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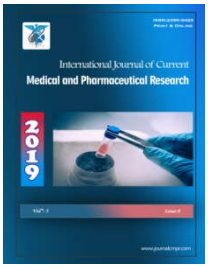

Research Article

FREQUENT ABERRATIONS IN CHROMOSOMES 1, 6 AND 13 IN YOUNG RETINOBLASTOMA PATIENTS

Jayakumar Rajarajeswaran and Venkatesan Ramachandran

Department of Zoology, Bharathiar University, Coimbatore, Tamil Nadu, India

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ABSTRACT

Retinoblastoma is the most common primary intraocular malignancy of childhood. Cytogenetic studies in retinoblastoma patients show the presence of aberrations in many chromosomes. In the present study chromosomal analysis of the peripheral blood leukocytes in retinoblastoma patients showed that the chromosomes 1, 3, 5, 6, 8, 10, 13 and 17 carry aberrations. The more frequent aberrations were 13q14, 6p- and 1q-, where deletion in the 13q14 is considered as a pre-requisite for tumorigenesis and aberrations in 6p and 1q are involved mainly in tumor progression. The less frequent aberrations identified were 3q-, 5p-, 17p-, 8q-, t(17p; 6p) and t(13q; 10q). The results of this study confirm that the retinoblastoma is associated with chromosomal aberrations.

INTRODUCTION

Retinoblastoma is the most common malignant ocular tumor of the eye that affects infants and young children (Grabowski & Abramson, 1987). It occurs throughout the world with no apparent racial or gender bias. An epidemiological assessment of retinoblastomas in a childhood population of Mumbai reported retinoblastoma to be 3.5% among total childhood cancers. Retinoblastoma has the lowest median age of all childhood malignancies, approximately 15 months (Yeole and Advani, 2002). Unilateral, bilateral and trilateral are the patterns of laterality expressed in retinoblastoma patients. The common patterns of laterality found in the population are unilateral and bilateral retinoblastoma. Many studies suggest that unilateral tumor patients are at equal risk for metastasis (Rubenfeld *et al*., 1986; Kopelman *et al*., 1987; Erwenne and Franco, 1989; Abramson *et al*., 1992; Moll *et al*., 1997). Genetic factors may be very important in retinoblastoma patients because, in most cases, these young patients have been minimally exposed to environmental mutagens and carcinogens (Arthur, 1986). From an epidemiological viewpoint, exposures of parents before the child's conception could influence the development of sporadic heritable retinoblastoma (Bunin *et al*., 1990). In sporadic heritable retinoblastoma, about 90% of new germinal mutations are of paternal origin (Hicks *et al*., 1984; Zhu *et al*., 1989). Thus, paternal exposures before the child's conception may indeed play a role in the etiology of sporadic heritable retinoblastoma.

The earliest cytogenetic studies on retinoblastoma patients described the presence of partial deletion of a D group chromosome (Stallard, 1962; Lele *et al*., 1963). The role of D chromosomes in the development of sporadic retinoblastoma was first reported by Hashem and Khalifa 1975. Orye *et al*. (1971) found deletion of a distal part of the long arm of chromosome 13, in a case of bilateral retinoblastoma. Orye *et al*. (1974) suggested that deletion of 13q21 is mainly responsible for retinoblastoma. Later, Francke (1976) identified the critical segment common to all deletions in retinoblastoma to be the band 13q14. In the present study, the chromosomal aberrations were analyzed in the retinoblastoma patients.

MATERIALS AND METHODS

Subjects

A total of 45 patient samples were collected. 37 mentally normal, physically healthy subjects with matching age groups were served as controls. All the subjects included in this study was below 10 years, hence an informed consent was obtained from their parents. Peripheral blood from the experimentals and controls were collected. All the samples were collected in sterile disposable syringes and stored in Lithium Heparin coated blood collection tubes.

Human Peripheral Blood Leukocyte Culture for Chromosomal Analysis

Peripheral blood Cultures were set-up following the method of Moorhead (1960) with modifications. In brief, 0.5ml of the

Corresponding author:* **Jayakumar Rajarajeswaran
Department of Zoology, Bharathiar University, Coimbatore, Tamil Nadu, India

blood was inoculated under aseptic conditions into a culture vial containing RPMI 1640 5.0ml of culture medium, 2ml of FB serum and 0.2ml of PHA. The cultures were inoculated at 37°C for a period of 72 hours and were shaken periodically twice a day to release carbon dioxide and to facilitate proper mixing of the medium and cells in the culture. 1 hour before harvesting the culture, 0.05ml of Colchicine (0.01%) was added to the culture to arrest the dividing cells at the metaphase stage. After 1 hour of colchicine treatment, the contents in the vial were transferred to centrifuge tube and centrifuged at 1000rpm for 5 minutes. The supernatant was discarded and 6ml of pre-warmed hypotonic solution (0.75M KCl) was added to the centrifuge tube after disturbing the cell button. The contents of the centrifuge tube were incubated for 7 minutes and centrifuged at 1000 rpm for 5 minutes. 6ml of freshly prepared fixative [Methanol and Glacial Acetic Acid (3:1 v/v)] was added to the centrifuge tube, incubated for 30 minutes and then centrifuged at 1000rpm for 10 minutes. Later, the supernatant was discarded and two or three changes of the fixative were given to obtain a colourless cell pellet. The cell suspension was placed on a microscopic slide and dried immediately.

Table 1 List of chromosomal aberrations in leucocytes of patients with retinoblastoma

Sample No.	Laterality	Age/sex	Karyotype
R1	URB	4/F	46, XX/46, XX del(1q-)
R2	URB	5/F	46, XX/46, XX del(13q14)
R3	URB	3/M	46, XY/46, XY del(17p-)
R4	URB	3/F	46, XX
R5	URB	4/M	46, XY
R6	URB	5/F	46, XX
R7	URB	4/F	46, XX/46, XX del(3q-)
R8	BRB	4/F	46, XX/46, XX (6p-)
R9	URB	6 months/F	46, XX
R10	URB	3/M	46, XY
R11	URB	5/M	46, XY
R12	BRB	5/M	46, XY
R13	URB	4/F	46, XX
R14	URB	5/F	46, XX/46, XX del(5p-)
R15	URB	7/F	46, XX
R16	URB	3/M	46, XY/46, XY del(8q-, 1q-)
R17	URB	2/F	46, XX
R18	URB	2/M	46, XY
R19	URB	2/M	46, XY/46 XY del(1q-)
R20	URB	3/F	46, XX
R21	URB	4/M	46, XY/46, XY t(10q-;13q-)
R22	BRB	5/F	46, XX
R23	URB	5/M	46, XY
R24	BRB	5/M	46, XX/46, XX del (13q14)
R25	URB	7/F	46, XX/46 XX del (13q14)
R26	URB	5/F	46, XX
R27	URB	7/F	46, XX
R28	URB	2/F	46, XX
R29	URB	3/F	46, XX/46, XX del(1q-)
R30	BRB	3/F	46, XX/46, XX del(3q-, 5p-)
R31	URB	5/M	46, XY
R32	URB	3/M	46, XY/46, XY (6p-)
R33	URB	3/M	46, XY
R34	URB	2/M	46, XY/46, XY del (13q14)
R35	URB	2/M	46, XX/46, XX (6p-)
R36	URB	4/M	46, XY
R37	URB	5/M	46, XX/46, XX del (13q14)
R38	URB	5/F	46, XX
R39	URB	4/F	46, XX
R40	URB	7/F	46, XX
R41	BRB	7/F	46, XX
R42	URB	4/F	46, XX/46, XX t(17p-; 6p-)
R43	BRB	5/F	46, XX
R44	URB	5/M	46, XX/46, XX (6p-)
R45	URB	5/M	46, XY

The chromosomes were banded using a modified Seabright technique (1973). The slides bearing chromosome spreads were treated with 0.25% trypsin for 3 - 10 seconds. The slides were then rinsed in distilled water, stained in 4% buffered Giemsa solution for 5 minutes. It was washed subsequently in running tap water and air dried. The slide was examined under light (Leica, Germany) microscope at 100X oil immersion and 50 metaphase spreads were analyzed for each sample.

RESULTS

Cytogenetic analysis of the leucocytes of the 45 patients revealed chromosomal aberrations only in 19 patients. No significant or notable aberrations were identified in the remaining 26 patients and controls (Table 1). Additions in the short arm of chromosome 6 were identified in 4 patients. Deletions in the arms of chromosomes were identified in 13 patients. Regions of the arms of the chromosomes 1q, 3q, 5p, 6p, 8q, 13q and 17p were deleted. Translocations were identified only in 2 patients between the chromosomes 13 and 10; 17 and 6. The percentage of abnormal cells present in the retinoblastoma patients ranged from 21 - 42%. Deletion in the region of the long arm of chromosome 1 was identified in 4 patients. Deletion in the region of the long arm of chromosome 3 was identified in 2 patients. A region of the short arm of chromosome 5 was found to be deleted in 2 patients. An addition in the short arm of chromosome 6 was identified in 4 patients. A deletion in the region of the long arm of chromosome 8 was identified in one female with unilateral retinoblastoma Translocation of a region of the short arm of chromosome 6 onto the short arm of chromosome 17 was identified in a female with unilateral retinoblastoma. Another translocation of a region of the long arm of chromosome 13 onto the long arm of chromosome 10 was identified in a male patient with unilateral retinoblastoma. A deletion in the region 13q14 was identified in 5 patients. A deletion in the region of the short arm of chromosome 17 was identified in a male with unilateral retinoblastoma.

DISCUSSION

Retinoblastoma is a rare malignant tumor of the developing retina with an incidence of 1 in 20000 live births in all human races, and this incidence does not vary with geography or level of industrialization. If retinoblastoma extends outside the eye mortality is very high (DiCiommo *et al*., 2000). Retinoblastoma, a hereditary cancer, is characterized by early age of onset, autosomal dominant pattern of inheritance, bilateral involvement of paired organs and presence of multiple primary malignant neoplasms (Arthur, 1986). It is highly malignant and, if left untreated, the mortality rate reaches 99% (Abramson *et al*., 1985).

Cytogenetic analysis allows the identification of individual chromosomes and subtle chromosome abnormalities that involve deletions and duplications associated with specific cancers. In addition to the detection of chromosomal imbalance, cytogenetic studies help in the identification of balanced chromosomal rearrangements and chromosomal mosaicism (Dave and Sanger, 2007). Difficulties encountered in the cytogenetic analysis of Retinoblastoma patients are their low mitotic index and relatively poor quality of the chromosomes derived from them. Despite these limitations, many studies addressing retinoblastoma cytogenetics have revealed chromosomal imbalances (Cano *et al*., 1994; Oliveros and Yunis 1995; Chen *et al*., 2001). Orye *et al*. (1974)

suggested that deletion of 13q21 is mainly responsible for retinoblastoma. Later on, the chromosome involved was identified as chromosome 13 and the critical segment common to all deletions as band 13q14 (Francke and Kung 1976; Knudson *et al*. 1976; Wilson *et al*. 1977; Francois *et al*. 1978). Abnormalities involving chromosomes other than No. 13 have also been reported in retinoblastoma. These include isochromosomes of both 17q and 6p, extra copies of 1q, monosomy 16, 1p- and two novel abnormalities, unique to cancer cells, homogeneously staining regions (HSR) and double minutes (DMS) (Balaban *et al*., 1981; Balaban *et al*., 1982; Gardner *et al*., 1982, Benedict *et al*., 1983; Chaum *et al*., 1984).

In the present study, deletions in the arms of chromosomes were identified in 13 patients. Deletions were found to be present in the chromosome arms- 1q, 3q, 5p, 6p, 8q, 13q14 and 17p. Translocations were identified only in 2 patients between the chromosomes 13 and 10; 17 and 6. Additions in the short arm of chromosome 6 were identified in 4 patients.

Cavenee *et al*. (1983) postulated homozygosity for a mutant allele at 13q14 to be a pre-requisite for tumorigenesis in retinoblastoma. About 20% of retinoblastoma tumors exhibit microscopic deletions of band 13q14 or monosomy 13 (Chaum *et al*., 1984). Potluri *et al*. (1986) suggested 13q abnormalities to be specific to retinoblastoma. Mechanisms involved in the production of effective homozygosity at a single locus include point mutations, submicroscopic deletions, mitotic recombination, non disjunction/chromosome reduplication and gene conversion (Cavenee *et al*., 1983). In the present study, deletions in chromosome 13q could be identified only in 5 among the 45 retinoblastoma patients. Deletions could not be identified in chromosome 13 of the remaining patients because mutations at 13q14 would most frequently be the product of changes other than visible deletions and chromosome loss (Potluri *et al*., 1986).

Additions on the short arm of chromosome 6 were identified in 4 among the 45 patients. Gain of 6p represented the most frequent event in retinoblastoma (Lillington *et al*., 2003). Most frequent mechanisms involved to produce additional 6p chromsomome was the isochromosome (6p). Isochromosome (6p) is a common abnormality found exclusively in retinoblastoma tumors and may be important for tumor progression (Squire *et al*., 1984; Horsthemke *et al*., 1992). Benedict *et al*. (1983) speculated that a gene on 6p may suppress or be suppressed by the Rb locus on 13q14. Cano *et al*., (1994) suggested an association between additional chromosome 6p and invasion of cancer cells into the optic nerve.

Abnormalities involving lq are the most commonly quoted in all tumor cells (Cowell and Hogg, 1992). Aberrations of chromosome 1 affecting both arms, particularly trisomy of 1q25-1q34, have been frequently detected in Rb tumors. Bands p36 and q11 were frequently involved (Amare *et al*., 2004). Changes in chromosome 1 play a significant role in tumor progression and evolution (Sandberg and Turc-Carel., 1987). In the current study, a deletion in the region of the long arm of the chromosome 1 was identified in 4 patients. No rearrangements or trisomy of chromosome 1 could be identified.

Aberrations resulting in monosmy, trisomy, addition and deletion of the arms of chromosome 17 were reported in retinoblastoma patients (Workman and Soukup, 1984; Potluri *et al*., 1986; Oliveros and Yunis, 1995). The most common aberration was an i(17q) chromosome. In the present study, a deletion in the short arm of chromosome 17 was identified in only one patient.

In the present study, deletions were present in the short arm of chromosome 5, long arms of the chromosomes 8 and 3 in 2, 1 and 2 patients respectively. Similarly additions and deletions in the arms of chromosomes 3, 5 and 8 were reported in retinoblastoma patients (Gardner *et al*., 1982; Kusnetsova *et al*., 1982; Benedict *et al*., 1983; Squire *et al*., 1984 and Chaum *et al*., 1984).

Two translocations, t(13q; 10q) and t(17p; 6p) were identified. The chromosome arms, 10q and 17p contain constitutional fragile sites which may predispose these regions to act as acceptors of translocations in malignant cells (Squire *et al*., 1985). Cano *et al*. (1994) reported translocations of 6p to other chromosomes as a mechanism to produce additional 6p chromosome in retinoblastoma patients. Other translocations observed in retinoblastoma patients were t(6p; 12q), t(10p; Xp), t(7; 10), t(12; 13), t(5; 13) and t(7; 17) (Gardner *et al*., 1982; Chaum *et al*., 1984; Squire *et al*., 1984; Workman and Soukup, 1984).

The rearrangements in chromosomes of retinoblastoma patients were classified as early or late according to their frequency. Early chromosome rearrangements were +1q, +6p, -13/del(13q), -16/del(16q), -17/del(17p), and late rearrangements were (in decreasing order) -8, -17/del(17p), -22, +3/+3q, -4, -19, +1q, +7/+7q, -14, +21 (Oliveros and Yunis, 1995).

Results of the present study also suggest that the more frequent aberrations (in decreasing order) were 13q-, 6p- and 1q-. Deletion in the 13q arm is considered as a pre-requisite for tumorigenesis whereas the arms 6p and 1q are involved mainly in tumor progression (Cavenee *et al*., 1983; Sandberg and Turc-Carel, 1987; Horsthemke *et al*., 1992). The less frequent aberrations in decreasing order were 3q-, 5p-, 17p-, 8q-, t(17p; 6p) and t(13q; 10q). The less frequent aberrations may not play a significant role in the tumorigenesis of retinoblastoma. In most of the cases, mosaicism was observed with the frequency of abnormal cells ranging between 21 and 42%. The degree of mosaicism may have a direct association with the risk of developing secondary tumors.

Very small deletions beyond the limits of the resolution of the microscope by the human eye could be present in patients diagnosed as having a normal karyotype or a mosaicism with a much lower proportion of abnormal cells than 8-14% could be present in lymphocytes, or lastly the possibility of tissue-limited mosaicism (Pagon *et al*., 1979) could not be excluded from the present study.

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