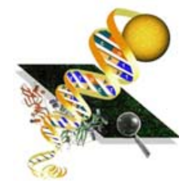
Успехи и перспективы геномных исследований для медицины, сельского и лесного хозяйства



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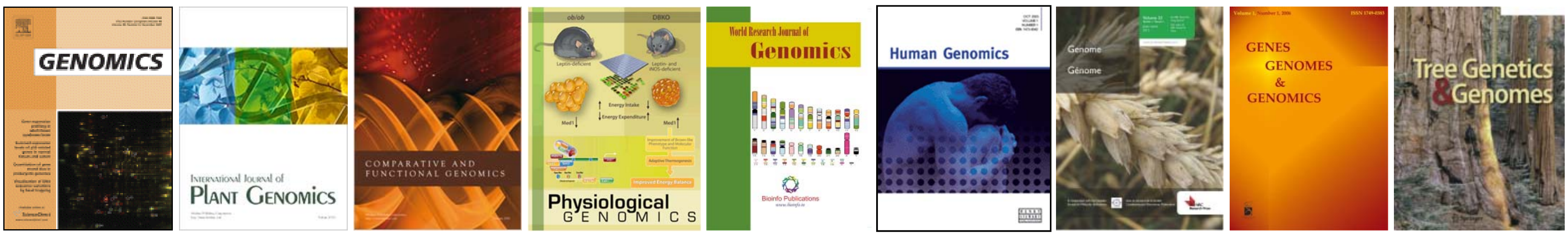
Лекция студентам СФУ 9 июня 2014 г.

Что такое «Геномика»?

- Термин «**геном**» (genome) был предложен немецким ботаником проф. **Hans Winkler** (1877- 1945) в 1920 г. (University of Hamburg), который объединил термины «**ген**» (“**gen**e”) и «хромос**ом**а» (“chromos**ome**”) для обозначения одновременно всех генов во всех хромосомах ядра клетки

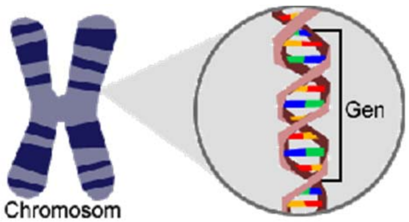
- Термин «**геномика**» (genomics) был предложен относительно недавно в 1986 г. **Thomas Roderick** (Jackson Laboratory, USA) для нового журнала *Genomics* и описания научной дисциплины связанной с секвенированием, картированием и анализом генома



- Геномика более широкое понятие в настоящее время и охватывает сравнение геномов разных видов (**comparative genomics**), их эволюцию (**evolutionary genomics**) и функционирование генома в целом (**functional genomics**)

Геномика – это изучение генов и их функций в их полной совокупности и взаимодействии

Основы геномной структуры

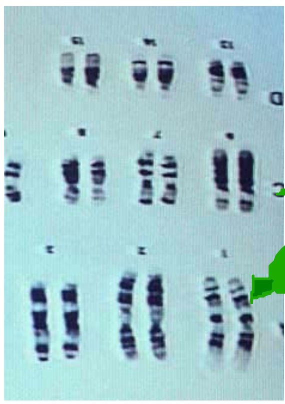


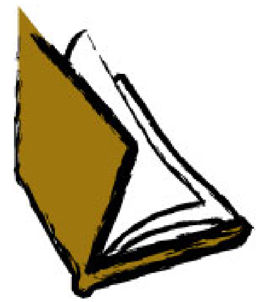
Ген

Строчка в тексте/Предложение
(состоящее из 4-х «букв»-нуклеотидов A, T, C и G, и 3-х буквенных «слов»-триплетов или кодонов)

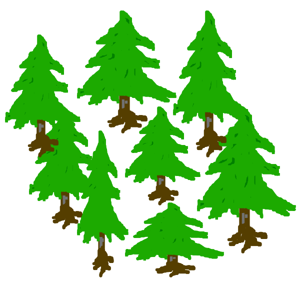
Хромосома

Глава





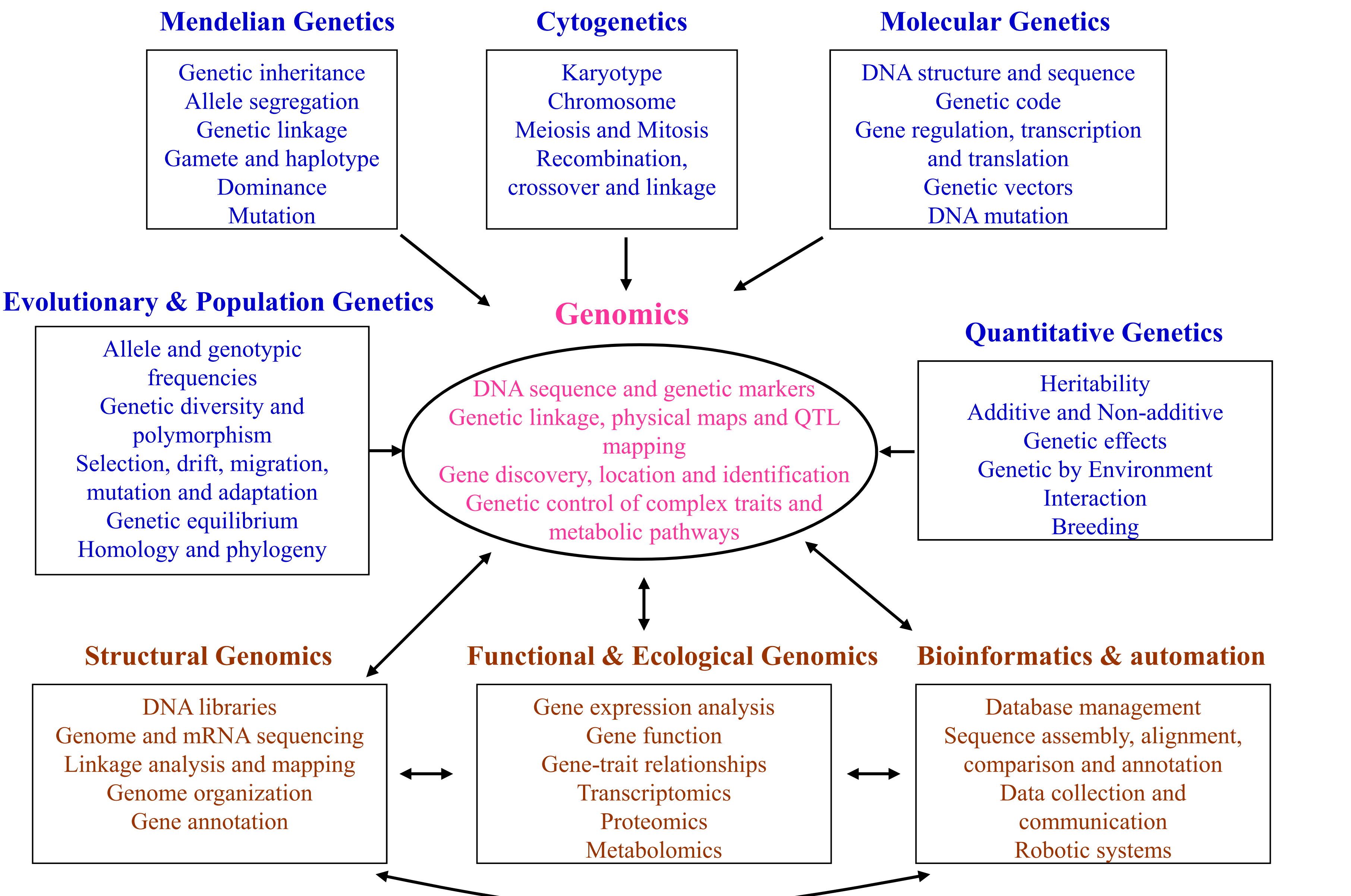
Геном



Генофонд

Основная задача геномики - полное секвенирование и расшифровка генома

Геномика - интеграционная научная дисциплина



Крутовский К.В. 2006. От популяционной генетики к популяционной геномике лесных древесных видов: интегрированный популяционно-геномный подход. *Генетика* Т. 42. №10. С. 1304–1318.

González-Martínez S.C., Krutovsky K.V., Neale D.B. 2006. Forest tree population genomics and adaptive evolution. *New Phytologist* **170**(2): 227-238.

Krutovsky K.V. & D.B. Neale. 2005 Forest genomics and new molecular genetic approaches to measuring and conserving adaptive genetic diversity in forest trees, pp. 369-390 in *Conservation and Management of Forest Genetic Resources in Europe*, edited by Th. Geburek and J. Turok. Arbora Publishers, Zvolen.

Основные разделы геномики

Structural Genomics

- ***DNA libraries and complete genome sequence***
- ***Gene annotation and homology search***
- ***Linkage analysis, genetic and physical mapping***
- ***Development of genome-wide genetic markers***

Functional Genomics

- ***Gene expression analysis*** (*transcriptome & metabolome profiling*)
- ***Gene function, gene-trait*** *and gene-environment* ***relationships***

Comparative & Evolutionary Genomics

- ***Comparative mapping and search for orthology and synteny***
- ***Gene and sequence comparison across different species***
- *Signatures of selection, evolutionary footprints*

Gene discovery

Statistical Genomics

- ***Mapping algorithms and associative analysis***
- ***Database management, data collection and communication***
- ***Sequence assembly, alignment, comparison and annotation***

Population & Ecological Genomics

- ***Genome wide scan for nucleotide diversity***
- ***Genome wide and candidate gene based mapping***
- ***Assessment of association between alleles and phenotypes and environments via association mapping***

Наиболее значительные события в Генетике, приведшие к Геномике

1944: идентификация ДНК как генетического материала для всех живых организмов

1953: расшифровка генетического кода (Watson & Crick, *Nature* 171, 737: 1953).

1977: первый полный сиквенс целого генома бактериофага phiX174; всего только 5386 нуклеотидов, в 60000 раз меньше генома человека (Sanger et al. *Nature* 265, 687: 1970).

mid-1980s: бурное развитие автоматизации и компьютеризации секвенирования

1990: начало проекта полного секвенирования генома человека

1997: полный сиквенс генома дрожжей (~12 Mbp)

1998: нематоды (~97 Mbp)

2000: арабидопсиса (~125 (Mbp)

2000: дрозофилы (~180 Mbp)

2001: человека (~3,200 Mbp)

2002: мыши (~3,500 Mbp) и риса (~420 Mbp)

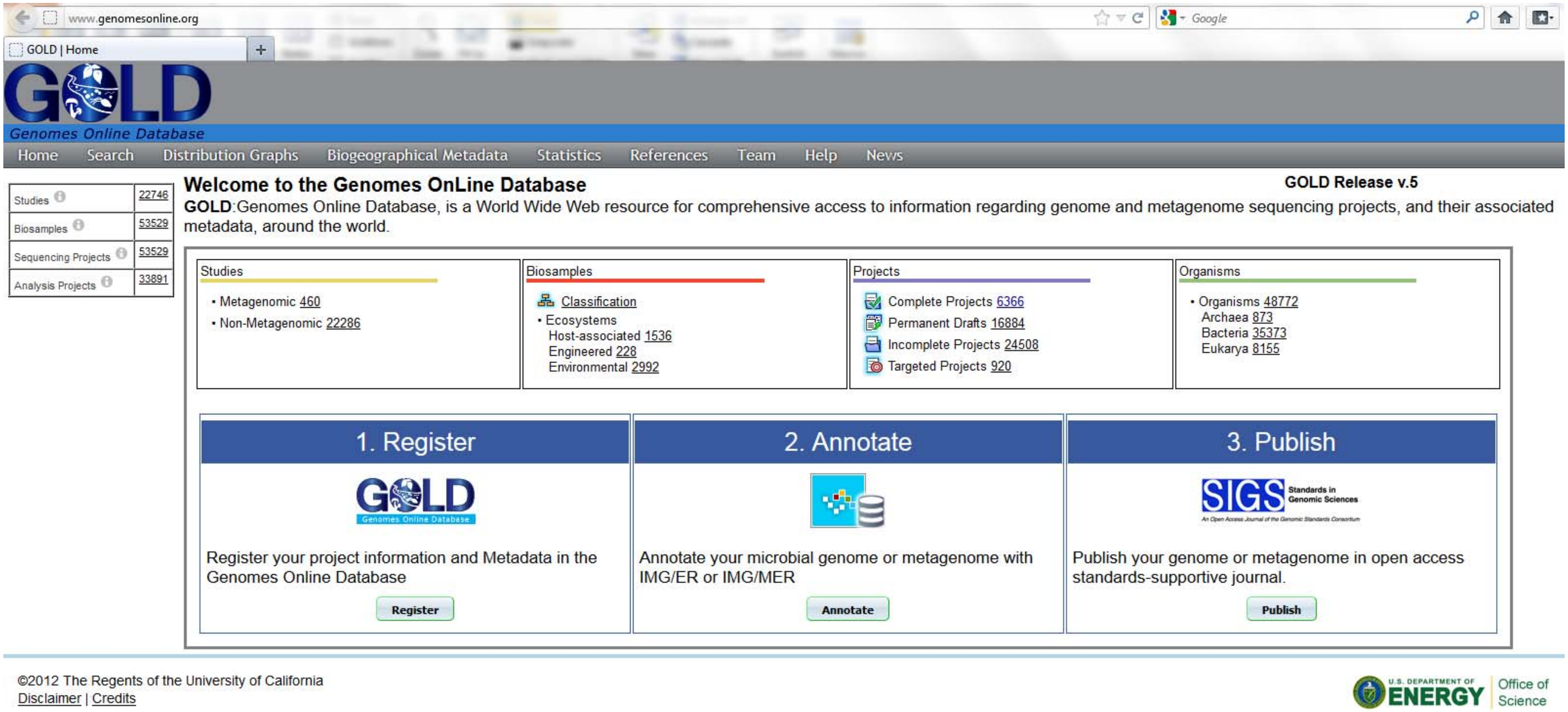
2006: тополя (~550 Mbp)

2008: Новое поколение секвенирующих платформ - **Next generation sequencing** (NGS) platforms - high-throughput massively parallel sequencing

2013: неандертальца (~3,200 Mbp)

2013: ели и 2014: сосны (~20,000 Mbp) 2015: кедр и лиственница?

База данных геномных проектов http://www.genomesonline.org



- Complete Projects 6366
- Permanent Drafts 16884
- Incomplete Projects 24508
- Targeted Projects 920

- Organisms 48772
  Archaea 873
  Bacteria 35373
  Eukarya 8155

Фундаментальная проблема генетики – связь фенотипа с генотипом!

Её можно решить для сложных признаков только изучая изменчивость по совокупности всех генов в геноме

Nature (genome) vs. *Nurture* (environment)

$$P = G + E + G \times E$$

Phenotype = *Genome(Genotype)* + *Environment* + ***Interaction***

Organisms are different because of the:

- **genomic/genetic (*G*) differences among individuals**
- **different environments (*E*) where individuals are growing**
- **and interactions between the genotypes and the environments in which they grow (*G*×*E*)**

Nature (genome) vs. *Nurture* (environment)

Сколько генотипа в фенотипе?

Mendelian traits vs. Complex traits

- Mendelian = Qualitative
  - single gene responsible for most of the observed phenotypic variance

- Complex = Quantitative
  - multiple genes with gene × gene, gene × environment interactions contributing to phenotypic variance

Single vs. Multiple Genes in Population

$$P^n = G^n + E^n + G^n \times E^n$$

n – multiple phenotypes, genes and environments

Great Ferma Theorem : $Z^n = X^n + Y^n$

does not have integer solutions X, Y, Z **for** $n > 2$

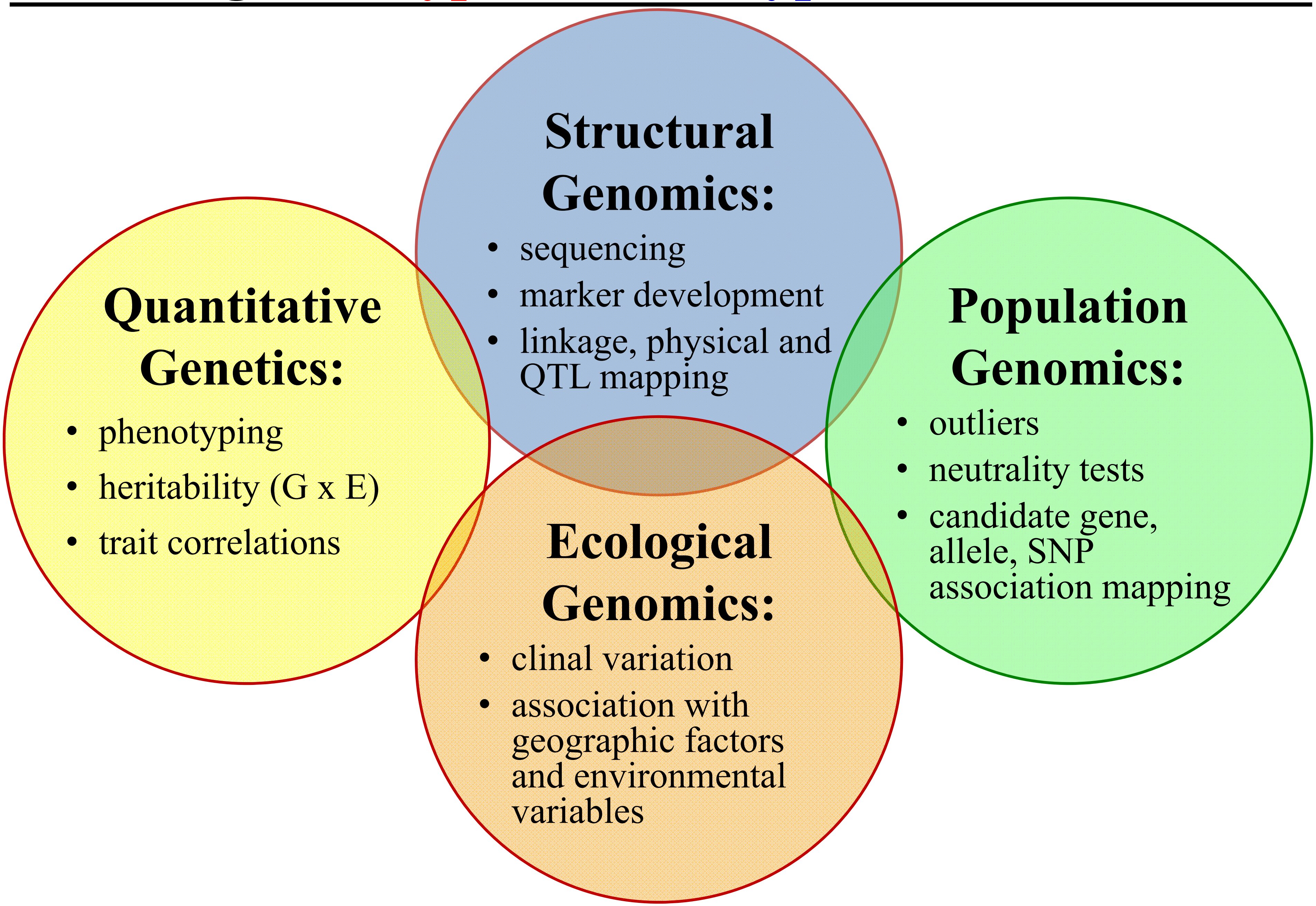
Andrew Wiles, 1994

My Theorem : $P^z = G^x + E^y$

My Great Theorem: $P^z = G^x + E^y + G^x \times E^y$

Геномика – единственное решение!

Linking Genotype to Phenotype & Environment



Nature (genome) vs. *Nurture* (environment)

Nature

Nurture

Phenotypic Expression

?

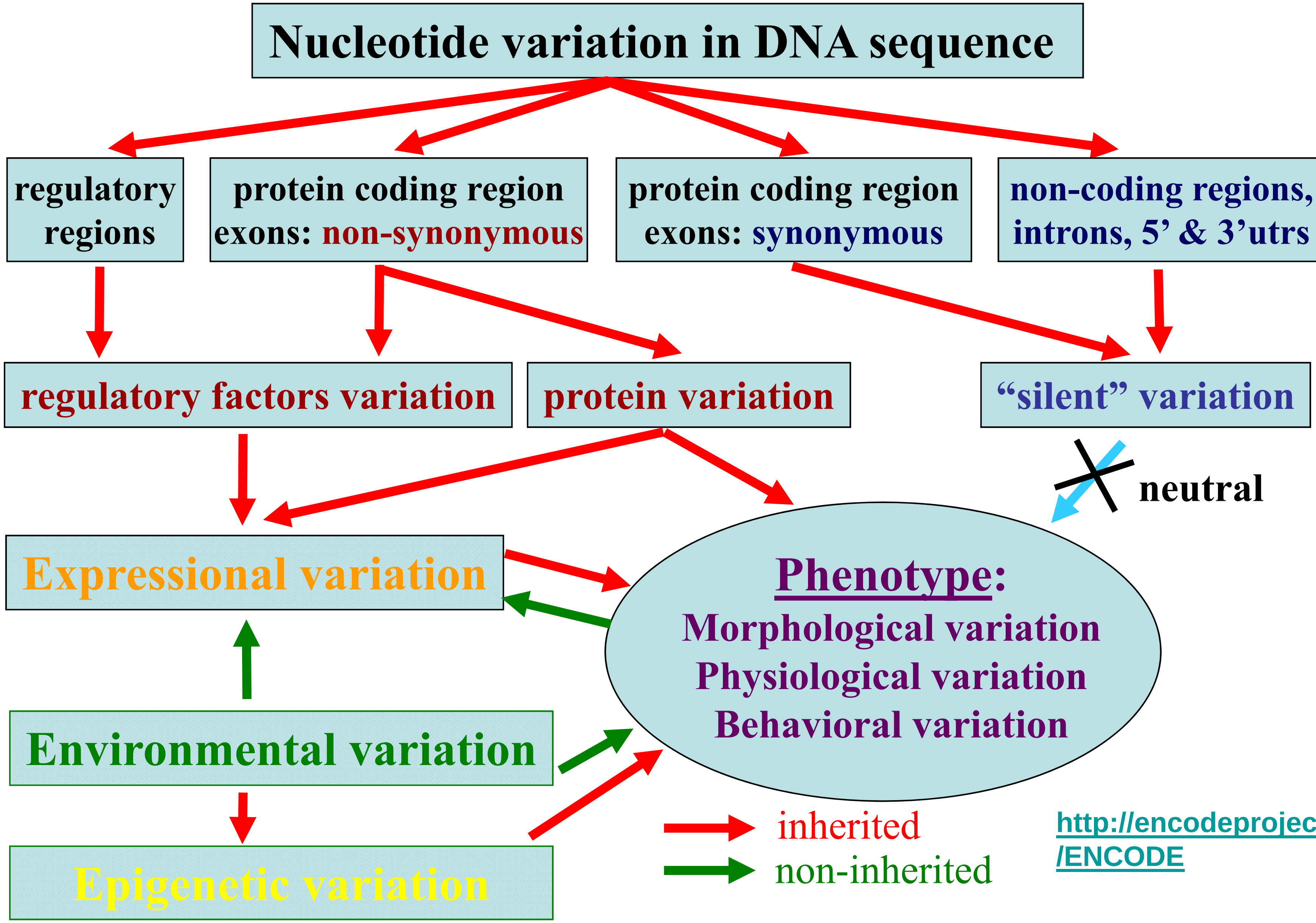
Proteins & Regulatory Factors

Environment

Genome (blueprint)

Я нашел ген, который заставляет нас верить, что все признаки основаны на генах!

Expression of genetic variation



http://encodeproject.org/ENCODE

Как связать сложную фенотипическую изменчивость с генетической?

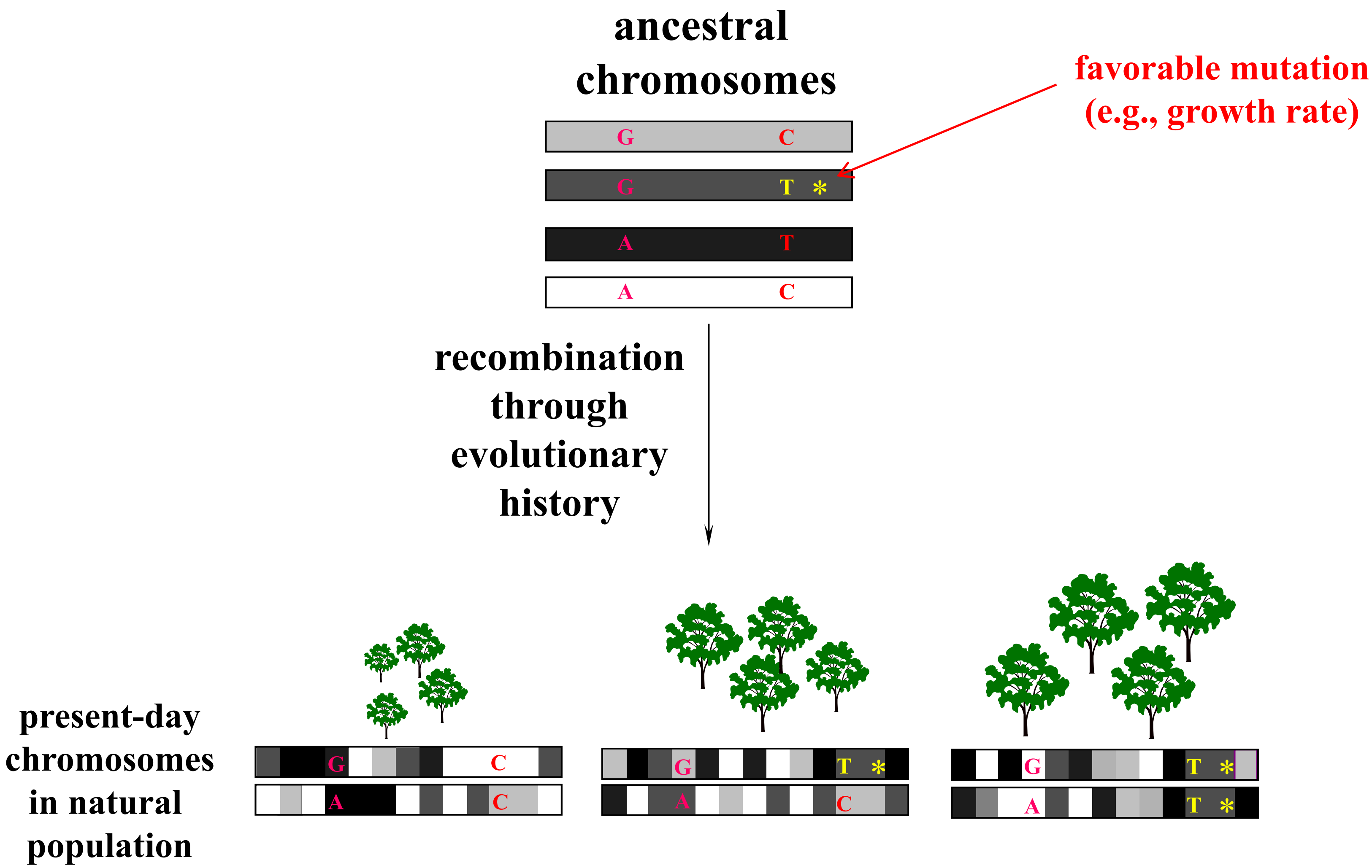
Современные популяционно-геномные подходы:

- **ассоциативное картирование**
- **обнаружение генов-«аутсайдеров» (outliers)**

Крутовский К.В. 2006. От популяционной генетики к популяционной геномике лесных древесных видов: интегрированный популяционно-геномный подход. *Генетика* Т. 42. №10. С. 1304–1318.

González-Martínez S.C., Krutovsky K.V., Neale D.B. 2006. Forest tree population genomics and adaptive evolution. *New Phytologist* **170**(2): 227-238.

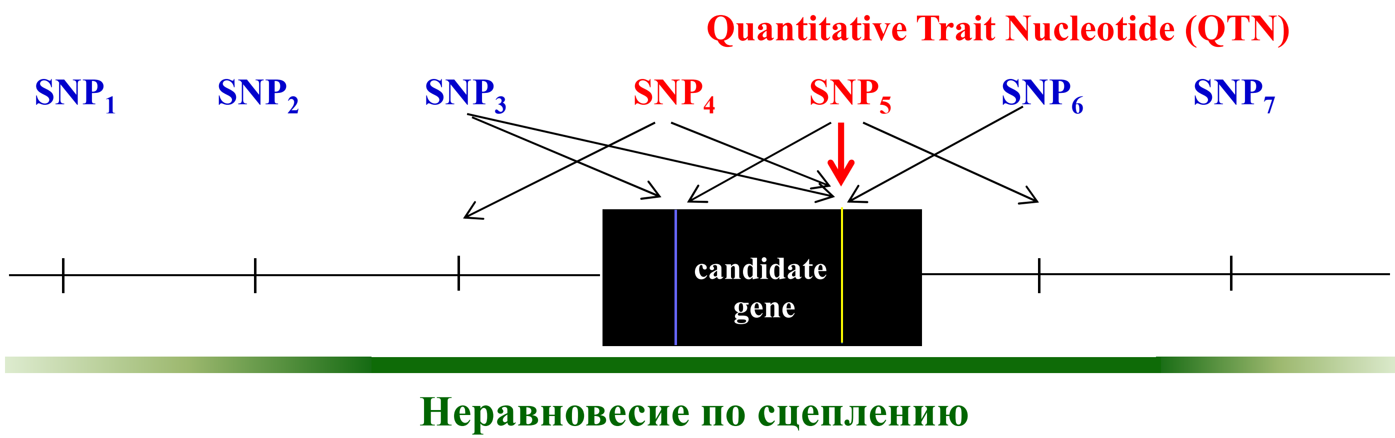
Ассоциативное картирование



Полно-геномное ассоциативное картирование с использованием случайных маркёров (например, «снипов» - SNPs – single nucleotide polymorphisms)

vs.

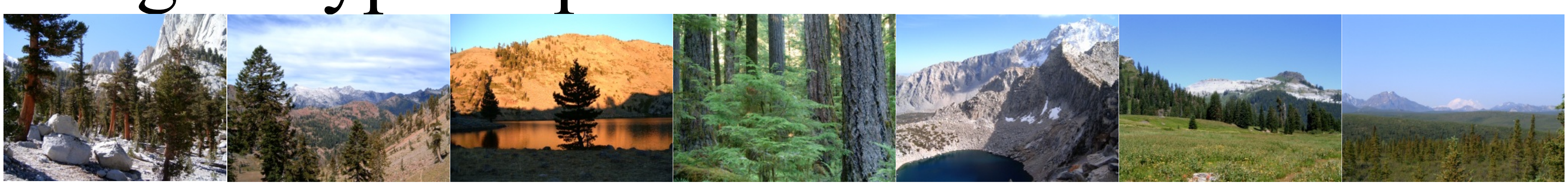
Избирательного ассоциативного картирования, основанного на фунциональных маркёрах в генах-кандидатах



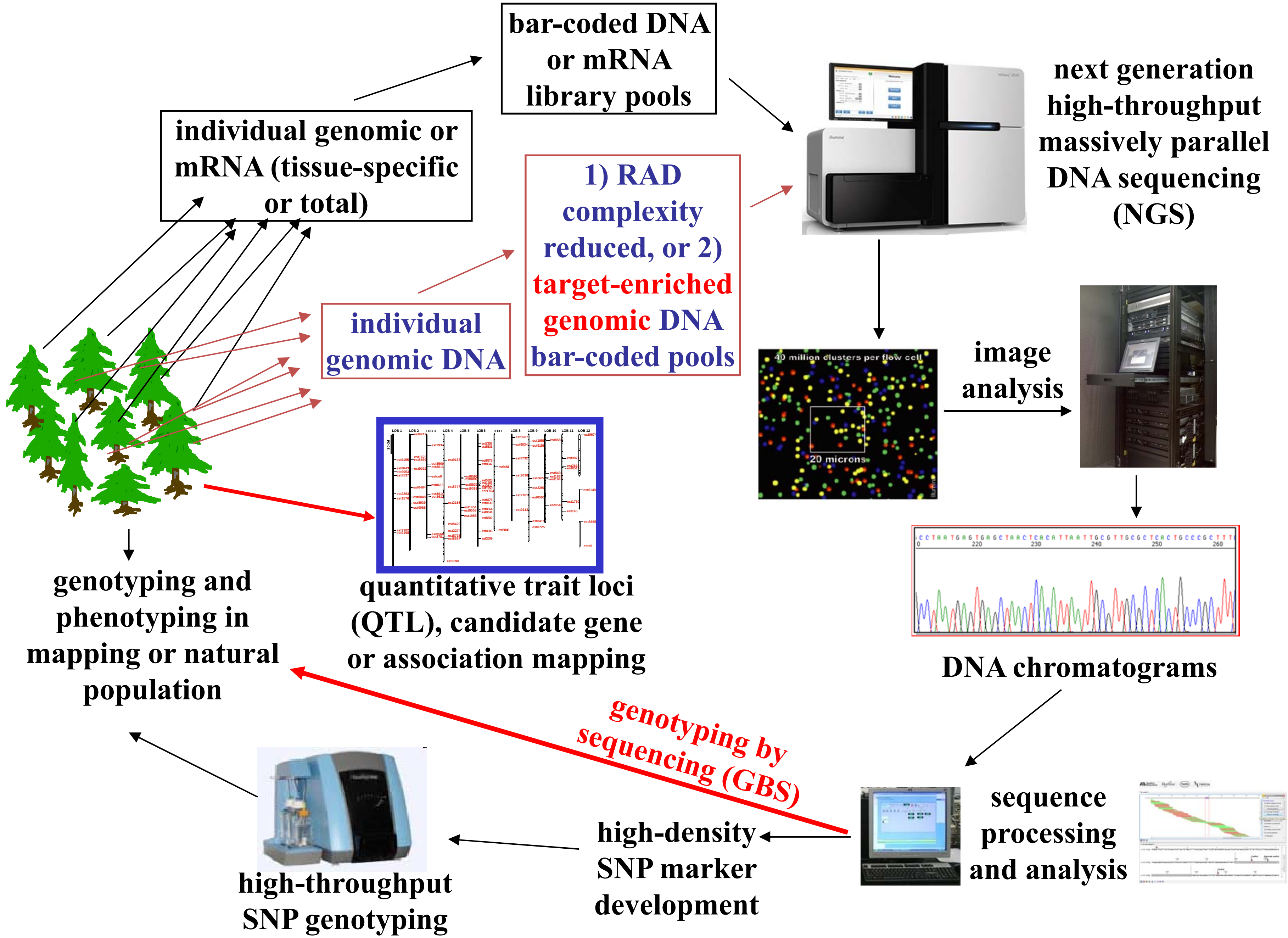
Неравновесие по сцеплению (Linkage Disequilibrium - LD) – это неслучайная ассоциация аллелей сцепленных локусов

Association Mapping Components

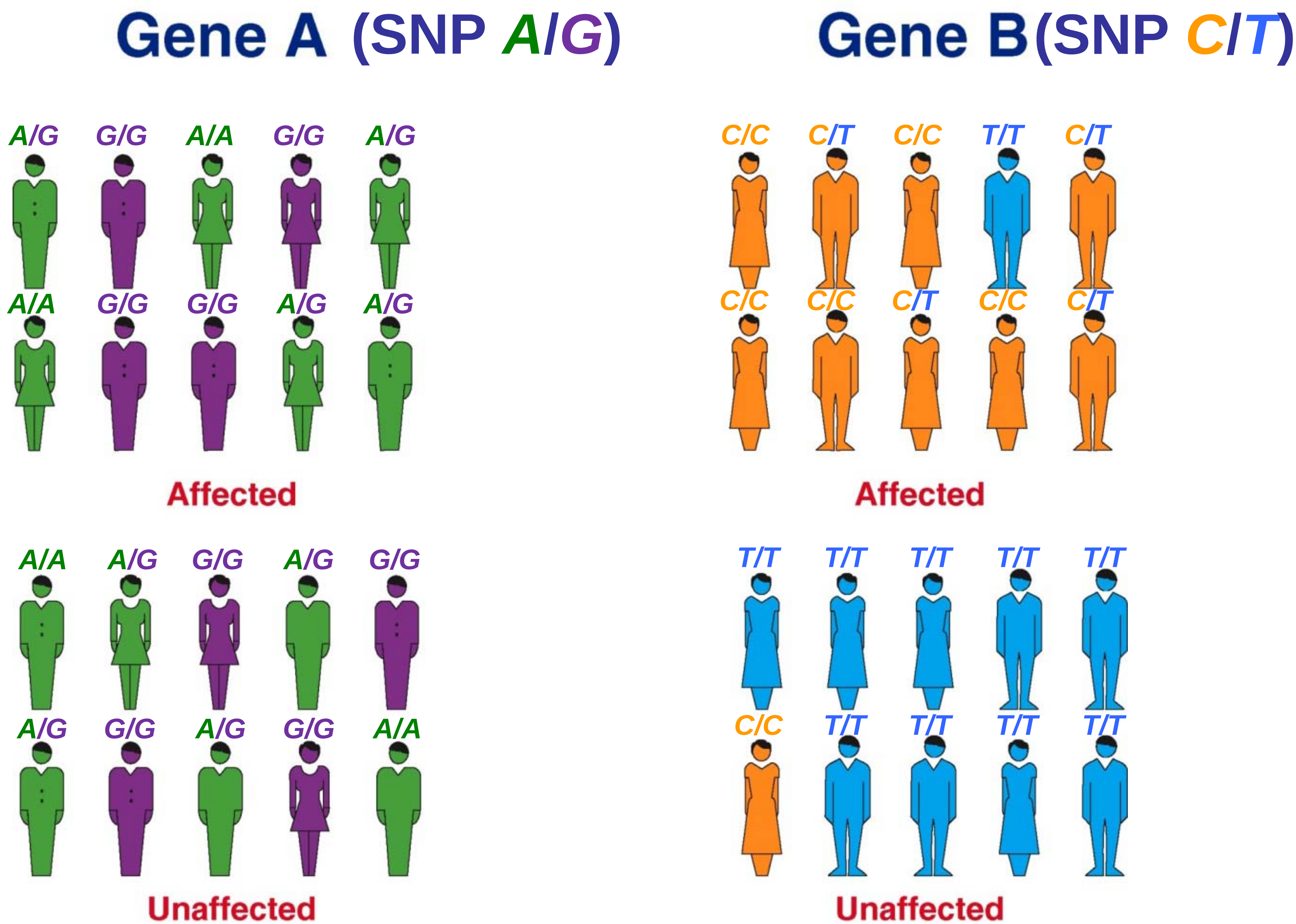
- **Phenotypes**
  - trait values
- **Numerous Molecular Markers**
  - SNPs
    - ✓ SNP genotyping assays based on preselected SNPs
    - ✓ SNP genotyping by sequencing
- **Statistical Models**
  - Linear model: phenotype as response and genotype as predictor



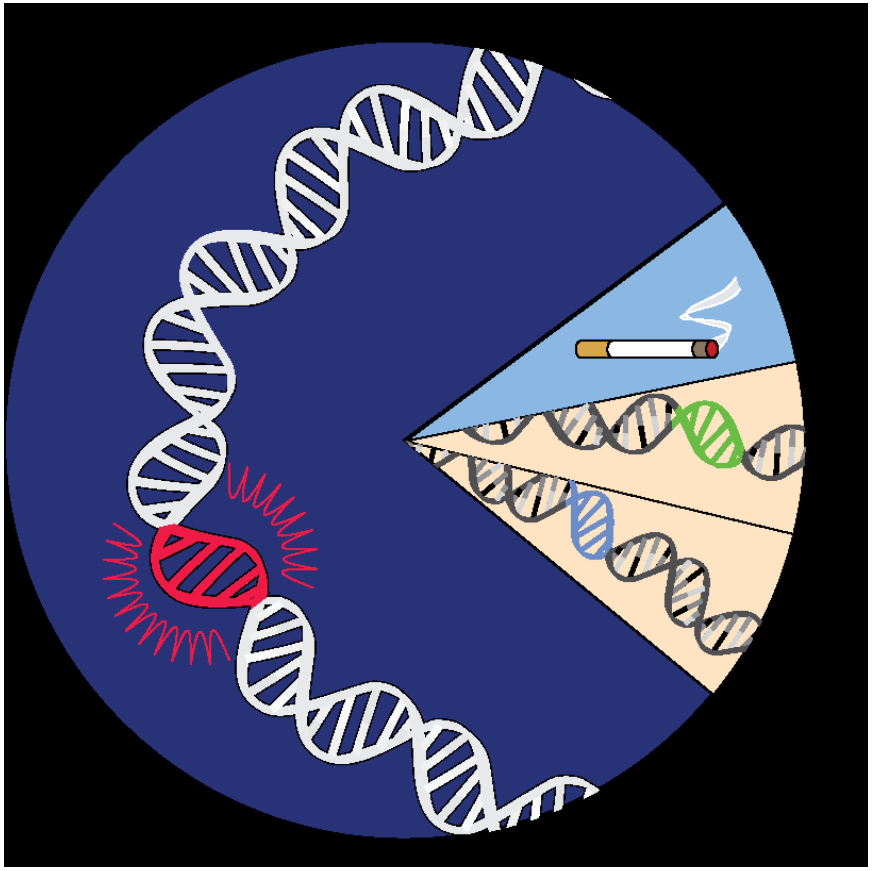
Современные методы получения маркёров и генотипирования путём прямого секвенирования



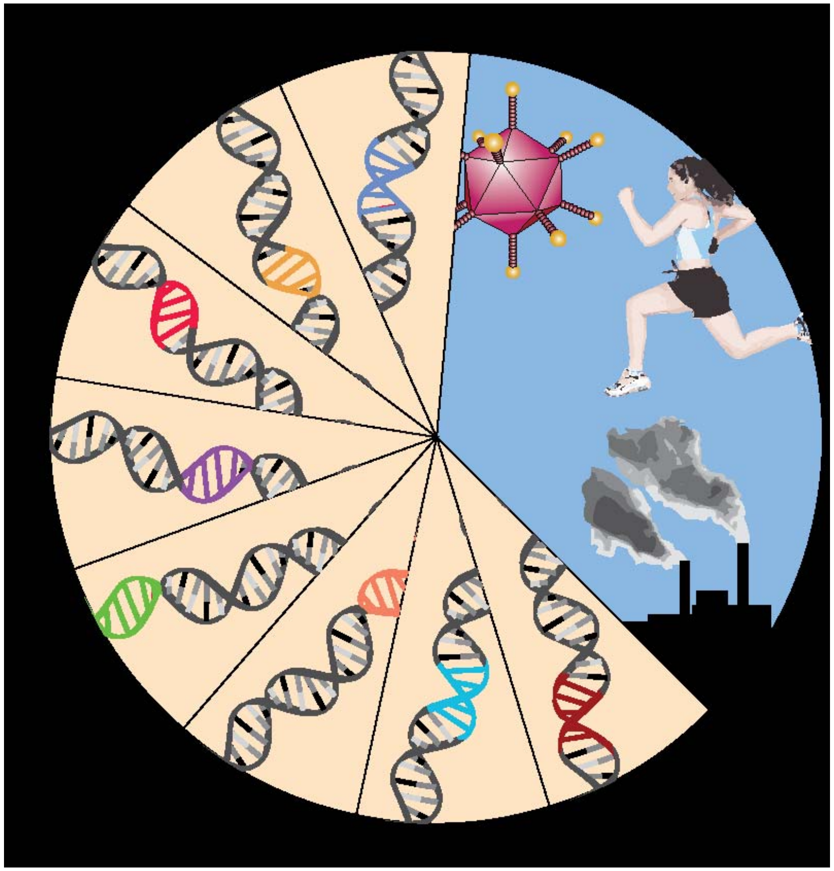
Genome-Wide Association Mapping (GWAS)



Genomic Architecture of Genetic Diseases



- rare
- simple
- monogenic
- Mendelian…
- mostly *protein coding* mutations



- common
- complex
- multigenic,
- non-Mendelian…
- mostly *regulatory* mutations

Example from traditional genetics for monogenic deceases:

Newborn screening for Phenylketonuria (PKU)

Screen for newborn for elevated phenylanaine

↓

Identify affected newborns

↓

Diet to prevent mental retardation

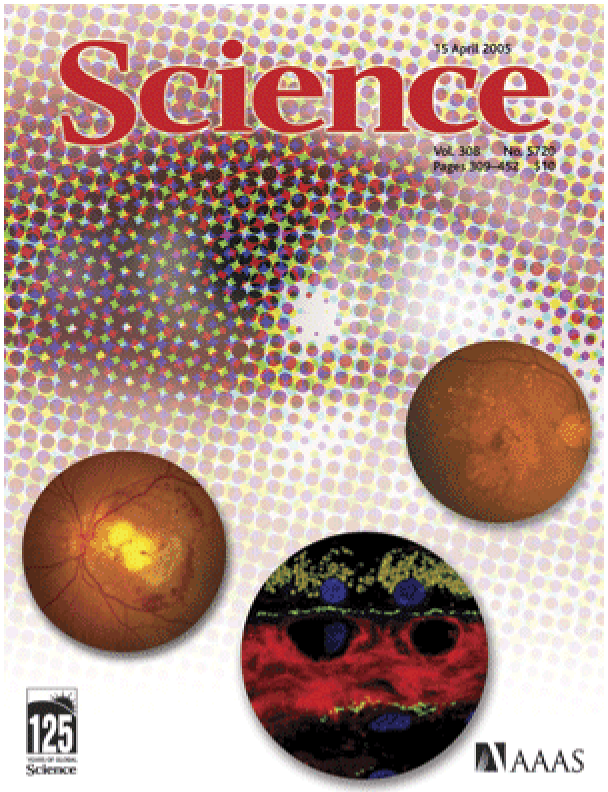
Spectrum of genetic contribution to disease

Mostly Genetic	Genes and Environment	Mostly Environment
↓	↓	↓
Cystic fibrosis	Diabetes, Asthma	Chicken pox

The First GWAM Success Story: Age-Related Macular Degeneration

Complement Factor H Polymorphism in Age-Related Macular Degeneration

Robert J. Klein,[1] Caroline Zeiss,[2*] Emily Y. Chew,[3*] Jen-Yue Tsai,[4*] Richard S. Sackler,[1] Chad Haynes,[1] Alice K. Henning,[5] John Paul SanGiovanni,[3] Shrikant M. Mane,[6] Susan T. Mayne,[7] Michael B. Bracken,[7] Frederick L. Ferris,[3] Jurg Ott,[1] Colin Barnstable,[2] Josephine Hoh[7†] ***Science* (2005)**



- Because of high costs, initial high-density screens are often conducted on a few hundred cases and controls
  - Age-Related Macular Degeneration: 96 cases, 50 controls, 105,980 markers analyzed (Science 2005; 308:385-389)
  - Breast Cancer: 390 cases, 364 controls (Nature 2007; 447:1087-1095)
  - Coronary Heart Disease: 322 cases, 312 controls (Science 2007; 316:1488-1491)

Example for complex polygenic deceases

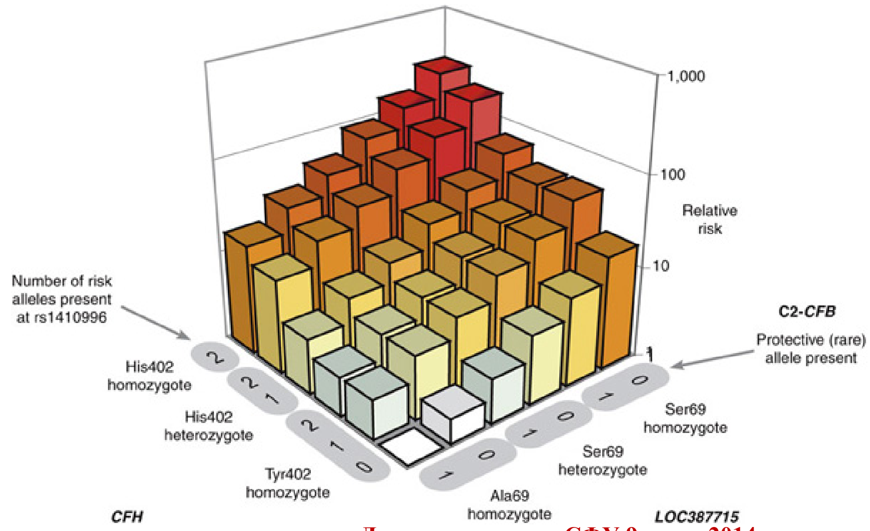
Medullary thyroid cancer & *RET* mutation testing: Multiple Endocrine Neoplasia 2 (MEN2) (If RET +, prophylactic thyroidectomy is offerred)

Predicting toxicity from chemotherapy based on retrospective analysis of clinical trial data. Toxicity and sensitivity depend on thiopurine methyltransferase (TPMT) activity. There is individual genetic polymorphisms that affect this enzymatic activity.

Multiple contributors to **asthma**: *Genetics (*beta-adrenergic receptor, GSTM1, GSTT1, IL-4, IL-4RA, IL-13, TNF-alpha, and 30-50 other genes) + *Environment* (mites, cockroaches, pollens, animal danders, cigarette smoke, diesel fuel)

Estimate of lifetime diabetes risk based on presence/absence of disease-associated mutations

Risk of age-related macular degeneration (AMD) depends on variation in 3 genes



1% have > 50% risk of AMD
most have risk close to average
(Nat Genet 2006; 38:1055-9)

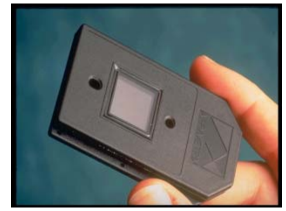
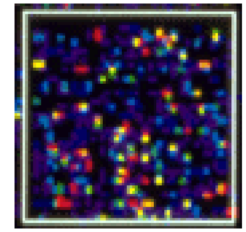
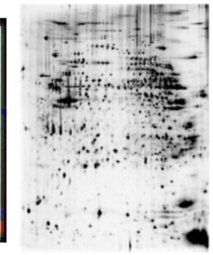
Общий вклад геномики в медицину

- Genomics can discover disease associated genes
- Genomics can discover disease causing genes.
- Genomics provides understanding of disease
- Genomics and bioinformatics provides basis for novel drug development
- Genomics provides basis for novel genetic and stem cell therapies
- Genomics provides the basis for preventive medicine

Использование геномной информации

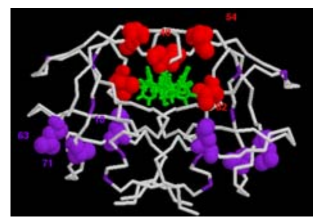
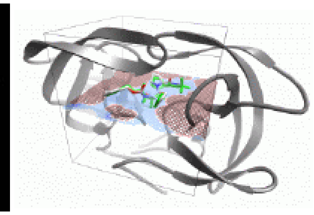
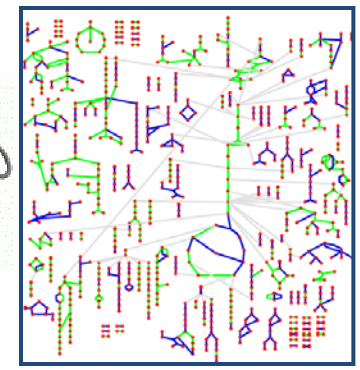
Novel Diagnostics

- Microchips & Microarrays - DNA
- Gene Expression - RNA
- Proteomics - Protein

Novel Therapeutics

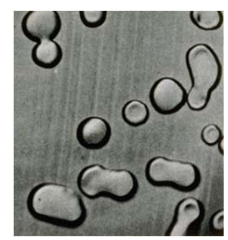
- Drug Target Discovery
- Rational Drug Design
- Molecular Docking
- Gene Therapy
- Stem Cell Therapy

Understanding Metabolism

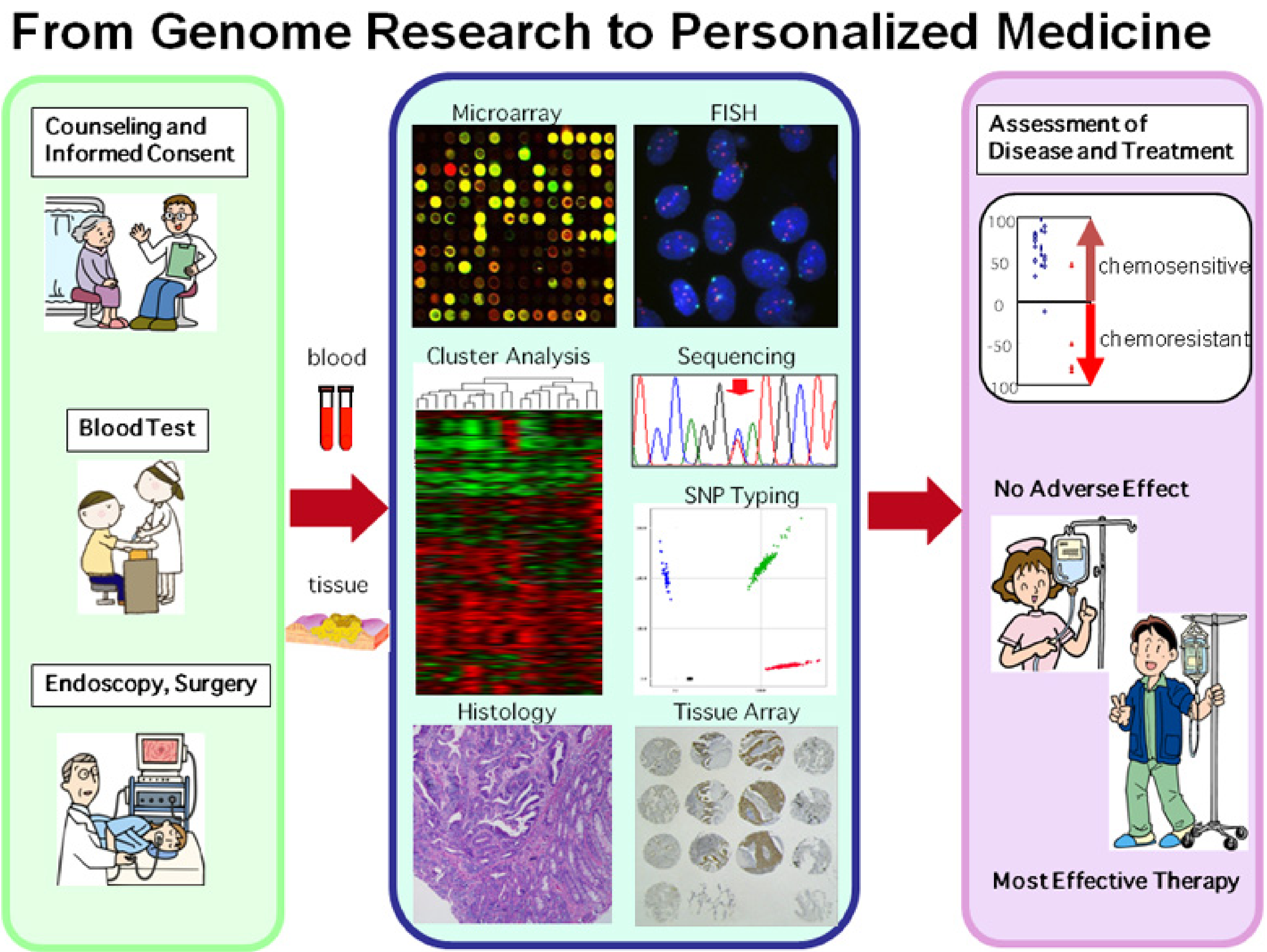
Understanding Disease

- Inherited Diseases - OMIM
- Infectious Diseases
- Pathogenic Bacteria
- Viruses



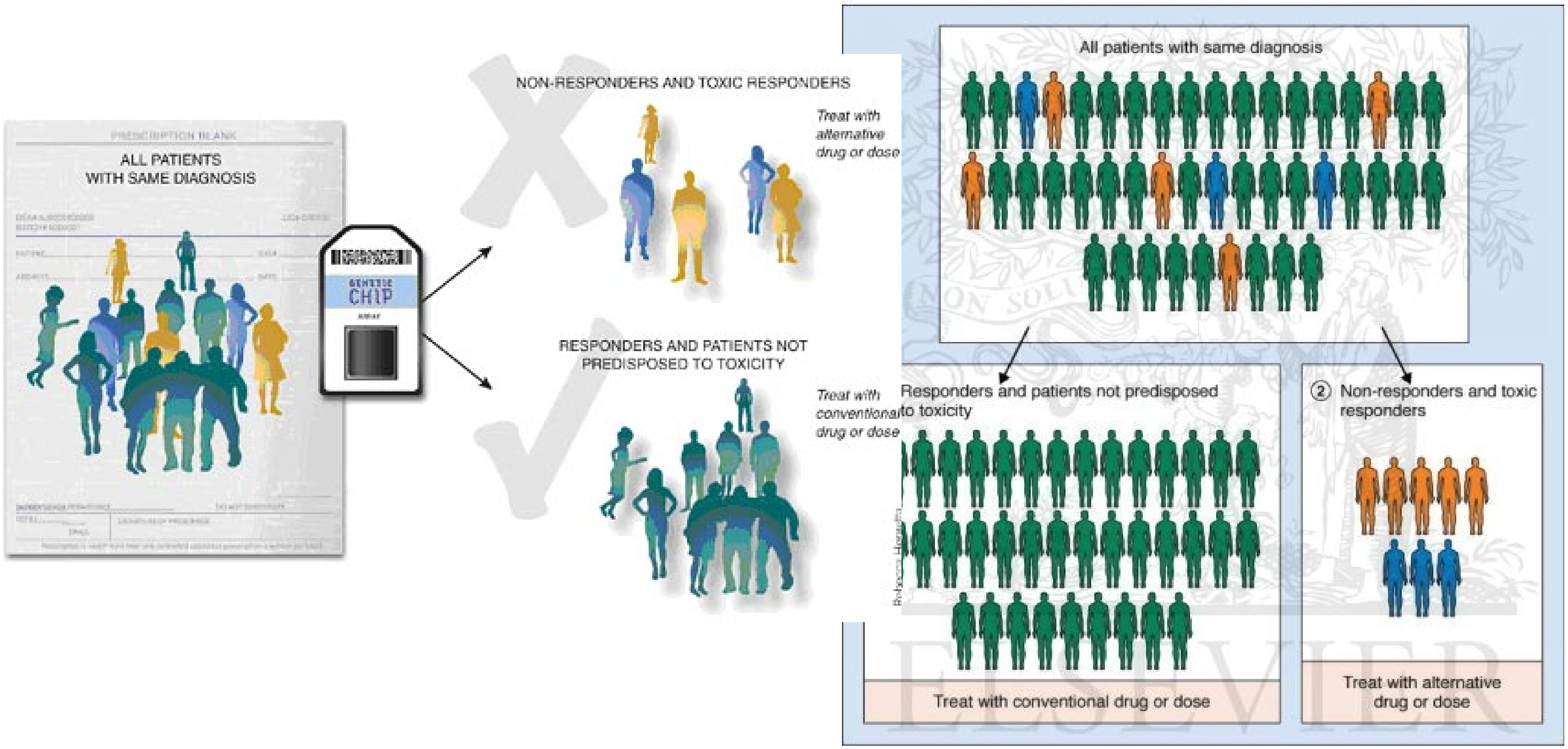

Personalized genomic medicine

The right treatment, for the right patient, at the right



Personalized genomic medicine

The right treatment, for the right patient, at the right time



Personalized genomic medicine

In a First, Test of DNA Finds Root of Illness - NYTimes.com - Mozilla Firefox

www.nytimes.com/2014/06/05/health/in-first-quick-dna-test-diagnoses-a-boys-i

The New York Times

HEALTH

152 COMMENTS

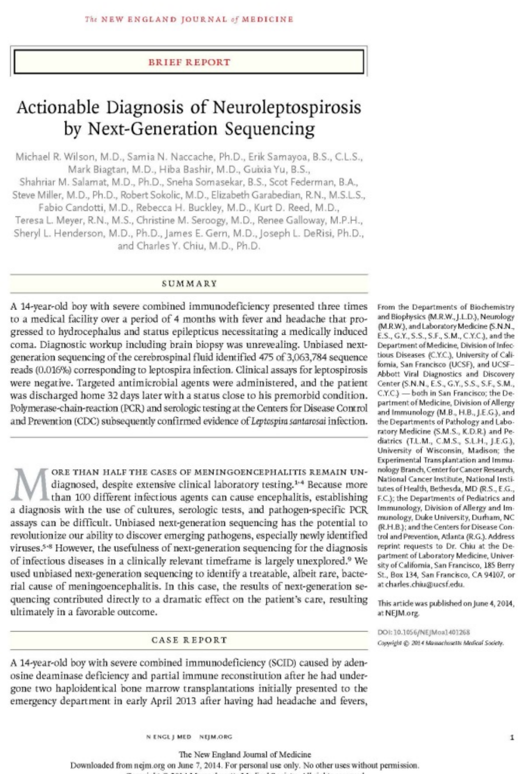
In a First, Test of DNA Finds Root of Illness

By CARL ZIMMER JUNE 4, 2014

Joshua Osborn, 14, lay in a coma at American Family Children's Hospital in Madison, Wis. For weeks his brain had been swelling with fluid, and a battery of tests had failed to reveal the cause.

The doctors told his parents, Clark and Julie, that they wanted to run one more test with an experimental new technology. Scientists would search

Joshua Osborn outside his home in Cottage Grove, Wis., with his father, Clark Osborn. Joshua suffered



The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Actionable Diagnosis of Neuroleptospirosis by Next-Generation Sequencing

Michael R. Wilson, M.D., Samia N. Naccache, Ph.D., Erik Samayoa, B.S., C.L.S., Mark Biagtan, M.D., Hiba Bashir, M.D., Guixia Yu, B.S., Shahriar M. Salamat, M.D., Ph.D., Sneha Somasekar, B.S., Scot Federman, B.A., Steve Miller, M.D., Ph.D., Robert Sokolic, M.D., Elizabeth Garabedian, R.N., M.S.L.S., Fabio Candotti, M.D., Rebecca H. Buckley, M.D., Kurt D. Reed, M.D., Teresa L. Meyer, R.N., M.S., Christine M. Seroogy, M.D., Renee Galloway, M.P.H., Sheryl L. Henderson, M.D., Ph.D., James E. Gern, M.D., Joseph L. DeRisi, Ph.D., and Charles Y. Chiu, M.D., Ph.D.

SUMMARY

A 14-year-old boy with severe combined immunodeficiency presented three times to a medical facility over a period of 4 months with fever and headache that progressed to hydrocephalus and status epilepticus necessitating a medically induced coma. Diagnostic workup including brain biopsy was unrevealing. Unbiased next-generation sequencing of the cerebrospinal fluid identified 475 of 3,063,784 sequence reads (0.016%) corresponding to leptospira infection. Clinical assays for leptospirosis were negative. Targeted antimicrobial agents were administered, and the patient was discharged home 32 days later with a status close to his premorbid condition. Polymerase-chain-reaction (PCR) and serologic testing at the Centers for Disease Control and Prevention (CDC) subsequently confirmed evidence of *Leptospira santarosai* infection.

More than half the cases of meningoencephalitis remain undiagnosed, despite extensive clinical laboratory testing.[1-4] Because more than 100 different infectious agents can cause encephalitis, establishing a diagnosis with the use of cultures, serologic tests, and pathogen-specific PCR assays can be difficult. Unbiased next-generation sequencing has the potential to revolutionize our ability to discover emerging pathogens, especially newly identified viruses.[5-8] However, the usefulness of next-generation sequencing for the diagnosis of infectious diseases in a clinically relevant timeframe is largely unexplored.[9] We used unbiased next-generation sequencing to identify a treatable, albeit rare, bacterial cause of meningoencephalitis. In this case, the results of next-generation sequencing contributed directly to a dramatic effect on the patient's care, resulting ultimately in a favorable outcome.

CASE REPORT

A 14-year-old boy with severe combined immunodeficiency (SCID) caused by adenosine deaminase deficiency and partial immune reconstitution after he had undergone two haploidentical bone marrow transplantations initially presented to the emergency department in early April 2013 after having had headache and fevers,

From the Departments of Biochemistry and Biophysics (M.R.W., J.L.D.), Neurology (M.R.W.), and Laboratory Medicine (S.N.N., E.S., G.Y., S.S., S.F., S.M., C.Y.C.), and the Department of Medicine, Division of Infectious Diseases (C.Y.C.), University of California, San Francisco (UCSF), and UCSF–Abbott Viral Diagnostics and Discovery Center (S.N.N., E.S., G.Y., S.S., S.F., S.M., C.Y.C.) — both in San Francisco; the Department of Medicine, Division of Allergy and Immunology (M.B., H.B., J.E.G.), and the Departments of Pathology and Laboratory Medicine (S.M.S., K.D.R.) and Pediatrics (T.L.M., C.M.S., S.L.H., J.E.G.), University of Wisconsin, Madison; the Experimental Transplantation and Immunology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD (R.S., E.G., F.C.); the Departments of Pediatrics and Immunology, Division of Allergy and Immunology, Duke University, Durham, NC (R.H.B.); and the Centers for Disease Control and Prevention, Atlanta (R.G.). Address reprint requests to Dr. Chiu at the Department of Laboratory Medicine, University of California, San Francisco, 185 Berry St., Box 134, San Francisco, CA 94107, or at charles.chiu@ucsf.edu.

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DOI: 10.1056/NEJMoa1401268

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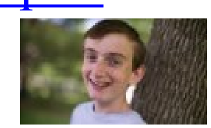
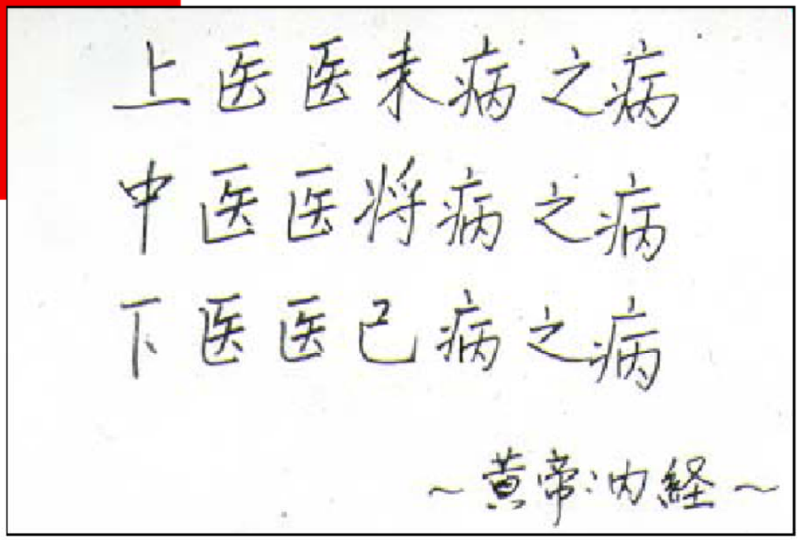
Статья в Нью-Йорк Таймс 4 мая 2014 г.: **«Экспресс-тест ДНК диагностировал заболевание у мальчика»** - рассказывает о чудесном исцелении благодаря новейшей диагностики с помощью новых геномных технологий – **нового поколения секвенирования - Next-Generation Sequencing (NGS)**, описанного в последнем выпуске журнала **The New England Journal of Medicine** в статье Wilson et al. 2014

- Joshua Osborn, 14, laid in a coma at American Family Children's Hospital in Madison, Wis. For weeks his brain had been swelling with fluid, and a battery of tests had failed to reveal the cause.
- DNA-based test for diagnosing elusive pathogens
- DNA was isolated from different tissues, sequenced and compared with database within 48 hours
- Joshua's cerebrospinal fluid contained DNA from a potentially lethal type of bacteria called Leptospira
- Leptospira was readily treated with penicillin.



Профилактическая медицина



"Superior Doctors Prevent the Disease.
Mediocre Doctors Treat the Disease Before Evident.
Inferior Doctors Treat the Full Blown Disease."

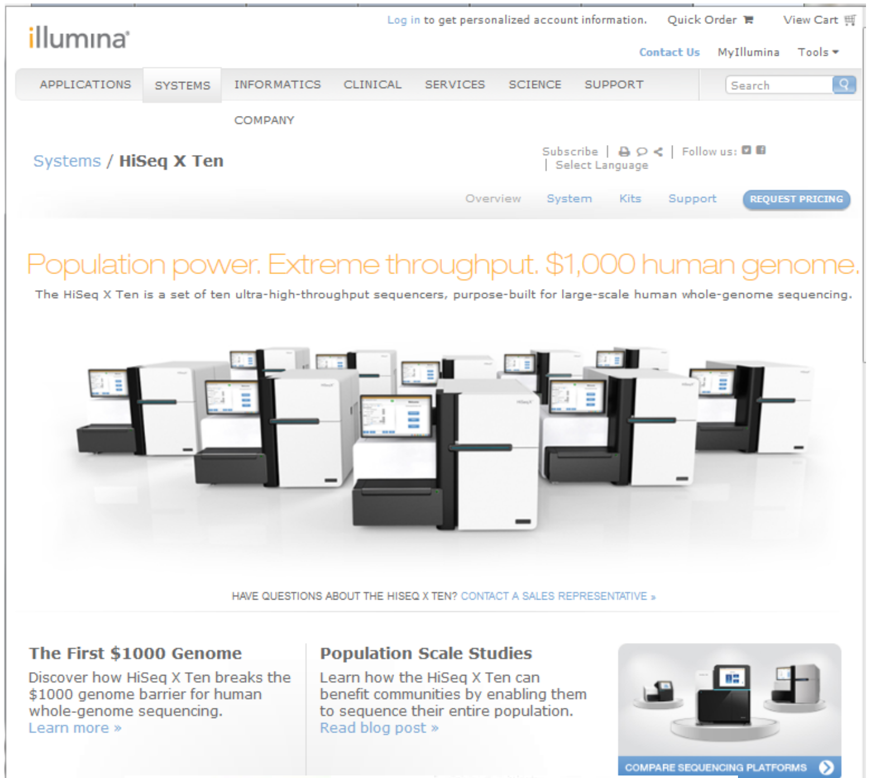
-Huang Dee: Nai - Ching (2600 B.C. 1st Chinese Medical Text

Геномика позволяет предвидеть заболевания, устанавливая их связь с генотипом, и таким образом создает основу для профилактики этих заболеваний.

When thinking about diseases, I never think about how to cure them, but instead I think about how to prevent them.

-Louis Pasteur (1822-1895)

Профилактическая медицина



- **ПМ на основе полногеномного секвенирования становится реальностью!**
- В январе этого года на международной конференции по геномике растений и животных в Сан-Диего компания Illumina представила новый самый мощный секвенатор **HiSeq X**
- In his presentation, Illumina's chief executive Jay Flatley said the **HiSeq X** would be able to deliver **a human genome for just under $1,000**
- He said the world is "entering the **supersonic age of genomics**".
- **1.6-1.8 Tb for 3 days = >500 human genomes**
- **Qatar's human genome project** (**http://www.qatartodayonline.com/qatar-genome-launched-at-wish**)

International Plant & Animal Genome Conference

PAG XXII - Home | http://campaig...-d4ae52754aa9

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January 11-15, 2014 San Diego, CA

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PAG History 1996-2014																			
	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010*	2011*	2012*	2013	2014*
	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Scientific	630	840	1,040	1,340	1,472	1,683	1,806	1,799	1,826	2,004	1,987	2,105	2,074	2,063	2,285	2,534	2,788	2,762	**2,851**
Exhibitor Staff	55	75	85	125	328	333	219	188	216	219	225	204	302	321	313	348	425	408	**546**
Total Attendance	685	915	1,125	1,465	1,800	2,016	2,025	1,987	2,042	2,223	2,212	2,309	2,376	2,384	2,598	2,882	3,213	3,170	**3,397**
USA	374	512	656	866	971	1,103	1,198	1,219	1,212	1,436	1,330	1,385	1,324	1,342	1,147	1,552	1,643	1,634	**1,543**
INTL	256	318	384	474	501	580	607	580	614	568	657	720	750	721	838	982	1,145	1,128	**1,308**
Plant				1,115	1,252	1,389	1,498	1,448	1,440	1,554	1,523	1,696	1,652	1,648	1,773	1,962	2,129	2,124	**2,173**
Animal				225	220	294	308	351	386	450	464	409	422	415	512	572	651	638	**678**
Ind. Workshops	0	1	1	3	6	10	14	12	16	18	14	16	22	21	23	24	27	26	**28**
Sci. Workshops	14	27	26	34	37	45	57	57	59	68	79	79	80	93	96	104	121	132	**140**
Booths	23	29	32	42	86	86	93	83	86	89	90	91	102	110	128	138	133	136	**129**
Abstracts	393	519	610	704	866	932	1,173	1,272	1,272	1,242	1,388	1,410	1,475	1,393	1,583	1,516	1,764	1,855	**1,957**
Posters	318	390	416	534	624	705	840	905	998	887	959	955	941	865	945	907	1,022	1,045	**1,160**
Reg/Poster Ratio	2	2.1	2.5	2.5	2.4	2.4	2.2	2.2	1.8	2.2	2.1	2.2	2.2	2.4	2.4	2.8	2.7	2.5	**2.5**
* Record Attendance																			

1	Country	Total Registrants
2	Argentina	7
3	Australia	50
4	Austria	4
5	Belgium	33
6	Benin	1
7	Brazil	83
8	Canada	115
9	Chile	7
10	China	128
11	Colombia	12
12	Costa Rica	2
13	Czech Republic	13
14	Denmark	22
15	Egypt	4
16	Ethiopia	3
17	Finland	5
18	France	115
19	Germany	76
20	Guatemala	1
21	Hong Kong	1
22	India	21
23	Ireland	8
24	Israel	22
25	Italy	26
26	Japan	76
27	Jordan	2
28	Kenya	10
29	Malaysia	5
30	Mauritius	1
31	Mexico	34
32	Montserrat	1
33	Morocco	4
34	Mozambique	1
35	Netherlands	45
36	New Zealand	13
37	Nigeria	24
38	Norway	5
39	Pakistan	2
40	Peru	2
41	Philippines	12
42	Poland	3
43	Portugal	1
44	Qatar	2
45	Rwanda	1
46	Saudi Arabia	7
47	Senegal	1
48	Singapore	5
49	Slovenia	2
50	South Africa	17
51	South Korea	94
52	Spain	11
53	Sweden	11
54	Switzerland	10
55	Taiwan	6
56	Tanzania	4
57	Thailand	9
58	Trinidad and Tobago	1
59	Turkey	9
60	Uganda	20
61	United Kingdom	95
62	Uruguay	3
63	US	1
64	USA	1546
65	Zambia	1

Палеогеномика и секвенирование геномов древней ДНК

Scientists create complete genetic map of a Neanderthal from a TOE - and put it online for free

- Scientists from Germany's Max Planck Institute sequenced genome from toe bone found in southern Siberia
- New techniques allowed them to sequence every position in the genome 50 times over for greater accuracy
- They hope it will help answer questions about our own genetic history and how we're related to Neanderthals

By DAMIEN GAYLE

PUBLISHED: 14:52 GMT, 20 March 2013 | UPDATED: 17:26 GMT, 20 March 2013

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The first complete Neanderthal genome sequence has been completed and made available free-of-charge to researchers across the world.

Scientists from the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, have made the data available as a free download from their website.

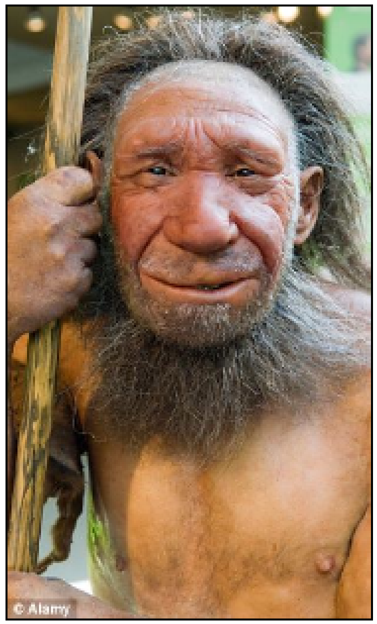
The group will present a paper describing the genome later this year.

'But we make the genome sequence freely available now to allow other scientists to profit from it even before it is published' said Dr Svante Pääbo, who led the project.

Dr Pääbo and his colleagues in 2010 presented the first draft of the Neanderthal genome from data collected from three bones found in a cave in Croatia.

They have now used a toe bone excavated in 2010 in Denisova Cave in southern Siberia to generate a high-quality genome from a single Neandertal individual.

The Leipzig team used sensitive techniques developed there over the past two years to sequence every position in the genome about 50 times over, using DNA extracted from 0.038 grams of the bone.



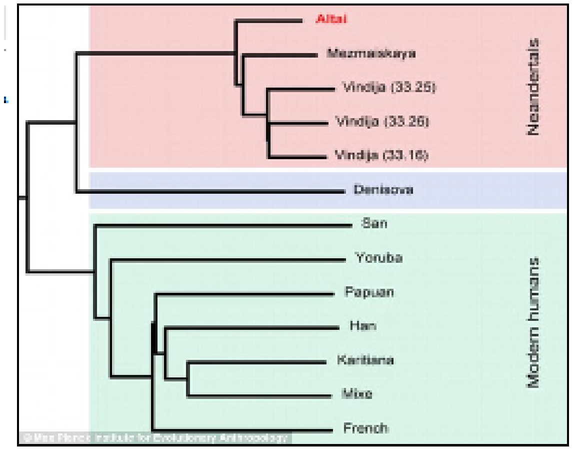
Sequenced: The first full Neanderthal genome has been sequenced and made available free-of-charge by the Max Planck Institute

The analysis of the genome together with partial genome sequences from other Neanderthals, and the genome from a small finger bone discovered in the same cave, shows that the individual is closely related to other Neanderthals in Europe and western Russia.

Remarkably, Neanderthals and their relatives, Denisovans, were both present in this unique cave in the Altai Mountains on the border between Russia, China, Mongolia and Kazakhstan.

In the 2010 draft version of the Neanderthal genome, each position was determined, on average, once. In the now-completed version of the genome every position was determined on average 50 times over.

This allows even the small differences between the copies of genes that this individual inherited from its mother and father to be distinguished.



This family tree relates this genome (top) to the genomes of Neanderthals from Croatia, Germany and the Caucasus as well as the Denisovan genome recovered from a finger bone also excavated at Denisova Cave

The Leipzig group has made the entire genome sequence freely available for the scientific community over the internet.

'The genome is of very high quality', said Dr Kay Prüfer, who coordinated the analyses. 'It matches the quality of the Denisovan genome, presented last year, and is as good as or even better than the multiple present-day human genomes available to date.'

Dr Pääbo added: 'We are in the process of comparing this Neanderthal genome to the Denisovan genome as well as to the draft genomes of other Neanderthals.'

'We will gain insights into many aspects of the history of both Neanderthals and Denisovans and refine our knowledge about the genetic changes that occurred in the genomes of modern humans after they parted ways with the ancestors of Neanderthals and Denisovans.'

The project, part of 30 years' worth of efforts by Dr. Pääbo's group to study ancient DNA, was made possible by financing from the Max Planck Society.

The bone used to sequence the genome was discovered by Professor Anatoly Derevianko and Professor Michael Shunkov from the Russian Academy of Sciences in 2010 during excavations at the Denisova Cave.

The cave is a unique archaeological site which contains cultural layers indicating it has been occupied by humans and our ancestors from as early as 280,000 years ago.

HOW THE DENISOVAN GENOME WAS SIMILARLY SEQUENCED

The Neanderthal genome was sequenced thanks to the discovery of just a toe bone, and it was an even tinier fragment of finger that allowed the same researchers to map out the entire genetic code of Denisovan man.

Evidence suggests that the Denisovans, a little-known ancient cousin of modern humans who lived in Siberia around 50,000 years ago, had dark skin, brown hair and brown eyes.

The existence of the Denisovans was only confirmed in 2010, but previous research has already suggested they co-existed with Neanderthals and interbred with our own species, Homo sapiens.

Scientists made the discovery after studying DNA from a piece of finger bone and two molars found at same Denisova Cave in the Altai Mountains of southern Siberia as the Neanderthal toe bone.

Because they had only a tiny sample of material from the finger bone, Svante Pääbo and his research team developed a treatment that unzipped the DNA so that each of its two strands can be used to generate molecules for sequencing.

This method allowed the team to generate an extremely thorough genome sequence (30X), similar in quality to what researchers can obtain for the modern human genome.

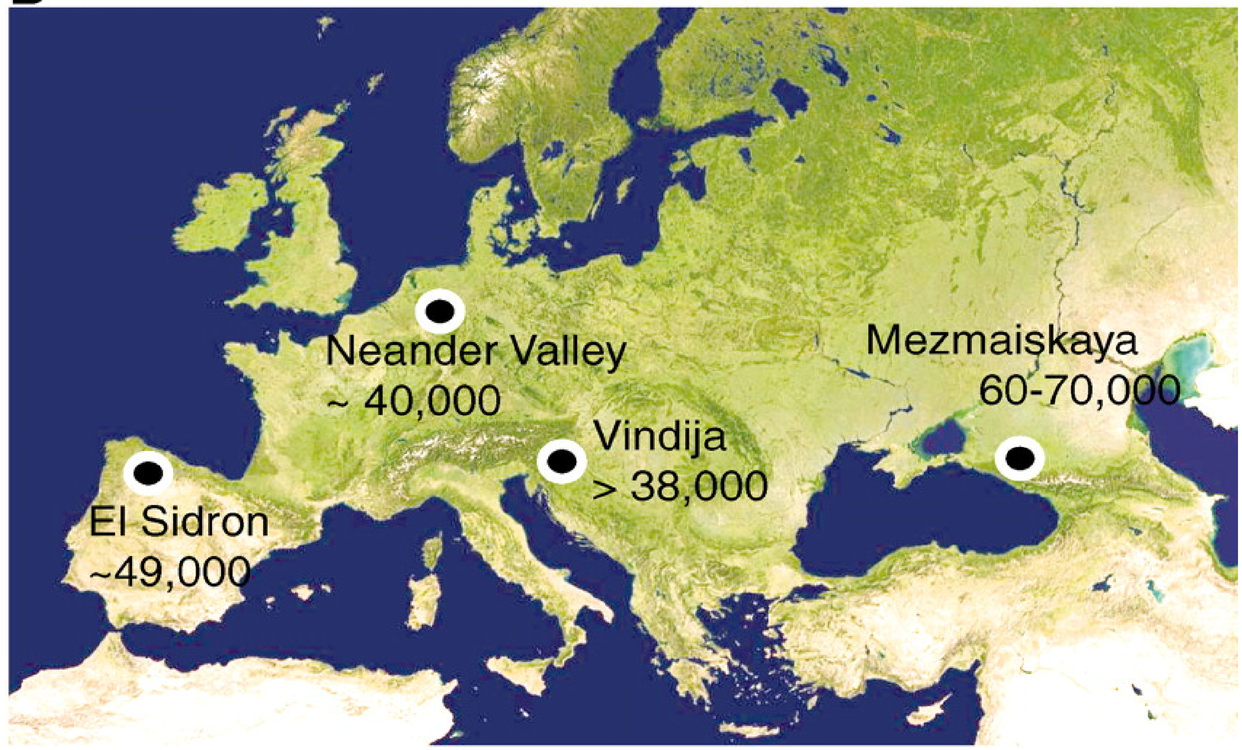
The scientists found that the Denisovans were most genetically similar to Australian aborigines and island populations from south-east Asia.

Палеогеномика и секвенирование геномов древней ДНК

Места и образцы костей неандертальцев, из которых была выделена ДНК

A

B

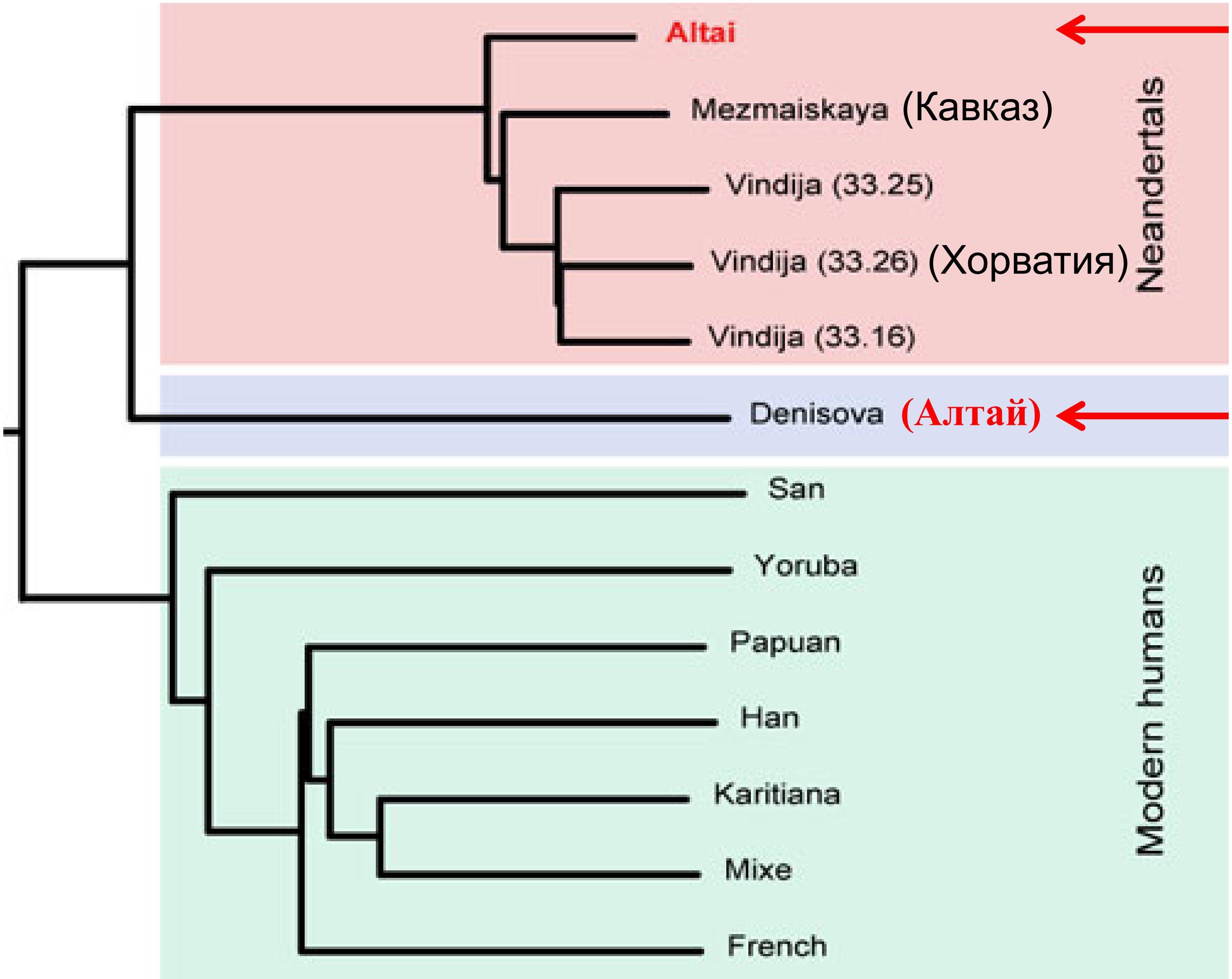


(A) The three bones from Vindija from which Neandertal DNA was sequenced.

(B) Map showing the four archaeological sites from which bones were used and their approximate dates (years B.P.)

R E Green et al. Science 2010;328:710-722

Палеогеномика и секвенирование геномов древней ДНК

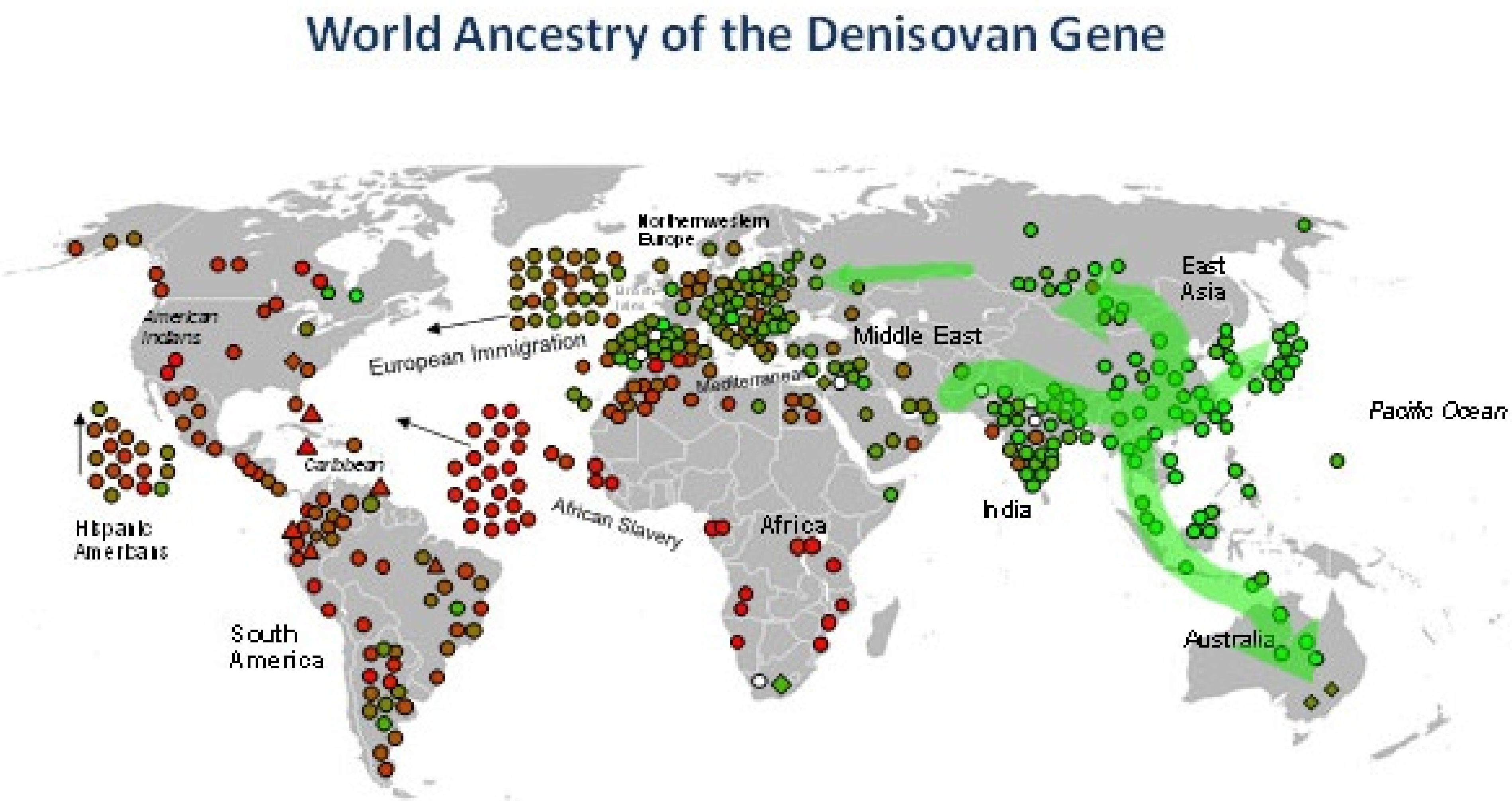


Геном неандертальца из ДНК зуба, обнаруженного в Денисовой пещере

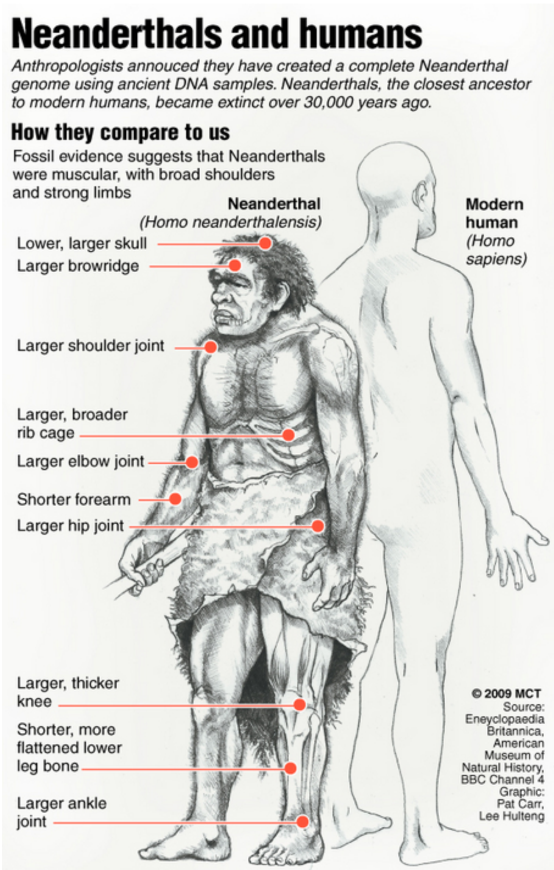
Геном из ДНК фаланги пальца, обнаруженной в Денисовой пещере в 2010 г. (Meyer et al. Pääbo 2012 Science 338(6104): 222-226)

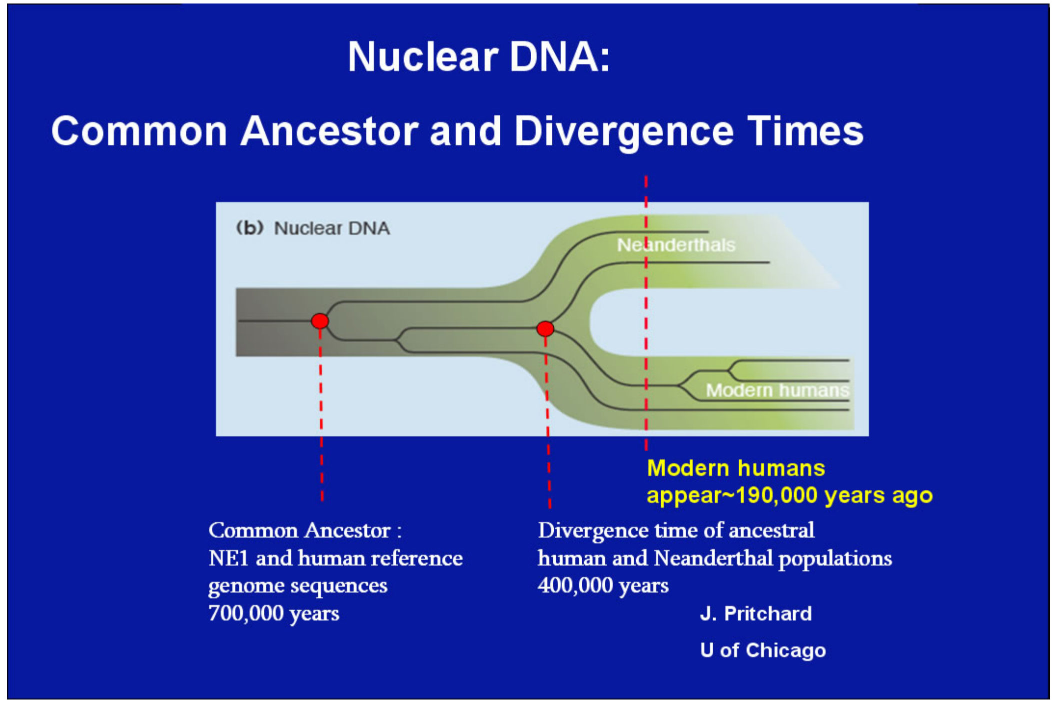
http://www.eva.mpg.de/neandertal/index.html

Палеогеномика и секвенирование геномов древней ДНК



Палеогеномика и секвенирование геномов древней ДНК

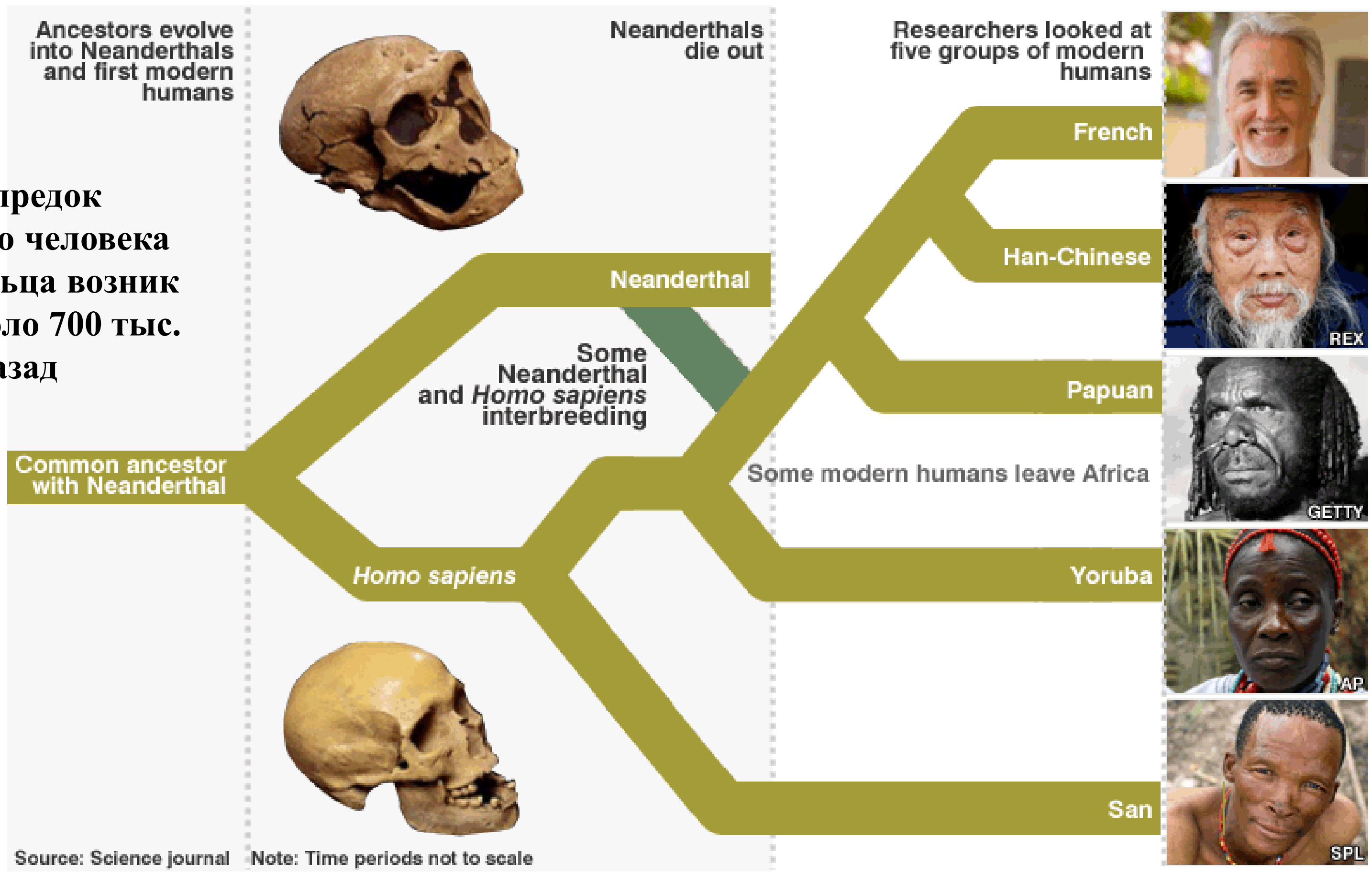




Analysis of genomic DNA from fossilized Neanderthal bones indicated that *Homo sapiens* and *Homo neanderthalensis* last shared a common ancestor approximately 700,000 years ago. The two hominids split into separate species approximately 400,000 years ago, with no evidence of any significant crossbreeding between the two after that time.

Палеогеномика и секвенирование геномов древней ДНК

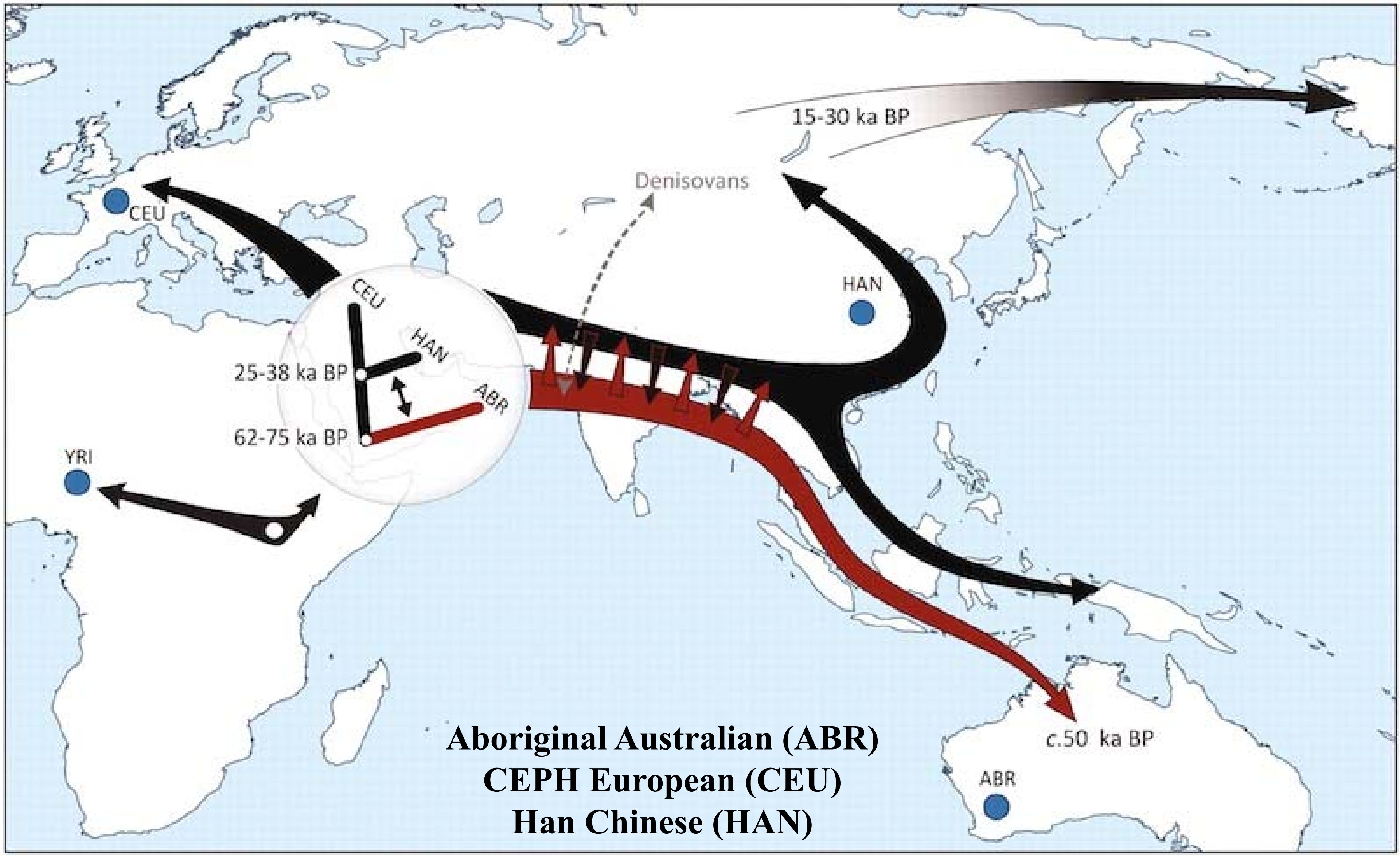
Общий предок современного человека и неандертальца возник в Африке около 700 тыс. лет назад



Разделение на современного человека и неандертальца произошло около 400 тыс. лет назад

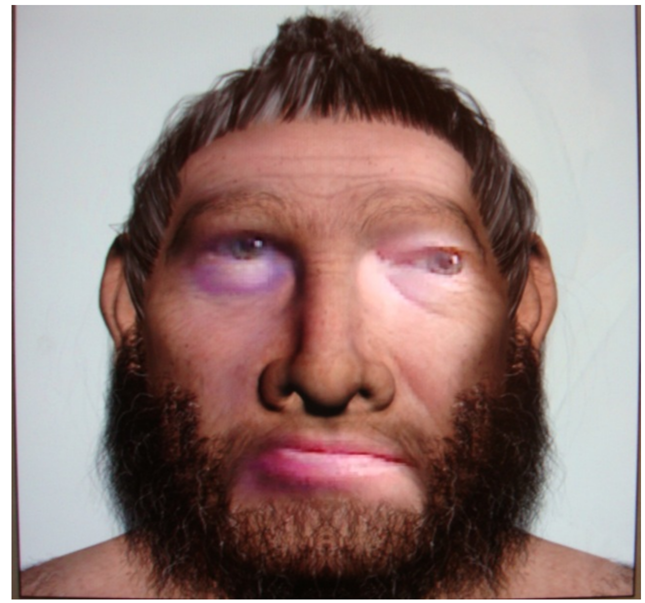
Расселение из Африки в Евразию современного человека и неандертальца началось около 40-70 тыс. лет назад

Расселение современного человека



Палеогеномика и секвенирование геномов древней ДНК

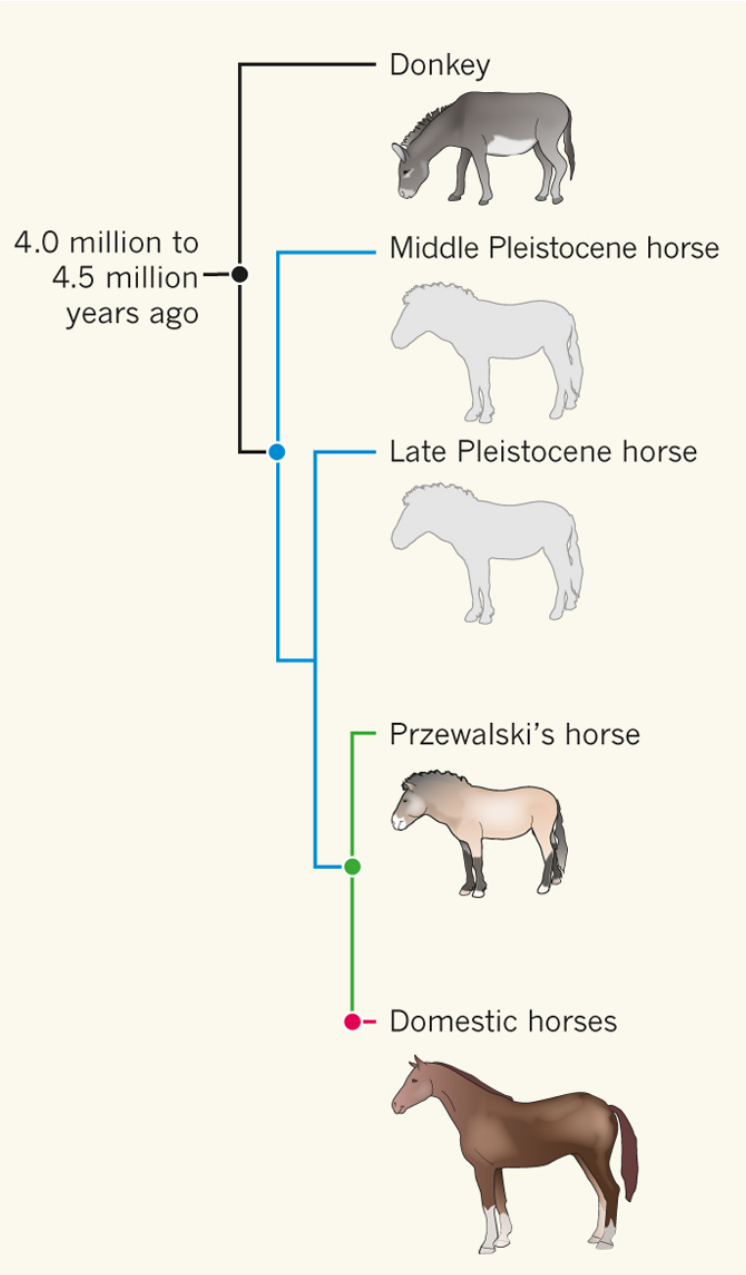
Special challenges:



- Ancient DNA is degraded by nucleases
- The majority of DNA in samples derives from unrelated organisms such as bacteria that invaded after death
- The majority of DNA in samples is contaminated by human DNA
- Determination of authenticity requires special controls, and analysis of multiple independent extracts

Green, R. E. *et al.* A draft sequence of the Neandertal genome. Science 328, 710–722 (2010)

Первые лошади возникли 4 миллиона лет назад



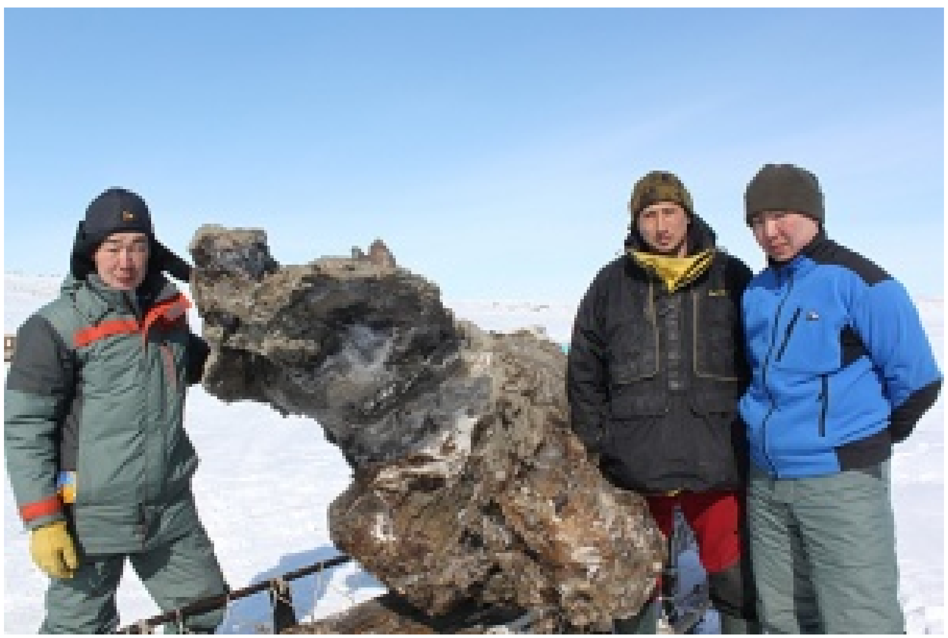
Палеогенетикам удалось восстановить геном древней лошади, чьи останки были захоронены в канадской вечной мерзлоте примерно 700 тысяч лет назад; его анализ показал, что последний общий предок домашних скакунов, зебр и их родичей жил 4 миллиона лет назад (Orlando, L. *et al*. Nature 2013 http://dx.doi.org/10.1038/nature12323).

Геном мамонта частично расшифрован в 2008 г.

Биологи из Университета штата Пенсильвания определили почти полную последовательность **генома (3.3 млрд нукл.) шерсистого мамонта (*Mammuthus primigenius*).** ДНК была получена из шерсти двух мамонтих возрастом 20 и 60 тысяч лет, найденных в Сибири (Miller et al. 2008 Nature 456: 387-390).

Находка Малоляховского мамонта в прекрасной сохранности в мае 2013 г. (НИИ прикладной экологии Севера (НИИПЭС) СВФУ, рук. программы **Семен Егорович Григорьев**, зав. лаб. Музей мамонта им. П.А. Лазарева).

В марте 2014 НОЦ геномных исследований СФУ взял образцы для секвенирования.

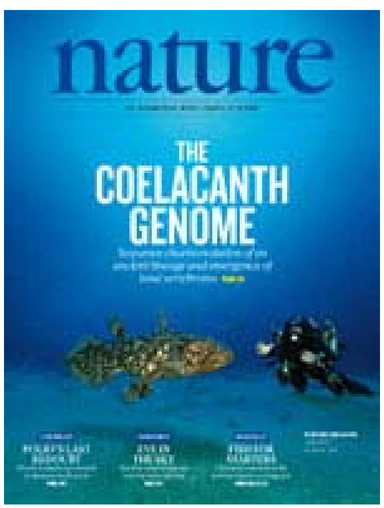


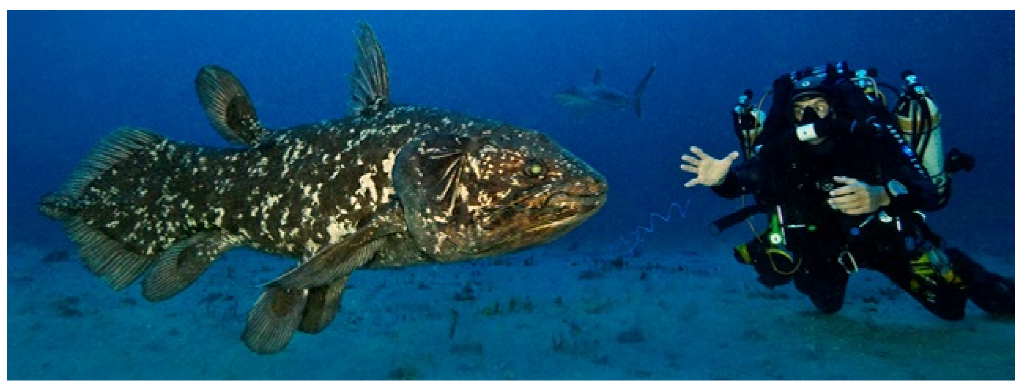
Геном Малоляховского мамонта

Взятие образцов для секвенирования сотрудником НОЦ геномных исследований СФУ Орешковой Натальей Викторовной в марте 2014 .

Расшифрован геном "живого ископаемого" африканского целаканта (*Latimeria chalumnae*) - древней кистеперой рыбы

- Расшифрован геном, **латимерии,** которую вплоть до конца 30-х годов XX века считали вымершей 70 млн лет назад. Исследование генома этих "живых ископаемых" обогатило науку массой ценных наблюдений. В частности, выяснилось, что частота мутаций у целакантов крайне низка, т.е., их гены не очень сильно изменились за миллионы лет.
- Также оказалось, что у целакантов нет генов, кодирующих иммуноглобулины M (IgM) - антитела, присутствующие у всех позвоночных и обеспечивающие первичный иммунный ответ. Возможно, функцию защиты от микробов берут на себя иммуноглобулины W (IgW) - молекулы, обнаруженные только у двоякодышащих и хрящевых рыб, а теперь и у латимерии.
- Филогенетический анализ показал, что, по-видимому, наиболее близкими родственниками четвероногих животных были не латимерии, а двоякодышащие рыбы. Было бы крайне интересно выяснить, какие именно молекулярные события позволили рыбам вылезти на сушу, однако геном двоякодышащих рыб чрезвычайно велик, что пока препятствует его расшифровке.





Amemiya et al. The African coelacanth genome provides insights into tetrapod evolution. Nature, 2013 Apr 18; 496(7445): 311-316.

Секвенирование смешанных микросообществ (Metagenomics)

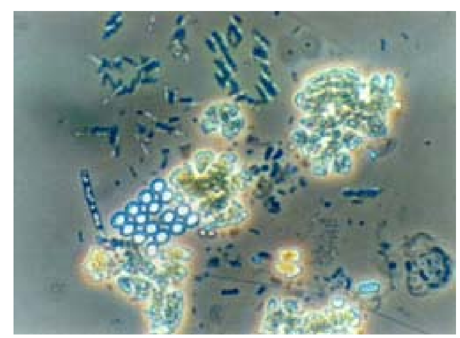
Metagenomics (also **Environmental Genomics**, **Ecogenomics** or **Community Genomics**) is the study of genetic material recovered directly from environmental samples:

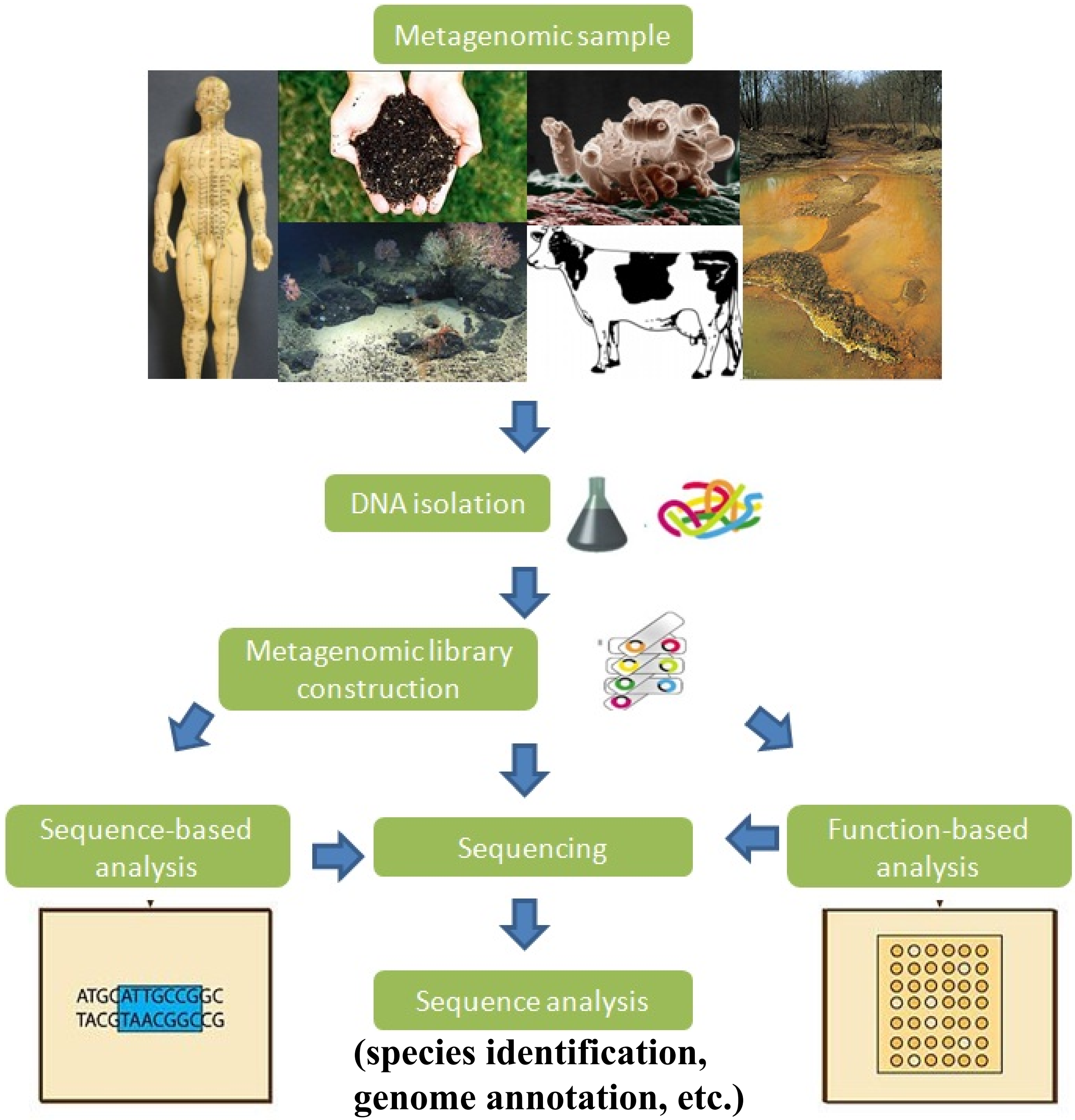
- <u>external environments (ecological)</u>

  hot spring, ocean, sludge, soil, etc.

- <u>internal environments (organismal)</u>

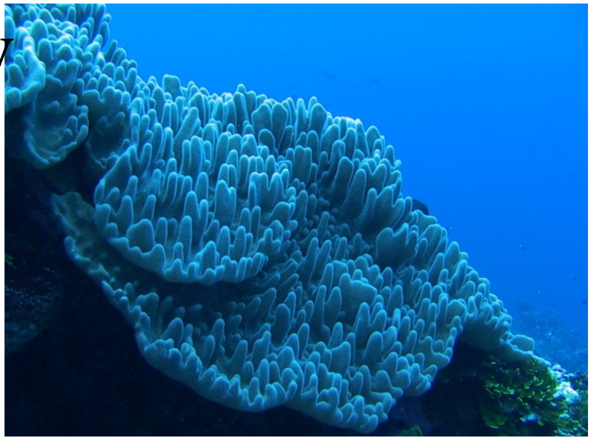
  guts, saliva, feces, lung, etc.



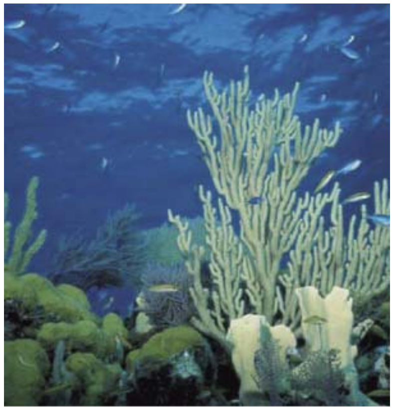

Metagenomic sample
DNA isolation
Metagenomic library construction
Sequence-based analysis
Sequencing
Function-based analysis
ATGCATTGCCGGC
TACGTAACGGCCG
Sequence analysis
(species identification, genome annotation, etc.)

Marine Metagenomics

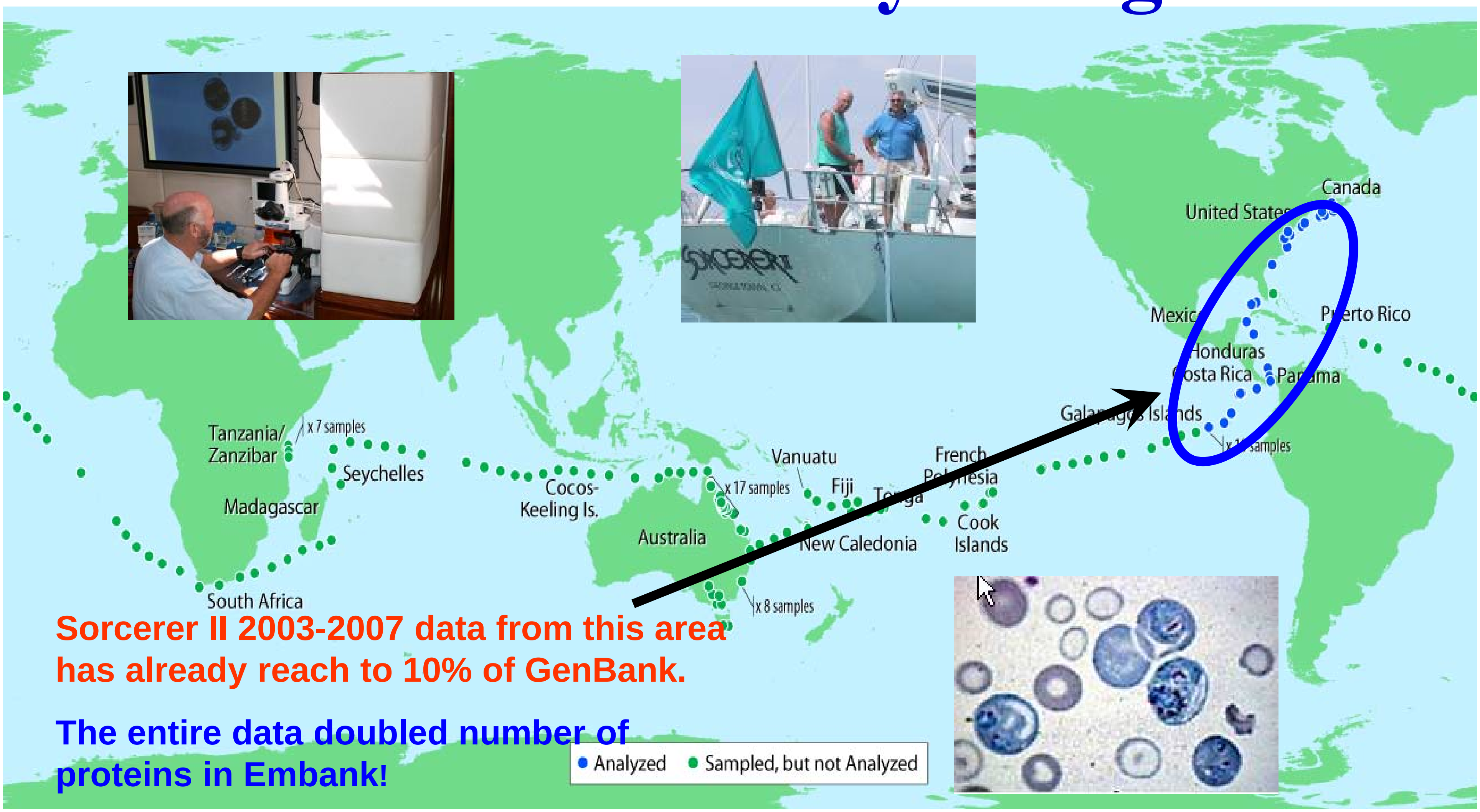
- Microbes account for more than **90% of ocean biomass**, mediate all biochemical cycles in the oceans and are responsible for **98% of primary production** in the sea.



- Metagenomics is a breakthrough sequencing approach to examine the open-space microbial species **without the need for isolation and lab cultivation of individual species**.



Marine Genome Sequencing Project Measuring the Genetic Diversity of Ocean Microbes led by Craig Venter



Sorcerer II 2003-2007 data from this area has already reach to 10% of GenBank.

The entire data doubled number of proteins in Embank!

Marine Metagenomics

Drug discovery

Metabolic pathway discovery

Microbial genetic survey

Environmental survey

Symbiosis

Who is there?

Evolution study

Endosymbiosis

Organism discovery

Microbial genomic survey

Bioenergy discovery

Biogeochemistry mapping

Marine conservation

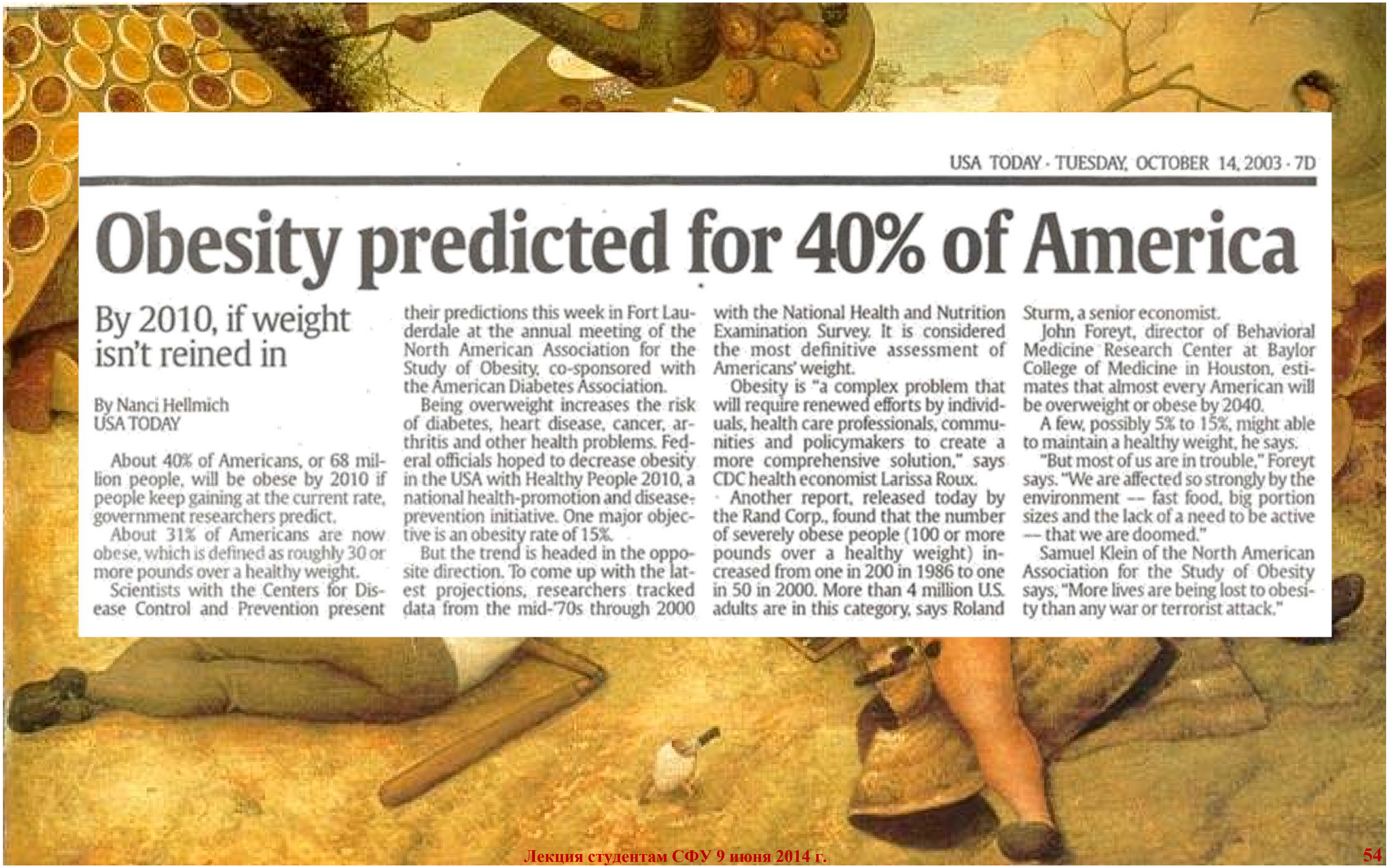
What is Nutrigenomics?

- Nutrigenomics is the science that examines the response of individuals to food compounds using post-genomic and related technologies.
- The long-term aim of nutrigenomics is to understand how the whole body responds to real foods using an integrated approach.
- Studies using this approach can examine people (i.e. populations, subpopulations - based on genes or disease - and individuals), food, life-stage and life-style without preconceived ideas.

Why is Nutrigenomics important?

- Most non-genetic diseases are **nutrition** related.
- **Diabetes, obesity and other nutrition related diseases are growing!!!** Of course genes are a factor.
- **Finding the right combination of nutrients for each genotype** can help in changing behavior and preventing many of these diseases.
- This combination may change with age, sex!

Nutrition – complex problem



USA TODAY · TUESDAY, OCTOBER 14, 2003 · 7D

Obesity predicted for 40% of America

By 2010, if weight isn't reined in

By Nanci Hellmich
USA TODAY

About 40% of Americans, or 68 million people, will be obese by 2010 if people keep gaining at the current rate, government researchers predict.

About 31% of Americans are now obese, which is defined as roughly 30 or more pounds over a healthy weight.

Scientists with the Centers for Disease Control and Prevention present their predictions this week in Fort Lauderdale at the annual meeting of the North American Association for the Study of Obesity, co-sponsored with the American Diabetes Association.

Being overweight increases the risk of diabetes, heart disease, cancer, arthritis and other health problems. Federal officials hoped to decrease obesity in the USA with Healthy People 2010, a national health-promotion and disease-prevention initiative. One major objective is an obesity rate of 15%.

But the trend is headed in the opposite direction. To come up with the latest projections, researchers tracked data from the mid-'70s through 2000 with the National Health and Nutrition Examination Survey. It is considered the most definitive assessment of Americans' weight.

Obesity is "a complex problem that will require renewed efforts by individuals, health care professionals, communities and policymakers to create a more comprehensive solution," says CDC health economist Larissa Roux.

Another report, released today by the Rand Corp., found that the number of severely obese people (100 or more pounds over a healthy weight) increased from one in 200 in 1986 to one in 50 in 2000. More than 4 million U.S. adults are in this category, says Roland Sturm, a senior economist.

John Foreyt, director of Behavioral Medicine Research Center at Baylor College of Medicine in Houston, estimates that almost every American will be overweight or obese by 2040.

A few, possibly 5% to 15%, might able to maintain a healthy weight, he says.

"But most of us are in trouble," Foreyt says. "We are affected so strongly by the environment — fast food, big portion sizes and the lack of a need to be active — that we are doomed."

Samuel Klein of the North American Association for the Study of Obesity says, "More lives are being lost to obesity than any war or terrorist attack."

Genes – Lifestyle – Calories

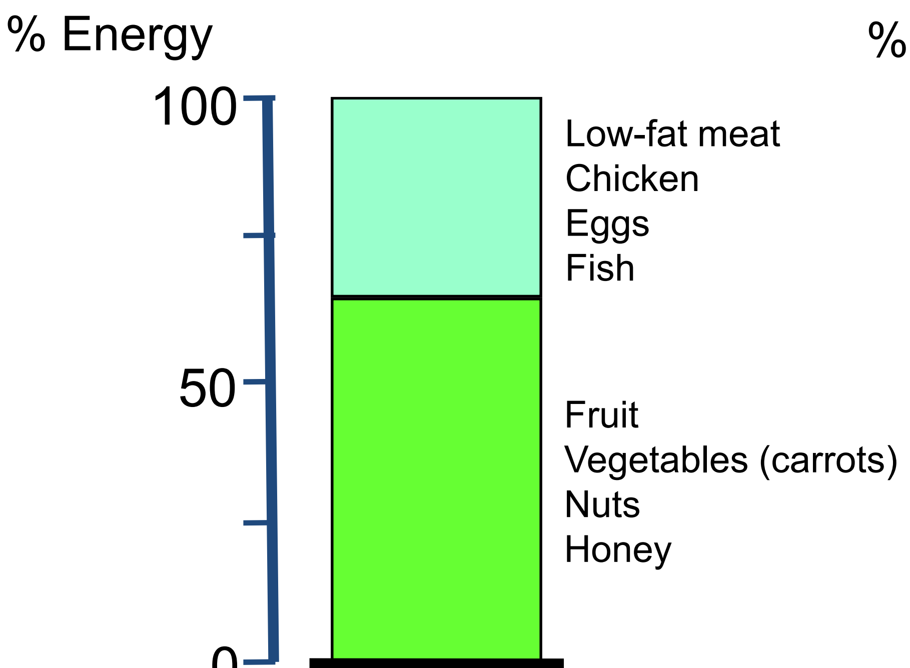
The same genes – The changed diet

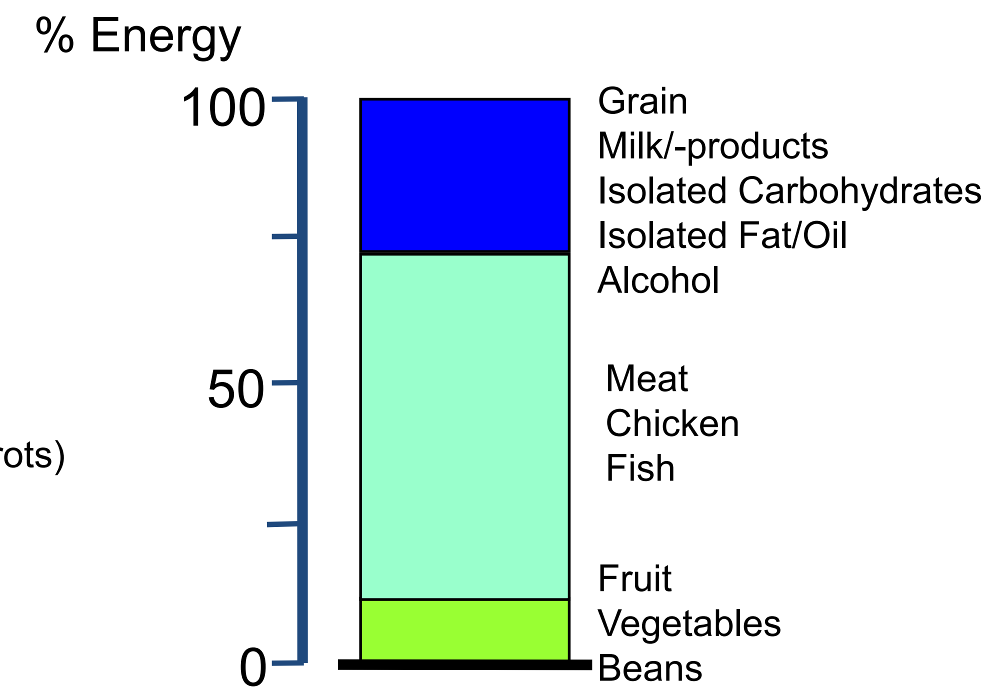
Paleolithic era

1.200.000 Generations between feast and famine

Modern Times

2-3 Generations in energy abundance



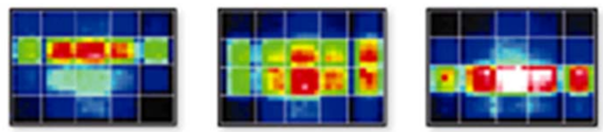


Molecular nutrition

Our "gene passports" and nutrition

Individual genotype
Functional phenotype

AA AB BB



Optimal Nutrition

Lifestyle

Improvement
Maintenance
of Health

"Eat right for your genotype??"

Personalized diets?

genelex
Science that benefits humanity

Nutritional Genetic Profile Request Form

Client Information

To order testing, either contact Genelex directly or complete this form and return it either by fax at (425) 825-1870 or mail to Genelex Corporation, 12277 134th Ct NE, Ste. 130 Redmond, WA 98052.

Name: ______________ Phone: ______________ E-mail: ______________

Address: ______________

City: ______________ State: ______________ Zip: ______________

Nutritional Genetic Profile Requested

Item	Number ordered	Cost (per item)	Total
Nutritional Genetic Panel		$445.00	
Nutritional Genetic Collection Kit (Additional $410 due with samples)		$35.00	
International Shipping		$50.00	
Amount Due			

Payment: Prepayment is required. Send Cash, Check, or Money Order to the address shown above.

Cash ☐ Check or Money Order ☐ Credit Card (all major cards) ☐

Type of credit card: ______________

Print cardholder's name: ______________

Card number: ______________ Expiration date: ______________

For immediate consultation Call 800-TEST-DNA (800-837-8362)
Hours 7:00 AM to 6:00 PM PST, 10:00 AM to 9:00 PM EST, fax 425-825-1870,
e-mail: info@genelex.com
www.genelex.com

Consumers warned that time is not yet ripe for nutrition profiling

Erika Check

One day, information about your genome may well help you decide what breakfast cereal to eat. But that day's a long way off, the second International Nutrigenomics Conference in Amsterdam was told last week. In the meantime, researchers at the meeting heard, the emerging field badly needs a regulatory framework that will stop its first customers from being scared off.

Nutrigenomics researchers aim to learn how nutrients interact with genes to lead to health or disease. But people eat wildly different levels of nutrients over their lifetimes, and teasing apart the precise interactions is notoriously difficult.

The researchers who gathered in Amsterdam on 6–7 November were in optimistic mood, however. Their science is progressing quickly, and food industry executives have expressed interest in the idea of using genetic information to customize their products.

In January, the US National Institutes of Health used a 5-year, $6.5-million grant to create a National Center of Excellence for Nutritional Genomics at the University of California, Davis, and the Children's Hospital Oakland Research Institute (CHORI) in Oakland. In July, the European Commission set up the European NutriGenomics Organisation to coordinate work. Now the Netherlands looks set to embark on a $20-million nutrigenomics project, jointly funded by the government and the food industry.

But some researchers warn that the field is in danger of developing too quickly. They want experts to back off from the sometimes-extravagant claims for the field's potential, and instead to sit down and patiently work out a scientific vision and ethical framework for the discipline.

"Our aim is to bring the field a little bit back down to Earth, because people tend to start with a lot of science fiction," says Michael Müller, a genomicist at Wageningen University in the Netherlands who helped to organize the meeting.

The main fruits of this field are still years away, researchers say. So far, most of the studies on profiling gene expression — measuring genome-wide responses to nutrients — have been done in mice. And much more work is needed on the basic mechanisms by which nutrients turn genes on or off. But that hasn't stopped a handful of companies from selling nutritional profiles directly to consumers over the Internet.

The companies test a tissue sample — such as a cheek swab — from a "patient". The patient can choose which genetic profile he or she wants to learn about, for example skin ageing or susceptibility to osteoporosis. The company then gives the patient a "personalized profile" based on its tests for single nucleotide polymorphisms (SNPs): genetic variants that have been linked to disease. For instance, one company, GeneLink of Margate, New Jersey, tells people what vitamins they should take, based on SNPs involved in cellular responses to certain toxins. GeneLink declined to comment on its products.

But many scientists argue that it's far too early for most of these tests to be useful. "The idea of marketing any individual genetic test at this point assumes there is information to justify the use of that test, and we really don't have evidence that any single genetic marker carries enough information to guide dietary treatments," says Ronald Krauss, director of atherosclerosis research at CHORI.

The direct-to-consumer tests also raise ethical issues that affect the whole field. For instance, some companies sell the results of their genetic profiles to other firms, which use the information for research on genes and disease. Although consumers must give their consent, they may not necessarily understand what they're agreeing to, says ethicist David Castle of the University of Guelph. Castle is collaborating with the University of Toronto Joint Center for Bioethics in soliciting comments on a joint working paper on ethics and nutrigenomics.

At the nutrigenomics meeting, Castle argued that even though the field is very young, scientists must begin talking to the public about such issues.

"This technology could end up affecting something that every person does every day, which is eat," Castle says. "It's not a situation where you want to roll out the science and the products and then go back and ask people how they feel about it." ■

Looks good, tastes good, and one day individuals may know exactly how much good it does them.

NATURE | VOL 426 | 13 NOVEMBER 2003 |

Nutrients acts as dietary signals

Nutritional factors

↓

Transcription factors

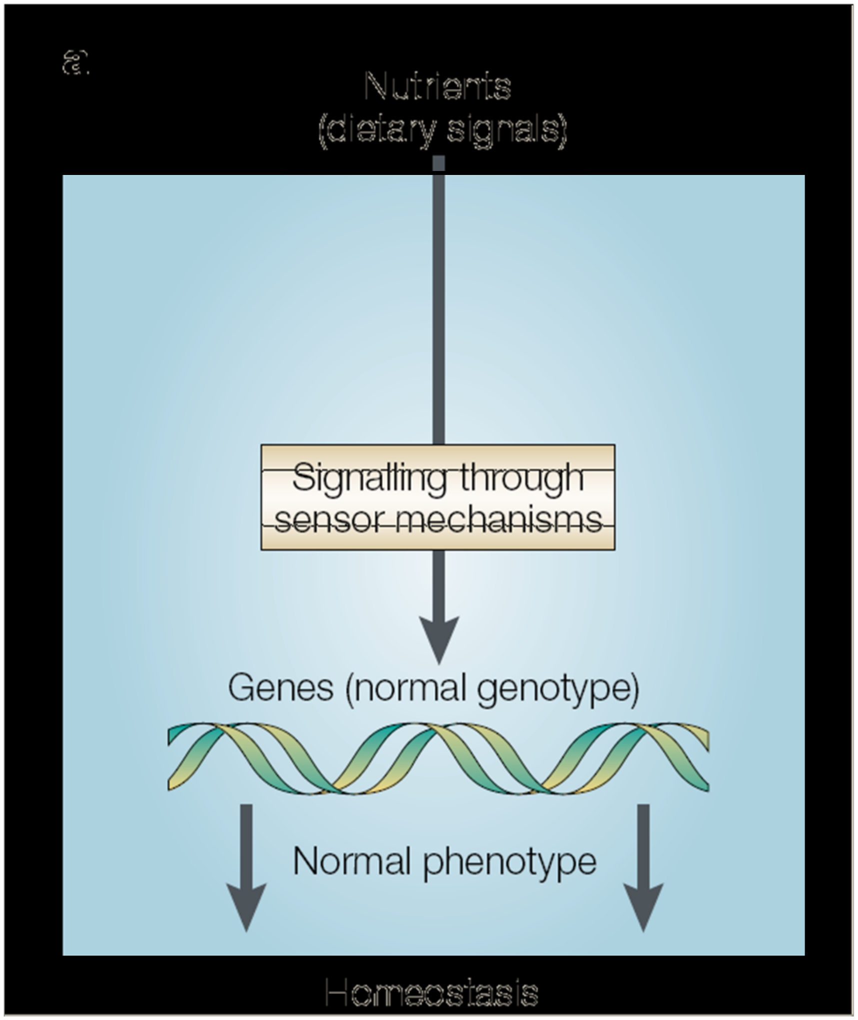
↓

Gene transcription

Energy homeostasis

Cell proliferation

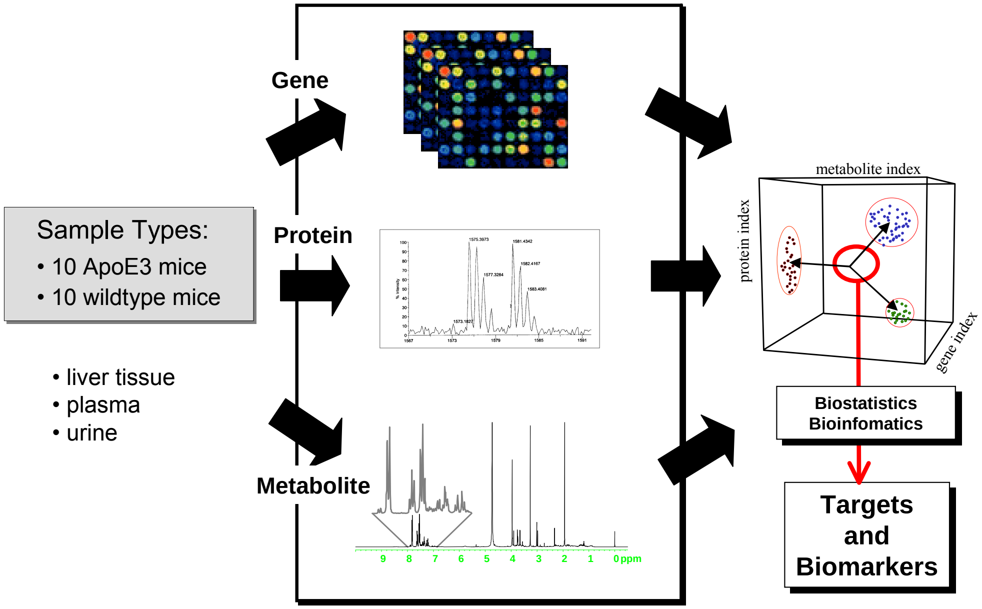
Nutrient absorption

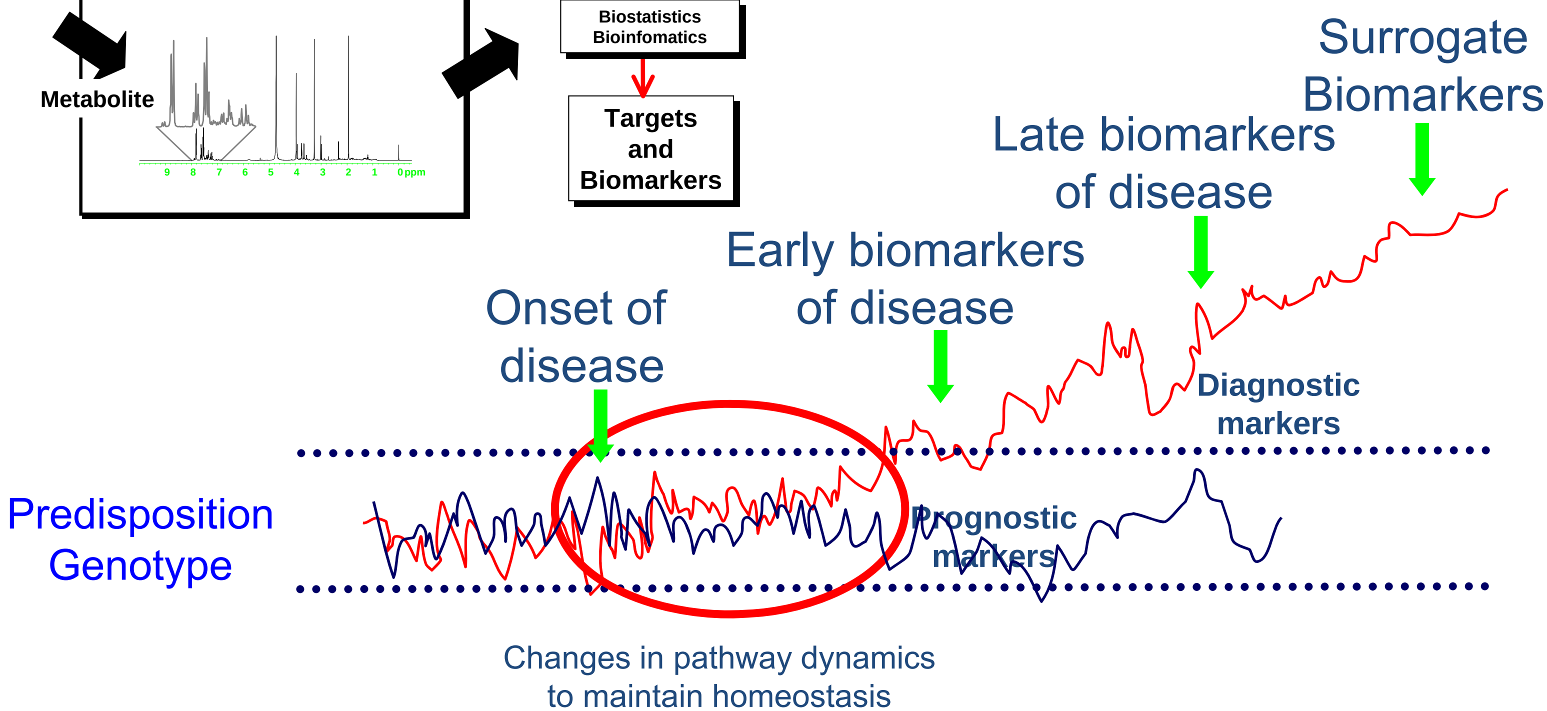


Transcription-factor pathways mediating nutrient-gene interaction

Nutrient	Compound	Transcription factor
Macronutrients		
Fats	Fatty acids Cholesterol	PPARs, SREBPs, LXR, HNF4, ChREBP SREBPs, LXRs, FXR
Carbohydrates	Glucose	USFs, SREBPs, ChREBP
Proteins	Amino acids	C/EBPs
Micronutrients		
Vitamins	Vitamin A Vitamin D Vitamin E	RAR, RXR VDR PXR
Minerals	Calcium Iron Zinc	Calcineurin/NF-ATs IRP1, IRP2 MTF1
Other food components		
	Flavonoids Xenobiotics	ER, NFκB, AP1 CAR, PXR

Nutritional Systems Biology





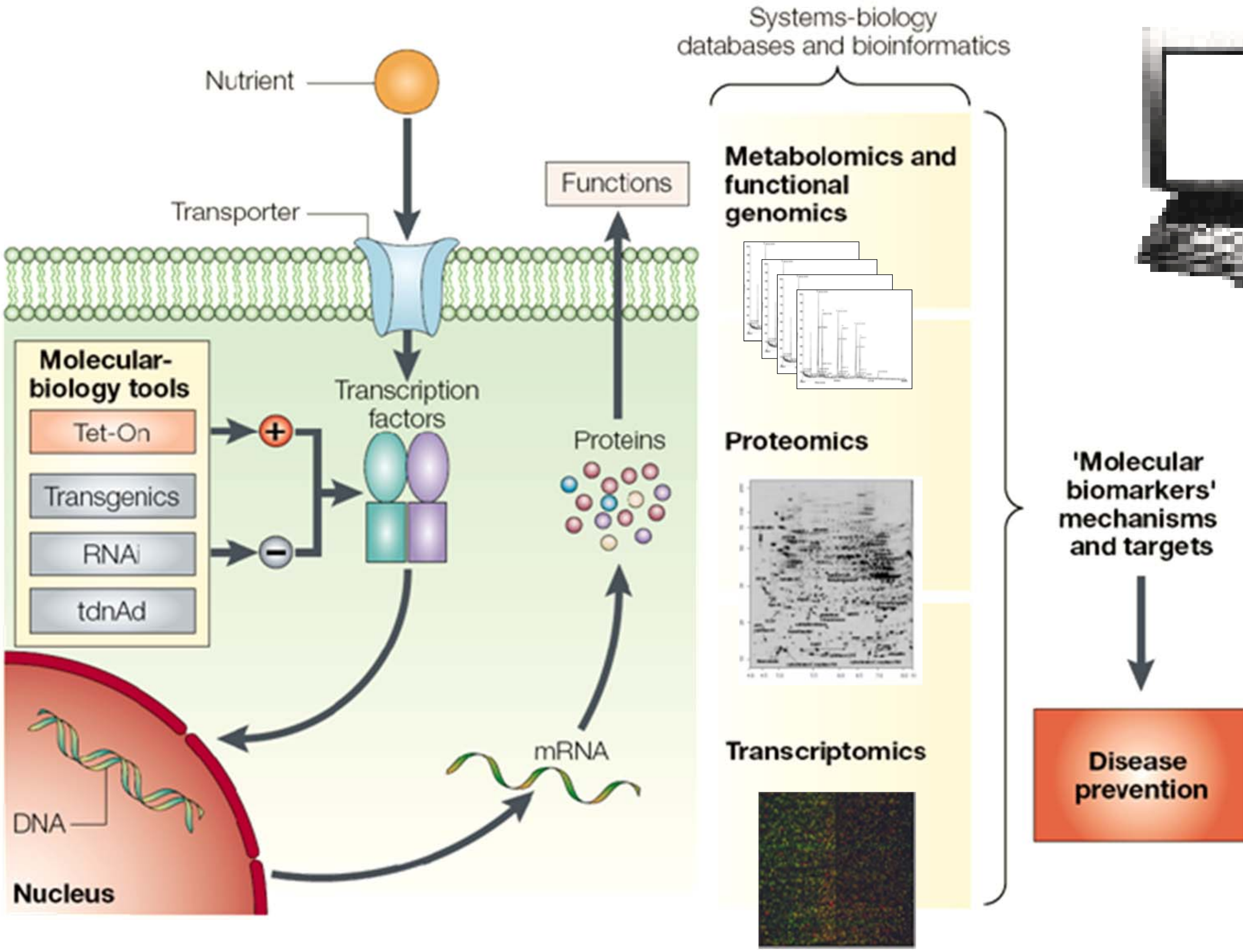
“Molecular Nutrition & Genomics”
The strategy of Nutrigenomics

50000 (?) metabolites

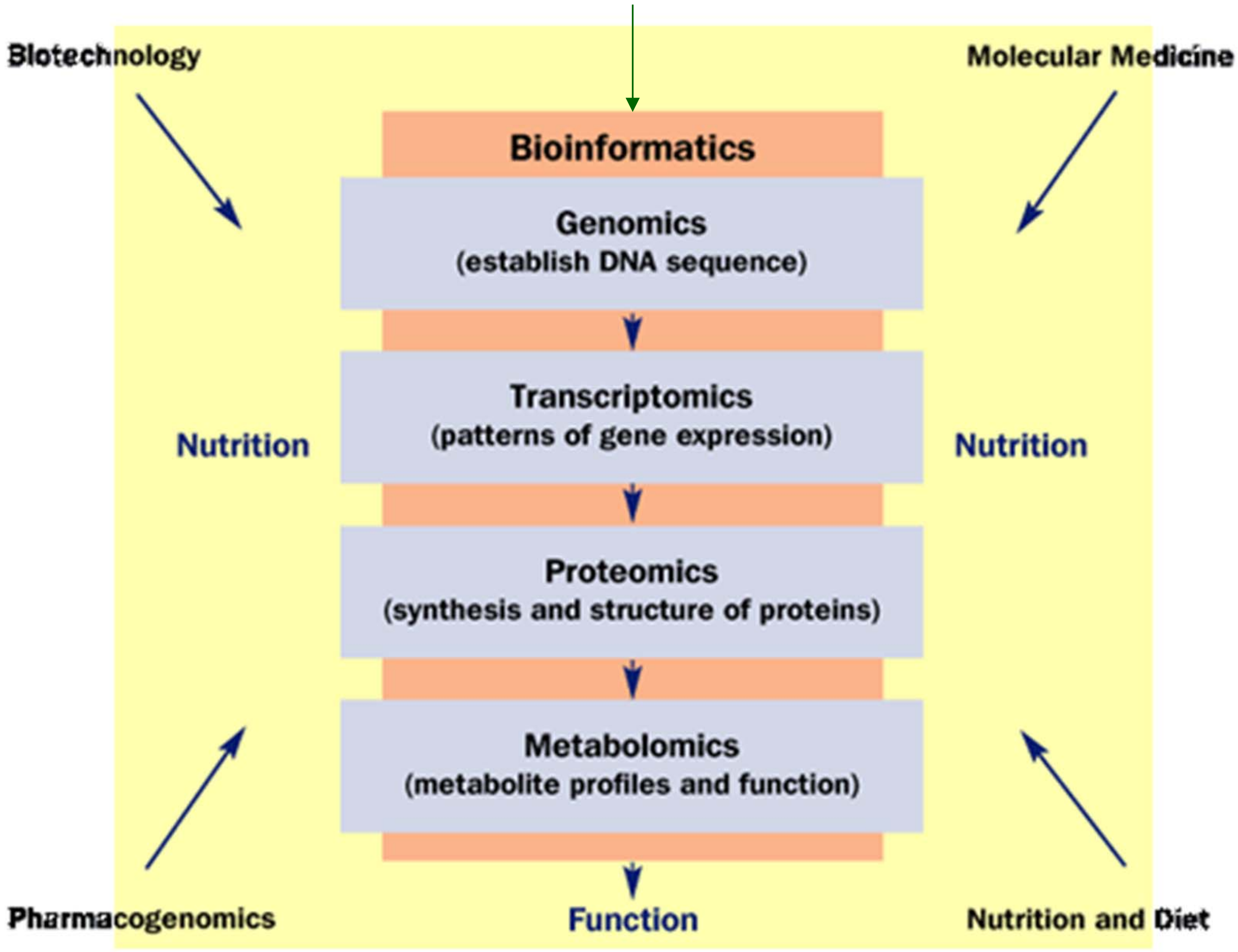
80-100000 proteins

100000 transcripts

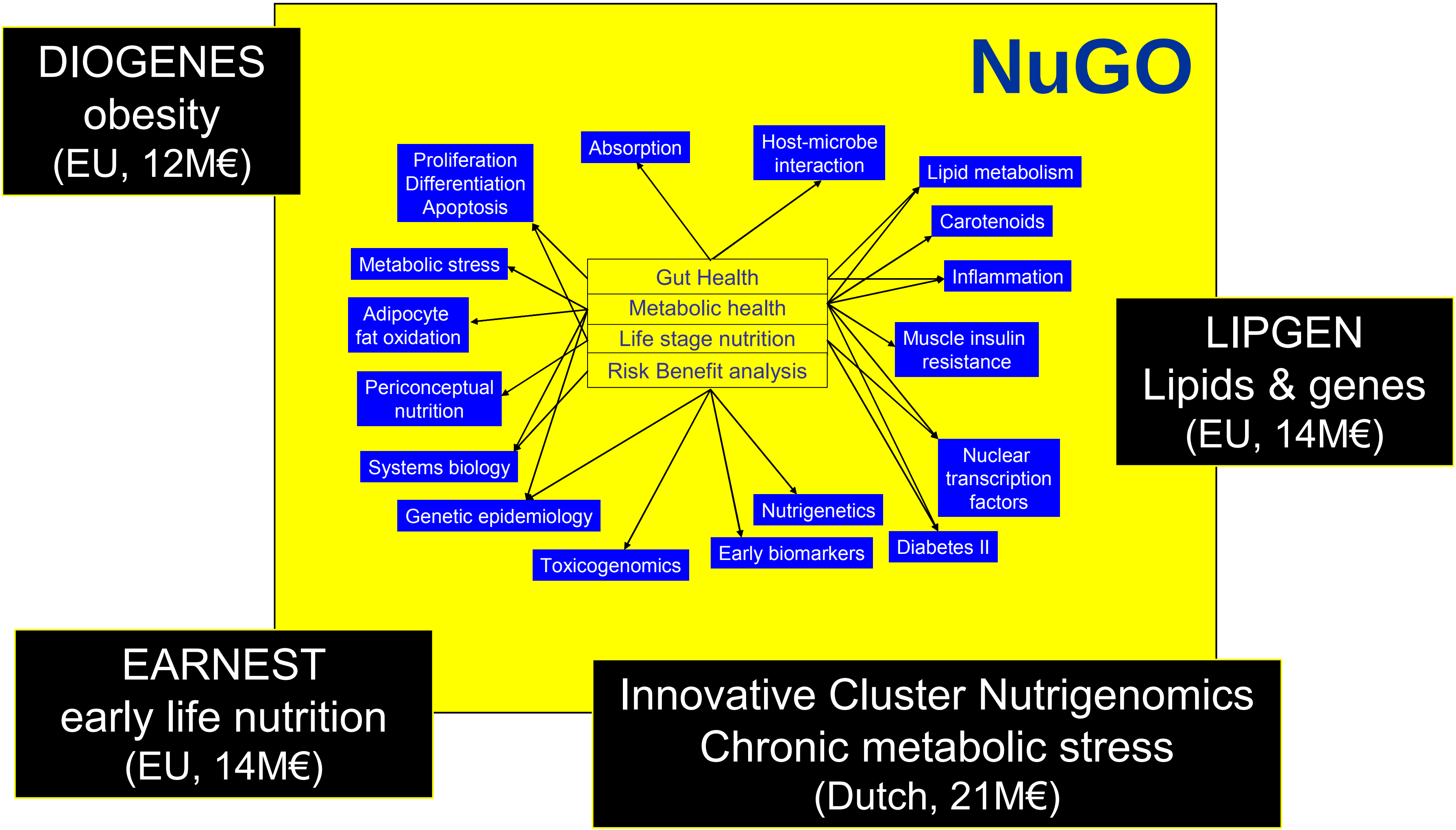
20-25000 genes



Integration of enabling technologies in nutrigenomics



EU programs


DIOGENES
obesity
(EU, 12M€)
NuGO
Proliferation
Differentiation
Apoptosis
Absorption
Host-microbe
interaction
Lipid metabolism
Carotenoids
Inflammation
Metabolic stress
Adipocyte
fat oxidation
Gut Health
Metabolic health
Life stage nutrition
Risk Benefit analysis
Muscle insulin
resistance
Periconceptual
nutrition
Systems biology
Genetic epidemiology
Toxicogenomics
Nutrigenetics
Early biomarkers
Diabetes II
Nuclear
transcription
factors
LIPGEN
Lipids & genes
(EU, 14M€)
EARNEST
early life nutrition
(EU, 14M€)
Innovative Cluster Nutrigenomics
Chronic metabolic stress
(Dutch, 21M€)

Conclusion and future perspective

(1) Nutrigenomics researchers must know the challenge of understanding polygenic diet related diseases.

(2) Short-term goals:

1. to identify the dietary signals.

2. to elucidate the dietary sensor mechanisms.

3. to characterize the target genes of these sensors.

4. to understand the interaction between these signalling pathways and pro-inflammatory signalling to search for sensitizing genotypes.

5. to find '**signatures**' (gene/protein expression and metabolite profiles).

(3) Long-term goals:

Nutrigenomics is to help to understand how we can use nutrition to prevent many of the same diseases for which pharmacogenomics is attempting to identify cures.

Future → **personalized diets**

Геронтогеномика (Gerontogenomics)

GerontoGenomics is the genomics of aging and senescence

Research

Somatic mutations found in the healthy blood compartment of a 115-yr-old woman demonstrate oligoclonal hematopoiesis

Henne Holstege,[1,10] Wayne Pfeiffer,[2] Daoud Sie,[3] Marc Hulsman,[4] Thomas J. Nicholas,[5] Clarence C. Lee,[6] Tristen Ross,[6] Jue Lin,[7] Mark A. Miller,[2] Bauke Ylstra,[3] Hanne Meijers-Heijboer,[1] Martijn H. Brugman,[8] Frank J.T. Staal,[8] Gert Holstege,[9] Marcel J.T. Reinders,[4] Timothy T. Harkins,[6] Samuel Levy,[5] and Erik A. Sistermans[1]

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The somatic mutation burden in healthy white blood cells (WBCs) is not well known. Based on deep whole-genome sequencing, we estimate that approximately 450 somatic mutations accumulated in the nonrepetitive genome within the healthy blood compartment of a 115-yr-old woman. The detected mutations appear to have been harmless passenger mutations: They were enriched in noncoding, AT-rich regions that are not evolutionarily conserved, and they were depleted for genomic elements where mutations might have favorable or adverse effects on cellular fitness, such as regions with actively transcribed genes. The distribution of variant allele frequencies of these mutations suggests that the majority of the peripheral white blood cells were offspring of two related hematopoietic stem cell (HSC) clones. Moreover, telomere lengths of the WBCs were significantly shorter than telomere lengths from other tissues. Together, this suggests that the finite lifespan of HSCs, rather than somatic mutation effects, may lead to hematopoietic clonal evolution at extreme ages.

[Supplemental material is available for this article.]

Mutations are called somatic if they were acquired in a tissue cell during organismal development or later in life, rather than being inherited from a germ cell. As such, somatic mutations lead to genotypic and possibly phenotypic heterogeneity within and between tissues, and they may compromise growth or lead to a growth advantage (Frank 2010). Because somatic mutations often occur during cell division, frequently dividing cell types are more prone to acquire somatic mutations than tissues that rarely divide (Youssoufian and Pyeritz 2002). Consequently, frequently dividing cell types, i.e., epithelial cells, hematopoietic cells, and male germ cells are vulnerable to somatic mutations that may lead to tumor development or other diseases and disorders. Therefore, most studies regarding somatic mutations have been attempts to discover mechanisms leading to cancer and disease (Youssoufian and Pyeritz 2002; Erickson 2010; Hanahan and Weinberg 2011).

It has been estimated that the adult human blood compartment is populated by the offspring of approximately 10,000–20,000 hematopoietic stem cells (HSCs) (Abkowitz et al. 2002). HSCs self-renew about once every 25–50 wk to create two daughter cells equivalent to their parent, and they differentiate to create offspring clones with multipotent progenitor cells that generate the much larger number of diverse blood cells via hematopoiesis (Catlin et al. 2011). Over time, somatic mutations will gradually accumulate within the HSCs, and the genotypes of the HSCs along with their offspring clones will diverge and lead to new clones of varying sizes.

Recent publications show that the genomes of patients with acute myeloid leukemia (AML) contain hundreds of somatic mutations that accumulate with age (Ley et al. 2008; Mardis et al. 2009; Ding et al. 2012), and that most of these mutations occur as random events in HSCs before one of them acquires a specific pathogenic mutation leading to AML (Welch et al. 2012). Similar patterns of clonal evolution have also been shown for the development of chronic lymphocytic leukemia (CLL) (Landau et al. 2013). However, it is currently unknown to what extent healthy HSCs acquire somatic mutations and which types of mutations can be tolerated in the genome during a lifetime without causing disease.

We set out to determine the prevalence and types of single nucleotide and small insertion/deletion mutations that are somatic within the healthy blood genome. Since the occurrence of somatic copy number changes has been shown to increase with age in sev-

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Article published online before print. Article, supplemental material, and publication date are at http://www.genome.org/cgi/doi/10.1101/gr.162131.113. Freely available online through the *Genome Research* Open Access option.

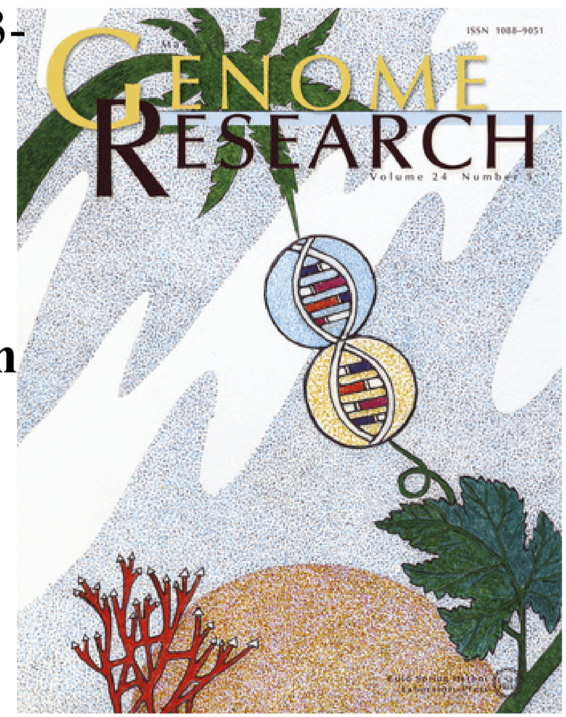
24:733–742 Published by Cold Spring Harbor Laboratory Press; ISSN 1088-9051/14; www.genome.org

Genome Research 733
www.genome.org

- Individual genome in the multiple blood cells of **Hendrikje van Andel-Schipper (1890-2005**), at one point the oldest woman in the world, were sequenced and compared (Holstege et al. 2014 *Genome Res*. 24(5): 733-742)

- She was remarkably healthy until her death

- **450 mutations were found in her cells, but none of them was detrimental**



- **Japanese project to sequence genome and metagenome of all centenarians**

Почему и зачем нужны геномные исследований в лесном хозяйстве

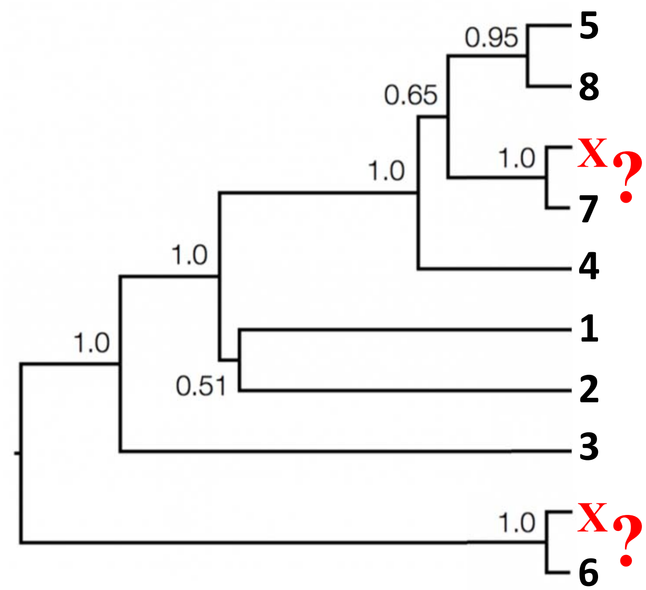
Какая выгода лесной генетике и защите леса от расшифровки генома основных видов хвойных?

- идентификация и аннотация всех функциональных генов и регуляторных элементов (включая короткие РНК, транскрипционные факторы и т.д.) и определение метаболических сетей генов, контролирующих адаптацию и устойчивость к болезням
- разработка высоко информативные генетические маркеры (прежде всего микросателлитных локусов и однонуклеотидных полиморфизмов - SNP – т.н. «снипов»), которые могут быть использованы в генетических исследований популяций и для создания генетической базы данных (наподобие молекулярно-генетических штрих-кодов для отдельных популяций) для борьбы с нелегальной заготовкой и торговлей древесины
- разработка полногеномных генетических маркеров для обнаружения связи между генетической изменчивостью (SNP, аллели , гаплотипы и генотипы) с изменчивостью адаптивных и селекционно-ценных признаков и фенотипов, и с факторами окружающей среды для лучшего понимания генетического контроля адаптивных, селекционных и экономически важных признаков
- разработка полногеномных генетических маркеров для геномной селекции быстрорастущих и более устойчивых пород с ценными признаками
- интеграция протеомики, транскриптомики и метаболомики
- референсный геном для картирования при повторном секвенировании (ресеквенировании)

Использование молекулярно-генетических маркёров для борьбы с нелегальной заготовкой и торговлей древесины

Условная лесная карта, на которой генетически различающиеся популяции выделены разными номерами

На дендрограмме эти популяции расположены на основе генетических различий между ними



Выделение ДНК и гено-типирование

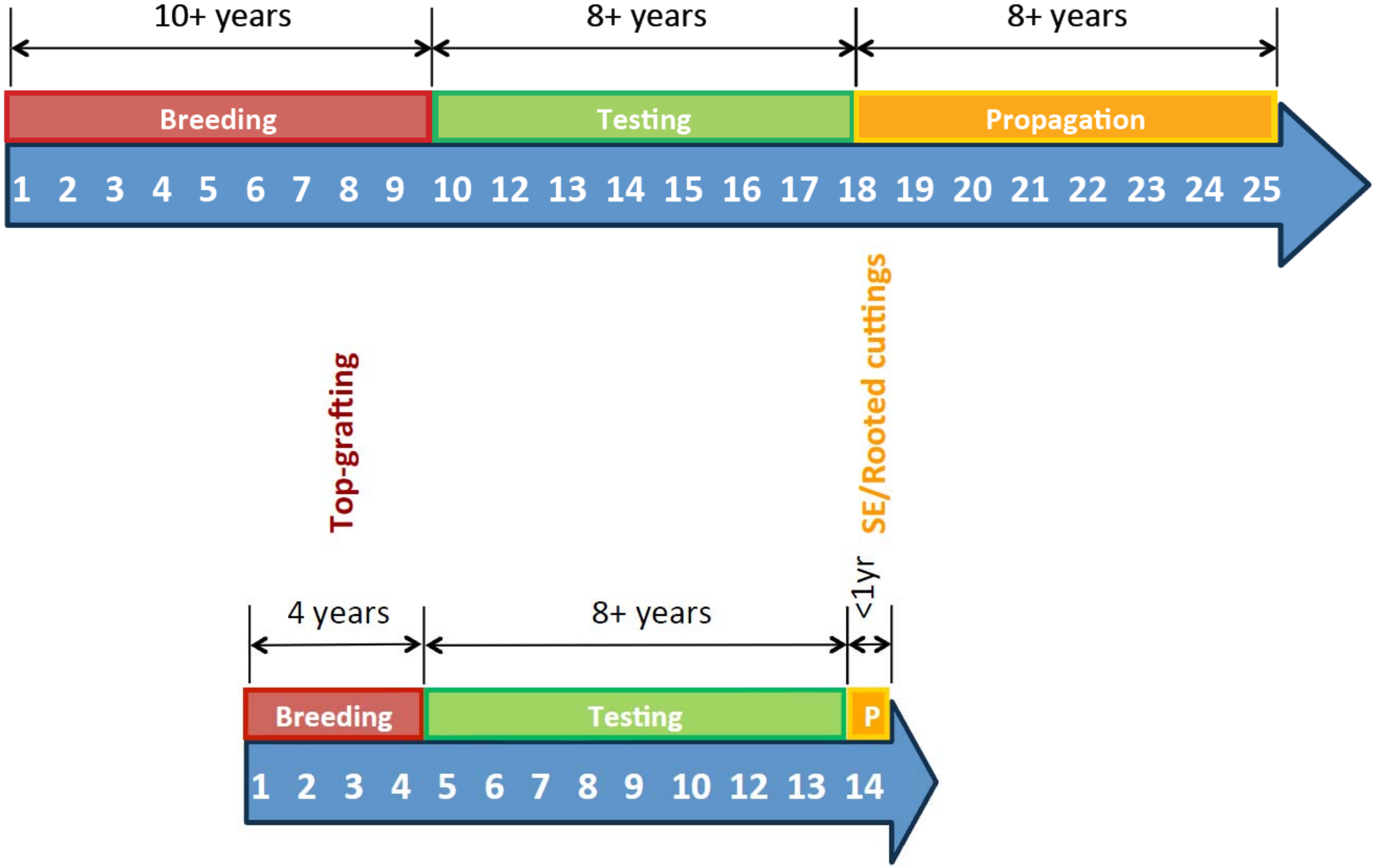
Сверка с компьютерной базой данных по частотам аллелей маркёров (микросателлитные локусы и «снипы») для всех основных популяциях данной породы в данном регионе

Построение новой дендрограммы


Геномика адаптивных признаков хвойных
Время раскрытия почки
Вторичное прорастание
Повреждение почек, хвои и стебля заморозками
Время закладки почки
Засухоустойчивость

Геномная селекция генетически-улучшенных пород животных и растений, в том числе древесных, устойчивых также к экстремальным факторам среды

Traditional pine breeding

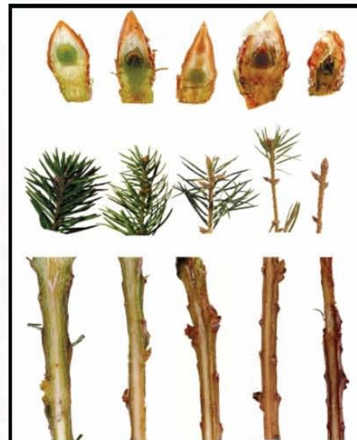


(*Adapted from Matias Kirst*)

Traditional molecular breeding and Marker-Aided Selection (MAS)

Growth

Adaptability



Straightness

Disease resistance

Insect resistance

Wood quality

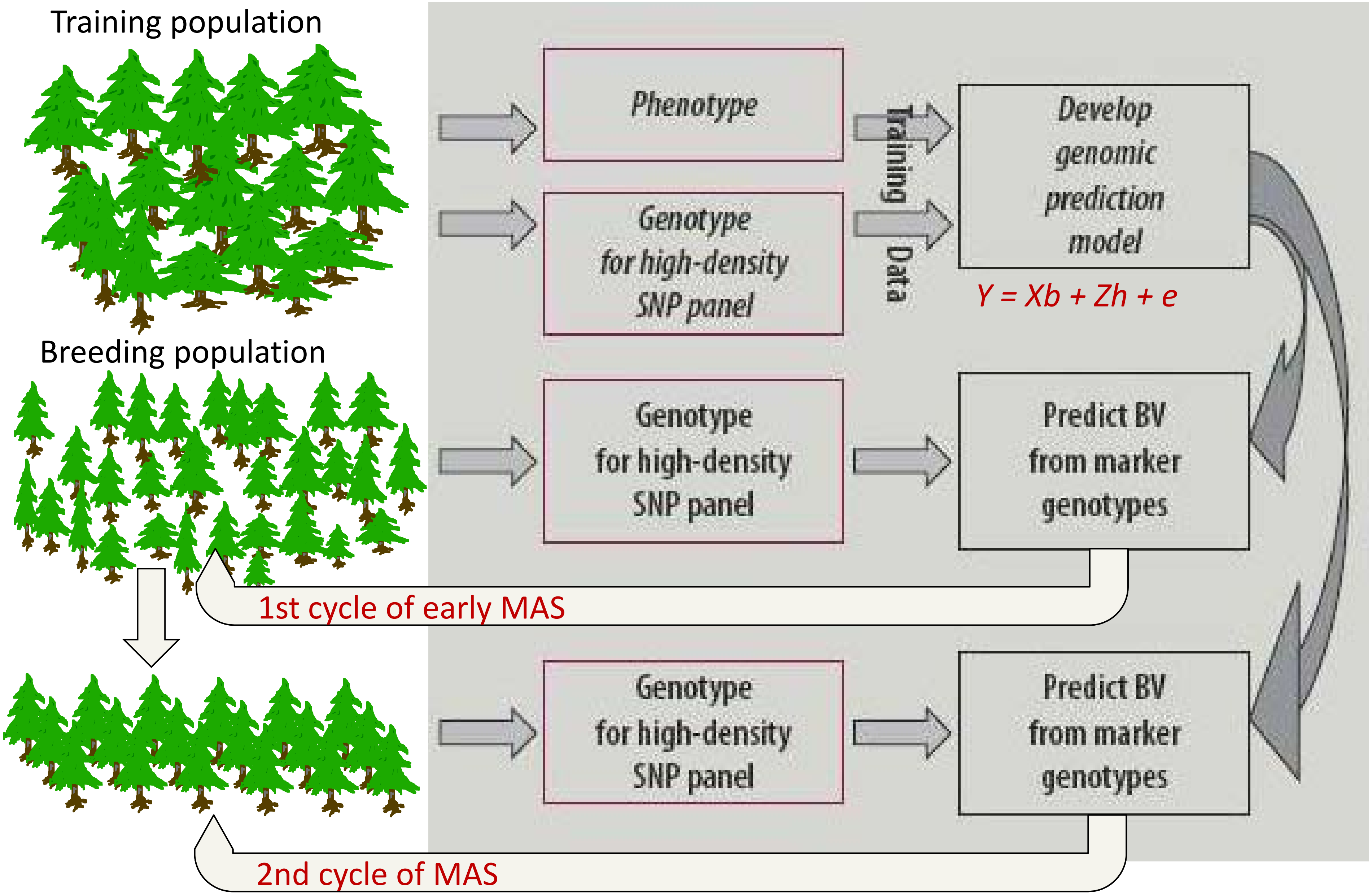
(*Adapted from Dave Neale*)

What we have learned from traditional forest tree breeding:

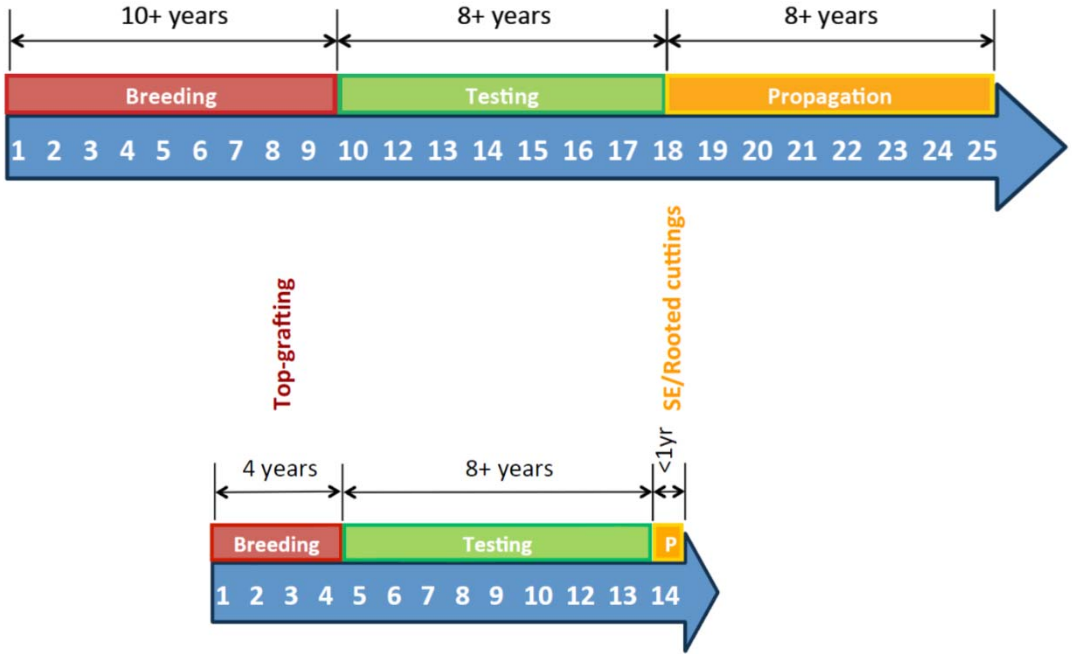
- Most breeding and adaptive traits are complex quantitative traits controlled by environment and multiple genes of small effect

- Genomic based selection is needed to accelerate breeding

Genomic selection

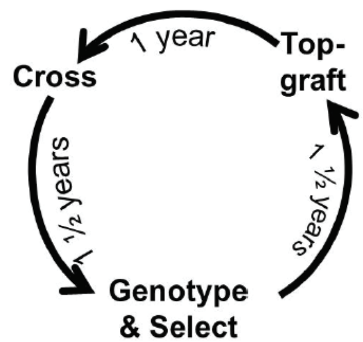


Traditional pine breeding:



Genomic selection:

Genomic Selection Guided Crosses



"Surgical" breeding

(*Adapted from Matias Kirst*)

USDA NIFA Climate Change Program 1: Regional Approaches to Climate Change
PI: Timothy Martin, 2011-2016, $19,976,825; "Integrating research, education and extension for enhancing southern pine climate change mitigation and adaptation".

ESSM Team of Scientists

Drs. Tom Byram, Carol Loopstra and Kostya Krutovsky will be the genetics team from Texas A&M University.

Among this project's main objectives are the study of loblolly pine's genetic adaptation to potential climate change. The goal is to use this knowledge to develop a new seed deployment tool that will help mitigate the detrimental effects of warmer and drier climate in the southeastern United States. Association and population genetics analysis will be used to characterize important adaptation and mitigation traits to support future breeding efforts. The genetics program will support development of growth and yield models, stand-level biophysical carbon balance modeling, multi-scale policy and economic analysis of market and non-market forest benefits and services, and an education program to deliver state-of-the-art forest management solutions. Texas A&M will assist collaborators at sister organizations in meeting these objectives through a local genetics team.

$20 million grant to study effects of climate change http://www.pinemap.org

Six scientists from Ecosystem Science and Management will be part of a $20 million grant to study effects of climate change on agricultural and forest production

On Friday, Feb. 18, the USDA National Institute of Food and Agriculture (NIFA) awarded three Coordinated Agriculture Projects (CAP) representing a major scientific investment in studying the effects of climate change on agriculture and forest production. NIFA Director Roger Beachy made the announcement at the annual meeting of the American Association for the Advancement of Science in Washington, D.C.

"Climate change has already had an impact on agriculture production. Going forward agriculture producers need sound scientific information to plan and make decisions to ensure their economic viability," Beachy said. "These projects ensure we have the best available tools to accurately measure the effects of climate change on agriculture, develop effective methods to sustain productivity in a changing environment and pass these resources on to the farmers and industry professionals who can put the research into practice."

Institute of Food and Agriculture announced the award of a five-year, $20 million grant, to fund research, outreach and education to develop and transfer better management methods for southern pine, notably loblolly pine. They will study climate change mitigation and adaptation as it relates to southern pines, particularly loblolly pine, which comprises 80 percent of the planted forestland in the Southeast. It's widely used for lumber, pulp and paper production, and has great potential for biofuel production.

NIFA made the awards through its Agriculture and Food Research Initiative funding opportunity. AFRI's Climate Change challenge area is focused on reducing greenhouse gas emissions and increasing carbon sequestration in agricultural and forest production systems and preparing the nation's agriculture and forests to adapt to changing climates.

Two-thirds of all the drinking water in the U.S. comes from forested watersheds.

USDA NIFA Climate Change Program 1: Regional Approaches to Climate Change
Project: "Integrating research, education and extension for enhancing southern pine climate change mitigation and adaptation" http://www.pinemap.org

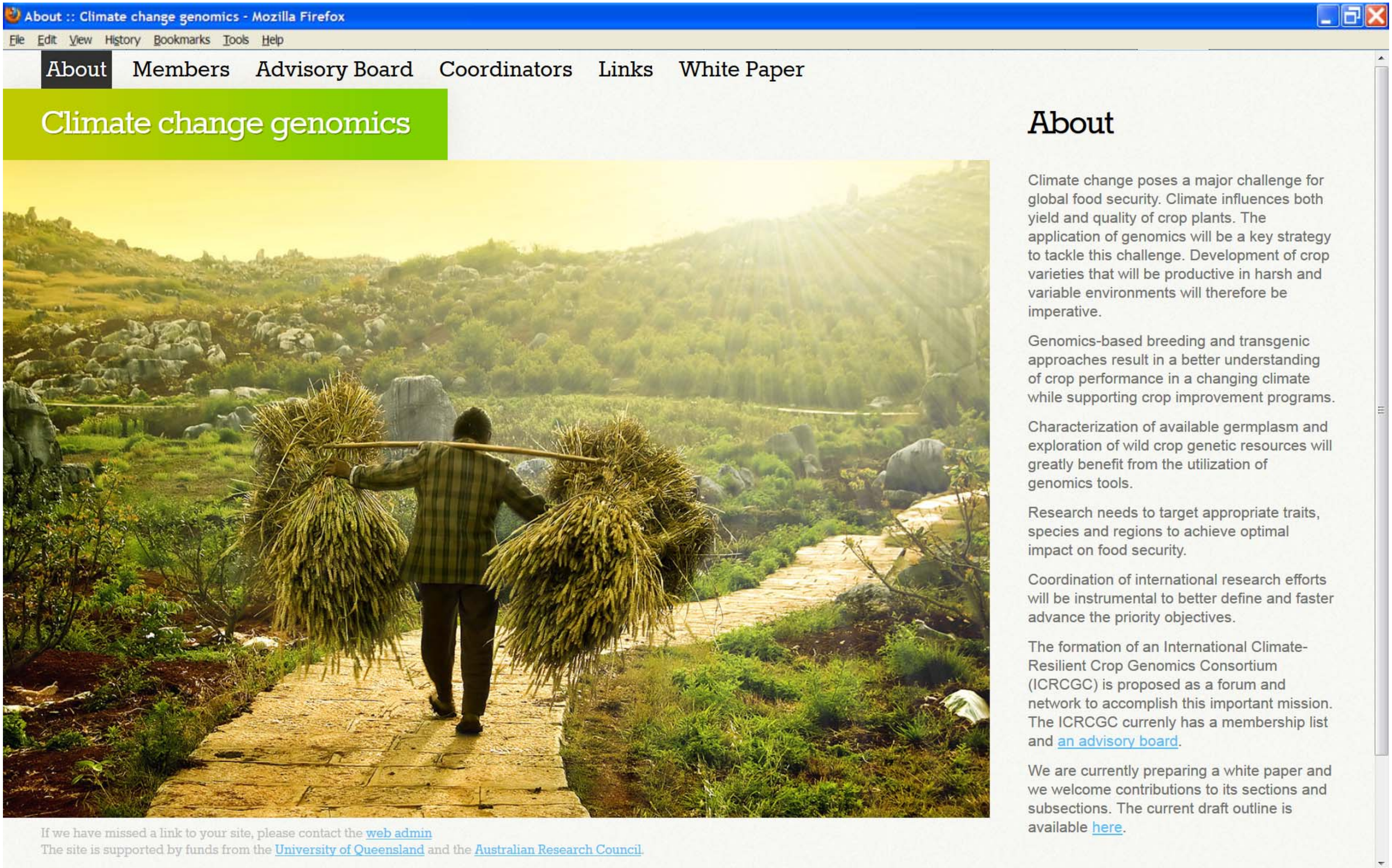
- **2,8 млн SNPs уже генотипировано в почти 40,000 генах ладанной сосны** в моей лаборатории в Texas A&M University в этом проекте путём прямого секвенирования геномной ДНК, обогащённой экзомными районами с помощью гибридизации тотальной ДНК с 600 млн олигонуклетидных проб, представляющих почти полный транскриптом (~40 тыс. экспрессируемых генов) ладанной сосны
- более чем **400 деревьях со всего ареала, профенотипированных по большому числу адаптивных и селекционно-ценных признаков**, а также изученных по большому числу средовых факторов **будут генотипированы по всем обнаруженным SNPs** для обнаружения аллелей и гаплотипов связанных с изменчивостью адаптивных признаков, а также с устойчивостью к средовым факторам
- фактически, это означает **переход от отдельных маркёров к полному генотированию через секвенирование!**
- **эра маркёров заканчивается – наступает эра полногеномного секвенирования!**
- **популяционная геномика вместе с молекулярной экологией (экогеномикой) позволят**:
  - обнаружить гены и аллели ответственные за адаптацию
  - связать генотипы с адаптивными фенотипами и средой

Заключение

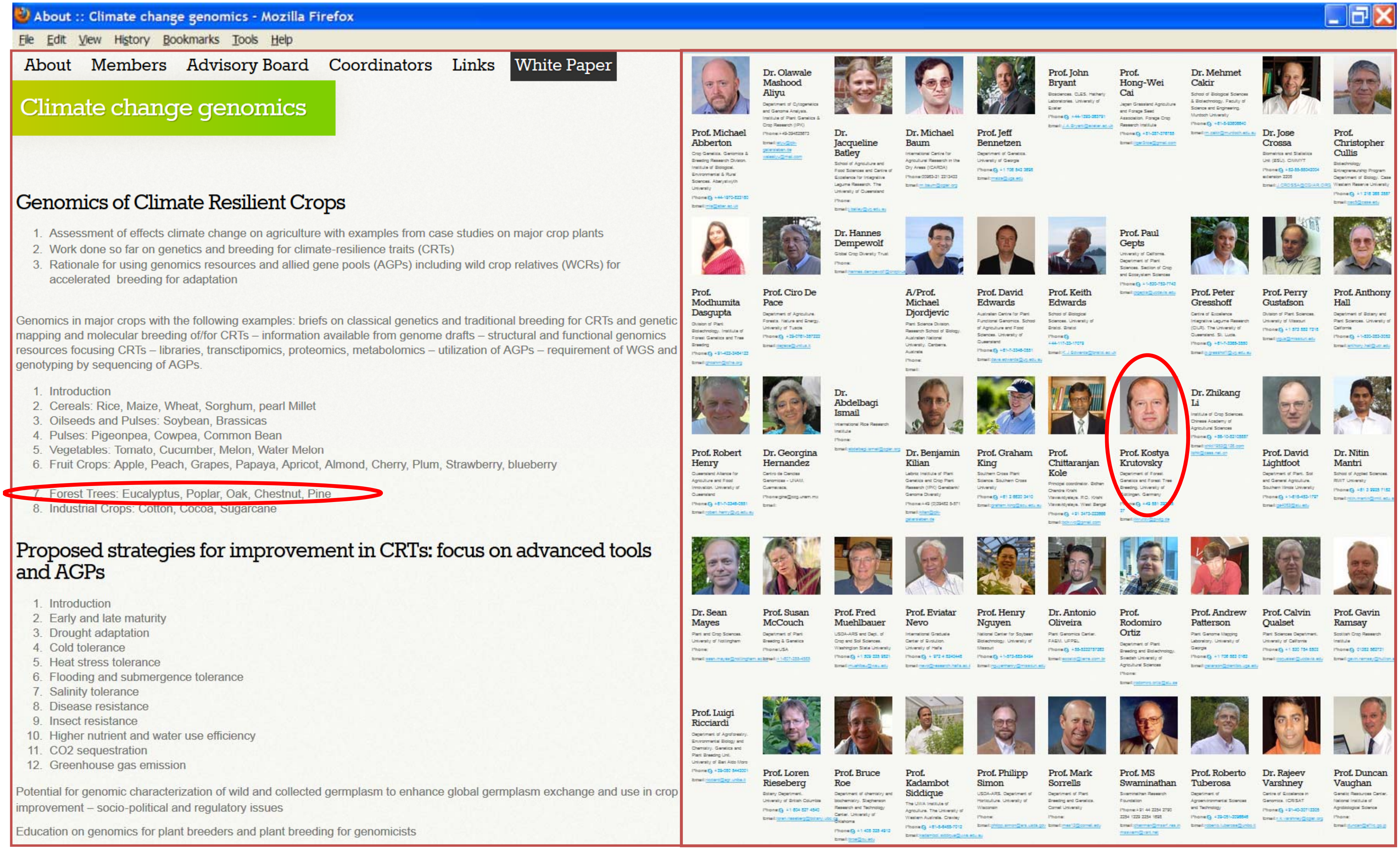
- **Полногеномное секвенирование стало реальностью и наиболее информационным способом генотипирования**

- **Интегрированный популяционно-геномный подход и полногеномное ассоциативное картирование позволяют обнаружить гены ответственные за заболевания у человека и за селекционно-ценные признаки и адаптацию у растений и животных**

The International Climate-Resilient Crop Genomics Consortium (ICRCGC) http://www.climatechangegenomics.org



The International Climate-Resilient Crop Genomics Consortium (ICRCGC) http://www.climatechangegenomics.org/members.php



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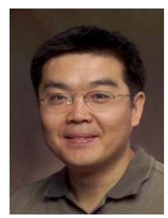

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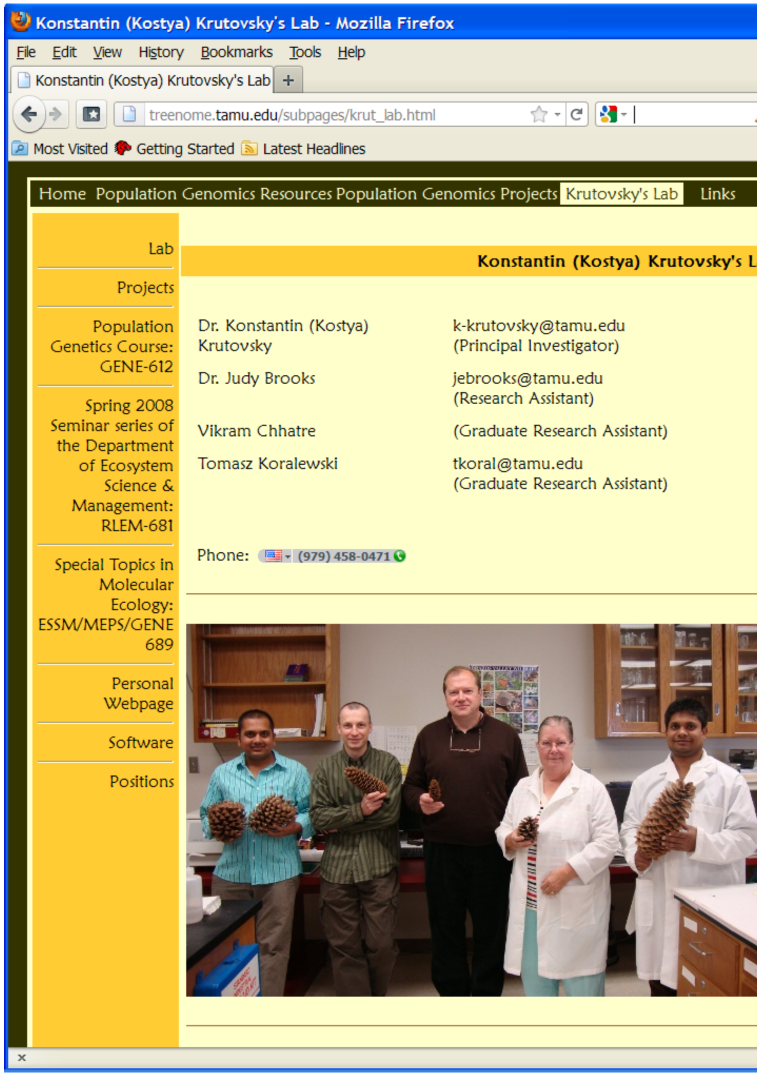

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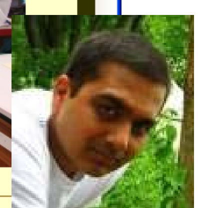

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http://genome.sfu-kras.ru/main

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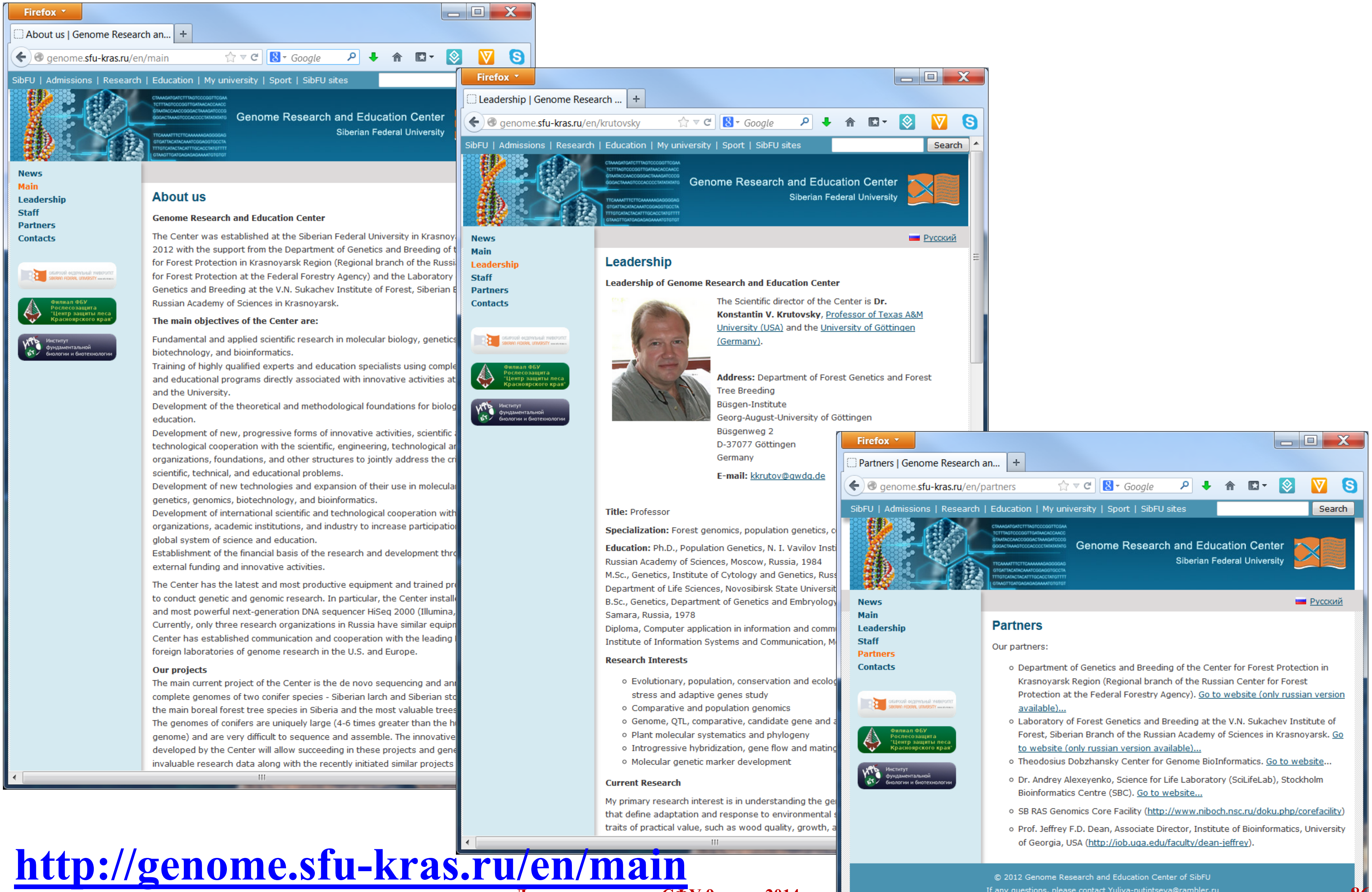

http://genome.sfu-kras.ru/en/main

- **20-ый век:**

  Эволюционное учение + Генетика = Синтетическая теория эволюции (Генетическая теория эволюции или Эволюционная генетика)

  ↓

  популяционный уровень мышления

Феодосий Добжанский
(1900-1975)

- **21-ый век:**

  Молекулярная генетика + Биоинформатика = Геномика

  ↓

  популяционно-геномный уровень мышления

Крутовский К. В. От популяционной генетики к популяционной геномике лесных древесных видов: Интегрированный популяционно-геномный подход // Генетика. 2006. Т. 42. №10. С. 1304–1318.

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