Published in final edited form as:
Fertil Steril. 2007 November ; 88(5): 1446–1448. doi:10.1016/j.fertnstert.2007.01.019.

Age has no effect on de novo constitutional t(11;22) translocation frequency in sperm

Takema Kato, M.Sc.[a,b], **Kouji Yamada, Ph.D.**[a], **Hidehito Inagaki, Ph.D.**[a], **Hiroshi Kogo, Ph.D.**[a], **Tamae Ohye, Ph.D.**[a], **Beverly S. Emanuel, Ph.D.**[c], and **Hiroki Kurahashi, M.D., Ph.D.**[a,b]

[a]Division of Molecular Genetics, Institute for Comprehensive Medical Science, Fujita Health University, Toyoake, Japan

[b]21st Century Center of Excellence (COE) Program, Development Center for Targeted and Minimally Invasive Diagnosis and Treatment, Fujita Health University, Toyoake, Japan

[c]Division of Human Genetics and Molecular Biology, The Children's Hospital of Philadelphia and Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Abstract

We analyzed de novo constitutional t(11;22) translocation frequency in sperm derived from normal healthy males as a function of the age of the sperm donors (from 25 to 51). Translocation-specific polymerase chain reaction demonstrated no age-dependent increment in the frequency of the rearrangements.

The effect of gender and age on the frequency of cytogenetic abnormalities is of significant interest. Because of the general tendency toward delay of reproduction in the industrialized countries and recent advances in assisted reproductive technologies, it is becoming an important issue. Mutation rates for single genes generally are higher in male gametogenesis than they are in female germ cell development. It is the result of the greater number of germline divisions to complete spermatogenesis (often >150 divisions) as compared with oogenesis, and the number increases with age. In contrast, the chromosomes of female germ cells undergo only 23 divisions before oogenesis, and the number is consistent (1).

Cytogenetic abnormalities also manifest a gender bias. Numerical abnormalities are more likely to arise in maternal gametogenesis. They primarily occur as a consequence of nondisjunction during meiotic cell division, and the rate increases exponentially with advanced maternal age (2). In contrast, for structural abnormalities, 80% of the chromosomal rearrangements are of paternal origin. Because structural abnormalities arise when double-strand breaks induced by endogenous or exogenous factors produce illegitimate recombination, it is not surprising that structural rearrangements demonstrate a male predominance. However, little is known regarding the effect of paternal age. Because technical problems exist in cytogenetic analysis of sperm, there have been no consistent results (3).

Reprint requests: Hiroki Kurahashi, M.D., Ph.D., Division of Molecular Genetics, Institute for Comprehensive Medical Science, Fujita Health University, 1-98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi 470-1192, Japan (FAX: 81-562-93-8831; kura@fujita-hu.ac.jp)..

The constitutional t(11;22) is the only known recurrent non-Robertsonian translocation in human beings. The translocation breakpoints are localized at palindromic AT-rich repeats on chromosomes 11q23 and 22q11 (PATRR11 and PATRR22) (4-7). We propose that the PATRRs adopt cruciform structure that induces genomic instability, leading to the recurrent translocation (8).

In our previous study, we established the translocation-specific polymerase chain reaction by using the sequences of the translocation junction fragments from both derivative translocation chromosomes (9). By using this method, we successfully detected de novo t(11;22)s in sperm derived from normal healthy males at the single-cell level (10). We calculated the de novo translocation frequency on the basis of the occurrence of positive polymerase chain reaction reactions and reported that polymorphisms of the PATRR11 affected the de novo translocation frequency (11). In this study, we analyzed the translocation frequency as a function of the age of the male sperm donors after obtaining the appropriate informed consent. The study was approved by the Ethical Review Boards for Human Genome Studies at Fujita Health University.

To avoid the effect of PATRR11 polymorphisms on translocation frequency, we selected 10 male volunteers who are homozygotes for the most common allele, the long PATRR11. Among these subjects, the frequency of translocation ranged from 1.46×10^{-5} to 1.57×10^{-4}, which is a relatively narrow range when compared with a frequency variation of more than three orders of magnitude induced by polymorphism of the PATRR11. This also suggests that we can almost ignore the unknown effect from polymorphism of the PATRR22. The age of the donors ranges from 25 to 51 years. As is indicated in Table 1, no age-dependent increment in the frequency of rearrangements was observed among these subjects. Standard linear regression analysis of log translocation frequency on donor age suggested no significant positive correlation [$y = -0.00009\ \mathrm{Ln}(x) + 0.0004$, $R^2 = 0.1862$].

Further, we obtained samples from two individuals at two different time points. Both of these subjects were heterozygotes for the long PATRR11 and the asymmetric short PATRR11. After a 6-year interval, the translocation frequency did not significantly change (Table 1). Although we do not know whether the constitutional t(11;22) can be considered representative of other structural chromosomal abnormalities, we conclude that the de novo frequency of the t(11;22) does not increase with increasing paternal age.

The mechanism of PATRR-mediated chromosomal translocation in human beings is still unknown. Palindromic sequences are known to be unstable in *Escherichia coli*, because replication of the palindromic region is slowed or even stalled because of intrastrand base pairing that produces a hairpin structure on the lagging strand template (12). Indeed, recent finding indicates that partial deficiency of DNA polymerase can induce palindrome-mediated translocations in an experimental yeast system (13). However, the age independence of the de novo translocation frequency may implicate a replication-independent mechanism for formation of the translocations. It is consistent with the fact that de novo translocations can only be detected in sperm and no other human tissues (10). Our results suggest that the t(11;22) translocations arise during meiosis or postmeiosis in male gametogenesis.

Acknowledgments

The authors thank Haruki Nishizawa, M.D., Ph.D., and Hasbaira Bolor, Ph.D., for helpful discussion and thank Kayuri Nagaoka, B.S., Terumi Mori, M.Sc., and Eriko Hosoba, B.S., for technical assistance.

Supported by grants-in-aid for Scientific Research, Genome and for the 21st Century COE Program of Fujita Health University from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (Tokyo, Japan; to H.K.), as well as by a grant (CA39926) from the National Institutes of Health (Bethesda, Maryland; to B.S.E.).

REFERENCES

1. Crow JF. The origins, patterns and implications of human spontaneous mutation. Nat Rev Genet 2000;1:40–7. [PubMed: 11262873]
2. Hassold T, Hunt P. To err (meiotically) is human: the genesis of human aneuploidy. Nat Rev Genet 2001;2:280–91. [PubMed: 11283700]
3. Buwe A, Guttenbach M, Schmid M. Effect of paternal age on the frequency of cytogenetic abnormalities in human spermatozoa. Cytogenet Genome Res 2005;111:213–28. [PubMed: 16192697]
4. Kurahashi H, Shaikh TH, Hu P, Roe BA, Emanuel BS, Budarf ML. Regions of genomic instability on 22q11 and 11q23 as the etiology for the recurrent constitutional t(11;22). Hum Mol Genet 2000;9:1665–70. [PubMed: 10861293]
5. Edelmann L, Spiteri E, Koren K, Pulijaal V, Bialer MG, Shanske A, et al. AT-rich palindromes mediate the constitutional t(11;22) translocation. Am J Hum Genet 2001;68:1–13. [PubMed: 11095996]
6. Tapia-Paez I, Kost-Alimova M, Hu P, Roe BA, Blennow E, Fedorova L, et al. The position of t(11;22)(q23;q11) constitutional translocation breakpoint is conserved among its carriers. Hum Genet 2001;109:167–77. [PubMed: 11511922]
7. Kurahashi H, Emanuel BS. Long AT-rich palindromes and the constitutional t(11;22) breakpoint. Hum Mol Genet 2001;10:2605–17. [PubMed: 11726547]
8. Kurahashi H, Inagaki H, Yamada K, Ohye T, Taniguchi M, Emanuel BS, et al. Cruciform DNA structure underlies the etiology for palindrome-mediated human chromosomal translocations. J Biol Chem 2004;279:35377–83. [PubMed: 15208332]
9. Kurahashi H, Shaikh TH, Zackai EH, Celle L, Driscoll DA, Budarf ML, et al. Tightly clustered 11q23 and 22q11 breakpoints permit PCR-based detection of the recurrent constitutional t(11;22). Am J Hum Genet 2000;67:763–8. [PubMed: 10903930]
10. Kurahashi H, Emanuel BS. Unexpectedly high rate of de novo constitutional t(11;22) translocations in sperm from normal males. Nat Genet 2001;29:139–40. [PubMed: 11586296]
11. Kato T, Inagaki H, Yamada K, Kogo H, Ohye T, Kowa H, et al. Genetic variation affects de novo translocation frequency. Science 2006;311:971. [PubMed: 16484486]
12. Leach DR. Long DNA palindromes, cruciform structures, genetic instability and secondary structure repair. Bioessays 1994;16:893–900. [PubMed: 7840768]
13. Lemoine FJ, Degtyareva NP, Lobachev K, Petes TD. Chromosomal translocations in yeast induced by low levels of DNA polymerase: a model for chromosome fragile sites. Cell 2005;120:587–98. [PubMed: 15766523]

TABLE 1

De novo translocation frequency in sperm from normal males.

Case no.	PATRR11	Age	Frequency		
			der(11)	der(22)	Total[a]
1[b]	L/L	25	4.12×10^{-5}	4.84×10^{-5}	4.53×10^{-5}
2[b]	L/L	26	1.11×10^{-4}	1.11×10^{-4}	1.11×10^{-4}
3[b]	L/L	31	1.11×10^{-4}	1.47×10^{-4}	1.28×10^{-4}
4[c]	L/L	31	3.22×10^{-5}	5.17×10^{-5}	3.35×10^{-5}
5[c]	L/L	33	9.46×10^{-5}	7.81×10^{-5}	9.31×10^{-5}
6[b]	L/L	34	1.19×10^{-5}	1.89×10^{-5}	1.52×10^{-5}
7[b]	L/L	35	1.67×10^{-4}	1.47×10^{-4}	1.57×10^{-4}
8	L/L	40	3.57×10^{-5}	4.12×10^{-5}	3.84×10^{-5}
9	L/L	51	1.20×10^{-5}	1.88×10^{-5}	1.46×10^{-5}
10	L/L	51	5.67×10^{-5}	4.12×10^{-5}	4.80×10^{-5}
11-1[c]	L/S	40	1.24×10^{-5}	1.37×10^{-5}	1.25×10^{-5}
11-2	L/S	45	1.23×10^{-5}	2.34×10^{-5}	1.92×10^{-5}
12-1[c]	L/S	37	2.16×10^{-5}	1.84×10^{-5}	2.13×10^{-5}
12-2	L/S	43	8.98×10^{-6}	1.88×10^{-5}	1.35×10^{-5}

Note: L = long PATRR; S = asymmetric short PATRR.

Kato. No age effect on de novo t(11;22). Fertil Steril 2007.

[a]The total frequency was calculated based on the total positive PCR reactions.

[b]Samples appearing in Kato et al. (11).

[c]Samples appearing Kurahashi et al. (10).