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Review Article

Many Developmental Errors and or Pathological Conditions May Be Associated with Marker Dots /Small Supernumerary Chromosomes

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- Chromosome definition; Marker dots and small marker chromosomes; Marker chromatin bodies as indicators of chromosomal mutagenesis; Genetic counselling; Marker dots and SMCs as synonyms

Abstract

In the modern context, chromosomes should be defined as "compound unit of inheritance loaded with sequences of nucleic acids following intracellular molecular events of transmission and cell division". The definition is based on observations which must differentiate between the specific chromosome structure and the chromatin structures expelled by chromosomes. During 1960s and 1970s, small chromatin dots were seen in addition to the normal chromosomal component among many metaphases prepared from tissues of brain tumours by various workers but the fact that certain specific chromosomes, under a triggered molecular mechanism, expel chromatin dots was realized as an important event by the present author in 1986. After observing clear pictures of various metaphases and identifying the specific chromosomes by G banding showing emanating chromatin dots, we had named these small chromosome structures as "Marker Dots" (MDs). These marker dots were repeatedly observed and defined (1986,1992) as being detached from a specific chromosome; sometimes also demonstrated as held or attached with a fine fibril to the chromosome. Lately, these expelled chromosome structures have been named as small Supernumerary Marker Chromosomes (SMCs) by various workers and with the help of most modern techniques like DNA hybridisation in situ, FISH techniques they have also reported exactly same results that chromatin structures are expelled from specific chromosomes. Since neither small marker chromosomes (SMCs) nor marker dots (MDs), though, both have been shown to be produced by any chromosome within a cell, have definite centromere, we can best designate them as marker dots. Our observations already published have exhibited marker dots to be found among some metaphases of normal persons without any phenotypic variable, sometimes in persons with malignant features or sometimes also associated with many pathological conditions as well as in recurrently aborting couples. Hence it would be logical to hypothesize that "Emanation of chromatin is an accelerated epigenetic molecular triggering within specific loci of chromosomes." Influence or impact of this expelled chromatin structure might be related with the activated DNA sequences on the chromosome loci from where and which specific chromosome, this has been "expelled. Since the mode of origin as well as functional aspects of both Marker Dots and SMCs are identical; both are present in normal persons and sometimes affiliated with some and the other disease, these should be considered as synonyms. Both appear to be the same and can help in genetic counselling.

INTRODUCTION

A few chromatin dots of variable sizes were reported in cells of many brain tumour tissues [1-4]. Our studies by standard lymphocyte cultures and staining with Giemsa, G and C banding and Feulgen's approaches on more than 600 persons revealed definite origin of these chromatin dots of variable sizes as the outcome of some triggered molecular mechanism operative on chromatin. We had published clear pictures of chromosomes, observed in many cases revealing direct detachment of these dots, termed as "Marker Dots (MDs). These emanating marker dots [5-11] varied in origin from different chromosomes (as identified by G banding) and were associated with many pathological features more commonly with malignancies and recurrent abortions. These expelled chromatin dots are being discovered by most modern molecular approaches including FISH and DNA hybridisation techniques by various workers and have been termed as small supernumerary marker chromosomes (SMCs). Nevertheless, Marker Dots or supernumerary marker chromosomes are those chromatin -structures which are expelled from a specific chromosome (s) as the consequence of "molecular triggering of the specific loci within a particular chromosome and any chromosome can be molecularly affected and involved in the process of chromatin attenuation [5,7,12-16]. There are evidences published by very many workers [17-23] that appearance of supernumerary marker chromosome is a definite denominator of chromosomal involvement representing onset of some or the other pathological condition. Similar to these small marker chromosomes we have described many years earlier [5,7] these larger dots as Marker Dots. Obviously, the nature of a pathological condition would depend mainly on the "genic" content of the Marker Dot / small Supernumerary marker chromosome and the site of chromatin attenuation at the chromosome from where the chromatin-log has been de-saddled (dislodged from or near centromere, telomere or any other site). This paper Obviously opines that marker dots and small marker chromosomes may be the same structures. Since marker dots have been seen and described as being detached from specific locus [5,6,12,13] as free dots in the vicinity or still attached with a fine stainable fibril, and several chromosomes have been reported to be involved, the "marker-dot emanation "should be listed as a definite kind of chromosomal aberration to be tagged with other standard aberrations (deletion, duplication, inversion and translocation). Formation or appearance of SMCs also is due to chromatin expelled from some or the other chromosome.

MATERIAL AND METHODS

Studies on genotoxic assessments by lymphocyte cultures on persons exposed to MIC gas as well as including various control subjects, family members of normal controls, patients with many syndromes and pathological conditions in and around Bhopal were studied over two decades. Comparative observations on more than 600 persons had established that chromosomal damages have been installed among seriously exposed persons. Studies have been based on standard protocols of cell cultures and chromosome studies with specific staining schedules [5,6,13-15]. Staining schedules of simple G staining, G & C banding and Feulgen's approach have been repeatedly carried out. Table 1 presents a list, though may be incomplete as there are many workers with similar results and the Table 2 presents our already published results. Figure 1 exhibits enhanced sister chromatid exchanges in a female patient exposed with toxic exposure to accidently released MIC gas in Bhopal during 1984. Figure 2 presents comparative histogram of the origin and association of release of marker dots (MDs) among various categories of persons studied and relationship of Mds with kind of aberrations.

Observations

This was a remarkable find to record in slides from lymphocyte cultures of exposed persons and confirms the presence of chromatin marker dots which were seen emanating from specific chromosomes. This was not only clearly identifiable by variously stained metaphases but even SCE studies (sister chromatid exchanges) have had exactly localised the place and modes of origin of chromatin material (Figure 1). The released material could be either linear or a dot and even chromosomes have been seen detaching a marker dot still attached with a fibril (see arrows and lines in Figure 1; [12]. Now that small chromatin structures, described by a large number of workers as small supernumerary chromosomes (SMCs), which originate from any chromosome within the cell are associated with some or the other pathological condition has been well established. Cytogeneticists from various

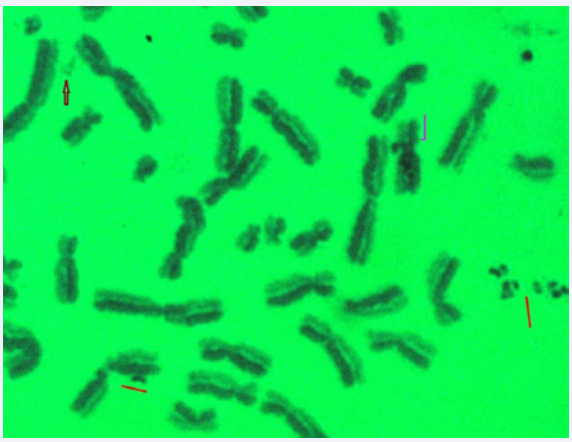

Figure 1 A metaphase from lymphocytes of a female patient seriously affected with exposure of Methylisocyanate gas during December 1984 exhibiting chromosomal mutagenesis as evidenced by many Sister chromatid exchanges; note the release of chromatin material from many chromosomes (arrowed and indicated with lines). The most significant part is that chromatin may be released as dots or linear structures which get round up to form Marker Dot or SMC. This woman died of multiple diseases including dyspnoea and cancer cervix.

Table 1: Association of Marker dots/Small supernumerary chromosomes with parental chromosome.

Authors	Observation	Comments
Cox et al., 1965; Lubs et al 1966; Dharker et al., 1973 a,b. Goswami, 1986	Small Chromatin dots Chromatin dots more than 1.5 to 2 mu were named as Marker dots	Chromatin bodies in malignant Tumours of child hood / brain tumours Observed in cells of methylcyanate exposed persons in Bhopal (after gas exposure in Dec -1984)
Goswami, 1993 , 2016, 2017a,b, 2018 Goswami & Chang, 2001; Goswami et al., 1990, 1992, 1997, 1998	Obo Chromosome SOME OR THE Other chromosomes numbers in involved to detected show detaching Mds 1,2,3, 4,5, 6,7,8, 9,11, 16,17,19; 20, Y	Observed attenuation of marker dots suggesting that marker dots are indicators of chromosomal mutagenesis. 1. Pelvic lipomatosis with Renal ectopia 2. Gradual Disappearnce of right ulna in achild 3. Recurrently aborting mothers 4. Mentally retarded children 5. Toxic effects of methylisocyanate gas exposure among hundreds of affected persons 6. EVEN in 5% seemingly normal persons 7. *Extremely important for GENETIC COUNSELLING for early detection of malignancy and or any embryological or developmental error (?).(Goswami & Chang,2001)*

Pietrzak J , Mrasek K, Obersztyn E , Stankiewicz P, Kosyakova N, Weise A, Cheung S W, Cai W W , Eggeling F, Mazurczak T, Bocian E , Liehr T (2007) Bae M H , Yoo HW , Lee JO, Maria Hong M and Seo EJ (2011)	Molecular cytogenetic characterization of eight small supernumerary marker chromosomes originating from chromosomes **2, 4, 8,18, and 21.** Case 1	Identified in three patients with dysmorphic features, psychomotor retardation and multiple congenital anomalies. We also attempted to correlate the patients' genotypes with phenotypes Analyzing SMCs using high-resolution chromosomal microarray can help identify specific gene contents and to offer proper genetic counseling by determining genotype-phenotype correlations
Huang,B , Pearle, P , Rauen KA ; ,Cotter P D. (2012) https://doi.org/10.1002/ajmg.a.35385	-Chromosome 6------- Clinical outcomes varied. The clinical manifestations observed in Case 1 included small for gestational age, feeding difficulty at birth, hydronephrosis, deviated septum and dysmorphic features, while the phenotype is apparently normal in Case 2. Array comparative genomic hybridization (CGH) was performed and showed increase in dosage for approximately 26 Mb of genetic material from the proximal short and long arms of chromosome 6 euchromatin.	The difference in the clinical presentation in patients may have resulted from the difference in the actual gene contents of the marker chromosomes and/or the differential distribution of the mosaicism
Reddy et al., 2013 Chen et al., (2017) SMCs detected in routine chromosomal analysis, SMCs originating from chromosome 21 Dalpra et al., (2005) Kurtas N E , Xumerle L , Leonardelli L, donne	SMCs Proved by genomic hybridization in a genome-wide analysis SMCs derived from chromosome 21. Extensive survey revealed that Acrocentric chromosomes also play definite role in generating SMCs. Studied observations on movements of SMCs during regular cell divisions and found as laggards	A small supernumerary marker chromosome is often seen in patients with developmental disorders. Prior to array-based comparative genomic hybridization markers were rarely genotyped end to end. In this study, a valid genotype-to-phenotype correlation was possible because the supernumerary marker chromosomes were fully characterized by array-based comparative genomic hybridization in a genome-wide analysis Prenatal diagnosis and molecular cytogenetic characterization of mosaicism for a small supernumerary marker chromosome derived from chromosome 21.
An Na, Y Yang, Xi Q, Yue F, Liu R, Li S, Wang R (2019) Molecular Characterization of Molecular Characterization of Mosaicism for a Small Supernumerary Marker Chromosome Derived from Chromosome Y in an Infertile Male with Apparently Normal Phenotype: A Case Report and Literature Review	Studied Proved that Y chromosome is involved and indicated that SMC may be responsible in causing oligospermia	A total of 113 of the 241 sSMCs were detected antenatally, and 128 were detected postnatally. There were 52 inherited and 172 de novo cases. Abnormal phenotype was present in 137 cases (57%), 38 of which were antenatally diagnosed. A mosaic condition was observed in 87 cases (36%).The chromosomes generating the sSMCs were acrocentric in 132 cases (69%) and non-acrocentric chromosomes in 60 cases (31%); a neocentromere was hypothesized in three cases involving chromosomes 6, 8, and 15 Authors have studied by a whole genomic approach and trios genotyping, 12 *de novo*, nonrecurrent small supernumerary marker chromosomes (sSMC), detected as mosaics during pre- or postnatal diagnosis and associated with increased maternal age. Findings strongly suggest that most sSMCs are the result of a multiple-step mechanism, initiated by maternal meiotic nondisjunction followed by postzygotic anaphase lagging of the supernumerary chromosome and its subsequent chromothripsis. Authors claim first report of the chromosomal Y anomalies, SRY gene translocated from der(Y) (pter ⟶ q11.23) to qter of normal chromosome Y, were not reported before. Our findings indicated that the mosaic presence of sSMC(Y) may be the main cause of severe oligospermia although no other apparent abnormalities were observed. A total of

laboratories [17-22] have established that appearance of SMCs is associated with the developmental errors leading to some or the other pathological condition or a syndrome (Table 1). Observations listed in the Table 1 perfectly match with our earlier published observations but offer more scientific importance on account of use of most modern investigational methodologies.

Our earlier observations [5,7] regarding these chromatin structures to which we had named as marker dots (MDs) and present discussions have been presented in Figure 2 and Table 2 and also briefly mentioned hereunder:

(1) This becomes imperative to reemphasize that these chromatin dots seen emanating from chromosomes are decidedly early indicators of chromosomal mutagenesis. We have confirmed by G, and C banding as well as by Feulgen's staining and fluorescence procedures that these are chromatin bodies found in patients of cancers (bone, breast, lung and colon in particular) and sometimes in a few of their family members (2). Family members prone to cancer were found to exhibit marker dots and developed clinical signs of cancer after 03 to 05 years after our report. Marker dots measuring 2-to-3 micron emanate from different chromosome in several metaphases in preparations from cancer patients obviously, it appears that the molecular attenuation of chromatin structures movable from chromosomes is related with triggering neoplastic transformations (3). These dots appear in those metaphases which exhibit translocations and acrocentric associations, which are precursors to installation of chromosomal mutagenesis as established since the time of Boveri. Marker dots can be reliable early indicators of precancerous patients; may help in early detection. We have evidences for this pronouncement. In the background we have a credited discovery of marker dots particularly in those families which have had a cancer patient and identify a possible susceptible person. Out of our 17 such cases adjudged, 13 had started showing signs of malignancy within 3-5 years of yearly follow up study. Our prognostic approaches were admired by surgeons during their treatments of various patients.

DISCUSSION

Chromosome involvement in malignancy has been known since the time of Boveri and hundreds of papers have been published in accordance with this concept that molecular mechanism of malignancy leading to clinical cancer is always associated with chromosomal aberrations including polyploidy as well as new small chromatin structures called as double minutes [24-26]. Double minutes, though are two small dots giving a small dumbel shape and can be well examined under light microscope, but molecularly are overloaded with oncogenes. Marker dots or SMCs as most other workers designate, are additional chromatin structures whose origin is from the chromosome(s) within the cell and these are affiliated to a large number of pathological conditions and developmental errors. There are strong reasons to suggest that neither Marker Dots nor SMCs should be referred as

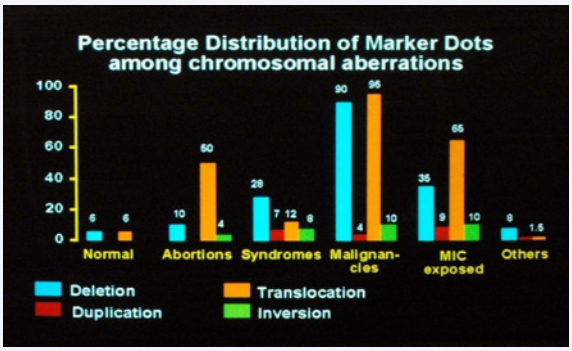

Figure 2 Based on computations of clear metaphases and counting of type of aberrations in each kind of patients and controls this figure displays a comparative picture of distribution of Marker Dots (MDS) . In all categories of subjects/ persons studied the aberration -translocation appears to be by and large more associated with "release of chromatin material".

Involvement of Chromosomes in Releasing Marker Dots (2106 metaphases)

Involvement of Chromosome	No.of metaphases	CG Bodies (= Marker dots) Arising			
		Centromere	Telomere	Arm p	Arm q
1	117	5	51	4	-
2	126	-	117	-	-
3	125	-	43	-	-
5	850	3	502	-	18
8	180	-	45	49	-
9	120	-	73	-	17
11	165	-	70	12	-
12	047	-	29	-	-
13	132	-	41	18	73
16	087	10	45	-	1
17	140	-	37	-	58
Y	017	-	12	-	27

Table 2 This table is based on computation of clear metaphases indicating the location of CG (Chromatin bodies or Marker Dots positively stainable with both C and G banding).

"chromosomes". Chromosomes should be defined as "compound unit of inheritance loaded with sequences of nucleic acids following intracellular molecular events of transmission and cell division". Since neither SMCs nor marker dots, though, both have been shown to be produced by any chromosome within a cell, have definite centromere, we can best designate them as marker dots. Both must have a fraction of heterochromatin with which these can sometimes attach to any chromosome and move to poles during anaphasic movements. Obviously, just like micro chromosomes in birds and reptiles these "expelled chromatin structures do possess some part of the heterochromatin which can facilitate retention in few (not all) cells. Both marker dots and also SMCs are not present in all cells.

CHROMOSOME SITE?

This is a moot question that from which part or specific locus does a Marker Dot or SMC arise?. [27] specified the origin from centromere all other workers have presented definitive evidences on the basis of most modern molecular genetic methods (including bandings, in situ hybridizations etc) that SMCs can arise from any (terminal or telomeric, interstitial or from any part of the chromosome). Goswami has also presented the origin of MDs (Marker Dots) from many parts including centromeric and telomeric regions and most remarkably in many cases the exact detaching perfectly stained fine thread or fibril has been shown (review, [13]. Almost all chromosomes in human genome can emanate the chromatin dot-structure. SMCs have been proved to be always associated with some or the other pathological disorder and or a developmental error (Table 1). With the help of very elegant studies by various workers [17,18,28] on genotype-to-phenotype correlation was possible because the supernumerary marker chromosomes were fully characterized by array-based comparative genomic hybridization in a genome-wide analysis. The genetic significance of these marker dots or SMCs as these were called later (without mentioning about marker dots) have been known for quite some time [6-10,12-16,29].

CHROMOSOMAL MECHANISM

Chromosome-assay is one of the most reliable approaches in assessing genetic damages induced by any environmental agent. Our group followed the conventional study of mutational damages both by SCE (sister chromatid exchanges) as well as by scoring chromosomal aberrations. Based on publications [5,8] and thereafter we have opined that there are individuals in Bhopal (to whom we could reinvestigate at least three times; a few of them were investigated in early 1994 as routine practice of cytogenetics unit of the department of Genetics, Bhopal University) who still show the induced aberrations particularly rare kinds of translocations. As shown in Figure 1, which is a metaphase cell showing increased mutagenesis by sister chromatid exchanges (SCE) many parts of several chromosomes show release chromatin fragment and dots expelled from respective or probably nearby chromatid (see Figure 1. for details). What we have categorically mentioned [12] is that "chromatin attenuation" at any or more loci is triggered by some molecular mechanism (may be an epigenetic phenomenon ?). Scoring such aberrant cells on large scale and statistically counting metaphases we have found that translocations are in greater proportion in those cells where MDs are observed but all aberrations do offer possibility involving several chromosomes (See Tables 1, 2 and Figure 2). Acrocentric associations and premature centromeric divisions are also highly pronounced which are apparently not normal events. But these aberrations always do not involve the same "parental chromosome" generating a SMC or marker dot.

Whatever is the molecular mechanism responsible for the generation or expulsion of chromatin from a chromosome ("marker dots" or small marker chromosomes) one physically visible process is the attenuation of a part of chromatin within a chromosome. These attenuated chromatin dots are being randomly expelled from specific chromosomes [5,8,12,13] (Figure 1). Results of genomic DNA studies and matching with some oncogenic expressions are still unpublished needing repetitions. But this appears logical that the type of abnormal developmental feature or a pathological condition or appearance of a syndrome should be related with the activated DNA sequences on the basis of the chromatin make up and the part from where and which chromosome this extra chromatin structure has been derived. Both, SMCs as well as Marker dots are found in some seemingly normal persons also [5]. Our follow-up studies of the same persons have indicated that in due course these could be early warnings [6,12-15] for a pathological anomaly including recurrent abortions and or malignancy. In other words, presence of marker dots can help in genetic counselling as well.

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