in addition to deficits in two or more adaptive behaviors that affect every day, general living. **Material and methods-** This hospital based observational study was carried out at Department of Paediatric Medicine, SPMCHI, SMS Medical College, Jaipur between May 2015 to April 2016 to identify the genetic defects of children with Idiopathic Mental Retardation.The study included 20 children with Idiopathic Mental Retardation. After detailed clinical history and physical examinations, specific investigations were done.Qualitative analysis of chromosomal microarray of idiopathic Mental Retardation have been done by using DECIPHER database. **Results-** Out of 20 children, 12(60%) were males and 8(40%) were females. out of 20 children, 11 had mild mental retardation contributing to 55% of the total and 9( 45%) children were of moderate mental retardation. In our study 3 CNV Gain on loci q21.31 on Chr. X in 40% children, 3 CNV Gain on loci q28 on Chr. X in 15% children, 3 CNV Gain on loci p11.23 on Chr. X in 5% children, Gain Mosaic on loci p22.33 on Chr. X in 5% children, Gain Mosaic on loci p11.3 on Chr. X in 5% children, Loss of CNV on loci q11.2 on Chr.14 in 5% children, 3 CNV Gain on loci q12.11 on Chr.13 in 5% children defects found. **Conclusion**-We found that most of the patients of idiopathic mental retardation had CNVs at chromosomes no X, 13th or 14th, so in cases of idiopathic mental retardation we should search for genetic defects at these chromosomes.

## INTRODUCTION

Intellectual disability (ID),[1]also known as general learning disability,[2]and mental retardation (MR)[3,4] is a generalized neuro developmental disorder characterized by significantly impaired intellectual and adaptive functioning. It is defined by an IQ score under 70 in addition to deficits in two or more adaptive behaviors that affect every day, general living.

Intellectual disability affects about 2–3% of the general population. Seventy-five to ninety percent of the affected people have mild intellectual disability. Non-syndromic or idiopathic cases account for 30–50% of cases. About a quarter of cases are caused by a genetic disorder. Mental retardation is a heterogeneous condition, affecting 1-3% of general population. In the last few years, several emerging clinical entities have been described, due to the advent of newest genetic techniques, such as Array Comparative Genomic Hybridization. The detection of cryptic microdeletion/microduplication abnormalities has allowed genotype-phenotype correlations, delineating recognizable syndromic conditions that are here in reviewed. With the aim to provide to Paediatrician a combined clinical and genetic approach to the child with mental retardation, a practical diagnostic algorithm is also illustrated.[5]Intellectual disability (ID) begins during childhood and involves deficits in mental abilities, social skills, and core activities of daily living (ADLs) when compared to same-aged peers.[6]Among children, the cause of intellectual disability is unknown for one-third to one-half of cases. In around 5% of cases Intellectual disability is inherited from their parents.[5] Genetic defects that cause intellectual disability but are not inherited can be caused by accidents or mutations in genetic development. Examples of such accidents are development of an extra chromosome 18 (trisomy18) and Down syndrome, which is the most common genetic cause.[5] Velocardiofacial syndrome and fetal alcohol spectrum disorders are two next most common causes.

**However, doctors have found many other causes.**
**The most common are:**

Genetic conditions: Sometimes disability is caused by abnormal genes inherited from parents, errors when genes combine, or other reasons.The most prevalent genetic condition Down syndrome, Klinefelter syndrome, Fragile X syndrome (common among boys) neurofibromatosis, congenital hypothyroidism, Williams syndrome, Phenylketonuria and Prader willi syndrome.Other genetic condition include Phelan McDermid Syndrome (22q13del), Mowat-Wilson syndrome, genetic ciliopathy[7] and Siderius type X-linked intellectual disability as caused by mutations in the *PHF8* gene.[8,9] In the rarest of cases, abnormalities with the X or Y chromosome may also cause intellectual disability. 48, XXXX and 49, XXXXX syndromes affect a small number of girls worldwide, while boys may be affected by 47, XYY, 49, XXXX, or 49, XYYYY.

Problems during pregnancy: Intellectual disability can result when the fetus does not develop properly. For example, there may be a problem with the way the fetus' cells divide as it grows. A pregnant person who drinks alcohol (fetal alcohol spectrum disorder) or gets an infection like rubella during pregnancy may also have a baby with intellectual disability.

Problems at birth: If a baby has problems during labor and birth, such as not getting enough oxygen, he or she may have developmental disability due to brain damage.

Exposure to certain types of disease like whooping cough, measles, or meningitis can cause intellectual disability if medical care is delayed or inadequate.
Exposure to poisons like lead or mercury may also affect mental ability.

With the advent of novel genetic techniques, several new cryptic chromosomal aberrations have been discovered in last few years.[10,11]and a consistent number of MR cases, previously considered "idiopathic" forms, are now classified as syndromic conditions with clinical recognizable phenotypes.[12] Microarrays techniques (such as array-Comparative Genomic Hybridization) revealed submicroscopic aberrations in 5-17% of MR patients with normal results from prior conventional cytogenetic testing[13] and higher-density platforms (such as Single-Nucleotide Polymorphism array) provided to increase diagnosis in about 6% of cases evaluated by lower-density oligonucleotide

arrays.Genetic testing is an emerging modality in finding etiology of MR. These tests have high diagnostic yield in unexplained/Idiopathic Mental Retardation. Microarray molecular genetic testing should be done for Idiopathic Mental Retardation.

## AIMS AND OBJECTIVES

To identify genetic defects by Microarray Based Comparative Genomic Hybridisation in children with Idiopathic Mental

## MATERIAL & METHODS

This study is carried out at the Department of Paediatrics and Genetic laboratory attached to SMS Medical College, Jaipur between MAY 2015 to APRIL 2016..This study is Hospital based descriptive type of observational study sample size was 20 cases.Patients with idiopathic mental retardation from the OPD and IPD of Department of Paediatrics, SMS Medical College, Jaipur ,between age 5 to 18 years were included in the study while Syndromic phenotype patient with Past history of Birth Asphyxia and Past history of whooping cough, measles, or meningitis and Radiological evidence of brain damage patients were excluded from study.2 ml EDTA sample was collected from each patient and sent to genetic lab SMS medical college jaipur where sample was stored at 4 degree Celsius.

### Chromosomal Micro -Arrays method:

Enable us to perform high-resolution genome-wide DNA copy number analysis. Also provides genotyping information, enabling detection of loss of heterozygosity (LOH), which can be used to detect UPDs. The combined high resolution DNA copy number data and the ability to detect gains, losses, and UPDs on a single array.

## OBSERVATION

Table 1 shows the demographic profile of study subjects. Out of 20 children, 12(60%) were males and 8(40%) were females. Table 2depicts that out of 20 children, 11 had mild mental retardation contributing to 55% of the total and 9( 45%) children were of moderate mental retardation. Table 3 shows about the chromosome loci in idiopathic mental retardation children where the genetic defects occurs, which is responsible for certain phenotype loci. Table 4 shows about type of genetic defects which have different size as mention in table 5.There are 3 type genetic defects present in idiopathic mental retardation child as CNV Gain(84.6%), Gain mosaic(13.5%),Loss(1.9%).

**Table No 1 Demographic Profile of the children with Idiopathic Mental Retardation**

| Sex | Frequency | Percent |
|---|---|---|
| Male | 12 | 60% |
| Female | 8 | 40% |
| Total | 20 | 100% |

**Table 2 Distribution of children according to extent of mental retardation**

| IQ(Intellectual Quotient) | Extent of delay | No. of children |
|---|---|---|
| 50-70% | Mild | 11 |
| 35-50% | Moderate | 9 |
| <35% | Severe | 0 |
| | | 20 |

**Table 3 Description of chromosome loci in idiopathic mental retardation children**

| Chromosome location | Frequency | Percent |
|---|---|---|
| Chr.13q12.11:23165649-25356053 | 1 | 1.9 |
| Chr.14q32.33: 105,953,562 - 106,982,195 | 1 | 1.9 |
| Chr.14q32.33: 106,003,519 - 106,599,191 | 2 | 3.8 |
| Chr.14q32.33: 106,005,011 - 107,047,902 | 4 | 7.7 |
| Chr.14q32.33: 106,154,277 - 106,956,015 | 2 | 3.8 |
| Chr.14q32.33: 106,159,204 - 106,955,372 | 5 | 9.6 |
| Chr.14q32.33: 106,163,508 - 106,939,177 | 3 | 5.8 |
| Chr.14q11.2: 22,434,043 - 23,007,517 | 1 | 1.9 |
| Chr.19p13.3: 356,673 - 1,848,519 | 2 | 3.8 |
| Chr.19p13.3: 477,360 - 1,832,777 | 1 | 1.9 |
| Chr.7p11.2: 56,977,684 - 63,513,897 | 2 | 3.8 |
| Chr.Xp22.33: 0 - 11,858,266 | 1 | 1.9 |
| Chr.Xq28: 152,667,967 - 153,201,181 | 3 | 5.8 |
| Chr.Xp11.3: 33,412,605 - 114,663,970 | 1 | 1.9 |
| Chr.Xp11.23: 48,837,021 - 49,428,483 | 3 | 5.8 |
| Chr.Xq21.31: 89,052,822 - 89,614,175 | 4 | 7.7 |
| Chr.Xq21.31: 89,129,617 - 89,735,437 | 2 | 3.8 |
| Chr.Xq21.31: 89,134,012 - 89,701,744 | 2 | 3.8 |
| Chr.Yp11.31: 0 - 32,722,038 | 5 | 9.6 |
| Chr.Yp11.31: 2,657,020 - 3,849,192 | 1 | 1.9 |
| Chr.Yp11.2: 4,085,981 - 6,373,862 | 3 | 5.8 |
| Chr.Yp11.2: 6,359,367 - 6,921,247 | 3 | 5.8 |
| Total | 52 | 100.0 |

**Table 4 Description of type of CNV**

| | Frequency | Percent | Valid Percent | Cumulative Percent | |
|---|---|---|---|---|---|
| Type | Gain | 44 | 84.6 | 84.6 | 84.6 |
| | GainMosaic | 7 | 13.5 | 13.5 | 98.1 |
| | Loss | 1 | 1.9 | 1.9 | 100.0 |
| | Total | 52 | 100.0 | 100.0 | |

## DISCUSSION

Mental Retardation is one of the most common reason for disability in paediatric population. Not only the affected children suffer from disability, the families of these children also get affected. These children as well as their families need special care and support. Thus, it is required that these children should be diagnosed at an early stage so that effective management can be issued early. Role of early intervention and stimulation therapy can definitely improve outcome in these children. Finding an underlying cause for a child's delay can directs the paediatrician for planning best management plan for the child. Timely targeting and treating co morbidities in these children is also of utmost importance as it can reduce the morbidity associated with the disability and can help these children lead active, self supporting and long lives. Only few studies are available till date that too from outside India, on children with Idiopathic Mental Retardation genetic analysis and defect in Genomes.This study was undertaken to study the genetic defect in idiopathic mental retardation children in a hospital based setting in our country. The study was conducted at Department of Paediatrics, SPMCHI, Jaipur from May 2015 to April 2016.Total of 20 children with IQ < 70% and age between 5-18yrs were selected as study subjects. Detailed history including family history was taken. Clinical examination including neurological examination was done. Specific investigations

neuro imaging, metabolic profile workup and thyroid profile have been done. All the information was entered in a set proforma then chromosomal microarray of idiopathic M R has been done and data was then arranged in an excel sheet and analyzed accordingly.We found 22 chromosomal loci in 20 idiopathic mental retardation children where the genetic defects detected, which are responsible for certain phenotype loci according to DECIFER database.In our study we analysed 20 idiopathic mental retardation and all below mention genetic defects are responsible for mental retardation in children as per explained in DECIFER Database, which has unknown/benign pathogenicity. Sharma et al[14] ( 2016) conducted study at Division of Genetics, Department of Paediatrics, All India Institute of Medical Sciences, New Delhi, India with chromosomal microarray analysis (CMA) in a clinical setting for the identification of sub microscopic copy number variations (CNVs), throughout the genome, associated with neurodevelopmental phenotypes including ID/GDD. In this study they investigated the utility of CMA in the detection of CNVs in 106 patients with unexplained ID/DD, dysmorphism with or without multiple congenital anomalies (MCA). CMA study was carried out using Agilent 8×60K chips and Illumina Human CytoSNP-12 chips. Pathogenic CNVs were found in 15 (14.2%) patients. In these patients, CNVs on single chromosome were detected in 10 patients while 5 patients showed co-occurrence CNVs on two chromosomes. The size of these CNVs ranged between 322kb to 13Mb. The yield of pathogenic CNVs was similar for both mild and severe ID/GDD cases. One patient described in this paper is considered to harbour a likely pathogenic CNV with deletion in 17q22 region. Only few cases have been described in literature for 17q22 deletion and patient reported here was found to have an atypical deletion in 17q22 region. This study re-affirms the view point that CMA is a powerful diagnostic tool in the evaluation of idiopathic ID/GDD patients irrespective of the degree of severity. Boggula et al[15]( 2015) conducted study at Department of Medical Genetics, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India with CMA in 86 Indian patients with idiopathic ID/DD with or without dysmorphic featuresPathogenic CNVs were found in 18 of 86 (20.9%) patients. One large (14 Mb size) de novo heterozygous copy number gain was found in one patient. VUS (total 31) were present in 17 of 86 (19.7%) patients. Five novel recurrent benign CNVs were also present in their patients.Their findings highlight the difficulties in interpretation of CNVs identified by CMA. More Indian data on VUS and recurrent benign CNVs will be helpful in the interpretation of CMA in patients with ID/DD. Pariltay et al[16] ( 2014) conducted study with new array technologies which have facilitated the analysis of sub microscopic chromosomal imbalances and structural variants. Copy number variation (CNV) analysis can reveal genetic imbalances in up to 10% of cases involving intellectual disability (ID), with or without multiple congenital anomalies (MCA). Here they present 4 cases, diagnosed by CNV analysis using Affymetrix Genome Wide Human SNP 6.0 array, and their parents. CNVs ranging from 18 to 196 per subject, with a size range of 100kb- 6093kb, were detected in all cases. One case revealed inherited CNVs, whilst de novo ins/dels were found in the other three which may be causative factors in the development of clinical pictures. Microarray technology may help to reveal the etiology of ID and is a potentially useful diagnostic tool for patients with ID.

## CONCLUSION:

We found that most of the patients of idiopathic mental retardation had CNVs at chromosomes no X, 13th or 14th, so in cases of idiopathic mental retardation we should search for genetic defects at these chromosomes. However we recommend that parental microarray should also be performed with patient`s microarray so that we can differentiate pathological CNV from benign CNV.

## REFERENCES


1. Wilmshurst Linda: "Clinical and Educational Child Psychology an Ecological-Transactional Approach to Understanding Child Problems and Intervention". Hoboken: Wiley. (2012) p. 168.
2. Tidy, Colin : "General Learning Disability" ( 2013) p.40
3. Harkin: 'Rosa law" (2013)p.36
4. Ansberry, Clare: "Erasing a Hurtful Label from the Books". The Wall Street Journal. ( 2010)p.21
5. Galasso C, Lo-Castro A, El-Malhany N, Curatolo P: "Idiopathic" mental retardation and new chromosomal abnormalities",Ital J Pediatr(2010) 14;36:17
6. Kaneshiro, Neil K: "Intellectual disability", MedlinePlus, U.S. National Library of Medicine, (2015)
7. Bendor M: "Intellectual disability" Queensland journel ( ,2015).
8. Badano, Jose L.; Norimasa Mitsuma; Phil L. Beales; Nicholas Katsanis (September 2006). "The Ciliopathies : An Emerging Class of Human Genetic Disorders" . Annual Review of Genomics and Human Genetics. (2006). 7: 125–148.
9. Siderius LE, Hamel BC, van Bokhoven H, et al. "X-linked mental retardation associated with cleft lip/palate maps to Xp11.3-q21.3". Am. J. Med. Genet. (2005) (3):216
10. Laumonnier F, Holbert S, Ronce N, et al. "Mutations in PHF8 are associated with X linked mental retardation a Shevell MI, Bejjani BA, Srour M, Rorem EA, Hall N, Shaffer LG: "Array comparative genomic hybridization in global developmental delay". Am J Med Genet. 2008, 147B: 1101-1108. 10.1002/ajmg.b.30730.
11. Shaffer LG, Bejjani BA, Torchia B, Kirkpatrick S, Coppinger J, Ballif BC:"The identification of microdeletion syndromes and other chromosome abnormalities: cytogenetic methods of the past, new technologies for the future". Am J Med Genet. 2009
12. Li MM, Andersson HC: "Clinical Application of Microarray-Based Molecular Cytogenetics": An Emerging New Era of Genomic Medicine. J Pediatr. 2009, 155:311-317.10.1016/j.jpeds.2009.04.001
13. Liang JS, Shimojima K, Yamamoto T:"Application of Array-based Comparative Genome Hybridization in Children with Developmental Delay or Mental Retardation". Pediatr Neonatol. 2008, 49: 213-217. 10.1016/S1875-9572(09)60013-
14. Sharma P, Gupta N, Chowdhury MR, Sapra S, Ghosh M, Gulati S, Kabra M."Application of chromosomal microarrays in the evaluation of intellectual disability/global developmental delay patients - A study from a tertiary care genetic centre in India".Gene. 2016 Sep 15;590(1):109-19.
15. Boggula VR, Agarwal M, Kumar R, Awasthi S, Phadke SR. "Recurrent benign copy number variants & issues in interpretation of variants of unknown significance identified by cytogenetic microarray in Indian patients with intellectual disability". Indian J Med Res. 2015 Dec;142(6):699-712.
16. Pariltay E, Durmaz A, Durmaz B, Aykut A, Onay H, Ak H, Aydin HH, Ozkinay F, Cogulu O."Genome-wide copy number variation analysis in idiopathic intellectual disability/multiple congenital anomalies".Genet Couns. 2014;25(2):221-9.


.