RESEARCH COMMUNICATION

Frequent Incidence of Double Minute Chromosomes in Cancers, with Special Up-to-date Reference to Leukemia

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Abstract

Double minute chromosomes (DMs) are small chromatin bodies consisting of gene amplification in an extrachromosomal location. Although found in an variety of human tumor cells, their presence in hematologic malignancies is rare and their role in leukemogenesis is controversial. However, they are thought to be involved in tumorigenesis and in drug resistance, representing a mechanism for upregulated oncogene expression generally associated with a poor prognosis. The presence of DMs has been associated with a rapid disease course, low response rate, and short survival. Little knowledge is, however, available on DMs in leukemias. To elucidate this issue, a web-based search for all types of articles published was initiated using MEDLINE/PubMed, the Mitelman database and other pertinent references on websites. We found that DMs have the highest frequency in adrenal carcinoma (28.6%), and lowest rate noted as 2.6% for large intestine. The large Mitelman database and other web based pertinent reports provide novel knowledge of DMs and their association in the wide field of cancers.

Keywords: DMs - incidence - cancer - leukemia

Asian Pacific J Cancer Prev, **13**, 3453-3456

Introduction

Double minute chromosomes (DMs) are paired Feulgen stain-positive bodies that was first described in a direct preparation of cells from the pleural effusion of a patients with untreated brochogenic carcinoma (Spriggs et al., 1962; Ariyama et al., 1998). Although found in a variety of human tumor cells, their presence in hematologic malignancies is rare. Their role in leukemogenesis is not clear, but they have been reported to be associated with rapid progression and short survival time (Barker & Hsu 1979; Thomas et al., 2004). DMs are found in tumor cell proliferations, characteristically varying in number from cell to cell (Cowell, 1982). They are thought to be involved in tumorgenesis and in drug resistance. Sait et al. (2002) reported for the first time that, DMs originating from chromosome 19.

Gene amplification causes an increase in the gene copy number and, subsequently, elevate the expression of the amplified genes, which modify normal growth control and survival pathway (Shoup et al., 1990; Fan et al., 2011; Fichter et al., 2011; Yan et al., 2011). In this connection, C-myc was the most frequently amplified gene, but cases with MLL gene amplification have also been reported elsewhere (Crossen et al., 1999; Streubel 2000; Thomas et al., 2004; Brothman et al., 2009). The semiconservative replication of DNA in DMs has been demonstrated to occur in both human and mouse cell line (Levan et al., 1977; Levan, 1978; Barker & Hsu, 1979 Bruckert et al., 2000). DMs can also stick to the ends of intact chromosomes and be passively transported along with the chromosomes into the daughter cells that form at mitosis cell cycle (Levan & Levan, 1978; Barker & Hsu, 1979; Clappier et al., 2007).

Little knowledge is, however, available on DMs chromosome on leukemia and tumors. Hence to unravel these issues, we retrieved the Mitelman database and other pertinent references reported in all DMs chromosomes of positive primary cancerous karyotypes.

Materials and Methods

Four databases were used for the literature search which were Medline, Pub Med, Science Direct, and Black Well Synergy. The search terms were DMs, incidence, cancer, leukemia, chromosomal abnormality.

Over 200 articles published between 1960-2011 were reviewed which included systematic reviews, quasi experimental reports, surveys and qualitative studies. Also, the large Mitelman database were the most supported knowledge of this article. All selected articles were followed according to International System for Chromosomes Nomenclature (ISCN) (Brothman et al., 2009).

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Table 1. AML Patients with Amplification of C-MYC

Ref .no.	Age/Sex	FAB Class	Primary/ Secondary	Karyotype	Response to chemo	Relapse	Survival (months)
28	58/M	M1	Primary	45,X,-Y+5-8,del(9)(q13q32),-10,-17+mar1,+mar2,12-28dmin	NR		Few hours
TA	27/M	M2	Primary	46,XY,del(8)(q24.2),2-16dmin/46,XY	CR	Chemo on study	16+
14	NM/F	M2	Primary	46,XX/46,XX,dmin	NM		NM
9	52/F	M2	Primary	46,XX/47,XX,+4,dmin	CR	3mths-NR	9
29	54/M	M2	Primary	45,X,-Y,del(8)(q13q22),9,del(9)(p22),t(17;17)(p11.2;p13),+18,dmin	NR		0.5
30	60/M	M2	Primary	46,XY,7 ~ 23dmin	PR		On consodialtion 15mths after diagnosis of AML
10	62/F	M2	Primary	46,XX/45,X,-X,266dmin	CR	5mths-NR	25
26	68/F	M2	Primary	45,XX,dup(1)(q11qter),-5,-7,-11,-17,+der(17)t(17;18)(p13;p11) +r,+mar/44,XX,-5,-7,-17,+mar,dmin	NR		2
11	68/F	M2	Primary	46,XX,dmin/46,XX	CR		6
30	69/M	M2	Primary	46,XY,2-58dmin	PR	12mths-NR	13
26	70/F	M2	Primary	46,XX/46,XX,dmin/47,XX,+4 ,dmin	CR	NM	45+
29	72/F	M2	Primary	45,X,-Y,add(4)(p16),del(5)(q13q35),del(8)(q21.3q24.1), del(9)(q12q23),del (17)(p11.2),dmin	NR		1
31	72/M	M2	Primary	46,XY/46,X,-Y,+19,dmin/47,X,-Y+6,+19/47,X,hsr(9)(q13),+18,+19	CR	5mths-NR	8
30	73/M	M2	Primary	46,XY,6-64dmin	CR	12mths-NR	12
26	75/F	M2	Primary	46,XX/45,XX,-7,der(16)t(16;20)(p13;q13), der(20)del(20)(q11Q13)t(16;20)(p13;q13),dmin	NR		6
11	75/M	M2	Primary	46,XY,-9,del(4) (q21),del(5)(p11),del(8)(q24),del(9)(q34),+mar,+DMs	NM		3
32	76/F	M2	Secondary	46,XX,2-17dmin/47,XX,+r,3-24dmin	NM		15+
32	78/F	M2	Primary	45,X,-Y,del(5)(q15q34),+13,-20,1-35dmin	NM	12mths	12mths
13	79/M	M2	Secondary	46,XY,dmin/47,XY+4,dmin/46,XY	NR		0.5
32	81/F	M2	Secondary	44,XX,inv(1)(p36q21),-5,del(7)(p11),der(7)t(7;?)(q22;?),-14, der(17)t(17;?)(p11;?),-22,+mar1,2-24dmin/44,idem,+mar2/44,XX,inv(1)(p36q1),-5,der(7)t(7;?),der(17)t(17;?),22	NM		0.75
27	79/F	M2	Secondary	46,XX/46,XX,1-22dmin/47,XX,+4,3-8dmin	No chemo		13+
15	59/F	M2	Primary	45,XX,-5,+6,add(9)(p?),del(10)(q24),der(16)t(8;16)(q22;q24), del(18)(p11),der(20)t(17;20)(q21;q11),-22,+mar,dmin	NR		1.5
12	79/F	M3	Primary	45,XX,der (5)t(5;17)(q?q12),del(8)(q22q24),-17,5,-32dmin	CR	NR	0.5
TA	78/M	M3	Primary	46,Y,t(X;1)(q28;q12),+6,del(8)(q24.2),-10/46,idem,2~24,dmin	NR		1
32	30/F	M5	Secondary	42-45,XX,?del(5)(q33q35),der(7)t(7;12)(q22;q13), -12,-16,-20,?t(21;22)(p11;q11),22,+r,+1-4mar,2dmin	NM		10
0	0	M6	Secondary				

CR,Complete remission; NM, not mentioned; NR, no remission

Table 2. AML Patients with DM Amplification of Other Genes

FAB class	Primary/ Secondary	Karyotype	Amplification
M1	Primary	85-87,XYY,-X,-2,-4,+8,+8,+8,-11,-12,-17,-17,-19,-20,-20,+mar,+mar,70-90 dmin	MLL
M2	Primary	45,XY,-5,-9,del(11)(q23q25),-14,+t(14;17)(q11.2;p13),-17,-18,+3mar,1-35dmin/46,XY	Not MYC/Not MLL
M4	Primary	46,XY,add(5)(q12),-7,add(11q23),-13,add(17q22),+2mar	MLL
M4	Primary	Hyperdiploid,XXXX,-3,del(3)(p11)2,-5,-5,-6,10,-11,del(11)(q23)2, -12,-14,-15,+i(17)(q10)2,-20,+2mar,1-4dmin	C-ETS 1
M5	Primary	39-43,XX,del(5)(q13q31),add(8)(q24),t(9;16)(q22;p11.2),der(11)t(11;17)(p11;q11.2), del(11)(q23q23),-16,-17,der(17)del(17)(q11q23)ins(17;14)(q11.2;q13q22),del(20)(q11),5-30dmin	MLL
M5	Primary	45,X,-Y,+6,+8,-11,add(17)(p13),-20,add(22)(p10),6-21dmin	MLL
M5	Secondary	41-46,XY,t(10;18),(p11;q11),t(11;17)(p15;q11)+mar,dmin	Htrx-1
M6	Secondary	44,XX,add(3)(p25),-5,del(11)(q13),-15,-16,del(17)(p11),-18,+r,+mar, 1-2dmin/43,XX,idem,der(3)t(3;?)9q27;?),add(8)(q12),-9,+mar	MLL

The Htrx-1 (human trithorax homologue) is the same gene as MLL, and different authors use them interchangeably; Thomas et.al.2004

Results

As the present results, there are a total of 54,398 cases in the Mitelman database. Among them ,787 (1.4%) cases are DMs-positive. In this cumulative data DMs positive cases, the ratio of males to females is 1.08 (401/373).

Frequencies of DMs in cancer according to topography are shown in Figure 1a. The frequency in this data noted as adrenal carcinoma is the highest (28.6%). Frequencies in the endocrine system, cerebellum, brain, central nervous system, prostate, stomach, soft tissue, digestive system, bone and soft tissues, respiratory system, lung, eye, ovary, skeleton, and large intestine carcinoma are 10.4%, 9%, 6.4%, 6%, 5.3%, 5.1%, 4.5%, 4.4%, 4%, 4%, 3.8%, 3.2%, 3.1%, 2.7%, and 2.6%, respectively. The number of analyzed cases in the above tumors is more than 200, thus, the frequencies are more credible. The Figure 1b, presents the frequencies of DMs in cancer according to morphology. In the tumors, which include more than 100 cases, neuroblastoma has the highest frequency of DMs (31.7%). The frequencies in embryonic nervous system tumors (all subtypes), asterocytoma (grade III–IV), primitive neuroectodermal tumor, osteosarcoma, neuroglial neoplasm (all subtypes), leiomyosarcoma, malignant peripheral nerve sheath tumor, atypical lipomatous tumor, fibrohistiocytic tumor (all subtypes),

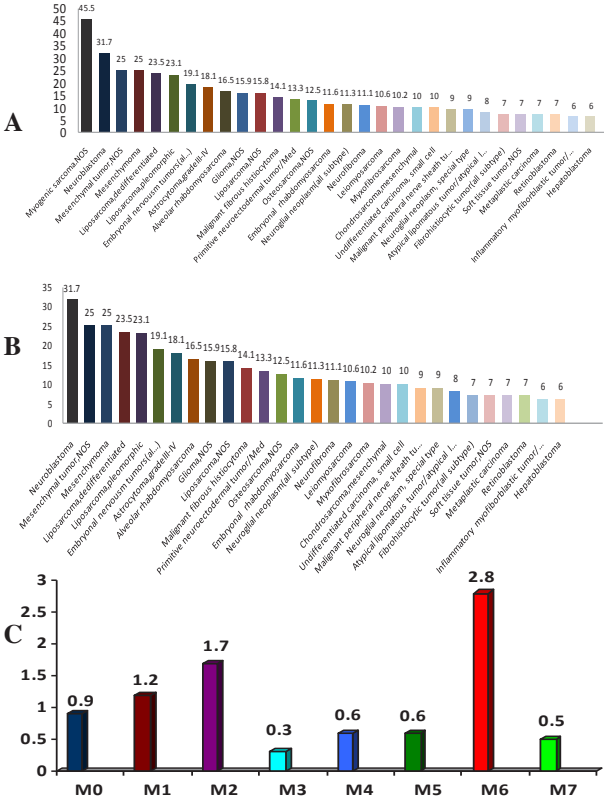

Figure 1. Frequencies of Double Minute Chromosomes (DMs) in Tumors and Leukemia. a- Frequencies of DMs in tumors. b- Frequencies of DMs in tumor classified by morphology. c- Frequencies of DMs in Leukemia

retinoblastoma, and hepatoblastoma are 19.1%, 18.1%, 13.3%, 12.5%, 11.3%, 10.6%, 9.3%, 7.7%, 7.1%, 6.6%, and 6.0%, respectively. The frequency of DMs in MO to M7 of Leukemia ranges from 0.3% to 2.8% (Figure 1c). In Table 1, summarizes a total of 25 AML cases associated with dmin which carry the C-MYC gene (Cowell 1982; Brukert et al., 2000). Patients with dmin associated with amplification of putative oncogenes other than C-MYC have also been documented in the current literature (Table 2) (Cox et al., 1965; Thomas et al., 2004; Fan et al., 2011).

Discussion

In the light of our previous reports (Movafagh et al., 1996) and utilizing the largest chromosome aberrations database in cancers (Mitelman database of chromosome, aberrations and gene fusions in cancers, http://cgapanci.nih.gov/chromosomes/Mitelman), an obvious source of DMs chromosomes in the current literatures described on the website (Shimizu et al., 2007; Fan et al., 2011; Fichter et al., 2011). Also, Benner et al. (1991) reported the presence of DMs in 93.5% of analytical tumors by reviewing 200 published tumors taken directly from website. Furthermore, Thomas et al. (2004) documented 33 cases with DMs in acute myeloid leukemia in the current literature.

Gene amplification cause an increase in the gene copy number and, subsequently, elevate the expression of the amplified genes, which modify normal growth control and survival pathway (Fan et al., 2011; Fichter et al., 2011; Yan et al., 2011).

Double minute chromosomes represent a mechanism for upregulated oncogene expression and are generally associated with a poor prognosis. This type of gene amplification has been found in various solid tumors, such as Colon, Pancreatic, Breast carcinoma, Brain tumors , and Neuroblastoma (Gebhart et al., 2005). However, it appears to be less common in AML (Thomas et al 2004). Generally C-myc amplification results in an overexpression of the myc protein, which is known to be a critical nuclear transcription factor (Crossen et al., 1999; Hoglund et al., 2005).

DMs chromosome, which are cytological manifestation of gene amplification, are rare abnormalities in leukemic cells (Martín-Subero et al., 2005; Clappier et al., 2007; Lahortiga et al., 2007; Kamath et al., 2008; Kawamata et al., 2008; 2009).

Amplification of the ETS1, FL11, SRPR, NFRKB, and KCNJ4 genes located at 11q23-24 distal to MLL was demonstrated in patients with AML (Ariyama et al., 1998; Crossen et al., 1999; Kamath et al., 2008; Kawamata et al., 2009). They have been found in a vast number of human neoplasia. Many oncogenes have been identified on DMs, for example, MYCN, C-myc, EIFA2, and MDM2 (Brukert et al., 2000; Thomas et al., 2004; Gebhart 2005; Höglund et al., 2005; Storlazzi et al., 2006; Kuttler & Mai, 2007; Kawamata et al., 2009; Morales et al., 2009; Fan et al., 2011).

The presence of DMs has been associated with a rapid disease course, low response rate, and short survival (Cowell et al., 1982; Kuttler and Mai, 2007). Several early reports concluded that DMs, whose number and size vary from cell to cell, were not viral or bacterial contamination (Cox et al., 1965; Lubs et al., 1966; Lahortiga et al., 2007). Also past medical history of both cases presented here recorded without history of any micro organism contaminations and history of previous malignancies. DMs do occur in leukemic patients without previous history of maligmnancy (Levan et al., 1978). On the contrary, a relation between DMs and previous mutagenetic exposure has been suggested by Weh et al. (1982).

Thus for, suggest that the demonstration of DMs in patients with AML might be an indication that such patients have a previous history of malignant disease treated with irradiation or chemotherapy or both.

In summary, the identification of DMs-positive associated with leukemia reported, together with large Mitelman database and other pertinent reports provides novel knowledge of double minute chromosomes and their association in the wide field of cancers and leukemia.

Acknowledgements

We thank Dr Fatemeh Isfahani, Dr Abbas Hajfathali, Dr Hamid Attarian, Dr Morteza Ghadiani, Dr Hamid Rezvani of the Departments of Medical Oncology and Internal Medicine. Thanks are also due to Miss Niloofar Safavi for excellent technical assistance and material collection. The authors further declare no conflict of interest.

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