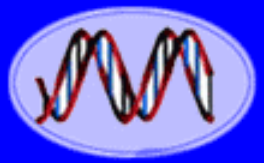
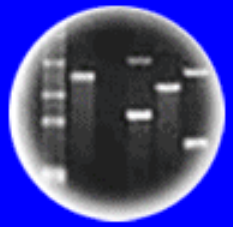


DNA
Genetic Code of Life

Entire Genetic Code
of a Bacteria



DNA Fingerprinting

Cloning: Ethical Issues
and Future Consequences

Plants of Tomorrow

HC70A & SAS70A Winter 2016
Genetic Engineering in Medicine, Agriculture, and Law

Professors Bob Goldberg & John Harada

Lecture 7
Human Genomes &
Tracing Human Ancestry

UCLA

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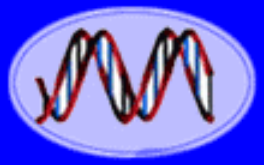

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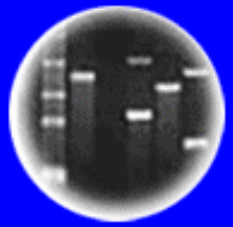

DNA Fingerprinting

Cloning: Ethical Issues
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Themes

UCLA

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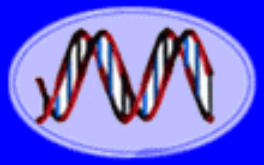

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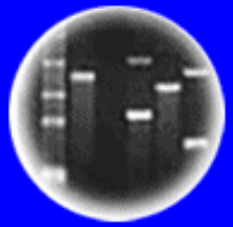

DNA Fingerprinting

Cloning: Ethical Issues and Future Consequences

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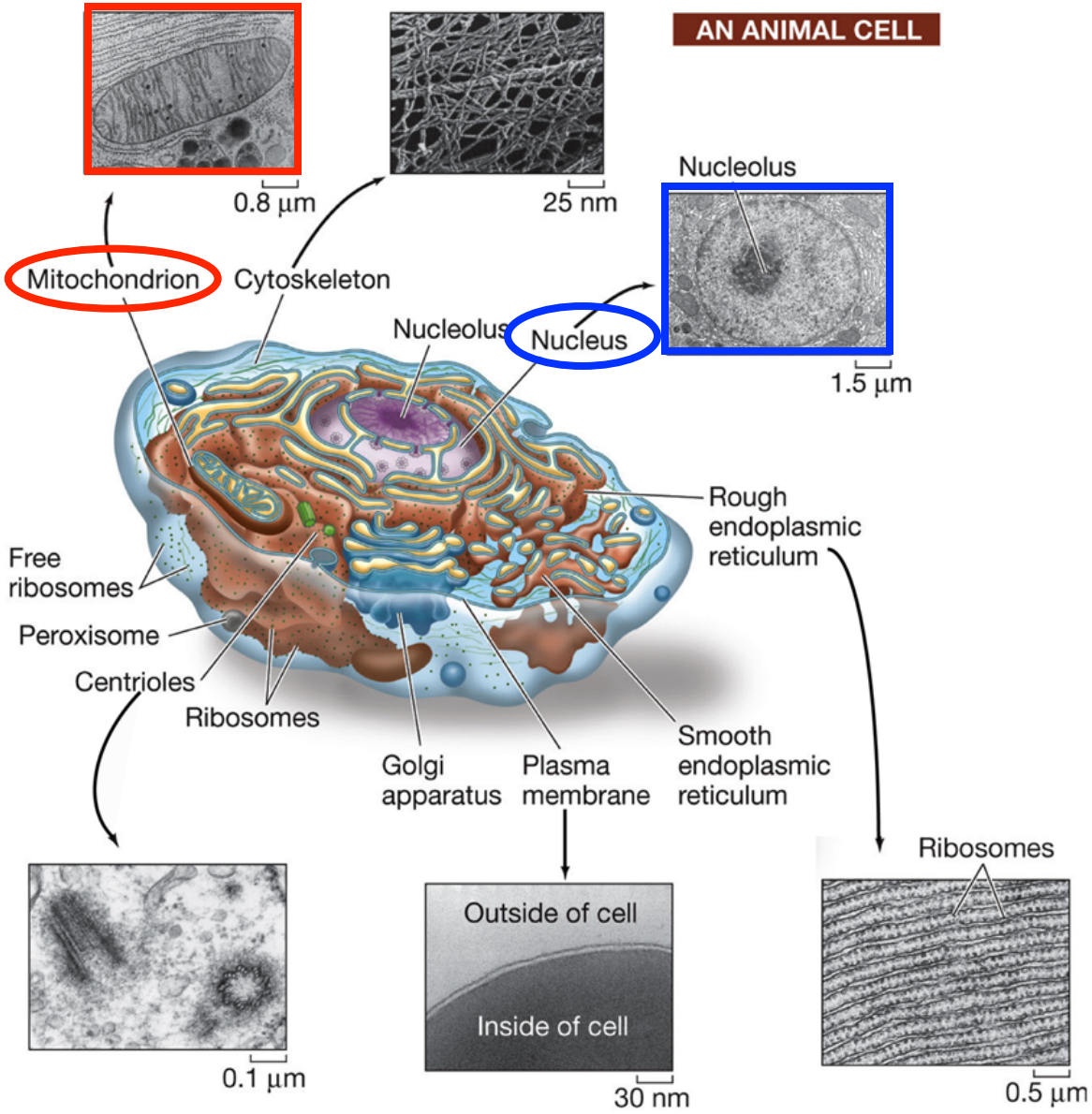
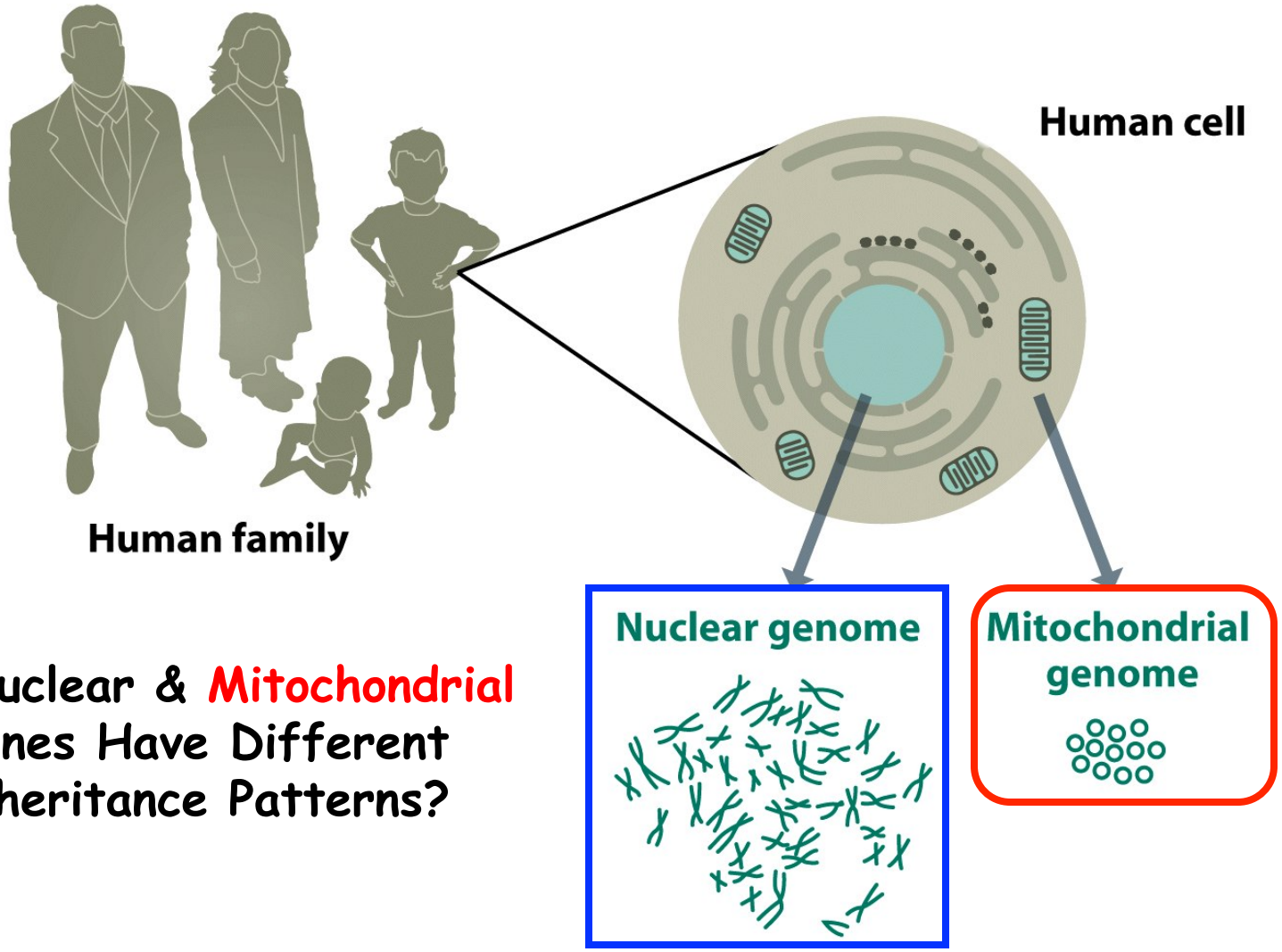
Human Cells Have Two Genomes



……One in the Nucleus and One in the Mitochondria



Do Nuclear & Mitochondrial Genes Have Different Inheritance Patterns?

Figure 1-1 Genomes 3 (© Garland Science 2007)

The Nuclear and Mitochondrial Genomes Differ in Size & Shape

Nuclear

3.2 Mb
25,000 Genes
24 Linear Pieces

Mitochondrial

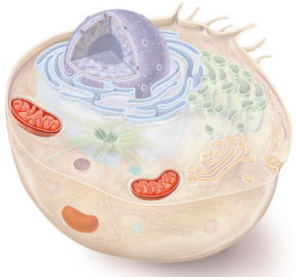
17 kb
30 Genes
1 Circle - 5 per Mt

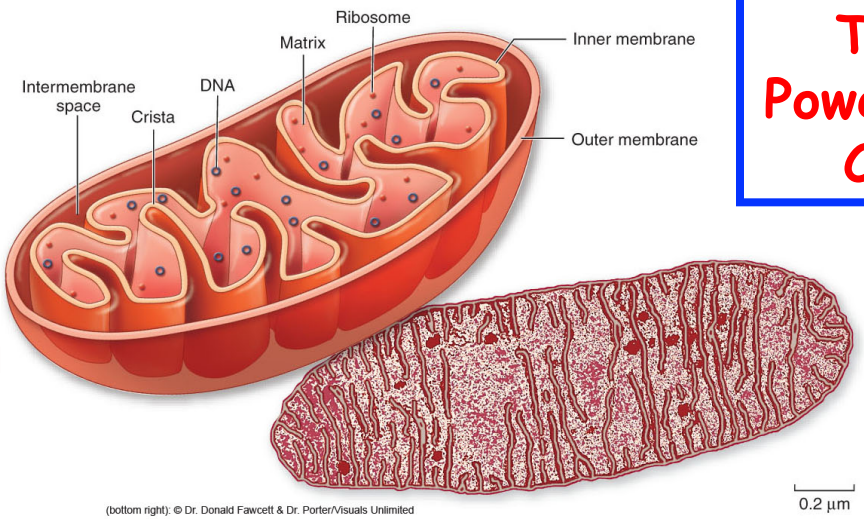
Table 9.1: The human nuclear and mitochondrial genomes

	Nuclear genome	Mitochondrial genome
Size	3200 Mb	16.6 kb
No. of different DNA molecules	23 (in XX cells) or 24 (in XY cells); all linear	One circular DNA molecule
Total no. of DNA molecules per cell	46 in diploid cells, but varies according to ploidy	Often several thousands (but variable – see *Box 9.1*)
Associated protein	Several classes of histone and nonhistone protein	Largely free of protein
No. of genes	~ 30 000–35 000	37
Gene density	~ 1/100 kb	1/0.45 kb
Repetitive DNA	Over 50% of genome, see *Figure 9.1*	Very little
Transcription	The great bulk of genes are transcribed individually (*monocistronic transcription units*)	Co-transcription of multiple genes from both the heavy and the light strands (*polycistronic transcription units*)
Introns	Found in most genes	Absent
% of coding DNA	~ 1.5%	~ 93%
Codon usage	See *Figure 1.22*	See *Figure 1.22*
Recombination	At least once for each pair of homologs at meiosis	Not evident
Inheritance	Mendelian for sequences on X and autosomes; paternal for sequences on Y	Exclusively maternal

Mitochondria Power Human Cells and Contain a Circular Genome

Each Cell Has Many Mitochondria
Blood Cells: 0
Liver Cells: 2000
Egg Cell: 50,000





(bottom right): © Dr. Donald Fawcett & Dr. Porter/Visuals Unlimited

Makes ATP Energy That Powers All Cells!

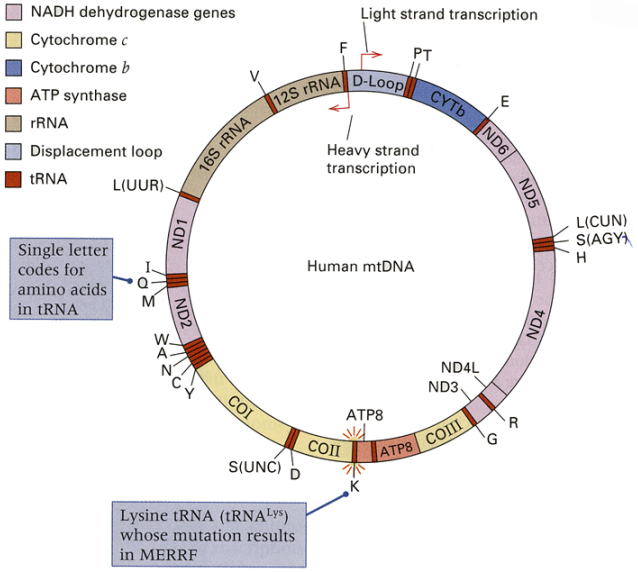


Figure 16.3 Genes in human mitochondrial DNA. The tRNA genes are indicated by the one-letter amino acid symbols; hence $tRNA^{Lys}$ is denoted K. The positions of these and other genes in the mitochondrial DNA are indicated by color according to the key at the upper left. The arrows indicate the promoters for transcription of the heavy and light strands. [Courtesy of N-G. Larsson and D. A. Clayton. With permission, from the *Annual Review of Genetics* 29: 151. Copyright 1995 by Annual Reviews, www.AnnualReviews.org.]

Semi-Autonomous Genome

DNA

Divides
Transcription
Translation

→ **Mitochondrial Proteins**

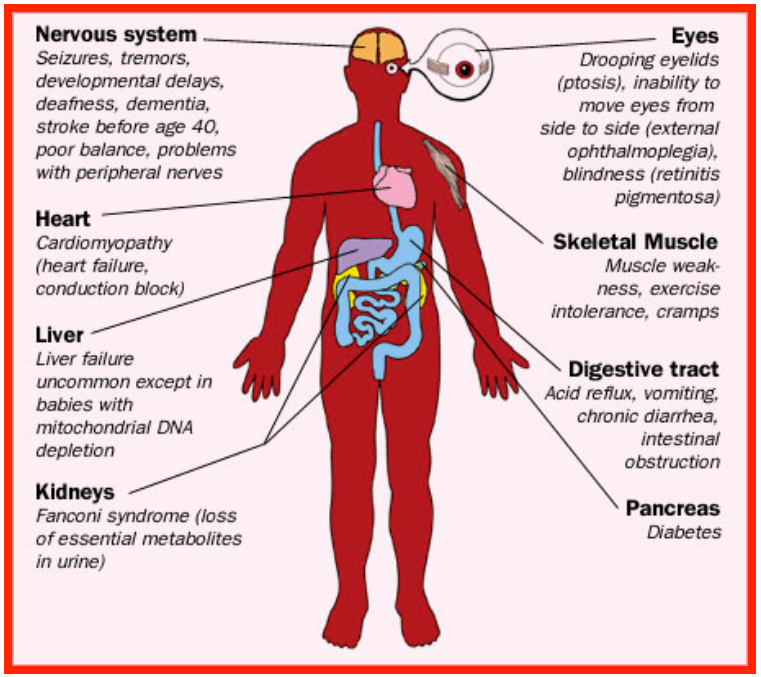
UNITED MITOCHONDRIAL DISEASE FOUNDATION.
HOPE. ENERGY. LIFE.

Mitochondrial DNA Diseases

Defects in Energy Production (ATP)

Affect 1/4000 People

- Alpers Disease
- Barth syndrome
- Beta-oxidation Defects
- Carnitine-Acyl-Carnitine Deficiency
- Carnitine Deficiency
- Creatine Deficiency Syndromes
- Co-Enzyme Q10 Deficiency
- Complex I Deficiency
- Complex II Deficiency
- Complex III Deficiency
- Complex IV Deficiency
- Complex V Deficiency
- COX Deficiency
- CPEO
- CPT I Deficiency
- CPT II Deficiency
- Glutaric Aciduria Type II
- KSS
- Lactic Acidosis
- LCAD
- LCHAD
- Leigh Disease or Syndrome
- LHON
- LIC (Lethal Infantile Cardiomyopathy)
- Luft Disease
- MAD
- MCAD
- MELAS
- MERRF
- MIRAS
- Mitochondrial Cytopathy
- Mitochondrial DNA Depletion
- Mitochondrial Encephalopathy
- Mitochondrial Myopathy
- MNGIE
- NARP
- Pearson Syndrome
- Pyruvate Carboxylase Deficiency
- Pyruvate Dehydrogenase Deficiency
- POLG Mutations
- Respiratory Chain
- SCAD
- SCHAD
- VLCAD

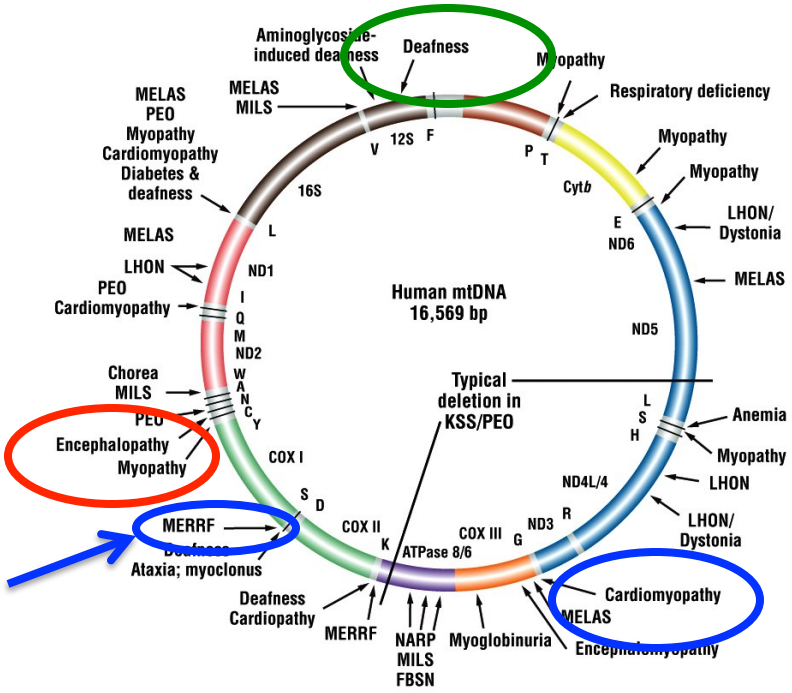


Treatment

At this time, there are no cures for these disorders.

The Circular Mitochondrial Genome is Inherited Maternally

One in Five People Have Mutations in <u>One</u> Mitochondrial Genome But They Do Not Have Disease Symptoms. Why?



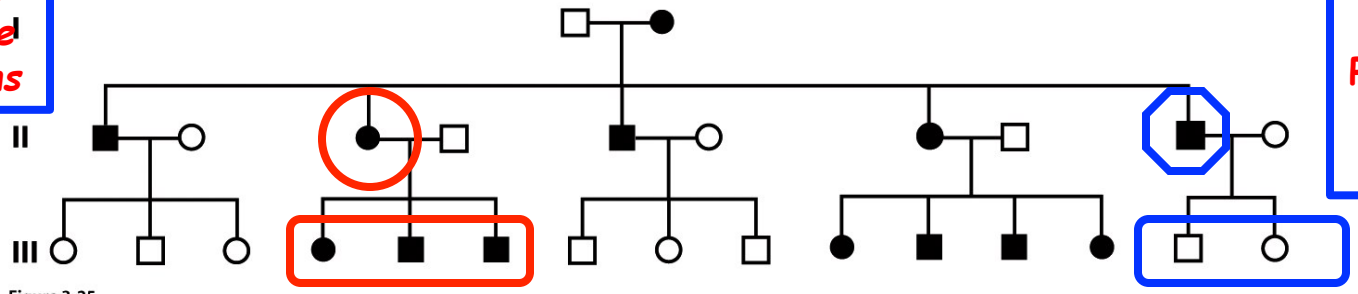
Disease Genes Present on the Mitochondrial Genome

Many Affect Muscles Because Mitochondria Produce Energy Needed For Muscle Activity

Provide a Hypothesis For the Variation in Disease Symptoms

Diseases:

MERRF	Myoclonic epilepsy and ragged red fiber disease	MMC	Maternally inherited myopathy and cardiomyopathy
LHON	Leber hereditary optic neuropathy	PEO	Progressive external opthalmoplegia
NARP	Neurogenic muscle weakness, ataxia, and retinitis pigmentosum	KSS	Kearns–Sayre syndrome
MELAS	Mitochondrial encephalomyopathy, lactic acidosis, and strokelike symptoms	MILS	Maternally inherited Leigh syndrome



Note: Passed on From Mother to All Children

Figure 3-25
Introduction to Genetic Analysis, Ninth Edition

Can Gene Therapy Be Used to "Cure" Mitochondrial Gene Defects?

NUCLEAR TRANSPLANTATION

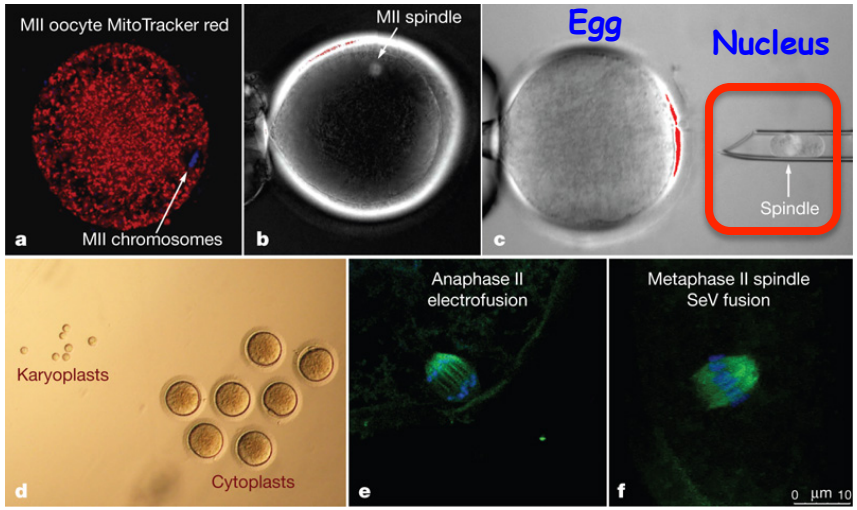
Researchers Prevent Inheritance of Faulty Mitochondria in Monkeys

Vol 461|17 September 2009|doi:10.1038/nature08368 nature

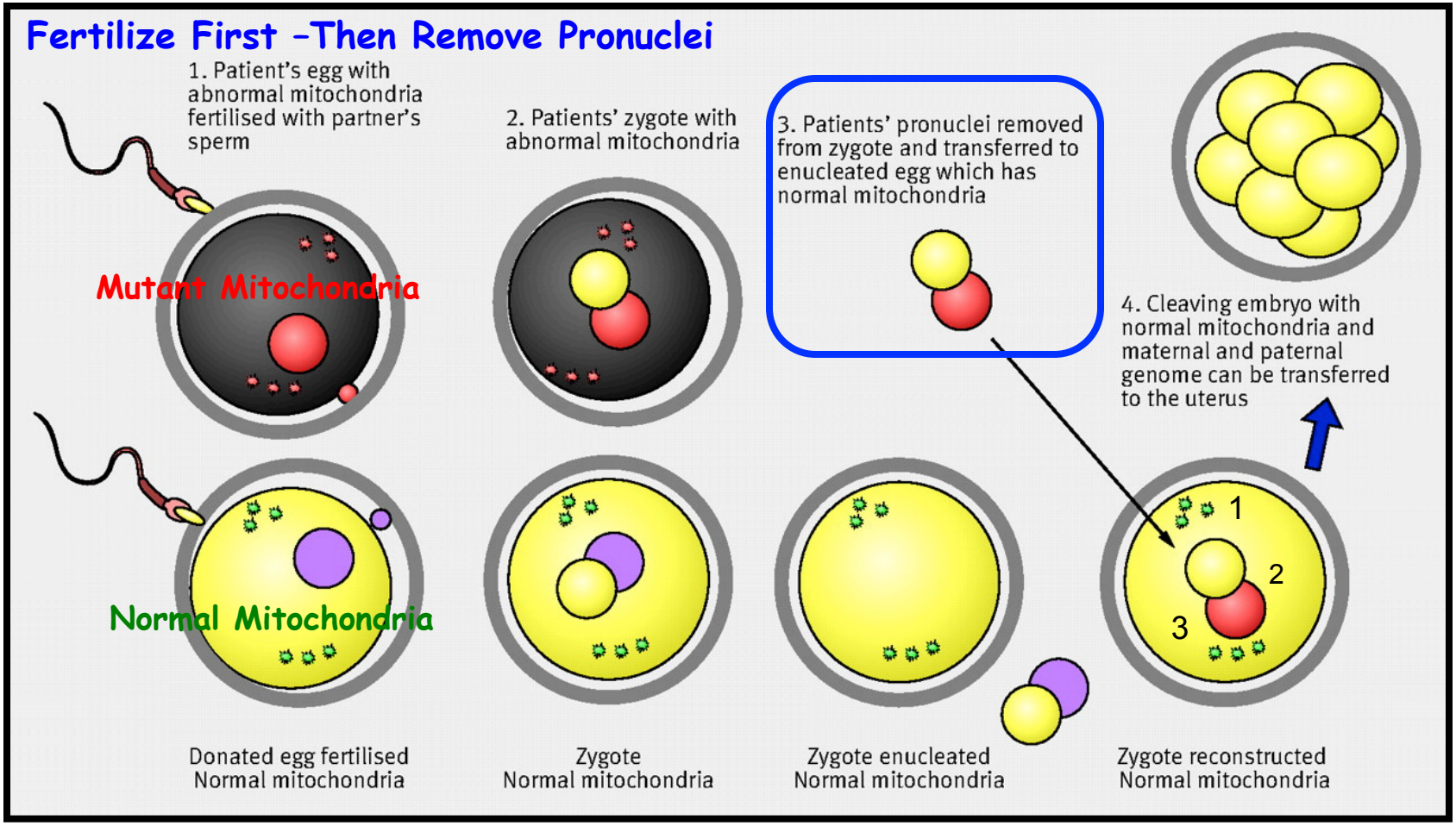
Nature 461, September 17, 2009

ARTICLES

Mitochondrial gene replacement in primate offspring and embryonic stem cells

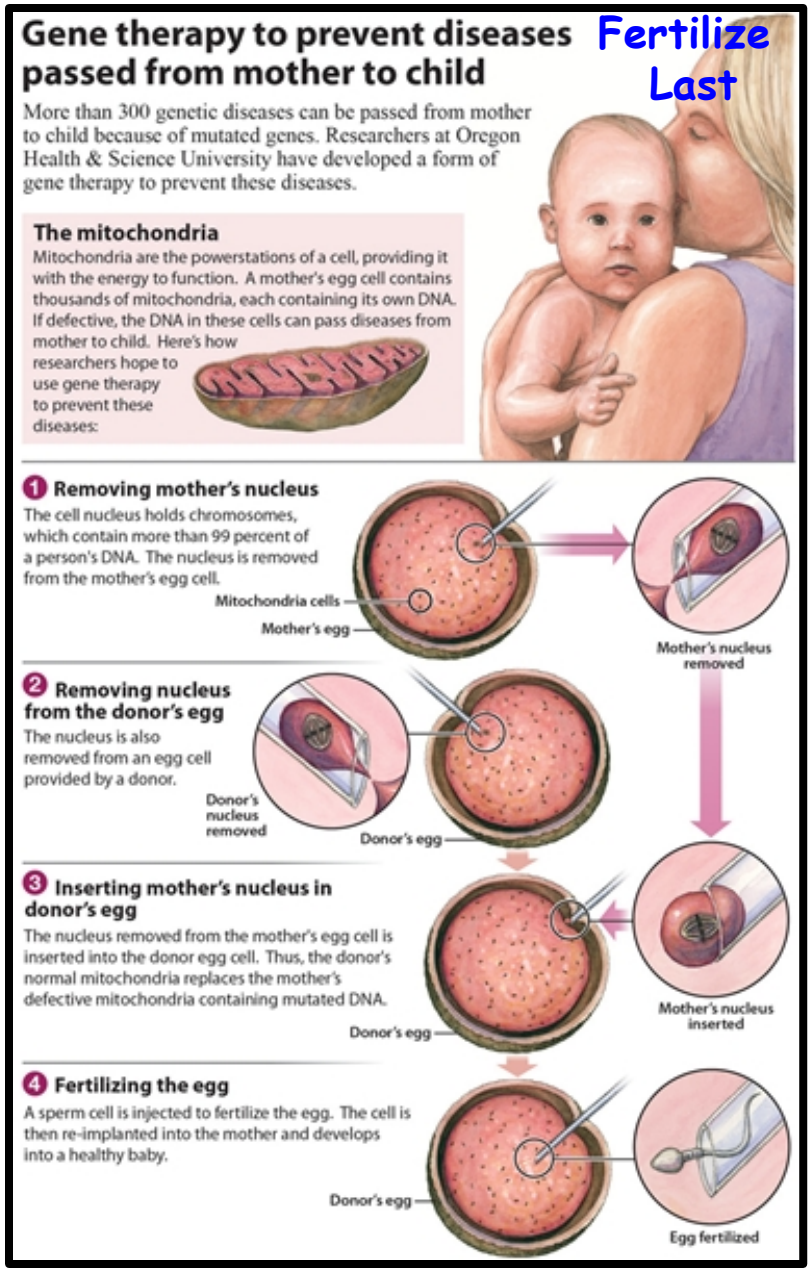


Mitochondrial Pronuclear Replacement Therapy



***Note:* The Zygote Contains THREE Genomes --**
One from Mother, One From Father, and One From Donor Mitochondria

Egg Spindle Replacement Therapy
An Alternative Approach



NATURE | NEWS

DNA-swap technology almost ready for fertility clinic

Mitochondrial transfer could reduce the risk of childhood disease.

David Cyranoski

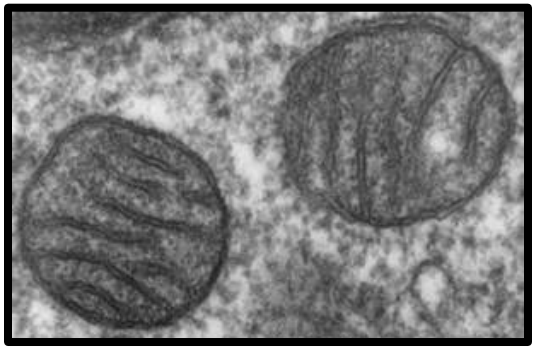
24 October 2012

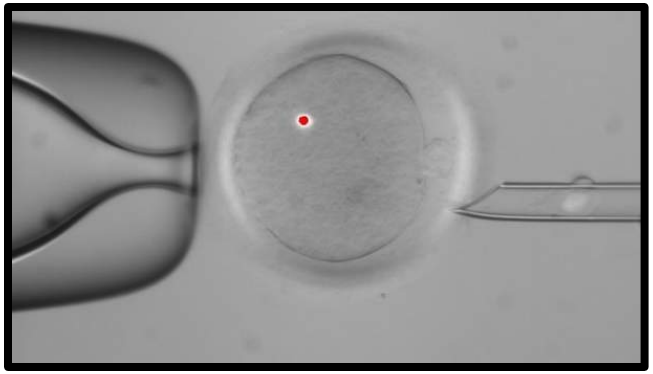
Geneticists Breach Ethical Taboo By Changing Genes Across Generations

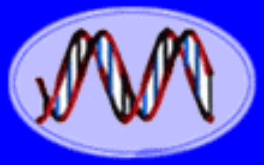
NATURE NEWS BLOG

Bioethics board backs embryo alteration for mitochondrial disease

11 Jun 2012 | 23:01 BST | Posted by Ewen Callaway | Category: Biology & Biotechnology, Health and medicine







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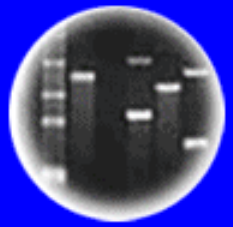

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Plants of Tomorrow

1

Zygote Destroyed

2

Egg Destroyed

GENOME TRANSPLANT

Two different techniques could be used to prevent children from inheriting their mothers' mutant mitochondria.

Pronuclear transfe

Spindle complex

Maternal spindle transfe

An egg from a woman carrying mitochondrial DNA mutations undergoes *in vitro* fertilization (IVF).

The 'spindle' of chromosomes is removed from an unfertilized egg with mitochondrial DNA mutations.

The resulting pronuclei are removed.

Pronuclei

This structure is added to a unfertilized donor egg that has had its spindle removed.

These genetic structures are ferried into a fertilized donor egg that has had its pronuclei removed.

Normal mitochondria

This fused egg goes through IVF.

http://www.nature.com/news/scientists-cheer-vote-to-allow-three-person-embryos-1.16843?WT.ec_id=NEWS-20150210 Page 3 of 6

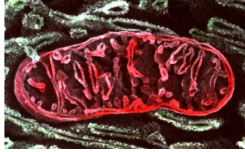
Scientists cheer vote to allow three-person embryos : Nature News & Comment 2/10/15, 2:00 PM

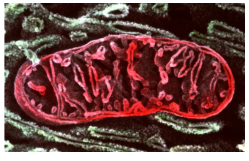
The fused egg goes on to form an embryo.

The fertilized egg then develops into an embryo.

Ethical questions

Two Methods of Mitochondrial Replacement Therapy

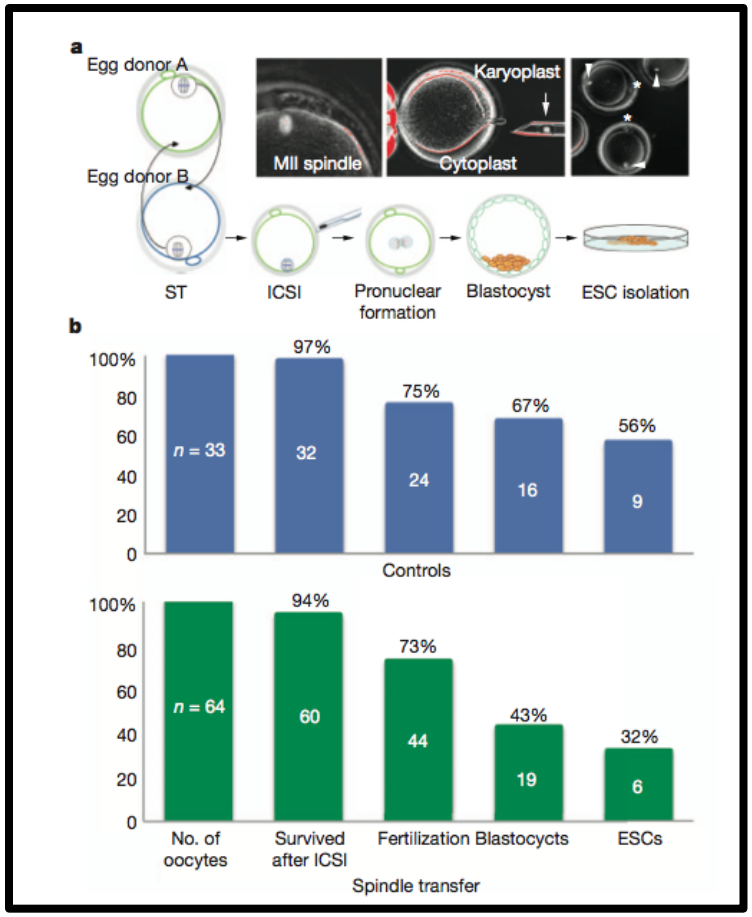




Towards germline gene therapy of inherited mitochondrial diseases

Nature, October, 2012

Using Human Eggs and Embryos



Spindle Transfer Pilot Study Only

Three-Parent Babies: Controversial IVF Procedure To Defeat Genetic Diseases One Step Closer To Being Legalised

Ethics of mitochondrial gene replacement: from bench to bedside

The prospect of using mitochondrial gene replacement to conceive children free of mitochondrial disease highlights the need for a sound ethical framework for reproductive genetic technology, say **Annelien Bredenoord** and **Peter Braude**

- How to Test Whether It Works?
- Testing on Live Human Embryos
- When To Test Its Effectiveness
- Safety & Long-Term Potential Problems
- Nuclear-Mitochondrial Genome Incompatibility?
- Approved Research Protocols
- IRB (Institutional Review Board) Oversight
- Informed Consent of Parents

British Medical Journal, January 8, 2011,342, 87-89

Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review

July, 2013

NUFFIELD COUNCIL ON BIOETHICS

We conclude

Due to the health and social benefits to individuals and families of living free from mitochondrial disorders, and where potential parents express a preference to have genetically-related children, on balance we believe that **if these novel techniques are adequately proven to be acceptably safe and effective as treatments, it would be ethical for families to use them**, if they wish to do so and have been offered an appropriate level of information and support.

Given the above and subject to the appropriate oversight, we believe that **as a research objective it is ethical to gather further information about pronuclear transfer and maternal spindle transfer** in order that they can be considered for treatment use.

UK Becomes First Country to Approve 'Three-Parent Babies'

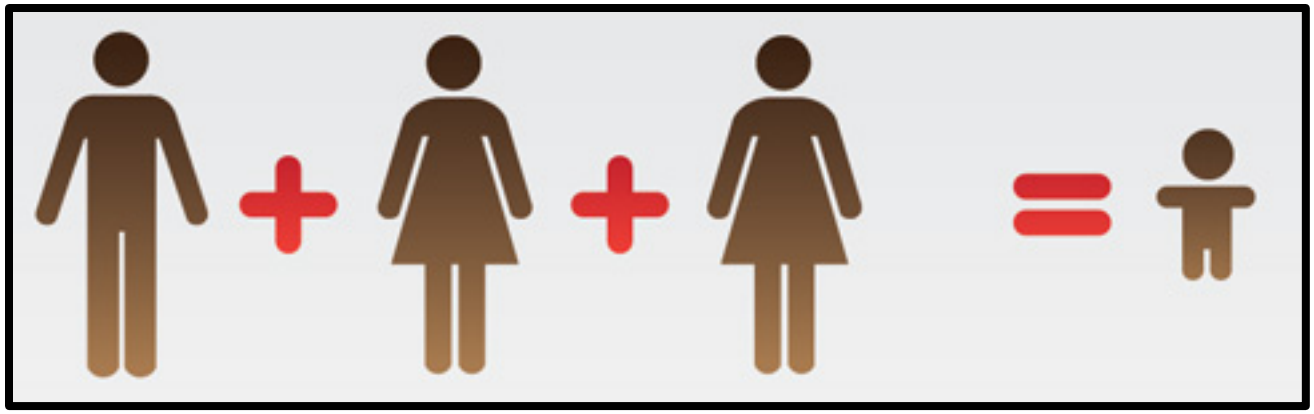
By Carl Engelking | February 3, 2015 1:58 pm

Scientists cheer vote to allow three-person embryos

British decision could be a watershed to approving mitochondrial replacement technique in other countries.

World hails UK vote on three-person embryos

British approval for pioneering fertility technique leads other nations to consider rule changes.



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Advisory Committee Calendar

- 2014 Advisory Committee Tentative Meetings
- 2014 Advisory Committee Calendar
- 2013 Advisory Committee Calendar
- 2012 Advisory Committee Calendar
- 2011 Advisory Committee Calendar
- 2010 Advisory Committee Calendar
- 2009 Advisory Committee Calendar

Resources for You

- 2014 Meeting Materials, Cellular, Tissue and Gene Therapies Advisory Committee
- FR Notice

February 25-26, 2014: Cellular, Tissue, and Gene Therapies Advisory Committee Meeting: Announcement

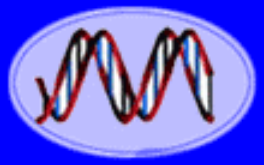
Center	Date	Time	Location
CBER	February 25, 2014 February 26, 2014	8 a.m. - 5:30 p.m. 8 a.m. - 5 p.m.	Hilton Washington, D.C. North/Gaithersburg, 620 Perry Pkwy., Grand Ballroom, Gaithersburg, MD 20877 (301-977-8900)

Agenda
On February 25, 2014, from 8 a.m. to 5:30 p.m. and on February 26, 2014, from 8 a.m. to approximately 11:15 a.m., the committee will discuss oocyte modification in assisted reproduction for the prevention of transmission of mitochondrial disease or treatment of infertility. On February 26, 2014, from approximately 11:15 a.m. to 11:30 a.m., the committee will hear updates on guidance documents issued from the Office of Cellular, Tissue, and Gene Therapies, Center for Biologics Evaluation and Research (CBER), FDA. On February 26, 2014, from 1 p.m. to approximately 5 p.m., the committee will discuss considerations for the design of early-phase clinical trials of cellular and gene therapy products. CBER published guidance on this topic in July 2013.

Meeting Materials
Materials for this meeting will be available at the Cellular, Tissue, and Gene Therapies Advisory Committee Meeting main page.

Public Participation Information
Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee.

- Written submissions may be made to the contact person on or before February 18, 2014.
- Oral presentations from the public w… heduled between approximately 2:15 p.m. and 3:15 p.m. on February 25, 2014 and between a… 1:45 p.m. and 2:15 p.m. on February 26, 2014. Those individuals interested in making f… sentations should notify the contact person and submit a brief statement of the general nature… r arguments they wish to present, the names and addresses of proposed particip… cation of the approximate time requested to make their presentation on or before Febru… me allotted for each presentation may be limited. If the number of registrants requesting to speak is greater than can be reasonably accommodated during the scheduled open public hearing session, FDA may conduct a lottery to determine the speakers for the scheduled open public hearing session. The contact person will notify interested persons regarding their request to speak by February 11, 2014.
- For those unable to attend in person, the meeting will also be Webcast. The link for the Webcast is available at:
  - February 25, 2014
  - February 26, 2014



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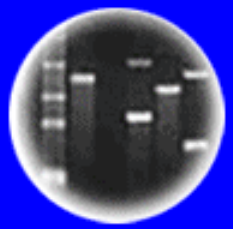

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What About The United States?
Recommendations to the FDA

NATIONAL ACADEMY OF SCIENCES

NATIONAL RESEARCH COUNCIL

OF THE NATIONAL ACADEMIES

Status: Prepublication
Downloads: 1,035

Mitochondrial Replacement Techniques:

Ethical, Social, and Policy Considerations (2016)

Board on Health Sciences Policy

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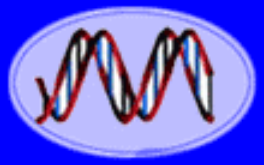

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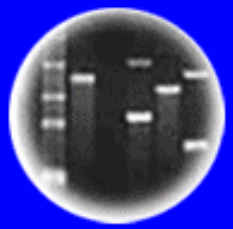


DNA Fingerprinting

Cloning: Ethical Issues and Future Consequences

Plants of Tomorrow

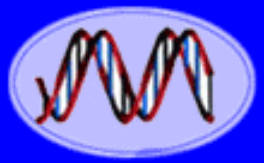
Finding an ethical path forward for mitochondrial replacement

NRC Report Summary - Science, February 3, 2016

Anne B. Claiborne[1*†], Rebecca A. English[1*], Jeffrey P. Kahn[2*†]

It is Ethically Permissible to Initiate Clinical Investigations of Mt Replacement Therapy in Humans So Long as *Significant Conditions and Restrictions* Are in Place

1. Initial Restriction to Transfer to Male Embryos
2. No Transfer to Females Until Robust Evidence is Obtained of the Safety & Efficacy of Technique By Following Children Long Term
3. Public Discussion Should Be Held to Determine If Ever Female Transfer Should Be Permitted as This Results in a Heritable Genetic Modification
4. Limit Clinical Investigations to Women Who Are At Risk of Transmitting a Serious Mt Disease
5. Primary Concern in Assessing the Benefits & Risks in Clinical Investigation is Minimizaiton of Risk of Harm to the Resulting Child



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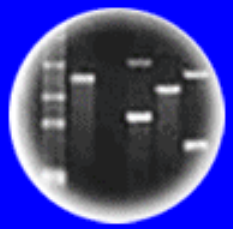

DNA Fingerprinting

Cloning: Ethical Issues and Future Consequences

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Road Blocks

Dickey-Wiker Amendment-1995

Federal Funds Cannot Be Used To:

- Create Human Embryos For Research Purposes
- Fund Research in Which a Human Embryo Will Be Destroyed, Discarded, or Knowingly Subjected to Risk or Injury of Death

2016 Congressional Budget

- FDA Cannot Spend Any Money to Review Applications For Clinical Trials That Involve Human Embryos With Heritable Genetic Modifications *(But… Male Mt Replacement Not Inherited & Egg Spindle Transfer Doesn't Destroy Embryo)*

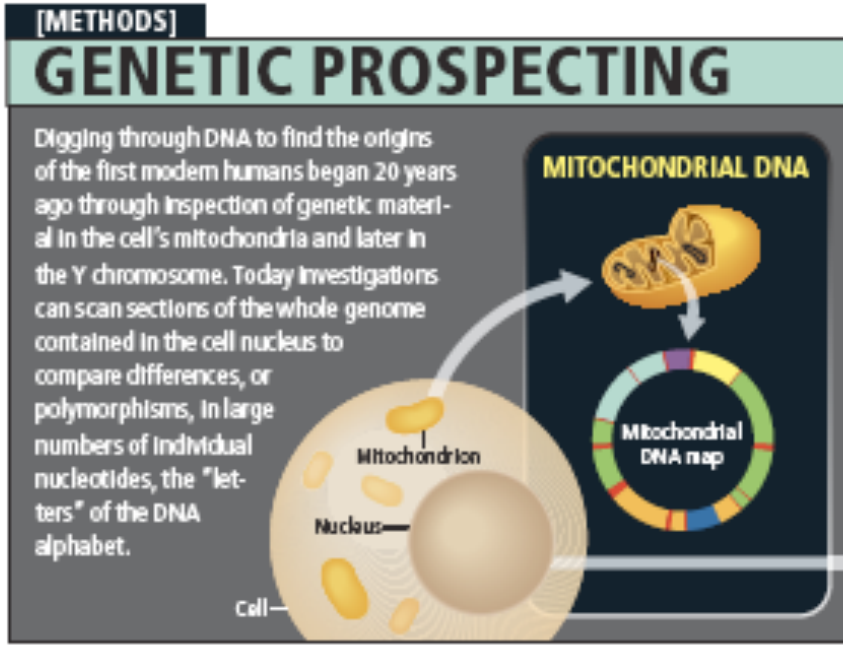
Country-Specific Approaches to Mitochondrial Replacement Therapy

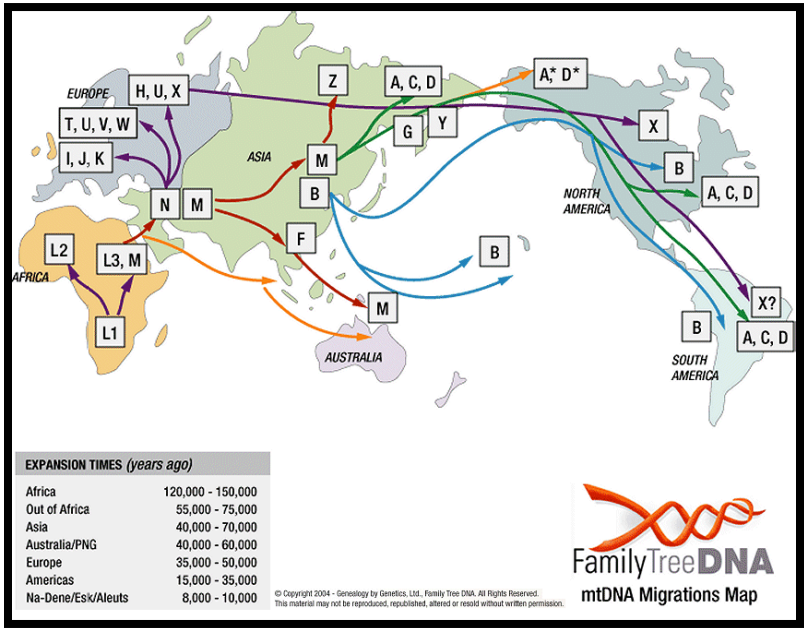
- Focus on All Therapeutics – View MRT as a "drug or biological product"
- National Values - "Moral" Objections to Working on Human Embryos
- Human Embryo Research Controversial and Funding Constrained (no funding for creation of human embryo for research or where human embryo destroyed – Dickey-Wicker Amendment)
- Embryo Research)
- Tangled in Political and Religious Debate Over Abortion, Rights of Embryos, & When Life Begins
- Minimal Public Consultation

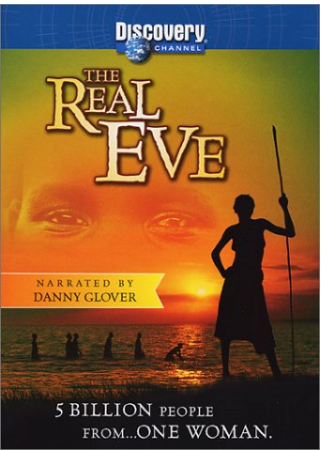
- Focus Specifically on Human Fertility & Reproductive Matters
- Legal in Great Britain to Conduct Research on Human Embryos up to Day 14
- Views MRT as an Extension of Existing and Familiar Technologies (e.g., IVF)
- National Values - No "Moral" Objections to Working on Human Embryos
- Extensive Public Consultation

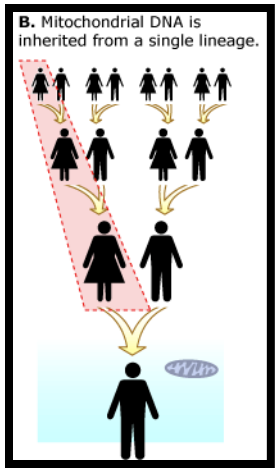
Science 348,178-180, April 10, 2015

Tracing Human Populations Using Mitochondrial DNA Polymorphisms (SNPs) - Back to Eve!



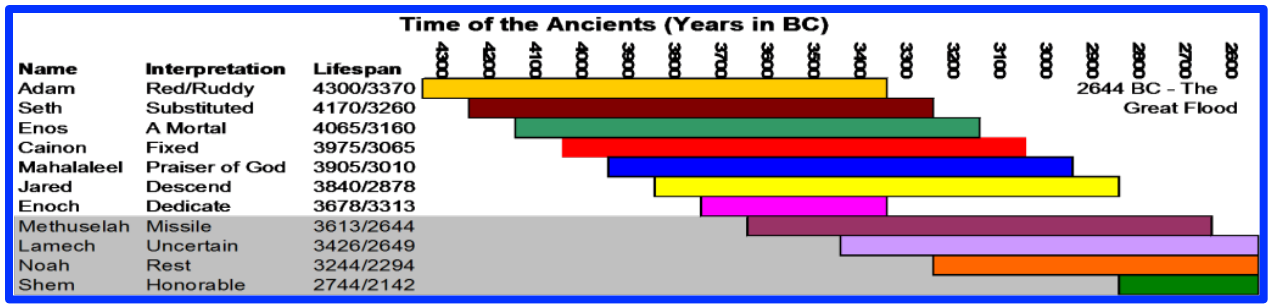






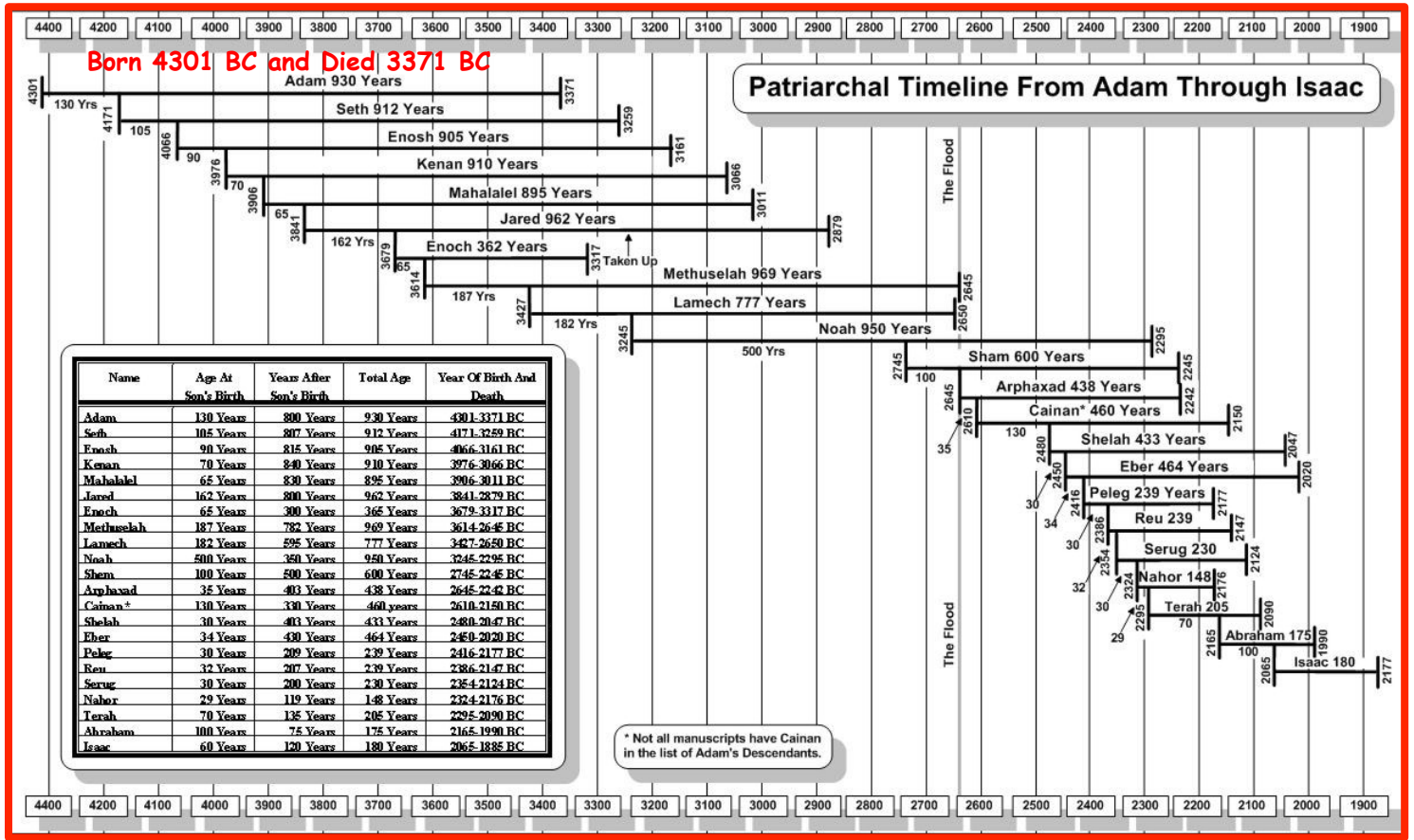
When Did Adam & Eve Live? According to the Book of Genesis ~ 6,000 Years Ago!!

The Book of Genesis



Name	Interpretation	Lifespan
Adam	Red/Ruddy	4300/3370
Seth	Substituted	4170/3260
Enos	A Mortal	4065/3160
Cainon	Fixed	3975/3065
Mahalaleel	Praiser of God	3905/3010
Jared	Descend	3840/2878
Enoch	Dedicate	3678/3313
Methuselah	Missile	3613/2644
Lamech	Uncertain	3426/2649
Noah	Rest	3244/2294
Shem	Honorable	2744/2142

The Book of Genesis



Name	Age At Son's Birth	Years After Son's Birth	Total Age	Year Of Birth And Death
Adam	130 Years	800 Years	930 Years	4301-3371 BC
Seth	105 Years	807 Years	912 Years	4171-3259 BC
Enosh	90 Years	815 Years	905 Years	4066-3161 BC
Kenan	70 Years	840 Years	910 Years	3976-3066 BC
Mahalalel	65 Years	830 Years	895 Years	3906-3011 BC
Jared	162 Years	800 Years	962 Years	3841-2879 BC
Enoch	65 Years	300 Years	365 Years	3679-3317 BC
Methuselah	187 Years	782 Years	969 Years	3614-2645 BC
Lamech	182 Years	595 Years	777 Years	3427-2650 BC
Noah	500 Years	350 Years	950 Years	3245-2295 BC
Shem	100 Years	500 Years	600 Years	2745-2245 BC
Arphaxad	35 Years	403 Years	438 Years	2645-2242 BC
Cainan*	130 Years	330 Years	460 years	2610-2150 BC
Shelah	30 Years	403 Years	433 Years	2480-2047 BC
Eber	34 Years	430 Years	464 Years	2450-2020 BC
Peleg	30 Years	209 Years	239 Years	2416-2177 BC
Reu	32 Years	207 Years	239 Years	2386-2147 BC
Serug	30 Years	200 Years	230 Years	2354-2124 BC
Nahor	29 Years	119 Years	148 Years	2324-2176 BC
Terah	70 Years	135 Years	205 Years	2295-2090 BC
Ahraham	100 Years	75 Years	175 Years	2165-1990 BC
Isaac	60 Years	120 Years	180 Years	2065-1885 BC

Mitochondrial DNA SNPs in Human Populations

What is an ancestral marker?

mtDNA is a circular chain consisting of 16,569 pairs of nucleotides. Let's unwind the DNA double helix and take a closer look at its genetic code.

DNA consists of two chains of nucleotides, designated A, C, T, and G. "A" is always linked to "T", and "C" is always linked to "G" on the opposite chain. In this diagram, we will take a closer look at a short segment of mtDNA, namely locations 1 to 45. The unique combination of nucleotides in the chain is called a "genetic code" and holds genetic information.

Ancestral markers are "mutations", little changes or "hiccups" that occur in the genetic code of the mtDNA. There are many types of mutations, but the type of mutation most commonly found in mtDNA is called a "SNP" (single nucleotide polymorphism). A SNP mutation occurs when a single nucleotide is replaced with a different nucleotide. For example, in this diagram, the "T" at location 40 is replaced by a "G".

TA to GC SNP
@ NT 45
Becomes a MARKER!

This mutation is documented as follows:

- Location: 40
- Nucleotide Change: T>g (also indicated as T40G)

RFLPs and SNPs Can Be Used to Identify Individuals and Ancestors Using Mitochondrial DNA

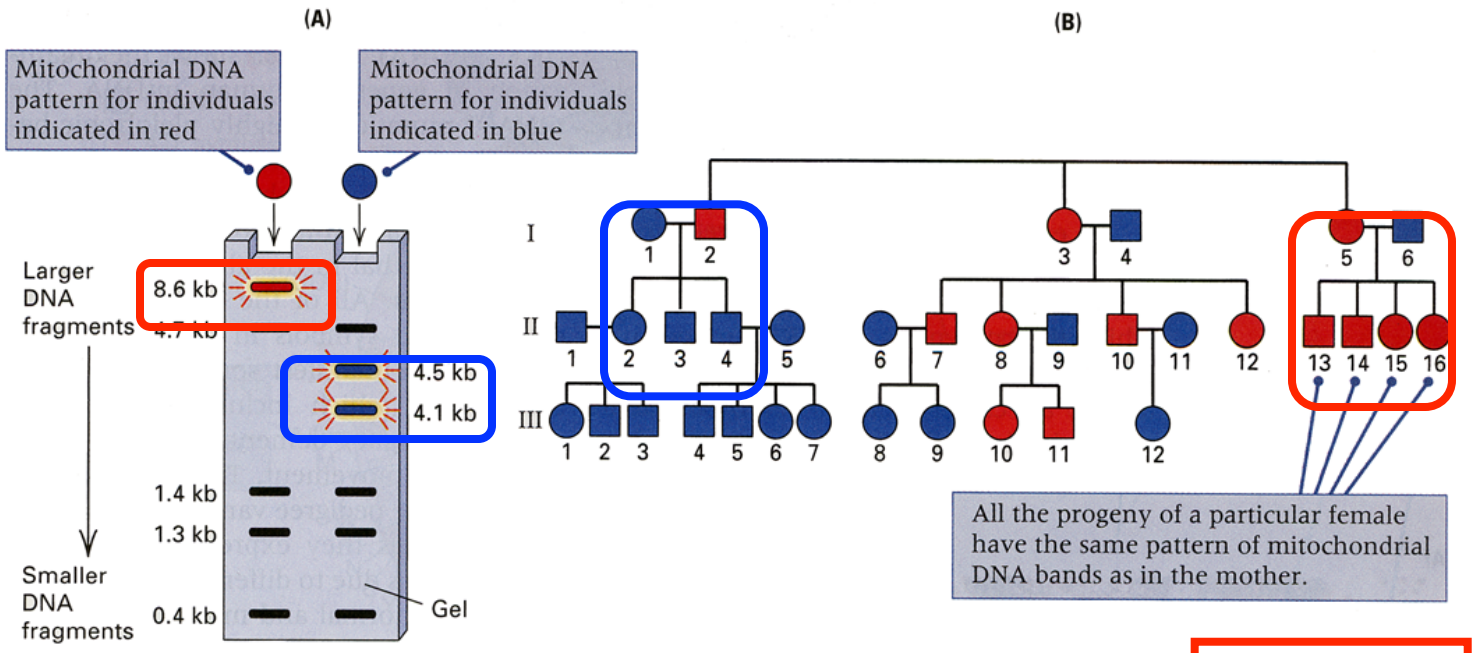
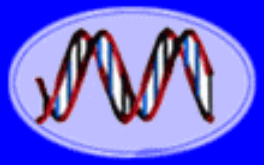


Figure 16.1 Maternal inheritance of human mitochondrial DNA. (A) Pattern of DNA fragments obtained when mitochondrial DNA is digested with the restriction enzyme *Hae*II. The DNA type at the left includes a fragment of 8.6 kb (red). The DNA type at the right contains a cleavage site for *Hae*II within the 8.6-kb fragment, which results in smaller fragments of 4.5 kb and 4.1 kb (blue). (B) Pedigree showing maternal inheritance of the DNA pattern with the 8.6-kb fragment (red symbols). The mitochondrial DNA type is transmitted only through the mother. [After D. C. Wallace. 1989. *Trends in Genetics* 5: 9.]

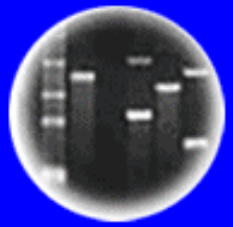
100% of Children Have 8.6 kb DNA Fragment From Mother

Note How Mitochondrial RFLP Markers Are Inherited !!



DNA
Genetic Code of Life

Entire Genetic Code of a Bacteria

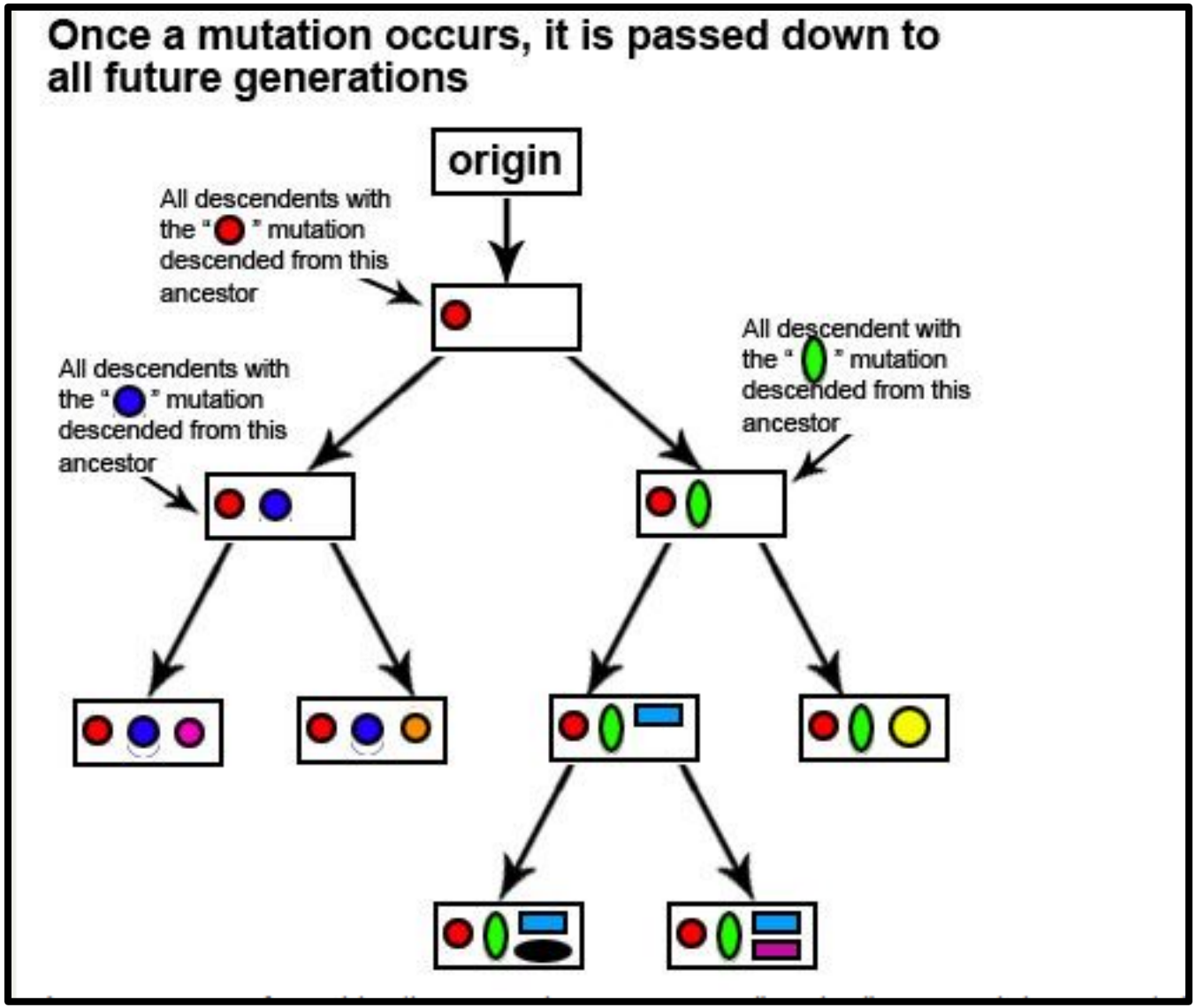


DNA Fingerprinting

Cloning: Ethical Issues and Future Consequences

Plants of Tomorrow

How Trace Ancestry Using Mitochondrial DNA SNPs?



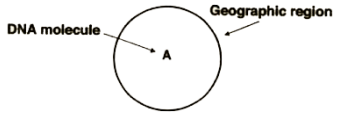
How Trace Ancestry Using Mitochondrial DNA SNPs
Oldest Populations Contain the Most Diversity

Analysis of human mtDNA led to the Mitochondrial Eve Hypothesis

In the 1980s, Allan Wilson pioneered the use of mtDNA to study human evolution.

In two papers published in 1987 and 1991, he and his colleagues at Cal proposed that we all come from a population of humans that lived in Africa approximately 200,000 years ago.

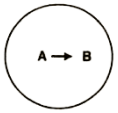
Here's the logic behind the hypothesis.



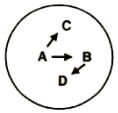
Start with A.

Time

Detected By Using Specific Markers (RFLPs or SNPS)



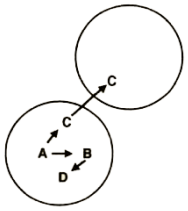
Mutation generates B from A; now have individuals with both A and B DNAs in population.



Additional mutations generate diversity; now have individuals with both A, B, C and D DNAs.

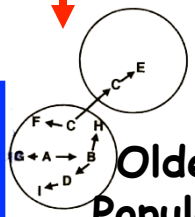
Newest Population

Subset of "Old" Variants + New Variants



C migrates to form separate population.

Lots of "Old" Variants



Oldest Population

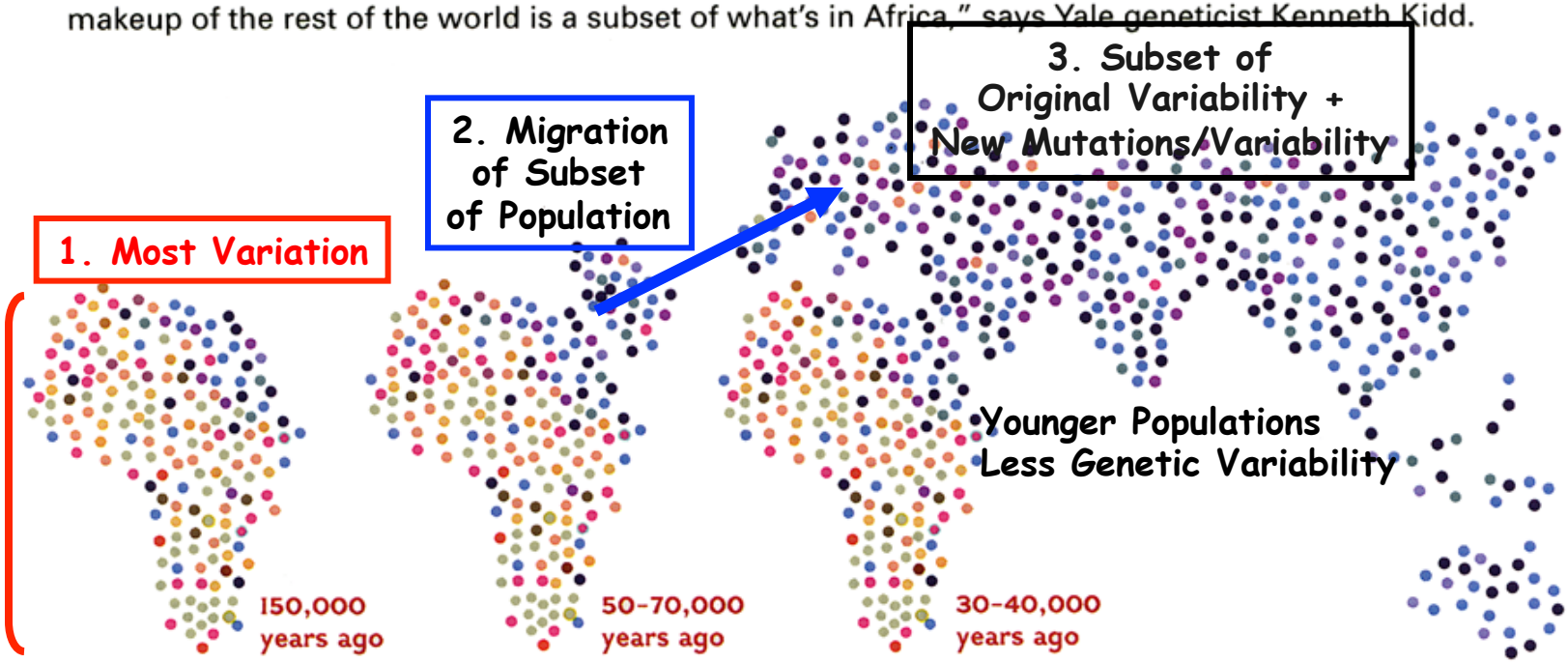
Additional mutations diversify DNAs in populations: original population more diverse (A, B, C, D, F, G, H, I) than newer population (C, E).

Old Variants Trace Ancient Lineage. New Variants Mark New Populations SPECIFICALLY

Most Genetic Diversity Originated in the Founder Populations to Modern Humans!

Diverse From the Start

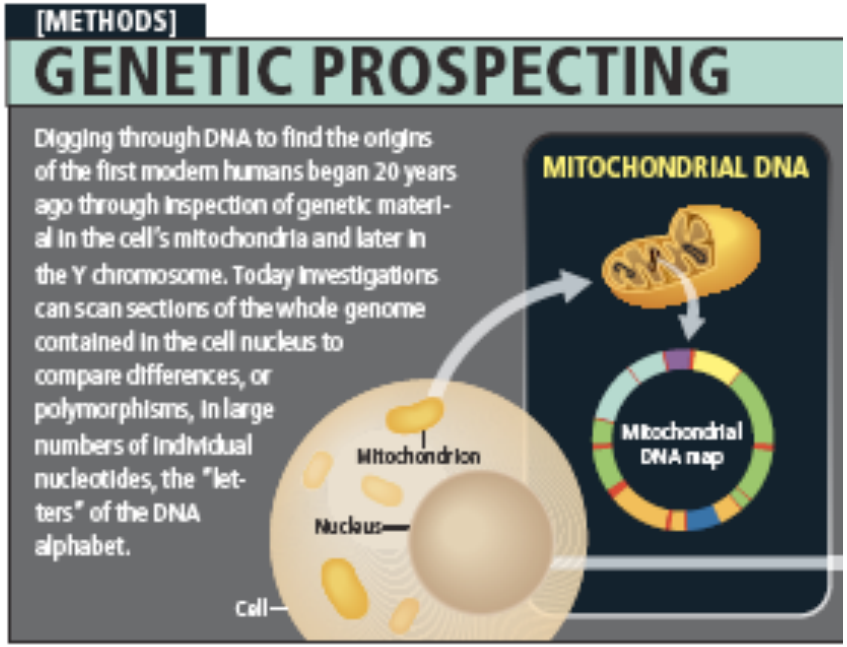
The diversity of genetic markers is greatest in Africa (multicolored dots in map), indicating it was the earliest home of modern humans. Only a handful of people, carrying a few of the markers, walked out of Africa (center) and, over tens of thousands of years, seeded other lands (right). "The genetic makeup of the rest of the world is a subset of what's in Africa," says Yale geneticist Kenneth Kidd.

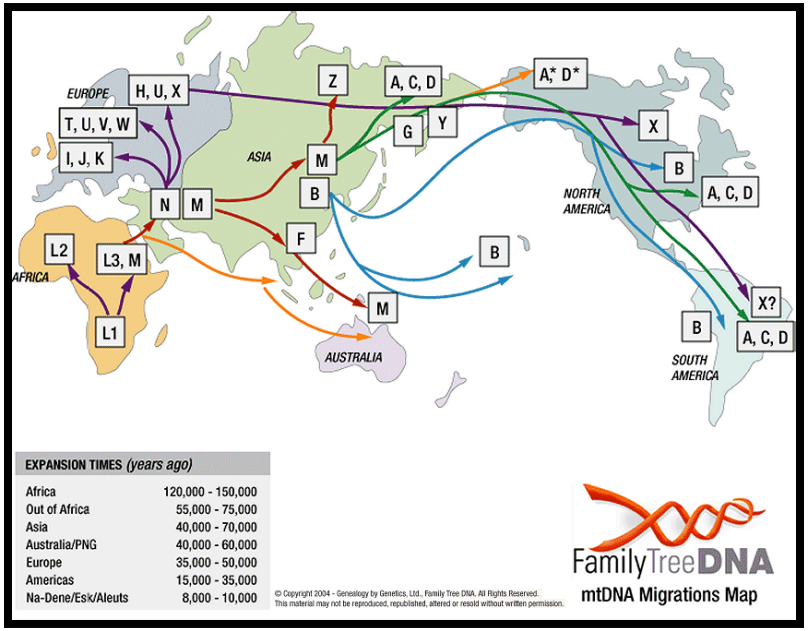


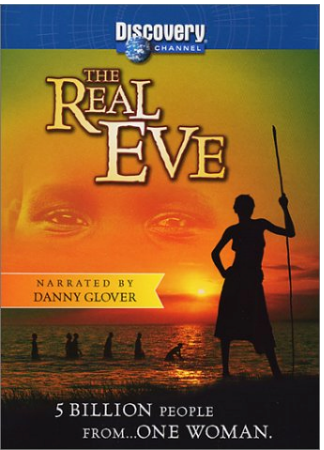
Genetic Variation Proportional to Population Age

Markers From Original Population + New Markers For "New" Population

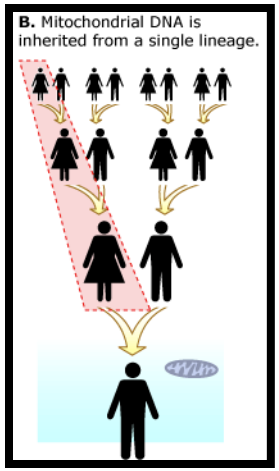
Tracing Human Populations Using Mitochondrial DNA Polymorphisms (SNPs) - Back to Eve!



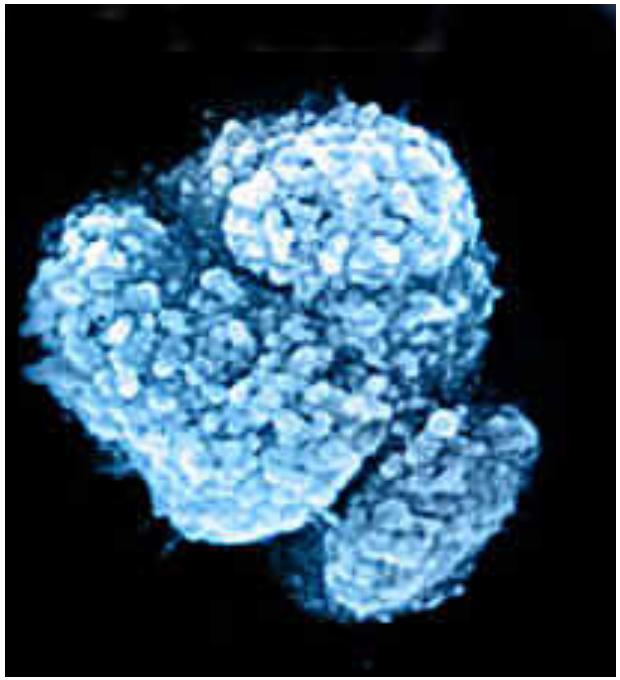


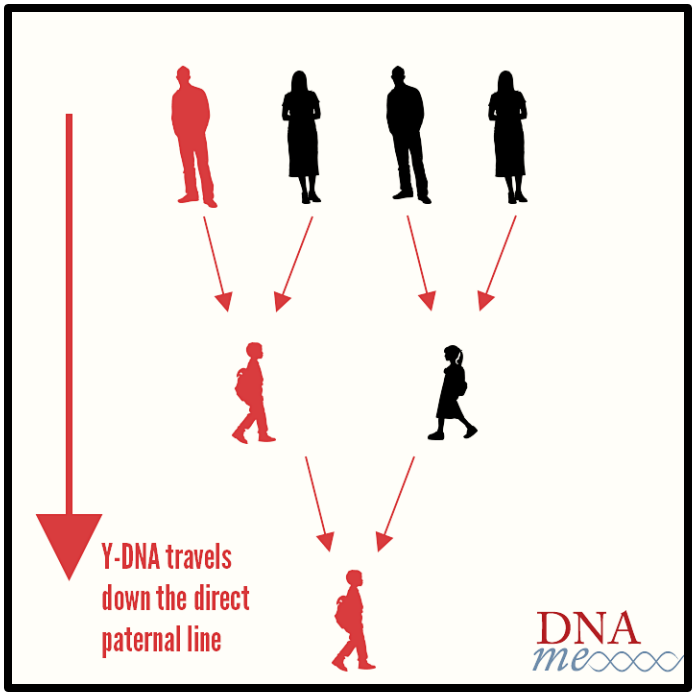


Eve Lived ~200,000 Years Ago!!

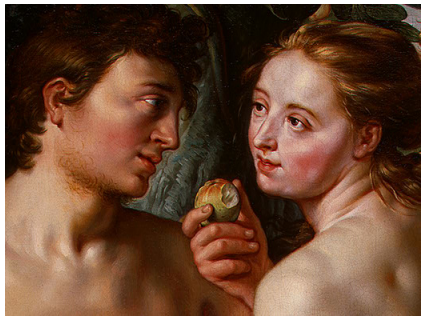


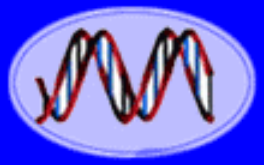
When Did Adam Live?
Tracing Human Populations Using Y DNA Polymorphisms





Adam Also Lived
~200,000
Years Ago!





DNA
Genetic Code of Life

Entire Genetic Code
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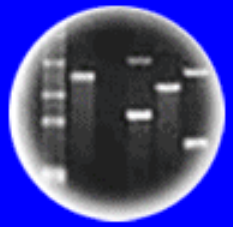

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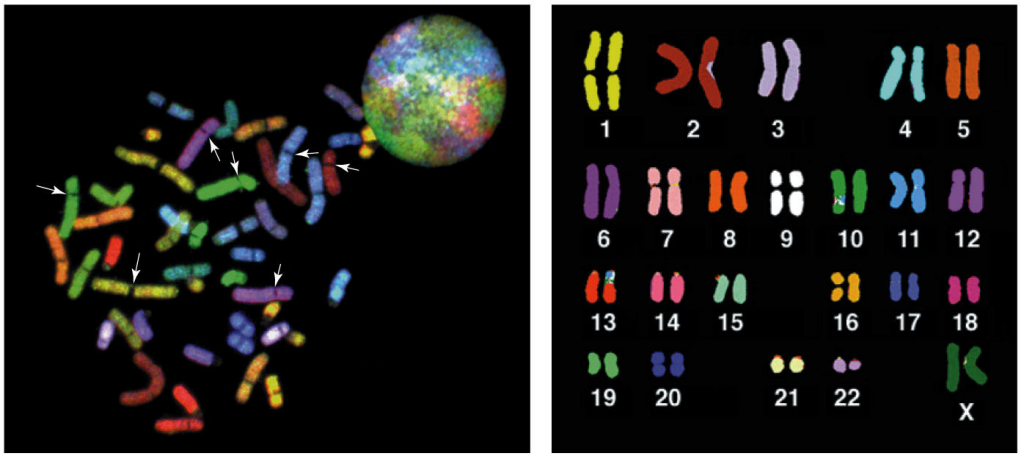
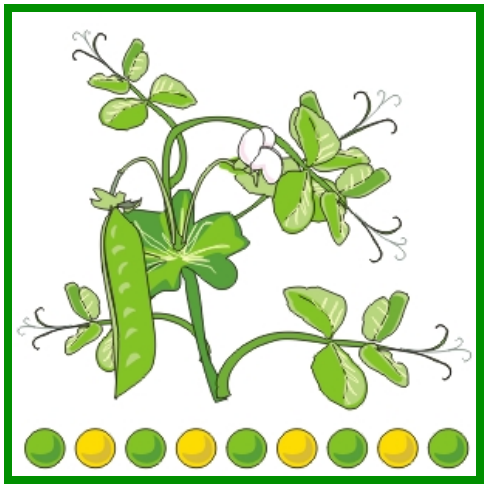
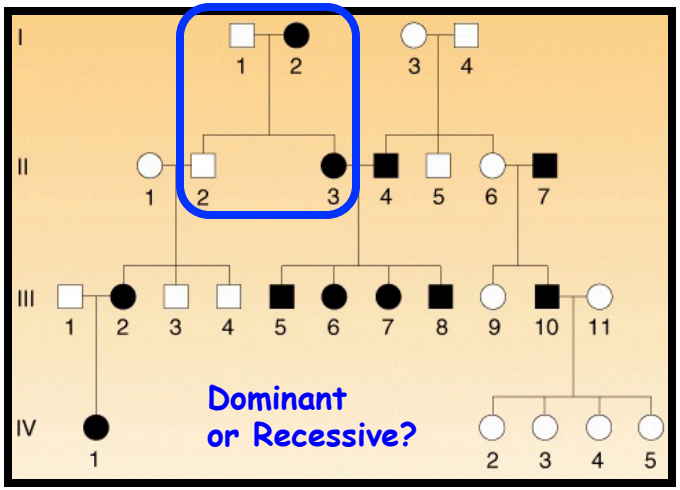
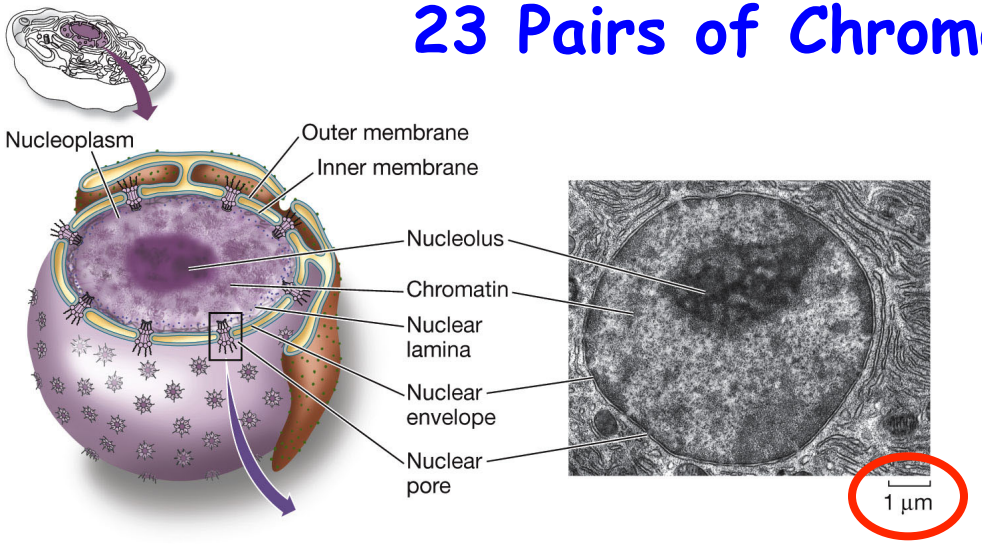


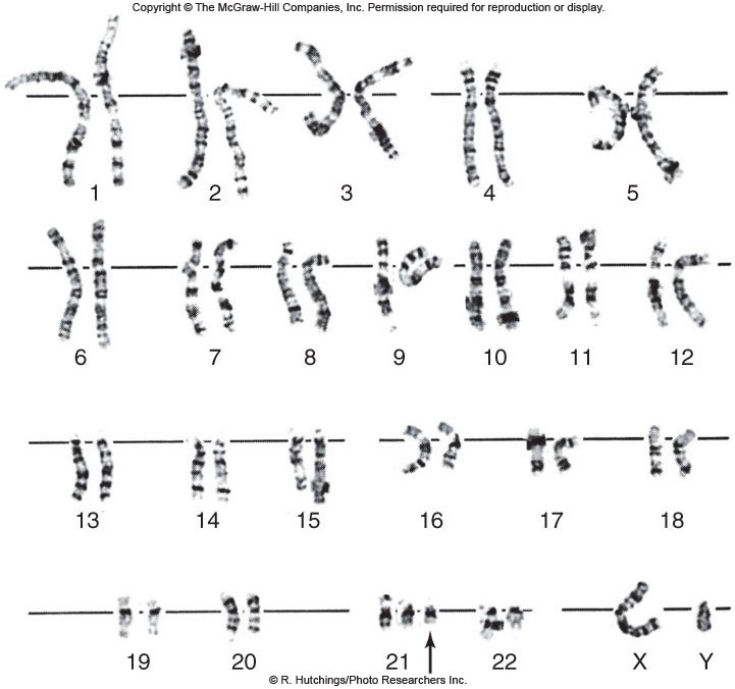




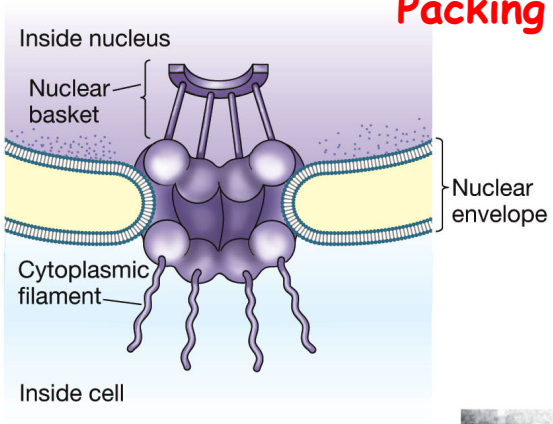
Note: Gene is Inherited in a Mendelian Pattern

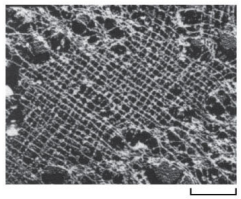
The Nucleus Is A Complex Organelle With 23 Pairs of Chromosomes (Humans)



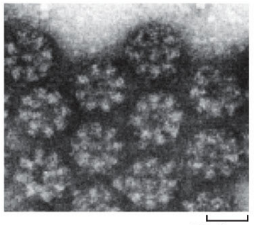


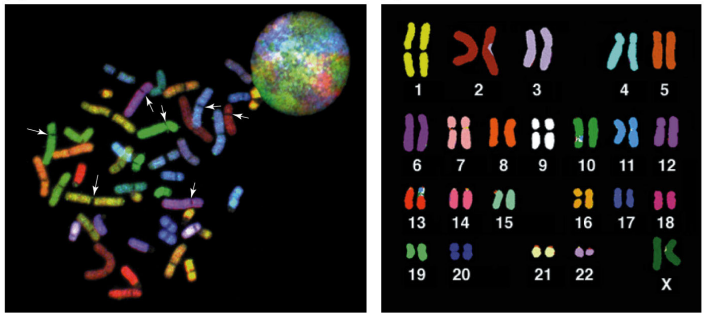
Packing Problem?





RNA & Protein Transport





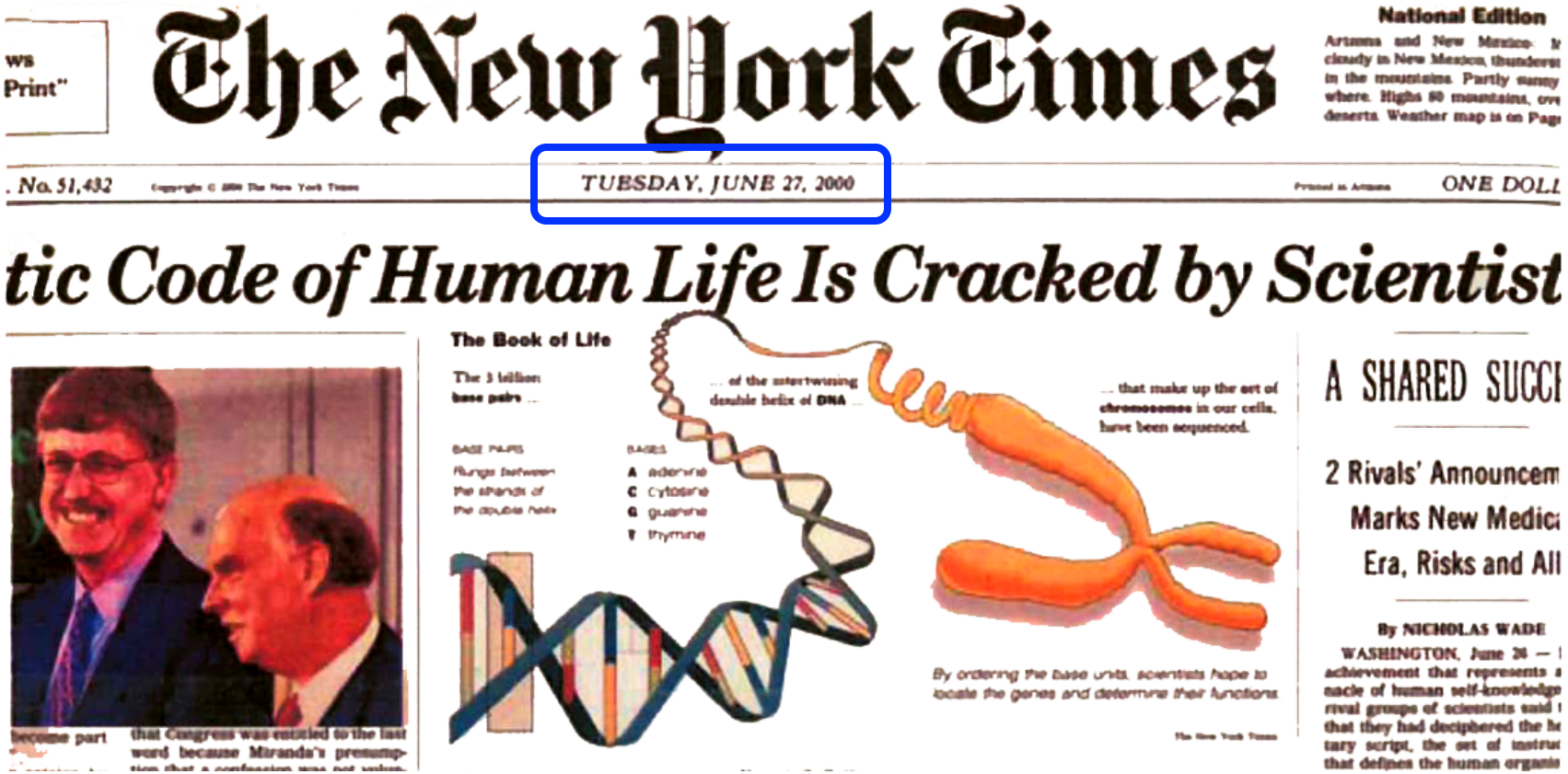
The Human Genome End to End is 1.1 Meters in Length!!!!!!

Note: Chromosome Sizes & Bands = Markers

LIFE 8e, Figure 4.8 (Part 2)

The Human Genome Was Sequenced Fifteen Years Ago!

The Human Genome Project



The New York Times

National Edition

. No. 51,432 TUESDAY, JUNE 27, 2000 ONE DOLL

tic Code of Human Life Is Cracked by Scientist

The Book of Life

A SHARED SUCCI

2 Rivals' Announcem

Marks New Medic

Era, Risks and All

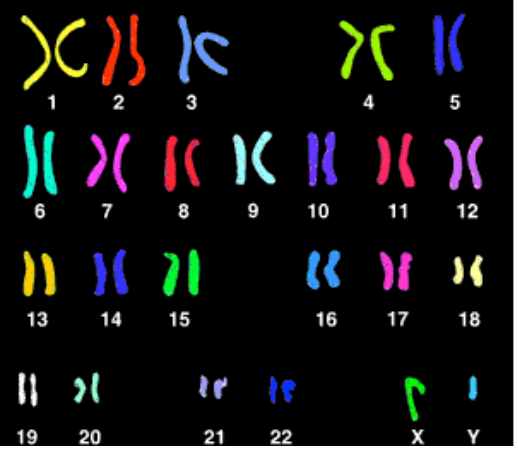
By NICHOLAS WADE

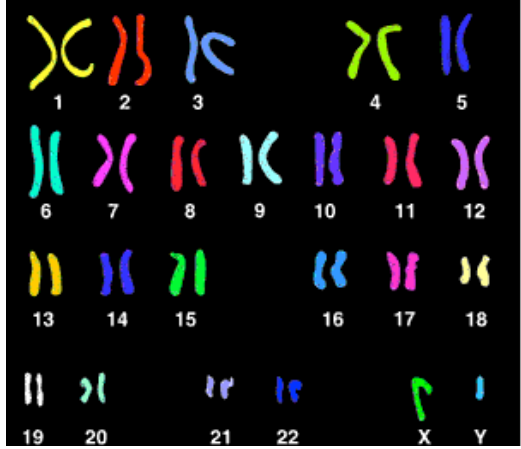
WASHINGTON, June 26 —

By ordering the base units, scientists hope to locate the genes and determine their functions.

Public & Private Effort Using Different Strategies - A Race!

3 Billion Dollars & Took 15 Years



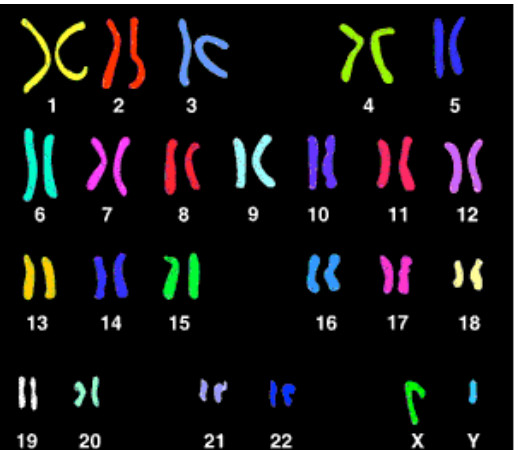


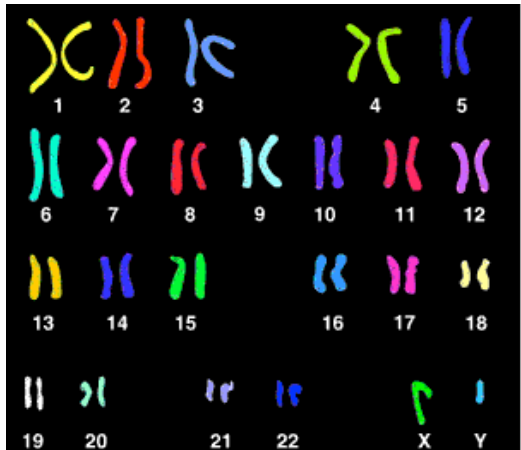
The Human Genome

Large

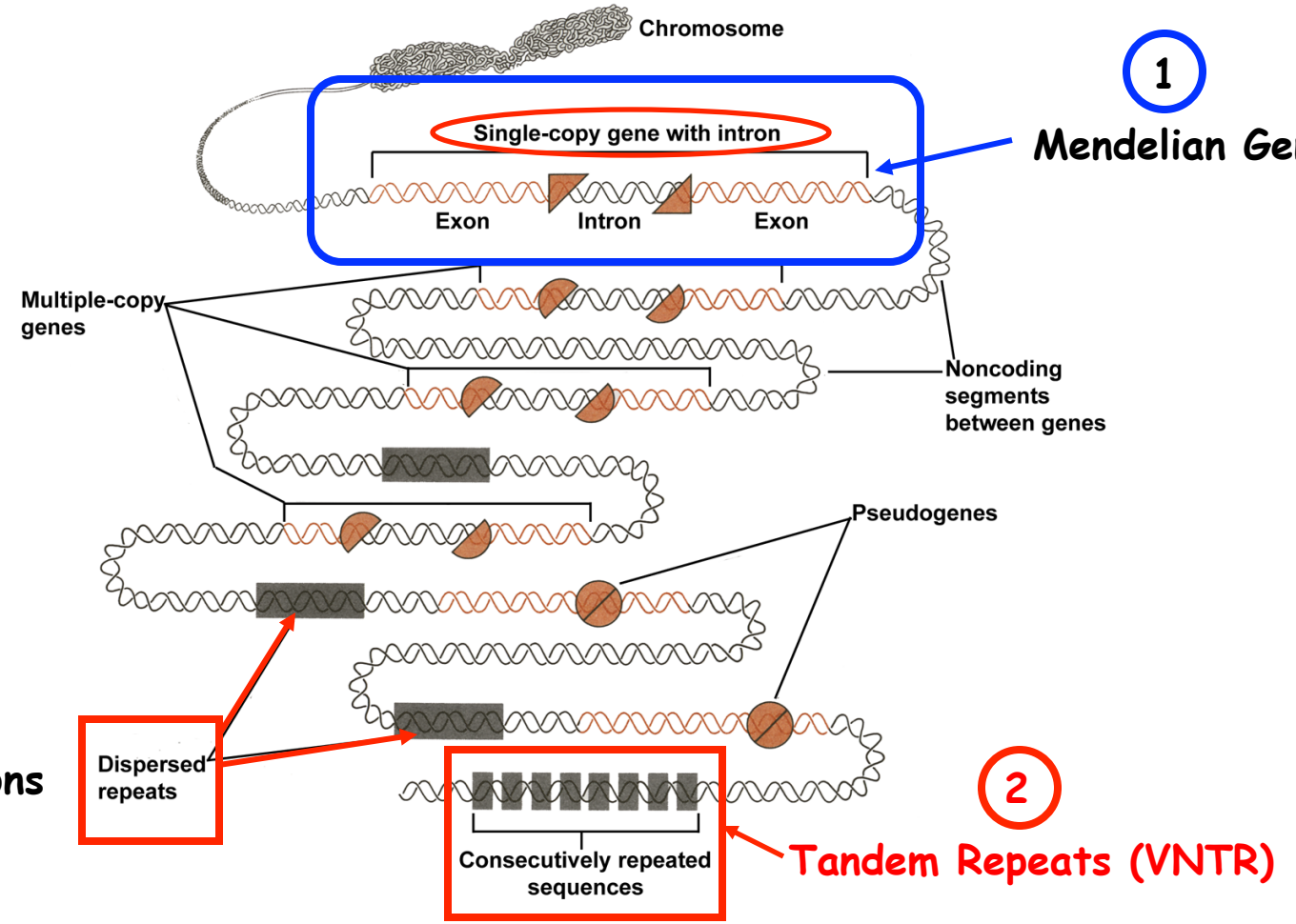
Small

Chromosome	Including gaps	Sequenced	Gaps
1	247,249,719	224,999,719	22,250,000
2	242,951,149	237,712,649	5,238,500
3	199,501,827	194,704,827	4,797,000
4	191,273,063	187,297,063	3,976,000
5	180,857,866	177,702,766	3,155,100
6	170,899,992	167,273,992	3,626,000
7	158,821,424	154,952,424	3,869,000
8	146,274,826	142,612,826	3,662,000
9	140,273,252	120,143,252	20,130,000
10	135,374,737	131,624,737	3,750,000
11	134,452,384	131,130,853	3,321,531
12	132,349,534	130,303,534	2,046,000
13	114,142,980	95,559,980	18,583,000
14	106,368,585	88,290,585	18,078,000
15	100,338,915	81,341,915	18,997,000
16	88,827,254	78,884,754	9,942,500
17	78,774,742	77,800,220	974,522
18	76,117,153	74,656,155	1,460,998
19	63,811,651	55,785,651	8,026,000
20	62,435,964	59,505,253	2,930,711
21	46,944,323	34,171,998	12,772,325
22	49,691,432	34,851,332	14,840,100
X	154,913,754	151,058,754	3,855,000
Y	57,772,954	25,652,954	32,120,000
M	16,571	16,571	0
Total genome	**3,080,436,051**	**2,858,034,764**	**222,401,287**





The Human Genome Landscape



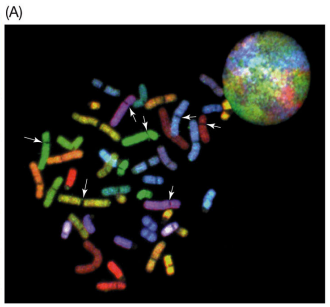
Tandem Repeats or VNTRs are Useful for DNA Fingerprinting Studies!

e.g., DIS80 Locus For Class DNA Fingerprint on Chromosome 4 Core = 16bp

Only A Small Fraction of the Human Genome Encodes Proteins

TABLE 18.1 Classes of DNA Sequences Found in the Human Genome

Class	Frequency (%)	Description
Protein-encoding genes	1.5	Translated portions of the 25,000 genes scattered about the chromosomes
Introns	24	Noncoding DNA that constitutes the great majority of each human gene
Segmental duplications	5	Regions of the genome that have been duplicated
Pseudogenes (inactive genes)	2	Sequence that has characteristics of a gene but is not a functional gene
Structural DNA	20	Constitutive heterochromatin, localized near centromeres and telomeres
Simple sequence repeats	3	Stuttering repeats of a few nucleotides such as CGG, repeated thousands of times
Transposable elements	45	21%: Long interspersed elements (LINEs), which are active transposons 13%: Short interspersed elements (SINEs), which are active transposons 8%: Retrotransposons, which contain long terminal repeats (LTRs) at each end 3%: DNA transposon fossils



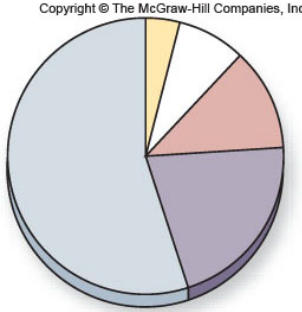
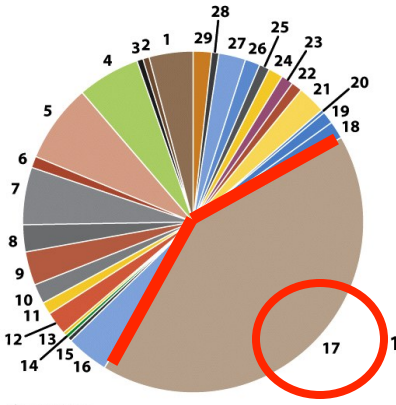


Table 20.6 Average characteristics of genes in the human genome

Characteristic	Average
Number of exons	8.8
Size of internal exon	145 bp
Size of intron	3,365 bp
Size of 5′ untranslated region	300 bp
Size of 3′ untranslated region	770 bp
Size of coding region	1,340 bp
Total length of gene	27,000 bp

Table 20-6

The Human Genome Has DNA Sequences Present Once As Well as Repeated Many Times

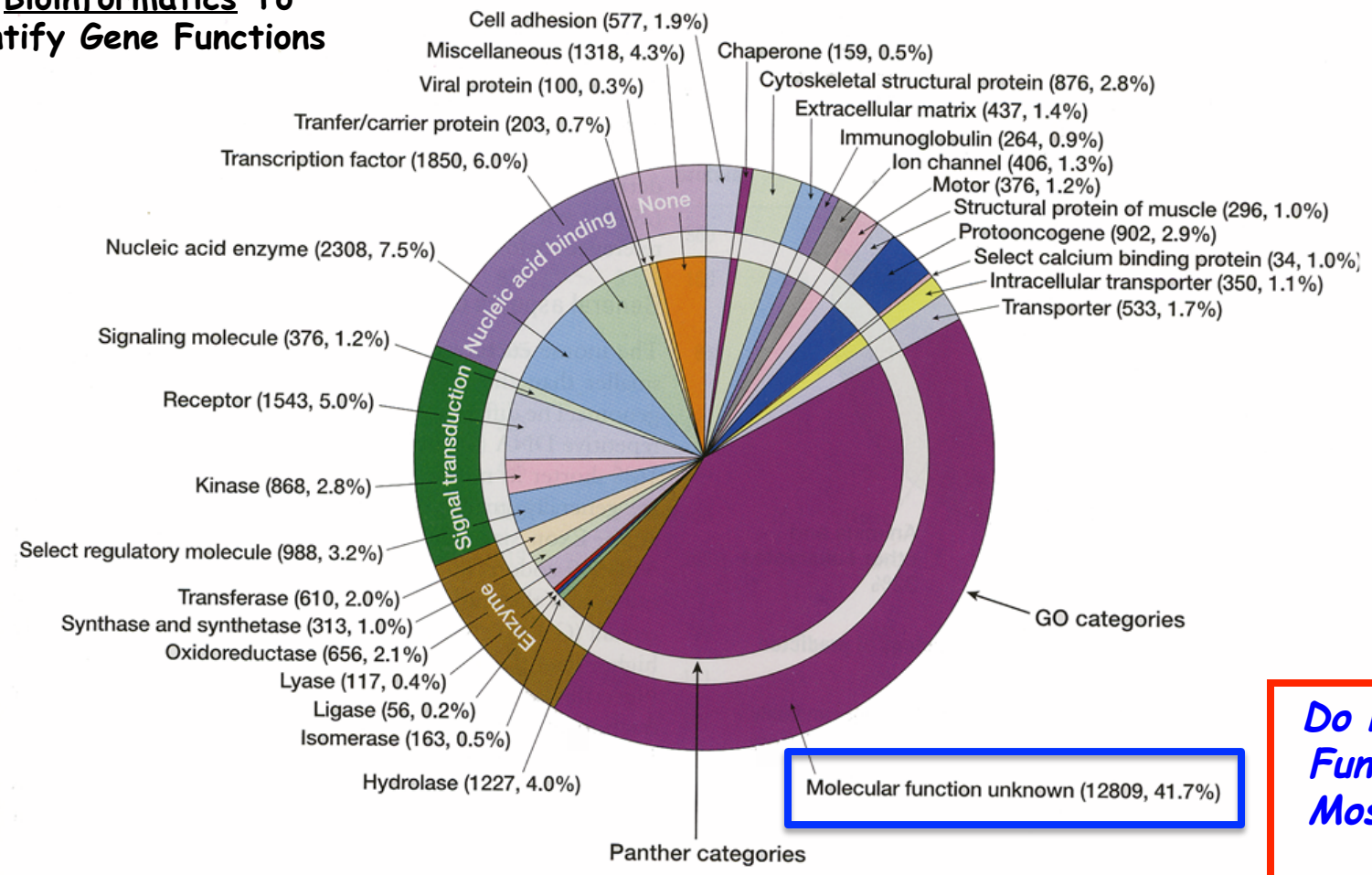


1. Miscellaneous
2. Viral protein
3. Transfer or carrier protein
4. Transcription factor
5. Nucleic acid enzyme
6. Signaling molecule
7. Receptor
8. Kinase
9. Select regulatory molecule
10. Transferase
11. Synthase and synthetase
12. Oxidoreductase
13. Lyase
14. Ligase
15. Isomerase
16. Hydrolase
17. Molecular function unknown
18. Transporter
19. Intracellular transporter
20. Select calcium-binding protein
21. Protooncogene
22. Structural protein of muscle
23. Motor
24. Ion channel
25. Immunoglobulin
26. Extracellular matrix
27. Cytoskeletal structural protein
28. Chaperone
29. Cell adhesion

Human Genes are Large but Contain Mostly Introns

The Human Genome Contains ~25,000 Different Genes

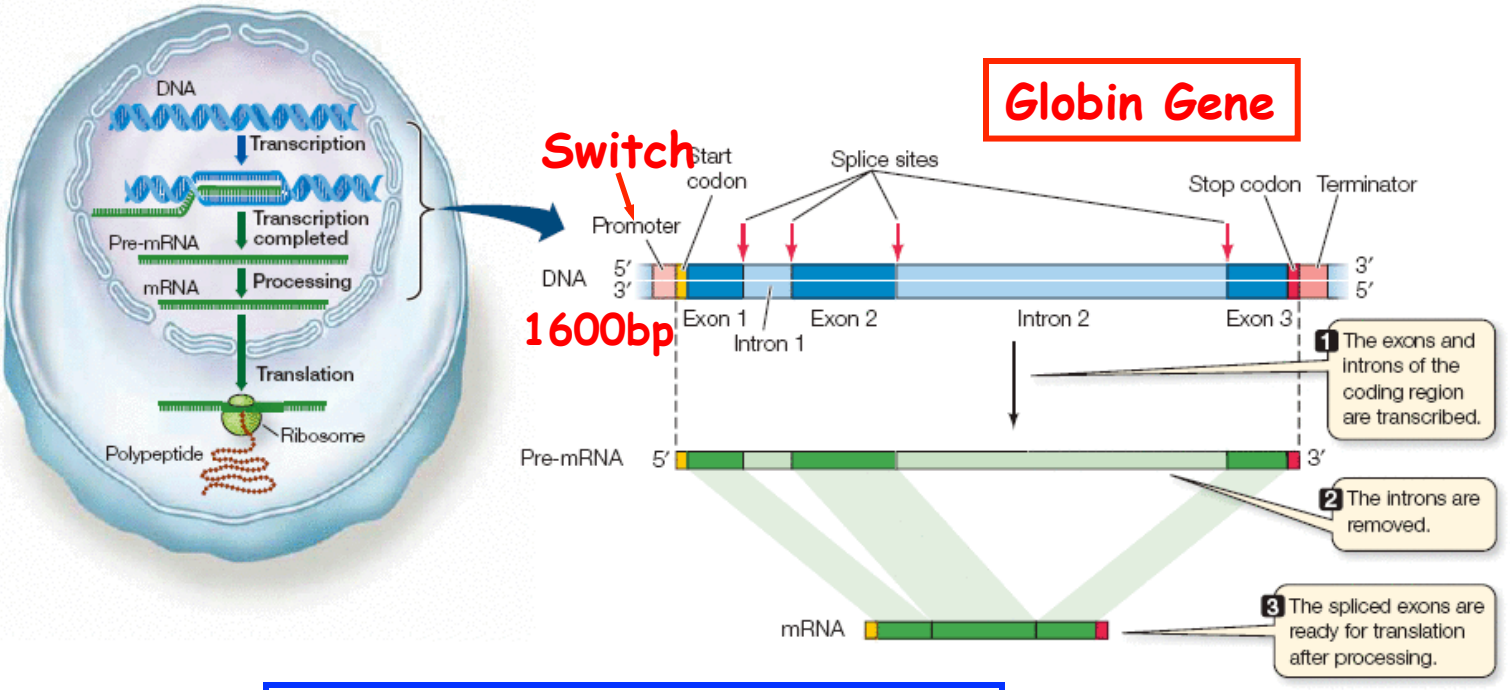
Use Bioinformatics To Identify Gene Functions



Do Not Know Functions of Most Human Genes!

How Many Encoded Proteins? Alternative Splicing?

RNA Splicing- Removing Non-Coding Sequences From Primary Transcripts & Generating Functional mRNAs



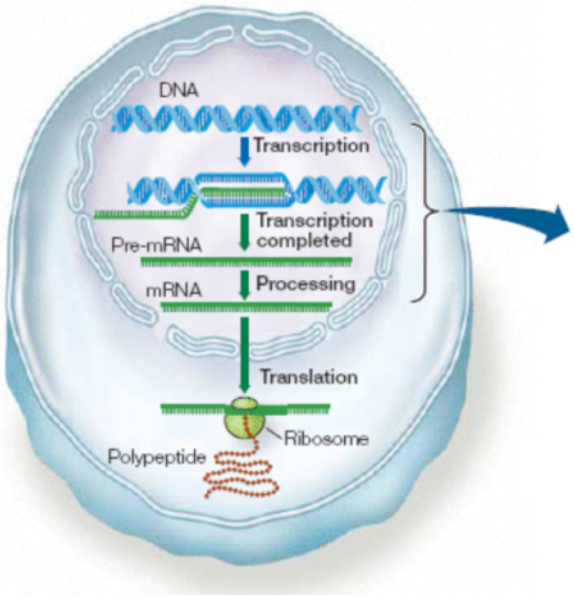
Mutations→ Blood Disorders
Where can these occur?

Mutations Can Occur in Coding Region, Switch, & RNA Splice Sites

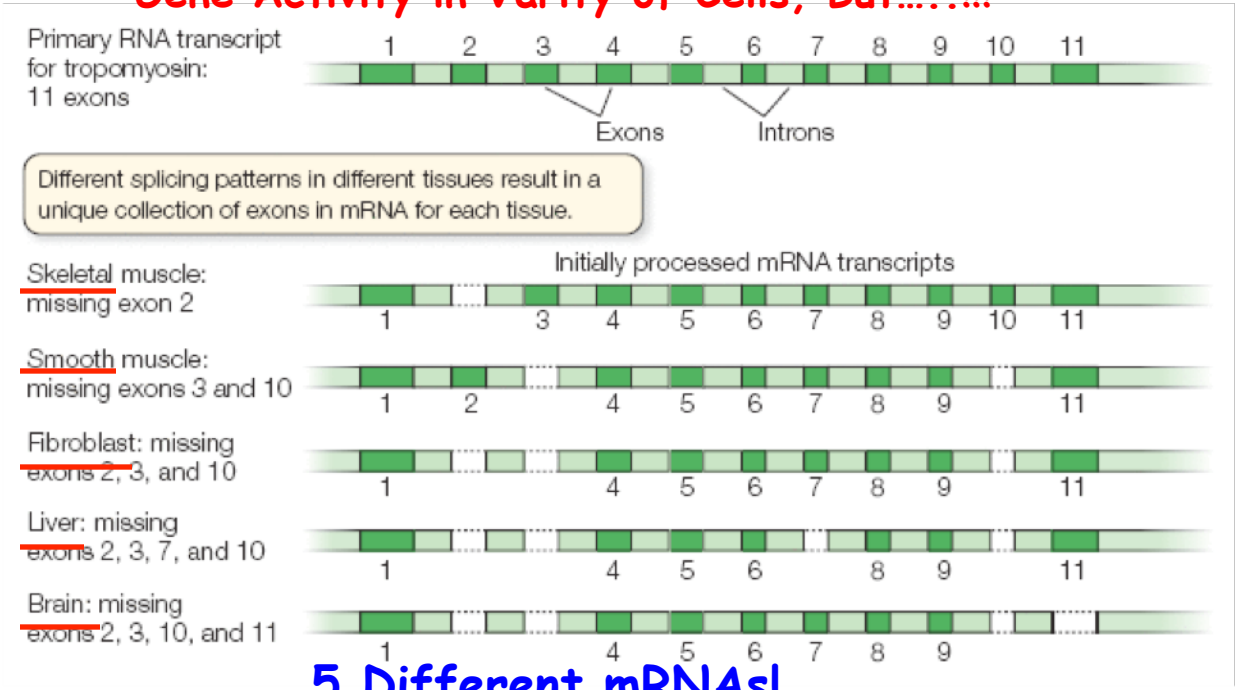
→ **Mutant Phenotype**

Implications For Engineering Eukaryotic Gene in Bacterial Cell For Expression?

Alternative Splicing- One Gene → Several mRNAs & Proteins



Gene Activity in Varity of Cells, But…..!!!



5 Different mRNAs!

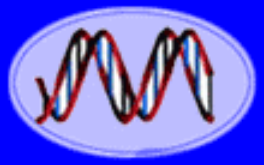
Different mRNA = Different Proteins = Different Functions!

Implication- Human Genome Has Only 25,000 Genes But Can Give Rise to Many More Proteins which Are Responsible For Producing the Phenotype

95% of Human Mutiexonic Genes Are Alternatively Spliced

Reason Why Human Genome Can Contain Same Number of Genes as Fly and Plant Genomes!!

Implications for Genetic Engineering? Use Specific cDNA!



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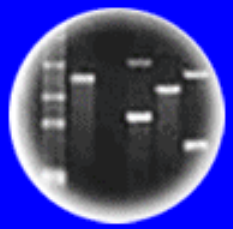

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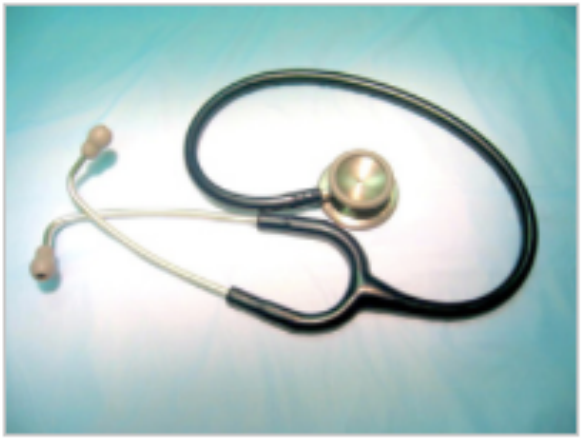
Mutations in Splicing Sequences Can Cause Human Diseases

Alternative Splicing and Disease



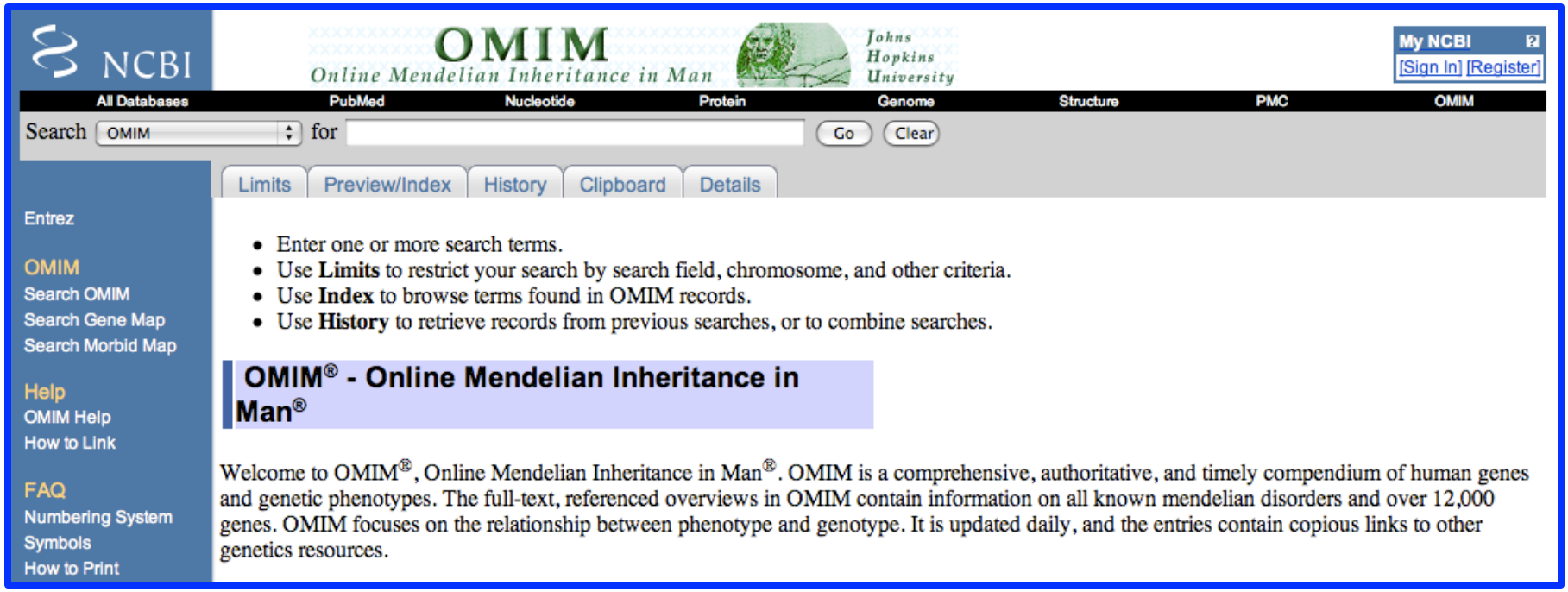
More than two thirds of the human protein-coding genes undergo alternative splicing, thus changes and misregulation of this mechanism can have severe effects and cause diseases.

About 15% of mutations connected with disease affect splicing.

Mutations completely impeding the splicing event cause severe disease patterns due to the lack of the correct gene product.

Mutations disturbing regulatory pathways lead to the appearance of misspliced gene products causing milder but more varied courses of disease.

How Many Human Disease Genes Have Been Identified?



There are ~25,000 Genes in The Human Genome

1. ~4653 Genes Correlate With a Disease Phenotype (832 on X & 53 on Y)
2. The Molecular Basis of These Genetic Diseases Are Known (e.g., Sickle Cell Anemia, Hemophilia A)
3. ~1635 Disease Genes – Molecular Basis Unknown

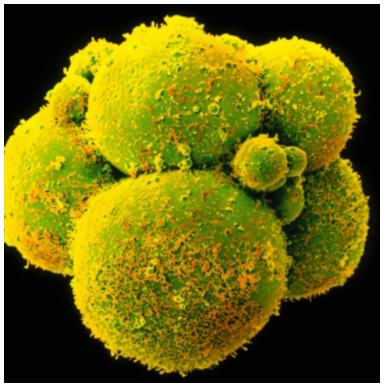
OMIM 2/15/16

http://omim.org/statistics/entry

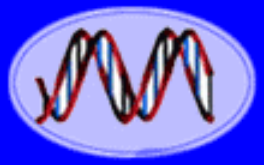
What's a GMO? Using Genetic Engineering to Cure Genetic Diseases

A Genetically Engineered Person With a Gene That They Weren't Born With That "Cures" a Lethal Genetic Disease?

A Genetically Engineered Baby With a Gene That They Weren't Born With That "Cures" a Lethal Genetic Disease?



A Human Embryo With a Defective Blood Disease Gene That Was "Edited" and Engineered to Be Normal?



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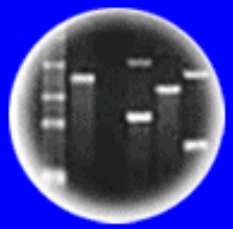

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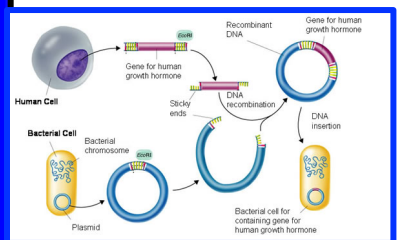
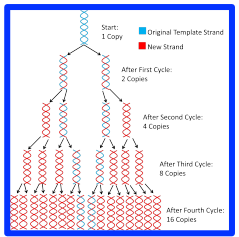
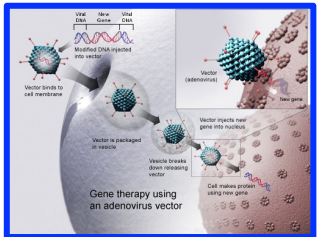
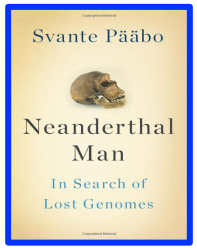
There Have Been Several Major Revolutions in Genetic Engineering

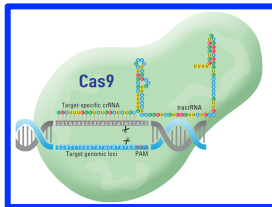
- 1970s - Genetic Engineering Origins
- 1980s – PCR Invented
- 1990s – Gene Therapy For Genetic Diseases
- 2000s – Genomics Revolution, Sequencing of the Human Genome
- 2000s - Ancient DNA & Human Origins
- 2015 – Genome Editing Using CRISPR

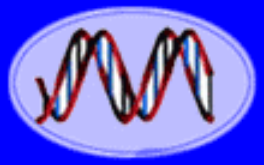












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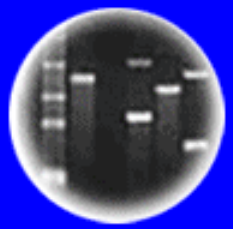

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Gene Editing Makes Possible To Correct Any Genetic Defect in Human Zygotes After Conception

Protein Cell
DOI 10.1007/s13238-015-0153-5

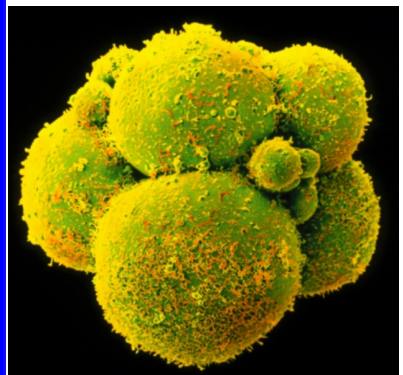
CrossMark Protein & Cell

RESEARCH ARTICLE

CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes

Puping Liang, Yanwen Xu, Xiya Zhang, Chenhui Ding, Rui Huang, Zhen Zhang, Jie Lv, Xiaowei Xie, Yuxi Chen, Yujing Li, Ying Sun, Yaofu Bai, Zhou Songyang, Wenbin Ma, Canquan Zhou✉, Junjiu Huang✉

Guangdong Province Key Laboratory of Reproductive Medicine, the First Affiliated Hospital, and Key Laboratory of Gene Engineering of the Ministry of Education, School of Life Sciences, Sun Yat-sen University, Guangzhou 510275, China
✉ Correspondence: hjunjiu@mail.sysu.edu.cn (J. Huang), zhoucanquan@hotmail.com (C. Zhou)
Received March 30, 2015 Accepted April 1, 2015



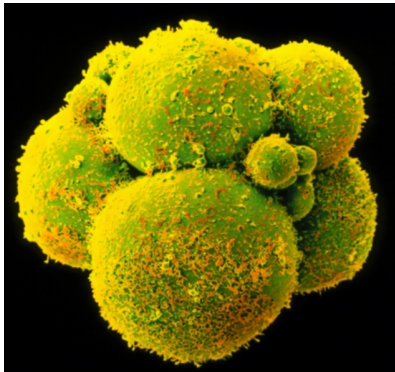
NATURE | NEWS

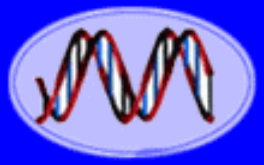
Chinese scientists genetically modify human embryos

Rumours of germline modification prove true — and look set to reignite an ethical debate.

David Cyranoski & Sara Reardon

22 April 2015





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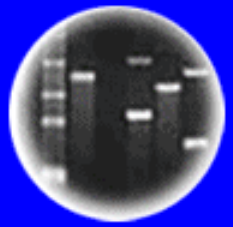

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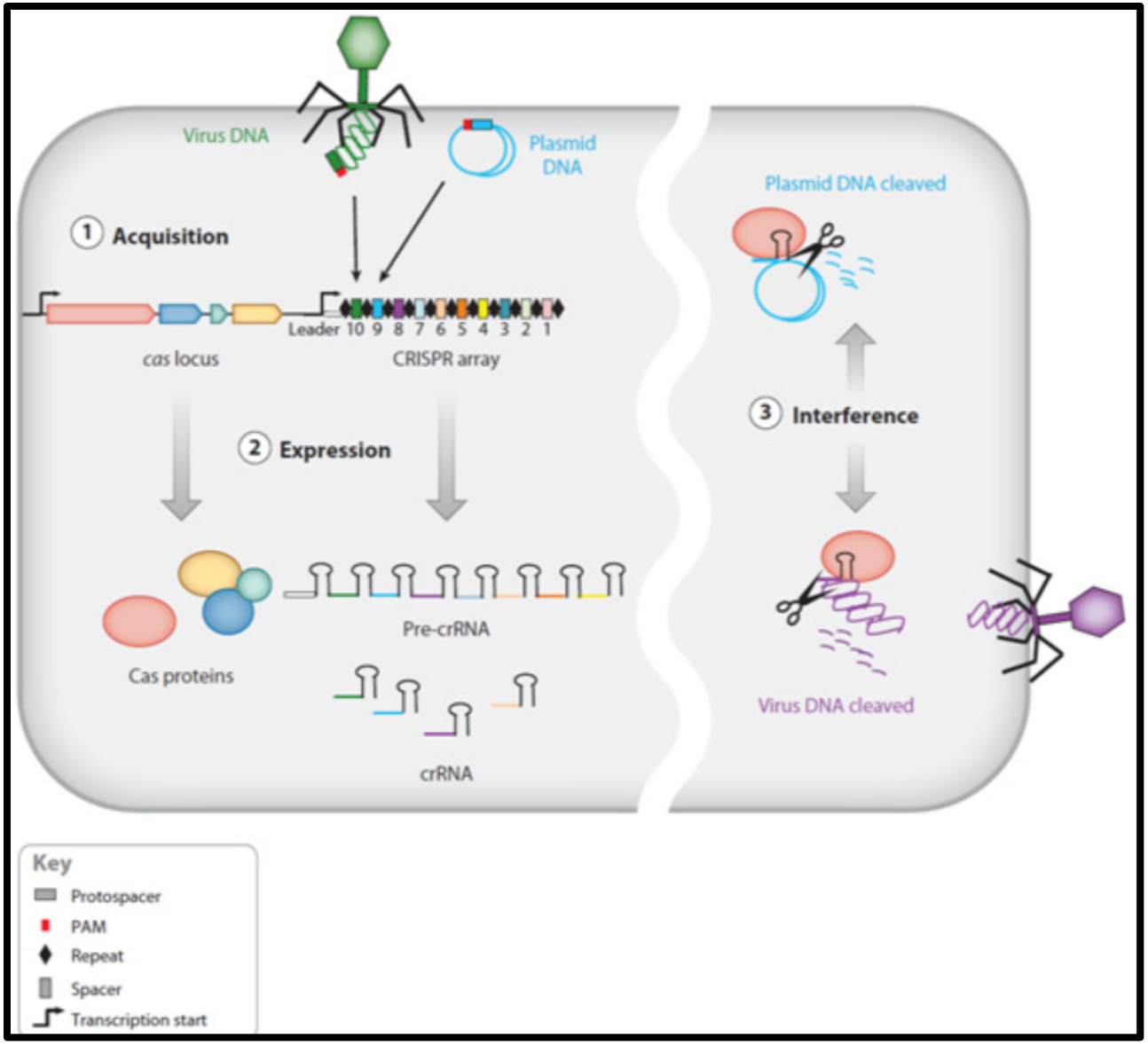
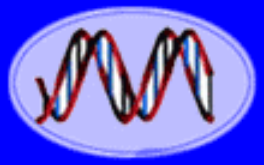
The CRISPR-CAS9 Bacterial Defense System





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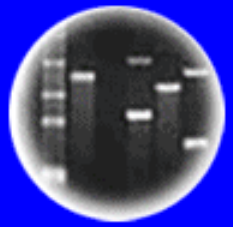

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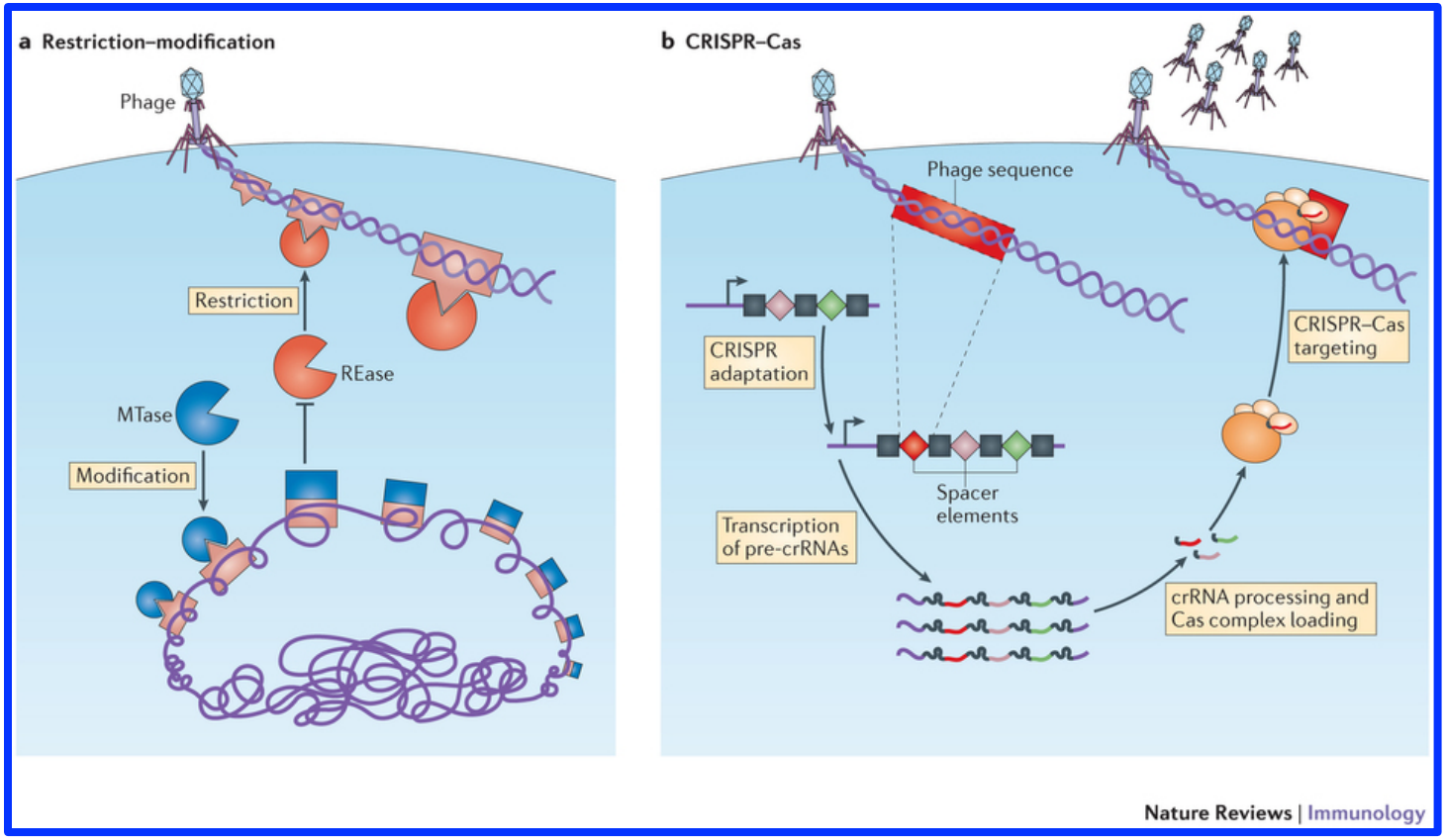
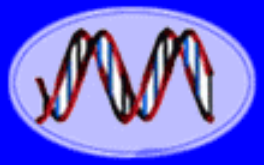
Another Bacterial Defense System That is Important For Genetic Engineering



Using CRISPR-CAS9 For Genetic Engineering



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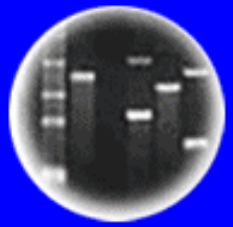

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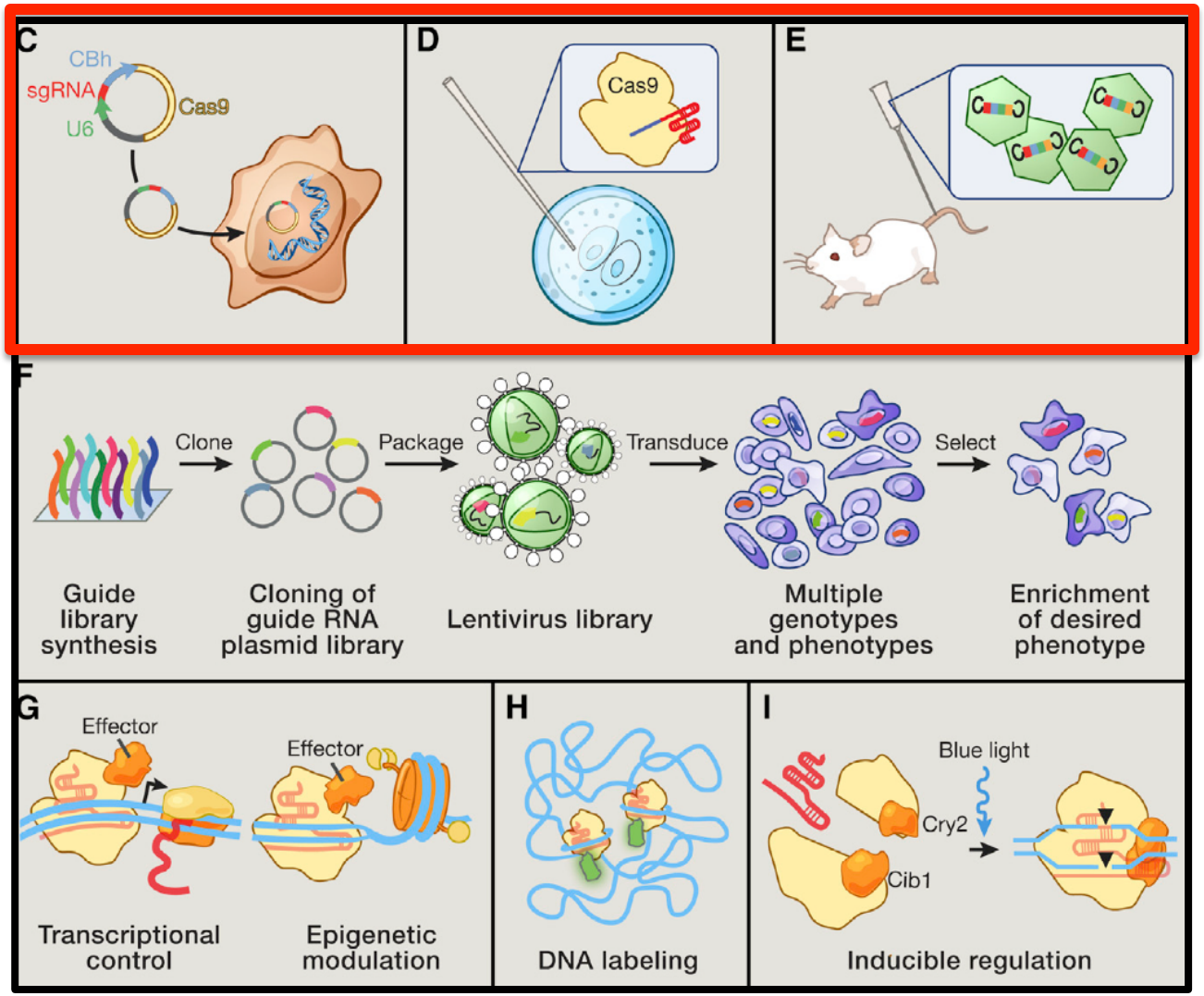

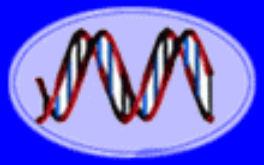

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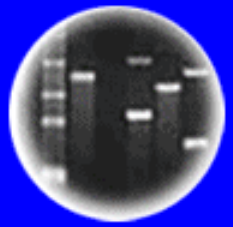

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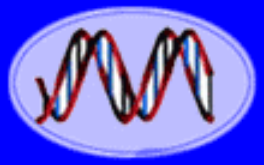
"Improving" Humans with Customized Genes Sparks Debate among Scientists

Scientists Seek Moratorium on Edits to Human Genome That Could Be Inherited



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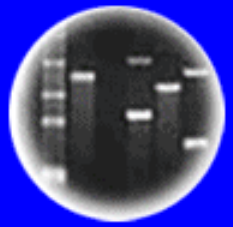

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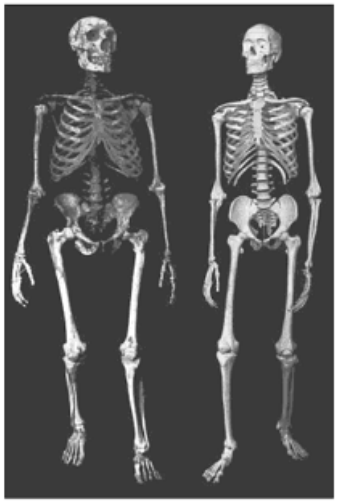
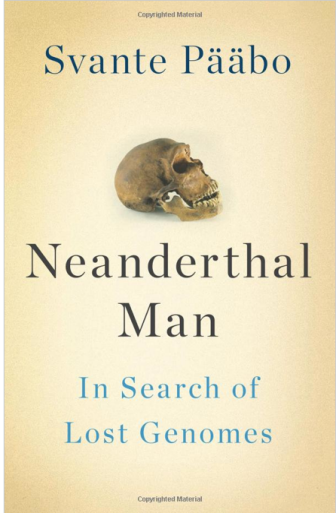
Gene Editing Summit Recommendations

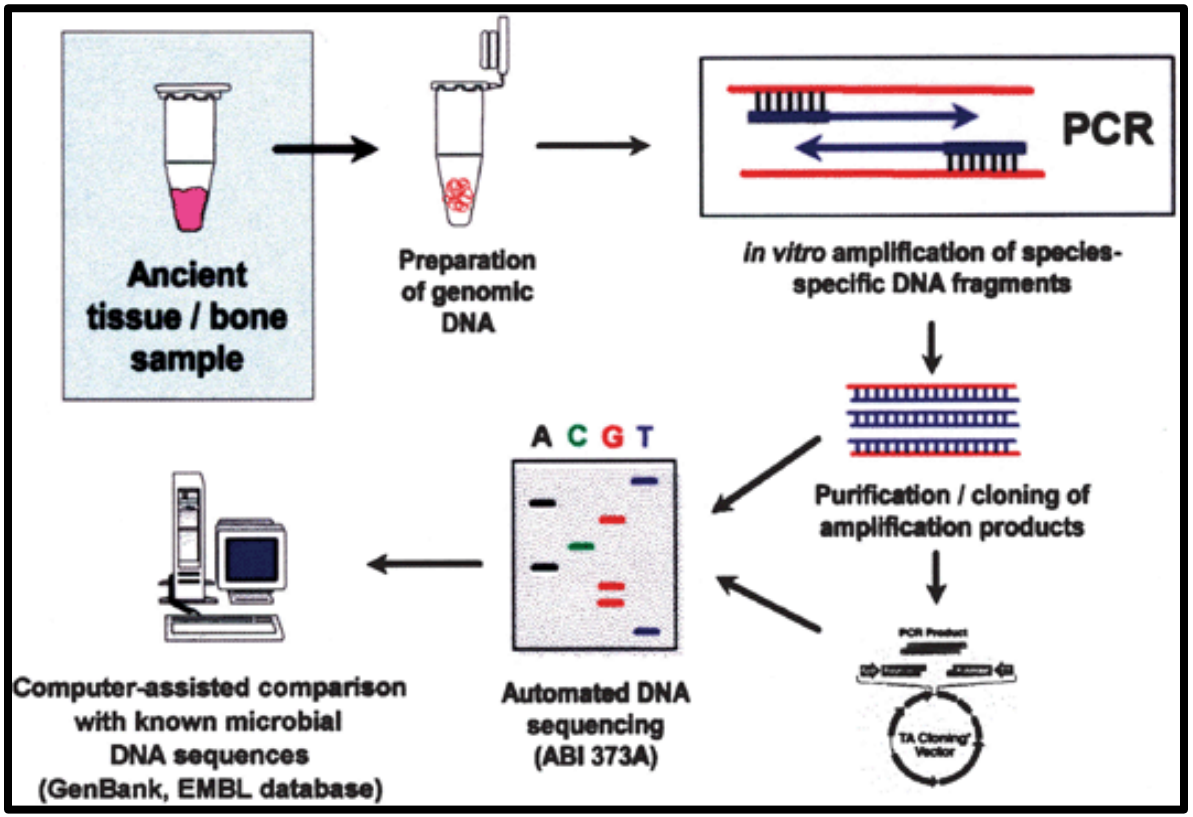
- **Basic & Preclinical Research** is Needed & Should Proceed. If in the Process Germline Cells or Early Embryos Are Edited, They Should Not Be Used To Establish Pregnancy
- **Clinical Use – Somatic** – Gene Editing of Somatic Cells Can Proceed Under Existing Regulations & Guidelines (e.g., Blood cells, Cancer Cells)
- **Clinical Use – Germline** – At Present the Safety Issues and Societal Consensus on Permanently Editing the Human Genome Have Not Been Resolved For Any Clinical Use. However, If They Are Resolved in The Future, This Issue Should Be Revisited. But the Most Compelling Cases For Germline Editing Are Limited.
- There is a Need For **Ongoing International Forum** & Consensus – Affects All of Humanity

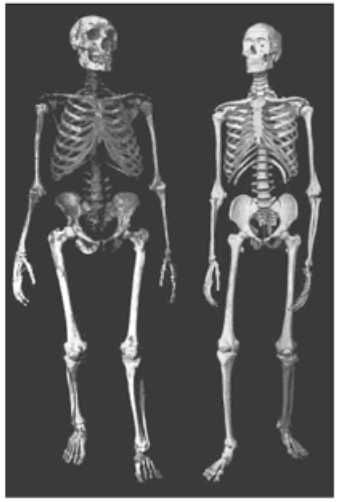
http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=12032015a



Using Ancient DNA to Unravel Our Human Heritage







RESEARCH ARTICLE

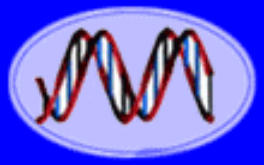
Science, May 7, 2010 (328, 710-722)

A Draft Sequence of the Neandertal Genome

From a 45,000 Year-Old Bone

Reconstruction by Kennis & Kennis / Photograph by Joe McNally

For the first time, a Neanderthal female peers from the past in a reconstruction informed by both fossil anatomy and ancient DNA. At least some of her kind carried a gene for red hair and pale skin.



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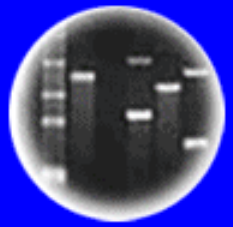

DNA Fingerprinting

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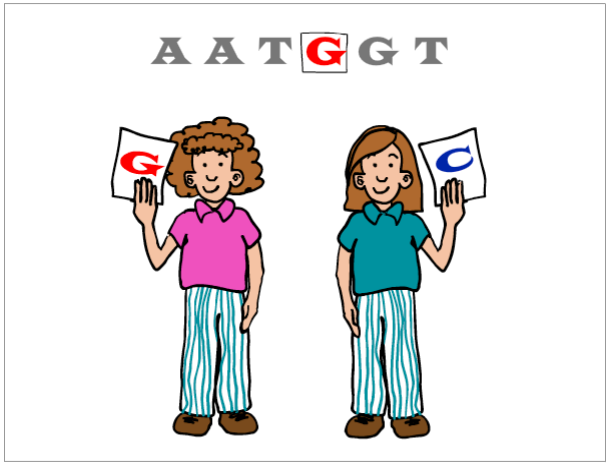
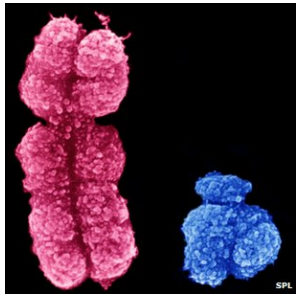
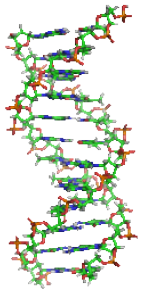
DNA Sequences From Humans Can Be Used To Specify Eye Color…..



…..As Well As Gender
& Other Traits





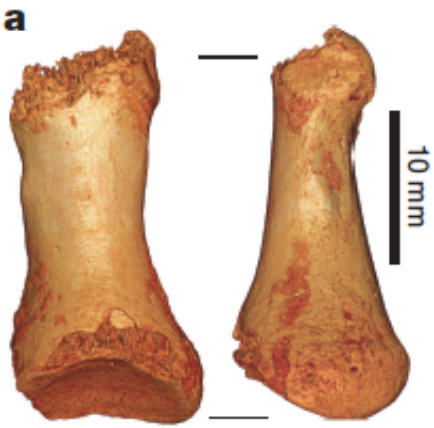
To Construct Phenotypes of Neanderthals & Other Ancient Relatives

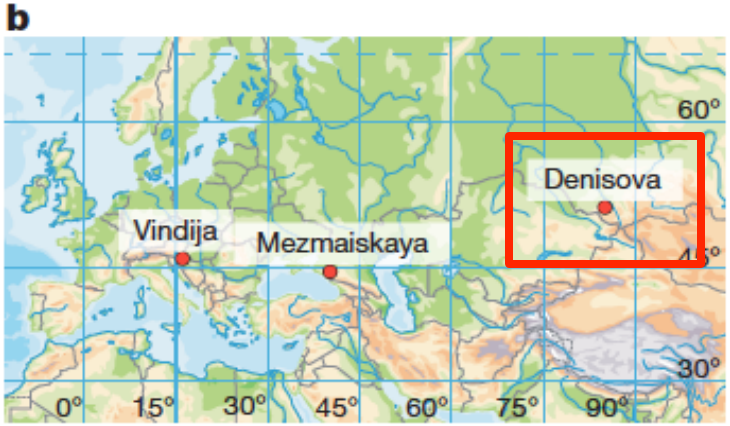
Nature, January 2, 2014 (505, 43-49)

The complete genome sequence of a Neanderthal from the Altai Mountains

130,000 Year-Old Neanderthal

Toe Fossil Provides Complete Neanderthal Genome





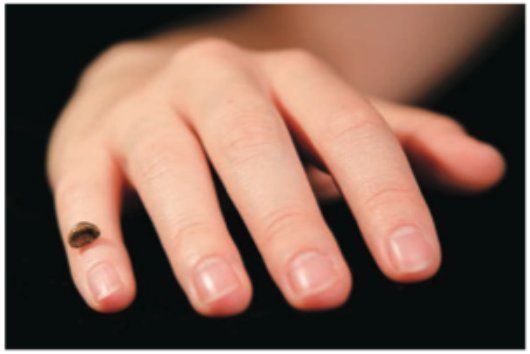
Science, October 12, 2012 (338,222-226)

ANCIENT DNA

A Crystal-Clear View Of an Extinct Girl's Genome

COMPLETE DNA Sequence From 40,000 Year Old Fossil DNA With Accuracy of Sequencing Our Own Genome!!

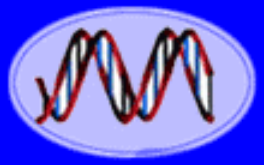
Had 23 Chromosomes Like "Us" and Split From Human Line Between 150k and 700k Years Ago



Slice of life. This replica of a tiny finger bone from Denisova Cave (*right*) yielded an entire genome.

New DNA Analysis Shows Ancient Humans Interbred with Denisovans

A new high-coverage DNA sequencing method reconstructs the full genome of Denisovans--relatives to both Neandertals and humans--from genetic fragments in a single finger bone



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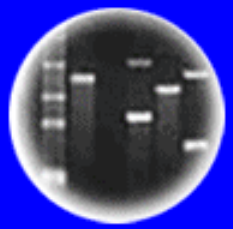

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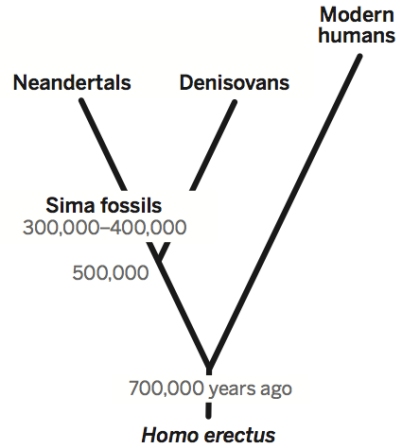
HUMAN EVOLUTION

Humanity's long, lonely road

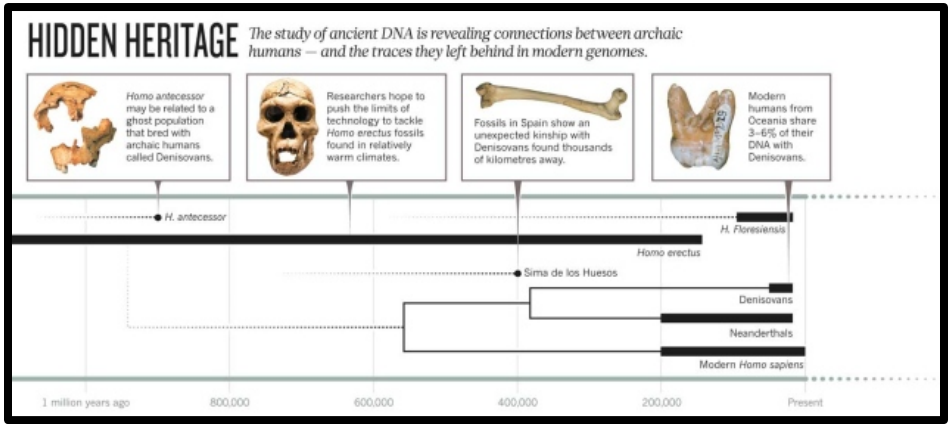
Oldest ancient nuclear DNA suggests humans and Neandertals parted ways early

Deeper branches

Putting the Sima fossils on the Neandertal lineage implies an earlier split between modern and some archaic humans.



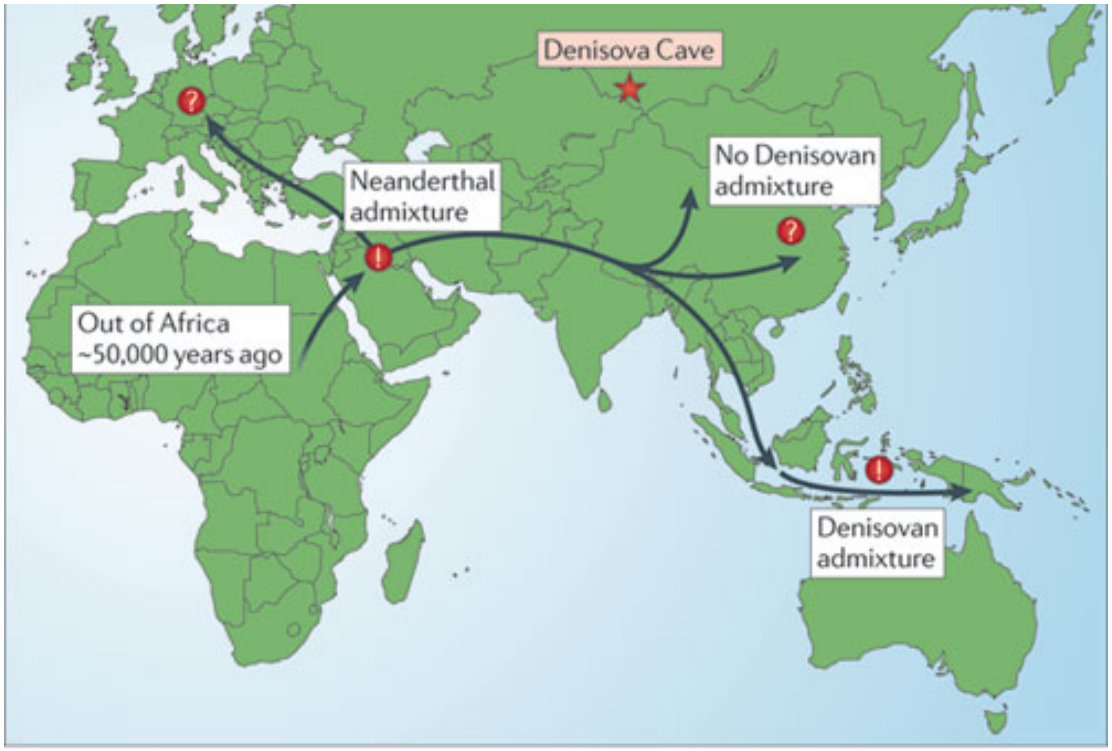
Creating a Map of Human History!



The Shaping of Modern Human Immune Systems by Multiregional Admixture with Archaic Humans

www.sciencemag.org **SCIENCE** VOL 334 7 OCTOBER 2011

Comparing 130,000 Year-Old Fossil Genomes to Our Genome Reveals Ancient "Matings" Between Diffferent Human Ancestor Lineages!!



Nature Reviews | Genetics
September, 2011

2-4% of Human Genome Consists of Neanderthal Sequences!

It's All in the DNA!

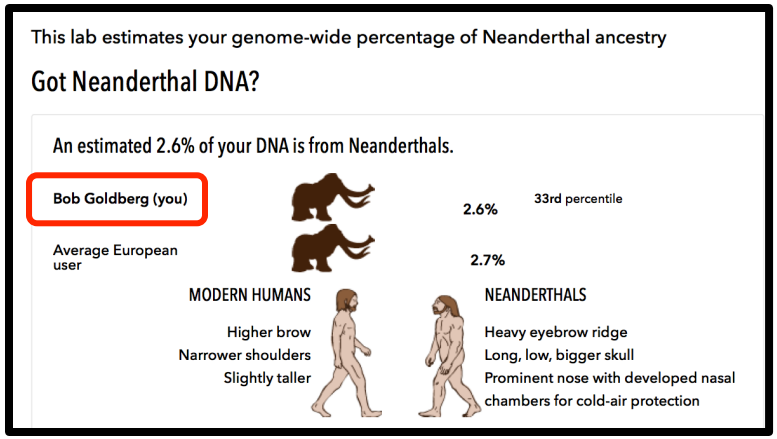
The genomic landscape of Neanderthal ancestry in present-day humans

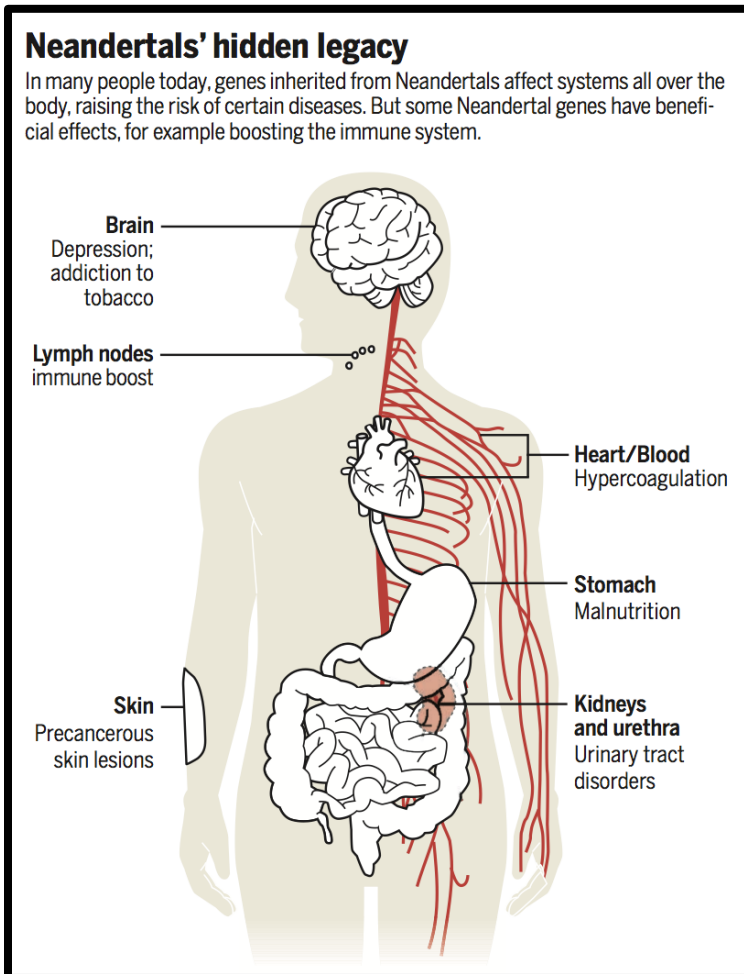
Nature, January 29, 2014

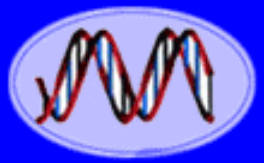
Neandertal genes linked to modern diseases

The phenotypic legacy of admixture between modern humans and Neandertals

Genomic Signatures of Selective Pressures and Introgression from Archaic Hominins at Human Innate Immunity Genes







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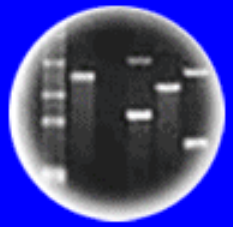

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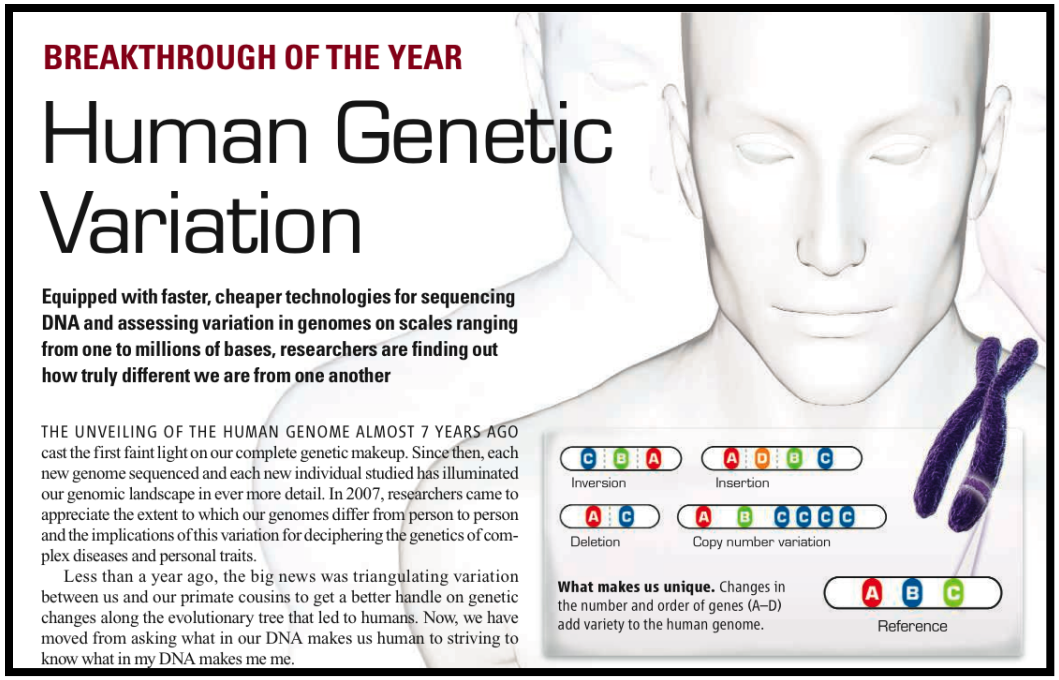
HUMAN DIVERSITY

RICHARD LEWONTIN

Scientific American Library
1982 ISBN 07167-14698

Using DNA Variations (SNPs) Between Individuals (Living & Dead) Has Many Uses

1. Marking and Identifying Disease Genes
2. Paternity, Individual Identification, Forensics
3. Human Population History and Origins
4. Identifying Neanderthal Alleles in Modern Human Populations



BREAKTHROUGH OF THE YEAR

Human Genetic Variation

Equipped with faster, cheaper technologies for sequencing DNA and assessing variation in genomes on scales ranging from one to millions of bases, researchers are finding out how truly different we are from one another

THE UNVEILING OF THE HUMAN GENOME ALMOST 7 YEARS AGO cast the first faint light on our complete genetic makeup. Since then, each new genome sequenced and each new individual studied has illuminated our genomic landscape in ever more detail. In 2007, researchers came to appreciate the extent to which our genomes differ from person to person and the implications of this variation for deciphering the genetics of complex diseases and personal traits.

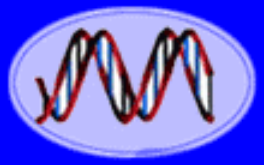
Less than a year ago, the big news was triangulating variation between us and our primate cousins to get a better handle on genetic changes along the evolutionary tree that led to humans. Now, we have moved from asking what in our DNA makes us human to striving to know what in my DNA makes me me.

What makes us unique. Changes in the number and order of genes (A–D) add variety to the human genome.

The 1,000 Genomes Project Will Provide Novel Insight in Human Genomes, Ancestry, & Disease Genes & Is Now the 100,000 Genome Project!!!

The 100,000 Genomes Project

You can read all about the 100,000 Genomes Project in the different sections below or download all of this information in our full narrative here: Narrative – Genomics England and the 100,000 Genomes Project.



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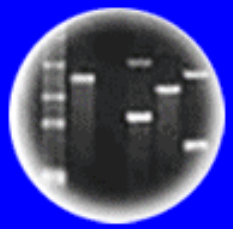

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ARTICLE

Nature, October 28, 2010

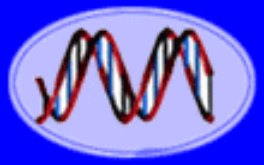
doi:10.1038/nature09534

A map of human genome variation from population-scale sequencing

The 1000 Genomes Project Consortium*

The 1000 Genomes Project aims to provide a deep characterization of human genome sequence variation as a foundation for investigating the relationship between genotype and phenotype. Here we present results of the pilot phase of the project, designed to develop and compare different strategies for genome-wide sequencing with high-throughput platforms. We undertook three projects: low-coverage whole-genome sequencing of 179 individuals from four populations; high-coverage sequencing of two mother–father–child trios; and exon-targeted sequencing of 697 individuals from seven populations. We describe the location, allele frequency and local haplotype structure of approximately 15 million single nucleotide polymorphisms, 1 million short insertions and deletions, and 20,000 structural variants, most of which were previously undescribed. We show that, because we have catalogued the vast majority of common variation, over 95% of the currently accessible variants found in any individual are present in this data set. On average, each person is found to carry approximately 250 to 300 loss-of-function variants in annotated genes and 50 to 100 variants previously implicated in inherited disorders. We demonstrate how these results can be used to inform association and functional studies. From the two trios, we directly estimate the rate of *de novo* germline base substitution mutations to be approximately 10^{-8} per base pair per generation. We explore the data with regard to signatures of natural selection, and identify a marked reduction of genetic variation in the neighbourhood of genes, due to selection at linked sites. These methods and public data will support the next phase of human genetic research.

- Sequenced Genomes of ~900 individuals
- From Seven Different Global Populations
- Identified 15,000,000 SNPs
- 50-100 Variants in Disease Genes Per Person
- 10^{-8} Mutations Per bp Per Generation (~30 per Genome)
- 3,000,000 Unique SNPs Per Person
- 750,000 Unique Indels Per Person



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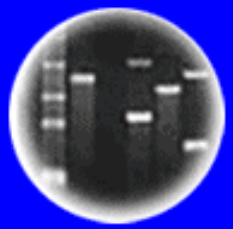

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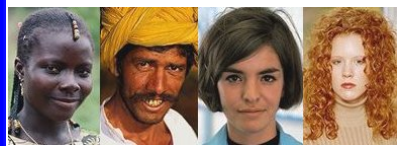
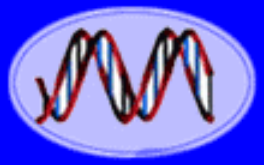
An integrated map of structural variation in 2,504 human genomes

The 1000 Genomes Project set out to provide a comprehensive description of common human genetic variation by applying whole-genome sequencing to a diverse set of individuals from multiple populations. Here we report completion of the project, having reconstructed the genomes of 2,504 individuals from 26 populations using a combination of low-coverage whole-genome sequencing, deep exome sequencing, and dense microarray genotyping. We characterized a broad spectrum of genetic variation, in total over 88 million variants (84.7 million single nucleotide polymorphisms (SNPs), 3.6 million short insertions/deletions (indels), and 60,000 structural variants), all phased onto high-quality haplotypes. This resource includes >99% of SNP variants with a frequency of >1% for a variety of ancestries. We describe the distribution of genetic variation across the global sample, and discuss the implications for common disease studies.

A global reference for human genetic variation

Structural variants are implicated in numerous diseases and make up the majority of varying nucleotides among human genomes. Here we describe an integrated set of eight structural variant classes comprising both balanced and unbalanced variants, which we constructed using short-read DNA sequencing data and statistically phased onto haplotype blocks in 26 human populations. Analysing this set, we identify numerous gene-intersecting structural variants exhibiting population stratification and describe naturally occurring homozygous gene knockouts that suggest the dispensability of a variety of human genes. We demonstrate that structural variants are enriched on haplotypes identified by genome-wide association studies and exhibit enrichment for expression quantitative trait loci. Additionally, we uncover appreciable levels of structural variant complexity at different scales, including genic loci subject to clusters of repeated rearrangement and complex structural variants with multiple breakpoints likely to have formed through individual mutational events. Our catalogue will enhance future studies into structural variant demography, functional impact and disease association.





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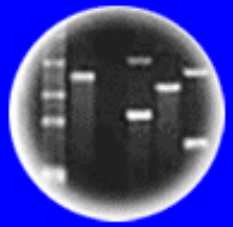

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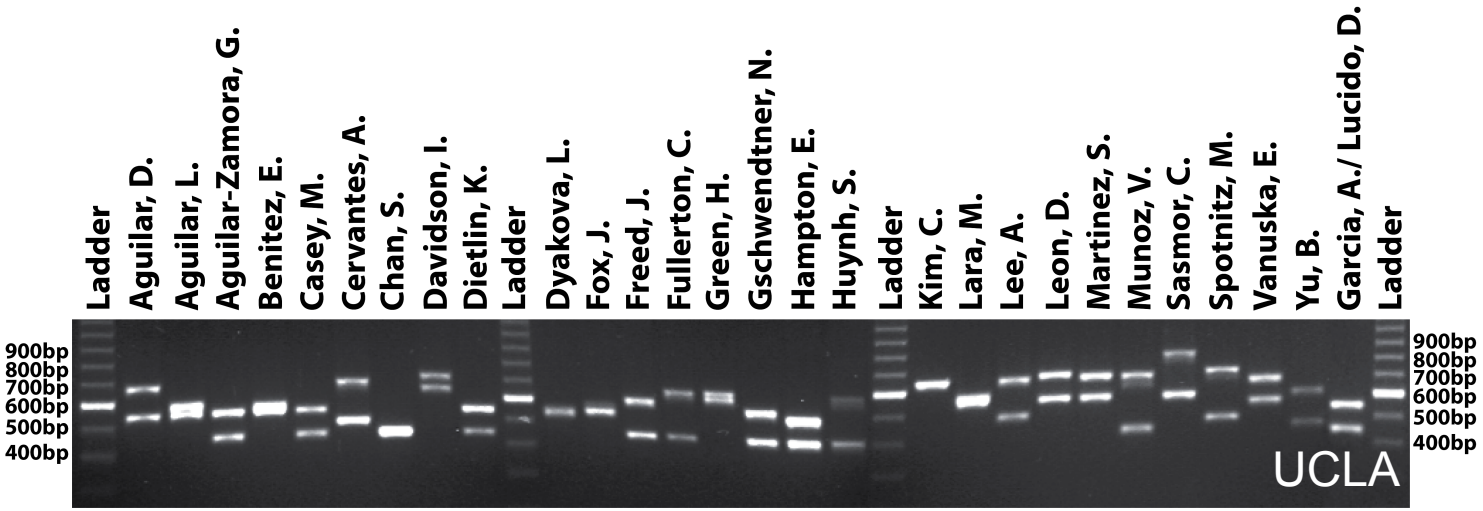
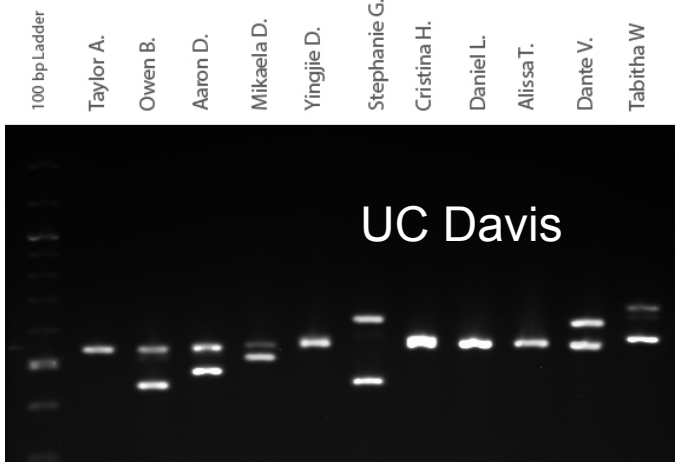
HC70A/SAS70A Class Allelic Variation
(Note Heterozygousity)

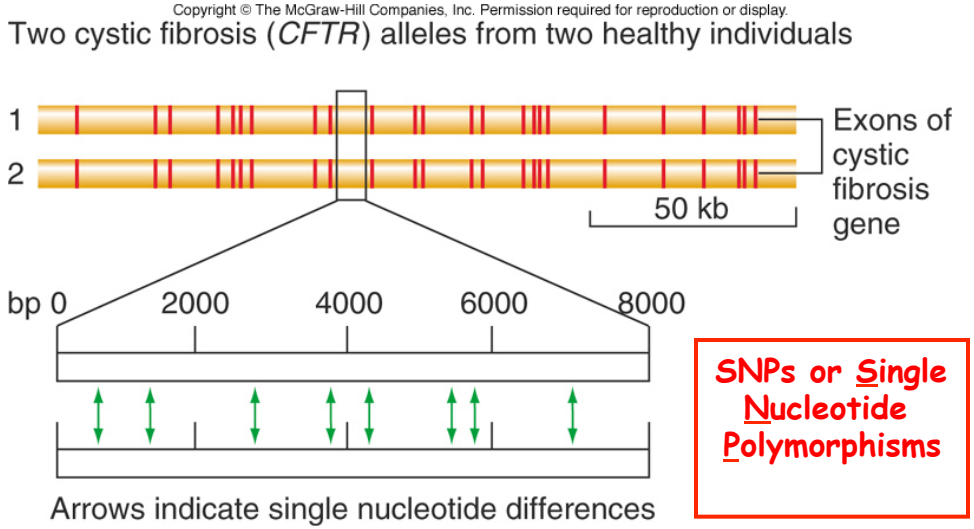


Note: the Class Allelic Diversity at the D1S80 Locus on Chromosome One!



Same Locus?
Same DNA Sequence?
Same Alleles?

Most DNA Variations Between Individuals Occur Because of Base-Pair Changes in Non-Coding Regions of the Genome



SNPs or Single Nucleotide Polymorphisms

To Be on the safe side, suppose you assume that only 80% (0.8) of the 3 billion base pairs in the genome are noncoding, and on average only 1 base pair in 700 is polymorphic. With these assumptions, you can determine the frequency of polymorphism within a single individual by multiplying 3 billion by 0.8 and then multiplying that amount by 1/700:

(3x109) x 0.8 = 2.4 x 109, (2.4 x 109) x 1/700 = 3.4 million.

The result of 3.4 million is astonishing: It means that there are millions of differences between any two haploid sets of human chromosomes. Combined with differences in coding and regulatory sequences (which occur much less frequently), the millions of polymorphisms at anonymous loci contribute to an enormous pool of potential DNA markers.

Types of DNA Polymorphisms

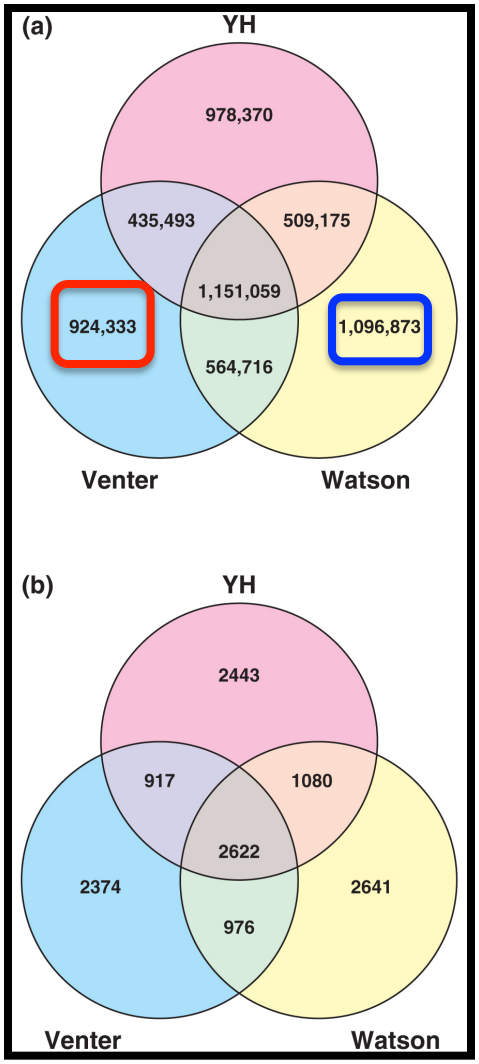
TABLE 11.1 Classes of DNA Polymorphisms

Class	Size of Locus	Number of Alleles	Number of Loci in Population	Rate of Mutation	Use	Method of Detection
SNP	Single base pair	2	100 million	10^{-9}	Linkage and association mapping	PCR followed by ASO hybridization or primer extension
Microsatellite	30–300 bp	2–10	200,000	10^{-3}	Linkage and association mapping	PCR and gel electrophoresis
Multilocus minisatellite	1–20 kb	2–10	30,000	10^{-3}	DNA fingerprinting	Southern blot and hybridization
Indels (deletions and duplications)	1–100 bp	2	N/A	$<10^{-9}$	Linkage and association mapping	PCR and gel electrophoresis

This is What Makes Us Unique Individuals!

There is ~1bp Change per 700bp in Human Genomes or ~3.4 Million bp Differences Between Individuals ~0.1% of Genome

Comparison of Watson's and Ventner's Genomes Indicates That Individuals Have Unique SNPs!



YH= Anonymous Chinese Man

(a)

Allele	Genome	Single-Strand Notation
1	AGCTCTGATAC TCGAGACTATG	AGCTCTGATAC
2	AGCTCCGATAC TCGAGGCTATG	AGCTCCGATAC

(b)

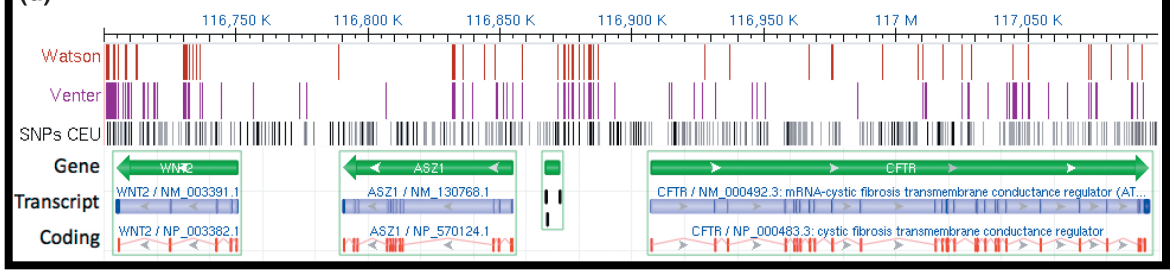
Genotype	Notation
Homozygous T	TT
Heterozygous T	TC
Homozygous C	CC

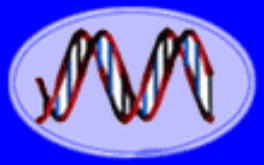
(c)

Human 1 TTGACGTATAAATGATCTTTATATTTTCAGAAGTC
Human 2 TTGACGTATAAATGATCTTTATATCTTCAGAAGTC
Chimp TTGACATATAAATGATCTTTATATCTTCAGAAGTC

These Are Alleles!

(d)





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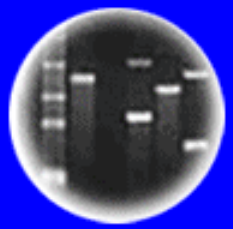

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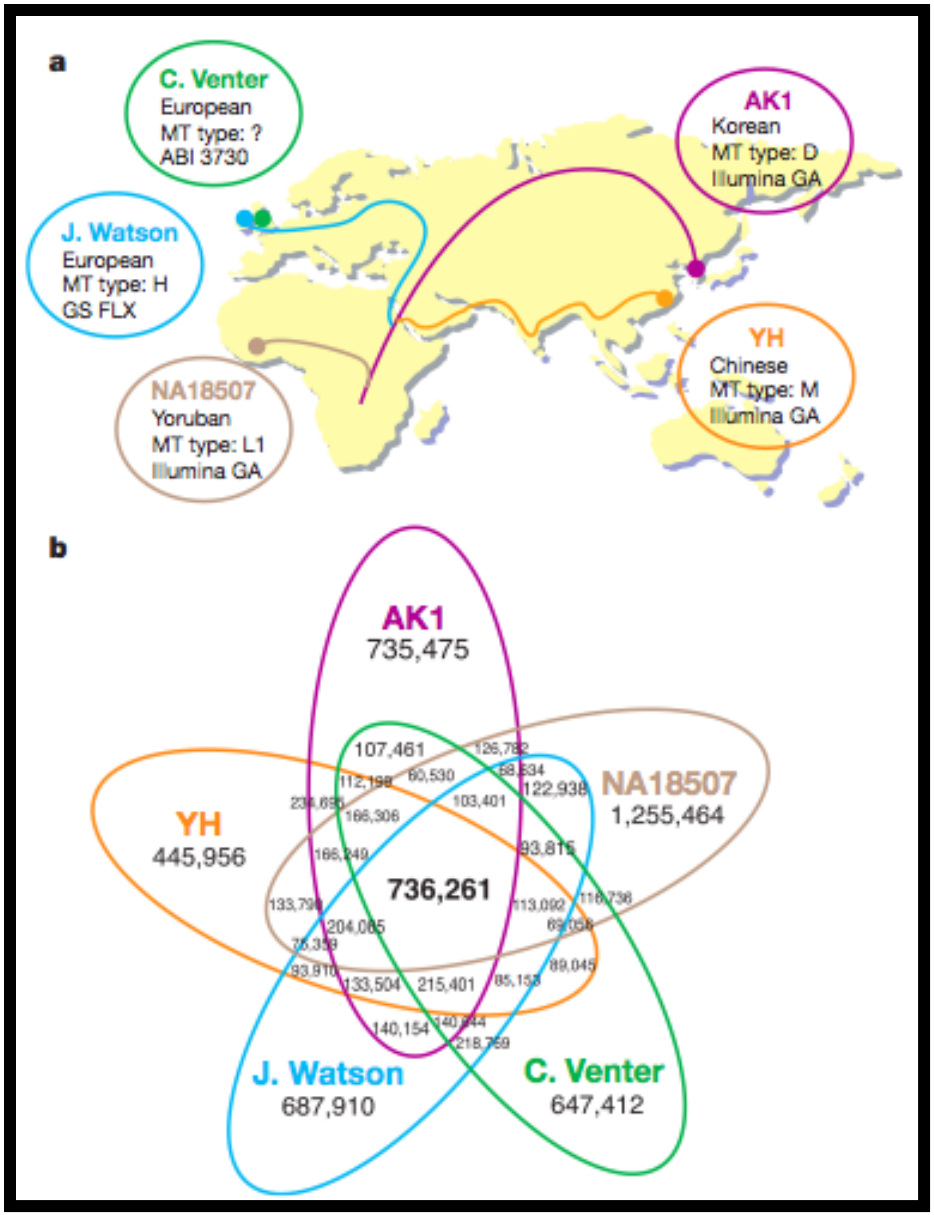
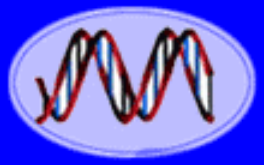
Everyone Has a Large Number of Unique SNPs!



Used to Trace Ancestry & Individuality



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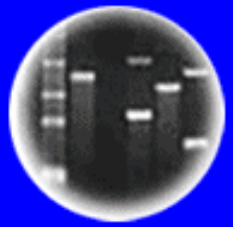

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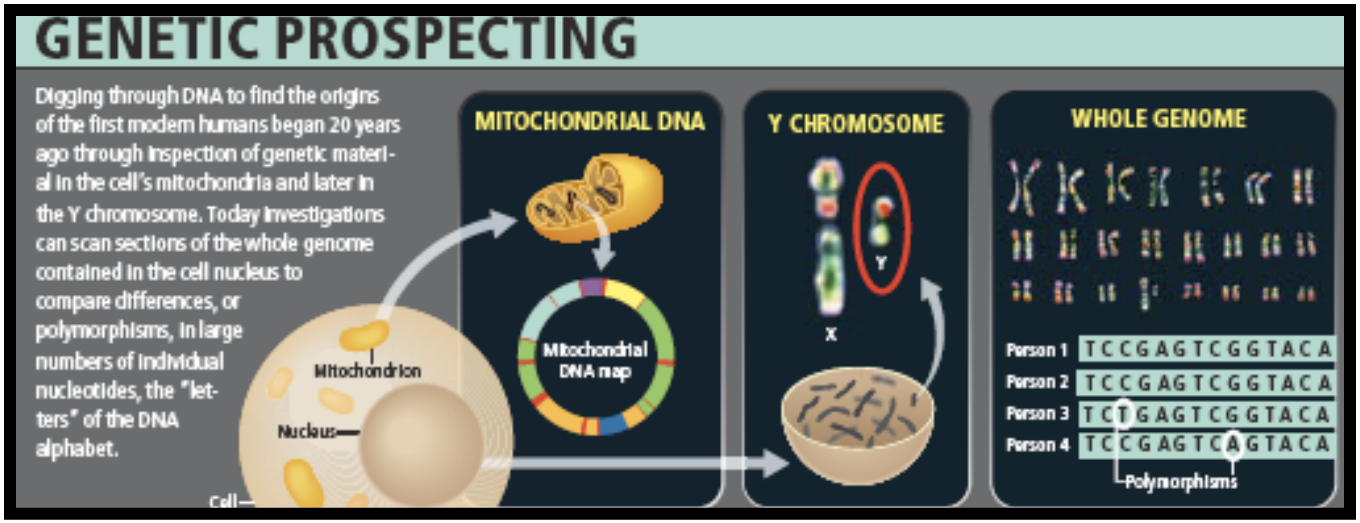
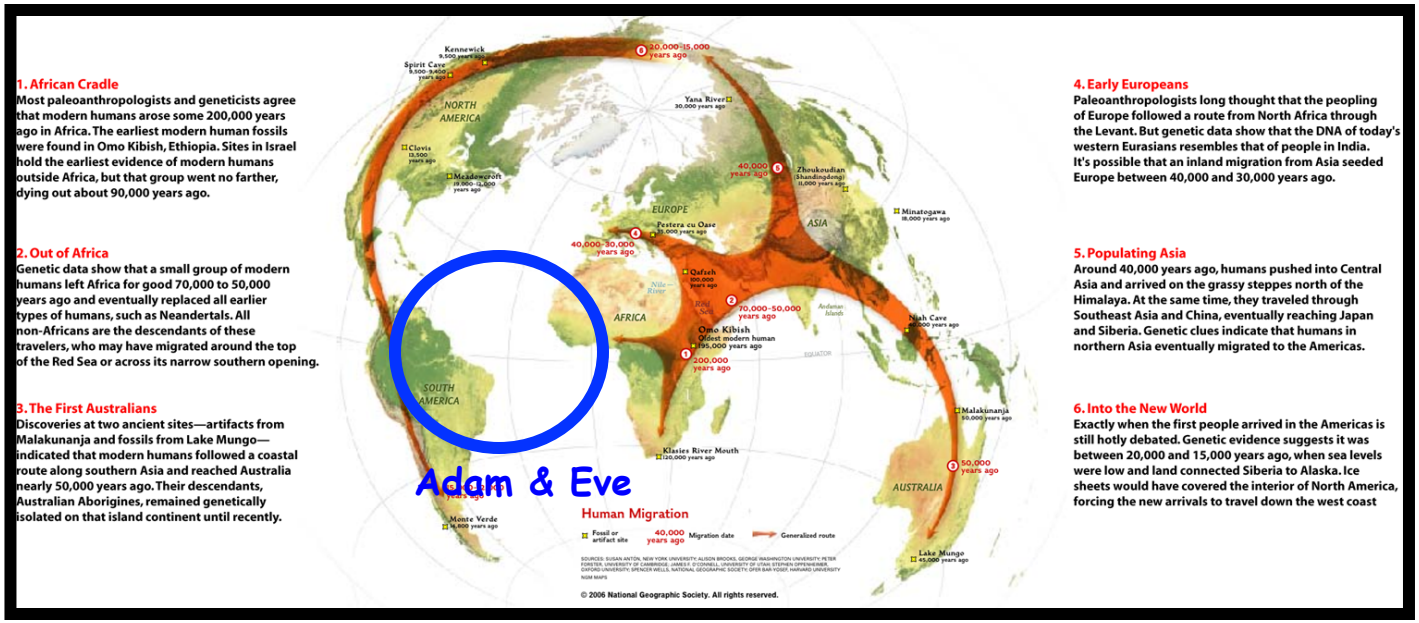
Nuclear DNA SNPS Can Be Used To Trace Human Populations & Origins

(Concept Same as For Mt DNA)



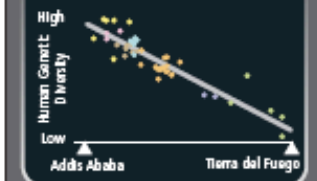


[WHOLE-GENOME RESULTS]

LOOKING FAR AND WIDE

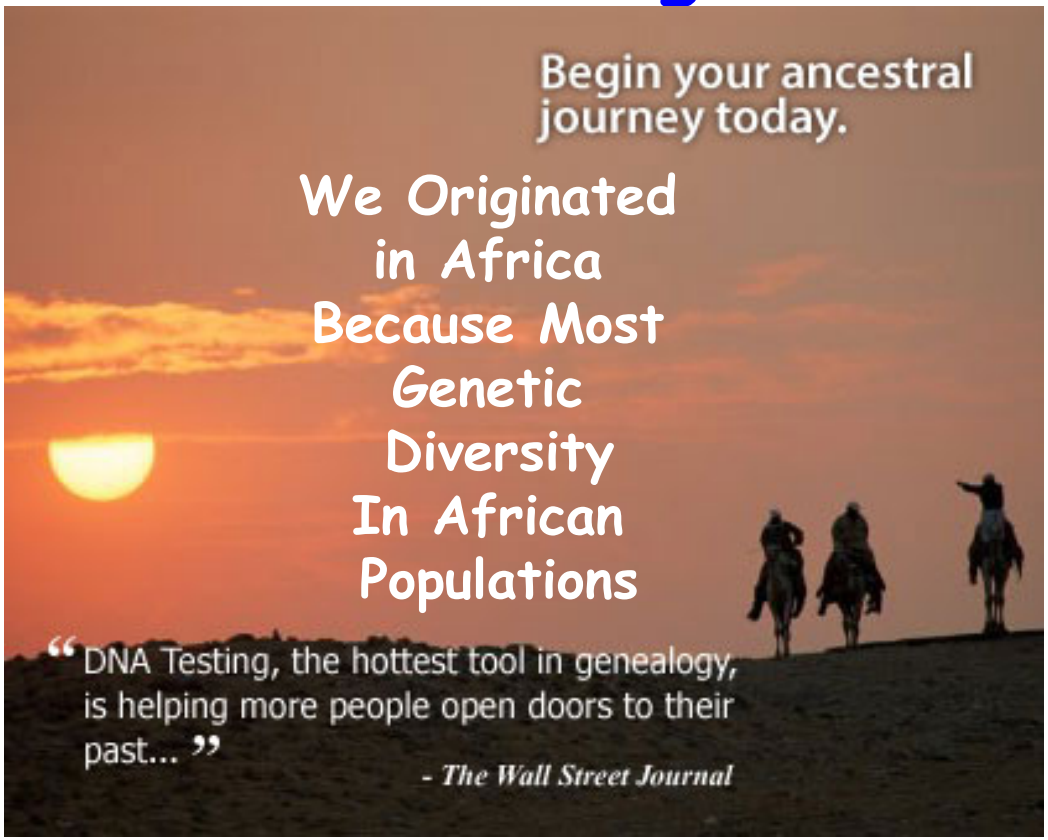
High-powered genetic sequencing and computational techniques developed for the Human Genome Project and in its aftermath have furnished a wealth of data that lets researchers compare genomes drawn from distinct populations around the globe.

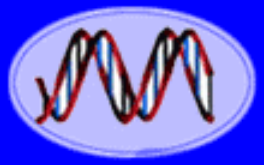
The diversity of DNA—measured as the variation of nucleotides within blocks of DNA called haplotypes—decreases with distance from Addis Ababa, Ethiopia, a pattern that corresponds to the chronology of human migrations.



A genomic map of the world, crafted by researchers at the University of Michigan at Ann Arbor, shows that genetic diversity decreases outside of Africa. Each colored tile represents a common haplotype. Africa has more tiles than found on other continents and ones that correspond to haplotypes found nowhere else.

All of Humanity is Related & Has the SAME Origin!





DNA
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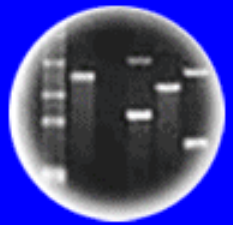

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Finally…Human Genome Diversity & The Concept of "Race"

There is More Genetic (Allelic) Diversity Within Populations than Between Populations!! So Much for the Concept of Racial "Purity"!!!!

Proportion of genetic diversity accounted for within and between populations and races

Gene	Total $H_{species}$	Proportion		
		Within Populations	Within Races between Populations	Between Races
Hp	.994	.893	.051	.056
Ag	.994	.834	—	—
Lp	.639	.939	—	—
Xm	.869	.997	—	—
Ap	.989	.927	.062	.011
6PGD	.327	.875	.058	.067
PGM	.758	.942	.033	.025
Ak	.184	.848	.021	.131
Kidd	.977	.741	.211	.048
Duffy	.938	.636	.105	.259
Lewis	.994	.966	.032	.002
Kell	.189	.901	.073	.026
Lutheran	.153	.694	.214	.092
P	1.000	.949	.029	.022
MNS	1.746	.911	.041	.048
Rh	1.900	.674	.073	.253
ABO	1.241	.907	.063	.030
Mean		.854	.083	.063

Source: R. C. Lewontin, *Genetic Basis of Evolutionary Change* (Columbia University Press, 1974).

More Genetic Diversity Within Any Population Than Between Polulations

1. 85% of Human Genetic Variations Occurs Within Populations & Between Individuals in that Populations!
2. Remaining 15% of Human Genetic Variation Split Between Different Populations of Same "race" (8%) & Between Different "races" (6%)
3. Only 6% of Human Genetic Variation are to Differences between races!!! Mostly Geographic. Note: THERE ARE GROUP DIFFERENCES! Most likely as a result of geographical isolation and adaptive significance in that population.

Within Population Differences Account For 95% of Human Genetic Variation

Genetic Structure of Human Populations

Noah A. Rosenberg,[1]* Jonathan K. Pritchard,[2] James L. Weber,[3] Howard M. Cann,[4] Kenneth K. Kidd,[5] Lev A. Zhivotovsky,[6] Marcus W. Feldman[7]

We studied human population structure using genotypes at 377 autosomal microsatellite loci in 1056 individuals from 52 populations. Within-population differences among individuals account for 93 to 95% of genetic variation; differences among major groups constitute only 3 to 5%. Nevertheless, without using prior information about the origins of individuals, we identified six main genetic clusters, five of which correspond to major geographic regions, and subclusters that often correspond to individual populations. General agreement of genetic and predefined populations suggests that self-reported ancestry can facilitate assessments of epidemiological risks but does not obviate the need to use genetic information in genetic association studies.

Table 1. Analysis of molecular variance (AMOVA). Eurasia, which encompasses Europe, the Middle East, and Central/South Asia, is treated as one region in the five-region AMOVA but is subdivided in the seven-region design. The World-B97 sample mimics a previous study (*6*).

Sample	Number of regions	Number of populations	Variance components and 95% confidence intervals (%)		
			Within populations	Among populations within regions	Among regions
World	1	52	94.6 (94.3, 94.8)	5.4 (5.2, 5.7)	
World	5	52	93.2 (92.9, 93.5)	2.5 (2.4, 2.6)	4.3 (4.0, 4.7)
World	7	52	94.1 (93.8, 94.3)	2.4 (2.3, 2.5)	3.6 (3.3, 3.9)
World-B97	5	14	89.8 (89.3, 90.2)	5.0 (4.8, 5.3)	5.2 (4.7, 5.7)
Africa	1	6	96.9 (96.7, 97.1)	3.1 (2.9, 3.3)	
Eurasia	1	21	98.5 (98.4, 98.6)	1.5 (1.4, 1.6)	
Eurasia	3	21	98.3 (98.2, 98.4)	1.2 (1.1, 1.3)	0.5 (0.4, 0.6)
Europe	1	8	99.3 (99.1, 99.4)	0.7 (0.6, 0.9)	
Middle East	1	4	98.7 (98.6, 98.8)	1.3 (1.2, 1.4)	
Central/South Asia	1	9	98.6 (98.5, 98.8)	1.4 (1.2, 1.5)	
East Asia	1	18	98.7 (98.6, 98.9)	1.3 (1.1, 1.4)	
Oceania	1	2	93.6 (92.8, 94.3)	6.4 (5.7, 7.2)	
America	1	5	88.4 (87.7, 89.0)	11.6 (11.0, 12.3)	

But - There Are Differences! But…They Fall Into Geographical Groups -- Groups Divided Originally by Geographic Barriers (Ocean, Desert, Mountains). The 5% Difference Allows Us to Mark and Trace Ancestry!

Conclusions

1. If 85% of Human Genetic Variation Occurs Between Different People Within Any Given Population (localized)
2. If only 7% of Human Genetic Variation Occurs Between "Races" (novel alleles specific to "races")
3. Then Losing all "Races" Except One Retains 93% of all Human Genetic Variation!

[85% + (15%-7%)]= 93%

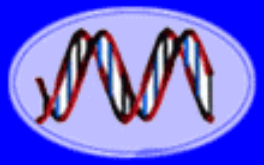
Variation That Occurs in Ancestral Population

85% Within Population genetic variability

8% Between Populations of Same "Race"

7% Between "Race" Genetic Variability

4. ∴ Humans Are Highly Heterozygous or Hybrids- & If Above Not True- Most of Us Would Not Be Here- Need Genetic Variation to Survive!



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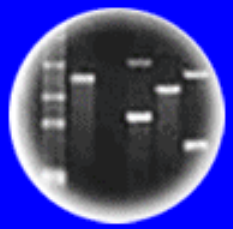

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So What is a "Race"?

1. Primarily a sociological concept- but could be a localized or "inbred population" that has a higher frequency of alleles at a *very small number of loci*. Affects few physical features.
2. High frequency alleles in one "race" are present at lower frequencies in other "races". All humans have same genes- differ in form mostly within populations!
3. Heterozygosity (variation) high in human populations- all populations. None homozygous at all loci!
4. No such thing as a "pure" race - would have little variation
5. Genes affecting physical features not representation of genes across genome — "selected" traits with adaptive significance (e.g., vitamin D synthesis, sexual selection, pathogen susceptibility, etc.

Geographical Ancestry is relevant-many "racial" groups now have multiple ancestries because of admixture and migration