Meiotic Drive in Chronic Lymphocytic Leukemia compared with other Malignant Blood Disorders

Viggo Jønsson (viggo.jonsson@medisin.uio.no)  
University of Oslo

Haneef Awan  
University of Oslo

Neil Deaton Jones  
University of Copenhagen

Tom Børge Johannesen  
Cancer Registry of Norway

Klaus Thøgersen  
www.tpuk.dk

Bjarni á Steig  
National Hospital of the Faroe Islands

Gudrid Andorsdottir  
Genetic Biobank of the Faroe Islands

Geir Erland Tjønnfjord  
University of Oslo

Research Article

Keywords: chronic lymphocytic leukemia, malignant blood disorders, susceptibility

Posted Date: February 11th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-155676/v1

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Version of Record: A version of this preprint was published at Scientific Reports on April 12th, 2022. See the published version at https://doi.org/10.1038/s41598-022-09602-1.
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Viggo Jønsson, Haneef Awan, Neil Deaton Jones, Tom Børge Johannesen, Klaus Thøgersen, Bjarni á Steig, Gudrid Andorsdottir, Geir Erland Tjønnfjord

Viggo Jønsson
Viggo.jonsson@medisin.uio.no
correspondence
Department of Hematology, Oslo University Hospital, and
Institute of Clinical Medicine, University of Oslo
P.O. box 4950 Nydalen
NO 0424 Oslo, Norway

Haneef Awan
Haneef.awan@usit.uio.no
Center for Information Technology Service (USIT), Oslo University Hospital, and
Institute of Clinical Medicine, University of Oslo
P.O. box 1059 Blindern
NO 0316 Oslo, Norway

Neil Deaton Jones
Jonesneil73@gmail.com
Department of Computer Science
University of Copenhagen
Universitetsparken5, Building B
DK 2100 Copenhagen, Denmark

Tom Børge Johannesen
Tom.borge.johannesen@kreftregisteret.no
Norwegian Cancer Registry
Ullernchausseen 64
NO 0379 Oslo, Norway

Klaus Thøgersen
kt@tpu.dk
Industrial Consultant, Technology & Product Development, Ltd.
www.tpu.dk
Mølledamsvej 10
DK 3460 Birkerød, Denmark

Bjarni á Steig
bjast@ls.fo
National Hospital of the Faroe Islands
Medical Department
J.C. Svaboe gøta 2
F 100 Torshavn, Faroe Islands and
Genetic Biobank of the Faroe Islands
J.C. Svaboe gøta 43
F 100 Torshavn, Faroe Islands

Gudrid Andorsdottir
Gudrid@biobank.gov.fo
Genetic Biobank of the Faroe Islands
Abstract

Studies of families with two or more cases of malignant blood disorders (lymphoproliferative and/or myeloproliferative) provide a description of the pathway of susceptibility down through the generations towards the proband. The united observations fit into a non-Mendelian operational model consisting of parental genomic imprinting combined with feto-maternal microchimerism. Male affected
relatives of a proband are predominant in paternal lines with maternal imprinting, while female affected relatives are predominant in lines with maternal affiliation and paternal imprinting. The findings suggest the influence of a so-called polymorphic equilibrium with segregation distortion related to parental imprinting (fitness optimalization). In the generations before a proband, affected relatives with the same diagnosis may covariate, viz. be present with a higher frequency than expected (relative superiority); or contravariate, that is a lower frequency than expected (mutual minority). Covariation has been observed especially among affected relatives with multiple myeloma, diffuse large B-cell lymphoma, acute myeloid leukemia, Hodgkin’s lymphoma and some few other diagnoses. Contravariation is only seen among affected relatives with chronic lymphocytic leukemia. The dynamic drive of susceptibility in an affected family with birth order effect and/or anticipation is regarded as an additional polymorphic equilibrium with segregation distortion caused by feto-maternal microchimerism.

[197 words, max. 200 words]
INTRODUCTION

Non-Mendelian inheritance (meiotic drive) of susceptibility to mutation in the hematopoietic stem cells is the etiology of malignant blood disorders (MBD) (1). Chronic lymphocytic leukemia (CLL), the most common leukemia in the Western World, is a subset of MBD (1, 2). Together with other types of malignant lymphoproliferative disorders (LPD) such as acute lymphoblastic leukemia, other subsets of lymphoid leukemia, malignant lymphomas including Hodgkin lymphoma, myeloma and the myeloproliferative disorders (MPD), these all depend on a monoclonal expansion of blood cells derived from a mutated hematopoietic stem cell (1 - 3). Each disorder has its own cytogenetic profile (4 - 10), forming an inherited polygenetic model of disease susceptibility (11 - 13) with an evident familial occurrence (14 - 21).

It has been difficult to get a comprehensive overview of the inheritance process in spite of an intensive search for decades. We have proposed a segregation pattern of MBD based on the interaction of parental genomic imprinting (22 - 25) and fetomaternal microchimerism (26 - 28) (Figure 1). That model (29) gathers and explains the details known about the inheritance pathway in general, but CLL stands out. Genealogical studies of pedigrees from affected families show that CLL seems to have a meiotic drive of its own paths with a unique distribution of affected ancestors to a CLL proband (29). Only CLL has a demonstrable birth order effect (Table 1) and clinically, CLL-males and females have a different course of disease (31). Female patients usually have a better crude survival than males, a higher age at onset of disease, and a better dose-response to chemotherapy (30). These clinical differences between male and female patients sometimes occur in non-Hodgkin lymphomas (NHL) (32, 33), but not as clear as in CLL. Furthermore, we have recently assessed the distribution in the pedigree of MBD-affected ancestors to a proband with MBD (29). This results in a pattern of segregation with co- and contravariation and here too, CLL stands out.

The purpose of the present paper is to describe the characteristics of the transgenerational segregation of susceptibility to CLL compared with other diagnoses within MBD and to outline the modifications of the general segregation model (Figure 1) that CLL causes.

MATERIAL AND METHODS
The material consists of two types of MBD-families: 1) Families with unrelated parents (112 families and 301 cases of MBD) from Norway and Denmark. 2) One big family with related parents (315 cases of MBD from the endemic, consanguineous Faroese population). Percentages of MBD (i.e., rates, prevalence or frequencies) are in use because no data from the Faroe Islands is available for calculations of incidences. Official data from the Cancer Registries or other public health institutions regarding familial MBD do not exist either. Parts of this joint database were in use for genealogical investigations elsewhere (29, 34, 35).

Birth order effect

Birth order effect (BOE), which is a rank order by age of the affected sibs in a sibship was systematically assessed in the families by means of the Haldane & Smith’s method (36). This method is based on a comparison of the sum of rank numbers in the test sample with a theoretical rank sum as if no BOE exists, expressed as the 95% confidence interval (CI 95%). For control, the Wilcoxon signed rank test was used, comparing the sum of older (positive scores) and younger (negative scores) of healthy sibs to the affected sib in the sib ship (significance P<0.05). Statistical analysis was programmed using language R version 3.3 (www.r-3-3 project.org).

Anticipation

The number of patients within each diagnosis in the Norwegian and Danish families has been compared with the number of patients with the same diagnosis in the Cancer Registries of Norway and Denmark (chi-squared test, significance P < 0.05). Age at onset of disease was also included in this comparison.

The Norwegian and Danish MBD-families

One hundred and twenty families have been found in our hematologic out-patient clinics by asking new patients about other family members with possible MBD. Families with two or more cases of MBD were included. There were 276 cases of LPD (lymphoproliferative disorders), and 24 cases of MPD (myeloproliferative disorders), and one case of Leukemia NOS (Not Otherwise Specified), giving 2.7 patients per family.

The included persons were all of Scandinavian origin, there were no twins, and none have had unrelated parents. The observation period was largely the same as for the Faroese material. The oldest patient is a female with CLL, born in 1864.

All patients were cross-checked with the National Cancer Registries, and all members of the family, the healthy persons as well, were checked with the Civil Person Registry. In case of doubt, we checked with church books, midwives protocols, and transcripts from alimony judgements. All medical files were examined, and all diagnoses were cross-checked with the SNOMED registration of
the pathologists (37). The ICD-10 nomenclature was used for a standardization of the diagnoses from different periods with different taxonomic systems (38).

Parental affiliation

Each case of MBD in the family tree (designated proband crude, Pc) was associated with its affected relatives (ARs) and used for a systematic registration of familial MBD. Strictly vertical pairs of affected Pc – affected AR (viz. affected parent – offspring pairs) were selected for an estimation of the parental affiliation to ensure that only patients with a position in the pedigree that allow direct, transgenerational transfer of susceptibility from parent to child were involved (Table 2). Horizontal pairs such as concordance of two affected siblings are not included in the table.

Co- and contravariation

Covariation indicates a greater number of observed ARs (OBS) to a Pc than expected (EXP), while contravariation indicates a smaller number of OBS than EXP (chi-squared test).

Pairs of affected Pc – affected parent were sorted by the diagnoses CLL or nonCLL (all other diagnoses of MBD than CLL. This makes it possible to compare groups of pairs with AR CLL and AR nonCLL (Table 2).

Legal permissions to do the study: cf. Acknowledgements.

The Faroese MBD-family

As of December 2011, 341 cases of MBD have been recorded in the Faroese Diagnostic Registry in Torshavn, the capital of the Faroese Islands. During the years after 2011, all patients were cross-checked and patients with a delayed diagnosis were included. Three patients were excluded because the medical records have been lost, and 23 failed inclusion because their position in the family tree was uncertain (e.g. extramatrimonial relationship). Thus, 315 MBD patients, designated proband crude (Pc), were included since the first person (a female with CLL, born in 1884).

The Faroese people are descended from the Vikings (39). Today, there are nearly 53,000 people from a few thousand founders who survived the plague during the Black Death about 20 generations ago around 1350 (40). The population was under the influence of isolation and consanguinity right up to a period after WW II (40). Foreign settlers (on an average of one or two per year one hundred years ago) were mainly Scandinavian sailors and priests. The Coefficient of Inbreeding has never been calculated (41). The Faroese parity is one of the highest in Europa (7.4 in 1900 and 2.7 today) (40). Until 1870-80, childbed fever was a common
cause of maternal death, and many men were married several times. Then, after the introduction of high-sea fishing from small boats, many men drowned and many women married again.

The course of disease, symptoms, the medical record and the pathologist’s SNOMED diagnoses (37) were cross-checked. All included diagnoses were grouped according to the ICD-10 diagnostic system (38), and reassessed according to the diagnostic criteria valid at the time of diagnosis. In 45 cases, NOS (not otherwise specified)-diagnoses were used: (25 cases of uncertain subtype of NHL, 15 cases with uncertain distinction between myelodysplasia (MDS) and other subsets of MPD, and in five cases of lymphoid leukemia in elderly desolate patients who were not further investigated. There were no twins among the patients. BOE and anticipation were included in the screening.

Pedigree and parental affiliation
One united pedigree showing all affected and unaffected family members was provided by the Faroese National Civil Registry. Each patient was appointed to be proband crude (Pc), and a systematic registration of the affected relatives (ARs) in up to 5 generations before each Pc allowed an estimation of the parental affiliation of each AR related to Pc. Up to five healthy family members between Pc and AR in the Faroese pedigree defined the association between Pc and AR. Since a given patient in the generations before Pc may act as AR to several Pcs at the same time, the total number of ARs is higher than the actual number of patients with MBD.

Co- and contravariation
The calculation of EXP for this comparison rests on the prevalence given in Table 1. In HL for example: HL represents 8.7 % of all Faroese LPD (Table 1). According to our joint database, 121 AR LPD (68 males and 53 females) are related to HL so that the expected number of AR HL is 8.7 % of 121 = 10.53 ~ 11 HL patients (males 10.53 x 12/19 = 6.65 ~ 7 patients; females 10.53 x 7/19 = 3.88 ~ 4 patients). Table 3 shows all detected significant discrepancies between OBS and EXP.

Legal permissions to do the study: cf. Acknowledgements.

Anonymity
To ensure anonymity at publication, the patients have numbers without names or initials, and without data on gender, age, or place of birth so that no person can be recognized from the outside.
Informed consent.

All patients older than 18 years got oral and written information about the purpose of the study, that participation was voluntary and could be interrupted at any time. It was stated that all data was confidential and made anonymous, and that the investigation was approved by the Scientific Ethical Committees, and the National Data Registry Agencies. Included patients accepted their participation by completing a signed questionnaire. Each patient provided informed consent to participate in the study, thus informed consent was taken from all patients. Patients under the age of 18 years were included with informed consent from a parent or a legal guardian.

This study was approved by ethics committee

of the Ministry of Health and Social Service, Government of the Faroe Islands, and (for Norway) the Norwegian Research Ethical Committees, that includes the Data Inspectorate, the Social and Health Directorate and the Regional Committee for Medical and Health Research Ethics, South-East Norway. For Denmark the Royal Danish National Archives, comprising the Provincial Archives of Zealand, the Danish Data Protection Office, the Danish Scientific-Ethical Committees and the Danish Board of Health.

RESULTS

The diagnoses of the two groups (continental families from Norway and Denmark with unrelated parents; and the endemic, Faroese family with related parents) comprise both LPD and MPD. Continental families: LPD 92%, MPD 8%; Faroese family: LPD 70%, MPD 28% (Table 1).

CLL is the most common diagnosis in the continental families (65.6%) compared with a prevalence of 22.8% in the Faroese family. Two of the most common types of malignant lymphoma (FL and DLBCL) have a significantly lower prevalence both in the Faroese family and in the families from Norway and Denmark the families than reported by the Cancer Registries of Norway and Denmark (P < 0.05).

Anticipation is pronounced in the Faroese family with a high prevalence of ALL (7.3%) compared with 4% in the Cancer Registries. The mean age at onset of disease is lower than in the continental families (P < 0.01). We are uncertain whether the high incidences of HL and MPD in the Faroese family are signs of anticipation.

Birth order effect (BOE) is only seen in the Continental families, when male CLL patients in paternal lines appear late in the sib ship (P < 0.001).
**Segregation of susceptibility to MBD, Continental families.** Affected parent – affected offspring pairs (P-O pairs) make up the predominant transgenerational components (Table 1). Table 2 shows whether the MBD-susceptibility comes from the father line (paternal, PA) or from the mother line (maternal, MA) related to gender of the affected offspring (Table 2). All pairs of this table are affected parent-affected offspring. Therefore, AR (affected relative) is equivalent with P, and Pc (proband crude) is equivalent with O.

In 154 P-O pairs extracted from the pedigrees, the diagnoses were either CLL or any other diagnosis within MBD, denoted nonCLL. The intention of this set up is to expose CLL versus nonCLL in four P-O groups: CLL – CLL, nonCLL – CLL, CLL – nonCLL and nonCLL – nonCLL (Table 2).

For all four groups (Table 2, 1 – 4) there is a bi-parental affiliation of AR to PA (40.9%) and to MA (59.9%). Male AR are predominant in PA, female AR are predominant in MA (P < 0.01). CLL is predominant in AR-MA (60.4%) while in AR-PA, the content of CLL is 50.8% of all ARs. In pairs estimated with CLL as the marker (Table 2, line 1 and 2), the number of female AR CLL is higher than the number of male AR CLL (male/female ratio < 1). In contrast, we found a male/female ratio > 1 in pairs estimated with nonCLL as the marker (Table 2, line 3 and 4).

Mother-son transfer of susceptibility is predominant in MA. Father-son transfer is predominant in PA (Table 2).

**Segregation of susceptibility to MBD, the Faroese family.** In contrast to the continental families, there are nearly no parent – offspring pairs in the Faroese family and therefore neither sib concordance nor birth order effect (Table 1).

All Faroese ARs to a Pc within 5 generations before Pc were recorded in order to evaluate the parental affiliation of AR related to Pc (Table 3). Hereby, co- and contravariation are visible thanks to the high number of patients (ARs) of one single family with the reservation that when comparing with the Continental families, the parents are kindred in the Faroese material. Table 3 shows the findings of a systematic study of co- and contravariation of all diagnoses in the Faroese material. Diagnoses not mentioned in Table 3 do not show detectable co- or contravariation. The observed number of patients (OBS) is compared with the calculated, expected number (EXP), cf. Material and Methods, co- and contravariation.

Since a given patient in the generations before Pc may act as AR to several Pcs at the same time, the total number of ARs given in Table 3 is higher than the observed total number of Faroese patients (315 patients) as mentioned in Table 1.

The occurrence of a few affected parent – affected offspring pairs (Table 1) is presumably interference (overlap of multiple pairs of affected non-parent – affected offspring).

**Covariation** concerns AR nonCLL (Table 2, line 3 and 4; Table 3; Table 4, line 1-6). The observed ARs in pairs involved in covariation (Table 4, line 1 and 4) differs from ARs of the same pairs (same diagnoses of Pc and AR combined), with and without covariation that are totally registered in our joint database (Table 4, line 2 and 5). The ARs from pairs involved in covariation have a significant correlation to MA (Table 4, line 3 and 6), (P < 0.01, chi-square test, 2 degrees of freedom).

**Contravariation** concerns only AR CLL (Table 2, line 2; Table 3; Table 4, line 7-9). The ARs from pairs involved in contravariation have a significant correlation to PA (Table 4, line 9), (P < 0.05, chi-square test, 2 degrees of freedom).
DISCUSSION

The findings from the present study on the segregation of susceptibility to MBD (Table 1-4), are fused with a model of parental genomic imprinting (22) (Figure 1). In this model, a proband crude (Pc) can have affected relatives (AR) in paternal lines (PA) with maternal imprinting, and AR in maternal lines (MA) with paternal imprinting.

We have previously argued that the genetic component of MBD may be reappearance of parts of the fetal residual-genome, which long after birth can produce mutated hematopoietic monoclonies, i.e. MBD (29). The regulating factor is a so-called polymorphic equilibrium with segregation distortion related to parental imprinting (23, 24) and mainly to the segregation of genes of early embryonic growth factors (23 - 25, 42).

In such cases, fitness (in a biological sense) is generally higher than in Mendelian segregation (24), and the mean fitness is maximized by complete but opposite drive in the two fractions, PA and MA (23, 24). In mammals, fitness usually means maternal drive and maternal predominance, protection of the oocyte, and tight regulation of genes affecting the feto-maternal interface in placenta (43, 44). In CLL (31) and sometimes in NHL (32, 33), fitness means specifically that the overall 10 years survival and the response to treatments are better in females than in males.

In general, genomic imprinting of a pluripotent stem cell with subsequent differentiation brings about the same number of affected males and females, carriers and healthy people in PA and MA. The allocation of the stem-cell descendants to either PA or MA is permanent, sometimes denoted «the specific fate” (25).

If, on the other hand, it is about somatic cell differentiation after the initial pluripotent stage, where newly developed descendants of the stem cell become mother cells for new maturation cell lines, the fate may change (45). The genes involved can change under the influence of even more polymorphic equilibria, e.g. restricted gene-expression, epigenetic modifies (DNA methylation modifications) and epigenetic reprogramming moderators (clonal development and loss of genomic integrity (25, 45). In following generations, specific monogenes in the segregation of susceptibility to MBD undergo further segregation distortion to fractions of male and female ARs in PA and MA. Our present findings on the strong dominance of male ARs in PA and the modest accumulation of male ARs in MA, can hardly be explained without a polymorphic equilibrium with segregation distortion.

Co- and contravariation of AR are such opposite drives of “the two fractions”, PA and MA. In MA, there is an observed predominance of groups with covariation where PA, however, is not zero. In PA, where groups with contravariation predominate, MA is not zero (Table 4). It might look like a discrepancy that so many female AR CLL from MA contravariate, m/f ratio < 1 (Table 2, 2). We believe that AR CLL’s association with PA is correctly reported (Table 4) and that we see an opposite drive between PA and
CLL, and between MA and nonCLL. However, Table 2 is showing a selected material of affected parent-affected offspring pairs. Solo cases of CLL that are not included in pairs are not included in the calculations. Because CLL in the whole material has a m/f ratio > 1, and a high prevalence in the families investigated (unrelated parents in families from Norway and Denmark), the loss of male AR CLL becomes relatively noticeable, turning the m/f ratio low.

The physiological HLA-related microchimerism between mother and fetus completes the model of segregation of susceptibility to MBD (46 - 49). In that perspective, microchimerism belongs to the group of physiological segregation modifiers. Without the notion of drive of susceptibility by HLA mismatch and chimerism, the model would have no reasonable explanation for birth order effect (per-generational enhancement) or anticipation (trans-generational enhancement) (Figure 1). Apparently, chimerism between mother and fetus exerts a drive for the susceptibility. We do see affected pairs of mother-son where the HLA mismatch is greatest in families with unrelated parents, but not, or nearly not in families with related parents and thus a higher degree of HLA compatibility (Table 1). Here, MBDs appear more widely distributed in the family tree, presumably at such positions where the susceptibility of the proband can be expressed distant from the father and mother at places with a slightly higher mismatch, for example in the Faroe Islands, where many islands are scattered in the ocean. This is also in accordance with observations from Saudi-Arabia, where consanguineous parents have children with a lower frequency of MBD than seen in families with unrelated parents (50).

Familial cases of two of the most common subtypes of malignant lymphoma, the diffuse large B-cell lymphoma (DLBCL) and the follicular lymphoma (FL) have been found to have a lower frequency than in solo cases as reported by the Cancer Registries (51, 52). This trend is also seen in the present investigation, but not statistically significant. Hodgkin lymphoma, on the other hand, is well known in familial clustering (53 -55) as also seen in the Faroese family (Table 3) The findings must be taken with the reservation that the patients are alive and without symptoms at the time of registration but they may later in life develop MBD which ought to be included.

Heads of the Tables:

Table 1. Proband crude (Pc) in familial malignant blood disorders

<table>
<thead>
<tr>
<th>LYMPHOPROLIFERATIVE DISORDERS - LPD</th>
<th>Norwegian and Danish Families</th>
<th>The Faroese Family</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD-10 Code</td>
<td>Total (males, females)</td>
<td>%</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia CLL C91.1</td>
<td>181 (98, 83)</td>
<td>65.6</td>
</tr>
<tr>
<td>Acute lymphoblastic leukemia ALL C91.0</td>
<td>4 (2, 2)</td>
<td>1.4</td>
</tr>
<tr>
<td>Disorder</td>
<td>Cases</td>
<td>(Low, High)</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-------</td>
<td>-------------</td>
</tr>
<tr>
<td>Other Leukemias</td>
<td>14</td>
<td>(7, 7)</td>
</tr>
<tr>
<td>Multiple myeloma MM C90</td>
<td>10</td>
<td>(6, 4)</td>
</tr>
<tr>
<td>Monoclonal gammapathy MGUS D47.2</td>
<td>2</td>
<td>(1, 1)</td>
</tr>
<tr>
<td>Hodgkin lymphoma HL C81.1</td>
<td>11</td>
<td>(8, 3)</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma DLBCL C83.3</td>
<td>16</td>
<td>(9, 7)</td>
</tr>
<tr>
<td>Follicular lymphoma FL C82</td>
<td>19</td>
<td>(13, 6)</td>
</tr>
<tr>
<td>Other lymphomas</td>
<td>19</td>
<td>(11, 8)</td>
</tr>
<tr>
<td>Lymphoproliferative disease LPD total</td>
<td>276</td>
<td>(155, 121)</td>
</tr>
<tr>
<td>Age at onset of disease Years (median)</td>
<td>67</td>
<td>(65, 69)</td>
</tr>
<tr>
<td>Birth Order Effect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLL males, paternally</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent Offspring pairs</td>
<td>142</td>
<td>pairs</td>
</tr>
<tr>
<td>Siblings</td>
<td>42</td>
<td>pairs</td>
</tr>
</tbody>
</table>

**MYELOPROLIFERATIVE DISORDERS - MPD**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Cases</th>
<th>(Low, High)</th>
<th>Median</th>
<th>N</th>
<th>(Low, High)</th>
<th>Median</th>
<th>N</th>
<th>(Low, High)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myeloid leukemia AML C92.0 and C92.2-9</td>
<td>9</td>
<td>(6, 3)</td>
<td>37.6</td>
<td>2</td>
<td>44</td>
<td>(28, 16)</td>
<td>50.6</td>
<td>1.8</td>
</tr>
<tr>
<td>Chronic myeloid leukemia CML C92.1</td>
<td>3</td>
<td>(1, 2)</td>
<td>12.5</td>
<td>0.5</td>
<td>14</td>
<td>(9, 5)</td>
<td>16.1</td>
<td>1.8</td>
</tr>
<tr>
<td>Other MPD</td>
<td>12</td>
<td>(6, 6)</td>
<td>50.0</td>
<td>1.0</td>
<td>29</td>
<td>(15, 14)</td>
<td>33.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Total MPD</td>
<td>24</td>
<td>(13, 11)</td>
<td>100</td>
<td>1.2</td>
<td>87</td>
<td>(52, 35)</td>
<td>100</td>
<td>1.5</td>
</tr>
<tr>
<td>Age at onset of disease Years (median)</td>
<td>63</td>
<td>(59, 68)</td>
<td>54</td>
<td>(49, 60)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affected parent (AR) – offspring (PC) pairs</td>
<td>Markers</td>
<td>PA</td>
<td>MA</td>
<td>Total</td>
<td>Male/female ratio of AR Total</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>-------------------------------------------</td>
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<td>-----------------------------</td>
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<td></td>
</tr>
<tr>
<td>1. CLL - CLL</td>
<td>CLL: AR: 25 (22, 3)</td>
<td>43 (7, 36)</td>
<td>68 (29, 39)</td>
<td>0.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PC: 25 (19, 6)</td>
<td>43 (24, 19)</td>
<td>68 (43, 25)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Non CLL – CLL and CLL – Non CLL</td>
<td>CLL: AR: 7 (7, 0)</td>
<td>12 (2, 10)</td>
<td>19 (9, 10)</td>
<td>0.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PC: 21 (12, 9)</td>
<td>18 (12, 6)</td>
<td>39 (24, 15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Non CLL – CLL and CLL – Non CLL</td>
<td>Non CLL: AR: 21 (19, 2)</td>
<td>18 (2, 16)</td>
<td>39 (21, 18)</td>
<td>1.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PC: 7 (2, 5)</td>
<td>12 (6, 6)</td>
<td>19 (8, 11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Non CLL – non CLL</td>
<td>Non CLL: AR: 10 (10, 0)</td>
<td>18 (5, 13)</td>
<td>28 (15, 13)</td>
<td>1.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PC: 10 (8, 2)</td>
<td>18 (10, 8)</td>
<td>28 (18, 10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Co- and contravariation of affected relatives to probands crude with familial malignant blood disorders (the Faroe Islands)

<table>
<thead>
<tr>
<th>ICD-10 codes</th>
<th>PROBANDS CRUDE (PC)</th>
<th>AFFECTED RELATIVES (AR)</th>
<th>INCREASE, COVARIATION</th>
<th>INCREASE, COVARIATION</th>
<th>DECREASE, CONTRAVARIATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>HL</td>
<td>OBS</td>
<td>OBS</td>
<td>HL: 17 (10, 7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C81</td>
<td>EXP</td>
<td>EXP</td>
<td>HL: 11 (7, 4)</td>
<td>P &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>FL</td>
<td>OBS</td>
<td>OBS</td>
<td>MM: 22 (14,8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C82</td>
<td>EXP</td>
<td>EXP</td>
<td>MM: 15 (9, 6)</td>
<td>P &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>DLBCL</td>
<td>OBS</td>
<td>OBS</td>
<td>DLBCL: 37 (14, 23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C88.3</td>
<td>EXP</td>
<td>EXP</td>
<td>DLBCL: 28 (17, 11)</td>
<td>P &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>NHL NOS</td>
<td>OBS</td>
<td>OBS</td>
<td>HL: 19 (12, 7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C85.9</td>
<td>EXP</td>
<td>EXP</td>
<td>HL: 12 (8, 4)</td>
<td>P &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>MM</td>
<td>OBS</td>
<td>OBS</td>
<td>FL: 27 (15, 12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C90</td>
<td>EXP</td>
<td>EXP</td>
<td>FL: 20 (13, 7)</td>
<td>P &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>OBS</td>
<td>OBS</td>
<td>ALL: 27 (11, 16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C92.0</td>
<td>EXP</td>
<td>EXP</td>
<td>ALL: 23 (14, 9)</td>
<td>P &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>MF</td>
<td>OBS</td>
<td>OBS</td>
<td>MF: 29 (16, 13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C92.1</td>
<td>EXP</td>
<td>EXP</td>
<td>MF: 12 (6, 6)</td>
<td>P &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>OBS</td>
<td>OBS</td>
<td>AML: 78 (45, 33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C92.0</td>
<td>EXP</td>
<td>EXP</td>
<td>AML: 60 (38, 22)</td>
<td>P &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>MM</td>
<td>OBS</td>
<td>OBS</td>
<td>MM: 73 (41, 32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C92.1</td>
<td>EXP</td>
<td>EXP</td>
<td>MM: 48 (30, 18)</td>
<td>P &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>OBS</td>
<td>OBS</td>
<td>AML: 37 (22, 15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C92.1</td>
<td>EXP</td>
<td>EXP</td>
<td>AML: 27 (17, 10)</td>
<td>P &lt; 0.05</td>
<td></td>
</tr>
</tbody>
</table>

Diagnosis abbreviations: Cf. TABLE 1
OBS: Number of patients observed
EXP: Calculated number of patients using prevalence given in Table 1.
Covariation: OBS > EXP
Contravariation: OBS < EXP
Table 4. Paternal (PA) and Maternal (MA) affiliation of Affected Relatives (AR) in co- and contravariation (the Faroe Islands)

Table 4. Paternal (PA) and Maternal (MA) affiliation of Affected relatives (AR) in co- and contravariation (shown in Table 3), the Faroe Island

<table>
<thead>
<tr>
<th>COVARIATION</th>
<th>AR in Pc-AR pairs, lymphoproliferative disorders (LPD) shown in Table 3 with covariation:</th>
<th>AR PA</th>
<th>AR MA</th>
<th>AR Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1. total (males , females)</td>
<td>86 (43, 43)</td>
<td>151 (83, 68)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>%</td>
<td>36 (34, 39)</td>
<td>64 (66, 61)</td>
</tr>
<tr>
<td></td>
<td>2. For comparison: AR in all PcLPD-AR pairs of the material</td>
<td>2. total (males, females)</td>
<td>593 (349, 244)</td>
<td>563 (329, 234)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>%</td>
<td>51 (51, 51)</td>
<td>49 (49, 49)</td>
</tr>
<tr>
<td></td>
<td>3. Difference between 1. and 2. (%)</td>
<td>AR PA</td>
<td>AR MA</td>
<td>AR Total</td>
</tr>
<tr>
<td></td>
<td></td>
<td>minus 15 ( minus 17, minus 12)</td>
<td>15(17, 12)</td>
<td></td>
</tr>
</tbody>
</table>

COVARIATION

AR in Pc-AR pairs, myeloproliferative disorders (MPD) and mixed LPD and MPD shown in Table 3 with covariation:

<table>
<thead>
<tr>
<th>AR PA</th>
<th>AR MA</th>
<th>AR Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. total (males , females)</td>
<td>110 (68 ,42)</td>
<td>187 (99, 88)</td>
</tr>
</tbody>
</table>
% 37 (41, 32) 63 (59, 68) 100

5. For comparison: AR in all PcMPD-AR pairs of the material

<table>
<thead>
<tr>
<th></th>
<th>AR PA</th>
<th>AR MA</th>
<th>AR Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>5. total (males, females)</td>
<td>398 (240, 158)</td>
<td>366 (213, 153)</td>
<td>764 (453, 311)</td>
</tr>
<tr>
<td>%</td>
<td>52 (53, 51)</td>
<td>48 (47, 49)</td>
<td>100</td>
</tr>
</tbody>
</table>

6. Difference between 4. and 5. (%):

<table>
<thead>
<tr>
<th></th>
<th>AR PA</th>
<th>AR MA</th>
</tr>
</thead>
<tbody>
<tr>
<td>minus 15 (minus 12, minus 19)</td>
<td>15 (12, 19)</td>
<td></td>
</tr>
</tbody>
</table>

CONTRAVARIATION

AR in PcLPD-ARCLL pairs and from PcMPD-ARCLL pairs, myeloproliferative disorders (MPD) and mixed LPD and MPD shown in Table 3 with contravariation:

<table>
<thead>
<tr>
<th></th>
<th>AR PA</th>
<th>AR MA</th>
<th>AR Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. total (males, females)</td>
<td>65 (42, 23)</td>
<td>54 (26, 28)</td>
<td>119 (68, 51)</td>
</tr>
<tr>
<td>%</td>
<td>55 (62, 45)</td>
<td>45 (38, 55)</td>
<td>100</td>
</tr>
</tbody>
</table>

8. For comparison: AR in all PcMPD-AR pairs of the material

<table>
<thead>
<tr>
<th></th>
<th>AR PA</th>
<th>AR MA</th>
<th>AR Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>8. total (males, females)</td>
<td>116 (72, 44)</td>
<td>159 (88, 71)</td>
<td>275 (160, 115)</td>
</tr>
<tr>
<td>%</td>
<td>42 (45, 38)</td>
<td>58 (55, 62)</td>
<td>100</td>
</tr>
</tbody>
</table>

9. Difference between 7. and 8. (%):

<table>
<thead>
<tr>
<th></th>
<th>AR PA</th>
<th>AR MA</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 (17, 7)</td>
<td>minus 13 (minus 17, minus 7)</td>
<td></td>
</tr>
</tbody>
</table>
Parent - Offspring
Maternal Imprinting
Mother - Son

[Generation]
I
II
III
IV
Legend to Figure 1:

Figure 1. Parental genomic imprinting denotes a transgenerational segregation that depends on the gender of the parents. One allele is transcriptionally inactivated (imprinted, silenced) while the other allele remains active. At each transgenerational passage, the imprint erases and then it regenerates making imprinting a lifelong mechanism. A distinction between maternal and paternal imprinting points out a stereotypic distribution of affected- and healthy persons, and carriers in the pedigree. The marked difference between maternal and paternal imprinting is visible in for example Prader-Willi and Angelman syndrome, where most cases have a q11-13 deletion of chromosome 15. A fetus that receives the chromosome with the deletion from the father will have Prader-Willi syndrome, and when the deleted gene comes from the mother, the child has Angelman syndrome. Thus, two imprinted genes are involved: One is maternally imprinted. A wild-type non-deleted gene from the mother with an imprinted copy of the gene (and a
deleted gene from the father) will give rise to Prader-Willi syndrome in the child. The other gene is paternally imprinted. A wild-type non-deleted gene from the father with an imprinted copy of the gene (and a deleted gene from the mother) will result in Angelman syndrome in the child.

**Signature, Figure 1:**
Square, male  
Circle, female  
Black, affected  
White, unaffected  
Black and white, carrier  
Black bold line, main pathway of segregation

**REFERENCES**


Danish Cancer Registry, http://www.nordcan.dk


ACKNOWLEDGEMENTS
We want to thank the Genetic Resource Centre, Ministry of Health and Social Service, Government of the Faroe Islands, Eirargardur 2, FO-100 Torshavn, Faroe Islands, for permission to do the study and for the access to data from the Faroe Islands (record no. July 18 and October 12, 2007). Special thanks to Mr. Hans Pauli Strøm, former Minister of Social Affairs and Health, Torshavn, for valuable information about the Faroese population. For permission to undertake the study in Norway, we thank the Norwegian Research Ethical Committees, Kongens gata 14, NO-0153 Oslo, Norway, that includes the Data Inspectorate (record no. 07/00254-2), the Social and Health Directorate in Oslo (record no. 07/324) and the Regional Committee for Medical and Health Research Ethics, South-East Norway (record no. S.-06353b). For permission to undertake the study in Denmark, we thank the Royal Danish National Archives, Kalvebod Brygge 34, DK-1560 Copenhagen K, comprising the Provincial Archives of Zealand (record no. 2000-441-0023), the Danish Data Protection Office (record no. 2000-41-0184), the Danish Scientific-Ethical Committees (record no. 01-224/01), and the Danish Board of Health (record no.123-63-2000), Faculty of Health and Medical Science, University of Copenhagen, Blegdamsvej 3B, DK-2200 Copenhagen N. The Travel Found, Oslo University, is thanked for financial support for a study trip to the Faroe Islands.

AUTHORS CONTRIBUTION

Viggo Jønsson prepared the draft for the manuscript and all authors reviewed and corrected the text. Haneef Awan did the bulk data processing and constructed the tables and the figure. Neil Deaton Jones and Klaus Thøgersen supervised the interpretation of data related to mathematical models. Tom Børge Johannesen made a cross-check of all patients and healthy family members of all included Continental persons. Bjarni á Steig and Gudrid Andorsdottir cross-checked all Faroese patients and provided the united pedigree of the Faroese patients. Geir Erl End Tjønnfjord supervised the final version of the manuscript.

DATA AVAILABILITY

Data are stored at the National Norwegian Cancer Registry, Ullernchausseen 64. NO 0379, Oslo, Norway, att. Dr. Tom Børge Johannesen.
COMPETING INTERESTS

None of the authors declare competing interests.

INFORMED CONSENT

The patients were informed about the purpose of the study, that it was free to decline at any time, and that the investigation was approved by the Scientific Ethical Committees and done according to the Declaration of Helsinki. It was clearly stated that data would remain confidential and unrecognizable outside the study. Each patient confirmed participation by completing a questionnaire, approved by the National Ethical Committees.