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Cytogenetic Instability of Gastric Cancer in and Around Coimbatore City, South India.

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Abstract: Gastric cancer (GC) is a major health issue in worldwide and genetic factors plays an important role in GC. The focal aim of the present study was the major chromosomal aberrations, deletion, translocation, inversion and mosaic in gastric cancer (GC) patients of coimbatore, Tamilnadu. Totally 20 blood samples were collected from various hospitals in and around coimbatore city and equal numbers of normal healthy subjects were selected. Cytogenetic studies were used by G-banding technique and results were guaranteed by SKY technique. In the present investigation, major CA like deletion, translocation, inversion and mosaic were identified in experimental subjects. A result shows frequent CA in chromosomes 1, 3, 6, 8, 11, 17, 20 and Y. In comparison with experimental subjects, the control subjects exhibited very low levels of major CA ($P<0.05$). Identification of chromosome alterations may be helpful in understanding the molecular basis of the disease in better manner.

Key words: Gastric cancer · Chromosome aberration · SKY · G-Banding

INTRODUCTION

Gastric cancer (GC) is a major health issue in worldwide. Close to one million new GC cases, 9% of all cancers were diagnosed in the year 2002 alone [1]. As an example of the scope of the problem, GC was the second most common cause of cancer-related death and fourth most common cancer after lung, breast and colorectal cancers [1]. The highest incidence areas are Asia, Eastern Europe, mainly more frequent in males than in females and usually affect elderly, as 75% of GC patients are over 50-55 years old.

Diet shows the most significant association with GC in many epidemiological studies [2]. Alcohol consumption and smoking are the main risk factors for GC [3]. Heavy alcohol usage is particularly associated with GC in asian populations.

Nevertheless genetic factors play an important role in GC. Chromosomal aberrations are fundamental to cancer formation because they interfere with the function of oncogenes and suppressor genes. Identification of recurrent chromosomal translocation may thus contribute to the cloning of cancer causing genes. Several genetic alterations associated with GC have been reported [4-8]. These specific alterations have been implicated in multi-stage carcinogenesis of GC.

At the same time, previous cytogenetic studies of GC have demonstrated frequent aberrations of chromosome nos. 1, 3, 6, 7, 8, 13, 17, 20 and Y, [9-12] while other chromosomes have also been found to be repeatedly involved in GC [13-16]. The chromosomal breakpoints identified were 1p22, 3p21, 3q23, 11p13-15 and 19p13 on primary GC [9, 10, 17].

However, specific chromosomal translocations have not yet been identified in GC, because complete karyotypic analysis was precluded by the complicated and cryptic nature of the rearrangements as well as the poor banding of condensed chromosomes. To overcome these limitations, multiplex fluorescence *in situ* hybridization (FISH) has been successfully used for two patients with GC [18].

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Furthermore our previous study to established peripheral blood samples and was able to identify and characterize recurrent chromosomal breakpoints in prostate cancer [19] and Liver cancer [20]. So the present study, selected SKY technique to analyse GC in and around Coimbatore city.

MATERIALS AND METHODS

Coimbatore, the Manchester of South India is located in the western region of Tamilnadu. The total population of the Coimbatore district is 42.25 lakhs (21, 56, 280 males and 20, 67, 817 females). Due to the existence and predominance of population and their food habituate the silent toll of human lives due to numerous diseases is on the rise.

A total of 40 subjects aged 40~65 years old including 20 gastric cancer patients and 20 healthy controls were recruited. Five milliliters of blood samples were collected from 20 cancer patients in various hospitals of city, who did not undergo any therapeutical treatment and also samples were collected from twenty healthy controls were selected from the same area as that of the patients. Data on medical and family history of cancer, smoking habits, alcohol and occupational history were obtained through an interviewer-administered questionnaire as well as from review of the patient's hospital records of both control and cancer patients. The work was carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Cultures were set up in RPMI 1640 medium (Hi-Media Lab., India) at 37°C for 72 hours according to standard culturing technique [21] with some modifications. The lymphocytes were treated with 0.075 M KCl at room temperature for 22 minutes and fixed with carnoy's fixative (1 part glacial acetic acid and 3 parts methanol). Slides were carefully dried on a hot plate (56 °C, 2 min) and then stained using the Giemsa-banding [22] and pretreated with trypsin and karyotyped according to the International System for Human Cytogenetic Nomenclature (ISCN 1995) [23]. The remaining chromosome pellets were stored at-20 for SKY analyses.

The SKY™ kit probe cocktail from Applied Spectral Imaging (ASI, Carlsbad, CA, USA) was hybridized to metaphase spreads from each slide according to standard protocols [24-26] and as per the manufacturer's instructions (ASI, Carlsbad, CA, USA). After destaining the G-banded slides with methanol for 10 min, the slides were rehydrated in a descending ethyl alcohol series (100%, 90%, 70%) and fixed with 1% formaldehyde in 50 mmol/L MgCl2/phosphate buffer solution for 10 min. The slides were then dehydrated using an ascending ethyl alcohol series and denatured for 30~45 s in 70% formamide/2× SSC at 75 °C. The SKY probe was denatured for 7 min at 75 °C, reannealed at 37 °C for 1 h, placed on the slide and covered with a glass coverslip. The coverslip was sealed with rubber cement and the slides placed in a damp container in a 37 °C incubator. After overnight hybridization, the post-hybridization washes were performed as per manufacturer's instructions (ASI, Carlsbad, CA, USA). The metaphase images were captured using an SD 200 spectral bio-imaging system attached to a Zeiss microscope and stored on a SKY image-capture workstation. The images were analyzed using the SKY View software version 1.2 which resolves individual fluorochrome spectra by Fourier spectroscopy and distinguishes the spectral signatures for each chromosome to provide a unique pseudocolour for each chromosome (classified image).

RESULTS

Selected GC patients with CA are shown in Table 1. It represents the chromosomal aberrations seen in the peripheral blood lymphocytes of GC patients were deletion, translocation, inversion and mosaicism in chromosomes 1, 3, 6, 7, 8, 11, 17, 20 and Y. Interestingly, experimental subjects displayed high level (4.3±1.91) of major CA (Table 2) compared with their respective control (0.95±0.87). Statistically significant results were obtained from both control and experimental subjects. From the above data inferred that significant elevation in CA was observed in GC patients.

DISCUSSION

Cancer is a consequence of genetic or epigenetic alterations in a variety of genes that are fundamental to the process of growth, cell proliferation, differentiation and programmed cell death [27]. The exact role of instability in the heterogeneity of the pathological status for a given genetic constitution can be determined by identifying the chromosomal breakpoints in tumor tissue as well as in peripheral lymphocytes. Each alteration whether an initiating or a progression associated event, may be mediated through gross chromosomal change and hence has the potential to be detected cytogenetically [28].

Table 1: Chromosomal abnormalities in Gastric cancer patients identified by sequential G-banding and SKY techniques

				Chromosomal abnormalities identified by G-banding and SKY				
S. No.	Case No	Age (Years)	Chromosome Number	Deletion	Translocation	Inversion	Mosaic	Total
1	GCP001	61	1,3,Y	3	-	1	-	4
2	GCP002	54	8,11	1	-	1	-	2
3	GCP003	60	3,7	-	1	-	1	2
4	GCP004	45	7	3	-	-	-	3
5	GCP005	60	3	1	1	-	-	2
6	GCP006	69	Y	-	-	-	2	2
7	GCP007	68	7,8,11,Y	5	1	-	1	7
8	GCP008	49	17	2	-	1	1	4
9	GCP009	52	20	-	2	1	-	3
10	GCP010	58	8,20	5	1	-	1	7
11	GCP011	54	3	3	1	-	-	4
12	GCP012	75	3	1	2	-	3	6
13	GCP013	55	7	-	4	-	1	5
14	GCP014	48	3,20	-	1	2	3	6
15	GCP015	67	8	-	-	2	-	2
16	GCP016	64	3,7	3	3	-	1	7
17	GCP017	63	8	1	-	3	-	4
18	GCP018	61	8,11,17	1	3	2	1	7
19	GCP019	49	8	-	-	3	1	4
20	GCP020	46	20,Y	3	1	-	1	5

Table 2: Chromosomal abnormalities in controls identified by sequential G-banding and SKY techniques

				Chromosomal abnormalities identified by G-banding and SKY				
S.No.	Case No	Age (Years)	Chromosome Number	Deletion	Translocation	Inversion	Mosaic	Total
1	CS001	49	3	1	-	-	-	1
2	CS002	53	8	-	-	-	-	0
3	CS003	47	0	-	-	-	-	0
4	CS004	62	0		-	-	-	0
5	CS005	60	17	1	-	-	1	2
6	CS006	54	3,8	-	-	1	-	1
7	CS007	60	1	-	1	-	1	2
8	CS008	45	0	-	-	1	-	1
9	CS009	52	0	-	-	-	-	0
10	CS010	58	0	-	-	-	-	0
11	CS011	61	3	-	-	1	-	1
12	CS012	51	1	-	2	-	-	2
13	CS013	55	0	-	-	-	-	0
14	CS014	56	16	2	-	-	-	2
15	CS015	49	0	-	-	-	-	0
16	CS016	46	6		1	-	1	2
17	CS017	63	0	-	-	-	-	0
18	CS018	61	0	-	-	-	-	0
19	CS019	54	0	-	-	-	-	0
20	CS020	65	17	3	1	-	1	5

However, a low level of chromosomal instability is detectable in the peripheral blood lymphocytes of patients with skin, breast and bladder cancers and lymphomas [29-31] reported a significant increase in the mortality ratio for all cancers in subjects who had shown increased levels of CA in their lymphocytes. Essentially, the data from both these studies when pooled indicated that the frequency of chromosome instability in peripheral blood lymphocytes is a relevant biomarker for cancer risks in humans, reflecting early biological effects of genotoxic carcinogens and individual cancer susceptibility [32, 33].

Although previous studies have shown the presence of chromosome instability in GC [11-17]. This is the first molecular cytogenetic study to investigate the major CA like deletion, translocation, inversion and mosaics in the peripheral blood lymphocytes of previously untreated GC patients in coimbatore city.

Chromosomal rearrangements frequently involved well-known oncogene loci that may be associated with genes of gastric carcinogenesis. GC may either implicate microsatellite instability or chromosome instability pathways [34]. Nevertheless the genetic alterations also implicate the GC, so the present study analyse the peripheral blood lymphocytes in GC patients by spectral karyotyping.

There are few published cytogenetic studies of gastric carcinoma cases reported to date [35, 36]. Furthermore critical cell biological mechanisms in gastric carcinogenesis include proliferation, apoptosis, invasion, degradation and remodeling of extracellular matrix and stroma induction including angiogenesis. These mechanisms are to a large extent caused by genetic changes that occur at the chromosomal level. Therefore, DNA copy number profiling is a sensible approach for genotyping in gastric cancer [14, 16, 37, 38].

In the present study, chromosome 1 3, 7, 8, 11, 17, 20 and Y showed the deletion, translocation, inversion and mosaicism in GC patients. The results of the present study have been supplemented with several reports relating to these chromosomal sites [9-17]. Chromosome 1 showed only deletion and inversion in GC patients. It is involved in GC whether through the presence of GC susceptibility genes or through the disruption of common pathways involved in cancer development.

Maximum numbers of CA were deletion, translocation, inversion and mosaics are identified in the short arm (3p) of chromosome 3 of GC patients. These results were supported by other studies on chromosome 3 [39-45]. Deletions of the short arm of chromosome 3 (3p24-26 and 3p22-12) were identified in over half of primary GC cases through cytogenetic studies. Further, 5q31-33 was strongly associated with aggressiveness of GC in a linkage analysis. But present study did not showed any genetic modification in chromosome 5 GC in GC patients.

Chromosome 7 and 8 showed deletion, translocation, inversion and mosaic in GC patients. Similar studies have reported the loss of alleles of chromosomes was detected in a subset of advanced-stage GC [46-48]. Many authors consider chromosome 8 numerical aberrations an important event to gastric cancer [46-51]. Ferti-Passantonopoulou [45] studying a few cases by conventional staining techniques, found that numerical aberrations of chromosome 8 and Xia *et al.* [49]. described trisomies of chromosomes 8 and 9 as a cytogenetic subgroup of gastric cancer. Xiao *et al.* [47] have also observed trisomy 8 in a case with minimal chromosomal changes, suggesting that this abnormality might be a non-random event in gastric tumorigenesis.

In the present investigation chromosome 11 showed deletion, translocation and inversion in GC patients, mainly in the long arm (11q) of chromosome 11. These results were further strengthened by other reports. Another common breakpoint of 11q13 contains a variety of genes associated with cell proliferation and differentiation [52, 53]. It has been demonstrated that HST1/FGF4 is co-amplified with INT2/FGF3 in human GC, although amplification of FGF4 and FGF3 does not correlate with mRNA overexpression [54], while high-level amplification of 11q13 has been frequently detected in CGH analysis [15,16].

Chromosome 17 and 20 showed deletion, translocation, inversion and mosaic in GC patients of the present analysis. Regarding chromosome 17, 17q, 20, 20p karyotype was found in few of the experimental subjects. SKY banding analysis led to the identification of recurrent co-localization of the chromosomal bands involved in translocations: 8q24.1 and 8q14, 8q24.1 and 11q13, 11q13 and 17q11.2 and 18q11.2 and 20q11.2. Many authors of previous studies consider these chromosomes numerical aberrations an important event to gastric cancer [40-44]. In chromosome Y showed elevated incidence of deletion, translocation, inversion and mosaic in GC patients.

Finally SKY analysis identified the frequently occurring breakpoints 8q24.1, 11q13, 20q11.1-13.1 and 11q14 and the translocations 8q24.1 and 8q24.1 and 11q13, 11q13 and 17q11.2 and 18q11.2 and 20q11.2 in chromosome 1, 3, 6, 7, 8, 11, 17, 20 and Y SKY thus proved to be extremely useful for a comprehensive analysis of chromosomal translocations in GC [55].

In conclusion the chromosomal breakpoints defined in our study may well contain critical genes which are involved in multistage carcinogenesis of GC and thus can serve as landmarks for crucial regions that warrant molecular dissection. In the present study, the high frequency of centromeric rearrangements indicates a potential role for mitotic irregularities associated with the centromere in GC tumorigenesis.

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