Anticipation in Families with Chronic Lymphocytic Leukemia and Other Lymphoproliferative Disorders

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Abstract: Fifty-one parent-offspring pairs with chronic lymphocytic leukemia (CLL) or other lymphoproliferative disorders (nonCLL) such as malignant lymphoma, multiple myeloma, or other types of lymphocytic leukemia than CLL were ascertained independently in 38 families. There were 30 CLL-CLL parent-offspring pairs and 21 pairs with nonCLL in parents and/or in offspring. The median age of onset of disease was 13 years lower in the offspring than in the parents when comparing all 51 pairs ($P < 0.001$). This difference was mainly caused by a significantly lower age at onset in offspring with parental nonCLL ($P < 0.001$) where paternal disease was transferred especially to sons, while affected offspring to parents with CLL have the same age at debut of disease than their parents ($P = 0.130$) and a nearly equal transfer to sons and daughters. The low-malignant follicular small B-cell lymphoma was the predominant diagnosis within nonCLL. Anticipation is pointed out as one likely mechanism behind the lower age at onset of disease in offspring than in parents, even if a part of this difference is ascribed to a generally earlier diagnosis with modern technology in offspring than in parents.

Keywords: chronic lymphocytic leukemia, malignant lymphomas, multiple myeloma, epigenetic inheritance, familial clustering
Introduction
Anticipation, which denotes a genetic pattern where the age at onset of disease decreases in successive generations with an increased severity and an increased number of affected family members, has been consistently reported in chronic lymphocytic leukemia (CLL) and in other types of lymphoproliferative disorders (LPD). However, anticipation could not be verified by means of life-table methods and marginal survival methods in a population-based sample from Sweden, neither in CLL nor in other types of LPD.

Anticipation is part of the pathogenesis of about twenty degenerative neurological disorders such as Huntington’s disease, familial Parkinson’s disease and the fragile X syndrome, where anticipation is caused by intergenerational increase of unstable nucleotide repeats in the disease-related genes, viz. expansion and genomic accumulation of tri-, tetra-, or pentanucleotide repeats in step with the progression of the disease down through the generations. Such unstable tri-nucleotide repeats have been reported in CLL related to variation in repeat length at certain FRA16A loci which may permit identification of susceptible family members while other mechanisms than accumulation of unstable CAG tri-nucleotide repeats were found to be involved in the generation of anticipation in familial CLL, e.g. accumulation of motif CCG. The male predominance in CLL has so far not been related to larger accumulation of unstable nucleotide repeats in male than in female patients. However, an earlier onset of disease in children than in their parents cannot be ascribed to anticipation alone, because bias from modern diagnostic techniques is likely if not inevitable: Easier access to the practitioner, efficient health care programs which include automatic white blood cell counting and screening procedures for enlarged lymph nodes with standard procedure for diagnostic biopsy will evidently provide an earlier CLL diagnosis today than in former generations. Furthermore, as stated in a study of familial Hodgkin’s disease, environmental factors such as simultaneous parent-offspring exposure to lymphotropic EBV virus could be related to anticipation.

The question about anticipation in CLL is crucial because it addresses whether or not unstable nucleotide repeat expansion is involved in the segregation of CLL and hence whether amplification or suppression in and outside coding repeats with “gain- or loss-phenomenon” is relevant to CLL and its otherwise unknown mode of segregation. Genealogical interpretations of pedigrees from affected families suggest a non-Mendelian, epigenetic segregation with a birth order effect and a male predominance of affected family members. The question is whether instability of the repeating nucleotides with manifestation in the form of anticipation as a possible error mechanism of the DNA reduplication can explain the meiotic drive behind such a pleiotropic and anticipative propagation of disease down through the generations.

The purpose of the present paper is to discuss whether genealogical interpretation of families with CLL by means of independent ascertainment technique reveals signs of a different age at onset of disease in parents and in children? And if so, whether this difference is equally seen in affected parent-offspring pairs with CLL compared with other LPD diagnoses?

Material and Methods
Parent-offspring pairs
Thirty eight consecutive families from our data base on familial LPD were included. Fifty one affected parent-offspring pairs were identified, 30 CLL-CLL pairs and 21 pairs with nonCLL in parent and/or in offspring (Table 1). LPD denotes the entity of CLL and nonCLL. NonCLL comprises the diagnoses reported in Table 2.

Families and pedigrees
Since 2002 all our CLL patients in Oslo and Copenhagen have been interviewed about other cases of LPD in their family. Each patient has also been asked about the number and positions of healthy members, stillborns and extra-marital individuals for a detailed description of the pedigree. Data were validated by crosschecking information in all cases.
with the Cancer Registry in Denmark and Norway, respectively. Hospital records, and review of histopathological and laboratory reports including information from flowcytometry and cytogenetics were crosschecked when available. All diagnoses were based on standard criteria.\textsuperscript{29–34} CLL was confirmed by multicolour flowcytometry according to consensus guidelines.\textsuperscript{34} Karyotyping by interphase fluorescence in-situ hybridization (FISH) using standard protocols and commercially available probes, and assessment of the IgHV mutation status by DNA based sequencing were performed in all patients alive at the time of investigation. All patients investigated were of Scandinavian origin.

Procurement of data was performed upon informed consent and that the study was approved by the Scientific-Ethical Committees and the Data Protection Agencies in Norway and Denmark.

Registration and inclusion
Since the affected parent-offspring pairs were independently ascertained from the pedigrees,\textsuperscript{29} doublet counting of affected family members was inevitable in the following situations (Fig. 1): (a) one affected parent having more than one affected offspring, so that the same affected parent is counted for each affected sibs (n), when n > 1. (b) affected family members in more than two generations, for example the combination of an affected grand parent, parent and offspring, from which two pairs are ascertained (a grand parent—parent pair and a parent—offspring pair, viz. 2 pairs with 4 patients) so that one parent is counted twice. (c) combinations of (a) and (b). Figure 1 shows that the present material comprises 12 such doublets, CLL 9 and nonCLL 3:follicular small B cell lymphoma (FL) 2 and lymphoplasmocytic lymphoma (LPCL) 1. Thus, the 51 parent-offspring pairs (102 affected patients) comprise 90 affected family members of whom 12 are counted twice in order to include all ascertained parent offspring pairs.

Pairs of affected aunt/uncle—niece/cousin and sib-sib concordance were not included. Therefore, the material does not allow a calculation of the rates and total number of affected family members per family or per generation.

Statistics
Comparison between parent and offspring was done by means of two-sided Wilcoxon Signed—Rank Test. Significant difference was accepted when $P \leq 0.05$.

| Table 1. Parent-offspring with lymphoproliferative disease. |
| --- | --- | --- | --- |
| Affected pairs | Parents | Offspring | |
| | CLL | nonCLL | CLL | nonCLL |
| | M | P | M | P | M | P |
| CLL-CLL | 17 | | | 7s | 10d | |
| CLL-CLL | | 13 | | 9s | 4d | |
| CLL-nonCLL | 3 | | | 1s | 2d | |
| CLL-nonCLL | | 4 | | 2s | 2d | |
| nonCLL-LPD | 6 | | | 2s | 0d | 2s |
| nonCLL-LPD | | 8 | | 6s | 0d | 2s |
| Total | 20 | 17 | 6 | 8 | 9s | 10d | 4d | 4d | 10d | 3s | 4d | 2d |
| Total CLL | 37 | | 38 | | | | | |
| Total nonCLL | | 14 | | | | | 13 | |

LPD, lymphoproliferative disease in the sum of CLL and nonCLL; For nonCLL, see Table 2.

Abbreviations: M, matrilineal; P, patrilineal; d, daughter; s, son.
Results

Parent-offspring pairs

Out of a total of 51 parent-offspring pairs, there were 37 (73%) pairs with parental CLL and 14 (27%) pairs with parental nonCLL (Table 1).

The most common parent-offspring combination was CLL-CLL, 30 pairs (69%) with a nearly equal distribution of matrilineal and patrilineal CLL (17 vs. 13 cases) and a nearly equal number of affected sons and daughters (16 vs. 14) but a marked predominance of affected sons in patrilineal pairs (9 sons vs. 4 daughters) (Table 1).

In parental nonCLL, the follicular small B cell lymphoma stage I-III (FL) and FL without definite staging, denoted “FL not otherwise specified” (FLNOS), was most common, 5 pairs (10%) seen together with a number of other nonCLL diagnoses in both parents and offspring (Table 2). Males were highly predominant among the offspring (12 affected sons vs. 2 affected daughters) and all patrilineal combinations (8 of 14 pairs) were father—son pairs (Table 2).

Age at onset of disease

LPD, viz. pooled data from CLL and nonCLL, showed a significantly lower age at onset of disease in the offspring than in the parents, most pronounced in patrilineal (P = 0.005) compared with matrilineal inheritance (P = 0.015), with an 13 years overall difference between the median value of parents and offspring (Table 3).

Only pairs with parental nonCLL contributed to this difference while pairs with parental CLL do not (Tables 4 and 5).

Parental CLL

Table 4 shows that no significant difference in the age at onset was seen, neither when investigated according to patrilineal and matrilineal inheritance, nor according to the gender of offspring, sons vs. daughters. All subgroups of pairs exhibited a generally lower age at debut of disease in the offspring than in the parents, but this difference was not statistically different (P > 0.05).

A number of nonCLL diagnoses in offspring with parental CLL was recorded, n = 7 (Table 2) but no specific pattern in the segregation of nonCLL from the parents with CLL could be seen (Table 2).

Parental nonCLL

In remarkable contrast to the group above, pairs with parental nonCLL (Table 5) showed a significantly lower age at onset of disease in the offspring than in the parents, also when the material is sorted out according to matrilineal vs. patrilineal inheritance, or in subgroups according to offspring CLL vs. offspring nonCLL. Sons are predominant in the group of parental nonCLL (12 sons vs. 2 daughters) (Tables 1 and 2) and CLL is far the most commonly seen diagnosis among the 12 sons: CLL 8, nonCLL 4 (Table 2).

We have been looking for a possible pattern in the pleiotropic repertoire of affected parents and offspring (Table 2). FL and FLNOS is predominant among the parents (FL and FLNOS 7 vs. all other types of
The independent ascertainment technique used in the present investigation for the identification of affected parent-offspring pairs caused double counting of affected family members in situations with one affected parent and more affected sibs (2 families), and in situations with affected family members in more than two subsequent generations (3 families), and in combinations thereof (3 families). Thus, 9 cases of cLL and 3 cases of noncLL were counted twice.

Abbreviations: cLL, chronic lymphocytic leukemia; FL, follicular B cell lymphoma stage I–III; HL, Hodgkin’s lymphoma; LPCL, lymphoplasmacytic lymphoma; MM, multiple myeloma; NOS, not otherwise specified; TL, small T cell lymphoma.

**Figure 1.** The independent ascertainment technique used in the present investigation for the identification of affected parent-offspring pairs caused double counting of affected family members in situations with one affected parent and more affected sibs (2 families), and in situations with affected family members in more than two subsequent generations (3 families), and in combinations thereof (3 families). Thus, 9 cases of cLL and 3 cases of noncLL were counted twice.
nonCLL 7), especially in patrilineal combinations (FL and FLNOS 6 vs. all other types of nonCLL 4) (Table 4).

**Discussion**

A different age at onset of disease between parent and offspring does not mean genetic anticipation as the only explanation. People of today see their doctor earlier and for less than their parents and grand parents, seemingly healthy people are checked in public health care programs with blood screening, and medical progress has provided a faster and safe diagnostic process today so that also pre-stages of malignant disorders such as MBL (monoclonal B-lymphocytosis of uncertain significance which can be a sign of smouldering CLL) and MGUS (monoclonal gammopathy of uncertain significanse, well known as a possible early manifestation of malingt B-lymphoproliferative disease) are diagnosed at an increasing scale today.\textsuperscript{35–37} We probably see this tendency in the present material, as the median value of age at onset of disease in all parent-offspring combinations investigated were lower in the offspring than in the parents. (Tables 3–5).

### Table 3. Age at onset of lymphoproliferative disease in parent-offspring pairs.

| Affected pairs | Min | I\textsubscript{75\%} | Max | M | P       |
|----------------|-----|----------------------|-----|---|---------|
| LPD-LPD parents | 40  | 52–75 | 86  | 66 | <0.001  |
| Total n = 51 offspring | 25  | 47–61 | 84  | 53 |         |
| LPD-LPD mothers | 40  | 50–77 | 84  | 68 | 0.015   |
| Matrilineal n = 26 offspring | 25  | 49–61 | 76  | 55 |         |
| LPD-LPD fathers | 46  | 54–75 | 86  | 65 | 0.005   |
| Patrilineal n = 25 offspring | 32  | 43–64 | 84  | 52 |         |

Notes: Wilcoxon signed-rank test showing the 75\% interquartile range (I\textsubscript{75\%}), median (M), minimum (min) and maximum (max) values, and the two-sided P value.

### Table 4. Age at onset of disease in parent-offspring pairs with parental cLL.

| Affected pairs | Min | I\textsubscript{75\%} | Max | M | P       |
|----------------|-----|----------------------|-----|---|---------|
| cLL-cLL parents | 40  | 48–77 | 86  | 66 | 0.130   |
| Total n = 30 offspring | 42  | 51–66 | 84  | 57 |         |
| cLL-cLL mothers | 40  | 46–78 | 84  | 57 | 0.370   |
| Matrilineal n = 17 offspring | 44  | 53–69 | 71  | 56 |         |
| cLL-cLL fathers | 46  | 55–75 | 86  | 68 | 0.240   |
| Patrilineal n = 13 offspring | 42  | 51–69 | 84  | 58 |         |
| cLL-cLL female child parents | 44  | 48–77 | 86  | 72 | 0.154   |
| n = 14 daughter | 44  | 49–66 | 84  | 58 |         |
| cLL-cLL male child parents | 40  | 46–75 | 81  | 65 | 0.215   |
| n = 16 sons | 42  | 51–69 | 75  | 56 |         |
| cLL-nonCLL parents | 48  | 54–71 | 78  | 65 | 0.110   |
| Total n = 7 offspring | 32  | 48–64 | 76  | 57 |         |

Notes: Wilcoxon signed-rank test showing the 75\% interquartile range (I\textsubscript{75\%}), median (M), minimum (min) and maximum (max) values, and the two-sided P value.
However, a striking difference between CLL and nonCLL is disclosed, since only parental nonCLL contributes to this difference (Table 5) while parental CLL does not (Table 4). In the group of parental nonCLL, the majority of pairs are father-son combinations, and all patrilineal pairs are father-son combinations (8 of 14 pairs) without any father-daughter combination. In 6 of the 8 father-son pairs, the offspring has CLL (Table 1).

The influence of bias or other systemic errors in the collection of data, including the influence of modern medical technology, will exert its action equally in the two groups parental CLL and parental nonCLL, and without doubt the difference in age at onset of disease between the two groups is real. Undetected low-grade LPD without clinical symptoms, for example MGUS, MBL and sometimes silent stage A CLL will cause truncation of data, but equally in both groups, as also the LPD diagnoses to come in family members who are healthy at the time of investigation based on the fact that only dead family members have been observed long enough to ensure whether they have or have had LPD or not.

The difference in age at onset of disease between parental CLL and parental nonCLL is furthermore surprising because in CLL, the mean age at onset of disease is generally higher than the mean age at onset in most of the nonCLL diagnoses so that the age in CLL parents should be expected to be higher than the age in nonCLL offspring, but seven pairs of CLL-nonCLL combination show no such difference in contrast to the pairs with parental nonCLL (Table 4). In spite of the low numbers, these observations focus attention on a biological mechanism like anticipation, and to interpret the extreme male predominance in offspring to parents with nonCLL as a sort of sex-related inheritance, which is not seen in the offspring to parental CLL (Table 2). The male predominance in affected offspring to parental CLL is in accordance with recent findings that non-Hodgkin’s lymphoma confer a stronger familial association among men than among women. Such a different pattern in the segregation of CLL and nonCLL can hardly be explained by a Mendelian mechanism but calls attention to an epigenetic modality. Pregnancy related genomic imprinting with a birth order effect has been suggested as one likely epigenetic mechanism in which selective DNA methylation and histone modifications of paternal genes, controlled by the pregnant mother, is the executive molecular mechanism. Without knowledge about the segregation of the CLL susceptibility genes and with the reservation that parts of the tumorigenesis in CLL depends on other genetic factors than susceptibility, e.g. antigenic- and autoimmune drive, the findings from the present study indicate that the genetics of CLL and nonCLL is linked, and that a meiotic drive directs the susceptibility especially in men towards a lower and lower

| Affected pairs           | Min | I_{75%} | Max | M | P    |
|-------------------------|-----|---------|-----|---|------|
| NonCLL-LPD parents      | 48  | 55–74   | 78  | 68| <0.001|
| Total n = 14            | offspring | 25 | 38–49 | 61 | 46| 0.032|
| NonCLL-LPD mothers      | 52  | 61–74   | 78  | 69|      |
| Matrilineal n = 6       | offspring | 25 | 36–49 | 52 | 47| 0.008|
| NonCLL-LPD fathers      | 48  | 54–75   | 75  | 67|      |
| Patrilineal n = 8       | offspring | 36 | 38–60 | 61 | 43| 0.031|
| NonCLL-nonCLL parents   | 52  | 61–75   | 78  | 69|      |
| n = 6                   | offspring | 25 | 36–52 | 60 | 49| 0.008|
| NonCLL-CLL parents      | 48  | 54–74   | 75  | 68|      |
| n = 8                   | offspring | 38 | 43–47 | 61 | 46|      |

Notes: Wilcoxon signed-rank test showing the 75% interquartile range (I_{75%}), median (M), minimum (min) and maximum (max) values, and the two-sided P-value.
age of onset of CLL from nonCLL predecessors. This is or mimics anticipation with regard to a lower age of onset. The other half of anticipation related to an increased severity of disease down through the generations cannot be statistically estimated in the present investigation because CLL was the only entry to study, but in accordance with anticipation, a single case of acute lymphoblastic leukemia, which is the most aggressive subset of LPD, was seen in a daughter to a mother with CLL (Table 2).

The present genealogical investigation based on independent ascertainment technique found a significant different age at onset of disease in nonCLL pairs, mean difference: 13 years between parents and children (Table 3). Genealogical studies of familial Hodgkin’s disease have showed 22 years between age at onset in parents and in children.45 These differences are in contrast to the findings from population based investigations based on data from Cancer Registries showing no anticipation.10,11 Most likely, the genealogical studies comprise all known cases of LPD in a given family, ensured from a meticulous crosscheck of all family members and a detailed family history so that the risk of incomplete ascertainment is eliminated.28 Furthermore, such genealogical investigations of pedigrees do not need a normal material for control in the same way as it is needed in population based studies. A normal material for such use must be roughly of the same period of time and from a similar environment which is certainly difficult for the observation window in question (from about 1900 to now) where a highly pronounced dynamic of the population took place at the same time as the diagnostic criteria for CLL and LPD were changed nearly every 10th year since the fifties. Finally, a normal material for comparison in population based studies will inevitably be contaminated with low-grade LPD such as undiagnosed cases of MGUS, MBL and stage A CLL without symptoms which is a matter of concern especially when to estimated rare disorders with low incidences.

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Disclosures

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