Chromosomal Aberrations in Squamous Cell Carcinoma and Solar Keratoses Revealed by Comparative Genomic Hybridization

Kevin J. Ashton, PhD; Stephen R. Weinstein, MD; David J. Maguire, PhD; Lyn R. Griffiths, PhD

Objective: To identify chromosomal copy numbers of frequent genetic aberrations within squamous cell carcinomas (SCCs) and solar keratoses (SKs), and provide further evidence to support or challenge current dogma concerning the relationship between these lesions.

Design: Retrospective analysis of genetic aberrations in DNA from SK and SCC biopsy specimens by comparative genomic hybridization.

Setting: University-based research laboratory in Queensland, Australia.

Patients: Twenty-two biopsy specimens from patients with diagnosed SKs (n=7), cutaneous SCCs (n=10), or adjoining lesions (n=5).

Main Outcome Measure: Identification of frequent genetic aberrations both specific to SK and SCC and shared by these lesions to investigate their clonal relationship.

Results: Shared genomic imbalances were identified in SK and SCC. Frequent gains were located at chromosome arms 3q, 17q, 4p, 14q, Xq, 5p, 9q, 8q, 17p, and 20q, whereas shared regional losses were observed at 9p, 3p, 13q, 17p, 11p, 8q, and 18p. Significant loss of 18q was observed only in SCC lesions.

Conclusions: Our results demonstrate that numerous chromosomal aberrations are shared by the 2 lesions, suggesting a clonal relationship between SK and SCC. Additionally, the genomic loss of 18q may be a significant event in SK progression to SCC. Finally, the type and frequency of aberrations suggests a common mode of tumorigenesis in SCC-derived tumors.

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It is widely accepted that solar keratoses (SKs) are premalignant precursors to cutaneous squamous cell carcinoma (SCC). However, estimates relating to the development of SK to SCC have been extremely variable. Clinical and histological studies have associated between 10% and 97% of SCCs with a contiguous SK, although these data alone do not establish a clonal relationship. As the clinical and histological presentations of SK and SCC are remarkably similar, with no sharp line of demarcation between the two, it has been proposed that they may be fundamentally one and the same.

Although SK is clinically benign, several genetic studies have shown nonrandom genetic abnormalities in SK similar in type and frequency to those found in SCC. Mutational analysis of the tumor suppressor gene TP53 identified a high frequency of UV radiation–induced mutations in both SK (30%-53%) and SCC (58%-69%). Loss of heterozygosity (LOH) at 17p suggests a further role of TP53 in SK and SCC development. Other chromosomal loci (3p, 9p, 9q, 13q, and 17q) of genomic loss are observed in similar frequencies in SCC and SK. In SCC, however, further nonrandom numerical chromosomal changes have been cytogenetically detected; in decreasing order of frequency, the involved chromosomes are 1, 11, 8, 9, 5, 3, and 7. Frequent isochromosomes of 1q, 8q, 5p, 1p, 9p, and 9q have also been detected. Interphase FISH analysis of SCC has detected a frequent deletion of 3p21 in 67% of cases and a surprising gain of 17p13 (TP53) in 27% of cases.

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Comparative genomic hybridization (CGH) is a powerful molecular cytogenetic tool for the genome-wide detection of gross DNA copy number aberrations (CNAs). With CGH, large contiguous regions of aberration can be detected within a cell population, as opposed to a more local investigation using arm-specific probes. The CGH technique reveals numerical or
unbalanced aberrations but cannot be used to detect changes that do not affect DNA sequence copy numbers—for instance, balanced translocations and inversions. Differentially labeled test and reference DNA are hybridized simultaneously to normal metaphase chromosomes generating an overview of DNA sequence imbalances, and this overcomes the often difficult interpretation of complex karyotypes frequently associated with solid tumor. The general pattern and degree of CNAs often reflect different tumor types and stages of progression.

Tumor DNA extracted from tissue may contain a significant proportion of contaminating nonneoplastic cells, which diminishes the ability to observe CNAs by CGH. The purity of tumor DNA can be increased by microdissecting histologically representative regions of the tumor, but DNA yields from such small tissue samples are often insufficient for CGH analysis. Universal amplification of DNA is therefore necessary to increase the yield to levels suitable for CGH. This can be achieved using a procedure known as degenerate oligonucleotide–primed polymerase chain reaction (DOP-PCR), which universally and linearly amplifies minute quantities of DNA. Many studies have demonstrated that universally amplified DNA is highly representative of the original genomic template. Tumor DNA isolated by tissue microdissection with subsequent DOP-PCR amplification can thus provide the macroscopic amounts of DNA required for CGH analysis. The integration of these 3 techniques can enable the rapid identification of CNAs across the entire genome in archival tissue samples. We have previously used this approach to investigate CNAs present in basal cell carcinoma.

Comparative genomic hybridization studies on keratinocyte–tumor–derived cell lines have demonstrated copy number gains at 3q, 5p, 7p, 8q, 9q, 11q, and 17q, and losses at 3p, 4p, 5q, 8p, 9p, 10p, and 17p. These findings are similar to findings for other SCC-derived tumors including head and neck, cervical, lung, and bladder carcinomas. At present, classic and molecular cytogenetic data concerning SK and SCC tissue obtained from direct biopsy are lacking. This study is aimed at characterizing the chromosomal abnormalities associated with these nonmelanoma skin cancer varieties.

### METHODS

#### TISSUE SAMPLES

Formalin-fixed, paraffin-embedded tissue sections from SCCs (n=9) and SKs (n=7) were obtained from the Department of Pathology of Gold Coast Hospital. In addition, separate tissue samples from 3 SCCs arising from an adjacent SK lesion were also obtained. All lesions were histologically examined and classified as characteristic sun-induced tumors. Five tissue sections of healthy skin (3 from the forearm and 2 from the back) displaying no histological evidence of sun damage were also obtained for use in hybridization efficiency and dynamic range determination.

#### MICRODISSECTION

Six consecutive 10-µm sections were cut from each paraffin-embedded tissue block. A hematoxylin–eosin–stained section was used to identify histologically representative regions of the tumor. Adjacent sections were stained with methyl green using standard techniques and manually microdissected. Tumor tissue was removed and incubated in 15 µL of digestion buffer (10mM Tris-hydrochloric acid [pH 8.3], 50mM potassium chloride, 1.5mM magnesium chloride, 0.4 mg/mL of proteinase K, and 0.5% polysorbate 20) at 55°C overnight. Digestion was then inhibited by heat inactivation.

#### DOP-PCR AND DNA LABELING

Experimental procedures were performed on 10-µm sections, essentially as we have previously described. Additionally, because of the small size of microdissected tissue, 2 to 3 DOP-PCR replicates of each sample were often pooled before labeling. This increased the quantity and quality of higher molecular weight DNA required for good labeling and subsequent hybridization. After pooling and concentration, tumor DNA yielding some fragments of 600 base pairs or greater was deemed suitable for fluorescent nucleotide labeling via nick translation.

#### CGH AND DIGITAL IMAGE ANALYSIS

Comparative genomic hybridization and subsequent analysis was performed essentially as described. Only metaphases showing a uniform hybridization without granularity were used. Data from 5 to 10 metaphases were used to generate a mean ratio profile for each chromosome. Gains and losses were scored if the means and standard deviations were above 1.15 or below 0.85, respectively. In addition, reciprocal labeling of tumor and normal DNA was applied to a subset of tumors to confirm the presence of CNAs. Analysis was not applied to regions prone to artificial hybridization (1pter, 16p, 19, 22, and Y). In addition, heterochromatin, acrocentric p arms, centromeres, and telomeres were excluded from analysis because of their naturally high polymorphic DNA content.

#### CONTROLS AND THRESHOLD DETERMINATION

Each hybridization batch included a previously characterized cell line control (MPE600 vs normal female DNA) and a sex-mismatch control (normal male vs normal female DNA) for determination of dynamic range. These controls verified hybridization sensitivity and detection specificity. Results were used only if all known CNAs in the cell line were detected and the dynamic range in the sex-mismatch control did not exceed a ratio of 0.65 at the X chromosome. Because of the heterogeneity of the tissue samples and the varying degrees of normal cell contamination, it was deemed necessary to set threshold limits for detection of gains and losses to 1.15 and 0.85, respectively. These cutoff values were determined by a series of sex-mismatch controls obtained from normal skin. In nonproblematic chromosomal regions, no observable deviations were apparent at the threshold limits of 1.1 and 0.9.

#### STATISTICAL ANALYSIS

Differences in the prevalence of the most frequent CNAs were analyzed using the Fisher exact test with 2-tailed P values (P≤.05 was considered significant). Percentage concordance was calculated for matched SK and SCC lesions as described. Finally, clustering analysis was used to compare patterns of aberrations in SK with those of SCC and to investigate the relationship between SCC and a contiguous SK. The hierarchical clustering algorithm was applied, and we used the Pearson correlation coefficient as the measure of similarity in conjunction with complete linkage clustering. Dendrograms were plotted using the J-Express clustering package (Molmine Bioinformatics Software Solutions, Bergen, Norway).
RESULTS

HISTOPATHOLOGICAL ANALYSIS OF SK AND SCC LESIONS

Histopathological diagnoses and selected clinical data for the biopsy samples of the 12 SKs and 15 SCCs characterized by CGH are presented in Table 1. In 5 subjects, an SCC and an associated SK at the same site were available for CGH analysis.

OVERVIEW OF ABERRATIONS DETECTED IN SK LESIONS

In SK dysplasia the average number of aberrations was 6.3 (95% confidence interval [CI], 5.5-7.1; range, 0-10). On average, 2.8 gains (95% CI, 1.9-3.7; range, 0-5) and 3.5 losses (95% CI, 2.7-4.4; range, 0-6) per dysplasia were observed. Only 1 SK lesion had no detectable CNAs. Gains were frequently observed at chromosomal regions 3q, 4p, and 17q (33% of the cases for each region), 5p, 9q, and 17p (25%). The most frequent losses in SKs were observed at both 9p and 13q in 7 tumors (58%). Other losses were detected at 3p, 4q, 11p, and 17p in 25% of cases each (Figure 1). A significant association (P = .045) was demonstrated between the occurrences of a 4q loss and a 5p gain, but no other significant correlations could be made.

OVERVIEW OF ABERRATIONS DETECTED IN SCC

Cutaneous SCCs displayed an average of 8.1 aberrations (95% CI, 6.8-9.4; range, 4-13), with averages of 4.1 gains (95% CI, 3.3-4.8; range, 1-7) and 4.1 losses (95% CI, 3.1-5.0, range, 1-7) per dysplasia. A high frequency of gains was observed at chromosomal regions 3q (47%) and 17q (40%). Other prevalent gains were demonstrated at 14q, Xq (33%), 4q, 8q (27%), 1q, 5p, 7q, 9q, 10q, and 20q (20%). The most frequent loss of genetic material was observed at 9p in 10 tumors (67%). Less prevalent losses were demonstrated at 3p (53%), 18q (47%), 17p (33%), 4q (27%), 5p, 8p, 11p, 13q, and 18p (20%). Significant correlation between 3p loss and 3q gain (P = .04), 1q gain and 8p loss (P = .002), 1q gain and 18p loss (P = .03), and 8p and 18p loss (P = .04) was observed. The results of CGH for all CNAs detected in SK and SCC lesions are summarized in Figure 1.

GENERAL COMPARISON BETWEEN SK AND SCC LESIONS

The total number of numerical chromosomal aberrations detected in SCC (mean, 8.1; 95% CI, 2.7-4.4) was significantly higher (P = .03) than those observed in SK (mean, 6.3; 95% CI, 5.5-7.1). Comparisons of the frequency of CNAs in both SK and SCC are summarized in Figure 1. Figure 2 demonstrates the total number of CNAs in both SK and SCC, and the increase in genetic imbalances from SK to SCC. In addition, trends concerning the total number of CNAs and the prevalence of 3p loss, 3q gain, and 18q loss can clearly be seen in Figure 2. Comparison of SK and SCC revealed a similar pattern of chromosomal imbalances, except at 18q. Loss of 18q was significantly more frequent (P = .04) in SCC than in SK.

Hierarchical clustering of SK and SCC based on their chromosomal copy number imbalances grouped the lesions into 4 distinct clusters (A-D) in Figure 3. We observe that SK and SCC cases are dispersed almost evenly throughout each group in the dendrogram. Matched pairs of SK and SCC samples for cases 8, 10, 11, and 12 also

Table 1. Histopathological and Clinical Data of Patients With SK and SCC

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age, y</th>
<th>Location</th>
<th>Clinical Diagnosis</th>
<th>Description of Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>SK01</td>
<td>M</td>
<td>76</td>
<td>Scalp</td>
<td>SK</td>
<td>Hypertrophic</td>
</tr>
<tr>
<td>SK02</td>
<td>M</td>
<td>42</td>
<td>Nose</td>
<td>SK</td>
<td>Extensive solar damage to skin</td>
</tr>
<tr>
<td>SK03</td>
<td>F</td>
<td>79</td>
<td>Unknown</td>
<td>SK</td>
<td>Bowenoid</td>
</tr>
<tr>
<td>SK04</td>
<td>F</td>
<td>81</td>
<td>Forearm</td>
<td>SK</td>
<td>Hyperkeratotic</td>
</tr>
<tr>
<td>SK05</td>
<td>M</td>
<td>43</td>
<td>Hand</td>
<td>SK</td>
<td>Hyperkeratotic</td>
</tr>
<tr>
<td>SK06</td>
<td>M</td>
<td>63</td>
<td>Lip</td>
<td>SK</td>
<td>Hyperkeratotic</td>
</tr>
<tr>
<td>SK07</td>
<td>M</td>
<td>80</td>
<td>Leg</td>
<td>SK</td>
<td>WD with SK in middle, extends to mid-dermis</td>
</tr>
<tr>
<td>SK08/SCC08m</td>
<td>M</td>
<td>64</td>
<td>Neck</td>
<td>SK/SCC</td>
<td>WD with hyperkeratotic SK, extends to deep dermis</td>
</tr>
<tr>
<td>SK09/SCC09m</td>
<td>M</td>
<td>81</td>
<td>Scalp</td>
<td>SK/SCC</td>
<td>WD, extensive SK</td>
</tr>
<tr>
<td>SK10/SCC10m</td>
<td>M</td>
<td>68</td>
<td>Scalp</td>
<td>SK/SCC</td>
<td>WD, SCC arising in SK</td>
</tr>
<tr>
<td>SK11/SCC11m</td>
<td>M</td>
<td>69</td>
<td>Calf</td>
<td>SK/SCC</td>
<td>WD, SCC arising in Bowenoid SK</td>
</tr>
<tr>
<td>SK12/SCC12m</td>
<td>M</td>
<td>75</td>
<td>Forehead</td>
<td>SK/SCC</td>
<td>WD, extends to subcutaneous fat</td>
</tr>
<tr>
<td>SCC13</td>
<td>M</td>
<td>74</td>
<td>Forehead</td>
<td>SCC</td>
<td>WD</td>
</tr>
<tr>
<td>SCC14</td>
<td>M</td>
<td>62</td>
<td>Ear</td>
<td>SCC</td>
<td>WD</td>
</tr>
<tr>
<td>SCC15</td>
<td>M</td>
<td>65</td>
<td>Hand</td>
<td>SCC</td>
<td>WD, keratinizing invasive, no perineural invasion</td>
</tr>
<tr>
<td>SCC16</td>
<td>M</td>
<td>71</td>
<td>Calf</td>
<td>SCC</td>
<td>WD, infiltrates into subcutaneous fat</td>
</tr>
<tr>
<td>SCC17</td>
<td>M</td>
<td>86</td>
<td>Scalp</td>
<td>SCC</td>
<td>WD</td>
</tr>
<tr>
<td>SCC18</td>
<td>M</td>
<td>70</td>
<td>Scalp</td>
<td>SCC</td>
<td>WD, multifocal, arising in association with multifocal SK</td>
</tr>
<tr>
<td>SCC19</td>
<td>M</td>
<td>54</td>
<td>Ear</td>
<td>SCC</td>
<td>MD, invades deeply</td>
</tr>
<tr>
<td>SCC20</td>
<td>M</td>
<td>51</td>
<td>Leg</td>
<td>SCC</td>
<td>WD, extends to mid-dermis</td>
</tr>
<tr>
<td>SCC21</td>
<td>M</td>
<td>52</td>
<td>Face</td>
<td>SCC</td>
<td>MD-WD, infiltrating, extends to subcutis, no perineural invasion</td>
</tr>
<tr>
<td>SCC22</td>
<td>M</td>
<td>54</td>
<td>Scalp</td>
<td>SCC</td>
<td>WD, invasive, no perineural invasion</td>
</tr>
</tbody>
</table>

Abbreviations: MD, moderately differentiated; SCC, squamous cell carcinoma; SK, solar keratosis; WD, well differentiated.
clustered into the same group as their respective partner; only case 9 did not pair correctly. To further test the hypothesis that SK and SCC are related lesions, associations between CNAs were investigated in the entire sample population (ie, SK and SCC were treated as a single group). As demonstrated in Table 2, many statistically significant correlations between frequent CNAs exist. The mean concordance for the matched samples was 46% (95% CI, 25%-66%; range, 25%-80%). Therefore, all matched cases demonstrated some degree of similarity between SK and SCC, and many of the frequent abnormalities seemed to occur together in the same dysplasia.

**COMMENT**

Whole-genome analysis of cutaneous SCCs and SKs by CGH identified many frequent CNAs acquired during carcinogenesis. The number of genetic imbalances in each type of dysplasia was significantly different, and this supports the role of SK as a precursor to SCC. Comparison of SKs and SCCs revealed a similar pattern of chromosomal aberrations, except for the loss of the chromosome 18q arm. This aberration, which was more prevalent in SCCs than in SKs, may be an important event in tumor progression and the invasion of the dermal layer by atypical squamous cells.

Chromosomal regions of frequent gain shared by both lesions, in decreasing order of recurrence, were located at 3q, 17q, 4p, 14q, Xq, 5p, 9q, 8q, 17p, and 20q. Shared regional losses were observed at 9p, 3p, 13q, 17p, 11p, 8q, and 18p. Many of these genetic imbalances coincide with previously reported karyotypic findings and CGH results of keratinocyte tumor–derived cell lines.17,25-27 Previous LOH studies have shown a similar degree of genetic alterations in SK and SCC dysplasias, as we found in our own observations. These studies also revealed that the 2 types of skin lesions shared regions of high-frequency genomic loss (3p, 9p, 9q, 13q, 17p, and 17q).15,16 The observations, reached with different molecular methods, of shared nonrandom CNAs further validate the importance of these genetic changes in skin tumorigenesis. A comparison of our observations with genetic data from CGH analysis of other types of tumors (head and neck, esophageal, bladder, cervical, and squamous cell of lung carcinomas28,29) also shows similarities between these and SCC data.
The relationship between SK and SCC has recently become a topic of discussion in the field of dermopa-

Figure 2. Accumulation of genetic alterations in solar keratosis (SK) and squamous cell carcinoma (SCC) lesions. A, The number of alterations detected by comparative genomic hybridization in an individual lesion is shown in each group; the mean ± SEM for both lesion types is displayed as perpendicular bars; and significant differences in copy number aberrations (CNAs) between SK and SCC are compared with values for SK (P<.05). B, Distribution of recurrent CNAs in SK. C, Distribution of recurrent CNAs in SCC. Black circles indicate carries the specified CNA; open circles, does not carry the specified CNA.

Figure 3. Dendrogram displaying clustering (using the Pearson correlation with complete clustering) of data obtained by comparative genomic hybridization from all solar keratosis (SK) and squamous cell carcinoma (SCC) lesions analyzed. Note the arrangement of 4 distinct groups (denoted A-D) within the dendrogram.

The relationship between SK and SCC has recently become a topic of discussion in the field of dermopa-

thology. Solar keratoses are so widely recognized as precursor lesions to SCC development that a reclassi-
cation of SK has been proposed. The histological obser-
vation of a high correlation of cutaneous SCC tumors with a concomitant SK (or SCC in situ) suggests that all SCCs evolve from SK lesions, and that when a contiguous SK is not present, the carcinoma has engulfed the preinva-
sive lesion. Expanding on this conjecture leads to con-
sider that SKs and SCCs are one and the same, and that SCC, as the earliest visible presentation of an SCC, should be reclassified as SCC in situ, superficial SCC, or kerat-
inocyte intraepithelial neoplasia. However, this view still generates a large degree of controversy.

The present study and others support the hypothe-
sis of a clonal relationship between the 2 lesions. As previously discussed, shared regions of genetic loss have been determined in LOH studies and CGH analysis, in this investigation, has also identified frequently shared aberrations. The prevalence of each genetic imbalance in each type of dysplasia identified significant differences at only 1 locus, the loss of the 18q arm in SCC. How-
ever, the frequency of total CNAs was significantly lower in SK than in SCC. The histological diagnosis of the lesion is based on this approach and using CGH data have also been derived from a small subpopulation of cells within the lesion, which may have not invaded the dermis. In SK, cell masses are therefore small, and have a greater heterogeneity than SCC cell populations. Because the CNAs identified by CGH represent a global view of predominant genetic im-
balances in the cell population, they can be masked by the presence of different clonal populations. Expansion of the tumor cell population would enrich for those cells with a higher mitotic index—generally those that are more genetically unstable. This would promote the growth of specific cell populations, and thus reduce heterogeneity and the masking of CNAs. Genetic analysis of several cases where SK was associated with an SCC further validates the clonal relationship between SK and SCC.

Hierarchical clustering is a conventional method used to classify and identify associations between similar and ident-
tical tumor types using microarray data. Several studies based on this approach and using CGH data have also been documented. Clustering of aberrations between SK and SCC demonstrates a dispersion of SK samples among the SCC population. If SK were a dysplasia distinct from SCC, most samples would cluster into a separate subset. This finding therefore provides further evidence to support a clonal relationship. Additionally, many samples containing an SCC and associated SK (cases 8-12) paired with their respective match within each cluster subset within the dendrogram (Figure 3). As all paired samples showed some degree of concordance, this observation further suggests a clonal relationship between the 2 lesions. In some cases the paired SK and SCC did not cluster. This may be explained by the heterogeneous nature of the SCC lesion, which may have been derived from a small subpopulation of cells within the SK. A disadvantage of the CGH technique is that it detects only the most prominent CNAs, and is unable to provide copy number information on a cellular level.

Many of the chromosomal regions observed to under-
gro copy number changes in SCC and SK contain nu-
meros known and putative oncogenes and tumor sup-
pressor genes. To discuss each region of aberration with
The delineation of several loci implicated in noncutaneous SCC have prompted some authors to attempt to identify the causative genes of SCC development. The gain of 3q may be linked to the human telomerase RNA gene, which maps to this arm. A disparate telomerase activity has been linked to cellular immortality and tumor progression in a wide array of tumor types, including nonmelanoma skin cancer, and in many of these types overexpression of the 3q arm can be observed. Interestingly, the loss of 3p and gain of 3q was a significant occurrence in SCC.

The inactivation of several genes has been associated with the development of nonmelanoma skin cancer progression is apparent by the prevalence of the loss of 18q in SCC was statistically different. This loss, though not significant at 9p21 in SK than in SCC. This observation suggests a possible mechanism of progression from SK to SCC through a loss of genes in this locus. Loss at 17p is characteristic of TP53 inactivation. This is one of the most consistently implicated genes in SK and SCC development. Numerous investigations have demonstrated deletion of this gene and/or the presence of UV radiation–induced inactivating mutations in SK and SCC. Interestingly, gain of 17p was also observed in this study and others, but its significance is poorly understood.

Table 2. Chromosomal Alterations Detected by Comparative Genomic Hybridization in Matched SCC and SK

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Concordance, %</th>
<th>Common to SK and SCC</th>
<th>Present Only in SK</th>
<th>Present Only in SCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>29</td>
<td>+Xq, −17p</td>
<td>+3q, +4q, +8q, −8p, +5q, +9p, −15q2-qter</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>27</td>
<td>−9p21-qter, −Xq</td>
<td>+4q, +9q22-qter, +15q, +4q, +9q22-qter, +15q, −13q, −14q11-q23</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>25</td>
<td>−9p26-qter, −9p</td>
<td>+5p, −4q</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>67</td>
<td>+Xpter-q21, −17p, −Xq22-qter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>80</td>
<td>+20p</td>
<td>+17p, −X</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: +, gain on chromosomal arm; −, loss on chromosomal arm.

In conclusion, we have identified chromosomal imbalances frequently shared by SK and SCC dysplasia. These aberrations are in line with current knowledge of genetic events involved in nonmelanoma skin cancer development. Additionally, the genetic changes observed overlap those identified in other SCC-derived tumors. This suggests the possibility of shared mechanisms in the tumorigenesis of this cellular subtype. Comparison of aberrations found in SK and SCC demonstrated shared genetic changes, and only the loss of 18q in SCC was statistically different. This loss, which may be a defining event in SCC progression into the dermal layers of the skin, has been associated with the more aggressive nature of other SCC-derived tumors. This could also explain the clinical benign nature of many SKs, as all but 1 lesion demonstrated retention of both copies of chromosome 18. Finally, these findings also exhibit further evidence to support a clonal relationship between SK and SCC. What is still unclear is whether an SK requires further mutations to progress to an SCC, or, alternatively, SK may in fact be small SCC lesions. This distinction cannot be substantiated on the basis of present data.

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Corresponding author and reprints: Lyn R. Griffiths, PhD, Genomics Research Centre, Griffith University–Gold Coast, PMB50 GCMC, Bundall, QLD 9726, Australia (e-mail: L.Griffiths@mailbox.gu.edu.au).
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