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LETTER TO THE EDITOR

Male Health

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 (JTs).[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 through spermatogenic defects or by an incidental finding in the absence of clinical symptoms.[3] 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 R54; https://yhrd.org),[5,6] 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

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Table 1: Haplotypes of the Y-STR loci in the father and son

	DYS456	*DYS389I*	*DYS390*	*DYS389II*	*DYS458*	*DYS19*	*DYS385*	*DYS393*	*DYS391*	*DYS439*	*DYS635*	*DYS392*	*YGATAH4*	*DYS437*	*DYS438*	*DYS448*
Father	16	14	23	29	18	16	10, 19	14	10	11	20	13	12	14	13	18
Son	16	14	23	29	18	16	10, 19	14	10	11	20	13	12	14	13	18

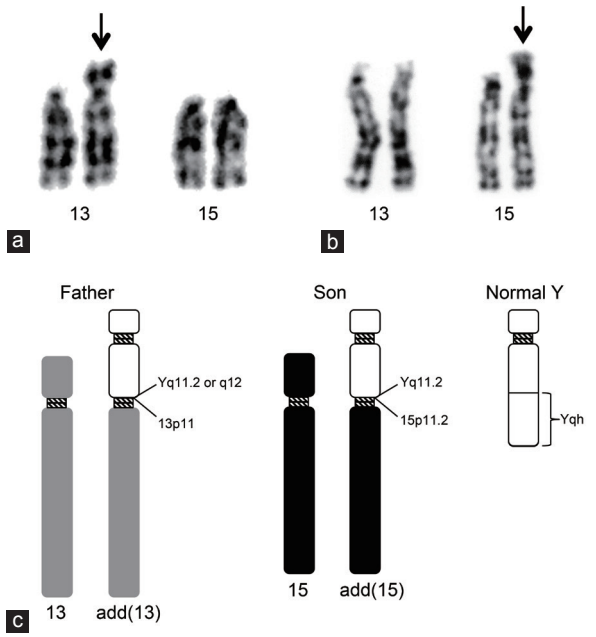

Figure 1: G-banded partial karyotypes of the father and son. (**a**) The arrow denotes the add(13) in the father. (**b**) The arrow indicates the add(15) in the son. (**c**) Schematic diagram of the translocated chromosomes. The breakpoints of each translocation are indicated. The Yqh regions are lost in both the father and son.

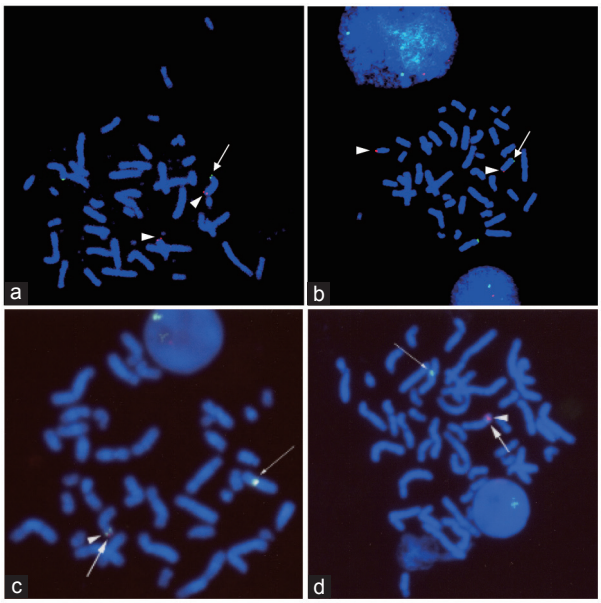

Figure 2: FISH analyses of the translocated chromosomes in the father and son. (**a**) Xp/Yp telomere (green) and 13q telomeres (red) in the father. The arrow and arrowheads denote the Yp and 13q probes, respectively. (**b**) Xp/Yp telomere (green) and 15q telomeres (red) in the son. The arrow and the arrowheads indicate the Yp and 15q probes, respectively. (**c**) *SRY* (red, large arrow), DYZ3 (green, arrowhead) and DXZ1 (green, small arrow) in the son. (**d**) *DAZ* (green, large arrow), DYZ3 (red, arrowhead) and DXZ1 (green, small arrow) in the son. Chromosomes were counterstained with DAPI (blue).

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.[2] JT breakpoints mostly reside in centromeric/pericentromeric regions or within telomeric sequences, which involve heterochromatin and are rich in repetitive DNA.[8] Chromosome breakages associated with JTs frequently occur at repetitive DNA regions because of their genomic instability.[9] 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.[10] 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.

AUTHOR CONTRIBUTIONS

MT carried out the cytogenetic analysis, STR analysis and drafting of the manuscript. NF and FS performed the cytogenetic analysis. TM and SF carried out the gynecological check and provided genetic counseling. MW provided the genetic counseling for the prenatal test. NT carried out the clinical management of the son. HT was responsible for the chromosomal analysis and the clinical genetics. OM conducted the fertility treatment. TE and HK conceived the study and participated in its design. HK drafted the manuscript. All authors read and approved the final manuscript and agreed with the order of presentation of the authors.

COMPETING INTERESTS

The authors declare no competing interests.

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