Summer Institute in Statistical Genetics 2017

Genetics and Genomics

5a. Integrative Genomics

ggibson.gt@gmail.com

http://www.gibsongroup.biology.gatech.edu

Georgia Tech

Center for Integrative Genomics

The Rationale for Gene Expression Profiling

Question: What makes a muscle cell different from a skin cell different from a liver cell?

Analogy: What makes a living room different from a bathroom different from the kitchen?

Answer: What furniture and appliances and windows re placed where and when

What genes are expressed where and when and how much

Strategy: Measure the abundance of mRNA transcripts in a bunch of samples, and use statistically rigorous approaches to identify differential expression

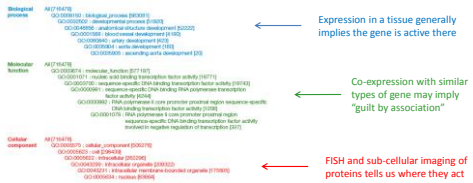
Methods: Prior to 1995: One gene at a time qPCR

1995-2015: Microarrays

Since 2015: RNAseq

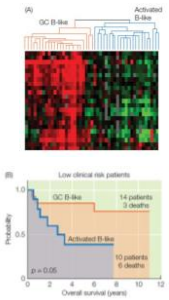
Annotation of Gene Function

Gene Ontology



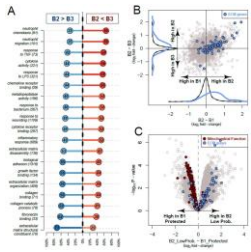
Differential Expression Analysis

Cancer



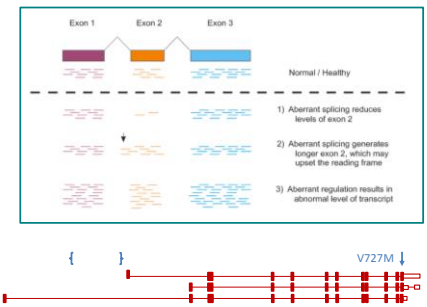
Alizadeh *et al* (2000) *Nature* **403**: 503-511

Inflammatory Bowel Disease



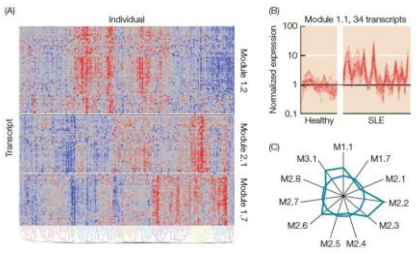
Kugathasan *et al* (2017) *Lancet* **389**: 1710-1718

Clinical Diagnostics



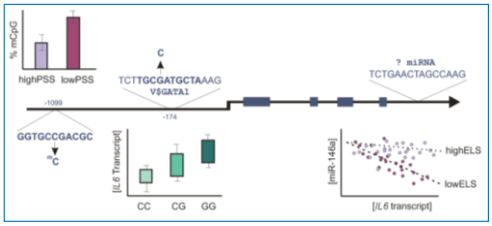
Cummings, MacArthur et al (2017) *Sci Transl Med* **9**: eaal5209

Population Profiling

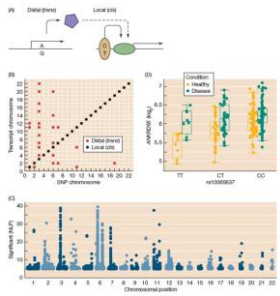


Chaussabel *et al* (2008) *Immunity* **29**: 150-164

Gene Regulation

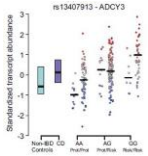


Expression QTL



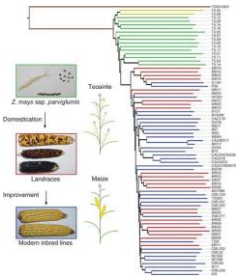
Expression QTL are polymorphisms that affect the expression of a gene.

They are particularly interesting when they overlap with GWAS hits.



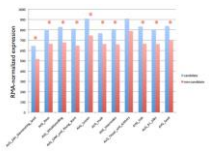
Ecology and Evolution

Comparative population genomics of maize domestication and improvement



~1000 Domestication and Improvement loci identified with s ~0.015

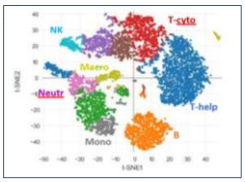
Improvement candidates tend to be more highly expressed in multiple tissues, suggesting selection targeted cis-regulatory sites.



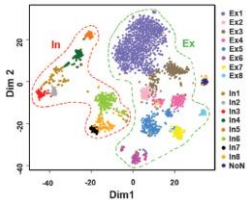
Hufford *et al* (2012) *Nature Genetics* **44**: 808-811

Single Cell RNASeq

Peripheral Blood Monocytes



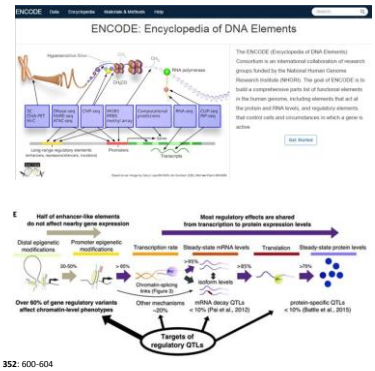
Neuronal nuclei



Zheng *et al* (2017) *Nature Comm* **8**: 14049

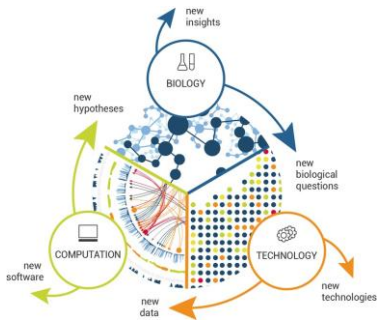
Lake *et al* (2016) *Science* **352**: 1586-1590

Additional Tiers of Gene Regulation



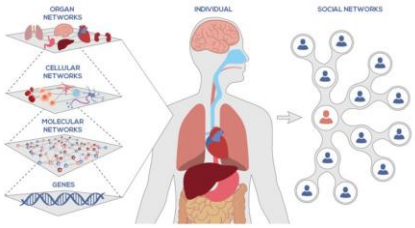
Li et al (2016) Science **352**: 600-604

Systems Biology



http://www.omicscouts.com/en/disease-and-systems-biology.html

Human Systems Biology



https://www.systemsbiology.org/about/what-is-systems-biology/

First genome sequencing success story

Diagnosed at age 5 with dopa-responsive dystonia

Worsening respiratory and neuromuscular disease not responsive to dopamine precursor therapy

WGS shows mutation in SPR "sepiapterin reductase" gene

5-HT serotonin precusor supplementation had immediate impact

The Beery twins

Bainbridge, *et al.* (2011) *Sci. Transl. Med.* **3,** 87re3

Some Personal Genomics Companies

Some Public Initiatives

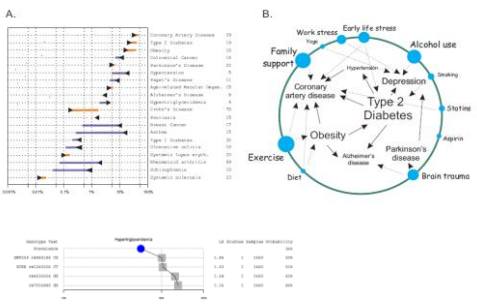
Precision Medicine and Predictive Health

Precision Medicine is molecular pathology based on a patient's genome sequence. It is about finding the mutation or perturbed genetic pathway that is largely responsible for a congenital birth defect, or for a specific cancer.

Predictive Health is about using your own clinical and genomic profile to make better decisions about wellness in an effort to prevent the onset of chronic disease.

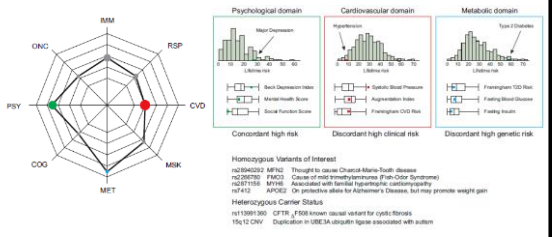
Personalized genomic medicine encompasses both, and essentially captures the idea that each person's individual genome sequence will eventually be part of their own medical care.

Common Variant Risk-o-Grams



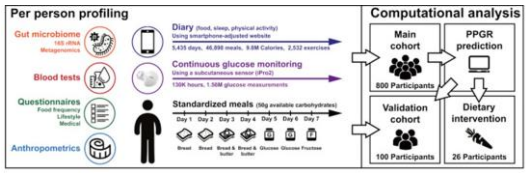
Ashley et al (2010) *Lancet* **375**: 1525-1535

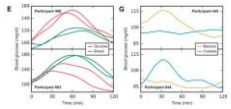
A Sample Predictive Health Profile



Patel, Sivadas et al (2013) *Genome Medicine* **5**: 58

Microbiome-directed personalized nutrition

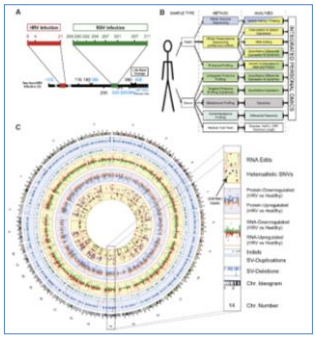




How can pre-diabetics control their blood glucose given that we each respond differently to different diets? In part, by monitoring our microbiome, which in combination with other tests, is remarkably predictive.

Zeevi et al (2015) *Cell* **163**: 1079-1094

Integrative Personal Omics: iPOP



- Whole genome
- Transcriptome
- microRNAome
- Proteome
- Metabolome
- Auto-antibodies
- Blood parameters

- Probably $200,000

Chen *et al* (2012) *Cell* **148**: 1293-1307

Then why don't we all get our PGS?

1. Cost: $500 for the lite version, $3000 the whole
2. Privacy: What if WikiLeaks releases it to the world
   Can providers sell information to companies?
3. Insurance: The Genetic Non-Discrimination Act protects from workplace and health discrimination only
4. Anxiety: Will I learn something I don't want to know? And will there be anything I can do about it?
5. Consent: How can I provide informed consent to something I don't really understand? Can I trust my doctor to help me decide?