Genetic Epidemiology

March 31, 2016

HLSC 2003

Learning Objectives

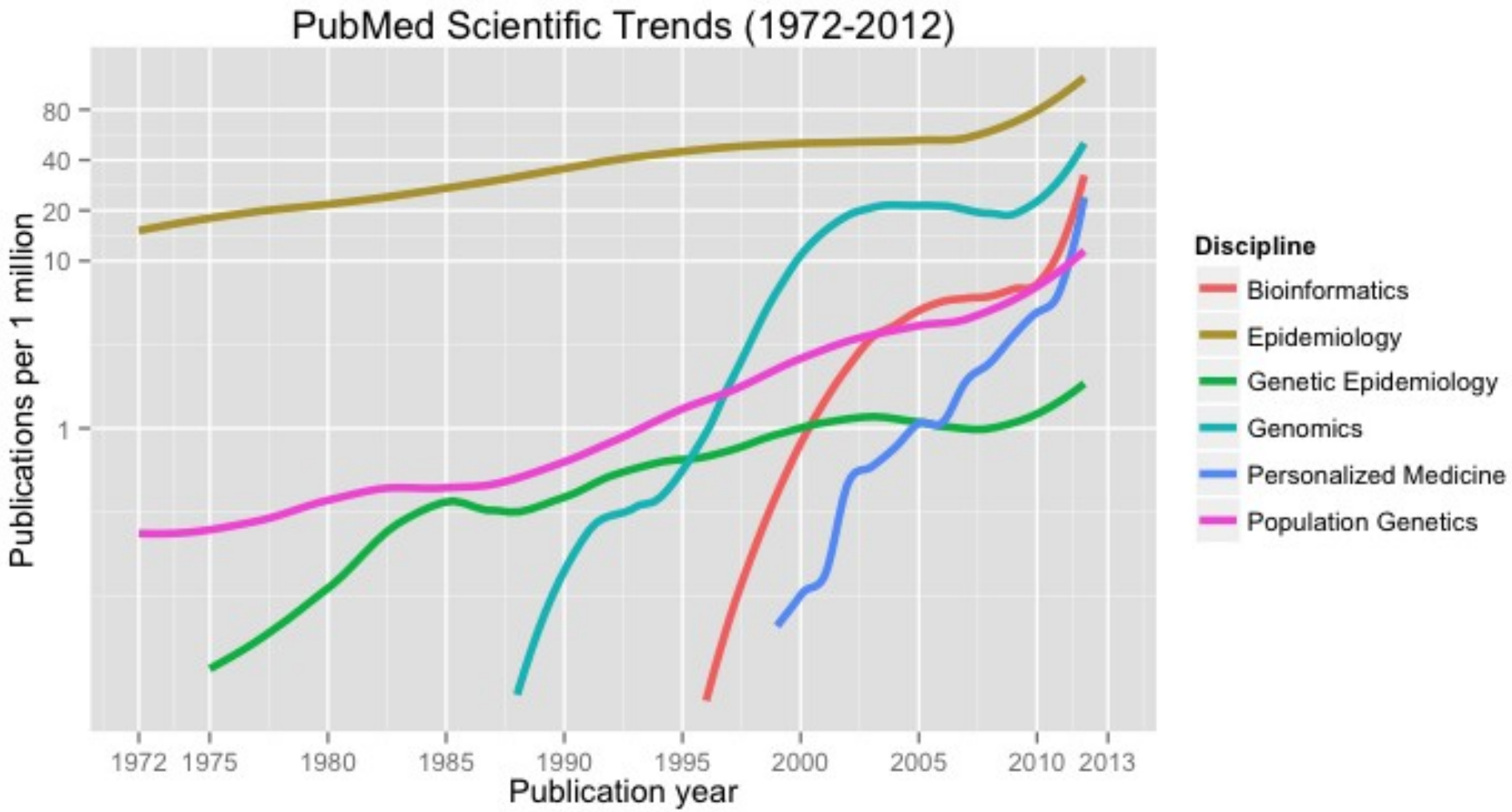
1. Understand difference between genetic epi and molecular epi.
2. Have a general understanding of **epigenetics** and its influence on research in epidemiology
3. Describe common genetic and epigenetic epidemiology **study designs** used in genetic and epigenetic epidemiology.
4. **Think critically** about the role of genetics in the health

Genetic vs. Molecular Epidemiology

- **Genetic epidemiology** - the study of the role of genetic factors in the occurrence of disease in families & populations.
  - Gene _____

- **Molecular epidemiology** – The use of biological markers to measure exposures and outcomes. Examples:
  - Hormone levels measured via salivary samples

Genetic Epi is a Relatively New Field



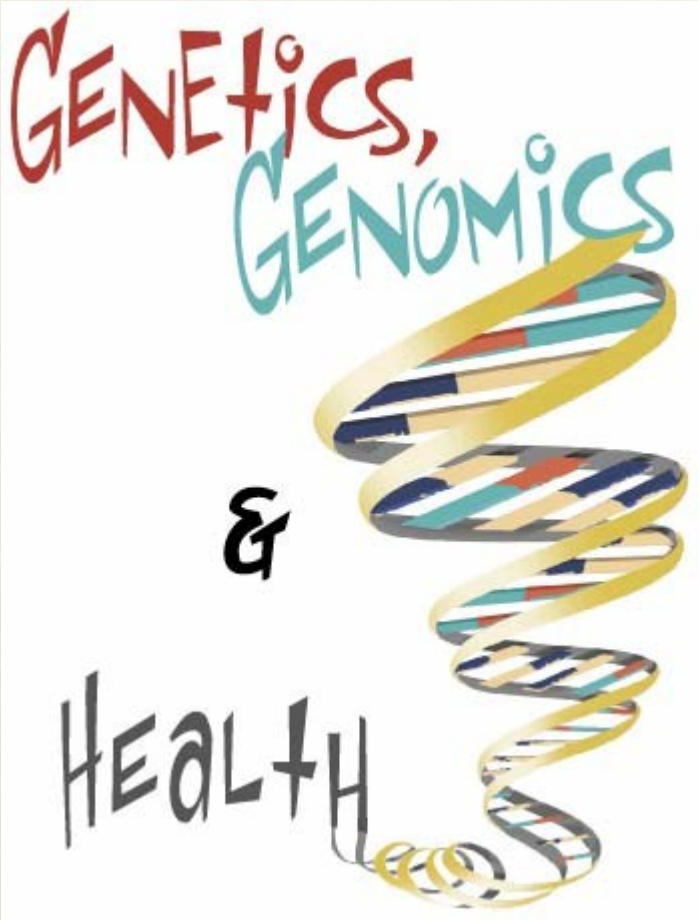
Genotype vs. Phenotype

- **Genotype** – The full hereditary information of an organism (expressed or not)

- **Phenotype** – The actual observed properties of an organism (outward appearance and bodily structure, their development, their behaviour).

The Fascination with Genetics

- **Finding the genetic roots of disease** has become an increasingly important focus in health – lots of $$$ directed at this.
- Is this a good use of funds?
- Emerging research suggests this pursuit may be misguided



Social Factors & Genetics Collide!

The Role of Epigenetics

What is Epigenetics?

- **Epigenetics** is the role of the physical & social environment in shaping gene expression.
- Most people do not realize there is a control system of **'switches' that turn genes on and off based on <u>environmental cues</u>**
  - Examples – Stress level, nutrition, social world, environmental toxins.

Why is Epigenetics Important in Epidemiology?

- Epigenetics blends the fields of **genetic** epidemiology, **social** epidemiology & **environmental** epidemiology.
- Tells us that features of the social and physical environment modify gene expression to

Why is Epigenetics Important?

- Severe adverse experiences create '**molecular scars**' in your body
- Features of the social and physical environment modify gene expression to impact health.
- Unnatural Causes - Video clip

Genetic & Epigenetic Epidemiology

Study Designs

Genetic Epi
Guiding Research Questions

- **Does a disease cluster in families?** - YES
- If so, is that clustering due to shared social & environmental risk factors alone or **is there a genetic component?**
  - EFFECT REMAINS AFTER CONTROL FOR CONFOUNDERS? Interesting!
- What gene(s) are responsible for the disease?

Study Designs used in Genetic Epi

Study Design	Application
1. Cross-Sectional Study	Prevalence of genetic & epigenetic markers in a population, associations.

Useful to:

- Estimate allele and genotype frequencies in a population.
- Examine associations between genotypes, exposures & phenotypes
- Develop hypotheses to be tested using more sophisticated methods

Key Weakness

- Does not measure incidence of disease, no

Study Designs used in Genetic Epi

Study Design	Application
1. Cross Sectional Study	Prevalence of genetic & epigenetic markers in a population, examine associations
2. Case-Control Study	Genetic & epigenetic markers in those with and w/o disease.

2. Case-Control Studies

Good study design in genetic epidemiology because:

- **Exposure of interest** (genetic heritage) - stable over time
- We can do a comprehensive search of several genetic markers within a sample of **people with a disease** (cases) and without the disease (controls).
- We can look at rare diseases (birth defects, rare cancers).

Key Weakness

- There are changes in social & environmental exposures over time. Difficult to separate

Study Designs used in Genetic Epi

Study Design	Application
1. Cross Sectional Study	Prevalence of genetic & epigenetic markers in a population
2. Case-Control Study	Genetic & epigenetic markers in those with and w/o disease.
3. Cohort Study	Gather genetic & epigenetic data before disease present. For epigenetics this provides temporal sequence.

3. Cohort Studies

Large cohort studies beginning to collect genetic data (e.g., the Framingham study)

Good study design in genetic epidemiology because:

- It permits repeated phenotypic and outcome measures on individuals over time.
- Can examine rare genetic exposures

Key Weakness

- Difficult to examine rare diseases.
- Expensive & time consuming

Canadian example - CARTaGENE Study in Quebec: link

Study Designs used in Genetic Epid

Study Design	Application
1. Cross Sectional Study	Prevalence of genetic & epigenetic markers in a population, associations
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3. Cohort Study	Gather genetic & epigenetic data before disease present. For epigenetics this provides temporal sequence.
4. Experimental Study (sort of….)	Effects of epigenetic therapies on disease. Genetic epi – twin studies

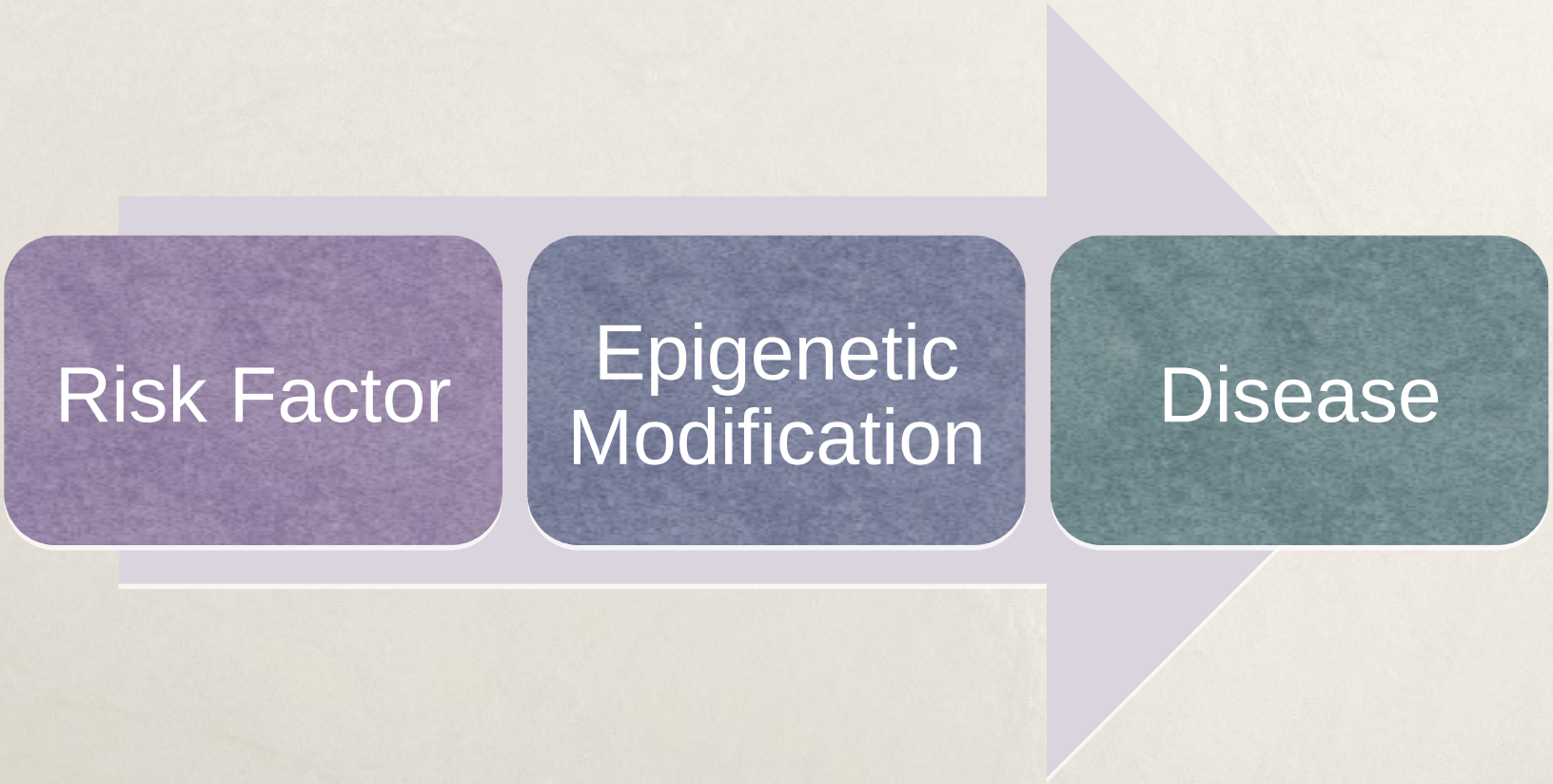
4: Experimental Studies (more like natural experiments)

Family-Based Studies – used to identify & quantify the heritability of human diseases

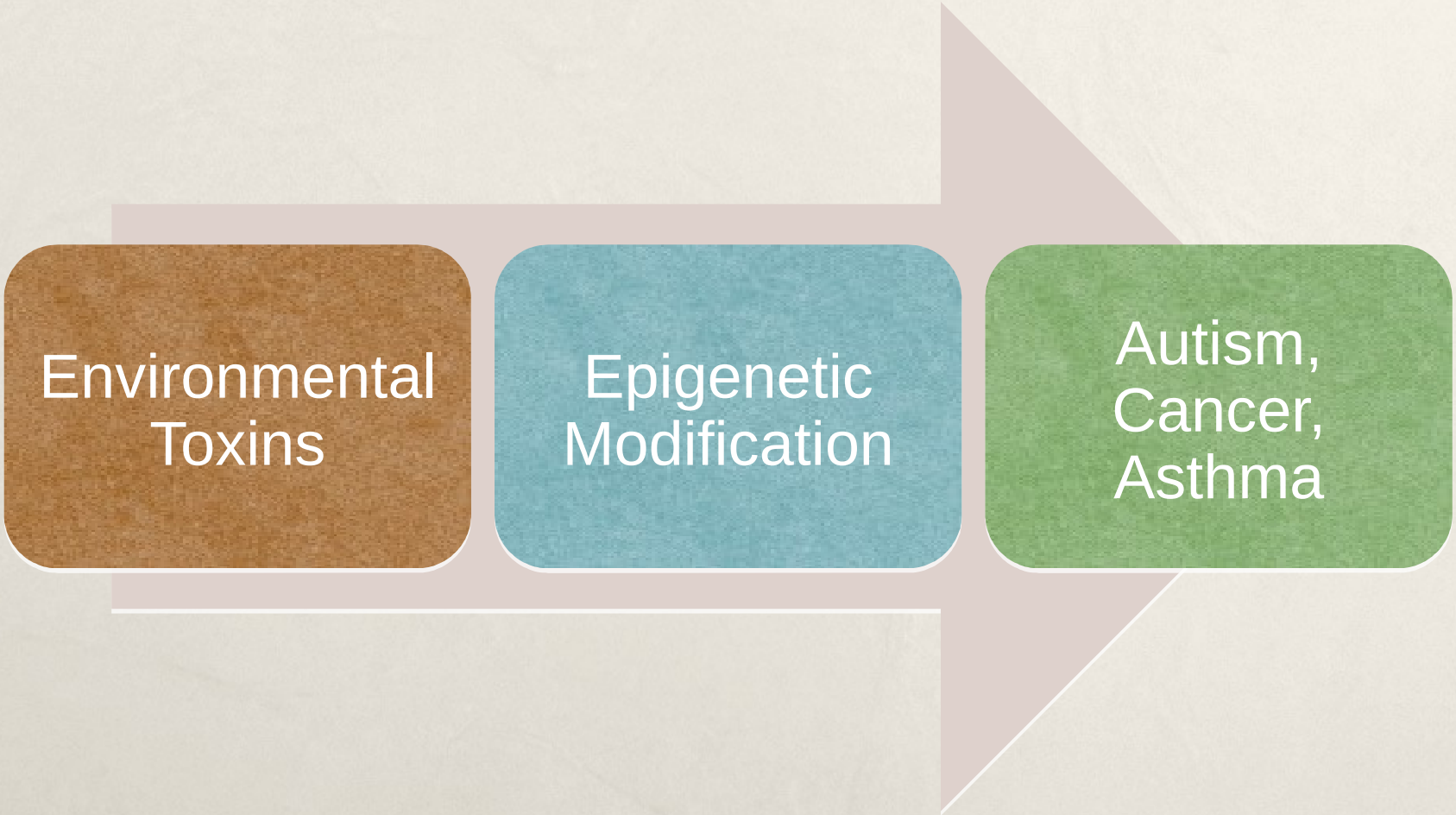
- **Twin Studies**
  - Monozygous (MZ) twins (identical)
  - Dizygous (DZ) twins (not identical)
  - Especially sought after – MZ twins reared apart
    - Example - Twins adopted and raised by unrelated foster parents

Goal: To measure the degree of genetic contribution to disease separate from environmental influence

Epigenetics **as a Mechanism** that explains association between X and Y



Epigenetics **as an Explanatory Mechanism** (on the causal pathway)



Carcinogenic Impacts of Alcohol

Thinking Critically about Genetics & Health

Thinking Critically about Genetics & Health

- There are genetic similarities between Aboriginal and Asian populations.
- Many Asians have genes that result in different alcohol metabolism (specifically variant alleles for the alcohol dehydrogenase gene cluster) (Edenberg, 2007)
- This provides **protection against alcoholism** in some Asian groups.
- This does not explain higher levels of alcoholism among Aboriginal peoples in Canada if genetic similarities are present.
- A review of the scientific evidence indicates that **alcohol use disorders and their transmission in families cannot be attributed to unique**

Alcohol & Genetics

- This explanation also **does not explain** elevated levels of alcohol use disorders across colonized Indigenous peoples **with varied genetic**

Indigenous Peoples of Scandinavia: **The Sami**

- The Sami are the Indigenous peoples of Northern Scandinavia
- Occupied area since 10,000 BC, highly adapted to arctic environment
- Have their own language and culture centering around reindeer herding, trapping and coastal fishing.

Sami Family – Norway circa 1900

Recognized as an Indigenous peoples under the international convention.

Indigenous Peoples of Scandinavia: **The Sami**

The Sami tradition of learning from the Elders is an important part of reindeer herding, and knowledge is passed down from generation to generation and not learned in books.

The Sami

- Scandinavian countries have spent considerable money in efforts to wipe out **Sami culture**.
  - Sami language forbidden, cultural & spiritual practices made illegal.
  - Incentives for settlers to move into Sami lands.
  - Sami children sent to residential schools.
  - Adults forced to work in slave mines.
  - Forced sterilization of Sami women in Sweden.

A Pite Sami Man

Sami Youth

- **Today – the Sami are slowly gaining their culture back.**

Indigenous Culture & Health

- What diverse **Indigenous peoples** share in common are **comparable social problems rooted in the experience of colonization**.
- **Alcoholism & other addictions** are higher in disenfranchised populations as individuals strive to cope with these experiences.

ORIGINAL ARTICLE

The relationship between internalizing and externalizing symptoms and cultural resilience factors in Indigenous Sami youth from Arctic Norway

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ABSTRACT

Objectives. To examine whether enculturation factors, like cultural activities, ethnic pride and native language competence, are related to decreased internalizing and externalizing symptoms in Indigenous Sami youth from Arctic Norway. The impact of self-efficacy on the relationship between enculturation factors and mental health problems was also examined.

Study design. Population-based, cross-sectional questionnaire study.

Methods. The Norwegian Arctic Adolescent Health Study was conducted among 10th graders in junior high schools in north Norway during 2003–2005. The study sample consisted of 450 Indigenous Sami youth, aged 15–16 years. Internalizing symptoms were measured with the Hopkins Symptom Check List-10 (HSCL-10), while externalizing symptoms were measured by two subscales of the Strengths and Difficulties Questionnaire (SDQ).

Results. For boys, self-efficacy and participation in cultural activities were associated with decreased internalizing symptoms. Additionally, self-efficacy interacted with Sami language competence and cultural activities: when self-efficacy increased, these enculturation factors were related to symptom reduction. For girls, self-efficacy had an independent effect on internalizing symptoms and also strengthened the relationship between participation in cultural activities and reduced externalizing symptoms. Sami language competence was related to the reduction of both internalizing and externalizing symptoms in girls.

Conclusions. In the present study, several enculturation factors as well as self-efficacy were identified as potential protective factors against mental health problems. In order to develop theoretical models that

Who are Indigenous Peoples?

Article 1b of the International Labour Organization (C169, 1989)

- Peoples who are regarded as indigenous on account of their descent from the populations which inhabited a geographical region at the time of conquest or colonisation or the first establishment of state boundaries and who retain some or all of their own social, economic, cultural and political institutions.
- Useful website to learn more

The Thrifty Gene?

Good review article on this topic

Racialized Genetics and the Study of Complex Diseases

the thrifty genotype revisited

Yin C. Paradies,* Michael J. Montoya,† and Stephanie M. Fullerton‡

ABSTRACT Current debate on the use of population genetic data for complex disease research is driven by the laudable goals of disease prevention and harm reduction for all, especially dispossessed, formerly enslaved, or colonized populations. This article examines one of the oldest gene-based theories of complex disease causation: the thrifty genotype hypothesis (THG). This hypothesis is emblematic of the way in which genetic research into complex disease attracts a high investment of scientific resources while contributing little to our capacity to understand these diseases and perpetuating problematic conceptions of human variation. Although there are compelling

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The Thrifty-Gene *Hypothesis*

- In 1962 James Neel speculated that because **humans lived as hunters and gathers for 99% of human history**, we lived in cycles of feast or famine.
- Thus, as the theory goes, genetic traits evolved to allow them to store excess calories during “feast” times, to help them survive during times of famine.
- Neel did not racialize this theory. However other researchers did so - saying the gene, if it exists, should be more common among Aboriginals. Why?

The Thrifty-Gene *Hypothesis*

- Groups who were hunter & gatherer societies until recently on remote islands now have very high diabetes.
  - They have always lived on islands that had generous food supplies all year - but they didn’t have problems with diabetes before colonization.

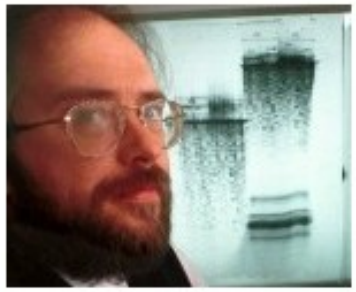
- Another problem – We know tha
  societies experience feast a
  cycles (not just hunter and gat
  - Greek & Roman empire
  - Europe over the millennia
  - The great depression –

a recent example

Link to article

FEBRUARY 28, 2011

By Carolyn Abraham
From Saturday's Globe and Mail



A post-mortem has already begun for the 'thrifty-gene' hypothesis, amid suggestions that science flirted with racism

Robert Hegele had doubts. Even in 1999, as the research attracted wide media attention and the British Medical Journal declared, "Thrifty gene identified in Manitoba Indians," Dr. Hegele could not be certain – which is telling, since he was the geneticist who had made the discovery.

But back then he still thought further work would bear it out. Part of a small research group, Dr. Hegele had been studying the astonishing prevalence of type 2 diabetes among the Ojibwa-Cree people of Sandy Lake, an isolated reserve in Northern Ontario not far from the Manitoba boundary.

At that time, gene hunting in remote populations was as fashionable as starting a dot-com, and the Sandy Lake project stood out as a model – a rare instance in which a community negotiated compensation for the DNA of its members. In exchange for fresh food, expanded medical services, school programs and a share of any profits, the band council allowed scientists to search for an explanation as to why the diabetes rate was five times the national average – why, in fact, it was the third-highest rate in the world.

The locals knew it as the *Sho-goh-wah-pee-nay*, the "sugar disease." It afflicted nearly half the adults, could be detected in children as young as 10 and cost many residents their kidneys, sight and limbs. Yet Sandy Lake had recorded no cases of diabetes until the 1960s.

The numbers seemed to have risen alongside its conversion to the unholy trinity of the couch, fast food and the television. When Dr. Hegele, a senior scientist at the University of Western Ontario, first heard the Sandy Lake story, he couldn't help but wonder if this was the work of the elusive thrifty gene.

Since James Van Gundia Neel proposed it almost 50 years ago, the thrifty-gene hypothesis has reigned as the dominant explanation for soaring rates of obesity and diabetes among many aboriginal groups. Native communities where diabetes didn't exist in the first half of the 20th century had, by the end of it, the world's highest prevalence, with Arizona's Pima Indians in first place, followed by the Nauru islanders of Micronesia and the Oji-Cree at Sandy Lake.

Aboriginal Peoples & Diabetes: Why the Genetic Preoccupation?

After 4 decades in search of thrifty genes - <u>no one can find them</u>. So why is this theory still considered?

- Poudrier - The theory **allows society to curl up with the notion that biology shoulders most of the blame** for the ill health of Aboriginal people.
- It promotes **the myth** that Aboriginal people all have the same genes that make their diabetes "**a special problem**" that has nothing to do with colonization.
- This **detracts** from a focus on **the social**

Hungry aboriginal people used in bureaucrats' experiments

Food historian published details of nutritional experiments that began in the 1940s

The Canadian Press Posted: Jul 16, 2013 3:20 PM CT | Last Updated: Jul 17, 2013 8:02 AM CT

A nurse takes a blood sample from a boy at the Indian School in Port Alberni, B.C., in 1948, during a period when nutritional experiments were being conducted on students there and in five other residential schools. (Library and Archives Canada/Canadian Press)

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The Canadian government says it's appalled to hear hungry aboriginal

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Question

How might epigenetics explain health inequalities within Aboriginal populations in Canada?

Grandma's Experiences Leave a Mark on Your Genes

Your ancestors' lousy childhoods or excellent adventures might change your personality, bequeathing anxiety or resilience by altering the epigenetic expressions of genes in the brain.

By Dan Hurley | Tuesday, June 11, 2013

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Alison Mackey/DISCOVER

When Considering Genetic Factors

Be Critical in your Thinking

- Aboriginal peoples experience health inequalities in Canada - people will often jump to a genetic deficiency to explain this.
- Remember: What appears to be differential genetic vulnerability for a health problem in a population, **may actually be differential exposure to social risk factors** that shape behaviour and shape illness.

Ghost in Your Genes

Highly recommended video on epigenetics

http://www.youtube.com/watch?v=fMxgkSgZojs

Additional References from Today's Lecture

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