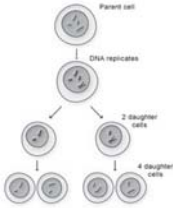
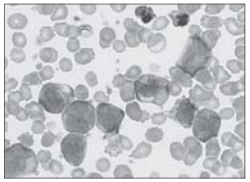
Is Leukemia Hereditary?





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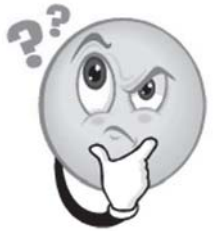
Michigan State University

drugline.org

Session Objectives

1. Discuss a basic understanding of cancer development
2. Explain how heredity can affect cancer development generally
3. List particular leukemias shown to have a hereditary association

What got me curious about this topic?



What this presentation is NOT about

- Genetic syndromes with well-known leukemia associations
  - Examples:
    - Down syndrome
    - Diamond-Blackfan syndrome
    - Fanconi anemia

What the presentation IS about

- Leukemias that run in families that seem otherwise healthy
- The genetics of familial leukemias

Presentation Content

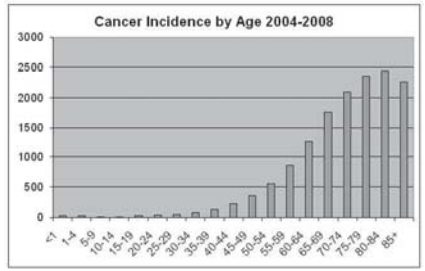
- What causes cancer – generic and basic
- Review of some basics of genetics
- What we know about heredity and leukemias
  - Lymphoproliferative disease
  - Myeloproliferative diseases
  - Myelodysplasia and acute myeloid leukemia
  - Acute lymphoblastic leukemia
- A side step into Li-Fraumeni syndrome

What causes cancer? (My simplified version)

- Mutations
  - Inherited: genes allow cancer to develop
  - Acquired: caused by insults (hits) to DNA
    - Radiation, viruses, toxins = xenobiotics
    - The insults damage the DNA (cause mutation) and when the cell divides, the mutated daughter cells carry the mutation and pass it on to their daughter cells, that pass it on to their daughter cells, etc
  - Combination: inherited genes plus DNA hits
    - Sometimes the inherited mutation makes the DNA more susceptible to insults or allows the mutated cells to perpetuate

- Multiple hits to a particular cell (and its progeny) are typically needed – more than one mutation
- Cells have defenses against insults = tumor suppression
  - Repair the damaged DNA before the cell divides
  - Prevent the damaged cells from dividing; induce it to die so the mutation is not propagated = apoptosis
- For a given cancer to develop, it may need a particular set of mutations occurring in a particular order

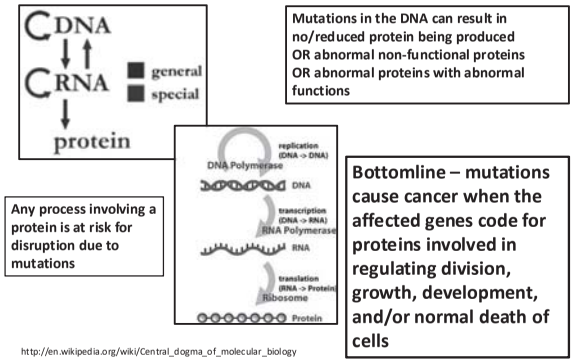
- Anyone can develop sporadic (non-inherited) cancers if a cell receives enough, and the right hits, to damage the DNA
  - Increased incidence of cancer with aging



www.freeby50.com

- Cancers with an inherited component (with or without environmental components) can occur earlier in life = anticipation; may be more aggressive

Central Dogma of Molecular Biology



Mutations in the DNA can result in no/reduced protein being produced OR abnormal non-functional proteins OR abnormal proteins with abnormal functions

Any process involving a protein is at risk for disruption due to mutations

Bottomline – mutations cause cancer when the affected genes code for proteins involved in regulating division, growth, development, and/or normal death of cells

http://en.wikipedia.org/wiki/Central_dogma_of_molecular_biology

Types of mutations causing cancer

- Mutations that impair normal cell cycle (division) and maturation
  - Affected proteins include growth factor receptors, signal transducers, transcription factors
  - Cells don't divide properly or mature normally
- Mutations that impair the DNA repair process
  - Mutations don't get fixed, cells divide and pass on the mutation
- Mutations that impede normal cell death (apoptosis)
  - Mutated cells live when they shouldn't
- Mutations that do not impair the gene's function BUT may make it more susceptible to insults that ultimately do affect its function

More on genes that contribute to cancer

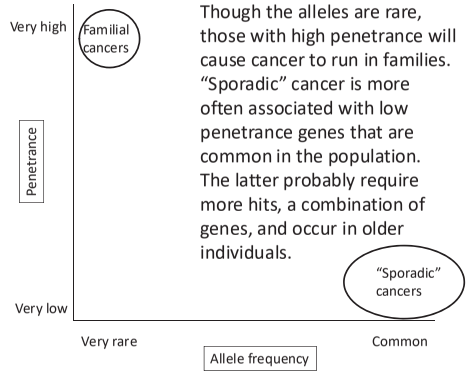
- High penetrance genes
  - The cancer is very likely to occur if you inherit the gene – Odds Ratio (OR) > 10
  - Rare (<0.1% population frequency)
  - Small risk to the overall population
  - Example: BRCA1 and BRCA2

Fletcher, 2010

More on genes that contribute to cancer

- Low penetrance genes
  - Carrying the gene does not confer a high risk of getting the cancer – OR 1.1-1.6
  - Common – Minor Allele Frequency (MAF)>10%
  - Contributes substantially to the overall population risk
  - Example: ESR1

Fletcher, 2010



Though the alleles are rare, those with high penetrance will cause cancer to run in families. "Sporadic" cancer is more often associated with low penetrance genes that are common in the population. The latter probably require more hits, a combination of genes, and occur in older individuals.

Not all mutated genes get expressed as disease

- Inheriting a mutated gene, particularly the common - low penetrance genes, may not be sufficient
  - May need multiple mutated genes = polygenic
- The development of cancer is multifactorial = genetics interacting with environment (i.e. insults)
  - So may need a certain hit to activate the oncogenic gene
- The sequencing of acquired mutations may be important

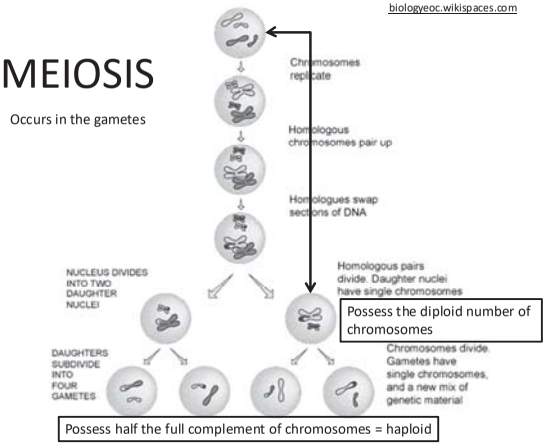
Genetic Basics

- **23 pairs of chromosomes = 46 chromosomes**
  - **22 pairs are autosomes**
  - **1 pair - the sex chromosomes**
- **Inherit one chromosome of each pair from each parent**
  - **Gametes (sperm and ova) only have 23 chromosomes because they undergo meiosis – reduction division**
  - **These are the germ cells (from the Latin – germin = to beget)**

MEIOSIS

biologyeoc.wikispaces.com

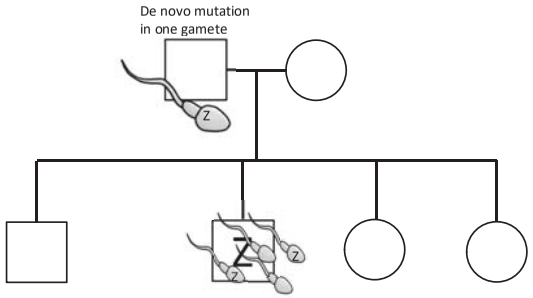
Occurs in the gametes



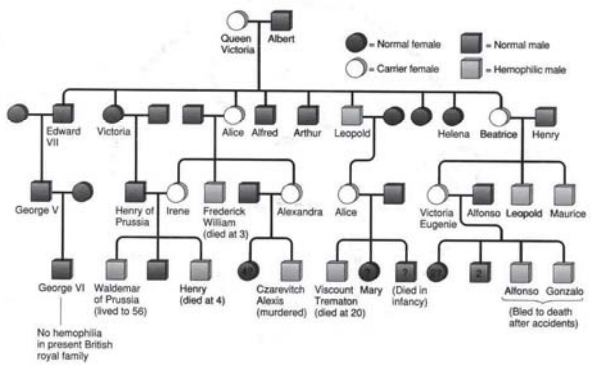
For a disease to be inherited:

- The mutation must be present in the gametes so that it can be transmitted from one generation to the next = germline mutation
- Two ways to have a germline mutation

1. Germline mutation can arise de novo in a healthy individual who passes it to their offspring
   - Mutation is occurring all the time during meiosis– it is actually good for maintaining genetic diversity in the population
   - Every somatic cell of the offspring, and ½ his/her gametes, will then carry the mutation

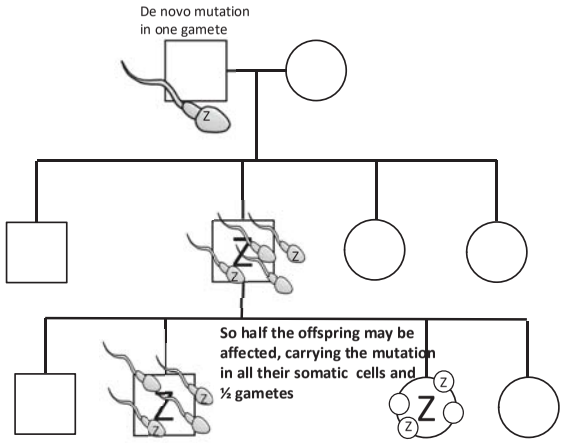


Every somatic cell of the child born from that gamete will carry the mutation. Half the gametes will carry the mutation.



http://www.biology-pages.info/Q/Queen_Victoria.html

2. If the parent inherited a germline mutation, it can be passed to progeny
   - Every somatic cell of the offspring, and ½ his/her gametes, will then carry the mutation



How is inherited cancer different from truly sporadic cancer?

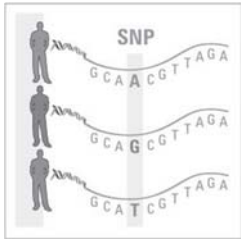
- In sporadic (non-inherited cancers), the mutation occurs in a cell other than a gamete
  - Examples: skin, lung, ovary, breast, liver
  - This cannot be transmitted to offspring because the gametes are not mutated
- The mutated genes can be different than the mutations seen in the inherited form of the disease
  - Often at least some are the same as in the inherited version of the disease

Remember: cancer can be inherited if the genes possess:

- Mutations affecting genes that:
  - Repair DNA
  - Control cell cycle, maturation and proliferation (i.e. growth factors)
  - Control normal cell death
  - Provide xenobiotic protection

We need to talk about SNPs

- Single nucleotide polymorphism (SNP)
  - In the string of nucleotides that comprise the DNA of an allele, ONE is different than the nucleotide at that position in the vast majority of the population



Wild type

SNP

Different SNP at the same location

www.broadinstitute.org

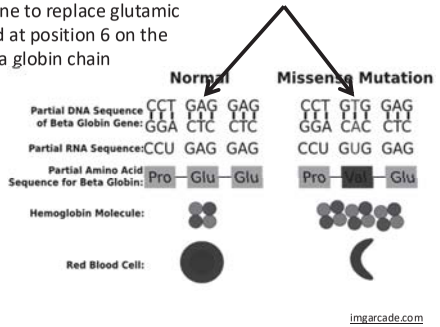
More on SNPs

- If at least 1% of people have that particular nucleotide substitution it is a SNP
  - People may have a different substitution at that position but if it is less than 1% of the population it is not considered to be a SNP

Can one nucleotide really make a difference?

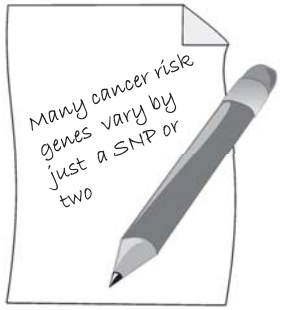
Sickle hemoglobin is a well-known SNP

- A is replaced with T causing valine to replace glutamic acid at position 6 on the beta globin chain



imgarcade.com

Here's the bottom line...



Lymphoproliferative Disorders

Lymphoproliferative Disorders

- Chronic Lymphocytic Leukemia (CLL)
- Non-Hodgkins Lymphoma (NHL)
- Hodgkins Lymphoma (HL)

From Brown et al

- Among CLL patients, nearly 60% have at least one 1st degree relative (parents, children, sibs – share 50% of DNA) with some kind of cancer
- 1 in 6 (17%) CLL patients has a 1st or 2nd degree relative (aunts, uncles, cousins) with a lymphoproliferative disorder
  - CLL is the most frequent of those
  - The mothers of CLL patients were more likely to also have a lymphoproliferative disease than fathers

Studies estimating increased risk to relatives

- First degree relatives of European patients with CLL had relative risk (RR) 7.52 times that of controls of developing CLL (Goldin 2004)
  - No anticipation was identified
  - Also increased risk for NHL and HL in relatives
- First degree relatives of patients with CLL have 8.5-fold increased risk of developing CLL(Goldin 2009)
  - About 2X risk for NHL

But Goldin says...

- Overall incidence of disease is low, so no value in monitoring first degree relatives
- Nat'l Cancer Institute – 4.5/100,000 new cases
  - =14-15,000/year in US
  - Lifetime risk of developing CLL – 0.6%

From Mauro et al

- Among CLL patients, 12.5% had a family history (1st and 2nd degree relatives) of hematologic malignancy
  - Women had a higher frequency of family history than men did
  - 9% were lymphoproliferative; 6% CLL
- Among parent-child subject pairs, children were diagnosed earlier than parents by a median of 22 years
- No prognostic differences for patients with familial vs sporadic CLL

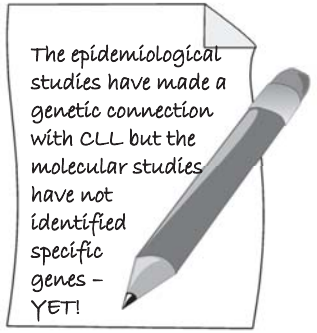
From Sellick et al

- Used linkage analysis of high-density SNP arrays of 206 families to develop evidence of
  - A major susceptibility locus on chromosome 2 – 2q21.2
    - Likely autosomal recessive
    - May be involved in B cell proliferation and differentiation
  - A second locus on chromosome 6 – 6p22.1
    - Likely autosomal recessive
    - Includes the HLA locus
  - A third locus on chromosome 18 – 18q21.1
    - Likely autosomal dominant
    - May be involved in B cell proliferation and differentiation

- Also found 3% of healthy relatives in the study had monoclonal B-cell lymphocytosis
  - These cells carry the same markers as the CLL cells
  - This was 14% of the first-degree relatives of CLL families
  - Individuals with actual lymphocytosis carry a 1-2% increased risk of progression to CLL (Shanafelt)
  - Maybe an indicator of familial predisposition to CLL (Slager)

- Now more than 25 GWAS-identified (genome-wide associated studies), and replicated, loci have been implicated (Slager)
  - Many are intergenic so may not be functional
  - Studies have not been restricted to studying families; included sporadic cases
    - One familial study - Most promising is 6p21.3 – includes MHC
- One reported study of Chinese families (in which CLL is very low incidence) (Lan)
  - 3 SNPs identified
- One study in African-Americans (Coombs)
  - No associated SNPs identified

Here's the bottom line on CLL



Chronic Myeloproliferative Neoplasms

The Myeloproliferative Neoplasms (MPN)

- Polycythemia (rubra) vera (PV)
- Essential thrombocythemia (ET)
- Primary myelofibrosis (PMF)

- Chronic myelogenous leukemia (CML) – Ph+

- 10X risk of MPN in Ashkenazi Jews (Chaiter)
- 5-7 fold increased relative risk of MPN among first degree relatives of MPN patients (Landgren)
  - 12 fold increased ET risk for ET patients' relatives
- The same disease will be present about 60% of the time in affected relatives
- One report that the transformation to acute leukemia is more frequent in familial MPN (Rumi)

www.clevelandclinicmeded.com

From [illegible]-analysis

- Mean age of [illegible]ilial MPD 46 (sporadic cases – 66)
- Mendelian autosomal dominant inheritance in about 60% of cases
- Incomplete penetrance

JAK2 mutation is important

- JAK2 protein transduces messages from outside the cell into the nucleus
  - Promotes proliferation and cell survival
  - Gene location: 9p24
- JAK2 V617F mutation present in MPN (not just familial):
  - 95+% of PV
  - 50-60% of ET
  - 50-60% of PMF

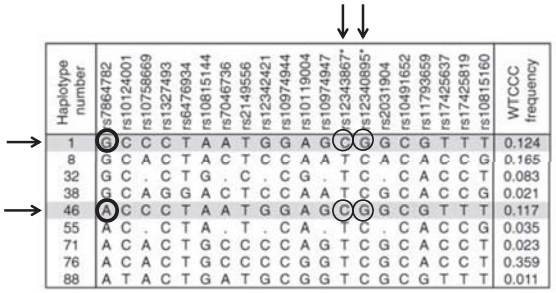
- JAK2 V617F mutation is constitutively activated
- Has not been reported to be inherited through the germline in MPN

Jones 2013

Haplotype 46/1 is a contributor

- JAK2 V617F arises preferentially on the 46/1 haplotype of chromosome 9 (Jones 2009)
- Haplotype 46/1
  - 19 nucleotides that get inherited together
  - Haplotypes 1 and 46 have 2 SNPs that differ from other common haplotypes (they also differ by one SNP from each other)

People with haplotypes 1 and 46 had increased incidence of JAK2 V617F



Haplotype number	rs7864782	rs10124001	rs10758669	rs1327493	rs6476934	rs10815144	rs7046736	rs2149556	rs12342421	rs10974944	rs10119004	rs10974947	rs12343867*	rs12340895*	rs2031904	rs10491652	rs11793659	rs17425637	rs17425819	rs10815160	WTCCC frequency
→ 1	G	C	C	C	T	A	A	T	G	G	A	G	C	C	G	C	G	T	T	T	0.124
8	G	C	A	C	T	A	C	T	C	C	A	A	T	C	A	C	A	C	C	G	0.165
32	G	C	.	C	T	G	.	C	.	C	G	.	T	C	.	C	A	C	C	T	0.083
38	G	C	A	G	G	A	C	T	C	C	A	A	T	C	G	C	A	C	C	G	0.021
→ 46	A	C	C	C	T	A	A	T	G	G	A	G	C	C	G	C	G	T	T	T	0.117
55	A	C	.	C	T	A	.	T	.	C	A	.	T	C	.	C	A	C	C	G	0.035
71	A	C	A	C	T	G	C	C	C	C	A	G	T	C	G	C	A	C	C	T	0.023
76	A	C	A	C	T	G	C	C	C	C	G	G	T	C	G	C	A	C	C	T	0.359
88	A	T	A	C	T	G	A	T	G	C	G	G	T	C	G	C	G	T	T	T	0.011

Jones 2009

Haplotype 46/1 is a contributor

- 46/1 (AKA GGCC) haplotype occurs:
  - In 24% of Europeans;
    - 50% have at least one chromosome carrying that haplotype
    - Also identified in other ethnic groups – Chinese and Japanese
- O.R. of developing a Ph neg MPN is 3.7 for people with 46/1 haplotype

"...JAK2 46/1 is one of the strongest predisposition factors linked to development of molecularly define malignancy indentified to date..."

Jones 2013

Why does 46/1 predispose to JAK2 mutation?

- Hypotheses
  - 46/1 is hypermutable = acquires JAK2 mutations more readily
  - 46/1 acquires JAK2 mutations at the same rate but once mutated, the 46/1 confers a selective advantage to the mutated clone
  - 46/1 creates a propensity to acquire mutations beyond JAK2 or otherwise contribute to disease development
  - Multiple of the above

JAK2 V617F and association with haplotype 46/1 is an example of the "inherited mutation" (i.e. the haplotype) predisposing to development of the disease-associated acquired mutation (JAK2 V417F)

46/1 is not required for development of MPD

- JAK2 V671F arises on a different haplotype about 25% of the time (Jones 2013)
  - Likely more sporadic cases

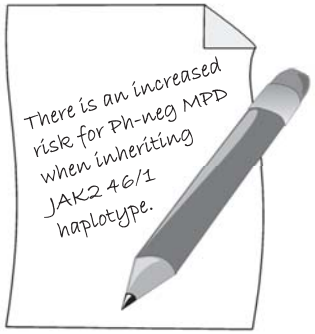
Other mutations have been implicated for familial MPN

- Also likely to be acquired but with strong evidence of some familial/inherited component as yet unknown
  - Myeloproliferative leukemia proto-oncogene (MPL W515L/K) – involved in making thrombopoietin receptor protein (which uses JAK to transmit its signal)
  - TET2 (tet methylcytosine dioxygenase 2) – tumor suppressor

What about CML?

- No clear evidence that JAK2 mutations play a role
- "there is no... familial predisposition" –
  - Deininger in Wintrobe's Clinical Hematology

Here's the bottom line on MPD



Myelodysplastic Syndromes (MDS)

AND Acute Myeloid Leukemia (AML)

Myelodysplasia

- Seven WHO sub-types – lumped together for our purposes
  - Characterized by cytopenias and dysplasia
  - Commonly progress to AML
- Not including discussion of bone marrow failure syndromes associated with syndromes like Fanconi anemia
- Inherited MDS/AML is RARE AND not in the WHO subtypes
  - Sources for this are Babushok and West reviews

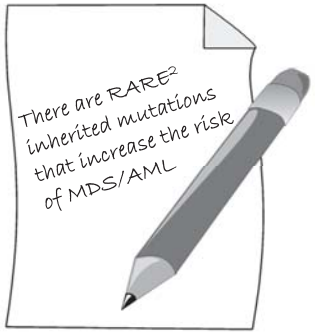
What is the incidence of MDS/AML?

- For MDS – literature says it is under-reported – these are improved incidence estimates
  - Australia– 103/100,000 (Mcquilten)
  - US– 75/100,000 (Cogle)
- 21,000 new cases/year AML (NCI)
  - 4/100,000 in US men and women
  - Lifetime risk of 0.5%
- About 1% of AML patients could have familial AML (Pabst)
  - And those WILL include the Fanconi anemias, all sporadic cases, etc

Known heritable MDSs (detailed slides at the end)

- Familial acute myelogenous leukemia with mutated CEBPA
- Familial MDS/AML with mutated GATA2
- Familial platelet disorder with propensity to myeloid malignancy

Here's the bottom line on MDS/AML



Acute Lymphocytic Leukemia

How frequent is ALL?

- Most common cancer in children in developed countries
- 6-7,000 new cases each year (NCI)
  - 1.7/100,000 in US men and women
  - Lifetime risk of 0.1%

From Sherborne, et al

- Four SNPs identified to confer small risk for development of B-cell ALL (mostly Europeans)

Tagging SNP	Gene	Chromosome/ position	Risk allele	Risk allele frequency in controls	Odds ratio	95% CI	
rs4132601	*IKZF1*	7p12.2	C	0.27	1.69	1.58-1.81	Normal function
rs3731217	*CDKN2A*	9p21.3	G	0.15	0.71	0.64-0.78	Tumor suppressor
rs7089424	*ARID5*	10q22.1	C	0.34	1.65	1.54-1.76	Tumor suppressor
rs2239633	*CEBPE*	14q11.2	G	0.52	1.34	1.22-1.45	Cell growth regulator
							Pro-apototic

- Homozygotes have about twice the risk of heterozygotes
- Increasing risk with increasing number of risk alleles = polygenic

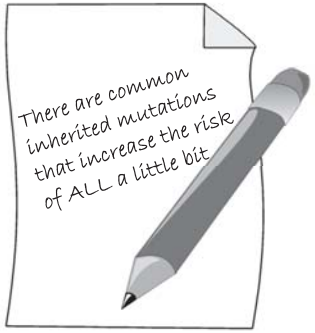
From Encisco-Mora, et al.

- Used genome wide association studies (GWAS)
- 3.93-fold increased risk of ALL in siblings of patients with B cell precursor ALL (BCP-ALL)
- Expects other low risk SNPs to be identified but unlikely to have relative risks >1.3
- Supports the polygenic nature of BCP-ALL

BTW...

- ALL has documented intrauterine associations with maternal xenobiotic exposures

Here's the bottom line on ALL

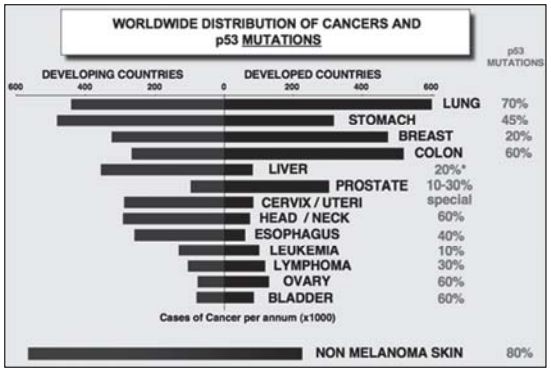


What about Li-Fraumeni Syndrome?

- Families in which there is:
  - High incidence of sarcomas (arise in mesenchymal cells; included leukemias) among first degree relatives
  - Occurring at early age (eg. <45)
    - Especially when adult cancers occur in children
  - Mutations of p53 are usually involved

P53 – Guardian of the Genome

- Activates DNA repair
- Can initiate apoptosis
- Inherit two copies of the gene – one from each parent
- If only one mutated gene is inherited, the normal gene protects until/unless it is affected by a sporadic mutation – a "second hit"
  - the acquired mutation of the second gene in a cell can result in loss of p53 tumor suppressor functions and result in cancer



http://p53.free.fr/p53_info/p53_cancer.html

p53 mutations and leukemia

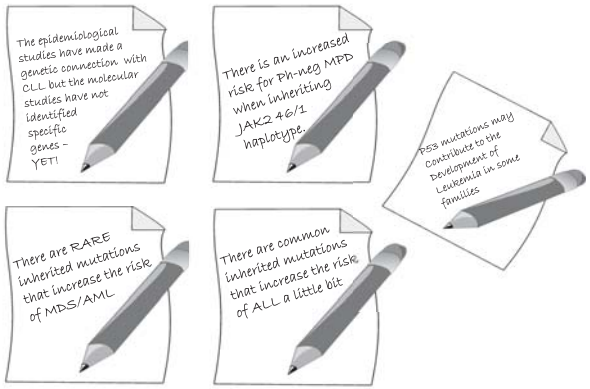
- Occur in about 15% of all leukemias
  - AML <9%
  - ALL ~5%
  - CLL reports of 15-50%
  - Hairy cell ~28%
  - CML develop during accelerated phase
- Are usually acquired
- May correlate with advanced disease, aggressive course, poor prognosis

Peller

BUT...

- The association of p53 mutations and Li-Fraumeni syndrome means, when leukemia is diagnosed, inquiring about sarcomas among other family members is important:
  - Patient prognosis
  - Monitoring other family members

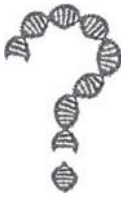
IN SUMMARY



Last words:

Most leukemias are sporadic

But there are familial leukemias and familial components to apparently sporadic leukemias. Recognizing it can affect treatment, prognosis, and other family members



Questions?

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Recommended Reading

- Fletcher O and Houlston RS. Architecture of inherited susceptibility to common cancer. Nature Reviews Cancer 2010; 10(5): 353-361.

Inherited MDS details

Familial acute myelogenous leukemia with mutated CEBPA

- CEBPA is a transcription factor in myeloid development
- Mutations diminish gene activity
- Autosomal dominant inheritance
- Near complete penetrance

Familial MDS/AML with mutated GATA2

- GATA2 is a transcription factor important to hematopoietic cell development
- Autosomal dominant inheritance – various mutations have been described
  - Often by haploinsufficiency
    - If the other chromosome is "hit", disease progresses
- GATA2 deficient individuals have a 50% chance of MDS/AML
- Typically affects younger individuals than sporadic MDS

Familial platelet disorder with propensity to myeloid malignancy

- Mutations to RUNX1 gene – component of a transcription factor complex necessary for normal hematopoiesis
- Autosomal dominant
- Can be due to haploinsufficiency
- Individuals with the RUNX1 mutations have a 35% increased chance of developing MDS/AML

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