CANCER GENOMICS & PROTEOMICS *18*: 167-196 (2021)
doi:10.21873/cgp.20251

Review

Interstitial Deletions Generating Fusion Genes

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Abstract. *A fusion gene is the physical juxtaposition of two different genes resulting in a structure consisting of the head of one gene and the tail of the other. Gene fusion is often a primary neoplasia-inducing event in leukemias, lymphomas, solid malignancies as well as benign tumors. Knowledge about fusion genes is crucial not only for our understanding of tumorigenesis, but also for the diagnosis, prognostication, and treatment of cancer. Balanced chromosomal rearrangements, in particular translocations and inversions, are the most frequent genetic events leading to the generation of fusion genes. In the present review, we summarize the existing knowledge on chromosome deletions as a mechanism for fusion gene formation. Such deletions are mostly submicroscopic and, hence, not detected by cytogenetic analyses but by array comparative genome hybridization (aCGH) and/or high throughput sequencing (HTS). They are found across the genome in a variety of neoplasias. As tumors are increasingly analyzed using aCGH and HTS, it is likely that more interstitial deletions giving rise to fusion genes will be found, significantly impacting our understanding and treatment of cancer.*

A fusion gene is defined as the physical juxtaposition of two different genes resulting in a chimeric structure consisting of the head of one gene and the tail of the other. It is an important class of mutations in both benign and malignant neoplasms where they often constitute the primary tumorigenic event (1-5). Clinically, fusion gene-detection may play a key role in the accurate diagnosis and sub-classification of cancers, may have prognostic significance, and the novel genes may even be the target of molecular therapy (6-9). Thus, they are key to an increased understanding of neoplastic processes and may serve as the ultimate biomarker. As such, they have attracted much attention.

Fusion genes have been detected in hematologic neoplasms as well as in both benign and malignant mesenchymal, epithelial, and other solid tumors (10, 11). During 1982-1988, 10 fusion genes were identified, followed by 162 during the next decade (1990-99). In the last update (January 15, 2021) of the "Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer", the number of fusion genes had risen to 32,618 (12). The list is certainly going to become longer as more tumor samples are investigated using high throughput sequencing methodologies (10). However, many of the fusion genes detected by these techniques alone, *i.e.* without subsequent, meticulous verification by other methods, are likely to represent stochastic events without any pathogenetic significance (13).

Chromosomal translocations, and to a lesser extent inversions, have traditionally been viewed as the most common genetic mechanisms whereby fusion genes are generated. The existence of such events has been known since the 1980s and the field has been repeatedly and extensively reviewed (1-5, 7, 14-17).

In contrast, unbalanced genomic rearrangements leading to loss of material, in particular terminal and interstitial chromosomal deletions, have mostly been pathogenetically associated with loss of tumor suppressor genes (11, 18-20). In the 1970s, the detection of a constitutional interstitial deletion of chromosome band 13q14 in some patients with retinoblastoma was key to Knudson's two-hit model of suppressor gene-mediated tumorigenesis and crucial for the

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Key Words: Interstitial deletion, chromosome, cytogenetics, fusion gene, review.

subsequent discovery of *RB1*, the classical tumor suppressor gene (21-27). Another example was the interstitial deletion of chromosome band 9p21 detected in many types of cancer, but particularly in acute lymphoblastic leukemia, which results in loss of the cyclin dependent kinase inhibitor 2A and 2B genes (*CDKN2A* and *CDK2NB*) (28-31). Chromosome deletions resulting in the loss of an important allele and, consequently, reduced levels of protein in the cells lacking that allele (haploinsufficiency) may also contribute to cancer development, even in the absence of subsequent loss of the second allele (20, 32-34).

A less known consequence of interstitial chromosomal deletions is the formation of fusion genes. In the present review, we discuss this genetic mechanism, *i.e.* the fusion genes that develop through it, and the neoplastic diseases in which this appears to be preferred.

Genes at the Rims of Interstitial Deletions May Fuse to Form Chimeric Genes/Transcripts

The principle for the formation of a fusion gene by interstitial deletion is the same as that for a translocation-generated fusion. The deletion starts within the 5'-end of one gene and finishes within the 3'-end of another, its fusion partner. Both genes are transcribed in the same orientation, *i.e.* from telomere to centromere or from centromere to telomere. Thus, juxtaposition of the two genes by removal of the chromosome segment between them results in a chimeric structure consisting of the head of one gene and the tail of the other (Figure 1A). Depending on the size of the deletion, loss of gene loci between the fusion partners may or may not accompany the fusion gene formation.

It is important to note that a fusion gene generated by a deletion could also be formed by a translocation between homologous chromosomes if the breaks and recombinations are the same as those for the deletion (Figure 1B). For example, deletion in chromosome bands 1q22-23 breaks the genes lamin A/C (*LMNA* in 1q22) and neurotrophic receptor tyrosine kinase 1 (*NTRK1* in 1q23.1), both of which are transcribed from centromere to telomere, to generate the *LMNA-NTRK1* fusion gene in many malignancies (see below). The same *LMNA-NTRK1* fusion gene can also be formed by a t(1;1)(q22;q23) chromosome translocation.

Most fusion genes have been detected using high throughput sequencing technologies. In fact, most were found as fusion transcripts in RNA sequencing analyses and were subsequently reported as fusion genes (35-39). For the majority of cases, no chromosome banding or other cytogenetic analysis, no fluorescence in situ hybridization (FISH), array comparative genome hybridization (aCGH), single nucleotide polymorphism (SNP) array, Southern blot or other methodologies were used to support this conclusion. As a consequence, no actual genome-level confirmation exists that fusion gene formation has taken place in these situations, *i.e.* no structural DNA rearrangement leading to the junction of two different genes has been proven. In order to fill this "gap" between fusion transcripts and fusion genes, Prof. Mitelman decided in his database that "chromosome abnormalities giving rise to gene fusions identified through RNA sequencing are by default designated as translocations (t), unless shown to arise by other types of chromosome rearrangements (del, dup, ins, inv)" (12, 40, 41). By way of example, the "Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer" lists the transcript emanating from a fusion between the transcriptional repressor GATA binding 1 (*TPRS1*) gene from 8q23.3 and the pleomorphic adenoma gene 1 (*PLAG1*) from 8q12.1 (*TRPS1-PLAG*1 chimera), found by RNA sequencing in a uterine myxoid leiomyosarcoma and a soft tissue myoepithelial tumor, as being generated by a t(8;8)(q12;q23) (12, 40, 41). However, no direct evidence for the presence of such a translocation is provided in the articles describing the genetic analyses of the above-mentioned tumors (40, 41). By contrast, we recently examined a chondroid syringoma carrying a del(8)(q12q23) as the only cytogenetic aberration (42). Using aCGH, FISH, reverse transcription polymerase chain reaction (RT-PCR), and Sanger sequencing methodologies, we showed that a *TRPS1-PLAG*1 chimeric gene was generated by the deletion (42) (Figure 2).

Chimeric transcripts may also be formed at the transcription level. In that case, two independently transcribed, neighboring genes with the same orientation give rise to a single chimeric RNA which may code for a chimeric protein (43-46). Various names have been given for these chimeric transcripts such as readthrough transcripts, transcription induced chimeras, tandem RNA chimeras *etc* (47). They have been found in many mammals (48). Whether they should be viewed as genuine chimeric transcripts is still under discussion (43-50). An example involves the genes solute carrier family 45 member 3 (*SLC45A3*) and ETS Like 4 transcription factor (*ELK4*) which are both transcribed from telomere to centromere and map on 1q32 with a distance of 25 kbp between them. The chimeric *SLC45A3-ELK4* transcript, detected in prostate cancer, was found to be generated by cis-splicing between the two neighboring genes *SLC45A3* and *ELK4* without any actual rearrangement of DNA (35, 51-53). That chimera is designed as resulting from a t(1;1)(q32;q32) in Mitelman's database (12).

With all these difficulties, caveats, and provisos in mind, we provide a chromosome-by-chromosome list of the unambiguous deletion-generated neoplasia-associated fusion genes that we have been able to ascertain from the relevant literature (Table I).

Chromosome 1

The SCL/TAL1 interrupting locus (*STIL* is also known as *SIL*) maps on 1p33, is transcribed from centromere to telomere, and codes for a protein which is part of the

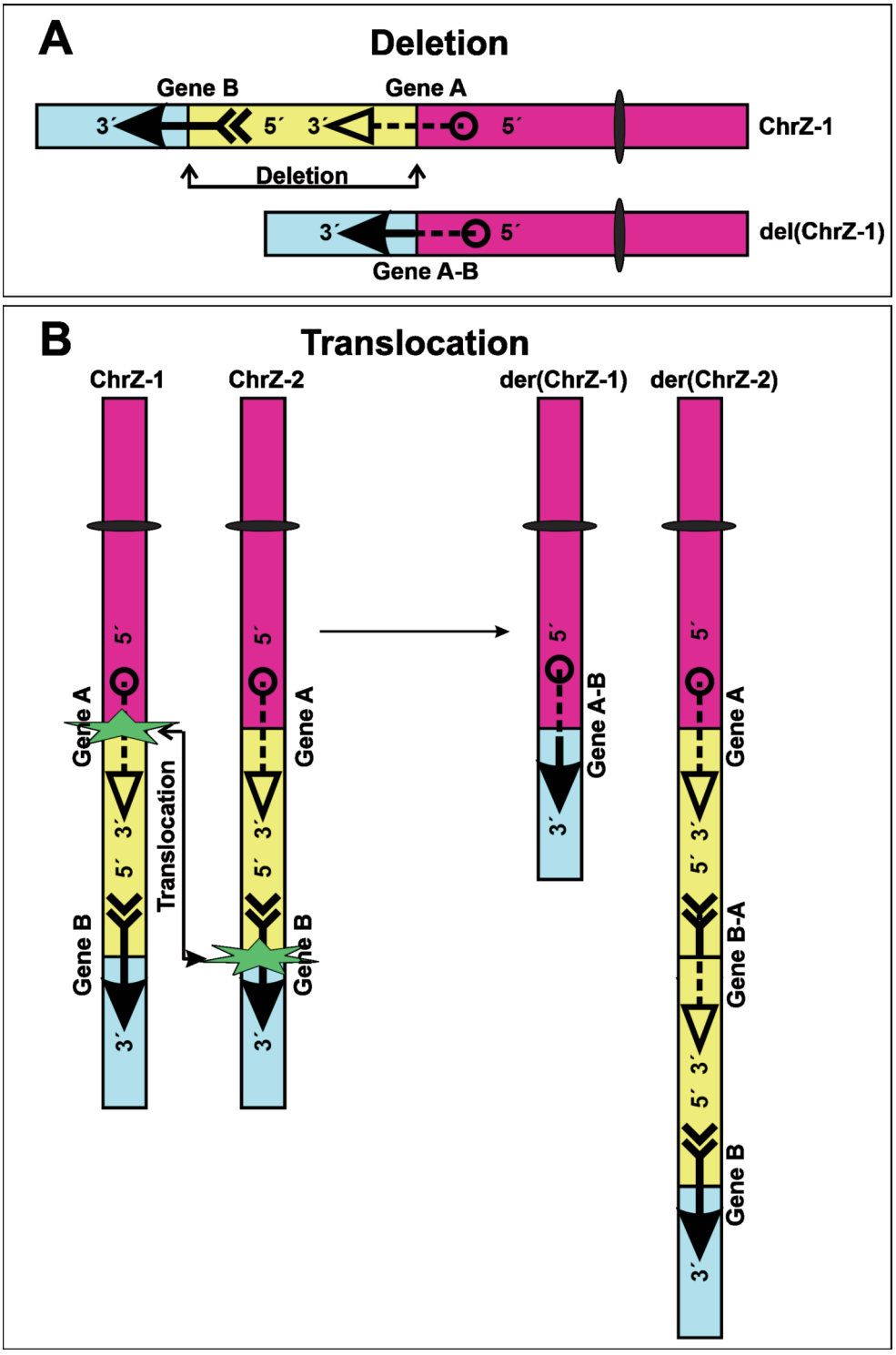

Figure 1. *Formation of a fusion gene (Gene A-B) by an interstitial deletion and a chromosome translocation. (A) The deletion starts within Gene A and finishes within Gene B. Both genes are transcribed from centromere to telomere. The juxtaposition of the two genes by removal of the chromosome segment (yellow region) between them results in the chimeric Gene A-B consisting of the head (5'-end) of Gene A and the tail (3'-end) of Gene B. Loss of gene loci mapping in the yellow region, between the fusion partners, accompanies the fusion gene formation. (B). Formation of Gene A-B fusion by chromosome translocation between the two homologous chromosomes ChrZ-1 and ChrZ-2. Gene A-B is formed on der(ChrZ-1) whereas the reciprocal Gene B-A is formed on the der(ChrZ-2) chromosome. Duplication of gene loci mapped in the yellow region accompanies the reciprocal Gene B-A formation.*

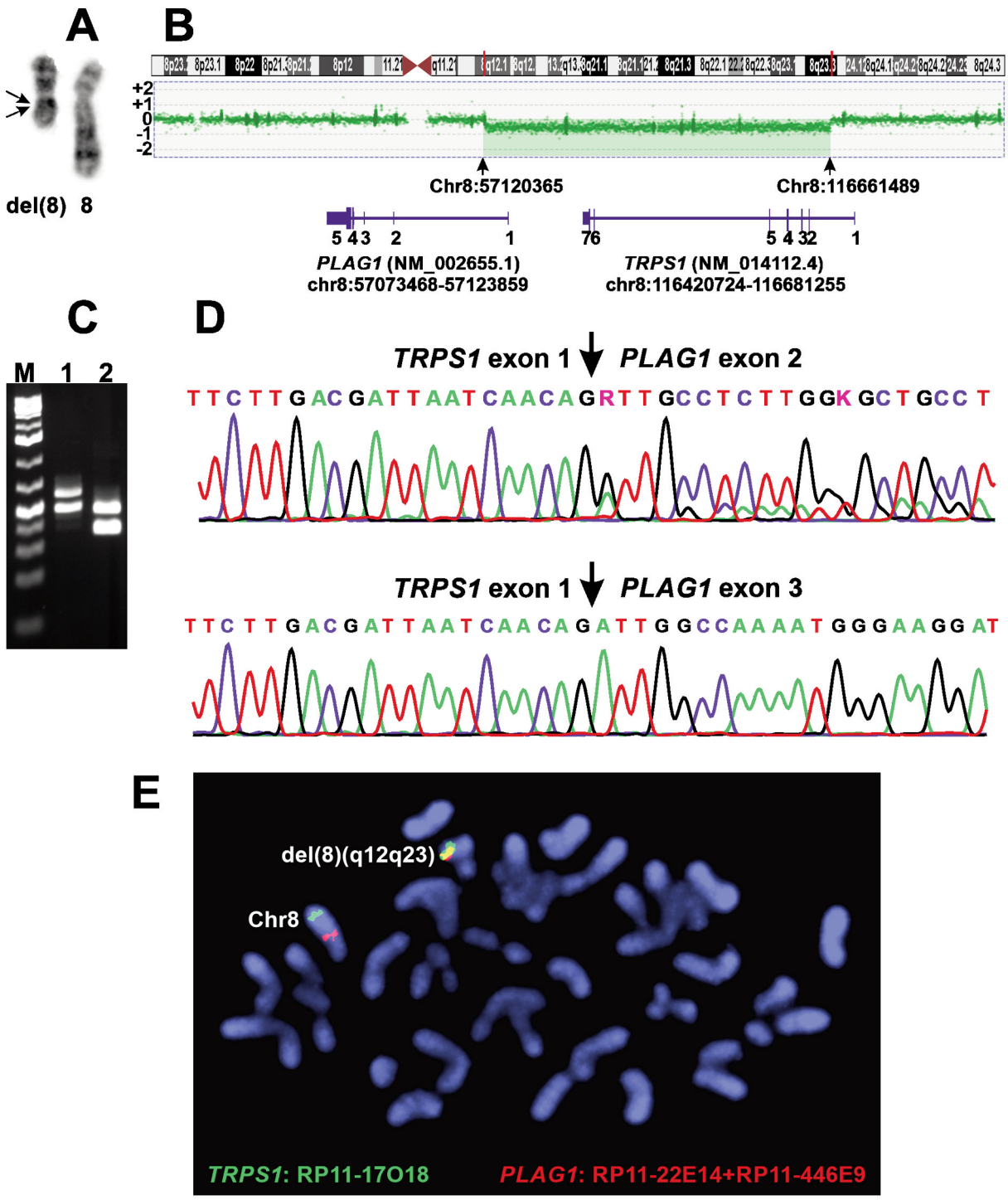

Figure 2. *Identification of a TRPS1-PLAG1 fusion gene which is generated by the interstitial deletion del(8)(q12q23). (A) Partial karyotype showing the del(8)(q12q23) and the normal chromosome 8 (breakpoints are shown by arrows). (B) Array comparative genomic hybridization showing the deletion in the q arm of chromosome 8. Based on the hg19 assembly, the deletion started at position Chr8:57120365 in intron1 of PLAG1 and ended at Chr8:116661489 in exon 1 of TRPS1. (C) Gel electrophoresis showing the amplified TRPS1-PLAG1 cDNA fragments. (D) Partial sequence chromatograms of the cDNA amplified fragment showing the junction positions of exon 1 of TRPS1 with exon 2 of PLAG1 and exon 1 of TRPS1 with exon 3 of PLAG1. E) FISH analysis on metaphase spreads with PLAG1 probe (red signal) and TRPS1 probe (green signal) showing that the TRPS1-PLAG1 fusion gene is on the del(8)(q12q23) (yellow signal). One copy of PLAG1 (red signal) and one of TRPS1 (red signal) are on chromosome 8. Data and figure are obtained from reference 42.*

Table I. *Fusion genes generated by interstitial deletions in cancer.*

Chromosome	Fusion gene	5'-end partner gene	Cytogenetic location of 5'-end partner gene	Genomic coordinates (GRCh38) of 5'-end partner gene	Transcription of 5'-end partner gene	3'-end partner gene	Cytogenetic location of 3'-end partner gene	Genomic coordinates (GRCh38) of 3'-end partner gene	Transcription of 3'-end partner gene	Distance between 5'-end and 3'-end partner genes (kbp)
1	*STIL-TAL*	*STIL*	1p33	chr1:47250139-47314147	Cen>Tel	*TAL1*	1p33	chr1:47216290-47231715	Cen>Tel	19
	PIP5K1A-NTRK1	*PIP5K1A*	1q21.3	chr1:151198551-151249536	Cen>Tel	*NTRK1*	1q23.1	chr1:156860894-156881642	Cen>Tel	5,500
	CGN-NTRK1	*CGN*	1q21.3	chr1:151511387-151538692	Cen>Tel	*NTRK1*	1q23.1	chr1:156860894-156881642	Cen>Tel	5,200
	CHTOP-NTRK1	*CHTOP*	1q21.3	chr1:153634066-153646306	Cen>Tel	*NTRK1*	1q23.1	chr1:156860894-156881642	Cen>Tel	3,140
	ZBTB7B-NTRK1	*ZBTB7B*	1q21.3	chr1:155002630-155018522	Cen>Tel	*NTRK1*	1q23.1	chr1:156860894-156881642	Cen>Tel	1,800
	LMNA-NTRK1	*LMNA*	1q22	chr1:156114711-156140081	Cen>Tel	*NTRK1*	1q23.1	chr1:156860894-156881642	Cen>Tel	670
	BCAN-NTRK1	*BCAN*	1q23.1	chr1:156642117-156659528	Cen>Tel	*NTRK1*	1q23.1	chr1:156860894-156881642	Cen>Tel	156
2	*DCTN1-ALK*	*DCTN1*	2p13.1	chr2:74361154-74380355	Cen>Tel	*ALK*	2p23.2-p23.1	chr2:29192774-29921586	Cen>Tel	44,440
	GFPT1-ALK	*GFPT1*	2p13.3	chr2:69319780-69387248	Cen>Tel	*ALK*	2p23.2-p23.1	chr2:29192774-29921586	Cen>Tel	39,400
	WDPCP-ALK	*WDPCP*	2p15	chr2:63119559-63588477	Cen>Tel	*ALK*	2p23.2-p23.1	chr2:29192774-29921586	Cen>Tel	33,200
	BCL11A-ALK	*BCL11A*	2p16.1	chr2:60457194-60553654	Cen>Tel	*ALK*	2p23.2-p23.1	chr2:29192774-29921586	Cen>Tel	30,535
	PPP4R3B-ALK	*PPP4R3B*	2p16.1	chr2:55548378-55617608	Cen>Tel	*ALK*	2p23.2-p23.1	chr2:29192774-29921586	Cen>Tel	25,630
	CCDC88A-ALK	*CCDC88A*	2p16.1	chr2:55287842-55419888	Cen>Tel	*ALK*	2p23.2-p23.1	chr2:29192774-29921586	Cen>Tel	25,370
	FBXO11-ALK	*FBXO11*	2p16.3	chr2:47806920-47888719	Cen>Tel	*ALK*	2p23.2-p23.1	chr2:29192774-29921586	Cen>Tel	17,890
	STPG4-ALK	*STPG4*	2p21	chr2:47086991-47155308	Cen>Tel	*ALK*	2p23.2-p23.1	chr2:29192774-29921586	Cen>Tel	17,165
	SRBD1-ALK	*SRBD1*	2p21	chr2:45388680-45611267	Cen>Tel	*ALK*	2p23.2-p23.1	chr2:29192774-29921586	Cen>Tel	15,500
	STRN-ALK	*STRN*	2p22.2	chr2:36837698-36966536	Cen>Tel	*ALK*	2p23.2-p23.1	chr2:29192774-29921586	Cen>Tel	6,900
4	*FIP1L1-PDGFRA*	*FIP1L1*	4q12	chr4:53377641-53460862	Cen>Tel	*PDGFRA*	4q12	chr4:54229293-54298245	Cen>Tel	770
5	*CD74-PDGFRB*	*CD74*	5q33.1	chr5:150400041-150412751	Tel>Cen	*PDGFRB*	5q32	chr5:150113839-150155845	Tel>Cen	244
	TNIP1-PDGFRB	*TNIP1*	5q33.1	chr5:151029949-151087158	Tel>Cen	*PDGFRB*	5q32	chr5:150113839-150155845	Tel>Cen	874
	SPARC-PDGFRB	*SPARC*	5q33.1	chr5:151661096-151686915	Tel>Cen	*PDGFRB*	5q32	chr5:150113839-150155845	Tel>Cen	1,500
	EBF1-PDGFRB	*EBF1*	5q33.3	chr5:158695920-159099916	Tel>Cen	*PDGFRB*	5q32	chr5:150113839-150155845	Tel>Cen	8,540
6	*GOPC-ROS1*	*GOPC*	6q22.1	chr6:117560269-117602528	Tel>Cen	*ROS1*	6q22.1	chr6:117288300-117425855	Tel>Cen	134
	CEP85L-ROS1	*CEP85L*	6q22.31	chr6:118460772-118651591	Tel>Cen	*ROS1*	6q22.1	chr6:117288300-117425855	Tel>Cen	1,035
	MAN1A1-ROS1	*MAN1A1*	6q22.31	chr6:119177205-119349761	Tel>Cen	*ROS1*	6q22.1	chr6:117288300-117425855	Tel>Cen	1,750
	PTPRK-ROS1	*PTPRK*	6q22.33	chr6:127968779-128520674	Tel>Cen	*ROS1*	6q22.1	chr6:117288300-117425855	Tel>Cen	10,540
	EZR-ROS1	*EZR*	6q25.3	chr6:158765748-158819368	Tel>Cen	*ROS1*	6q22.1	chr6:117288300-117425855	Tel>Cen	41,340
	SFT2D1-ROS1	*SFT2D1*	6q27	chr6:166319728-166342545	Tel>Cen	*ROS1*	6q22.1	chr6:117288300-117425855	Tel>Cen	48,900
	MYB-QKI	*MYB*	6q23.3	chr6:135181315-135219167	Cen>Tel	*QKI*	6q26	chr6:163414718-163578592	Cen>Tel	28,200
7	*FAM131B-BRAF*	*FAM131B*	7q34	chr7:143353400-143362752	Tel>Cen	*BRAF*	7q34	chr7:140730665-140924928	Tel>Cen	2,430
8	*HEY1-NCOA2*	*HEY1*	8q21.13	chr8:79764010-79767767	Tel>Cen	*NCOA2*	8q13.3	chr8:70109782-70403808	Tel>Cen	9,360
	HAS2-PLAG1	*HAS2*	8q24.13	chr8:121612116-121641440	Tel>Cen	*PLAG1*	8q12.1	chr8:56160909-56211273	Tel>Cen	65,401
	TRPS1-PLAG1	*TRPS1*	8q23.3	chr8:115408496-115669001	Tel>Cen	*PLAG1*	8q12.1	chr8:56160909-56211273	Tel>Cen	59,197
	NDRG1-PLAG1	*NDRG1*	8q24.22	chr8:133237176-133297586	Tel>Cen	*PLAG1*	8q12.1	chr8:56160909-56211273	Tel>Cen	77,026
9	*SET-NUP214*	*SET*	9q34.11	chr9:128683655-128696400	Cen>Tel	*NUP214*	9q34.13	chr9:131125586-131234663	Cen>Tel	2,430
10	*VTI1A-TCF7L2*	*VTI1A*	10q25.2	chr10:112447258-112818744	Cen>Tel	*TCF7L2*	10q25.2-q25.3	chr10:112950452-113167678	Cen>Tel	132
11	*KMT2A-ARHGEF12*	*KMT2A*	11q23.3	chr11:118436490-118523917	Cen>Tel	*ARHGEF12*	11q23.3	chr11:120336413-120489937	Cen>Tel	1,812
	KMT2A-CBL	*KMT2A*	11q23.3	chr11:118436490-118523917	Cen>Tel	*CBL*	11q23.3	chr11:119206276-119308149	Cen>Tel	682
	KMT2A-FOXR1	*KMT2A*	11q23.3	chr11:118436490-118523917	Cen>Tel	*FOXR1*	11q23.3	chr11:118971761-118981287	Cen>Tel	448
	KMT2A-TIRAP	*KMT2A*	11q23.3	chr11:118436490-118523917	Cen>Tel	*TIRAP*	11q24.2	chr11:126283087-126294933	Cen>Tel	7,759
	PAFAH1B2-FOXR1	*PAFAH1B2*	11q23.3	chr11:117144287-117171045	Cen>Tel	*FOXR1*	11q23.3	chr11:118971761-118981287	Cen>Tel	1,801
19	*DNAJB1-PRKACA*	*DNAJB1*	19p13.12	chr19:14514769-14518397	Cen>Tel	*PRKACA*	19p13.12	chr19:14091688-14117762	Cen>Tel	400
21	*TMPRSS2-ERG*	*TMPRSS2*	21q22.3	chr21:41464305-41508158	Tel>Cen	*ERG*	21q22.2	chr21:38380027-38661694	Tel>Cen	2,800
X/Y	*P2RY8-CRLF2*	*P2RY8*	Yp11.2/ Xp22.33	chrY/chrX:1462581-1537185	Cen>Tel	*CRLF2*	Yp11.2/Xp22.33	chrY/chrX:1190490-1212649	Cen>Tel	248

pericentriolar material surrounding the parental centrioles, which is essential for centriole duplication during the cell cycle (54). The T-cell acute leukemia 1 (*TAL1* also known as *SCL*, *tal-1*) gene maps just 18 kbp distal to *STIL*, is transcribed from centromere to telomere and codes for a transcription factor that harbors the basic helix-loop-helix domain (bHLH) which is a protein dimerization and DNA-binding motif common to many eukaryotic transcription factors (55).

In 1990, two independent research groups working on T-lineage acute lymphoblastic leukemias detected an approximately 90 kbp interstitial deletion in 1p33 which caused the 5'-untranslated part of *STIL* to fuse with the coding part of *TAL1* (56, 57). The deletion placed the expression of *TAL1* under the control of the *STIL* promoter, causing aberrant overexpression of the TAL1 protein (56, 57). To the best of our knowledge, this was the first description of a fusion gene resulting from an interstitial, submicroscopic deletion.

The *STIL-TAL1* fusion gene has been reported in 15-25 % of pediatric and young adult T-lineage acute lymphoblastic leukemia (T-ALL) but much less frequently in older T-ALL patients (58-60). Compared to T-ALL patients without *STIL-TAL1* fusions, those with the chimera have a higher white blood cell count at diagnosis, express CD2 on their leukemic cells and show a poor response to the steroid drug prednisone (59, 61, 62). The prognosis of *STIL-TAL1* fusion-positive leukemias has been reported as both better, poorer or about equal to that of other T-ALL groups (59, 61-64). In murine models, abnormal expression of *TAL1* has been reported to result in the development of T-cell malignances (65, 66).

Fusion of the gene coding for lamin A and C (*LMNA*) with the gene coding for neurotrophic receptor tyrosine kinase 1 (*NTRK1*) was reported to occur as the result of a 750 kbp interstitial deletion in chromosome bands 1q22-23 in a spitzoid melanoma (67). Both genes are transcribed from centromere to telomere. Subsequently, *LMNA-NTRK1* fusion was also described in other neoplasias such as colon cancer, thyroid cancer, breast cancer, cholangiocarcinoma, soft tissue sarcoma, and uterine sarcoma (68-80). The *LMNA-NTRK1* codes for a chimeric tyrosine kinase. Patients with this fusion can be treated with kinase inhibitors such as crizotinib, entrectinib, and larotrectinib with significant clinical response (71, 72, 79, 81-85).

In the 1q21-23 chromosomal region, 15 fusion genes involving *NTRK1* have been reported. Based on the orientation of the transcription (from centromere to telomere), interstitial deletions come across as the probable cause of fusions between *NTRK*1 (3'-fusion partner) and zinc finger and BTB domain containing 7B (*ZBTB7B*), brevican (*BCAN*), chromatin target of protein arginine methyltransferase 1 (*CHTOP*), cingulin (*CGN*), platelet endothelial aggregation receptor 1 (PEAR1), or phosphatidylinositol-4-phosphate 5-kinase type 1 alpha (*PIP5K1A*). The fusions have been found in various tumors of the brain, breast, bladder, and neuroendocrine cells (75, 80, 86-89). Most fusions have been detected using high throughput sequencing methodologies. Cytogenetic, FISH, aCGH, or any other data confirming the said deletions at the genomic level are lacking.

Using CRISP-Cas9, Cook *et al*. (90) generated a microdeletion leading to a Bcan-Ntrk1 fusion gene in mice. The mice developed high-grade gliomas which responded to the Ntrk1 inhibitor entrectinib. In general, patients whose cancers carry *NTRK1* fusion genes have responded satisfactorily to treatment with tyrosine kinase inhibitors (85, 91-95).

Chromosome 2

The anaplastic lymphoma kinase (*ALK*) gene maps to 2p23 (position chr2:29,192,774-29,921,586) and is transcribed from centromere to telomere. More than 20 *ALK*-chimeras have been reported in which the *ALK* 5'-fusion partner comes from another gene which also resides on the short arm of chromosome 2. In 10 of these *ALK*-chimeras, the 5'-fusion partner maps proximal to *ALK* (*i.e.* closer to chromosome 2 centromere) and is also transcribed from the centromere towards the telomere (Table I). Thus, an interstitial deletion could be the genomic mechanism behind the generation of these chimeras.

Fusion of the coiled-coil domain-containing protein 88A (*CCDC88A*) gene with *ALK*, giving a *CCDC88A-ALK* chimera, was found in an anaplastic ependymoma of an 8-month-old girl. An interstitial deletion del(2)(p16p23) was seen by G-banding examination of the tumor cells and confirmed by FISH. Genomic PCR showed that the deletion started within intron 12 of *CCDC88* (2p16.1) and ended within intron 19 of *ALK* (2p32.2) (96).

ALK-fusions were detected with the genes dynactin 1 (*DCTN1*) in uterine inflammatory myofibroblastic tumor and pancreatic ductal adenocarcinoma (*DCTN1-ALK* chimera) (97, 98), glutamine:fructose-6-phosphate amidotransferase 1 (*GFPT1*) in medullary thyroid cancer (*GFPT1-ALK* chimera) (99), WD repeat-containing planar cell polarity effector (*WDPCP*) in lung adenocarcinoma (*WDPCP-ALK* chimera) (100), BAF chromatin remodeling complex subunit BCL11A in lung adenocarcinoma (*BCL11A-ALK* chimera) (101, 102), S1 RNA binding domain 1 (SRBD1) in lung adenocarcinoma (*SRBD1-ALK* chimera) (103, 104), and striatin (*STRN*) in lung adenocarcinoma, malignant peritoneal mesothelioma, and thyroid carcinoma (*STRN-ALK* chimera) (105-108). These were true chimeric genes resulting from DNA rearrangements, possibly deletions between the 5'-fusion partner and *ALK* (the 3'partner). In all the above-mentioned fusion genes, the genomic breakpoint in *ALK* was within the 1932 bp long intron 19 of the gene.

Irrespective of the 5'-fusion partner gene, all *ALK*-chimeras seem to code for chimeric protein tyrosine kinases (109). Patients whose tumors carry *ALK*-chimeras, respond well to treatment with ALK inhibitors (110-115). More specifically, patients whose tumors carry the fusions *DCTN1-ALK*, *BCL11A-ALK*, *SRBD1-ALK*, *STPG4-ALK*, and *STRN-ALK* have reportedly shown excellent response to ALK inhibitors such as Crizotinib, Ceritinib, and Alectinib (98, 101-103, 105-107, 116).

Chromosome 4

The factor interacting with PAPOLA and CPSF1 (*FIP1L1*) gene and the platelet derived growth factor receptor alpha (*PDGFRA*) gene both map to chromosome band 4q12 and are transcribed from centromere to telomere. The distance between them is 800 kbp. *FIP1L1* codes for a subunit of the cleavage and polyadenylation specificity factor complex that polyadenylates the 3' end of mRNA precursors (117). *PDGFRA* codes for a cell surface tyrosine kinase receptor for members of the platelet-derived growth factor family (118-120). *PDGFRA* together with its paralog gene platelet derived growth factor receptor beta (*PDGFRB*), and the genes colony stimulating factor 1 receptor (*CSFR1*), KIT proto-oncogene receptor tyrosine kinase (*KIT*), and fms related receptor tyrosine kinase 3 (*FLT3*) code for the class III family of receptor tyrosine kinases that have important roles in leukemo- and tumorigenesis (120-124).

In 2003, the *FIP1L1-PDGFRA* fusion gene was, as a result of an 800 kbp interstitial chromosomal deletion in 4q12, detected in nine out of 16 patients with hypereosinophilic syndrome (125). *FIP1L1-PDGFRA* codes for a chimeric, constitutively active tyrosine kinase which consists of the first 233 amino acids of FIP1L1 and the last 523 amino acids of PDGFRA. Imatinib inhibits tyrosine phosphorylation by the FIP1L1-PDGFRA fusion protein (125). Nowadays, the World Health Organization's "Classification of tumours of haematopoietic and lymphoid tissues" lists, under the category "Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFRA, PDGFRB, or FGFR1, or with PCM1-JAK2", the new subgroup "Myeloid/lymphoid neoplasms with *PDGFRA* rearrangement" in which *FIP1L1-PDGFRA* is the most commonly detected gene fusion (126-128). Patients with this disease usually respond well to imatinib (129, 130).

Chromosome 5

The *PDGFRB* gene maps to 5q32 and is transcribed from telomere to centromere. It encodes, similarly to its homologous *PDGFRA* gene, a cell surface tyrosine kinase receptor for members of the platelet-derived growth factor family (119, 120, 123, 124). In 1994, Golub *et al*. reported that the t(5;12)(q33;p13) chromosome translocation sometimes seen in chronic myelomonocytic leukemia results in fusion of the ETS variant transcription factor 6 gene (*ETV6*, also known as *TEL*) from 12p13 with *PDGFRB* (131). According to the January 15, 2021 version of the Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer, 49 *PDGFRB* chimeras have been reported, most of them in hematologic malignancies (12). The consequence of the *PDGFRB* fusions is constitutive activation of the PDGFRB tyrosine kinase (120, 123). Patients with hematologic malignancies bearing *PDGFRB* chimeras can be successfully treated with imatinib (132-140).

The genes EBF transcription factor 1 (*EBF1* on 5q33.3), CD74 molecule (*CD74* on 5q33.1), secreted protein acidic and cysteine rich (*SPARC* on 5q33.1), and TNFAIP3 interacting protein 1 (*TNIP1* on 5q33.1) are transcribed from telomere to centromere and have been found to fuse as 5'-end partner genes with *PDGFRB* (Table I). The *EBF1-PDGFRB* chimera, which is found in B-lineage acute lymphoblastic leukemia, in the majority of cases results from an 8.6 Mbp interstitial deletion, del(5)(q32q33.3), with breakpoints within the *EBF1* and *PDGFRB* genes (132, 133, 141-143). In very few cases, a chromosome translocation has instead been shown to generate the *EBF1-PDGFRB* chimera (142). The *TNIP1-PDGFRB* chimera results from a 900 kbp interstitial deletion with breakpoints located within *TNIP1* and *PDGFRB* (6, 144-146).

No information exists about DNA rearrangements behind the formation of the *CD74-PDFGRB* and *SPARC-PDGFRB* chimeras found in a patient with B-ALL and a case of lipofibromatosis, respectively (147, 148). *CD74* and SPARC are located 240 kb and 1.5 Mbp distal to *PDGFRB*, respectively. Since both genes are transcribed from telomere to centromere, as is *PDGFRB*, and since both are distal to *PDGFRB*, we see it as probable that both fusions are the product of interstitial deletions.

Chromosome 6

The ROS proto-oncogene 1, receptor tyrosine kinase (*ROS1*) gene maps on 6q22.1, is transcribed from telomere to centromere, and codes for a tyrosine kinase receptor with similarities to the Drosophila sevenless tyrosine kinase receptor (149-155). Neither the expression nor the cellular function of *ROS1* has been well studied but the gene seems to be widely expressed. Examining the expression of *ROS1* in 45 different human cell lines, the majority from various neoplasias, Birchmeier *et al*. (152, 155-158) found high-level expression in glioblastoma-derived cell lines but no to very low expression in the remainder. Further studies have shown ectopic expression of *ROS1* also in other brain tumors (152, 155-158). *ROS1* chimeras have been reported in various types of cancer, more and more as tumors are increasingly being

screened for fusion genes/transcripts. In 2016, a review of ROS*1* fusions in cancer reported 26 genes as having been found to fuse with *ROS1* (159) whereas a similar recent review reported the number of *ROS1* fusion partners to be 54 (160). In 2020, the year before the review by Drilon *et al.* (160) was published, another 14 novel *ROS1* fusion partner genes were added to the list (161-165), raising the total currently known number of *ROS1* chimeras to 68. Regardless of their large number and variability, *ROS1* chimeras encode chimeric ROS1 proteins which are constitutively active kinases and which, consequently, may be targets for treatment with kinase inhibitors (13, 160, 166-171).

In 2003, Charest *et al.* (172) showed that cells from a glioblastoma contained a 250 kbp submicroscopic interstitial deletion causing fusion of the golgi associated PDZ and coiled-coil motif containing *GOPC* (also known as *FIG*) gene with *ROS1*. The *GOPC-ROS1* transcript, which consists of the first seven exons of *GOPC* and the last nine exons of *ROS1*, was in-frame and coded for a constitutively active GOPC-ROS1 chimeric protein that seems to be oncogenic (172, 173). At present, the GOPC-*ROS1* chimera is considered to be a rare, but recurrent, fusion found in glioma, lung adenocarcinoma, cholangiocarcinoma, and high-grade serous ovarian carcinoma (166, 168, 172, 174-177). The chimeric GOPC-ROS1 protein may be the target for kinase inhibitors (160, 166-169, 177).

In 2013, a 41.5 Mbp interstitial deletion, del(6)(q22q25), was reported to fuse the first 10 exons of the ezrin (*EZR*) gene, which is transcribed from telomere to centromere and maps on 6q25.3, with exons 34-43 of the *ROS1* gene in lung adenocarcinomas from four female patients, three of whom had never been smokers (178). The *EZR-ROS1* gene coded for a chimeric protein with oncogenic activity. It contained the FERM domain of the EZR protein joined to the transmembrane and kinase domains of ROS1 (178). Additional studies confirmed the recurrence of EZR-*ROS1* in lung cancer and also that the finding was clinically important: the chimeric protein could be the target of kinase inhibitors with very good results (160, 161, 167, 169, 179-184).

A chimera with the centrosomal protein 85 like (*CEP85L*) gene, which maps on 6q22.31, 1.0 Mbp distal to *ROS1*, and is transcribed from telomere to centromere, as the 5'-end partner gene and *ROS1* as the 3'-end partner gene has been reported in an angiosarcoma as well as a few glioblastomas (87, 166, 185-188). The chimeric *CEP85L–ROS1* transcript was accompanied by deletion of the 5'-end of *ROS1* suggesting that an interstitial 1.1 Mbp submicroscopic deletion within band 6q22 caused the *CEP85L–ROS1* chimera (166, 185). The *CEP85L–ROS1* transcript codes for a chimeric protein with oncogenic activity. The protein can be targeted with kinase inhibitors (87, 166, 185-188).

Recently, three novel in-frame *ROS1* chimeric transcripts were detected (161, 164) using high throughput technology, probably corresponding to microdeletions between *ROS1* (as the 3'-end partner gene) and 5'-end partner genes (161, 164). In the first chimeric transcript, found in a melanoma of the skin, the SFT2 domain containing 1 (*SFT2D1*) gene was fused to *ROS1* (161). In the second transcript, found in a serous carcinoma of the ovary, an invasive ductal breast carcinoma, and in a carcinoma of unknown origin, the protein tyrosine phosphatase receptor type K (*PTPRK*) gene was fused to *ROS1* (161). In the third transcript, found in a leiomyosarcoma, the mannosidase alpha class 1A member 1 (*MAN1A1*) gene was fused with *ROS1* (164). *In vitro* assays showed that the MAN1A1-ROS1 protein had strong transformation potential and that the kinase inhibitor crizotinib inhibited growth of MAN1A1-ROS1 transformed cells in a dose-dependent manner (164).

The *SFT2D1*, *PTPRK*, and *MAN1A1* genes are distal to ROS1 and map on 6q27, 6q22.33, and 6q22.31, respectively. They are transcribed from telomere to centromere. Thus, a 49 Mbp deletion is predicted to have caused the *SFT2D1-ROS1*, an 11 Mbp deletion the *PTPRK-ROS1*, whereas a 2 Mbp deletion probably resulted in the *MAN1A1-ROS1* chimera.

The MYB proto-oncogene (*MYB* is also known as *c-MYB*) gene codes for a transcription regulator with three helix-turn-helix (HTH) DNA-binding domains, maps on 6q23.3, and is transcribed from centromere to telomere (189, 190). The gene and its paralogues *MYBL1* (also known as *A-MYB*, on 8q13.1) and *MYBL2* (also known as *B-MYB,* on 20q13.12) compose the MYB family of transcription factors which play important roles in cell growth, differentiation, and apoptosis (191-193). MYB regulates hematopoiesis, is crucial for colon development in murine animals, and is required for the proliferation of neural progenitor cells and maintenance of the neural stem cell niche (189, 193-196). Because *MYB* is involved in many malignancies such as leukemias and solid cancers of breast, colon, and brain, it has been considered as an attractive target for anti-tumor therapy (193, 197, 198).

The QKI, KH domain containing RNA binding (*QKI*) gene, which codes for a protein that regulates pre-mRNA splicing, export of mRNAs from the nucleus, protein translation, and mRNA stability, maps on 6q26 and is transcribed from centromere to telomere (199-201). In 2014, Roth *et al.* (202) used high-resolution SNP array methodology to detect, in a pediatric ganglioglioma, a 30 Mbp deletion in 6q23.3-26 with the proximal breakpoint in the last intron of *MYB* and the distal one within the *QKI* gene. They proposed that the result of this deletion would be a *MYB-QKI* fusion gene, a chimera that had previously been reported in a pediatric low-grade glioma (203). The *MYB-QKI* fusion gene was subsequently found to characterize angiocentric gliomas (204-207). Interstitial deletion as a mechanism for the generation of the MYB-*QKI* fusion was reported in two of the studies (204-207).

Chromosome 7

The B-Raf proto-oncogene, serine/threonine kinase (*BRAF*) gene maps to 7q34 and transcribes from telomere to centromere (208-210). It codes for a member of the RAF family of serine/threonine protein kinases which is involved in regulating the MAP kinase/ERK signaling pathway and affects cell division, differentiation, and secretion (211-214).

Mutations in *BRAF*, most commonly the V600E mutation, have been found in many malignancies such as melanoma, colorectal cancer, thyroid carcinoma, non-small cell lung carcinoma, hairy cell leukemia, non-Hodgkin lymphoma, and adenocarcinoma of lung (214-216). The mutations play a fundamental role in cancer development. They constitutively activate *BRAF* resulting in an over-performing RAF-MEK-ERK signaling cascade, promotion of cell proliferation and survival, and inhibition of apoptosis (214-216). The identification and characterization of pathogenic *BRAF* mutations have led to the development of BRAF kinase inhibitors used to treat patients whose cancers carry this particular genetic abnormality (214, 215, 217, 218).

BRAF chimeras have also been reported (12). In Mitelman's Database of Chromosome Aberrations and Gene Fusions in Cancer (updated October 15, 2020), 95 *BRAF* chimeras were registered with 30 of them involving a partner gene in 7q.

Using aCGH, Cin *et al*. (219) found in three pilocytic astrocytomas a 2.5 Mbp interstitial deletion in chromosome band 7q34. The deletion led to in-frame fusion of the currently uncharacterized gene with the name "family with sequence similarity 131-member B" (*FAM131B*) with *BRAF*. The chimeric FAM131B-BRAF protein was a constitutively active kinase with MEK phosphorylation potential and transforming activity *in vitro* (219). Subsequent studies confirmed the existence of a submicroscopic interstitial deletion in 7q34 and the recurrent generation of a *FAM131B-BRAF* chimeric gene in pilocytic astrocytomas (202, 206, 220, 221).

Chromosome 8

The gene with the name "hes related family bHLH transcription factor with YRPW motif 1" (*HEY1*) maps on 8q21.13, is transcribed from telomere to centromere, and codes for a nuclear protein belonging to the hairy and enhancer of split-related (HESR) family of basic helix-loop-helix (bHLH)-type transcriptional repressors (222-225). The nuclear receptor coactivator 2 (*NCOA2*) gene maps on 8q13.3, is also transcribed from telomere to centromere, and codes for a transcriptional coactivator of nuclear hormone receptors (226-229). A *HEY1-NCOA2* fusion gene has been reported to be pathognomonic for mesenchymal chondrosarcoma (230-236). SNP array analyses of a few such chondrosarcomas indicated an interstitial deletion as the cause of the *HEY1-NCOA2* chimeric gene (221, 231).

The pleomorphic adenoma gene 1 (*PLAG1*) maps to 8q12.1, is transcribed from telomere to centromere, and codes for a zinc finger transcription factor (237-240). *PLAG1* spans 50 kbp and contains 5 exons, the first 3 of which are untranslated (NCBI reference: NM_002655.3) (237, 241). *PLAG1* was initially found to be rearranged in pleomorphic adenomas carrying a t(3;8)(p22;q12) translocation which led to its fusion as a 3'-end partner with the catenin beta 1 (*CTNNB1*) gene from 3p22.1 (237). Subsequently, various *PLAG1*-fusion genes were found in pleomorphic adenomas of the salivary glands, lipoblastomas, as well as other tumors (40-42, 242-246). In *PLAG1* chimeras, the two fusion partner genes exchange their promoters and the 5'-end untranslated exons. Consequently, the expression of *PLAG1* is controlled and regulated by the fusion partner gene promoter. The *PLAG1* gene is either overexpressed or activated which results in deregulation of its targeted genes and leading thus to tumor development (240, 247-251).

The hyaluronan synthase 2 (*HAS2*) gene maps on 8q24.13, is transcribed from telomere to centromere, and codes for the isoform 2 of hyaluronan synthase (252-256). *HAS2* spans 29 kb and has 4 exons, the first of which is untranslated (NCBI reference: NM_005328.3). In 2000, a recurrent *HAS2-PLAG1* fusion gene was detected in three lipoblastomas, two of which had del(8)(q12q24) and the third a ring chromosome 8 (244). The genomic breakpoints were in introns 1 of both *HAS2* and *PLAG1*, and in the chimeric *HAS2-PLAG1* transcripts, the untranslated exon 1 of *HAS2* fused to either exon 2 or exon 3 of *PLAG1* (244). Thus, the *HAS2-PLAG1* fusion gene was the result of a 65.5 Mbp interstitial del(8)(q12q24) deletion. Subsequent reports on lipobastomas confirmed that the *HAS2-PLAG1* fusion resulted from a del(8)(q12q24) (257-259).

The transcriptional repressor GATA binding 1 (*TRPS1*) gene maps on 8q23.3, is transcribed from telomere to centromere, and codes for a transcription factor that represses GATA-regulated genes and binds to a dynein light-chain protein (260). *TRPS1* spans 260 kbp and has seven exons, the first of which is untranslated (NCBI reference: NM_014112.5). Chimeric *TRPS1-PLAG1* transcripts in which exon 1 of *TRPS1* was fused to exon 2 or exon 3 of *PLAG1*, were reported in soft tissue myoepithelial tumor, uterine myxoid leiomyosarcoma, and chondroid syringoma (40-42). G-banding analysis of the chondroid syringoma revealed an interstial deletion, del(8)(q12q23) (Figure 2A). aCGH examination confirmed the deletion and showed that it started in intron 1 of *PLAG1* and ended in exon 1 of *TRPS1* (Figure 2B). RT-PCR (Figure 2C) and Sanger sequencing (Figure 2D) confirmed the presence of the *TRPS1-PLAG1* fusion transcripts. FISH analysis on metaphase spreads showed that the *TRPS1-PLAG1* fusion

gene was on the del(8)(q12q23) chromosome (Figure 2E). Thus, both the aCGH and karyotyping data indicated that a *TRPS1-PLAG1* fusion gene had been formed as the result of a deletion (42).

The N-myc downstream regulated 1 gene (*NDRG1*) maps to 8q24.22, is transcribed from telomere to centromere and codes for a cytoplasmic protein involved in stress and hormonal responses, cell growth, and differentiation (261-264). The *NDRG1* gene spans 60 kbp and has sixteen exons of which the first is untranslated (NCBI reference: NM_006096.4). A chimeric *NDRG1-PLAG1* transcript in which exon 1 of *NDRG1* was fused to exon 3 of *PLAG1* was found in a chondroid syringoma (42). FISH analysis showed that the *NDRG1-PLAG1* chimeric gene was on a ring chromosome 8. No reciprocal *PLAG1-NDRG1* chimeric gene was seen. The data indicated that an interstitial deletion had caused the *NDRG1-PLAG1* chimera (42).

Chromosome 9

A fusion of the SET nuclear proto-oncogene (*SET*) with the nucleoporin 214 (*NUP214*) gene, also known as *CAN*, was discovered by von Linden *et al*. in an acute undifferentiated leukemia with normal karyotype. The discovery was made while they were looking for the *DEK-NUP214* (alias *DEK-CAN*) fusion gene generated by t(6;9)(p22;q34) in acute myeloid leukemias (265-267).

SET and *NUP214* map on 9q34.11 and 9q34.13, respectively, and are both transcribed from centromere to telomere. *SET* codes for a nuclear protein which inhibits both histone acetyltransferase and demethylation of DNA (268, 269), whereas *NUP214* codes for a nuclear envelop protein which is a subunit of the nuclear pore complex (270). The SET-NUP214 protein is found within the nucleus. It causes disturbed intracellular localization of the chromosomal maintenance 1 (CRM1) protein that facilitates transport of RNA and protein across the nuclear membrane into the cytoplasm (271). As a consequence, disruption of the nuclear export system occurs. Recruitment of the SET-NUP214 protein onto *HOX* gene clusters leads to aberrant expression of *HOX* genes in leukemic cells (271, 272). Expression of SET-NUP214 in transgenic mice was shown to block hematopoietic differentiation (273).

In 2006, Rosati *et al*. reported that a 2.5 Mbp deletion generated *SET-NUP214* fusion in an AML-patient (274). Subsequent studies confirmed that the submicroscopic deletion did indeed lead to *SET-CAN* chimeras in leukemias (274-281).

The *SET-NUP214* chimera has been detected in AML as well as in undifferentiated acute leukemia (AUL) and B- and T-differentiated lymphoblastic leukemias (B-ALL and T-ALL). Its overall frequency in T-ALL is 3-8 % (275, 277, 282). *SET-NUP214* is rare in pediatric T-ALL but was found in as many as 13 % of adult T-ALLs (60, 282). In a recent study of 24 patients whose leukemic cells carried a *SET-NUP214* and who had undergone allogeneic hematopoietic stem cell transplantation, those who expressed SET-NUP214 after transplantation fared badly (283).

Chromosome 10

Vesicle transport through interaction with t-SNAREs 1A (*VTI1A*) and transcription factor 7 like 2 (*TCF7L2*) are neighboring genes in 10q25.2-25.3, separated by 130 kbp. Both are transcribed from centromere to telomere (284). The *VTI1A* gene codes for a soluble N-ethylmaleimide-sensitive fusion protein-attachment protein receptor that is active in intracellular trafficking (285, 286). The *TCF7L2* gene codes for a high mobility group (HMG) box-containing transcription factor that plays a key role in the Wnt signaling pathway (287, 288). Although several *TCF7L2* tissue specific splice variants have been found, all of them code for a protein which has an N-terminal beta-catenin (CTNNB1)-binding domain and a HMG-box region (287-289).

Genomic sequencing of colorectal adenocarcinomas identified a 540 kbp deletion starting in intron 2 of the *VTI1A* gene and ending in intron 3 of the *TCF7L2* gene, thus generating a *VTI1A-TCF7L2* chimera which is in-frame transcribed and translated to a chimeric protein lacking the CTNNB1-binding domain of TCF7L2 (284). In the first study, the chimeric *VTI1A-TCF7L2* gene was present in 3 % of the examined colorectal carcinomas (284). Later, Nome *et al*. (290) detected the *VTI1A-TCF7L2* fusion transcript in 42 % of colorectal cancers but also in 28 % of normal colonic mucosa samples as well as in 25 % of normal tissue samples taken from various other anatomical sites. They also detected seven different splice variants of the *VTI1A-TCF7L2* transcript (290). These data indicate that *VTI1A-TCF7L2* is not specific for cancer nor for cells emanating from the large bowel. Nevertheless, functional studies of the VTI1A-TCF4 chimeric protein have shown that it acts as a dominant negative regulator of the Wnt signaling pathway, and that its transcription is activated by CDX2 (291). It is possible that it plays a pathogenetic role in cancer in spite of its lack of specificity.

Chromosome 11

The histone-lysine N-methyltransferase 2A gene (*KMT2A*, also known as *MLL*) maps to 11q23 and is transcribed from centromere to telomere. It encodes a transcriptional coactivator with multiple functional motifs and domains, among them a menin-binding motif at the amino-terminus, DNA binding AT hooks, a cysteine rich CXXC domain, plant homeodomain finger motifs, a bromodomain, a transactivation domain, and a SET domain at the carboxyl-terminus responsible for histone

H3 lysine 4 (H3K4) methyltransferase activity (292-297). *KMT2A* is known to recombine with more than 100 different partners in hematologic malignances and solid tumors with most of the fusions coding for chimeric proteins (12). All KMT2A-chimeric proteins retain the menin-binding motif, the DNA binding AT hooks, and the CXXC domain indicating that they are essential for the transformation potential of the fusion proteins (282, 298-300).

Fusions of *KMT2A* with three genes - Rho guanine nucleotide exchange factor 12 (*ARHGEF12*), Casitas B-lineage lymphoma proto-oncogene (*CBL*), and decapping enzyme scavenger (*DCPS*) - were found to result from interstitial deletions in various hematologic malignancies (Table I) (147, 282, 298-305).

KMT2A-ARHGEF12 fusion is brought about by a 2Mbp deletion stretching from the major breakpoint cluster region of *KMT2A*, which spans from exon 7 to exon 13, to intron 11 or 13 of *ARHGEF12* (Figure 3) (299-301, 304, 305). The result is an in-frame *KMT2A-ARHGEF12* chimeric transcript that gives rise to a protein composed of the KMT2A amino-terminus and the ARHGEF12 carboxyl-terminus (299-301, 304, 305). So far, seven cases with *KMT2A-ARHGEF12* fusion have been reported: three AMLs, three B-ALLs, and one high-grade B-cell lymphoma (147, 299-305). Figure 3 presents, in brief, our results on identification of a *KMT2A-ARHGEF12* fusion gene generated by a therapy induced interstitial deletion in subband 11q23.3 in a child treated for acute myeloid leukemia (301). aCGH detects a deletion which starts in the KMT2A gene and ends in the ARHGEF12 gene (Figure 3A). The deletion is also confirmed by FISH (Figure 3B). Finally, molecular methodologies (genomic PCR and Sanger sequencing of the PCR amplified fragments) show that an intronic sequence of *KMT2A* fuses to an intronic sequence of *ARHGEF12*, generating a chimeric *KMT2A-ARHGEF12* gene (Figure 3C).

A *KMT2A-CBL* fusion is generated by an 800 kbp deletion starting within *KMT2A* and ending in *CBL* gene (282, 298-300). It gives rise to an in-frame *KMT2A-CBL* chimeric transcript that translates into a chimeric protein. Up to now, *KMT2A-CBL* fusion has been described in two AML and one T-Lineage ALL (282, 298-300).

Mayer *et al*. (306) described an AML patient with a del(11)(q23) in the diagnostic karyotype. Detailed investigation showed that the leukemic cells carried a 7.8 Mbp interstitial deletion which fused a genomic sequence from intron 8 of *KMT2A* with an intergenic sequence 7.2 kbp upstream of the *DCPS* gene. *DCPS* maps on 11q24.2, 10 kbp distal to *TIRAP*, and is transcribed, as is *KMT2A*, from centromere to telomere (306). At the transcription level, the deletion results in in-frame fusion of exon 8 of *KMT2A* with exon 2 of the *DCPS* gene (306).

The forkhead box R1 (*FOXR1*) gene maps to 11q23.3 (chr11:118,971,761-119,018,638), is transcribed from centromere to telomere, and codes for a member of the forkhead box (FOX) family of transcription factors which are expressed in the testis, predominantly in spermatogonia and meiotic spermatocytes (307, 308). Santo *et al*. (309) identified interstitial microdeletions activating the *FOXR1* gene in three neuroblastomas. In two of them, a 500 kbp deletion between intron 1 of *KMT2A* upstream of the *FOXR1* gene resulted in a *KMT2A-FOXR1* chimeric transcript in which the entire coding region of *FOXR1* was fused to exon 1 of KMT2A. In the third neuroblastoma, a 1.9 Mbp deletion within 11q23.3, starting within the platelet activating factor acetylhydrolase 1b catalytic subunit 2 (*PAFAH1B2*) and ending just upstream of *FOXR1*, resulted in two *PAFAH1B-FOXR1* chimeric transcripts in which the entire coding region of *FOXR1* was fused to exon 2 of *PAFAH1B*. Thus, both KMT2*A-FOXR1* and *PAFAH1B-FOXR1* resulted in *FOXR1* expression (309).

Chromosome 19

In 2014, a 400 kbp submicroscopic deletion in 19p13.12 was found to fuse the DnaJ heat shock protein family (Hsp40) member B1 (*DNAJB1*) gene with the protein kinase cAMP-activated catalytic subunit alpha *(PRKACA*) gene in all fifteen examined cases of fibrolamellar hepatocellular carcinoma, a rare liver cancer (310). Both *DNAJB1* and *PRKACA* are transcribed from centromere to telomere. Although the breakpoints were different in the examined cases, each deletion started either in intron 1 or exon 2 of *DNAJB1* and ended in intron 1 of PRKACA. The resulting *DNAJB1-PRKACA* chimeric transcript thus comprised the first exon of *DNAJB1* and exons 2-10 of *PRKACA* (310). The correlation between *DNAJB1-PRKACA* fusion gene formation and fibrolamellar hepatocellular carcinoma was quickly confirmed by other groups (311-316). Recently, the same fusion gene was reported to be recurrent also in intraductal oncocytic papillary neoplasms of the pancreas and bile ducts, cystic precursors to invasive carcinoma (317, 318).

The *DNAJB1* gene codes for a member of the heat shock protein 40 family (HSP40) which interact with HSP70s and are involved in numerous cellular processes such as refolding, interaction, and transport of proteins (319, 320). *PRKACA* codes for one of the catalytic subunits of protein kinase A (321, 322). The *DNAJB1-PRKACA* gene codes for a chimeric protein kinase with oncogenic potential (310, 315, 323, 324). Both the first exon of *DNAJB1* and the kinase domain of *PRKACA* were required for tumorigenesis (324).

Chromosome 21

In 2005, Tomlins *et al*. (325) reported a recurrent fusion transcript of transmembrane serine protease 2 (*TMPRSS2*) with the E26 transformation-specific (ETS) related gene (*ERG*), resulting in strong overexpression of *ERG,* in

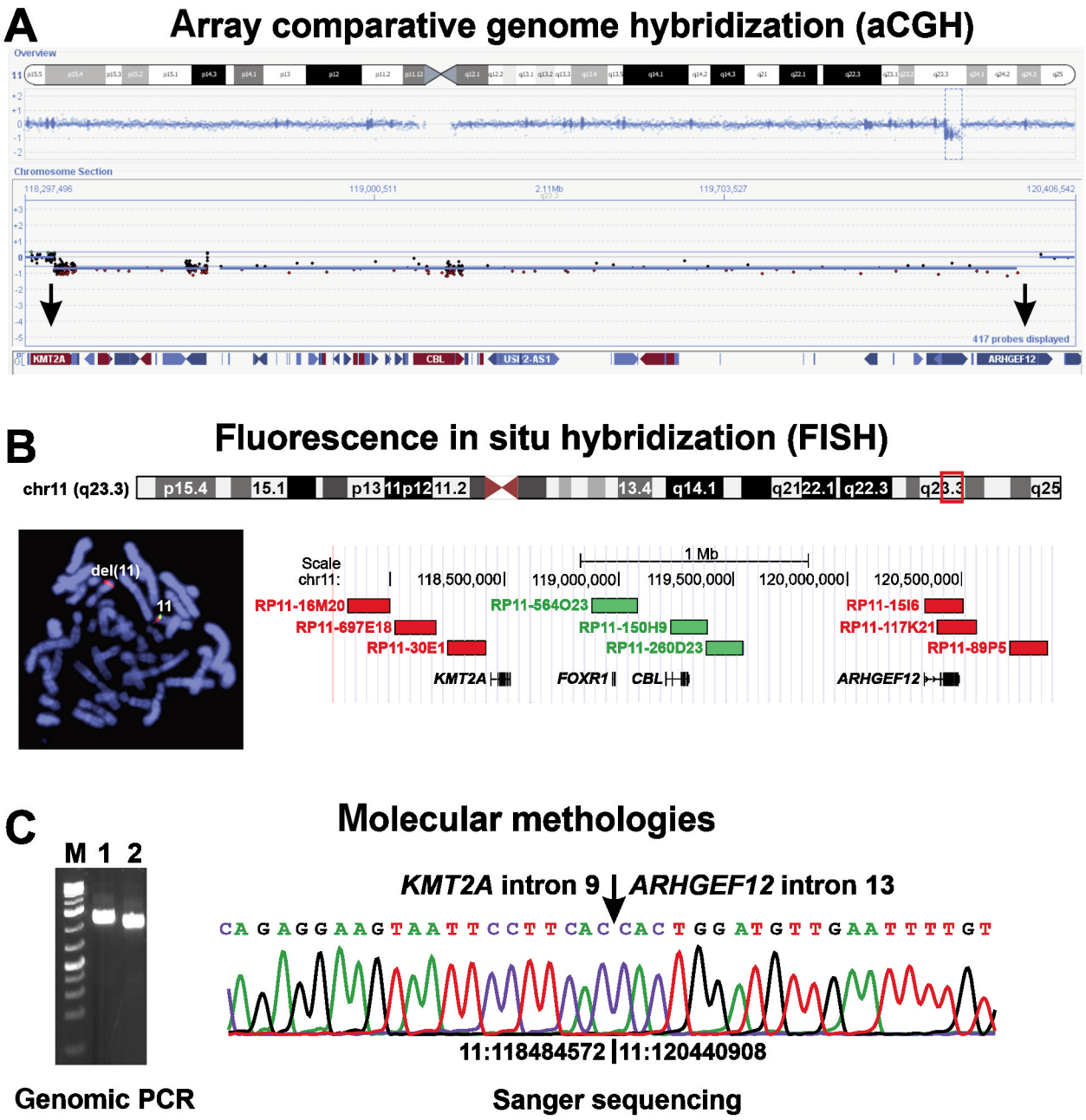

Figure 3. *Identification of a KMT2A-ARHGEF12 fusion gene generated by an interstitial deletion in subband 11q23.3. (A) Array comparative genome hybridization detects a deletion which starts in the KMT2A gene and ends in the ARHGEF12 gene. (B) Fluorescence in situ hybridization confirms the deletion between the KMT2A and ARHGEF12 genes. The green and red probes hybridized on the normal chromosome 11. Only the red probes hybridized on the del(11) indicating the deleted area (green signals missing). (C) Examinations using molecular methodologies (genomic PCR and Sanger sequencing of the PCR amplified fragments) show that an intronic sequence of KMT2A fuses to an intronic sequence of ARHGEF12, generating a chimeric KMT2A-ARHGEF12 gene. Data and figure are from reference 305.*

prostate cancer. The *TMPRSS2-ERG* fusion transcript was quickly confirmed by other groups and was found to be present in at least 40 % of prostate cancers (see below) and 20 % of high-grade prostatic intraepithelial neoplasia (326-331). The *TPPRSS2* gene maps on 21q22.3, is transcribed from telomere to centromere, and codes for a type II transmembrane serine protease (332-334) which in prostate cancer is regulated by androgen (335, 336). The *ERG* gene

maps on 21q22.2, 3.1 Mbp centromeric (proximal) to *TMPRSS2*. It is transcribed from telomere to centromere and codes for a member of the ETS family of transcription factors (337-339).

FISH and aCGH analyses show that the *TMPRSS2-ERG* fusion gene is generated by an approximately 3.0 Mbp interstitial deletion which starts in *ERG* and ends in *TMPRSS2*, by translocation between the two chromosomes 21 or by microdeletion and concurrent translocation (326, 327, 329-331, 340-344). Roughly 40 % to 60 % of *TMPRSS2-ERG* fusion genes in patients with prostate cancer are generated by deletions (345, 346). Furthermore, prostate cancer patients whose tumor cells have a *TMPRSS2-ERG* fusion stemming from deletion, seem to have worse prognosis than those with a fusion resulting from translocation (346, 347). The 3 Mbp region between *ERG* and *TMPRSS2* contains many genes which are involved in cancer and may function as tumor suppressor genes. The fact that the interstitial deletion which generates the *TMPRSS2-ERG* fusion gene, simultaneously results in haploinsufficiency for these genes, may explain the clinical difference. In a murine model, Linn *et al*. (348) showed that only mice lacking the interstitial region developed prostate adenocarcinoma marked by poor differentiation and epithelial-to-mesenchymal transition.

Chromosome X/Y

The genes cytokine receptor like factor 2 (*CRLF2*, also known as *TSLPR*) and P2Y receptor family member 8 (*P2RY8*) map to the pseudoautosomal regions Xp22.33 and Yp11.2, are transcribed from centromere to telomere, and are separated by a 250 kbp genomic region (349-353). *CRLF2* codes for a receptor for thymic stromal lymphoprotein (TSLP) (349-352). CRLF2 together with interleukin 7 receptor (IL7R) and TSLP form the TSLPR complex which is capable of activating multiple signaling transduction pathways, among them the JAK/STAT pathway and the PI-3 kinase pathway (354-356).

P2RY8 codes for a member of the family of G-protein coupled receptors (357-359). The P2RY8 protein together with its ligand, S-geranylgeranyl-L-glutathione, and the enzyme gamma-glutamyltransferase-5, which metabolizes S-geranylgeranyl-L-glutathione to a form that does not activate the P2RY8 receptor, promote confinement of B-cells in germinal centers (357-359).

In 2009, two groups reported that in B-progenitor ALL a 300 kbp interstitial deletion within the pseudoautosomal region Xp22.33/Yp11.2 juxtaposed the first, noncoding exon of *P2RY8* with the coding region of *CRLF2* resulting in overexpression of *CRLF2* (360, 361). The *P2RY8-CRLF2* fusion was found in 5-7 % of patients with B-progenitor ALL but in more than 50 % of B-ALL patients with Down syndrome (360-365). The *P2RY8-CRLF2* fusion could be both an early and a clearly secondary genomic event in B-ALL development, making its role in leukemogenesis all the more intriguing (363, 366, 367).

Conclusion

Although it may seem more likely that fusion genes or activated oncogenes are mainly caused by balanced genomic rearrangements, and although the early history of fusion gene detection in cancer apparently corroborated this view, we show here that interstitial chromosomal deletions are not an uncommon mechanism for the formation of similar fusion genes. Most of these deletions are below the detection level of chromosome banding methodologies and, hence, were detected using other techniques, including aCGH and high throughput sequencing. The detected interstitial deletions/fusion genes are not restricted to one or only a few chromosomes or a single type of cancer; instead, they have been found across almost the entire genome and in various neoplasias. Their detection has improved significantly our understanding of tumorigenesis and leukemogenesis and they are increasingly used for diagnosis and classification of neoplasms, prognostication, and as targets for molecular therapy. As more neoplasms are being analyzed, especially as high throughput sequencing is increasingly being relied on in laboratory diagnostic routines, even more such interstitial deletions/fusion genes are likely to be found, something that is going to have a significant impact both clinically and scientifically. The challenge in this context, however, is to apply proper verification/falsification measures to all new discoveries that will be made so that the field does not become swamped by data of questionable significance.

Conflicts of Interest

The Authors declare that they have no potential conflicts of interest with regards to this study.

Authors' Contributions

Both authors (IP and SH) wrote the manuscript.

Acknowledgements

This work was supported by grants from Radiumhospitalets Legater.

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Received February 26, 2021
Revised March 15, 2021
Accepted March 16, 2021