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Review

DNA Copy Number Losses in Human Neoplasms

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This review summarizes reports of recurrent DNA sequence copy number losses in human neoplasms detected by comparative genomic hybridization. Recurrent losses that affect each of the chromosome arms in 73 tumor types are tabulated from 169 reports. The tables are available online at http://www.amjpathol.org and http://www.helsinki.fi/~lgl_www/CMG.html. The genes relevant to the lost regions are discussed for each of the chromosomes. The review is supplemented also by a list of known and putative tumor suppressor genes and DNA repair genes (see Table 1, online). Losses are found in all chromosome arms, but they seem to be relatively rare at 1q, 2p, 3q, 5p, 6p, 7p, 7q, 8q, 12p, and 20q. Losses and their minimal common overlapping areas that were present in a great proportion of the 73 tumor entities reported in Table 2 (see online) are (in descending order of frequency): 9p23-p24 (48%), 13q21 (47%), 6q16 (44%), 6q26-q27 (44%), 8p23 (37%), 18q22-q23 (37%), 17p12-p13 (34%), 1p36.1 (34%), 11q23 (33%), 1p22 (32%), 4q32-qter (31%), 14q22-q23 (25%), 10q23 (25%), 10q25-qter (25%),15q21 (23%), 16q22 (23%), 5q21 (23%), 3p12-p14 (22%), 22q12 (22%), Xp21 (21%), Xq21 (21%), and 10p12 (20%). The frequency of losses at chromosomes 7 and 20 was less than 10% in all tumors. The chromosomal regions in which the most frequent losses are found implicate locations of essential tumor suppressor genes and DNA repair genes that may be involved in the pathogenesis of several tumor types. *(Am J Pathol 1999, 155:683–694)*

Knowledge of chromosomal deletions has significantly contributed to the detection of tumor suppressor genes, since the inactivation of one allele, according to the two-hit hypothesis, often results from a deletion on the chromosomal level.[1] Massive deletions often obliterate entire chromosomes (monosomy) or chromosome arms in tumor tissue. A typical example of this underlying event led to the discovery of the *RB1* (retinoblastoma 1) gene. Chromosome studies have revealed a great number of deletions which indicate presence of tumor suppressor genes or DNA repair genes in corresponding regions.[2]

As methodological problems in the cytogenetic analysis of solid tumors have restrained attempts to apply standard techniques to screening for deleted chromosomal areas, comparative genomic hybridization (CGH) has been proven to be a powerful genome-wide screening method. Since the CGH technique was introduced in 1992, studies using this method have been reported in about 200 papers that describe a great number of recurrent deleted chromosomal areas in a wide variety of human neoplasms.[3,4] The Peutz-Jeghers syndrome is the first example of how CGH suggested the chromosomal region to which the tumor suppressor gene *STH11/LKB1* (serine/threonine kinase) was mapped.[4] Here we summarize 170 reports of DNA sequence copy number losses detected by CGH in 73 tumor types. We aimed to cover all relevant papers published by the end of 1998.

Comparative Genomic Hybridization Reveals DNA Copy Number Imbalances

Comparative genomic hybridization allows DNA copy number losses and gains to be studied in one hybridization experiment.[3] CGH methodology has been described and discussed in detail previously.[5,6]

Comparative genomic hybridization is sensitive for detecting deletions that are 10 to 20 megabases in size.[7,8]

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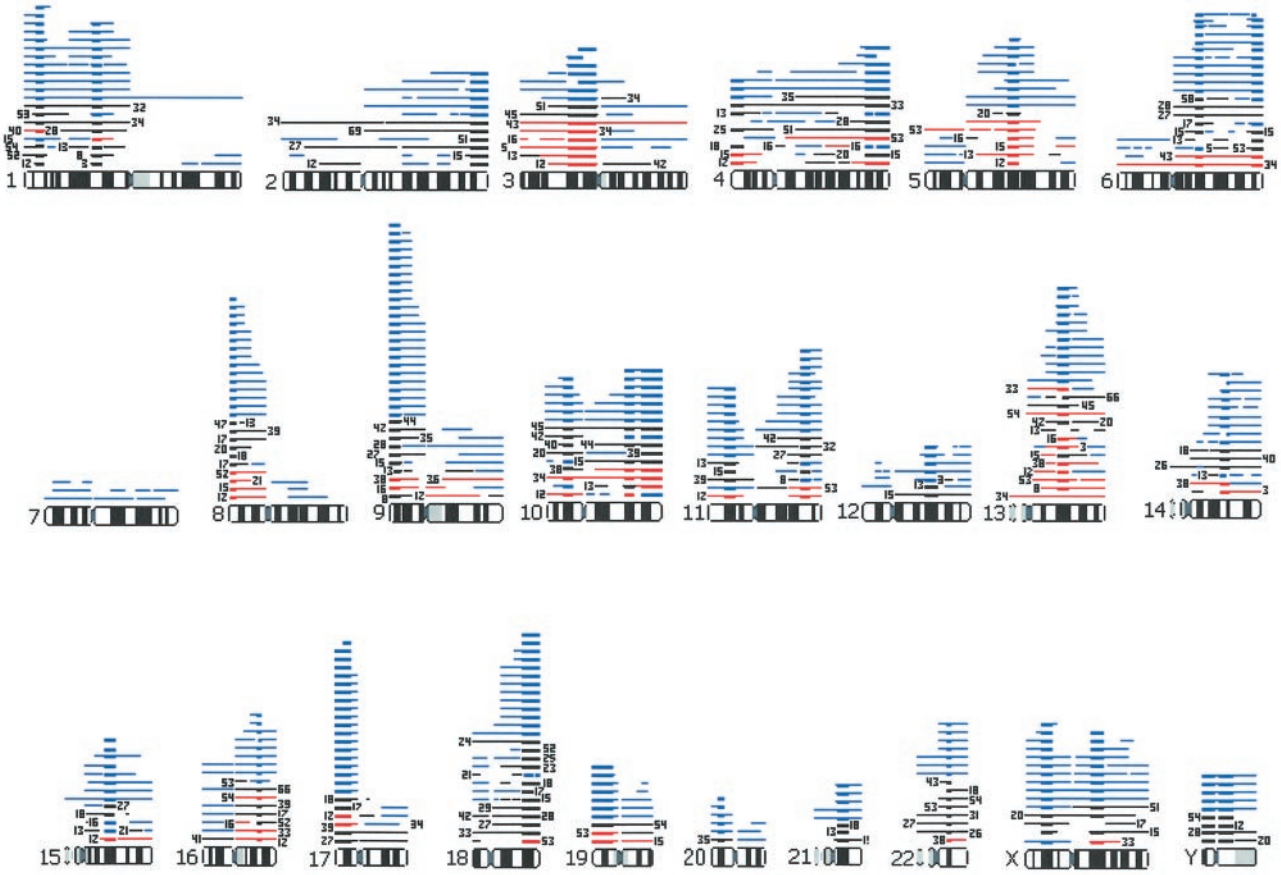

Figure 1. Summary of losses in 73 tumor entities reported in Table 2. Each line by a chromosome arm represents a tumor entity. Red and black lines indicate that the loss was found in at least 30% of the cases in that particular tumor type (numbers refer to numbering in Table 2 online). A red line signifies that two different publications reported the loss, and a black line shows that the loss was published in one report only. A blue line indicates that the loss was involved in 10 to 29% of the cases. A bold line shows the smallest common overlapping area of the losses.

The present paper and our previous review of DNA copy number amplifications can be accessed electronically at http://www.amjpathol.org and http://www.helsinki.fi/~lgl_www/CMG.html.

Recurrent DNA Copy Number Losses

Recurrent losses in different tumor types are shown in Table 2[197] (online). We define a loss to be recurrent when its frequency in a certain tumor type is at least 10% and the number of aberrant cases is at least three. If a particular loss is observed in at least 30% of the cases and the loss has been reported in at least two publications, it is considered to be an established loss and indicated in bold type in Table 2. An asterisk in Table 2 indicates that the loss was located within the area but did not necessarily affect the whole area in all cases. As a whole, the description should be considered a flexible way to summarize critical areas of recurrent DNA copy number changes in each tumor type. A description without an asterisk indicates minimal overlapping areas. Figure 1 is a compilation of the recurrent losses in 73 tumor entities presented in Table 2. The most common losses (Figure 1) were 9p, 13q, and 6q, found in 35, 34, and 32 of the 73 tumor entities (48%, 47%, and 44%). The corresponding minimal overlapping regions were 9p23-p24, 13q21, 6q16, and 6q26-q27. Other frequent losses involved 8p (37%), 18q (37%), 17p (34%), 1p (34%), 11q (33%), and 4q (31%), with minimal overlapping regions at 8p23, 18q22-q23, 17p12-p13, 1p36.1, 11q23, 1p22, and 4q32-qter. Other recurrent losses involved 2q (16%), 3p (22%), 4p (21%), 5q (23%), 10p (21%), 10q (25%), 11p (19%), 12q (13%), 14q (25%), 15q (23%), 19p (13%), 21q (10%), 22q (22%), X (22%), and Y (12%), with minimal overlapping regions at 2q36-qter, 3p12-p14, 4p16, 5q21, 10p12, 10q23, 10q25-q26, 11p14, 12q21, 14q22-q23, 15q21, 19p13.1-pter, 21q21, 22q12, Xp21, Xq21, Yp, and Yq11-q12. The frequency of recurrent losses at chromosomes 7 and 20 was less than 10% in all tumors.

Known and Putative Tumor Suppressor Genes and DNA Repair Genes in Chromosomal Regions with Recurrent Losses

Table 1[197] (online) shows examples of known and putative tumor suppressor genes and DNA repair genes. Their association with each of the chromosomes is discussed below.

Chromosome 1

The most relevant candidates may be *MTS1/SA1/TFS1* (1pter-p22.1; malignant transformation suppression-1), *ID3* (1p36.13-p36.12; inhibitor of DNA binding 3), *NB/NBS* (1p36.13-p36.11; neuroblastoma suppressor), *TNFR2* (1p36.3-p36.2; tumor necrosis factor receptor 2), *DAN* (1p36.13-p36.11; differential-screening-selected gene aberrant in neuroblastoma), *CDC2L1* (1p36; cell division cycle 2-like 1), *MOM1/PLASG2* (1p35; phospholipase A2), and *BRCD2* (1p36; breast cancer suppressor-2). Recently the *P73* gene was mapped to 1p36 and its protein is known to share considerable homology with the tumor suppressor *p53*. 1p36 is a frequently deleted region in neuroblastoma and other tumors. Disregulation of P73 may therefore contribute to their tumorigenesis.[9,10] However, no clear evidence supporting the importance of the loss of any of these genes has been published.

Chromosome 2

The mismatch repair genes *MSH2, MSH6/GTBP*, and *PMS1* have been assigned to 2p22-p21, 2p16, and 2q32, respectively.[11]

Chromosome 3

Losses of DNA sequences at chromosome 3 mostly involve the short arm. Using standard cytogenetic and loss of heterozygosity (LOH) methods, four regions at 3p, which have been implicated to encompass putative tumor suppressor genes, have been recognized. They span bands p12, p14.2, p21.3, and p25 (reviewed by Le Beau et al).[12] The tumor suppressor gene *VHL* (von Hippel-Lindau) locates at 3p25-p26. Germline mutations of this gene are found in patients with the von Hippel-Lindau disease, a familial cancer syndrome with susceptibility to the development of several neoplasms, such as renal cell carcinoma.[13] Mutations in *VHL* have also been reported to occur in sporadic renal cell carcinoma tumors (30 to 60%), with most of them displaying homozygous loss (reviewed by Decker et al),[14] as well as in other tumor types.[13] Another important gene in 3p is the *FHIT* (fragile histidine triad) gene that spans the fragile site FRA3B at 3p14.2. Several tumor types, including lung, pancreatic, and head and neck squamous cell carcinomas as well as gastrointestinal cancers, have been reported to display alterations of the *FHIT* gene.[15–18] However, because some analyses have shown similar alterations of *FHIT* in both malignant and nonmalignant tissues[19,20] and because studies using a non-nested polymerase chain reaction technique[20,21] show some discrepancies with the first reports, the role of *FHIT* as a possible tumor suppressor gene needs to be further clarified (reviewed by Le Beau et al).[12] A recent paper reports progress in the search of putative tumor suppressor gene(s) at 3p21.3 by the identification of a homozygous deletion in a breast cancer cell line and its corresponding tumor.[22] DNA mismatch repair gene *MLH1* resides at 3p21.3-p23 and DNA repair gene *XPC*, which was found mutated in xeroderma pigmentosum syndrome type C, is located at 3p25.[23]

Chromosome 4

In breast cancer, loss of chromosome 4 was significantly more common in hypodiploid tumors.[24] So far no tumor suppressor gene has been identified on chromosome 4, but some CGH and LOH results clearly indicate regions in chromosome 4 to which a yet unidentified tumor suppressor gene will be assigned.[24–28] In esophageal adenocarcinoma, high frequency of LOH has been observed in regions 4q21–25, 4q21-qter, and 4q33-q35.[25] One of the critical areas in testicular cancer is 4cen-q13. Three candidate genes located in or close to this area have been suggested, *AFP* (α-fetoprotein gene), *ALB* (embryonal protein gene), and *KIT* (tyrosine kinase receptor gene).[26]

Chromosome 5

A myeloid tumor suppressor locus was recently mapped to 5q31.1,[29,30] which is consistently lost in myeloid neoplasms with 5q aberrations.[30] Two tumor suppressor genes, *APC* (adenomatosis polyposis coli) and *MCC* (mutated in colorectal cancer), which have been mapped to 5q21-q22, are mainly involved in colorectal cancer. Somatic mutations in *APC* have been identified in colorectal tumors as well as in some cancers of stomach, pancreas, thyroid, and ovary.[31] DNA mismatch repair gene *MSH3* is located at 5q11-q12.

Chromosome 6

p21/WAF/CDKN1A (6p21.2; cyclin-dependent kinase inhibitor 1A) is considered to be a putative tumor suppressor gene. So far no tumor suppressor gene has been identified at 6q. However, microsatellite marker analyses on different malignancies, such as breast and ovarian carcinoma, NHL, and malignant mesothelioma have revealed several regions at 6q showing allelic imbalance suggesting the existence of one or more tumor suppressor genes.[32–37] Moreover, chromosome 6 transfer experiments have implicated the chromosomal regions 6q23-q25 and 6q24-q25 as the locations for putative tumor suppressor genes involved in breast and ovarian cancer, respectively.[33,38] One candidate tumor suppressor gene is *LOT-1/hZAC* (lost on transformation 1) at 6q24-q25.[39,40]

Chromosome 7

Cytogenetic data indicate that complete and interstitial deletions of chromosome 7 are among the most common solely occurring cytogenetic aberrations in myeloid neoplasms.[41] Both 7p and 7q have been suggested to be locations of putative tumor suppressor genes. However, no tumor suppressor gene has so far been identified, but at least two distinct critical areas, 7q22 and q31, have

been suggested in different solid tumors.[42–45] Involvement of more than one critical region in 7q has been shown in myeloid disorders as well,[46,47] and correlation between poor prognosis and a factor located at 7q31 has been reported.[48] DNA mismatch repair gene *PMS2* is located at 7p22.

Chromosome 8

In bladder carcinomas loss of 8p has been associated with invasive tumor growth.[49,50] In breast, prostate, and small-cell lung carcinomas loss of 8p is often detected in association with gain at 8q, suggesting isochromosome 8q formation. LOH studies on different tumor types have often shown two or three independent regions of deletion at 8p, which may indicate that more than one tumor suppressor gene is located on this chromosome arm.[51–54] The 8p region has been suggested to harbor several candidate tumor suppressor genes. Recently, a gene frequently deleted in human liver cancer (*DLC1*, dynein light-chain gene 1) was isolated and localized at 8p21.3-p22.[55] Located at the same band is *PRLTS* (PDGF-receptor β-like tumor suppressor), which has been found to be altered in a few cases of hepatocellular, colorectal, and non-small-cell lung carcinomas.[56] A third breast cancer susceptibility gene has been suggested to reside at 8p12-p22,[57] and recently a third *EXT*-like gene [*EXTL3*, exostoses (multiple)-like 3] has been identified in the same region.[58] *EXT1*, a putative tumor suppressor gene, is located at 8q24.1.

Chromosome 9

Band 9p21 contains a tumor suppressor gene, *CDKN2A* (cyclin-dependent kinase inhibitor 2A), which encodes a cell-cycle inhibitor, p16.[59,60] Deletions at the locus often encompass and inactivate a gene nearby, *CDKN2B (p15)*, which has similar functions as *CDKN2A*.[61] High frequency of *CDKN2A* alterations has been observed in many primary malignancies. Small homozygous deletions represent a major mechanism of the inactivation of the gene.[61–74] Germline alterations of *CDKN2A* are frequent in kindreds with familial melanoma, and *CDKN2A* has been suggested to be a familial melanoma gene.[66,75–77] In some reports of acute lymphoblastic leukemia, *CDKN2A* deletions have been associated with adverse prognostic factors[71–73] and also with poor rate of event-free survival.[74,78]

LOH studies of transitional cell carcinoma of the bladder have revealed at least three common regions of deletion at 9q: 9q13-q31, 9q32-q33, and 9q34.[79–81]

The locus for the nevoid basal cell carcinoma syndrome, an autosomal dominant disorder that predisposes to basal cell carcinomas, ovarian fibroma, and medulloblastoma, has been mapped to the 9q22.3-q31 region by linkage analysis.[82–85]

In bladder cancer (9q32–33; *DBCCR1*, deleted in bladder cancer chromosome region candidate 1) and in ovarian carcinoma (9q31 and 9q32-q34) three candidate tumor suppressor genes/areas have been suggested,[68,86] and in lung carcinoma Suzuki et al[87] suggested tuberous sclerosis complex 1 (*TSC1*)-associated region at 9q34 as a candidate locus for a tumor suppressor gene.

DNA repair gene *XPA*, which was found mutated in xeroderma pigmentosum syndrome type A, is located at 9q22.3-q31.[88] Nearby, at 9q22.3 resides *PTCH*, a candidate gene for basal cell nevus syndrome characterized by postnatal cell carcinomas and developmental abnormalities.[89]

Chromosome 10

Although no tumor suppressor gene has been mapped to 10p, both functional studies and direct analysis of human tumors strongly support the idea that at least one, and possibly two, tumor suppressor genes for prostate cancer and human gliomas are present on 10p.[90,91]

Recent studies of the 10q23 region have led to the isolation of a candidate tumor suppressor gene, *PTEN* (phosphatase and tensin homolog), that appears to be mutated at a considerably high frequency in human cancers, eg, in breast cancer and thyroid cancer. In preliminary screenings, mutations of *PTEN* have been detected in glioblastoma, prostate cancer, breast cancer, and endometrial carcinoma.[92–94] Moreover, the 10q region is known to contain the *MXI1* gene assigned to 10q24-q25. The *MXI1* (MAX-interacting protein 1) gene may negatively regulate *CMYC* oncogene (V-MYC avian myelocytomatosis viral oncogene homolog) activity and have a tumor suppressing function. Altered *MXI1* function as such might contribute to tumorigenesis.[95,96]

Chromosome 11

The short arm of chromosome 11 harbors a number of known tumor suppressor genes, eg, *WT1* (Wilms' tumor 1) at 11p13 and *WT2* (Wilms' tumor 2) and a cyclin-dependent kinase inhibitor (*CDKN1C*) at 11p15.5, a tumor susceptibility gene 101 (*TSG101*) at 11p15.1–p15.2, a metastasis suppressor gene for prostate cancer *KAI1* (Kangai 1) at 11p11.2, and a putative tumor suppressor gene *EXT2* at 11p11-p12. Furthermore, a liver tumor suppressor gene has been localized at 11p11.2-p12.[97] It is not known whether these genes are lost in the above-mentioned tumor types, but the involvement of the known tumor suppressor genes or novel genes deserves further study.

In breast cancer, CGH studies have shown that the entire 11q or the region at 11q14-qter are most commonly affected. In several tumors, the minimal common region of 11q deletion has been mapped to 11q22-q23 by LOH studies.[98–107]

11q is a very gene-rich area but contains only a few identified tumor suppressor genes. The *ATM* (11q22.3, ataxia telangiectasia mutated) gene, altered in some forms of leukemia, has a role in cell cycle check point control, genome surveillance, and cellular defense against oxidative stress, and has been considered to function as a tumor suppressor gene.[108] Recently *PPP2R1B* [protein phosphatase 2 (formerly ZA at 11q22-

q24), regulatory subunit A(PR6) β isoform], a gene which encodes a subunit for serine/threonine protein phosphatase, was identified as a putative tumor suppressor gene in lung and colon cancer.[109] In most cases the mutation in one allele was accompanied by the deletion of the other allele. *MEN1*, a gene located at 11q13, is defective in multiple endocrine neoplasia type 1 which is characterized by the occurrence of tumors of the parathyroid glands, the pancreas, and the pituitary gland.

Chromosome 12

The 12p13 region contains the *TEL* [for translocation, E Twenty-six Specific (ETS), leukemia] (*ETV6)* gene, which encodes a member of the ETS-like family of transcription factors.[110] In the cryptic translocation t(12;21) (p13;q22) of childhood acute lymphoblastic leukemia (ALL), *TEL* is fused to the *AML1* gene.[111,112] *AML1* encodes a DNA-binding subunit of the AML1/CBFB transcription factor complex.[113] This translocation is the most common molecular genetic aberration of childhood ALL, occurring in approximately 25% of the patients, and it is associated with a favorable outcome.[114–118] The nontranslocated allele of *TEL* is frequently deleted in connection with the translocation.[119,120] Raynaud et al[121] showed this deletion to be a secondary event that occurred after the translocation. Cavé et al[120] reported deletion of *TEL* in 34 of 44 patients with t(12;21) (77%). In contrast, homozygous deletion of *TEL* is a rare event in childhood ALL.[119] 12q13 harbors also a cyclin-dependent kinase inhibitor, *CDKN1B*, that using a mouse model has been shown to have a role in cell proliferation control. So far, little is known of putative candidate genes located at 12q.

Chromosome 13

RB1 (retinoblastoma 1) at 13q14.3 is one of the best studied tumor suppressor genes.[122–124] Hereditary retinoblastoma is caused by a germline mutation of *RB1*.[125,126] This finding gave support to the two-hit hypothesis proposed by Knudson in 1971.[1] *RB1* is defective in several cancers, eg, osteosarcoma, soft tissue sarcoma, small-cell lung carcinoma, breast, and bladder cancer.[122]

13q14 contains the recently reported genes *LEU1* (leukemia associated gene 1) and *LEU2* (leukemia associated gene 2) which are strong candidates as tumor suppressor genes relevant to chronic lymphocytic leukemia.[127] 13q14 losses in this region have been detected by CGH in 11 to 12% of chronic lymphocytic leukemia.[128,129]

Germline mutations in *BRCA2* (13q12.3; breast cancer 2) confer an increased risk for breast cancer.[130,131] Germline mutations predispose the carriers also to ovarian cancer, prostate cancer, and male breast cancer. A CGH study of breast cancers from mutation carriers revealed a loss at the *BRCA2* locus at a high frequency (73%), indicating the loss of the wild-type allele.[132]

ING1 (inhibitor of growth 1), a candidate tumor suppressor gene, was recently cloned and mapped to 13q34.[133,134] This region is known to contain alterations in squamous cell carcinomas of the head and neck.[135] By CGH, losses in this region have been detected in 50% of squamous cell carcinoma of the head and neck.[136]

Chromosome 14

There is no known tumor suppressor gene at 14q. Several LOH studies at 14q have been performed on different tumors. Analyses on ovarian and bladder carcinomas have shown similar results revealing two regions, one at 14q12-q13 and another at 14q32, to be the most frequent areas to show LOH.[137,138] 14q32.1-q32.2 was also found to exhibit LOH in renal oncocytomas.[139] 14q23-q24.3 and 14q24.2-qter were implicated as regions for frequent deletions in renal oncocytomas and nonpapillary renal cell carcinomas, respectively.[139,140] These data implicate the possibility of several tumor suppressor genes at 14q, which could be important in many different types of tumor.

Chromosome 15

It has been suggested that a putative tumor suppressor gene, which may play a role in the later stages of carcinogenesis and be associated with metastasis in breast cancer, is located at 15q14.[141]

Chromosome 16

The level of *RB2/p130* (16q12.2, retinoblastoma-like 2) expression is inversely related to histological grade and the development of metastases in lung cancer,[142] and a decreased level of pRb2/p130 is associated with increased risk of recurrence and death in endometrial cancer.[143] Expression of *CMAR* (16q24.3; cell matrix adhesion regulator) mRNA is frequently diminished in colorectal cancer[144] and in hepatocellular carcinoma.[145] Recently a putative tumor suppressor gene *CTCF* (CCCTC-binding factor) has been localized to 16q22.1 and it is a candidate for breast cancer tumorigenesis.[146] Mutations including large deletions in *TSC2* (tuberous sclerosis 2), located at 16p13.3, are found in patients with tuberous sclerosis, indicating its role to act as a tumor suppressor.[147] E-cadherin, the *CDH1* gene (16q22.1, cadherin 1) has been suggested to act as a tumor/invasion suppressor for sporadic infiltrative lobular breast carcinomas.[148] H-cadherin, the *CDH13* gene (16q24.2-q23, cadherin 13), has been reported to be inactivated due to deletions and hypermethylations in lung cancer.[149]

Chromosome 17

One of the best known tumor suppressor genes, *TP53*, is located at 17p13.[150] It codes for a protein, p53, that acts as a transcription factor and prevents damaged DNA from replicating.[151,152] Losses or other inactivating mutations in *TP53* are possibly the most common genetic

changes in cancer.[153,154] Other well known tumor suppressor genes located at chromosome 17 are *BRCA1* (breast cancer 1) (17q21) and *NF1* (neurofibromatosis 1) (17q11.2). *BRCA1* codes for a component of the RNA polymerase II holoenzyme.[155] Mutations in *BRCA1* are thought to be responsible for 52% of inherited breast cancer and 81% of inherited breast and ovarian cancer.[156] *NF1* codes for neurofibromin, which stimulates the GTPase activity of ras.[157] Mutations in neurofibromin are associated with type 1 neurofibromatosis.

Chromosome 18

The band q21 includes two known tumor suppressor genes, *DPC4* (deleted in pancreatic carcinoma 4) (*SMAD4*) and *DCC* (deleted in colorectal cancer). *DPC4*, a member of the *MAD* gene family, is involved in signal transduction of serine threonine kinase receptors.[158] Its inactivation occurs in almost half of pancreatic carcinomas[158] but is uncommon in other tumor types.[159–161] However, studies in colorectal cancer cells and *DPC4* mutated mice have suggested that *DPC4* has a role in the progression of colorectal tumors.[162,163] The *DCC* gene (deleted in colorectal cancer) encodes a netrin receptor.[164] Recently, *DCC* has been found to induce apoptosis in the absence of ligand binding.[165] Originally, deletions and mutations of *DCC* have been found in colorectal carcinomas.[166] Moreover, inactivation of *DCC* has been found in breast, prostate, pancreatic, and gastric cancer, in glioma and osteosarcoma, and in some hematological malignancies.[167–173] The 18q21 region harbors also another member of the *MAD* gene family, *MADR2* (MAD-related protein 2) (*SMAD2*), which has been proposed to be a tumor suppressor gene.[174] No currently known tumor suppressor gene has been assigned to 18p.

Chromosome 19

A serine/threonine kinase *STK11/LKB1* (19p13.3), found to be responsible for the Peutz-Jeghers syndrome, has been cloned recently.[4] *STK11/LKB1* is the first example of cloning in which the role of CGH was essential in indicating the chromosomal location.[175] Another candidate gene in 19 is *EXT3* [exostoses (multiple) 3]. By using linkage analysis, one of the loci of hereditary multiple exostoses, *EXT3*, has been assigned to 19p.[176] It has been suggested that *EXT3* has tumor suppressing functions. Cyclin-dependent kinase inhibitor 2D (19p13; *CDKN2D*) belongs to the INK4 family. One member of the *INK4* family, *CDKN2A*, has been shown to function as a tumor suppressor in a variety of cancers (Table 1).

The *BAX* (BCL2-associated X protein) gene (19q13.3) is a primary-response gene for *p53*, involved in a *p53*-regulated pathway for induction of apoptosis.[177] *BAX* forms heterodimers with *BCL2* and reduces the death-repressing activity of *BCL2*.[178] The gene coding for ZIP kinase is also located in 19q13.3. ZIP kinase induces morphological changes in apoptosis in mammalian cells when overexpressed, suggesting that it plays an important role in the induction of apoptosis.[179] Three functionally related genes, *XRCC1* (X-ray-repair complementing defective in Chinese hamster 1),[180] *ERCC1* (excision repair complementing defective repair in Chinese hamster 1),[181] and *ERCC2* (excision repair complementing defective repair in Chinese hamster 2),[182] are located close to 19q13.2-q13.3. Several different lines of evidence have shown that these gene products play an important role in both UV cross-link repair and nucleotide excision repair.

Chromosome 20

Chromosome banding analysis has revealed recurrent deletions at 20q in myeloproliferative diseases and myeloid leukemias.[2] No CGH study of a large series of patients with these diseases has been reported so far.

No known tumor suppressor genes have been found in chromosome 20. Several candidate genes and novel ESTs (expressed sequence tags) have been identified in studies of deletions of chromosome 20q in myeloid disorders. The common deleted region (CDR) in cells of myeloid leukemia patients was narrowed down to 8 megabases at 20q12 by Wang et al[183] and a YAC contig was constructed on the CDR.[184] The plausible candidate genes in the CDR include *PLCG1* (phospholipase C, γ 1), *HNF4* (hepatocyte nuclear factor 4), *TOP1* (topoisomerase 1), *MYBB* (myeloblastosis viral oncogene homolog-like 2), *ADA* (adenosine deaminase), and *CD40*.[183–186]

Chromosome 21

No known tumor suppressor genes have been found on chromosome 21. Furthermore, evidence of any candidate gene for tumor suppression in this chromosome appears to be very scarce.

Chromosome 22

The long arm of chromosome 22 contains the tumor suppressor gene neurofibromatosis type 2 (*NF2*) at 22q12,[187] but there is also evidence for the presence of another putative tumor suppressor gene distal to *NF2*.[188]

Chromosome X

No currently known tumor suppressor gene has been located to chromosome X. LOH studies of chromosome X on ovarian, endometrial, cervical, and breast cancer and on renal oncocytomas,[97,189–196] however, suggest that the chromosomal regions Xp11-p22, Xq12, X25-q26, and Xq28 could harbor tumor suppressor genes.

Chromosome Y

The genes involved with loss of Y have not yet been identified.

Conclusion

Our review (Table 2) shows that CGH has provided an enormous amount of data on DNA sequence copy number losses. Because the number of cases studied for many tumor types is less than 20, it is hardly possible to draw reliable conclusions based on the frequencies of losses. At this stage we can, however, conclude the following. Losses are found in all chromosome arms, but they seem to be relatively rare at 1q, 2p, 3q, 5p, 6p, 7p, 7q, 8q, 12p, and 20q (Figure 1). Losses and their minimal common overlapping areas that were present in a great proportion of the 73 tumor entities reported in Table 2 are (in descending order of frequency): 9p23-p24 (48%), 13q21 (47%), 6q16 (44%), 6q26-q27 (44%), 8p23 (37%), 18q22-q23 (37%), 17p12-p13 (34%), 1p36.1 (34%), 11q23 (33%), 1p22 (32%), 4q32-qter (31%), 14q22-q23 (25%), 10q23 (25%), 10q25-qter (25%),15q21 (23%), 16q22 (23%), 5q21 (23%), 3p12-p14 (22%), 22q12 (22%), Xp21 (21%), Xq21 (21%), and 10p12 (20%).

The minimal overlapping areas presented above are merely approximations derived from the large number of original results. The reader should also take into consideration that in many original papers the results from subtelomeric and subcentromeric areas as well as from the problematic chromosomal regions at 1p, 16p, 17p, 19, 22, and Y have been interpreted with great caution. Despite the inaccuracy, the common losses are chromosomal areas in which essential (known and putative) tumor suppressor genes most probably reside. Relevant cancer genes or candidate genes have been discussed above in connection with each of the chromosomes under the heading Recurrent DNA Copy Number Losses.

Even when the above-mentioned common losses are seen in a wide variety of tumor entities, there seem to be tumor types that do not contain these losses or the frequency of these losses is very low. For example, in hematological neoplasms the loss at 11q23 seems to be restricted to mantle cell lymphoma and chronic lymphocytic leukemia. Losses at 7 and 20q are usually rare, but according to karyotype analysis these losses are recurrent in myeloid neoplasias. Excluding these examples, it is too early to draw conclusions about tumor-specific losses. Before the clinical significance of recurrent losses can be interpreted, more data need to be analyzed.

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