Nonrandom Cell-Cycle Timing of a Somatic Chromosomal Translocation: the t(X;17) of Alveolar Soft-Part Sarcoma Occurs in G2

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The cell-cycle timing of somatic chromosomal translocations in cancer remains poorly understood but may be relevant to their etiology and the mechanism of their formation. Alveolar soft-part sarcoma (ASPS) is a rare malignant soft-tissue tumor of uncertain lineage that provides an opportunity to address this question. The great majority of ASPSs have relatively simple near-diploid karyotypes characterized by an unbalanced der(17)t(X;17)(p11.2;q25), resulting in nonreciprocal fusion of *TFE3* with *ASPSCR1* (a.k.a. *ASPL*), with consequent net gain of Xp11.2→pter and loss of 17q25→qter. The presence of a normal X along with the der(17)t(X;17) in ASPSs that occur in men has been well described in previous cytogenetic reports and is most readily explained by a translocation in the G2 phase of the cell cycle. To establish whether formation in G2 is a general feature of the t(X;17), we examined polymorphic loci in Xp11.2→qter in ASPS from 9 women, including 7 with an unbalanced t(X;17). Our analysis showed that all 7 displayed retention of heterozygosity at all informative markers on Xp11.2→qter, supporting preferential formation of the t(X;17) in the G2 phase of the cell cycle. Given that the two derivative chromosomes of a translocation in G2 would be expected to segregate together half the time, the predominance of an unbalanced der(17)t(X;17) also raises the possibility of a selective advantage in ASPS cells for gain of Xp11.2→pter or loss of 17q25.3→qter or retention of an active copy of *TFE3*. © 2005 Wiley-Liss, Inc.

INTRODUCTION

Remarkably little information is available regarding the cell-cycle timing of somatic chromosomal translocations (Paulsson et al., 2005). The der(17)t(X;17)(p11.2:q25) of alveolar soft-part sarcoma (ASPS) provides a setting in which to address this question. We previously showed that this unbalanced translocation fuses *TFE3*, a gene at Xp11.2 that encodes a member of the microphthalmia-TFE subfamily of basic-helix-loop-helix leucine zipper transcription factors, to *ASPSCR1* (also known as *ASPL*), a novel gene at 17q25 (Ladanyi et al., 2001). The resulting fusion gene encodes chimeric *ASPSCR1–TFE3* RNA transcripts. In ASPS, this translocation more often is unbalanced and nonreciprocal than it is reciprocal. A review of karyotypic, fluorescence in situ hybridization (FISH), and RT-PCR data from our laboratory and from published studies (Table 1) showed evidence of a balanced translocation structure in only 4 of 20 (20%) ASPSs. Furthermore, the der(17)t(X;17) of ASPS is usually observed in the absence of the corresponding der(X)t(X;17), such that most ASPSs in men show a normal X chromosome. Specifically, data support there being an unbalanced t(X;17) with a normal X in 5 of 7 males with ASPS (Table 1). The predominance of ASPS with a der(17)t(X;17)

and a normal X in men is in sharp contrast to the general trend in cancers with somatic translocations involving the X chromosome arising in men. For instance, the Mitelman Database of Chromosome Aberrations in Cancer (http://cgap.nci.nih.gov/Chromosomes/Mitelman) contains more than 500 near-diploid tumor karyotypes (40–52 chromosomes) with X chromosome breakpoints from men, of which only 12% also contain a normal X chromosome ($P = 0.0005$).

The cytogenetic observation of a normal X in most ASPSs arising in men suggests that in men, the der(17)t(X;17) forms in the G2 phase. Although the presence in men of a normal X and a der(17)t(X;17) is most parsimoniously explained by its formation occurring during G2, it could also be

TABLE 1. 20 ASPS Cases with Cytogenetic or Molecular Evidence of t(X;17) and Data on Translocation Structure

					Evidence for t(X;17) structure		
Case[a]	Age/Sex/Site	Fusion type[b]	t(X;17) Structure	Karyotypic data	17q25→qter copy number by FISH[c]	RT-PCR evidence for reciprocal structure[c]
ASPS-1	19 F thigh	1	Unbalanced	n.a.	1	-
ASPS-2	36 F thigh	2	Unbalanced	n.a.	1	-
ASPS-3	31 F thigh	1	Unbalanced	n.a.	1	-
ASPS-4	38 M arm	2	Unbalanced	n.a.	1	-
ASPS-5	29 F thigh	1	Unbalanced	n.a.	1	-
ASPS-6	14 F thigh	1	Unbalanced	der(17) only	1	-
ASPS-7	40 F thigh	1	Balanced	n.a.	2	+
ASPS-8	40 M hand	2	Unbalanced	der(17), del(Xp11)	n.a.	-
ASPS-9	7 M thigh	1	Unbalanced	der(17) only	n.a.	-
ASPS-11	9 M lower leg	1	Unbalanced	n.a.	1	-
ASPS-13	27 M thigh	1	Unbalanced	n.a.	1	-
ASPS-14	36 F thigh	1	Balanced	n.a.	2	+
ASPS-17	21 F thigh	**	Unbalanced	der(17) only	n.a.	n.a.
Cullinane et al., 1992	15 F thigh	**	Unbalanced***	der(17) only	n.a.	n.a.
van Echten et al., 1995	58 F neck	**	Unbalanced***	der(17) only	n.a.	n.a.
van Echten et al., 1995	32 F thigh	**	Unbalanced***	der(17) only	n.a.	n.a.
Heimann et al., 1998	10 F uterine cervix	**	Unbalanced	der(17), del(Xp11)	1	n.a.
Lasudry and Heimann, 2000	2 M orbit	**	Balanced	t(X;17)	n.a.	n.a.
Uppal et al., 2003	31 F forearm	1	Balanced	t(X;17)	n.a.	-
Unpublished*	10 M forearm	**	Unbalanced	der(17) only	n.a.	n.a.

[a]Unique case numbers indicate ASPS cases previously studied in our laboratory (Argani et al., 2001; Ladanyi et al., 2001, 2002). ASPS-13 and ASPS-14 were previously unpublished. ASPS-17 was published (Sciot et al., 1993), but the karyotype was revised in Ladanyi et al. (2001), and the tumor was further studied in Ladanyi et al. (2002).
[b]Refers to type of *ASPSCRI–TFE3* fusion (a.k.a. *ASPL–TFE3*). The type 2 fusion includes an additional exon of *TFE3*. RT-PCR data are from Ladanyi et al. (2001), except for those from Uppal et al. (2003).
[c]FISH and RT-PCR data from (Argani et al. 2001), except for those from Uppal et al. (2003) and Heimann et al. (1998). RT-PCR evidence refers to detection of *TFE3–ASPSCRI* transcripts.
*The full karyotye of this unpublished case (Griffiths et al., unpublished data) is 46,XY, der(17)t(X;17)(p11.2;q25)[20].
**Cytogenetic data only.
***Published karyotypes contained der(17), in retrospect consistent with der(17)t(X;17)(p11.2;q25).

explained by X duplication prior to a G1 translocation. In ASPS arising in women, there is yet another possible scenario that could result in two normal X chromosomes and the der(17)t(X;17), namely, a G1 translocation followed by missegregation of the duplicated remaining X in a later mitosis. These different mechanisms of formation are depicted in Figure 1. In G1 translocation scenario A (Fig. 1), missegregation of 2 der(X) and 2 normal X chromosomes at the next mitosis would result in homozygosity for Xp11.2→qter markers in all cases. In G1 translocation scenario B (Fig. 1), one third of cases would show homozygosity for these same markers. However, in a G2 translocation scenario (Fig. 1), the der(17) would segregate with 2 normal X chromosomes, usually of different parental origin (assuming that the chromatids of the unaffected X chromosome segregated normally), leading to heterozygosity for Xp11.2→qter markers in all cases. We therefore performed an analysis of polymorphic markers on the X chromosome in ASPSs from women to determine whether the preferential cell-cycle timing of this translocation was related to the sex of the patient.

MATERIALS AND METHODS

We studied matched pairs of normal and tumor tissue from archival paraffin blocks of 9 women with ASPS ranging in age from 14 to 40 years. Six of these ASPS cases are described in Table 1 (ASPS-1, -2, -3, -5, -7, and -14); the other 3, ASPS-16, -19, and -20, were archival cases for which cytogenetic and molecular data were unavailable, but which all showed intense nuclear immunoreactivity for TFE3, a finding that we previously showed to be a highly specific and sensitive marker for the presence of a TFE3 fusion protein (Argani et al., 2003). Furthermore, all 3 cases showed evidence of an unbalanced t(X;17) structure, as determined on the basis of allelic imbalances for Xp markers (see Results section, below). The phenotype of case ASPS-16 was described in more detail previously (Ladanyi et al., 2002). Overall, of the 9 cases
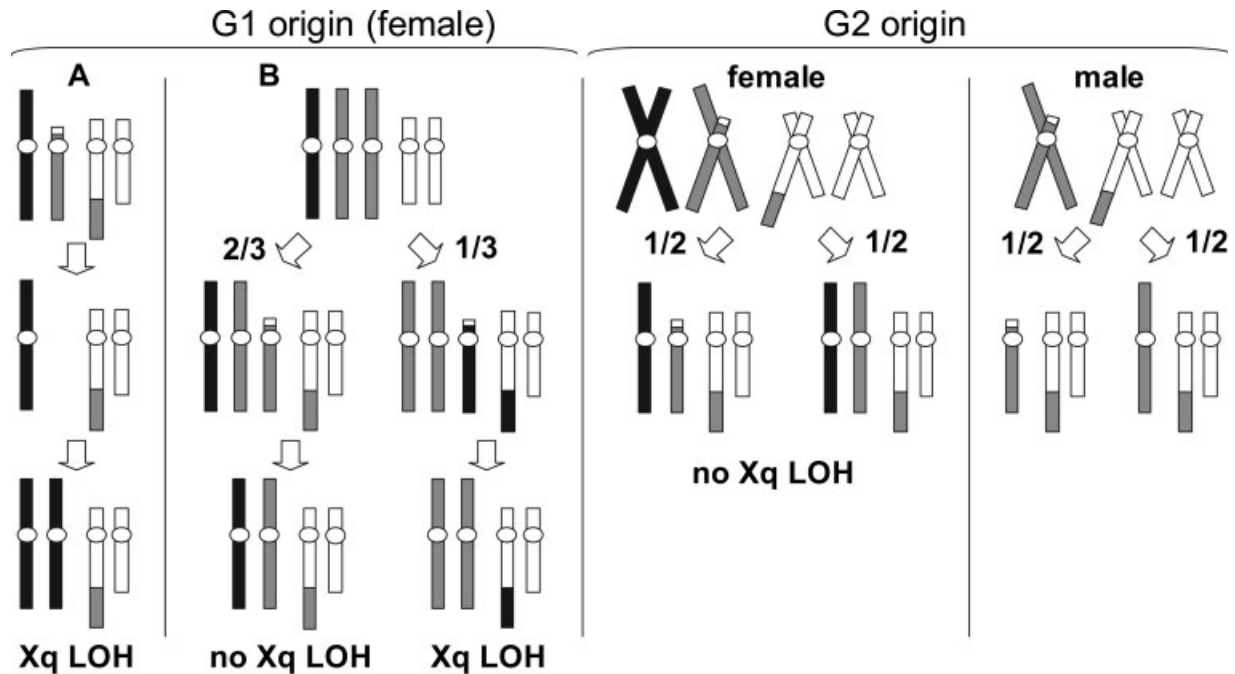
Figure 1.   Three possible scenarios for the formation of der(17)-t(X;17)(p11.2:q25) of ASPS. For G1 translocation scenarios (left), only those resulting in a der(17) in females are shown. There are two possible mechanisms by which a G1 translocation could result in a der(17): (A) translocation followed by loss of the der(X) and duplication or mis-segregation of the normal homolog, resulting in LOH for Xq loci; and (B) trisomy X preceding the t(X;17) followed by loss of the der(X), resulting in retained heterozygosity for Xq loci in two thirds of the cases and LOH for Xq loci in one third of the cases. For the G2 translocation scenario (right), all outcomes resulting in the der(17) with or without the der(X) are shown for both females and males. In females, translocation in the G2 phase of the cell cycle resulted in retention of heterozygosity for all X loci in all cases.

studied, only 2, cases ASPS-7 and ASPS-14, showed evidence of a balanced t(X;17).

We microdissected the tumor specimens to reduce nonneoplastic tissue contamination and to obtain at least 90% of tumor content in the portion used for DNA extraction. We performed allelotyping of 4 highly polymorphic microsatellite loci in Xp11.2→qter and of 3 loci in Xp11.2→pter (Fig. 2). The broad regions to be analyzed in the X chromosomes allowed us to select easily typed tetranucleotide-repeat loci. The primers used for the Xp and Xq polymorphic loci were in the NCBI human UniSTS database (www.ncbi.nlm.nih.gov/entrez/query.fcgi?db= unists). We also studied two novel polymorphic dinucleotide-repeat loci that we had identified in 17q25.3→qter, approximately 500 kb telomeric to *ASPSCR1*. The first one, which we designated CHR17-Di-4 in the Genbank #AC124287 sequence, was amplified by primers GAACACGTGGCC CCCAGC and GAACCGAAACCCCTCCTCGTGC. The second locus, designated CHR17-Di-5, in the Genbank #AC124283 sequence, was amplified by primers CTCTATAAAACTGAGGCTGTGCTT CA and AAAGCCATGGTCACTGGAACATG. DNA samples were amplified using primers labeled with 6-FAM fluorescent amidites. PCR products

were then diluted appropriately, admixed with Hi-Di formamide and Tamra-500 size standard, and loaded into an ABI 310 (Applied Biosystems, Foster City, CA) automated genetic analyzer; the allele sizes were defined by GeneScan™ software (Applied Biosystems, Foster City, CA).

RESULTS

The results of the allelotyping studies are shown and summarized in Figure 2. A minimum of 3 of the 7 markers tested were informative (range, 3–6) in all 9 cases, 8 of which also were informative for both the p and the q arms in at least one locus. Only case ASPS-20 was uninformative at the Xp loci. We found that, in all 9 cases, all Xp11.2→qter loci that were informative in normal tissue remained heterozygous in the corresponding tumor genomic DNA. This was true for every informative microsatellite locus in each case (Fig. 2). Overall, for all 7 markers spanning both arms of the X chromosome, all 9 ASPS cases displayed this consistent match of allelotypes between normal and tumor tissue. An incidental observation in case ASPS-20 was that the tumor genomic DNA showed one additional peak at both *DXS6810* and *DXS6797*, indicative of microsatellite instability (Fig. 2). A
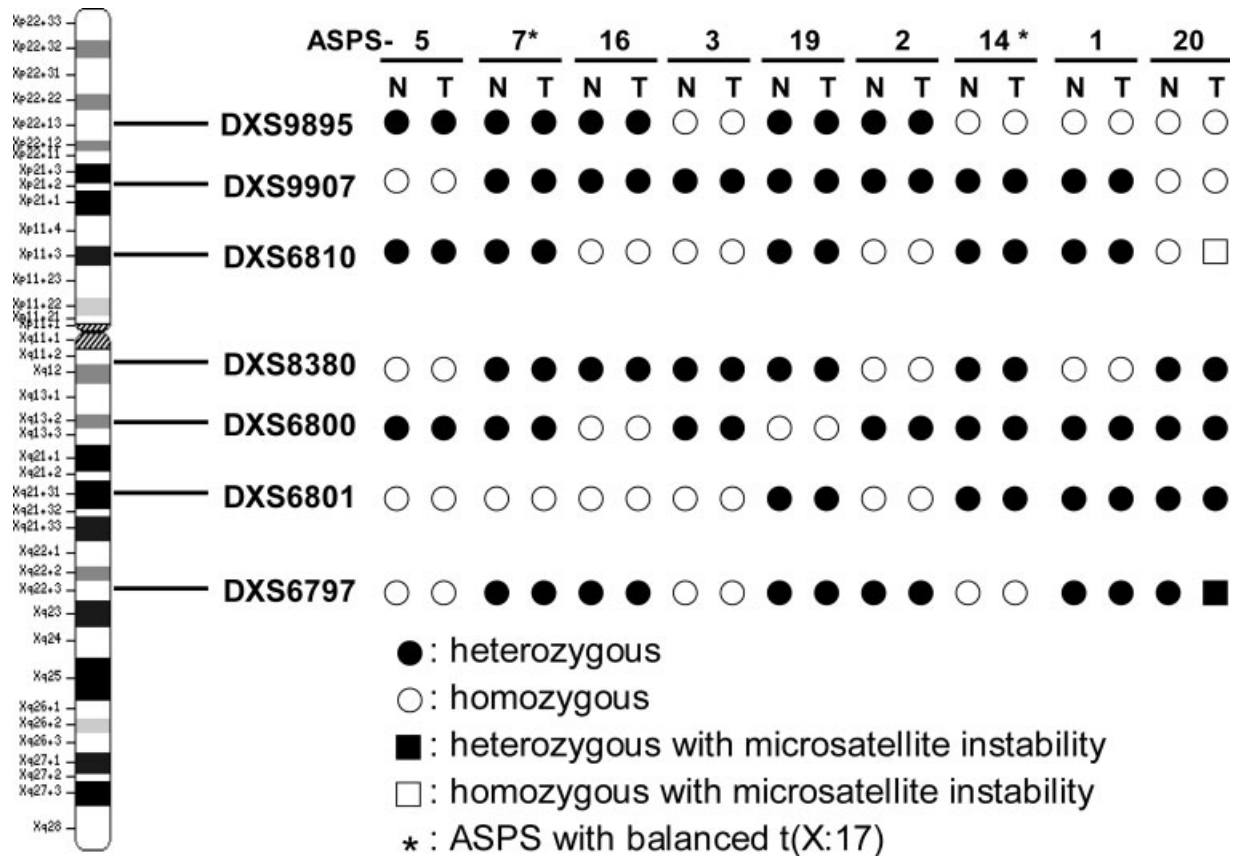
Figure 2. Summary of allelotyping results of the X chromosome for 9 females with ASPS showing that all informative markers on Xp11.2→qter were heterozygous.

previous study of ASPS showed low-level microsatellite instability in a minority of the cases (Saito et al., 2003).

In addition, we also observed the expected differences in allele ratios at Xp loci between the 2 ASPS cases with balanced t(X;17) translocations and the 7 cases with unbalanced t(X;17) translocations. For markers telomeric to the Xp11 breakpoint, the relative allele ratios of tumor DNA to normal tissue DNA were approximately 1.0 in the former, whereas they were close to 2.0 in the latter (Fig. 3). The nearly twofold increase in the allele ratios of the Xp markers seen in the unbalanced ASPSs reflects previous cytogenetic studies demonstrating a net gain of one copy of Xp11.2→pter because of the unbalanced t(X;17) in most ASPSs. Conversely, this discrepancy was not present in each heterozygous locus of Xq, with the allele ratios approaching 1.0 in both balanced and unbalanced cases. To confirm that the pattern of allelic imbalances in 17q also was in accordance with the previous cytogenetic and RT-PCR findings indicating a net loss of one copy of 17q25→ qter in unbalanced ASPS cases, we compared the allelotypes of

unbalanced and balanced cases by using polymorphic markers telomeric to the 17q25.3 breakpoint. As expected, heterozygosity was lost in unbalanced ASPSs but was retained in the two balanced cases (Fig. 3). This finding also largely excluded the possibility that the samples contained too many non-neoplastic cells to allow the detection of loss of heterozygosity (LOH).

DISCUSSION

The results of our allelotyping, which showed retention of Xq heterozygosity in all 7 female patients with an unbalanced t(X;17), along with published male cases with an unbalanced t(X;17), are most consistent with the t(X;17) of ASPS occurring in the G2 phase of the cell cycle, regardless of patient sex. A similar analysis of the der(19)t(1;19)(q23;p13) of acute lymphoblastic leukemia (which encodes the *E2A–PBX1* fusion gene) was recently published (Paulsson et al., 2005). Because, in that study, none of the 4 der(19) cases showed LOH for chromosome 1, the authors excluded a translocation occurring in G0/G1, followed by duplication of the remaining normal
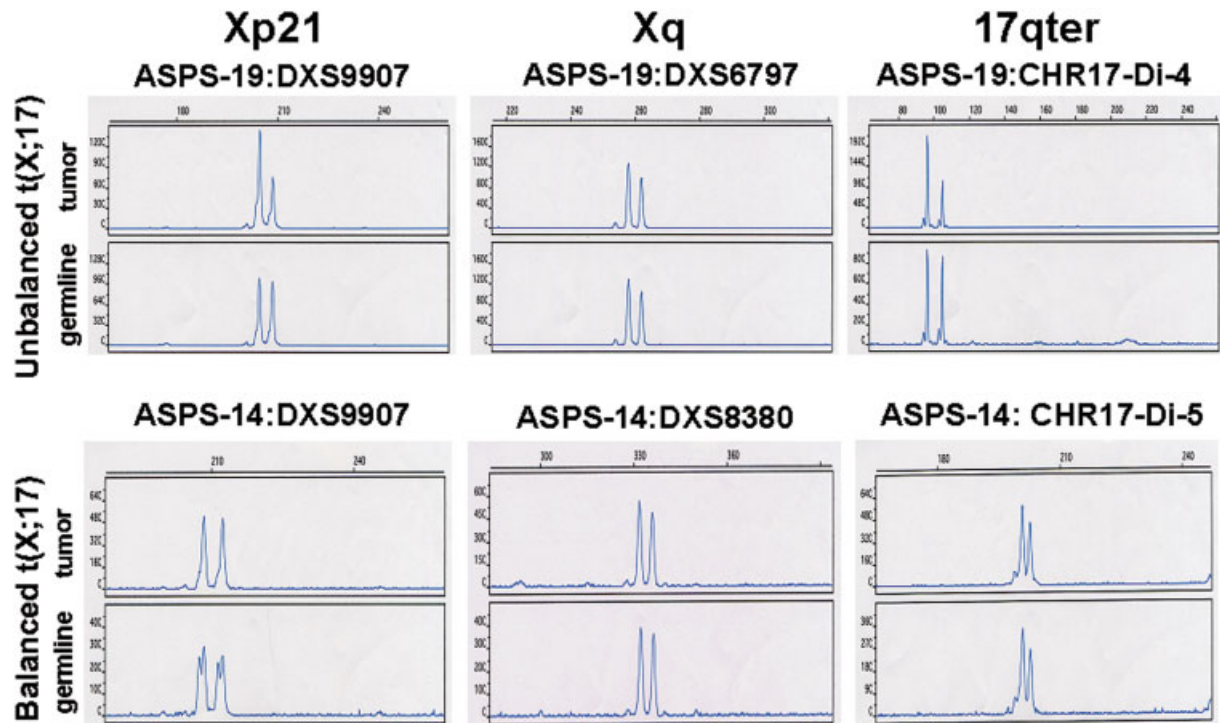
Figure 3. Electrophoretograms showing allelotype differences between an ASPS bearing an unbalanced t(X;17) (case ASPS-19) and an ASPS bearing a balanced t(X;17) (case ASPS-14). Heterozygosity was retained in tumor DNA from both cases at informative polymorphic markers on Xq. This finding in case ASPS-19 is most readily explained by a G2 translocation (see text). The difference in peak ratios between tumor and germ-line DNA in case ASPS-19 at the Xp21 and 17qter markers (500 kb telomeric to *ASPSCR1*) is evidence that its translocation structure is unbalanced. The 17qter markers are two novel polymorphic dinucleotide repeat loci in 17q25.3→qter, designated CHR17-Di-4 (in Genbank No. AC124287) and CHR17-Di-5 (in Genbank No. AC124283); for more detail, see the Materials and Methods section. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

chromosome 1. The remaining possibilities included formation of the der(19) in G2 or formation in G1 preceded by trisomy 1. Paulsson et al. (2005) favored the latter scenario because coexisting t(1;19)/der(19) clones and trisomy 1 have been observed in some cases. However, such a mechanism has less support in ASPS because cases with coexisting t(X;17)/der(17) clones or +X have not been reported. However, the caveat to this statement is that the total number of ASPS cases studied remains limited. If the der(17)t(X;17) in ASPS in women arises consistently during G2, as is likely the case in men, this would suggest a peculiar intrinsic propensity for the translocation to occur in G2 in these cells, of which the unbalanced translocation structure might merely be a frequent consequence.

Most chromosomal translocations producing fusion genes are cytogenetically reciprocal, with no net gain or loss of genetic material, even though only one of the two resulting chimeric genes is pathogenetically significant. Thus, the predominantly nonreciprocal structure of the t(X;17) of ASPS stands in sharp contrast to most translocations encoding fusion oncogenes (reviewed in Rego and Pandolfi, 2002). The unbalanced t(X;17) structure in ASPS thus combines fusion protein formation with gain of most of the short arm of X and loss of the relatively small region 17q25.3→ qter. The Xp imbalance also was detected in a CGH study of ASPS (Kiuru-Kuhlefelt et al., 1998). These genomic imbalances associated with an unbalanced t(X;17) could be biologically advantageous to ASPS cells, but this remains purely hypothetical.

Cytogenetic progression from a balanced to an unbalanced translocation structure through loss of the reciprocal derivative chromosome has been described in some soft-tissue tumors in association with histologic or clinical progression. Examples include the der(14)t(12;14)(q15;q24) in intravenous leiomyomatosis arising from uterine leiomyomas (Dal Cin et al., 2003) and the der(22)t(17;22) (q22;q13) of adult dermatofibrosarcoma protuberans compared to its pediatric counterpart, giant cell fibroblastoma (Maire et al., 2002). However, such a cytogenetic progression has not been described in ASPS. Individuals whose ASPS contains a balanced t(X;17) have not been found to be younger, on average, than those with an unbalanced t(X;17),

and no cases with coexisting balanced and unbalanced clones have been seen.

Interestingly, the cell-cycle timing of somatic chromosomal translocations may be linked to the mechanism of their formation. In experimental models, two double-strand breaks (DSBs) are sufficient to result in frequent reciprocal translocations (Richardson and Jasin, 2000). Mammalian cells are currently known to repair DSBs by pathways involving either homologous recombination (HR) or nonhomologous end-joining (NHEJ). In experimental systems, more than 99% of DSBs are repaired by NHEJ (Honma et al., 2003). Although the factors affecting the preferential use of the HR or NHEJ repair pathway are unclear, mounting evidence suggests that in cells of vertebrates, the NHEJ pathway plays a major role in DSB repair during the G0/G1 phase. In contrast, the HR-mediated repair system tends to work efficiently during the late S/G2 phase but appears to be suppressed in the G0/G1 phase (Ferguson and Alt, 2001). Given the selectivity of these DSB repair mechanisms for different phases of the cell cycle, the observation that most specific chromosomal translocations that produce fusion genes in human cancers show evidence of an NHEJ mechanism in the form of small duplications, deletions, or inversions at their genomic fusion points (Zucman-Rossi et al., 1998; Gillert et al., 1999; Wiemels and Greaves, 1999; Rassool, 2003; Reiter et al., 2003) is consistent with the presumption that they occur during G0/G1, which, in turn, also is consistent with them typically having a reciprocal structure. The G2/S timing of the t(X;17) of ASPS might point, instead, to HR as a mechanism. In this regard, it is interesting that alignment of *ASPSCR1* intron 7 (12.19 kb) and *TFE3* intron 5 (3.769 kb), predicted to be rearranged in type 1 fusions, revealed several substantial stretches (>200 bp) of significant identity (>85%) and shorter stretches (>100 bp) with 95% identity because of multiple *ALU* subfamily S repeats in both introns. HR-mediated rearrangements between homologous *ALU* repeats have been described in a number of settings (Kolomietz et al., 2002).

Of note, some pediatric renal carcinomas contain a balanced t(X;17)(p11.2:q25), with breakpoints cytogenetically identical to the translocation observed in ASPS. By both FISH and RT-PCR for the reciprocal *TFE3–ASPSCR1* fusion transcript, we confirmed that t(X;17)-associated renal carcinomas retained both copies of 17q25.3 telomeric to the breakpoint, whereas in almost all ASPS cases, this subtelomeric region of chromosome arm 17q

was deleted during translocation, accompanied by net gain of the Xp sequence telomeric to *TFE3*, with only 2 of our 14 previously reported ASPS cases deviating from this pattern (Argani et al., 2001). The finding of two distinctive tumors associated with balanced and unbalanced forms of the same translocation is highly unusual and suggests mechanistically that the t(X;17) may occur in different phases of the cell cycle in these two tumors. It raises the possibility that the biology of these cancers differs in the impact of the genomic imbalances associated with an unbalanced rearrangement or in the requirement for an intact copy of *TFE3*. *TFE3* is only minimally expressed by the inactive X, at least in fibroblasts (Carrel and Willard, 2005).

In summary, our data in ASPS are consistent with a model in which the somatic chromosomal translocation, t(X;17), occurs predominantly or exclusively in the G2 phase of the cell cycle regardless of the sex of the patient. The development of t(X;17) during G2 could reflect an intrinsic property of this genetic rearrangement, or it could reflect selection for retention of an intact copy of *TFE3* or for the genomic imbalances associated with the presence of a normal X chromosome.

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