Disclosures

The views presented today are my own and do not necessarily represent the views of the National Cancer Institute.
Waldenström macroglobulinemia (WM)

Family Studies

The Questions

- Why does WM sometime cluster in families?
- Is WM in families different from non-familial WM?
- Why are some people susceptible to WM?
  - Are there factors that increase risk for WM?
    - Genetic?
    - Environmental?
    - Lifestyle?
Our Approach

High – risk Families

Population Registries

Case - Control

Population Genetics
The NCI Family Study

- Identify families having
  - 2 or more family members with WM
  - 1 family member with WM + 1 with a related B-cell cancer
  - 1 family member with WM
Study Components

- Questionnaire(s)
  - Family History
  - Individual
- Permission to obtain pertinent medical records
- Blood and/or saliva sample
- Possible visit to NIH for clinical evaluation
What have we learned so far?
Familial WM is rare, but not as rare as we first thought

- ~100 families enrolled in the NCI National Familial WM Registry
- In a referral hospital setting, about 5% of WM patients report having a family member with WM
Are family members of WM patients at risk for WM or other conditions?
Healthy

Disorder

CLL

MGUS

WM

NHL

National Cancer Institute
WM and B-cell disorders

• Study subjects: 2144 LPL/WM patients, >8000 controls, and 1st-degree relatives of both groups in Sweden

Are family members of WM patients at higher risk of B-cell cancers?

YES (some)

MGUS is usually IgM

National Cancer Institute
WM and Autoimmunity

- Study subjects: 2470 LPL/WM patients, >9000 controls, and 1st-degree relatives of both groups in Sweden
- Question: Compared to people who do NOT have WM, do close family members of WM patients have higher risk for autoimmune diseases?

Kristinsson SY, . . . McMaster ML, et al. JNCI 2010
Understanding risk

“How many times must I tell you people who live in glass houses should not throw stones...”
Understanding risk
Are environmental exposures associated with WM?

High-risk Families

Population Registries

Case-Control

Population Genetics
Environmental exposures in WM families

- Study subjects: 103 familial WM patients
  273 unaffected relatives

- Question: In WM families, are any environmental exposures associated with increased risk for WM?

YES
Are there genes that predispose to WM?
What does ‘genetic susceptibility’ mean?

- One or more genes that are important for normal cell growth have changes (variants) that affect their function.

- These changes are present at birth and can be passed from one generation to the next.

- These changes may not be able to cause WM by themselves – may need:
  - more than 1 gene change or
  - combination of gene variants + environment.
Genes can be studied on many levels.
Genes can have different effects

- Genes with “Big effect”
  - Rare
  - Lead to high risk for disease
  - May be modified by other genes or environmental factors
  - Strategies: Chromosome, linkage & sequencing studies

- Genes with “Small effect”
  - Common
  - Lead to small increase in risk, so disease results from many genes + environment
  - Strategies: Association studies

Manolio T et al., JCI 2008
Searching for rare WM genes

Variety of chromosome abnormalities observed

Similar to nonfamilial WM

Abnormalities differ among members of same family

Chromosomes

McMaster et al., Clin Lymphoma 2005
Searching for rare WM genes

**Linkage Study**

- Linkage – close association of genes on the same chromosome
- We saw linkage to more than one region of the genome
- When we included IgM MGUS, the linkage signal was stronger
- Not every family linked to the same region

_McMaster et al., Am J Hum Genet 2006_
Searching for rare WM genes

What are we looking for?

• Genes contain the instructions to make proteins
• Genes can have changes in “spelling”

COLOR
COLOUR  Same meaning
COLON    Different meaning
COLR
COLOOR  Meaningless
CMLOR

• We call these changes “Variants”
• Genetic studies look for variants in genes
Searching for rare WM genes

Whole-genome and whole-exome sequencing

- Use patient’s DNA, not the tumor
- Look for variants in the ‘spelling’ of DNA
- “Whole-exome” = genes only
- “Whole-genome” = all DNA: genes + DNA between genes
- Best for identifying rare genes with “big effects”
- Studies in progress
Searching for common WM genes

Association studies

• Scan genomes from many different people
• Look for genetic markers that can predict presence of disease
• Compare WM patients to unrelated people
Searching for common WM genes

Association studies

1. Family-based association study
   - Studied specific genes – important in the immune system
   - Found a few genes that may contribute to risk
   - Need confirmation

2. Genome-wide association study
   - Scan entire genome using genetic “mile-markers”
   - Compare results from many different WM patients with healthy people
   - In progress

Summary I

1. Relatives of WM patients are more likely than other people to have:
   - WM or a related B-cell disorder
   - IgM MGUS
   - Certain autoimmune conditions

2. Risk is increased, but SMALL
3. A single gene is NOT likely to account for all familial WM

We found:

- Linkage to more than one region of the genome
- Associations with more than one “small effect” gene
- Evidence suggesting that environmental exposures might contribute to WM

4. These results need more study and the use of new approaches

- We still need your help to answer questions about WM
THANK YOU!

International Waldenström’s Macroglobulinemia Foundation

All our families and WM patients
who have so generously given their support

The Family Studies Team
Deborah Zametkin
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Our many scientific collaborators
and colleagues
Ask me about the new WM study at NCI!

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MGUS: Mono (= one) + clonal (= clone)
Gammopathy (= Ig)
of Undetermined (= unknown)
Significance
WM is a clinicopathological syndrome

- A specific type of lymphoma cells (lymphoplasmacytic lymphoma [LPL]) in bone marrow
- IgM monoclonal protein in blood