Nationwide Registry-Based Analysis of Cancer Clustering Detects Strong Familial Occurrence of Kaposi Sarcoma

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Abstract

Many cancer predisposition syndromes are rare or have incomplete penetrance, and traditional epidemiological tools are not well suited for their detection. Here we have used an approach that employs the entire population based data in the Finnish Cancer Registry (FCR) for analyzing familial aggregation of all types of cancer, in order to find evidence for previously unrecognized cancer susceptibility conditions. We performed a systematic clustering of 878,593 patients in FCR based on family name at birth, municipality of birth, and tumor type, diagnosed between years 1952 and 2011. We also estimated the familial occurrence of the tumor types using cluster score that reflects the proportion of patients belonging to the most significant clusters compared to all patients in Finland. The clustering effort identified 25,910 birth name-municipality based clusters representing 183 different tumor types characterized by topography and morphology. We produced information about familial occurrence of hundreds of tumor types, and many of the tumor types with high cluster score represented known cancer syndromes. Unexpectedly, Kaposi sarcoma (KS) also produced a very high score (cluster score 1.91, p-value <0.0001). We verified from population records that many of the KS patients forming the clusters were indeed close relatives, and identified one family with five affected individuals in two generations and several families with two first degree relatives. Our approach is unique in enabling systematic examination of a national epidemiological database to derive evidence of aberrant familial aggregation of all tumor types, both common and rare. It allowed effortless identification of families displaying features of both known as well as potentially novel cancer predisposition conditions, including striking familial aggregation of KS. Further work with high-throughput methods should elucidate the molecular basis of the potentially novel predisposition conditions found in this study.


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Introduction

Identification of inherited genetic factors that contribute to the development of cancer has been a subject of extensive research since the discovery of the first tumor susceptibility genes. Various approaches have been used to estimate the proportion of the inherited versus environmental factors in the etiology of different cancers. Twin studies have elucidated a large heritable fraction (26%–42%) for many common cancers, such as those of stomach, colon/rectum, breast, prostate, and lung [1]. Systematic registry-based analyses have shown a significantly increased risk for colon/rectum, breast, prostate, and lung [1]. Systematic registry-based analyses have shown a significantly increased risk for colon/rectum, breast, prostate, and lung [1].

Some degree of genetic admixture and migration due to a whole is relatively small. For example, high-penetration mutations in genes such as MLH1, MSH2, APC, and MTH account for only about 5% of all colorectal cancer cases [6]. However, identification of cancer predisposing genes has contributed significantly to our understanding of cancer biology, since they are often central also in the development of sporadic tumors.

The genetic background of the Finnish population (currently 5.4 million) is relatively well-studied and, even though considered relatively homogenous, has been shown to harbor substantial substructuring [7]. Ten distinct subpopulations of Finns have been characterized with high-density SNP genotyping suggesting multiple bottlenecks in the history of the Finnish population. After internal migration in the 1500s, population size of the wide inland areas of Finland grew in isolation because of long distances, and small villages formed genetically distinct subpopulations. Some degree of genetic admixture and migration due to
urbanization started taking place after World War II. Single-origin mutations which have spread without negative effect on biological fitness have accounted for highly prevalent diseases in some of these isolated populations. This founder effect has enabled successful identification of genetic susceptibility to diseases in Finland (reviewed in [8]). As an example, the discovery of familial pituitary adenoma clusters in Northern Finland led to the identification of aryl hydrocarbon receptor interacting protein (AIP) defects in patients with pituitary adenoma predisposition [9]. Mutations in AIP originally identified in Finland have subsequently been found from similar patients worldwide [10].

The Finnish Cancer Registry (FCR) is a nationwide database covering currently more than one million patients, and practically all incident cancers and cancer deaths in Finland since 1953 [11]. Physicians, hospitals, and pathology and hematology laboratories send cancer notifications to FCR. This reporting was made obligatory by law in 1961. Thus, FCR has also a link to sample information, such as archival tissue blocks, for all the patients that have been examined in pathology laboratories. Information about family history and family relationships is not recorded in the cancer notifications, but identification of patients’ relatives is possible through the National Population Registry (NPR) and the Parish Registries (PRs). PRs have kept records of citizens since 1580 until NPR was established. The personal identity code (PIC) system was implemented in Finland in the 1960s, and PIC is used as the identification key also in FCR for all patients except for those who died before 1967. Both FCR and NPR have an excellent coverage and high quality data [11,12].

Conventional epidemiological tools are poorly suited to search for evidence of cancer predisposition, in particular if the conditions in question are uncommon. Here we describe an effective method that utilizes the extensive patient data in FCR, and information about family name at birth and municipality of birth in NPR, to systematically identify familial aggregation of all different tumor types on a nation-wide scale. The method enables identification of families suitable for sample collection and further research of the underlying genetic predisposition. Similar approach in a smaller scale has earlier been exploited in a search for prostate cancer families in Finland [13]. In this study, we apply our method to cluster all available patients in FCR. We calculate statistical significance for each cluster, and produce information about familial occurrence of hundreds of tumor types with at least two patients in FCR were included, resulting in 846 combinations of topography and morphology (Table S3). To obtain information on patients’ family names at birth and municipalities of birth, we linked the 878,593 patients with PIC to NPR.

For each tumor type, systematic clustering was performed based on municipality of birth and family name at birth (MN-clusters). The observed number of patients (O) with each tumor type in FCR was calculated in a stratum defined by municipality (M), family name (N), sex, and year of birth. The proportion of persons in each M, N, sex, and year of birth category in the entire population of same gender and year of birth was calculated from the same version of NPR database that was linked with FCR patients. When that proportion was multiplied with the total sex and birth-year specific number of cancer cases of the cancer type in question in the NPR-linked subset of FCR, the expected number of cases (E) in each stratum was obtained. The stratum-specific observed and expected numbers were added up over the gender and birth year categories. O/E ratios were calculated for each MN category, and their 95% confidence intervals were defined assuming a Poisson distribution of observed numbers.

**Estimation of Familial Occurrence with Cluster Score**

To estimate the familial occurrence of various tumor types, cluster score was calculated. For each tumor type i, we selected clusters with the lower limit of confidence interval (CI-low) greater than or equal to α, and calculated the number of patients (Xαi) in these clusters.

We define the cluster score of tumor type i to be $X_{α_i}/Y$ divided by the total number of patients with the same tumor type (Y) per 100,000 persons in Finland. For example, cluster score with α = 10 for Kaposi sarcoma was calculated as following ($X = 19$ and $Y = 537$ from Table 1):

$$\frac{19}{537} \times \frac{1}{5,400,000} = 1.91.$$

To estimate whether $X_{α_i}/Y$ was different than expected ratio $Y \times X_{α_i}/Y$ (where $X_{α_i}/Y$ is the respective ratio over all tumor types in Finland; 0.0029 for α = 10), two-sided Poisson test was calculated with 95% confidence level. The p-values were adjusted for multiple test comparisons with false discovery rate method [14].

**Confirmation of Kinship in the Clustered Kaposi Sarcoma Cases**

Relatedness of patients in KS clusters was confirmed using information from NPR and PRs. NPR includes a link to parents for persons born since 1950s and who had not died before the PIC system was implemented in the 1960s. For the rest of the patients, we utilized PRs to identify first degree relatives and their children. PRs were also utilized for more thorough genealogy research. The relatives of the clustered KS cases were traced back at least three generations. To identify additional affected cases in the families, the cancer histories were checked from FCR for individuals identified through genealogy.

**Geographical Illustration of Kaposi Sarcoma in Finland**

The O/E ratios for Kaposi sarcoma cases in each municipality of birth were calculated as described previously for MN-clusters, and illustrated using the small-area mapping method developed in FCR [15]. The twenty-one largest cities in Finland, including Vyborg (currently part of Russia), are shown as circles with...
Table 1. Tumor types showing the strongest evidence for familial occurrence.

<table>
<thead>
<tr>
<th>Topography</th>
<th>Morphology</th>
<th>Cluster score</th>
<th>p-value*</th>
<th>Number of patients in FCR</th>
<th>Number of clusters**</th>
<th>Number of patients in clusters**</th>
<th>Suggestive predisposition gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>central nervous system</td>
<td>hemangioblastoma</td>
<td>4.98</td>
<td>2.77E−14</td>
<td>141</td>
<td>5</td>
<td>13</td>
<td>VHL</td>
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<tr>
<td>thyroid gland</td>
<td>medullary carcinoma</td>
<td>3.55</td>
<td>7.86E−21</td>
<td>335</td>
<td>9</td>
<td>22</td>
<td>RET</td>
</tr>
<tr>
<td>Skin</td>
<td>Kaposi sarcoma</td>
<td>1.91</td>
<td>2.05E−13</td>
<td>537</td>
<td>9</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>neuroendocrine carcinoma</td>
<td>1.40</td>
<td>2.75E−06</td>
<td>386</td>
<td>5</td>
<td>10</td>
<td>MEN1, RET</td>
</tr>
<tr>
<td>Kidney</td>
<td>nephroblastoma</td>
<td>1.26</td>
<td>5.98E−06</td>
<td>428</td>
<td>5</td>
<td>10</td>
<td>WTI</td>
</tr>
<tr>
<td>small intestine</td>
<td>neuroendocrine carcinoma</td>
<td>0.98</td>
<td>1.19E−09</td>
<td>1154</td>
<td>10</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>hematopoetic and reticuloendothelial system</td>
<td>myelosclerosis</td>
<td>0.69</td>
<td>2.75E−09</td>
<td>2186</td>
<td>14</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>vulva and vagina</td>
<td>squamous cell neoplasms and carcinoma</td>
<td>0.63</td>
<td>1.37E−10</td>
<td>3092</td>
<td>17</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>mesothelium</td>
<td>mesothelioma</td>
<td>0.62</td>
<td>3.49E−06</td>
<td>1750</td>
<td>10</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>mucinous and mucinous cystic tumor</td>
<td>0.57</td>
<td>2.45E−07</td>
<td>2564</td>
<td>13</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>thyroid gland</td>
<td>papillary adenocarcinoma</td>
<td>0.56</td>
<td>2.77E−20</td>
<td>7863</td>
<td>41</td>
<td>82</td>
<td></td>
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<tr>
<td>central nervous system</td>
<td>neurofibroma</td>
<td>0.55</td>
<td>1.02E−05</td>
<td>2062</td>
<td>9</td>
<td>21</td>
<td>NFI</td>
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<tr>
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<td>neoplasm malignant</td>
<td>0.51</td>
<td>1.89E−05</td>
<td>2346</td>
<td>11</td>
<td>22</td>
<td></td>
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<tr>
<td>hematopoetic and reticuloendothelial system</td>
<td>polycythemia vera</td>
<td>0.50</td>
<td>0.97E−05</td>
<td>2173</td>
<td>10</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>hematopoetic and reticuloendothelial system</td>
<td>chronic lymphatic leukemia, b-cell</td>
<td>0.48</td>
<td>3.37E−13</td>
<td>7478</td>
<td>31</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>neoplasm malignant</td>
<td>0.47</td>
<td>1.20E−05</td>
<td>3015</td>
<td>13</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>lymph node</td>
<td>Hodgkin lymphoma</td>
<td>0.46</td>
<td>2.77E−09</td>
<td>5499</td>
<td>22</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>esophagus</td>
<td>squamous cell neoplasms and carcinoma</td>
<td>0.45</td>
<td>8.37E−09</td>
<td>5514</td>
<td>23</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>epithelial neoplasm and carcinoma</td>
<td>0.44</td>
<td>2.82E−05</td>
<td>3187</td>
<td>13</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Lip</td>
<td>squamous cell neoplasms and carcinoma</td>
<td>0.35</td>
<td>1.94E−05</td>
<td>7167</td>
<td>22</td>
<td>46</td>
<td></td>
</tr>
</tbody>
</table>

*Poisson distribution, two-sided test with 95% confidence level, p-values adjusted with FDR for multiple comparisons** CI-low ≈1.
doi:10.1371/journal.pone.0055209.t001
a diameter relative to E, and with the color shading indicating the O/E ratio in that city. The remaining map area illustrates the floating averages of the O/E ratios of the neighboring municipalities, excluding the largest cities. The map was based on borders of Finland before year 1940 because a large proportion of the KS patients were born before that.

**Determination of HHV8 Seroprevalence in Finland**

To estimate Human herpesvirus 8 (HHV8) infection rate in Finland, serological testing was performed in age and sex matched serum samples of 200 Eastern and 200 Western Finns obtained from the National Public Health Institute’s Health 2000 cohort. The serological analyses were done at HUSLAB (Helsinki, Finland) with direct HHV8 IgG antibody Enzyme Linked ImmunoSorbent Assay.

**Results**

We clustered 878,593 cases in FCR to assess the familial aggregation of various tumor types defined by topography and morphology. The clustering was performed based on tumor type, municipality of birth, and family name at birth (MN-clusters). As a result, we identified 25,910 MN-clusters representing 183 combinations of topography and morphology (see Table S3 for distribution of cases). All the clusters fulfilled the criterion that the number of cases in the cluster was higher than the expected number based on the distribution of family names and birth municipalities in Finland, with CI-low $\geq$ 1.

We also sought to estimate the tumor types that showed strongest evidence for familial occurrence, and for that we calculated cluster score for tumor types that produced significant MN-clusters. The clusters with the strongest confidence, CI-low $\geq$ 10, were considered, encompassing 4.7% of all MN-clusters and representing 169 tumor types (Table S3). This corresponds to 0.3% of the patients in FCR.

Tumor types and respective cluster scores with FDR adjusted p-values $< 0.0001$ are displayed in Table 1. Cluster scores and p-values for all tumor types are listed in Table S3. Most of the top scoring tumor types indicated rare cancer predisposition syndromes. The most frequently clustered tumor type was hemangio-blastoma, a common finding in patients with the Von Hippel-Lindau syndrome (VHL [MIM #193300]) (cluster score 4.98). The second most frequently clustered tumor type was medullary thyroid carcinoma indicative of patients with Multiple Endocrine Neoplasia type 2 (MEN2A [#171400] and MEN2B [#162300]) (cluster score 3.55). Among the most common tumor types showing strong evidence for familial occurrence were papillary thyroid adenocarcinoma (cluster score 0.56), chronic lymphatic leukemia (cluster score 0.48), and squamous cell carcinoma of the lip (cluster score 0.35), all with over 7000 registered patients in FCR (Table 1).

**Kaposi Sarcoma**

Familial occurrence of KS, the third most frequently clustered tumor type (cluster score 1.91), was further studied through genealogy as an example of the procedure to be followed with promising clusters in the systematic search. Out of the 23 KS patients in the MN-clusters, 16 (70%) were shown to be first-degree relatives within the cluster, and 14 of these belonged to clusters with CI-low $\geq$ 10 (Fig. 1). The genealogy revealed a family of five affected individuals with KS in two generations (Fig. 2). Two family members belonged to the same MN-cluster, and a third sibling and an affected cousin were connected to the family through genealogy work. We were able to confirm the mother’s KS diagnosis (she had died in 1962) from the radiotherapy records after it was verbally reported by her daughter.

The geographical distribution of KS incidence according to municipality of birth of the 537 KS patients in FCR showed a strikingly uneven pattern (Fig. 3). Patients accumulate almost entirely to the rural areas of Western Finland. Another aggrega-
Cases originate from Western Finland (Fig. 1). Eastern Finland, whereas most of the other ascertained familial
Interestingly, the family of five patients (Fig. 2) originates from

division of KS patients is seen in Northeastern Finland, while Eastern
Finland displays much less KS cases than expected by chance.
Interestingly, the family of five patients (Fig. 2) originates from
Eastern Finland, whereas most of the other ascertained familial
cases originate from Western Finland (Fig. 1).

Human herpesvirus 8, also known as Kaposi sarcoma-associated
herpesvirus, is a well-known etiologic factor for KS. To study
whether the uneven clustering of KS cases resulted from the
uneven distribution of HHV8 infections in Finland, we studied the
seroprevalence of HHV8 in 400 individuals from Eastern and
Western Finland. Four out of 400 individuals (1%) were HHV8
positive. Two of them originated from Eastern Finland and two
from Western Finland, suggesting similar seroprevalence of HHV8
in Eastern and Western Finland. However, the numbers are far
too small for a proper conclusion on possible geographical
variation of HHV8 infection in Finland.

Discussion

Here we have used an approach to systematically analyze
familial aggregation of all tumor types in nation-wide registry-

Figure 3. The observed/expected (O/E) ratios of Kaposi
sarcoma (KS) incidence according to municipality of birth.
Persons born in rural Western Finland have much higher incidence of KS
than persons born in Eastern Finland. Twenty-one largest cities are
indicated by circles. The white lining is superimposed on the colors of
the sparsely populated areas in Northern Finland (less than 1 inhabitant
per km²). The borders of Finland are based on those before year 1940.

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both common and rare tumor types. Tumor types showing the

greatest potential for familial occurrence were those that are
mainly seen in rare cancer predisposition syndrome patients -
a proof of concept that the method works well in estimating
familial occurrence. Unexpectedly, one of the top scoring tumor
types was Kaposi sarcoma with strong familial aggregation and
uneven geographical distribution. We were able to identify seven
families with two first-degree relatives with KS, and a family with
five KS cases, which to our knowledge is the third largest reported
KS family worldwide [16,17].

The described clustering method is designed to identify cancer
cases with similar phenotype and common family name at birth,
thus the method is able to detect also potential relatives outside the
nuclear family. The method is also applicable to other registered
diseases than cancer. Primary requirement is to obtain information
about family names and municipalities of patients, while
population-scaled data is needed for calculation of statistical
significance. Populations with enough diversity in family names
are suitable for similar clustering efforts and allow the formation of
statistically significant clusters. Due to the fact that family name in
Finland is usually inherited from father, the birth name-
municipality based clustering method is restricted to finding
family links only from the paternal side.

In this study, we were able to cover significantly more cases and
more detailed tumor types compared to previous familial
clustering efforts, such as those conducted in Icelandic [18] or
Utah population databases [19,20]. One limitation of our effort is the
lack of such extensive genealogy data for the studied individuals as in the studies in Iceland or Utah. However, the
diversity of family names in Finland (~100,000) and relatively little
migration before World War II – the time period when most of the
cancer cases in FCR were born – warrants our search for familial
occurrence with MN-clustering. In our example case of KS, we
were able to ensure familial relations through NPs and PRs for
70% of the cases in MN-clusters, and 88% of these clusters were of
high statistical significance with the lower confidence limit greater
than ten. Thus, calculating the statistical significance of clustering,
and choosing clusters with the high O/E and CI-low values
obviously increase the probability of identifying true relatives.

We concentrated on the most significant MN-clusters to
estimate the familial occurrence of the tumor types using cluster
score. Top two tumor types indicated known rare cancer
syndromes, namely Von Hippel-Lindau syndrome and Multiple
Endocrine Neoplasia type 2, suggesting that our approach is
feasible in identifying families with high-penetrance cancer
predisposition. One of the most interesting phenotypes with a high
cluster score was KS, which showed high tendency to cluster with
a frequency exceeding, for example, that seen in Wilms’ tumor.
Another phenotype among the top tumor types without known
gene etiology was neuroendocrine carcinoma of small intestine,
for which high familial risk has been described earlier [3,21].

Twin studies and systematic registry-based studies of all cancers
have been restricted to demonstrate the hereditary effect
concerning the most common cancer sites. In our study, the
strongest evidence for familial occurrence among the most
common tumor types was shown for papillary thyroid adenocarci-

oma, chronic lymphatic leukemia, and squamous cell carcino-
ma of the lip, each with over 7000 registered patients in FCR. The
very same cancer sites, although without detailed morphology
definitions, showed significant relatedness also in distant familial
relationships (no closer than first cousins) in Utah [20].

KS is a prevalent tumor type especially among HIV-infected
patients and in sub-Saharan Africa [22]. HHV8 is a well-
established etiologic factor for KS, and it is well acknowledged that
patients suffering from immunosuppressive conditions have higher risk for KS [16,17,25–28]. A recent study has suggested that the HHV8 infection rate is similar to that of other infections with similar risk factors [29–33]. However, no conclusive mutations predisposing to HHV8 infection have thus far been reported. KS is a vascular tumor with a predominance of 0.1–0.2 per 100,000 person-years in Finland in 1963–2010, adjusted for age to the World Standard Population. The incidence of KS according to municipality of birth is higher among family members of classic KS patients, and person-to-person transmission has been confirmed by the observation that in almost all cases the same viral genotype was shared within the family [37,38]. While intrafamilial transmission of HHV8 probably plays a role in the familial occurrence of KS in our data, it cannot explain in itself the number of KS patients as high as five within a single family without additional susceptibility to develop tumors.

It is likely that some high-penetrance tumor predisposing genes – particularly those of recessive inheritance and those that do not display easily recognizable syndromic features – remain unidentified. Poorly characterized combinations of multiple germline variants with moderate penetrance are likely to explain some proportion of the hereditary cancer burden. While such genetic susceptibility factors have previously been difficult to study, the molecular tools available for hereditary cancer gene identification have improved dramatically in recent years. Next-generation sequencing has highlighted the utility of very small numbers of carefully chosen affected individuals in genetic analyses [33,39,40]. Our approach is useful in deriving the most valuable specimens from the whole population for analyses of new cancer susceptibility conditions, including archival tissue blocks that can be utilized for generation of high-throughput DNA data for predisposition variant detection.

Supporting Information

Table S1 ICD-O-3 based morphology code groups used in the birth name-municipality based clustering. (DOCX)

Table S2 ICD-O-3 based topography code groups used in the birth name-municipality based clustering. (DOCX)

Table S3 Topography and morphology combinations in the birth name-municipality based clustering, distribution of patients, and cluster scores. (DOCX)

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Author Contributions

Conceived and designed the experiments: EM Aavikko PV RA E. Pukkala. Performed the experiments: EM TP E. Pukkala. Analyzed the data: EM M. Aavikko PV RL LA E. Pukkala. Contributed reagents/materials/analysis tools: PK ML. Wrote the paper: EM M. Aavikko PV TP SS OK E. Pukkala M. Artama RL LA E. Pukkala.

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