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Karyotyping as a preliminary screening tool for learning disabled children

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Abstract

LD refers to a heterogeneous group of disorders manifested by significant difficulties in the acquisition and use of listening, reading, writing, reasoning or mathematical abilities. Fragile X Syndrome is the most common inherited cause of LD. The affected children show a characteristic fragile site in the long arm of X chromosome. Cytogenetic visualization of fragile X chromosome is one of the main marker which helps in the diagnosis of Fragile X Syndrome

Keywords: Learning disability**,** Fragile X Syndrome, Fragile site, Cytogenetic analysis

Introduction

Learning disability (LD) is a neuro- developmental problem that affects brain's ability to receive process, analyze or store information. LD is a general term which refers to a heterogeneous group of disorders manifested by significant difficulties in the acquisition and use of listening, reading, writing, reasoning or mathematical abilities. The term LD does not include children who have learning problems, which are primarily the result of visual, hearing, or motor handicaps, or of mental retardation, or of emotional disturbance, or of environmental, cultural or economic disadvantages. Children with LD have average or above average intelligence. Currently the most accepted approach to defining LD is one in which there is a significant discrepancy between a child's potential for learning and his/her achievement

The current definition of LD

'LD includes the presence of a significantly reduced ability to understand new or complex information, to learn new skills with a reduced ability to cope independently which started before adulthood, with a lasting effect on development' (Adelman, 1989)[1]. This definition is broadly consistent with the current version of the World Health Organization's International Classification of Disease (ICD-10).

Incidence of LD in India and Kerala

The twentieth century has undergone a sudden spurt in the identification of LD in India. This outlook has benefited some children who have to cope with the invisible LD. It is a painful truth that LD is real and a stumbling block for a nation's developmental process. In 1985, the National Institute for Mentally Handicapped, Secunderabad, India conducted a study, in 550 school children, which claimed the incidence of LD to be 4%. In another survey conducted by the institute in 1995, the occurrence of LD was reported to be 20%. In India, around 13 – 14% of all school children suffer from learning disabilities.

Importance of genetics in LD

Genetics was one of the major scientific accomplishments of the twentieth century, beginning with the rediscovery of Mendel's laws of heredity,

continuing with the first draft of the complete DNA sequence of the human genome. Genetics plays a significant role in all phases of life starting from prenatal, neonatal, childhood, adolescence, adult and old age. A number of environmental and genetic factors are thought to be significant in the development of LD. British Institute of Learning Disabilities suggests that in people with severe or profound learning disabilities, the chromosomal abnormalities cause about 40% and genetic factors account for 20%, prenatal and perinatal problems 10%, and postnatal issues a further 10%. Cases which are of unknown cause are fewer, but still high at around 20%. Twin studies have shown that if one twin has the reading disability, the probability of its occurrence in the other twin is 68% for monozygotic twins and 40 % for dizygotic twins. Familial disorders associated with LD often do not show simple Mendelian inheritance.

Fragile X Syndrome orMartin–Bell syndrome, or Escalante's syndrome (more commonly used in South American countries), is a geneticsyndrome that is the most commonly known single-gene cause of autism and the most common inherited cause of LD. It has been observed in several studies that, in this condition there is over expression of features by males, than females (Turner, 1974)[2]. Fragile X Syndrome is a distinct entity among X-linked mental retardation conditions, estimated to account for the majority of the male predominance detected (Opitz and Sutherland[3], 1984; Neri*et al.* [4], 1992). It occurs due to the mutation of the genes on the X- chromosomes. Simola, (1984)[5]. It is believed that mutations of genes on the X chromosome contribute significantly to this gender inequality (Opitz, 1986[6]and Turner *et al*., 1996)[7].

So it really important to examine the genetics underlying the disease. Fragile X Syndrome is known to be X-linked which means that the disease will appear roughly in twice as many male cases than females. This is because males, who have only a single copy of X chromosome, which they inherit from their mothers, are hemizygous for all genes on that chromosome. The consequence of this is that, if a male inherits an X chromosome with mutant alleles at any locus, he lacks the second dose of paternal X, which may counter the deleterious effects of those mutations. Males who exhibit the behaviors associated with Fragile X Syndrome, usually inherit the disease from their mothers. To continue with the transmission genetics pertaining to this syndrome, it is also known that there are more than twice as many female carriers of the disease than male carriers.

The gene responsible for Fragile X Syndrome was identified as Fragile X mental Retardation (FMR1) gene in 1991. Fragile X Syndrome derives its name from a characteristic fragile site in the long arm of X chromosome at 27.3.A **c**hromosomal fragile site is a non-staining gap or discontinuity in chromatids or chromosome due to the failure of chromatin condensation during mitosis. These break points usually have a strand of visible material across them under microscope or chromosome is broken at the fragile sites. Lubs, (1969)[8] identified the fragile site at band X 27.3 of the long arm of X- chromosome, and Sutherland, in (1977)[9] induced special culture medium for the expression of fragile site.

Cytogenetic approach to LD

Karyotype analysis determines the number of chromosomes in the cells and whether there are any pieces of chromosomal material that are missing, extra, or rearranged. Any variation from the normal chromosome number and arrangement can have implications for a person's character and the risk for having a child with birth defects. Karyotypes are usually constructed by laboratory technologists and analyzed by cytogeneticists. The cells must be grown and advanced to a specific cell stage that is optimal for analysis. The process of growing the cells, dropping them onto slides, arranging the chromosomes into a karyotype, and analysis by cytogeneticists usually takes between one and three weeks. Each chromosome contains hundreds or thousands of genes each, depending on the size of the chromosome, individual genes are too small to be seen even through a powerful microscope. Webb *et al*., (1986)[10,] reported that the incidence was 1/1200-1/2600 in males and 1/1600-1/2400 in females after studying Fragile X Syndrome cytogenetically. Cytogenetic analysis done by Kahkonen *et al*., *(*1987)[11]also reported almost the same incidence rates.

Cytogenetic detection of chromosome fragile site

Cytogenetic investigations of Fragile X Syndrome became possible when the chromosomal fragile site at Xq27.3 was found to be linked to the disease phenotype. Cytogenetic methods for detecting this folate-sensitive fragile site, FRAXA, were developed during the early 1980's (reviewed by Sutherland, 1983)[12]. The fragile site at Xq27.3 (FRAXA) is one of

the rare folate-sensitive fragile sites found in human chromosomes (Sutherland, 1977) [9] and 1979)[13]. Cytogenetic visualization of fragile X chromosome is one of the main marker which helps in the diagnosis ofFragile X Syndrome (Sutherland, 1977)[9]; Reiss and Freund, 1990)[14]; Sujatha*et al*., (1998)[15]. Because these fragile sites are expressed in low percentages, a cut off point of 4% fragile X expression has been recommended to be taken as positive for both the male and female subjects. (Howard Peebles, 1981)[16];Jacobs*et al*., 1986)[17].

Cytogenetic identification of fragile site at Xq27.3 became possible as a result of greatly improved culturetechniques and thishelped in accurate diagnosis of Fragile X Syndrome (Glover, 1981[18]; Matte*iet al.*, 1981[19]). Fragile site can be induced in metaphase spreads of peripheral lymphocytes by using specific culture media deficient in folic acid and thymidine. G-banding is necessary for the proper diagnosis of Fragile X Syndrome, as recommended by Webb, (1986)[20]. In spite of improvements in cytogenetic methods, expression of fragile site never detected in all studied characters. In cells of the fragile X syndrome patients, the expression varying from as low as 2% up to 60% of the mitosis examined has been encountered. For diagnostic purposes the minimum frequency recommended to be diagnostic in fragile X expression has been recommended as 4% (Jacky *et al*., 1991)[21], but even lower cut-off points have been commonly used in diagnostic laboratories.

Cytogenetic diagnosis appeared to be reliable only in affected individuals. Practically all affected males and the great majority of affected females (approximately > 90%) were found to express the site. The limitations of the cytogenetic test were evident in detecting clinically normal carriers. Based on present knowledge, this group includes mostly full mutation carriers but also a few with premutation carriers. In order to achieve more accurate prenatal diagnosis, but false negative and also false positive results were not totally eliminated (Shapiro *et al*., 1988[22]; Jenkins *et al*., 1991) [23]. The physical signs are neither specific nor constant and are generally more apparent after childhood. Thus, no early diagnosis can be made on clinical grounds alone, and here lies the importance of cytogenetic analysis.

References

1.Adelman HS. (1989). Toward solving the problems of misidentification and limited intervention efficacy. *J Learn Disabil* 22:608.

2. Turner G and Turner B. (1974). X-linked mental retardation. *JMed Genet*11:109-113.

3. Opitz JM and Sutherland G. (1984). International workshop on the Fragile X and X-linked mental retardation. *Am J MedGenet*17:5-94.

4. Neri G, Chiurazzi P, Arena F, Lubs H and Glass I. (1992). XLMR genes: update 1992. *Am JMedGenet*43:373-382.

5.Simola KO. (1984). X-linked mental retardation with the marker X chromosome - A clinical and cytogenetic study. MD thesis, Univ Helsinki, Dpt of Medical Genetics.

6. Opitz JM. (1986).On the gates of hell and a most unusual gene. *Am JMed Genet*23:1-10.

7. Turner G, Webb T and Wake S.(1996).Prevalence of Fragile X syndrome. *Am J Med Genet* 64:196–197.

8.Lubs HA. (1969).A marker X chromosome. *AmJ Hum Genet*21:231-244.71

9.Sutherland GR. (1977). Fragile sites on chromosomes: demonstration of their dependence on the type of tissue culture medium. *Science*197:265-266.

10.Webb TB, Bundey S, ThakeA and Todd J. (1986). Population incidence and segregation ratios in the Martin-Bell syndrome. *Am J Med Genet* 23:573-580.

11.Kahkonen M, Alitalo T, Airaksinen E, Matilainen R, Launiala K, Autio S andLeisti J. (1987). Prevalence of the fragile X syndrome in four birth cohorts of children of school age. *Hum Genet*77:85-87.

12. Sutherland GR. (1983). The Fragile X chromosome. *Int RevCytol* 81:107-143.

13.Sutherland GR. (1979). Heritable fragile sites on human chromosomes I. Factors affecting expression in lymphocyte culture. *Am J Hum Genet* 31:125-135.

14.Reiss AL and Freund LS.(1990). Cognitive profiles associated with the fra (X) syndrome in males and females. *Am J Med Genet*38:542-547.

15.Sujatha B, Naseerulla MK, Manjunatha KR, Chetan GK, Arathi R, Bhaskar GV, Girimaji SR, Shoba S.(1998).Cytogenetics of Fragile X chromosomes 95 Sheshadri S, RadhaRamadevi, BrahmachariVaniTriplet repeat polymorphism and fragile X syndrome in the Indian context. *Ind J Med Res*107: 29-36.

16.Howard Peebles PN. (1981). Chromosome banding in X linked mental retardation. *Lancet* 1: 494.

17.Jacobs PA, Mayer M andAbruzzo MA. (1986). Studies of the Fragile (X)syndrome in populations of mentally retarded individuals in Hawaii.*Am J Med Genet* 23(1-2):567-572.
18.GloverTW. (1981).FUdr induction of the X chromosome fragile site: evidence for the mechanism of folic acid and thymidine deprivation. *Am J Hum Genet*33:234-242.
19.Mattei MG, Mattei JF, Vidal J and Giraud P. (1981). Expression in lymphocyte and fibroblast culture of the fragile X chromosome: a new technical approach. *Hum Genet* 59:166-169.
20.Webb TB, Bundey S, ThakeA and Todd J. (1986). Population incidence and segregation ratios in the Martin-Bell syndrome. *Am J Med Genet* 23:573-580.
21.Jacky PB, Ahuja YR, Anyane-Yeboa K, Breg WR, Carpenter N, Froster-Iskenius U, Fryns JP, Glover TW, Gustavson K, Hoegerman S, Holmgren G, Howard-Peebles P, Jenkins E, Krawczun M, Neri G, Pettigrew A, Schaap T, Schonber S, Shapiro L, Spinner N, Steinbach P,Vianna-Morgante A, Watson M and Wilmot PL. (1991). Guidelines for the preparation and analysis of the fragile X chromosome in lymphocytes. *Am J Med Genet*38:400-403.
22.Shapiro L, Wilmot P, Murphy P andBregg W. (1988). Experience with multiple approaches to the prenatal diagnosis of the Fragile X syndrome: amniotic fluid, chorionic villi, fetal blood and molecular methods. *AmJ Med Genet*30:347-354.
23.Jenkins E, Krawczun M, Stark-Houck S, Duncan C, Kunaport S, Gu H, Schwartz-Richstein C, Howard-Peebles P, Gross A, Sherman S and Brown T. (1991). Improved prenatal detection of Fra(X)(q27.3): Methods for prevention of false negatives in chorionic villus and amniotic fluid cell cultures. *Am J Med Genet* 38:447-452.

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