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Genetic Variation Affects de Novo Translocation Frequency

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Translocation is one of the most frequently occurring human chromosomal aberrations. Balanced carriers usually manifest no phenotype but experience problems with reproduction. These include infertility, recurrent abortion, and offspring with chromosomal imbalance. The constitutional t(11;22)(q23;q11) is a balanced translocation between chromosomes 11 and 22, with breakpoints at bands 11q23 and 22q11. It is the only known recurrent non-Robertsonian translocation and represents a good model for studying translocations in humans (1). The recurrent nature of this translocation prompted us to examine t(11;22) breakpoints for a specific genomic structure. The analysis of many unrelated t(11;22) cases revealed that the breakpoints occur within palindromic AT-rich repeats (PATRRs) on 11q23 and 22q11 (PATRR11 and PATRR22) (2–4). The majority of the breakpoints are localized at the center of the PATRRs, suggesting that the center of the palindrome is susceptible to double-strand breaks (DSBs), thereby inducing illegitimate chromosomal rearrangement (3,5). Recent findings of PATRR-like sequences at the breakpoints of other translocations support the possibility that palindrome-mediated chromosomal translocation is a general pathway for human genomic rearrangements (6–8).

The PATRR11 is variable in size in normal healthy individuals (Fig. 1 and table S1). The most common allele is a ~450–base pair (bp) PATRR11 (L-PATRR11) that forms a nearly perfect palindrome (5). Several types of short variants were identified (S-PATRR11) that appear to be derived from the longer version primarily by deletion near the symmetric center of the palindromic structure. We can classify the S-PATRR11s into four groups. The most frequent 350-bp variant, S1-PATRR11, has a 50-bp deletion at both of the palindromic arms but still remains completely symmetrical. S2-PATRR11 has an asymmetric deletion at its center, but the new center manifests a symmetric palindrome. S3-PATRR11 does not possess palindromic features by virtue of a deletion at the center of the palindrome. We identified a rare 434-bp S-PATRR11, which sustained an asymmetric central deletion followed by the insertion of an AT-rich sequence of unknown origin (S4-PATRR11). We also identified another rare allele with a duplication of the proximal arm, which constitutes a 603-bp asymmetric palindrome (EL-PATRR11). On the basis of the palindrome-mediated mechanism of the translocation, it is reasonable to hypothesize that the polymorphism of the PATRR11 could affect the frequency of de novo t(11;22) translocations.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/311/5763/971/DC1

Materials and Methods

Tables S1 to S3

Translocation-specific polymerase chain reaction (PCR) detects de novo t(11;22) translocations in normal sperm samples from healthy individuals with a normal karyotype (9). We analyzed sperm DNA from individuals with various genotypes for the PATRR11. Five men homozygous for the L-PATRR11 genotype produced de novo translocations at a frequency ranging between 1.52×10^{-5} and 1.57×10^{-4} (table S2). A heterozygote for the L-PATRR11 and S1- or S2-PATRR11 alleles produced de novo translocations at a similar overall frequency, as did homozygotes for the L-PATRR11. Sequence analysis of the PCR products revealed that products derived from the symmetrical S1- or S2-PATRR were less frequently observed than products originating from the L-PATRR11, with a low estimated frequency of de novo translocations ($\sim 10^{-6}$), suggesting that the frequency of de novo translocation depends on the size of the PATRR. On the other hand, although two individuals heterozygous for L-PATRR11 and S3-PATRR11 produced de novo translocations at a similar overall frequency, sequence analysis revealed that virtually all of the de novo translocations appeared to originate from the L-PATRR11. This finding suggests that the asymmetric S-PATRR does not produce de novo translocations (table S2).

Sperm from one individual, who was a rare compound heterozygote for the S1- and S3-PATRR11, contained de novo translocations at a very low frequency. Sequence analysis of the junction fragments showed that the translocations were exclusively derived from the S1-PATRR11. Because both the S2- and S4-PATRR11s alleles produced translocations at a low frequency ($\sim 10^{-6}$ and $\sim 10^{-7}$, respectively), a compound heterozygote for this genotype had a very low translocation frequency overall. We identified another individual heterozygous for the S3-PATRR and EL-PATRR. This individual is the only person who carried asymmetric PATRR11s on both alleles. He did not produce any de novo translocations (table S2). The frequencies for each allele are summarized in Fig. 1.

This work demonstrates genetic variation over more than three orders of magnitude in the susceptibility for generating the recurrent translocation in humans. Our results point to the importance of genomic sequence variation on the frequency of chromosomal rearrangements, a class of human mutation that is generally thought to be random. Our data imply that genetic variation plays an important role in this process.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References and Notes

1. Zackai EH, Emanuel BS. Am J Med Genet 1980;7:507. [PubMed: 7211960]
2. Kurahashi H, et al. Hum Mol Genet 2000;9:1665. [PubMed: 10861293]
3. Edelmann L, et al. Am J Hum Genet 2001;68:1. [PubMed: 11095996]
4. Tapia-Paez I, et al. Hum Genet 2001;109:167. [PubMed: 11511922]
5. Kurahashi H, Emanuel BS. Hum Mol Genet 2001;10:2605. [PubMed: 11726547]
6. Kurahashi H, et al. Am J Hum Genet 2003;72:733. [PubMed: 12557125]
7. Nimmakayalu MA, Gotter AL, Shaikh TH, Emanuel BS. Hum Mol Genet 2003;12:2817. [PubMed: 12952865]
8. Gotter AL, et al. Hum Mol Genet 2004;13:103. [PubMed: 14613967]
9. Kurahashi H, Emanuel BS. Nat Genet 2001;29:139. [PubMed: 11586296]
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Allele type	Subtype	Size (bp)	Number	Allele frequency (%)	Structure	Translocation frequency
L-PATRR11		442-450	343	87.1		$1.07-2.27 \times 10^{-5}$
S-PATRR11	Type 1	350	20	(40.0)		$1.20-2.93 \times 10^{-6}$
	Type 2	292-410	5	(10.0)		$1.55-1.71 \times 10^{-6}$
	Type 3	63-380	24	(48.0)		$<3.05 \times 10^{-7}$
	Type 4	434	1	(2.0)		6.81×10^{-7}
	Subtotal		50	12.7		
EL-PATRR11		603	1	0.3		$<1.69 \times 10^{-7}$
Total			394	100.0		

Fig. 1.

Polymorphic PATRR11 alleles and their translocation frequencies. Arrows indicate each unit of inverted repeats. Vertical arrowheads indicate the center of the palindrome. Dotted blue lines show deleted regions, whereas red lines indicate insertions. Calculated frequencies of de novo translocation produced from each allele are shown at the right.