National Cancer Institute

Family Studies in Waldenström Macroglobulinemia

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Disclosures

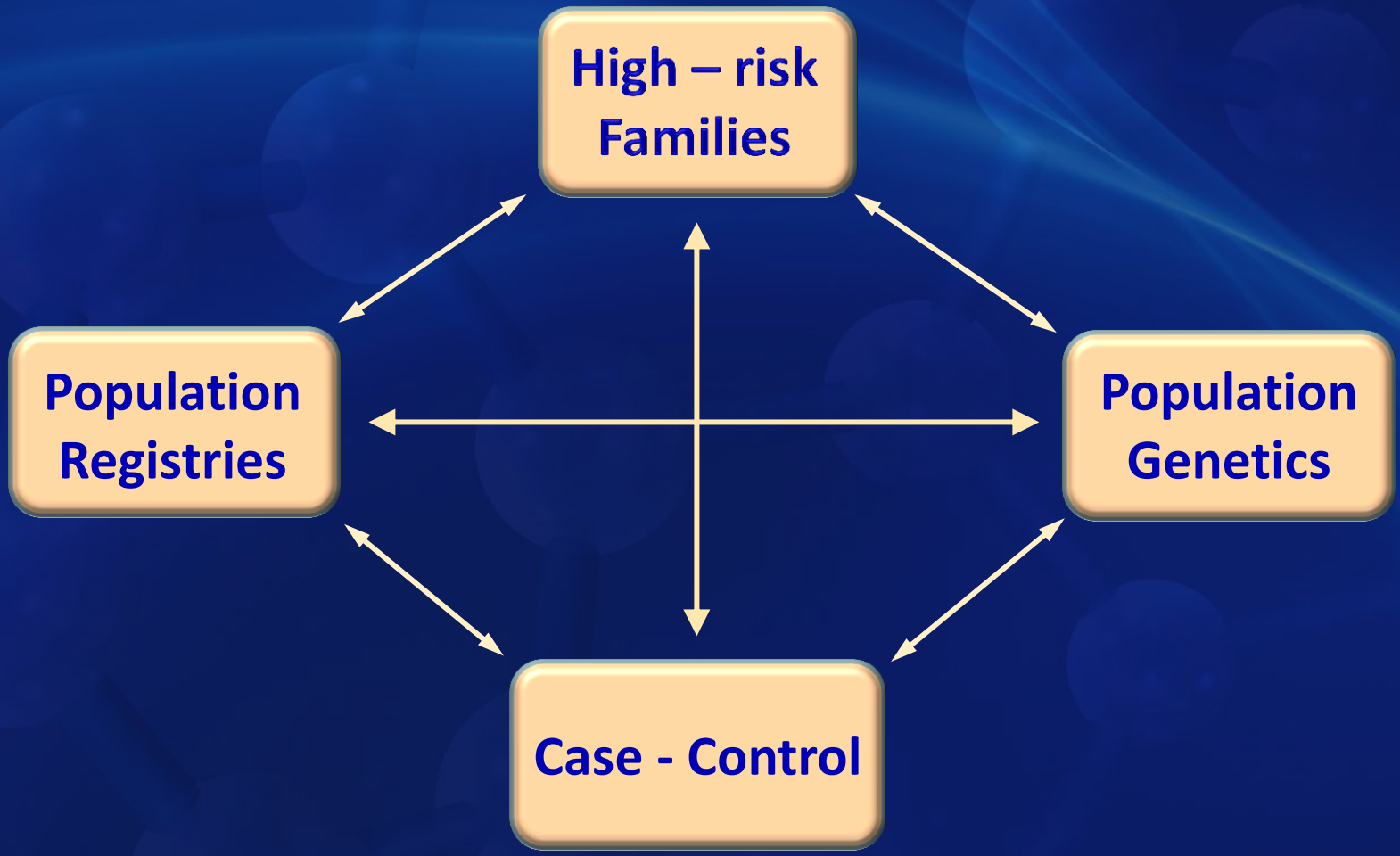
The views presented today are my own and do not necessarily represent the views of the National Cancer Institute

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



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

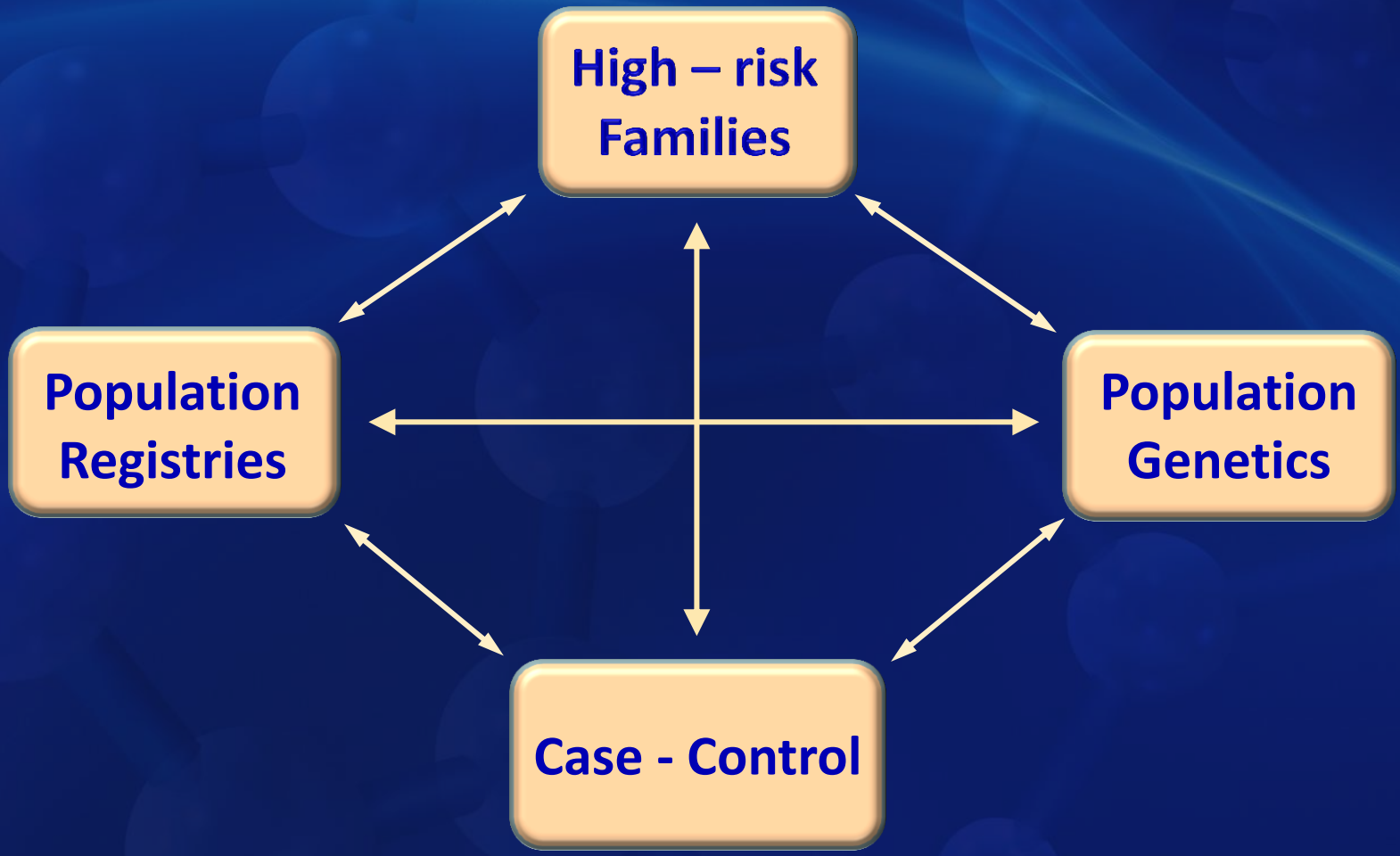
What have we learned so far?

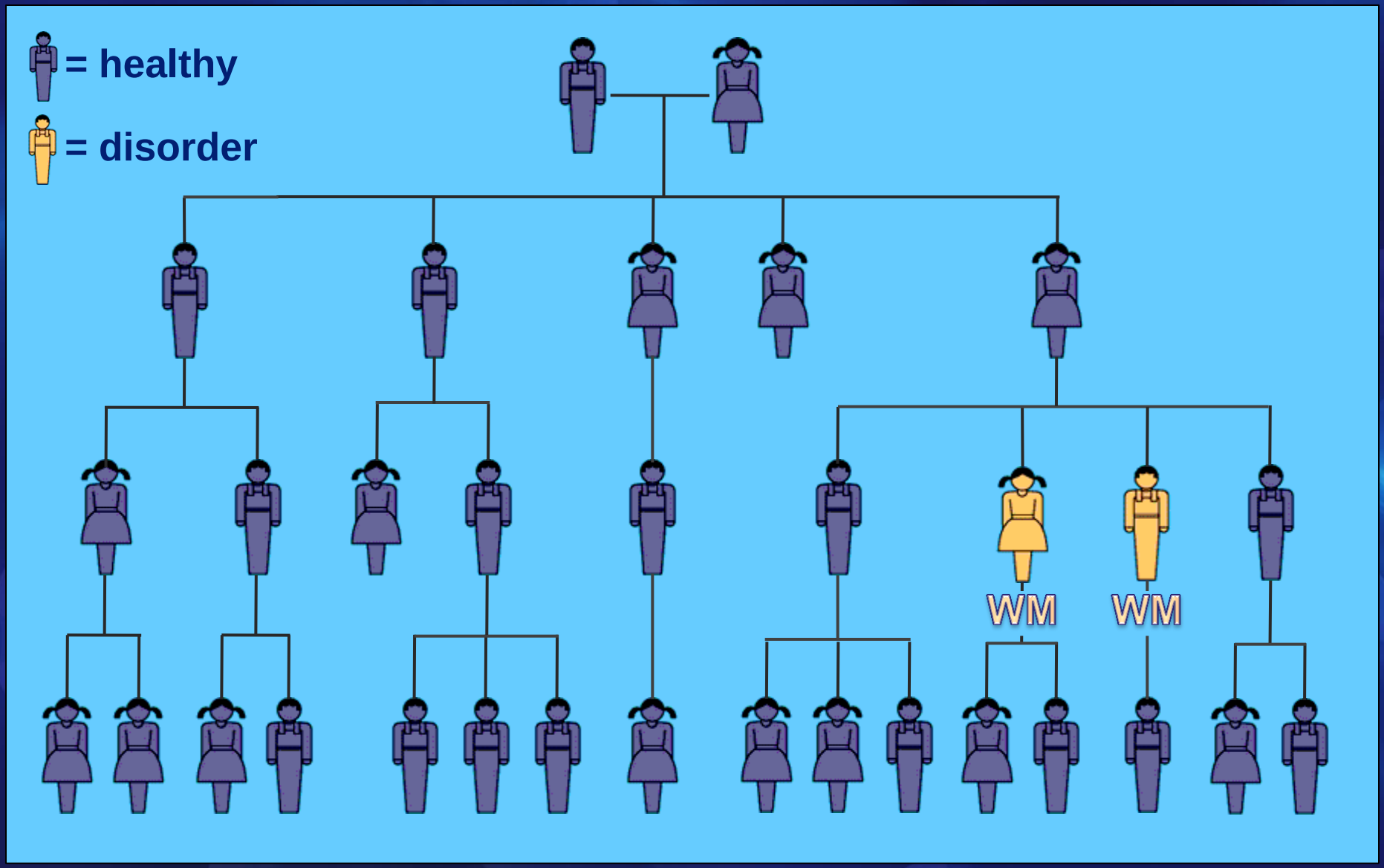
Is Familial WM rare?

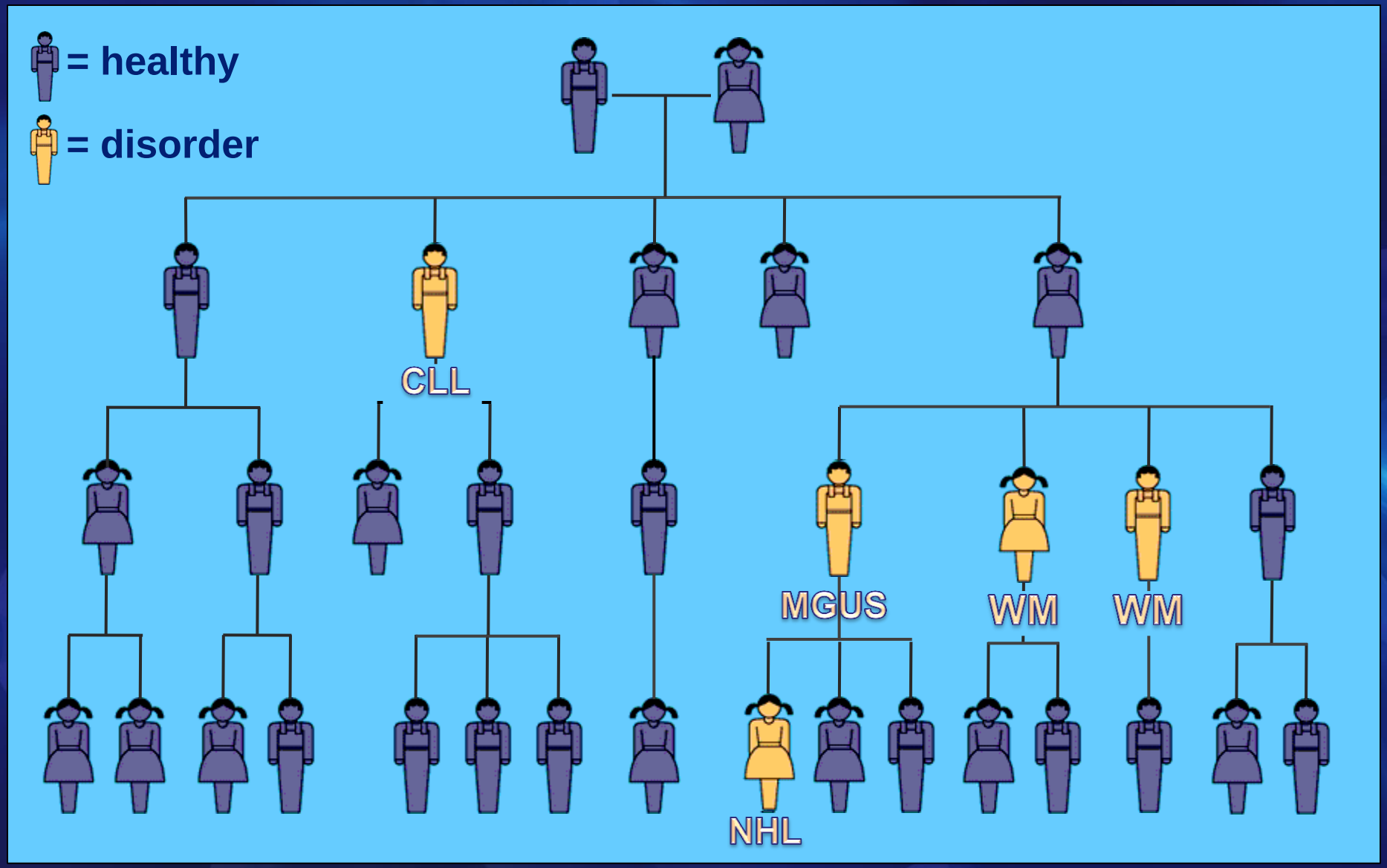
Familial WM is rare,
but not as rare as we first thought

- ~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?







WM and B-cell disorders

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

WM Patient

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

Person without WM

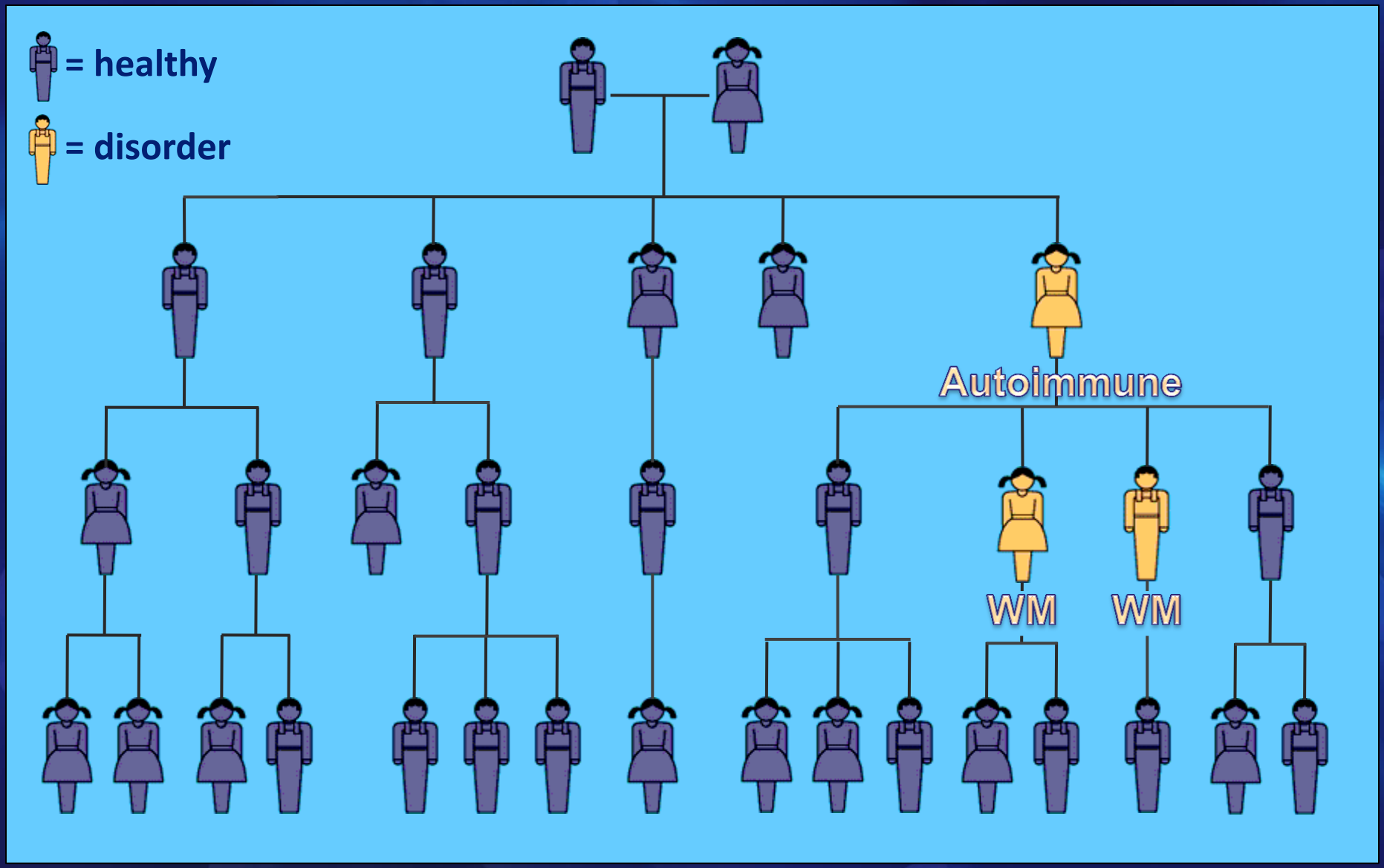
Close Family Members

YES

(some)

MGUS is usually IgM

Close Family Members



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?

WM Patient

Close Family Members

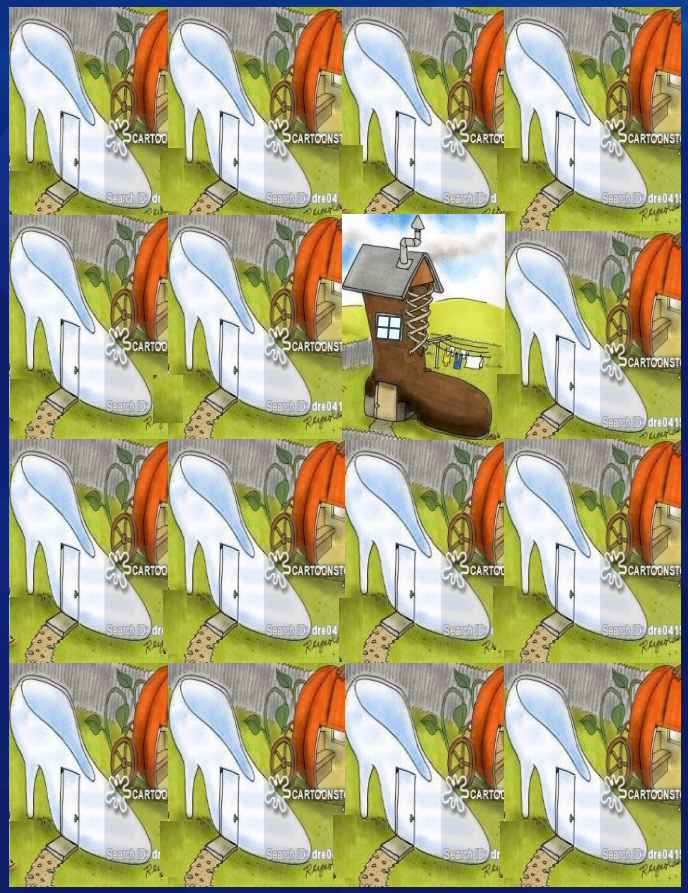
YES

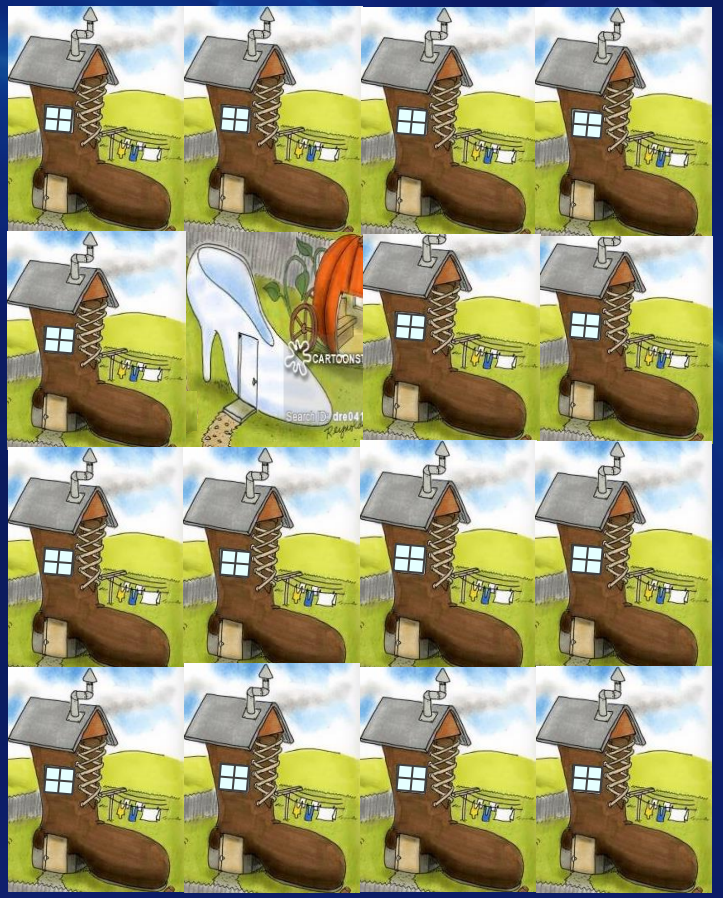
(some)

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

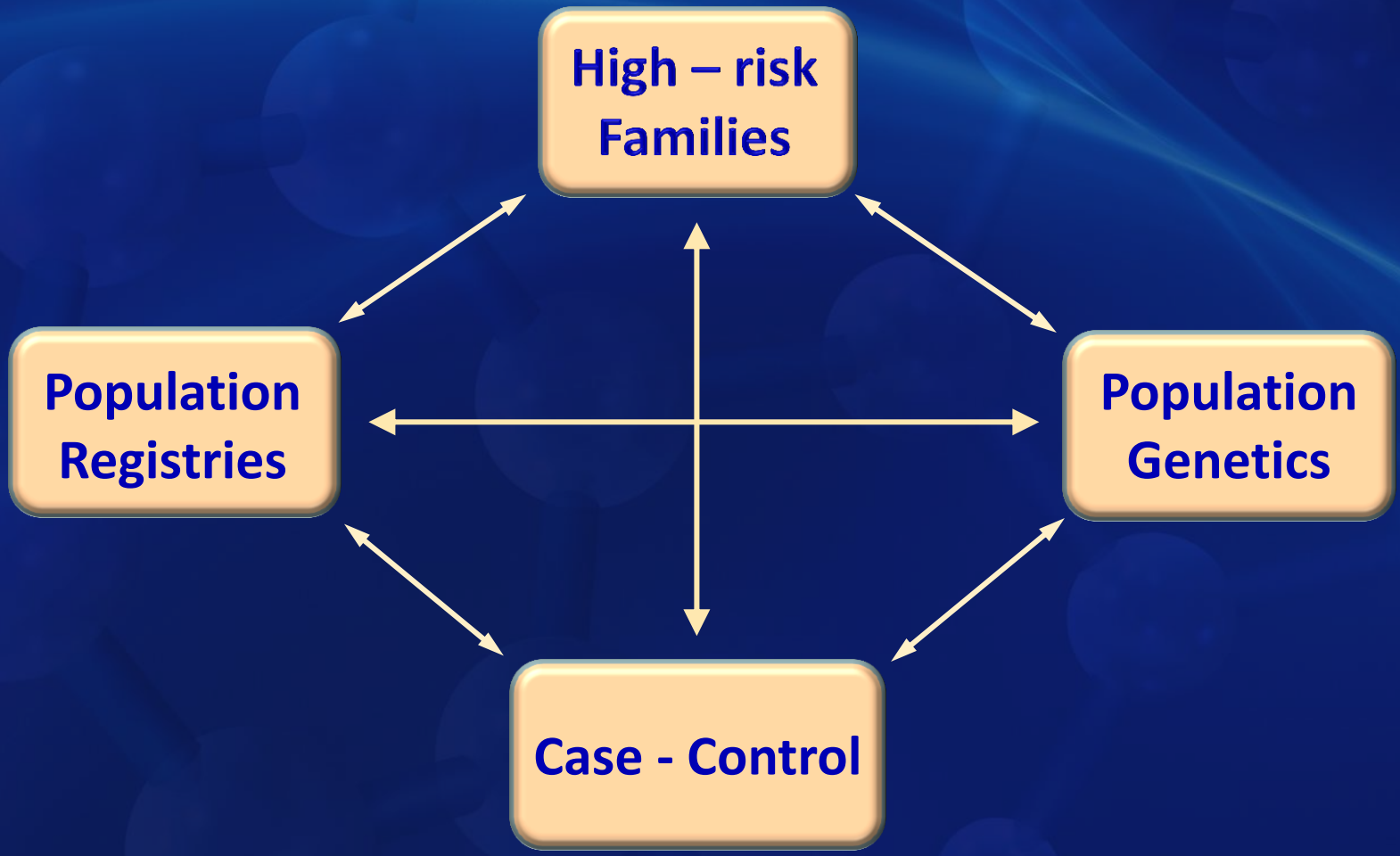
Understanding risk

Understanding risk





Are environmental exposures associated with WM?



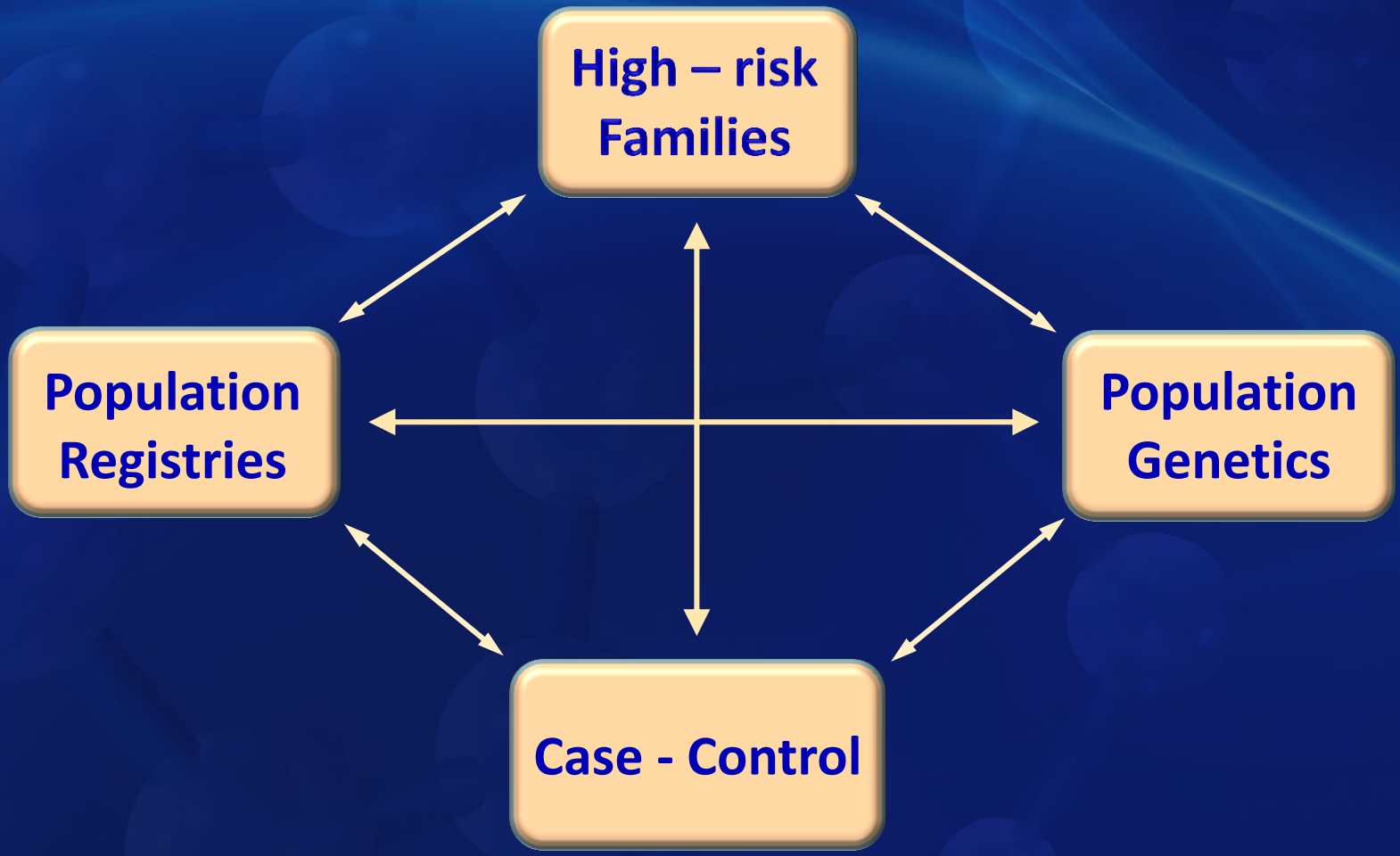
Environmental exposures in WM families

- Study subjects: 103 familial WM patients
  273 unaffected relatives
- Question: In WM families, are any environmental exposures associated with increased risk for WM?

YES

Royer RH. . . McMaster ML. Blood 2010

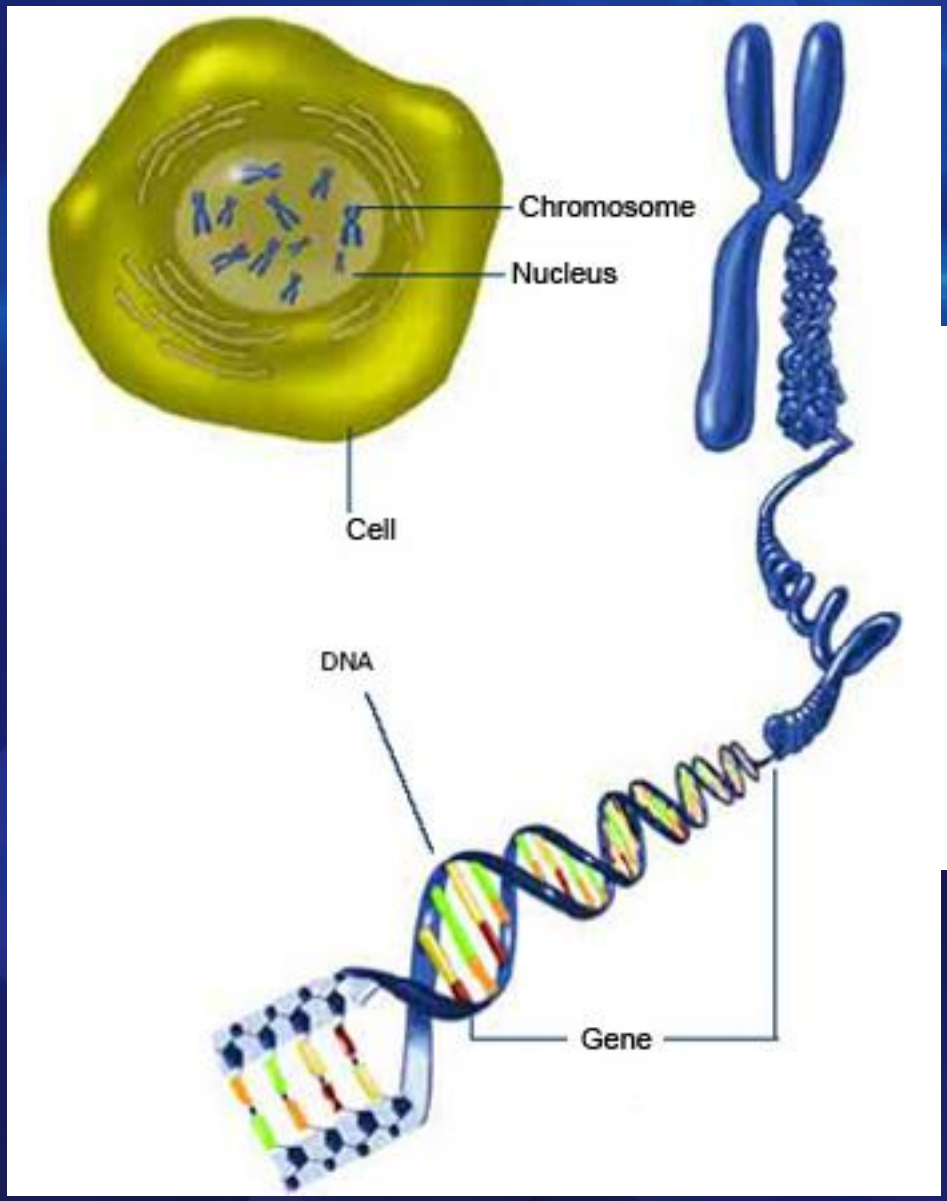
Are there genes that predispose to WM?

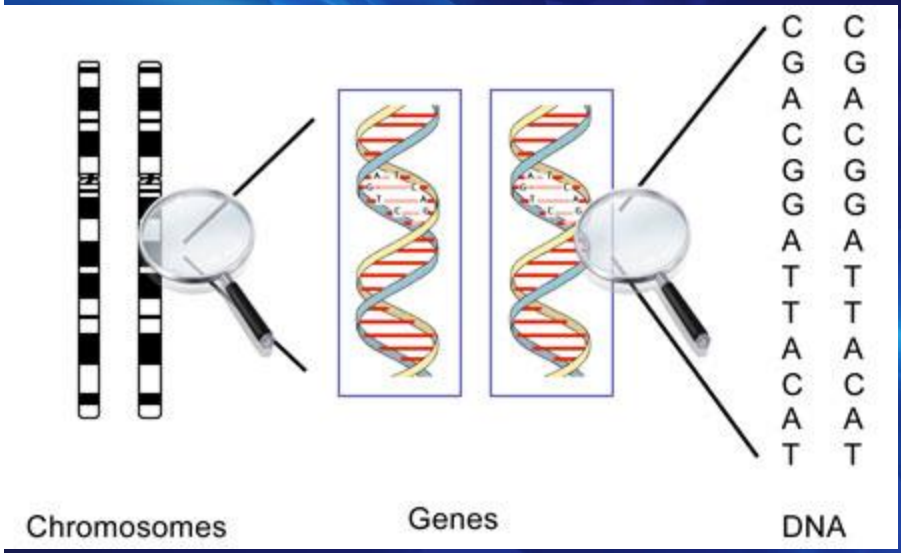


What does ‘genetic susceptibility’ mean?

- 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





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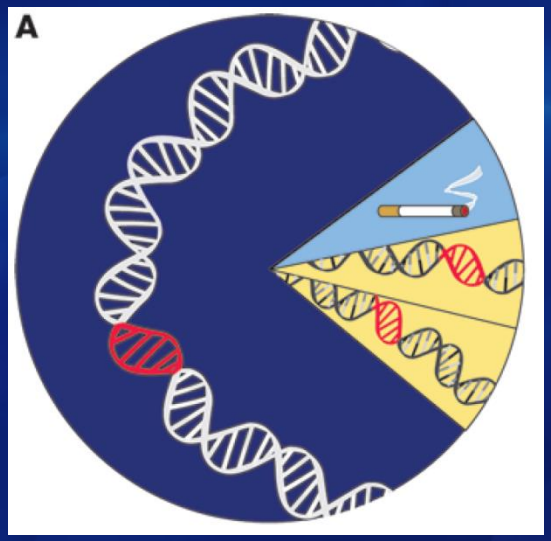
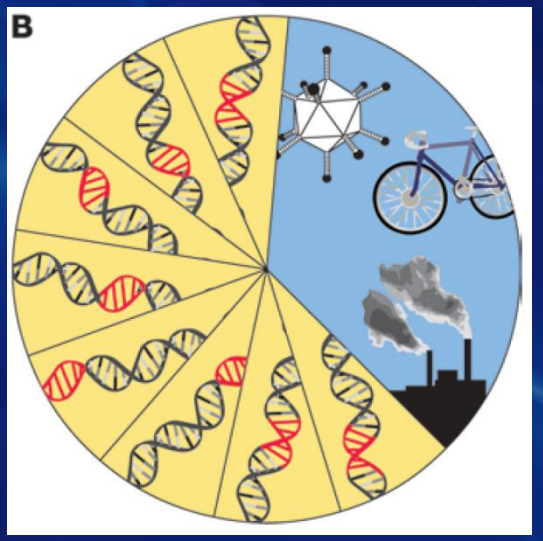
Genes can have different effects





- 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

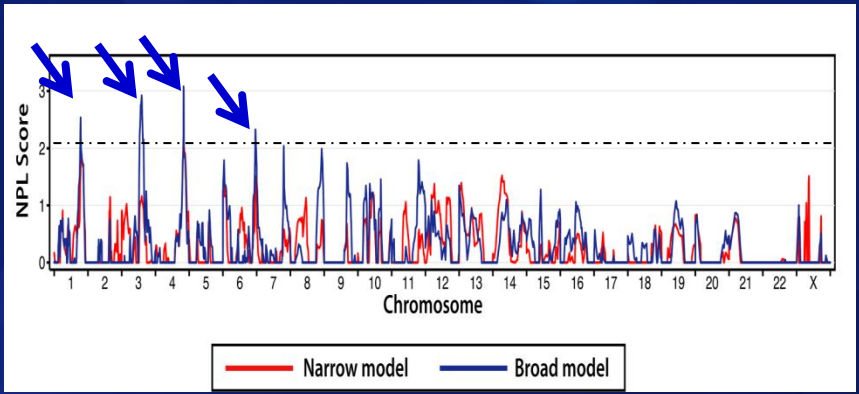
Chromosomes

- Variety of chromosome abnormalities observed
- Similar to nonfamilial WM
- Abnormalities differ among members of same family

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
CMLOR — Meaningless

- 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

Liang X. . . McMaster ML, et al., Br J Haematol 2009

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

Summary II

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
Ginny Pichler
Laura Fontaine

Our many scientific collaborators and colleagues

National Cancer Institute

Ask me about the new WM study at NCI!

For more information, contact:

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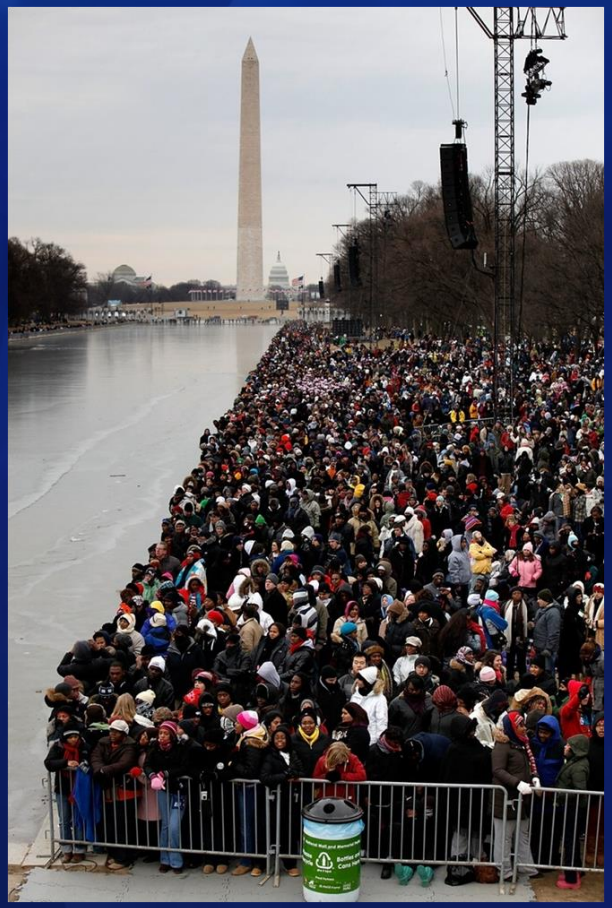
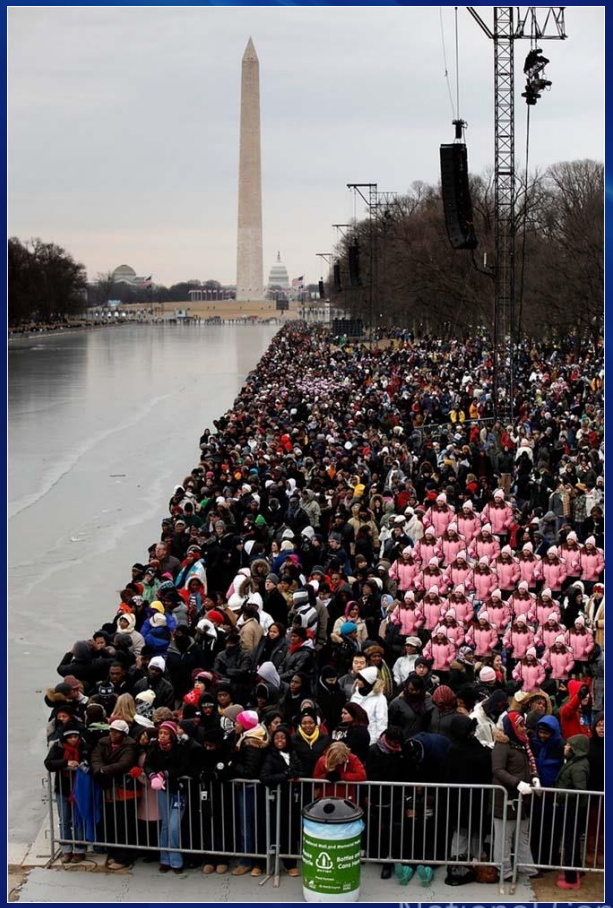
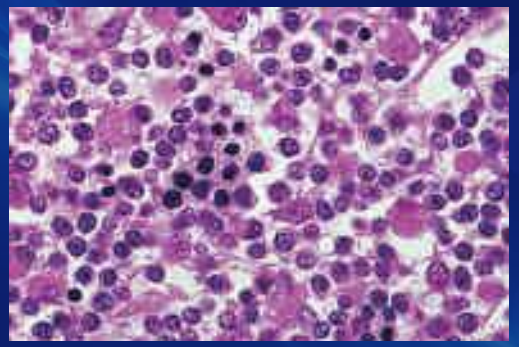
MGUS: Mono (= one) + clonal (= clone)
Gammopathy (= Ig)
of Undetermined (= unknown)
Significance





WM is a clinicopathological syndrome

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



- IgM monoclonal protein in blood