LETTER TO THE EDITOR

A constitutional jumping translocation involving the Y and acrocentric chromosomes

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Dear Editor,

Translocations of the same chromosomal fragments to two or more different chromosomes in different somatic cell lineages are referred to as jumping translocations (JT).1 JTs have been mainly reported in hematological malignancies but have been observed in rare instances also as constitutional chromosomal aberrations.2 The underlying JT mechanism remains unclear, however.

The frequency of Y-autosome translocations is 1 in 2000 and carriers are often identified by means of somatic translocations or by an incidental finding in the absence of clinical symptoms.1 Notably, translocations of the heterochromatin region of the Y long arm to the short arm of chromosome 15 or 22 are commonly observed as normal variants.4 We here present an intriguing case of a constitutional Y;13 translocation in a male with oligozoospermia but a Y;15 translocation in his son, who was born with the assistance of reproductive technologies. To uncover the origin of this inconsistency, we examined the Y-autosome translocated chromosomes and concluded that this represented an instance of JT.

Our study family included a 40-year-old male partner of a Japanese infertile couple who was healthy except for a severe oligozoospermia identified during a prior examination for causes of the couple’s infertility. As detailed below, he was found to carry a Y;13 translocation. The female partner was 38-year-old with a 46,XX karyotype. This couple had three prior miscarriages before becoming pregnant via intracytoplasmic sperm injection, which produced a healthy boy with normal external genitalia. The genetic testing used in our current analyses was approved by the ethics committee of Fujita Health University (Toyoake, Japan). Blood samples from the participants were obtained following written informed consent in accordance with Local Institutional Review Board guidelines.

G-banding analysis of the father revealed a 45,X,add(13)(p11) karyotype (Figure 1a). Fluorescent in situ hybridization (FISH) analyses with Y chromosome probes were conducted to determine the origin of the additional chromosomal material. A Yp telomere probe produced a positive signal at the add(13) chromosome (Figure 2a). SRY (sex-determining region Y), DYZ3 (alphoid satellite DNA) and DAZ (deleted in azoospermia) probes were also positive at add(13) (data not shown). No signal for DYZ1, a Y-specific heterochromatin repeat (Yqh), was evident on add(13) or on other chromosomes (data not shown).

These results indicated that the additional chromosome in the father was a Y chromosome lacking the distal part of the long arm that had fused with the short arm of chromosome 13 (Figure 1c and 2a). The breakpoint on the Y chromosome was located in the proximity of the boundary region between DAZ and the heterochromatin region, and that on chromosome 13 was located in its short arm (Figure 1c).

Thus, the add(13) chromosome was dicentric, lacking the 13p region. Consequently, the father’s karyotype was 45,X,add(13)(p11).ish dic(Y;13)(q11.2 or q12;p11)(SRY+,DYZ3+,DAZ+).

Interestingly, both an amniocentesis and analysis of peripheral blood from the son obtained after birth indicated a karyotype of 45,X,add(15)(p11.2).ish psu dic(15;Y)(p11.2;q11.2)(SRY+,DYZ3+,DAZ+) (Figure 1b and 2b–2d). Unlike father, the Y chromosome material of the son was joined to chromosome 15 and not chromosome 13 (Figure 1c).

The haplotypes of the Y chromosomal regions in both the father and son were analyzed by evaluating common STR markers using the AmpFLSTR Yfiler PCR Amplification Kit (Thermo Fisher Scientific, Waltham, MA, USA). The amplification of 17 Y-chromosomal STR loci in both father and son indicated a perfect match (Table 1). Furthermore, as the frequency of this haplotype would be expected to be approximately 1 in 6135 in Japan, as calculated using the Kappa method (release RS4; https://yhrd.org),1,6 this finding was very unlikely to have been coincidental. Our analysis thus indicated that the son inherited his Y chromosomal material from his father and that a second translocation event involving the Y chromosomal region occurred during paternal spermatogenesis.

We therefore here report a rare event in which a translocated Y chromosome changed partner chromosomes during its transmission to the next generation. We refer to this as JT. To the best of our knowledge, only one other family has been previously described in which a constitutional JT involving the Y chromosome occurred between a father, tas(Y;19), and son, tas(Y;15).7 Telomeric associations (TAS) refer to a fusion between telomeres of different chromosomes. As defective
telomeric repeats at the junction can elicit conformational instability, it is quite possible that one TAS event could induce another and thereby lead to JT. Our present case was not the result of a TAS event however because the Yqter was lacking at the junction, although it is possible that the junction of the first translocation was unstable due to an unknown sequence-specific mechanism leading to a susceptibility for a second translocation.

Like most constitutional JTs thus far described, our present case family involved acrocentric chromosomes in both translocations. JT breakpoints mostly reside in centromeric/pericentromeric regions or within telomeric sequences, which involve heterochromatin and are rich in repetitive DNA. Chromosome breakages associated with JTs frequently occur at repetitive DNA regions because of their genomic instability. In our current subject family, it is likely that the dic(Y;13) junction comprising a fusion of repetitive DNA of both chromosomal regions produced increased instability as a result of the first translocation. It has been shown that the short arms of the acrocentric bivalents associate with the nucleoli during prophase of meiosis I. The dic (Y;13) paired with the normal chromosome 13 should, therefore, be involved in the nucleolus and come close to the short arm of the bivalent chromosome 15. It is possible that this proximity and the unstable junction might have induced the second translocation in a spermatocyte.

In conclusion, a rare JT event occurred during spermatogenesis in a Japanese man with oligozoospermia and was transmitted to his son. Although it is rare, a JT should be considered in cases where there is an inconsistency between the translocated chromosomes in a parent and child.
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