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Genomics meets physics – are there any links between modern human genetics and physics?

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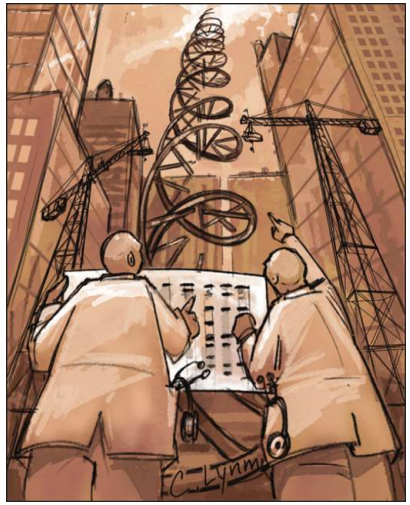
Basic idea – understand genome

- 2001 – Human Genome Project completed
- First human sequence
- 100 mil USD
- 10 years



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Why didn't genetics change the world (yet)?

- P1: Complex genome structure and organization
- P2: Difficulties in definition of our phenotypes
- P3: Epigenetics
- P4: Cost
- P5: People…

Problem 1: Genome structure

- **A lot of data:** $3^{*}10^{9}$ base pairs (**ACGT**)
- About 2m long molecule (if assembled together)
- 23 chromosome pairs (22+XX/XY)
- 17-25k genes expected (based on homology with other species and gene structure)
- Gene: piece of DNA that has a (almost) unique start and end signals
- Furthermore …

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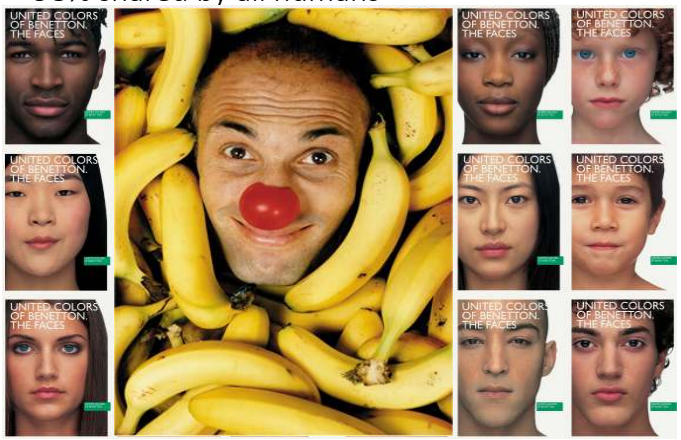
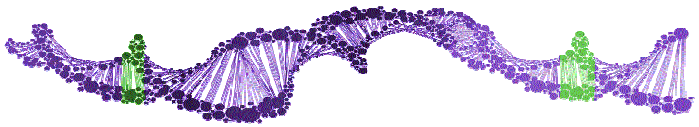
98% shared by all humans



2% of DNA ($3*10^{7}$ base pairs)

- All variation in humans is stored in those 2% called the exome
- The rest is "**dark matter**", of unknown function (so far) - the introns
- Only recently we started producing some data related to the biological role of introns



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Meiosis

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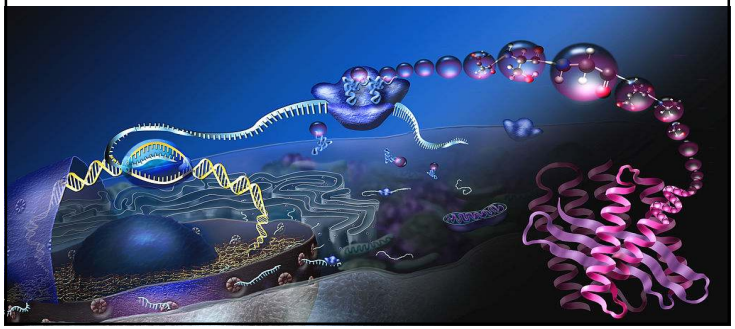
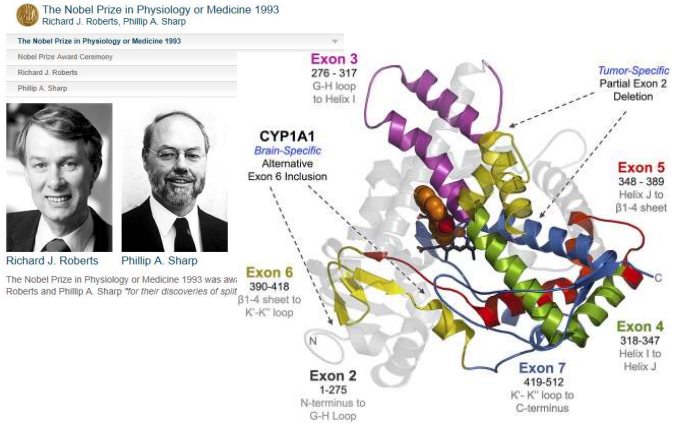
Central dogma of genetics

- DNA encodes RNA which produces proteins that build our bodies and govern all other processes in the body

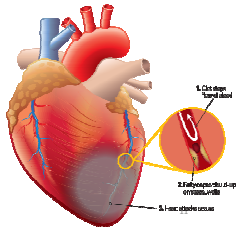


Alternative splicing



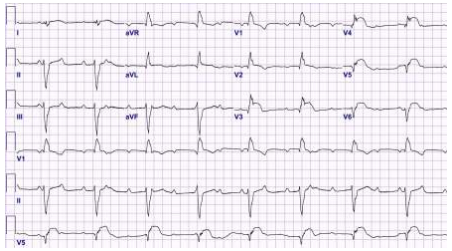
Problem 2: Difficult phenotypes

- Many disease occur as the result of numerous reasons
- Mycoardial infarction – occlusion of the blood vessel in heart that leads to death of a heart muscle
  - Embolus (blood cloth, air bubble)
  - Atherosclerosis (blood vessel hardening)
  - Hyperlipidaemia (elevated lipids)
  - Lack of physical activity
  - Smoking
  - Salt overuse*
  - Chemical injury (homocysteine)



Solutions?

- Quantitative trait analysis
- Instead of going after the disease, why not investigate the trait that is related to the disease?
- ECG – a recording of electrical impulse travel through the heart muscle



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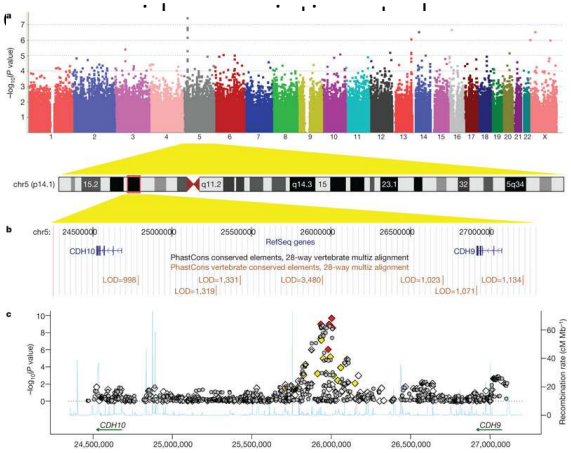

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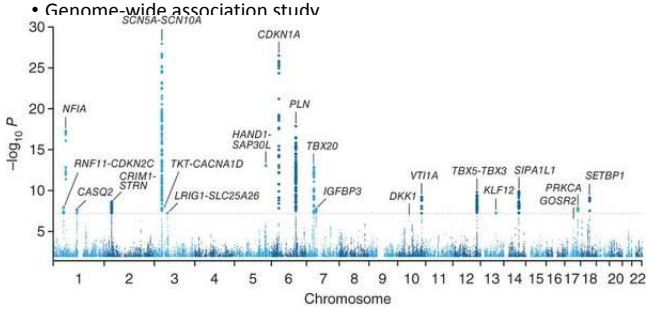
Result?

- Genome-wide association study



Sotoodehnia N, et al. Common variants in 22 loci are associated with QRS duration and cardiac ventricular conduction. Nat Genet. 2010;42(12):1068-76

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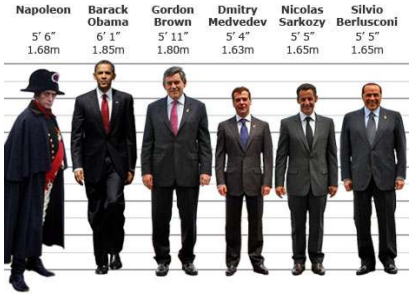
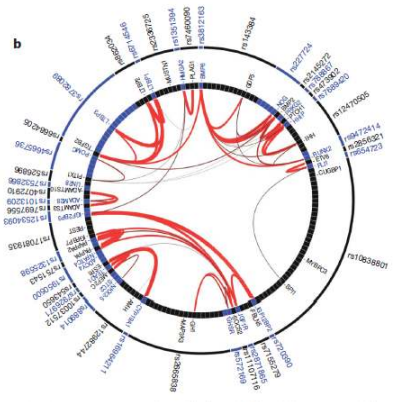
Maximising the possibilities…

- Use meta-analytic approach and create **global consortia**
- Select a very stable trait
- Maximise sample size
- Height



Result?

- 203 institutions
- 130k subjects+
  60k replication
- 263 authors
- 130 new genes
- But…



Lango Allen H, et al. Hundreds of variants clustered in genomic loci and biological pathways affect human height. Nature. 2010;467(7317):832-8.

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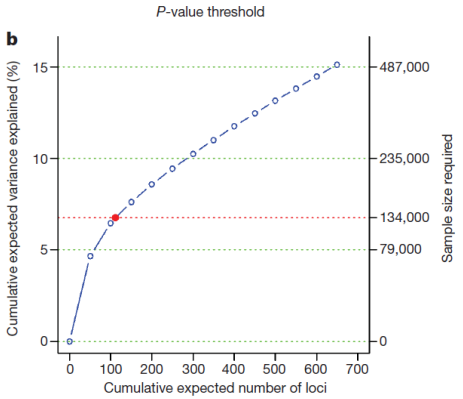
Variance



Lango Allen H, et al. Hundreds of variants clustered in genomic loci and biological pathways affect human height. Nature. 2010;467(7317):832-8.

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Problem 3: Epigenetics and interactions

- Our bodies are full of different molecules that are activated in time-sensitive manner and that can **interact**
- DNA activation and inactivation
- Interactions: gene-gene, gene-environment, random effects
- Molecular interactions: proteins+lipids (proteolipids), proteins+sugars (glycans), lipids+sugars (glycolipids)
- Several groups of *omics* variables – **producing more data than we can analyze and understand**

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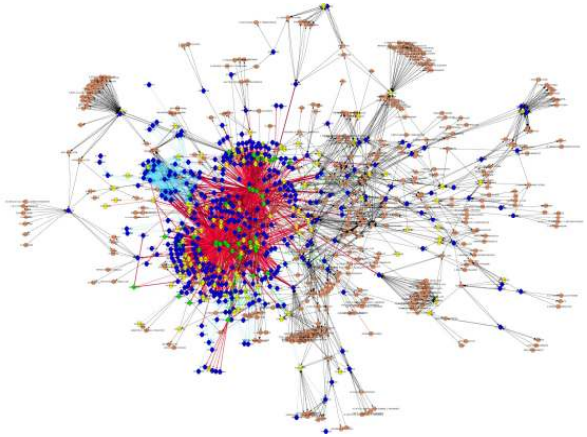
Systems biology and gene networks



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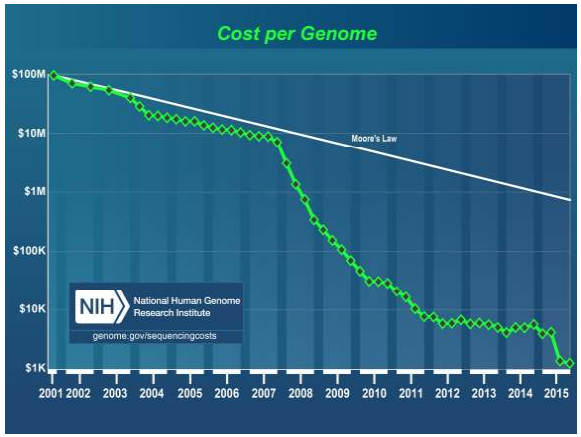
Problem 4: Cost



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10,001 Dalmatians project

- Research project initiated in 2001
- Uses isolated human populations to map genes
- Isolation leads to genetic and environmental homogeneity-> increases chances of success
- We developed a large biobank of blood, serum and urine samples, with nearly 1600 quantitative traits, currently with over 6,500 samples

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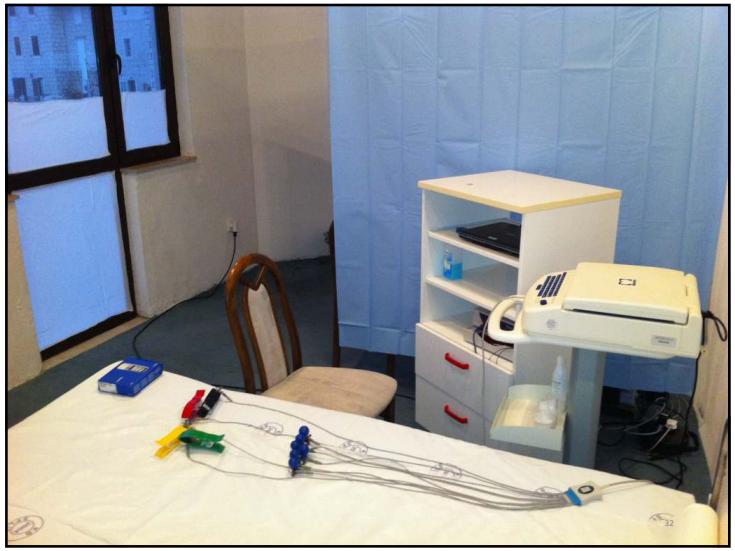

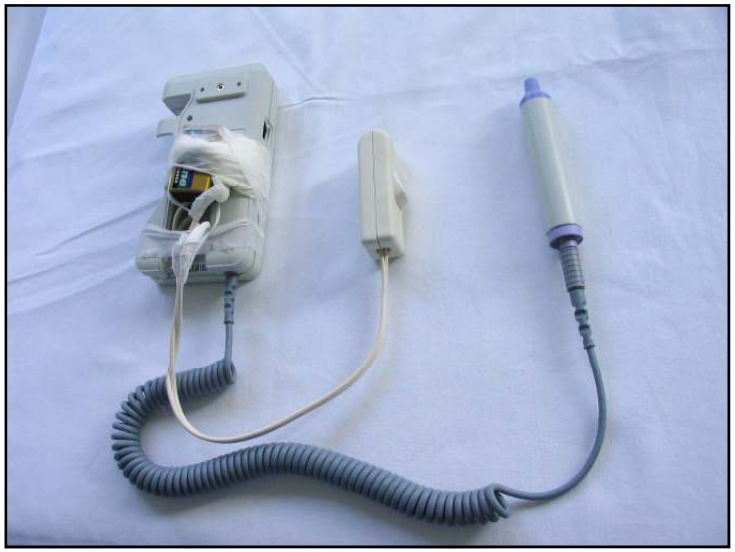


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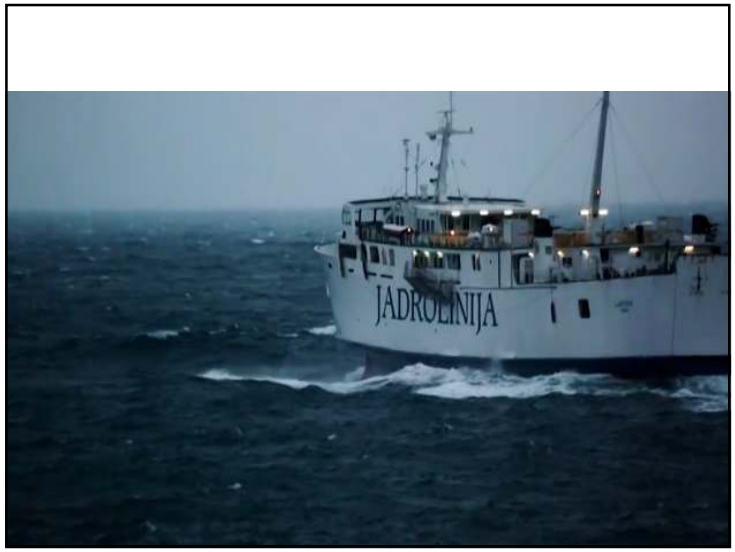
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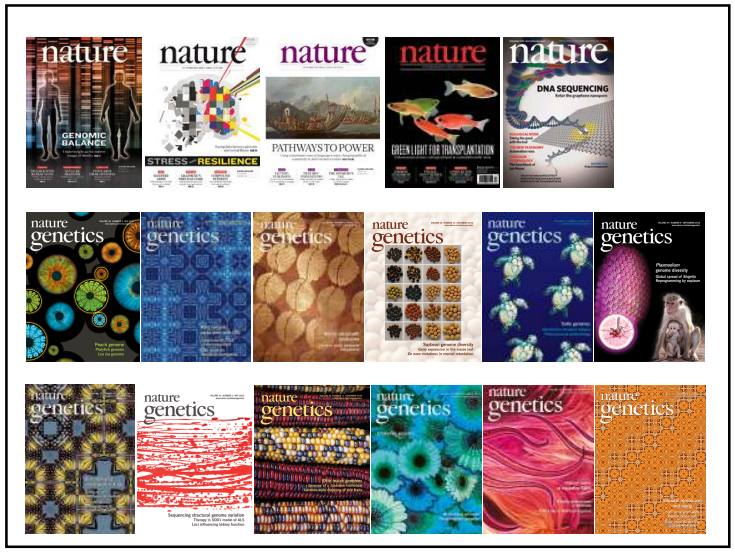
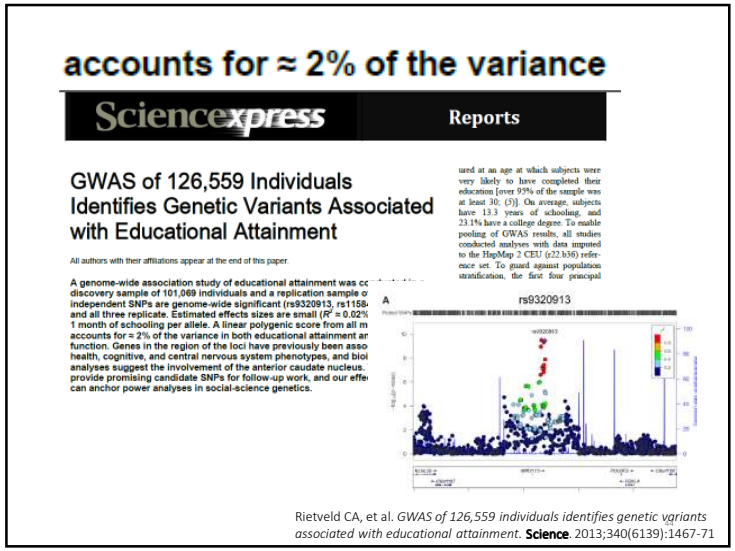


Height and intelliegence

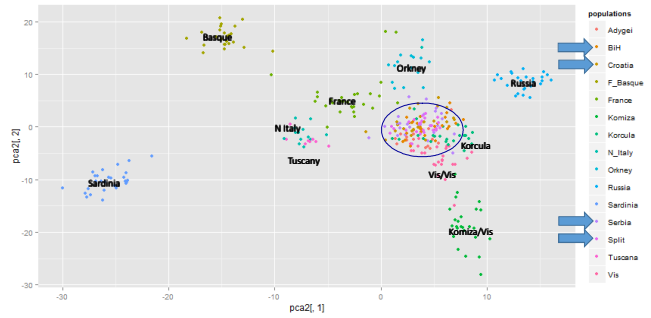
Joshi P, et al. *Directional dominance on stature and cognition in diverse human populations.* **Nature**. 2015;523(7561):459-62

accounts for ≈ 2% of the variance

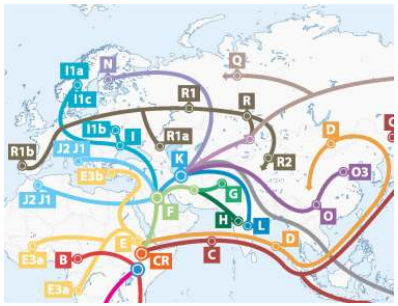


Rietveld CA, et al. *GWAS of 126,559 individuals identifies genetic variants associated with educational attainment.* **Science**. 2013;340(6139):1467-71

Unpublished…



Glimpses of past in DNA



An estimated 3.0% of your DNA is from Neanderthals.

88th percentile

23andMe

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Glimpses of future in DNA

Elevated Risk

NAME	CONFIDENCE	YOUR RISK	AVG. RISK	COMPARED TO AVERAGE
Celiac Disease	★★★★	2.7%	0.1%	23.02x
Psoriasis	★★★★	22.4%	11.4%	1.98x
Prostate Cancer ♂	★★★★	28.2%	17.8%	1.58x
Atrial Fibrillation	★★★★	33.9%	27.2%	1.25x
Ulcerative Colitis	★★★★	1.00%	0.77%	1.30x
Parkinson's Disease	★★★★	2.0%	1.6%	1.23x

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Differences of physics and genetics

- Our truth is moving – **no universal truths in biology***
- Our DNA is changing – selection
- Evolution is happening
- Our environment is undergoing substantial changes
- Our biology adapts to the environment to ensure our survival (*and in the craziest ways non-imaginable*)

- *We could be living in a simulation*

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Genomics meets physics

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