



# Special Topics on Genetics

## Section 1: Introduction to genomics

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Ευρωπαϊκή Ένωση  
Ευρωπαϊκό Κοινωνικό Ταμείο



ΥΠΟΥΡΓΕΙΟ ΠΑΙΔΕΙΑΣ & ΘΡΗΣΚΕΥΜΑΤΩΝ, ΠΟΛΙΤΙΣΜΟΥ & ΑΘΛΗΤΙΣΜΟΥ  
ΕΙΔΙΚΗ ΥΠΗΡΕΣΙΑ ΔΙΑΧΕΙΡΙΣΗΣ

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# Funding

- The offered educational material has been developed as part of the educational work of the Instructor.
- The project "Open Academic Courses at Aristotle University of Thessaloniki" has financially supported only the reorganization of the educational material.
- The project is implemented under the Operational Program "Education and Lifelong Learning" and is co-funded by the European Union (European Social Fund) and national resources.



# Section Contents

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- Introduction
- Terminology
- Model organisms
- The increase of genome data
- A new era for genomics and human studies
- Examples of large genome studies



# Introduction (1/4)

## Three basic discoveries gave impetus to genetics:

- Mendel (1860): Discovery of the fundamental laws of heredity
- Watson & Crick (1953): Determination of DNA structure
- Human Genome Project (1986-2003...): Decoding the human genome

[http://www.youtube.com/watch?feature=player\\_embedded&v=TwXXgEz9o4w#!](http://www.youtube.com/watch?feature=player_embedded&v=TwXXgEz9o4w#!)



# Introduction (2/4)

## Chromosomal Theory of Inheritance (1857-1865)

- G. Mendel studied the inheritance of characteristics in pea
- The laws of heredity or laws of Mendel laid the foundations of genetics



Figure 2: Peas in pods



# Introduction (3/4)

## Watson, Crick & Wilkins

Saturday 7 March 1953

Three publications - Nature, issue of April 25, 1953 –  
The model for the secondary structure of the DNA molecule was suggested

1962 - Nobel Prize for the  
discovery of DNA structure



Figure 3: James Watson & Francis Crick



# Introduction (4/4)

## Decoding the human genome (1986-2003)

- The initial aim was to discover its sequence. Was followed by focus on its function in conjunction with the comparison with other **model organisms**
- Two parallel efforts
  - **Public sector:** the US National Institutes of Health (NIH) and the US Department of Energy (DOE) led by **Francis Collins**. The largest part of the program was conducted at universities and research centers in China, France, Germany, Japan, Spain, UK and USA. Its results were published in **Nature** magazine
  - **Private sector:** Celera Corporation under the direction of **Craig Venter**. Its results were published in **Science** magazine



# Terminology (1/7)

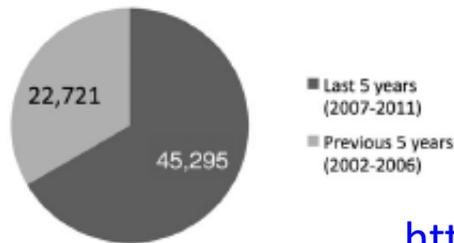
- **Genome**: includes all the information in a (haploid) series from the set of chromosomes found in the nucleus (or outside of it) of each cell of an organism
- The **Human Genome** (for example) includes 24 different chromosomes (22 autosomal chromosomes and the sex chromosomes X and Y) and the mitochondrial DNA, i.e. the human genome contains 25 different DNA macromolecules. – A total of 3.2 Gb ( $3.2 \times 10^9$  base pairs).
- The size of each chromosome ranges ~50-300 Mbp, while
- The size of mitochondrial genome is 16,571 bp



# Terminology (2/7)

- **“Genomics Science”** studies and analyses completed genomes
- The terminology was firstly used in 1986.
- Applies laboratory mapping methods, sequencing analyses, compares results and reaches conclusions
- Computers are required for analyzing large amounts of data generated
- Related Journals: Genome, BMC Genomics, Genome Research, Comparative and Functional Genomics...
- There is a large increase in the number of publications in recent years (genome analysis, bioinformatics)

PubMed MeSH index: Computational Biology



**Figure 4:** The diagram shows the increase in the number of publications in years 2007-2011 Kerfeld (2013). *Biochem Mol Biol Educ* 41, 12-15.

<http://onlinelibrary.wiley.com/doi/10.1002/bmb.20660/pdf>



# Terminology (3/7)

The changes that occur are as large as those of the Agricultural and Industrial Revolution, with applications in:

- **Fundamental research** - Information on cell division, differentiation, growth, reproduction and the diversity within populations
- **Applied research** - Information on new drugs, treatment and prevention of diseases, determination of traits (qualitative and quantitative) with financial interest



# Terminology (4/7)

- **Structural Genomics** - analyse the genome structure (genetic mapping, physical mapping, sequencing). It has grown very rapidly since the start of the genomics era.
- **Functional Genomics** - analyse the function of the genome, i.e.. The phenotype. Includes analysis of all RNAs transcribed in the cell (**transcriptome**) and all proteins coding the genome (**proteome**). It's the next step: "**post-genome era**".



# Terminology (5/7)

- **DNA microarrays (DNA chips)** allow the monitoring of the expression of the entire genome at various developmental stages or different organs or, finally, in response to environmental changes.
- These technologies are believed to give answers on how genes interact with each other and with the environment, in order to produce the final phenotype. This was impossible until now.

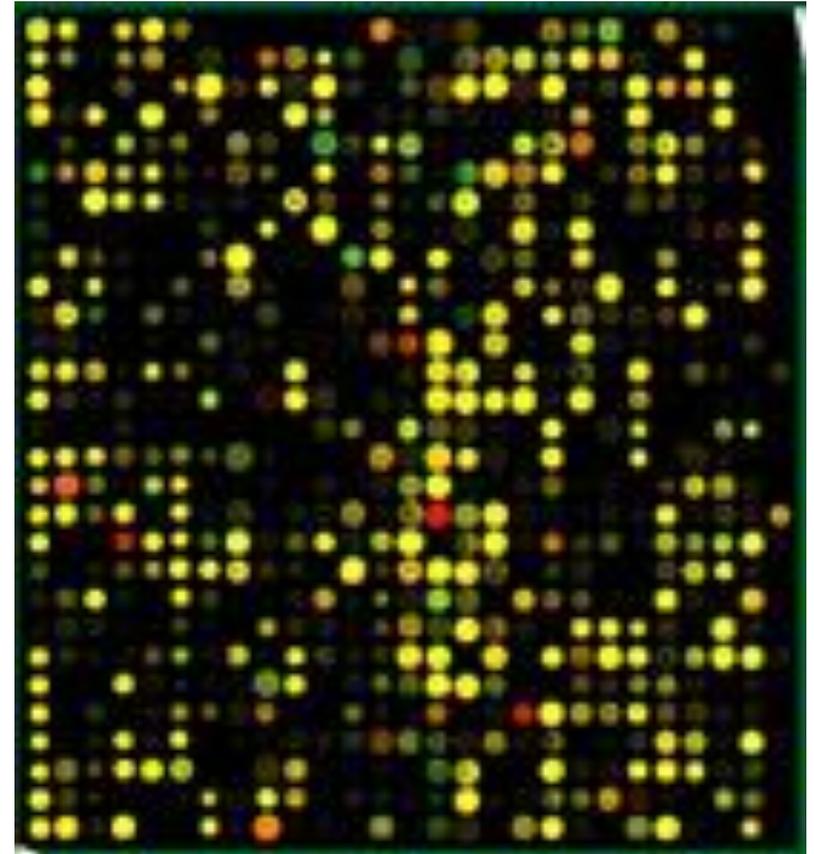


Figure 5: DNA microarray



# Terminology (6/7)

**Proteomics:** Study the expression, the structure, the function and the temporal and spatial placement of proteins, contributing to the study of the phenotype.

**Bioinformatics:** Computational-Algorithmic approaches to the production and processing of information from large biological datasets. **It is among the most important sectors of modern biology.**



# Terminology (7/7)

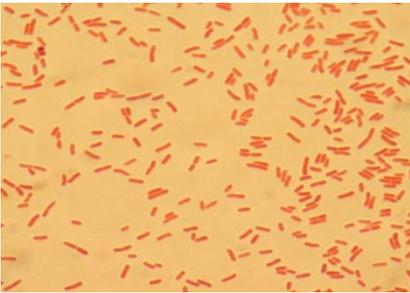
- **Comparative Genomics** – Application of knowledge from one species to other organisms (even evolutionary remote )
- This information is collected on model organisms and has implications on agricultural and medical problems → analysis of the genotype-phenotype relationship



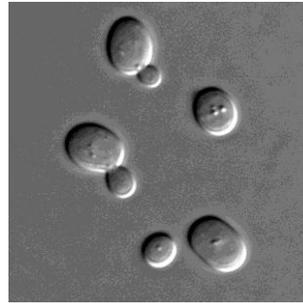
# Model Organisms (1/3)

The first 6 model organisms in which genomic analyses were carried out  
(Figure 6):

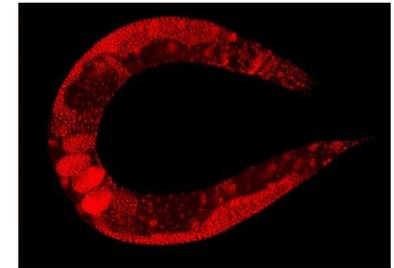
*E. coli*



*S. cerevisiae*



*C. elegans*



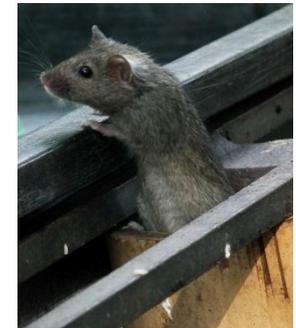
*D. melanogaster*



*A. thaliana*



*M. musculus*



# Model Organisms (2/3)

- They have numerous shared genetic mechanisms and pathways among themselves and with human.
- There are no major ethical problems regarding experiments on them.
- Experiments including controlled intersections and directed modification of genetic material are not considered unethical.
- They were not chosen randomly – They are located at different steps along the evolutionary chain.
- A lot of biological data is already available since they have been studied for many years.



# Model Organisms (3/3)

## First Sequencing Projects

Organism	# of Genes	% of genes with known function	Completion date
<i>E. coli</i>	4,288	60	1997
<i>S. cerevisiae</i>	6,600	40	1996
<i>C. elegans</i>	20,000	40	1998
<i>Drosophila</i>	15,000	25	1999
<i>Arabidopsis</i>	25,000	40	2000
Mouse	~30,000	20	2002
Human	~30,000	20	2001/4



# The increase of data (1/2)

1976/79: First viral genome – MS2/fX174

1995: First prokaryote genome – *H. influenzae*

1996: First genome of single cell eukaryote - Ζύμη

1997: First genome of multicellular eukaryote - *C. elegans*

2001: The human genome ~3Gb

2014: 3141 complete prokaryotic genomes (+ 25000 in progress), + 1700 eukaryotic genomes (only 21 fully completed)

In recent years there has been a rapid increase in the number of both completed and draft genomes published:

(<http://www.ncbi.nlm.nih.gov/genome/browse/>)



# The increase of data (2/2)

- Many sequencing projects are currently in progress
- Archaea, Bacteria: A significant number of genomes have been sequenced and some drafts have been published
- Eukaryotes: a few genomes have been completely sequenced, while a few draft genomes have been published
- Most programs involve the analysis of the genome, while in eukaryotes a considerable number of projects investigate the transcriptomics
- These species specific programs cannot be applied to certain groups of archaea and bacteria, since their culture is difficult

<http://www.ncbi.nlm.nih.gov/genomes/static/gpstat.html>



# A New Era

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- The completion of the HGP signaled the beginning of a new era in Genomics and Proteomics.
- New methods are developed.
- New results are produced.



# New organisms

New organisms are continuously the target of their genome's sequencing. These include: *Guillardia theta*, *Encephalitozoon cuniculi*, *Plasmodium falciparum*, *Schizosaccharomyces pombe*, *Anopheles gambiae*, Chimpanzee, macaque, orangutan, cat, elephant of African savannah, rat, horse, cow, dog, pig (+10 mammals) zebrafish, pufferfish, cod, oats, barley, soybean, rice, wheat, corn, tomato.

The (NHGRI) National Human Genome Research Institute is a pioneer in the analysis of new genomes.

<http://www.genome.gov/>



# Production of data

The table shows the advances in the coverage of different taxonomic classes in archaea and bacteria (see related programs below) and eukaryotes. More effort is needed especially for eukaryote organisms.

Domain	Projects		Phyla		Class		Order		Family		Genus	
	2011	2009	2011	2009	2011	2009	2011	2009	2011	2009	2011	2009
Archaea	327	179	5/5	5/5	10/10	10/10	18/18	18/18	28/29	24/26	96/118	85/109
Percentage coverage			100	100	100	100	100	100	97	92	81	78
Bacteria	8458	4184	32/34	27/29	51/53	45/47	109/118	234/281	254/298	234/281	885/2106	730/1930
Percentage coverage			94	93	100	96	92	83	85	83	42	38
Eukarya	2205	1280	33/57	29/55	93/182	80/188	258/1037	350/6288	458/6689	350/6288	729/54 K	536/48 K
Percentage coverage			58	53	51	43	25	6	7	6	1	1

DOE Joint Genome Institute

- A Genomic Encyclopedia of Bacteria and Archaea

<http://genome.jgi.doe.gov/programs/bacteria-archaea/GEBA.jsf>



# Data storage

**GOLD** (Genomes online database) is an online source that provides comprehensive access to information of genomic and post-genomic sequencing programs and the data generated from these. Its data have increased in recent years at a large rate (October 2014: 58,311 programs)

[http://genomesonline.org/cgi-bin/GOLD/index.cgi?page\\_requested=Statistics](http://genomesonline.org/cgi-bin/GOLD/index.cgi?page_requested=Statistics)

Related publications:

**The Genomes On Line Database (GOLD) in 2009: status of genomic and metagenomic projects and their associated metadata**

Liolios K., *et al.* 2010, *Nucleic Acid Research* , Vol. 38, D346–D354

**The Genomes OnLine Database (GOLD) v.4: status of genomic and metagenomic projects and their associated metadata**

Pagani I., *et al.* 2012, *Nucleic Acid Research* , Vol. 40, D571-D579



# Production of data (1/3)

- ✓ Today data from genomic research are produced in 31 countries worldwide
- ✓ In the following link these countries are shown as well as the number of programs in each of them:

[http://genomesonline.org/cgi-bin/GOLD/index.cgi?page\\_requested=GenomeMap](http://genomesonline.org/cgi-bin/GOLD/index.cgi?page_requested=GenomeMap)

- ✓ USA: The country with the most genomic programs (holds the lead with a difference from the others, > 3,000 programs)
- ✓ Below USA we find the U. K. (~ 250 programs), Japan (~ 200 programs) and France (~ 200 programs)
- ✓ The most significant sequencing centers are: JGI (Joint Genome Institute), JCVI (J. Craig Venter Institute), Broad Institute

[http://genomesonline.org/cgi-bin/GOLD/index.cgi?page\\_requested=Statistics](http://genomesonline.org/cgi-bin/GOLD/index.cgi?page_requested=Statistics)

<http://www.jgi.doe.gov/>

<http://www.jcvi.org/>

<http://www.broadinstitute.org/>

<http://www.hgsc.bcm.tmc.edu/>



# Production of data (2/3)

**Archaea:** The majority of the programs refer to the analysis of the entire genome (92.3%), while in a less percentage to the analysis of transcriptome and resequencing.

**Bacteria:** Programs associated with bacteria mainly include the analysis of the entire genome (96.3%).

**Eukaryotic :** 66.3% of programs for eukaryotes are associated with analysis of the entire genome, 19% with resequencing programs and 12.2% with transcriptome analysis.



# Production of data (3/3)

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## Definitions

Metagenome sequencing programs: programs where the focus is the entire environmental sample including the DNA of all organisms living there without an initial separation of the organisms habiting the environment.

Resequencing programs: Sequencing of additional individuals from a species whose genome has already been obtained from one individual.



# Increase of data / Decrease of prices

- 2000: Publication of the first draft of the human genome  
In the following years data growth is exponential  
<http://www.nature.com/news/2010/100331/pdf/464670a.pdf>
- *Nature* 28/10/10: By the end of 2011 30,000 human genomes have been completed
- New technologies which are constantly being developed, allow sequencing of genomes with increasingly reduced cost  
[http://www.nature.com/nature/journal/v464/n7289/fig\\_tab/464674a\\_F1.html#figure-title](http://www.nature.com/nature/journal/v464/n7289/fig_tab/464674a_F1.html#figure-title)



# Publications on sequencing human genomes (1/2)

- The Diploid Genome Sequence of an Individual Human

<http://www.plosbiology.org/article/fetchObject.action?uri=info%3Adoi%2F10.1371%2Fjournal.pbio.0050254&representation=PDF>

- Accurate whole genome sequencing using reversible terminator chemistry

<http://www.nature.com/nature/journal/v456/n7218/pdf/nature07517.pdf>

- DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome

<http://www.nature.com/nature/journal/v456/n7218/pdf/nature07485.pdf>

- The diploid genome sequence of an Asian individual

<http://www.nature.com/nature/journal/v456/n7218/pdf/nature07484.pdf>



# Publications on sequencing human genomes (2/2)

- Complete Khoisan and Bantu genomes from southern Africa  
<http://www.nature.com/nature/journal/v463/n7283/pdf/nature08795.pdf>
- Illumina sequences DNA of American actress Glenn Close  
<http://www.news-medical.net/news/20100311/Illumina-sequences-DNA-of-American-actress-Glenn-Close.aspx>
- The characterization of Twenty Sequenced Human Genomes  
<http://www.plosgenetics.org/article/fetchObject.action?uri=info%3Adoi%2F10.1371%2Fjournal.pgen.1001111&representation=PDF>
- Sequencing only the exome of the genome  
<http://www.nimblegen.com/>



# 1000 genomes project (1/2)

- It was the first program that its main objective was to sequence the genomes from a large number of humans, thus providing a more complete source of information on human genetic diversity
- An ambitious program that aimed to detect low-frequency mutations associated with susceptibility to diseases
- It became possible thanks to sequencing with new machines and elaborate bioinformatics analysis

<http://www.1000genomes.org/>



# 1000 genomes project (2/2)

Now we definitely know that **we certainly are not perfect ...** <sup>28/10/2010</sup>

Based on scientific evidence

A map of human genome variation from  
population-scale sequencing

The 1000 Genomes Project Consortium

<http://www.nature.com/nature/journal/v467/n7319/full/nature09534.html>



On average, every man carries 250-300 null mutations and 50-100 alleles associated with hereditary diseases



# Publications of sequencing genomes of other organisms

Sequencing programs of genomes were not performed only in humans but also in a number of animals:

- Whole genome sequencing of a single *Bos taurus* animal for single nucleotide polymorphism discovery

Eck *et al.*, 2009, *Genome Biology*, **10**:R82

The genome of a cow

- Drosophila Population Genomics Project

The genomes of 50 Drosophila

<http://www.dpgp.org/>

- Population Genomics of Parallel Adaptation in Threespine Stickleback using Sequenced RAD Tags

Hohenlohe *et al.* 2010, *PLoS Genetics*, 6(2)

The genome diversity of 45000 SNPs in 100 stickleback fish



# A new era

According to data from GenBank/NCBI:

- ✓ 2000: 8 billion bases deposited
- ✓ April 2011: 126 billion bases deposited



☞ **2013**: Doubling of the NCBI data in less than a year

<http://www.ncbi.nlm.nih.gov/Genbank/genbankstats.htm>

!

Just for 2014 the production target  
of the DOE JGI in America is 68 billion bases

<http://jgi.doe.gov/our-projects/statistics/>



# The increase of data

□ The increase of the deposited data in the last decade is due to the explosive production of data of sequence (previously ... short) read archive (SRA) from next generation sequencing machines (especially in humans).

**We have reached 2 petabases ( $10^{15}$ )**

<http://www.ncbi.nlm.nih.gov/Traces/sra/>

□ On the other hand the production of trace data from first generation sequencing machines has decreased  
(<http://www.ncbi.nlm.nih.gov/Traces/trace.cgi?view=statistics>)  
[http://openi.nlm.nih.gov/detailedresult.php?img=3013722\\_gkq1150f1&req=4](http://openi.nlm.nih.gov/detailedresult.php?img=3013722_gkq1150f1&req=4)

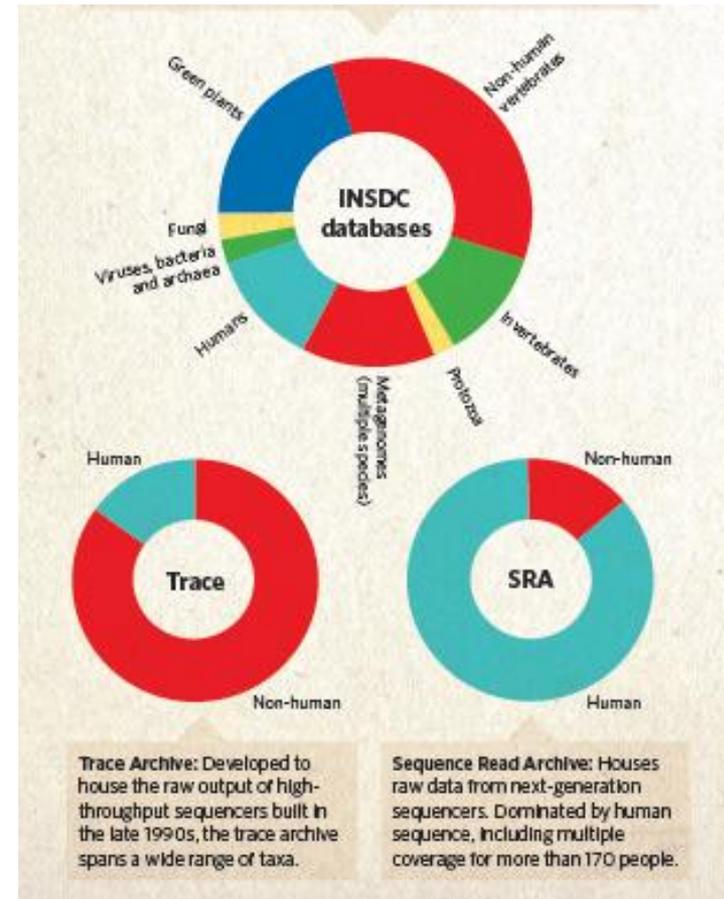


# A new era

Figure 7:

**Trace archive** – data from classic sequencing machines (chromatograms), usually 600 bases long, wherein a DNA segment is read/sequenced once

**Sequence read archive** – data from next generation sequencing machines, with a length from a few tens (previously) to hundreds of bases (today), where a DNA segment is read several times and requires assembling with bioinformatics methods



# The prices fall

- Since 1990 the cost of sequencing of the human genome has dropped  $> 50$  times
- Today  $< 10.000$  \$ required
- In the not too distant future the aim is **1.000 \$ !!!**
- Sequencing only coding regions already costs \$1.000. Costs are related to the resequencing of an available genome

<http://www.genome.gov/sequencingcosts/>



# The future is now

## The 1000\$ genome

15/1/2014

**HiSeq:** Production of 16 Human Genomes / 3 days = 18,000 HG / year 30X coverage, thanks to better packaging of reactions in microprobes, better recording of signal through improved camera, cheaper polymerase

But ... you have to buy 10 such machines = 10 M \$

<http://www.nature.com/news/is-the-1-000-genome-for-real-1.14530>



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**New discoveries have completely  
changed what we' ve known so far**



# A new era

**Widespread RNA and DNA Sequence Differences in the Human Transcriptome**-*Science* May 19 2011 (vol. 333, p. 53-58) <http://www.sciencemag.org/content/333/6038/53.full.pdf>

## RNA-DNA differences (RDDs)

Scientists compared RNA sequences from human B cells of 27 individuals to the corresponding DNA sequences from the same individuals and uncovered more than 10,000 exonic sites where the RNA sequences do not match that of the DNA. All 12 possible categories of discordances were observed.

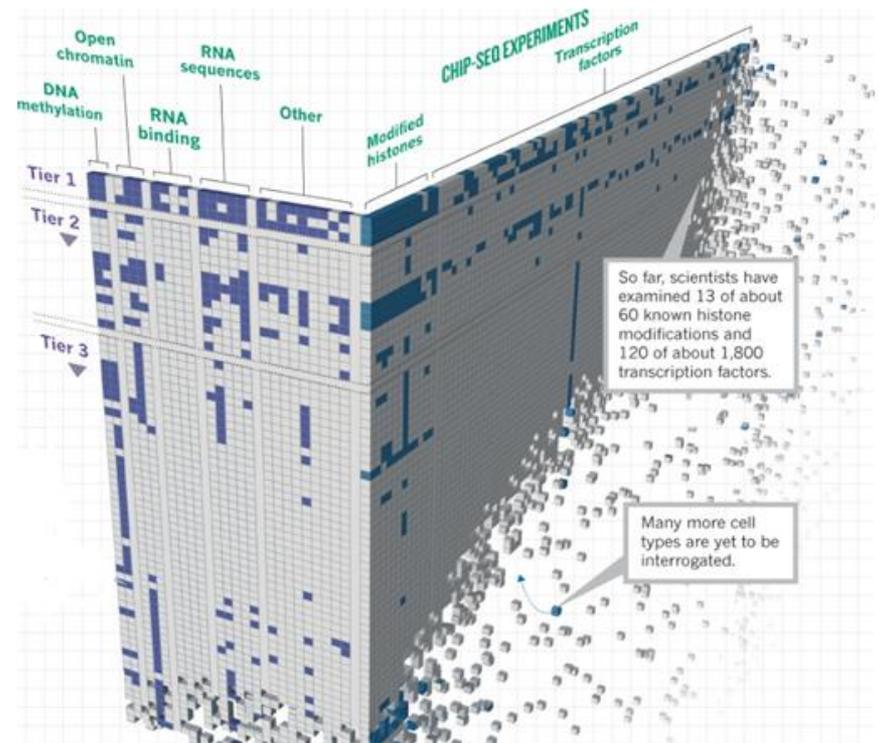
Using mass spectrometry, scientists detected peptides that are translated from the discordant RNA sequences and thus do not correspond exactly to the DNA sequences

But see also ... DOI: 10.1371/journal.pone.0025842



# A new era

6/9/2012- The program **ENCODE** (result of large research efforts of 32 research groups, which simultaneously published 30 scientific papers) studies the regulatory factors which determine the expression of the genome. They found that at least 80% of the genome has some function with >70,000 promoter regions and 400,000 enhancer regions. The genome is transcribed for the most part in non-coding RNA



**Figure 8** shows the effort of ENCODE's researchers in 24 different analyses (along the figure) in 150 different cell lines (from top to bottom). Many analyses are still being processed...

<http://www.nature.com/news/encode-the-human-encyclopaedia-1.11312>



# A new era

**Exonic Transcription Factor Binding Directs Codon Choice and Affects Protein Evolution** *Science* 13 December 2013: Vol. 342 no. 6164 pp. 1325-1326

**Genomes contain two types of genetic code** 1) one that determines the amino acid 2) a regulatory code indicating the binding sites for transcription factors (TF). Analysis of human exome in 81 different cell lines showed that ~15% of human codons are dual-use codons (“**duons**”). These positions are conserved. 17% of mutations in duons affect the binding of transcription factors.



# The genome of Neanderthal

## A Draft Sequence of the Neanderthal Genome

<http://www.sciencemag.org/content/328/5979/710.full.pdf>

<http://www.mpg.de/914714/Neandertal>

Modern humans outside Africa possess ~ 4% of the genome of Neandertal

The history of human expansion is very complex!!

Prufer et al 2014, Meyer et al 2014, Huerta-Sanchez et al. 2014

Richard E. Green *et al.* *Science* 328, 710 (2010)

<http://www.mpg.de/914714/Neandertal>



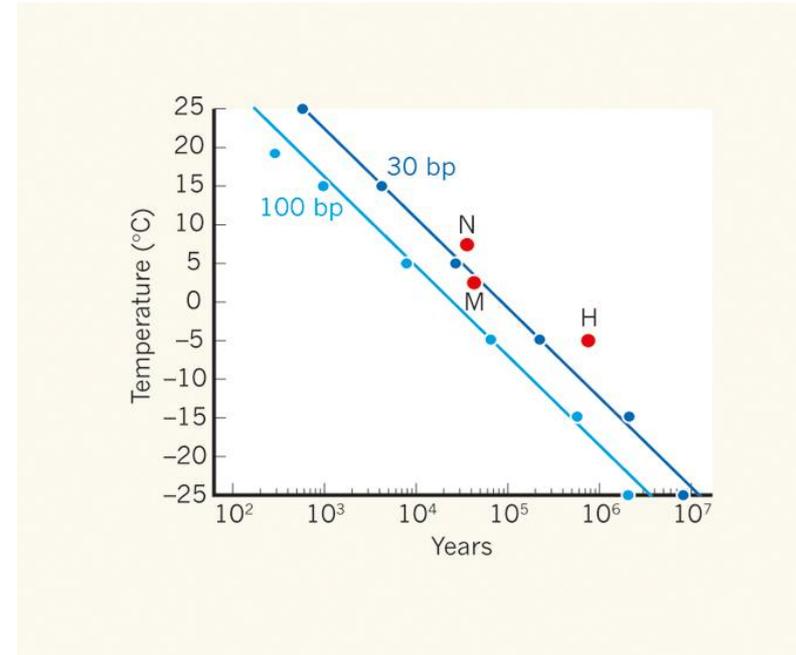
# Publications on sequencing ancient genomes

Recalibrating *Equus* evolution using the genome sequence of an early Middle Pleistocene horse

Nature 499, 34–35 (04 July 2013)

Researchers were able to study the genome from a horse bone of 560-780 thousand years ago!!!

As evident in **Figure 9** the decomposition rate of DNA (into segments of 30 or 100 bases) depends on the storage temperature of the tissue. Reference is made to the published genomes of Neanderthal (N), Mammoth (M) and horse (H).



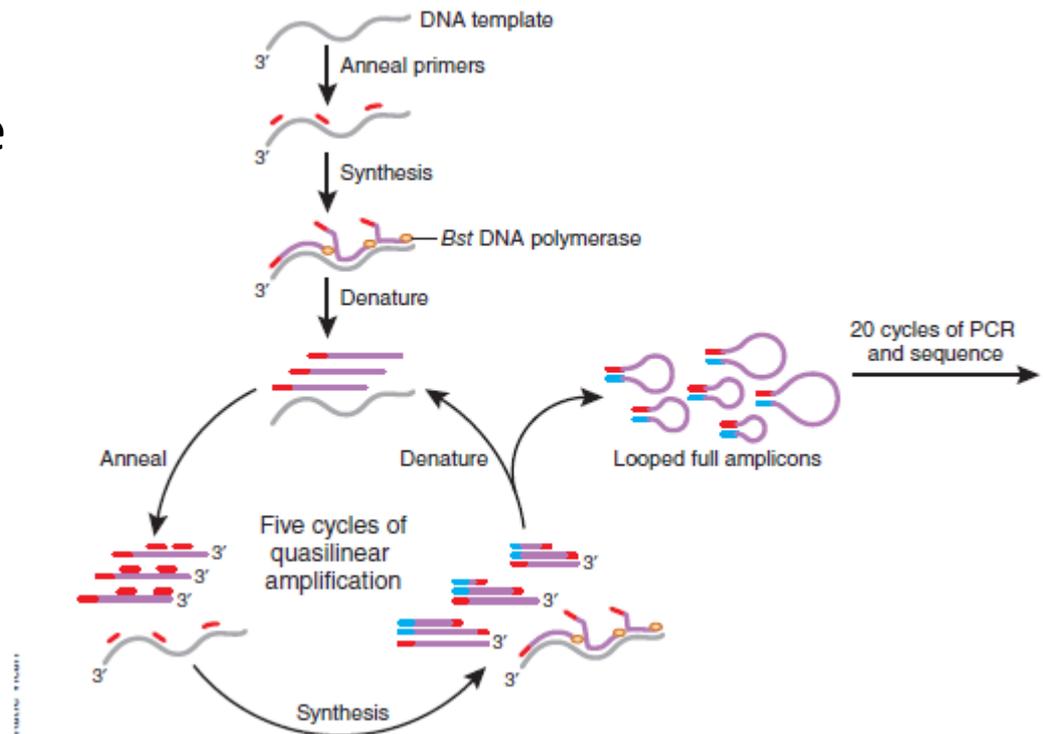
# The genome of a single cell

## Single-cell sequencing in its prime

Lasken R.S., 2013, Nature Biotechnology 31, 211–212

New technologies have allowed the sequencing of the genome of a **single** cell

The methodology used for the sequencing of a single cell. (**Figure 10**)



# Applications with economic and medical interest

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5/7/2013 : Sequencing of the genome of 100,000 British ... until 2017

Ministry of Health NHS – Welcome Trust - Illumina

<http://www.genomicsengland.co.uk/>

<https://www.youtube.com/watch?v=KiQgrK3tge8#t=26>



# Applications with economic and medical interest

Sequencing of 50 different types of cancer

- **ICGC Goal:** To obtain a **comprehensive** description of **genomic, transcriptomic and epigenomic changes** in **50 different tumor types and/or subtypes** which are of clinical and societal importance across the globe

<https://icgc.org/>



# Metagenomics human microbiome analysis program

- HMP (**Human Microbiome Project**): An effort that lasted five years, using metagenomics
- Purpose: The complete characterization of the human microbiota and analysis of its role in human health and diseases
- Allowed the analysis of genetic material collected directly from microbial communities without culturing the microorganisms
- The results showed a correlation between changes in the microbial community composition in the human body and health



# Metagenomics human microbiome analysis program

## Papers which study the human microbiome:

✓ **A human gut microbial gene catalogue established by metagenomic sequencing** Nature, 464, 59-65 (4 March 2010), doi:10.1038/nature08821

- 576.7 Gb sequence, from stool samples of 124 Europeans

- A Gene set 150x of human genes

- Includes ~1000 – 1150 basic species of bacteria

- Everyone has ~ 160 species, many are in common

<http://www.nature.com/nature/journal/v464/n7285/pdf/nature08821.pdf>

✓ **Chimpanzees and humans harbour compositionally similar gut enterotypes**

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3520023/pdf/nihms425633.pdf>

✓ **Genomic variation landscape of the human gut microbiome**

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3536929/pdf/nihms-417625.pdf>



# Genomic services

➤ The GenoGraphic Project

Find out your ancestry with 150,000 markers for \$200

<https://genographic.nationalgeographic.com/>

➤ GenePartner

\$250 for testing HLA genes in order to find the right partner

<http://www.genepartner.com/>

➤ 23andMe

Was prohibited by FDA to provide information on the possible occurrence of hereditary diseases

<https://www.23andme.com/>



# The time of - omics

**Phenome** – complete description of the phenotype (using knockout genes)

**Interactome** – The king of omics - the molecular interaction of all

**Intergrome** – the placement of data in databases easily understandable

**Incidentalome** – genetic data discovered 'accidentally' e.g. 99 common genetic variations related to diseases

**Toxome** – how the body reacts to toxic compounds

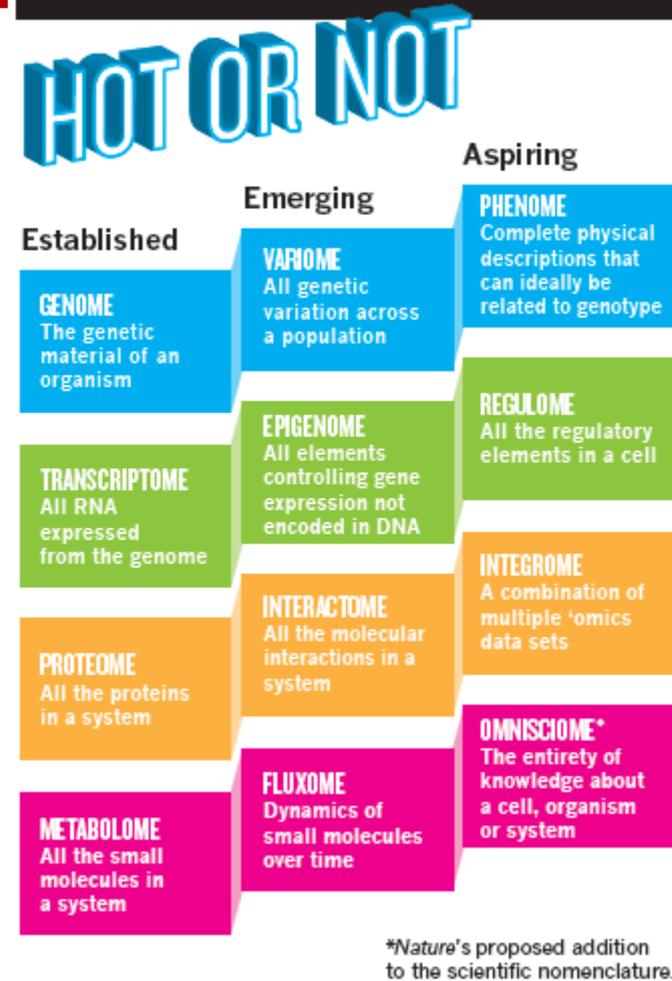


Figure 11: Nature 494, 2013, 416-419



# The future ?

Even the USA Department of Health admits that we should wait until 2020, so we can have a real improvement in health services and increased protection from diseases based on the results of genomics science.

<http://www.nature.com/news/specials/humangenome/index.html>

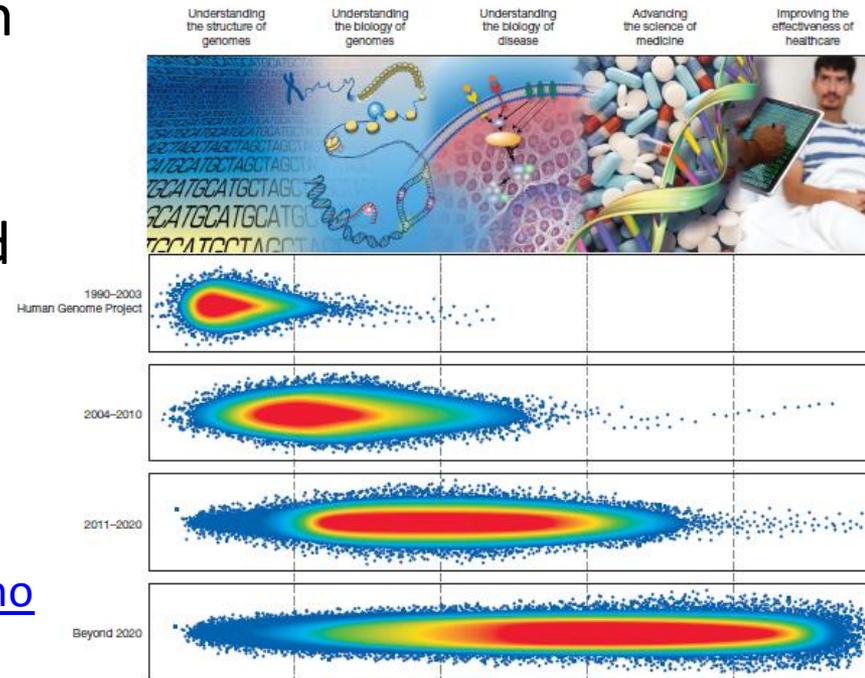
5/9/2013 - genome sequencing and newborn screening disorders

<http://www.genome.gov/27554886>

<http://www.nature.com/news/fast-genetic-sequencing-saves-newborn-lives-1.16027>

<http://www.technologyreview.com/featuredstory/513691/prenatal-dna-sequencing>

Figure 12



# Note of use of third party works

**Peas in pods**, [http://commons.wikimedia.org/wiki/File:Peas\\_in\\_pods\\_-\\_Studio.jpg](http://commons.wikimedia.org/wiki/File:Peas_in_pods_-_Studio.jpg) by Bill Ebbesen, CC-BY-SA-3.0 (creativecommons.org/licenses/by-sa/3.0/gr/), μέσω wikimedia commons

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# Reference note

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Processing: Minoudi Styliani  
Thessaloniki, Winter Semester 2014-2015



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Ευρωπαϊκό Κοινωνικό Ταμείο



ΕΠΙΧΕΙΡΗΣΙΑΚΟ ΠΡΟΓΡΑΜΜΑ  
ΕΚΠΑΙΔΕΥΣΗ ΚΑΙ ΔΙΑ ΒΙΟΥ ΜΑΘΗΣΗ  
*επένδυση στην κοινωνία της γνώσης*

ΥΠΟΥΡΓΕΙΟ ΠΑΙΔΕΙΑΣ & ΘΡΗΣΚΕΥΜΑΤΩΝ, ΠΟΛΙΤΙΣΜΟΥ & ΑΘΛΗΤΙΣΜΟΥ  
ΕΙΔΙΚΗ ΥΠΗΡΕΣΙΑ ΔΙΑΧΕΙΡΙΣΗΣ

Με τη συγχρηματοδότηση της Ελλάδας και της Ευρωπαϊκής Ένωσης



ΕΣΠΑ  
2007-2013  
πρόγραμμα για την ανάπτυξη  
ΕΥΡΩΠΑΪΚΟ ΚΟΙΝΩΝΙΚΟ ΤΑΜΕΙΟ



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