Multivariate Analysis of Chromosomal Imbalances in Breast Cancer Delineates Cytogenetic Pathways and Reveals Complex Relationships among Imbalances

Mattias Höglund, David Gisselsson, Gunnar B. Hansen, Torbjörn Säll, and Felix Mitelman

Department of Clinical Genetics, University Hospital, SE-221 85 Lund [M. H., D. G., G. B. H., F. M.], and Department of Genetics, Lund University, SE-223 62 Lund [T. S.], Sweden

INTRODUCTION

Rapid progress in our understanding of the biology of human neoplasms has been achieved during the past decades. It is now well established that cancer arises through a multistep accumulation of somatic mutations (1, 2), and that this process may proceed over many years. In many tumors, genetic changes are microscopically visible as nonrandom and often disease-specific chromosomal abnormalities (3). Chromosome aberrations have been classified as primary and secondary (4). Primary changes are believed to initiate the cellular transformation, whereas secondary changes are important for tumor progression. Unlike hematological neoplasms, in which specific translocations are observed frequently, solid tumors often show a complex set of recurrent chromosomal aberrations resulting in highly complex karyotypes. The high degree of karyotypic complexity makes it very difficult to discern the primary anomalies. To overcome some of these difficulties, we have developed adapted several statistical methods that allow identification and interpretation of karyotypic pathways. These methods were applied on 538 breast cancer karyotypes. The distribution of the number of imbalances/tumor showed a monomodal appearance, indicating that one single mode of karyotypic evolution is operating in this tumor type. We show that there exists a temporal order with respect to the appearance of chromosomal imbalances. The imbalances +1pq, 1q-, 3p-, and +7 appear earlier than expected from random events, and two cytogenetic pathways, one initiated by +1q and followed by 11q- and +22, the other initiated by either 3p- or 1q- and followed by 1p-, 3q-, and 6q-, can be discerned. We also show that +7 and +8q behave independently of the other imbalances and cannot, by simple means, be incorporated in the identified pathway scheme. Although the cytogenetic pathways are well separated at earlier stages, they later converge and include a common set of late imbalances.

ABSTRACT

More than 550 breast adenocarcinomas with clonal chromosomal abnormalities have been reported. Although the aberration pattern is clearly nonrandom, no specific primary or secondary karyotypic abnormality has been identified, and furthermore the chronological order in which the aberrations appear during disease progression is not well known. The high degree of karyotypic complexity in epithelial tumors such as breast cancer is one reason why our understanding of the sequential order of cytogenetic evolution is unclear. To overcome some of these difficulties, we have used several statistical methods that allow identification and interpretation of karyotypic pathways. These methods were applied on 538 breast cancer karyotypes. The distribution of the number of imbalances/tumor showed a monomodal appearance, indicating that one single mode of karyotypic evolution is operating in this tumor type. We show that there exists a temporal order with respect to the appearance of chromosomal imbalances. The imbalances +1pq, 1q-, 3p-, and +7 appear earlier than expected from random events, and two cytogenetic pathways, one initiated by +1q and followed by 11q- and +22, the other initiated by either 3p- or 1q- and followed by 1p-, 3q-, and 6q-, can be discerned. We also show that +7 and +8q behave independently of the other imbalances and cannot, by simple means, be incorporated in the identified pathway scheme. Although the cytogenetic pathways are well separated at earlier stages, they later converge and include a common set of late imbalances.

MATERIALS AND METHODS

Selection of Data. All adenocarcinomas of the breast with abnormal karyotypes were retrieved from the Mitelman Database of Chromosome Aberrations in Cancer. A total of 569 karyotypes were ascertained and used to construct an imbalance map. On the basis of this map, 34 segments affected by imbalances in >10% of the cases were identified, including deletions of 10 single terminal bands (Table 1). Each karyotype was then assessed for the presence or absence of the selected imbalances. The NIPT was then calculated, and the 538 tumors with at least one imbalance were selected. Because the identification of single band deletions is unclear, these were excluded when calculating NIPT. Tumor grade was recorded when reported. This information was present for 204 tumors; 27 were grade I, 98 grade II, and 79 grade III.

Temporal Analysis. We defined early and late imbalances as those predominantly present in tumors with few and many imbalances, respectively. To obtain a value for lateness, all tumors with a given imbalance were selected, and the distributions of NIPT were plotted. The modes of these distributions were used as an estimate of lateness and referred to as the TO (6). TO is thus a function of karyotypic complexity. To obtain a better estimate of the TO, the selected distributions were resampled with replacement (bootstrapped) 1000 times, and the TO was scored after each resampling (9). The mean of the bootstrapped TO values was then used as the TO for the given imbalance. The bootstrapped 2.5, 25, 75, and 97.5 percentiles were also calculated. For the bootstrap estimates, resampling software from Resampling Stats (Arlington, VA) was used. To evaluate whether an imbalance occurred earlier or later than expected from random events, a simulation procedure was used in which the distribution of NIPT for the whole tumor population as well as the frequencies of the imbalances was identical to the observed. The simulation was performed as described earlier (5). An imbalance was considered to occur significantly earlier (observed TO < simulated TO) or significantly later (observed TO > simulated TO) than expected when >95% of the simulated TO values deviated from the observed values.

Principal Component Analysis. To search for possible patterns of correlations between the imbalances, PCA was performed using the Statistica software package (Statsoft, Tulsa, OK). PCA is a standard multivariate method used frequently to search for underlying structures in data sets (10). In short, principal components are linear combinations of the original variables, orthogonal, and ordered with respect to their variance so that the first principal component has the largest variance. To analyze imbalances, these were used as variables and the individual tumors as the observations; this will group imbalances seen frequently in the same tumors. To determine the appropriate number of factors to extract, the scree test was used (11). The factor models arrived at were evaluated at three levels, total variance accounted for, communalities, and by the residual correlation matrix. The fraction of the original variance accounted for by the specific factor model is given by the cumulative percentage of the explained variance for each component in the factor model. The communality of a given variable (imbalance) is an estimate of how well

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1 Supported by the Swedish Cancer Society, the Crafoord Foundations, and the Nilsson Family Foundation.
2 To whom requests for reprints should be addressed, at Department of Clinical Genetics, University Hospital, SE-221 85 Lund, Sweden. Phone: 46-46-131061; E-mail: mattias.hoglund@klingen.lu.se.
3 Internet address: http://cgap.nci.nih.gov/Chromosomes/Mitelman.

Received 1/10/02; accepted 2/27/02.
the factor model predicts the behavior of the given variable. The communality ranges from 0 to 1, where a value of 1 indicates full explanation of the variance. The residual matrix is obtained by subtracting the original correlation matrix with the one produced by the given factor model. This analysis indicates how well the factor model accounts for relationships between specific pairs of imbalances.

To test the robustness of the correlation-based PCA, the relationships between the imbalances were also investigated by using χ² statistics. The χ² value for independence was calculated for each combination, and weighted distances were computed using the Correspondence Analysis Module of the Statistica software. Factors (dimensions) were then extracted by means of the factor model. To establish the relative order of appearance of the imbalances, tumors containing either of the early imbalances +1pq, 1q-, 3p-, and +7 were selected for analysis. This amounted to 348 cases. In Fig. 3, the means of the bootstrapped TO values using this set of tumors are plotted together with the 2.5, 25, 75, and 97.5 percentiles. Early imbalances (TO = 1–2) were +1pq, 1q-, 3p-, +7, and −16q. These are followed by the moderately early imbalances (TO = 4.5–6) 1p-, 3q-, and +8q. Intermediate imbalances (TO = 8.5–10) were 6q-, 11q-, and −22, followed by the late imbalances (TO = 10.5–12) 10p-, −13, −17, 18q, −X and the very late imbalances (TO = 12–14) 4p-, 4q-, 9p-, −15q, 14p-, and 21p-. The simulation study revealed the imbalances +1pq, 1q-, 3p-, and +7 to occur earlier than expected from random events.

Identification of Cytogenetic Pathways. A correlation matrix for the imbalances was produced and analyzed by PCA. The loadings on the first component for each imbalance correlated well with the TO values obtained from the temporal analysis (r = 0.88), and thus the first principal component represents a time axis. The two-factor PCA solution (Fig. 4a) explained 32% of the variability and delineated two major cytogenetic pathways. One originated with +1pq and chromosome 7 and loss of 1q and 3p and was identified as early imbalances because their distributions showed modal values of 1. To establish the relative order of appearance of the imbalances, tumors containing either of the early imbalances +1pq, 1q-, 3p-, and +7 were selected for analysis. This amounted to 348 cases. In Fig. 3, the means of the bootstrapped TO values using this set of tumors are plotted together with the 2.5, 25, 75, and 97.5 percentiles. Early imbalances (TO = 1–2) were +1pq, 1q-, 3p-, +7, and −16q. These are followed by the moderately early imbalances (TO = 4.5–6) 1p-, 3q-, and +8q. Intermediate imbalances (TO = 8.5–10) were 6q-, 11q-, and −22, followed by the late imbalances (TO = 10.5–12) 10p-, −13, −17, 18q, −X and the very late imbalances (TO = 12–14) 4p-, 4q-, 9p-, −15q, 14p-, and 21p-. The simulation study revealed the imbalances +1pq, 1q-, 3p-, and +7 to occur earlier than expected from random events.

RESULTS

Basic Statistics. The frequencies of the imbalances are given in Table 1. The most frequent were +1pq, 1p-, 3p-, 6q-, and −16q. Deletions of the most terminal bands were seen at 2q, 5p, 7q, 8q, 10q, 12q, 15q, 16q, 19p, and 19q with frequencies spanning from 12 to 15%. The average number of such terminal deletions/tumor increased linearly from 0.2 to 4.4, with NIPT = 1–13 (r = 0.96). The imbalances 4q-, 6q-, and 8p- were negatively correlated with grade I (P = 0.042, 0.020, and 0.047, respectively), whereas +7 was posi-
Correlations between Imbalances. Because the obtained PCA model represents a compromise of all correlations and may lack important information on specific imbalances, the part of the correlation matrix that included the imbalances $+1pq$, $1q-$, $3p-$, $+7$, and $+8q$ were analyzed in more detail (Table 2). Gain of $1pq$ and $3p-$ showed significant ($P < 0.01$) correlations with most of the other imbalances, whereas $+8q$ and $1q-$ only showed association with a limited number of imbalances, and $+7$ behaved in an intermediate fashion (Table 2). All of the remaining, and later, imbalances showed significant multiple correlations with coefficients ranging from 0.12 to 0.57 (data not shown). Several of the imbalances that showed correlation with $+1pq$ also show significant correlation with $3p-$, i.e., $8p-$, $10p-$, $11p-$, $-13$, $14p-$, $15p-$, and $18q$. The imbalances $+7$, $+8q$, $11q-$, $16q-$, $21p-$, and $-22$ were, however, more associated with $+1pq$, whereas $1p-$, $3q-$, $4p-$, $4q-$, and $6q-$ were more associated with $3p-$.

Imbalances occurring in both pathways were predominantly late, as determined by the temporal analysis. Gain of $8q$ showed significant ($P < 0.01$) correlation with $+1pq$ and $+7$ but was independent of the other imbalances. Similarly, $1q-$ showed, apart from negative correlation with $+1pq$, significant correlation with $1p-$ and $3q-$ but was otherwise independent of the other imbalances. Trisomy 7 showed associations with fewer imbalances than did $+1pq$ and $3p-$, and these were also of mixed character. Three were in common with the $+1pq$ pathway ($+8q$, $21p-$, and $-22$), two with the $3p-$ pathway ($4p-$ and $4q-$), and two were in common with both pathways ($10p-$ and $18q$). No significant correlation specific for $+7$ was seen. As a measure for how autonomous $+7$ was relative to the $+1pq$, $1q-$, and $3p-$ imbalances, the proportion of $+7$ cases not showing concomitant presence of $+1pq$, $1q-$, or $3p-$ was compared with the equivalent proportions for $+1pq$, $1q-$, and $3p-$, respectively. The proportion for $+7$ (14 of 102) was significantly smaller ($P < 0.012$) than for $+1pq$ (68 of 153), $1q-$ (47 of 86), and $3p-$ (54 of 139), respectively. Cases with $+1pq$ and $+7$ showed a significantly higher proportion of grade III tumors ($P = 0.02$) than did $+1pq$ cases without $+7$. A similar pattern, albeit at borderline significance ($P = 0.06$), was seen for cases with either $1q-$ or $3p$ with or without $+7$.

Analysis of the Tumor Population. Because two major pathways were identified characterized by $+1pq$ and $3p-$, the tumors were divided into $+1pq$-positive and $+1pq$-negative tumors in the subsequent analyses. The PCA of the $+1pq$ tumors revealed four well-separated clusters determined by the presence or absence of $1p-$ and $16q-$ (Fig. 5a). The tumors could thus be classified as $1p-$ positive but $-16q$ negative, $1p-$ and $-16q$ positive, $16q-$ positive but $1p-$ negative, and tumors negative for both $1p-$ and $-16q$. These groups had NIP averages of 5.5, 8.7, 4.5, and 5.9, respectively. The PCA of the $+1pq$-negative tumors also revealed four clusters, determined by the presence or absence of $1q-$ and $3p-$, respectively (Fig. 5b). The $1q-$ group of tumors had an average NIP of 3.5, the $3p-$ group 5.4, the $1q-$ and $3p-$ group 9.3, and the group of tumors showing absence of both imbalances an average NIP of 2.7. The latter group, which also showed absence of $+1pq$ because of the selection criteria, constituted 41% (223 cases) of all tumors. The majority of these (>95%) had fewer than seven imbalances. The proportion of grade III/grade II tumors in this group (43 of 43) was significantly higher than the...
equivalent proportion for cases having one of the early imbalances +1pq, −1q and 3p−, and fewer than seven imbalances, 13 of 30 (P = 0.033).

DISCUSSION

The present study indicates that the acquisition of chromosomal changes in breast adenocarcinomas is dominated by one mode of chromosomal evolution. The monotonous nature of the distribution indicates that the investigated material is homogeneous. No tumor subtypes with elevated chromosomal instability were seen. We have previously (5, 6, 13) interpreted this type of distribution as being close to geometrical. Such distributions may reflect that imbalances occur at low frequencies and that their occurrence is independent of the presence of previous imbalances. This is in accordance with the prevailing understanding of how tumors develop, by the successive acquisition of random changes that may or may not have a selective advantage (14).

Deletions of single terminal bands were seen at unexpectedly high frequencies. Furthermore, they were nonrandom with respect to the chromosome arms involved. The deletions were present in both low- and high-complexity karyotypes, and the frequency increased linearly with NIPT. This suggests that the mode of acquisition of these imbalances is the same as for the more extensive losses. The correlation of terminal deletions to the overall cytogenetic complexity could indicate that telomeric crisis (15) plays a role in the cytogenetic evolution of breast cancer. Recent investigations have shown that shortening of telomeric TTAGGG sequences can cause widespread chromosomal instability in neoplastic cells (15). It is thus possible that at least some of the chromosomal imbalances result from telomeric dysfunction, leading to chromosomal missegregation and breakage during mitosis (16). On the other hand, the high frequency of telomeric deletions could merely be a side effect of cellular proliferation beyond the normal replicative life span of breast epithelium, with little if any pathogenetic significance. However, only a limited number of chromosome arms showed high frequencies of terminal rearrangements. Because short telomeres could make the arms more liable to deletion of terminal bands, a comparison was made with the reported

Table 2. Correlations of +1pq, +7, +8q, 1q−, +3p− with other imbalances

<table>
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<th>+8q</th>
<th>1q−</th>
<th>3p−</th>
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<tr>
<td>8p−</td>
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<td>0.10</td>
<td>0.08</td>
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<td>0.04</td>
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* Significant correlations (P < 0.01) in bold.
length of telomeres in normal chromosomes (17), but no association was seen. Whether this preference of certain chromosome arms is caused by a selective advantage from deletion of specific genes in these regions or whether the terminal chromosome material is dispensable and may be lost with no affect on cellular fitness remains an open question.

To evaluate the temporal order of the imbalances, we used the karyotypic complexity at which a given imbalance was most frequent as a measure for lateness (6). We have shown previously that this variable correlates well with tumor progression (13), i.e., imbalances predominantly seen in high-grade tumors have large TO values. To acquire more reliable estimates of the TO, bootstrapped estimates of both TO values and confidence intervals for the mean TO were calculated for each imbalance. The obtained results showed a clear order of appearance. Four major early imbalances (TO = 1), +1pq, 3p-, 1q-, and +7, were identified; moderately early imbalances were 16q-, 1p-, 3q-, and +8q, whereas the remaining may be classified as late, among which 9p-, 21p-, and 4q- were the latest. The simulation study showed that TO values for +1pq, 1q-, 3p-, and +7 were significantly smaller in the observed data as compared with the expected. This suggests that +1pq, 1q-, 3p-, and +7 have a larger selective value at earlier stages than other imbalances, underscoring the presence of a certain temporal specificity among the imbalances. However, because the bootstrapped TO values show substantial overlap, no strict order of imbalances may be arrived at; the data rather point to a preferred order of events from which deviations occur frequently in individual cases.

The temporal analysis and the three-factor PCA solution emphasized the importance of +1pq, 1q-, 3p-, and +7 in breast cancer development; all were classified as early events and were well separated by the PCA. Of these, +7 was atypical. The proportion of +7 cases that did not also show the presence of +1pq, 1q-, or 3p- was significantly smaller than the equivalent proportions for +1pq, 1q-, and 3p-. This makes +7 more of a secondary imbalance than the temporal analysis would suggest. Although gain of chromosome 7 was correlated with at least eight other imbalances, it also demonstrated a substantial independent behavior, seen by the sharp increase in communality when including a forth dimension, an increase that was only paralleled by +8q. Thus, +7 behaves as a promiscuous secondary imbalance. Furthermore, +7 was associated with grade III tumors, irrespective of the preceding imbalance. This feature of +7, to be associated with high-grade tumors, was also seen in a recent investigation of urinary bladder cancer (13). However, in this tumor type +7 seems to represent a separate cytogenetic pathway.

Gain of 8q was the most atypical of the investigated imbalances. The three first components could not account for the behavior of this imbalance. Not until the fourth principal component was added could some of the variance of the +8q be captured. All other imbalances were sufficiently described by the three-factor model, and adding a fourth factor provided no significant increase in communalities, with the possible exception of +7. Gain of 8q was, however, significantly correlated with +1pq and +7. A second feature of +8q was the dependence on preceding imbalances, seen by the very low frequency of +8q tumors with 1pq (Fig. 2c). Thus, the data indicate that +8q shows a great deal of independent behavior but may only have a selective value at very specific stages of tumor progression.

The PCA clearly delineated two major cytogenetic pathways, one characterized by +1pq and one by 3p- and possibly 1q-. This was particularly well seen in the two-factor PCA solution, where these imbalances occupied two opposite ends of the second principal component. Similar pathways were seen irrespective of the matrices used, either being based on product moment correlation or on $\chi^2$ statistics. Gain of 1pq showed positive correlation with 13 of the imbalances, of which +7, +8q, −11q, −16q, −21p, and −22 were specific for +1pq, and the remaining, mostly late, imbalances were shared with 3p-. The PCA of the 1pq-containing tumors resulted in four clusters, each determined by the presence or absence of 1p- or −16q. This could indicate four cytogenetic subtypes. However, these imbalances are mechanistically related to +1pq through i(1q) or der(1;16), and hence the clusters may rather reflect mutational mechanisms than pathways promoted by different types of selection. The fact that 1p- was not significantly correlated with +1pq but with 3p- underscores the mechanistic aspect of the +1pq subgroups.

The most frequent imbalances in the 3p- pathway were 1p-, 3q-, 4p-, 6q-, −13, 15p-, and −17. Imbalances that were significantly more associated with 3p- than with +1pq were 1p-, 3q-, 4p-, 4q-, and 6q-. Loss of 1q was positioned close to 3p- by the PCA, and consequently, the 1q- and 3p- pathways demonstrated several similarities; both showed lower frequencies of +7, +8q, and 16q- than did tumors with +1pq. The major importance of 3p- and 1q- in the tumors without 1pq was also indicated by the fact that the PCA identified 1q- and 3p- as classifying imbalances.

The analysis of the tumor population revealed a group of tumors that lacked the early imbalances +1pq, 1q-, and 3p-. This group had a lower average NIPT but had, despite this, progressed further because...
they showed a significantly higher proportion of high-grade tumors. Because the temporal analysis displayed a highly ordered appearance of genetic events, directed toward the more advanced stages, this suggests that these tumors may have cryptic changes equivalent to the early cytogenetic events, therefore showing a lower NPI. Thus, given a multistep model for tumorigenesis, the initiating events may not always be detected by cytogenetic banding methods. Conversely, high-grade tumors with few and early imbalances may be expected to harbor cryptic changes equivalent to late imbalances.

In conclusion, the accumulated cytogenetic data on breast cancer reveal a highly complex pattern of chromosomal aberrations. This not withstanding, we were able to show that imbalances appear in a temporally ordered fashion with distinctively early and late imbalances. Furthermore, two major cytogenetic pathways were identified, temporally ordered with distinctively early and late imbalances. We were able to show that imbalances appear in a temporally ordered fashion with distinctively early and late imbalances. Consequently, high-grade tumors with few and early imbalances may be expected to harbor cryptic changes equivalent to late imbalances.

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