Arvagongdin innan illkynjaðar blóðsjúkur í Føroyum

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Inheritance of Susceptibility to Malignant Blood Disorders

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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 diseases[1–7], 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 monoclone[8,9]. 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 families[18,19], and large-scale screenings from cancer registries[20–24] 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].

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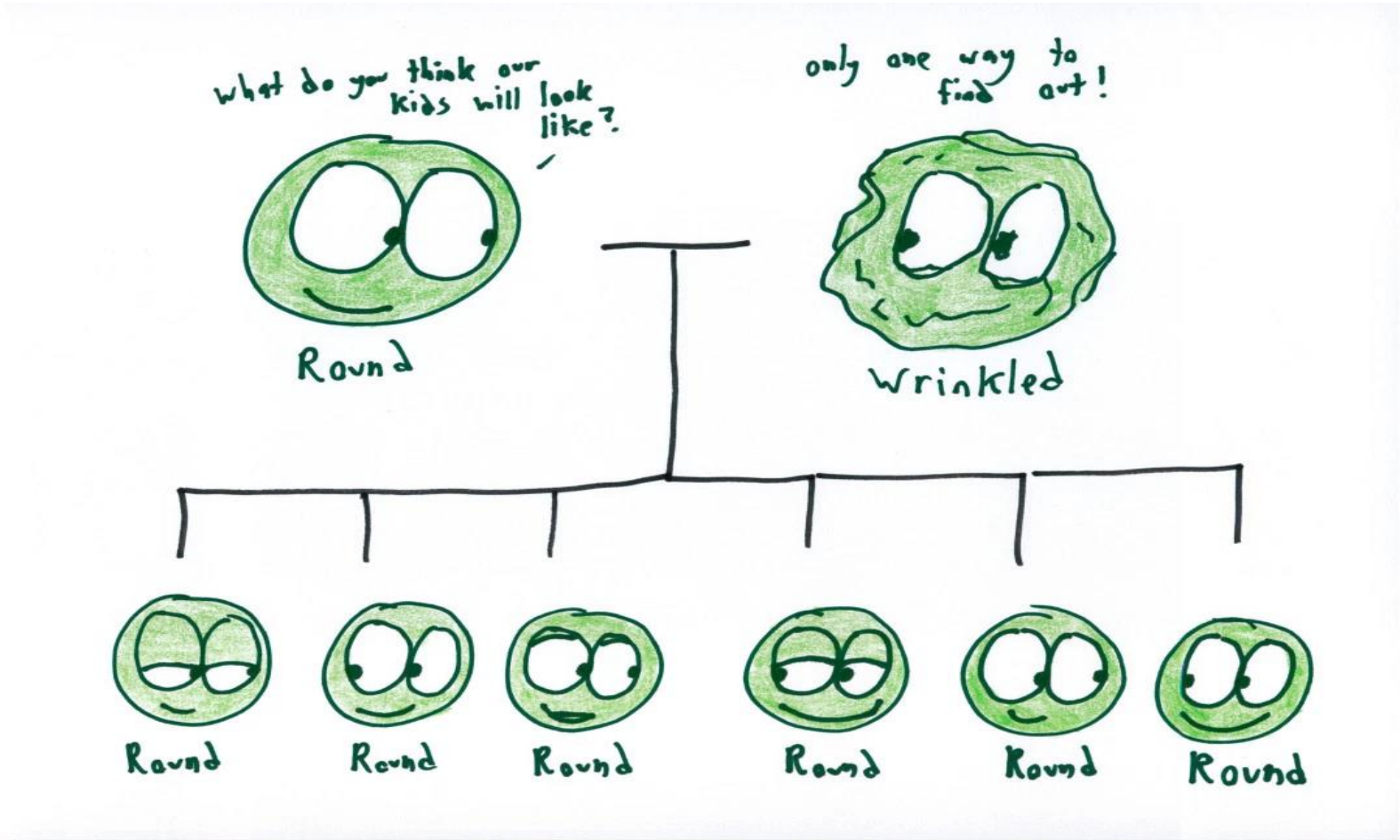
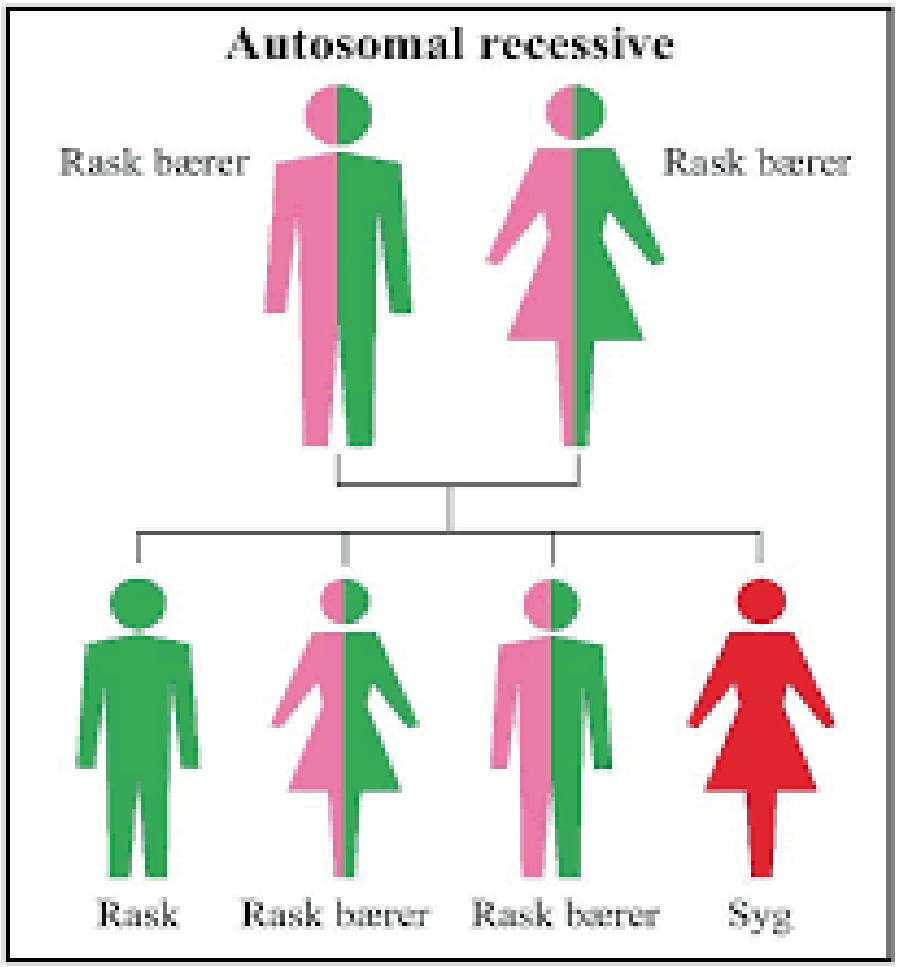

what do you think our kids will look like?
only one way to find out!
Round
Wrinkled
Round
Round
Round
Round
Round
Round

- 1994
- 1999 **BRIC (mutatión á kromosom 18)**

- 2004
- 2007
- 2019 **MBD**



- *Mendel var ikki nøktandi*

- **Professor Viggo Jønsson**

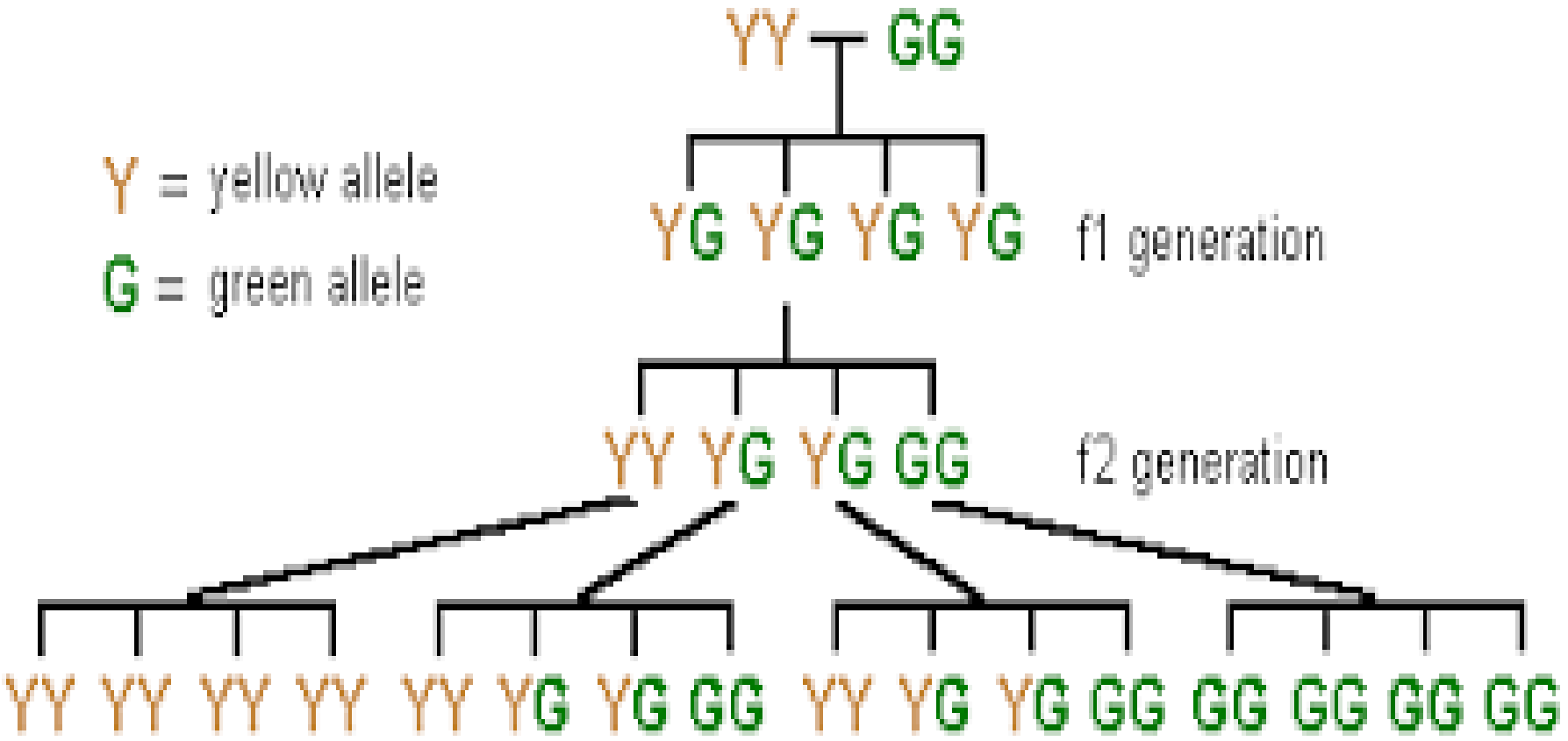
Diagnoses	Familial Diagnoses Observed							Cancer Registries
ICD-10 code numbers	The Faroe Islands			Norway and Denmark				Norway and Denmark
Lymphoproliferative Disorders	Pc			Pc				All cases recorded
	Total	(males, females)	%	Total	(males, females)	%		% (mean)
Hodgkin's lymphoma HL C81	13	(12, 1)	8.7	11	(8, 3)	4.0		6
Follicular lymphoma FL C82	14	(3, 5)	6.4	19	(13, 6)	6.9		12
Mantle cell lymphoma MCL C82.7	0			4	(4, 0)	1.4		<2
Diffuse Non-Hodgkin's lymphoma DLBCL C83.3	55	(31, 13)	25.6	16	(9, 7)	5.8		23
Peripheral T cell lymphoma PTCL C84	6	(2, 4)	2.7	2	(2, 0)	0.7		3
Monomorphic B cell lymphoma MONO C85.7	0			4	(3, 1)	1.4		2
Non-Hodgkin lymphoma NOS NHL NOS C85.9	23	(14, 11)	11.4	9	(4, 5)	3.3		6
Waldenstrom's disease WA C88	3	(2, 1)	0.9	8	(5, 3)	2.9		3
Multiple myeloma MM C92	53	(30, 19)	22.8	13	(8, 4)	3.6		14
Acute lymphoblastic leukemia ALL C91.0	18	(10, 8)	7.5	6	(4, 2)	1.4		4
Chronic lymphocytic leukemia CLL C91.1	50	(29, 21)	22.6	161	(88, 83)	55.8		22
Prolymphocytic leukemia PLL C91.5	2	(1, 1)	0.9	2	(1, 1)	0.7		1
Hairy cell leukemia HCL C91.4	1	(1, 0)	0.5	1	(1, 0)	0.4		1
Large granular T-cell leukemia LGL C91.0	0			3	(2, 1)	1.1		<1
Mucosa-associated lymphoma MALIS B47.5	0			2	(1, 1)	0.7		3
Lymphoproliferative disease LPD total	310	(181, 88)	100	278	(155, 123)	96.9		100
Male/Female ratio		1.5			1.3			
Age at onset of disease Years (median)	61	(58, 64)		67	(65, 68)			
Birth order effect		NO			Positional CLL, ons			
Myeloproliferative Disorders								
Acute myeloblastic leukemia AML C92.0 and C92.2–9	64	(28, 16)	20.6	9	(6, 3)		3.5	20
Chronic myeloid leukemia CML C92.1	14	(9, 5)	6.1	7	(3, 3)		12.5	18
Polycythemia vera PV C94.0	4	(2, 2)	4.6	8	(4, 2)		23.0	9
Myelodysplasia MDS D46	2	(0, 2)	2.3	2	(1, 1)		8.3	5
Myelofibrosis MF D47.1	9	(4, 4)	9.2	1	(0, 1)		4.2	5
Essential thrombocytosis ET D47.3	0			3	(1, 2)		12.5	<2
Myeloid leukemia unspecified ML NOS C97.9	15	(9, 6)	17.2	0				<2
Myeloproliferative disease MPD total	87	(52, 35)	100	24	(15, 12)		99.9	100
Male/Female ratio		1.5			1.3			
Age at onset of disease Years (median)	54	(49, 61)		63	(59, 68)			
Birth order effect		NO			NO			
Other Malignant Disorders								
Leukemia, uncertain L NOS C95.9	7	(2, 5)		1	(1, 0)			
Malignant histiocytosis MH C96.9	2	(0, 2)		0				

Table 1. Diagnoses. Comments: Pc, Proband crude; number of patients observed. NOS, not otherwise specified.

Nøkur heiti

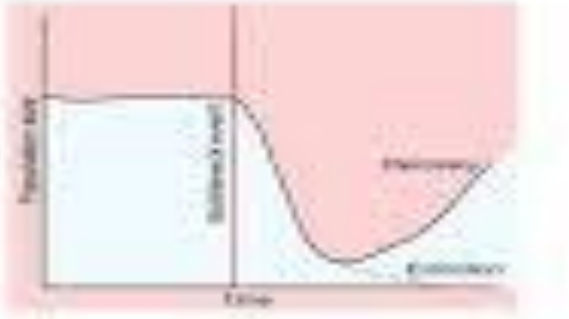
- ***Genetic drift***
- Meiotic drive
- ***Pattern recognition (ProGeny)***
- ***Anticipation (malignitetur hækkar og debutaldur lækkar)***
- ***Bottleneck effect ("loss of genes")***
- ***Microchimerisme***

Genetic drift og anticipation

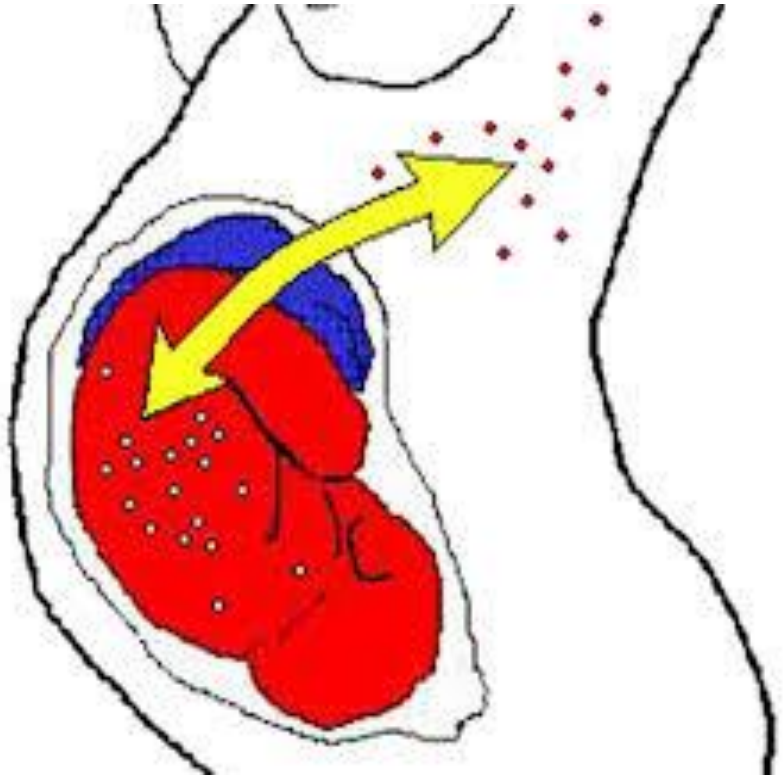


BOTTLENECK EFFECT

- Sudden change in environment drastically reduces population size (ex. famine, loss of habitat)



Microchimerism



- Samstarv

- Oslo Universitet
- DK
- Landssjúkrahúsið
- Ílegusavnið

- **Malignar Hæmatologiskar sjúkur eru monoklonalar**
- Lymfoproliferativar (Myelomatosa, Lymfom, Hodgkin, CLL og ALL)
- Myeloproliferativar (AML,MDS,MPN,CML,Myelofibrosa)

- 301 frá112 familiur í Norra og Danmark (ikki í slekt)
- Sjúk Foreldur - sjúkt barn (oftast son)

- 301 patientar í Føroyum (í slekt)
- Sjúk mostur/fastur ella mammu-/pápabeiggi - sjúkt barn

- MBD hægri incidens í Føroyum

Úrslit

- **Myeloprolierativar hægri í Føroyum**

- ***MPN hægri í Fø (28 % versus 8%)***
- AML hægri í Fø (50 % versus 37 %)
- CML hægri í Fø (16 % versus 12 %)
- Male/female ratio 1,5 : 1
- Debut 54 versus 63 ár
- Malignitetur versnar

Lymfoproliferativ hægri í Føroyum

- Mb Hodgkin hægri í Fø (8,7 % versus 4 %)
- DSCBCL hægri í Fø (15,6 % versus 5,8 %)
- NHL hægri í Fø (11,4 % versus 5,8 %)
- ***Myelomatosa væl hægri í Fø (22,8 versus 3,6 %)***
- Male/female ratio 1,5 : 1
- Debut 61 versus 67 ár
- Maligniteturin versnar

Niðurstøða

- Hægri incidens av MBD í Føroyum
- Ratio 1,5 : 1 fyri mann/kvinnu í Føroyum
- Eingin ella sjáldan afficeraði foreldur – barn í Føroyum
- Anticipatión í Føroyum

- ***Mendel ikki galdandi innan arvagongina fyri MBD***

- ***Microchimerisma og gentic drive vísa arvagongd í Føroyum***
- ***Debutaldur lækkar og og at enda terminerast sjúkan (Anticipation)***
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