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Genetic diagnostics the gateway to personalized medicine

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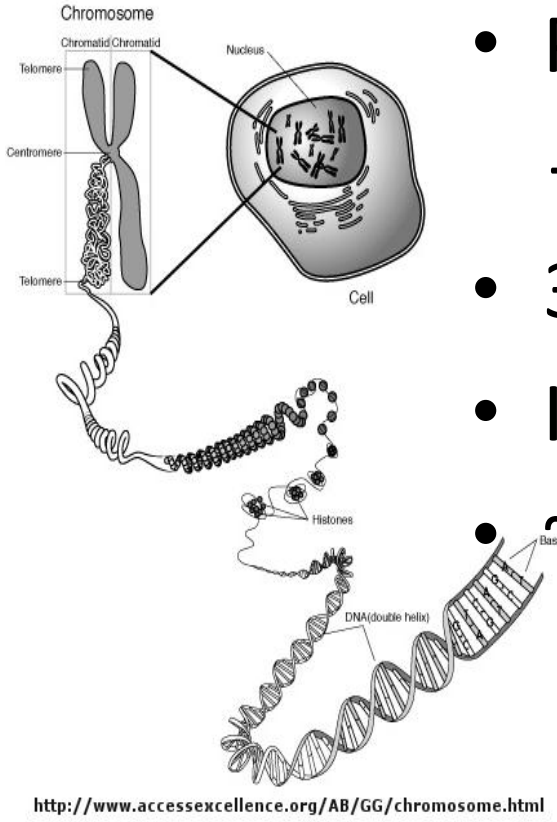
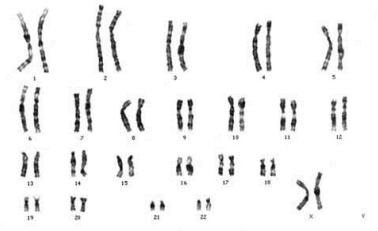
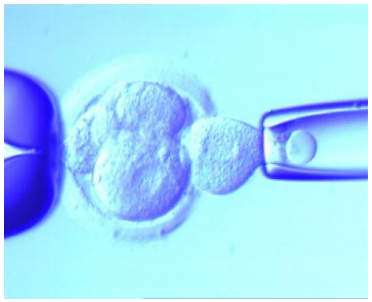
The Human Genome

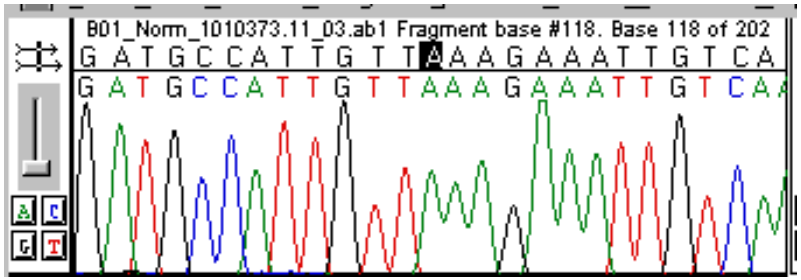


http://www.accessexcellence.org/AB/GG/chromosome.html

- Packed in 46 chromosomes
  + mitochondrial DNA
- 3 000 000 000 bp
- Includes 23 000 genes
- ~ 1% of DNA is protein coding genes





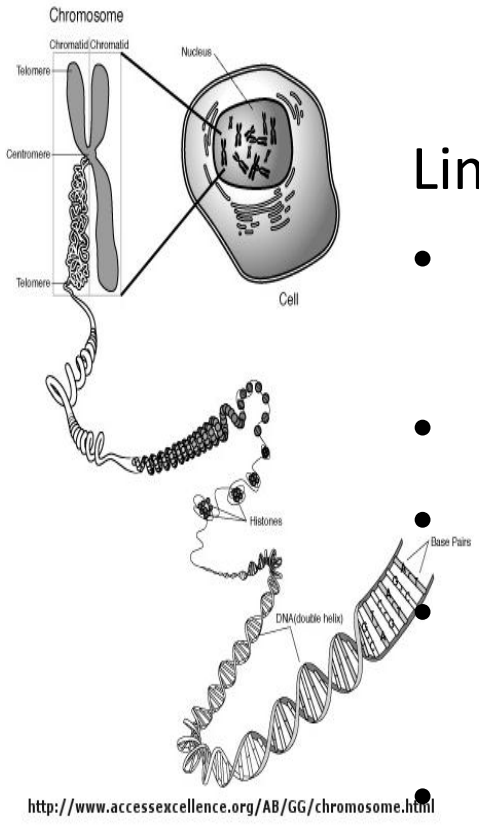


Genetic diagnostics to date

- To date, genetic diagnostics has dealt with inherited diseases and their causative individual genes and mutations
- Clinically important as there are some 7000 inherited diseases (genetic background known in detail in ~50%)

- Confirmation of diagnosis
- Information on prognosis
- Genetic testing of (unaffected) family members
- Prenatal testing and PGD
- **Molecular genetic diagnosis is an integral part of present day medicine**

Genetic diagnostics to date



Limitations of present day diagnostics:

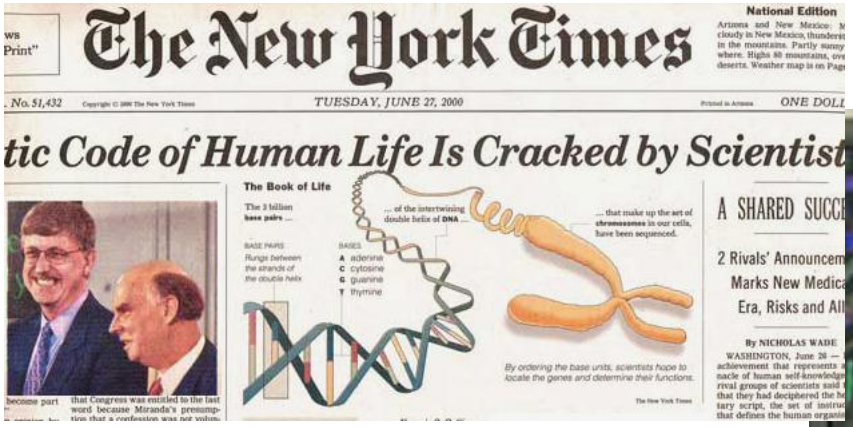
- time consuming, not always available when needed for clinical purposes
- High cost, not used as often as desirable
- Through-put limitations (one gene at a time)
- Diagnostic yield low in some diseases

  Of note!

- Human diseases are greatly heterogeneous
  - common diseases
  - rare inherited disorders (Retinistis pigmentosa, RP, all modes of inheritance with ~ 50 genes)

Human DNA sequence

(Collins & Venter 2001)


The New York Times

National Edition

TUESDAY, JUNE 27, 2000

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tic Code of Human Life Is Cracked by Scientist

The Book of Life

A SHARED SUCCE

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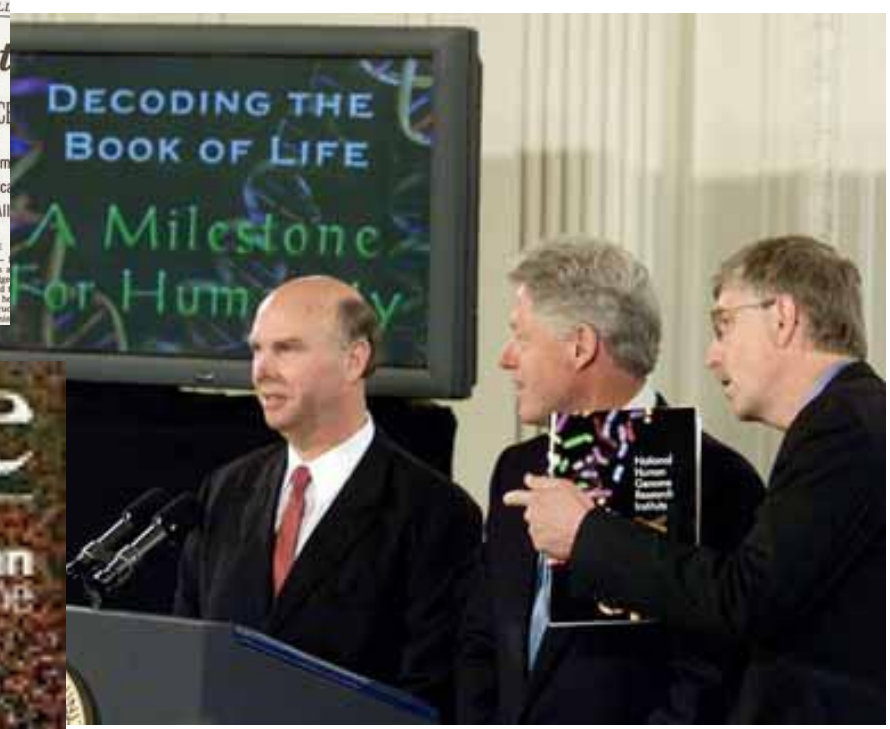
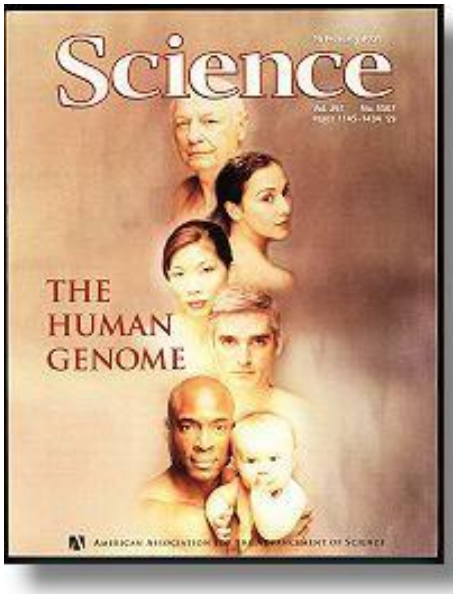
By NICHOLAS WADE





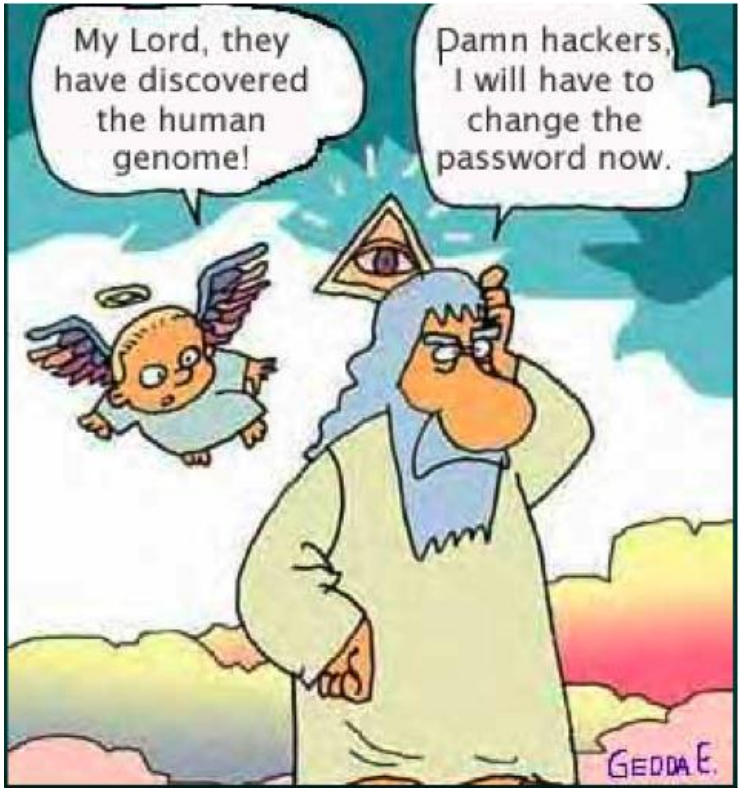
Two major developments

- The Human Genome Project
  Joint effort to decipher the sequence of the Human Genome
  - took 13 yrs
  - cost 2.7 billion $

- 4 years later new methodology

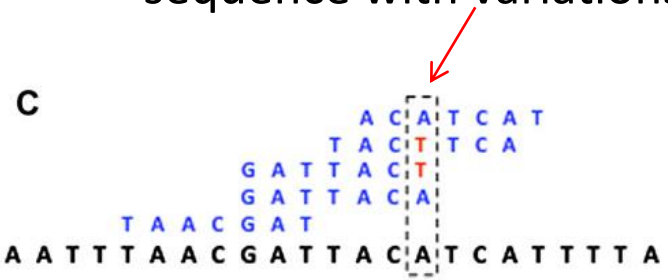
for DNA sequencing Next Generation Sequencing (NGS) became available

Today, the sequensing of the entire human genome in few days, < 10 000 $

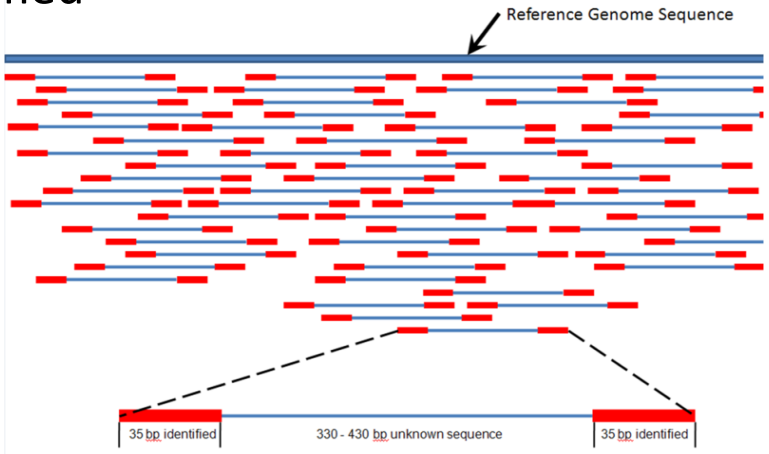


Next Generation Sequencing

- High-throughput methodology, where short reads of sequence are produced simultaenously in parallel
- In ultra-high-throughput sequencing as many as 500,000 sequencing-by-synthesis operations may be run in parallel
- The sequence capacity can be used to study large sequences of one DNA sample or divided to sequence fewer genes from many samples
- The short reads are bioinformatically aligned with reference sequence with variations identified

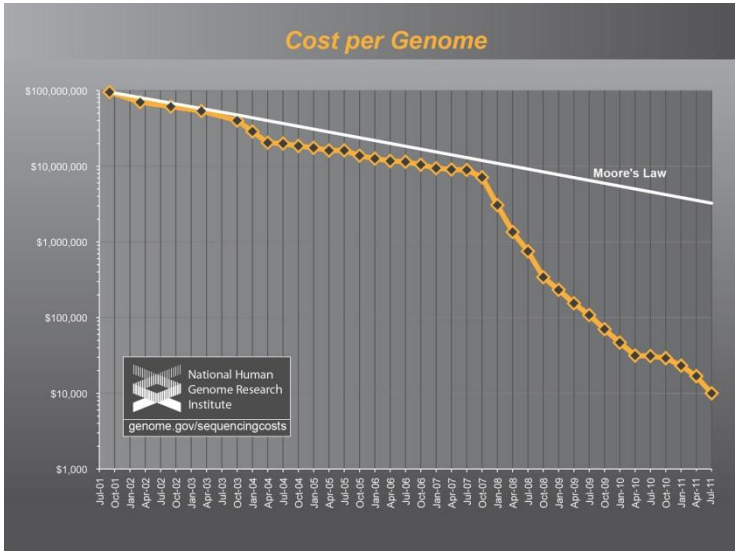


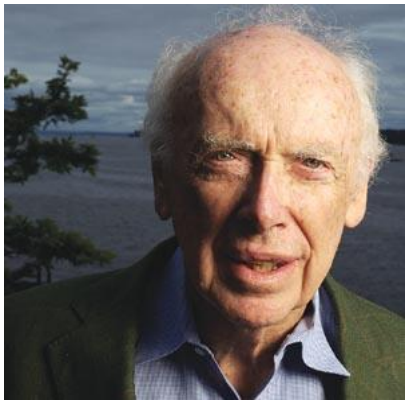
Each sequence fragment is bioinformatically aligned to the genome, and potential sequence variants identified. Here we see a possible heterozygous A>T single nucleotide polymorphism



Next Generation Sequencing

- Sequencing of entire genomes affordable
- Data of the variation in human genome collected
- Exome sequencing to clinical use

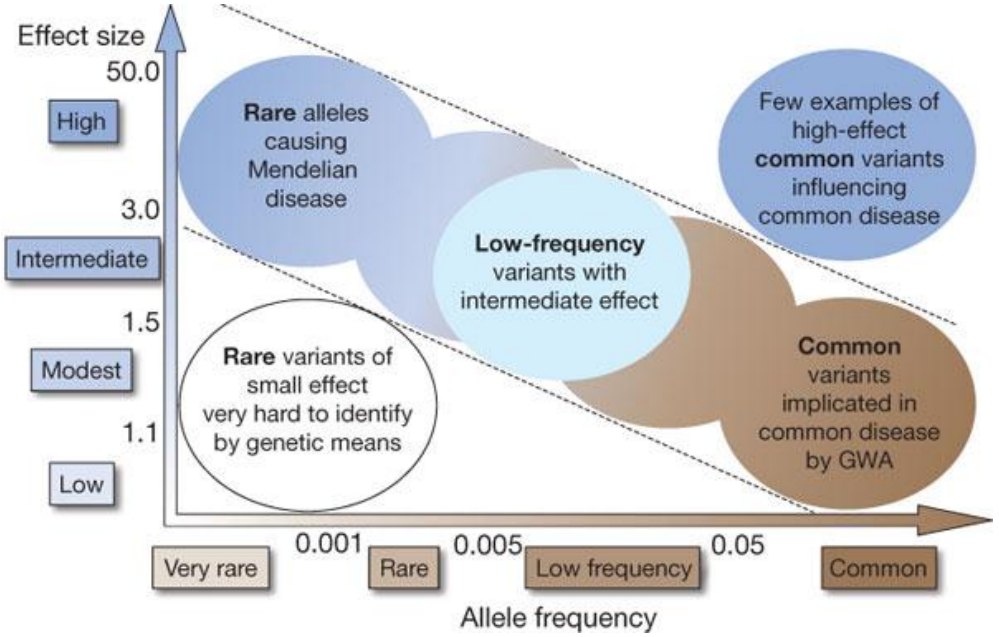




The genomes of Watson and Kriek sequenced!

NGS in diagnosis of inherited diseases

- Entirely new approach!
- Significantly cheaper and faster than classical Sanger sequencing
- Genetically heterogeneous diseases can be studied by sequencing target regions including all relevant genes or
- Exome sequencing and analysing only the genes of interest
- In clinical setting, also patients/families with a disease with unknown genetic background can be studied by exome sequencing with NGS



Genetic variation and disease risk

TA Manolio *et al. Nature* **461**, 747-753 (2009) doi:10.1038/nature084[illegible]

Identification of risk alleles with NGS

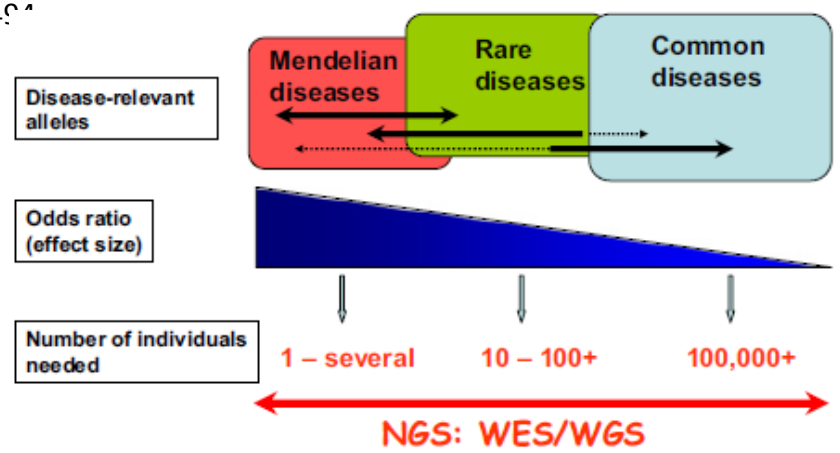


Figure 1 Roadmap for the application of next generation sequencing technologies for the identification of disease-relevant genomic variations.

Towards personalized medicine

- Risk allele identification
  - Personalized risk profiling
  - Enabling preventive measures

Molecular characterization of diseases

- human disesases are heterogeneous in genetic background
- different backgrounds respond to different treatments
- in cancer genetics certain cancers with specific mutations are resistant to first-line treatments
  - the cancer will not respond to treatment
  - the patient is exposed to development of serious side-effets
- molecular characterization of diseases will allow the development of most effetive treatment while avoiding unnecessary side-effects

Towards personalized medicine

- Risk allele identification
  - Personalized risk profiling
  - Enabling preventive measures
- Molecular characterization of the disease
  - Specific treatment for specific molecular background

Pharmacogenetics

- Pharmacological agents have complex metabolism within the cell
- Pharmacodynamics is determined by genetic variation
  - quick metabolizers, slow metabolizers
  - side-effects
    - statin myopathy, SLCO1B1 allelle 18% vs 0.6% risk
- We need genetic information before prescribing treatment to ensure effective treatment and to avoid side-effects

Towards personalized medicine

- Risk allele identification
  - Personalized risk profiling
  - Enable preventive measures
- Molecular characterization of the disease
  - Specific treatments to specific disease
- Pharmacogenetic profiling
  - Personalized, effective treatmer
  - Avoid untoward side effects
- Cost-effective treatment

NGS challenges

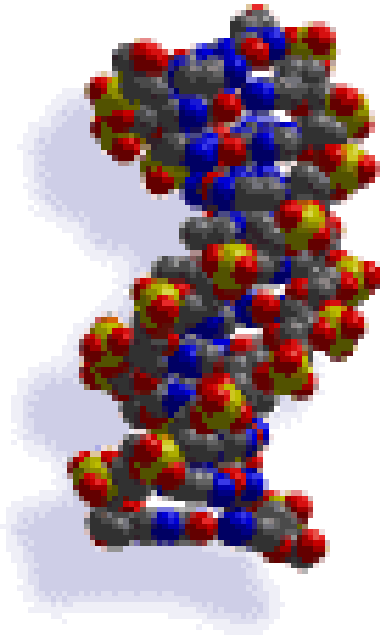
- NGS produces enormous amounts of genetic data
  - To analyze this data, better and faster software is needed
  - Specialists in bioinformatics, statistics, genetic epidemiology are needed
- Human genome includes more variation than anticipated
  - Comprehensive databases with annotation of known variants are essential
  - Effective methods to determine the nature of identified variants
- Large amounts of data are produced
  - Where, how and how long is this data stored?
  - Who can access the stored data?
  - Can we ensure privacy of genetic information?

New genomics has the potential to change medicine

- Investment to develop the targeted treatments required
- Disease backgrounds may very in different populations, need to provide the relevant information for Finland
- Personalized, targeted treatments may require a change from mass production of pharmaceutical agents to smaller subgroups of targeted treatment regimens
- This approach is likely to be more expensive, but less money is lost in uneffective treatments and untoward side-effects
- None of this will take place, unless people decide to be tested

Genetic discrimination

- Is there a threat for genetic discrimination?
- If so, people will not want to be tested in fear of
  - difficulties in employment
  - difficulties in getting insured
  - having to pay higher premiums
  - not receiving best of care, if not insured
  - Shadowing the life of their children with genetic information
- Must be ensured that this will not happen!



NGS and the new genomics open entirely new avenues to genetic diagnostics and development of personalized medicine!

Much effort is still needed to use this information for the benefit of an individual patient!

Thank you!