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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...

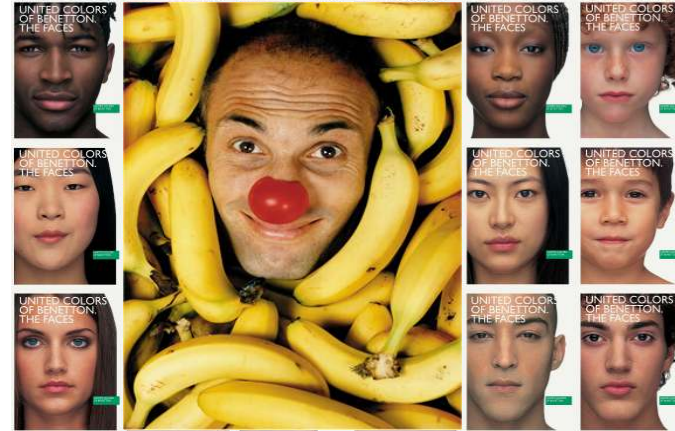


### Problem 1: Genome structure

- **A lot of data:**  $3 \times 10^9$  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 ...

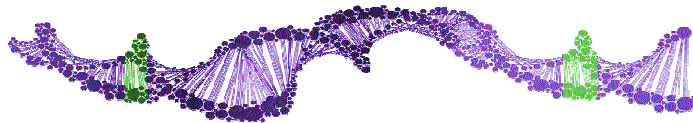
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98% shared by all humans



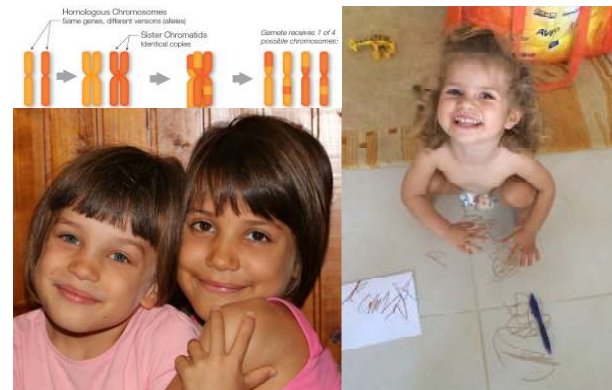
2% of DNA ( $3 \times 10^7$  base pairs)

- 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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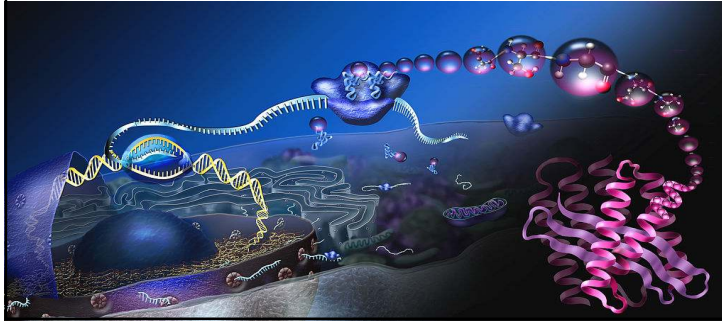
### Meiosis



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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

The Nobel Prize in Physiology or Medicine 1993

Richard J. Roberts, Philip A. Sharp

The Nobel Prize in Physiology or Medicine 1993

Nobel Prize Award Ceremony

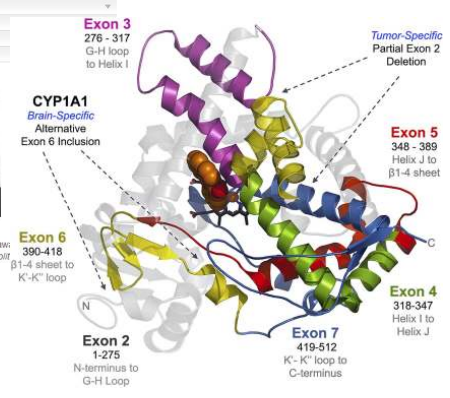
Richard J. Roberts

Philip A. Sharp



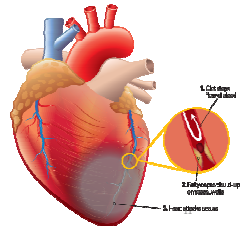
Richard J. Roberts Philip A. Sharp

The Nobel Prize in Physiology or Medicine 1993 was awarded to Roberts and Philip A. Sharp for their discoveries of splicing



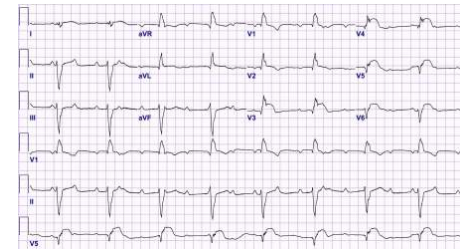
## Problem 2: Difficult phenotypes

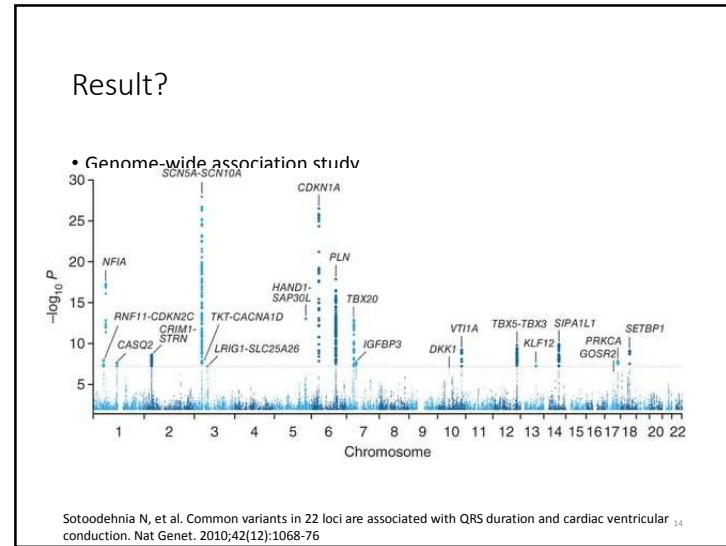
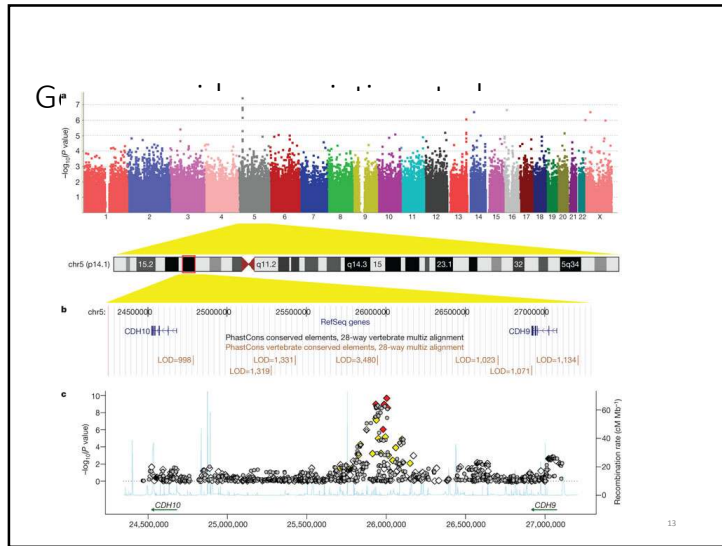
- Many disease occur as the result of numerous reasons
- Myocardial infarction – occlusion of the blood vessel in heart that leads to death of a heart muscle
  - Embolus (blood clot, air bubble)
  - Atherosclerosis (blood vessel hardening)
  - Hyperlipidaemia (elevated lipids)
  - Lack of physical activity
  - 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





### Maximising the possibilities...

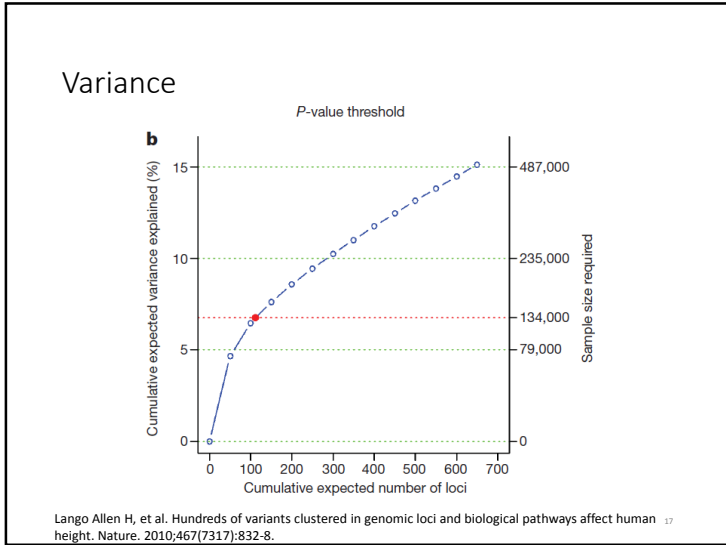
- Use meta-analytic approach and create **global consortia**
- Select a very stable trait
- Maximise sample size
- Height

Napoleon	Barack Obama	Gordon Brown	Dmitry Medvedev	Nicolas Sarkozy	Silvio Berlusconi
5' 6"	6' 1"	5' 11"	5' 4"	5' 5"	5' 5"
1.68m	1.85m	1.80m	1.63m	1.65m	1.65m

### Result?

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

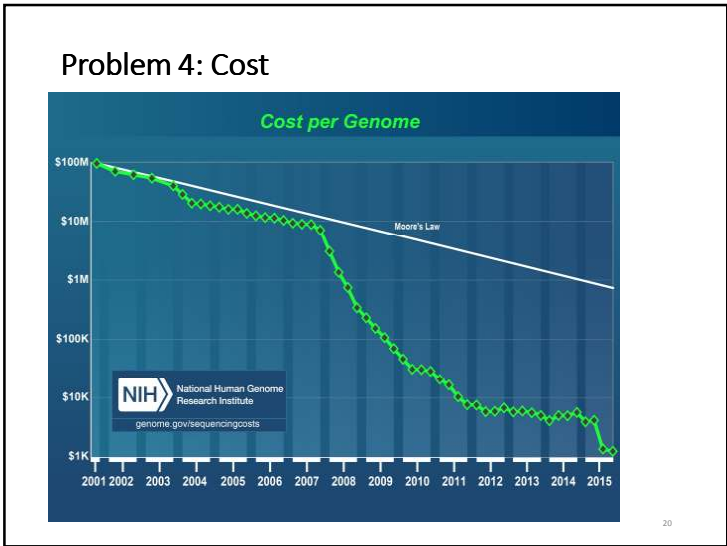
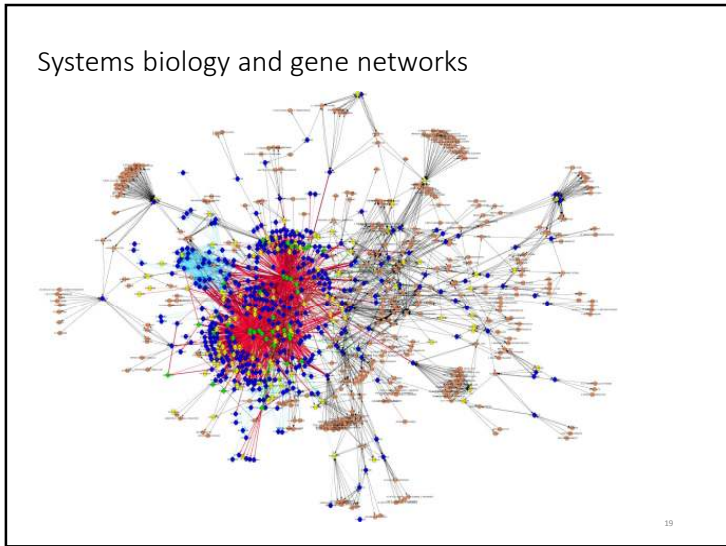
Lango Allen H, et al. Hundreds of variants clustered in genomic loci and biological pathways affect human height. *Nature.* 2010;467(7317):832-8.



### 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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Problem 5:  
People

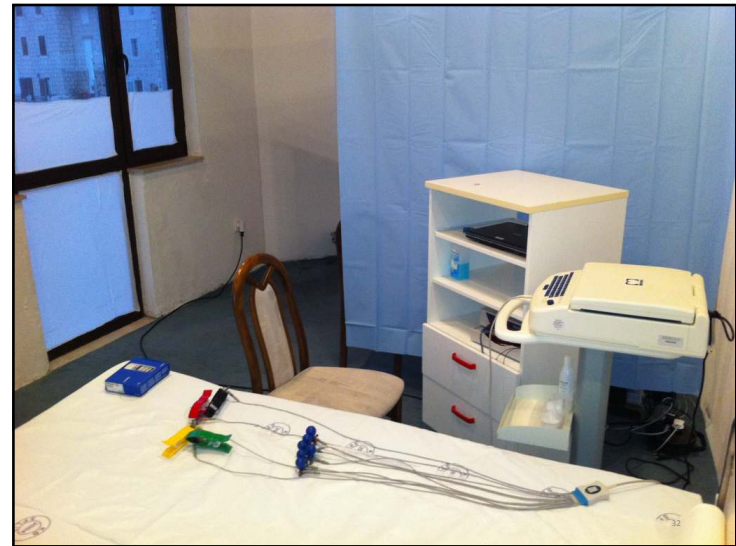
## 10,001 Dalmatians project

- 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

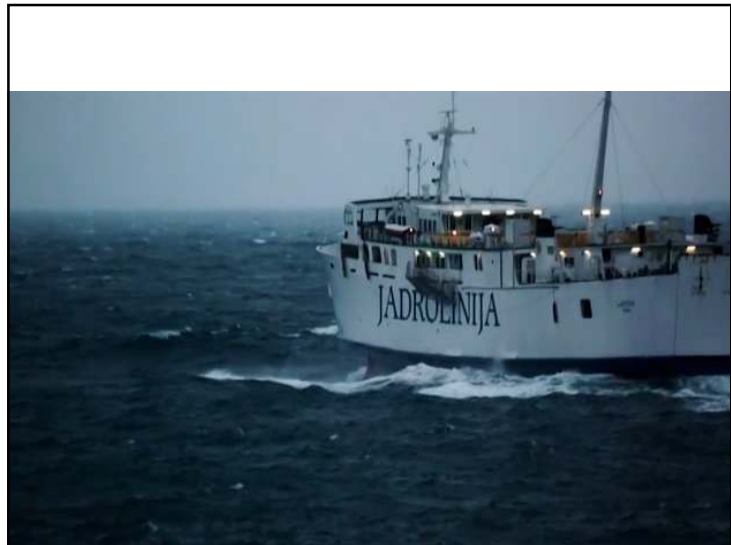
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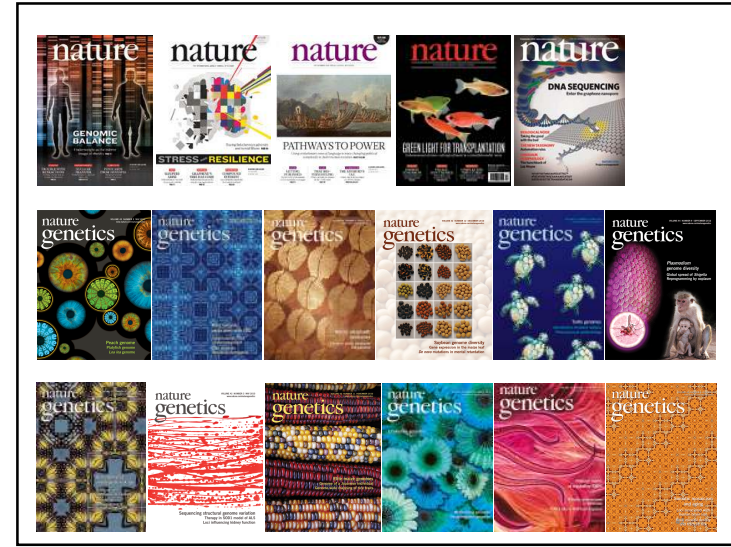












### Height and intelligence

- Taller and more intelligent people – more offspring
- Proof of selection (and evolution) in humans




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

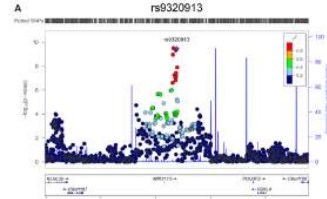
Scienceexpress Reports

#### GWAS of 126,559 Individuals Identifies Genetic Variants Associated with Educational Attainment

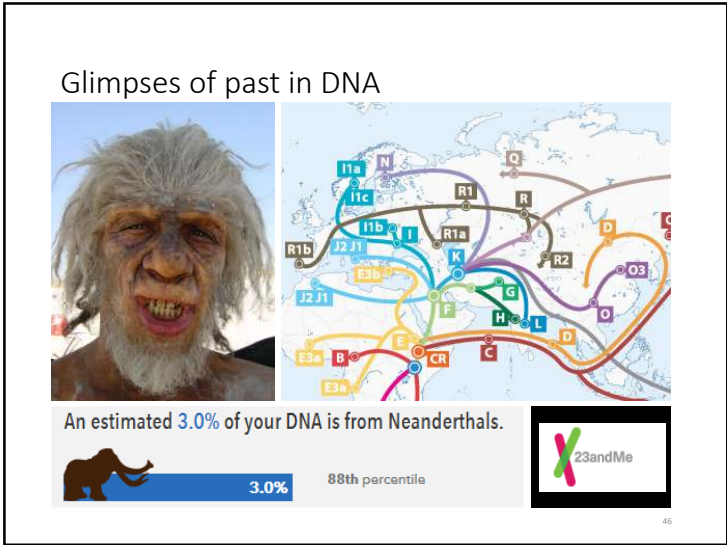
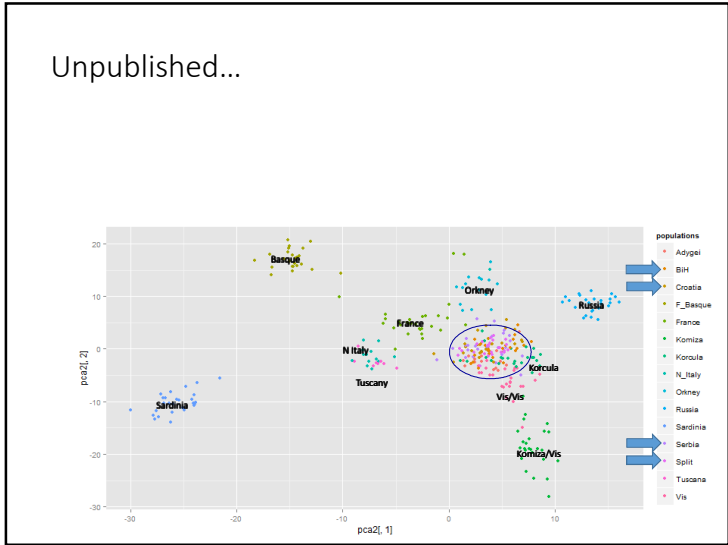
All authors with their affiliations appear at the end of this paper.

A genome-wide association study of educational attainment was conducted in a discovery sample of 101,069 individuals and a replication sample of independent SNPs are genome-wide significant (rs9320913, rs1158, and all three replicates. Estimated effects sizes are small ( $R^2 = 0.02\%$ ), 1 month of schooling per allele. A linear polygenic score from all m accounts for ≈ 2% of the variance in both educational attainment and function. Genes in the region of the loci have previously been associated with health, cognitive, and central nervous system phenotypes, and bioanalyses suggest the involvement of the anterior caudate nucleus. We provide promising candidate SNPs for follow-up work, and our efforts can anchor power analyses in social-science genetics.

used at an age at which subjects were very likely to have completed their education (over 95% of the sample was at least 16 (15). On average, subjects have 13.3 years of schooling, and 23.1% have a college degree. To enable pooling of GWAS results, all studies conducted analyses with data imputed to the HapMap 2 CEU (G23385) reference set. To guard against population stratification, the first four principal



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




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


- 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*


# Genomics meets physics


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SEVENTH FRAMEWORK PROGRAMME

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znanosti  
obrazovanja  
i športa



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