Celiac Disease in Families: How Genes Determine Your Risk

with David Kastenberg, MD, Co-Director, Jefferson Celiac Center, TJUH and Stephanie Winheld, MS, LCGC, Jefferson Kimmel Cancer Center Network, TJUH

Important Reminders!

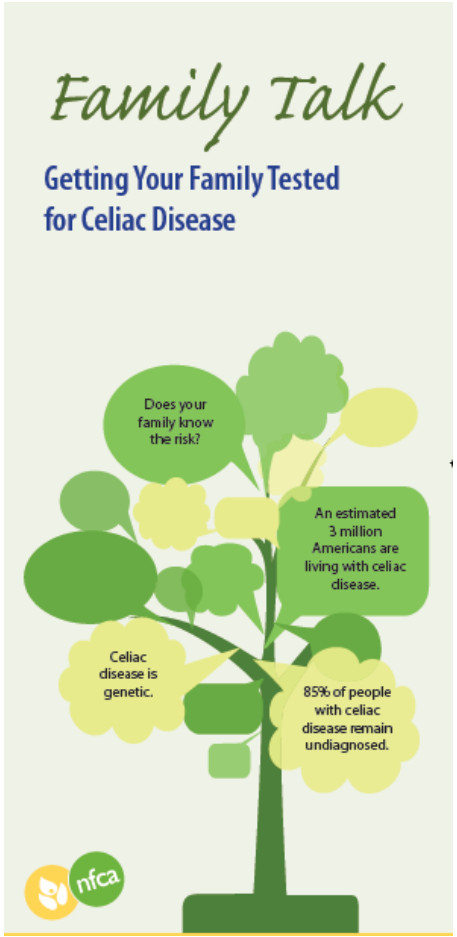
① **Will this information be available at a later date?**

- Yes, always!
- **Webinar recording will be posted along with the webinar slides within 72 hours after the live webinar ends.** Download recorded webinars and slides at the Archived Webinars page: CeliacCentral.org/webinars/archive/

② **Are continuing education credits available?**

- Yes!
- NFCA will provide a certificate as proof of participation for each webinar. **Attendees must complete the follow-up survey in order to access this certificate. Program participants will receive a link to complete the follow-up survey on Monday, April 14th through an email from NFCA.**
- **To ensure that you receive this email, make sure that NFCA (National_Foundation_for_Celiac_A@gmail.vresp.com) is on your allowed senders list.** If you have unsubscribed from any NFCA emails, please register for the webinar with a new email address. Make sure your email address is spelled correctly when registering, as we will use this for our follow-up communications.
- Please note that RDs and DTRs are not permitted to claim credits by viewing archived webinars. **Only those who register and attend live webinars will receive the opportunity to obtain continuing education credits.**
- Each participant must register for and log in to the webinar in order to receive credit. **In the case of group viewing, only the registered and logged in participant will receive credit for the webinar.**

History of NFCA's Family Education & Testing



- 2012 research project "*Celiac Disease Testing: Attitudes and Beliefs of At-Risk Family Members*," a collaboration with Emerson College and Celiac Center at BIDMC
  - At-risk relatives want to hear from their diagnosed family members!
- 2013 research project "*Physician Recommendations for Celiac Disease Screening in First-Degree Relatives,*" a collaboration with the Jefferson Celiac Center
- Thank you for participating! These projects are still ongoing
- Learn more and initiate your own conversation: **CeliacCentral.org/family**

Learning Objectives

① Understand the basics of genetics and their role in celiac disease

② Learn about the increased risk for developing celiac disease in families who have a medical history

③ Understand the importance of family member testing for celiac disease

④ Discuss the role of genetic testing in celiac disease diagnosis

Welcome!

David Kastenberg, MD, Co-Director, Jefferson Celiac Center

- Co-Director of Jefferson Celiac Center
- Associate Professor at Thomas Jefferson University
- MD, New York University School of Medicine
- BA, Rutgers College

Welcome!

Stephanie Winheld, MS, LCGC,

•Licensed Certified Genetic Counselor at Jefferson Kimmel Cancer Center Network

•Specializes in hereditary predispositions to cancer, especially hereditary GI cancer

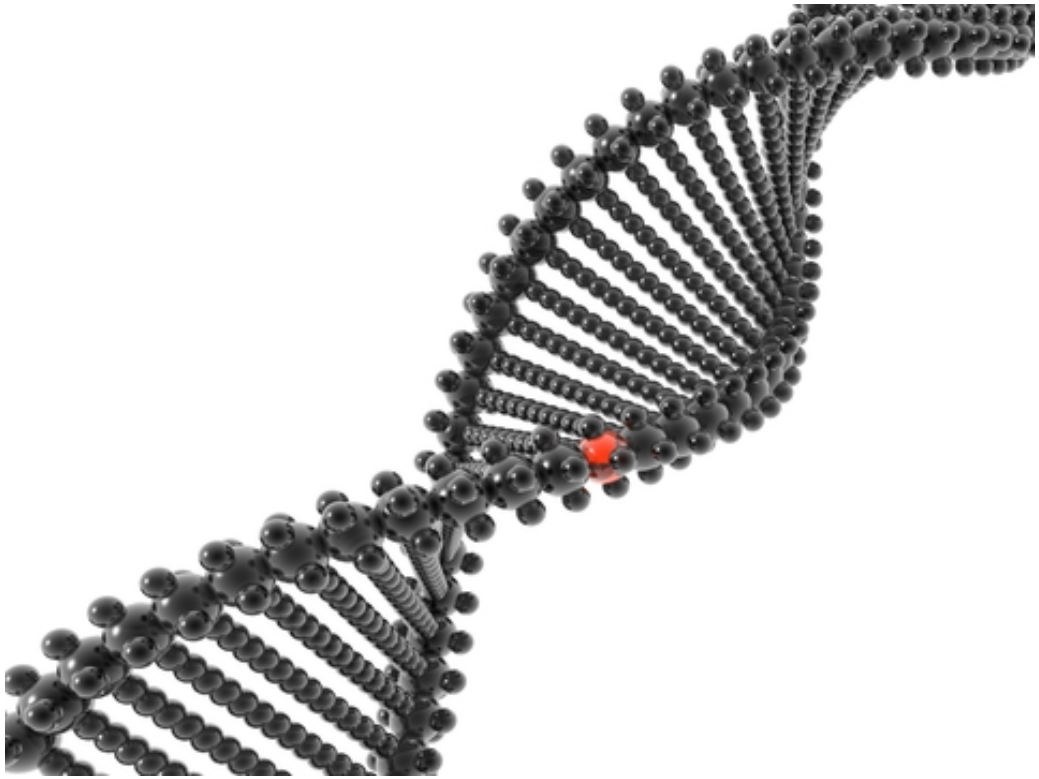
•Regularly travels to Jefferson's network hospital to provide genetic counseling services

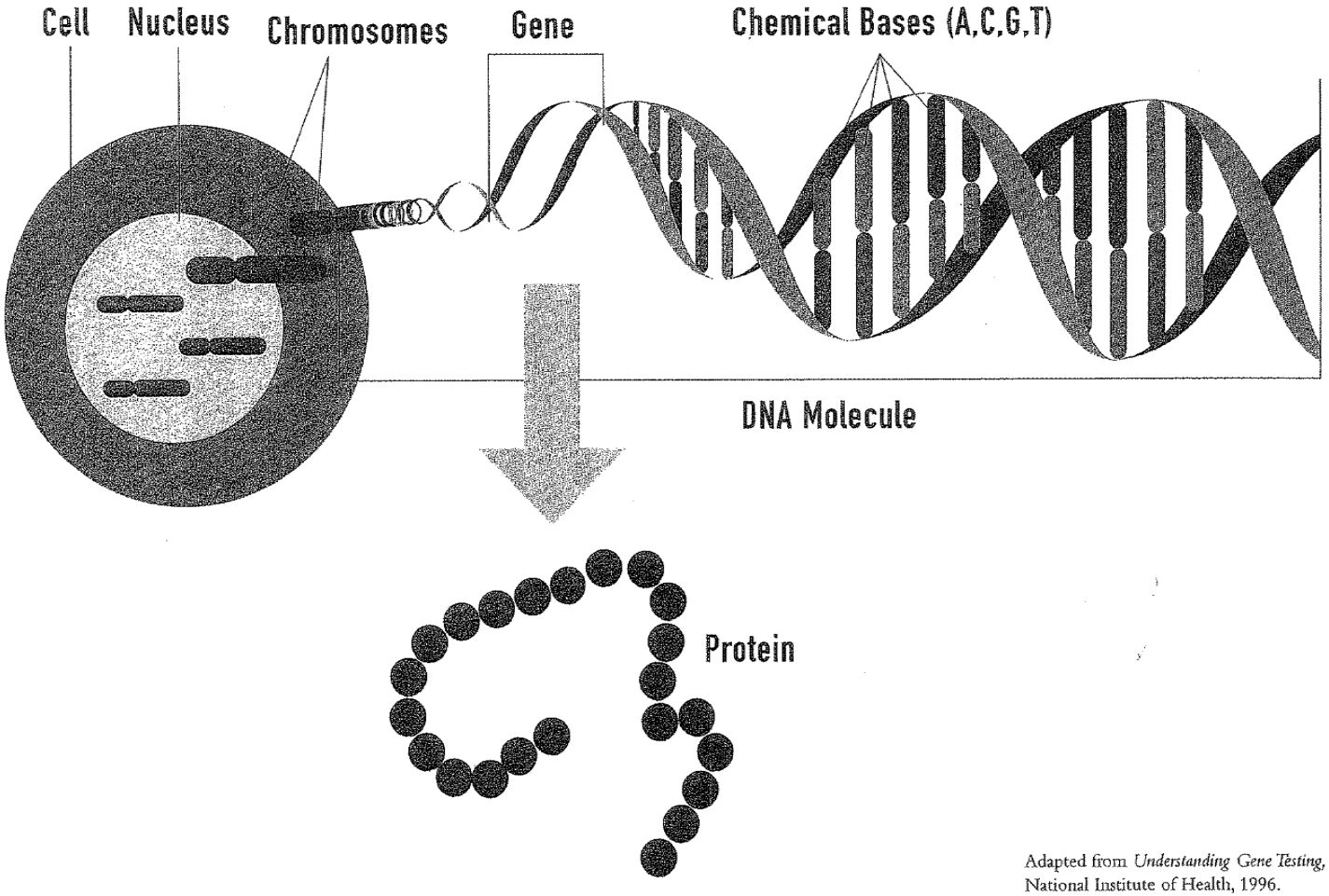
•Bachelor of Science from Penn State in Biobehavorial Health

•Master of Science from Arcardia University in Genetic Counseling

•Certified in genetic counseling by American Board of Genetic Counseling and licensed by the Commonwealth of Pennsylvania

Part 1:
Setting the Stage



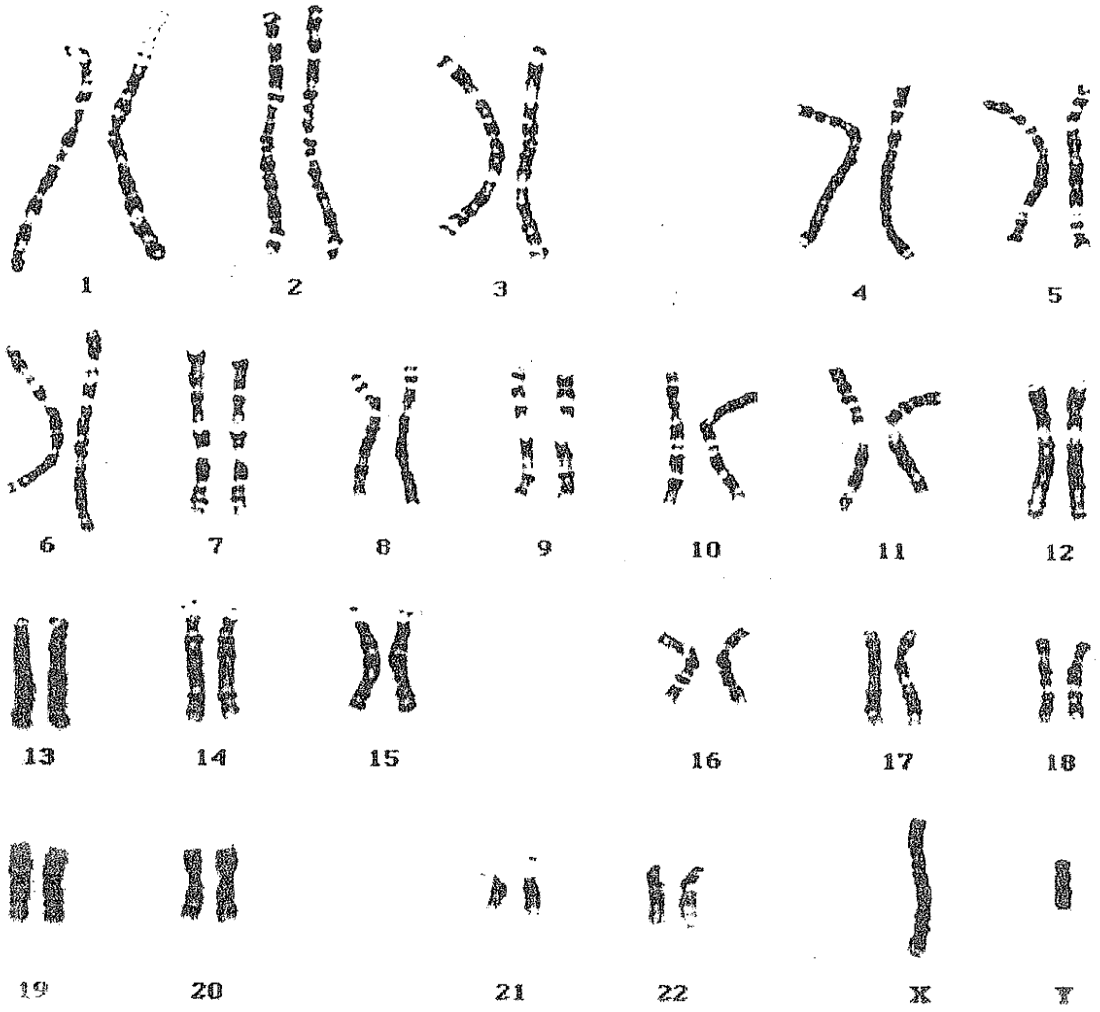


Adapted from *Understanding Gene Testing*, National Institute of Health, 1996.

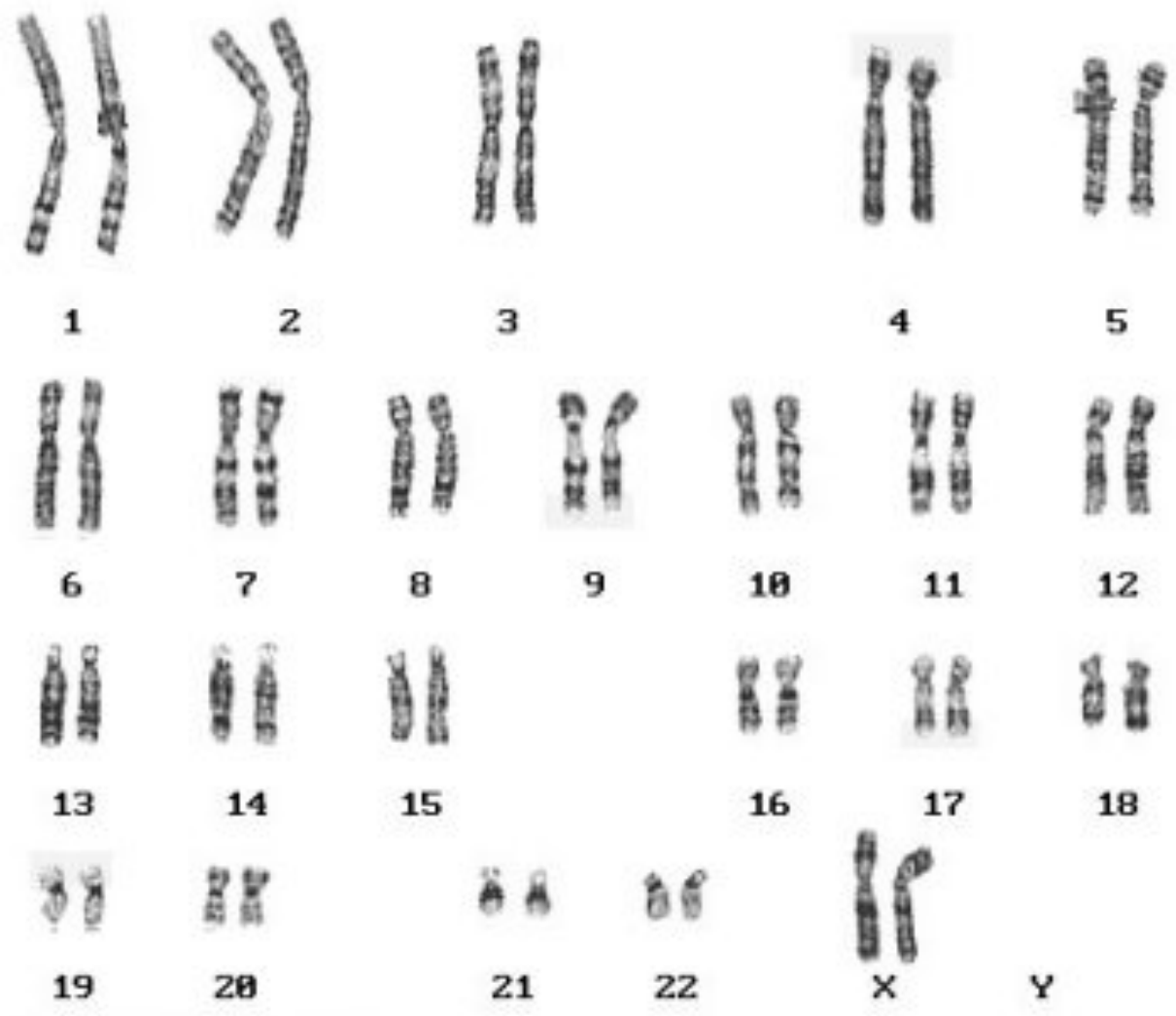
What are chromosomes?

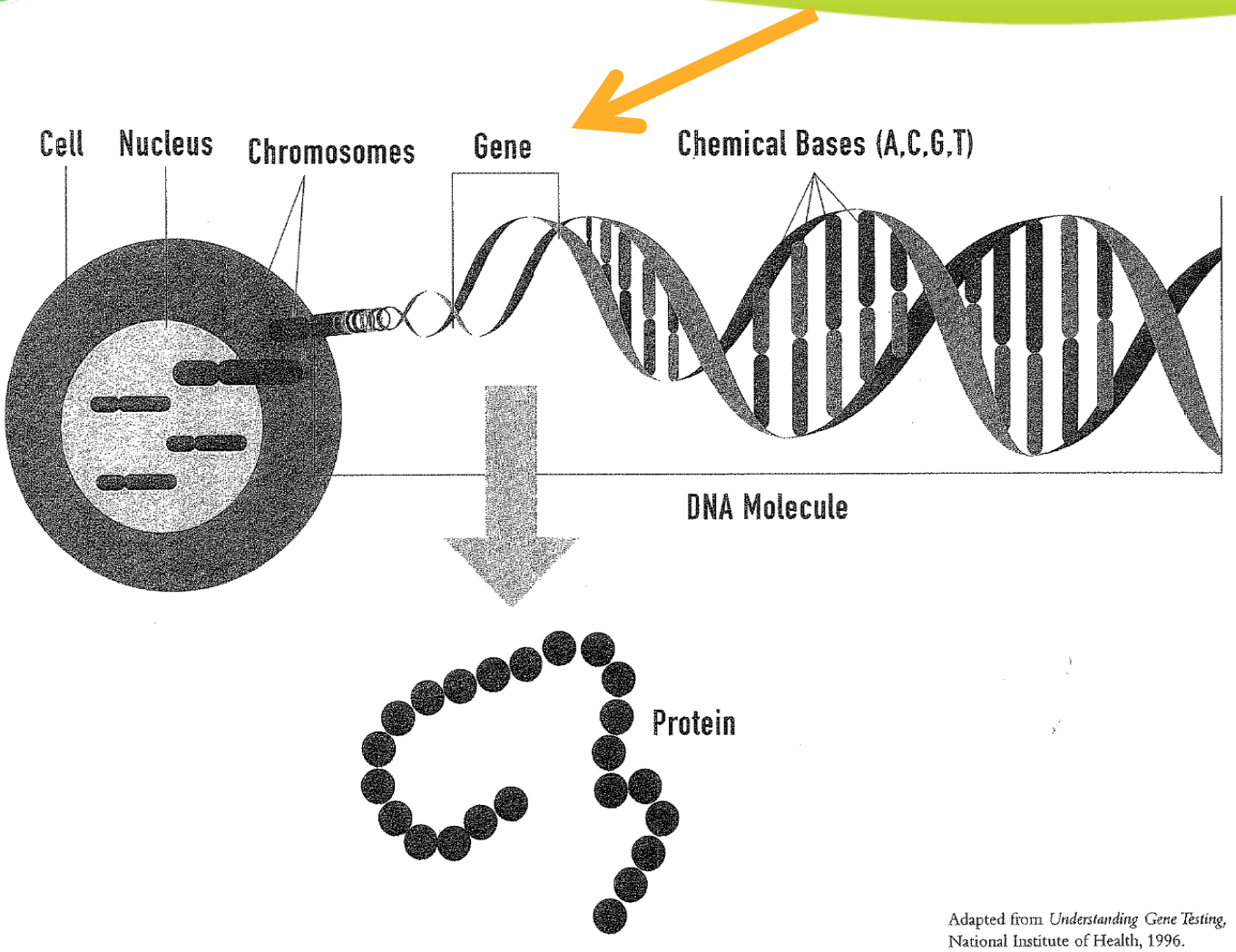
- Structures that hold all of our genes within them
- 46 chromosomes in each cell in our bodies
  - They come in pairs
  - Within each pair of chromosomes, one comes from the mother, the other from the father
  - One pair determines the sex of a person
    - XY = Male
    - XX = Female

Chromosomes



Chromosomes

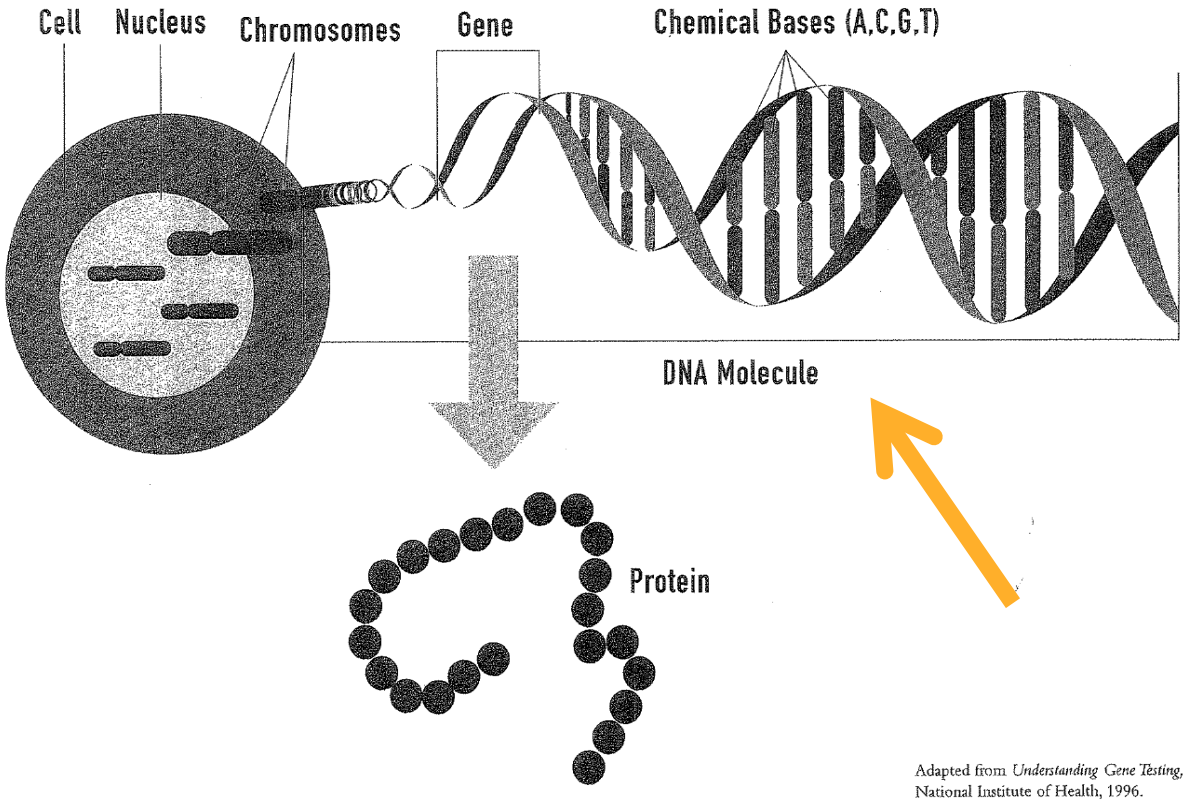




Adapted from *Understanding Gene Testing*, National Institute of Health, 1996.

What is a gene?

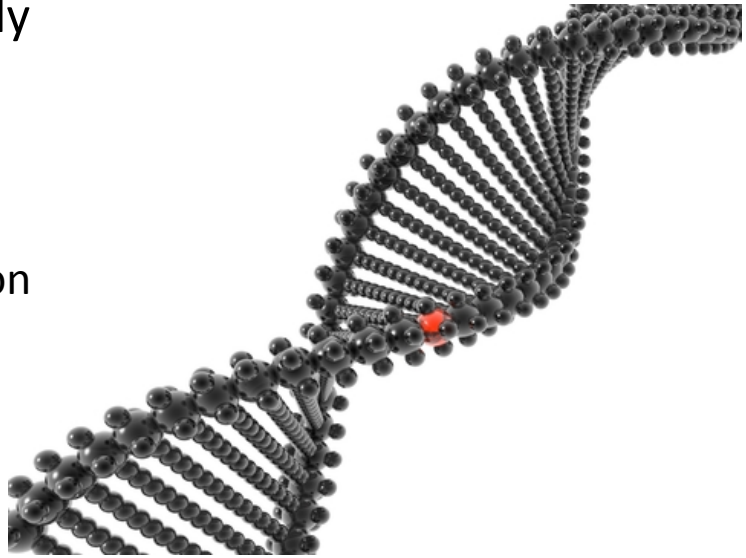
- Functional unit of heredity
- 20,000 – 25,000 within the human genome
  - **Provide instructions for making us who we are**
    - Eye color, hair color, height, etc.
- Made up of DNA
- **Provides instructions or the "code" for our bodies to make proteins**



Adapted from *Understanding Gene Testing*, National Institute of Health, 1996.

What is DNA?

- Deoxyribonucleic Acid
- Stored in every cell in a person's entire body
- DNA can make copies of itself:
  - For creation of new cells
  - For passing information from one generation of people to the next



What is a mutation?

- A change or alteration in the transcript of DNA
- Can be benign or pathogenic
  - Benign: A difference in the DNA that makes one person unique from another
  - Pathogenic: A difference in the DNA that can cause disease

Passing on Disease vs. Susceptibility

With some conditions:

- Passing on a mutated gene results in disease
- Examples include:
  - Huntington's Disease
  - Cystic Fibrosis

Other conditions:

- **Passing on a mutated gene MAY result in disease (susceptibility)**
- Examples include:
  - Hereditary Breast and Ovarian Cancer Syndrome
  - **Celiac Disease**

Class II Human Leukocyte Antigens (HLA)

- **Part of a group of proteins that help the immune system recognize self from non-self**
  - Found on white blood cells (WBCs)
  - Identifies viruses and bacteria anc initiates an attack
  - **Non-self in people with celiac disease = gluten proteins**

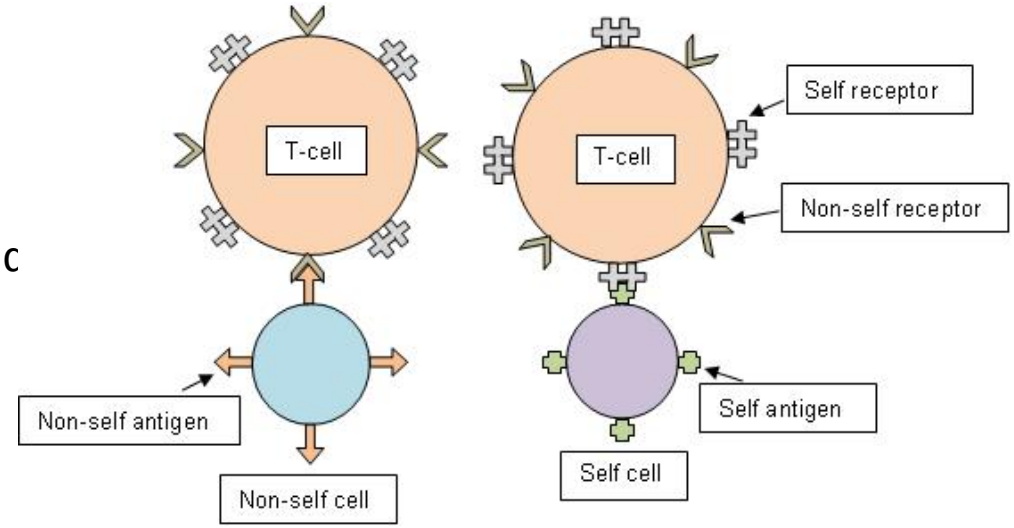


Image adapted from Kinnear & Martin, 2006

Class II Human Leukocyte Antigens (HLA)

- Includes more than 200 genes within chromosome 6
- Other conditions related to HLA genes:
  - Hashimoto thyroiditis, Type 1 diabetes, Multiple sclerosis, etc.
  - All of these diseases are located on chromosome 6

National Institutes of Health (NIH) Genetics Home Reference http://ghr.nlm.nih.gov/geneFamily/hla

Human Leukocyte Antigens (HLAs)

- Provides instructions for making proteins
  - The proteins exist exclusively on certain immune cells
- Many variations within the genes
  - Allow a person's immune system to respond to many types of foreign invaders

Genes Associated with Celiac Disease

•Complex genetic disorder!

• HLA-DQ2 and DQ8 account for 35-40% of the total celiac disease genes

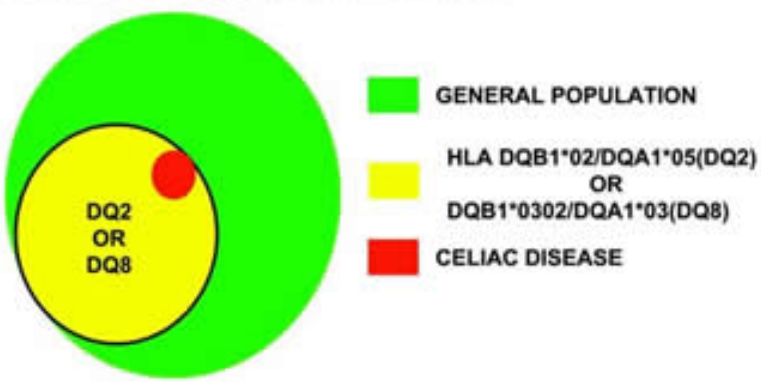
• Scientists have also identified other non-HLA genes that significantly increase a person's risk for celiac disease , but are not as well understood

• Getting the genes from the same parent may put a person at higher risk than receiving the genes from different parents

Pietzak M (2010) Genetic Testing in Celiac Disease. In M.D. & D.L. (Eds), Real Life with Celiac Disease: Troubleshooting and Thriving Gluten-Free (41-48). AGA Press.

Facts about HLA-DQ2 and HLA-DQ8

- Up to 40% of the general population carry these genes
  - Only 2 – 3% of these people will go on to develop celiac disease
- Celiac disease occurs in 1% of the general population overall
- Take home message: Your risk of developing celiac disease is related to how many DQ2 and/or DQ8 genes you have



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Snyder, Cara L., Danielle O. Young, Peter H. Green, and Annette K. Taylor. "Celiac Disease." *GeneReviews*. N.p., 3 July 2008. Web. 1 Mar. 2014. <http://www.ncbi.nlm.nih.gov/books/NBK1727/>.

Facts about HLA-DQ2 and DQ8

- Global distribution of these genes
- Examples of common regions:
  - DQ2: Western Europe, Central Asia and Northern/Western Africa
  - DQ8: Central and Southern America
- HLA-DQ2 is found in 78 – 95% of patients with celiac disease
  - For the remainder of celiac disease patients, they carry either HLA-DQ8 or a combination of HLA-DQ2/DQ8

Pietzak M (2010) Genetic Testing in Celiac Disease. In M.D. & D.L. (Eds),
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HLA-DQ2

- Having two copies of HLA-DQ2 = extremely high risk of developing celiac disease:
  - Research has found that 28-31% of people at risk for celiac disease who have two copies of HLA-DQ2 had a positive celiac disease blood test (EMA positive)
- Carrying one copy of HLA-DQ2:
  - Ranges from very high to low risk
  - Risk depends on if DQ2 is accompanied by other high-risk or low-risk genes

Pietzak M (2010) Genetic Testing in Celiac Disease. In M.D. & D.L. (Eds),
Real Life with Celiac Disease: Troubleshooting and Thriving Gluten-Free (41-48). AGA Press.

HLA-DQ8

- Two copies of this marker leads to a high risk of developing celiac disease
  - 8-10% of those at-risk had a positive celiac disease (EMA) blood test

- One copy gives a moderate celiac disease risk (2% of those at-risk had a positive blood test)

Pietzak M (2010) Genetic Testing in Celiac Disease. In M.D. & D.L. (Eds),
Real Life with Celiac Disease: Troubleshooting and Thriving Gluten-Free (41-48). AGA Press.

Part 2:
Understanding Celiac Disease Genetics and the Increased Risk Among Families

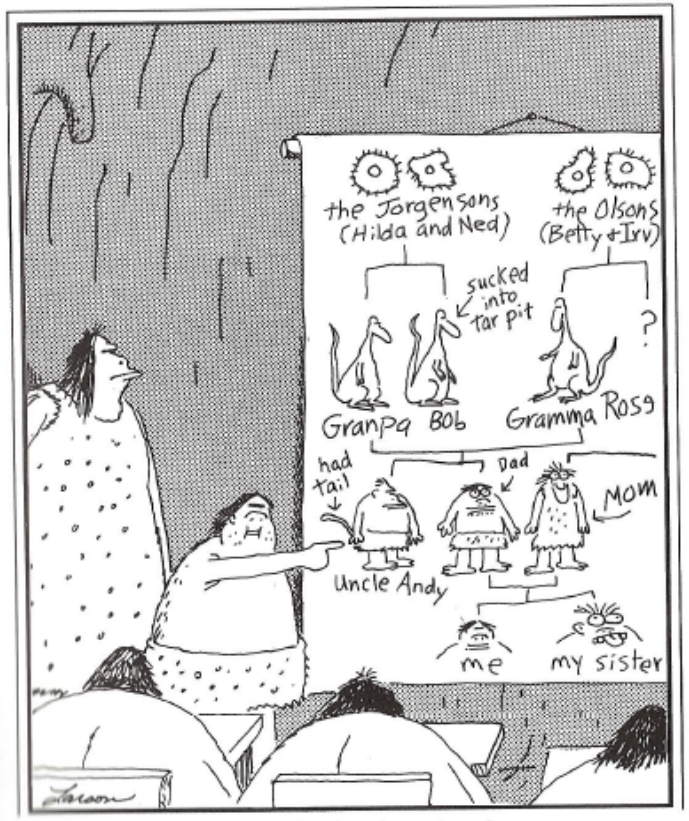
Defining Celiac Disease

- **Chronic inflammatory** disorder of the small intestine triggered by gluten proteins from wheat, rye, and barley leading to malabsorption and related conditions
- **Genetically vulnerable**
- **Variable** presentation
  - Intestinal symptoms
  - Extra-intestinal symptoms
  - Asymptomatic (no outward symptoms)
- **Treatment** is consistent and permanent withdrawal of gluten

American Gastroenterological Association (AGA) Statement

How common is celiac disease?

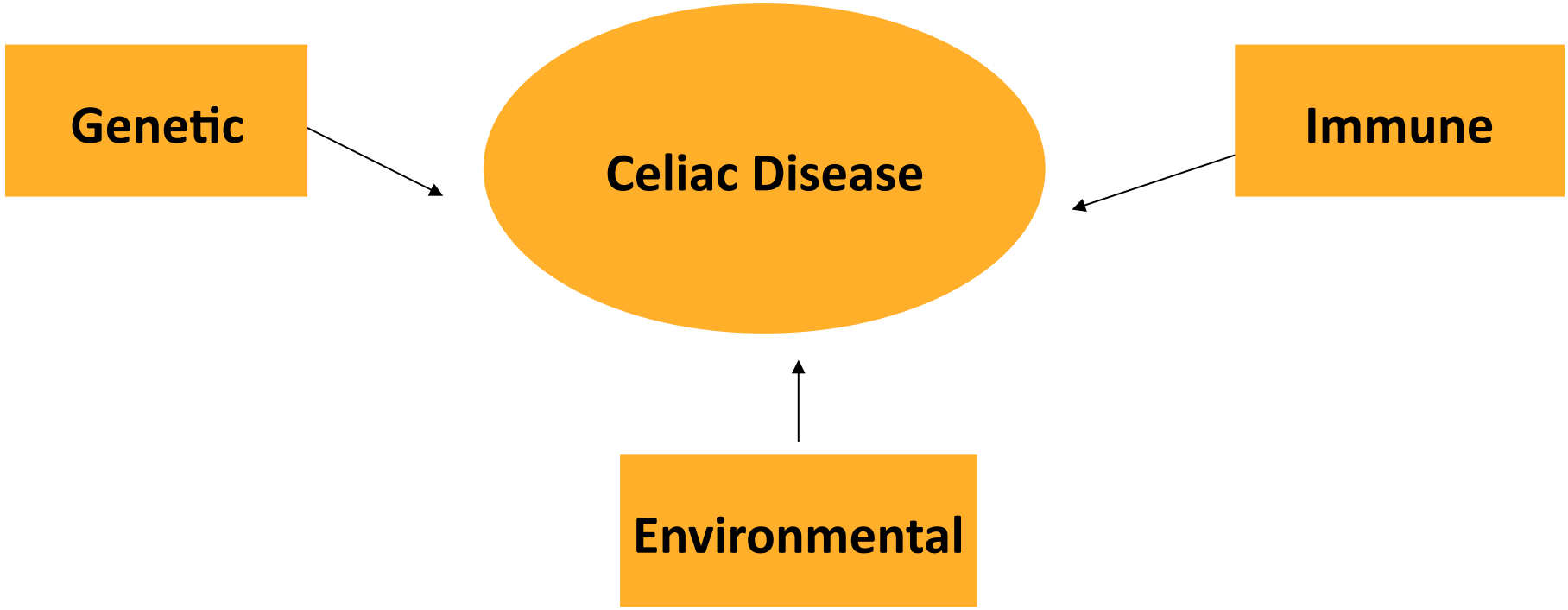
- U.S./Western:
  - 0.6-1%
- Identical twins:
  - 70-80%
- 1st degree and fraternal twins:
  - 10-15%
- 2nd degree relatives:
  - 2-6%



Dirk brings his family tree to class.

Fasano A, Arch Intern Med 2006; Roston, Gastro 2006; Kupfer, Gastrointest Endosc Clin N Am 2012; Fasano, NEJM 2012

Many Different Factors at Play



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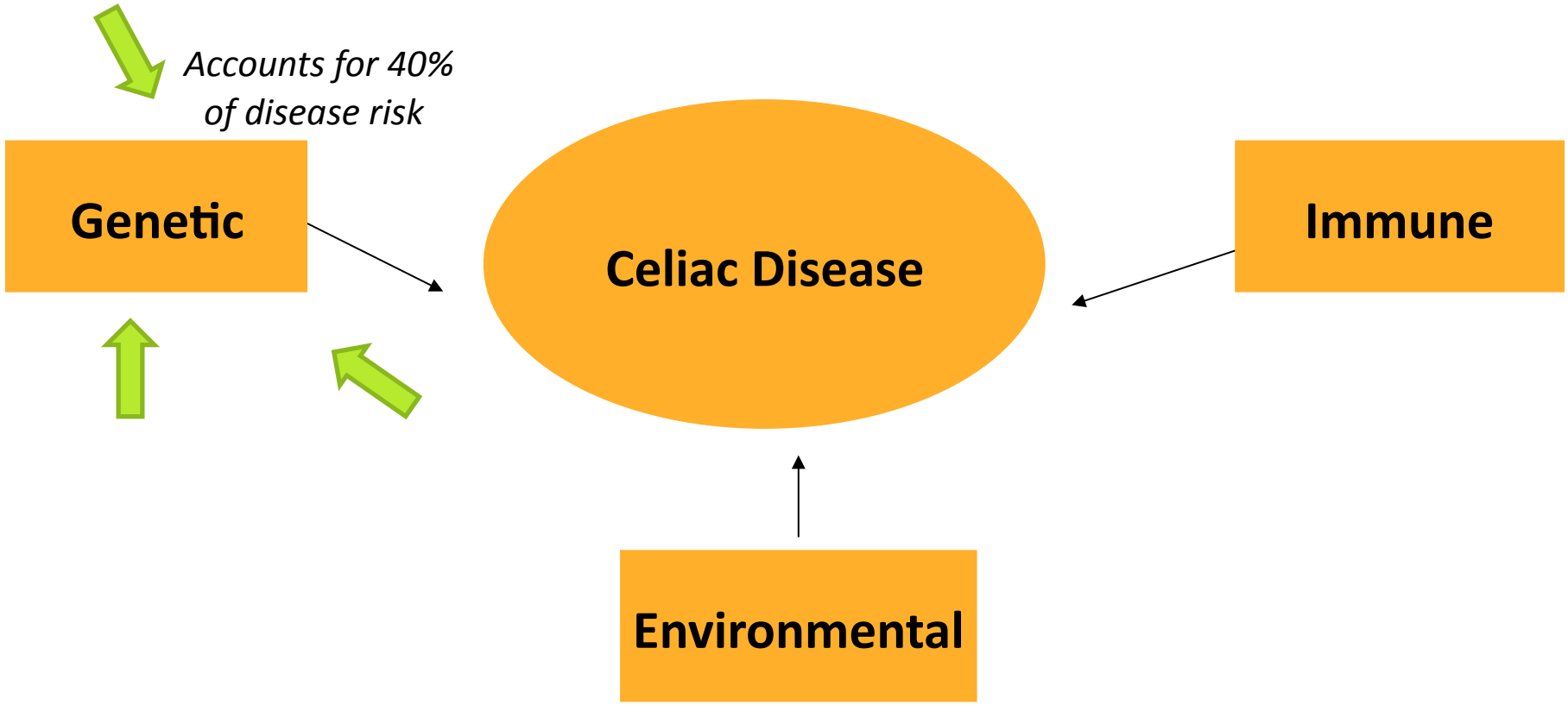
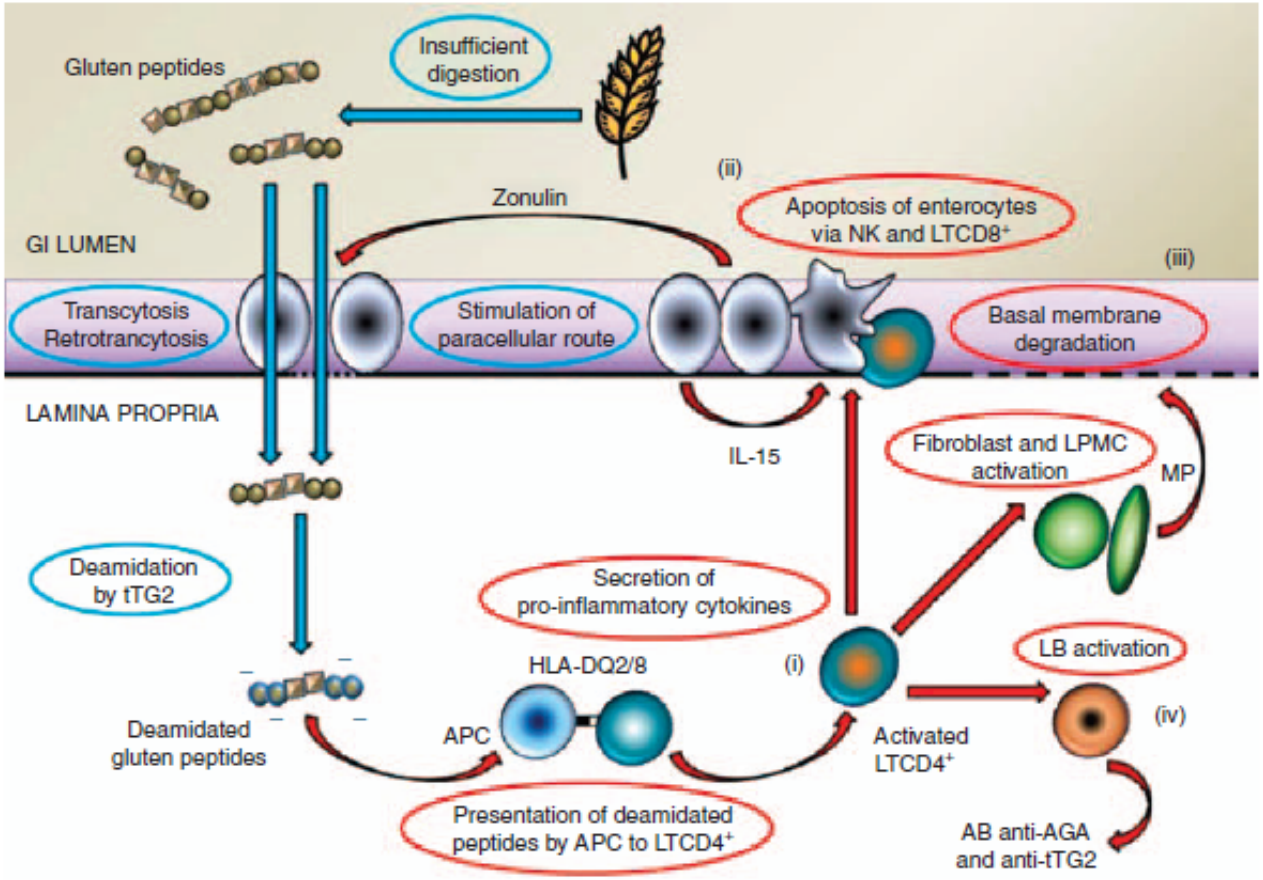


Pathophysiology: A Series of Unfortunate Events



Pinnier, Am J Gastro 2010

HLA and Celiac Disease

- HLA-DQ2 haplotype (DQA1*0501/DQB1*0201)
  - 90% of celiac disease patients
  - 33% general population
- HLA-DQ8 haplotype (DQA1*0301/DQB1*0302)
  - 5% of celiac disease patients
- At least one of the two genes encoding DQ2 (DQB1*0201 or DQA1*0501)
  - 5% of celiac disease patients

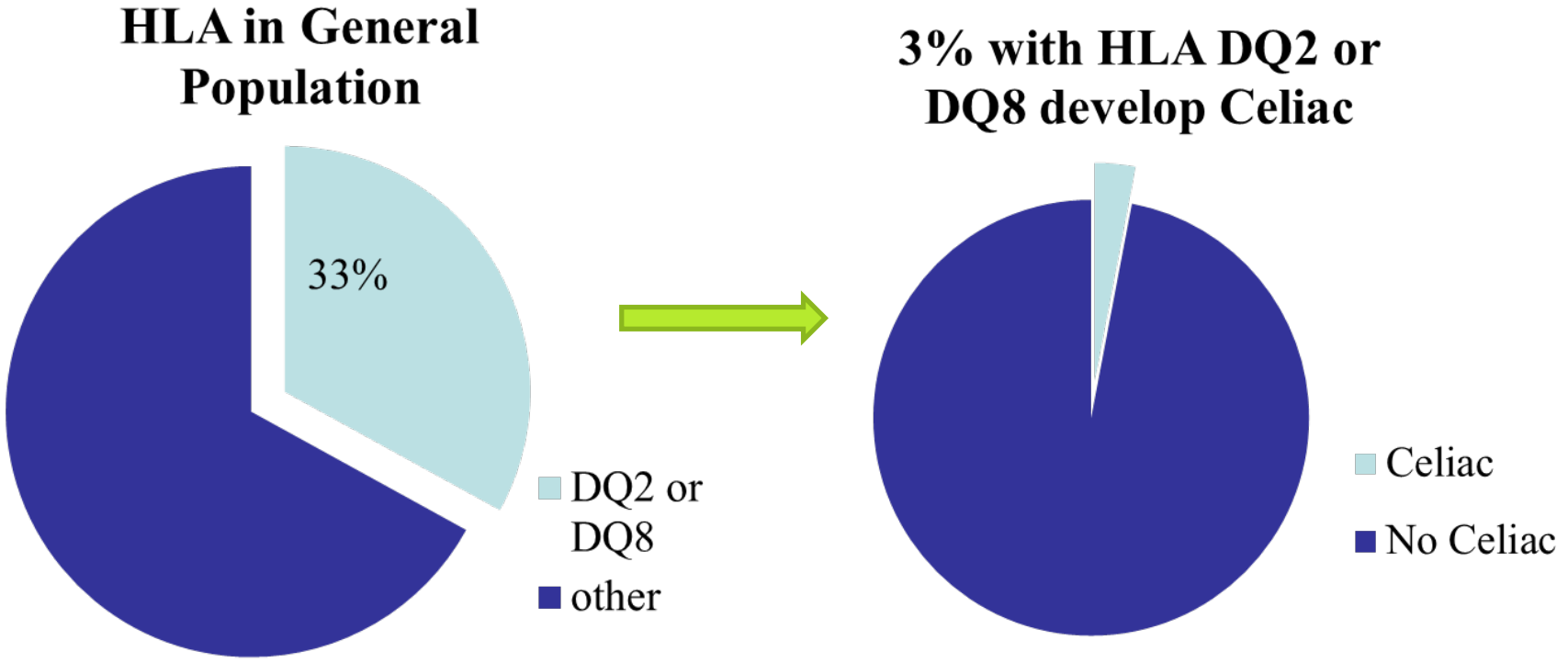
Fasano, NEJM 2012

HLA DQ2 and DQ8 and Celiac Disease

- These genes are necessary for celiac disease:
  - Less than 1% of celiac disease patients are negative carriers
- Does **NOT** establish diagnosis of celiac disease:
  - 1/3 of Western Caucasians are positive for DQ2/DQ8
  - *Most useful when test is negative because it rules out celiac disease*
- Worldwide, HLA prevalence in population mirrors prevalence of celiac disease
- Multiple non-HLA genes also contribute to the disease risk, but their roles are poorly understood

Green, NEJM 2007; Greco, Gut 2002

HLA: Necessary, But Not Sufficient



HLA Predicts Risk of Celiac Disease

Disease risk

	Patients%	Controls%	Risk	F	M
DQ2 and DQ8	2.5	0.2	1:7	1:7	1:8
DQ2, *B1*02/*02*	23.1	2.4	1:10	1:8	1:13
DQ8, *B1*02* pos.	3.0	0.7	1:24	1:16	1:52
β2, *B1*02/*02*	1.4	0.4	1:26	1:27	1:26
DQ2, *B1*02/X*	55.1	19.2	1:35	1:26	1:54
DQ8, *B1*02* neg.	7.3	6.5	1:89	1:62	1:157
β2, *B1*02/X*	4.6	9.7	1:210	1:211	1:208
α5	2.1	37.9	1:1842	1:8327	1:1027
Other	0.9	23.0	1:2518	1:2530	1:2497

Megiorni, Hum Immunol 2008

How does the environment contribute?

- Breast feeding
- Timing of gluten introduction, as well as coordination with breast feeding
- Childhood infections such as rotavirus and adenovirus
- Microbiome, the community of trillions of bacteria that live in our bodies:
  - Antibiotics
  - Elective C-section
- Degree of gluten exposure
- Hygiene hypothesis
- Others:
  - Summer season of birth
  - Use of acid suppression medications
- ????

Fasano, NEJM 2012; Stene, Am J Gastroenterol 2006; Kagnoff, J Exp Med 1984

Essential Environmental Factor: Gluten

- Gluten:
  - Storage protein in wheat, rye and barley
  - Up to 100 gluten proteins in a single variety of wheat
  - Average U.S. consumption is 15-20 grams/day (2.5 g/slice of bread)
    - 10-50 mg is the amount needed to stimulate response in celiac disease, which is estimated to be less than a crumb of gluten-containing food
  - Proline rich fraction (prolamines) responsible for toxicity
    - Resistant to digestion by stomach, pancreas, small intestine

Rostom, Gastroenterol 2006

Infant Diet and Risk for Celiac

- Breast feeding:
  - Protective effect on developing celiac disease
  - Continue during introduction of gluten
  - Risk for celiac disease may increase if continue beyond 12 months
- Introduction of gluten:
  - Gradually, in small amounts
  - After month 4, and before month 7
- Endorsed by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN)
- Exciting new research from Dr. Carlo Catassi's group is expected to be published soon

Akobeng, Arch Dis Child 2006; Rostom, Gastroenterol 2006; Stordal, Pediatrics 2013; Husby, JPGN 2012

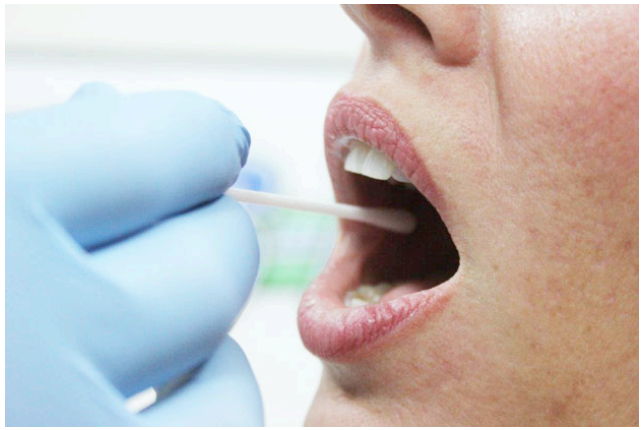
Microbiome

- Composition of gut bacteria may influence immunity
- Hypothesis: Intestinal microbial ecosystem dictates switch from tolerance to immune response in genetically susceptible individuals
- Preliminary studies show microbiome differs between:
  - Infants at risk for celiac disease vs. those without risk
- Research is consistent with this theory:
  - History of antibiotic use associated with increased risk for celiac disease

Sellitto, PLoS ONE 2012; Marild, BMC Gastroenterol 2012

HLA Testing

- How is it done?
  - Blood test
  - Mouth swab



When to Consider HLA Testing

Important! Unlike blood test and biopsy, genetic testing does not need to be done on a gluten-free diet

- **No symptoms but at-risk for celiac disease:**
  - 1st degree relatives (particularly children)
  - Autoimmune and other high risk conditions
- **Children with clinical and serologic evidence of celiac disease if a biopsy is *not* performed**
- **Clinical suspicion but supporting evidence is ambiguous**
- Celiac disease is possible but blood testing is unreliable:
  - **People who are already following a gluten-free diet**

Autoimmune Disease and Celiac Disease

- Autoimmune disease is more common with celiac disease:
  - 14% celiac disease vs. 2.8% controls
  - Risk increases with:
    - Longer duration of gluten exposure
    - Older age at time of celiac disease diagnosis
- Type 1 diabetes:
  - Prevalence of celiac disease is 2-5%
- Autoimmune thyroid disease (Hashimoto's)
  - Prevalence of celiac disease is 3%

Ventura, Gastroenterology 1999

Additional Autoimmune Diseases Associated with Celiac Disease

- Having an autoimmune disorder makes you more likely to develop other autoimmune diseases
- Other examples include:
  - Addison disease
  - Autoimmune liver disease
  - Behcets
  - Dermatomyositis
  - Myasthenia gravis
  - Psoriasis
  - Sjogrens
  - Vitiligo

Additional Individuals Have Increased Risk for Developing Celiac Disease

- Down syndrome: 5.5%
- Turner syndrome: 6.5%
- Williams syndrome: 9.5%
- IgA Nephropathy: 4%
- IgA Deficiency : 3%
  - Note: Important to order total IgA because people with IgA deficiency may have a false negative blood test for celiac disease
  - Talk to your doctor about ordering the IgG-DGP, IgG-tTG blood tests instead

Husby, JPGN 2012

When ***Not*** to Perform HLA testing

- As part of routine evaluation for signs or symptoms of celiac disease – having the genes is not sufficient for a diagnosis
- Celiac disease is already well established
- Test results will not impact patient management

Tips for HLA Testing

- Discuss with a doctor skilled in celiac disease whether it is appropriate
- *Before* HLA testing, understand:
  - The implications of a positive or negative result
  - How it will be helpful?
  - Will it affect care going forward?
- Check with your insurer to make sure it will be covered – it can be costly
- Know that different laboratories may interpret/report their information differently (e.g. it's not always apples to apples)

Take Home Points

- With rare exception, all patients with celiac disease have HLA-DQ2 and/or HLA-DQ8:
  - HLA can predict the risk of developing celiac disease
- Most people with a positive HLA, regardless of family history, do not develop celiac disease
  - However, helping relatives understand their risk is important
- The development of celiac disease in genetically vulnerable individuals is affected by numerous factors, many environmental:
  - We still have much to learn in this area
- HLA testing should be done selectively and is most helpful to exclude celiac disease

Questions & Answers

Watch & Win!

- Three webinar participants will each receive Jefferson swag:
  - Insulated lunch bag, black frame sunglasses with blue stems, a clip hand sanitizer and pen

**Note: NFCA will select winners from participants who complete follow-up survey. If you do not respond you will forfeit the prize.*

Thomas Jefferson University Hospitals

- Jefferson Celiac Center:
  - 215-9-CELIAC
  - www.JeffersonHospital.org/celiac

Resources on Celiac Disease Genetics

- *Real Life with Celiac Disease: Troubleshooting and Thriving Gluten-Free* by Melinda Dennis, MS, RD, LDN and Daniel A. Leffler, MD, MS
- *Celiac Disease for Dummies* by Ian Blumer, MD and Sheila Crowe, MD

“Family Talk”

- **Getting tested is easy and you can lead the way:**
  1. Tell your story
  2. Emphasize that not everyone has symptoms or even the same symptoms
  3. Explain that a blood test is the first step
- NFCA has made a commitment and we’re asking you to do the same!
- **CeliacCentral.org/family**

Upcoming Free Webinars

CeliacCentral.org/Webinars

- **May 15, 2014 at 2pm Eastern - "Best Practices in Celiac Disease Diagnosis"** with Dr. Ritu Verma, Director, Center for Celiac Disease at CHOP and Dr. Dan Leffler, Director of Clinical Research for Celiac Center at BIDMC
- **July 15, 2014 at 2:30pm Eastern – "Environmental Based Theory of Increased Wheat Consumption & Excess Gluten in Food Supply"** with Julie Miller Jones, PhD, CNS, LN, Distinguished Scholar and Professor Emerita, Foods and Nutrition, St. Catherine University
- **TBD – "Understanding the FDA's Gluten-Free Labeling Part 2: A Focus on Compliance"**

We want to hear from you!

- Webinar questions, comments and feedback: webinars@celiaccentral.org
- Connect with NFCA:

- Learn more about the Jefferson Celiac Center: www.JeffersonHospital.org/celiac

