Breakpoint Cloning and Haplotype Analysis Indicate a Single Origin of the Common Inv(10)(p11.2q21.2) Mutation among Northern Europeans

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The pericentric inv(10)(p11.2q21.2) mutation has been frequently identified in cytogenetic laboratories, is phenotypically silent, and is considered to be a polymorphic variant. Cloning and sequencing of the junction fragments on 10p11 and 10q21 revealed that neither inversion breakpoint directly involved any genes or repetitive sequences, although both breakpoint regions contain a number of repeats. All 20 apparently unrelated inv(10) families in our study had identical breakpoints, and detailed haplotype analysis showed that the inversions were identical by descent. Thus, although considered a common variant, inv(10)(p11.2q21.2) has a single ancestral founder among northern Europeans.

A small number of cytogenetically visible human chromosome rearrangements are considered to be polymorphic variants, including several common pericentric inversions.[1] These inversions fall into two classes: one in which both breakpoints occur within heterochromatin (chromosomes 1, 3, 9, and 16) and the other in which both breakpoints occur within euchromatin (chromosomes 2, 5, and 10). The heterochromatic variants are the most frequent but may be a consequence of alterations in the amount and distribution of heterochromatin rather than true inversions.

The pericentric inv(10)(p11.2q21.2) mutation is not associated with any phenotypic abnormalities[2] and has been frequently identified in cytogenetic laboratories in the United Kingdom,[2] France,[3] Denmark and Sweden,[4] and North America.[5] The estimated frequency of inv(10) among prenatal diagnostic referrals to the laboratories taking part in this study is 1 in 3,600 in Germany, 1 in 7,100 in Denmark, and 1 in 12,800 in the United Kingdom. Thus, although the great majority of chromosome inversions appear to be unique rearrangements, the frequency and wide geographical distribution of inv(10)(p11.2q21.2) suggest that it might be a recurrent variation that has arisen independently in different populations.[6]

Repetitive sequence elements have been implicated in the formation of a range of recurrent structural rearrangements.[7] For example, the breakpoints of the most frequently occurring non-Robertsonian translocation, t(11;22), are within palindromic AT-rich repeat sequences,[8] and low copy number repeats (LCRs), or duplicons, mediate the formation of microdeletions and microduplications.[9]

We have studied a series of 20 apparently unrelated families with cytogenetically identical inv(10)s, comprising 9 families from the United Kingdom, 5 from Germany, 3 from Denmark, 2 from Sweden, and 1 from northwestern Russia (table 1). Our study had two specific aims: (1) characterization of the inv(10) breakpoints at the molecular level, to ascertain whether the formation of the inversion is mediated by repetitive sequence elements, and (2) haplotype analysis, to determine the proportion of inv(10)s that arose independently and the proportion that share an ancestral founder and are identical by descent (IBD).

The inv(10) breakpoints of patients 1 and 2 were lo-

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Table 1

Study Population

Family	Patient	Country of Origin
1	Ger1	Germany
2	***Sw1***	***Sweden***
3	***Sw2***	***Sweden***
4	Dk1	Denmark
5	Dk2	Denmark
6	Dk3	Denmark
7	UK1	United Kingdom
8	***UK3***	***United Kingdom***
9	***UK4***	***United Kingdom***
10	UK5	United Kingdom
11	UK6	United Kingdom
12	UK7	United Kingdom
13	UK8	United Kingdom
14	UK9	United Kingdom
15	***UK10***	***United Kingdom***
16	Ger2	Germany
17	Ger3	Germany
18	Ger4	Germany
19	Ger5	Germany
20	Rus1	Northwestern Russia

NOTE.—Bold italic type = phase known.

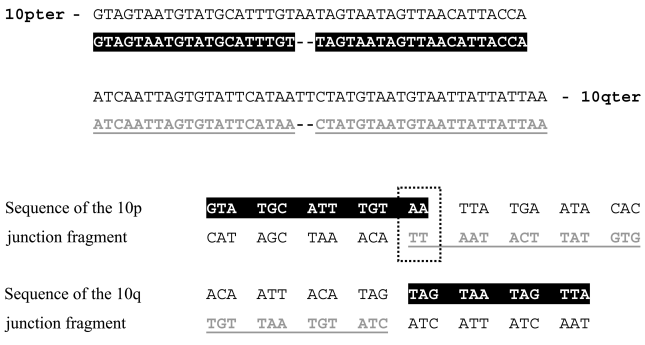

Figure 1 Sequence analysis of junction fragments. *A*, Genomic sequence encompassing breakpoints. *B*, Sequence of PCR-amplified junction fragments showing the chromosome 10 genomic sequence (*normal text*), the sequence flanking the 10p11 breakpoint (*white text*), the sequence flanking the 10q21 breakpoint (*underlined text*), and the sequence from either 10p11 or 10q21 (*boxed*). The genomic sequences shown have the following coordinates in NCBI 35 (November 2005): 10p: 37,148,066–37,148,108/AL390061.9; 4,483–4,525 and 10q: 59,748,173–59,748,217/AC016396.6; 120,582–120,626.

cated by FISH in the cytogenetic bands 10p11.21 and 10q21.1. For both inv(10) carriers, the BAC clone RP11-92B19 spans the breakpoint on 10p11.21. On 10q21.1, the breakpoints of both carriers were within the overlapping region of BAC clones RP11-22H3 and RP11-806B6. Subsequent analysis showed that the breakpoints of a further seven inv(10) carriers fell in the same spanning BAC clones.[10]

The inversion breakpoints of patient 1 were further refined by Southern blot analysis and were subsequently cloned. Sequence analysis revealed an overall loss of two nucleotides. The break in the 10q junction fragment could be unambiguously assigned, but, in the 10p junction fragment, there was a 2-bp overlap common to both 10p11 and 10q21 sequences (fig. 1). Thus, it is not possible to tell at which breakpoint site the deletion occurred. Apart from the 2-bp identity at the breakpoint, there was no extensive homology between the 10p11 and 10q21 sequences.

To determine whether other inv(10) carriers in our series contained the same breakpoints, we designed PCR assays to specifically amplify the rearranged chromosome 10 (table 2). PCR fragments of identical length were amplified at both breakpoints in the remaining 19 families, and sequencing revealed that the breakpoints were identical in all the inv(10) carriers.

The 10p11 breakpoint maps to 37,148 kb from 10pter (NCBI 35, November 2005) in a gene desert with no known gene for 300 kb on either side of the breakpoint. The 10q21 breakpoint maps to 59,748 kb within a cluster of four genes (*IPMK, CJ070, UBE2D1* [MIM 602961], and *TFAM* [MIM 600438]). Although a position effect cannot be excluded, no genes are directly disrupted by either breakpoint. This observation is consistent with the benign nature of the inversion.

The breakpoints did not directly involve any repetitive sequences. However, although the breaks occurred within short stretches of unique single-copy sequence, in both cases these were flanked by several repeats. The RepeatMasker program showed that the sequence around both breakpoints was enriched for interspersed repetitive elements. The 10-kb interval on 10p11—5 kb

Table 2

Amplification of 10p11 and 10q21 Junction Fragments

Breakpoint	Primer Sequences		Fragment Size (bp)	PCR Conditions
	Forward	Reverse		
10p11.2	GAGGCCAGGCTTAAAGCAAC	CCCACTATGGTCTGCACCAG	354	39 cycles: 95°C 30 s, 57°C 30 s, 72°C 40 s
10q21.2	AGCTGCTGTAGCCTTTGCAC	AACTGGTAAAAGAAGATCCTTGG	513	39 cycles: 95°C 30 s, 56°C 30 s, 68°C 40 s

Table 3

Microsatellite Analysis in Phase-Known Families

Locus	Locus Size (Mb)	Heterozygosity	No. of Alleles	Allele Size[a]					Founder
				Family 2	Family 3	Family 8	Family 9	Family 15	
D10S600	28.7	.84	10	*178*	*182*	*190*	*186*	*182*	-
D10S213	29.5	.83	9	*188*	*180/188*	*188*	*172*	*182*	-
D10S204	29.7	.76	12	*291*	*291*	*319*	*329*	*295*	-
D10S193	30.6	.82	9	*214*	*220*	*224*	*224*	*220*	-
D10S208	31.7	.80	9	*180*	*182*	*182*	*178*	*182*	-
D10S199	32.4	.86	12	*173*	*173*	*173*	*179*	*179*	-
D10S1666	33.7	.72	10	*266*	*258*	*276*	*274*	*256*	-
D10S1175	33.9	1.00	Unknown	*320*	*320*	*316*	*310*	*348*	-
D10S176	36.8	.70	10	*114*	*94*	*94*	*94*	*94*	-
D10S1791	37.1	.73	6	*207*	*201*	*201/207*	*201*	*201*	-
10p11.21	37.1								
D10S508	37.8	.67	Unknown	***184***	***184***	***184***	***184***	***184***	***184***
Centromere	39–41								
D10S141	42.8	.85	13	***115***	***115***	***115***/131	***115***	***115***	***115***
D10S469	42.8	.87	10	***123***	***123***	***123***/137	***123***	***123***	***123***
ZNF22	44.8	.84	10	***151***	***151***	***151***	***151***	***151***	***151***
sJRH	48.0	.90	17	303	***299***	***299***	***299***	***299***	***299***
D10S1793	49.5	.86	11	***254***	***254***	***254***	252	***254***	***254***
D10S1766	50.4	.75	5	***171***	***171***	***171***	***171***	***171***	***171***
D10S220	51.7	.84	10	***107***	***107***	***107***	***107***	109	***107***
D10S196	51.8	.79	6	***100***	94	***100***	***100***	94/***100***	***100***
D10S1790	54.6	.84	11	191	***193***	***193***	***193***	***193***	***193***
D10S539	54.7	.76	8	***93***	***93***	***93***	***93***	***93***	***93***
D10S1124	56.8	.88	14	***231***	***231***	***231***	***231***	***231***	***231***
D10S1788	57.3	.78	7	***249***	***249***	***249***	***249***	***249***	***249***
D10S1767	58.0	.71	13	***256***	***256***	***256***	***256***	***256***	***256***
D10S1756	58.4	.84	9	***192***	***192***/194	***192***	***192***	***192***	***192***
D10S524	58.6	.88	Unknown	***369***	365	***369***	***369***	***369***	***369***
D10S1659	58.7	.75	8	***184***	***184***	***184***	***184***	***184***/194	***184***
10q21.1	59.8								
D10S589	60.8	.79	8	*190*	*186*	*184*	*184*	*186*	-
D10S464	60.9	.78	8	*140*	*140*	*144*	*134*	*140*	-
D10S1652	63.8	.78	10	*167*	*163*	*165*	*161*	*171*	-
D10S581	65.2	.80	12	*142*	*134/138*	*136*	*136*	*148*	-
D10S1743	66.8	.78	9	*227*	-	*235*	*243*	*241*	-
D10S1670	68.2	.76	12	*305*	*301*	*305*	*305/307*	*321*	-
D10S210	69.4	.80	6	*135*	-	*133*	*129/133*	*131*	-
D10S1647	70.3	.82	9	*204*	*208*	*212*	*208*	*206*	-
D10S1665	70.6	.87	12	*240*	-	*238*	*218*	*234/240*	-
D10S537	71.7	.83	9	-	-	*298*	*290*	*292*	-
D10S1650	72.6	.85	12	*136*	-	*132*	*124*	*138*	-

Note.—Breakpoints and the centromere are shaded in gray. All microsatellite details are available from the Genome Database, and distances were taken from Ensembl. Alleles outside the inversion are in italics. Shared alleles and the common haplotype are shown in bold italics, and allele differences are underlined.

[a] Allele sizes are taken from the total size of the PCR product and are given in base pairs, rounded to the nearest whole number.

on either side of the breakpoint—contained 34% repetitive sequences (15% short interspersed transposable elements [SINEs] and 14% LTRs), and the 10-kb interval on 10q21 contained 47% repetitive sequences (20% long interspersed transposable elements [LINEs], 10% LTRs, and 9% SINEs). Interspersed repeats may promote instability and the formation of DNA double-strand breaks and/or act as substrates for recombination.[7] Therefore, although it seems unlikely that the sequences around each breakpoint are predisposed to the formation of the inversion, we cannot exclude this possibility.

The presence of the same breakpoints in all inv(10) carriers and the lack of obvious predisposing factors suggest a founder effect—that is, that all 20 families share a common ancestor. To determine whether the inv(10)s were all IBD, we undertook detailed haplotype analysis, using microsatellites and SNPs. DNA was avail-

Table 4

Microsatellite Results for All 20 Inv(10) Families

Locus	Ancestral Haplotype	Family Allele Size																			
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
10p11.21																					
D10S508	184	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Centromere																					
D10S141	115	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
D10S469	123	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ZNF22	151	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
sJRH	299	-	303	-	-	-	-	-	-	-	-	-	-	-	-	-	-	303	303	-	-
D10S1793	254	-	-	-	-	-	-	-	-	252	-	-	-	-	-	-	-	-	-	-	-
D10S1766	171	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
D10S220	107	109	-	-	-	-	-	-	-	-	109	109	-	-	-	109	-	-	-	-	109
D10S196	100	-	-	94	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
D10S1790	193	-	191	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
D10S539	93	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
D10S1124	231	-	-	-	-	-	-	-	-	-	-	213/223	-	-	-	-	-	-	-	-	-
D10S1788	249	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
D10S1767	256	-	-	-	-	-	-	-	-	-	-	-	254	254	-	-	-	-	-	-	-
D10S1756	192	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	190	190	-	-
D10S524	369	-	-	365	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
D10S1659	184	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
10q21.1																					

Note.—Breakpoints and the centromere are shaded in gray. A hyphen indicates that the same allele is present as that in the ancestral haplotype. Where no allele is shared with the ancestral haplotype (i.e., a microsatellite mutation), the size of the divergent allele is shown. Allele sizes are taken from the total size of the PCR product and are given in base pairs, rounded to the nearest whole number. Only microsatellites within the inverted region are shown.

able for more than one inversion carrier from 5 of the 20 families. The five haplotypes for which phase was known were identical or differed at no more than 2 of the 17 microsatellites tested within the inversion (table 3). This suggests that all five inv(10)s are IBD and allowed us to predict the likely ancestral haplotype that was identical to that observed for family 8 (UK3). In contrast to the degree of allele sharing within the inverted region, the flanking haplotypes were completely divergent outside the inversion breakpoints.

We also typed the same microsatellites in the 15 families where DNA was available from only a single carrier (table 4). This demonstrated that all 20 families are IBD. The alleles in 8 of the 20 families were consistent with the common haplotype, whereas in 12 families there was at least one difference. In total, there were nine allele differences: five were private mutations, whereas four were seen in more than one family. The most common allele change observed was at the microsatellite *D10S220,* from a PCR product length of 107 bp in the ancestral haplotype to 109 bp in five families.

Table 5

dbSNP Accession Numbers and Details for the Analyzed SNPs

The table is available in its entirety in the online edition of *The American Journal of Human Genetics.*

For SNP analysis (table 5), we compared three families for which phase was known and four families for which phase was unknown. In contrast to the microsatellites, which spanned the whole inversion, SNPs were chosen over a few kilobases in the immediate vicinity of the breakpoints. All seven inv(10) families tested had exactly the same haplotype (table 6), providing further evidence that the inversions are IBD. Families 2 (Sw1) and 3 (Sw2) had identical haplotypes even though they differed at 4 of the 17 microsatellites. This is likely to be due to the higher mutation rates in microsatellites compared with SNPs. Thirty-six control SNP haplotypes were generated from 18 normal individuals (from 9 trios) to assess the frequency of the inversion haplotype. There were 19 different haplotypes and, in total, 6 of the 36 control chromosomes carried the inversion haplotype (one homozygous and four heterozygous individuals). Thus, it is unlikely that the SNP haplotype shared by the inv(10) carriers is coincidental.

The haplotype analysis demonstrated complete suppression of recombination within the inverted segment. Our data cannot distinguish between a direct effect—namely, that crossing over does not occur—and indirect selection against unbalanced recombinant products. The inversion breakpoints are close to the centromeric areas of low recombination. No recombinants were seen in two studies of 33 and 15 inv(10) families.[2,4]

Table 6

Conserved SNP Haplotype

Chromosome and dbSNP Accession Number	Alleles	Inv(10)
10p:		
rs3898062	A/G	G
rs2488748	C/G	G
rs12257945	A/G	A
rs12572077	A/C	A
rs2695081	C/G	G
rs4934835	C/G	C
rs11010897	A/G	A
	Breakpoint	
rs2463226	A/T	A
rs10827731	C/T	C
rs11817755	G/T	T
rs3867222	C/T	T
rs2490841	G/T	T
10q:		
rs16851	C/T	T
rs11818916	A/C	A
rs2486489	G/T	T
rs12248484	A/G	G
	Breakpoint	
rs7072568	A/G	G
rs12241885	C/T	C
rs1007915	C/T	T

NOTE.—Twelve SNPs around the 10p breakpoint and seven SNPs around the 10q breakpoint were selected for SNP analysis by enzyme digestion or sequencing. All details are given in table 5.

It is difficult to make an accurate estimation of the age of the inversion. The geographical distribution of the 20 inversion carriers, the accumulation of microsatellite mutations within the inversion—estimates for which range from 10^{-2} to 10^{-4} per locus per generation—and the occurrence of crossovers very close to both the 10p11 and 10q21 breakpoints in most, if not all, families suggest that the rearrangement is not a recent event. This is consistent with the calculation of average reproductive fitness for inversions of 0.926 ± 0.085.[11]

The breakpoints of a small number of other pericentric inversions have also been determined. In contrast to inv(10), these inversions were studied because they were associated with specific abnormal phenotypes, and, consequently, the majority of breakpoints were identified within the introns of genes.[12–16] Graw et al.[17] cloned the breakpoints of the inv(8)(p23.1q22.1), which is associated with various clinical manifestations, including mental retardation and heart defects in unbalanced carriers (Rec 8 syndrome [MIM 179613]). The results were similar to inv(10) in a number of ways: No genes were directly disrupted by the inversion, the breakpoint sequences showed little homology, the breakpoints lay in unique sequences flanked by repetitive elements, and the inversion has spread widely from a single founder.

The 20 inv(10) families studied were all from northern Europe. It would be interesting to establish whether all cases worldwide are also derived from the same founder. Of the inv(10) cases in the literature, only one has been reported as de novo.[18] Breakpoint sequencing and haplotype analysis should be applied to any potentially unrelated or non-European inv(10) carriers. We have contacted several cytogenetic laboratories worldwide whose populations are unlikely to be of European origin. To date, we have had replies from three laboratories (in Egypt, Mexico, and Singapore), none of which have identified a single inv(10). The only non-European cases in the literature are from the United States and Canada,[3] and these individuals could conceivably be of European origin.

Thus, the overall evidence suggests that, although it is considered a common variant, inv(10) may well be a unique rather than a recurrent rearrangement, with a single European founder. It would be interesting to apply the approaches used in this study to other common inversions, such as the variant inv(2)(p11q13), to establish whether they are also IBD.

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Web Resources

URLs for data presented herein are as follows:

dbSNP, http://www.ncbi.nlm.nih.gov/SNP/
Ensembl, http://www.ensembl.org/
Genome Database, http://www.gdb.org/
National Center for Biotechnology Information (NCBI), http://www.ncbi.nlm.nih.gov/
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for *UBE2D1, TFAM,* and Rec 8 syndrome)
RepeatMasker, http://www.repeatmasker.org/
UCSC Genome Browser, http://genome.ucsc.edu/

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