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Mapping the X chromosome breakpoint in two papillary renal cell carcinoma cell lines with a t(X;1)(p11.2;q21.2) and the first report of a female case

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Abstract. A t(X;1)(p11.2;q21.2) has been reported in cases of papillary renal cell tumors arising in males. In this study two cell lines derived from this tumor type have been used to indicate the breakpoint region on the X chromosome. Both cell lines have the translocation in addition to other rearrangements and one is derived from the first female case to be reported with the t(X;1)(p11.2;q21.2). Fluorescence in situ hybridization (FISH) has been used to position YACs belonging to contigs in the Xp11.2 region relative to the breakpoint. When considered together with detailed mapping information from the Xp11.2 region the position of the breakpoint in both cell lines was suggested as follows: Xpter→Xp11.23–OATL1 – GATA1 – WAS – TFE3 – SYP – **t(X;1)** – DXS255 – CLCN5–DXS146–OATL2–Xp11.22→Xcen. The breakpoint was determined to lie in an uncloned region between SYP and a YAC called FTDM/1 which extends 1 Mb distal to DXS255. These results are contrary to the conclusion from previous FISH studies that the breakpoint was near the OATL2 locus, but are consistent with, and considerably refine, the position that had been established by molecular analysis.

Renal cell carcinoma (RCC), the most common cancer of the kidney, can be divided into papillary and non-papillary clear cell tumor subgroups (Whelan et al., 1990; Savage, 1994). The clear cell carcinomas are characterized in cytogenetic and molecular studies by frequent abnormalities of the short arm of chromosome 3, including loss of heterozygosity. The von Hippel-Lindau (VHL) disease, a dominantly inherited cancer syndrome in which family members develop multiple bilateral clear cell renal carcinomas, as well as tumors of the brain, spine and eye, has also been mapped to this chromosome region. The VHL gene has now been cloned (Latif et al., 1993) and mutations of this gene are found in a high proportion of sporadic clear cell renal carcinomas (Gnarra et al., 1994; Shuin et al., 1994; Whaley et al., 1994). Papillary renal tumors, which account for around 15–20% of renal carcinomas, also occur in both sporadic and familial forms (Mancilla-Jimenez et al., 1976; Zbar et al., 1994). Abnormalities and loss of 3p are not observed in these tumors but recurrent numerical abnormalities of other chromosomes have been detected including trisomy or tetrasomy 7, trisomy 10, 12, 16, 17, and 20 and loss of the Y chromosome (Mitelman, 1994; Kovacs et al., 1987; Kovacs et al., 1991; Berg et al., 1993). Evidence suggests that some of these alterations may also be present in the surrounding normal tissue and thus not tumor specific (Elfving et al., 1995).

A specific reciprocal translocation between chromosomes X and 1, t(X;1)(p11.2;q21.2), has been described in a case of trabecular papillary renal adenocarcinoma (de Jong et al., 1986). The same rearrangement was subsequently found in four additional cases of papillary renal tumors and this translocation has been suggested as being characteristic of a specific subset of papillary RCC (Meloni et al., 1993). A t(X;17)(p11.2;q25) and a del(X)(p11) have also been found in two separate papillary RCC (Tomlinson et al., 1991; Ohjimi et al., 1993). Notably all these tumors with a rearrangement at Xp11 had arisen in males. Two other cases involving Xp11 have been documented in unspecified types of renal cell tumors. These were both trans-

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locations involving 1p34 and one was from a female patient (Yoshida et al., 1985; Kovacs et al., 1987).

As a step towards identifying the gene at Xp11.2 and its specific fusion partner at 1q21.2 it is important to localize the precise position of the breakpoints in the t(X;1)(p11.2;q21.2) of papillary RCC. However, mapping studies to position the breakpoint at Xp11.2 have yielded inconsistent results. Studies using a panel of tumor derived somatic cell hybrids mapped the breakpoint relative to 9 markers from the X chromosome (Sinke et al., 1993). When considered together with recent mapping data from this region, the results indicated that the breakpoint lay between the marker DXS146 and the locus for the gene SYP. Analysis using FISH, including the tumor used in the molecular studies, found that a YAC corresponding to the more telomeric OATL1 locus hybridized to the derivative 1, der(1), chromosome and a YAC for the more centomeric OATL2 locus hybridized to both the derivative X, der(X), and the der(1), chromosomes. This led to the conclusion that the OATL2 YAC spanned the breakpoint (Suijkerbuijk et al., 1993). In order to resolve these inconsistencies and to define, as precisely as possible, the position of the breakpoint, we have used FISH to determine the X chromosome breakpoint in two independent papillary renal cell tumors containing the t(X;1)(p11.2;q21.2).

Materials and methods

Cell lines

The UOK120 and UOK124 cell lines were derived from the papillary renal cell carcinoma from a 30-year-old male and a 21-year-old female respectively. These were maintained in Dulbecco's minimal essential medium with 10% fetal calf serum. Slides of metaphase chromosomes from the cell lines and normal peripheral blood lymphocytes were prepared and stained by standard procedures.

DNA probes

An X chromosome specific centromere probe, pSV2X5, and a probe for the pericentric region on chromosome 1, pUC1.77, were used to unambiguously identify the derivative chromosomes in FISH experiments. The following YAC clones were available for the FISH studies; OATL2.7, pTAK8/3, PTM, M27B/2, FTDM/4, FTDM/1, Y67, SAE/1, TFE3/3, GATA/2 and OATL1.2. The YACs were grown for 4 days and DNA isolated by standard procedures.

FISH

The YAC DNA probes were biotinylated or labeled with digoxigenin (Boehringer Mannheim) by nick translation (Bionick kit, Gibco, BRL). 400 ng of YAC DNA and 20 ng of centromere specific probe was hybridized to the slides of metaphase chromosomes and detected as previously described (Shipley et al., 1993). An X chromosome specific paint was used according to the manufacturers instructions (Cambio, Cambridge UK). The preparations were counterstained with DAPI and analysed using a Zeiss Axioplan microscope and a cooled CCD camera (Photometrics) linked to a digital imaging system with software from Digital Scientific (Cambridge, UK).

Results

Cytogenetics of papillary renal cell carcinoma cell lines

Cytogenetic analysis showed that both the cell lines UOK120 and UOK124 contained the t(X;1)(p11.2;q21.2) amidst a heterogeneous and complex karyotype. The composite karyotype of UOK120 was 68–78,–Y,t(X;1)(p11.2;q21.2)×2,+3,+5,der(6)t(6;?)b(q24;?),+7,der(11)t(11;Y)(q14;q21),+13,der(15)t(15;?)(p11;?)×2,+mar1×2,+mar2[cp20]. The karyotype of UOK124 was 64–81,–X,t(X;1)(p11.2;q21.2),der(X)t(X;1)(p11.2;q21.2),der(1)del(1)(p31)t(X;1)(p11.2;q21.2),der(18)t(5;18)(q11.2;q23),der(19)t(19;?)(p13.2;?)[cp20]. The chromosomes derived from chromosomes X and 1 in this case are shown in Fig. 1 and no normal X chromosome was found (confirmed by analysis with an X chromosome specific-paint). The der(1)del(1) is likely to have arisen by a deletion in the long arm of a duplicated der(1).

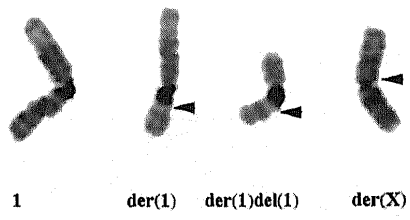

Fig. 1. Partial karyotype of the cell line UOK124 illustrating the rearrangements involving chromosomes X and 1. The karyotype contained a normal chromosome 1 but no normal X. The der(1) and the der(X) result from the t(X;1)(p11.2;q21.2) that is associated with papillary renal cell carcinoma and the der(1)del(1)(p31)t(X;1)(p11.2;q21.2) is thought to be derived by deletion following the duplication of the der(1) chromosome. The arrows indicate the position of the translocation breakpoints.

FISH studies to map the Xp11.2 breakpoint

To determine whether the chromosome breakpoint in the t(X;1) was located in the ornithine aminotransferase pseudogene region, OATL2, as previously reported (Suijkerbuijk et al., 1993) the 450-kb YAC, OATL2.7, that spans the OATL2 locus was hybridized to the metaphase chromosomes of UOK120 and UOK124. This probe produced signal on both the der(X) and the der(1), in both UOK120 and UOK124 and also hybridized to the der(1)del(1) of UOK124. The strongest signal was generally observed on the der(X) in both cell lines (Fig. 2Ai and 2Bi). A 650-kb YAC for the OATL1 region (OATL1.2) that maps 3–4 Mb telomeric to the OATL2 locus was also hybridized to the chromosomes of the two cell lines. Signal on both derivative chromosomes was also demonstrated, although the signal was usually strongest on the der(1) (Fig. 2Aii and 2Bii). It is known that the OATL1 and OATL2 regions have many sequences in common and cross hybridization of OATL2 sequences with the OATL1 region has previously been noted in FISH experiments (Shipley et al., 1994; Crew et al., 1995). The present results can therefore be explained by cross hybridization if the breakpoint lies between the OATL1 and OATL2 region. To investigate this explanation of the results, additional markers from characterized contigs in the region were positioned relative to the breakpoint.

Detailed mapping between the OATL1 and OATL2 loci has allowed the following order of genes and markers to be determined: Xpter→Xp11.23–OATL1–GATA1–WAS–TFE3–SYP–M27β(DXS255)–CLCN5–pTAK8(DXS146)–OATL2–Xp11.22→Xcen (Lafreniere et al., 1991a, 1991b; Derry et al., 1994; Fisher et al., 1994a; Fisher et al., 1995). A YAC contig with a minimum size of 2 Mb spans the pTAK8(DXS146),

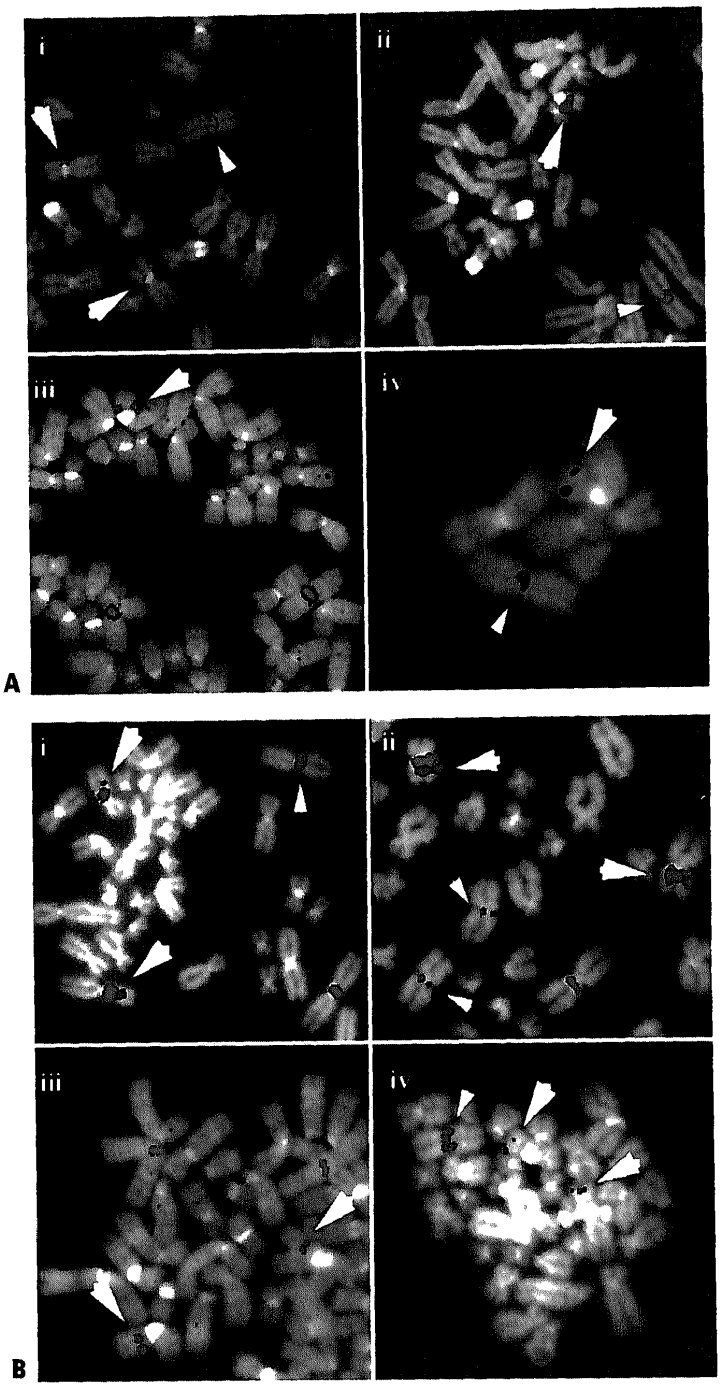

Fig. 2. FISH analysis illustrating the hybridization of YACs to the derivative chromosomes of (**A**) UOK120 and (**B**) UOK124 which both have the t(X;1)(p11.2;q21.2) that is associated with papillary renal cell carcinoma. The large arrow indicates signal from the YAC probes (red) on the der(1) chromosome and on the smaller der(1)del(1) chromosome found in UOK124 (**B**). The smaller arrow indicates signal from the YAC on the der(X) chromosome. The green signal corresponds to the X centromere probe, with the exception of Bi and Bii where it corresponds to the probe for the pericentric region of chromosome 1. The YACs shown are (i) OATL2.7, (ii) OATL1.2 which hybridized to both the der(1) and der(X) chromosomes, (iii) GATA/2 which localized to the der(1) and (iv) FTDM/1 which hybridized to both the der(1) and the der(X) but not to the breakpoint region on the der(X).

CLCN5, and M27β(DXS255) loci. This contig includes the YACs pTAK8/3, PTM, M27β/2, FTDM/4 and FTDM/1 with the YAC FTDM/1, at the end of the contig, extending 1 Mb telomeric to M27β(DXS255). A second YAC contig which is greater than 1.4 Mb spans the SYP, TFE3, WAS, GATA1 and OATL1 loci and includes the YACs Y67, SAE/1, TFE3/3, and GATA/2 (Fisher et al., 1995; Table I).

Various YAC clones that make up the two contigs were used as probes in the FISH experiments (Table I). The majority of YACs hybridized to Xp11.2 only, however, YACs SAE/1, Y67 and FTDM/1 also hybridized to an additional site in normal metaphase chromosomes. This is likely to be due to YAC chimerism but the possibility of regions of homology cannot be excluded. The YAC designated SAE/1 containing both the TFE3 and SYP genes was shown by FISH to hybridize to normal chromosomes at 7q34 as well as Xp11.2 indicating that this is a chimeric YAC clone. This YAC also appears to have a deletion of approximately 250 kb of DNA between the two genes. Another YAC designated Y67 that contains the SYP gene was shown to hybridize strongly to 3q26 as well as weakly to Xp11.2, suggesting that the SYP region is unstable in yeast. Signal at Xp11.2 and Xp22→p21 was found following hybridization of the 660-kb YAC clone FTDM/1 to normal metaphases.

In FISH experiments with the UOK120 and UOK124 cell lines, YAC clones Y67, SAE/1, TFE3/3, and GATA/2 all hybridized to the der(1) and in UOK124 the der(1)del(1) chromosome but not to the der(X) chromosome (Fig. 2Aiii and 2Biii). Conversely, the YAC clones pTAK8/3, PTM, M27β/2 and FTDM/4 all hybridized to the der(X) chromosome but not to the der(1) or the der(1)del(1). The clone FTDM/1 gave a strong hybridization signal on the der(X) and a weaker signal on the der(1) and the der(1)del(1) chromosomes (Fig. 2Aiv and 2Biv). However, the position of the signal on the der(1) and the der(1)del(1) did not correspond to the cytogenetic position of the breakpoint and was consistent with hybridization to the Xp22→p21 region seen in normal X chromosomes. This probe was therefore considered to lie centromeric to the breakpoint. Individual YACs hybridized to the same derivative chromosomes in both UOK120 and UOK124 indicating that these cell lines have Xp11.2 breakpoints at a similar position. In addition, the pattern of hybridization was the same for the der(1)del(1) chromosome as the der(1) which is consistent with its derivation from a der(1) chromosome. These results are summarized in Table I and place the breakpoint at Xp11.2 between the YAC markers FDTM/1, which extends 1 Mb telomeric from the DXS255 marker and Y67 (which contains the SYP gene).

Genes in the region, SSX1 and SSX2, which are disrupted by the t(X;18) associated with synovial sarcoma and map within the OATL1 and OATL2 regions respectively (Clark et al., 1994; Crew et al., 1995); TFE3, a transcription factor (Beckmann et al., 1990) and CLCN5, a strong candidate for involvement in a hereditary nephrolithiasis Dent's disease (Fisher et al., 1994b), were considered candidate genes for involvement in the t(X;1)(p11.2;q21.2) of papillary renal cell carcinoma. Southern and Northern blots including DNA and RNA from UOK120 and UOK124 were screened with probes for these genes but there was no evidence for their involvement in the t(X;1) (data not shown). GATA1, another transcription factor

Table I. Fluorescence in situ hybridization of Xp11.23→p11.22 probes to the papillary renal cell carcinoma derived cell lines UOK120 and UOK124 containing the t(X;1)(p11.2;q21.2)

YAC[a]	Library	YAC ID	YAC size (kb)	Genes/markers present	Signal
OATL1.2	ICRF	F0501	550	OATL1	der(X), der(1)
GATA/2	ICRF	B102	300	GATA1, WAS	der(1)
TFE3/3	Nussbaum	E11	230	TFE3	der(1)
SAE/1b	ICRF	E021	375	SYP, TFE3	der(1)
Y67b	CEPH	66G1	390	SYP	der(1)
FDTM/1[b]	ICRF	E0250	660		der(X)[c]
FDTM/4	ICI	36HB8	345		der(X)
M27b/2	St Louis	6129	185	M27b, DXS255, CLCN5	der(X)
PTM	ICRF	C0191	365		der(X)
pTAK8/3	ICRF	G0101	300	pTAK8, DXS146	der(X)
OATL2.7	ICRF		450	OATL2	der(X), der(1)

[a] In order, telomere to centromere.
[b] Chimeric YACs.
[c] Hybridization to the der(1) was also seen but not at the breakpoint region.

Clones were hybridized to the chromosomes of the cell lines UOK120 and UOK124 and localized to the derivative X, der(X) or derivative 1, der (1) chromosome (including the der(1)del(1) of UOK124). Bold indicates clones belonging to a contig of greater than 2 Mb that spans DXS255–CLCN5–DXS146. Italics indicates the clones in the contig of approximately 1.4 Mb that span OATL1–GATA1– WAS–TFE3– SYP (Fisher et al., 1995).

(Merika and Orkin, 1993), WAS, implicated in Wiscott-Aldrich syndrome (Derry et al., 1994), SSX1 and SSX2 are considered to be at least 100 kb from the breakpoint.

Discussion

As a first step towards isolating the genes involved in the t(X;1)(p11.2;q21.2) of papillary RCC we have localized the breakpoint position on the X chromosome in two cases relative to various markers from Xp11.2. Previous studies concluded that the breakpoint was in the OATL2 region (Suijkerbuijk et al., 1993). Although the pattern of hybridization that we observed with the YAC clone OATL2.7 in the FISH analysis was similar to that seen by Suijkerbuijk et al. (1993), the signal on both the der(1), including the der(1)del(1), and the der(X) chromosomes is interpreted here as being due to cross hybridization of the probe with the OATL1 region some 3–4 Mb more telomeric (Lafreniere et al., 1991b; Fisher et al., 1994a). Cross hybridization in FISH experiments has been seen between the OATL1 and OATL2 region in synovial sarcoma samples which are associated with a t(X;18)(p11.2;q11.2) and have a breakpoint in either the OATL1 or OATL2 region (Shipley et al., 1994). In addition, considerable sequence homology has been shown between the OATL1 and OATL2 regions (Crew et al., 1995). Confirmation of this interpretation was obtained using probes prepared from YAC clones that mapped to this region. The results showed that the X chromosome breakpoint in both cell lines containing the t(X;1)(p11.2;q21.2) lay between sequences detected by the YACs FTDM/1 and Y67. The nearest flanking markers/genes are therefore DXS255 and SYP. This result is consistent with the data previously obtained using somatic cell hybrids containing a der(X) chromosome from a papillary RCC which, when considered together with more recent mapping data, places the breakpoint between DXS146, which lies centromeric to DXS255, and SYP (Sinke et al., 1993). We conclude that the breakpoint lies within an uncloned genomic region between the Xp11.2 region of the YAC FTDM/1, which lies distal to DXS255, and the SYP gene. Our data therefore both resolve the discrepancy regarding the mapping of the t(X;1) breakpoint that exists in the literature and have considerably refined the position of the breakpoint since the YAC FTDM/1 extends approximately 1.5 Mb telomeric from DXS146 towards the breakpoint.

Several solid tumor specific translocations have been shown to involve transcription factors (Shipley et al., 1993; Rabbitts, 1994). Candidate genes for involvement in the t(X;1)(p11.2;q11.2) which encode transcription factors include TFE3 (Beckmann et al., 1990) and GATA1 (Merika and Orkin, 1993). Two other genes, SSX1 and SSX2, map to the region near the OATL1 and OATL2 loci respectively and either of these is disrupted in the t(X;18)(p11.2;q11.2) associated with synovial sarcoma (Shipley et al., 1994; Clark et al., 1994; Crew et al., 1995). These genes are also believed to encode transcription factors (Crew et al., 1995). In addition, a gene CLCN5 is a strong candidate for involvement in Dent's disease, a familial syndrome associated with proximal renal tubular disorder, based on its position defined by a micro-deletion in the DSX255 region, its expression pattern, and its proposed function as a chloride channel gene (Pook et al., 1993; Fisher et al., 1994). Due to the implication of this gene in a renal disorder, it was also of interest to assess its potential involvement in papillary renal cell carcinomas. However, neither CLCN5, SSX1, SSX2 nor TFE3 could be directly implicated by molecular studies. The genes for GATA1 (Merika amd Orkin, 1993) and WAS, implicated in Wiscott-Aldrich syndrome (Derry et al., 1994), map some distance from the breakpoint and are therefore unlikely to be involved. The closest known gene to the breakpoint, SYP, encodes a membrane protein of synaptic vesicles called synaptophysin (Ozcelik et al., 1990) which on functional grounds is an unlikely candidate for involvement in RCC.

The first female case of papillary renal cell carcinoma with the reciprocal translocation t(X;1)(p11.2;q21.2) is reported here. However, no normal X chromosome was found in the cell line which was predominately hypertriploid. In addition to the two der(X) chromosomes and one der(1) chromosome, a rearranged der(1) chromosome described as

der(1)del(1)(p31)t(X;1)(p11.2;q21.2) was found. This chromosome is probably derived from the standard der(1) following its duplication. The previously described male cases with a t(X;1)(p11.2;q21.2) were near diploid and it is possible that the more complex karyotypes in the cell lines have arisen during tissue culture. All nine cases reported with rearrangement at Xp11 were in males with the exception of a t(X;1)(p11.2;q34) found in an unspecified type of renal cell carcinoma from a female patient where an apparently normal X chromosome was present (Kovacs et al., 1987). Further cases of papilliary renal cell carcinoma with Xp11.2 rearrangements need to be characterized to determine whether there is a genetic explanation for the unequal sex distribution. Defining the position of the breakpoint associated with the t(X;1)(p11.2;q21.2) of papillary renal cell carcinomas should facilitate identifying the genes involved and ultimately lead to elucidating their function in both normal and papillary renal cell carcinoma cells.

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