Complex Genotype Sarcomas Display Familial Inheritance Independent of Known Cancer Predisposition Syndromes

Kevin B. Jones1,2, Joshua D. Schiffman2,4, Wendy Kohlmann3, R. Lor Randall1,2, Stephen L. Lessnick2,4, and Lisa A. Cannon-Albright5

Abstract

Background: The low incidence of sarcomas in the general population makes heritable contribution to disease risk difficult to discern beyond highly penetrant Mendelian syndromes.

Methods: The Utah Cancer Registry (UCR) and Utah Population Database were interrogated for sarcoma diagnostic codes grouped by genetic type, either complex genotype/karyotype sarcoma or balanced translocation-associated sarcoma. The genealogic index of familiality (GIF) was calculated and relative risks (RR) of disease estimated for first-, second-, and third-degree relatives of sarcoma probands. Cancer patterns in pedigrees of sarcoma probands were examined to rule out known hereditary cancer syndromes.

Results: A total of 229 balanced translocation type and 1,161 complex genotype type sarcomas with at least three generations of ancestral genealogy data were identified in the UCR. There was no evidence for excess relatedness for the balanced translocation group by using the GIF test (P = 0.657) and no significantly elevated RRs. In the complex genotype group, we observed significantly elevated GIF (P = 0.03). Modest RRs corroborated the GIF analysis, in which excess relatedness existed in distant relationships. No recognized cancer syndromes were identified among high-risk pedigrees.

Discussion: We identified strong familiality among complex genotype sarcomas, independent from known cancer predisposition syndromes. In the absence of significantly elevated RRs for close relatives, the high GIF argues for a strong genetic—rather than environmental—component to complex genotype sarcoma risk. We observed no significant familial risk of developing balanced translocation-associated sarcomas, but the sample was small.

Impact: There exists yet to be deciphered heritable risk for developing complex genotype sarcomas. Cancer Epidemiol Biomarkers Prev; 20(5); 751–7. ©2011 AACR.

Introduction

Sarcomas, cancers of mesenchymal tissues, remain challenging diseases to treat. Sarcomas are rare cancers and directly affect a small portion of the general population (1). However, their impact is heightened by their deadly incidence among adolescents and young adults.

Mesenchymal tissues line neither the body surface nor ingesting/inhaling organ cavities exposed directly to environmental toxins. The development of cancer in mesenchyme therefore may depend more on biologically intrinsic factors than environmental exposures. This thought is supported by the relative rarity of sarcomas despite the fact that mesenchymal tissues comprise a strong majority of tissue volumes and body mass percentages in the human body (2). The major determinant of tissue-intrinsic characteristics beyond the chance accrual of replication errors, mis-recombinations, and erroneous chromosomal segregations is the inherited genome from which each cell begins. This raises the possibility for heritable risks for sarcomagenesis.

The major challenge to studying the familiality of sarcoma is its scarcity in the general population. If the brother or sister of a sarcoma patient had even a 5-fold relative risk for developing sarcoma, that risk would not be readily detected unless the patient had tens or hundreds of thousands of siblings. The Utah Population Database (UPDB) has proven valuable to the study of heritability, especially for rare diseases, given the depth of genealogies recorded and its careful linking to the Utah Cancer Registry (UCR), which is part of the Surveillance, Epidemiology, and End Results (SEER) program and has been maintained for the last 50 years (3). Nonetheless, an investigation of familiality for any individual subtype of...
sarcoma is likely to be underpowered even over this 50-year population accrual because of insufficient case numbers. A potential route forward from this challenge is the meaningful grouping of sarcoma subtypes. Although individual sarcoma subtypes tend to derive their identities from known or presumed tissues of origin, there is a variety of ways to lump subtypes together. For example, sarcomas may be grouped according to the population affected, adolescents, and young adults versus the elderly. Alternatively, they can be grouped according to bone versus soft-tissue locations; many current treatment paradigms roughly follow this crude grouping, with chemotherapeutic adjuvants for bone sarcomas and adjuvant radiation for soft-tissue sarcomas, generally.

Sarcomas can also be classified according to tumor cell genetics. Many are associated with balanced chromosomal translocations, which generate subtype specific fusion oncogenes, such as EWS-FLI1 in Ewing’s sarcoma and SYT-SSX1 in synovial sarcoma (4). Other sarcomas can be termed complex karyotype sarcomas. This latter group exhibits genomic and chromosomal instability, with mutations and copy number alterations common throughout the genome and wild, nondiploid karyotypes frequent (4). Familiality has been suspected, but not proven, for both types of sarcoma. It has been most carefully explored in the bone sarcomas, osteosarcoma, and Ewing’s sarcoma.

Osteosarcoma, the prototype complex genotype sarcoma, arises more frequently in 3 heritable Mendelian cancer predisposition syndromes, Li Fraumeni syndrome (5), hereditary retinoblastoma (6), and Rothmund Thompson syndrome (7). However, these syndromes contribute only a scant number of cases to the overall population incidence of osteosarcoma. Beyond these syndromes, there may be other complex heritable predispositions not yet recognized that engender the genomic instability, resulting in complex genotype sarcomas such as osteosarcoma.

Ewing’s sarcoma, the most common balanced translocation-associated sarcoma does not arise commonly in any heritable cancer predisposition syndrome. Individual cases have been reported following diagnosis and treatment of retinoblastoma (8, 9). The general association between Ewing’s sarcoma and other cancers in families has been suggested by a few small series only (10). Four sibling pairs with Ewing’s sarcoma have been described (11–13). Ewing’s sarcoma also has been associated in families with both umbilical and inguinal hernias (14–16). Finally, Ewing’s sarcoma has a much lower incidence among American individuals of African descent than among Americans of European or Asian ancestry (17). These epidemiologic findings all suggest a modest but discernable genetic contribution to disease risk despite the lack of Ewing’s sarcoma with any known hereditary cancer syndrome (18).

There are 2 hypothesized heritable risks for the group of balanced translocation-associated sarcomas such as Ewing’s sarcoma. First, there may be a heritable predisposition to generate the translocations themselves. Such heritable predispositions to generate translocations could be either generalized or locus (sarcoma subtype) specific. The latter, are obviously difficult to detect without large numbers of cases and deep genealogies. Second, there may be heritable tendencies for a cell that has undergone such a translocation to complete transformation rather than apoptose. Silencing of the p53 pathway, for example, is common even among balanced translocation-associated sarcomas (19).

Methods

The UPDB is a computerized data resource consisting of genealogic and demographic data representing the Utah population (3). The genealogic data in the UPDB have been record linked to the UCR. The Utah genealogy database was created in the 1970s to investigate the familial aggregation of cancer and now spans up to 12 generations in some Utah pedigrees (20). Several studies using the genealogy data linked to the UCR have defined familial cancer predispositions and syndromes (21–27). The UCR was established in 1966 and became part of the NCI SEER program in 1973. All cancers occurring in the state are reportable by law to the UCR; follow-up rates exceed 95%. The UCR data include primary site, histology, stage, grade, survival months, and age at diagnosis data for each cancer. The Utah population is genetically representative of northern Europe and has low inbreeding levels, similar to the rest of the United States (28, 29).

Our analysis was restricted to the 2.3 million subjects in the UPDB with at least 3 generations of genealogy data for each cancer. The Utah population is genetically representative of northern Europe and has low inbreeding levels, similar to the rest of the United States (28, 29).

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All individuals in the UCR with a sarcoma diagnosis who also had at least 3 generations of genealogy data in the UPDB were identified by searching for International Classification of Diseases (ICD)-O codes, grouped into translocation-associated sarcomas and complex karyotype sarcomas as shown in Table 1. Malignant peripheral nerve sheath tumors (MPNST), although fitting into the complex karyotype sarcomas, were excluded from the analysis due to fact that roughly half of these malignancies arise in the setting of the Mendelian syndrome, neurofibromatosis type I, which might bias the data set toward familiality. Dermatofibrosarcoma protubersans and gastrointestinal stromal tumor cases were also excluded. These patients typically bear point mutations in specific genes, rather than balanced translocations, but are otherwise simple genetic sarcomas.

Genealogic index of familiality method

The genealogic index of familiality (GIF) statistic was designed to identify familial aggregation of specific traits within the Utah genealogy (30). The GIF method of analysis has been used in previous studies of familiality for cancers (21, 22, 26, 27). A similar method of...
The GIF statistic measures the average relatedness between all pairs of individuals with a specific phenotype (cases). The Malecot coefficient of kinship is used to measure the degree of relatedness between all pairs of cases. The coefficient of kinship is defined as the probability that randomly selected homologous genes from 2 individuals are identical by descent from a common ancestor (24). The coefficient is one-half for parent/offspring, one-fourth for siblings, one-eighth for grandparent/grandchild, and so forth. The case GIF is the mean of all coefficients of kinship between all possible pairs of cases. The coefficient of kinship for any two individuals in a population is expected to be close to zero. For ease of presentation, the case GIF is multiplied by 10^5. The GIF statistic takes into account all genetic relationships between all cases.

To test the null hypothesis of no excess relatedness among cases, we created an empirical control distribution. For each sarcoma case, we selected a control at random from the UPDB genealogy resource (also limited to individuals with at least 3 generations recorded), matched on sex, 5-year birth cohort, and place of birth (in or out of Utah), resulting in a control set of the same size as the case set. The matching strategy is employed to account for potential differences in kinship based on differences in birth year, sex, and place of birth. One thousand independent 1:1 matched control sets were selected and the GIF was measured for each set to create an empirical distribution of average relatedness under the null hypothesis of no excess relatedness among cases. We then tested this hypothesis by comparing the case GIF to the empirical distribution of the 1,000 GIFs of the control groups.

The degree of shared genetic composition between pairs of cases representing different genetic distances is quantifiable through the GIF analysis. We assume that the degree of shared environment among individuals diminishes to a population level of sharing beyond second- or third-degree relatives for the Utah population. Among close relationships, it is difficult to determine whether excess familiality is due to shared environment or to shared genetics, or to a combination of both. Among more distant relationships, however, significant excess relatedness most likely indicates a genetic contribution. The empirical significance of the GIF test tells us whether overall excess familiality is observed. When this same test

<table>
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<tr>
<th>Diagnosis</th>
<th>Histology ICD-O codes</th>
<th>n</th>
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<tbody>
<tr>
<td>Complex genotype/karyotype sarcoma</td>
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<td></td>
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<td>Pleiomorphic liposarcoma</td>
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<td>Osteosarcoma</td>
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<td>120</td>
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<td>Fibrosarcoma</td>
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<tr>
<td>Balanced translocation-associated sarcoma</td>
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<td>Synovial sarcoma</td>
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<td>Alveolar soft parts sarcoma</td>
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<td>Clear cell sarcoma</td>
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<tr>
<td>Desmoplastic small round cell tumor</td>
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Table 1. Diagnoses included in each group
is done excluding all close relationships (first- and second-degree relatives), it allows us to determine whether significant excess familiality exists in distant relationships, further supporting the hypothesis of a genetic contribution (this test is termed the distant or dGIF).

Relative risks

Estimation of relative risks (RR) in relatives is an alternative approach to test the hypothesis of a familial contribution to disease. The GIF analysis utilizes all relationships between all cases, regardless of genetic distance, whereas the RR analysis typically relies on comparisons in close relatives only. The RR, or the risk of the disease in the relatives compared with the risk in the general population (also termed standardized mortality ratio), was also calculated. This ratio is directly related to the power to identify disease predisposition genes and is typically a primary test for a genetic component to a disease. The RR approach compares observed rates of sarcoma in relatives of probands with the expected rates of sarcoma as estimated in the UPDB. All individuals in the UPDB with genealogy were used to estimate cohort-specific cancer rates.

We estimated RR as follows: All 2.3 million individuals in the UPDB with at least 3 generations of genealogy were assigned to 1 of 132 cohorts on the basis of birthplace (in or out of Utah), sex, and 5-year birth cohorts. For each cohort, internal cohort-specific cancer rates are calculated by summing the number of individuals in each cohort with sarcoma and dividing by the total number of individuals in the cohort. These internal cohort-specific sarcoma rates estimate the expected rate of sarcoma for each cohort. The expected number of sarcoma cases among first-degree relatives of sarcoma cases is calculated by multiplying the number of first-degree relatives of sarcoma cases in each cohort by the cohort-specific internal rate of sarcoma and then summing over all cohorts. The number of observed sarcoma cases among relatives is a count (without duplication) of all of the relatives of sarcoma cases who also were diagnosed with sarcoma. The first-degree RR statistic is the ratio of the number of observed sarcoma cases among first-degree relatives of sarcoma cases in each cohort to the number of expected sarcoma cases among first-degree relatives of sarcoma cases. The RR was similarly estimated for second- and third-degree relatives.

The RR is assumed to follow a Poisson distribution, with the mean value equal to the number of expected sarcoma cases among relatives of sarcoma cases. The Poisson distribution is an approximation of the sum of multiple binomial distributions, representing the number of expected deaths in each cohort. This approximation is appropriate for both rare and common phenotypes, being more conservative for common diseases. Probability values for 1-sided tests of significance and 95% CIs for the RR statistic can be calculated by Poisson distribution under the null hypothesis that the RR is equal to unity. Although significantly elevated risks in first-degree relatives suggest a genetic contribution to disease, they may result either from shared environment or from a combination of both genes and environment. However, significantly elevated risks for second- or third-degree relatives would strongly suggest a heritable component.

High-risk pedigrees

We also identified as high-risk pedigrees those families with an excess of cases identified among the progeny by RR and a total of more than 5 sarcoma cases. Among these high-risk pedigrees, we examined coaggregation of each sarcoma group with other cancers. This analysis was used to rule out the inclusion of recognizable cancer predisposition syndromes in the final data set. These analytic methods to identify familial contribution to disease (average relatedness, RR, and high-risk pedigree identification) previously have been shown to be unbiased, but conservative (22, 23, 27, 32–36).

Results

Genealogic index of familiality

There were 229 individuals with balanced translocation or simple genetic sarcomas identified in the UCR with at least 3 generations of ancestral genealogy recorded in the UPDB. The breakdown into specific diagnoses represented is given in Table 1. There was no overall excess relatedness for the balanced translocation group by using the GIF test, with case GIF of 2.05 and mean control GIF of 2.32 (GIF empirical \( P = 0.657 \)), and no excess distant relatedness (dGIF empirical \( P = 0.530 \)), as shown in Figure 1. The complex genotype karyotype sarcoma group of 1,161 patients, however, did show excess overall relatedness, with case GIF of 3.05 and mean control GIF of 2.73 (GIF empirical \( P = 0.034 \)), and borderline significance when close relationships were done excluding all close relationships (first- and second-degree relatives).
were ignored (dGIF empirical $P = 0.054$), as shown in Figure 2.

**Relative risks**

For translocation sarcomas, the RR estimates corroborated the GIF data; no translocation sarcoma cases were observed among the first-, second-, or third-degree relatives of balanced translocation probands.

For complex genotype karyotype sarcomas, RR estimates were greater than 1.0 for both first- and second-degree relatives but were not significantly elevated. The RR for third-degree relatives was estimated to be less than 1.0 but, again, not significantly. These RRs (Table 2) corroborate the GIF analysis, in which excess relatedness exists primarily at more distant relationships.

**High-risk pedigrees**

We identified “high-risk” pedigrees for complex genotype/karyotype sarcomas defined as having a significant excess of complex genetic sarcoma cases among all descendants of the founding couples compared with calculated general rates across the UPDB population. Twenty pedigrees in this category had more than 5 complex genotype sarcomas in related individuals. Interestingly, in these 20 high-risk complex genetic sarcoma pedigrees, other cancer types were also observed in excess. These associated cancers and the number of high-risk pedigrees in which they were found in excess are listed in Table 3. Notably, none of the pedigrees had inheritance patterns and cancer types that would fit with any of the well-documented cancer predisposition syndromes such as Li Fraumeni syndrome, hereditary retinoblastoma, or Werner, Bloom, or Rothmund Thompson syndromes.

**Discussion**

Recognizing the heritable genetic contribution to the risk of rare diseases such as individual sarcoma subtypes

![Figure 2. Chart displaying the contribution to the GIF statistic for 229 balanced translocation-associated sarcoma (BTAS) cases compared with the mean distribution for 1,000 sets of matched controls. The genetic distance (x-axis) represents relationships: 1, parent/offspring; 2, siblings; 3, avunculars; 4, first cousins; and so forth. There is no significant excess relatedness among balanced translocation-associated sarcomas compared with control data, but statistical power is low given the small number of cases.](image)
is very difficult because of relatively low patient numbers and insufficient statistical power. Traditional means of suspecting familial cancer risk depend on clinically oriented family histories, which rarely probe deeper than 2 generations beyond the proband. These methods have identified familial sarcomas as potential manifestations of otherwise penetrant and recognizable heritable disorders. Examples, include Li Fraumeni syndrome (5), arising from inherited disruption of p53, recognized for the strong predisposition to a variety of carcinomas but also including osteosarcoma and pleomorphic rhabdomyosarcoma; hereditary retinoblastoma (6), in which syndrome osteosarcoma is the second most common cancer but the first is almost universally penetrant; and neurofibromatosis type I (37), which is recognized from a broad array of nononcologic clinical manifestations but also predisposes patients to MPNST. Beyond these, familiality has been suspected but never explored for sarcomas.

In this study, therefore, we used 2 methods to strengthen our general detection of familiality among relatively rare sarcomas: the probing of deep genealogies (at least 3 generations and often many more) and the pooling of specific sarcoma diagnoses into genetically defined categories. This dual approach utilizing the unique resource of the UPDB allowed us to identify evidence for excess familiality among complex genotype sarcomas. This excess familiality was particularly strong in fifth- through seventh-degree relatives, suggesting a genetic component to risk for developing complex genotype sarcomas rather than an environmental influence from nuclear family surroundings and occupations. We presume that this genetic risk is inherited in the form of multiple minor susceptibility loci, but we have not strictly ruled out unrecognized, strong, single-gene susceptibilities. That these complex genotype sarcomas colocalize in families with other cancers in patterns that do not fit any known syndromes suggests a broader relevance to our findings. Identifying the susceptibility loci in these high-risk families may impact cancers beyond sarcoma and increase our overall understanding of oncogenesis more generally. We actively participate in a new intercontinental collaboration to collect germ line genetic samples from sarcoma patients, to define genetic loci carrying risk for sarcomagenesis.

Of interest are the specific cancers that arise more commonly in the families with an excess prevalence of complex genotype sarcomas. An excess of Ewing’s sarcoma family of tumors cases was apparent in 3 of the 20 pedigrees with more than 5 complex genotype sarcomas. Certainly, the development of an osteosarcoma or pleomorphic soft-tissue sarcoma as a radiation-induced secondary cancer following treatments of Ewing’s sarcoma has been reported (38), but these associations in the pedigrees were not in the same patients and merit further exploration. The excess of lymphoma cases in half of the pedigrees with an excess of complex genotype sarcomas follows to the extent that lymphoma is one of very few solid tumors that is neither a carcinoma nor a sarcoma. Interestingly, species, such as rodents, canines, and felines, more prone to sarcomas than humans are also more prone to lymphomas (39). Lymphoma and sarcoma have previously been linked in terms of risk factors in the settings of acquired immunodeficiency (40) and herbicide exposure (41). Beyond these, a few families with both sarcomas and lymphomas have been reported in isolation in the literature (42–44). Again, further investigation is required.

Similar evidence for familiality was not identified in the smaller set of balanced translocation-associated sarcomas. Although we did not see evidence for familial clustering, the small sample size may have affected our power to see such an effect for a rare disease. Furthermore, our negative findings in these families for balanced translocation-associated sarcomas as a pooled group give no suggestion for or against the possibility of familiality for any given specific subtype of sarcoma even in the same population. Pooling of all of the balanced translocation-associated sarcomas together in 1 analysis would also dilute the effect seen if any single balanced translocation-associated sarcoma subtype was familial, independent from the group. For example, the suggestion of familiality in prior studies of Ewing’s sarcoma is not significantly challenged by these data, as it was not tested individually. Efforts are ongoing to gather resources that will permit the specific testing of familial risk for developing Ewing’s sarcoma family of tumors.

Although the accumulation of random genetic changes is certainly involved in sarcomagenesis, our study indicates that perhaps more than chance plays a role in complex genotype sarcomagenesis. We report evidence for the contribution of familiality to the risk of developing one from this group of sarcomas, which, if deciphered, could lead to important insights into sarcomagenesis and perhaps oncogenesis more generally.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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