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Original Research Article

Evaluation of constitutional chromosomal abnormalities: experience of a tertiary healthcare diagnostic laboratory in India

Vidya Salaskar[1], Gauri Pradhan[1], Anurita Pais[1]*, Chaitali Kadam[1], Sunmeet Matkar[2]

[1]Department of Cytogenetics, [2]Department of Medical Communication, Research and Development, Metropolis Healthcare Limited, Kurla (W), Mumbai, Maharashtra, India

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***Correspondence:**
Dr. Anurita Pais,
E-mail: anurita.pais@metropolisindia.com

ABSTRACT

Background: Structural and numerical chromosomal aberrations contribute significantly to genetic disease. Unbalanced aberrations are associated with congenital anomalies, mental retardation and underdevelopment of secondary sexual characters while balanced structural chromosomal abnormalities contribute to an increased risk for infertility, bad obstetric history and chromosomally unbalanced offspring with multiple congenital abnormalities and intellectual impairment. Aim of the current study was to determine the prevalence and characterization of cytogenetic aberrations in 8445 cases referred during the years 2010-2013 for cytogenetic evaluation.
Methods: Metaphase chromosomes from 72-hour blood lymphocyte culture were prepared for Giemsa-Trypsin-G banding. Characterization of marker chromosomes were done by M-FISH and subtle chromosomal aberrations were evaluated by targeted FISH using centromeric probes for chromosome 13,18,21, X and Y and loci specific probes for microdeletion syndromes and SRY gene.
Results: Variant forms of trisomies i.e. partial trisomies were seen in cases with Edwards and Patau syndrome. Sex chromosomal abnormalities associated with puberty and reproductive problems were seen in cases with Turner syndrome, Klinefelter syndrome and also in females with primary amenorrhea. Autosomal reciprocal translocations were the most common chromosomal changes in couples with recurrent abortions. In order to increase the diagnostic yield and evaluate variations, FISH and m-FISH were additional tests done to characterize the genetic variations.
Conclusions: Along with Karyotyping SRY, XIST, SHOX9 gene analysis and Y microdeletion analysis are also critial tests to assess the possibilities for normal development or assisted reproduction in individuals with sex chromosomal abnormalities.

Keywords: Chromosomal abnormalities, Cytogenetic evaluation, Klinefelter syndrome, Turner syndrome

INTRODUCTION

Chromosomal aberrations are abnormalities in the structure or number of chromosomes and are often responsible for genetic disorders.[1] Numerical abnormalities result in trisomy or monosomy of chromosomes which can be de novo or may be inherited from carrier parents.[2] The rearrangement of chromosomes results in different types of structural changes such as translocations, deletions, inversions and duplications.[3] Structural abnormalities result in either balanced or unbalanced translocations. Carriers of balanced chromosomal rearrangements are usually clinically normal but can produce unbalanced gametes and have an increased risk for chromosomally abnormal offspring.[4] Heterozygous carriers have an increased risk for infertility, miscarriages. Unbalanced constitutional rearrangements are generally associated with

developmental delay or intellectual impairment, birth defects and poor growth.[5] Disorders of the sex chromosome can be either numerical or structural, and can be present in all cells or in a mosaic form. Clinical indications that raise suspicions of a sex chromosome abnormality are delay in onset of puberty; primary or secondary amenorrhea; infertility; and ambiguous genitalia.[6] A cytogenetic study in cases with sex chromosome abnormalities is essential for proper genetic counseling and normal development. Depending on the resolution of the genetic variation further characterization of chromosomal abnormalities using different technologies need to be applied. Therefore, the aim of the current study was to determine the prevalence and characterization of cytogenetic aberrations in 8445 cases referred during in two years year-2011 to year-2013 for cytogenetic evaluation.

METHODS

Metaphase chromosomes from 72hour blood lymphocyte culture were prepared for Giemsa-Trypsin-G banding. Characterization of marker chromosomes were done by M-FISH and subtle chromosomal aberrations were evaluated by targeted FISH using centromeric probes for chromosome 13,18,21, X and Y and loci specific probes for microdeletion syndromes and SRY gene.

RESULTS

Of the total 8445 cases analysed, clinical indications were available for 6712 cases. Out of the total cases, around 1108 cases were of children referred for various disorders such as Down syndrome, Edwards Syndrome, Patau Syndrome, Multiple congenital abnormalities, dysmorphic features, developmental delays, mental retardation and ambiguous genitalia. While, 929 cases were referred for ambiguous genitalia and puberty related issues. And lastly, 4675 cases were referred for Bad Obstetric history and Infertility. Of the total 1108 cases (Figure 1), 301 cases showed complete trisomy 21, 20 cases showed trisomy due to robertsonian translocation and 50 cases showed mosaic pattern. Trisomy 21 was also identified in cases with klinefelter syndrome and XY females and one case with balanced translocation involving chromosomes 1 and 11. Marker chromosome 21 was identified as iso-21 by FISH. Apart from trisomy 13 in Patau syndrome (4cases), trisomy 18 in Edwards Syndrome (5 cases) and 4p deletion in Wolf Hirshom Syndrome (3 cases), Deletion of 5p in Cri-Du-Chat syndrome (5 cases) our study reported unbalanced translocations involving chromosomes like 3, 5, 15, 16, 18, 21 and 22.

Along with these, number of structural abnormalities of chromosome 18 such as deletion 18q, addition 18q, ring 18 and translocation between chromosomes 5 and 18 were also identified. FISH-analysis was carried out in suspected cases of Di-George Syndrome, Prader-Villi/Angelman syndrome and to identify marker chromsomes. M-FISH done in a case revealed a mosaic pattern with ring chromosome 8 which was responsible for genetic instability and a cause for mental retardation. FISH remains an important tool to map and characterize both balanced and unbalanced rearrangements and to unravel the complexity of the genomic imbalance.

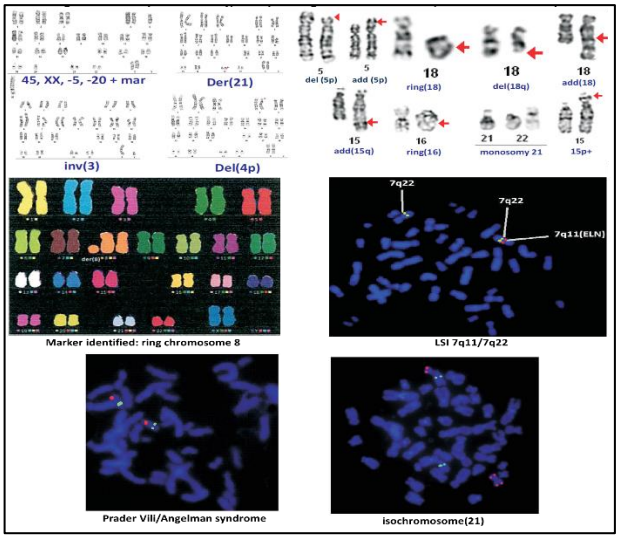

Figure 1: Development delay/multiple congenital abnormalities/ intellectual disability from the image.

Our study also focused on the Sex chromosome abnormalities. Apart from abnormalities of X and Y chromosomes, cases with autosomal abnormalities were also identified. Structural abnormalities of the Y chromosome result in a spectrum of abnormalities from primary infertility (male or female) to various forms of ambiguous genitalia.

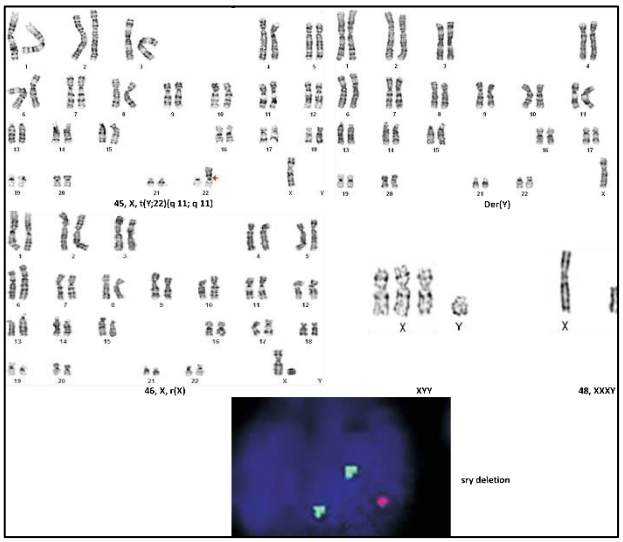

Figure 2: Sex chromosome abnormalities in men

With respect to sex chromosome abnormalities in Males (Figure 2), in few males with XX karyotype SRY gene studies were carried out as the SRY (sex-determining

region on the Y chromosome) gene is required for normal embryonic wolffian (male) genital development, although numerous other genes are involved in completing the process of normal male development. Cases with small Y and Inversion in Y chromosome were further evaluated for Y micro deletion studies. Translocation of Sex chromosome with autosomes were also noted such as t (Y;22) and t (11;22) in a case of Klinefelter syndrome.

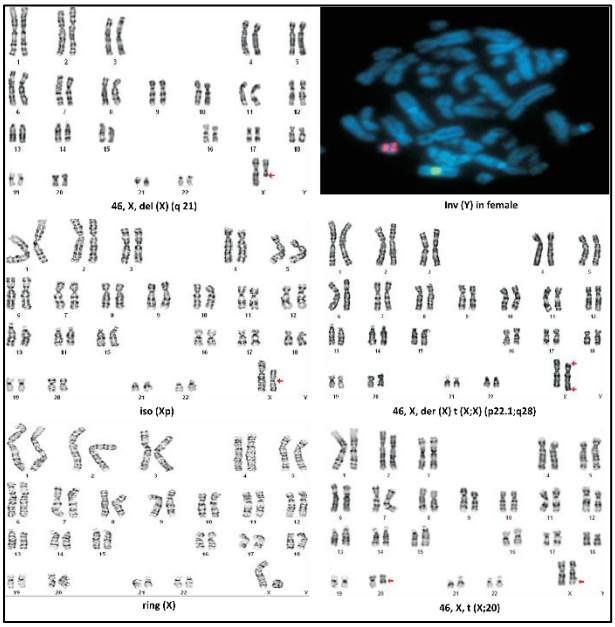

Figure 3: Sex chromosome abnormalities in female.

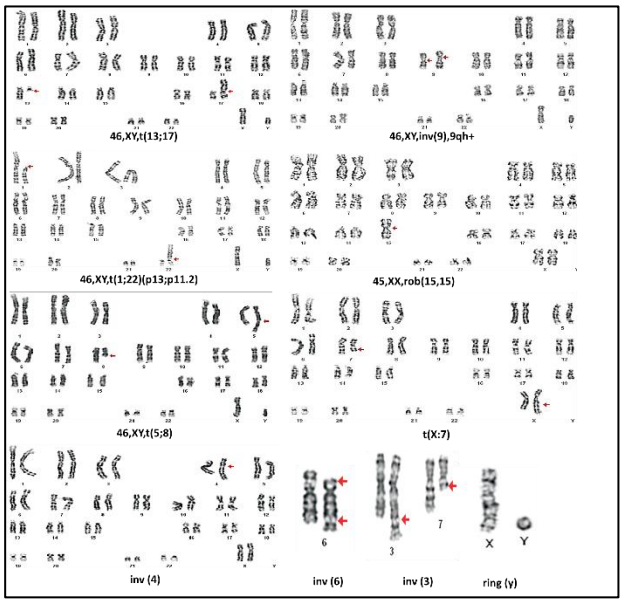

Figure 4: BOH/recurrent abortions/infertility.

While, the sex chromosome abnormalities in Females (Figure 3) reported that among the sex chromosome abnormalities 33% showed complete monosomy of chromosome X, 33% showed variant turner patterns such as Mosaic XX RING XXX ISOXP ISOXQ Deletion Xp Deletion Xq. Around 33% were identified with 46, XY karyotype in females with primary amenorrhea. Translocation of sex chromosome with autosomes were also noted such as t (X;16), t (X;X) and t (X;20). To determine low degree mosaicism FISH studies were carried out wherever required.

Although there were 2340 couples that were refereed for abortions and infertility, 480 couples had a history of recurrent abortions and or previous abnormal child (Figure 4). Of these 480 cases, 70 cases showed balanced aberrations like reciprocal translocations, robertsonian translocations and inversions. Sex chromosome abnormalities such as ring X, ring Y, translocations involving X chromosome, triple X syndrome were noted. Y chromosome abnormalities like small Y and inversion Y were also commonly observed.

Although inversion of chromosome 9 and increase in heterochromatin 9 are considered to be normal variants, we observed number of cases showing these abnormalities and as per literature these variants may have a role in causing imbalances during recombination in gametogenesis. One case showed presence of both these variants on both homologue 9.

DISCUSSION

The chromosomal rearrangements may be balanced or unbalanced. Unbalanced translocations may result in microdeletions and microduplications causing copy number variations in the genome leading to functional disability of genes responsible for phenotypic changes and intellectual impairment. Balanced translocations may also lead to functional changes in genes at the break point causing various disorders such as developmental delay, multiple congenital abnormalities, ambiguous genitalia, infertility, and primary amenorrhea.[7]

In cases with apparently balanced rearrangements showing phenotypic variations further characterization is needed by techniques such as targeted FISH or m-FISH to identify marker chromosomes and array CGH. In individuals with sex chromosomal abnormalities besides Karyotyping SRY, XIST, SHOX9 gene analysis and Y microdeletion analysis are also some of the important tests in assessing the possibilities for normal development or assisted reproduction.[8]

Identification of individuals with balanced translocations is important as the risk of recurrence is high and hence prenatal cytogenetic testing is necessary.

CONCLUSION

Along with Karyotyping SRY, XIST, SHOX9 gene analysis and Y microdeletion analysis are also critial tests to assess the possibilities for normal development or assisted reproduction in individuals with sex chromosomal abnormalities.

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