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Cytogenetic biomarkers for human cancer

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1. ABSTRACT

Human cancer cytogenetics is the study of chromosomal rearrangements and numerical abnormalities in malignant tissue. Since the 1960s and the discovery of the Philadelphia chromosome, hundreds of common and characteristic chromosomal aberrations have been observed in various neoplasias. Because these cytogenetic aberrations provide diagnostic, prognostic, and treatment-related information for the associated cancers, they are considered biomarkers for disease. Here we describe many of the best-known chromosome rearrangements and variant rearrangements in hematologic disease and solid tumors, indicate the genes and underlying molecular mechanisms known to be involved in development and progression of disease, and describe the newer molecular cytogenetic technologies and how they are currently being used in cancer diagnostics. We also highlight many important pit-falls in obtaining, transporting, and analyzing neoplastic samples which can compromise cytogenetic studies and preclude its use as a diagnostic tool.

2. INTRODUCTION

Cancer is a genetic disease characterized by DNA changes at either the nucleotide or chromosomal level, or both. Malignancies can develop either from a genetic predisposition followed by acquired somatic mutations, or from an accumulation of somatic mutations that develop into a cancer phenotype. At the chromosome level, these mutations include changes in chromosome number, loss of heterozygosity (LOH, whole chromosome or segmental region loss), chromosomal rearrangements (translocations and inversions), and gene amplification. Many of these cytogenetically visible and cryptic (submicroscopic) aberrations are characteristic for a particular disease or disease subtype. Because characteristic chromosomal aberrations provide diagnostic, prognostic, and/or treatment information for many cancers, they are in many ways true biomarkers for human cancer.

There are three main types of cytogenetic aberrations in human cancer: 1) gain or loss of whole

chromosomes (aneuploidy), or part of a chromosome (segmental aneuploidy), 2) apparently balanced chromosomal rearrangements (translocations or inversions), and 3) loss of heterozygosity (LOH). These three types of chromosomal aberrations typically cause cell overgrowth through over-expression/activation of an oncogene, or by deletion of a tumor suppressor gene.

Chromosomal aneuploidy is extremely common in cancer, and can be either a primary or secondary event. Chromosomal gains (whole or partial) are designated in the karyotype with "+" or "add," and typically result in the over-expression of an oncogene. Supernumerary marker chromosomes (SMCs), double minutes, and homologous staining regions (HSRs) are special types of chromosomal gains that are often observed in human cancers. SMCs are small additional chromosomes whose origins are not readily identifiable by banding methodologies, and are designated as "mar" in the karyotype. Double minutes are specific types of SMCs that are characterized by a typical dumbbell shape, and represent extra-chromosomal oncogene amplification. For example, *MYCN* gene amplification in the form of double minutes is commonly observed in neuroblastoma. HSRs are amplified oncogenes within the structure of a chromosome, and are designated as "hsr" in the karyotype. Usually *ERBB2* (*HER2/neu*) gene amplification on chromosome 17 in breast cancer is an example of an HSR that is typically detected with florescence in situ hybridization (FISH). Chromosomal losses (whole or partial) are designated in the karyotype by "-" or "del," and are thought to result in deletion (or decreased activity) of tumor suppressor genes.

Balanced rearrangements in cancer include translocations (exchange between two or more chromosomes) and inversions (orientation change relative to the centromere, within a single chromosome). These rearrangements disrupt the normal function of critical genes involved in normal cell growth or differentiation, resulting in an abnormal process. More than 500 recurrent balanced cytogenetic aberrations have been reported to date (1). Translocations and inversions usually cause cancer by fusing together two genes, resulting in aberrant expression. Currently, more than two hundred fusion genes responsible for human cancers have been reported in the literature (2). One classic example of an important translocation in human cancer is the t(9:22) in CML. The t(9;22) results in aberrant expression of a gene (*ABL1*) that normally functions in cellular proliferation, by coming under control of a constitutively expressed gene (*BCR*). Approximately 50% of hematopoietic neoplasms acquire translocations somatically; most of these neoplasms are restricted to a single cell lineage (that in which the translocation originated) and are arrested in a particular stage of developmental maturation (2). On occasion more than one cell lineage is affected (e.g. *MLL* gene-related malignancies), suggesting that the involved genes were affected at the pluripotent stem cell stage.

Defined as the loss of one parent's contribution to the cell, LOH can be caused by deletion, gene conversion, mitotic recombination, or loss of a chromosome. LOH often occurs in cancer, where the second copy of a gene (typically a tumor suppressor gene) has been inactivated by other mechanisms, such as point mutation or hypermethylation. When a whole chromosome or a large segment of a chromosome is lost, the remaining chromosome or segment is often duplicated. With complete duplication of the remaining genetic material, the karyotype may appear normal, even though no normal genes are present. Though not easily detected by cytogenetic techniques, this duplication of the remaining chromosome or segment has been shown using molecular genetic techniques (3). At least in theory this type of LOH can be detected cytogenetically using chromosome heteromorphisms, though it is not often pursued.

In the current article we aim to describe the most commonly observed and characteristic cytogenetic aberrations associated with human cancers of the blood and solid tumors. We have tailored our discussions for physicians, students, and scientists who are not intimately involved in the cytogenetics laboratory. We emphasize diagnostic, prognostic, and treatment implications of the characteristic rearrangements, highlight many of the known genes and genetic mechanisms, and note technical issues of sample collection, handling, and transport that may affect the laboratory's ability to obtain quality cytogenetic results. It is beyond the scope of this article to list all cytogenetic aberrations observed in cancer; thorough reviews of cancer cytogenetics can be found elsewhere (4-6).

3. FUNDAMENTALS OF CANCER CYTOGENETICS

Cancer cytogenetics determines the genetic content of cells on a chromosomal level. Through several decades of clinical cytogenetic analysis of cancer cells it has become apparent that suboptimal collection, transport, and culture of clinical specimens can lead to inappropriate (e.g. normal) results. Molecular genetic techniques such as PCR can be used to detect specific chromosomal rearrangements (e.g. *BCR-ABL1* translocation); however, cytogenetic techniques (i.e. chromosome analysis) are needed to detect changes in chromosome number, atypical chromosomal rearrangement, or large (>10kb) deletions and duplications. Newer molecular cytogenetic techniques, such as FISH and comparative genomic hybridization (CGH) are capable of detecting aberrations of an intermediate size (~10kb to 5Mb), and are commonly used in cancer cytogenetics laboratories today. In this section we discuss several common pit-falls that preclude cytogenetic analysis and describe the newer technologies used today in cytogenetics laboratories.

A number of factors determine the success of the clinical cytogenetic laboratory to obtain useful diagnostic results. Classical clinical cytogenetics (i.e. karyotype) depends upon the laboratory's ability to grow cells in situ and obtain metaphase nuclei; therefore any factor that prevents the laboratory from obtaining sterile living cells may preclude complete cytogenetic analysis. Therefore important considerations for cytogenetic analysis include sample collection, handling, and transport which may affect the completion of cytogenetic studies. Because actively

dividing cells are required to obtain sufficient metaphase nuclei for cytogenetic analysis, care should be taken to provide the cytogenetics laboratory with good quality viable tissue, devoid of necrosis, when possible. Some specimens (e.g. bone marrow, lymph nodes, and pleural effusions) contain spontaneously proliferating cells which can be utilized to obtain "direct" chromosome preparations. As such, the first few milliliters of the bone marrow tap is the best specimen for cytogenetic analysis because it contains the highest proportion of dividing cells. Other sample types can be cultured for short-term (i.e. 24 - 72 hours, commonly without stimulants) to obtain metaphase nuclei for analysis.

Inappropriate or insufficient specimens that are submitted to the laboratory may not yield results. For example, a peripheral blood sample lacking circulating blasts will produce normal results or no analyzable metaphases. Similarly, some bone marrow samples may not be suitable for the detection of blasts (e.g. CML). Insufficient specimen often results in culture failure, although FISH on non-dividing nuclei may obtain results if a specific abnormality is suspected. Finally, samples fixed in formalin or paraffin embedded will not grow in culture and therefore can not be used for classic cytogenetic studies; although fixed samples may be appropriate for FISH.

Newer molecular cytogenetic techniques, such as FISH and array comparative genomic hybridization (aCGH), can be used to obtain rapid results. Both techniques can either be performed following culture, or directly from patient tissue without culturing.

FISH is a useful technique for the detection and monitoring of cells with low-level mosaicism (clonal chimerism) or subtle submicroscopic chromosomal changes that are not easily detectable under the microscope. It is also commonly used when rapid or direct (i.e. without culturing) results are needed, and can be performed on formalin fixed paraffin-embedded tissue. FISH uses fluorescently labeled DNA probes (e.g. bacterial artificial chromosomes, BACs) hybridized to either metaphase chromosomes or interphase nuclei, depending on the application. Three main probe strategies are utilized in FISH: 1) enumerating probes, 2) fusion probes, and 3) break-apart probes.

The enumerating or counting probe strategy, as its name implies, is useful for counting the number of a particular locus or whole chromosomes within the cell. Counting probes are used to detect gains or losses of whole chromosomes (e.g. chromosomes 5, 7, 8, and 20 in MDS), or deletions and duplications of genes involved in a disease (e.g. *TP53* and *RB1* gene probes in myeloma). These probes can be either BACs containing the gene or genes of interest, or alpha-satellite repeat sequences specific for the centromeric region of each chromosome. This strategy is also useful for detecting cryptic deletions that can not be detected by classical metaphase chromosome analysis.

The fusion probe strategy is classically used to detect translocations or inversions [e.g. the t(9;22) in CML and the t(15;17) in APL]. BAC probes complementary to chromosomal regions involved in the rearrangements are labeled with two different florophores (e.g. red and green) and analyzed under the microscope for signal overlap. Normal nuclei will have two red and two green signals, corresponding to the two normal (un-rearranged) chromosomes, while nuclei with rearrangements will have one or more yellow signals, corresponding to the overlap of the red and green signals and suggestive of rearranged chromosomes. Dual-fusion strategies are used to reduce false-positive signals produced by artifactual overlap caused by the three-dimensional structure of DNA compaction within the nucleus. Dual-fusion approaches utilize probes that overlap the two reciprocal translocation breakpoints and result in two yellow fusion signals corresponding to the two derivative chromosomes. This probe strategy is also useful to distinguish between variants, such as an extra Philadelphia chromosome in CML blast crisis.

The break-apart probe strategy is essentially the opposite of the fusion probe strategy, and is most useful when a single locus is involved in several different rearrangements (translocations, inversions, deletions, etc). For example, the *MLL* gene locus is involved in >70 recurrent translocations (7), all of which can be detected with the break-apart strategy. Two differently labeled BAC probes (e.g. red and green) normally bind to a single locus and produce the overlapped signal color (e.g. yellow). When the locus of interest is rearranged, the colors split apart. Normal nuclei will have two yellow (overlapped) signals, while nuclei with a rearrangement will have one yellow, one red, and one green signals.

While FISH can provide rapid results, and is applicable for various sample types that are otherwise not amenable to classic cytogenetic analyses, it has limitations. FISH will only answer the particular question being asked regarding an exact probed locus. For example, cells probed with a *BCR-ABL1* fusion probe set may be positive for the t(9;22), but trisomy 8 cells within the sample (often seen in CML-blast crisis) would not be detected unless a chromosome 8 enumerating probe set is used in the probe mix. Similarly, an enumerating probe set consisting only of the alpha repeats from the chromosome 5-centromere will not detect a deletion of the long arm of chromosome 5 (5q-). Physicians ordering tests should be mindful of the questions they are trying to address and order FISH and/or karyotypes appropriately. When questions arise regarding which FISH test to order, the laboratory should be consulted, as ordering a FISH test without specifying the probe set is inaccurate.

CGH is a relatively new molecular technique for identifying gains and losses in a test sample (e.g. a patient sample), relative to a control sample. DNA is extracted from both the test and control samples and digested with restriction enzymes or sonicated to break it into short (~500bp) fragments. The test and control samples are differentially labeled with florescent dyes (e.g. red and green), denatured, and hybridized to metaphase

Table 1. Common cytogenetic aberrations in chronic myeloprolifereative disease

Chromosomal aberration	Comments[1]
-Y	CML-blast crisis
Chromosome 1 aberrations	All MPD subtypes
t(1;6)(q11;p21)	PV
t(1;9)(q10;p10)	PV
del(3)(p11p14)	PV
-5	CIMF
del(5)(q13q33)	All MPD subtypes
t(5;12)(q33;p13)	CEL
-7	All MPD subtypes
+8	All MPD subtypes and CML-blast crisis
+9	PV, CNL, CIMF
t(9;22)(q34;q11.2)	BCR1-ABL gene fusion and diagnostic for CML
del(11)(q14)	CNL
del(12)(p12)	CIMF
del(13)(q12q14)	All MPD subtypes
del(14)(q12q12)	CEL
i(17q)	PV and CML-blast crisis
+19	CML-blast crisis
del(20)(q11q13)	All MPD subtypes
+21	CNL

[1] See text for a detailed explanation of the aberrations listed.

chromosomes. Chromosomal regions that are equally represented in the test and control samples will hybridize equally to the chromosomes and produce an overlapped color (e.g. yellow). A loss (deletion) is detected when the control DNA fluoresces stronger within a region of the metaphase chromosomes, and a gain (duplication) is detected when the patient DNA fluoresces stronger. In array CGH (aCGH), the fluorescently labeled test and control samples are hybridized to an array of DNA sequences (e.g. BACs or oligonucleotides) rather than metaphase chromosomes. aCGH has a much higher resolution than classic metaphase CGH. Although CGH and aCGH have been well-established for use in detecting submicroscopic gains and losses in constitutional (inherited) disease (8), neither are currently appropriately established as a stand alone technology for diagnosis in cancer. One reason is that the CGH technique cannot detect balanced chromosomal aberrations (translocations and inversions), which are very common in cancers, especially in hematological disorders. Also, because of tumor heterogeneity and general genomic instability (i.e. several clonal populations) CGH and aCGH do not necessarily provide narrow and consistent genomic regions of interest that can be definitively implicated or identify previously unknown genomic regions of primary etiology (9). However, the authors are optimistic about the refinements in the CGH technology in the future and its potential use in identifying new cancer biomarkers.

While the genetic tools and strategies described above have been applied to cancer for fewer than fifty years, they are clearly invaluable for the study and diagnosis of malignancy; the importance of cytogenetics in oncology is evidenced by the reclassification of certain hematological diseases by the World Health Organization (5). The application of cytogenetic methods to hematologic disease and solid tumors is described below.

4. CLINICAL CYTOGENETIC EVALUATION OF HEMATOLOGIC MALIGNANCIES

The Philadelphia (Ph) chromosome in chronic myelogenous leukemia, CML, was the first somatically acquired chromosomal aberration observed. At the time of its discovery, Nowell and Hungerford knew only that the Ph chromosome was present in cancerous cells but not in the normal cells of their patients (10, 11). Today we know that the Ph chromosome is due to a balanced chromosomal 9;22 translocation that fuses the *ABL1* kinase gene on chromosome 9q34 with the constitutively active *BCR* gene on 22q11.2, creating a new tyrosine kinase gene with oncogenic properties. One critical aspect of Nowell and Hungerford's work was the comparison of chromosomes from cancer cells to the chromosomes isolated from normal cells. In fact, the observation that cancer cells from patients contained chromosomal aberrations that were not present in normal cells was key to their success, and led to the subsequent discovery of hundreds of characteristic numerical and structural aberrations and the impact of clinical cytogenetics as we know it today. Diagnostic, prognostic, and treatment information for human cancers are routinely provided by clinical cytogenetics laboratories. In this section we describe the common and characteristic chromosomal aberrations observed in hematologic malignancies, the genes and mechanisms known to be involved, and the prognostic and treatment information provided by these aberrations.

4.1. Chronic myeloproliferative disorders

WHO classifies myeloproliferative disorders (MPD) into CML, chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia/hypereosinophilic syndrome (CEL), polycythemia vera (PV), chronic idiopathic myelofibrosis (CIMF), essential thrombocythemia (ET), and unclassifiable chronic MPD (MPD-U) (12). CML is discussed separately.

Cytogenetic abnormalities in MPD subtypes other than CML occur at different frequencies ranging from 3% - 40%, depending on the subtype. Compared to CML, the other MPD subtypes are more clinically and cytogenetically heterogeneous. In fact, at least 27 different chromosomal anomalies have been associated with MPD. The most common of these anomalies are listed in Table 1. Chromosomal anomalies are found most frequently in CIMF (up to 50%), followed by PV, while anomalies in ET and CEL are so infrequent that cytogenetics can be omitted when the diagnosis is clear (13). The most common structural chromosomal anomalies of MPD in order of frequency are t(9;22)(q34;q11.2), del(20)(q11q13), del(13)(q12q14), del(5)(q13q33), and del(12)(p12). The most common numeric anomalies are -Y, +8, +9, and -7. Only the t(9;22) (or variant 9;22) is diagnostic of any specific type of MPD (CML), although relatively strong associations are observed for the del(13) in CIMF, the t(5;12)(q33;p13) in CEL and the del(20), +8, and +9 in PV (14).

No consistent chromosomal anomaly has been associated with CNL, and the primary genetic event is

likely cryptic (submicroscopic). Chromosomal anomalies reported to date may reflect secondary anomalies associated with chromosomal evolution in CNL. Sporadic reports of patients with +8, +9, del(20)(q11q13), del(11)(q14), +21, and complex karyotypes are described in the literature (15).

Although no specific cytogenetic abnormalities have been associated with CEL, the presence of another clonal anomaly that is associated with MPD can help in the differential diagnosis between CEL and a reactive disease that involves the eosinophils. Cytogenetic anomalies in CEL often have been associated with a poor prognosis (16). One important chromosomal aberration that has been linked with CEL is t(5;12). The t(5;12) results in the fusion of the *PDGFRβ* tyrosine kinase gene on chromosome 5q33 and the *TEL* gene on chromosome 12p12. Various investigators have assigned the breakpoints within chromosome 5 as 5q33 or 5q31, and within chromosome 12 as p12 or p13; however the investigators are most likely describing the same translocation (17). Variant translocations that involve the *PDGFR* gene include the t(5;7)(q33;q11.2) and t(5;10)(q33;21.2). Fusion of the *FIP1L1* gene to the platelet derived growth factor receptor alpha (*PDGFRα*) gene has recently been described in patients with hypereosinophilic syndrome (18). These two genes lie very close to one another within chromosome 4q12, so the fusion can not be detected by karyotype. However, the fusion results in a submicroscopic deletion of the intervening DNA sequences, which can only be detected by FISH or aCGH. The del(4)(q12q12) is a target for imatinib mesylate (IM) treatment (18).

In PV, cytogenetic results do not predict evolution of the disease, but they can provide clues to hematologic phenotype, duration of the disease, and consequences of myelosuppressive therapy (19). A greater proportion of patients with advanced disease (and poorer prognosis) have chromosomally abnormal clones than patients with early stage PV (14, 19). In addition, abnormal clones are more frequent among patients who have PV with myeloid metaplasia (78%) than among patients who had PV alone (19%) or PV with myelofibrosis (40%) (14). The most common chromosomal anomalies at PV diagnosis are del(20)(q11q13), +8, and +9, with +8 and +9 often occurring together in the same clone. Additional abnormalities observed include del(1)(p11), del(3)(p11p14), t(1;6)(q11;p21), and t(1;9)(q10;p10). In some patients with PV, a de novo leukemia or MDS develops; in these patients, chromosomal anomalies are more similar to the secondary disease than those associated with untreated PV. Still other patients with PV develop a chromosomally abnormal clone as a consequence of therapy. The most common chromosomal anomaly associated with therapy-related leukemia involves anomalies of chromosome 5 or 7 or both and unbalanced translocations derived from t(1;7)(p11;p11) (20).

No consistent chromosomal anomaly was associated with ET, but chromosomal abnormalities have been observed in about 5% - 7% of patients. Anomalies in ET may have developed as a consequence of therapy or as a de novo leukemic clone (14, 21). However, one group detected a low percentage (less than 10%) of trisomy 8 and/or 9 in about 55% of their patients by FISH (22).

Although the proportion of cases of CIMF with abnormal karyotypes ranges from 30% - 75%, distinct recurrent chromosomal aberrations have been reported in 40% - 50% of patients. This discrepancy is mostly due to difficulty in sampling adequate numbers of quality metaphases from few cells aspirated from fibrotic marrow (23, 24). Although no "specific" chromosome anomalies are observed in patients with CIMF, +1q, del(13q), del(20q), and +8 appear in approximately two-thirds of patients with pathologic karyotypes (24), and rarer anomalies include +9 and del(12p). The most common anomalies, the del(13) and translocations involving chromosome 13, likely interrupt the *RB1* gene, an important tumor-suppressor gene in retinoblastoma, osteosarcoma, and other solid tumors (14). Although balanced translocations are uncommon, some reports document isolated cases with balanced translocations mostly involving chromosomes 1 and 12 with different partners (14, 24). Specific cytogenetic abnormalities in CIMF are associated with significantly different survival outcomes (25, 26). Prognostically favorable aberrations include the 13q- and 20q-, while prognostically unfavorable clones may contain 12p- and +8 (27).

The observation of a subclone or stem line with multiple chromosomal anomalies is often an indication of disease progression or clonal evolution (28). This evolution is seen in at least 12% of patients with MPD. Multiple clones have been observed in 2.1% of patients with hematologic malignancies, and in 1.8% of patients with MPD. The observation of multiple clones is most common among patients with a clone harboring t(9;22), del(20q) or +8 (14).

4.1.1. Chronic myeloid leukemia

As described above, the Ph chromosome was the first consistent cytogenetic rearrangement found in a hematologic disease (10, 11). Banding techniques developed during the 1970s allowed for the identification of the Ph chromosome as being derived from a translocation between chromosomes 9 and 22, t(9;22)(q34;q11) (29). The translocation was subsequently described as resulting in the fusion of the *ABL1* protooncogene (a homologue of the Abelson murine leukemia virus oncogene) on chromosome 9q34 with gene called *BCR* (breakpoint cluster region) on chromosome 22q11 (30). The *ABL1* gene encodes a tyrosine kinase that phosphorylates several proteins and signaling for cell proliferation*, and the BCR* gene encodes a 160kD phosphoprotein with kinase activity. Expression of the Bcr-Abl chimeric protein has aberrant tyrosine kinase activity (31) and is leukemogenic (32).

The unambiguous presence of the *BCR-ABL1* fusion gene is required for a clinical diagnosis of CML, and in typical cases remains the sole abnormality observed through most of the chronic phase. Approximately 90-95% of patients present with the t(9;22) while the remaining 5-

Table 2. Common cytogenetic aberrations in myelodysplastic syndrome

Chromosomal aberration	Comments[1]
-Y	Also associated with normal aging process
Chromosome 3 aberrations	Poor chemotherapy response
-5	Low risk MDS
del(5)(q13q31), del(5)(q13q33)	Low risk MDS; 5q31 deletions associated with more aggressive disease course
-7	Secondary MDS and high risk disease
del(7q)	Secondary MDS and high risk disease
del(11)(q23)	MLL gene aberrations and high risk disease
del(12p)	Intermediate risk MDS
del(13q)	All MDS risk groups
del(17q)	P53 gene deletion and high risk disease
del(20)(q11q13)	As sole aberration, associated with low-risk MDS

[1] See text for a detailed explanation of the aberrations listed.

10% of patients have cryptic or complex rearrangements, but eventually fuse *BCR* and *ABL1*. Variant translocations with deletions at the involved breakpoints signify a poorer prognosis than the more common t(9;22) (33, 34). FISH or molecular techniques can be used to establish diagnosis in cases where the t(9;22) can not be identified by standard karyotyping.

CML-blast crisis is often predicted by cytogenetic findings prior to pathologic changes. 75% - 80% of patients develop additional chromosome aberrations as the disease progresses. Aberrations of chromosomes 8, 17, 19 and 22 are most often involved in disease evolution (major route), accounting for approximately 70% of patients with evolving disease. Trisomy 8, isochromosome 17, trisomy 19, or an extra Ph chromosome (derivative chromosome 22) are the most frequently observed secondary changes in blast crisis (4). The remaining 30% of patients with evolving disease develop various secondary aberrations that may include trisomy 21, loss of the Y, monosomy 7 or 17, trisomy 17, or others (6, 35). Genes known to have roles in transformation include *TP53*, *RB1*, *CDKN2A*, *INK4alpha*, *MINK*, *AML1*, and *EVL1*, although their role in transformation is currently unknown (28, 36).

The *BCR-ABL1* fusion gene has several different genetic breakpoints, which are important for disease characterization and prognosis. The *ABL1* gene breakpoint usually occurs in exon 2; however the *BCR* gene has two different breakpoints which result in different sized hybrid genes and different course of disease. Originally, almost all of the breakpoints identified within the *BCR* gene localized to exons 12-16 (named the major breakpoint cluster region, M-bcr) resulting in a *BCR-ABL1* fusion gene encoding an 8.5kb hybrid mRNA that translates into a 210kD tyrosine kinase protein (37). An identical M-bcr breakpoint is found in approximately 50% of adult Ph-positive acute leukemias, without bias toward AML or ALL (4). A variant *BCR* breakpoint within intron 1 was later observed in Ph-positive acute leukemias and was termed the minor breakpoint cluster region (m-bcr) (37). The m-bcr is observed in the remaining approximately 50% of adults and nearly 80% of children with Ph-positive acute leukemias. The m-bcr transcribes a 7.5kb mRNA which is translated into a 190kD kinase with substrate specificities similar to the 210kD enzyme (38).

The most exciting breakthrough in the treatment of CML has been the development of imatinib mesylate (IM, or Gleevec®) as an oral therapeutic agent. IM binds to a cleft between the N-terminal adenosine triphosphate binding domain and the C-terminal activation loop that forms the catalytic site of the Abl tyrosine kinase, locking the protein into the inactive conformation (39). Although IM appears to be extremely effective in CML, it has markedly reduced effectiveness in the acute leukemias. Patients with deletions at the *BCR-ABL1* breakpoint may not respond to therapy, and drug resistance can occur. IM resistance can occur via four main mechanisms: 1) Expression of the multidrug resistance P-glycoprotein increases drug efflux and decreases intracellular drug levels, thus decreasing drug effectiveness (40). 2) Genomic amplification of the *BCR-ABL1* gene by gain of a second Ph chromosome or cellular aneuploidy is associated with resistance (41). 3) Clonal evolution and development of chromosomal aberrations in addition to the t(9;22) may allow the clone to develop non-Bcr-Abl1 dependent growth mechanisms (42) 4) Finally, *ABL1* gene mutations within the tyrosine kinase domain appear to prevent binding of IM to the protein (41). Currently only allogenic hematopoietic stem cell transplantation conclusively provides long-term and prolonged disease-free survival for patients with CML (43).

4.2. Myelodysplastic syndromes

Several recurrent and well-established cytogenetic changes have been described in myelodysplastic syndromes (MDS), and the detection of these changes can greatly facilitate diagnosis, prognosis, follow up, and treatment of patients (44). The most common chromosomal aberrations associated with MDS are presented in Table 2. Although chromosomal abnormalities occur in almost half of de novo cases, aberrations are observed in up to 95% of secondary MDS. Most chromosomal defects in MDS are nonspecific, and with the exception of 5q-, none are specifically associated with any FAB or WHO subtypes (45, 46).

Observed in nearly 50% of patients, chromosomal deletions are the most common defects observed in both de novo and secondary MDS. Deletions are generally interstitial, rather than terminal, and frequently occur in 5q, 7q, 20q, 11q, 13q, 12p and 17q. Although a deletion observed as a sole abnormality is associated with low-risk MDS, deletions observed with other abnormalities are associated with more advanced cases (45, 47).

A normal karyotype, monosomies, trisomies and unbalanced translocations are the next most common aberrations, occurring in 15% of patients. The most common monosomies in MDS involve chromosomes 5, 7 and Y. Deletions and monosomies cause MDS through the same mechanism; both cause the loss of one allele of a tumor suppressor gene with the subsequent submicroscopic

deletion of the second allele on the homologous chromosome (48). This recessive mechanism inactivates the cell's ability to control the cell cycle, DNA repair, and apoptosis (44, 45). Although balanced translocations are relatively common aberrations in myeloid disorders, they are very rare in MDS.

The incidence of 5q-/-5 is 10% - 20% in de novo and 40% in secondary MDS. The long arm of chromosome 5 has genes coding many hematopoietic growth factors and growth factor receptors, including IL-3, IL-4, IL-5, IL-9 and GMCSF. Two commonly deleted regions are 5q31 and 5q33. 5q33 deletions correspond to the 5q- syndrome and lead to a mild type of MDS. 5q31 deletions are reported in other de novo and secondary subtypes and exhibit a more aggressive course (47, 48).

7q-/-7 is present in all MDS subtypes, though it is much more common in advanced forms. 7q-/-7 occurs as a sole chromosomal abnormality in 1% of cases. Further karyotypic defects (e.g. rearrangements of long arm of chromosome 3) occur in 5% - 10% of de novo MDS cases. 7q-/-7 is more common in secondary MDS, seen in up to 60% of the patients, and is therefore considered a secondary event in pathogenesis of the disease. Monosomy 7 is the most common chromosomal defect in bone marrow of patients with constitutional syndromes (e.g. Fanconi's anemia, type I neurofibromatosis, and severe congenital neutropenia) that predispose to myeloid disorders (49). Also, a recently described pediatric monosomy 7 syndrome presents with hepatosplenomegaly, leukocytosis, thrombocytopenia, males predominance, and an unfavorable outcome. Patients harboring deletions in 7q31 to 7q36 regions have an inferior response to chemotherapy and shorter survival than those with deletions in the 7q22 region (45, 48).

Deletion of long arm of chromosome 20 occurs in 5% of de novo and 7% of secondary MDS. This incidence might be an under estimation, since monosomy 20 and unbalanced translocations involving chromosome 20 occur as frequently as deletions. Although the critical region seems to be 20q11.2 to 20q12, deletions are rather large and involve most of the long arm of chromosome 20. Patients with del(20q) as a sole abnormality are in the low-risk MDS categories (RARS and RA), whereas those presenting with this deletion as a part of a complex karyotype (3 or more abnormalities in karyotypes) have a poor prognosis (47).

Deletion of the short arm of chromosome 17 encompasses not only simple deletions, but also unbalanced translocations, isochromosome 17q, and (rarer) monosomies. del(17q) is rather rare in de novo MDS (~7%), but occurs more frequently in secondary MDS. Despite its heterogeneity, all of the above mentioned aberrations of the short arm of chromosome 17 lead to the loss of one p53 allele. Mutation or submicroscopic deletion of the other p53 allele occurs in 70% of the patients and cause inactivation of the gene.

Loss of the Y chromosome occurs both in disease and as a normal event in elderly men. Loss of the Y is observed in about 10% of MDS patients. It also occurs in about 7% of the elderly men without any hematological disorder. Therefore, MDS diagnosis cannot be based on the presence of –Y alone. When biological and clinical parameters point to an MDS diagnosis, loss of the Y chromosome identifies patients with a favorable clinical outcome.

Interstitial deletions or balanced translocations involving band 12p13 are found in about 5% of patients with RAEB and RAEB-t. These patients usually belong to an intermediate-risk cytogenetic category for MDS. However, recent studies suggest that 12p13 aberrations signify a clinical outcome similar to that of patients included within the low-risk category (47).

Several other chromosomal aberrations are observed in MDS, but are not specific to the disease. Trisomy 8 occurs in 10% of all MDS cases, but can be found in other oncohematological disorders. Trisomy 8 is more often associated with RARS and RAEB. Chromosome 3 rearrangements, typically translocations or inversions, occur in 2 - 5% of patients with MDS (also in AML). Chromosome 3 changes are frequently associated with -7/7q and 5q-, and are associated with a short survival and a poor response to chemotherapy. Aberrations within 11q23 (the *MLL* gene locus) are found in 5% of MDS patients.

Using cytogenetics abnormalities, MDS patients have been divided into three prognostic categories. Patients in the first, low-risk category exhibit a normal karyotype, deletion of long arm of chromosome 5 as a sole abnormality, or harbor an isolated deletion of long arm of chromosome 20. Patients with either a deletion of the short arm of chromosome 12 or trisomy 8 are categorized as an intermediate-risk group. Finally, the presence of complex karyotypes, monosomy 7, deletion of short arm of chromosome 17, rearrangements involving chromosome 3 and aberrations of long arm of chromosome 11 (*MLL*), indicate a high-risk group of MDS patients (45, 46, 50).

4.3. Acute myeloid leukemia

The most common acute leukemia in adults, acute myeloid leukemia (AML), is very heterogeneous cytogenetically. More than 160 recurrent structural chromosomal abnormalities have been reported in AML (51, 52). The most commonly observed chromosomal aberrations in AML are presented in Table 3. Most patients present with chromosomal changes, such that approximately 77% - 85% of children and about 55% - 78% of adults have cytogenetic aberrations. Recent studies have shown that even patients with normal karyotypes have cryptic (submicroscopic) gene alterations, such as a duplication or deletion of the *MLL* gene on chromosome 11, underscoring the importance of cytogenetics in AML.

Chromosomal aberrations in AML can be either primary or secondary. Primary aberrations are frequently found as the sole abnormality, and are often associated with a particular AML subtype. Approximately 55% of patients

Table 3. Common cytogenetic aberrations in acute myeloid leukemia

Chromosomal aberration	Comments[1]
3q26 aberrations	Multilineage AML and MDS with increased platelet production and high risk disease
-5	AML with multilineage dysplasia
del(5q)	AML with multilineage dysplasia
t(5;17)(q23;q12)	APL and NPM-RARA gene fusion
-7	AML with multilineage dysplasia
+8	AML with multilineage dysplasia
t(8;21)(q22;q22)	AML1-ETO gene fusion and childhood leukemia
t(9;22)(q34;q11.2)	BCR1-ABL gene fusion and m-bcr breakpoint
11q23 aberrations	MLL gene interruption and high risk disease
t(11;17)(q13;q12)	APL and NuMA-RARA gene fusion
t(11;17)(q23;q12)	APL, PLZF-RARA gene fusion and poor ATRA resonse
t(15;17)(q22;q21)	APL and PML-RARA gene fusion
inv(16)(p13q22)	Abnormal eosinophilia and CBFα gene interruption
t(16;16)(p13;q22)	Abnormal eosinophilia and CBFα gene interruption
del(16)(q22)	Abnormal eosinophilia and CBFα gene interruption

[1] See text for a detailed explanation of the aberrations listed.

with karyotypic abnormalities present with a single aberration. The most common sole aberrations [e.g. t(8;21), t(15;17), and inv(16)] are balanced translocations or inversions which disrupt critical genes involved in normal hematopoisis, resulting in abnormal expression. Then again, unbalanced rearrangements, including gains and losses of whole or partial chromosomes can also be primary changes. Common unbalanced chromosomal alterations include +1, del(5q), -7, del(7q), +8, del(9q), +11, and +13.

Secondary aberrations in AML are rarely found alone, but seem to be important in the progression of disease. Approximately 45% of patients with abnormal karyotypes have more than one chromosomal aberration. About 30% – 50% of AML patients have complex aberrant karyotypes (at least three cytogenetic abnormalities), which is associated with a very poor prognosis. The detection of these chromosomal aberrations can be essential regarding the available treatment options for certain types of AML.

4.3.1. AML with t(8;21)(q22;q22)

The t(8;21) is the most common structural abnormality in AML (FAB AML-M2); approximately 12% of all AML cases with discernable chromosomal translocations and about 17% of children with karyotypically abnormal AML exhibit this translocation (53). The t(8;21) fuses the *ETO* gene in 8q22 with the *AML1* gene in 21q22 to form the *AML1-ETO* fusion gene. *AML1* gene breakpoints are mostly located within intron 5 and *ETO* breakpoints are typically located within intron 1b (54). This aberration appears to be more frequent in the young and is rare past the age of 50 years. Patients with the t(8;21) as a sole aberration usually have a good prognosis when treated with chemotherapy. However, the presence of additional secondary changes, including expression of CD5, appears to adversely affect survival (55-57).

Approximately 70% - 80% of cases have additional karyotypic aberrations. Of the cases with additional aberrations, two-thirds have numerical anomalies, and one-third have structural anomalies. Loss of the Y or X chromosome, abnormal chromosomes 7 and/or 9 with a deletion of the long arm [del(7q) and del(9q), respectively], -7, or +8 are common secondary aberrations (58).

The Aml1 protein is one of three members in the Runt domain family (including Aml1, Aml2, and Aml3) that regulate transcription in normal hematopoiesis and/or oncogenesis (59). Although the Aml1 protein is a relatively weak transcriptional activator alone, coupled with core binding factor beta (Cbfβ) it binds to consensus DNA motifs called Runt domain binding elements. Runt binding domains are present in the transcriptional regulatory regions of genes important in myelopoiesis (e.g. IL-3, GM-CSF, CSF1 receptor, myeloperoxidase, and subunits of the T- and B-cell antigen receptor) (60-65). Abnormal Aml1 fusion proteins, including the Aml1-Eto fusion protein, inhibit the expression of genes normally transactivated by Aml1, thus interfering with normal myelopoiesis (66-68).

4.3.2. AML with inv(16)(p13q22), t(16;16)(p13;q22), or del(16)(q22)

Three chromosome 16 rearrangements, inv(16)(p13q22), t(16;16)(p13;q22), and del(16)(q22), share identical clinical features and genetic pathogenesis in AML (FAB AML-M4EO). The abnormal chromosome 16 is found in approximately 5% - 10% of all AML cases, and is associated with the presence of abnormal eosinophilia in the marrow. Found mainly in AML with eosinophilia, these chromosome rearrangements are occasionally found in AML without eosinophilia, and rarely in MDS. They are also found as secondary rearrangements in CML. AML patients with chromosome 16 rearrangements tend to have a favorable prognosis compared to patients with other cytogenetic aberrations (69).

All three chromosome 16 aberrations interrupt the *CBFα* gene in 16q22; the inv(16) and t(16;16) fuse the *MYH11* gene in 16p13 with the *CBFα* gene. The *CBFα* gene encodes a 22kD protein which forms the beta subunit of the Cbf transcription factor, which normally regulates the expression of myeloid and T-cell specific genes such as: *GM-CSF*, *M-CSFR*, *IL3*, and T- Cell receptor genes *TCRA-D*, *TCRB*, and *TCRG*. The *MYH11* gene encodes a 214kD protein called MYST which binds actin, and functions in muscle contraction. The fusion protein functions by diminishing the quantity of active Cbf protein and by accumulating Cbfα-Myh11/Cbfα multimeres in the nucleus to compete with the remaining active Cbf (70).

Secondary changes in AML with eosinophilia and chromosome 16 aberrations occur in about 30 – 50% of patients. +8, +21, and +22 are the most frequently observed secondary aberrations.

Identification of the inv(16) can be difficult by conventional cytogenetics, especially when chromosome morphology is poor; for this reason, FISH is often used to aid in the detection of inv(16). The break-apart gene rearrangement strategy is typically applied to detection of the inv(16) and t(16;16).

4.3.3. AML with t(15;17)(q22;q21)

Although considered somewhat rare among hematopoietic malignancies, acute promyelocytic leukemia (APL, FAB AML-M3) has gained attention by becoming the first human cancer for which complete remission can be induced by a pharmacological agent, all-*trans*-retinoic acid (ATRA). APL accounts for only approximately 5% - 8% of AML cases (71), and is typified by a translocation between the long arms of chromosomes 15 and 17, t(15;17)(q22;q21) (72). The t(15;17) fuses the gene encoding the retinoic acid receptor alpha (*RARα*) within chromosome 17q21 to the promyelocytic leukemia (*PML*) locus on chromosome 15q22, causing expression of the *PML- RARα* chimeric oncoprotein and cellular transformation (73, 74). Additional aberrations are present in 35% - 45% of cases; trisomy 8, del(9q), or an isochromosome derived from the t(15;17) are among the most common secondary rearrangements (71).

Retinoic acid (RA), the active vitamin A metabolite, plays an important role in development, differentiation, and homeostasis. Its effects are mediated through binding to specific nuclear receptors: the RARs (alpha, beta, and gamma) and the RXRs (alpha, beta, and gamma). RARs and RXRs regulate gene transcription through RA signaling. The receptors bind to DNA motifs known as RA-response elements (RAREs) as RAR/RXR heterodimers or RXR homodimers, thereby activating transcription of RA target genes (reviewed in 75, 76). RARs and RXRs activate or repress gene transcription by recruiting multiprotein co-activator and/or co-repressor complexes with histone acetyltransferase or histone deacetyltransferase (DHAC) activity. It is currently thought that the oncogenic potential of the APL fusion proteins results from the aberrant repression of gene transcription through HDAC-dependent chromatin remodeling. ATRA restores the normal granulocytic differentiation pathway by binding to one of three known retinoic acid receptors (RARs) and retinoid X receptors (RXRs), rather than by inducing rapid cell death (as is typical of conventional chemotherapy). Binding of ATRA to RAR activates gene transcription, which restores granulocytic differentiation (77).

Three variant translocations, t(11;17)(q23;q12), t(5;17)(q23;q12), and t(11;17)(q13;q12), lead to the fusion of the *RARα* gene and fusion partners *PLZF*, *NPM*, and *NuMA*, respectively. Morphologic differences exist between true APL and disease with the variant translocations though. The t(11;17)(q23;q12) occurs in ~0.8% of APL, and in contrast to the more frequent t(15;17), is associated with an unfavorable prognosis and poor ATRA response (71, 78). The t(5;17) and t(11;17)(q13;q12) translocations respond to ATRA (79-81).

The fusion probe FISH strategy is typically employed for detection of the t(15;17) translocation. Clinicians often order FISH in addition to a karyotype can be employed whenever APL is suspected, since FISH results can be obtained on a rapid basis, allowing patients to receive therapy as quickly as possible.

4.3.4. AML with 11q23 abnormalities

Translocations and other rearrangements involving chromosome 11q23 and the *MLL* gene occur in approximately 5% - 6% of patients with AML (FAB AML-M5). *MLL1* gene rearrangements can take the form of balanced translocations, partial tandem duplication of internal coding sequences, or through amplification of rearranged forms of the locus. However, balanced translocations appear to be the most common mechanism in human cancer (82).

A wide range of chromosomes serve as donors in the reciprocal interchanges with chromosome 11. The t(4;11)(q21;q23) and t(11;19)(q23;p13) translocations predominate in ALL (83, 84), while the t(6;11)(q27;q23), t(9;11)(q34;q23), and t(11;19)(q23;p13) translocations are most common in AMLs (85, 86). Additional 11q23 translocation partners include: Xq24, 1q32, 2q37, 7q22, 7q32, 8q11, 9p11, 9q33, 12p13, 12q24, 14q11, 14q32, 17q11, 18q12, 20q13, and others. Alternatively, about 10% of AML cases without cytogenetic evidence of 11q23 rearrangements show internal tandem duplication of *MLL*, often in association with trisomy 11 (87, 88). In addition, more than 20% of patients with intragenic aberrations of *MLL* demonstrate a mutation/deletion involving *FLT3* (CD135), but this occurs in only about 10% of AML cases with *MLL* translocations and only in 5% of adult AML with normal *MLL* status (89).

The *MLL* gene (also known as *MLL1*) encodes a transcription factor and homeobox gene that is homologous to the *Drosophila Trithorax* gene. Mll protein is widely expressed during development, is expressed in most adult tissues including myeloid and lymphoid cells, and is required for complete hematopoiesis (90). Balanced translocations of 11q23 cluster between exons 8 and 14 of *MLL*, resulting in deletion of the so-called PHD domain which is implicated in binding of histone deacetylases HDAC1 and 2 (91). Experimental evidence suggests that the Mll fusion proteins transform by a gain-of-function, rather than loss-of-function mechanism. For example, hematopoietic progenitors are impaired by null mutations (complete deletion) of *MLL* (92), while in-frame fusions of *MLL* to *AF9*, found in the t(9;11), develop expansion of myeloid progenitors and ultimately AML in mouse models (93). Retroviral transduction of Mll fusion proteins such as Mll-Enl, found in the t(11;19), has shown similar findings (94).

MLL gene rearrangements can be detected by FISH using the break-apart gene rearrangement probe strategy, similar to the strategy used in detection of the inv (16). Occasionally, this probe detects not only a reciprocal translocation, but also a deletion of at least 190kb from the 3' region of the *MLL* gene.

4.3.5. Other commonly observed chromosomal aberrations in AML

Approximately 3% of AML patients with cytogenetic abnormalities have a Philadelphia chromosome, the t(9;22). In contrast to CML, patients with Ph+ acute leukemias often have a mixture of

Table 4. Common cytogenetic aberrations in precursor B- and T-cell neoplasms

Chromosomal aberration	Comments[1]
t(1;7)(p32;q34)	TAL1 gene interruption; T lineage
t(1;11)(p32;q23)	TAL1 gene interruption; T lineage
t(4;11)(q21;q23)	MLL and AF4 gene fusion; early pre-B and biphenotypic
t(9;22)(q34;q11)	BCR1-ABL gene fusion and m-bcr breakpoint; B-, T-, and pre-B lineage
11q23 aberrations	MLL gene interruption and high risk disease
t(11;19)(q23;p13.1)	MLL and ENL gene fusion; biphenotypic and multilineage
t(12;21)(p13;q22)	TEL-AML1 gene fusion and favorable prognosis; pre-B lineage

[1] See text for a detailed explanation of the aberrations listed.

cytogenetically normal and abnormal cells at diagnosis. Approximately half of Ph+ AML cases exhibit the M-bcr breakpoint and the 210kD Bcr-Abl1 fusion protein that is observed in CML. The remaining patients have the minor breakpoint m-bcr.

AML with multilineage dysplasia is associated with chromosomal aberrations similar to those found in MDS [e.g. -5, del(5q), -7, +8, and others]. Abnormalities of 3q26, including inv(3)(q21q26), t(3;3)(q21;q26), or ins(3;3)(q21;q26) are associated with multilineage AML and MDS with increased platelet production. 3q aberrations in AML with multilineage dysplasia are typically associated with an adverse prognosis.

Primary trisomies in AML include those of chromosomes 4, 8, 11, 13, 16, 19, 21, and 22. AML with partial trisomy 4 is believed to originate from an early myeloid precursor, and is commonly found with double minutes consisting of many duplicated copies of the *MYC* protooncogene. Other gene mutations commonly seen in AML include *KIT*, *CEBPA*, *WT1*, *NRAS*, and *KRAS*.

Several hundred cytogenetic aberrations have been reported in AML, in addition to the common characteristic chromosomal aberrations in AML listed above. It is beyond the scope of this article to list all aberrations associated with AML. For a complete listing of chromosomal aberrations observed in AML, the reader is referred to any of several thorough reviews of cancer cytogenetics, such as (4, 5).

4.4. Precursor B- and T-cell neoplasms

Precursor B- and T-cell neoplasms are predominantly acute lymphocytic leukemias (ALL). Pre-B ALL is primarily a disease of children, while pre-T ALL is found in both children and adults. The most common cytogenetic aberrations associated with precursor B- and T-cell neoplasms are presented in Table 4.

Approximately 75% of all ALL cases occur in children under six years of age, and about 80% - 85% of all ALL cases are of a pre-B phenotype. Because children are most often affected, prognostication has been the focus of many studies, and cytogenetics plays an important role in determining the outcome of disease. Cytogenetic abnormalities in pre-B ALL fall into four main groups with different prognoses: 1) hypodiploid, 2) pseudodiploid 3) hyperdiploid with fewer than 50 chromosomes, 4) hyperdiploid with more than 50 chromosomes, 5) ALL with one of several specific translocations or rearrangements.

Hypodiploid pre-B ALL is associated with a poor prognosis. Most hypodiploid cases have a modal number of 45 chromosomes and arise from the loss of whole chromosomes, unbalanced translocations, or the formation of dicentric chromosomes. Near-haploid clones usually have at least one copy of each chromosome, two sex chromosomes, and two copies of the chromosome 21, and like other hypodiploid clones are associated with a poor prognosis. A second pseudodiploid clone can arise by duplication of the near-haploid clone, and usually contains exactly two copies of the chromosomes present in the near-haploid cell line and is associated with a poor prognosis. About 2% of adults with ALL have clones with 30 - 39 chromosomes.

Karyotypes exhibiting between 51 and 65 chromosomes (hyperdiploid) are associated with a good prognosis in the current treatment protocols. Karyotypes of these massively hyperdiploid ALL cases commonly exhibit extra copies of chromosomes X, 4, 6, 10, 14, 17, 18, 20, and 21, duplication of 1q, and an isochromosome 17q. Trisomies +6, +4 and +10 are strongly associated with favorable outcomes. About 3% of adults with ALL have karyotypes exhibiting triploidy, which can also be associated with a favorable prognosis. Moderately hyperdiploid pre-B ALL cases (47 - 50 chromosomes) have an intermediate prognosis.

Several translocations are commonly observed in ALL, including t(12;21)(p13;q22), t(9;22)(q34;q11), and translocations involving the *MLL* gene on chromosome 11q23. The t(12;21) translocation fuses the *TEL* gene on chromosome 12p13 with the *AML1* gene (95), and is found in about 25% of children with pre-B ALL (96, 97). The *TEL-AML1* fusion gene defines a distinct sub-group of patients aged 1-10 years with a favorable prognosis; the 5 year event-free survival rate is 91%, compared to 65% in patients lacking the translocation (98). The *TEL* gene is deleted on the other chromosome 12 in most patients with *TEL-AML1* fusion (99), leading to dominant effects of the Tel-Aml1 fusion protein. Although it is the most common translocation in childhood ALL, it can not be identified using classic cytogenetics because there is no change in the morphology to identify the rearranged chromosomes. FISH or molecular genetics techniques (e.g. RT-PCR) are needed to detect the presence of this translocation. The fusion probe FISH strategy is most often employed for detection of the various *AML1* translocations, including the *TEL-AML1* fusion.

As described above, the t(9;22) is observed in patients with CML, AML, and ALL. Present in 15% - 20% of all cases of ALL, the t(9;22) is the most common of all ALL-associated chromosomal aberrations (100, 101). The t(9;22) is found more frequently in adults (15% - 20% of

Table 5. Common cytogenetic aberrations in mature B- and T-cell neoplasms

Chromosomal aberration	Comments[1]
+3	MALT lymphoma
del(6q)	CLL
t(8;14)(q24;q23)	Burkitt lymphoma
del(11)(q22)	ATM gene deletion, CLL
t(11;14)(q13;q23)	CCND1-IGH gene fusion, mantle cell lymphoma
t(11;18)(q21;q21)	MALT lymphoma
+12	CLL and mantle cell lymphoma
del(13)(q14)	RB1 gene deletion, CLL, mantle cell lymphoma, MM
t(14;18)(q23;q21)	CCND1-IGH gene fusion, follicular lymphoma
14q32 rearrangements	IGH gene interruption, all B-cell neoplasms
del(17)(p13)	P53 gene deletion, CLL, mantle cell lymphoma, MM

[1] See text for a detailed explanation of the aberrations listed.

cases) than in children (5% of cases) (102), and is characterized by the m-bcr breakpoint and 190kD fusion protein (described in detail above). Variant translocations occur in ALL, just as in CML, though less often (<5%, see reference 103). Ph positive patients respond better to therapy than CML patients in blast crisis, although they are at the same time worse off than patients in other cytogenetic subgroups of ALL. In contrast to CML disease progression, the Ph marker tends to disappear during remission in the acute leukemias.

Translocations involving the *MLL* gene locus on chromosome 11q23 occur in approximately 7% - 10% of patients with ALL. Importantly, about 70% of all infants with both AML and ALL have 11q23 translocations, likely occurring in utero (104), making 11q23 rearrangements the single most common cytogenetic abnormality in infants with acute leukemia (105, 106). Infants and adults with AML or ALL and 11q23 rearrangements have aggressive clinical features and often present with hyperleukocytosis and early involvement of the central nervous system; therefore, 11q23 rearrangements are generally associated with a poor prognosis and a high risk of treatment failure (107-109). However, children aged 1-9 years with 11q23 rearrangements and patients with an inversion of 11q23 appear to have a better outcome (110). The most frequent 11q23 translocations in ALL are of pre-B cell lineage or mixed lineage phenotype and include the t(4;11)(q21;q23) and t(11;19)(q23;p13.1), which fuse *MLL* with the *AF4* and *ENL* genes, respectively (83, 84). 11q23 rearrangements are also associated with therapy-related leukemias, especially in patients previously treated with topoisomerase II inhibitors (111). For example, the t(4;11) is commonly found in treatment-related disease.

A smaller percentage of T-cell ALL cases (60% – 70%) have cytogenetic abnormalities than B-ALLs (~80%), and the majority of the aberrations observed in T-ALL are cryptic. For example, nearly 80% of children with T-ALL have cryptic deletions of the *CDKN2A* (*INK4A*) gene locus on 9p21 (112). Also, in contrast to B-ALL where cytogenetic abnormalities provide strong prognostication, T-ALL aberrations have little predictive value. Ph+ T-ALL cases have an aggressive course and poor prognosis, as in B-ALL (113, 114). Interestingly, *MLL* gene rearrangements appear to have a better prognosis in T-ALL cases than in B-ALL cases (115, 116). Many of the chromosomal aberrations observed in T-ALL are submicroscopic and must be detected by FISH or molecular techniques. Finally, the *TAL1* gene locus on chromosome 1p32 is involved in at least two recurring chromosomal rearrangements including t(1;7)(p32;q34) and t(1;11)(p32;q23).

4.5. Mature B-cell neoplasms

About 90% of all lymphoid neoplasms are mature B-cell neoplasms. Within this diverse group, large cell lymphoma and follicular lymphoma are the most common, comprising approximately 50% of all non-Hodgkin's lymphomas (117). In WHO classification, B-cell lymphomas are listed according to their major clinical presentations. These are predominantly disseminated leukemic types, primary extranodal lymphomas, and predominately nodal lymphomas, which might involve extranodal sites as well. Chronic lymphocytic leukemia (CLL) and plasma cell myeloma are discussed separately. The most frequently observed cytogenetic rearrangements observed in mature B-cell disease are presented in Table 5.

Several characteristic translocations in mature B-cell neoplasms are important in determining differential diagnosis; these include the t(11;14)(q13;q23) in mantle cell lymphoma, the t(14;18)(q23;q21) in follicular lymphoma, the t(8;14)(q24;q23) in Burkitt lymphoma (BL), and the t(11;18)(q21;q21) in MALT lymphoma. These four rearrangements each bring together different proto-oncogenes with a constitutively expressed gene, causing abnormal expression of the oncogene. Specifically, oncogene fusions with the immunoglobulin heavy chain gene (*IGH*) on chromosome 14q23, and with the *MALT* gene on chromosome 18q21, result in abnormal proliferation. For example, in the t(11;14) of mantle cell lymphoma, the gene encoding cyclin D1 (*CCND1*, also called *BCL1*) on chromosome 11q13 is constitutively expressed when fused with the *IGH* locus. Other rearrangements observed in mantle cell lymphoma include those observed in CLL, such as 13q14 deletions, trisomy 12, 17p13 deletions, which predict poor outcomes relative to the t(11;14) and normal karyotypes (118). In follicular lymphoma, the *BCL2* gene on chromosome 18q21 is fused to *IGH* in the t(14;18), preventing normal Bcl2 protein function and cellular apoptosis. In BL, the *MYC* (8q24) gene is fused with *IGH* in the t(8;14), causing uncontrolled proliferation. MYC rearrangement is a consistent feature of BL and is now considered diagnostic (119, 120). Variants include the t(2;8)(p12;q24.1) involving the Ig κ light chain region (*IGK* gene) locus, and the t(8;22)(q24.1;q11.2) involving the Ig light-chain region (*IGL*) on chromosomes 2p12 and 22q11.2, respectively. It should be noted that *MYC* translocations are not specific for BL; *MYC* translocation has also been reported in secondary pre-B ALL following follicular lymphoma. In MALT lymphoma, the t(11;18) results in a chimeric fusion of the apoptosis inhibitor *API2* on chromosome 11q21 with the *MALT1* gene on chromosome 18q21 is observed in 25% - 50% of cases (121). Trisomy 3 is observed in about 60% of cases (122, 123).

In general, mature B-cell neoplasms are extremely heterogeneous, and correct diagnosis is essential to predict the outcome and direct therapy. More precise subclassifications of these neoplasms that is afforded by cytogenetic analysis have led to innovative therapies, including localized radiation therapy for eradication of MALT lymphoma and humanized anti-CD20 as an adjunct therapy for CD20-positive B-cell lymphomas.

Cytogenetic aberrations in mature T-cell neoplasms are cryptic (i.e. complex karyotypes). However, anaplastic large cell lymphoma (ALCL)

4.5.1. Chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the US and Europe (124-126), accounting for approximately 30% of all leukemia cases. Approximately 95% of these cases are of B-cell origin (124, 127), while the remaining are of T cell origin.

Conventional cytogenetics detects structural chromosome abnormalities in about 40% – 50% of CLL patients (128, 129). However, chromosomal aberrations are not always detected in CLL patient's B-cells because the cells are often not stimulated to grow in culture. For this reason, molecular cytogenetic techniques are more sensitive for the detection of clinically significant chromosome abnormalities than standard chromosome analysis. FISH serves to unravel cryptic chromosomal aberrations that may not otherwise be detected due to the low mitotic index achieved in cultures obtained from most CLL patient samples, even in the presence of B-cell mitogens (125, 127, 128, 130). Additionally, when metaphases can be obtained, they are often so poor in quality that many aberrations escape detection. Therefore, FISH performed in conjunction with conventional cytogenetics is the testing methodology of choice for these disorders. All molecular cytogenetics techniques (i.e. FISH, CGH, and array CGH) have increased the detection rate of CLL to about 80% (129-131).

Among patients with abnormal karyotypes, as many as 65% have one chromosome abnormality, 25% have two abnormalities, and the remainder have more complex abnormalities (6%) (127). A 13q14 deletion, involving the *RB1* gene, is the most common finding (36% to 50% of the patients) (124, 125); this deletion is believed to be a primary event in B-CLL, as it is present in a majority of the tumor cells and is frequently the sole abnormality. The second most common abnormality, and the most common abnormality to be detected by conventional cytogenetics, is trisomy 12 (11% to 21% of the patients). Trisomy 12 usually displays an excess of large lymphocytes identifying the CLL mixed-cell-type variant of the FAB classification (128). Trisomy 12 may be a secondary event in the course of CLL, since it is typically identified in a minority of the tumor cells. Less frequent primary aberrations in CLL include 14q32 rearrangements (*IGH* locus, up to 21%) (127), 11q22.3 deletion (involving the *ATM* gene, 9% - 15%) (132), and a 17p13 deletion (involving the *P53* gene locus, 7% to 12%) (131). Cases with trisomy 12 predominately have non-mutated immunoglobulin variable-region genes, whereas those with 13q14 abnormalities more often have mutations in this region (133). Other less frequent chromosome abnormalities also occur (e.g. complex karyotypes).

A chromosome 6q deletion occurs in 7% of all CLL patients (as a primary event in 4%) and represents a cytogenetic and clinicobiological entity that exhibits a distinct phenotypic and hematologic profile (134). Patients with del6q usually present with a relatively high WBC count, classical immunophenotype, and CD38 positivity, which are associated with the acceleration to the more aggressive prolymphocytic leukemia (PLL) (126). Therefore, del6q patients require immediate therapy to achieve remission (128).

The recommended FISH panel for CLL detection consists of 11q22.3 (*ATM* gene), 13q14 (D13S319), *IGH* locus-specific probe (14q32), the centromere of chromosome 12 (D12Z3) and 17p13.1 (P53 gene). In addition, there are recommendations to add 6q21 probe to the panel (127, 128).

Cytogenetics is also helpful in predicting the course of CLL (128, 130). In fact, chromosomal abnormalities are independent predictors of disease regression and survival (124, 126, 129). Patients with diploid karyotypes or a 13q deletion as a sole abnormality have the best prognosis and a benign clinical course (median survival 79 - 133 months) (125, 126, 130). The presence of the del(6q) or trisomy 12 usually has an adverse effect on patient survival and results in intermediate prognosis (median survival 33 - 114 months) (125). Patients with 11q22–23 (median survival 13 - 79 months), 17p13 deletion (median survival 9 - 32 months), or complex karyotypes have the worst prognosis (126-128, 135).

Although data related to chromosomal abnormalities is important in determining a diagnosis and prognosis for CLL patients, it is also useful for additional applications, such as finding minimal residual disease, and possibly indicating potential target sites for therapeutic interventions. Jahrsdorfer et al. showed that cytogenetic status correlates with the biological behavior of B-CLL in vitro (124). Poor prognosis cytogenetics was associated with more rapid spontaneous apoptosis in vitro, lower immunogenicity, and higher lactose dehydrogenase (LDH). Good prognosis cytogenetics was associated with less spontaneous apoptosis, higher Bcl-2 levels, stronger immunogenicity, and lower levels of LDH (124).

4.5.2. Plasma cell myeloma

Multiple myeloma (MM) represents the malignant culmination and clonal expansion of genetically transformed plasma cells. Several pre-malignant stages have been described, which include monoclonal gammopathy of undetermined significance (MGUS) and smoldering myeloma (SMM). Active myeloma is often preceded by an indolent phase of MGUS, where the plasma cells are already abnormal with an aneuploid DNA content. In fact, almost all myeloma tumors and most cases of

MGUS are aneuploid as demonstrated by DNA content measurements using flow cytometry, conventional cytogenetics, or molecular cytogenetics (FISH) (136, 137).

By classical cytogenetics, only one-third of MM patients have a complex abnormal karyotype. The remaining two-thirds of patients have normal karyotypes (138, 139). However, the observed normal karyotypes are often derived from the other non-neoplastic hematopoietic cells, rather than from abnormal plasma cells because the plasma cells fail to grow. There are three reasons plasma cells may fail to grow in culture, resulting in the analysis of metaphases from normal cells. First, samples from MM patients may fail because of the low proliferative capacity of the myeloma cells (140). Myeloma cells (especially early myeloma) are stroma dependent, so removing the cells from their supportive microenvironment results in apoptosis and lack of growth. However, if myeloma cells have become stroma-independent (i.e. in advanced stages of the disease), removal of the myeloma cells from their microenvironment can result in proliferation and an abnormal karyotype (140). Another explanation for the laboratory's inability to obtain abnormal metaphases lies in the quality of the bone marrow aspirates received for cytogenetic studies. Aspirates frequently contain drastically fewer plasma cells than the corresponding smear used for morphological assessment since the number of tumor cells in a given specimen largely depends on the level of local bone marrow infiltration, and the degree of sample dilution by bone marrow blood (139). For this reason, it is essential that the first few milliliters of the bone marrow draw be sent for cytogenetic analysis. Also, the needle should be repositioned during aspiration, rather than simply continuing to withdraw marrow from the initial puncture site, to ensure that abnormal cells are submitted to the laboratory. Finally, aspirates should be processed as soon as possible if FISH is requested. Several techniques have been created to selectively culture plasma cells (141), although these methods are imperfect when the sample provided to the laboratory is poor.

Several recurring aberrations are observed in karyotypically abnormal MM. The majority of MM cases are characterized by chromosomal aneuploidy. Four categories of aneuploidy can be defined by karyotyping: hypodiploidy (44 – 45 chromosomes), pseudodiploidy (44/45 - 46/47 chromosomes), hyperdiploidy (HRD, >46/ 47 chromosomes), and near-tetraploidy (>75 chromosomes). Due to the frequent occurrence of chromosomal losses in tetraploid MM cells, near-tetraploidy has been classified together with hypo- and pseudodiploidy as ''non-HRD." Non-HRD is observed in approximately half of tumors. Multiple nonrandom trisomies are associated with HRD tumors (142), especially trisomies of odd numbered chromosomes (141). Karyotypes are typically complex and exhibit more than 10 abnormalities in almost half of patients and even more than 20 aberrations in about 10% of cases.

Translocation of the *IGH* gene on 14q32 to one of several non-random partners is an initial event in the genesis of MM and is seen in about 40% of patients (141). Cyclin D1, D2 and D3 genes (*CCND1*, *CCND2*, and *CCND3*) on chromosomes 11q13, 12p13, and 6p21, respectively, MAF family member genes (*MAF*, *MAFA*, and *MAFB*) on chromosomes 16q23, 8q24, and 20q11, respectively, and the fibroblast growth factor receptor 3 gene (*FGFR3*) on chromosome 4p16, are commonly observed as *IGH* translocation partners (136). *IGH* gene translocations are found more frequently in non-HRD tumors (70%) than in HRD tumors (20%). The t(11;14) and t(4;14) are the most common *IGH* translocations, followed by t(14;16), and the t(14;20) is the least common (139, 141). The overall rate of 14q32 translocations, however, significantly increases with disease progression and reaches up to 90% in advanced tumors and human myeloma cell lines. *IGH* translocation and hyperdiploidy act similarly, through the up-regulation of one of the cyclins (D1, D2 or D3) (140, 142).

While numerical and gross structural changes can be diagnosed without difficulty using the karyotype, small interstitial deletions, partial genomic gains and cryptic translocations (e.g. *IGH* translocations) can be easily overlooked due to the karyotype's limited spatial resolution. Modern molecular-based techniques, such as CGH and FISH, allow the detection of genetic abnormalities independent of proliferating cells. With these methods, chromosomal aberrations are found in more than 90% of patients with MM and most (if not all) patients with MGUS. FISH permits the reliable identification of both translocations and small deletions or gains in MM (139). Most clinical laboratories currently test for 13q34 (*RB1*) and 17p13.1 (*TP52*) deletions as well as the primary translocations t(4;14)(p16.3;q32) and t(11;14)(q13;q32). Ploidy should be determined in all tumors; for example, disomy of chromosome band 13q14 in a near-tetraploid karyotype is functionally a deletion of the region. Polyploidy can be reliably excluded by the use of control probes mapped to genomic regions that rarely display aneuploidy (e.g. chromosomes 2, 10, and 12) (136, 138). Finally, some laboratories test for t(6;14)(p21;q32), t(14;16)(q32;q23) and t(14;20), and detection of the most frequent chromosomal abnormalities (e.g. +1q, +9q, +11q) has also been recommended (137).

Cytogenetics is helpful in determining myeloma patients outcomes (137). Normal metaphases and normal FISH, HRD tumors, and *CCND1* gene activation are associated with a better prognosis (136). However, patients with *MAF*, *MAFB*, or *FGFR3* activation, del(13q), del(17p), hypodiploidy, 1q abnormalities, or 9q trisomies are associated with a worse prognosis (136, 138, 140).

5. CLINICAL CYTOGENETIC EVALUATION OF SOLID TUMORS

Few recurrent cytogenetic aberrations have been reported in solid tumors, relative to their importance in human cancer. For example, malignant epithelial tumors, which cause 80% of human cancer deaths, constitute only about 10% of the reported cytogenetic aberrations in human malignancies (1). A number of analytical problems associated with solid tumor chromosome analysis and

Table 6. Common cytogenetic aberrations in solid tumors

Chromosomal aberration	Comments[1]
t(X;18)(p11.2q11.2)	synovial sarcoma
t(2;13)(q35;q14)	alveolar rhbdomyosarcomas
del(3p)	non-papillary clear cell and granular renal carcinomas
del(11)(p13)	Wilms tumor
t(11;22)(q24;q12)	Ewing's sarcoma
12q15 rearrangements	benign lipomas
t(12;16)(q13;p11.2)	myxoid liposarcoma
t(12;22)(q13;q12)	clear cell sarcomas

[1] See text for a detailed explanation of the aberrations listed.

diminish the value of the existing data. First, the quality of metaphase chromosomes obtained from solid tumors is often poor, complicating analysis and interpretation. Second, unlike in hematological disorders which often exhibit few cytogenetic changes, most solid tumors have excessive numbers of secondary changes already at the time of sampling and diagnosis, making the identification of the various abnormalities difficult at best. Even when the quality of chromosomes is good and each abnormality can be characterized, the distinction between primary and secondary aberrations is more difficult in solid tumors than in hematological malignancies. For example, balanced, simple, and disease-specific changes are found in about one-third of the acute leukemias and malignant lymphomas and 20% of the mesenchymal tumors, but in less than 5% of the epithelial tumors (1). Consequently, large numbers of cytogenetically well-analyzed tumors are required in order to identify the relevant abnormalities for each tumor type. Third, while hematological neoplasms are sampled through minimally invasive procedures (bone marrow aspiration or phlebotomy), solid tumors are obtained via biopsy or surgical resection. Normal tissue within the sample can outgrow the tumor, resulting in a normal karyotype instead of the true tumor karyotype. Similarly, tumors obtained via fine-needle aspiration can result in a minimal sample that is difficult to culture. FISH can be used for minimal or fixed material if the presence of a specific aberration is sought (e.g. *EWSR1* gene rearrangements in bone and soft tissue tumors). Finally, clonal heterogeneity (i.e. cytogenetically unrelated clones) introduces a further dimension of complexity in the analysis of solid tumors. For example, approximately 80% of carcinomas exhibit clonal heterogeneity, compared with less than 5% of leukemias, lymphomas, and mesenchymal tumors (1).

Cytogenetic studies in solid tumors are more often used for a confirmation of a clinical diagnosis, rather than for prognostication, as is common in hematological neoplasms. Cytogenetics does provide prognostic information in some cases (e.g. 1p and N-MYC aberrations in neoblasoma), though further study is clearly needed in this area. The most common cytogenetic aberrations observed in solid tumors are presented in Table 6.

5.1.Bone and Soft tissue tumors

Perhaps the best characterized cytogenetic aberration in mesenchymal tumors is the t(11;22)(q24;q12) translocation in Ewing's sarcoma. In the t(11;22), the *EWSR1* gene on chromosome 22 fuses with the *FL1* gene on chromosome 11 (143). The EWSR1 gene encodes a serine- tyrosine kinase, and the *FL1* gene encodes a member of the ETS transcription factor family (144). The der(22) chromosome results in the fusion of the Ews protein N-terminal kinase domain with the DNA binding domain of human Fli1 protein. Variant translocations exist; virtually all Ewing's sarcomas fuse the *EWSR1* gene to other ETS transcription factor genes.

The most common types of rhabdomyosarcoma are the embryonal and alveolar subtypes, which are difficult to distinguish histologically. However, cytogenetic studies have confirmed that the subtypes are distinct and can be useful in confirmation of diagnosis. Alveolar rhbdomyosarcomas are characterized by reciprocal translocations involving chromosome 13q14, and specifically the *FKHR* gene (forkhead transcription factor). The most common translocation observed in alveolar rhbdomyosarcomas is the t(2;13)(q35;q14) fusing the *PAX3* gene on chromosome 2 to the *FKHR* gene, though variants do occur. Embryonal rhbdomyosarcomas, in contrast, are hyperdiploid with gains of extra copies of chromosomes 2, 8, and 20 frequently occurring. Embryonal rhbdomyosarcomas typically lack *FKHR* translocations.

More than 90% of synovial sarcomas have a characteristic t(X;18)(p11.2q11.2) translocation (145). The t(X;18) fuses the oncogenic *SYT* gene on chromosome 18 with one of two neighboring genes on the X chromosome, *SSX1* or *SSX2* (146). Biphasic synovial sarcoma nearly always exhibits the *SYT-SSX1* fusion. Conversely, the *SYT-SSX2* fusion is found in either biphasic or monophasic synovial sarcoma, and apparently indicates a better long-term prognosis (147).

Nearly all adipose tumors, whether benign or malignant, contain distinctive chromosomal aberrations, making cytogenetics an important diagnostic and/or confirmatory test. Benign lipomas often exhibit chromosome 12q15 rearrangements which disrupt the *HMGIC* gene (148). Other aberrations in benign lipomas include rearrangement of the short arm of chromosome 6 or deletion of the long arm of chromosome 13. Lipoblastomas generally contain translocations involving the long arm of chromosome 8, at bands 8q11-q12. Hibernomas generally have rearrangements of chromosome 11q. A t(12;16)(q13;p11.2) translocation is found in myxoid liposarcoma and is retained in cells that acquire round cell features (149). The t(12;16) fuses the *CHOP* gene on chromosome 12 with the *TLS* gene on chromosome 16, and is not observed in any other liposarcoma subtype. Finally, the well-differentiated liposarcomas (atypical lipomas) usually have characteristic giant marker chromosomes or rings. Both of these SMC subtypes contain various amplified genes from chromosome 12 and other chromosomes, however the essential gene amplification targets for this tumor subtype have not yet been found.

EWSR1 gene rearrangements are observed in more than 75% of clear cell sarcomas in the form of a t(12;22)(q13;q12). This specific translocation has never been observed in cutaneous melanoma and therefore serves as a reliable marker to distinguish the two tumor types. The

t(12;22) fuses the *EWSR1* gene to the *ATF1* gene on chromosome 12. Since the *ATF1* gene codes for a transcription factor, the translocation mechanism is probably similar to that in the Ewing's sarcoma translocations.

Neuroblastomas can be assigned to one of two cytogenetically prognostic groups. Near-diploid or near-tetraploid karyotypes, 1p deletions, or *MYCN* gene amplification are associated with aggressive tumors that respond poorly to therapy. Tumors with near-triploid karyotypes (without 1p or *MYCN* amplification) respond well to chemotherapy and can even undergo spontaneous regression.

5.2. Renal tumors

Many renal tumors contain distinctive chromosomal aberrations that are very specific to the tumor subtype, making cytogenetics an important diagnostic and/or confirmatory test. Characteristic aberrations have been observed in nearly all types of renal cancer, and include deletion of the short arm of chromosome 3 in non-papillary clear cell and granular carcinomas, hypodiploidy in chromophobe tumors, trisomies in papillary carcinoma, and 11p deletions in pediatric tumors.

More than 80% of clear cell and granular non-papillary renal cell carcinomas have 3p deletions, whereas fewer than 10% of papillary renal cell carcinomas disrupt 3p. Chromosome 3p deletions are the most frequently observed cytogenetic aberrations in clear cell and granular non-papillary renal cell carcinomas, found in 70% – 90% in some series (150, 151). The von Hippel-Lindau tumor suppressor gene, *VHL*, located near the telomere of 3p is one target gene deletion. The *FHIT* tumor suppressor locus in band 3p14 is another potential target of these deletions. Because most non-papillary tumors have 3p aberrations, the region may be an attractive target for future therapeutic interventions. At least 10% of clear cell and granular renal cell carcinomas exhibit other nonrandom chromosomal aberrations including extra copies of 5q, trisomy 7, deletion of 17p, and loss of the Y chromosome. However, isolated trisomy 7 or loss of the Y chromosome are often observed in other non-neoplastic tissues (particularly in elderly men) and therefore may not be distinctly associated with cancer.

Most chromophobe carcinomas have extremely hypodiploid karyotypes containing thirty-one to thirty-seven chromosomes, typically with monosomies of chromosomes 1, 2, 6, 10, 13, 17, and 21. Demonstration of a hypodiploid karyotype can be useful in distinguishing chromophobe tumors from clear cell/granular renal cell carcinoma and oncocytoma, since chromosome counts below 40 are rarely observed in the other types.

Renal adenomas and papillary carcinomas often have trisomies of chromosomes 7, 16, or 17, and loss of the Y chromosome, which are each found in at least 50% of these tumor subtypes. Trisomies of chromosomes 3, 8, 12, and 20 are also non-randomly found; they are observed in 10% – 50% of papillary carcinoma.

Wilms tumor is the most common type of renal cancer in children. At least 10% of cases display one or more cytogenetic aberration (152). These include trisomies of chromosomes 6, 8, 12, and 18, deletions of 11p13, 11p15, and 16q (152-154). The 11p13 deletion is the best studied aberration in Wilms tumor because children with the contiguous gene deletion syndrome WAGR (Wilms tumor, aniridia, genitourinary malformations, and retardation) have constitutional deletions of this region. The Wilms tumor suppressor gene (*WT1*) is completely inactivated in most if not all WAGR patients, although it is interrupted in only about 20% of sporadic Wilms tumors.

Benign oncocytomas have distinctive cytogenetic features and lack the various cytogenetic aberrations found in malignant renal tumors. About 30% - 50% of oncocytomas exhibit the loss of one copy of chromosomes 1 and a sex chromosome (either X or Y). Translocations involving 11q13 are also frequently observed. Importantly, oncocytomas lack the 3p deletions that characterize the clear cell/granular renal cell carcinomas.

5.3. Breast carcinoma

Traditional cytogenetic studies are typically not performed in the routine diagnostic evaluation of breast cancer, but FISH studies are hugely important in the prognostic and therapeutic evaluation of tumors. Amplification of either the *ERBB2* gene (chromosome 17q11.2) or *MYC* (chromosome 8q24), as detected by FISH, is associated with a poor prognosis. However, *ERBB2* amplification indicates that the patient may benefit from antibody therapy with Herceptin, an antibody therapy which targets the protein encoded by *ERBB2*, Her2/neu. Although Her2/neu over expression can be detected by immunohistochemistry (IHC), FISH has the advantage of internal control, and is therefore considered by some the "gold standard" for detection of *ERBB2* gene amplification. In *ERBB2* FISH, technologists not only look for an increase in the number of copies of the gene, but can detect polysomy (increase in number of all chromosomes in the cell) and can observe the expected two *ERBB2* signals in normal tissue surrounding the tumor. FISH does have some disadvantages over IHC; FISH is more expensive, takes longer to prepare and interpret, and the slides are difficult to preserve for future analysis. Two versions of the FISH assay have been approved by the Food and Drug Administration (FDA), Ventana's Inform™, and Abbott-Vysis's PathVysion™. Published studies indicate that FISH and IHC are highly correlative (155).

5.4. Bladder cancer

The cytogenetic profiles of bladder cancers are not as well characterized as renal tumors. However, trisomy 7 and deletions of several chromosomal regions (e.g. 8p, 9p, 9q, and 17p) are associated with bladder cancer (156, 157). FISH is routinely used to detect these cytogenetic aberrations, which are associated with histologic progression in bladder cancer. Abbott-Vysis sells an FDA-approved version of the FISH assay, called UroVysion, which detects gains of chromosomes 3, 7, and/or 17, and loss of 9p21. FISH is particularly useful in studies of sample types where few cells are likely to be available for

analysis, such as urine specimens. FISH might be useful for detection of bladder neoplasms in high-risk individuals (e.g. unexplained hematuria), though the clinical utility for uses other than bladder cancer need to be further evaluated.

5. CONCLUSIONS AND PERSPECTIVES

As described above and evidenced by several examples provided, tumor markers are commonly used for screening, diagnosis and prognosis of specific malignancies. The number of clinically significant molecular markers described in different cancers is rapidly increasing. The methods used to detect these markers commonly involve IHC and cytogenetics, including FISH, and RT-PCR. These techniques and the emerging microarray technology combined with highly sophisticated bioinformatics have begun to satisfy the perpetual demand for new markers that predict the outcome of a certain treatment regimen and especially for specific molecular alterations to which cancer therapy can be targeted. The genetic markers will allow elucidation of the underlying pathogenetic mechanisms and the differing biology disease subtypes. Cytogenetic and molecular genetic methods have thus ushered in a completely new era in the follow-up of custom-tailored treatments. In addition, screening for these genetic changes will not only lead to the discovery of novel tumor-specific fusion, amplified, or deleted genes, but will be used in the future for evaluation of prognosis and therapy choices. This will undoubtedly play a major role in future treatment strategies.

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Abbreviations: aCGH: array-based comparative genomic hybridization, ALCL: anaplastic large cell lymphoma, ALL: acute lymphocytic leukemia, AML: acute myeloid leukemia, BAC: bacterial artificial chromosome, BL: Burkitt lymphoma, CEL: chronic eosinophilic leukemia/hypereosinophilic syndrome, CGH: comparative genomic hybridization, CIMF: chronic idiopathic myelofibrosis, CLL: chronic lymphocytic leukemia, CML: chronic myelogenous leukemia, CNL: chronic neutrophilic leukemia, ET: essential thrombocythemia, FISH: florescent in situ hybridization, HMCL: human myeloma cell lines, HRD: hyperdiploid, HSR: homologously staining region, IHC: immunohistochemistry, LDH: lactose dehydrogenase, LOH: loss of heterozygocity, MDS: myelodysplastic syndromes, MGUS: monoclonal gammopathy of undetermined significance, MM: multiple myeloma, MPD: myeloproliferative disorders, MPD-U: unclassifiable chronic MPD, Ph: Philadelphia chromosome, PLL: prolymphocytic leukemia, PV: polycythemia vera, SMC: supernumerary marker chromosome, SMM: smoldering myeloma.

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