ELECTRONIC LETTER

Transmission of an unbalanced (Y;1) translocation in Brittany, France

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Unbalanced and balanced Y;autosome translocations are rare structural rearrangements that constitute a heterogeneous group. According to Nielsen and Rasmussen,[1] the frequency of these translocations in the general population is approximately 1 in 2000 (six cases out of 11 148 newborn infants). All these six cases were in an unbalanced form.

In the majority of cases, there is a non-reciprocal translocation of the heterochromatic region of the long arm of the Y chromosome to the short arm of an acrocentric chromosome, most frequently a chromosome 15.[2 3] Most of these translocations are familial and transmitted down several generations through both sexes. No increased incidence of infertility or spontaneous abortions has been reported in these families.[1] Invariably, subjects with this type of translocation have a normal male or female phenotype. The majority of carriers with an unbalanced Y;acrocentric chromosome translocation are detected incidentally through newborn cytogenetic surveys[1] or during the familial investigation of an infant with congenital anomalies.[4]

Another group is composed of balanced reciprocal Y;autosome translocations. This group consists of translocations between the Y chromosome and any autosome excluding the short arm of the acrocentric chromosomes. About 80% of males with this type of translocation, which arises almost exclusively de novo, have azoospermia.[5] The translocation is mainly discovered during a consultation for infertility.

Finally, unbalanced Y;autosome translocations, with or without other chromosome abnormalities, are seen in children with malformations and/or sexual ambiguity owing to deletions, duplications, or rearrangements.[5–7]

The cases reported here share similarities with those of the first category but concern a chromosome 1 instead of an acrocentric. To our knowledge, this is the first segregation study of such an unbalanced (Y;1) translocation.

PATIENTS AND METHODS

Patients

Two unrelated couples (couples A and B) were referred to the cytogenetics laboratory because of repeated miscarriages (three and two, respectively). The ages of the men and women were 32 and 30 years, respectively (couple A) and 27 and 26 years, respectively (couple B). All four had a normal phenotype.

Cytogenetic studies

Investigations were carried out on peripheral blood cultures using standard methods. Chromosomes from phytohaemagglutinin stimulated lymphocytes were examined after R banding; at least 16 cells were karyotyped from each person. Metaphase chromosomes were also stained with quinacrine dihydrochloride.[8]

Fluorescence in situ hybridisation (FISH)

Dual colour FISH with DNA probes for the 1p telomere (TelVysion 1p, spectrum green, Vysis, Voisins le Bretonneux, France) and CEPY (locus DYZ1, spectrum orange, Vysis) was performed.

Briefly, before hybridisation, DNA slides were immersed in a flask of 2 × SSC/0.4% NP40 solution for 30 minutes at 37°C and then immediately passed through an ethanol series (70, 90, 100%) for three minutes and finally air dried. The probes were applied to target DNA and the denaturation was performed simultaneously for one minute at 75°C. The slides were then hybridised overnight in a dark humidity chamber at 37°C.

The slides were washed in 0.4 × SSC/0.3% NP40 for one minute at 72°C and then washed in 2 × SSC/0.1% NP40 for 20 seconds at room temperature. Finally, the slides were counterstained with 4-6-diamino-2-phenyl-indole-dihydrochloride (DAPI).

The slides were analysed using a Zeiss AxioPlan Microscope (Zeiss, Le Pecq, France). Subsequent image acquisition was performed using a CCD camera with isis (in situ imaging system) (MetaSystems, Altlussheim, Germany).

Molecular analysis

DNA was extracted from peripheral blood using standard methods. PCR amplification of Y specific sequences was performed using the following primer pairs located on Yp: the testis determining gene, *SRY*, and on Yq: sY611 (in the proximal AZFa region; GenBank accession No G65841), sY254 (*DAZ* gene family), sY158, sY1124 (GenBank accession No G66138), sY160 (heterochromatin DYZ1[9 10]). PCR conditions were as previously described.[9 10]

Pedigree reconstruction

Since both families originated from western Brittany, a pedigree reconstruction was performed using the civic details kept

Figure 1 46,XX,der(1)t(Y;1)(q12;p36) karyotype.

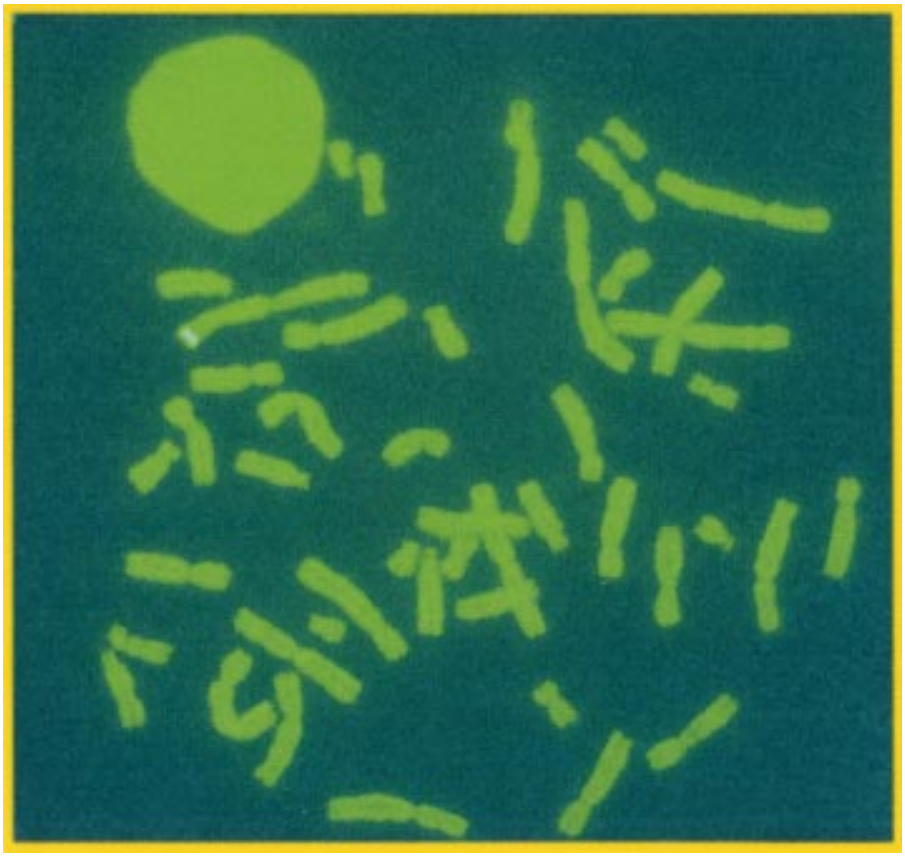

Figure 2 Staining with quinacrine dihydrochloride.

in the town halls and the archives department, as we wanted to determine whether these two families were related.

RESULTS

Cytogenetic studies showed a normal male karyotype (46,XY) in both husbands while their wives had a female karyotype, 46,XX, which included a 1p+ chromosome in all 16 metaphases examined (fig 1). The quinacrine fluorescent stain showed a highly fluorescent spot on the short arm of chromosome 1, similar in appearance to that of a Y chromosome (fig 2). The karyotype was interpreted as 46,XX,der(1)t(Y;1)(q12;p36) on the basis of R banding and quinacrine analyses.

FISH analysis with the probe for CEPY (DYZ1) confirmed the presence of the heterochromatin region (Yq12) on the short arm of chromosome 1 while no partial 1p deletion was observed with the probe for the 1p telomere (fig 3). Thus, the karyotype was 46,XX, der(1)t(Y;1)(q12;p36).ish der(1)t(Y;1)(q12;p36)(tel1p+,DYZ1+).

PCR amplification showed Y specific fragments corresponding to sY160 (heterochromatin) in both patients, but not in a control female (fig 4). There was no amplification of the markers SRY, sY611, sY254, sY158, or sY1124 in either patient. This confirmed that the translocated Y material in both patients contained only the heterochromatin present in band Yq12.

Familial cytogenetic investigations showed that this translocation was inherited from the father (VII.4 for couple A, VI.2 for couple B) in both cases (fig 5). Their karyotype was 46,XY,t(Y;1)(q12;p36). Couple A (VIII.1 and VIII.2) had a son (IX.1) and a daughter (IX.2), both carriers of the same translocation.

The pedigree reconstruction identified a common ancestral couple (I.1 and I.2) who were married in 1773 in the small village of Goulven, in north Finistère (the most westerly department of Brittany).

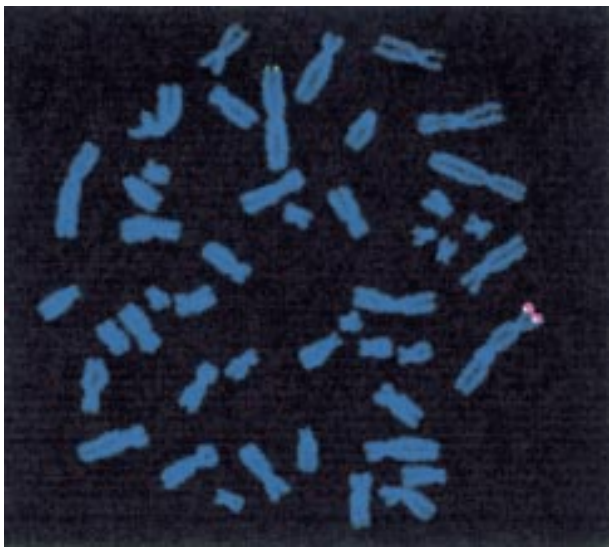

Figure 3 Fluorescence in situ hybridisation with DNA probes for the 1p telomere (spectrum green) and CEPY (locus DYZ1, spectrum orange).

DISCUSSION

To the best of our knowledge, five cases of Y;1 translocation have previously been published.[11–15] All these cases were in a balanced form (table 1).

Four of the five cases were discovered in men referred for couple infertility. Semen analysis showed azoospermia in two cases[13 15] and severe oligozoospermia in another.[14] Meiotic

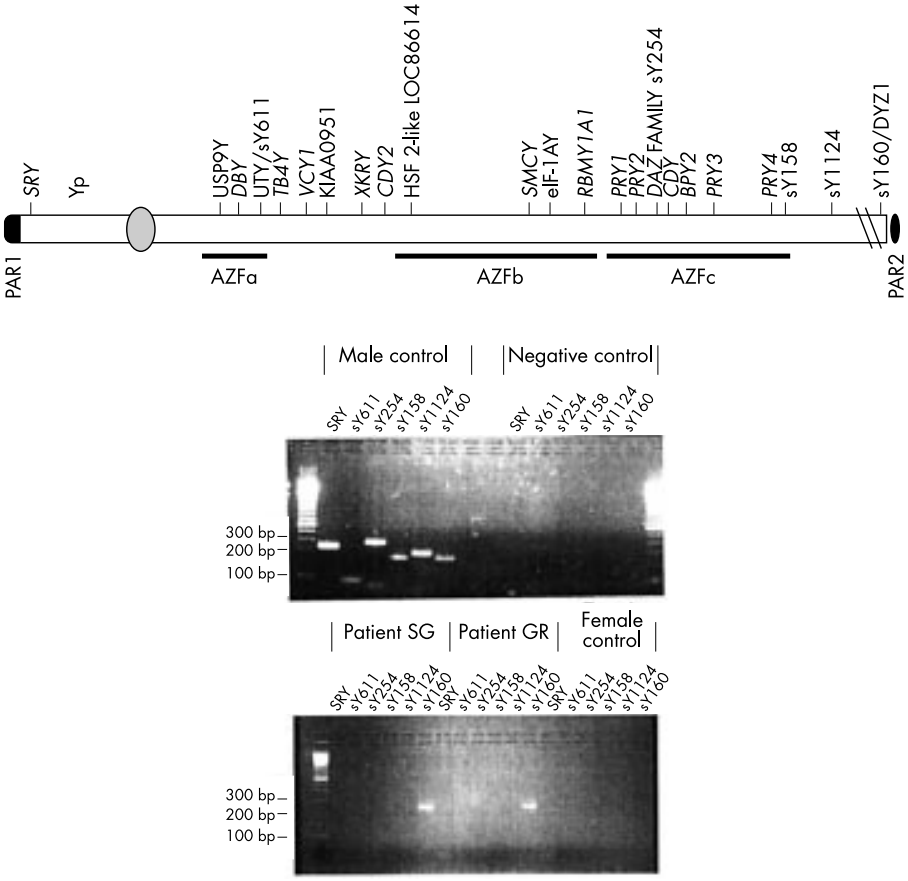

Figure 4 (Top) Schematic diagram of the human Y chromosome showing the main genes present on the long arm of the Y chromosome, the two Y chromosome pseudoautosomal regions (PAR), and the markers used in this study. The absence of three non-overlapping regions of the long arm (AZFa, AZFb, and AZFc) are specifically associated with a severe impairment of spermatogenesis. (Bottom) PCR amplification of Y chromosome specific markers *SRY* (314 bp), sY611 (76 bp), sY254 (379 bp), sY158 (231 bp), sY1124 (272 bp), and sY160 (236 bp) in a male control, negative control (H20), proband of couple B (fig 5, VII.2), proband of couple A (fig 5, VIII.2), and a female control. Amplification of the heterochromatin (sY160) was observed in the two patients.

studies showed that the infertility was the result of an arrest of spermatogenesis at pachytene[12] or diakinesis.[15]

The fifth balanced Y;1 translocation was found in a 4 month old child referred for poor weight gain, psychomotor retardation, and massive myoclonic spasms.[11] According to the authors, the presence of these phenotypic abnormalities and the apparently balanced translocation could be coincidental or the result of a small, microscopically undetectable loss of genetic material in the chromosomes involved in the translocation.

The balanced Y;1 translocation was de novo in three cases[11 13 15] and familial in one[14]; the origin of the fifth translocation was not reported.[12] In the familial case, the patient with severe oligoasthenozoospermia had inherited the translocation from his father who had had four children; thus, this abnormality does not necessarily cause infertility.

The breakpoint is often located on the long arm of the Y chromosome. It is either in band q12, a heterochromatic region consisting of highly repeated DNA sequences which are not transcribed in fertile males, or in the distal q11 euchromatin region, at the azoospermia factor (AZF) locus, in sterile males.[16] However, variable effects on fertility might be seen in translocations involving a breakpoint in Yq11 or Yq12.[14 15]

In our case, the unbalanced t(Y;1) was discovered in women. They had a normal phenotype because, as shown by molecular cytogenetics, there was no apparent partial 1p deletion and only Yq heterochromatic material, which is genetically inert and thus without consequence, on the translocated segment.

Indeed, both patients carried sequences recognised by PCR amplification of the marker sY160. The marker sY160 corresponds to the repetitive sequence DYZ1.[9] An average Y chromosome contains about 3000 copies of the DYZ1 repeat, which can be further subdivided into different families.[17] DYZ1 consists of a 3.4 kb repeat which mainly consists of a tandem array of pentanucleotides (TTCCA[18]). There are also about 2000 copies of the DYZ2 repeat family.[19] The human Y chromosome exhibits considerable variation in the size of the heterochromatin, correlated with the number of DYZ1 and DYZ2 repeats[20] between different populations; it may even be lacking in some subjects, without any phenotypic effect.

Familial cytogenetic investigations showed that this translocation was familial, inherited from the father in both cases. The men have no reproductive problems because they also have a normal Y chromosome. In the balanced Y;autosome translocations, the Y heterochromatic translocated segment onto the autosome is found to be associated with the XY bivalent[21]; therefore, the absence or abnormalities of the sex vesicle could explain the degeneration of most of the spermatocytes after the pachytene stage,[22] which causes infertility. In the unbalanced Y;autosome translocations, meiotic study showed a normal sex vesicle independent of the translocated supernumerary Y chromosome segment.[23]

Here, the breakpoint arose at the junction of the heterochromatin and the euchromatin of Yq but there was no effect on fertility because the men had a normal Y chromosome, so they must certainly have a normal sex vesicle and testicular

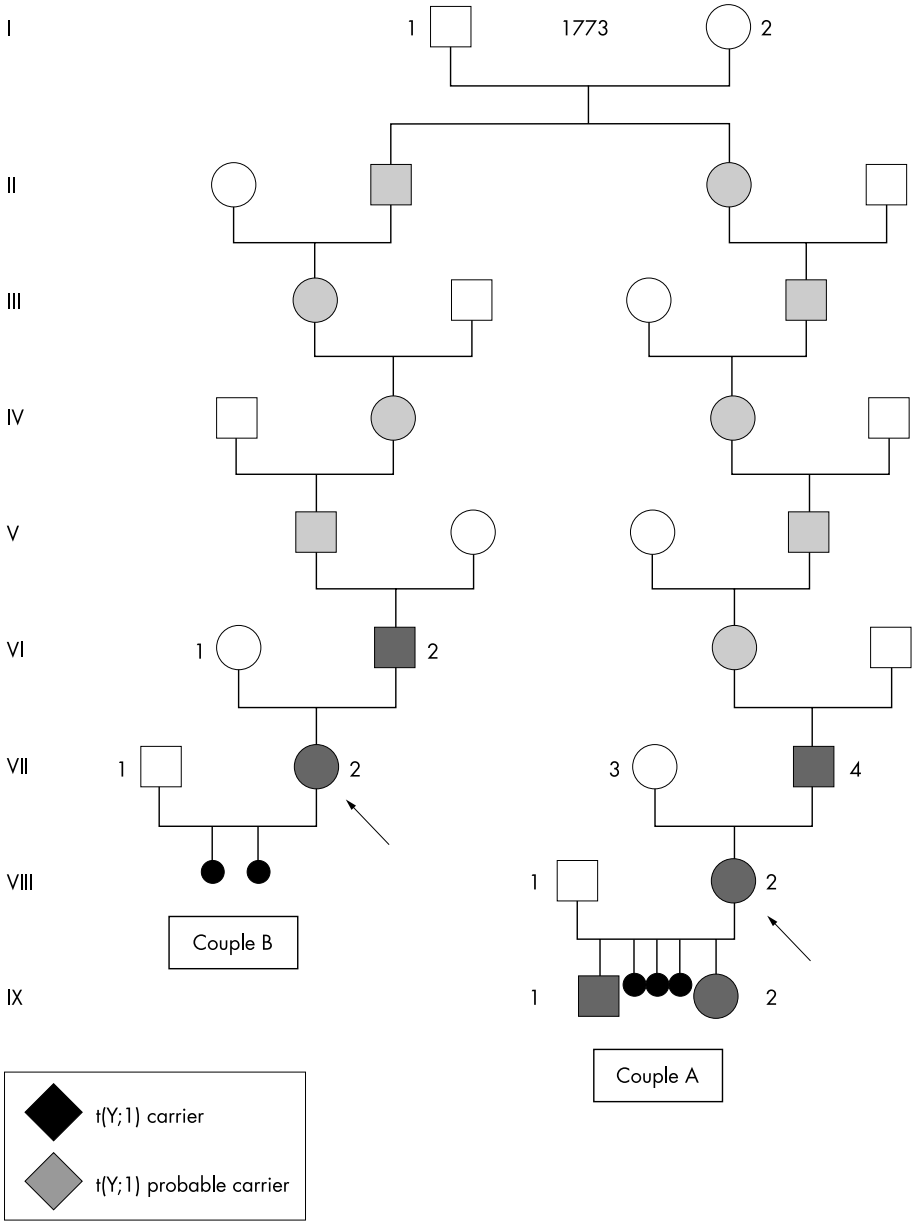

Figure 5 Family pedigrees.

differentiation. Recently, a familial chromosomal insertion of Y chromosome heterochromatin in band 11q24 was described in a family in which there were also no apparent phenotypic consequences.[24]

However, we can still ask whether there is a relationship between the translocation and the recurrent spontaneous abortions observed in both families or whether both occurrences are purely coincidental.

The identification of a common ancestral couple is not proof that these two couples are genetically related. However, this is most likely because this extremely rare and apparently identical translocation was found in two families who lived within a distance of 20 kilometres of each other.

In conclusion, this unbalanced translocation, der(1)t(Y;1)(q12;p36), has been transmitted as a chromosomal variant through both males and females down several

Table 1 Reported cases of Y;1 balanced translocations

References	Cytogenetics	Discovery	Translocation origin	Sperm parameters	Meitoc studies
11	t(Y;1)(q11;q21)	Psychomotor retardation	De novo	*	*
12	t(Y;1)(q21;p13)	Consultation for infertility	Not referred	–	+
13	t(Y;1)(cen-q11;cen-p11)	Consultation for infertility	De novo	Azoospermia	–
14	t(Y;1)(q11;q11)	Consultation for infertility	Familial	Severe oligozoospermia	–
15	t(Y;1)(q12;p34.3)	Consultation for infertility	De novo	Azoospermia	+

generations and does not appear to affect the phenotype of men or women.

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