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ARTICLE

Parental and chromosomal origins of microdeletion and duplication syndromes involving 7q11.23, 15q11-q13 and 22q11

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Non-allelic homologous recombination between chromosome-specific LCRs is the most common mechanism leading to recurrent microdeletions and duplications. To look for locus-specific differences, we have used microsatellites to determine the parental and chromosomal origins of a large series of patients with *de novo* deletions of chromosome 7q11.23 (Williams syndrome), 15q11–q13 (Angelman syndrome, Prader–Willi syndrome) and 22q11 (Di George syndrome) and duplications of 15q11–q13. Overall the majority of rearrangements were interchromosomal, so arising from unequal meiotic exchange, and there were approximately equal numbers of maternal and paternal deletions. Duplications and deletions of 15q11–q13 appear to be reciprocal products that arise by the same mechanisms. The proportion arising from interchromosomal exchanges varied among deletions with 22q11 the highest and 15q11–q13 the lowest. However, parental and chromosomal origins were not always independent. For 15q11–q13, maternal deletions tended to be interchromosomal while paternal deletions tended to be intrachromosomal; for 22q11 there was a possible excess of maternal cases among intrachromosomal deletions. Several factors are likely to be involved in the formation of recurrent rearrangements and the relative importance of these appear to be locus-specific.
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Introduction

Certain regions of the human genome are especially prone to structural rearrangements due to the presence of repetitive sequence elements. Genome architecture has been implicated in the formation of increasing numbers of genomic disorders.[1] The best-studied example is the association between segmental duplications or low-copy repeats (LCRs) and microdeletion and microduplication syndromes.[2] Interaction between chromosome-specific LCRs leads to gain, loss or inversion of the intervening sequence. Where a particular region contains dosage sensitive or imprinted genes this can lead to a specific genetic disease: loss of 7q11.23 results in Williams syndrome (MIM 194050), loss of 22q11 results in Di George syndrome/VCFS (MIM 192430/188400) and loss of 15q11–q13 results in either Prader–Willi syndrome (MIM 176270) or Angelman syndrome (MIM 105830).

Non-allelic homologous recombination (NAHR) between misaligned LCRs is the mechanism underlying the majority of genomic disorders.[1] This process may involve either

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both chromosome homologues (interchromosomal) or separate chromatids of only a single chromosome (intrachromosomal), referred to as the chromosomal origin. NAHR may also occur on the chromosome transmitted from either the mother or the father. However, there appear to be differences in the way this mechanism generates specific microdeletions. For example, variations have been reported in the proportion of maternal and paternal deletions, with an excess of maternal deletions for NF1,[3] an excess of paternal deletions for Sotos syndrome[4,5] or approximately equal numbers of maternal and paternal deletions for Smith–Magenis syndrome.[6] Similarly the relative contribution of interchromosomal and intrachromosomal rearrangements varies between microdeletions: 22q11 deletions[7] show a much higher proportion of interchromosomal rearrangements than deletions causing Smith–Magenis syndrome[6] or 15q11–q13 deletions.[8]

NAHR, whether interchromosomal or intrachromosomal, should generate reciprocal deletion and duplication products and for most microdeletion regions, the reciprocal duplication has been identified. Generally microduplications appear to arise by similar mechanisms to the corresponding microdeletion,[6,9] with the exception of 17p11.2–p12 imbalances. While duplications causing CMT1A are predominantly paternal and interchromosomal, deletions causing HNPP are predominantly maternal and intrachromosomal.[10] However, to date only relatively small numbers of microduplications have been characterised because they are technically more difficult to identify and because the associated phenotypes are either much milder than microdeletions or are not well defined.

We have undertaken a comprehensive study into the parental and chromosomal origins of deletions of chromosomes 7q11, 15q11–q13, 22q11 and the corresponding duplications of chromosome 15q11–q13. Our findings are compared with each other and with relevant studies from the literature.

Methods

All rearrangements were originally identified by FISH in patients referred to the Wessex Regional Genetics Laboratory. Follow-up analysis of both parents was then undertaken to determine whether the rearrangement was inherited or *de novo*. Only *de novo* rearrangements were included in the study.

DNA was extracted from each proband, both parents and any available first degree relatives using a salt precipitation technique. Parental origins were determined using microsatellites within the deleted or duplicated region. For microdeletions, chromosomal origin was determined from microsatellites flanking the deleted interval using first-degree relatives to reconstruct the haplotype of the transmitting parent. Where siblings were used, recombination was assumed to be absent in the haplotype inherited by the normal sibling from the transmitting parent (given the genetic distances covered by the haplotype, recombination would be expected to occur between the alleles flanking the deletion in a small percentage of normal siblings). At each locus flanking the microdeletion, the allele transmitted to the proband was then scored as either 'shared' or 'not shared' with the allele transmitted to the normal sibling. Scoring of informative alleles as either 'shared' or 'not shared' on both sides of the deletion indicated an intrachromosomal origin. Transition from 'shared' to 'not shared' or vice versa indicated an interchromosomal origin. For an additional explanation of these approaches, see references.[6,7]

For 15q11–q13 duplications chromosome origin was determined by microsatellites within the duplication. Inheritance of both alleles at loci heterozygous in the transmitting parent indicated an interchromosomal origin. Inheritance of two copies of the same allele where the transmitting parent is heterozygous indicated an intrachromosomal origin.

The primers used and their physical and genetic locations are shown in Table 1. All microsatellite details are available from the Genome Database (www.gdb.org), except those used to determine the chromosomal origin of the larger type I deletions of chromosome 15q11–q13. These were identified using the tandemrepeat finder program (tandem.bu.edu/) Table 2. One primer from each pair was fluorescently labelled to allow detection using an ABI 3100 automated DNA sequencer. Alleles were scored using the Genescan Analysis and Genotyper programs. Statistical analyses were carried out using χ^2 and four-fold contingency table tests.

Results and discussion

Deletions of chromosome 7q11. 23 (Williams syndrome)

No significant bias was observed in the parental origin of 7q11.23 deletions. Among the 27 cases 12 had arisen maternally and 15 paternally (Table 3). Adding our results to those from the literature[11–16] gave a total of 148 cases of maternal origin and 130 of paternal origin, a nonsignificant excess of maternal cases.

Haplotype analysis to determine chromosomal origin was performed on eight cases: in six cases the grandparents of the transmitting parent were available and in two cases a non-deleted sibling was available (Table 4). There was a strong preference for the formation of deletions through interchromosomal exchanges with seven interchromosomal rearrangements and one intrachromosomal rearrangement. This is consistent with all previous studies of Williams syndrome in which chromosomal origin was investigated.[12,13,16,17] Including our results there were 61

Table 1 Details of all primers used. (a) Chromosome 7q11.23, (b) Chromosome 15q11-q13 and (c) Chromosome 22q11

Locus	*Mb*	*mcM*	*fcM*
(a)			
D7S502	66.5	**54.32**	**105.39**
D7S1816	70.7	**57.25**	**112.77**
D7S2415	71.1	**57.25**	**112.77**
D7S653	71.2	**57.25**	**113.09**
Proximal breakpoint			
D7S489(U)	71.9	*57.41*	*113.54*
D7S2476	72.5	**57.61**	**114.07**
D7S613	73.0	**57.61**	**114.07**
D7S2472	73.3	**58.43**	**115.89**
D7S1870	73.6	**58.47**	**115.89**
D7S489(L)	74.6	**58.47**	**116.60**
Distal breakpoint			
D7S2490	74.9	**58.47**	**117.16**
D7S2518	75.0	**58.47**	**117.16**
D7S675	77.2	**59.58**	**120.12**
D7S2421	77.3	**59.58**	**120.53**
D7S524	84.3	**67.90**	**130.50**
(b)			
AC127381[a]	18.4	*0.00*	*0.00*
AC126335[a]	18.5	*0.00*	*0.00*
AC134980[a]	19.9	*0.00*	*0.00*
Proximal breakpoint class I			
D15S542	20.4	**0.00**	**0.00**
D15S541	20.5	*0.13*	*0.17*
Proximal breakpoint class II			
D15S543	21.1	*1.99*	*2.55*
D15S11	21.6	**3.56**	**4.57**
D15S128	22.7	**5.28**	**5.05**
D15S1506	23.1	*5.28*	*5.05*
D15S122	23.1	**5.28**	**5.05**
D15S822	24.9	**9.55**	**14.29**
D15S1002	25.6	**11.94**	**15.60**
D15S217	25.8	**13.23**	**16.51**
Distal deletion breakpoint			
D15S1019	27.5	**16.32**	**21.24**
D15S1048	27.7	**17.07**	**21.24**
D15S165	29.1	**18.50**	**22.66**
(c)			
F8VWFP	15.4	**0.00**	**2.50**
D22S420	16.2	**3.05**	**9.99**
D22S427	17.0	**6.22**	**16.74**
Proximal breakpoint			
D22S1638	17.4	*9.64*	*18.27*
D22S941	17.8	**10.09**	**18.27**
D22S944	18.0	**10.43**	**18.27**
D22S1623	—	—	—
D22S264	19.1	**11.60**	**18.27**
D22S311	19.5	**12.25**	**18.27**
D22S1709	19.7	*12.35*	*18.95*
Distal breakpoint			
D22S539	20.6	**12.35**	**25.12**
D22S308	20.8	*12.35*	*25.84*
D22S306	20.8	*12.35*	*25.84*
D22S425	21.4	**12.35**	**29.72**
D22S303	21.6	*12.35*	*29.72*

Physical distance: Mb from pter from ensembl; Genetic distance: centiMorgan: bold taken directly from the location database; italics inferred from physical distance in location database. (mcM = male centiMorgan; fcM = female centiMorgan).
[a]New primers designed using the Tandem Repeat Finder program. See Table 2. For 15q both proximal deletion breakpoints are shown, for 7q and 22q only the common breakpoints are shown.

interchromosomal deletions (73%) and 23 intrachromosomal deletions (27%).

The alleles transmitted proximal to the deletion were grandmaternal in two cases and grandpaternal in four cases. Among all cases in the literature, there were similar numbers of grandmaternal ($n=29$) and grandpaternal ($n=23$) alleles proximal to deletions of interchromosomal origin and there was no parental origin bias for intrachromosomal deletions.

Deletions of chromosome 22q11 (DiGeorge syndrome)

The majority of the deletions studied were of the common 3 Mb size. There were three smaller 1.5 Mb deletions and in eight cases insufficient markers were informative to determine the exact deletion size.

Parental origins were determined in 67 cases. There was no significant bias in parental origin: in 37 cases the origin was maternal and in 30 cases the origin was paternal (Table 3). From the literature, we have found a further 148 cases of maternal origin and 103 of paternal origin.[7,17–27] Thus, there is a slight overall excess of maternal cases, 185 compared to 133 paternal cases, that just reaches statistical significance ($\chi^2=4.09$; $P=0.05$).

Haplotype analysis was performed on 30 cases (all 3 Mb deletions): in 23 cases the grandparents of the transmitting parent were available and in seven cases a non-deleted sibling was available (Table 5). The great majority of deletions, 26 of 30, arose through an interchromosomal event, consistent with other published studies. Adding our results to those in the literature, the total number of interchromosomal cases is 73 (86%) compared to only 12 (14%) of intrachromosomal origin.

Baumer *et al*[17] reported the transmission of a significant excess of grandmaternal alleles proximal to the deletion breakpoint irrespective of the parental origin of the deletion. In contrast, Saitto *et al*,[7] reported equal number of grandmaternal and grandpaternal alleles. Among the interchromosomal rearrangements in our study the alleles transmitted proximal to the breakpoint were grandmaternal in 13 cases and grandpaternal in eight cases. Combining the results of these three studies with a fourth smaller one[26] gave 39 cases of grandmaternal origin compared to

Table 2 Sequences of new chromosome 15 primers

BAC	*Primer sequence*	*Repeat unit*	*Product size*
AC127381.4	For: TTCGGGGATGCTTTATCTTG Rev: TATCCATGTAGGGGGTGCTC	AC	244–256 bp
AC126335.16	For: TGGCCATTTGTATGGCATATT Rev: AGGCAGGAGAATTGCTTGAA	GT	222–232 bp
AC134980.3	For: CTCTGTCCTCCACCCTTCAC Rev: AGGTGCTTGTTCTTCCTTGAA	AC	199–217 bp

Table 3 Summary

	7q	*22q*	*15q del*	*15q dup*	*Total*
Parental origin					
Maternal	12	37	14[a]	7[a]	49[a]
Paternal	15	30	7[a]	2[a]	45[a]
Chromosomal origin					
Inter	7	26	13	5	51
Intra	1	4	8	4	17
Inter-chromosomal					
Maternal	4	12	11	4	31
Paternal	3	14	2	1	20
Intra-chromosomal					
Maternal	0	4	3	3	10
Paternal	1	0	5	1	7
Grandparental origin					
GM[b] proximal	2	13	6	—	21
GP[b] proximal	4	8	2	—	14

[a]Imprinted loci excluded from parental origin total column.
[b]GM = grandmaternal; GP = grandpaternal.

20 of grandpaternal origin. This is not statisticaly significanct ($\chi^2 = 2.75$; $P = 0.1$).

All four intrachromosomal deletions identified in our study were of maternal origin. The parental origin of a further six intrachromosomal deletions are reported in the literature,[7,17,21] with four of maternal origin and two of paternal origin. Thus, while intrachromosomal deletions can arise in either parent, there may an excess of maternal cases.

Deletions of chromosome 15q11–q13 (Prader–Willi syndrome/Angelman Syndrome)

15q11–q13 contains an imprinted domain and the phenotype associated with deletions of this region is determined by the parental origin: paternal deletions cause Prader–Willi syndrome (PWS) and maternal deletions cause Angelman syndrome (AS). Therefore, parental origin studies were not required and the number of cases reflects the ascertainment of two distinct syndromes. Of the 21 patients with 15q11–q13 deletions there were seven paternal cases and 14 maternal cases (Table 3).

Table 4 Chromosomal origins of 7q11.23 deletions

Family No	*Parental origin*	*Proximal*[a]	*Distal*[a]	*Chromosomal origin*
1	Mat	GP	GM	Interchromosomal
4	Mat	GP	GM	Interchromosomal
9	Mat	GM	GP	Interchromosomal
24	Mat	GP	GM	Interchromosomal
5	Pat	GM	GP	Interchromosomal
12	Pat	GP	GM	Interchromosomal
23	Pat	Shared	Not shared	Interchromosomal
28	Pat	Not shared	Not shared	Intrachromosomal

[a]GM = grandmaternal; GP = grandpaternal.

Table 5 Chromosomal origins of 22q11 deletions

Family No	*Parental origin*	*Proximal*[a]	*Distal*[a]	*Chromosomal origin*
2	Mat	GM	GM	Intrachromosomal
21	Mat	GP	GM	Interchromosomal
26	Mat	GM	GP	Interchromosomal
29	Mat	GM	GM	Intrachromosomal
30	Mat	GM	GP	Interchromosomal
33	Mat	GM	GP	Interchromosomal
34	Mat	GP	GM	Interchromosomal
36	Mat	GP	GM	Interchromosomal
46	Mat	GM	GP	Interchromosomal
49	Mat	Not shared	Not shared	Intrachromosomal
52	Mat	GM	GP	Interchromosomal
56	Mat	GM	GP	Interchromosomal
58	Mat	GM	GP	Interchromosomal
50	Mat	Not shared	Shared	Interchromosomal
59	Mat	Shared	Shared	Intrachromosomal
60	Mat	Not shared	Shared	Interchromosomal
3	Pat	Shared	Not shared	Interchromosomal
8	Pat	GM	GP	Interchromosomal
20	Pat	GP	GM	Interchromosomal
22	Pat	GM	GP	Interchromosomal
25	Pat	Not shared	Shared	Interchromosomal
32	Pat	GP	GM	Interchromosomal
38	Pat	GM	GP	Interchromosomal
40	Pat	GM	GP	Interchromosomal
47	Pat	GP	GM	Interchromosomal
53	Pat	GM	GP	Interchromosomal
57	Pat	GM	GP	Interchromosomal
61	Pat	GP	GM	Interchromosomal
65	Pat	GP	GM	Interchromosomal
76	Pat	Shared	Not shared	Interchromosomal

[a]GM = grandmaternal; GP = grandpaternal.

Taking all 21 deletions of 15q11–q13, irrespective of parental origin, there was an overall excess of interchromosomal rearrangements. Combining our data with two published studies[28,29] there were 23 interchromosomal rearrangements (62%) and 14 intrachromosomal rearrangements (38%).

For maternal deletions, haplotype analysis was performed using grandparents in nine cases and a sibling in five cases. There were 11 interchromosomal rearrangements and three intrachromosomal rearrangements. Analysis of the paternal deletions used grandparents in five cases and a sibling in two cases. There were two interchromosomal rearrangements and five intrachromosomal rearrangements (Table 6).

Thus the nature of the exchange event between LCRs was different for maternal and paternal deletions. Among maternal deletions there was a significant excess of interchromosomal cases while for paternal deletions there was an excess of intrachromosomal cases. These results extend the findings of Robinson *et al*[8] who reported that three out of three maternal cases and only two out of six paternal cases were interchromosomal. In contrast, Carrozzo *et al*[28] reported, an excess of interchromosomal cases among paternal deletions. Combining all these data together there are 14 maternal interchromosomal cases compared to three maternal intrachromosomal cases. In contrast, there are nine paternal interchromosomal cases compared to 11 intrachromosomal deletions. Thus, while maternal deletions can arise by both mechanisms there is a strong preference for recombination between both maternal chromosome 15 homologues. In contrast the formation of paternal deletions is more likely to involve only a single homologue. As a result of the small numbers, this result is significant only at the 5% level ($\chi^2 = 3.94$; $P = 0.05$).

Deletions of 15q11–q13 have a single common distal breakpoint, but can be divided into class I or class II according to their proximal breakpoints.[29] The proportion of class I and class II breakpoints was similar for maternal and paternal deletions. Among maternal deletions both classes showed an excess of interchromosomal deletions: six of eight for class I and five of six for class II. For paternal class II deletions, there were almost equal numbers of interchromosomal ($n = 8$) and intrachromosomal cases ($n = 7$). However, among the small number of paternal deletions with class I breakpoints four of the five cases had an intrachromosomal origin. Thus, for deletions arising paternally, recombination between different combinations of LCRs may be associated with different chromosomal origins.

Duplications of chromosome 15q11–q13

Seven of the *de novo* duplications studied had arisen maternally and two paternally (Table 3, family numbers 6, 7, 8, 11, 14, 15 have been reported previously[31]). Duplications of this region are also subject to ascertainment bias because of imprinting.[30] The phenotype associated with maternal duplications is much more severe than paternal duplications and thus the number of *de novo* maternal duplications is higher.

Maternal and paternal duplications of both interchromosomal and intrachromosomal origin were identified and overall there were approximately equal numbers of interchromosomal and intrachromosomal rearrangements

Table 6 Chromosomal origins of 15q11-q13 deletions

Family no	*Parental origin*	*Deletion class*	*Proximal*[a]	*Distal*[a]	*Chromosomal origin*
3	Mat	I	GM	GP	Interchromosomal
4	Mat	I	GP	GM	Interchromosomal
8	Mat	I	GP	GM	Interchromosomal
9	Mat	I	GM	GP	Interchromosomal
18	Mat	I	Shared	Not shared	Interchromosomal
19	Mat	I	Not shared	Shared	Interchromosomal
20	Mat	I	Shared	Shared	Intrachromosomal
24	Mat	I	GP	GP	Intrachromosomal
6	Mat	II	GM	GP	Interchromosomal
10	Mat	II	GM	GP	Interchromosomal
13	Mat	II	GP	GP	Intrachromosomal
17	Mat	II	Shared	Not shared	Interchromosomal
22	Mat	II	Shared	Not shared	Interchromosomal
23	Mat	II	GM	GP	Interchromosomal
14	Pat	I	GM	GM	Intrachromosomal
16	Pat	I	Not shared	Not shared	Intrachromosomal
21	Pat	I	Not shared	Shared	Interchromosomal
26	Pat	I	GP	GP	Intrachromosomal
27	Pat	I	GP	GP	Intrachromosomal
1	Pat	II	GM	GM	Intrachromosomal
11	Pat	II	GM	GP	Interchromosomal

[a]GM = grandmaternal; GP = grandpaternal.

(Table 7). Thus, chromosomal origin appears to be independent of both parental origin and deletion class. However, the number of duplications available to study was too small to validate the differences observed in chromosomal origin between maternal and paternal deletions and between paternal class I and class II deletions.

Combining our results with published data, the division of chromosomal origin was very similar to 15q11–q13 deletions with a total of 10 interchromosomal duplications (67%) and five intrachromosomal duplications (33%). Only one duplication of 7q11.23 has been described, which had the common deletion breakpoints and was maternal and interchomosomal in origin.[32] Over 20 independent duplications of 22q11 have been reported. The majority, but not all, had the common 3 Mb deletion breakpoints and among the *de novo* cases analysed with microsatellites all nine were interchromosomal.[9,33] Thus, unlike CMT duplications and HNPP deletions, reciprocal imbalances involving 7q11, 15q11–q13 and 22q11 appear to arise by the same mechanism. The results also confirm that for these regions, NAHR is the predominant mechanism and that other deletion-specific mechanisms, such as loop formation with loss of the intervening sequence, do not contribute substantially.

General discussion and conclusion

Combining all data from this study the majority of rearrangements, approximately three of four, are interchromosomal. Therefore, they are likely to have arisen as the result of unequal meiotic crossing over between LCRs on different chromosome homologues. The remaining intrachromosomal rearrangements are also likely to be meiotic, although for these cases a post zygotic error during mitosis cannot be excluded. Despite well-documented differences in male and female meiosis,[34] there were roughly equal numbers of maternal and paternal rearrangements when imprinted regions were excluded.

While combining all the data allows general conclusions to be drawn, this approach is of questionable relevance and overlooks factors specific to only certain microdeletions. The proportion of interchromosomal rearrangements ranged from 86 to 62% with from highest to lowest: 22q11 deletions; 7q deletions; 15q11–q13 deletions; and 15q11–q13 duplications. When considered separately, the proportion of maternal 15q11–q13 deletions with an interchromosomal origin was equivalent to that of 22q11 deletions. At 4–4.5 Mb, rearrangements of 15q11–q13 are larger than the common 7q11 and 22q deletions, of 1.6 and 3.0 Mb, respectively. It would be interesting to compare these data with other microdeletions to investigate whether the distance between LCRs has any influence on chromosomal origin.

Table 7 Chromosomal origins of 15q11-q13 duplications

Family no	*Parental origin*	*Deletion class*	*Chromosomal origin*
11	Mat	I	Intrachromosomal
15	Mat	I	Intrachromosomal
17	Mat	I	Interchromosomal
6	Mat	II	Interchromosomal
7	Mat	II	Interchromosomal
14	Mat	II	Intrachromosomal
17	Mat	II	Interchromosomal
18	Pat	I	Interchromosomal
8	Pat	II	Intrachromosomal

For 15q deletions those of maternal origin tended to be interchromosomal, while those of paternal origin tended to be intrachromosomal especially with type I breakpoints. The excess of paternal intrachromosomal deletions of 15q11–q13 contrasts with 22q11 deletions and CMT/HNPP rearrangements where intrachromosomal rearrangements are predominantly maternal. Thus, there is evidence that for at least some regions, the mechanism through which microdeletions are generated may be related to parental origin. However, given the extent of the differences in recombination between males and females it is surprising that there are not more extensive effects associated with parental origin. For example, the vast majority of human trisomies are maternal in origin[35] while terminal deletions are predominantly paternal except chromosome arms 1p[36] and 2q[37] for which there is an excess of maternal cases.

Results from molecular studies need to be put in the context of cytogenetic chromosomal studies. For example, inversions between LCRs predispose to the formation of 7q11 deletions[12,38] and maternal deletions of 15q11–q13.[39] For 7q11 deletions, the presence of the inversion in the transmitting parent causes a bias towards interchromosomal exchanges. Yet no inversions have been identified for 22q11 deletions[40] which have an even higher proportion of interchromosomal cases. The frequency, size and chromosomal origin of microdeletions causing Sotos syndrome differ between Caucasian[5] and Japanese[4] populations, possibly reflecting differences in genetic background.

Similarly gross mechanisms of microdeletion formation need to be correlated with investigation at the nucleotide sequence level. Every genomic disorder characterised at this level of resolution has shown positional preference for recombination at specific sites within the much larger LCR.[41] Thus cytogenetic background, parental origin, chromosomal origin, LCR combination and location of recombination are all involved in the formation of recurrent structural rearrangements and the relative importance of these factors appears to be specific for each locus.

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