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Gene assignment by means of somatic cell hybrids: a new method for the analysis of data

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Summary. A statistical approach to the interpretation of data from gene assignment with somatic cell hybrids is presented. The observed data are analysed under a variety of hypotheses. The fit to the hypotheses is compared by means of the likelihood obtained under a given hypothesis. Two of these hypotheses are related to fundamental questions: is a gene responsible for the enzyme observation and if so, is that gene located on a specific chromosome or could it change its position and be sometimes on chromosome j and, in another hybrid line, on chromosome k? The other hypotheses concern the assignment of the gene to just one of the chromosomes.

To improve the traditional data analysis approach we considered additional information: the uncertainties and possible errors of laboratory methods in all our calculations and the length of the donor chromosomes in connection with one specific hypothesis.

This method allows us to account for the reliability of the investigation methods and the nature of the hybrid lines involved. Data can be evaluated at different error probabilities within a realistic range in order to compare and discuss results.

Key words: Gene assignment – Somatic cell hybrids – Data analysis – Likelihood ratio

Introduction

In the traditional gene assignment approach with somatic cell hybrids, a perfect assignment would include only concordant observations of the gene product and the chromosome concerned. For the rest of the donor chromosomes concordance occurs only by chance association. However, very often we also find discordance with the best possible assignment. This discordance must be caused by technical errors and the limits of the methods involved. In the past, several approaches have been worked out in order to cope with this kind of discordance. They have been critically surveyed by Dolf and coworkers (1984). Although they all can lead to assignments, they offer no means of interpretation in the case where the best and the second best assignment differ very little in the amount of discordance.

We propose a new, statistical method that allows us to consider the kind of discordance mentioned above. In order to illustrate this new method we will develop the procedure using the following example:

We tried to map the pig gene for the enzyme mannosephosphate isomerase EC 5.3.1.8 (MPI). For this purpose 10 hybrid cell lines (pig × a3 Chinese hamster) were investigated (Dolf 1984). These hybrid cell lines originated from three different fusion experiments that were carried out according to Pontecorvo (1975) and Hales (1977). The enzyme MPI was analyzed by cellulose acetate gel electrophoresis (Meera Khan 1971; van Someren et al. 1974) and the pig chromosomes identified by their Q-band pattern (Caspersson et al. 1969) according to the Reading Conference (1980). The resulting data are listed in Table 1.

A donor chromosome was scored present if it was observed in at least 10% of the metaphases that were analyzed. It is remarkable that no telocentric pig chromosomes could be detected in these hybrid cell lines at any donor chromosome level. Table 2 contains the number of concordant and discordant observations for each pig chromosome. Also listed is the percentage of discordance for each pig chromosome.

The lowest rate of discordance we find with chromosome no. 7 (20%) followed by the chromosomes

Table 1. The 10 investigated hybrid lines: MPI and chromosome observations

Line i	MPI	Chromosome j																		
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19[a]
1	−	−	−	−	−	−	−	−	−	−	+	−	+	−	−	−	−	−	−	−
2	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−
3	−	+	−	+	−	+	−	−	−	+	−	+	+	−	−	−	−	−	−	−
4	+	−	−	−	−	−	+	+	+	+	+	−	+	−	−	−	−	−	−	−
5	+	−	−	+	−	−	−	+	+	+	−	−	+	−	−	−	−	−	−	−
6	+	−	−	−	+	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−
7	+	+	−	+	−	−	−	+	+	+	+	−	+	−	−	−	−	−	−	−
8	+	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
9	+	−	−	−	−	−	+	+	−	+	+	−	−	−	−	−	−	−	−	−
10	+	−	−	+	−	−	+	+	−	−	−	−	+	−	−	−	−	−	−	−

[a] Chromosome no. 19 is the X-chromosome

Table 2. The number of hybrid lines with observed combinations and the amount of total discordance for each chromosome

Combination	Chromosome j																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
$g+/c_j+$	1	1	3	1	0	3	5	3	4	3	0	5	0	0	0	0	0	0	0
$g-/c_j+$	1	0	1	0	1	1	0	0	1	1	1	2	0	0	0	0	0	0	0
$g+/c_j-$	6	6	4	6	7	4	2	4	3	4	7	2	7	7	7	7	7	7	7
$g-/c_j-$	2	3	2	3	2	2	3	3	2	2	2	1	3	3	3	3	3	3	3
Discordance (%)	70	60	50	60	80	50	20	40	40	50	80	40	70	70	70	70	70	70	70

nos. 8, 9 and 12 (40%). The question now arises whether, based on these data, we can assign the locus for MPI to a certain chromosome. The obvious choice would be chromosome no. 7 with the lowest rate of discordance. But can we really assume an assignment at all and is the assignment to chromosome no. 7 really better than an assignment to any of the other chromosomes? In order to answer these two questions, we first have to evaluate the accuracy of our observations concerning the presence or absence of the gene product (MPI) and the pig chromosomes.

Procedure

The error probabilities considering the technical limitations

If we believe we have observed the donor chromosome j in a metaphase there always is a possibility that our observation is wrong. Therefore, if it is observed (c_j+), in reality it is either present (c_jr+) or absent (c_jr-). The corresponding conditional probabilities sum up to 1:

$$P(c_jr- \mid c_j+) = 1 - P(c_jr+ \mid c_j+) . \quad (1)$$

In the case where the chromosome j is not observed (c_j-) the probabilities concerning the real state are defined in a similar way:

$$P(c_jr+ \mid c_j-) = 1 - P(c_jr- \mid c_j-) . \quad (2)$$

In many situations it is convenient to assume that the observational errors are the same for each donor chromosome so that the index j in the equations (1) and (2) can be omitted.

If the gene for MPI is present in a hybrid line ($gr+$) we would expect to observe the gene product ($g+$) with the probability $P(g+ \mid gr+) = 1$. But this is not true, as it is known that events like gene suppression do occur, in which case we cannot observe the gene product. Therefore, we have to introduce the probability $P(g- \mid gr+)$ for this kind of error:

$$P(g- \mid gr+) = 1 - P(g+ \mid gr+) . \quad (3)$$

If in reality the gene is not present ($gr-$) in that hybrid line, in most cases we would not observe the gene product ($g-$). But we still might falsely observe the gene product ($g+$) due to technical errors, so that:

$$P(g+ \mid gr-) = 1 - P(g- \mid gr-) . \quad (4)$$

All the probabilities defined up to this point are related to the experimenter's resources and his skills. These probabilities have to be chosen by the experimenter according to his experience.

In our example we have chosen the error probabilities according to the following considerations: the hybrid cell lines showed many chromosome aberrations. Very often they were the same as in the a3 Chinese hamster cell line. But we found some, especially small fragments, that were possibly formed after the fusion. These fragments could not be identified with certainty. Therefore, we chose $P(c_j r+ \mid c_j+)$ to be 0.90 which makes $P(c_j r- \mid c_j+) = 0.10$. That is, we expected to err in 10% of the cases where we thought chromosome j to be present.

In the case where we did not observe chromosome j, we suspected to err at a much higher rate. In addition to these unidentifiable fragments we also assumed the occurrence of submicroscopic aberrations. Thus $P(c_j r+ \mid c_j-) = 0.30$ seems to be appropriate. This implies that $P(c_j r- \mid c_j-)$ is only 0.70. In our example we considered the errors in chromosome observation to be the same for all donor chromosomes.

As we have more faith in our observations concerning the presence or absence of the gene product MPI, we chose the probabilities of correct observations to be 0.90 for $P(g+ \mid gr+)$ and to be 0.99 for $P(g- \mid gr-)$. Therefore, the error probabilities are $P(g- \mid gr+) = 0.1$ and $P(g+ \mid gr-) = 0.01$. In the first case we allowed for an error of 10% because of dilution and age effects that can deteriorate the enzyme probes. In the latter case we chose the error to be so small, because we think the techniques in enzyme detection are quite reliable.

The different hypotheses

With a set of J donor chromosomes it is possible to formulate J hypotheses of the form:

H_j: the gene coding for the enzyme is located on chromosome j (j = 1 to J).

But the following hypotheses also have to be considered:

$H_{anywhere}$: the gene is not located on a specific chromosome but can freely move around, that is, be at different times located on different chromosomes.

$H_{mistake}$: the enzyme observation has no genetic explanation.

If at all, only one of these hypotheses is correct. It is possible to analyse the observed data under the assumption that any of these J + 2 hypotheses is the correct one.

The probability of observing the gene product under the hypothesis that the gene is located on chromosome number j. Let us assume that the gene for MPI is located only on chromosome j. For all hybrid cell lines in which the donor chromosome j has been observed (c_j+), it is possible to indicate the conditional probability of observing or not observing the gene product (g+ and g− respectively):

$$P(g+ \mid c_j+) = P(g+ \mid gr+) \times P(c_j r+ \mid c_j+) + P(g+ \mid gr-) \times P(c_j r- \mid c_j+), \quad (5)$$

$$P(g- \mid c_j+) = 1 - P(g+ \mid c_j+). \quad (6)$$

If the chromosome j is not observed, the conditional probabilities turn out to be:

$$P(g+ \mid c_j-) = P(g+ \mid gr+) \times P(c_j r+ \mid c_j-) + P(g+ \mid gr-) \times P(c_j r- \mid c_j-), \quad (7)$$

$$P(g- \mid c_j-) = 1 - P(g+ \mid c_j-). \quad (8)$$

By coming back to our example we obtain from the equations (5) to (8):

$$P(g+ \mid c_j+) = 0.90 \times 0.90 + 0.01 \times 0.10 = 0.811$$
$$P(g- \mid c_j+) = 1 - 0.811 = 0.189$$
$$P(g+ \mid c_j-) = 0.90 \times 0.30 + 0.01 \times 0.70 = 0.277$$
$$P(g- \mid c_j-) = 1 - 0.277 = 0.723.$$

Under our hypothesis we expect to observe MPI in only 81.1% of the hybrid lines where the chromosome j has been observed and, due to possible errors, in 27.7% of the hybrid lines where this chromosome has not been observed.

The probability of observing a gene product under the hypothesis that the gene has no definite locus. The hypothesis $H_{anywhere}$ states that the gene has no definite locus and therefore is located randomly in the genome. This implies that the occurrence of the gene product depends not directly on the presence of a specific donor chromosome, but on the presence (gr+) or absence (gr−) of the gene in question. First of all the probabilities of these two events should be calculated for every hybrid cell line.

The chance to have this gene in a cell line is proportional to the total physical length of all donor chromosomes present in that line. We assume that a large chromosome is likely to harbor more genes than a small one. Therefore, to each donor chromosome its relative length l is attached, so that

$$\sum_{j=1}^{J} l_j = 1, \quad (9)$$

where J designates the haploid number of donor chromosomes included in the investigation. Without uncertainty we would have to sum up the relative length of each donor chromosome present in the i-th line to get the probability $P_i(gr+)$ of the presence of the gene concerned. In our approach we use the formula:

$$P_i(gr+) = \sum (l_j \times P(c_j r+ \mid c_j+)) + \sum (l_j \times P(c_j r+ \mid c_j-)). \quad (10)$$

The first sum considers the donor chromosomes observed whereas the second sum considers those perhaps falsely not observed. The probability of the gene's absence is

$$P_i(gr-) = 1 - P_i(gr+) . \quad (11)$$

We are now able to calculate the probability of observing the gene product in that particular hybrid line:

$$P_i(g+) = P(g+ \mid gr+) \times P_i(gr+) + P(g+ \mid gr-) \times P_i(gr-) , \quad (12)$$

$$P_i(g-) = 1 - P_i(g+) . \quad (13)$$

The relative length of the pig chromosomes we used were based on the values found by Fries (1982), but we omitted the Y chromosome (Table 3). Thus, by using (10) and (11), the probabilities $P_i(gr+)$ and $P_i(gr-)$, e.g. for the hybrid line number 10 turned out to be:

$$P_{10}(gr+) = 0.2172 \times 0.90 + 0.7828 \times 0.30 = 0.4303$$
$$P_{10}(gr-) = 1 - 0.4303 = 0.5697$$

The probability of observing MPI in the hybrid line number 10 is according to (12):

$$P_{10}(g+) = 0.90 \times 0.4303 + 0.01 \times 0.5697 = 0.3930$$

The probability of not observing MPI in the same hybrid line therefore is:

$$P_{10}(g-) = 1 - 0.3930 = 0.6070 .$$

The values of $P_i(gr+)$, $P_i(g+)$ and $P_i(g-)$ for the 10 hybrid lines that were investigated are listed in Table 4.

The probability of observing a "gene product" under the hypothesis that the enzyme observation has no genetic explanation. Under the hypothesis $H_{mistake}$ we have the probability of a positive observation equal to the error probability defined in (4)

$$P(g+) = P(g+ \mid gr-) \times P(gr-) = P(g+ \mid gr-) \quad (14)$$

since the probability $P(gr-)$ is under this hypothesis equal to one. A negative observation has therefore a probability

$$P(g-) = 1 - P(g+) = P(g- \mid gr-) . \quad (15)$$

The likelihood under the different hypotheses

The following procedure is well known and applied in many fields of application (Edwards 1972). Under every hypothesis we have calculated for each hybrid cell line a probability $P(g+)$ of a positive enzyme observation and a probability $P(g-)$ of a negative observation. If in an experiment N hybrid cell lines have been investigated with respect to a certain gene product, we have to multiply N probabilities corresponding to the realized observations. The resulting likelihood value is closely related to the probability of the observed gene product data under the chosen hypothesis.

Under the hypothesis H_j the gene is located on chromosome number j. The corresponding likelihood L_j is then

$$L_j = P(g+ \mid c_j+)^a \times P(g- \mid c_j+)^b \times P(g+ \mid c_j-)^c \times P(g- \mid c_j-)^d , \quad (16)$$

where a, b, c, d are the number of $g+/c_j+$, $g-/c_j+$, $g+/c_j-$, $g-/c_j-$ combinations, respectively, and

$$a + b + c + d = N . \quad (17)$$

This procedure can be applied to the whole set of donor chromosomes. In doing so we end up with J likelihood values calculated under the J similar hypotheses.

In our experiment we observed the following combinations of MPI and chromosome no. 7 (Table 2): $5 \times (g+/c_7+)$, $0 \times (g-/c_7+)$, $2 \times (g+/c_7-)$, and $3 \times$

Table 3. Relative length of the 19 pig chromosomes

Chromosome j	Length l_j	Chromosome j	Length l_j
1	0.10514	11	0.03975
2	0.06328	12	0.03515
3	0.05747	13	0.07259
4	0.05577	14	0.05257
5	0.04876	15	0.04846
6	0.06919	16	0.03164
7	0.05537	17	0.02423
8	0.05828	18	0.02263
9	0.05707	19	0.05507
10	0.04756		
Total			1.00000

Table 4. The probabilities $P_i(gr+)$, $P_i(g+)$, $P_i(g-)$ and P_i

Line i	$P_i(gr+)$	$P_i(g+)$	$P_i(g-)$	MPI	P_i[a]
1	0.3496	0.3212	0.6788	–	0.6788
2	0.3415	0.3139	0.6861	–	0.6861
3	0.5060	0.4603	0.5397	–	0.5397
4	0.4936	0.4493	0.5507	+	0.4493
5	0.4580	0.4176	0.5824	+	0.4176
6	0.3546	0.3256	0.6744	+	0.3256
7	0.5496	0.4992	0.5008	+	0.4992
8	0.3380	0.3108	0.6892	+	0.3108
9	0.4375	0.3994	0.6006	+	0.3994
10	0.4303	0.3930	0.6070	+	0.3930

[a] Probability of the realized observation outcome used to calculate the likelihood value under the hypothesis $H_{anywhere}$

Table 5. The likelihood values calculated under the different hypotheses

Hypothesis	Likelihood	Relative likelihood	
		R_j	
H_1	0.36194E-04	0.09683	0.0036
H_2	0.13846E-03	0.37041	0.0136
H_3	0.31026E-03	0.83001	0.0305
H_4	0.13846E-03	0.37041	0.0136
H_5	0.12362E-04	0.03307	0.0012
H_6	0.31026E-03	0.83001	0.0305
H_7	0.10174E-01	27.21716	1.0000
H_8	0.11869E-02	3.17512	0.1167
H_9	0.90837E-03	2.43011	0.0893
H_{10}	0.31026E-03	0.83001	0.0305
H_{11}	0.12362E-04	0.03307	0.0012
H_{12}	0.69523E-03	1.85990	0.0683
H_{13}	0.47290E-04	0.12651	0.0046
H_{14}	0.47290E-04	0.12651	0.0046
H_{15}	0.47290E-04	0.12651	0.0046
H_{16}	0.47290E-04	0.12651	0.0046
H_{17}	0.47290E-04	0.12651	0.0046
H_{18}	0.47290E-04	0.12651	0.0046
H_{19}	0.47290E-04	0.12651	0.0046
$H_{anywhere}$	0.37380E-03	1.00000	0.0367
$H_{mistake}$	0.97030E-14	0.00000	0.0000

$(g-/c_7-)$. The corresponding likelihood is then:

$$L_7 = 0.811^5 \times 0.189^0 \times 0.277^2 \times 0.723^3$$
$$= 0.3508 \times 1.0000 \times 0.0767 \times 0.3779 = 0.01017 .$$

Under the hypothesis $H_{anywhere}$ we have to multiply the probabilities calculated in (12) and (13). Let P_i be equal to $P_i(g+)$ in the case where MPI has been observed in the i-th cell line and equal to $P_i(g-)$ in the case where MPI has not been observed (Table 4). By multiplying the N values P_i we get the likelihood $L_{anywhere}$:

$$L_{anywhere} = P_1 \times P_2 \times \ldots \times P_N . \quad (18)$$

Under the hypothesis $H_{mistake}$ the likelihood is very quickly calculated:

$$L_{mistake} = P(g+ \mid gr-)^{N+} \times P(g- \mid gr-)^{N-} , \quad (19)$$

where N+ and N− are the number of positive and negative observations.

In our example $L_{anywhere}$ and $L_{mistake}$ turned out to be:

$$L_{anywhere} = 0.6788 \times 0.6861 \times \ldots \times 0.3930 = 0.3738 \times 10^{-3}$$
$$L_{mistake} = 0.01^7 \times 0.99^3 = 0.9703 \times 10^{-14} .$$

The likelihood ratios

One interesting point is to compare the J hypotheses of chromosomal assignment with the hypothesis that the gene has no definite locus. This can be done by the examination of the J likelihood ratios R_j:

$$R_j = L_j / L_{anywhere} \quad \text{where } j = 1 \text{ to } J . \quad (20)$$

This likelihood ratio indicates how many times our observations are more likely under H_j than under $H_{anywhere}$. A reasonable hypothesis H_j should lead to a value R_j which is distinctly greater than 1. According to Edwards (1972) a likelihood ratio, $R = 7.4$ (or $\log R = 2$), or higher provides a substantial support for one hypothesis over another.

As is shown in Table 5, the relative likelihood R_7 indicates a likelihood ratio of 27 to 1 that the gene for MPI is located on chromosome 7 as opposed to the hypothesis of absence of a definite locus.

The difference between the best two hypotheses, H_7 and H_8 in our example, can also be evaluated with the corresponding likelihood ratio:

$$R_{7,8} = L_7 / L_8 = 27.21716 / 3.17512 = 8.57 .$$

The data support strongly an assignment of the gene for MPI to the pig chromosome 7.

Discussion

The new method presented in this paper is a useful means to evaluate data resulting from experiments in gene assignment with somatic cell hybrids. The main advantage of this method lies in the consideration of technical errors and errors caused by the limitations of the approach itself. By choosing the error probabilities according to a given realistic situation, the data can be analyzed under different hypotheses. This leads to reasonable criteria for the acceptance or rejection of an assignment.

In our example we assumed the same probabilities of error for all donor chromosome observations. But it is possible to set individual probabilities of error, if this would be desirable. For instance, in the case where a donor chromosome is very similar to a recipient chromosome, one would expect the observational error to be greater than that of the other donor chromosomes.

Many parameters like the error probabilities, the number of the hybrid cell lines, the distribution of the donor chromosomes in the hybrid cell lines and the relative length of the donor chromosomes influence the outcome of the likelihood values and their ratios. One possibility is to investigate the data of a single experiment under different error probabilities in order to discuss the quality of an assignment and the influence of possible errors: For different error probabilities we looked for the highest R_j in order to get the likelihood

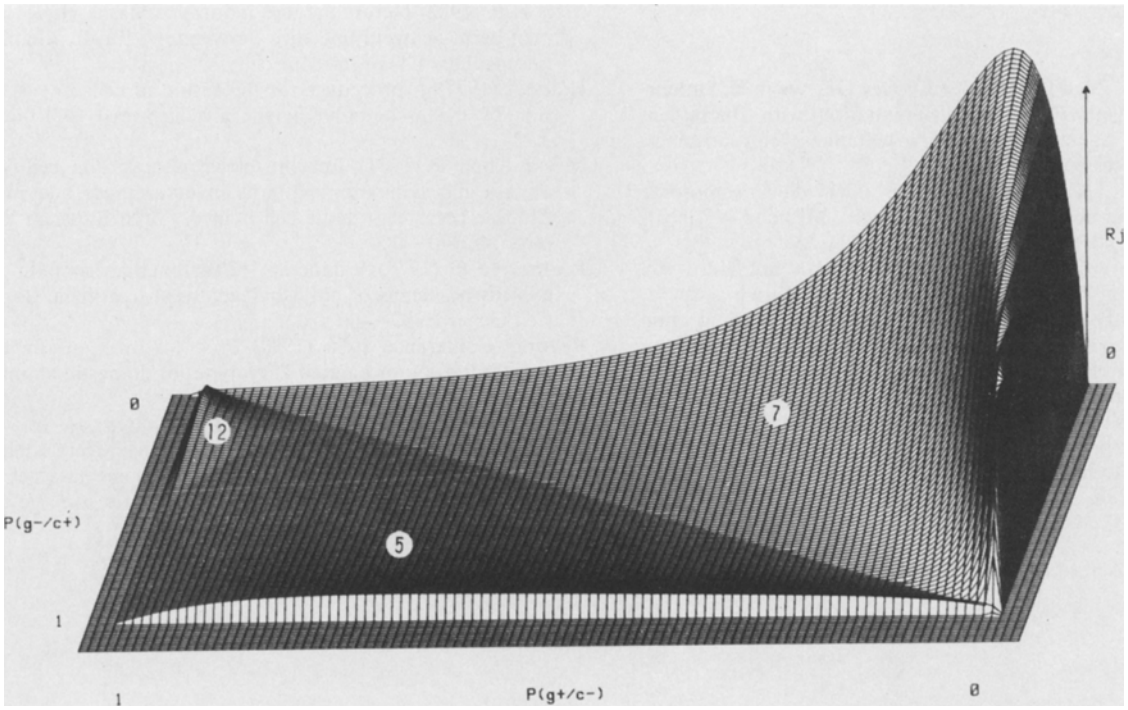

Fig. 1. R_j plotted against $P(g+|c-)$ and $P(g-|c+)$, the probabilities of discordant observations. In the range where both $P(g+|c-)$ and $P(g-|c+)$ are smaller than 0.5, R_7 is always greater than any other R_j

Table 6. The values belonging to the local maxima for R_j and the corresponding values as calculated in our example

	The three local maxima			Our example
	1	2	3	
$P(g+\|c+)$	0.98	0.02	0.91	0.81
$P(g-\|c+)$	0.02	0.98	0.09	0.19
$P(g+\|c-)$	0.09	0.69	0.99	0.28
$P(g-\|c-)$	0.91	0.31	0.01	0.72
$1.R_j$	109.78	8.46	6.11	27.22
assignment to	7	5 or 11	12	7
$2.R_j$	0.91[a]		1.12[b]	3.18[a]
$1.R_j/2.R_j$	120		5	8

[a] Corresponds to chromosome no. 8
[b] Corresponds to chromosome nos. 5 or 11

contours. In Fig. 1 the highest R_j was plotted against the probabilities of the discordant combined observations $P(g+|c-)$ and $P(g-|c+)$ ranging from 0.01 to 0.99.

Chromosome no. 7 always supersedes the other chromosomes in the range where

$$P(g+|c-) + P(g-|c+) < 1 .$$

In the range where

$$P(g+|c-) + P(g-|c+) > 1$$

we find an area where chromosome no. 12 and an area where chromosome no. 5 and no. 11 supersede the other chromosomes. As for both, chromosome no. 5 and no. 11, the combined observations are the same, R_5 and R_{11} are identical. Altogether three distinct areas with a local maximum can be seen in Fig. 1. The set of values that belong to these maxima are listed in Table 6 together with the likelihood ratio of the second best placed chromosome. For comparison, the corresponding values, as calculated in our example, are added.

Reasonable values for both, $P(g+|c-)$ and $P(g-|c+)$, have to be smaller than 0.5. In this area, based on our data, we can assign the gene for MPI only to chromosome no. 7. This assignment is in agreement with the findings of Förster and Hecht (1984) and Christensen and coworkers (1985).

One should keep in mind that this method is designed to map genes that have only one locus. For genes that have more loci or gene families, the hypothesis of an assignment would have to be changed appropriately.

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