Mapping of Novel Regions of DNA Gain and Loss by Comparative Genomic Hybridization in Esophageal Carcinoma in the Black and Colored Populations of South Africa

Lana Du Plessis, Erin Dietzsch, Mireille Van Gele, Nadine Van Roy, Paul Van Helden, M. Iqbal Parker, David K. Mugwanya, Mark De Groot, Munro P. Marx, Maritha J. Kotze, and Frank Speleman

Division Human Genetics, Medical School [L. D. P., M. P. M., M. J. K.], and MRC Center for Molecular and Cellular Biology, Department of Medical Biochemistry [P.V.H.], University of Stellenbosch; 7505 Tygerberg, South Africa; Department of Medical Biochemistry, University of Cape Town Medical School, Observatory, 7925 Cape Town, South Africa [E. D., M. I. P.]; Department of Human Genetics, University Hospital Ziekenhuis, Gent, Belgium [M. V. G., N. V. R., F. S.]; Department Cardiothoracic & Vascular Surgery, Faculty of Medicine, University of Transkei, UNITRA, 5100 Umtata, South Africa [D. K. M.], Department of Cardio-Thoracic Surgery, Groote Schuur Hospital, Observatory, 7925 Cape Town, South Africa [M. D. G.]

ABSTRACT

Esophageal cancer (EC) is the leading cause of cancer death in the Black male population in South Africa. Although several oncogenes and tumor suppressor genes have previously been found altered in this cancer, many novel genes remain to be identified. To identify the chromosomal location of these unknown genes, we have analyzed DNA of 29 South African EC patients by comparative genomic hybridization. Frequent loss occurred at chromosome 1p (52%), 4p (52%), 18q (48%), 19p (52%), 19q (55%), and 22q (41%). The most common gains were detected at 1q (41%), 2q (52%), 3q (72%), 5p (31%), 7p (48%), 7q (45%), 8q (55%), and Xq (69%). High level amplification was detected at 2q24–33, 6p21.1–q14, 7p12–q21, 7q11.2–31, 8q22–24, 8q31–qter, 13q21–34, and at 13q32–34. The present comparative genomic hybridization study opens the way for additional targeted studies on these particular chromosomal regions to identify the specific genes involved in the higher susceptibility to specific subtypes of esophageal carcinoma in different geographical regions. The loss of 8p (28%) and Xp (17%) in tumors of male individuals may provide clues to the basis of the sex-biased frequency of occurrence of EC favoring men.

INTRODUCTION

EC is known for its aggressive clinical behavior and poor prognosis. EC is not widespread globally, but this neoplasm occurs at high incidences in certain countries, such as China and Iran (1). Even higher incidences have been reported in certain parts of Africa and in particular among the Black population in the Transkei region of South Africa (2, 3). In this particular region, EC accounted for 45.8% of all cancer deaths, mostly among the Black population (6).

Several environmental and chemical risk factors have been implicated in the etiology of EC. These include combined smoking and alcohol use, dietary factors, mycotoxins, nitrosamines, infection, history of injury to the esophagus, and chronic inflammation (1, 7, and 8). Some of these factors have been suggested as contributing factors to the high incidence of this neoplasm in the South African Black population (6, 9).

Apart from these factors, many genes normally involved in cell growth and regulatory pathways have been found altered in EC (reviewed in Refs. 3 and 10). LOH at chromosomal loci on 1p, 3p, 5q, 9q, 11q13, 13q, 17p, and 18q has been shown using microsatellite markers (11–15). Allelic loss and mutations at tumor suppressor loci, e.g., TP53 (16, 17), retinoblastoma (RB1; Refs. 17 and 18), MTS1 (19, 20), and adenomatous polyposis coli (21) have also been identified in EC. Overexpression, inactivation, or amplification of growth-related genes, such as EGFR (22), MYCC (23), cyclin D1 (24), vascular endothelial growth factor (25), have also been reported in EC. Some of the earlier cytogenetic studies of chromosomal aberrations in EC reported structural changes affecting chromosomes 1, 2, 3, 6, 7, 9, and 11. Most of the frequent breakpoints involved were 3p11, 6q15, 6q33, 7p22, 7q22, 9p11, 9q12, 11p11.2, 11p14, and 11q12 (1, 26, 27). Recently, a report on cytogenetic analysis of Barrett’s mucosa and adenocarcinoma of the distal esophagus and cardium showed changes affecting chromosomes 1p, 3q, 11p, and 22p, losses of chromosomes 4, 18, 21, and Y, and gains of chromosomes 14 and 20 (28).

Like cytogenetic analysis, CGH also offers the advantage of the analysis of the entire tumor genome. Although CGH does not detect balanced chromosomal changes, as compared with the cytogenetic analysis of complex chromosome rearrangements, instead it offers a straightforward approach to the detection of gains and losses of DNA. Only three CGH studies on EC cancer have been reported, mostly describing changes occurring in limited numbers of esophageal adenocarcinomas (29), cell lines (30), or in leiomysomas of the esophagus (31). Most of the available genetic information on EC comes from studies of EAC rather than ESSC. The high incidence of ESSC in certain South African populations leads us to postulate that particular genes may be responsible for individual susceptibility to this cancer. To identify chromosomal regions, which harbor these genes, we performed CGH on a panel of 29 EC tumors including mostly ESSC tumors of the Black and Colored populations.

MATERIALS AND METHODS

Tumor Material from Patients and DNA Samples. The study material was collected from 29 patients who had been clinically diagnosed with esophageal cancer and had been referred to clinics at the Department of Thoracic Surgery, Groote Schuur Hospital, Cape Town, and the Umtata General Hospital.

Received 10/21/98; accepted 2/18/99.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

1 This work was supported by grants from the Cytogenetic Research Fund, Human Genetics, Tygerberg; by FWO Grant G.0085.96; and by GOA Grant 12051397. This study was further supported by grants from the Universities of Stellenbosch and Cape Town, the South African Medical Research Council, and the National Cancer Association of South Africa. This work is part of a thesis to be submitted in fulfillment of the requirements for the degree of Doctor of Philosophy, University of Stellenbosch.

2 To whom requests for reprints should be addressed, at Department of Human Genetics, Faculty of Medicine, University of Stellenbosch, P. O. Box 19063, Tygerberg, 7505, South Africa. Phone: 27-21-938 9103; Fax: 27-21-931 7810; E-mail: ldp@maties.sun.ac.za.

3 The abbreviations used are: EC, esophageal carcinoma; ESSC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; EGFR, epidermal growth factor receptor; CGH, comparative genomic hybridization; LOH, loss of heterozygosity; SCLC, small cell lung carcinoma; PGE, prostaglandin E; PTGER1, PGE receptor 1-EP1 subtype; PTGS2, prostaglandin-endoperoxidase synthase 2; HGF, hepatocyte growth factor; HGF, HGF receptor.
pital in Transkei for biopsy and histopathological classification. The patients included South Africans from different population groups, i.e., 11 Colored (2 females and 9 males), 17 Black Xhosa-speaking (8 females and 9 males), and 1 White male. In this study, “Colored” refers to an individual of mixed ancestry, including San, Khoi, West African Negro, Madagascar, Javanese, and Western European origin; “Black Xhosa” refers to South Africans of central African descent with cultural habits originating from Xhosa tribes; “White” refers to an individual of European descent, mainly Dutch, French, German, and British. The esophageal tumors were classified according to Tumor-Node-Metastasis classification (32). Twenty-seven tumors were squamous cell carcinomas. Tumors from two Colored South African males were esophageal adenocarcinomas (Table 1). Genomic DNA was extracted from fresh tumor biopsies by standard procedures (33). Control reference DNA was extracted from peripheral blood of healthy volunteers.

**CGH Analysis.** Target metaphases for CGH were obtained from phytohemagglutinin-stimulated lymphocytes. Cell culturing and preparation of metaphases were done according to routine procedures. The quality of slides was tested essentially as described by Van Gele et al. (34). Procedures for DNA labeling, in situ hybridization, fluorescence microscopy, and digital imaging and processing were according to du Manoir et al. (35, 36). Equal amounts of tumor and reference DNA were hybridized to normal metaphases in CGH experiments, and detection of digoxigenin- and biotin-modified probes were performed prior to counterstaining with 4',6-diamidino-2-phenylidole and digital image analysis.

**Digital Image Analysis.** CGH metaphase images were resolved on a Leitz DM microscope equipped with a high sensitivity integrated monochrome charge-coupled device camera (Sony IMAC-CCD S30) and dedicated software (ISIS: MetaSystems GmbH, Aihlhusheim, Germany). ISIS CGH image analysis software (MetaSystems) was further used for acquiring CGH DNA profiles. An average of 20 metaphases was analyzed for each of the 29 EC tumors. Testing for reliability of CGH and software was performed previously, with detail given to known small deletions and amplification (37). Analysis of individual ratio profiles and average ratio profiles with fixed limits at 1.25 and 0.75 and SD limits (the width of the confidence interval being three times the SD) were performed during evaluation for gains and losses. Gain or loss of DNA copies was assigned when the ratio profile crossed the SD limit. Amplification was defined at a ratio greater than 1.5.

**RESULTS**

Fig. 1 and Table 1 summarizes the chromosomal DNA gain and loss detected by CGH analysis in the 29 EC patients. Changes in DNA copy numbers were detected by CGH in all 29 EC tumors. Fig. 2 indicates CGH ratio profiles of some tumors with high level amplification and novel regions of gain and loss. Table 2 provides a summary of the mean frequency of DNA gain and loss detected in male and female populations, Black and Colored males, and Black females. The frequency of gain and loss in the Colored females and White male patients were not included in the table because of their small numbers. In males, the mean number of loci showing gain was 7.4 (range, 2–12), and the mean number of loss was 9 (range, 3–17). In females, the mean gain was 6.9 (range, 3–10), and the mean loss was 5.1 (range, 1–9). In male and female Blacks, the mean gain was 9.1 (range, 5–13) and 7.1 (range, 3–10), respectively, and the mean

Fig. 1. Summary of all chromosomal abnormalities detected by CGH in 29 esophageal carcinoma patients. Numbers indicated above correspond to case numbers as indicated in Table 1. Vertical lines on the left and right of chromosomes, loss and gain of DNA copy number, respectively. Dark boxes, high copy number amplification. Open boxes, multiple copies of DNA gain. When gain (loss) in a patient is indicated on both the short and long arm but the line is not connected, it indicates that in that tumor not the whole chromosome shows gain (loss).
Clinicopathological features and DNA copy number gains of 29 EC patients are summarized in Table 1. The most frequent gain was observed in chromosome 1q [12 of 29 tumors (41%)], chromosome 2q [15 tumors (52%)], chromosome 5p [9 tumors (31%)], chromosome 7p [14 tumors (48%)], chromosome 7q [13 tumors (45%)], chromosome 8q [16 tumors (55%)], and the X chromosome [20 tumors (69%)]. Chromosome 1 displayed a minimal region of gain at 1q24–31. Gain of 1p proximal to the centromere was found in seven (24%) tumors, and this 1p gain occurred in tumors of Black patients only (Fig. 1, tumors 12, 14, 15, 18, 19, 22–25, and 28). Thirteen tumors showed gain of partial 2q or partial 2q and 2p, but all excluded the most distal part of chromosome 2q33–37. A minimal common region of gain was assigned at 2q31–32. In one tumor, the ratio profile shows the gain of chromosome 5p and is represented by the presence of multiple copies of the short arm (Fig. 2g). Other regions of gain (in order of frequency) were on chromosomes 4q (28%), 9q (24%), 11q (24%), 12p (24%), 12q (28%), 13q (34%), 14q (28%), and 19q (24%).

High level amplification was observed on eight different chromosomal regions 2q24–33 (Fig. 2a), 6p21.1–q14 (Fig. 2b), 7p12–q21, and 7q11.2–31 (Fig. 2c), 8q22–24.1 (Fig. 2d), and 8q13–qter (Fig. 2f) and on chromosome 13q21–34 and 13q32–34 (Fig. 2e).

Loss of DNA Copy Number. The most frequent loss of DNA was found on chromosome 19 (17 of 29 tumors, 59%), either throughout whole chromosome loss (12 tumors, 41%), loss of 19p (15 tumors, 52%), or loss of 19q (16 tumors, 55%). Other regions of frequent loss included chromosome 1p [15 of 29 (52%)], 4p [15 of 29 tumors (52%)], 18q [14 tumors (48%)], and 22q (12 tumors [41%]). A minimal common region of loss was identified on 1p36–pter. Three of the Colored male patients showed no loss at this distal region but instead showed loss of the proximal part of 1p. This is in contrast to the Black EC patients that showed gain at this region. Other frequently overrepresented regions were on chromosomes 4q (28%), 9q (24%), 11q (24%), 12p (24%), 12q (28%), 13q (34%), 14q (28%), and 19q (24%).
**DISCUSSION**

ESSC has a high incidence in the Black populations and, to a lesser extent, in the Colored populations of South Africa. Very little information is available on the genetic alterations occurring in this tumor, in particular in the aforementioned populations. Using CGH, we have performed a genome wide screen for detection of DNA losses and gains in ESSC occurring in these population groups.

Chromosomal imbalances were observed in all tumors. The average number of imbalances per tumor was 16. Although at least one or more gains or losses were observed for all chromosome arms, some chromosomal regions were particularly frequently lost or overrepresented. Frequent loss (in order of highest to lowest frequency) occurred at chromosome 19q (55%), 1p (52%), 4p (52%), 19p (52%), 18q (48%), 22q (41%), 3p (38%), 5q14–21 (28%), 5q31–qter (24%), and 2q35–37 (21%). The most common gains (in order of frequency) were detected at 3q (72%), Xq (69%), 8q (55%), 2q (52%), 7p (48%), 7q (45%), 1q (41%), and 5p (31%).

Specific changes associated with the male and Black EC patient group were observed, including loss of chromosome 8p in males, loss of Xp in Black males, and gain of 1p in Black EC tumors. In view of the predominance of males affected by ESSC globally (including the South African population), we looked for differences in gains and losses between tumors from males and females. A higher frequency of DNA copy number change was observed in males than in females. The Black males showed a marked increase in the frequency of gain and loss compared with Colored males. These frequencies of changes could be indicative of the high occurrence of EC in males and specifically in the Black male population of South Africa. Loss of chromosome 8p was identified in 28% of EC tumors, and this loss occurred in males only. In a CGH study on 16 gastric and esophageal adenocarcinomas, high level amplification of 8p, in contrast to our data of loss of 8p, was found (29). Recently, a putative prostate cancer tumor suppressor gene, identified on 8p22, has shown involvement in prostate, lung, liver, and colon carcinoma (38, 39).

Additional studies aimed at the detection of loss of 8p in precursor lesions, EAC tumors, and additional ESSC tumors of both sexes and both Black and Colored population groups may elucidate the possible role of this gene in male EC patients in South Africa. In the same context, the loss of Xp only occurred in five of nine tumors from the Black male patient population. The minimal common region of loss on Xp21–22.3 may therefore harbor a putative tumor suppressor gene(s) that may contribute to the pathogenesis and/or specific susceptibility of EC in the Black population. We found specific gain of 1p (proximal to the centromere) in 24% tumors from only Black males and females. Five of these seven tumors showed simultaneous loss of distal 1p, in contrast to loss of a more proximal 1p region in three tumors from Colored males at 1p13–22. Additional studies, using high density allelotypes, are needed to verify whether distinct genetic changes on chromosome 1p are involved in EC.

![Fig. 2. Average CGH ratio profiles indicating regions of high level amplification on: a, 2q24–33 in case 25; b, 6p21.1–q14 in case 18; c, 7q11.2–31 in case 9; d, 8q22–24.1 in case 6; e, 13q12–34 in case 18; f, amplification on 8q13–qter and loss of 8p in a tumor from a Colored male patient (case 1); g, average CGH ratio profile showing multiple DNA copy number gain of chromosome 5p in case 24; h and i, average ratio profiles of novel loss on chromosome 8p (case 7) and Xp (case 1), respectively.](#)
Other gains and losses occurred equally frequently in tumors from male and female patients. Chromosome 19p and 19q was underrepresented in 52 and 55% of EC tumors, respectively (12 of 17 representing entire loss). Candidate tumor suppressor genes on chromosome 19p13.1 include PTGER1. It is hypothesized that excess PGF2α could contribute to chronic irritation in the lower esophagus, which may ultimately contribute to cancer development (40). The biological effects of PGF2α are mediated through interaction with specific membrane-bound G protein-coupled prostaglandin EP receptors including PTGER1. Therefore, PTGER1 may play a role in deregulation of the signal transduction pathways, involving PGF2α (40, 41). Recent evidence to substantiate the role of prostaglandins in EC has emerged, in that the PTGS2 gene (located on 1q25) involved in epithelial cell growth regulation was found highly expressed in metaplastic Barrett’s and esophageal adenocarcinomas (42–44).

Loss of distal 1p occurred in a total of 41% EC tumors (3 of 15 tumors showed loss at a more proximal locus on 1p). The minimal common region of deletion encompasses the most distal band 1p33–pter, which is clearly distinct from the 1p22–33 region identified in EAC by cytogenetic analysis (28). Loss of chromosome band 1p36 is a frequent finding in many malignancies including neuroblastoma, colon cancer, and breast cancer (45). Loss of chromosome 4 short arm material was found in 52% of cases. The minimal common region for deletion was the most distal band 4p16. CGH studies on EC indicated loss of 4p at a more proximal region (29), which is in contrast to our study indicating a more distal region of loss. Similar losses at distal 4p have been described in subsets of neuroblastomas and in bladder cancer (46, 47). To our knowledge, no candidate tumor suppressor genes have been described in this region.

Loss on 18q was found in 48% of tumors, with a minimal common region of deletion at 18q21–ter. Whole chromosome 18 loss has been reported at a low frequency in EAC (28, 29). Possible candidate tumor suppressor genes located on chromosome 18q have been associated with EC, i.e., the deleted in colon cancer on 18q21.3 and two mothers against decapentaplegic-related genes, SMAD4/DPC4 on 18q21.1 and the SMAD2 on 18q21; however, discrepancies exist for their role in the etiology of EC (48–53).

Loss of 3p material was observed in 38% of tumors; the consensus region was defined as 3p23–pter. The shortest region of overlap of 3p deletion as defined by cytogenetic analysis was 3p14. In a LOH study of Chinese EC patients, two regions of allelic loss were reported, a distal region on 3p24 and a proximal region on 3p14.2 (1, 12). These regions coincide with consensus regions of loss 3p21–pter and 3p13–21.1 found in a CGH study of SCLC (54). The FHIT (55, 56), β-catenin (CTNNB1; Ref. 57), von Hippel-Lindau gene (58), and thyroid hormone receptor β (THRβ/ERβA2; Refs. 59 and 60) are some of the candidate tumor suppressor genes that have been identified on 3p, of which only the THRβ/ERβA2 and von Hippel-Lindau genes fall within our minimal common region of deletion. In a LOH study of EC tumors in China (12), distal 3p loss was associated with tumors from geographical areas with high incidences of EC, whereas proximal 3p loss occurred in tumors from low incidence areas. Our results of distal 3p loss in mainly ESSC tumors from Black and Colored patients of South Africa may therefore indicate a similar involvement of a specific tumor suppressor gene at this more distal 3p23–pter locus involved in EC in high risk areas.

The loss of chromosome 5q has been widely reported in EC and other cancers (11, 21). In our study, underrepresentation of 5q was found in 28% tumors at 5q14–21 and in 24% at 5q31–qter. A similar observation was made in SCLC (54), where two distinct regions of loss, 5q21–22 and 5q31–qter, were identified. Previous LOH studies on primary EC implicated the distal region of loss as important in the pathogenesis of EC (61). Our data therefore indicate that a more proximal region of loss on 5q, other than implied for SCLC, may exist in EC. Another region of loss was at 2q35–37 in 21% of cases, which could suggest the involvement of an as yet unknown tumor suppressor gene in EC. Recently, a putative cellular senescence gene on 2q37 has been identified in a human cervical carcinoma cell line (62).

The highest frequency of DNA gain occurred at chromosome 3q in 72% of tumors, at a minimal common region of 3q25–27. CGH studies have revealed a similar high incidence of 3q gain in other tumors, including Merkel cell carcinoma, SCLC, and squamous cell carcinoma of the head and neck (34, 63–65). The simultaneous gain of 3q and loss of 3p might indicate the formation of an isochromosome 3q, and this phenomenon is frequently found in alveolar rhabdomyosarcoma and other cancers. Recently, evidence for the role of an iso(3q) chromosome in cellular transformation was confirmed, whereby the concurrent duplication of ataxia-telangiectasia and rad3-related (ATR) locus resulted in limiting terminal differentiation, invoking aneuploidy, and abolishment of G1 arrest after DNA damage (66).

Preferential gain of chromosomal material at a minimal common region of 2q24–33 was found in 52% EC tumors. Trisomy 2 has been reported in several neoplasms, including hepatoblastoma, embryonal rhabdomyosarcomas, papillomas, and squamous cell carcinoma of the skin (67, 68). A recent report on sporadic and hereditary ovarian carcinomas stated the sole difference between the two forms as the frequent gain of 2q24–32 in inherited tumors, indicating the specific involvement of an oncogene located at 2q24–32 (69). In contrast, the gain of 2q in this region in our sporadic EC tumors may suggest the involvement of an oncogene in EC that is distinct from that implicated in ovarian carcinomas.

DNA overrepresentation of 1q occurred in 41% of EC tumors with a minimal common region at 1q24–31. Other cancers found by CGH to involve gain of 1q, include Merkel cell carcinoma, primary SCLCs, and squamous cell carcinomas of the head, neck, and larynx (1, 28, 32, 63, 64, 70, 71). The PTGS2/COX2 maps to this region and has been found highly expressed in esophageal adenocarcinomas and Barrett’s metaplasia (42–44).

Gain of 5p was demonstrated in 31% of EC tumors. Although no EC-associated genes have been localized to chromosome 5p, the PTGER2 maps to 5p13.1 (40, 41). The changes found by CGH in regions involving genes related to prostaglandin synthesis (e.g., PTGER1 on 19p, PTGS2/COX2 on 1q, and PTGER2 on 5p) may serve to further substantiate the role of prostaglandins in the etiology of EC.

High-level DNA amplification was observed for chromosomal regions 2q24–33, 6p21.1–q14, 7p12–q21, 7q11.2–31, 8q22–24, 13q1–qter, 13q21–34, and at 13q32–34, but none of these regions were involved in more than two tumors. Region 6p21.2–6q14 harbors the CCND3 gene, which shares 53.1% homology to CCND1. The CCND1 gene is amplified in 30% of EC (24). Two tumors showed high level amplification on 7p12–q21 (which harbors the EGFR and HGF genes) and on 7q11.2–31 (which harbors the HGFR/MET gene), and these genes have been implicated in EC (72–74). High-level amplification of 8q22–24.1 was found in one case and contained in this region is MYCC (8q24.1), which is often amplified in EC (23). Another region of high-level amplification was demonstrated in two EC tumors, respectively, on 13q21–ter and 13q32–ter. Recently, high-level amplification of a region on 13q14 was found in EAC, suggesting the possible involvement of the PAX3 in EC (29). The two cases with high level amplification on 13q exclude the PAX3 locus, and this gene is unlikely to be amplified in ESSC.

Furthermore, known regions of frequent gain, harboring oncogenes associated with EC, were seen, i.e., on chromosome 11q13 (INT-2, HST-1, CCND1/PRAD1; Ref. 24), 7p11–15 (EGFR; Ref. 22), 7q21.1 (HGF; Ref. 73), and 7q31 (HGF; Ref. 74). Likewise, regions show-
ing high frequency of loss, containing tumor suppressor genes implicated in EC, were noticed, i.e., on 9p (MTS1/CDKN2), 11p (WT1, KAI1), 13q (RB1), 17p (TP53), and 17q (ERBB2).

In conclusion, the present CGH study provides the first record of chromosomal imbalances occurring in EC tumors (predominantly ESSC) in the Black and Colored populations of South Africa. Two regions, Xp and 8p, were specifically implicated in EC tumors of the Black male population. This finding may lead toward an understanding of the striking sex-biased occurrence of EC observed globally. Regions of frequent gain and loss were observed, confirming known and identifying novel changes in the EC genome. The role of these apparent sex-biased and other specific chromosomal areas highlighted here, in relation to the etiology of EC, may be substantiated by extended analysis of genes putatively implicated in different EC subtypes and population groups in South Africa.

ACKNOWLEDGMENTS

We gratefully acknowledge the contribution of biological material from the CANSAMRC Esophageal Cancer Research Consortium. We also acknowledge J. Grobbelaar for assistance in this study.

REFERENCES


Mapping of Novel Regions of DNA Gain and Loss by Comparative Genomic Hybridization in Esophageal Carcinoma in the Black and Colored Populations of South Africa

Lana Du Plessis, Erin Dietzsch, Mireille Van Gele, et al.


Updated version  Access the most recent version of this article at:  
http://cancerres.aacrjournals.org/content/59/8/1877

Cited articles  This article cites 68 articles, 17 of which you can access for free at:  
http://cancerres.aacrjournals.org/content/59/8/1877.full#ref-list-1

Citing articles  This article has been cited by 6 HighWire-hosted articles. Access the articles at:  
http://cancerres.aacrjournals.org/content/59/8/1877.full#related-urls

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, use this link  
http://cancerres.aacrjournals.org/content/59/8/1877.  
Click on "Request Permissions" which will take you to the Copyright Clearance Center’s (CCC) Rightslink site.