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Pathogenesis and Consequences of Uniparental Disomy in Cancer

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Abstract

Systematic application of new genome-wide single nucleotide polymorphism arrays has demonstrated that somatically acquired regions of loss of heterozygosity (LOH) without changes in copy number frequently occur in many types of cancer. Until recently, the ubiquity of this type of chromosomal defect had remained unrecognized as it cannot be detected using routine cytogenetic technologies. Random and recurrent patterns of copy-neutral LOH, also referred to as uniparental disomy (UPD), can be found in specific cancer types and probably contribute to clonal outgrowth owing to various mechanisms. In this review we explore the types, topography, genesis, pathophysiological consequences and clinical implications of UPD.

Keywords

UPD; LOH; SNP-A

Introduction

Chromosomal aberrations constitute a hallmark of a cancer genome. Recurrent balanced chromosomal abnormalities, for example, those occurring in distinct types of leukemia or lymphoma, can be diagnostic and often explain pathogenesis of these conditions. Chromosomal defects also constitute excellent clonal markers, essential for the diagnosis of a malignant clone, or for the detection of minimal residual disease or relapse, especially in cancers arising in the hematopoietic system (1-3). By contrast, the frequent complexity of chromosomal defects and inability to obtain viable cells, makes the diagnostic application of cytogenetic testing in solid tumors more difficult. Consequently, fewer chromosomal defects that can function as diagnostic or prognostic markers have been identified, although this has begun to change in recent years. Loss of heterozygosity (LOH) owing to segmental or numerical chromosomal deletion has been of particular importance and forms part of a number of paradigms of malignant transformation, including the concept of tumor suppressor gene inactivation and the Knudson two-hit hypothesis (4). After the loss of chromosomal materials containing one allele, the remaining allele can be affected by somatic mutation or harbor a disease-prone polymorphic variant. Similarly, loss of chromosomal material can lead to LOH and conversion of heterozygous inherited (potentially functionally silent) mutation to a hemizygous mutation. However, the discovery of uniparental disomy (UPD), also referred to as copy-neutral LOH, has indicated that LOH

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may not be necessarily due to loss of chromosomal material. Under normal circumstances, 2 copies (paternal and maternal) of each autosome exist that carry discrete differences encoded by single nucleotide polymorphisms (SNPs) and can thereby be distinguished. In regions of UPD, portions of one of the chromosomes are lost and replaced by the exact copy of the remaining chromosome (either paternal or maternal) resulting in retention of two copies of genetic information but loss of polymorphic differences which existed due to the presence of maternal and paternal genes in this region of a diploid chromosome set. Due to the lack of copy number change, UPD remains undetected by metaphase cytogenetics. However, the widespread use of microsatellite analysis or genotyping sequential SNPs combined with copy number determination has shown that various types of UPD frequently occur in the cancer genome (5, 6). Consequently, in this review we discuss the genesis and types of UPD seen in malignant and normal cells; we focus on mechanisms of selective growth advantage that can result from this lesion and discuss their mechanistic role in cancer pathogenesis. We also review the recurrent regions of UPD identified in various forms of cancer and the clinical implications associated with these defects.

Genetic and genomic implications of UPD

LOH due to loss of chromosomal material versus UPD

Until recently, LOH has been most consistently linked to deletions of chromosomal material in somatic cytogenetic defects encountered in cancer. In contrast, UPD has been identified through the study of inherited diseases as UPD can occur as a germ line lesion leading to isodisomy. Heterodisomy, another possible outcome of germ line UPD, does not result in LOH (7). Inherited UPD was first described by Engel (8) and can affect whole chromosomes or fragments of chromosomes, where UPD can be interstitial or telomeric (Fig. 1). Principally, UPD corresponds to a duplication of either paternal (unipaternal disomy) or maternal (unimaternal disomy) alleles and thereby homozygosity for germ line allelic variants. Consequently, LOH due to deletion results in hemizygosity, while UPD results in homozygosity (Fig. 1). Theoretically, it is also possible that trisomy is associated with LOH in form of uniparental trisomy, which is invariably related to numerical aberrations (Fig. 1). Conceptually, any trisomy might represent a form of UPD without LOH as the both parental alleles are retained while one is duplicated.

Unlike constitutional UPD, the genesis of somatic UPD is not well understood but might be a result of mitotic recombination or a successful attempt to correct loss of chromosomal material through the duplication of the remaining allele (Fig. 2A).

The mechanics of UPD

The chromosomal mechanics behind UPD have been intensely investigated in embryology and inherited conditions. In consanguineous populations, homozygosity is frequent and can accumulate in the form of stretches of autozygosity. Although such changes do not always result in pathology, autozygosity represents a risk for inherited disease, including genetic predisposition to various cancers (9). In contrast to autozygosity, germ line UPD can arise as a result of mistakes in meiosis, in which all cells in the organism contain the change or in the initial mitoses after fertilization resulting in tissue mosaicism. Autozygosity and meiotic UPD are not distinguishable without pedigree analysis (Fig. 2B). Germ line UPD can be due to meiotic chromosomal mis-segregation and subsequent mitotic re-assortment leading to a balanced genome. Various scenarios can lead to germ line meiotic UPD and heterodisomy and isodisomy (resulting in LOH) have to be distinguished from numerical chromosomal defects. Trisomic rescue following errors in meiosis I or II can result in UPD as one of the possible outcomes (Fig. 2B) (10).

Unlike germ line UPD and autozygosity, somatic UPD results from mitotic homologous recombination events or represents an attempt to correct the unbalanced loss of chromosomal material by using the remaining alleles as a template (Fig. 2A). Numerical somatic UPD can occur due to mitotic errors including non-disjunction or loss of a chromosome due to anaphase lag followed by reduplication of the remaining chromosome (11). Segmental telomeric UPD might be due to mitotic homologous recombination between highly homologous, low copy number repeats (12, 13). However, such a mechanism would be more difficult to invoke for segmental interstitial UPD as it would require 2 consecutive or simultaneous homologous recombination steps. It is possible that segmental UPD could also be a result of initial deletion followed by a compensatory reduplication of the remaining chromosomal fragment (Fig. 2A and 2B). For diagnostic and investigational purposes the distinction between a somatic, clonal UPD and germ line UPD or autozygosity is of the utmost importance.

UPD and cancer

Specific chromosomal regions affected by UPD in cancer

The pivotal description of UPD in a hematological malignancy was reported in polycythemia vera (PV) (14), in which UPD9p was found in 33% of patients, constituting the most common chromosomal lesion in this disease (15). Later this chromosomal defect was linked to *JAK2*V617F mutation (16). More comprehensive studies demonstrated that *JAK2*V617F mutations with UPD9p can also be found in other MPN (17, 18). For example, primary myelofibrosis (PMF) reveales a high frequency of UPD9p with *JAK2*V617F mutations (44%) (19). However, the homozygous mutational burden varies, because of differences in population size of mutant cells. Even in purified myeloid cell populations, heterozygous and homozygous cells can be found. Moreover, patients with essential thrombocytosis (ET) exhibit lower frequency of UPD9p and the resultant *JAK2*V617F mutational burden in ET is low compared with PMF and PV (16, 20).

Systemic application of SNP arrays as a karyotyping tool (Fig. 3A) led to further discoveries of recurrent regions of UPD in various myeloid and lymphoid malignancies with secondary acute myeloid leukemia (sAML), myelodysplastic syndrome (MDS) or myeloproliferative neoplasm (MPN) and chronic myelomonocytic leukemia (CMML) showing particularly high frequencies of this type of chromosomal lesion. Investigations of solid tumors produced comparable results with the identification of recurrent areas of acquired UPD in a wide spectrum of cancers some of which show a remarkable predilection for this type of chromosomal defect (Table 1).

Tumor-specific recurrent regions of UPD can be mapped for AML and MDS for example (Fig. 3B), as well as for a representative collection of cell lines derived from various malignancies (Supplemental Fig. 1). Many of the commonly affected areas contain important genes implicated in malignant pathogenesis. Of note is that in many studies, the frequency of somatic UPD is probably overestimated owing to the lack of distinction from frequent germline-encoded UPD. Nevertheless, based on the size and location of the reported regions of UPD and their recurrence, somatic nature of alterations can be clearly deduced. The impact of specific regions of UPD in terms of prognosis or diagnosis is currently being evaluated. For example, UPD7q, UPD11q or UPD17p have been linked to poor outcomes in myeloid malignancies (21-23).

Predisposition to UPD in cancer

That certain cancers display a higher frequency of somatic UPD, such as *MUTYH*-associated polyposis colon carcinomas (24), and also can accumulate multiple areas of UPD (complex UPD) implies that there is an inherited or acquired predisposition to this type of

defect owing to the presence of fragile sites prone to recombination or a specific type of chromosomal instability, for example. For some malignancies, particularly high frequencies of somatic UPD have been described, suggesting that this type of defect may be related to pathological pathways common in some but absent in other cancers. For instance, in sporadic colon cancer, physical loss of chromosomal material is characteristic and UPD is less common (25).

Preferred sites of mitotic recombination leading to UPD have been identified, with a clustering of the centromeric and telomeric breakpoints (12). In mantle cell lymphoma (MCL) the breakpoints flanking all the genomic UPDs were significantly associated with genomic regions enriched in copy number variants and segmental duplications, suggesting that the recombination at these regions might play a role in the genomic instability of MCL (26). Similarly, a careful analysis of the sites of acquired UPD origin in low-risk MDS showed that 43% of UPD regions were localized to or as part of a previously identified fragile site (27). Fragile sites correspond to known locations of frequent genomic instability and are associated with breakpoints occurring in the generation of chromosomal aberrations in hematological malignancies (28). Fragile sites have also been associated with regulatory micro RNA amplifications and deletions (29).

Risk factors for the acquisition of UPD also include the presence of *BRCA* mutations, which were shown to be associated with an increased frequency of UPD not observed in cases of spontaneous breast cancer (30). In ovarian cancer, UPD was frequently observed in tumors with an inherited *BRCA* mutation (31). Microsatellite instability (MSI) has been shown to be associated with the increased frequency of UPD (32). MSI was present in 60% of patients with AML that had regions of UPD (Fig. 3B), whereas single locus MSI was absent in patients with AML in whom UPD was not detected (33).

Pathogenic consequences of UPD in cancer

Although it is likely that chromosomal deletions occur randomly, those resulting in a proliferative advantage or resistance to physiological apoptosis for example, could initiate clonal outgrowth. Selection for clones with a specific region of LOH could be related to a somatic or germ line loss of a wild type allele resulting in hemizygosity for an SNP-encoded disease-prone allele or a somatic or germ line mutated allele (Fig. 1). If the affected area includes promoters of alleles that are differentially silenced (imprinted), deletion can lead to either a gain of imprinting (GOI) or loss of imprinting (LOI). This can result in changes in gene expression. UPD can also lead to the duplication of an imprinted expressed allele or a silenced (methylated), imprinted allele. In cases where the transcription of both alleles is required for normal cellular physiology, deletions can result in pathological haploinsufficiency and thereby LOH is less likely to play a pathogenic role (Fig. 1).

There are similarities and important differences between the consequences of LOH due to deletion or UPD. UPD could convey a permissive growth advantage when, in accordance with the 2-hit hypothesis, an initial heterozygous mutation is duplicated through UPD. This might result in homozygosity of a somatic mutation that inactivates a tumor suppressor gene, such as occurs in *TP53* in UPD17p, *RUNX1* in UPD21q and many others (Fig. 4). Activating oncogenic mutations can be duplicated through UPD leading to increased proliferative drive though a double dose of the mutated gene product. Such a scenario has been encountered with *JAK2* (UPD9p) (14, 16, 34), *FLT3* internal tandem duplication (ITD) (UPD13q) (35, 36), *WT1* (UPD11p) (37, 38) and *MPL* (UPD1p) (19, 39). Recently, we and other groups found loss of function mutations of *EZH2*, encoding trimethyltransferase of H3K27, in the patients with UPD7q (Fig. 4) (40-42). Because methylation of H3K27 is a histone repressive mark associated with condensation of chromatin, its loss of function mutation results in chromatin relaxation and accelerating gene transcriptions, for example,

WNT1 and *HOXA* family genes. *EZH2* mutations are more commonly homozygous (UPD7q) than heterozygous (40, 42). In myeloid malignancies, UPD is frequently observed on chromosome 11q specifically in MDS/MPN phenotype. *CBL* mutations were observed in 76% of the patients with UPD11q, however relatively rare (<5%) in the patients with deletion or without LOH 11q. In mutations associated with recurrent UPD, homozygosity might provide malignant clone with further growth advantage. Theoretically, a similar effect could be produced by LOH as a result of deletion, but for some genes, such as *CBL*, most mutations are homozygous and corresponding deletions were not found to harbor hemizygous mutations (22, 43, 44). Consequently, *CBL* knock out is less leukemogenic than ring finger domain mutant knock in *CBL* null mice (43, 45). By contrast, *TP53* or *TET2* mutations are associated with both deletions and UPD. UPD can also affect germ line heterozygous mutations. Examples of such mutations include UPD11q and UPD17q leading to duplication of *CBL* and *NF1* mutations in juvenile myelomonocytic leukemia (JMML) (Fig. 4) (46-48).

Somatic UPD can also lead to duplication and thereby homozygosity of disease prone SNPs that are silent in a heterozygous configuration. Typically, such SNPs show an exceeding low frequency of homozygosity for the minor allele in the general population. Of note is that although duplication of initially heterozygous mutations is a driving force for clonal dominance, areas of UPD contain a large number of genes that can include germline polymorphisms and imprinted sites. For example, on chromosome 9p, which is frequently affected by UPD, *CNTLN, KANK1, DMRT1, TOPORS* and *MLANA* genes were reported to be either imprinted or differentially methylated. Therefore UPD at this site can lead to GOI and LOI for specific genes (49-52). In addition, UPD9p contains a large number of nonsynonymous polymorphisms for which either minor or major allele can be duplicated and result in discrete changes of the phenotype. These findings indicate that association of high allelic burden of *JAK2*V617F mutation due to UPD9p may be influenced by homozygous SNPs and/or loss or gain of expression of monoallelically expressed genes in the region affected by UPD (53). More recently, multiple groups reported the relationship between the *JAK2* genetic predisposition and *JAK2*V617F and the 46/1 *JAK2* haplotype predisposes to the development of *JAK2*V617F-associated MPN (54-56). After these studies, Tefferi et.al. clarified that a *JAK2* germline genetic variation (rs12343867 genotype CC) was less frequent in PMF with high *JAK2*V617F burden. This suggests that the allelic distortion from acquired UPD contributes to the appearance of a more pronounced effect on disease susceptibility in *JAK2*V617F-positive patients (57).

Examples of changes LOI and GOI can also be found cancer-prone inherited disorders associated with UPD: GOI of *H19* and LOI of *IGF2* (58, 59). A similar alteration of imprinting patterns has been found in hepatoblastoma, a tumor characterized with frequent UPD11p affecting *H19* and *IGF2* (60). LOI for *IGF2* and *H19* due to UPD is evident in colon carcinoma (61) and Wilms' tumor (62), *ARH1* LOI is evident in ovarian and breast cancer (63) and *H19* LOI is evident in AML (64). Some of these events might be due to a shared mechanism of UPD. Thus, it is possible that although deletion or duplication can randomly affect each parental chromosome, clonal selection might favor the expressed or silenced imprinted allele and so might not be random. In MDS for example, the *FZD9* promoter has been found to be consistently hypermethylated in patients with LOH7q as a result of UPD or chromosomal deletion (65). Theoretically, several of these mechanisms can be operative in UPD affecting large number of genes and contributing to the heterogeneity of resulting tumor phenotype and clinical behavior (Fig. 4).

Conclusions

UPD is a previously cryptic type of chromosomal aberration ubiquitously occurring in cancer and often mapping to the regions affected by loss of chromosomal material. During malignant evolution, the clonal selection process favors duplication of heterozygous somatic or germline mutations, disease-prone SNP alleles or imprinting patterns that can produce a selective advantage. Whole genome scanning technologies with SNP arrays greatly facilitated detection of UPD. In addition to the somatic form of UPD, stretches of homozygosity due to inherited UPD or autozygosity can be detected through SNP arrays necessitating the distinction of truly clonal events from non-clonal homozygosity. Inherited UPD or autozygosity might constitute an independent predisposition factor for the development of malignancy. This theory, supported by the increased prevalence of cancer in inbred populations, needs to be further explored. Similarly, the mechanisms leading to the acquisition of somatic UPD also have to be clarified — distinct pathways are probably involved in the development of numerical and segmental (interstitial or telomeric) UPD. Similar to other chromosomal lesions, including gains, losses and balanced translocations, various acquired or inherited defects of the mitotic machinery or DNA repair pathways might be involved in UPD. If such mechanisms could be identified, they might allow for the identification of people at risk of developing cancer as a result of UPD and new drug targets for the treatment of tumors associated with UPD. In the diagnostic setting, identification of UPD allows for the distinction between truly homozygous genetic changes from contamination with wild type cells and cells with heterozygous mutations. This distinction helps to more precisely assess the extent of a mutation and to better understand the effect of specific mutations in a particular genetic context. For example, mutations in *TP53* occur most often in homo- or hemizygous form and the presence of a wild type allele is protective. The prognostic significance of some of the recurrent regions of UPD has been evaluated and such defects could be included in a cytogenetically-based prognostic scoring system. Should UPD prove to be of diagnostic value, cytogenetic methods should be introduced to allow for routine detection of this type of defect (2994 words).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TRANSLATIONAL RELEVANCE

We have prepared a review on uniparental disomy (UPD) in cancer, a new genomic defect which shed light on cancer pathogenesis and interaction between mutations and chromosomal defects. UPD helps to understand why certain mutations occur in homozygous form. The review explains to a non-specialist medical/pathogenetic implications of UPD in the embryogenesis and also in cancer evolution. In the past, Clinical Cancer Research has published identification of several important gene mutations which were greatly facilitated through detection of UPD in the affected areas. UPD highlights areas containing gene mutations with homozygous configuration. We and others have found this way *CBL* and *TET2* mutations in myelodysplastic syndrome, and now novel *EZH2* mutations have been found in association with UPD7q. Newer genomic tools allow easy detection of UPD. I think that the manuscript we have prepared would be educational to all oncologists and of interest to any reader.

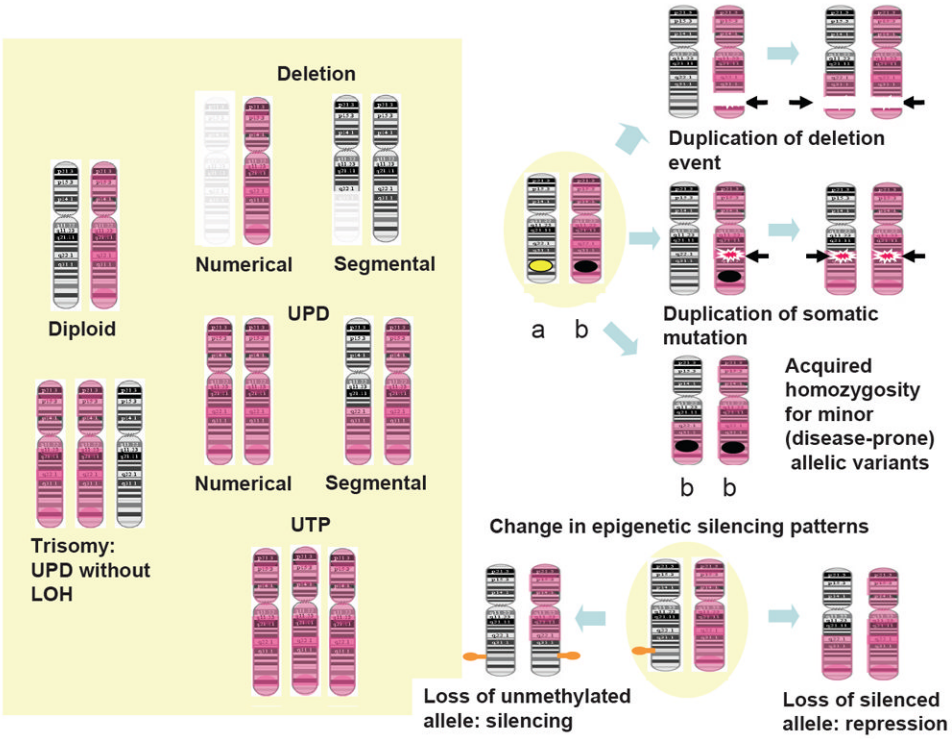
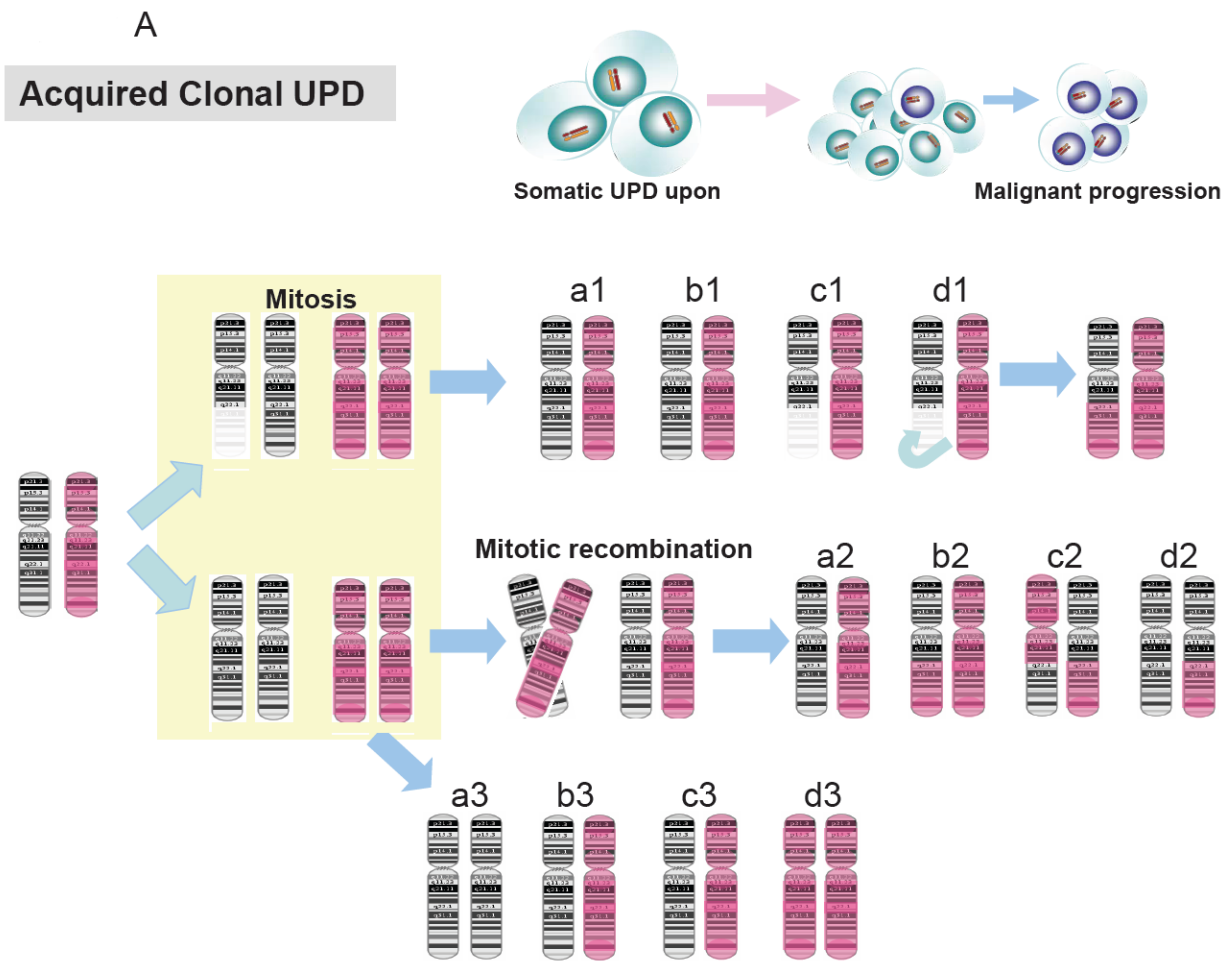


Fig. 1. Pathogenetic consequences of UPD

On yellow background: types of somatic UPD: segmental, numerical, uniparental trisomy (UPT) and trisomy with UPD without LOH as the both parental alleles are retained while one is duplicated. On the right: consequences of UPD including duplication of monoallelic deletion leading to biallelic deletion, duplication of disease-prone germ line polymorphism or mutation, duplication of somatic mutational event, gain or loss of imprinting.



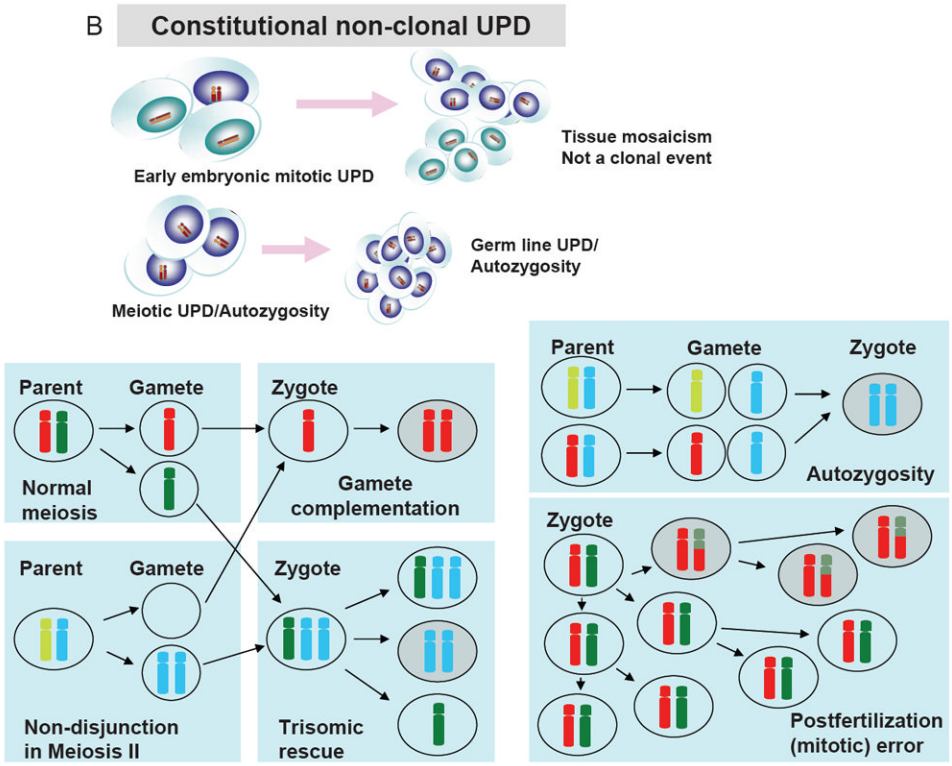


Fig. 2.

(A) Possible mechanisms leading to somatic UPD.

Upper portion. Occurrence of somatic UPD may lead to clonal progression. UPD will be present in clonal cells only. Lower portion. Panels 1 and 2: Segmental UPD, Panel 3: Numerical UPD. Panel 1: Segmental deletion event is corrected through duplication of deleted region using remaining chromosome as a template. a1-d1 depict possible outcomes of chromosome segregation in the progeny that could lead to various types of segmental UPD. Panel 2: Mitotic recombination event leads to exchange of chromatids with various possible outcomes (a2-d2). Panel 3: a3-d3: numerical UPD can be a result of chromosomal mis-segregation.

(B) Constitutional versus somatic causes of UPD.

Upper portion: Early embryonic UPD results in nonclonal tissue mosaicism, while in autozygosity and meiotic UPD all cells of the body will be affected. If occurring during meiosis I gamete contains 2 chromosomes inherited from sperm (ovum) and one chromosome from ovum (sperm) leading to heterodisomy (2 different chromosomes inherited from one of the parents), while if occurring in meiosis II, gametes could contain 2 homologous chromosomes inherited from the ovum (sperm) resulting in isodisomy (lower portion). Heterodisomy can also result from fertilization of nullisomic gamete and disomic gamete and isodisomy by fertilization between nullisomic and monozygous gamete followed by duplication of the remaining copy of the chromosome. Segmental disomy is likely to occur via nonhomologous recombination.

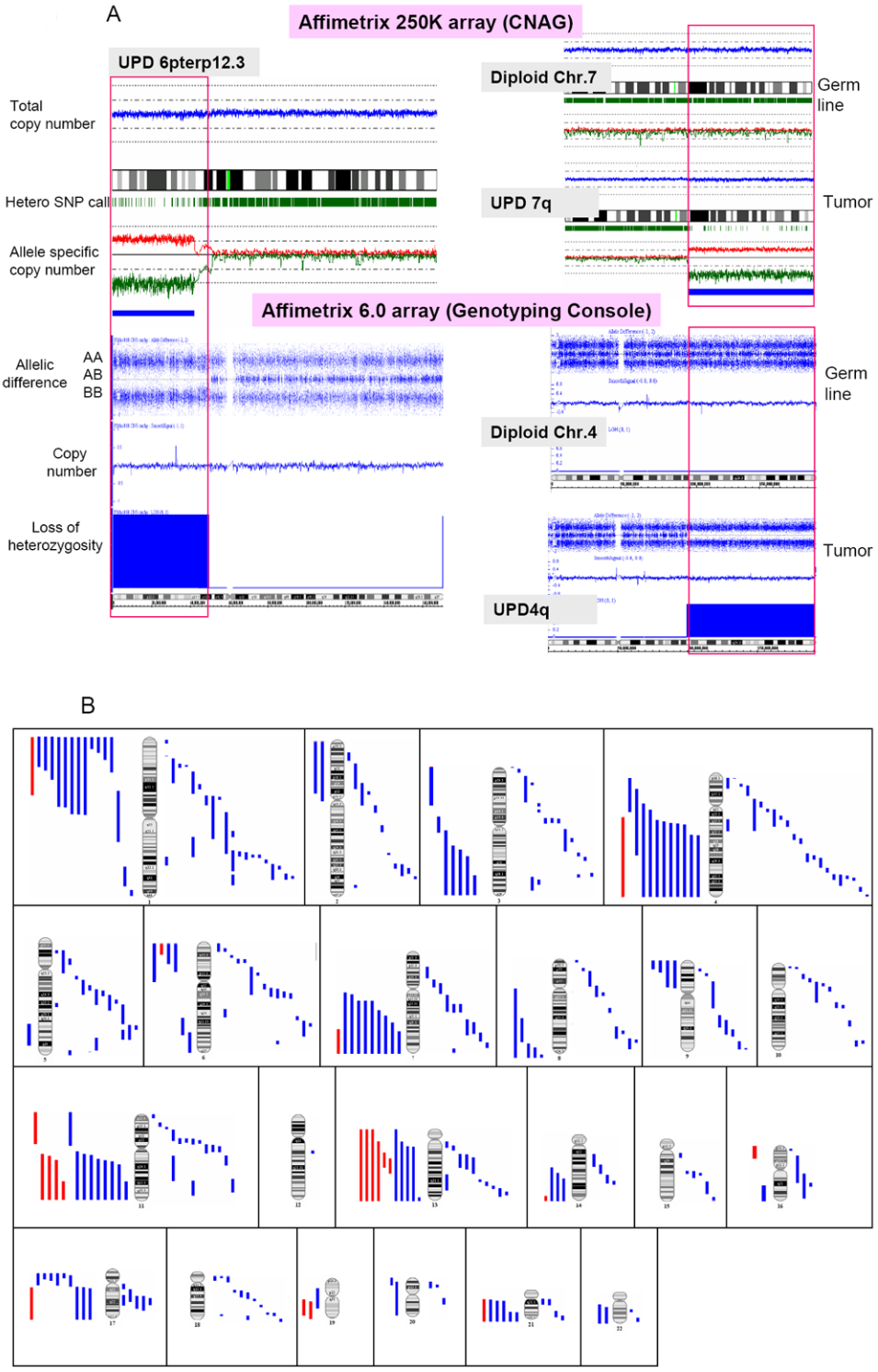


Fig. 3.

(A) Detection of UPD using SNP arrays. On the left: Chromosome ideograms showing exemplary UPD of chromosome 6 detected by (upper portion) 250K Affymetrix array (CNAG soft ware) and (lower portion) Affmetrix 6.0 arrays (Genotyping console). On the right: examples of UPD: UPD7q (250K array) and UPD4q (6.0 arrays).

(B) Mapping of recurrent UPD by chromosome in AML and MDS. Ideograms of chromosomes: on the left of the chromosome: blue and red bars indicate somatic UPD in MDS and AML, respectively. On the right: blue bars depict regions of UPD detected in DNA from 1003 controls. In our own analysis of healthy controls, nonclonal UPD and autozygosity have been found in 12% of samples; the majority (97%) of these regions of homozygosity are interstitial and <25 Mb in length. The topography and size of the somatic areas of UPD strikingly differ from those of the copy-neutral regions of LOH in the germline.

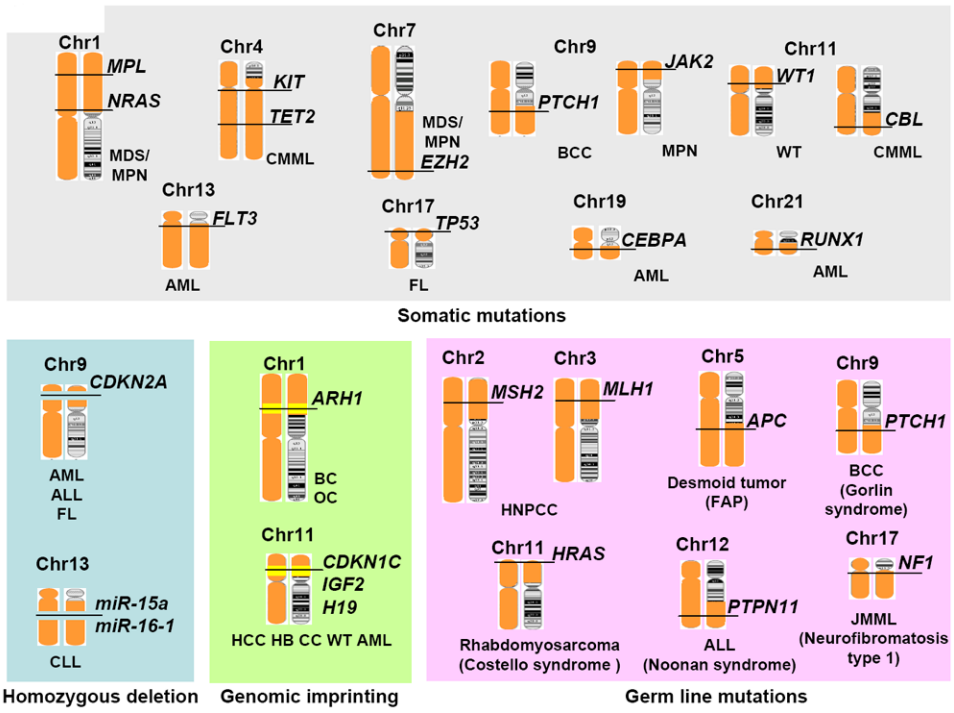


Fig. 4.

Examples of recurrent UPDs and corresponding homozygous mutations. Examples of recurrent areas of UPD in various human cancers associated with specific molecular lesions. Grey background: duplications of somatic mutations; blue background: duplication of segmental losses of chromosomal material leading to biallelic deletions; green background: changes of genomic imprinting due to UPD; margenta: duplication of germline mutations. MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; FL, follicular lymphoma; BCC, basal cell carcinoma; WT, Wilms' tumor; ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; BC, breast cancer; OC, ovarian cancer; HCC, hepatocellular carcinoma; HB, hepatoblastoma; CC, colorectal cancer; HNPCC, Hereditary nonpolyposis colorectal cancer; FAP, familial adenomatous polyposis; JMML, juvenile myelomonocytic leukemia.

Table 1

UPD and affected genes in various cancers

UPD	Disease	Frequency of UPD	Affected gene	Abnormalilty
1p	MDS/MPN, MPN	8.9% (MDS/MPN), 16.7% (RARST), 4.7% (MPN)	*MPL*	mutation
2p	Colorectal cancer	11.1% (Cell line), 52% (Hereditary non-polyposis colorectal cancer (HNPCC))	*MSH2*	mutation deletion
2q	Mantle cell lymphoma	10-16.7% (Cell line)	*MAP2*	deletion
3p	Colorectal cancer	22.2% (Cell line), 4% (Hereditary non-polyposis colorectal cancer (HNPCC))	*MLH1*	mutation
	Colorectal cancer, Esophageal cancer	73.9% (esophageal cancer), 1.1% (colorectal cancer)	*FHIT*	deletion
4q	MDS, MPN, MDS/MPN, AML	8.8% (MDS/MPN), 3.9-8.7% (MDS)	*TET2*	mutation
5q	Colorectal cancer	28.6-44.4% (Cell line)	*APC*	mutation
6p	Loss of graft versus leukemia effect	29.4% (Leukemia relapse after haploidentical transplantation)	*HLA-A, B, C*	loss of mismatch
6q	B cell lymphomas	8% (FL), 3.1% (DLBCL), 10.3% (MALT)	*A20*	mutation deletion
7q	MDS, MDS/MPN, AML	6% (MDS/MPN)	*EZH2*	mutation
9p	AML	2.6-3.1% (AML with normal karyotype), 5% (AML)		mutation
	MPN, MDS/MPN	11% (MDS/MPD), 25-43% (MPD), 41-80% (PV), 5.9-17% (ET), 43.8-67% (PMF)	*JAK2*	mutation
	AML	2.6% (AML with normal karyotype)		deletion
	ALL	7.1-29% (Pediatric ALL)		deletion
	Follicular lymphoma	33% (Cell line)		deletion
	MCL	60% (Cell line), 7.1% (primary sample)	*CDKN2A*	deletion
	Esophageal carcinoma	26.1% (primary sample)		deletion
	Ovarian cancer	7.5% (primary sample)		deletion
	Glioblastoma	3.3% (primary sample)		deletion
	Neuloblastoma	4.3% (primary sample)		deletion
	CNS lymphoma	21.1% (primary sample)	*CDKN2A*	methylation deletion
	Colorectal cancer	55.6% (Cell line)		methylation
9q	BCC	35.7% (primary sample)	*PTCH*	mutation
11p	AML	3.2-4.5% (AML primary sample), 6.4% (APL)	*WT1*	mutation
	AML	4.7% (primary sample)	*H19*	methylation
	Hepatoblastoma	23.5% (primary sample)	*IGF2, H19*	methylation
	Rhabdomyosarcoma	33.3% (primary samples)	*HRAS*	mutation
	Wilms' tumor	2.5-5.6% (primary samples)	*CDKN1C, IGF2, H19*	methylation
	Wilms' tumor	36% (primary samples)	*WT1*	mutation

UPD	Disease	Frequency of UPD	Affected gene	Abnormalilty
	Beckwith-Wiedemann syndrome	7.2-16.8% (primary samples)	*CDKN1C, IGF2, H19*	methylation
11q	MDS/MPN	4.9% (primary samples)	*CBL*	mutation
13q	AML	2.3-5.4% (primary sample)	*FLT3*	mutation
	CLL	3.6% (primary sample)	*miR-15a, miR-16-1*	deletion
	Mantle cell lymphoma	10% (MCL cell line)		deletion
	Breast cancer	6% (primary sample)	*RB1*	deletion
	Ovarian cancer	23.8% (primary sample)		deletion
	Retinoblastoma	59.5% (primary sample)		mutation
	Ovarian cancer	15% (primary sample)	*BRCA2*	mutation
17p	MDS, CLL	1.8% (MDS), 6.1% (CLL)	*P53*	mutation
	Follicular lymphoma	19.2% (Transformed case)		mutation
	Mantle cell lymphoma	3.8-10.7% (MCL), 10% (Cell line)		mutation
	Colorectal cancer	57.1% (Cell line)		mutation
	Breast cancer	6% (primary sample)		mutation
	Glioblastoma	3.3% (primary sample)		mutation
17q	JMML	25-80% (primary sample)	*NF1*	mutation
	Ovarian cancer	40% (primary sample)	*BRCA1*	mutation
19q	AML	0.6-1.6% (primary sample)	*CEBPA*	mutation
21q	AML	2.6% (AML with normal karyotype)	*RUNX1*	mutation