Comparative genomic hybridization and chromosomal instability in solid tumours

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The rational development of new diagnostic or prognostic tumour markers and the identification of novel cellular targets for anticancer chemotherapy relies on a more definitive understanding of tumour biology. Classical approaches using cellular pharmacology, and more recently molecular pharmacology, have led to the discovery of a number of growth factors and their receptors as well as other proteins which has resulted in novel therapies (e.g. inhibitors of epidermal growth factor receptor tyrosine kinase) and prognostic markers (e.g. oestrogen receptor levels in breast cancer) (Levitzki et al, 1995; Dowsett et al, 1997). Using classical metaphase cytogenetic techniques, many chromosomal aberrations have been identified in human cancer cell lines and primary tumours. However, the use of metaphase cytogenetic analysis has been limited in solid tumours, mainly due to the difficulties in growing primary cultures in which to generate tumour metaphase chromosomes. However, this has changed with the development of comparative genomic hybridization (CGH) and its ability to globally assess the genome of solid tumours for areas of loss and/or gain without the need for tissue culture (Kallioniemi et al, 1992; Forozan et al, 1997; Ried et al, 1997). CGH involves a competitive in situ hybridization of fluorescently labelled tumour DNA and healthy control DNA to normal metaphase chromosomes (Figure 1). Computer-assisted fluorescence microscopy is then used to assess the intensity of fluorochrome across each human chromosome. The differences in tumour and control fluorescence intensity along each chromosome on the reference metaphase spread are a reflection of the copy number changes of corresponding sequences in the tumour DNA. If chromosomes or chromosomal subregions are present in identical copy number within both the tumour and the normal DNA, an equal contribution from each fluorochrome is seen. However, a change in the fluorescent signal is seen if certain chromosomal subregions are gained or lost in the tumour DNA (Figure 1). The intensity of this signal is proportional to the amount of gain and loss seen for each region in the tumour DNA (Kallioniemi et al, 1992; Forozan et al, 1997). Regions with a high level of heterochromatin and centromeric regions are not informative with CGH, CGH data for the p regions of acrocentric chromosomes (e.g. 13p, 14p and 15p) must be interpreted with caution as repetitive sequences in these regions can affect the efficiency of competitive hybridization. With current technology, CGH has a theoretical limit of detection for gain and loss of genetic material of 5–10 Mb. However, gain of DNA in regions as small as 50 kb have been described in situations where high level amplification has occurred (Ried et al, 1997).

Initial studies with CGH were restricted to DNA prepared from fresh or snap-frozen tumour material. More recently, technical advances have allowed the extraction of DNA from formalin-fixed paraffin-embedded sections through the use of degenerate oligonucleotide primed polymerase chain reaction (DOP-PCR) (Isola et al, 1994; Kuukasjarvi et al, 1997). The DOP-PCR technique allows genome-wide amplification of tumour DNA from nanogram quantities to the micrograms needed for CGH, and has enabled retrospective analysis of genomic loss and gain to be performed using DNA from archival material.

Although CGH analysis has been performed in a wide variety of adult and paediatric tumours, these results have not been extensively interpreted in the context of the CGH findings from other tumour types. In this review, the results of CGH analysis in 27 tumour types are evaluated to identify regions of loss or gain which are common to all malignancies as well as those which are specific for a given tumour type or tumour subtype. In addition, the degree of overall genomic instability for specific tumour types has been assessed.

REVIEW OF THE LITERATURE

The Institute for Scientific Information (ISI) database from March 1992 to August 1998 identified 100 papers which described CGH findings in 2210 solid tumours of 27 cancer types (Appendix). This included common tumours (colon, breast, lung), gender-specific tumours (ovarian, cervix, testicular, prostate), paediatric tumours (neuroblastoma, rhabdomyosarcoma) and less common tumours (brain, renal, uveal melanoma). For each paper, the patterns of loss and gain in the p and q arms of each chromosome were recorded separately. Such an approach may not always be sufficient, as variation in subregions of the same chromosomal arm could be masked in some cases. However, a narrower definition for regions of gain and/or loss was not possible due to differences in the way CGH results have been presented in the
literature. Studies of CGH in patients with leukaemia, lymphoma or studies with incomplete details of results for individual chromosomes were not included in this review. Cell line data were not included due to the difficulty in differentiating between initial chromosomal aberrations and those ‘acquired’ during cell culture. The frequency of overall loss or gain for each chromosome arm was determined by pooling the data from all tumours, from a given tumour type and from specific tumour subtypes.

**PATTERNS OF CHROMOSOMAL LOSS AND GAIN**

**Solid tumours**

The frequency of loss or gain for each chromosome arm was determined for all the solid tumours by pooling the data found in the literature for 2210 tumours (Table 1). Gain of chromosomal material was found more frequently than loss among the solid tumours.

![Diagram of CGH experiment](image)
tumours (mean 4.2 gain per tumour vs 3.1 loss per tumour). A variable pattern of chromosomal gain was observed, with the highest frequency of gain found in 8q (27.7%) and 1q (25.1%) (Table 1). This contrasts with chromosome 22p (0.3%) and 15p (0.4%) where gain of chromosomal material was rarely observed (Table 1). The most common regions of chromosomal loss were found on 13q (16.3% of all tumours), 9p (16.1%) and 8p (15.0%) (Table 1). Loss of chromosomal material was rarely seen on chromosome 21p (0.1%), 13p (0.4%) and 14p (0.5%). From Figure 2 it can be seen that levels of loss and gain are not uniform across all chromosomal regions. Certain chromosomal regions, such as 8q, are often gained (27.7%) but rarely lost (2.9%). Similarly, loss in chromosome 4q was more common (13.4%) than gain (5.3%). This pattern was not seen for all chromosomes, with loss of 13q (16.3%) only 1.8 times more common than gain (9.2%). Patterns of nearly equal frequency of loss and gain were also observed for chromosomes 14q (9% gain vs 8.2% loss) and 15q (7.8% gain vs 7.2% loss). However, this does not take into account the specific region of a chromosomal arm to which the genetic loss or gene amplification in solid tumours is mapped. It also does not account for tumour-specific patterns of chromosomal gain and loss (Table 2), where the same chromosomal arm is rarely lost and gained to an equal extent for a particular tumour type.

Table 1: Loss and gain for each chromosomal arm when available CGH data from 2210 tumours (including 27 different solid tumour types) were pooled

| Chromosomal region | Total tumour gain (%) n = 2210 | Chromosomal region | Total tumour loss (%) n = 2210 |
|--------------------|-------------------------------|--------------------|-----------------------------|
| 8q + gains         | 616                           | 13q – losses       | 363                          |
| 1q + gains         | 558                           | 9p – losses        | 357                          |
| 7q + gains         | 513                           | 8p – losses        | 333                          |
| 7p + gains         | 477                           | 10q – losses       | 304                          |
| 17q + gains        | 412                           | 3p – losses        | 297                          |
| 3q + gains         | 365                           | 4q – losses        | 297                          |
| 20q + gains        | 344                           | 6q – losses        | 296                          |
| 5p + gains         | 292                           | 17p – losses       | 260                          |
| 12q + gains        | 290                           | 18q – losses       | 245                          |
| 12p + gains        | 277                           | 1p – losses        | 226                          |
| 11q + gains        | 252                           | 11q – losses       | 218                          |
| 6p + gains         | 246                           | 5q – losses        | 206                          |
| 20p + gains        | 223                           | 10p – losses       | 202                          |
| 19q + gains        | 223                           | 16q – losses       | 196                          |
| 2p + gains         | 214                           | 8q – losses        | 188                          |
| 13q + gains        | 205                           | 22q – losses       | 184                          |
| 19p + gains        | 203                           | 14q – losses       | 183                          |
| 1p + gains         | 201                           | 9q – losses        | 170                          |
| 14q + gains        | 201                           | 11p – losses       | 167                          |
| 2q + gains         | 198                           | 15q – losses       | 161                          |
| 17p + gains        | 179                           | 7q – losses        | 153                          |
| 16p + gains        | 176                           | 8q – losses        | 152                          |
| 8p + gains         | 175                           | 9q – losses        | 126                          |
| 15q + gains        | 174                           | Xq – losses        | 122                          |
| 5q + gains         | 168                           | Y – losses         | 119                          |
| 6q + gains         | 164                           | 18p – losses       | 112                          |
| 9q + gains         | 156                           | 17q – losses       | 105                          |
| 18p + gains        | 153                           | 3q – losses        | 102                          |
| 16q + gains        | 140                           | 12q – losses       | 98                            |
| 18q + gains        | 136                           | 19q – losses       | 96                            |
| 22q + gains        | 133                           | 1q – losses        | 89                            |
| 10p + gains        | 131                           | 9q – losses        | 82                            |
| Xq + gains         | 129                           | 5p – losses        | 83                            |
| 9p + gains         | 116                           | 6p – losses        | 84                            |
| Xp + gains         | 115                           | 16p – losses       | 83                            |
| 3p + gains         | 104                           | 5p – losses        | 83                            |
| 21q + gains        | 101                           | 2p – losses        | 82                            |
| 11p + gains        | 97                            | 8q – losses        | 64                            |
| 4q + gains         | 95                            | 10q – losses       | 56                            |
| 10q + gains        | 117                           | 4q – losses        | 53                            |
| 9p + gains         | 116                           | 4.5               | 53                            |
| Xp + gains         | 115                           | 7p – losses        | 52                            |
| 3p + gains         | 104                           | 1p – losses        | 50                            |
| 21q + gains        | 101                           | 15p – losses       | 36                            |
| 11p + gains        | 97                            | 1p – losses        | 36                            |
| 4p + gains         | 95                            | 15p – losses       | 21                            |
| Y + gains          | 55                            | 14p – losses       | 21                            |
| 14p + gains        | 24                            | 13p – losses       | 10                            |
| 21p + gains        | 22                            | 13p – losses       | 9                             |
| 13p + gains        | 17                            | 15p – losses       | 9                             |
| 15p + gains        | 9                             | 22p – losses       | 3                             |
| 22p + gains        | 6                             | 0.3               | 0.1                           |

Total gains 9320/2210 4.2 per tumour Total losses 6988/2210 3.1 per tumour
Specific tumour types

The frequency of chromosomal loss and gain varied between the individual tumour types, ranging from multiple regions per tumour (average gains: head and neck 12.2 per tumour, testicular 8.2 per tumour; loss: liver 7.5 per tumour, prostate 4.5 per tumour) to relatively rare events (average gains: neuroblastoma 0.5 per tumour, Wilms’ 1.6 per tumour; loss: sarcoma 0.8 per tumour, Wilms’ 1.3 per tumour (Table 3). The specific chromosomal regions of loss and gain differ substantially between specific tumour types. For example, gain in chromosome 12p occurred in 96.3% of testicular cancers and 0% of renal cancers (Table 2). New information on chromosomal loss or gain (Table 1) can be further specified amongst the various tumour types. For example, gain in chromosome 8q occurred in 27.7% of all tumours evaluated. However, on closer examination, frequency of 8q gain was high in tumours of the testis (40.7%), ovary (42.8%) and endometrium (45.5%), but was rarely found in renal tumours (1.3%) and neuroblastoma (3.0%). There is no chromosomal arm which demonstrated a consistent pattern of gain for all tumour types. Similar findings were demonstrated for chromosomal loss. For instance, 9p was lost in 16.1% of all tumours, but varied from a high frequency event (cutaneous melanoma 58.2%, pancreas 50.1%, brain 36.3%) to low (colon 7.5%, gastric cancer 7%) depending on the tumour type (Table 2).

Specific tumour subtypes

For several tumours, CGH analysis was available for multiple histological subtypes (Table 4). This allowed assessment of both the frequency at which loss and gain occurred and the extent to which each specific chromosomal arm is involved for each subtype.

Colon

Information on genomic alterations in colon cancer was available for low- and high-grade adenoma, primary carcinomas, liver metastases, and also carcinomas for which replication error repair status was known (Table 4). Ried et al (1995) found the frequency and degree of genetic aberrations increases with progression from low-grade adenoma through high-grade adenoma to carcinoma (Table 4). For example, gain in chromosome 7p was 7.1% in low-grade adenoma, 33.3% in high-grade adenoma and 50% in carcinoma. Similarly, gain in chromosome 20q was not detected in low-grade adenoma, but was at 33.3% and 75% in high-grade adenoma and carcinoma respectively. The frequency of alterations also increased with tumour progression: 3/47 chromosomal arms in low-grade adenoma, 21/47 high-grade adenoma, 32/47 carcinomas. A separate study by Paredes-Zaglul et al (1998) comparing primary carcinomas and liver metastases from patients with colorectal cancer found that the frequency of alteration remained constant at ~ 35/47 chromosomal arms between these two stages. However, a change was noted in the extent to which these arms were involved. The most obvious change being the increase in loss of genetic material between primary tumour and liver metastases. For example, loss at 8p was 30% in primary carcinomas compared with 80% in metastases. Similarly, loss of 18q was found in 50% of primary cases, but 90% of liver metastases. Changes in gain did not always follow the same pattern seen for loss. An increase in genetic instability was seen for some chromosomal regions in the transition from primary to metastases (e.g. 13q was gained in 30% of primary tumours compared with 50% in metastases). However, this was not the case for other regions, such as 12q, which was gained in 20% of primary carcinomas, but was normal in liver metastases. A difference in genetic instability was also seen between tumours with intact mismatch repair genes compared to
Table 2  The ten most frequently lost and gained chromosomal regions for each tumour type studied. Percentage of tumours with alterations of the specific chromosomal arm are shown. Fewer than ten altered arms were found in MCC.

| CR   | GC   | H&N | CR   | Pancreas | CR   | Colon | CR   | Prostate | CR   | Testicular | CR   | Breast | CR   | Ovary | CR   | Cervical | CR   | C mel | MCC | CR mel | U mel | CR   | Renal |
|------|------|-----|------|---------|------|-------|------|----------|------|------------|------|--------|------|-------|------|---------|------|------|------|--------|------|-------|-------|
| Y    | 22.1 | 3p  | 53.2 | 9p  | 50.1  | 1q/2 | 31.3 | 8p  | 42      | 13q/2 | 33.3  | 17q  | 18.2 | 8p  | 26.6 | 15q  | 21.2 | 3p  | 50  | 9p  | 58.2 | 10q  | 33.3 | 3p  | 45.5 | 3p  | 39.1 |
| 4q   | 16.2 | 5q  | 42.6 | 18q | 47.8  | 17p  | 22.5 | 16q | 39      | 4q/6  | 26    | 11q  | 12.3 | 17p | 16.7 | 18q  | 12.1 | 2q  | 33.3 | 10q  | 44.8 | 11q  | 33.3 | 3q  | 45.5 | 13q | 27.2 |
| 1q/2 | 14.7 | 4p/4 | 40.4 | 6q/5 | 33.8 | 18p  | 15   | 16q | 21      | 26    | 11q  | 17.1 | 16q  | 16.3 | 14q | 12.1 | 6q  | 26.6 | 10p  | 28.3 | 6q  | 45.4 | 6q  | 20.5 |
| 1p   | 13.2 | 4q  | 32   | 21q | 30.4  | 4p/6 | 12.5 | 16q | 39      | 6q/2  | 22.2 | 6q  | 11.2 | 18q | 14.8 | 16q  | 9.1  | 1q  | 23.3 | 6q  | 25.3 | 9p  | 27.3 | 4q  | 17.9 | 8q  | 17.2 |
| 5q/2 | 9.0  | 13q | 30  | 26   | 31.2 | 17q  | 25.2 | 13q | 35      | 5q/6  | 18.5 | 13q  | 10.7 | 17q | 12.8 | 9p  | 9.1  | 4p/3 | 23.3 | 6q  | 25.3 | 11p | 27.3 | 1q  | 17.9 | 8p  | 17.2 |
| 5q   | 10.0 | 13q | 52  | 26   | 31.2 | 17q  | 25.2 | 13q | 35      | 5q/6  | 18.5 | 13q  | 10.7 | 17q | 12.8 | 9p  | 9.1  | 4p/3 | 23.3 | 6q  | 25.3 | 11p | 27.3 | 1q  | 17.9 | 8p  | 17.2 |
| 5q   | 10.0 | 13q | 52  | 26   | 31.2 | 17q  | 25.2 | 13q | 35      | 5q/6  | 18.5 | 13q  | 10.7 | 17q | 12.8 | 9p  | 9.1  | 4p/3 | 23.3 | 6q  | 25.3 | 11p | 27.3 | 1q  | 17.9 | 8p  | 17.2 |
| 5q   | 10.0 | 13q | 52  | 26   | 31.2 | 17q  | 25.2 | 13q | 35      | 5q/6  | 18.5 | 13q  | 10.7 | 17q | 12.8 | 9p  | 9.1  | 4p/3 | 23.3 | 6q  | 25.3 | 11p | 27.3 | 1q  | 17.9 | 8p  | 17.2 |
| 5q   | 10.0 | 13q | 52  | 26   | 31.2 | 17q  | 25.2 | 13q | 35      | 5q/6  | 18.5 | 13q  | 10.7 | 17q | 12.8 | 9p  | 9.1  | 4p/3 | 23.3 | 6q  | 25.3 | 11p | 27.3 | 1q  | 17.9 | 8p  | 17.2 |
| 5q   | 10.0 | 13q | 52  | 26   | 31.2 | 17q  | 25.2 | 13q | 35      | 5q/6  | 18.5 | 13q  | 10.7 | 17q | 12.8 | 9p  | 9.1  | 4p/3 | 23.3 | 6q  | 25.3 | 11p | 27.3 | 1q  | 17.9 | 8p  | 17.2 |
| 5q   | 10.0 | 13q | 52  | 26   | 31.2 | 17q  | 25.2 | 13q | 35      | 5q/6  | 18.5 | 13q  | 10.7 | 17q | 12.8 | 9p  | 9.1  | 4p/3 | 23.3 | 6q  | 25.3 | 11p | 27.3 | 1q  | 17.9 | 8p  | 17.2 |
| 5q   | 10.0 | 13q | 52  | 26   | 31.2 | 17q  | 25.2 | 13q | 35      | 5q/6  | 18.5 | 13q  | 10.7 | 17q | 12.8 | 9p  | 9.1  | 4p/3 | 23.3 | 6q  | 25.3 | 11p | 27.3 | 1q  | 17.9 | 8p  | 17.2 |
| 5q   | 10.0 | 13q | 52  | 26   | 31.2 | 17q  | 25.2 | 13q | 35      | 5q/6  | 18.5 | 13q  | 10.7 | 17q | 12.8 | 9p  | 9.1  | 4p/3 | 23.3 | 6q  | 25.3 | 11p | 27.3 | 1q  | 17.9 | 8p  | 17.2 |

CR = Chromosomal region; C mel = Cutaneous melanoma; Endo = Endometrial; H&N = Head and neck; MCC = Merkel cell carcinoma; Neuro = Neuroblastoma; Rhab = Rhabdomyosarcoma; GC = Gastric carcinoma; U mel = Uveal melanoma; OSCC = Oral squamous cell carcinoma; GISST = Gastrointestinal stromal tumours; GE = Gastro-oesophageal adenocarcinoma; Para = Parathyroid adenomas; Pit = Non-functioning pituitary; C mel = Cutaneous melanoma; Neuro = Neuroblastoma; Rhab = Rhabdomyosarcoma; GC = Gastric carcinoma; U mel = Uveal melanoma; OSCC = Oral squamous cell carcinoma; GISST = Gastrointestinal stromal tumours; GE = Gastro-oesophageal adenocarcinoma; Para = Parathyroid adenomas; Pit = Non-functioning pituitary; N endo = Sporadic neuroendocrine tumours of the digestive system. No distinction was made between oesophageal adenocarcinoma from Barrett’s mucosa and gastric adenocarcinoma arising at the fundus of the stomach. As a result, CGH data for GC and GE could not be merged.
those with deficient repair ability (Table 4). As expected, the tumours lacking repair function had a higher frequency of instability. For example, gain of 7p and 7q was seen in 33% of tumours with non-functioning repair genes, while these aberrations were absent in tumours with intact DNA repair phenotype. Although a relationship between genomic instability and both tumour progression and repair deficiency had been previously suggested, CGH has provided strong data to support this hypothesis in tumour specimens.

Ovary

Several studies have been published assessing the genomes of ovarian cancer cases. The available data were split into ovarian cancers derived from the epithelia and those derived from germ cells. Cancers of the epithelia were then further subdivided into sporadic and hereditary cases. The hereditary cases were defined as such based on BRCA1 and BRCA2 status. It is appreciated that some papers did not assess their cases for BRCA1 and BRCA2 and that a small percentage of the sporadic cases may have altered BRCA genes. Overall, however, this division of ovarian tumours has yielded some useful observations. Firstly, it was found that the frequency of genetic aberrations was greatest in the sporadic cases at 41/47 chromosomal arms, compared with 33/47 in hereditary cases and 30/47 in the germ cell tumours. The greatest level of concordance was at 1q and 8q where gains occurred at approximately 30% and 50%, respectively, in all three tumour types. Both hereditary and sporadic cases had a high degree of gain at 3q (40.6% in sporadic and 50% in inherited cases). This is in contrast to the same region being gained in only 5.3% of germ cell tumours. However, all three tumour subtypes are likely to have some common genetic origin based on the observation that regions such as 1q and 8q are gained to an equal extent in all ovarian cancer types so far studied by CGH.

Prostate

The data on prostate cancer allowed comparison of CGH results in patient cohorts with primary resected carcinomas or tumours that recurred after hormone therapy. It has been speculated that further genetic damage allows a subclone of tumour cells to acquire resistance to chemotherapy and such studies can test this hypothesis. Very little change in the frequency of genetic aberration between primary carcinoma and recurrent carcinoma was seen (39/47 in primary vs 42/47 in recurrent). However, differences were seen in the degree of genetic aberration when specific chromosomal regions were considered. For example, gain in chromosome 8q was seen in 25.9% primary carcinomas compared with 73.9% in recurrent cases. Similarly, 19p was lost in 3.7% of primary tumours and 34.8% in recurrent cases. Gain in the region containing the androgen receptor gene, Xp, increased from 7.4% in primary tumour to 28.3% in patients with recurrent disease. This is consistent with androgen receptor gene amplification as a mechanism of resistance to hormone therapy. However, this was not always the case with some regions of the genome only slightly changed in the degree of the aberration between primary and recurrent. For example, 3p was lost in 1.9% of primary tumours and 4.3% in recurrent cases. Generally, the data support the hypothesis that increased tumour aggression is the phenotype of a more unstable genome.

### Table 3

The number of altered chromosomal arms observed among the different tumour types

| Cancer type            | Gains/tumour | Losses/tumour | Total instability (loss + gain) per tumour |
|------------------------|--------------|---------------|-------------------------------------------|
| Gastric carcinoma      | 365/68       | 128/68        | 7.3                                       |
| Gastrointestinal stromal | 52/32        | 71/32         | 8                                          |
| Head and neck          | 588/47       | 245/47        | 17.7                                      |
| Pancreatic             | 231/51       | 188/51        | 8.2                                       |
| Colorectal             | 204/80       | 190/80        | 5                                         |
| Prostate               | 312/100      | 447/100       | 7.6                                       |
| Testicular             | 337/41       | 171/41        | 12.4                                      |
| Breast                 | 752/187      | 549/187       | 6.9                                       |
| Ovarian                | 1136/203     | 499/203       | 8.1                                       |
| Endometrial            | 186/33       | 50/33         | 7.1                                       |
| Cervical               | 163/30       | 124/30        | 9.5                                       |
| Cutaneous melanoma     | 203/67       | 227/67        | 6.4                                       |
| Merkel cell carcinoma  | 23/3         | 13/3          | 12.3                                      |
| Uveal melanoma         | 23/11        | 27/11         | 4.6                                       |
| Renal                  | 346/151      | 530/151       | 5.8                                       |
| Bladder                | 222/96       | 278/96        | 5.2                                       |
| Wilms’                 | 89/54        | 71/54         | 2.9                                       |
| Connective tissue sarcoma | 530/193    | 154/193       | 3.5                                       |
| Rhabdomyosarcoma        | 158/224      | 61/24         | 9.1                                       |
| Lung                   | 845/142      | 599/142       | 10.2                                      |
| Liver                  | 201/43       | 322/43        | 12.2                                      |
| Neuroblastoma          | 56/118       | 439/118       | 4.2                                       |
| Brain                  | 1152/325     | 1076/325      | 6.8                                       |
| Gastro-oesophageal      | 100/15       | 50/15         | 10                                        |
| Parathyroid            | 36/53        | 121/53        | 9.5                                       |
| Plituary               | 92/23        | 22/23         | 8.2                                       |
| Neuroendocrine*        | 162/20       | 57/20         | 11                                        |

*Sporadic neuroendocrine tumours of the digestive system.
Connective tissue tumours

CGH data were available for several tumour types (liposarcoma, alveolar soft part sarcoma, osteosarcoma, Ewing’s, rhabdomyosarcoma and osteochondroma). Unlike the other subtypes discussed (colon, ovary and prostate), tumours of the connective tissue are found in many different sites throughout the body. Considering the frequency of genetic aberration, the widest range of variation between subtypes among any tumour type in the literature is observed in the sarcomas. At one end of the spectrum a study on osteochondromas reports no genetic aberrations in 15 cases of this benign tumour type (Larramendy et al, 1997). Such a paper is unique in the CGH literature as all other investigations report some genomic change detectable by CGH. The alveolar soft part- and osteosarcomas show low to moderate frequency of genetic aberration at 14 and 19 out of 47 chromosomal arms respectively. While the other subtypes showed moderate to high numbers of arms involved (range 28–38 of 47). Another unique observation in the CGH literature was seen in an osteosarcoma study where only gain of genetic material was detected (Forus et al, 1995). Caution must be exercised when interpreting such results as it is unlikely that this cancer is the exception where no loss of genetic material is required for its development. More likely any loss, such as that of a tumour suppressor gene, is below detection by CGH.

| Tumour type            | Colon† | Hga | Carcinoma | Min– | Min+ | Primary | Metastases |
|------------------------|--------|-----|-----------|------|------|---------|------------|
| CR                     | Iga    | Hga | n=14      | n=12 | n=16 | n=6     | n=12       | n=10      | n=10     |
| 7p                     | 7.1    | 33.3| 50        | 0    | 33.3 | 10      | 10         |
| 7q                     | 0      | 25  | 31.3      | 0    | 33.3 | 30      | 30         |
| 8p                     | 0      | 0   | 0         | 0    | 0    | 10–30   | 10–80      |
| 12q                    | 0      | 8.3 | 6.3       | 0    | 0    | 20      | 0          |
| 13q                    | 0      | 8.3 | 50        | −16.7| 41.7 | 30–10   | 50         |
| 18q                    | 0      | −16.7| −37.5   | 0    | −25  | −50     | −90        |
| 20q                    | 0      | 33.3| 75        | 0    | 25   | 50      | 40         |
| Involved arms          | 5/47   | 21/47| 32/47     | 3/47 | 34/47| 35/47   |

| Tumour type            | Ovary | Sporadic* | Inherited | OGCT |
|------------------------|-------|-----------|-----------|------|
| CR                     |       | n=148     | n=20      | n=19 |
| 1q                     | 34.8±0.7| 30        | 31.6      |
| 2q                     | 18.1±1.4| 50±5      | 0         |
| 3q                     | 40.6   | 50        | 5.3±5.3   |
| 8q                     | 52.9±0.7| 55        | 42.1      |
| 21q                    | 5.8±7.2| 0         | 47.4      |
| Involved arms          | 41/47 | 33/47     | 30/47     |

| Tumour type            | Prostate | Primary | Recurrent |
|------------------------|-----------|---------|-----------|
| CR                     |           | n=54    | n=46      |
| 3p                     | −1.9      | 4.3±4.3 |           |
| 7p                     | 3.7       | 34.8±2.2|           |
| 7q                     | 13±1.9    | 34.8±2.2|           |
| 8p                     | −46.5     | 8.7±60.9|           |
| 8q                     | 25.9      | 73.9    |           |
| 13p                    | 7.4±3.7   | −34.8   |           |
| Xp                     | 7.48±1.9  | 28.3±8.7|           |
| Xq                     | 14.8      | 15.2±6.5|           |
| Involved arms          | 39/47     | 42/47   |

| Tumour type            | Sarcoma | RMS-E | RMS-A | Liposarcoma | ASPS | Ewing’s |
|------------------------|---------|-------|-------|-------------|------|---------|
| CR                     | RMS-A   | n=14  | n=14  | n=14        | n=13 | n=20    |
| 2p                     | 0       | 50    | 50    | 0           | 0    | 5       |
| 6p                     | 28.6    | 0     | 7.1   | 0           | 0    | 10      |
| 2q                     | 17.1    | 60    | −14.3 | 14.3        | 0    | 5       |
| 13q                    | 14.3    | 60±10 | 35.7±7.1| 7.1±21.4 | 0   | 5       |
| 16q                    | 0       | 2±20  | 7.1±7.1| −7.7       | 56±5|
| Involved arms          | 19/47   | 38/47 | 35/47 | 38/47       | 14/47| 28/47   |

In several tumour subtypes both loss and gain were observed on the same chromosomal arm. Variation in the number of chromosomal arms involved in genetic instability was also observed between subtypes. *Contains tumours which were not evaluated for BRCA1 and BRCA2 status. †represents data from three separate studies evaluating tumour progression, microsatellite instability and metastasis respectively. CR = chromosomal region; Iga = low-grade adenoma; Hga = high-grade adenoma; OGCT = ovarian germ cell tumours; Min+ = without microsatellite instability; Min− = with microsatellite instability; RMS-E = rhabdomyosarcoma embryonal; RMS-A = rhabdomyosarcoma alveolar; ASPS = alveolar soft part sarcoma.
with alveolar rhabdomyosarcoma (Weber-Hall et al, 1996). For example, a sub-chromosomal region of 13q is gained in 60% and lost in 10% of embryonal, while the same region is gained in 35.7% and lost in 7.1% of alveolar, rhabdomyosarcomas. The exception is 2p, which is lost in 50% of cases in both subtypes. Comparing both subtypes of rhabdomyosarcoma with other sarcomas it is observed that a gain of 2q is not present in a high proportion in all sarcomas. In fact no change in 2q is detected in liposarcoma or alveolar soft part sarcoma and gain in Ewing’s sarcoma is detected in less than 10% of all cases. This pattern of a certain chromosomal region commonly occurring in a specific subtype, but not in any other, continues for many chromosomal regions, suggesting that sarcomas are very distinct in terms of their genetic origin, with each subtype having its own marker chromosomal aberrations. This may be due to the variation in tissue type in which these tumours arise. No single chromosomal aberration was found to be present in a high proportion of all sarcomas.

PATTERNS OF GENOMIC IMBALANCE OR INSTABILITY IN SOLID TUMOURS

The degree of genomic imbalance detectable by CGH differs significantly between the various solid tumours (Table 3). Chromosomal gain varied from 0.5 to 12.5 chromosome arms per tumour with a median of 4.5, while loss varied from 0.8 to 7.5 chromosomal arms per tumour with a median of 3.3. Total instability (chromosomal loss + chromosomal gain per number of tumours) was highest in head and neck tumours (17.7 lesions per tumour) and testicular (12.4 lesions per tumour) and lowest in Wilms’ (2.9 lesions per tumour) and sarcoma (3.5 lesions per tumour) tumours. These frequencies represent an overall value for each specific tumour type, as information on the chromosomal alterations found within an individual tumour was not available in most literature reports of CGH in human solid tumours. Difference in the degree of loss or gain was also observed between the various solid tumours (Table 3). For example, chromosomal gain was observed more frequently than loss in the sarcomas and endometrial tumours, while loss was more frequently observed for renal and liver tumours. It is unknown whether these patterns represent coincidental changes from generalized genomic instability or suggest that some cancers are more likely to be influenced by the loss of tumour suppressor genes (genomic loss), while others are more frequently influenced by oncogene over expression (genomic gain). In addition, several studies have identified an association between the acquisition of genetic aberrations and patient survival (Iwabuchi et al, 1995; Tanner et al, 1995). However, there are discrepancies in this association found in Table 3, and any correlations between biological markers and patient survival need to be interpreted cautiously in the context of modern therapy.

COMPARISON WITH SOLID TUMOUR KARYOTYPE ANALYSIS

Classical karyotyping of metaphase chromosomes has been successfully performed for some solid tumours. A recent review reported the frequencies and distribution of chromosomal imbalances detected in 3185 solid tumours from 11 tumour types using chromosomal banding (Merkel et al, 1997). Overall, deletions were more common than gains in this analysis. Our review has found the opposite, with gains more commonly detected by CGH than losses. This difference may reflect the difficulties with using tumour karyotyping to identify the chromosomal changes that have occurred in tumours with highly complex rearrangements and will be influenced to some extent by amplified segments being hidden among unidentified marker chromosomes. CGH should be more sensitive for the detection of the presence of gains than losses and therefore the discrepancies with the above study are likely to reflect technical limitations of the two methods. By restricting analysis to common alterations (i.e. the gain or loss was detected in at least 15% of the tumours studied for that particular tumour type), the classical karyotyping studies described fewer regions of gain and loss than CGH for every tumour type evaluated. CGH appeared to identify the same alterations described using the karyotyping approach (with the exception of balanced translocations which are not detectable by CGH), but also observed additional regions of loss or gain. For example, only two regions of gain were detected in ovarian carcinoma by traditional cytogenetic analysis compared with 26 regions of gain seen by CGH. However, there have been too few studies of solid tumour cytogenetics using both CGH and chromosome banding for any firm conclusions regarding concordance between the two techniques. Nevertheless, the accumulating body of evidence in the literature suggests that CGH is more sensitive than other current technologies available for global assessment of loss and/or gain in solid tumour genomes.

CONCLUSION

From this review, it is apparent that no specific chromosomal imbalances are found in all cancers, with the most frequently identified regions of gain or loss occurring in 27.7% and 16.3% of tumours respectively. This reflects the heterogeneity in genomic alterations identified in different tumour types. In addition, much variation within tumour subtypes was observed.

The development of CGH has provided the technology to identify many new areas of genomic alteration which were not previously recognized to be altered in tumorigenesis. This has now expanded the number of areas of the genome for which more detailed molecular study is required to give a clearer more complete understanding of cancer biology.

Other areas where CGH could potentially make a significant contribution include its application in tumour diagnosis, as a prognostic tool, or for investigations into chemoresistance. The ability to assess the entire genome in a single experiment makes this technique potentially useful as an adjunct to routine histopathology. Several studies have established the feasibility of using CGH to detect genomic regions involved in the acquisition of resistance in human cancer cell lines and have detected novel regions of the genome not previously recognized to be involved in drug resistance (du Manoir et al, 1997; Wasenius et al, 1997; Leyland-Jones et al, 1998; Rooney et al, 1998). This provides the impetus to apply CGH to human tumour specimens in the context of modern drug therapy to assess its role in optimizing patient treatment.

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British Journal of Cancer (1999) 80(5/6), 862–873
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British Journal of Cancer (1999) 80(5/6), 862–873

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