Acta Genet Med Gemellol 46: 193-198 (1997)

Absence of Pericentromeric Heterochromatin (9qh-) in a Patient with Bilateral Retinoblastoma

T. A. Sivakumaran[1], S. Ghose[2], H. Kumar[2], U. Singha[2], K. Kucheria[1]

[1]Division of Genetics, Department of Anatomy; [2]Pediatric Ophthalmology Service, Dr. Rajendra Prasad Center for Ophthalmic Sciences, All India of Medical Sciences, New Delhi, India

Abstract. The polymorphisms of constitutive heterochromatin regions, present on chromosomes 1, 9, 16 and Y, are inherited in a Mendelian fashion. The C-band heteromorphism has been reported to be associated with various types of cancer. Heterochromatin is considered to play a role in protecting genome against the mutagens. Changes in the quantity and proportion of the different types of satellite DNA might increase the genetic susceptibility in people with heterochromatic variations, which in turn cause chromosome instability and predispose the individual to cancer. We report a case of bilateral retinoblastoma with complete absence of pericentromeric heterochromatin on one of the chromosomes number 9. A similar deficiency of pericentromeric heterochromatin on chromosome number 9 and 16 has been reported in a phenotypically normal individual and a Down syndrome case, respectively. This deficiency was found to be inherited from the father in all the three cases. Complete absence of pericentromeric heterochromatin of chromosome 9 is not being reported in association with cancer syndromes. Further studies are necessary to understand the role of this factor in normals and in those with cancer susceptibility, specially with retinoblastoma and the paternal origin of this deficiency.

Key words: C-band, Heteromorphism, Absence of pericentromeric heterochromatin, Familial inheritance, Retinoblastoma, Paternal origin

INTRODUCTION

The constitutive heterochromatin (contains highly repetitive DNA) shows most notable morphological variation of chromosome (Heteromorphism). These heteromorphisms are commonly seen in human chromosomes 1, 9, 16 and Y. These can be readily demonstrated by C-banding. Family studies have indicated that the variants of centromeric heterochromatic regions are inherited in a Mendelian fashion [10]. Among these C-band heteromorphisms, heteromorphism of chromosome number 9 is most frequently seen in

normal population. The centromeric region of chromosome number 9 is composed of alphoid DNA, while pericentromeric heterochromatin region is composed primarily of classical satellite III DNA and beta satellite DNA [9].

Atkin and Brito-Babapulle [2] have proposed a hypothesis that heteromorphism might cause chromosomal instability which in turn predisposes the individual to neoplastic changes. Supporting this, several studies have shown an association of larger or smaller C-band polymorphism on the chromosome number 1 and 9 with various types of cancers such as haematologic, oral, colon, rectal, breast, cervix, head, neck, etc. [13, 5]. At the same time the reduction or loss is more deleterious than the gain of heterochromatin [6].

The available literature rarely reports about the complete absence of pericentromeric heterochromatin in normal population [3, 4]. Its association with cancer is unknown. Here, we report a case of bilateral retinoblastoma with complete absence of pericentromeric heterochromatin on one of the chromosomes 9.

MATERIALS AND METHODS

Case report

A one-year old male child presenting with white reflex in both the eyes was diagnosed as a case of bilateral retinoblastoma. There was no family history of retinoblastoma in his family or among his parents. The proband was the second child born to a non-consanguineous couple. The father was 29 years old and the mother was 25 years old, when the child was born. The mother had an uneventful pregnancy and had not taken any multivitamins or known teratogenic drugs during her pregnancy. She had undergone a routine ultrasound of the abdomen at three months of pregnancy. Father had no history of any recreational drug intake, except having alcohol occasionally.

Ophthalmological examination

The child exhibited no vision in the left eye (PL negative), but fixation of light in his right eye was present. The intraocular pressure was normal in both the eyes. The ophthalmoscopy examination revealed 2 tumor masses in the right eye: one 5 disc diameter (DD) X 3.2 mm ht, and the other 4 DD X 3mm ht, 1 DD and 4 DD temporal to the disc respectively, along the inferior arcade. The left eye was full of tumor with vitreous seeding.

Clinical investigation

Ultrasonography showed the typical V-W pattern confirming retinoblastoma [15]. The contrast enhanced CT scan of the head and orbit showed moderate sized soft tissue masses with typical nodular calcifications in both globes. No definite evidence of retrobulbar, perineural or perivascular spread was seen. Extraocular muscles and optic nerves were identical on both sides. Sellar and suprasellar regions were normal. On the basis of examination and investigation, the left eye was enucleated, the diagnosis of retinoblas-

toma was confirmed by histopathology, and the right eye was then treated with radiotherapy followed by chemotherapy. The histopathology of left eye showed a well differentiated retinoblastoma with the optic nerve, choroid, iris, anterior chamber and other intra ocular structures free of tumor.

Cytogenetic analysis

Metaphase chromosomes obtained from lymphocyte cultured for 72 hours using standard method showed 46, XY karyotype with complete absence of the pericentromeric heterochromatin region of chromosome 9 (46, XY, 9qh-) and the other was normal. The results were confirmed using C-banding (Fig. 1, 2). When cytogenetic analysis of the other family members was carried out, the father was found to have a similar karyotype, though he was phenotypically normal.

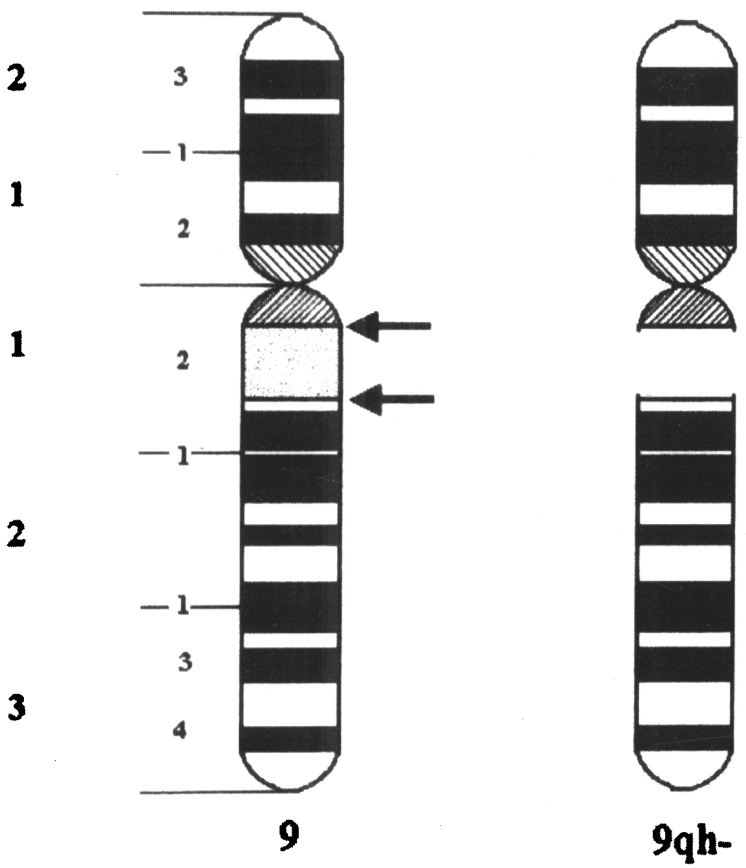

Fig. 1 - Arrows show normal pericentromeric Heterochromatin region on chromosome number 9. The other chromosome number 9 shows complete absence of pericentromeric heterochromatin region (9qh-).

https://doi.org/10.1017/S0001566000000428 Published online by Cambridge University Press

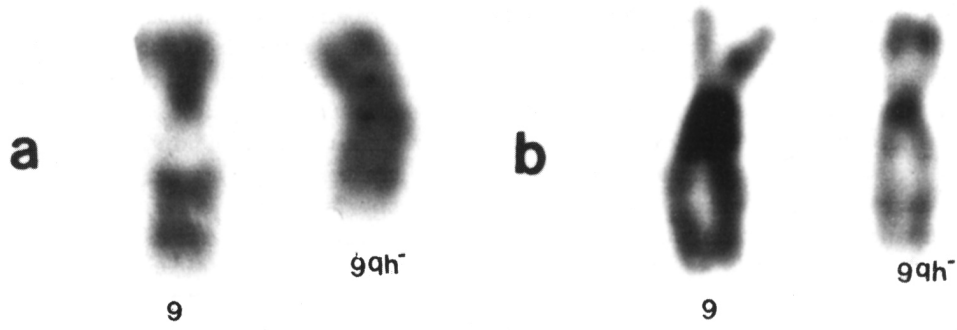

Fig. 2 - Partial karyotype showing normal chromosome number 9 (G-banded (a) and C-banded (b)) on left and chromosome number 9 with complete absence of pericentromeric heterochromatin region on right.

DISCUSSION

A male child with bilateral retinoblastoma was found to have a complete absence of pericentromeric heterochromatin in one of the chromosomes 9 (46, XY, 9qh-). The variant was an inherited trait from the father, who was apparently normal. A similar absence of pericentromeric heterochromatin region was reported in cultured amniotic cells and also in cultured blood cells from the father [3, 4]. Both the father and the child (after birth) were phenotypically normal. Another case of female newborn with Down syndrome had absence of heterochromatin on one of the chromosomes 16. A similar variation of chromosome number 16 was also observed in her phenotypically normal father [4]. None of these cases had any symptoms of cancer.

An association of complete absence of pericentromeric heterochromatin region with cancer, specially retinoblastoma is not being reported. However, available literature reports about the heterochromatic variations in retinoblastoma patients. Mao et al. [11] found abnormal karyotypes in 10 of the 80 retinoblastoma patients studied. Of these, 3 showed pericentric inversion of heterochromatic region of chromosome 9. Munier and colleagues [12] observed a long heterochromatin region on one of the chromosomes 9 (9qh+) in patients with bilateral retinoblastoma. Reports on the association of cancer with variable size of pericentromeric heterochromatin on chromosome 1 and 9 are available [14, 1].

It has long been known that heteromorphism is one of the genetic factors involved in carcinogenesis. Heterochromatin is considered to play a role in protecting the genome against the breaking agents such as viruses or other mutagens, serving in the form of bodyguard [7]. Changes in the quantity or proportions of the different types of satellite DNA may be responsible for failure in protecting function [13]. In a study of patients with malignant or premalignant hematologic diseases, Shabtai and Halbrecht [13] observed significantly increased incidence of heteromorphism in the patients and these variants were found to be inherited in healthy members of the family. It was further suggested that there is a genetically increased susceptibility to breaking agents in people with such heterochromatic variations, which in turn results in the increased chromosomal

breakage rate and predispose the individual to various malignant or premalignant diseases. In a family with hereditary predisposition to cancer, Kopf et al. [8] observed the malignant diseases in nine of the 35 family members. Cytogenetic analysis from peripheral blood showed a distinct heteromorphism on chromosome (1qh region) in 15 of the 19 family members, including all three cancer patients, investigated.

Two cases from the literature and the present case, with complete absence of pericentromeric heterochromatin on chromosomes 9 (9qh-) and 16 (16qh-) have shown a paternal origin. Further analysis at molecular level on large number of cases with absence of pericentromeric heterochromatin region might throw light on the role of paternal origin of this deficiency in clinical abnormalities.

The absence of pericentromeric heterochromatin (9qh-) found in the present family may have increased the cancer susceptibility in the child. Further investigations, on large number of families with retinoblastoma are necessary to clarify the role of this factor on cancer susceptibility.

Acknowledgements: One of the authors (T.A. Sivakumaran) is supported by Senior Research Fellowship of Indian Council of Medical Research, which is gratefully acknowledged.

REFERENCES

1. Advaryu SG, Dave BJ, Trivedi AH, Jani KH, Vyas RC (1987): Heteromorphism of C-band positive chromosomal regions in CML patients. Cancer Genet Cytogenet 27: 33-37.
2. Atkin NB, Brito-Babapulle V (1981): Heterochromatin polymorphism and human cancer. Cancer Genet Cytogenet 3: 261-272.
3. Buys CHCM, Ypma JMM, Gouw WL (1979a): Complete deficiency of constitutive heterochromatin on a Human chromosome 9. Hum Genet 49: 129-132.
4. Buys CHCM, Anders GJPA, Gouw WL, Borkent-Ypma JMM, Blenkers-Platter JAM (1979b): A comparison of constitutive heterochromatin staining methods in two cases of familial heterochromatin deficiencies. Hum Genet 52: 133-138.
5. Dave BJ, Trivedi AH, Advaryu SG (1991): Variations in centromeric heterochromatin among patients with premalignant and malignant oral diseases. Int J Cancer 48: 386-389.
6. Erdtmann B (1982): Aspects of evaluation, significance and evolution of human C-band heteromorphism. Hum Genet 61: 281-294.
7. Hsu TC (1975): A possible function of constitutive heterochromatin: The bodyguard hypothesis. Genetics (Suppl.) 79: 137-150.
8. Kopf I, Islam MQ, Friberg LG, Levan G (1989): Familial occurence of cancer and heteromorphism of the heterochromatic segment of chromosome 1. Hereditas 110: 79-83.
9. Luke S, Verma RS, Conte RA, Mathews T (1992): Molecular characterization of the secondary constriction region (qh) of human chromosome 9 with pericentric inversion. J Cell Sci 103: 919-923.
10. Magenis RE, Palmer CG, Wang L, Brown M, Chamberlin J, Parks M, Merritt AD, Rivas M, Yu PL (1977): Heritability of chromosome banding variants. In Hook EB, Porter IH (eds.) "Population cytogenetic studies in humans". New York, San Francisco, London, Academic Press, pp 179-188.

11. Mao WS, Lin XH, Ma QY, Chen YZ, Zeng LH, Dai ZY (1989): Lymphocyte chromosome survey in 80 patients with retinoblastoma. Yen-Ko-Hsueh-Pao 5: 7-13.
12. Munier F, Pescia G, Jotterand-Bellomo M, Balmer A, Gailloud C, Thonney F (1989): Constitutional karyotype in retinoblastoma: case report and review of literature. Oph Ped Genet 10: 129-149.
13. Shabtai F, Halbrecht I (1979): Risk of malignancy and chromosomal polymorphism: a possible mechanism of association. Clin Genet 15: 73-77.
14. Shabtai F, Antebi E, Klar D, Hart J, Halbrecht I (1985): Cytogenetic study in patients with carcinoma of colon and rectum: particular C-band variants as possible markers for cancer proneness. Cancer Genet Cytogenet 14: 235-245.
15. Verma N, Ghose S, Sekhar GC (1984): Ultrasonic evaluation of Retinoblastoma. Jap J Ophthalmol 28: 222-229.

Correspondence: Dr. (Mrs.) Kiran Kucheria, M.Sc., Ph.D. (Lond), Professor of Genetics, Division of Genetics, Department of Anatomy, All India Institute of Medical Sciences, New Delhi 110 029, INDIA, e-mail: kucheria@medinst.ernet.in.