Maternal and Paternal Imprinting in the Segregation of Malignant Blood Disorders

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Abstract

The malignant lymphoproliferative and myeloproliferative disorders are an entity of blood disorders derived from mutated clones on the hematopoietic stem cell line. One hundred and twelve families with two or more cases of malignant blood disease were included in the study after cross-check with the national cancer registries. Based on the pedigree of each family, the parental affiliation of pairs of affected parent-offspring was recorded. Chronic Lymphocytic Leukemia (CLL) showed a pattern of predominant matrilineal inheritance with an equal number of CLL male and CLL female offspring while in patrilineal inheritance, numerically fewer pairs were seen with a surplus of male CLL. Pronounced clustering was found in CLL as offspring were only seen in two generations after the parents. In non-CLL, i.e., all other cases of malignant blood disease than CLL, the same trend was seen, but with most non-CLL female offspring in the matrilineal line and no clustering. Compared with diagonal, so-called oblique inheritance, i.e., the segregation from the first and oldest patient in the pedigree, the proband, non-vertically to uncles, aunts, nephews, and nieces, recovered the trend from vertical inheritance with predominance of matrilineal affiliations and predominance of unaffected female «healthy» family members on the transgenerational route down through the pedigrees. With CLL as parents in such diagonal lines, the highest degree of anticipation i.e., increasing aggressive malignant disease with decreasing age at onset was seen. Our findings indicate that the overall picture of inheritance is compatible with combined bi-parental imprinting with maternal dominance and signs of antagonistic co-evolution of fitness.

Keywords: Parental genomic imprinting; Anticipation; Female predominance; Familial malignant lymphoproliferative disorders; Familial malignant myeloproliferative disorders

Introduction

The Malignant Blood Disorders (MBD) include lymphoproliferative diseases (lymphocytic leukemias, malignant lymphomas and multiple myeloma) and myeloproliferative diseases (myeloid leukemias, chromic myeloproliferative diseases, myelodysplastic diseases and histiocytic diseases) (Table 1) [1,2].

In each disorder, there is one or a few diagnosis-specific monoclonals originated from mutations in a hematopoietic stem cell, mixed in a diversity of other chromosomal defects [1-4]. It is a common feature of these diseases that they are hereditary with familial occurrence and ethnic restriction [3-6]. The diagnosis-specific mutations depend on germline mutations inherited from the parents [7]. These mutations form a subgroup, the predisposition, which is a subset of hematopoietic germ line variants that affect basic cell metabolism that alter a person's lifetime risk for developing malignancy [7]. The mutated DNA alterations are stably included into the genome and master the inherited oncogenic effect in clonal lineages, e.g., clonal cell proliferation and chromosomal aberrations such as deletion, insertion and trisomy [8]. Thus, a single, or possibly a few, cytogenetic alterations are diagnostic and decisive for the disease. Other mutations have a wide occurrence within MBD, for example the DDX4 mutation in both myeloproliferative and lymphoproliferative disorders [9]. The large number of inherited mutations at each diagnosis, demonstrated by Genome Wide Association Studies, GWAS [3,4,10] can explain pleiotropy [5,11-13], i.e., the occurrence of several different disorders within the same family. Furthermore, the diversity of mutations can provide

an explanation of the variations seen in the clinical presentation of each disease, such as the range of symptoms, effect of treatment, and prognosis [1,2].

The single strand of the twisted DNA double helix exposes coding and non-coding regions, the latter formerly denoted nonsense or junk regions [7]. Germline mutations attached to the non-coding regions comprise the epigenes, present in large mega-base loops, denoted Topologically Associated Domains (TAD) [7, 8]. TAD occur in between the coding regions and have the genes and their promotors and modifiers, non-coding drivers of the monoclonal, that cause disruptions of the gene expression and thereby normal biological regulation of cell growth [7]. The functional units, non-coding epigenetic Quantitative Traits Loci (eQTL), organizes interactive genes in such a way that genetically identical cells become stable phenotypes during repeated transgenerational passages [8]. In CLL for example, the epigenetic non-coding mutations involve 43 risk loci with 63 variants, where most GWAS signals map to the non-coding genome. Affected mechanisms are e.g., DNA methylation, histone modification, NOTCH aberrant splicing events, and MYC and BCL2 activity [7,14].

Moreover, the epigenetic eQTL traits in familial MBD are modulated during meiosis between each generation under the influence of epigenetic parental genomic imprinting. This develops stable phenotypes during segregation that promote fitness (in the biological sense) in each generation [15-18].

Genomic imprinting is monoallelic inheritance that depends on whether the dominant gene originates from the father or the mother [15-19].

In maternal imprinting, the active allele is paternally expressed and paternally transmitted down through the generations, so that sons transmit the active allele to sons and daughters in each subsequent generation while half of the daughters' children both sons and daughters will have the inactive (silenced) copy of disease-causing allele.

In paternal imprinting, where the active allele is maternally expressed and maternally transmitted, so that the daughters transmit the active allele to sons and daughters in each subsequent generation, while half of the sons' children have the silenced copy of the disease-causing allele [15-19]. At the end of this process, erased imprinting occur in either oogenesis or spermatogenesis [19-25], leaving the genetic message of the imprinted allele available for future generations. We assume that in the imprinting process there is a moment of microchimerism [26,27].

Parental genomic imprinting concerns the segregation of embryonic growth factors [28-32], and it was therefore not entirely surprising that segregation of susceptibility to MBD should turn out to follow genomic imprinting because this susceptibility is thought to code for monoclonal hematopoiesis early in embryogenesis [33].

The genealogical description of the occurrence of MBD in vertical and direct inheritance from parents to children has previously been reported [34-39]. CLL seems to have its own pathway down through the generations in families with MBD [13,34]. The influence of modifier genes that regulate the effects of the monoallelic genes [25,40-42] and shifts the distribution of male and female patients in relation to what one would expect from traditional maternal and paternal non-Mendelian genomic imprinting is obvious. Especially,

the occurrence of MBD in so-called oblique or diagonal position in the pedigrees, i.e., the occurrence of MBD in uncle, aunt, niece, and nephew in relation to a proband with otherwise vertical, parent to offspring, inheritance raises many questions about the pattern in the inheritance of MBD. The purpose of the present paper is to include diagonal inheritance in order to obtain a more nuanced picture of the inheritance of MBD as a supplement to the picture known from vertical segregation.

Material and Methods

MBD in Norwegian and Danish families with unrelated parents

One hundred and twelve families have been identified 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 familial cases of LPD (Lymphoproliferative Disorders), together with 24 familial cases of MPD (Myeloproliferative Disorders), and one case of Leukemia NOS (Not Otherwise Specified) (Table 1), giving 2.7 patients per family.

The included persons were all of Scandinavian origin, there were no twins, and none had related parents. The observation period comprises all confirmed cases of MBD, since the beginning of registration by the National Cancer Registries in Norway and Denmark. The oldest patient is a female with CLL, born in 1864.

Vertical inheritance denotes direct vertical family relation, e.g., parent-offspring or grandparent-offspring, detected in all 112 included families. For each family, the oldest patient from the pedigree, designated Proband crude (Pc), defines generation one. Affected Relatives (AR) in later generations in AR-AR was furthermore included. In each line of Pc-AR and AR-AR down through the pedigree, it was determined from the sex of Pc whether the line was Paternally (PA) or Maternally (MA) derived (Table 2).

Diagonal or oblique inheritance is not-vertical family relationship, such as the combination of uncle/aunt-nephew/niece or cousin in pairs, demonstrated in 24 of the included families. In some cases of diagonal inheritance, the parental affiliation was uncertain or impossible to determine from the pedigree, denoted UC (Table 3, 4). Especially in large families, the same Pc could be the ancestor of vertical and diagonal rows [43]. Therefore, such a Pc may have been repeatedly included. In the same way, the same AR may sometimes be included in several combinations of parent-offspring pairs. For that reason, the total number of patients in the parental series exceeds the actual number of registered patients as indicated in Table 1.

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 [44]. The ICD-10 nomenclature for standardization of the diagnoses from different periods with different taxonomic systems was used [45].

Each case of MBD in the family tree was associated with its Affected Relatives (ARs) and used for a systematic registration of familial MBD. Strictly vertical pairs of 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 in vertical inheritance (Table 2). Table 3, 4 shows a separate registration of so-called oblique or diagonal pairs.

Horizontal pairs such as two concordantly affected siblings are not included. Steps denote the number of normal healthy person interposed in the pedigree between two MBD patients on the shortest possible direct route between the two patients. Parts of our joint database were in use for genealogical investigations elsewhere [4,5,12,13,34,43].

Anonymity

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 and 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. Informed consent was given by 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 the ethics committee of the Ministry of Health and Social Service, Government of Denmark, and by the Norwegian Directorate of Health, the Norwegian Data Protection Authority, 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. Legal permissions to do the study: cf. Acknowledgements.

Results

Diagnosis and pleiotropy

Table 1- 4 show the pronounced pleiotropy occurring in the family material. The family material has significantly more cases of CLL, and significantly fewer cases of FL, DLBCL and MM than the population material (P<0.05). The proportion of lymphoproliferative and myeloproliferative diseases in vertical and diagonal inheritance corresponds to the composition of disorders in the total family material as shown in Table 1.

Percentages of MBD (i.e., rates, prevalence or frequencies) in the population are official data from the Cancer Registries [46,47] or other public health institutions [48]. Specific registration of familial MBD does not appear in these official registers, incidences are not specified either. Therefore, to compare MBD in the population (as stated in the registries) with MBD in the families (as enumerated in the present material), we compared the percentage values.

Vertical inheritance

Table 2 shows vertical pairs of affected parents-affected offspring, *viz.* pairs with a direct, transgenerational transfer of susceptibility from affected parent to affected child.

CLL

Table 2 shows that male CLL offspring in sheer parent-offspring

Table 1: Familial MBD. Cumulative findings in 112 families.

Diagnosis ICD-10 code	Families from Norway and Denmark			Cancer registries Norway and Denmark
Lymphoproliferative disorders	Total	Males, females	%	All cases recorded % (mean)
Hodgkin lymphoma HL C81	11	8, 3	4.0	6
Follicular lymphoma FL C82	19	13, 6	6.9	12
Mantle cell lymphoma MCL C82.7	4	4, 0	1.4	<1
Diffuse large B-cell lymphoma DLBCL 83.3	16	9, 7	5.8	25
Peripheral T-cell lymphoma TNHL C84	2	2, 0	0.7	2
Monocytoid B-cell lymphoma MONOCL C85.7	4	1, 3	1.4	2
NHL-lymphoma NOS NHL NOS C85.9	9	4, 5	3.3	6
Waldenstrom's macroglobulinemia WA C88.0	8	5, 3	2.9	3
Multiple myeloma MM C90.0	10	6, 4	3.6	14
Acute lymphoblastic leukemia ALL C91.0	4	2, 2	1.4	4
Chronic lymphocytic leukemia CLL C91.1	181	98, 83	65.6	22
B-Prolymphocytic leukemia PLL C91.3	2	0, 2	0.7	1
Hairy cell leukemia HCL C91.4	1	0, 1	0.4	1
Large granular T-cell leukemia LGTL C91.7	3	2, 1	1.1	<1
Monoclonal gammopathy MGUS D47.2	2	1, 1	0.7	2
Lymphoproliferative disease Total	276	155, 121	99.9	100
Myeloproliferative disorders				
Acute myeloid leukemia AML C92.2-9	9	6,3	37.6	
Chronic myeloid leukemia CML C92.1	3	1, 2	12.5	
Polycythemia vera PV D45.0	6	4, 2	25.0	
Primary myelofibrosis MF D47.1	1	0, 1	4.2	
Essential thrombocytosis ET D47.3	3	1, 2	12.5	
Myelodysplasia MDS D46	2	1, 1	8.3	
Myeloid leukemia NOS ML C92.9	0			
Myeloproliferative disease				
Total	24	13, 11	99.9	
Other hematological malignancies				
Leukemia NOS C95.9	1	1, 0		
Malignant histiocytosis C96.1	0			

NOS: Not Otherwise Specified

combinations (CLL-CLL parent-offspring pairs) are predominant in paternal affiliation, PA, (12 males and 4 females), P<0.05, while in Maternal Affiliation (MA), there is an almost equal distribution of CLL offspring males and females (11 males and 15 females, not significantly different P>0.05. (X^2-test, 1 Degree of Freedom, df).

This tendency holds in pairs of CLL grandparent-CLL grandchild but disappears in pairs of non-CLL parents-CLL children, i.e., disappears when parents do not have CLL.

There were significantly more pairs in maternal affiliations than in paternal affiliations (P<0.05).

Table 2: Vertical inheritance.

CLL parents	Paternal affiliation Number (males. females)	Maternal affiliation Number (males. females)
CLL-CLL parent-offspring pairs	16 (16.0)	26 (0.26)
CLL-CLL grandparent-grandchild pairs	1 (1.0)	13 (8.5)
CLL-nonCLL parent-offspring pairs	7 (7.0)	11 (0.11)
Total	24 (24.0)	50 (8.42)
CLL offspring		
CLL-CLL parent-offspring pairs	16 (14.2)	26 (11.15)
CLL-CLL grandparent-grandchild pairs	1 (1.0)	13 (8.5)
nonCLL-CLL parent-offspring pairs	17 (7.10)	16 (10.6)
Total	34 (20.14)	55 (29.26)
CLL offspring (generations)		
1st generation	25 (14.11)	35 (16.19)
2nd generation	9 (6.3)	20.(13.7)
3rd generation	0	0
NonCLL parents		
NonCLL-nonCLL parent-offspring pairs	9 (9.0)	16 (0.16)
NonCLL-CLL parent-offspring pairs	9 (9.0)	9 (0.9)
NonCLL-CLL grandparent-grandchild pairs	8 (8.0)	7 (4.3)
Total	26 (26.0)	32 (4.28)
NonCLL offspring		
NonCLL-nonCLL parent-offspring pairs	9 (7.2)	16 (5.11)
CLL-nonCLL parent-offspring pairs	7 (2.5)	11 (5.6)
NonCLL-nonCLL grandparent-grandchild pairs	0	6 (2.4)
Total	16 (9.7)	33 (12.21)
NonCLL offspring (generations)		
1st generation	2 (2.0)	4 (1 3)
2nd generation	3 (3.0)	17 (4.13)
3rd generation	9 (4.5)	9 (6.3)
4th generation	2.(0.2)	3 (1.2)
5th generation	0	0

CLL offspring only occur widely in the first two generations after the parental generation as an expression of clustering (accumulation) in the family.

Non-CLL

Table 2 shows that non-CLL in a sheer parent-offspring combination in PA is mainly distributed to males (7 males and 2 females) and in MA mainly to females (11 females and 5 males), P<0.05.

This trend, yet not quite as clearly, is also seen when estimating CLL- non-CLL parent-offspring pairs. There were significantly more pairs with maternal affiliations than paternal affiliations (P<0.05).

Offspring with non-CLL occur widely for up to four generations after Pc, in contrast to the distinct clustering seen in offspring of parents with CLL (Table 2).

Diagonal, oblique inheritance

Table 3, 4 shows segregation between uncle/aunt and nephew/

Table 3: Oblique inheritance, CLL parents.

Generation and combinations	Parental affiliation						Steps			
	Uncertain		Paternal		Maternal		Paternal		Maternal	
	m	f	m	f	m	f	m	f	m	f
CLL-CLL (10 pairs)										
1st generation	7	3								
2nd generation			1	1	7					
Between 1st and 2nd generation							6	1	6	7
3rd generation						1				
Between 1st and 3rd generation									2	2
Total	7	3	1	1	8		6	1	8	9
CLL-nonCLL (9 pairs)										
CLL	3		1			5				
NonCLL 2nd generation										
Follicular lymphoma						1				
ALL			2			1				
AML			1		1					
TNHL-lymphoma					1					
Between 1st and 2nd generation							2	1	3	8
NonCLL 3rd generation										
Lymphoblastic lymphoma					1					
AML					1					
Between 1st and 3rd generation									1	6
Total CLL	3		1			5				
Total nonCLL			3		3	3				
Total steps							2	1	4	14

Males: m; females: f; Steps, the number of healthy persons interposed in the pedigree between two patients on the shortest possible direct route between the two patients; diagnoses abbreviated cf. Table 1

niece/cousin. The findings from each table are numerically too small for a statistical calculation. Together, the four tables show a high proportion of uncertain parental affiliation, UC (39%), as expected in diagonal inheritance (UC Tables 4 to 7, total (males, females): 28 (16, 12); MA total 38 (17.21); PA total 10 (8.2) due to well-known difficulties in identifying Pc of diagonal lines in such pedigrees, cf. Material and Methods.

Estimated from the identified lines of paternal and maternal affiliation, PA 10 (8, 2) and MA 38, it is seen that MA is greatest (P<0.05) with a slight predominance of female offspring when CLL is the diagnosis of the parents (P<0.05, Table 4, 5). We have furthermore seen a slight predominance of male offspring in MA when non-CLL is the diagnosis of the parents (P<0.05, Table 4). Regarding steps, i.e., "stepping stones" in the form of normal healthy individuals on the shortest possible route down through the pedigree between a pair of patients, MA and females are predominant, MA 50 (15, 35); PA 16 (14, 2); (males, not significantly different in MA and PA: P>0.05); (females significantly fewer in PA: P<0.001).

Compared to the findings in vertical inheritance, oblique inheritance shows numerically the most maternal affiliations with a predominance of female offspring and a smaller number of paternal affiliations (P<0.05), but without a statistically significant predominance of male offspring in PA.

Table 4: Oblique inheritance, nonCLL parents.

Generation and combinations	Parental affiliation						Steps			
	Uncertain		Paternal		Maternal		Paternal		Maternal	
	M	f	m	f	m	f	m	f	m	f
Non-CLL-CLL (13 pairs)										
1st non-CLL generation										
MDS	1									
DLBCL	1									
AML		1								
Multiple myeloma	1	2								
Hodgkin lymphoma	1				1					
CML		1								
Follicular lymphoma		1			1	2				
2nd CLL generation			3	1	4	1				
Between 1st and 2nd generation							5		1	5
3rd CLL generation					4					
Between 1st and 3rd generation							1		1	2
Total CLL	4	5			1	3				
Total nonCLL			3	1	8	1				
Total steps							6	0	2	7
NonCLL-nonCLL (6 pairs)										
1st nonCLL generation										
CMML.MDS		3								
Multiple myeloma	2									
CML		1								
2nd nonCLL generation										
DLBCL					1					
Multiple myeloma						1				
AML			1							
Between 1st and 2nd generation									1	2
3rd NonCLL generation										
Monoclonal gammopathy					1					
DLBCL					1					
Mantle cell lymphoma					1					
Between 2nd and 3rd generation										3
Total nonCLL	2	4	1	0	4	1				
Total steps							0	0	1	5

Males: m; females: f; Steps, the number of healthy persons interposed in the pedigree between two patients on the shortest possible direct route between the two patients; diagnoses abbreviated cf. Table 1

Anticipation

We have registered 14 cases of highly malignant disorder in the family material (Table 1: total (males, females); ALL 4 (2, 2); AML 9 (6, 3); lymphoblast lymphoma 1 (0, 1)). Nine (64%) are found in oblique inheritances (Table 3, 4: ALL 3 (2, 1); AML 5 (3, 2); lymphoblast lymphoma 1 (0, 1)), including 7 pairs with CLL as parents. Of the remaining 5 cases of highly malignant disease in vertical inheritance, all pairs have parents with CLL. Thus, 12 of 14 pairs (86%) with highly malignant disease among the children have parents with CLL.

Discussion

Our data (Tables 1 to 4) show that in the inheritance of MBD a pattern compatible with parental genomic imprinting is on question, i.e., monoallelic specific expression according to the parental origin of the allele [15-19]. Interpreted in this way, we find that CLL (Table 2) has a maternal imprinting in PA with a dominance of father-son pairs, and a predominantly paternal mixed imprinting in MA with almost equal numbers of mother-son and mother-daughter pairs. In non-CLL (Table 2), we find evidence of maternal imprinting in PA, and mixed paternal and maternal imprinting in MA. We also see the predominance of matrilineal affiliations in diagonal (oblique) inheritance (Table 3, 4).

In both CLL and non-CLL, there are signs of simultaneous paternal and maternal imprinting, which seems plausible because there is considerable genotypic and phenotypic polymorphism within each disease. As for example in CLL, where the clinical phenotype is so variable with different stages, different cytogenetic groups and different treatment indications, etc. [1,2] that one can doubt whether CLL designates the same disease. We assume that this polymorphism within the same diagnosis is the explanation for the fact that for the same disease there can actually be both maternal and paternal imprinting at the same time.

In maternal imprinting the allele of the mother is silenced (imprinted) while the paternal allele is active and paternally expressed and paternally transmitted to the offspring, where sons transfer to offspring of both sexes while offspring of females do only transfer the inactivated copy of the allele. This pattern is particularly recognizable when inheriting CLL in the paternal line, Table 2.

In paternal imprinting, the allele from the father is silenced, while the active maternal allele is maternally expressed and maternally transferred to offspring so that sons pass on the inactivated copy of the allele, while daughters pass on the active copy to offspring of both sexes as also seen in non-CLL in the maternal line, Table 3. Imprinted genes are influenced by modifier genes [25,40-42] that may be linked to female sex, so-called maternal genomic dominance [42].

Our material shows a general tendency in CLL and non-CLL that MA lineages are overrepresented in the pedigrees. The same is seen in the diagonal inheritances (Table 3, 4), where large number of Uncertain (UC) affiliations create doubt about the actual sizes of PA and MA. The close relationship between female gender and inheritance of MBD also manifests from the number of steps in diagonal inheritance, i.e., passages of normal persons on the shortest path in the family tree between two patients, steppingstones on the route of segregation (Table 3, 4). The calculations of steps are uncertain because among the family members there are currently living healthy people who, despite being symptom-free at the time of registration, may have susceptibility to MBD and possibly may later develop MBD.

The dominance of maternal genes [42] among imprinted alleles with mixed maternal and paternal imprinting is possibly due to fast evolving antagonistic co-evolution [49] as part of overall control of embryonic growth [28-32] and development of evolutionary fitness [15-18]. The dominance of maternal genes in our material is most likely reflected in the ratio for CLL male/female in the families with MBD (ratio 1.18 (m:98, f:83) Table 1). This is lower than the ratio normally indicated for CLL of around 1.5 in unselected patient materials, e.g., from the National Cancer Registries [46,47] including

all known CLL patients, also solitary non-familial cases.

The diversity of inheritance by parental imprinting is under the influence of modifier genes [25,40-43] sometimes linked to female sex, so-called maternal genomic dominance [43]. We currently do not know why CLL is over-represented in the family material, nor why FL, DLBCL and MM are under-represented when compared to unselected registry materials (Table 1).

A study of birth order in CLL showed that affected sons appear late in the sibship, i.e., after repeated sensitizations with CLL susceptibility of the mother during her previous pregnancies. In contrast, affected daughters occur randomly in the sibship without rank of birth order [12]. This is interpreted in the way that the mother accepts susceptibility from female fetuses more easily than from male fetuses due to the microchimeristic gender difference [26,27]. The difference in the gender of the offspring may be relevant in the explanation of predominance of MA and female gender in the inheritance of MBD.

A high degree of anticipation in diagonal inheritance from CLL parents (Table 3) happens in an area of the family among pairs of uncles or aunts-nephews, nieces or cousins) where the HLA incompatibility is greater than in sheer parent-offspring pairs (Table 2, 3). At the same time as there is a surplus of healthy female family members as estimated from the steps in CLL- non-CLL pairs (Table 3). The question arises whether there are maternal genomic modifier genes that "microchimeristic cleanse" the MBD families of highly malignant disorders so that, biologically speaking, patients with highly malignant disorders die before childbearing age, and thereby building up a steady state of fitness related to the vital susceptibility genes among the remaining MBD patients in the family.

Acknowledgement

References

1. Knowles DM. Immunophenotypic markers useful in the diagnosis and classification of hematopoietic neoplasms. In: Knowles DM, editor. Hematopthology. Lippincott Williams & Wilkins Publ. 2001. p. 93-226, 2nd Ed.

2. Cousa JB. Hematopoietic-lymphoid neoplasms, principles of diagnosis. In: Greer JP, Foerster J, Lukens JN, Rogers GM, Paraskevas F, Glader B, editors. Wintrobe's Clinical Hematology. Lippincott Williams & Wilkins Publ. 2001. p. 1913-5.

3. Wang SS, Slager SL, Brennan P, Holly EA, de Sanjose S, Bernstein L, et al. Family history of hematopoietic malignancies and risk of Non-Hodgkin Lymphoma (NHL), a pooled analysis of 10 211 cases and 11 905 controls from the International Lymphoma Epidemiology Consortium (InterLymph). Blood. 2007;109(8):3479-88.

4. Crowther-Swanepoel D, Wild R, Sellick G, Dyer MJS, Mauro FR, Cuthbert RJG, et al. Insight into the pathogenesis of Chronic Lymphocytic Leukemia (CLL) through analysis of IgVH gene usage and mutation status in familial CLL. Blood. 2008;111(12):5691-3.

5. Awan H, Furuholmen J, Tjønnfjord GE, Ly B, Johannesen TB, Tierens A, et al. Segregation of malignant hematological diseases in families with malignant lymphomas. J Genet Syndr Gene Ther. 2014;5:6.

6. Sud A, Chattopadhyay S, Thomsen H, Sundquist K, Sundquist J, Houlston RS, et al. Analysis of 153 115 patients with hematological malignancies refines the spectrum of familial risk. Blood. 2019;134(12):960-9.

7. Pudjihartono M, Perry JK, Print C, O'Sullivan JM, Schierding W. Interpretation of the role of germline and somatic non-coding mutations in cancer, expression of chromatin conformation informed analysis. Clin Epigenetics. 2022;14(1):120.

8. Shen H, Laird PW. Interplay between the cancer genome and epigenome. Cell. 2013;153(1):38-55.

9. Lewinsohn M, Brown AL, Weinel LM, Phung C, Rafidi G, Lee MK, et al. Novel germ line DDX41 mutations define families with a lower age of MDS/AML onset and lymphoid malignancies. Blood. 2016;127(8):1017-23.

10. Speedy HE, Beekman R, Chapaprieta V, Orlando G, Law PJ, Martin-Garcia D, et al. Insight into genetic predisposition to chronic lymphocytic leukemia from integrative epigenomics. Nature Com. 2019;10:3615.

11. Goldin LR, Pfeiffer RM, Li X, Hemminki K. Familial risk of lymphoproliferative tumors in families of patients with chronic lymphocytic leukemia, results from the Swedish family-cancer database. Blood. 2004;104(6):1850-4.

12. Jønsson V, Tjønnfjord GE, Johannesen TB, Ly B, Olsen JH, Yuille M. Familial chronic lymphocytic leukemia in Norway and Denmark, comments on pleiotropy and birth order. In Vivo. 2010;24(1):85-95.

13. Jønsson V, Awan H, Jones ND, Johannesen TB, á Steig B, Andorsdottir G, et al. Inheritance of susceptibility to malignant blood disorders. Sci Rep. 2019;9:2444.

14. Beekman R, Chapaprieta V, Russinol N, Vilarassa-Blasi R, Verdaquer-Dot N, Martens JHA, et al. The reference epigenome and regulatory chromatin landscape of chronic lymophocytic leukemia. Nature Med. 2018;24(6):868-80.

15. Haig D. The kindship theory of genomic imprinting. Annu Rev Ecol Sys. 2000;31:9-32.

16. Ubeda F, Haig D. Sex-specific meiotic drive and selection at an imprinted locus. Genetics. 2004;167(4):2083-95.

17. Ubeda F, Haig D. On the evolutionary stability of Mendelian segregation. Genetics. 2005;170(3):1345-57.

18. Bertram J, Masel J. Density-dependent selection and limits of relative fitness. Ther Popul Bio. 2019;129:81-92.

19. Hartwell LH. Genomic imprinting, parental origin affects the expression of some genes in mammals. In: Genetics, from genes to genomes, chapter 11. McGraw-Hill Comp. 2000. p. 408-10.

20. Sasaki H, Matsui Y. Epigenetic events in mammalian germ-cell development, reprogramming and beyond. Nat Rev Genet. 2008;9(2):129-40.

21. Hiura H, Obata Y, Korniyama J, Shirai M, Kono T. Oocyte growth-dependent progression of maternal imprinting in mice. Genes Cells. 2006;11(4):353-61.

22. Delaval K, Feil R. Epigenetic regulation of mammalian genomic imprinting. Curr Opin Genet Dev. 2004;14(2):188-95.

23. Lucifero D, Mann MRW, Bartolomei MS, Trasler JM. Gene-specific timing and epigenetic memory in oocyte imprinting. Hum Mol Genet. 2004;13(8):839-49.

24. Reik W, Dean W, Walter J. Epigenetic reprogramming in mammalian development. Science. 2001;293(5532):1089-93.

25. Reik W, Walter J. Genomic imprinting, parental influence on the genome. Nat Rev Genet. 2001;2(1):21-32.

26. Nelson JL. Microchimerism in health and disease. Autoimmunity. 2003;36(1):5-9.

27. Adams KM, Zhan Y, Stevens A, Nelson JL. The changing maternal "self" hypothesis, a mechanism for maternal tolerance of the fetus. Placenta. 2007;28(5-6):378-82.

28. Isles AR, Holland AJ. Imprinted genes and mother-offspring interactions. Early Hum Dev. 2005;81(1):73-7.

29. Tycko B, Morison IM. Physiological functions of imprinted genes. J Cell Physiol. 2002;192(3):245-58.

30. Moore T, Haig D. Genomic imprinting in mammalian development, a parental tug-of-war. Trends Genet. 1991;7(2):45-9.

31. Morison IM, Ramsay JP, Spencer HG. Census of mammalian imprinting. Trends Genet. 2005;21(8):457-65.

32. Peters J. The role of genomic imprinting in biology and disease, an expanding view. Nat Rev Genet. 2014;15(8):517-30.

33. Jønsson V, Awan H, Johannesen TB, Tjønnfjord GE. Chronic lymphocytic leukemia. Advantage of monoclones? J Leuk. 2014;2:3.

34. Jønsson V, Awan H, Jones ND, Johannesen TB, Thøgersen K, á Steig B, et al. Meiotic drive in chronic lymphocytic leukemia compared with other malignant blood disorders. Sci Rep. 2022;12:6138.

35. Cerhan JR, Slager SL. Familial predispose and genetic risk factors for lymphoma. Blood. 2015;126(20):2265-73.

36. Schinasi LH, Brown EE, Camp NJ, Wang SS, Hofman NJ, Chiu BC, et al. Multiple myeloma and family history of lymphohaematopoietic cancers: Results from the International Multiple Myeloma Consortium. Br J Haematol. 2016;175(1):87-101.

37. Jones SJ, Voong J, Thomas R, English A, Schuetz J, Graham J, et al. Non-random occurrence of lymphoid cancer types in 140 families. Leuk Lymph. 2017;58(9):1-10.

38. Kleinstern G, Camp NJ, Goldin LR, Vachon CM, Vajdic CM, de Sanjose S, et al. Association of polygenic risk score with the risk of chronic lymphocytic leukemia and monoclonal B-cell lymphocytosis. Blood. 2018;131(23):2541-51.

39. Yan H, Tian S, Kleinstern G, Wang Z, Lee JH, Boddicker NJ, et al. Chronic Lymphocytic Leukemia (CLL) risk is mediated by multiple enhancer variants within CLL risk loci. Hum Mol Genet. 2020;29(16):2761-74.

40. Martin CC, Sapinesa C. A role for modifier genes in genomic imprinting. In: Genomic Imprinting. Ohlsson R, editor. Springer-Verlag, Berlin, Heidelberg. 1999. p. 251-70.

41. Morcos L, GeB, Koka V, Lam KC, Pokholok DK, Gundersen KL, et al. Genome-wide assessment of imprinted expression in human cells. Genome Biol. 2011;12(3):R25.

42. Keverne EB, Curley JP. Epigenetics, brain evolution and behavior. Front Neuroendocrinol. 2008;29(3):398-412.

43. Jønsson V, Houlston RS, Catovsky D, Yuille MR, Hilden J, Olsen JH, et al. CLL family "pedigree 14" revisited: 1947-2004. Leukemia. 2005;19(6):1025-8.

44. Sonomed. Sonomed International. 2023.

45. ICD10Data. 2023.

46. Report from the Norwegian Cancer Registry. 2023.

47. Danish Cancer Registry. 2023.

48. LYFO. Danish lymphoma group. 2023.

49. O'Connell MJ, Loughran NB, Walsh TA, Donoghue MTA, Schmid KJ, Spillane C. A phylogenetic approach to test for evidence of parental conflict or gene duplications associated with protein-encoding imprinted orthologous genes in placental mammals. Mamm Genome. 2010;21(9-10):486-98.