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Different break-points in Philadelphia chromosome variant translocations and in constitutional and sporadic translocations

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SUMMARY

Three different samples of translocations were considered in an attempt to identify those chromosomal bands preferentially involved in variant Philadelphia chromosome (Ph^1) translocations, and to compare them with bands preferentially broken in constitutional and sporadic translocations. The first sample included 204 cases of variant Ph^1 translocations with 221 identified break-points (bp), the second consisted of 106 cases of non-Robertsonian constitutional translocations with 213 bp identified, and the third one of 185 bp identified in sporadic translocations found occasionally in single cells of subjects with normal karyotypes and without haematological disorders.

A statistical analysis demonstrated that there are some bands preferentially broken in each of the samples, and this with a high level of significance ($P < 0{\cdot}001$). The analysis of the distributions of the χ^2 components permitted us to identify the 12 bands preferentially involved in variant Ph^1 translocations and the 13 and 9 bands preferentially involved in constitutional and sporadic translocations, respectively. The comparison among the groups of preferential bp showed that the bands most involved in the three samples are different.

Some theoretical problems related to the origin of the Ph^1 chromosome are discussed.

INTRODUCTION

In no more than 5 % of the patients with Ph^1-positive Chronic Myelocytic Leukaemia (CML) does the Philadelphia chromosome originate from translocations different from the standard one, (9;22)(q34;q11) (Sandberg, 1980; Hagemeijer *et al.* 1984). These variant rearrangements were classified usually into two types, namely the two-chromosome variants, apparently involving one chromosome 22 and another chromosome different from a 9, and the complex variants in which more than two chromosomes (three in most cases) are involved. Recently Hagemeijer *et al.* (1984), mainly on the basis of data obtained with *in situ* hybridization techniques, challenged this classification and suggested that all two-chromosome variants are in effect undetected complex ones. These authors postulate that all variants involve also a chromosome 9, even when this is not apparent, thus confirming the hypothesis advanced by Pasquali *et al.* (1979) and based on the formal analysis of translocation patterns and on some theoretical considerations.

In fact, the break-points (bp) on chromosomes 9 and 22 are consistently at bands 9q34 and 22q11, but few attempts have been made to analyse the bp on the other chromosomes involved (Sandberg, 1980; Mitelman & Levan, 1981). These studies indicated 'some measure of

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nonrandomness' (Mitelman & Levan, 1981) and the first objective of our work was to search for evidence of the preferential involvement of bands other than 9q34 and 22q11 in the origin of the Ph[1] chromosome from variant translocations.

A second step was to compare the bands preferentially involved in variant Ph[1] translocations with the bp of constitutional balanced translocation, i.e. with the same type of chromosomal changes which are not obviously related to neoplasms. A comparison was made also with those sporadic translocations occasionally found in the single cell of individuals with a normal karyotype and no haematologic disorder. The rationale for this comparison was to test whether a somatic cell in which a translocation arises could be the one from which the neoplastic growth begins. This event was postulated either in a general sense (de Grouchy, 1967), or for specific cases such as the malignancies in patients with ataxia-telangiectasia (Zech & Haglund, 1978; Hecht & Kaiser-McCaw, 1982).

MATERIAL

Three groups of translocations were taken into consideration in the present study.

Samples A, A.1 and A.2: variant Ph[1] translocations

Seventeen cases of variant Ph[1] translocations were observed in our laboratory (Pasquali *et al.* 1983), while 159 different ones are entered in the 'Catalogue of chromosome aberrations in cancer' (Mitelman, 1983). To these we added 28 further cases from the literature (Rowley, 1978; Van den Berghe *et al.* 1978; Cimino *et al.* 1979; Ross *et al.* 1979; Sandberg, 1980; Hagemeijer *et al.* 1981; Geurts van Kessel *et al.* 1981; Tomiyasu *et al.* 1982; Yao *et al.* 1982; Liu Yin *et al.* 1983; Hagemeijer, 1983; Turchini *et al.* 1983; Puchkova *et al.* 1983; Fraisse *et al.* 1983; M. Sessarego, 1983, pers. commun.; P. Simi, 1984, pers. commun.), making the total number of cases of Sample A up to 204. In a few instances we changed the interpretation of the translocation patterns given by the authors, as in the cases reported by Pasquali *et al.* (1979), or when misinterpretation was obvious. In this sample a total of 221 bp were identified. It includes all kinds of variants, that is the rearrangements involving two, three and more chromosomes, including the so-called 'masked' Ph[1]s (Sandberg, 1980).

We did not change the interpretation of the two-chromosome variants according to the hypothesis mentioned above (Hagemeijer *et al.* 1984), as this would not be relevant to our study. However, we did also analyse separately the bp of the two-chromosome and of the three-chromosome variants. Thus, we isolated from the total two more samples of translocations, here called A.1 and A.2, which include respectively 72 cases of two-chromosome variants with 73 bp identified, and 103 three-chromosome variants with 116 bp identified. In these two samples we did not include the 'masked' Ph[1]s.

Sample B: constitutional translocations

In order to get a sample of constitutional translocations homogeneous for the techniques and criteria of analysis, we assembled the constitutional translocations observed in our Institute in the period 1973–1983, with exclusion of the Robertsonian translocations. We included both balanced and unbalanced translocations, but only the index case was taken into account in the

familial cases. A total of 106 different translocations were collected, with 213 bp identified. Appendix I lists all the translocations of Sample B.

Sample C: sporadic translocations

From the files of our Institute we collected 38 patients with normal karyotype and without haematologic disorders in whom we found a single cell with a non-Robertsonian translocation. Appendix II lists these translocations, in which 74 bp were identified. This sample was rather small, and we pooled our data with one of the most extensive reports of sporadic translocations in the literature, that is the one by Mattei *et al.* (1979), in which 111 bp had been identified. Thus the total number of bp in Sample C became 185.

METHODS

For each of the three samples there are two alternative hypotheses: either the bp take place at random or some of the chromosomal bands are preferentially involved. In the first case one could expect that the probability of breaking for each single band is proportional to its width, as suggested by Yu *et al.* (1978). We measured all the bands of the ideogram of the human karyotype (ISCN, 1981), ignoring the subdivisions because bp in our samples were not assigned to sub-bands. We used a total of 320 bands. The band 1p31 is the widest and was taken as a standard measuring unit.

For each of the five samples, we then calculated the number of bp for each band expected under the random hypothesis (b_{exp}) with the formula

$$b_{exp} = \frac{B \times w}{W}, \tag{1}$$

where B is the total number of bp in the sample, w is the width of the band considered and W is the sum of the widths of all the 320 bands. The difference between the distribution of the bp expected under the random hypothesis and the distribution of the bp observed was tested by χ^2. In the cases of a significant difference, the analysis of the distribution of the χ^2 components would identify bands preferentially broken in each sample.

The Ψ heterogeneity test (Smith, 1952) was then used to compare the distributions of bp on these 'hot spots' in the different samples.

RESULTS

The values of χ^2 for the five samples are given in Table 1. Unfortunately, as the expected numbers b_{exp} in many bands are quite small, we cannot legitimately find the correct significance level by using the customary table of χ^2. The following method has been suggested to us as suitable by Professor C. A. B. Smith, and we owe to him the following explanation.

Let n be the number of bands, so that the number of degrees of freedom for χ^2, calculated in the usual way, is $N = n-1$. Then it turns out that the expected value of χ^2 (on the hypothesis of a random distribution of break-points) is exactly N, even when the expected numbers are small. The exact value of the variance V of χ^2 turns out to be

$$V = 2N(1-3/B)+[W\Sigma(w^{-1})-(N-1)^2]/B, \tag{2}$$

Table 1. *The χ^2 analysis of the five samples ($N=319$, $P<0{\cdot}001$)*

Sample	No. bp (B)	χ^2	V	$\frac{\sqrt{\chi^2}-m}{\sqrt{v}}$
A	221	583·256	818·095	7·88
A.1	73	584·050	1183·220	6·58
A.2	116	588·235	981·112	7·31
B	213	678·089	824·859	10·19
C	185	4173·240	853·141	57·18

approximating to $2N$ when B is large, so that the expected numbers are large. As a first approximation, we could say that the expected value of χ^2 is N and its standard error is $\sqrt{V}$, so that we would compute

$$t = (\chi^2 - N)/\sqrt{V} \tag{3}$$

in the usual way, and compare it with tables of the normal distribution.

However, this is not entirely satisfactory, because the distribution of χ^2 tends to be skewed, while the normal distribution is symmetrical. To overcome this, we use a device apparently originally due to R. A. Fisher, who observed that the distribution of $\sqrt{\chi^2}$ is much nearer to the normal form than that of χ^2 itself (provided that not many of the expected values are much smaller than 1). The variance of $\sqrt{\chi^2}$ is approximately $v = V/4N$ and the expected value of $\sqrt{\chi^2}$ is approximately

$$m = \sqrt{(N-v)}. \tag{4}$$

Hence, if we define t by

$$t = (\sqrt{\chi^2} - m)/\sqrt{v} \tag{5}$$

instead of as in equation (3), then we can compare t with the normal distribution with reasonable confidence, so that $t > 2{\cdot}33$ indicates significance at the 1 % level, and $t > 3{\cdot}09$ at the 0·1 % level. The values of t so obtained are given in Table 1, and are all highly significant, indicating a non-random distribution of break-points.

The values of the χ^2 components for each band in the five samples were ranked in increasing order and a comparison of the distribution of these values with the expected number of values in different ranges of χ^2 is shown in Table 2. So the bands preferentially involved were identified. In fact, in the last column of this table, on the hypothesis of random distribution, the expected number of χ^2 components higher than 10·827 should be 0·32, while the observed ones are 12, 9, 12, 13 and 9 respectively. We can then assume that the bands corresponding to the values of the last column of Table 2 are preferentially involved in the five samples, and these bands are listed in Table 3.

We compared the distribution of bp on the bands preferentially involved in samples A, B and C by means of the Ψ heterogeneity test (Smith, 1952). This was because this test is not sensitive to small numbers in the classes, unlike the customary χ^2 test for heterogeneity. The values of $(\sqrt{\Psi} - \sqrt{\epsilon})/\zeta$ (where Ψ, ϵ, ζ are as defined by Smith) are given in Table 4. They are all considerably greater than the 0·1 % significance point 3·09, and hence are highly significant. This indicates differences between the distributions of break-points in the three samples A, B and C.

Table 2. *Numbers of values of χ^2 in different ranges in the five samples*

	Range of χ^2 in percentiles														
	1	1	3	5	10	10	20	20	10	10	5	3	1	0.9	0.1
No. of values expected	3·20	3·20	9·6	16	32	32	64	64	32	32	16	9·6	3·2	2·88	0·32
A	—	—	3	2	13	15	92	118	32	6	3	14	2	8	12
A.1	—	—	—	—	19	65	181	16	2	4	6	4	6	8	9
A.2	—	1	1	—	2	23	172	73	10	6	6	4	2	8	12
B	2	1	1	6	9	16	86	121	30	15	4	7	6	3	13
C	3	2	2	3	11	22	93	141	19	5	—	4	4	2	9

Table 3. *The bands preferentially involved in the five samples*

A	A.1	A.2	B	C
3p21	17q25	3p21	9p22	14q11
4q23	12p13	4q23	15q11	7p13
17q25	7p22	3q21	22q11	7q35
17p13	17p13	11q13	21q22	14q32
3q21	11p15	5q13	18q11	14q12
11q13	9p24	15q15	Xq22	7q36
12p13	6p25	6p21	1q11	7p12
17q21	13q34	14q24	18q23	7q34
9p24	19p11	3q23	2p21	2p15
6p21		7q22	11q23	
14q32		17q21	2p13	
5q13		14q13	20q11	
			15q13	

Table 4. *Ψ heterogeneity test applied to the distributions of bp on the bands preferentially involved in Samples A, B and C*

(Ψ is significant at the 0·01 level when the value of the expression $\sqrt{\Psi}-\sqrt{\epsilon/\zeta}$ is $> 2{\cdot}5$, where ϵ and ζ are as defined by Smith (1952).)

Samples compared	
A/B	5·30
B/C	10·45
C/A	10·43

DISCUSSION

We obtained evidence that twelve bands are preferentially broken, together with bands 9q34 and 22q11, in the origin of the Ph[1] by variant translocations (Table 3). In addition, there are eight more bands for which the evidence is not as strong as for the group already mentioned, but again statistically significant ($P < 0{\cdot}01$). They are the bands whose χ^2 values are in the range 10·827–6·635, namely 15q15, 7p22, 2q37, 11p15, 2q11, 14q24, 3q23 and 4q31. A possible bias could be due to misinterpretation of the translocation patterns, which is indeed possible because we deal with chromosomes of leukaemic cells which are not always of the best quality. However, this should lead to an error of minor relevance, as it could be the exclusion or the inclusion of one or two bands in the list of those preferentially involved.

The comparative analysis of the results of the three samples of variant Ph[1] translocations deserves a comment. Obviously, the list of the bands preferentially involved in Sample A includes most of the ones of Samples A.1 and A.2. On the contrary, no correspondence exists between the bands preferentially broken in the two- and three-chromosome variants (Table 3). It is of interest that eight out of nine of the bands preferentially involved in two-chromosome variants are terminal, while none of the bands of the three-chromosome rearrangements is of this type. This fact is in agreement with the previous observations of Sandberg (1980) and Mitelman & Levan (1981), and strongly supports the view already expressed by us (Pasquali *et al.* 1979) and Hagemeijer *et al.* (1984) that two-chromosome variants do not exist. All variants should involve a third chromosome together with a 9 and a 22, and when the bp on this third chromosome is in the terminal band the part transposed may not be recognized and the translocation may be misinterpreted.

As to the constitutional and sporadic translocations of Samples B and C, a few comments are appropriate. The only data on the bp of constitutional translocations available in the literature refer to the higher frequency in G-negative bands (Yu *et al.* 1978; Nakagome *et al.* 1983), to a possible preferential localization in centromeric and telomeric regions (Yu *et al.* 1978; Aurias *et al.* 1978) and to the preferential involvement of some chromosome arms (Aurias *et al.* 1978). In our sample of constitutional translocations there is a highly significant preferential involvement of thirteen specific bands. There are two possible sources of bias in this result, but we think that neither should be of major relevance. The first might again be due to mistakes in bp interpretation, not due in this case to the quality of the preparations, but to the banding techniques applied. In our Institute GTG- and QFQ-banding techniques are used for routine work, and this can lead one to attribute the bp more easily to a G-negative than to a G-positive band. The possible outcome of this source of bias would be simply the shifting of some bp to adjacent bands, and this could be true also for some of the preferential bp found. The second and more serious possible bias could be due to ascertainment, as we took into account all the translocations we observed, irrespective of the reasons for which the patients had undergone chromosome analysis. However, the fact that the analyses were made over a 10-year period (1973–1983) and were part of routine work should have substantially reduced the possible effect of the ascertainment bias, to some extent introducing a randomizing factor. It is well known that translocations between chromosomes 7 and 14 are the most frequent ones among the sporadic translocations (Mattei *et al.* 1979). This was clear also in our Sample C, and only one band out of the nine found preferentially involved in these translocations was not on chromosome 7 or 14 (Table 3).

As to the preferential breaking of the G-negative bands, we observe that if this is true for the constitutional translocations (Nakagome *et al.* 1983), the Ph[1] variant translocations have a similar tendency, and all the bands preferentially broken in Samples A, A.1, A.2 and B are G-negative (Table 3). As we mentioned above, the type of banding techniques may blur the significance of these observations and, as a matter of fact, the only sample in which we found also G-positive preferential bp (three out of nine) is Sample C, in which 111 bp out of 185 were identified by mean of R-banding by Mattei *et al.* (1979).

The comparison we performed among the groups of bands preferentially broken in the different samples of translocations is illustrated in Fig. 1. It is immediately evident that the

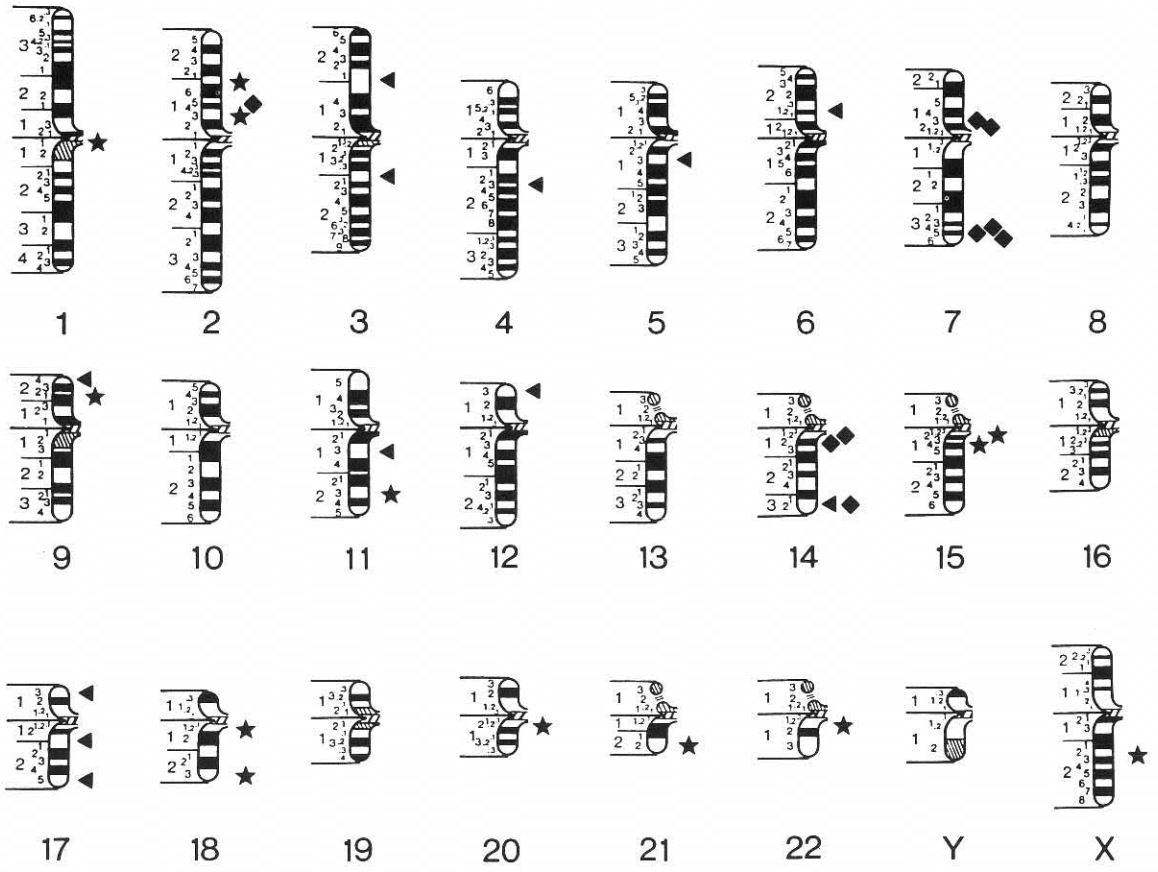

Fig. 1. The bands preferentially involved in the translocations of samples A, B and C. ★, Constitutional translocations; ◀, variant Ph¹ translocations; ◆, sporadic translocations.

bp preferentially involved in variant Ph¹ translocations are different from those preferentially involved in the constitutional and sporadic translocations, with the one exception of band 14q32. The heterogeneity test we performed showed beyond any doubt that in effect this difference is significant (Table 4). It should be noted that Yu *et al.* (1978), analysing 1134 bp of constitutional structural rearrangements from various sources, identified 21 bands, which they called 'hot spots', as those involved at least ten times. This threshold was arbitrary, but these authors suggested that these could be the bands with an increased chance of breaking spontaneously. Among these 21 bands are included only two of those which we demonstrated to be preferentially involved in variant Ph¹ translocations. This further confirms our conclusion and leads us to postulate that the preferential breaks of variant Ph¹ translocations do not correspond to the chromosomal regions more frequently involved in all types of constitutional structural changes.

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APPENDIX I

Sample B – Constitutional translocations

1 t(1;3)(p13;p21)
2 t(1;4)(p36;q31)
3 t(1;6)(p32;q25)
4 t(1;8)(p34;q24)
5 t(1;11)(p34;p15)
6 t(1;16)(p21;q23)
7 t(1;19)(q11;q13)
8 t(1;21)(q32;q22)
9 t(1;22)(q11;q13)
10 t(1;22)(q21;q11)
11 t(X;1)(p11;q24)
12 t(2;6)(p15;q15)
13 t(2;6)(p13;p23)
14 t(2;6)(p12;p12)
15 t(2;7;11)(2q31;2q37.1;7q34;11q35)
16 t(2;9)(p21;q34)
17 t(2;10)(p21;q26)
18 t(2;11)(q31;q23)
19 t(2;11)(p25;q23.2)
20 t(2;12)(p25;q21)
21 t(2;13)(q21;q12)
22 t(2;14)(p13;q32)
23 t(2;14)(p13;q11)
24 t(2;17)(q31;q25)
25 t(2;18)(q13;q21)
26 t(2;18)(p21;q23)
27 t(2;18)(q22;q23)
28 t(2;21)(p21;q22.1)
29 t(2;22)(q13;q11)
30 t(3;?)(q29;?)
31 t(3;6)(p14;q25)
32 t(3;8)(p21;p23)
33 t(3;9)(q22;p22)
34 t(3;10)(p13;q26)
35 t(3;14)(q27;q24)
36 t(3;19)(p25;q11)
37 t(3;19)(q21;p11)
38 t(3;21)(p23;q11)
39 t(X;3)(p22;q11)
40 t(4;7)(p14;q36)
41 t(4;10)(q33;q24)
42 t(4;11)(p14;p14)
43 t(4;15)(q11;q11)
44 t(4;16)(q23;q23)
45 t(4;16)(q25;p13)
46 t(5;6)(p15;q16)
47 t(5;6)(q13;p21)
48 t(5;12)(q13;p11)
49 t(5;15)(p11;q22)
50 t(5;15)(q35;q11)
51 t(5;18)(q34;q12)
52 t(6;8)(q15;q24.3)
53 t(6;11)(q13;p13)
54 t(6;17)(q11;q24)
55 t(7;8)(p13;p11)
56 t(7;17)(p12;p11)
57 t(7;20)(p15;q13)
58 t(X;7)(q21;p13)
59 t(8;10)(q11;q22)
60 t(8;15)(p11.32;p13)
61 t(8;16)(p21;q13)
62 t(8;17)(q11;q21)
63 t(9;13)(q22;q12)
64 t(9;14)(p22;q13)
65 t[inv(9)(p12q21);15](p12;q11)
66 t(9;15)(q34;q11)
67 t(9;15)(p22;q11)
68 t(9;21)(q22;q22)
69 t(9;22)(q11;q11.1)
70 t(10;13)(p13;q22)
71 t(10;14)(q24;q24)
72 t(10;22)(q11;q13)
73 t(11;17)(q13;q21)
74 t(11;18)(q25;q11)
75 t(11;20)(p15;q11)
76 t(11;20)(p11.3;q11)
77 t(11;21)(p11;q22)
78 t(11;22)(q23;q11.2)
79 t(11;22)(q23;q11.2)
80 t(11;22)(q23;q11.2)
81 t(11;22)(q23;q11.2)
82 t(X;11)(p11;p15)
83 t(12;18)(q22;q23)
84 t(13;18)(p11;q11)
85 t(X;13)(q22;q32)
86 t(15;18)(p12;q11)
87 t(15;18)(q13;q22)
88 t(15;19)(q13;q13)
89 t(15;20)(q15;q12)
90 t(15;21)(p13;p11)
91 t(X;15)(p11.3;p12)
92 t(16;21)(p12;q22)
93 t(18;18)(p11.4;p11.4)
94 t(18;21)(q11;p11)
95 t(X;18)(q22;q23)
96 t(X;19)(p11.3;q13.3)
97 t(20;21)(q11;q22)
98 t(20;21)(q11;q22)
99 t(21;21)(p13;q11)
100 t(22;22)(p11;p11)
101 t(Y;22)(q12;p13)
102 t(X;X)(q27;q23)
103 t(X;X)(p11;q13)
104 t(X;X)(q22;q22)
105 t(X;Y)(p22;q11)
106 t(X;Y)(p22.2;q11)

APPENDIX II

Sample C – Sporadic translocations

1 t(1;?)(q11;?)
2 t(1;7)(p31;q22)
3 t(1;13)(p21;q32)
4 t(2;11)(p15;p14)
5 t(2;13)(q13;q34)
6 t(2;14)(p11;q32)
7 t(3;16)(q12;p13)
8 t(3;18)(p11;q23)
9 t(4;5)(q31;q11)
10 t(5;10)(q31;q11)
11 t(7;11)(q11;q23)
12–24 t(7;14)(p13;q11)
25–28 t(7;14)(q36;q11)
29–30 t(7;14)(q34;q11)
31 t(8;9)(q13;p21)
32 t(12;14)(q15;p11)
33 t(13;13)(p11;q11)
34 t(13;14)(q14;q32)
35–36 t(14;14)(q32;q11)
37 t(14;?)(p11;?)
38 t(14;17)(q11;q25)