Genetics for Bioregulatory Medicine

October 21, 2017

BRMI
Bioregulatory Medicine Institute

Mapping Human Genetics: An Overview

- What is a gene?
- From his extraordinary experiments, Mendel conceptualized a discreet determinant, transmitted intact across generations, that specified a visible property: seed texture or color in pea plants
- He coined the word ‘gene’ to represent an abstract idea of inheritance

History

- Beadle solved the mechanism of action of a gene, which is to specify the structure of a protein
- Watson, Crick and Franklin discovered that the structure of DNA was a double helix
- Brenner and Jacob identified an RNA copy required for translating the genetic message

Genetics: The Early Days

- The chemical structure for genes is DNA: genetic information is carried in DNA
- DNA is surprisingly simple: composed of ONLY 4 nucleic acids “letters” which create only two pairs
- Cytosine, Adenine, Guanine and Thymine

Genetics: The Early Days

- Initially, DNA was characterized as an “unsophisticated” structure
- DNA was the long monotonous repetition of only 4 bases in a defined order
- ACGT-AGCT-AGCT and so forth, ad nauseum
- DNA was dubbed the “stupid” molecule!

Recent History of Genetics

- Monod and Jacob demonstrated that genes can be turned on and off by increasing and decreasing the RNA message
- There are regulatory switches appended to each gene which turn the gene “on” and “off”
- In the latter part of the 20th Century, the race to map the entire genome of a species began

The Book Of Man: The Map of the Genome

- It has 3,088,286,401 letters of DNA
- There are only 4 letters in the genetic alphabet, each made of nucleic acids
- If published in a book with standard font, the pages would contain only 4 letters …AGCTTGCAGGGG... and it would be ***1.5 million pages*** long

The Book of Man

- All of the human genome is distributed into 23 chromosomes; all other apes have 24 pairs
- At some point in evolution, 2 chromosomes in some ancestral ape fused into 1
- The human genome distinguished itself several million years ago - we lost a chromosome and gained a thumb!

Human Genome

- **OUR GENOME IS FIERCELY INVENTIVE**
- It squeezes complexity and individuality out of simplicity
- It produces a near infinite functional variation out of its limited repertoire
- It is the ingenuity of our genome that is the secret to complexity and individuality

Human Genome

- The 3 billion DNA letters in the human genome encode about 20,687 genes, only 1,796 more genes than worms
- Our genome has 12,000 genes fewer than corn, 25,000 fewer than rice or wheat
- The difference between a human and a hamburger bun is not in the number of genes but what we do with it

Human Genome

- It is **Dynamic** (as is the matrix)
  - In some cell lines, it reshuffles itself to make novel variants of itself
  - For example, immune cells make antibodies against presenting pathogens - pathogens change and so must the antibodies
- Genes can be activated and deactivated, and gene expression (epigenetics) is fluid and ever changing

The Human Genome

- 98% of the human genome does not contain genes
- There are enormous stretches of DNA, interspersed between genes, that have no function
- The length of the genome if unwound into a single line would be about 3,500 miles long
- Only about 70 miles of that 3,500 miles is DNA that carries genetic information

Human Genome

- Is encrusted with history/herstory
- Contains ancient fragments of DNA that were inserted into the genome millions of years ago and have been passively carried forward
- Has repeated sequences that appear frequently with no apparent function: a 300 base-pair sequence occurs tens of thousands of times

Human Genome

- It accommodates enough variation to make each of us distinct from one another
- The human genome has enough consistency to make us a species profoundly different from chimps and bonobos despite genomes that are 96% similar

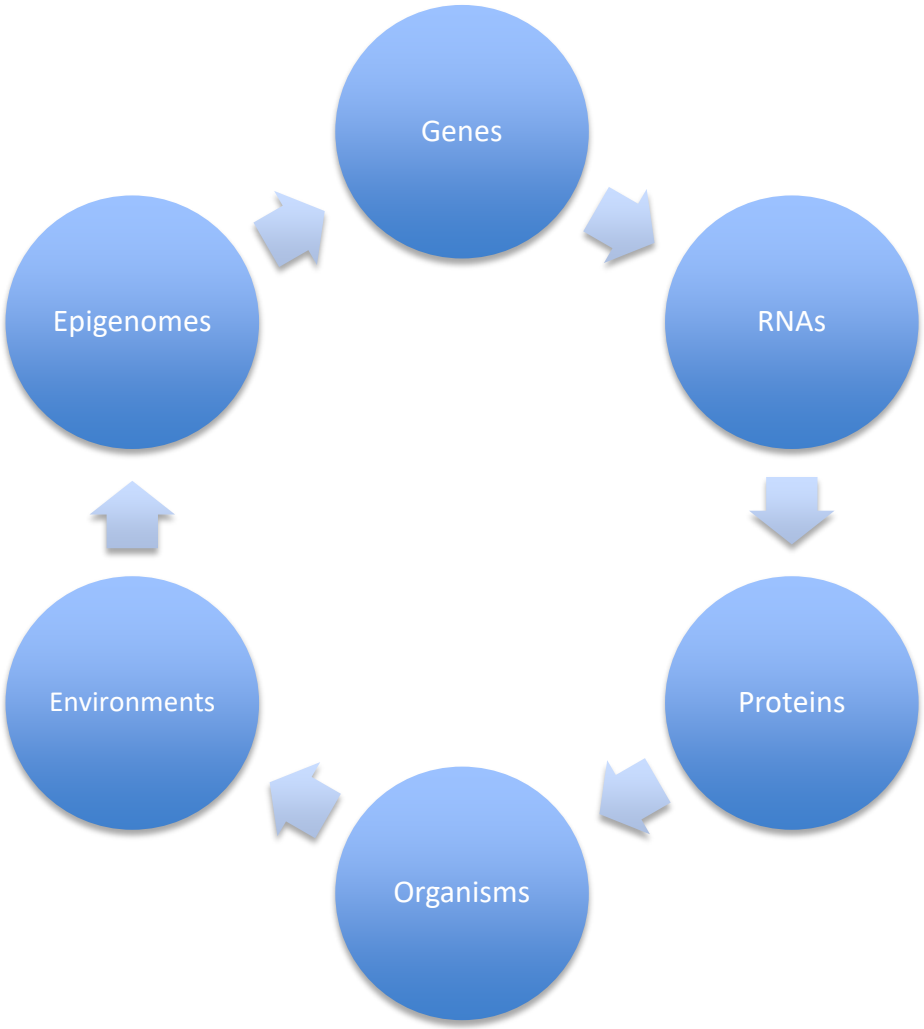
Human Genome

- We have unlocked the entire human genome but we have no understanding of the genomic code
- Genetic systems are extremely complex, dynamic, interdependent and chaotic
- Genomic codes can only be deciphered from within a specific understanding of the living matrix

Human Genome

Appended to each gene are DNA sequences that carry information on when and where to express the gene: there are codes beyond codes

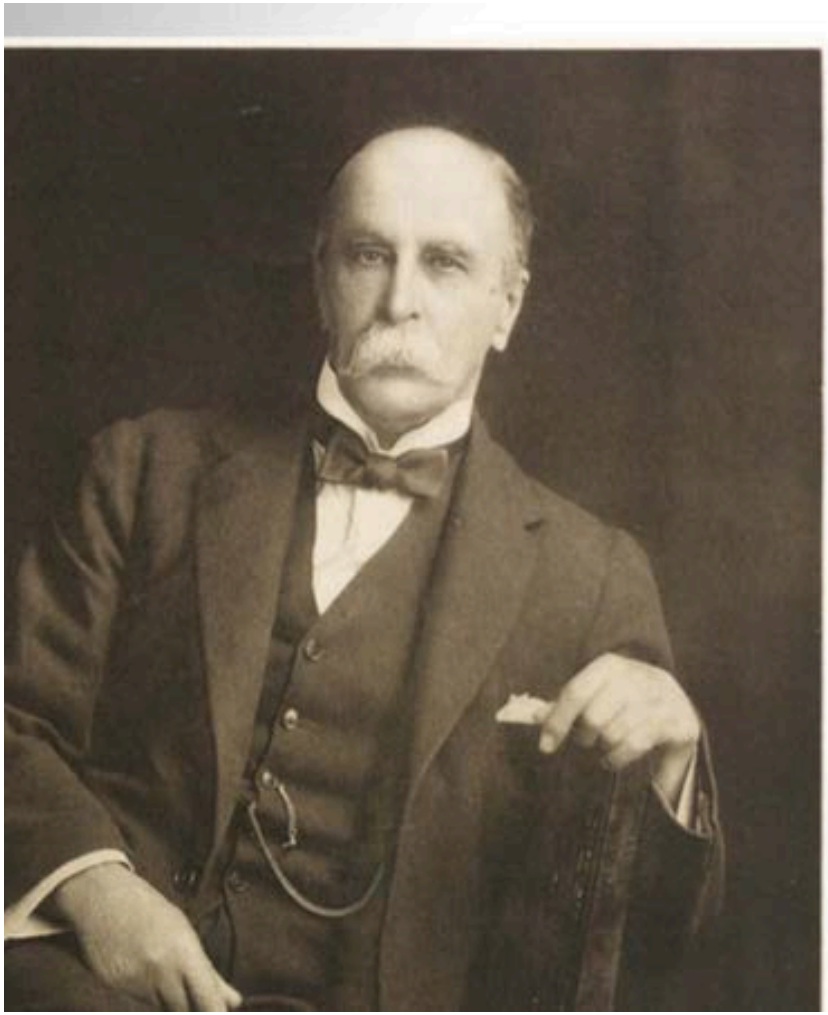
It imprints and erases chemical marks on itself in response to alterations in the environment - encoding cellular memory


Genes
RNAs
Proteins
Organisms
Environments
Epigenomes

Human Genome

- Mitochondrial Eve
- At conception, genetic material from the sperm and the egg combine
- But the cellular material of the embryo comes only from the egg / from the mother
- The mitochondrial information of each of us comes only from the maternal lineage
- Mitochondria carries a small genome itself

Understanding the Genome



Variability is the law of life, and as no two faces are the same, so no two bodies are alike, and no two individuals react alike and behave alike under the abnormal conditions which we know as disease.

Sir William Osler

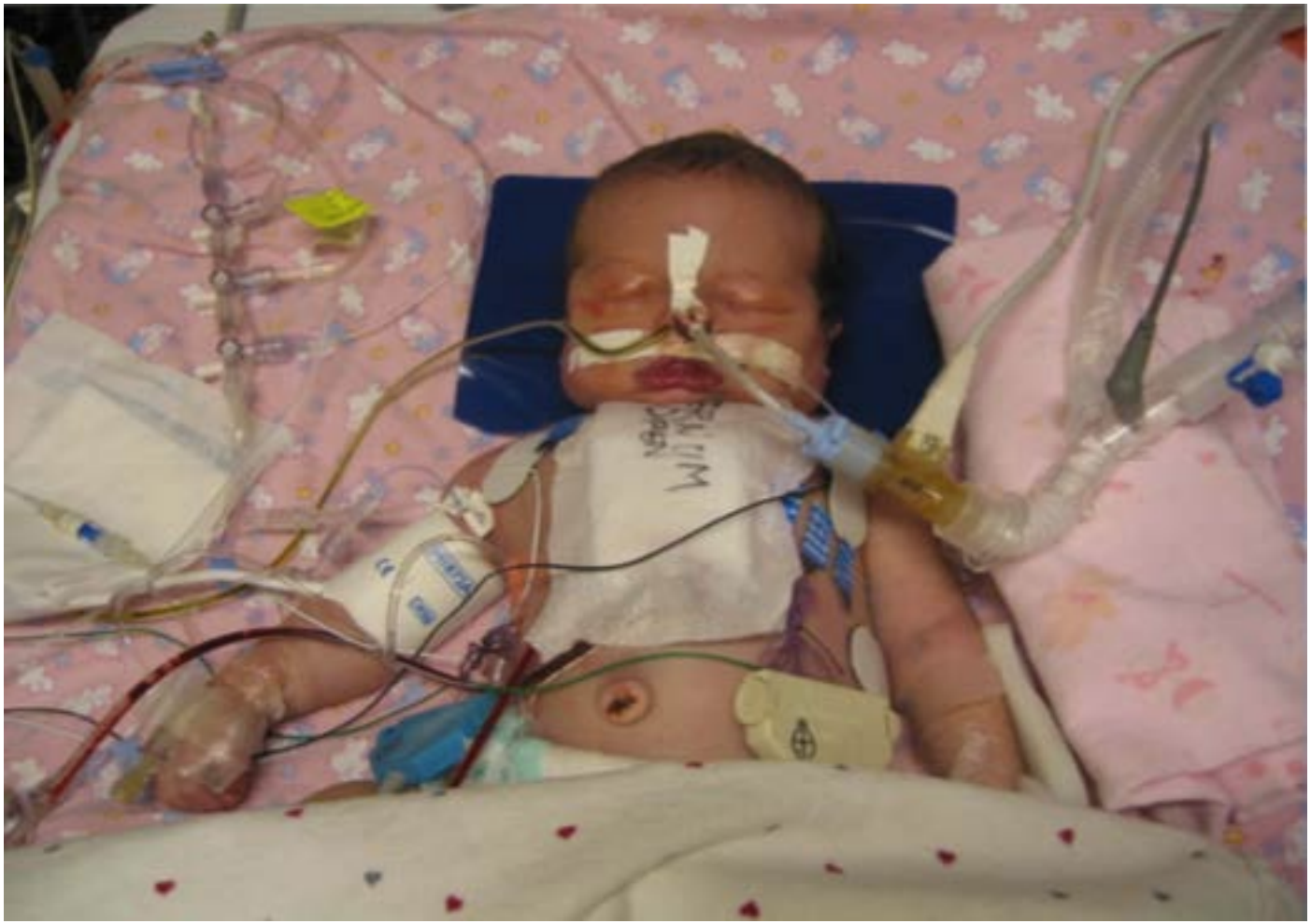
DiGeorge Syndrome

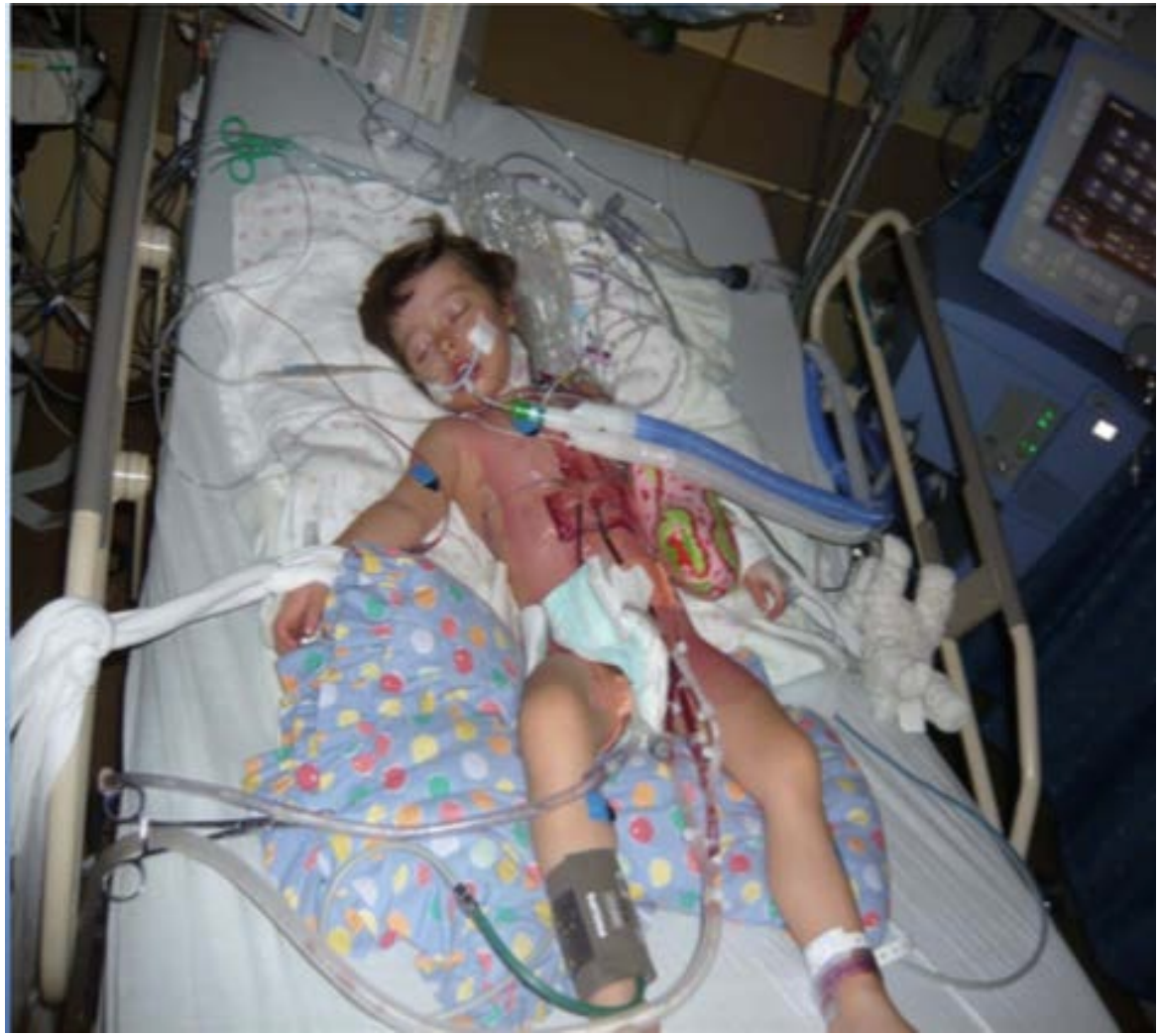
- Velo-Cardio-Facial Syndrome
- 22q11.2 deletion
- Majority of cases are new deletions
- 180 anomalies have been reported
  - Cardiac abnormalities (VSD, Pulmonic Stenosis, TOF, ASD)
  - Suppressed immune function
  - Palate abnormalities
  - Characteristic facial appearance
  - Hypotonia
  - Delayed development, etc., etc.

DiGeorge Syndrome

- 22q11 deletion is on one chromosome
  - Contains a number of genes, including COMT
- An example of haplo-insufficiency
  - When only a single copy of a functional gene cannot produce enough of a gene product to create a “wild-type” condition
  - Seen in many copy number sensitive genes
- Different diagnoses have been made in different members of the same family segregating the same deletion
  - The presentation of the same genetic change is quite variable

Amelie





Amelie

- 8 year old girl
- 2 open heart surgeries, 5 catheterizations, 3 angioplasties
- TA, PDA, ASD, VSD, interrupted aortic arch
- Aberrant subclavian arteries
- Von Willebrands disease
- Febrile seizures
- Tortuous retinal vessels
- Conductive hearing loss
- Narrow external ear canals
- Narrow trachea, structurally asymmetric pharynx
- Reactive airways

Amelie (cont'd)

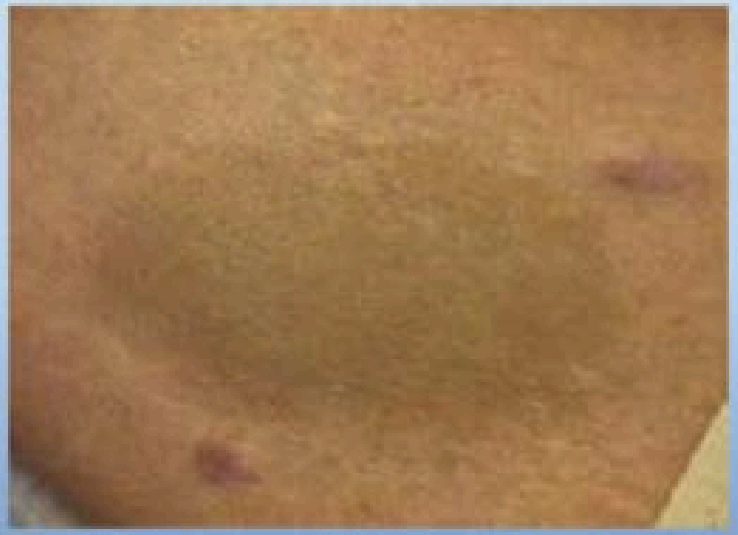
- Diaphragmatic hernia
- Frequent infections, 14 hospitalizations for pneumonia
- Learning disabilities/distractibility
- No thymus
- Poor sleep/periodic limb movement
- Congenital c-spine abnormality
- Raynaud's
- Chronic constipation
- Stomach aches, anal fissures

Genetics Meet Functional Medicine

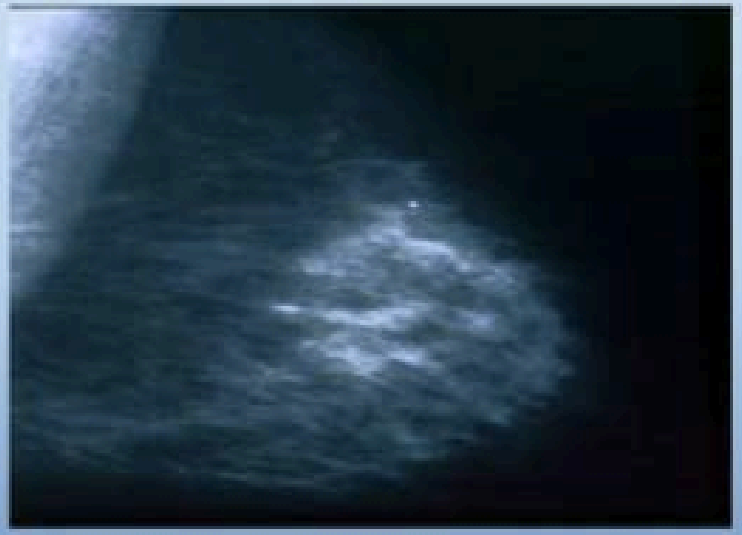
- A genetic disease or syndrome is a small part of a genome
- Don’t forget the rest of the person
- By focusing on the **matrix** we were able to:
  - Correct her digestive issues, including stomach aches, constipation and anal fissures
  - Decrease asthma symptoms
  - Help with sleep and restless legs
  - Decrease number of infections, no hospital admissons

Penetrance

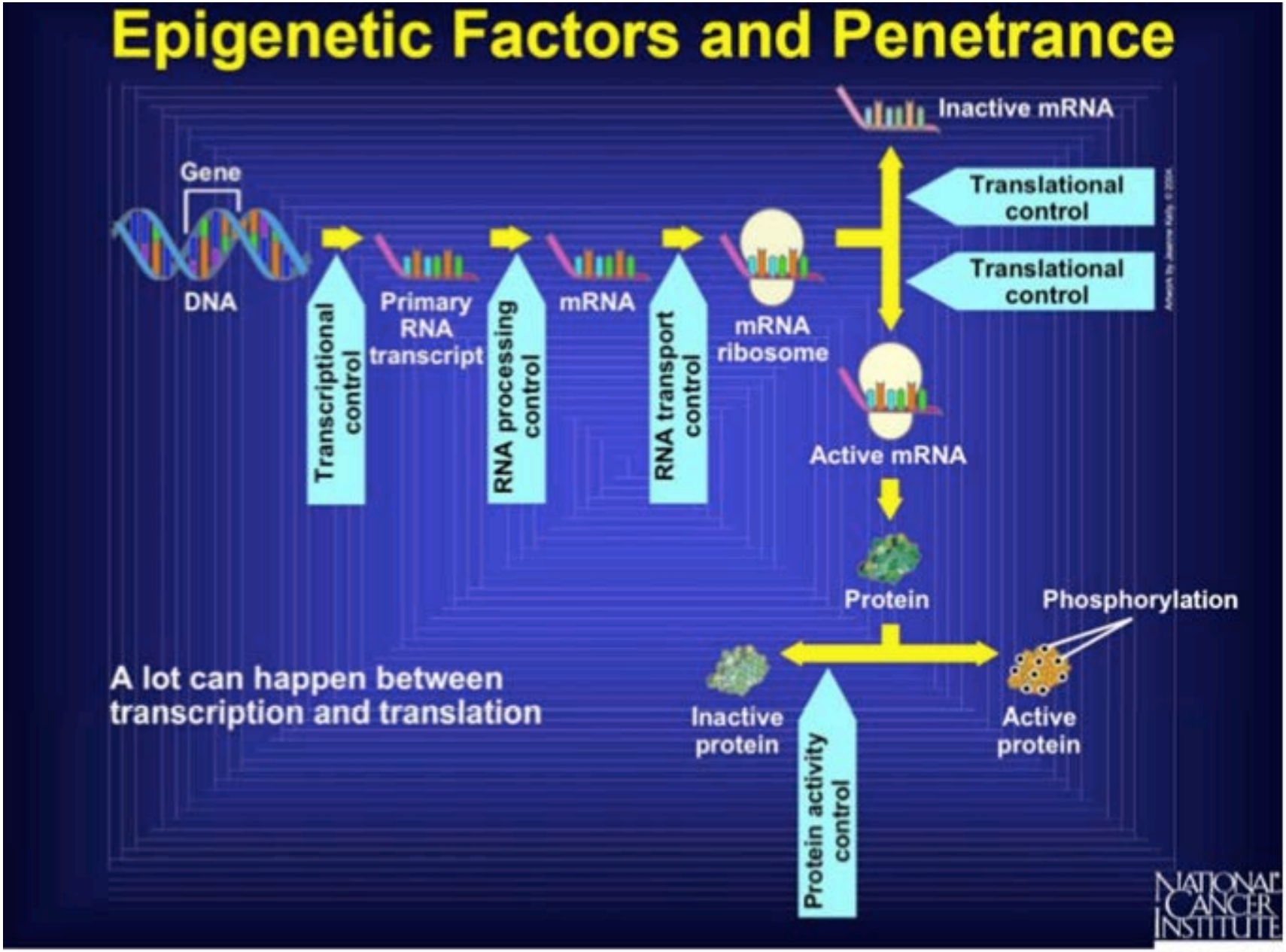
The proportion of people who have clinical symptoms when a particular variant or mutation is present.



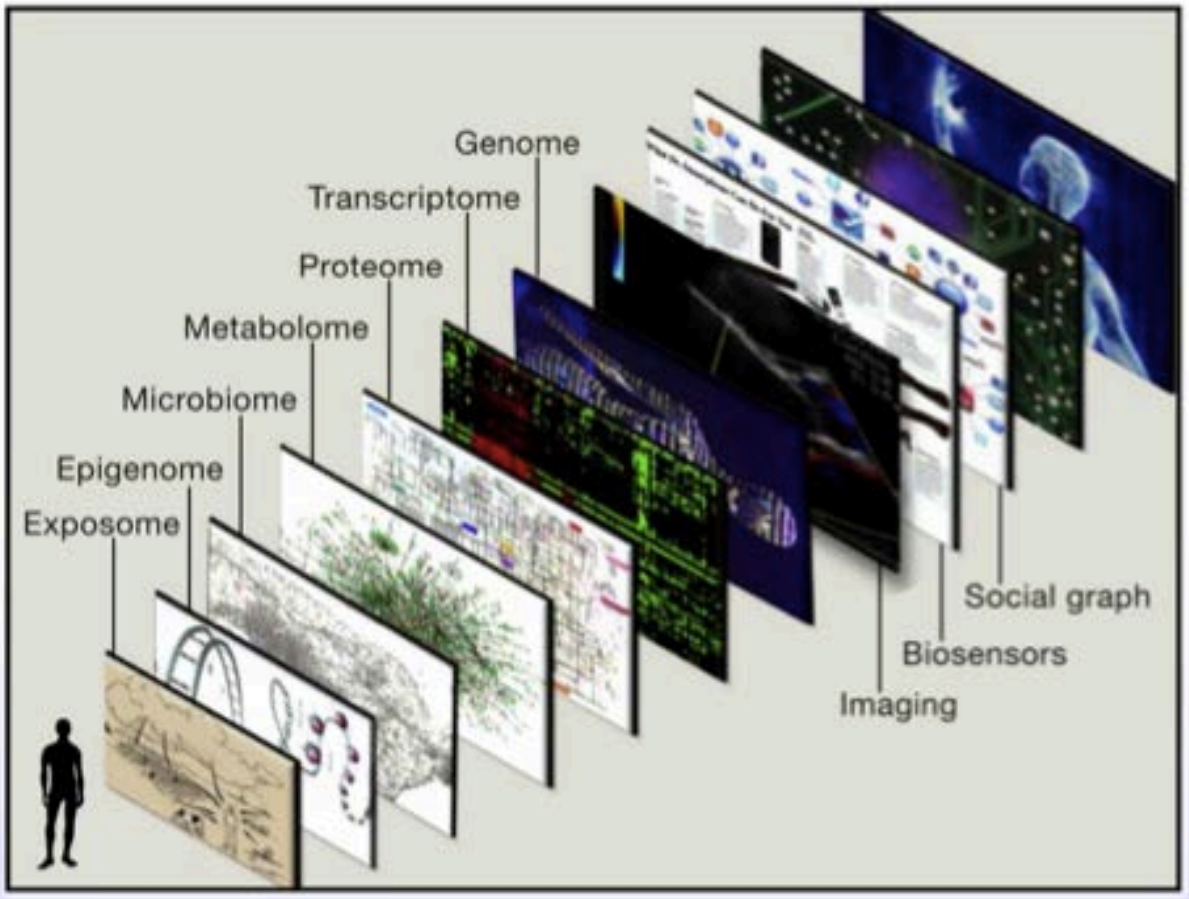
Neurofibromatosis – mutations is NF-1 gene are highly penetrant. Almost 100% of those with a mutation have a phenotypic trait, although the severity will still vary.



Breast cancer – mutations in BRCA-1 are lower penetrance, 45 to 60% of women up to age 40 will develop breast cancer and 45 to 87% by age 70.


Epigenetic Factors and Penetrance
Inactive mRNA
Gene
DNA
Transcriptional control
Primary RNA transcript
RNA processing control
mRNA
RNA transport control
mRNA ribosome
Translational control
Translational control
Active mRNA
Protein
Phosphorylation
A lot can happen between transcription and translation
Inactive protein
Protein activity control
Active protein
NATIONAL CANCER INSTITUTE

“Omics” Systems Biology



Geographic Information System of a Human Being

Cell 2014 157, 241-253DOI: (10.1016/j.cell.2014.02.012)

DISEASE GENE NETWORK

Reality Check !

Cystic Fibrosis- *a single gene defects disease*- > 2000 variants of the transmembrane conductance regulator gene (CFTR)
70% have 2 copies of a 3 base deletion AF508- mechanism understood
The Rest: 159 further variants at frequency >0.01% and the remaining >1850 singleton defects mechanism not understood

Comparisons of *CYP1A2* genetic polymorphisms, enzyme activity and the genotype-phenotype relationship in Swedes and Koreans

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Received: 19 December 2006 / Accepted: 20 February 2007 / Published online: 17 March 2007

Abstract

Objectives To investigate the CYP1A2 genotype-phenotype re
morphi
smokin
Korean
Method
and 15
on the
137X)
matography. Genotyping for the −3860G>A, −2467delT, −739 T>G, −729 C>T, −163C>A and −3113A>G polymorphisms was performed by PCR-restriction fragment length polymorphism analysis.

Results The mean 17X/137X ratio was 1.54-fold higher in Swedes than in Koreans (mean difference: 0.16; 95% CI of the mean difference: 0.12, 0.20; $p<0.0001$). Smokers had a significantly higher 17X/137X ratio (higher CYP1A2 activity) than non-smokers, while Swedish OC users had a significantly lower 17X/137X ratio than non-users (mean difference: 0.31, 95% CI of the mean difference: 0.23, 0.39;

We found significant differences in CYP1A2 enzyme activity between Swedes and Koreans that could not be explained by environmental factors or the CYP1A2 haplotypes examined.

played a significantly lower mean 17X/137X ratio than Swedes having the same *CYP1A2* genotype, smoking habit and OC use.

Conclusions We found significant differences in CYP1A2 enzyme activity between Swedes and Koreans that could not be explained by environmental factors or the *CYP1A2* haplotypes examined, despite differences in allele frequencies. None of the investigated *CYP1A2* haplotypes are critical in inducing variations in enzyme activity, with the exception of *CYP1A2**1F.

The Bacterial Microbiome: By the Numbers

- Every bodily surface hosts a myriad of microorganisms:
  - Skin = 10^{12} (one trillion) resident bacteria
  - Mouth = 10^{10} (ten billion)
  - Gut = 10^{14} (100 trillion)
    total weight approximately 2-5 lbs;
    most are anaerobes

What are the functions (ecosystem services) provided by these gene clusters?

(The Metagenome)

Vol 464|4 March 2010|doi:10.1038/nature08821 nature

ARTICLES

A human gut microbial gene catalogue established by metagenomic sequencing

Junjie Qin[1]*, Ruiqiang Li[1]*, Jeroen Raes[2,3], Manimozhiyan Arumugam[2], Kristoffer Solvsten Burgdorf[4], Chaysavanh Manichanh[5], Trine Nielsen[4], Nicolas Pons[6], Florence Levenez[6], Takuji Yamada[2], Daniel R. Mende[2], Junhua Li[1,7], Junming Xu[1], Shaochuan Li[1], Dongfang Li[1,8], Jianjun Cao[1], Bo Wang[1], Huiqing Liang[1], Huisong Zheng[1], Yinlong Xie[1,7], Julien Tap[6], Patricia Lepage[6], Marcelo Bertalan[9], Jean-Michel Batto[6], Torben Hansen[4], Denis Le Paslier[10], Allan Linneberg[11], H. Bjørn Nielsen[9], Eric Pelletier[10], Pierre Renault[6], Thomas Sicheritz-Ponten[9], Keith Turner[12], Hongmei Zhu[1], Chang Yu[1], Shengting Li[1], Min Jian[1], Yan Zhou[1], Yingrui Li[1], Xiuqing Zhang[1], Songgang Li[1], Nan Qin[1], Huanming Yang[1], Jian Wang[1], Søren Brunak[9], Joel Doré[6], Francisco Guarner[5], Karsten Kristiansen[13], Oluf Pedersen[4,14], Julian Parkhill[12], Jean Weissenbach[10], MetaHIT Consortium†, Peer Bork[2], S. Dusko Ehrlich[6] & Jun Wang[1,13]

>5 Million Microbial Genes (current estimate)
in 100 trillion cells - the Symbiotic Microbiome….
….what are they all doing?

Microbial Genetic "Dark Matter"

A Primer on Metagenomics

PLoS Computational Biology, 2010, Vol 6(2): e1000667

- Given our intimate relationship with microbes, sequencing the genomes of our own microbes is essential for understanding the human condition
- The metagenome = genomic analysis of microbial DNA extracted directly from communities in environmental samples

Gut Microbes and Host Gene Regulation

Front Microbiol. 2011 Vol 2(166): 1-14

- There is a dynamic interaction between host and bacteria that profoundly affects genetic expression: e.g., metabolites interact with transcription factors
- Intestinal bacteria alter host cellular function by influencing complex networks

Major Influences on Individual Microbiomes

- Host genotype
- Type of birth (vaginal vs C-section)
- Excessive hygiene (excessive)
  PLoS One, 2011;6(12):e28284
- Diet (macronutrients, fiber, phytochemicals, alcohol)
- Stress (social, emotional)
- Xenobiotics / pesticides

Humans vs. Bacteria

- Human somatic & germ cells: approximate average = 10^{13} (10 trillion)
- Total microbiota > 100 trillion – outnumbering human cells by 10:1
- Human genes ~20,000
- Common microbial genes > 3.3 million – outnumbering human genes >150:1
- **One of the most complex microbial ecosystems on the planet!**

The Human Gut Virome

Minot, et al Genome Research, 2011(10): 1616-1625

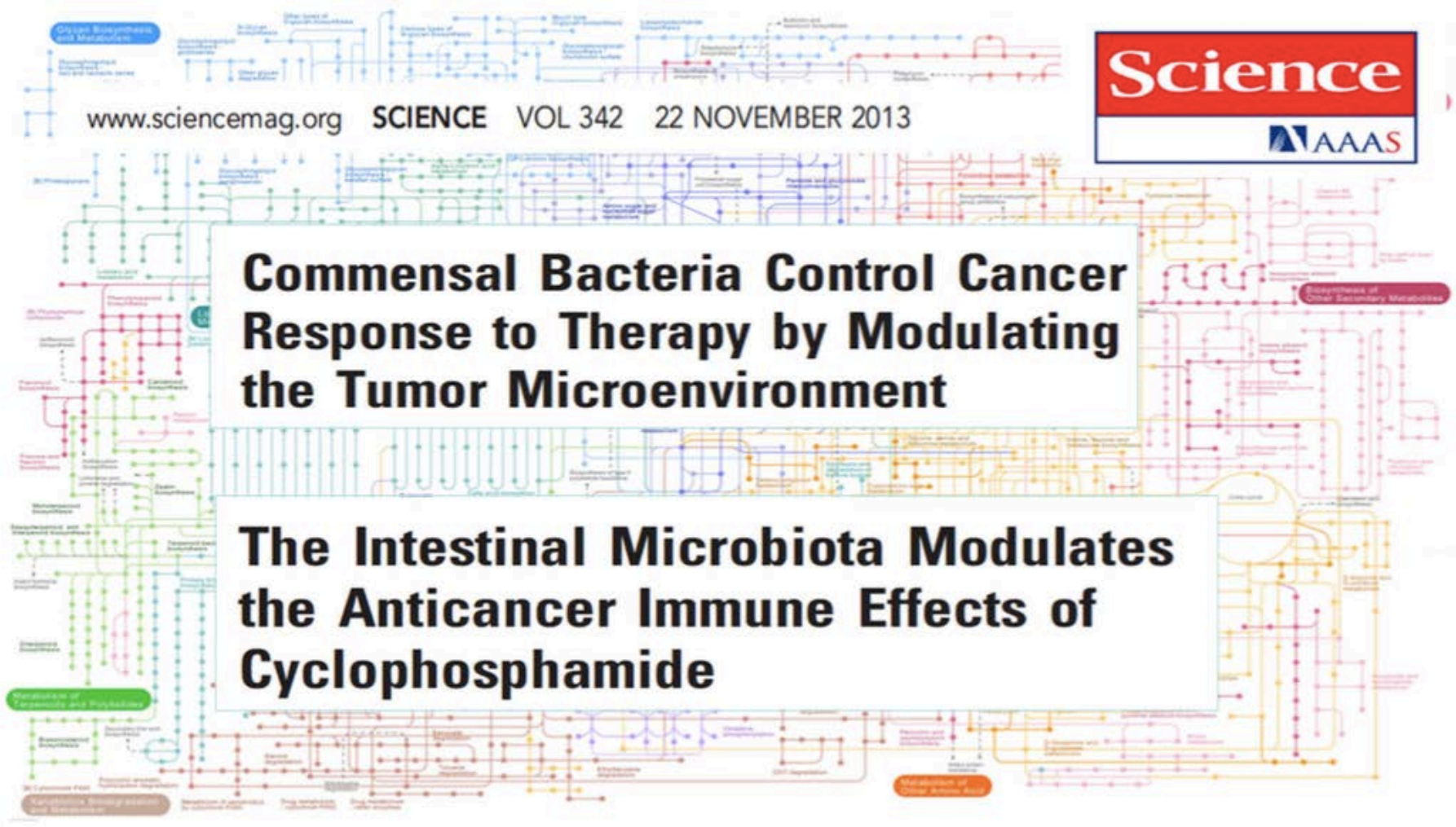
- Viral DNA analyzed in stool samples has shown:
  - several thousand distinct viruses, with
  - marked inter-individual variability

Immune Functions of the Healthy Gut Microbiome

Kalliomaki, M, et al, Lancet, 2001, Vol 357: 1076-1079

- Enhanced barrier function: trophic affects on epithelial tissue
- Initial development of gastrointestinal associated lymphoid tissue (GALT)
- C.R.A.P.: Colonized resistance against pathogens

Genetics



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Epigenetics

- Is changing the widely linear conception of genome function
- Explains how environmental and psychological influences change the expression of genes
- Epigenetic factors change the expression of genes without changing the genetic sequence

Epigenetics

- The history of science teaches us that what starts as heresy becomes orthodoxy
- Genetics research continues to be directed by reductionist thinking
- Bioregulatory medicine requires us to think differently, to restore regulatory balance to dynamic complex and chaotic systems

Epigenetics

"It's the environment, dummy."

Thank you for being here.

Resources

IFM "Omics" Article Series

Juy – December 2015

www.functionalmedicine.com

PLMI Free Online Education Portal

and

2015 Thought Leaders Consortium:

October 24-25, 2015 Chicago, IL

"From Personalized Cancer Therapy to Wellness"

www.plminstitute.org

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