

A practical guide to

Human cancer genetics

Second edition

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and

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Chromosomes and cancer

Boveri (1914) suggested that chromosome abnormalities were responsible for the transformation of normal to malignant cells. However, confirmation of this hypothesis had to wait until the development of modern cytogenetic techniques. In 1960, the first consistent chromosome abnormality in human cancer, the Philadelphia chromosome in chronic myeloid leukaemia, was identified by Nowell and Hungerford (1960). Thereafter, a huge number of numerical and structural chromosome changes were described in a wide variety of cancers. In many cases (except for the Philadelphia chromosome) these changes appeared to be random, non-specific findings and further progress was slow until the development of chromosome banding techniques (Heim and Mitelman, 1987). These techniques allowed the identification of individual chromosomes, and the definition of specific abnormalities in individual tumour types. Recent advances in molecular genetics have allowed the molecular pathology of specific chromosome abnormalities (e.g. Philadelphia chromosome) to be defined. Cytogenetics now plays an important role both in cancer research and in the clinical management of cancer patients: it can identify those areas of the genome which contain cancer-related genes and, in some cancers such as leukaemia, provides clinical prognostic information. In addition to cytogenetic analysis of tumour cells, the detection of patients with constitutional chromosome abnormalities and a predisposition to cancer has important research and clinical applications. In the following sections, each of these aspects is discussed in general terms.

Tumour cytogenetics

Chromosomal analysis of human cancer cells has yielded a huge amount of information about the incidence and nature of chromosomal abnormalities in malignant cells (Mitelman et al., 1997). Haematological malignancies, particularly leukaemias, are the best studied, and analysis of these tumours has yielded significant clinical–cytogenetic correlations which have been of diagnostic and prognostic importance. Cytogenetic examination of solid tumours is technically more difficult and for some human cancers information is sparse. However, advances in culture techniques and methods of analysis are increasing the success rate for analysis of solid tumours. It is now clear that although there is a wide variety of cancer-related

cytogenetic abnormalities, these are non-randomly distributed throughout the genome. Mitelman (1986) found in a survey of more than 5000 tumours that chromosome abnormalities were clustered in specific areas of the genome. This implied that these areas contained cancer-related genes and that there was a relatively small number of such genes.

Chromosome aberrations in human cancer may be divided into primary and secondary. Primary chromosome aberrations are directly related to the genesis of cancer, are frequently found as the sole abnormality, and are often specifically associated with particular tumours. Secondary chromosome aberrations are rarely the only abnormality, and occur in the presence of the primary change. Secondary abnormalities may be epiphenomena or may determine the biological behaviour of the tumour, including invasion, metastasis and response to therapy. Primary abnormalities would be expected to occur early in tumorigenesis, whereas secondary changes would become more frequent in the later stages. Secondary chromosome aberrations, although not specific, do not occur randomly and their occurrence may depend on the primary aberration and the particular tumour type involved. A partial list of well-established primary chromosome aberrations in human cancer is given in Table 1.1. A comprehensive map of recurrent chromosomal rearrangements in haematological malignancies and solid tumours has been described by Mitelman et al. (1997). Some chromosome aberrations are discussed in more detail under the relevant tumour type in Part two of this book. The type of chromosome aberration may be classified into three groups: (i) deletion of part of or an entire chromosome (this might inactivate tumour suppressor genes); (ii) translocation (this may activate an oncogene (see below) or inactivate a tumour suppressor gene); and (iii) gain of chromosomal material (this might promote cell proliferation by amplification of an oncogene or interfere with normal cell development by a dose-dependent effect). A discussion of oncogenes and tumour suppressor genes follows.

Constitutional chromosome abnormalities and cancer

These may be divided into two groups: (i) cancer predisposition associated with numerical or structural abnormalities of chromosomes, and (ii) chromosome breakage syndromes. Examples of the first group are shown in Table 1.2. In some cases, the molecular pathology of the chromosome rearrangement has been delineated and a translocation or deletion has been demonstrated to inactivate a tumour suppressor gene, as in *del(11p13)* and the Wilms' tumour (*WT1*) gene. Indeed, the identification of constitutional chromosome rearrangements in people who have a familial cancer syndrome has been important in the mapping and cloning of the retinoblastoma, neurofibromatosis type 1 (NF1) and Wilms' tumour genes. For the patients and their families, the detection of such a chromosome rearrangement allows carriers to be

Table 1.1. *Examples of primary chromosomal aberrations in human neoplasia*

Key:

ALL = acute lymphoblastic leukaemia, AML = acute myeloid leukaemia, CLL = chronic lymphoblastic leukaemia, CML = chronic myeloid leukaemia, MDS = myelodysplastic syndrome, NHL = non-Hodgkin's lymphoma.

| Region or band | Type of aberration | Disease |
|---------------------|----------------------------------|---------------------------|
| Chromosome 1 | | |
| 1p36 | t(1;;3)(p36;q21) | AML, MDS |
| 1p36-p32 | Deletions, translocations | Neuroblastoma |
| 1p32 | t(1;11)(p32;q23) | ALL |
| 1q21 | t(1;11)(q21;q23) | AML-M4,M5 |
| 1q23 | t(1;19)(q23;p13) | ALL |
| Chromosome 2 | | |
| 2p12 | t(2;8)(p12;q24) | NHL |
| 2q35 | t(2;13)(q35;q14) | NHL |
| Chromosome 3 | | |
| 3p23-p14 | del(3)(p14p23) | Small cell lung carcinoma |
| 3p26-p14 | Deletions | Renal cell carcinoma |
| 3q21 | t(1;3)(p36;q21) | AML, MDS |
| 3q21, 3q26 | inv(3)(q21q26) t(3;3)q21;q26) | AML, MDS AML |
| 3q25 | t(3;5)(q25;q34) | AML |
| 3q27-q28 | t(3;12)(q28;q15) | Lipoma |
| Chromosome 4 | | |
| 4p16-q35 | Trisomy | AML |
| 4q21 | t(4;11)(q21;q23) | ALL |
| Chromosome 5 | | |
| 5q12-q35 | Deletions | AML, MDS |
| 5q32-q34 | t(3;5)(q25;q34-35) | AML |
| 5q35 | t(2;5)(p23;q35) | NHL |
| Chromosome 6 | | |
| 6p25-q27 | Trisomy | MDS |
| 6p21 | Deletion | NHL |
| 6q22-q25 | del(6)(q21q25) | ALL, NHL |

Table 1.1. (*cont.*)

| Region or band | Type of aberration | Disease |
|----------------------|--------------------------------|--|
| Chromosome 7 | | |
| 7p22-q36 | Deletion | AML, MDS, myeloproliferative disorder |
| 7p22-q36 | Trisomy | Adenocarcinoma colon and kidney |
| 7p15 | t(7;11)(p15;p15) | AML |
| 7q21 q31 | deletion (7)(q21q32) | Uterine leiomyoma |
| 7q11-q36 | Deletion | AML |
| | del(7)(q22) most common | MDS |
| Chromosome 8 | | |
| 8p23-q24 | Trisomy | ALL, AML, MDS Myeloproliferative disorder Polycythaemia vera |
| 8p11 | t(8;16)(p11;p13) | AML-M5 |
| 8q22 | t(8;21)(q22;q22) | AML-M2 |
| 8q24 | t(2;8)(p12;q24) | NHL |
| | t(8;14)(q24;q11) | T-ALL |
| | t(8;14)(q24;q32) | ALL, NHL, ALL |
| | t(8;22)(q24;q11) | NHL |
| Chromosome 9 | | |
| 9p21 | del(9)(p21) | ALL |
| | t(9;11)(p22;q23) | AML-M4 and M5 |
| 9p12-p11 | t(9;12)(p11-12;p12) | ALL |
| 9p11-q11 | dic(9;12)(p11;p12) | ALL, B-lineage |
| 9q11-q32 | Various interstitial deletions | AML |
| 9q34 | t(6;9)(p23;q34) | AML |
| | t(9;22)(q34;q11) | CML, ALL, AML |
| Chromosome 10 | | |
| 10p15-q26 | Trisomy | Carcinoma kidney and uterus |
| 10q11 | inv(10)(q11q21) | Thyroid cancer (papillary) |
| 10q24 | t(10;14)(q24;q11) | ALL |
| Chromosome 11 | | |
| 11p15-q25 | Duplication | AML, MDS |
| 11p15 | t(7;11)(p15;p15) | AML |
| 11p13 | del(11)(p13p13) | Wilms' tumour |
| | t(11;14)(p13;q11) | T-ALL |
| 11q13 | t(11;14)(q13;q32) | Chronic lymphoproliferative disorder, NHL |

Table 1.1. (*cont.*)

| Region or band | Type of aberration | Disease |
|----------------------|--|---|
| 11q14-q23 | Deletion del(11)(q23) most common | AML |
| 11q23 | t(11;19)(q23;p13) | ALL, AML |
| | t(4;11)(q21;q23) | ALL |
| | t(9;11)(p22;q23) | AML |
| 11q24 | t(11;22)(q24;q12) | Ewing's sarcoma |
| Chromosome 12 | | |
| 12p13-q24 | Trisomy | CLL, chronic lymphoproliferative disorder, germ cell tumour, uterine leiomyoma, NHL |
| 12p13-p11 | del(12)(p13-p11) del(12)(p12) most common | ALL, AML, MDS |
| 12q13 | t(12;16)(q13;p11) | Liposarcoma (myxoid) |
| 12q14-q15 | t(12;14)(q15;q24) | Uterine leiomyoma |
| Chromosome 13 | | |
| 13p13-q34 | Trisomy | AML |
| 13q11-q34 | Deletions del(13)(q12q14) most common | ALL, MDS, myeloproliferative disorder |
| 13q14 | t(2;13)(q35;q14) | Rhabdoid sarcoma |
| 13q14 | del(13)(q14q14) | Retinoblastoma |
| Chromosome 14 | | |
| 14p13-q32 | Trisomy | Myeloproliferative disorder |
| 14q11 | t(11;14)(p13;q11) | T cell-ALL |
| | t(8;14)(q24;q11) | T cell-ALL |
| | t(10;14)(q24;q11) | T cell-ALL |
| 14q11,14q32 | inv(14)(q11q32) | T cell-CLL, T cell chronic lymphoproliferative disorder, NHL |
| 14q11-q32 | Deletion | NHL |
| 14q32 | t(14;18)(q32;q21) | NHL |
| | t(8;14)(q24;q32) | ALL, Burkitt's lymphoma, NHL |
| | t(11;14)(q13;q32) | Chronic lymphoproliferative disease, NHL |
| Chromosome 15 | | |
| 15q22 | t(15;17)(q22;q12) | AML |

Table 1.1. (*cont.*)

| Region or band | Type of aberration | Disease |
|----------------------|--------------------------|---|
| Chromosome 16 | | |
| 16p13 | t(8;16)(p11;p13) | AML |
| 16p13, 16q22 | inv(16)(p13q22) | AML-M4EO |
| 16p11 | t(12;16)(q13;p11) | Liposarcoma (myxoid) |
| 16q22 | del(16)(q22) | AML-M4EO |
| | inv(16)(p13q22) | AML-M4EO |
| Chromosome 17 | | |
| 17p13-q25 | Deletion | CLL |
| 17p11-q11 | i(17q) | AML, chronic lymphoproliferative disease, MDS, myeloproliferative disorder |
| 17q11-q12 | t(15;17)(q22;q11-q12) | AML-M3 |
| Chromosome 18 | | |
| 18p11-q23 | Deletion | Chronic lymphoproliferative disorder |
| 18p11-q23 | Trisomy | CLL |
| 18q11 | t(X;18)(p11;q11) | Synovial sarcoma |
| 18q21 | t(14;18)(q32;q21) | NHL |
| Chromosome 19 | | |
| 19p13-q13 | Trisomy | AML, MDS |
| 19p13 | t(1;19)(q23;p13) | ALL |
| | t(11;19)(q23;p13) | ALL, AML |
| Chromosome 20 | | |
| 20q11-q13 | del(20)(q11-13) | AML, MDS, myeloproliferative disease |
| | del(20)(q11) most common | Polycythaemia vera |
| Chromosome 21 | | |
| 21p13-q22 | Deletion | AML |
| 21p13-q22 | Trisomy | ALL, AML, CLL, MDS, myeloproliferative disorder |
| 21q22 | t(8;21)(q22;q22) | AML-M2 |
| Chromosome 22 | | |
| 22p13-q13 | Deletion | Meningioma, neurinoma |
| 22p13-q13 | Trisomy | AML |
| 22q11 | t(8;22)(q24;q11) | ALL, Burkitt's lymphoma |
| | t(9;22)(q34;q11) | CML, AML, ALL, MDS, myeloproliferative disease |

Table 1.1. (*cont.*)

| Region or band | Type of aberration | Disease |
|---------------------|--------------------|-----------------------|
| 22q11-q13 | del(22)(q11-q13) | Meningioma |
| 22q12 | t(11;22)(q24;q12) | Ewing's sarcoma |
| Chromosome X | | |
| Xp22-q28 | Deletion | Astrocytoma, MDS, NHL |
| Xp22-q28 | Trisomy | NHL |
| Xp11 | t(X;18)(p11;q11) | Synovial sarcoma |

Table 1.2. *Examples of constitutional chromosome abnormalities associated with cancer predisposition. (Further details under specific tumours in Part two)*

| Location | Abnormality | Cancer/syndrome |
|----------|-----------------|---|
| 3p13-14 | t | Renal cell carcinoma |
| 5q21-22 | del, t | Colon cancer (adenomatous polyposis coli) |
| 11p13 | del | Wilms' tumour (WAGR syndrome) |
| 11p15 | dupl | Beckwith–Wiedemann syndrome |
| 13q | t, del | Retinoblastoma |
| 17q | t | Neurofibromatosis 1 |
| 21 | trisomy | Leukaemia |
| 22 | ring | Meningioma |
| X | 47XXY | Breast |
| Y | 45X/46XY mosaic | Gonadoblastoma |

offered screening for asymptomatic tumours and genetic counselling (including discussion of the risks of offspring having unbalanced chromosome rearrangements). Indications for chromosome analysis in an individual with an inherited cancer syndrome or early-onset multiple tumours include associated mental retardation or recurrent miscarriages.

Fragile sites are codominantly inherited locations at which chromosomal gaps and breaks occur non-randomly. Although fragile sites, cancer chromosome breakpoints and oncogenes cluster in specific regions of the genome (Hecht, 1988), there is no convincing evidence of a causal relationship between cancer predisposition and a specific fragile site.

The chromosome breakage syndromes constitute a group of disorders characterised by genomic instability that can be recognised by increased spontaneous

chromosome breakage in cultured cells. Diseases in this category include Bloom syndrome, ataxia telangiectasia, Fanconi's anaemia, Werner's syndrome, xeroderma pigmentosum and Nijmegen breakage syndrome (see Part three). The pattern of chromosome breakage is specific for each disorder: in Bloom's syndrome there is an increased incidence of homologous sister and non-sister chromatid exchanges; in ataxia telangiectasia there is an increased incidence of chromosome rearrangements (typically involving chromosome 14) but sister chromatid exchanges are normal; Fanconi's anaemia is associated with an increased incidence of chromatid breaks, gaps and exchanges; Werner's syndrome is characterised by clonal expansion of chromosomally rearranged fibroblasts in long-term culture; and in xeroderma pigmentosum the frequency of chromosomal aberrations is not elevated under baseline conditions, but is elevated with ultraviolet irradiation.