Inheritance of Susceptibility to Malignant Blood Disorders

Viggo Jønsson1,2, Haneef Awan2,3, Neil D. Jones4, Tom B. Johannesen5, Bjarni á Steig6,7, Gudrid Andosdottir6,7 & Geir E. Tjønnfjord1,2

Malignant blood disorders depend on heritable susceptibility genes and occur in familial aggregations. We suggest a model of transgenerational segregation of the susceptibility genes based on the study of malignant blood disorders in Norwegian and Danish families with unrelated parents, and in the inbred Faroese population with related parents. This model, consisting of parental genomic imprinting and mother-son microchimerism, can explain the male predominance in most of the diseases, the predominance of affected parent-offspring when parents are not related, and the different modes of segregation in males and females. The model displays a specific pattern in the distribution of affected relatives for each diagnosis, viz. a characteristic distribution in the pedigrees of family members with malignant blood disorder related to the proband. Three such patterns, each reflecting a specific transgenerational passage, were identified: (1) alterations in the number of affected relatives in paternal lines alone, e.g. in patterns for probands with multiple myeloma; (2) alterations in the number of affected relatives in both paternal and maternal lines for probands with chronic lymphocytic leukemia; and (3) no alterations in the numbers of male and female affected relatives in the parental lines, e.g. for probands with some types of malignant lymphoma.

Strong evidence supports the notion that leukemia, lymphoma, myeloma and other malignant blood disorders (MBD) in man constitute an entity of heritable diseases1–7, but the transgenerational transfer of the susceptibility to MBD is still largely unknown. Heritable susceptibility genes, so called risk genes, are necessary for the production of tumor in the form of a mutated blood cell monoclonal8,9. A repertoire of susceptibility genes for each diagnosis comprises one or a few specific genes combined with a number of unspecific genes that differ from patient to patient with the same diagnosis. Genome-wide association studies clearly show this so-called "genomic landscape", e.g. in the lymphoproliferative diseases (LPD) including chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), Hodgkin’s lymphoma (HL), non-Hodgkin’s lymphomas (NHL) and multiple myeloma (MM); and in the myeloproliferative diseases (MPD), e.g. chronic myeloid leukemia (CML), acute myelogenous leukemia (AML), myelofibrosis (MF), polycythemia vera (PV), and essential thrombocytosis (ET)10–17.

There are silent bystanders within this polygenic model of susceptibility (persons having congenic susceptibility without developing the pathognomonic mutation), and there is a range of aggressiveness (stage of disease) in patients with the same diagnosis, so that low-stage diseases with weak or no symptoms are easily overlooked and not included in the registration of hereditary, familial MBD. Genealogical studies of MBD in families18,19, and large-scale screenings from cancer registries20–24 confirm a wide variety of different diagnoses within LPD and MPD (pleiotropy), but show no clear signs of a Mendelian or other specific pattern in the transgenerational transfer. Until now, no satisfactory explanation of the predominance of males has been given, e.g. in CLL. Further open questions concern anticipation (increased severity of malignancy down through the generations and low age at onset of disease)4, and sib ship birth order effect (non-random in the ages of affected siblings)25, and a pronounced inconsistency with regard to co- and contravariation of diagnoses (degree of linking)23,24.

1Department of Hematology, Oslo University Hospital, KG Jebsen Center for B cell malignancies P.O. box 4950, Nydalen, NO 0424, Oslo, Norway. 2Institute of Clinical Medicine, University of Oslo, P.O. box 4950, Nydalen, NO 0424, Oslo, Norway. 3Department of Research Computing, University of Oslo, P.O. box 1059, Blindern, NO 0316, Oslo, Norway. 4Department of Computer Science, University of Copenhagen, Universitetsparken 5, Building B, DK 2100, Copenhagen, Denmark. 5Norwegian Cancer Registry, Ullernchausseen 64, NO 0379, Oslo, Norway. 6National Hospital of the Faroe Islands, Medical Department, J.C. Svabos gøta 1, FO 100, Torshavn, Faroe Islands. 7Genetic Biobank of the Faroe Islands, J.C. Svaboe gøta 43, FO 100, Torshavn, Faroe Islands. Correspondence and requests for materials should be addressed to V.J. (email: viggo.jonsson@medisin.uio.no)
We now describe a novel model of the segregation of susceptibility to MBD. Based on new genealogical investigations of a large number of families with MBD, we are able to recognize distinct transgenerational pathways of the susceptibility genes and to identify the mechanisms likely involved in the inheritance of MBD.

Material and Methods

Our study is based on a genealogical investigation of familial MBD in two groups. One group comprises 315 patients from the inbred population of the Faroe Islands. The other group comprises 301 patients from 112 families with MBD and unrelated parents from Norway and Denmark. In both groups, cross-checked pedigrees were used for study. For comparison, diagnosis frequencies were extracted from the National Cancer Registries in Norway and Denmark.

The Faroe Islands. Patients and diagnoses. Based on data from the Diagnostic Registry in Torshavn (capital of the Faroe Islands), all 341 known cases of MBD from the Faroe Islands up to December 2011 were considered for study. In a five year period after 2011, it was ensured that all patients with delayed diagnoses were enrolled after proper cross-check. Three patients failed inclusion due to lost medical record or insufficient data for the verification of MBD, and 23 patients failed because their exact position in the family tree was uncertain due to extramatrietal relationship and unauthorized adoption. They hardly represent a selective loss, the diagnoses were MM 4, AML 4, ALL 3, CLL 3, NHL NOS 3, ML 3, DLBCL 2, CML 1. (Names and abbreviations of diagnoses, cf. Table 1) Thus, 315 patients (LPD 219, MPD 87, others 9, Table 1) were included after cross-check, comprising a review of the medical record and the pathologist’s SNOMED registration related to clinical diagnosis, laboratory findings, radiological assessments, symptoms and course of disease. The diagnosis of each patient was reassessed according to the diagnostic criteria valid at the time of diagnosis. In malignant lymphomas, for example, the Faroese Diagnostic Registry includes during the observation period cases according to the American Registry of Pathology (1934), Rappaport- (1956, 1966), Lennert- (1967), Kiel- (1974), WHO- (1976) Working- (1982) and Real- (1994) classifications. Therefore, in order to obtain a common denominator for the study group, all included patients were grouped according to the ICD-10 diagnostic system. NOS-diagnoses (not otherwise specified) have been used in 45 cases: 25 cases where the cross-check could not definitely confirm the subtype of NHL (NHL NOS, ICD-10 C85.9), in 15 cases in which a clear distinction between myelodysplasia (MDS) and other types of MPD was not ascertained (ML NOS, ICD-10 C92.9), and in five cases of lymphoid leukemia in elderly desolate patients who died without further diagnostic procedure (Leukemia NOS, ICD-10 C91.3–91.5).

To assure anonymity, the patients were numbered for study and no name, initials or birthplace were used so that no recognition from the outside was possible. For each patient, data on gender, age at entry in the study, year of birth, age and year of diagnosis, aliveness or age and year at death, and the birth rank order of the patient with the number and gender of older and younger sibs were available. There were no twins among the patients.

Families and pedigrees. The National Civil Registry in Torshavn provided the pedigrees showing the position of patients with MBD and their kinship with unaffected family members over 5 to 6 generations in one big family. Progeny Software was used for the processing and storage of the pedigrees. The 315 included patients were designated Proband crude (Pc).

Population and sampling history. The genetic founders are the nearly two thousand descendants of the original Vikings who survived the Black Death around 1350 and reproduced themselves in about 20 generations to the approximately 50,000 inhabitants of today. Before 1900 foreign settlers, mainly European traders, crafts, Danish priests and administrative staff, constituted a minority with minimal effect on the Faroese genome. One hundred years ago, the influx of foreign people, mainly from other Scandinavian countries, was only about 10 persons per 5 years. The population increased from about 15,600 people in 1900 to about 49,700 in 2011, and the mean lifespan increased from about 45 years in 1900 to about 82 years in 2011. In this inbred population, fishermen and sailors from abroad and later British soldiers during WW II who found a bride on the Faroe Islands most often brought the females home, so the Faroese genome remained largely unaffected. The Coefficient of Inbreeding has never been calculated.

The Faroese parity is unique. The mean number of live births per female was 7.4 in 1900 and 2.7 in 2011, some of the highest figures in Europe. The age of the mother at first delivery was nearly the same as in Norway and in Denmark. The late fetal death rate per 1000 live births was 11.0 on the Faroe Islands compared with 5.0 in Norway and 5.6 in Denmark when investigated in the late 1990s. Estimated from data on first born singletons, the mean Faroese live born birth weight is significantly higher (3610 g plus/minus standard deviation 609 g) than that of Norway (3520 g plus/minus 574 g) and that of Denmark (3411 g plus/minus 585 g), the live born weight increasing with mother’s age and parity. These data on parity and birth weight are used in the discussion of growth factors (cf. Discussion).

The oldest patient included was a female with CLL, born 1884. Data from the Cancer Registries in Norway and Denmark was used for comparison with the familial cases. Within the observation period, the diagnostic intensity in the main islands appears to be nearly the same as in Denmark and Norway, but lower elsewhere on the Faroe Islands, especially in the beginning of the period and on small, remote islands far out in the ocean with few or no general practitioners. Apart from the last few decades there has been no tradition for a systematic report to the National Danish Cancer Registry in Copenhagen, and no Faroese cancer statistic on incidence and prevalence is available.

All methods were carried out in accordance with relevant guidelines and regulations concerning Cancer Registry Data and all protocols were approved by relevant licensing authorities (cf. Acknowledgements). Further, all patients were included with informed consent (cf. Informed consent). Participants under the age of 18 years were included with informed consent from a parent or a legal guardian.
### Table 1. Diagnoses. Comments: Pc, Proband crude, number of patients observed. NOS, not otherwise specified.

| Diagnoses                              | Familial Diagnoses Observed | Cancer Registries |
|----------------------------------------|-----------------------------|-------------------|
|                                        | The Faroe Islands | Norway and Denmark | Norway and Denmark |
|                                        | Pc | (males, females) | % | Total | (males, females) | % | % (mean) |
| **Lymphoproliferative Disorders**      |                |                      |               |                    |                      |               |
| Hodgkin’s lymphoma                     | 19 | (12, 7) | 8.7 | 11 | (8, 3) | 4.0 | 6 |
| Follicular lymphoma                    | 14 | (9, 5) | 6.4 | 19 | (13, 6) | 6.9 | 12 |
| Mantle cell lymphoma                   | 0 | 4 | (4, 0) | 1.4 | <1 |  |
| Diffuse Non-Hodgkin’s lymphoma         | 34 | (21, 13) | 15.6 | 16 | (9, 7) | 5.8 | 25 |
| Peripheral T-cell lymphoma             | 6 | (2, 4) | 2.7 | 2 | (2, 0) | 0.7 | 2 |
| Peripheral T-cell lymphoma             | 0 | 4 | (1, 3) | 1.4 | 2 |  |
| Non-Hodgkin lymphoma                   | 25 | (14, 11) | 11.4 | 9 | (4, 5) | 3.3 | 6 |
| Waldenström’s disease                  | 2 | (1, 1) | 0.9 | 8 | (5, 3) | 2.9 | 3 |
| Multiple myeloma                       | 50 | (31, 19) | 22.8 | 10 | (6, 4) | 3.6 | 14 |
| Acute lymphoblastic leukemia           | 16 | (10, 6) | 7.3 | 4 | (2, 2) | 1.4 | 4 |
| Chronic lymphocytic leukemia           | 50 | (29, 21) | 22.8 | 181 | (98, 83) | 65.6 | 22 |
| Prolymphocytic leukemia                | 2 | (1, 1) | 0.9 | 2 | (0, 2) | 0.7 | 1 |
| Hairy cell leukemia                    | 1 | (1, 0) | 0.5 | 1 | (0, 1) | 0.4 | 1 |
| Large granular T-cell leukemia         | 0 | 3 | (2, 1) | 1.1 | <1 |  |
| Monoclonal gammopathy                  | 0 | 2 | (1, 1) | 0.7 | 2 |  |
| Lymphoproliferative disease            | 219 | (131, 88) | 100 | 276 | (155, 121) | 99.9 | 100 |
| Male/Female ratio                      | 1.5 | 1.3 |  |  |  |  |  |
| Age at onset of disease                | 61 | (58, 64) | 67 | (65, 69) |  |  |  |
| Birth order effect                     | NO | Patrilineal CLL, only |  |  |  |  |  |
| **Myeloproliferative Disorders**       |                |                      |               |                    |                      |               |
| Acute myeloblastic leukaemia           | 44 | (28, 16) | 50.6 | 9 | (6, 3) | 37.6 | 70 |
| Chronic myeloid leukemia               | 14 | (9, 5) | 16.1 | 3 | (1, 2) | 12.5 | 15 |
| Polycythemia vera                      | 4 | (2, 2) | 4.6 | 6 | (4, 2) | 25.0 | 5 |
| Myelodysplasia                         | 2 | (0, 2) | 2.3 | 2 | (1, 1) | 8.3 | 5 |
| Myelofibrosis                          | 8 | (4, 4) | 9.2 | 1 | (0, 1) | 4.2 | 5 |
| Essential thrombocytosis               | 0 | 3 | (1, 2) | 12.5 | <1 |  |
| Myeloid leukemia, uncertain            | 15 | (9, 6) | 17.2 | 0 |  | <1 |  |
| Myeloproliferative disease             | 87 | (52, 35) | 100 | 24 | (13, 11) | 99.9 | 100 |
| Male/Female ratio                      | 1.5 | 1.2 |  |  |  |  |  |
| Age at onset of disease                | 54 | (49, 60) | 63 | (59, 68) |  |  |  |
| Birth order effect                     | NO | NO |  |  |  |  |  |
| **Other Malignant Disorders**          |                |                      |               |                    |                      |               |
| Leukemia, uncertain                    | 7 | (2, 5) | 1 (1, 0) |  |  |  |  |
| Malignant histiocytosis                | 2 | (0, 2) | 0 |  |  |  |  |
Norway and Denmark. Patients and diagnoses. Our joint database on familial MBD has 301 patients (LPD 276, MPD 24, other 1) up to December 2011 (Table 1). These families were observed for new cases of MBD in a five year period after 2011. All diagnoses were cross-checked with reports from the pathology departments, medical records of the hospitals, and registrations in national cancer registries in Norway and Denmark. The diagnoses were sorted according to the ICD-10 nomenclature[27], in the same way as described for the Faroese material. All patients belonged to the genuine Scandinavian population of Norway and Denmark. There were no twins and no consanguinity. The first known cases of CLL, a 51-year-old man born in Norway in 1872 with CLL since 1923, and a 54-year-old female from Denmark, born 1864 with CLL in 1918 were included.

Families, population and sampling history. The 301 patients were extracted from 112 families in our database with two or more cases of MBD and unrelated parents. Several thousands of MBD patients have been screened for familial disease during the past two decades or more. From an overall assessment, our database is extensive in the sense that a large and representative number of patients have been available for the present study.

The parity in Norway and Denmark is nearly the same. The mean number of live births per female was 4.2 in 1900 and 1.7 in 2011[25,26]. The mean late fetal death rate per 1000 live births was 5.3 in the late 1900s[21]. However, parity comprises children born alive, stillborn, and abortions where especially the early spontaneous abortions, experienced as a late, strong menstruation, are practically impossible to enumerate. Taken together, about 15% of all pregnancies end with a miscarriage in Scandinavia[25,26], but that figure too, is uncertain when estimating parity related to the mother in a mother-son microchimeristic scenario, because such elusive factors as the number of male partners and expected changes in male fertility during the observation period exert their influence.

All methods were carried out in accordance with rules and regulations concerning Cancer Registry Data (cf. Acknowledgements) and all patients were included with informed consent (cf. Information consent). Participants under the age of 18 years were included with informed consent from a parent or a legal guardian.

Statistics. Diseases. The MBD-patients observed in the Faroese family and in MBD-families from Norway and Denmark were compared with “a normal material” based on data from the whole population National Cancer Registries in Oslo[28] and Copenhagen[29], and from the LYFO-Registry[30] (Table 1). The diagnoses observed were expressed in per cent of the total LPD and total MPD, respectively, and the percentages (frequencies) were used for comparison of the findings in the Faroese family with the families from Norway and Denmark, and for comparison with the normal material. Significance was accepted for P < 0.05. Sex- and age-adjusted incidences and prevalences would have been ideal, but these parameters are not available in the Faroese material and cannot reliably be constructed retrospectively as described (cf. Material and Methods, the Faroe Islands, Population and sampling history). Age at onset of disease in the two groups of familial MBD was described and compared by means of two-sided Mann-Whitney's test.

Genealogy. Each patient with familial MBD (Table 1) was appointed Proband crude (Pc) and the number, diagnoses and position in the pedigree of his or her affected relatives (AR) were recorded (Fig. 1, Table 2).

The pedigrees of all Faroese Pc were manually formatted into one united pedigree to describe the inbred family in which the AR were registered only once with ties of kinship in paternal (PA) and/or maternal (MA) lines (Fig. 1). The AR associated a given Pc in the united Faroese pedigree were recorded with up to five healthy family members between Pc and AR in vertical (parental) lines and/or in other vertical, oblique lines (uncle, aunt). The AR included were allocated to one of the following groups (1) AR in both patrilineal and matrilineal lines (PA + MA), (2) in PA only (PA), (3) in MA only (MA), or (4) entirely mixed or unknown (PA = MA), which means that ancestors to the proband of father’s and mother’s lines are mixed due to inbreeding to such an extent that their parental affiliation could not be determined (Fig. 1). In the same way, Fig. 1 also shows the parental affiliation added from the smaller 112 families with unrelated parents from Norway and Denmark.

A given AR was registered only once per Pc in either PA or MA, the one chosen being the one closest to the proband. The united pedigree with the total overview of the large, inbred Faroese family made it feasible to rule out double entry of a given AR to the same Pc. However, a given patient in the pedigree could act as AR to several Pc, especially in parts of the pedigree with many patients, viz. a high density of Pc and many shared AR. This explains why the total number of observed AR (Table 2) can be significantly higher than the total number of Pc (Table 1), both in LPD and in MPD. Data from the smaller Norwegian and Danish MBD-families shows the same tendency although the number of shared AR per Pc is much lower (301 Pc from 112 MBD-families) than in the Faroese material.

In order to expose a common pattern in the transgenerational transfer of MBD-susceptibility, the united Faroese pedigree was used as a master for inferential visual pattern recognition[31,32] to identify the mechanism behind the distribution of AR and Pc. We considered all relevant mechanisms we could think of (the Mendelian modalities, genomic imprinting, mother-son and mother-daughter microchimerism, gene linkage etc.). There are four different groups of Pc-AR with different parental affiliation (Fig. 1). In order to estimate paternal and maternal inheritances separately as part of the pattern recognition, a uniform, monoparental assessment of AR was required. Proband standard (Ps) denotes such a monoparental affiliation of AR to a given Pc. In contrast to Pc, Ps counts only one parental affiliation with its ARs in either patrilineal (Ps-PA) or in matrilineal (Ps-MA) lines. The following guidelines were used to convert Pc to Ps: Group (1), Pc having ARs in both father’s and mother’s lines at the same time gave rise to twice the number of Ps, one for PA and one for MA. In Group (2) and (3), the number of Pc was equal to Ps. Data from Group (4) was allocated to either Ps-PA or to Ps-MA based on an estimation of which parental line that brought Ps and the majority of AR closest together. In other words the lowest number of healthy family members between Ps and AR compared in the father’s and mother’s line in the pedigree. Some 21 Faroese Pc (12 males and 9 females) had a very peripheral position in the pedigree so that no affected
predecessors could be seen. These cases of unknown parental affiliation were shared equally between Ps-PA and Ps-MA. The numbers of observed ARs are reported in Table 2, denoted OBS.

The number of OBS (Table 2) was compared with the expected number of AR (total, males, females), denoted EXP (Table 2). EXP (the null-hypothesis) was based on an equal distribution of the AR among the four groups: Psm-PA, Psm-MA, Psf-PA and Psf-MA, viz. 25% of OBS for each of the four groups.

The birth order effect, i.e., the rank in the sibship by age of affected sibs, was estimated for every Pc by means of the Haldane Smith test, in which the sum of rank numbers in the test sample (6A) was compared with the theoretical value and expressed as the 95% confidence interval (CI 95%). The Wilcoxon signed-ranks test was used for control, comparing the sum of positive (older) and negative (younger) rank numbers of affected sibs in the sibship with zero representing the median age of all healthy and affected sibs in the sibship.

To estimate anticipation, the number of patients in each diagnosis in the familial material (“observed”) was compared with the National Cancer Registry findings (“expected”) by chi-squared test.

Co- and contra variation in the Faroese material was estimated by means of a systematic comparison of AR per Pc, observed versus expected (chi-squared test, significance $P < 0.05$).

Statistical analysis was done with programming language R version 3.3 (www.r-3-3project.org).

Informed Consent. The patients were informed about the purpose of the study, that it was free to decline, of course, and that the investigation was approved by the Scientific Ethical Committee. Furthermore, that data would remain confidential and unrecognizable outside the study, and that data could be crosschecked with the National Cancer Registry and with the Civil Person Registry if necessary. Each patient confirmed participation by completing a questionnaire, approved by the National Ethical Committees.

Results

Diagnoses. The myeloproliferative disorders are more frequent in the Faroe material (28% of all MBD) than in the families from Norway and Denmark (8%). (Table 1) AML is predominant but with a frequency lower than expected when comparing with the percentage of AML reported by the whole-population Norwegian and Danish Cancer Registries ($P < 0.05$). In contrast, CML has nearly the same frequency in the families and in the cancer registries.

Regarding the lymphoproliferative pleiotropic diversity, CLL is increased in the Norwegian and Danish families compared with the percentage of CLL reported by the cancer registries ($P < 0.01$). A reduction of familial DLBCL compared with the occurrence of DLBCL in the cancer registries is confirmed in both the Norwegian and Danish families ($P < 0.01$) and in the Faroese family ($P < 0.05$). A near halving of FL is seen in families with...
MBD (P < 0.05), even when the uncertainty related to NHL NOS is taken into account (50% united NHL, ICD-10 C82–C85, reported by the cancer registries compared with 19.6% of the Norwegian and Danish families, and 36.1% of the Faroese families).

| Affected Relatives (mean)/Pc | Affected Relatives Total (males, females) in Ps groups |
|-----------------------------|-----------------------------|
| m/m | f/m | m/f | f/f | Ps/PA | Ps/MA | Psf/PA | Psf/MA | Totals |
| LPD/HL | 5.7 | 4.4 | 9.7 | 7.6 | OBS | 65(37, 28) | 25(13, 12) | 13(6, 7) | 18(12, 6) | 121(68, 53) |
| EXP | OBS | 30(17, 13) | 30(17, 13) | 30(17, 13) | 30(17, 13) | OBS/EXP (P) | 3(3, 3) | 0(0, 0) | −2(−2, 0) | −1(−1, 0) |
| LPD/NHL FL | 4.9 | 2.2 | 8.8 | 4.0 | OBS | 13(12, 1) | 19(12, 7) | 7(2, 5) | 25(18, 7) | 64(44, 20) |
| EXP | OBS | 16(11, 5) | 16(11, 5) | 16(11, 5) | 16(11, 5) | OBS/EXP (P) | 0(0, 0) | 0(0, 0) | −1(−1, 0) | 0(0, 0) |
| LPD/NHL DLBCL | 4.7 | 3.9 | 7.6 | 6.3 | OBS | 59(32, 27) | 42(23, 19) | 39(24, 15) | 41(20, 21) | 181(99, 82) |
| EXP | OBS | 45(25, 20) | 45(25, 20) | 45(25, 20) | 45(25, 20) | OBS/EXP (P) | 1(0, 0) | 0(0, 0) | 0(0, 0) | 0(0, 0) |
| LPD/NHL NOS | 5.9 | 3.7 | 7.5 | 4.7 | OBS | 28(19, 9) | 37(22, 15) | 39(23, 16) | 34(21, 13) | 134(82, 52) |
| EXP | OBS | 34(21, 13) | 34(21, 13) | 34(21, 13) | 34(21, 13) | OBS/EXP (P) | 0(0, 0) | 0(0, 0) | 0(0, 0) | 0(0, 0) |
| LPD/MM | 5.8 | 4.3 | 9.5 | 7.0 | OBS | 102(63, 39) | 88(46, 42) | 46(23, 23) | 77(48, 29) | 313(180, 133) |
| EXP | OBS | 78(45, 33) | 78(45, 33) | 78(45, 33) | 78(45, 33) | OBS/EXP (P) | 0(0, 0) | 0(0, 0) | −1(−1, 0) | −2(−2, 0) |
| LPD/CLL | 5.0 | 3.2 | 7.0 | 4.5 | OBS | 82(53, 29) | 77(51, 26) | 43(19, 24) | 38(23, 15) | 240(146, 94) |
| EXP | OBS | 60(37, 23) | 60(37, 23) | 60(37, 23) | 60(37, 23) | OBS/EXP (P) | 1(1, 0) | 0(0, 0) | −2(−2, 0) | −3(−3, 0) |

Table 2. Affected Relatives and Proband Pc and Ps, The Faroe Islands. Comments: Abbreviations, cf. Tables 1 and 2. m, males; f, females. OBS/EXP (P): observed versus expected (P, chi-squared test). Zero: observed not different from expected (P > 0.05). Positive values, observed higher than expected. Negative values, observed lower than expected. At the following levels: P < 0.05 score 1, P < 0.01 score 2 and P < 0.001 score 3.
The male/female ratio is higher on the Faroe Islands (P < 0.01) where affected sons appeared late in the sibship (P < 0.01).

The percentage of ALL reported by the cancer registries is not significantly different from the percentage in the Norwegian and Danish families (P > 0.05) while in the Faroese material, the proportion of ALL is nearly twice as high (P < 0.01).

The Faroese material has the most pronounced signs of malignancy and anticipation, for example the highest frequency of ALL and the lowest frequency of some indolent lymphomas, e.g. FL, and the lowest age at onset of disease, LPD (P < 0.05), MPD (P < 0.01). Male patients had in general a lower mean age at onset of disease than female patients in both the Faroese and in the Norwegian and Danish material, LPD (P < 0.05), MPD (P < 0.01). The male/female ratio is higher on the Faroe Islands (P < 0.05).

A significant birth order effect is only observed in the Norwegian and Danish CLL-families related to patrilineal inheritance where affected sons appeared late in the sibship (P < 0.05).

**Proband**

Each patient referred to in Table 1 was appointed as Proband crude (Pc). (Fig. 1) The positions in the pedigree of a patient's affected relatives (AR) were counted as described in section "Material and Methods, Statistics, Genealogy": PA + MA (AR in both parental lines; PA (paternal only); MA (maternal only); and PA = MA (mixed or uncertain). Analysis of Ps (Pc formatted into monoparental lines) in the inbred Faroese family showed that the number of Ps-PA and Ps-MA is not significantly different in LPD (P > 0.05) and MPD (P > 0.05), and that Ps-males are predominant compared with Ps-females in both in PA and MA (P < 0.01). Parent-offspring affected pairs are rare compared with oblique affected pairs between Ps and uncle, aunt, denoted "other vertical pairs", LPD 98%, MPD 100% (P < 0.001).

In contrast, the Norwegian and Danish families with unrelated parents shows that Ps-MA is larger than Ps-PA (LPD: P < 0.05; MPD: same tendency with small sample sizes). In both PA and MA, parent-offspring pairs are predominant (P < 0.01).

**Proband and parental affiliation.** All LPD and MPD in the Faroese material have an entirely stereotypic pattern where Pc-females have more AR than Pc-males (P < 0.001), and the AR/Pc ratio m/m is larger than f/f (P < 0.001) and m/f is larger than f/f (P < 0.001) (Table 2 to the left).

(Table 2) In AR/Ps (Table 2 to the right), OBS is the number of AR counted in the pedigree for Pc and transformed into AR/Ps. EXP is the expected ratio AR/Ps. The expected number of AR has been calculated as one fourth of the total observed AR equally distributed among the four Ps-groups Psm-PA, Psm-MA, Psf-PA and Psf-MA (cf. Material and Methods, Statistics, Genealogy). OBS and EXP were compared using chi-squared test.

AR/Ps displays three distinct patterns of distribution (PD). Each PD has a characteristic configuration of the probands and their affected relatives, males and females, related to the parental affiliations. (1) The most common PD, seen in LPD/MM, LPD/LPD, MPD/LPD, LDP/MPD, MPD/MPD, MPD/AML and MPD/CML, has in PA a higher number of AR-males related to Ps males and fewer AR-males related to Ps females than expected while in MA, the numbers of AR-males and AR-females are as expected. (2) A PD for Ps-CLL with increased male-AR to Ps-males in both PA and MA combined with decreased male-AR related to Ps-females in both PA and MA. This tendency was also seen in MM/CLL, CLL/CLL and LPD/other LPD, even though consisting of only small sample sizes. Finally, (3) a PD for NHL and ALL, where the numbers of AR-males and AR-females were generally not different from what was expected in PA and MA.

In contrast to the Faroese AR, belonging to one big family, there are 112 Norwegian and Danish families with a total of 301 MBD-patients, so that the mean number of MBD-patients per family is only 2.7, and the mean number of AR per Pc, (301-112)/112, is 1.7, too small for a reliable comparison with the huge numbers of AR in the Faroese material. However, taking data from Table 2 into account, it can be concluded that the parental affiliation of AR to Norwegian and Danish Ps is stronger in MA than in PA in LPD and MPD (P < 0.01), compared with an equal affiliation to PA and MA in the Faroese material (P > 0.05).

**Co- and contravariations.** All diagnoses have been systematically screened for co- and conra variation, comparing observed data versus expected. In HL, for example, Pc is 19 (12, 7), total (males, females), and the total of Pc-LPD is 219 (131, 88) (Table 1). The number of AR to HL is 121 (68, 53) (Table 2). Thus, if AR were equally expected, the expected number of total AR would be 19 × 121/219 = 10.5 compared with the observed 19 (chi-squared test = 4.90). Observed versus expected total ARs were males were compared in the same way. Significant results from the Faroe Islands:

- PcMM-contravariation AR: CLL
- PcMM-covariation AR: ALL, CML and ML NOS.
- PcDLBCL-contravariation AR: DLBCL and MM.
- PcDLBCL-contravariation AR: CLL
- PcnHL NOS-covariation AR: HL and DLBCL.
- PcaML-covariation AR: AML, MM and DLBCL.
- PcaML-contravariation AR: CLL and ML NOS.
- PcCLL-co- and contravariation AR: none.
- Covariation of the same diagnosis in Pc and AR (clustering): HL, DLBCL, MM, AML.

All diagnoses have been systematically screened for co- and contra variation, comparing observed data versus expected. In HL, for example, Pc is 19 (12, 7), total (males, females), and the total of Pc-LPD is 219 (131, 88) (Table 1). The number of AR to HL is 121 (68, 53) (Table 2). Thus, if AR were equally expected, the expected number of total AR would be 19 × 121/219 = 10.5 compared with the observed 19 (chi-squared test = 4.90). Observed versus expected total ARs were males were compared in the same way. Significant results from the Faroe Islands:
from IIaC to IIIaC, and from IIIacG to IVacG, Fig. 3) explaining the PD 2 in MA of pathway 2. Here, the pro-

duction of affected males by paternal imprinting, restricted to MA-lines (Fig. 3), is higher (more intensive) than 

expected, viz. higher than an equal distribution of AR, expressed by assigning one fourth of the total AR to each 

generation. Manifest disease depends on a certain load of susceptibility genes, for example black 

signature (imprinted genes) and at least two red letters (microchimeristic genomic changes). Paternal (PA) lines: 

 Manifest male disease accumulates e.g. in the father-son line to the left in the figure from IIIaB to IVaBD and 

farther on in the PA males in the next generations with highly expressed microchimeristic genomic changes 

(red capitals only). And in the PA lines of sons of carrier fathers, e.g. IVaCF and further down in the next 

generations, all with partial expression of the microchimeristic genomic changes (mixed red capital and red 

small letters). Thus, the male probands in PA lines have a greater number of male affected relatives than female 

probands, because the female probands create carriers that break up the continuous lines of affected males 

and thereby reduce the number of available affected relative males per female proband. Maternal (MA) lines: 

An equal number of carrier males and females are produced from affected females. Transgenerational lines of 

female carriers are produced in MA lines, e.g. to the right in the figure from IIIacG to IVacg and further on in 

the subsequent generations of MA.

Discussion

New cumulative data from families with multiple cases blood disorders (MBD) reveal three patterns of the distri-

bution (PD) of the patients in the family (Table 2). Assuming that a systematic description of the mutual positions 

of the patients in the pedigree to some extent reflects the segregation of the genetic susceptibility to MBD, pattern 

recognition37,38 exposes parental genomic imprinting39 together with mother-offspring microchimerism40–44 as 

the likely mechanisms involved in the transgenerational segregation of the susceptibility genes. Figures 2 and 3 

were used to describe the interaction of these mechanisms in the conversion of the static PD into the dynamic 

operative algorithms (pathways).

Pathway 1 contains a higher number of male affected relatives (AR) related to male-Ps (proband standard) 

and fewer AR-males related to female-Ps in paternal (PA) lines than expected, and no significant changes in 

maternal (MA) lines (cf. Results, Proband and Affected Relatives, Table 2). Maternal imprinting combined with 

mother-son microchimerism can explain an increasing number of affected males with highly expressed suscepti-

bility (Fig. 2) and seems a plausible explanation of the surplus of males in LPD/MM, LPD/LPD, MP D/LPD, LDP/ 

MPD, MPD/MPD, MPD/AML and MPD/CML (Table 2). These PA-lines receive in addition affected males (e.g. 

IVaCF in Fig. 2) from father carriers (e.g. IIIaC) where the sons will proceed into the next generations as PA-lines 

with affected males in every generation. In contrast, affected females are produced only in every other generation 
on one line of descent with low expressive microchimeristic genomic changes, with offspring along the MA-lines 

that break up the continuous lines of AR-males available per female proband. Thus, affected females in PA-lines 

will have fewer affected males available, “spread of the AR in the pedigree”, than the affected males (Table 2).

Concomitant paternal imprinting and mother-son microchimerism (Fig. 3) of susceptibility genes from the 
genomic landscape of the diagnosis can explain the presence of affected mother-offspring pairs in a functionally 
balanced interaction between PD 1 and PD 2. A near equal number of affected males and females are produced. 
The affected males have a relatively weak expression of microchimeristic genomic changes (mixed red capital and 
red small letters) and no males have a strong expression (red capital only) like that seen in maternal imprinting. 
In other words, the microchimeristic genomic changes in males and females are more alike in MA-lines than in 
PA-lines. This can explain the non-significant difference when comparing the distribution of observed (OBS) 
males versus expected (EXP) males in MA-lines of PD 1 and pathway 1.

Pathway 2, related to CLL, has increased male-AR to male-Ps in both PA and MA-lines combined with 
decreased male-AR related to female-Ps in both PA and MA-lines (cf. Results, Proband and Affected Relatives, 
Table 2). Concomitant maternal imprinting and mother-son microchimerism is assumed to exert its action as 
described above related to PD1 and pathway 1. In CLL, however, especially in families with unrelated parents, 
affected mother-son pairs are the most frequent transgenerational combination (Fig. 1), indicating a stronger 
affinity of mother’s susceptibility to sons than to daughters. That concerns the paternal imprinting and its 
mother-son microchimerism in such a way that affected males become predominant (e.g. in the combinations 
from IIAc to IIIaC, and from IIIaG to IVaC, Fig. 3) explaining the PD 2 in MA of pathway 2. Here, the pro-
duction of affected males by paternal imprinting, restricted to MA-lines (Fig. 3), is higher (more intensive) than 
expected, viz. higher than an equal distribution of AR, expressed by assigning one fourth of the total AR to each 


of the four Ps-groups Psm-PA, Psm-MA, Psf-PA and Psf-MA. That’s exactly what is seen in the distribution of male-AR to CLL female-Ps in MA-lines (e.g. LPD/CLL, Table 2).

Pathway 3, related to NHL and ALL (Table 2), exhibits an expected number of affected males and females in both PA and MA-lines, which is easily explained as a merge of Figs 2 and 3 where affected males and females have nearly the same microchimeristic genomic expression (A = a, B = b, C = c etc.) without predominance of affected males.

Figures 2 and 3 depict a situation with stronger microchimeristic genomic charge in males (red capitals) than in females (red small letters) but otherwise, the pathways are assumed to act in concert depending upon the MBD-diagnoses related to the pleiotropic susceptibility genes present in the patient (“the genomic landscape”). Gradual deviations from the pathways, for example in LPD/HL (Table 2), are theoretically expected in advance due to degrees of gene expressivity (penetrance), variations in trigger-environmental epigenetic stimuli, co- and contravariation, and the number and range order by age of the sons in the sib ship. By means of the AR/Pc ratios as a kind of control (Table 2 to the left) it is easy to see that the ratios AR/Pc-females are generally higher than AR/Pc-males as expected when the number of affected females is lower than the number of affected males (Table 1). Ratios with AR males are generally higher than ratios with AR females as expected when the number of affected males is higher than the number of affected females (Table 1), especially in CLL. The increased number of male CLL-patients has been a mystery for decades so far, there have been no evident hormonal or any other pathophysiological explanations.

The genetic mode of segregation in the three pathways emerged while trying to match our findings against all known Mendelian and non-Mendelian modalities. Parental genomic imprinting combined with mother-son microchimerism appeared as a comprehensive correct solution bringing about a strong match, especially when both maternal and paternal imprinting are combined. Maternal imprinting causes accumulation of susceptibility in males (Fig. 2 to the left) and the formation of female carrier lines (to the right). Paternal imprinting causes accumulation of susceptibility in females (Fig. 3 to the right) and the formation of male carrier lines (to the left). Pattern recognition suggests that one combine both mechanisms to explain the presence in the pedigrees of affected father-offspring lines (in Fig. 2) and affected mother-offspring lines (in Fig. 3).

The many small families with unrelated parents from Norway and Denmark with a mean of only about 3 patients per family would never deliver such a clear PD as the Faroese with 315 patients in one family. However, the families from Norway and Denmark deserve attention because they support the idea of the model (Figs 2 and 3) that the degree of tissue-type compatibility (microchimerism) is relevant. We got a better match between our data and mother-son microchimerism than mother-son added daughter microchimerism. That could well be in accordance with the fact that mother-son microchimerism is the strongest due to difference in gender (“the gender barrier”). Thus, affected mother-son pairs are the most frequent parent-offspring combination in families with unrelated parents (Fig. 1). A birth order effect late in patrilineal sib ships was only seen in male CLL with unrelated parents (Table 1) at that precise place where mother’s acquired and accumulated tolerance to HLA of the father and of the male haploloads of the sons is assumed to be highest. That, however, does not exclude a certain degree of mother-daughter microchimerism at the same time which may even be theoretically expected by powerful mother-son microchimerism. Most likely so in Pathway 3, where the numbers of affected males and females in PA and MA are as expected. No birth order effect, nearly no affected parent-offspring pairs, and no sib concordance were seen in the Faroese material, where the HLA compatibility between mother-offspring and father is assumed to be relatively high due to consanguinity so that the microchimerism reaction is relatively weak. In consanguinity, the difference between maternal and paternal haploloads of the fetus may furthermore be evened out because both parents theoretically may confer different imprinted susceptibility, causing alterations in the stochastic, independent regulation of the proband.

Figure 3. Paternal imprinting and mother male-feto microchimeristic genomic change. Proposed model of the segregation of susceptibility. Paternal imprinting, otherwise the same signature as for Fig. 1. Paternal lines (PA): An equal number of carrier males and females are produced from carrier males under the formation of a continuous male carrier line (to the very left in Fig. 2). Maternal lines (MA): Accumulation of manifest female disease, e.g. in the mother-daughter line to the right in the figure from generation IIaC to IIIacG to IVacg and further on to the females in MA lines in the next generations. And in the MA lines of females of carrier mothers, e.g. IVabe and down with the females in MA lines in the subsequent generations, all with predominantly low expression of microchimeristic genomic changes (mainly small red letters). All affected males are produced in MA lines, and the affected males have in general a stronger expression of microchimeristic genomic changes than the affected females.
The statistical power of our findings can be discussed, especially since the patients have been sorted up in many diagnostic subsets and transgenerational groups. Compared with thousands of investigated patients with MBD from cancer registries and from genome-wide association studies, our patients represent small sample sizes. However, our findings get strength from being systematically cross-checked over several generations. This is especially true of the Faroese material, as far as we know the largest consanguineous population with MBD described up to now.

It is not really surprising to see parental genomic imprinting and microchimeristic genomic changes as the predicted mechanisms of the model, because both are well known to be related to MBD.

Parental genomic imprinting is seen in the segregation of mammalian growth factor genes, where subsets of genes required for the development are expressed at specific stages of life and in specific tissues from only one chromosome copy, depending upon the parental origin of that chromosome copy. Parental genomic imprinting has earlier been discussed as a possible mechanism behind the non-Mendelian genomic output in CLL. A common feature in the segregation of this group of genomic imprinted genes is a pronounced different outcome in paternal and in maternal imprinting. One classic example is the Prader-Willi and Angelman syndromes, caused by a partial deletion of chromosome 15 in most of the cases. If a fetus receives the chromosome with the deletion from the father, and the inactivated, imprinted copy of the gene from the mother (paternal imprinting), the fetus will have Prader-Willi syndrome. In contrast, a fetus receiving the partially deleted chromosome from the mother and the imprinted gene from the father (paternal imprinting) will have Angelman syndrome. Similarly, MBD is a syndrome closely related to the growth of monoclonal hematopoietic cells. Women with CLL or NHL have in general a better prognosis than male patients, including a better response to treatment with less toxicity and generally a higher age at onset of disease. These differences in MBD between the sexes, otherwise not definitely explained, could be seen as a different inheritance of susceptibility according to pathway 1 to 3. All known systems of mitotic drive (Non-Mendelian segregation) cause segregation ratios that are different between the sexes.

The relationship between alterations in growth factors and MBD is also seen, most likely, from the combined data on the high frequency of MBD on the Faroe Islands, the high birthweight and the high rate of miscarriages and stillborn. A relationship between development of MBD (ALL is the most studied) and a high body weight of the patient as newborn has been shown in other studies as well as an increased frequency of miscarriages and abortions in mothers to MBD patients.

In such systems of interacting genes, modifier genes may invade the system during the evolution. Therefore, a modifier to our model was theoretically expected. Microchimerism was an option in our pattern recognition for such a modifier. Microchimerism has previously been described in MBD as a mechanism for development of autoimmunity, graft-versus-leukemia effect, and the mechanism of birth order effect due to increased acquired tolerance of the mother in step with her parities and the number of her male partners. Also, the specific type of microchimerism in MBD has been discussed in the light of tolerance related to the degree of tissue-type compatibility (HLA-match) between mother, offspring and father. Microchimerism has furthermore been related to the pathophysiology of some types of solid cancer, e.g. breast cancer.

Microchimeristic susceptibility could be one mechanism behind anticipation, seen in the accumulation of susceptibility in the pedigree with increased genomic diversity in "the genomic landscape" down through the generations. Anticipation can be interpreted as a process that enhances the expression of the susceptibility. It is fascinating that the model also suggests a strategy for loss of susceptibility and thereby a delicate balance between genomic accumulation and depletion, so that affected families after a number of generations will not be overloaded with susceptibility. Anticipation produces an increased number of high-malignant diseases, especially in younger patients. ALL, having a high frequency in the inbred Faroese material, is such an example with a very high mortality if untreated. In such cases, death leads to depletion of susceptibility in the population before and during fertile life.

The familial clustering of HL, seen in the present study (cf. Results, co- and contravariations) has previously been reported and ascribed to familial HLA-association. Also, the modest risk of familial NHL seen in the present study (percentage of familial FL and DLBCL below the percentage of FL and DLBCL reported by the Cancer Registries, Table 1) has been described. Comparing the findings in the Faroese family (related parents) with the families with MBD in Norway and Denmark (unrelated parents), HL and DLBCL have the highest percentage in the Faroese family where both parents due to inbreeding theoretically can transfer interfering with the families with MBD in Norway and Denmark (unrelated parents). HL and DLBCL have the highest degree of tissue-type compatibility (HLA-match) between mother, offspring and father. Microchimerism has furthermore been related to the pathophysiology of some types of solid cancer, e.g. breast cancer.

In conclusion, the model suggested is an operational interaction between parental genomic imprinting of susceptibility genes and mother-son microchimerism. Theoretically, the intensity of the mother-son microchimerism depends on the tissue-type compatibility among mother, sons and the father. This may well explain why the segregation has been observed to be tardive with related parents, and immediate (from parent to offspring) with unrelated parents. The model explains the male predominance, the unique pathway 2 in the segregation of susceptibility to chronic lymphocytic leukemia, and draws attention to the relevance of growth factor genes for monoclonal expansion.

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

References
1. Houlston, R. S. et al. Causation of chronic lymphocytic leukaemia, insight from familial disease. Leukemia Res. 27, 871–876 (2003).
2. Marti, G. E. et al. B-cell monoclonal lymphocytosis and B-cell, abnormalities in the setting of familial B-cell CLL. Cytometry B, Clin. Cytom. 52, 1–12 (2003).
3. Goldin, L. R. et al. Familial aggregation of Hodgkin lymphoma and related tumors. Cancer 100, 1902–1908 (2004).
4. Rumi, E., Passamonti, F. & Della Porta, M. G. Familial chronic myeloproliferative disorders, clinical phenotype and evidence of disease anticipation. J. Clin. Oncol. 25, 5630–5635 (2007).
5. Speedy, H. E., Sava, G. & Houlston, R. S. Inherited susceptibility to CLL. Adv. Exp. Med. Biol. 792, 293–308 (2013).
6. Morgan, G. J. et al. Inherited genetic susceptibility to multiple myeloma. Leukemia 28, 518–524 (2014).
7. Cerhan, J. R. & Slager, S. L. Familial predisposition and genetic risk factors for lymphoma. Blood 126, 2265–2273 (2015).
8. Couto, J. B. Hematopoietic-lymphoid neoplasms: principles of diagnosis. In: Greer, J. P., Forster, J., Lukens, J. N., Rogers, G. M., Passamonti, F. & Glader, B. (Editors) Wintrobe’s Clinical Hematology. Lippincott Williams & Wilkins, pp. 1913–1915 (2004).
9. Jan, M. & Majeti, R. Clonal evolution of acute leukemia genomes. Oncogene 32, 135–140 (2013).
10. Conde, L. et al. Genome-wide association study of follicular lymphoma identifies a risk focus at 6p21.3. Nat. Genet. 42, 661–664 (2010).
11. Crowther-Swanepoel, D. et al. Common variants at 2q37, 8q24.21, 15q21.3 and 16q24.1 influence chronic lymphocytic leukemia risk. Nat. Genet. 42, 133–136 (2010).
12. Enciso-Mora, V. et al. A genome-wide association study of Hodgkin’s lymphoma identifies new susceptibility loci at 2p16.1(REL), 8q24.21 and 10p14(GATA3). Nat. Genet. 42, 1126–1130 (2010).
13. Slager, S. L., Caporaso, N. E., de Sanjose, S. & Goldin, L. R. Genetic susceptibility to chronic lymphocytic leukemia. Semin. Hematol. 50, 296–302 (2013).
14. Speedy, H. E. et al. A genome-wide association study identifies multiple susceptibility loci for chronic lymphocytic leukemia. Nat. Genet. 46, 56–60 (2014).
15. Skibola, C. F. et al. Genome-wide association study identifies five susceptibility loci for follicular lymphoma outside the HLA-region. Am. J. Hum. Genet. 95, 462–471 (2014).
16. Perez-Andreu, V. et al. A genome-wide association study of susceptibility to acute lymphoblastic leukemia in adolescents and young adults. Blood 125, 680–686 (2015).
17. Berndt, S. I. et al. Meta-analysis of genome-wide association studies discovers multiple loci for chronic lymphocytic leukemia. Nat. Com. 7, https://doi.org/10.1038/ncomms10933 (2016).
18. Thompson, E. A. Pedigree analysis of Hodgkin’s disease in a Newfoundland genealogy. Ann. Hum. Genet. 45, 279–292 (1981).
19. Jonsson, V. et al. CLL family “pedigree 14” revisited: 1947–2004. Leukemia 19, 1025–1028 (2005).
20. Goldgar, D. E., Easton, D. F., Cannon-Albright, L. A. & Skolnick, M. H. Chronic lymphocytic leukemia: population-based assessment of cancer risk in first-degree relatives of cancer probands. J. Natl. Cancer Inst. 86, 1600–1608 (1994).
21. Amundadottir, L. T. et al. Cancer as a complex phenotype, pattern of cancer distribution within and beyond the nuclear family. PLoS Med. https://doi.org/10.1371/journal.pmed.0010065 (2004).
22. Goldin, L. R., Pfeiffer, R. M., Li, X. & Hemminki, K. Familial risk of lymphoproliferative tumors in families of patients with chronic lymphocytic leukaemia, results from the Swedish Family-Cancer Data Base. Blood 104, 1850–1854 (2004).
23. Wang, S. S. et al. Family history of hematopoietic malignancies and risk of non-Hodgkin lymphoma (NHL), a pooled analysis of 10211 cases and 11905 controls from the International Lymphoma Epidemiology Consortium (InterLymph). Blood 109, 3479–3488 (2007).
24. Landgren, O. et al. Risk of plasma cell and lymphoproliferative disorders among 14621 first-degree relatives of 4458 patients with monoclonal gammopathy of undetermined significance in Sweden. Blood 114, 791–795 (2009).
25. Emery, A. E. H. Parental age and birth order. In: Emery, A. E. H. (editor) Methodology in medical genetics, 2nd Edition. Churchill Livingstone, pp. 40–53 (1986).
26. http://www.snomed.org.
27. http://www.icd10data.com.
28. http://www.progeny/software/genetics.com.
29. Statistics Faroe Islands, http://www.hagsfova.no.
30. Genetic Biobank, Iegusaniid, http://www.biobank.gov.no.
31. Olsen, S. F. & Joenssen, H. D. High liverborn birth weights in the Faroese, a comparison between birth weights in the Faroese and in Denmark. J. Epidemiol. Community Health 39, 27–32 (1985).
32. Norwegian Institute of Public Health, http://www.folkehelseinstitut.no/hn/statistikk (birth and pregnancy statistics).
33. Statistics Denmark, http://www.statistikbanken.dk (population and birth).
34. Report from the Norwegian Cancer Registry, http://www.kreftregisteret.noregistries/cancer statistics.
35. Danish Cancer Registry, http://www.nordcan.dk.
36. LåFO, D Lymphoma Group, http://www.lymphoma.dk.
37. Sneth P. H. & Sokal R. R. Numerical Taxonomy: the Principles and Practice of Numerical Classification. San Francisco, W.H. Freeman and Comp. Publ., pp. 28–29 (1973).
38. Bishop, C. M. Pattern recognition and machine learning, graphical models. Heidelberg, Springer Publ., pp. 359–418 (2006).
39. Hartwell, L. H., et al. Genomic imprinting, parental origin affects the expression of some genes in mammals. In: Genetics, from genes to genomes, chapter 11, the eukaryotic chromosome. Boston, McGraw-Hill Comp., pp. 408–410 (2000).
40. Tanaka, A., Lindor, K., Ansari, A. & Gershwin, M. E. Fetal microchimerism in the mother, immunologic implications. Liver Transpl. 6, 138–143 (2000).
41. Nelson, L. J. Pregnancy and microchimerism in autoimmune disease, protector or insurgent? Arthritis. Rheum. 46, 291–297 (2001).
42. Nelson, L. J. Microchimerism in health and disease. Autoimmunity 36, 5–9 (2003).
43. Adams, K. M. & Gadi, V. K. Autoimmunity in CLL: grave consequences of gravidity. Leuk Lymphoma 47, 1445–1446 (2006).
44. Adams, K., Zhan, Y., Zhan, Y., Stevens, A. & Nelson, J. L. The changing maternal “self” hypothesis: A mechanism for maternal tolerance of the fetus. Placenta 28, 378–382 (2007).
45. Mihali, S. Sex differences in incidence and outcome of chronic lymphocytic leukemia patients. Leuk. Lymphoma 47, 1477–1480 (2006).
46. Catoovsky, D., Wadie, R. & Else, M. The clinical significance of patients’ sex in chronic lymphocytic leukemia. Hematologica 99, 1088–1094 (2014).
47. Gentile, M. et al. Italian external multicentric validation of the MD Anderson Cancer Center monogram and prognostic index for chronic lymphocytic leukemia patients, analysis of 1502 cases. Br. J. Haematol. 167, 224–232 (2014).
48. Pflug, N. et al. Development of comprehensive prognostic index for patients with chronic lymphocytic leukemia. Blood 124, 49–62 (2014).
49. Eckerlesey-Maslin, M. A. & Spector, D. L. Random monoallelic expression, regulating gene expression one allele at a time. Trends Genet. 30, 237–244 (2014).
50. Ubeda, F. & Haig, D. Sex-specific meiotic drive and selection at an imprinted locus. Genetics 167, 2083–2095 (2004).
51. Ubeda, F. & Haig, D. On the evolutionary stability of Mendelian segregation. Genetics 170, 1345–1357 (2005).
52. Sasaki, H. & Matsui, Y. Epigenetic events in mammalian germ-cell development, reprogramming and beyond. Nat. Genet. 9, 129–140 (2008).
53. Jonsson, V. et al. Familial chronic lymphocytic leukemia in Norway and Denmark, comments on pleiotropy and birth order. In Vivo 24, 85–96 (2010).
54. Cassidy, S. B. & Driscoll, D. J. Prader-Willi syndrome. Eur. J. Hum. Genet. 17, 3–13 (2009).
55. Hedström, G., Peterson, S., Berglund, M., Jerkeman, M. & Enblad, G. Male gender is an adverse risk factor only in young patients with diffuse large B-cell lymphoma, a Swedish population-based study. *Acta Oncol.* **54**, 924–932 (2015).

56. Roman, E. *et al.* Childhood lymphoblastic leukaemia and and birthweight, insight from pooled analysis of case-control data from Germany, the United Kingdom and the United States. *Eur. J. Cancer* **49**, 1437–1447 (2013).

57. O’Neill, K. A. *et al.* Infant birthweight and risk of childhood cancer, international population-based case control studies of 40 000 cases. *Int. J. Epidemiol.* **44**, 153–168 (2015).

58. Hartl, D. L. Modifier theory and meiotic drive. *Theor. Popul. Biol.* **7**, 168–174 (1975).

59. Reik, W. Stability and flexibility of epigenetic gene regulation in mammalian development. *Nature* **447**, 425–432 (2007).

60. Van Rood, J. J., Scaradavou, A. & Stevens, C. E. Indirect evidence that maternal microchimerism in cord blood mediates a graft-versus-leukemia effect in cord blood transplantation. *Proc. Natl. Acad. Sci. USA* **109**, 2509–2514 (2012).

61. Bianch, D. W. & Roberts, E. Fetomaternal cell trafficking, a story that begins with prenatal diagnosis and may end with stem cell therapy. *J. Pediatr. Surg.* **42**, 12–18 (2007).

62. Dawe, G. S., Tan, X. W. & Xiao, Z. C. Cell migration from baby to mother. *Cell Adh. Migr.* **1**, 19–27 (2007).

63. Gadi, V. K. Fetal microchimerism in breast from women with and without breast cancer. *Breast Cancer Res. Treat.* **121**, 241–244 (2010).

Acknowledgements

The study was undertaken in accordance with the Declaration of Helsinki. We thank the Genetics Resource Centre, Ministry of Health and Social Service, Government of the Faroe Islands for permission to do the study and for access to data, (record no. July 18, October 12, 2007) and the Norwegian 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. S-06353b), the Royal Danish Archives and the Provincial Archives of Zealand (record no. 2000-441-0023), the Danish Data Protection Agency (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) for approving the study. One of us, Viggo Jønsson, received the Oslo University Travel Fund for travel to the Faroe Islands in connection with the present study.

Author Contributions

Viggo Jønsson, Haneef Awan and Neil Deaton Jones wrote the main manuscript text. All authors reviewed the manuscript. Haneef Awan did the bulk data processing and administrated the pedigrees. Neil Deaton Jones supervised the data processing and the interpretation of data. Tom Børge Johannesen cross-checked the family of each patient. Bjarni á Steig administrated the Faroese patient registry and guided the cross-check of the Faroese medical files. Gudrid Andorsdottir provided the pedigree of the inbred Faroese family. Geir E. Tjønnfjord participated in the interpretation of data.

Additional Information

Competing Interests: The authors declare no competing interests.

Publisher’s note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2019