Genetic and epigenetic regulation of the immune response
- DNA sequence data **doubled in 18 month**
- The number of known **genomes doubled in 18 month**
- **Cost of sequencing halved in 18 month**
Encyclopedia of DNA elements of human genome released: April, 2012
The human genome

- Exon (1.5%)
- Intron (5%)
- Regulatory elements (~20%)
- Mobile "jumping" elements (45%)
- L1 elements (17%)
- Alu elements (10%)
- Repetitive elements (14%)
- Individual non-coding DNA (15%)
- Large, common non-coding DNA (5–6%)
Sequencing DNA gets cheaper (<$3000), GWAS soon < $1000

Figure 1. The number of publications related to next-generation sequencing and indexed in PubMed has been increasing exponentially. The numbers reflect the PubMed search results by using the following query on 11 October, 2010:


MacConaill, L. Journal of Clinical Oncology (2010)
Some diseases with relevant environmental (epigenetic) background

- Fetal and neonatal disorders
- Autism
- Schizophrenia
- Crohn’s disease
- Neuromuscular disorders
- Psychotic diseases
- Tumors
- Type 1 and 2 diabetes
- Multiple sclerosis
- Asthma
- Gout and pseudogout
MISSING HERITABILITY
(after a disappointment)
as a major challenge

- Ethnic differences
- Multifactorial biological networks
- Environment-epigenetics
- coding-non-coding genome
- rare disease alleles
- metagenomics- (microbiota)
Definition of EPIGENETICS

- Covalent and reversible modifications of chromatin without changes in nucleotide sequence
- Regulates gene expression (…)

The epigenome tightly wraps **inactive** genes, making them unreadable.

The epigenome relaxes **active** genes, making them easily accessible.
EPIGENETIC INHERITANCE:

Same genotype - different phenotype

Mitotic transmission: « cellular memory »
Epigenetics of twins

- Kids: Right weighs 4 pounds less.
- Teens: Left has more smoking.
- Elders: Left has more sun.
Obesity epigenetics

- exercise
- eating
- Social status
- gut microbiome
- viruses
- medical care
- food excess
- in utero development
- psychology
- environmental pollution
- technology development
- hormones
- social effects
Human miRNAs block mRNA translation

- Total number of miRNAs known: 21,513
- Number human miRNAs identified: 3,756
- Number of human mRNA targets: 49,887
- miRNAs can have multiple targets
- Target mRNAs can have multiple miRNA binding sites

(July 31, 2013)

miRBase @ http://www.mirbase.org/
MicroCosm @ http://www.diana.pcbi.upenn.edu
Department of Medicine, University of California, San Francisco, CA, USA.

**Increased telomerase activity and comprehensive lifestyle changes: a pilot study.**

Heritable germline epimutation of \textit{MSH2} in a family with hereditary nonpolyposis colorectal cancer

Tsun Leung Chan\textsuperscript{1,2}, Siu Tsan Yuen\textsuperscript{1,2,3}, Chi Kwan Kong\textsuperscript{4}, Yee Wai Chan\textsuperscript{1,2}, Annie SY Chan\textsuperscript{1}, Wai Fu Ng\textsuperscript{5}, Wai Yin Tsui\textsuperscript{1}, Michelle WS Lo\textsuperscript{1}, Wing Yip Tam\textsuperscript{1}, Vivian SW Li\textsuperscript{1} & Suet Yi Leung\textsuperscript{1}

Epimutations in the germline, such as methylation of the \textit{MLH1} gene, may contribute to hereditary cancer syndrome in human, but their transmission to offspring has never been documented. Here we report a family with inheritance, in three successive generations, of germline allele-specific and mosaic hypermethylation of the \textit{MSH2} gene, without evidence of DNA mismatch repair gene mutation. Three siblings carrying the limited\textsuperscript{4}. During germ cell development and in early embryogenesis, the genome normally undergoes two rounds of demethylation and \textit{de novo} methylation\textsuperscript{5}. Consequently, epigenetic marks are substantially modified, and if their inheritance exists, it may manifest as an obscure pattern and could contribute to an unrecognized source of disease susceptibility inheritance. Indeed, epigenetic inheritance leading to cancer in humans was first suggested based on the discovery of

\textbf{Epigenetics in human disease and prospects for epigenetic therapy}

Gerda Egger, Gangning Liang, Ana Aparicio & Peter A. Jones

Departments of Biochemistry and Molecular Biology and Urology, USC/Norris Comprehensive Cancer Center, Keck School of Medicine of the University of Southern California, 1441 Eastlake Avenue, Room 8302L, Los Angeles, California 90089-9181, USA
(e-mail: jones_p@ccnt.hsc.usc.edu)
Epigenetic inputs

- maternal effect
- food
- medications, drugs, toxins
- infections
- radiation
- physical activity, sport
- light
- stress, behaviour, psychosocial effects
- etc....
1. danger requires rapid reaction

2. Restitution and maintenance of homeostasis (reversible changes)

- immunoregulation
- epigenetics
- chromatin rearrangement
- covalent, reversible
The immune genome

Kelley, de Bono & Trowsdale, 2005
GWAS analysis of SNP associations in asthma by Bayes informatics tool

Csorba et al, PlosOne, 2013
DC, monocyte/macrophage
PAMP/MAMP/DAMP signals are regulated by miRNA
B-lymphocyte
An epigenetic model of helper T cell differentiation

Methylation regulates T cell polarization
miR-155 elevates proliferation of activated T cells in atopic dermatitis

Sonkoly et al., J All Clin Immunol, 2010
Network Medicine

Genomics-epigenomics

• Heredity (genetics) is **irreversible**

• Egigenetic changes are **reversible**

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✓ Understand it,
✓ Like it!

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