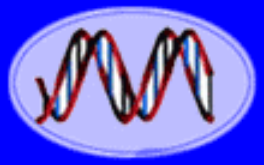

DNA
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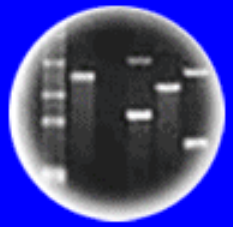
Entire Genetic Code
of a Bacteria



DNA Fingerprinting

Cloning: Ethical Issues
and Future Consequences

Plants of Tomorrow

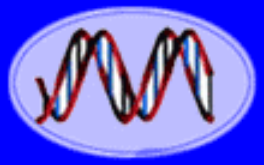
HC70A & PLSS059
Winter 2020
Genetic Engineering in Medicine, Agriculture, and Law

Professors Bob Goldberg &
Channapatna Prakash

Lecture 7
The Age of Genomics: Three-Parent Babies, Human Origins, & Race

UCLA

TUSKEGEE
UNIVERSITY



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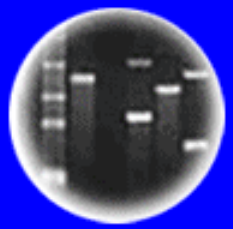

DNA Fingerprinting

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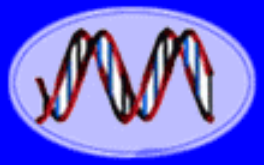
Themes

- The Human Genome – Two!
- Mitochondrial Genome, Diseases, & Ancestry
- Mitochondrial Replacement Therapy – Science, Ethics, & Politics
- The Human Genome
- Human Disease Genes
- Correcting Human Gene Disorders
- Using Ancient DNA To Trace Human Ancestry
- Human Genetic Diversity & 1000 Genome Project
- Using Human Genetic Diversity to Unravel Our Recent Human History
- Using Human Genetic Diversity to Unravel the Concept of "Race"
- Knowledge vs. Certainty – Dogma in Science



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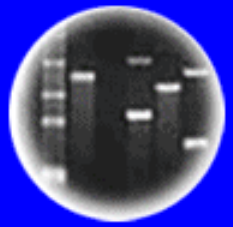

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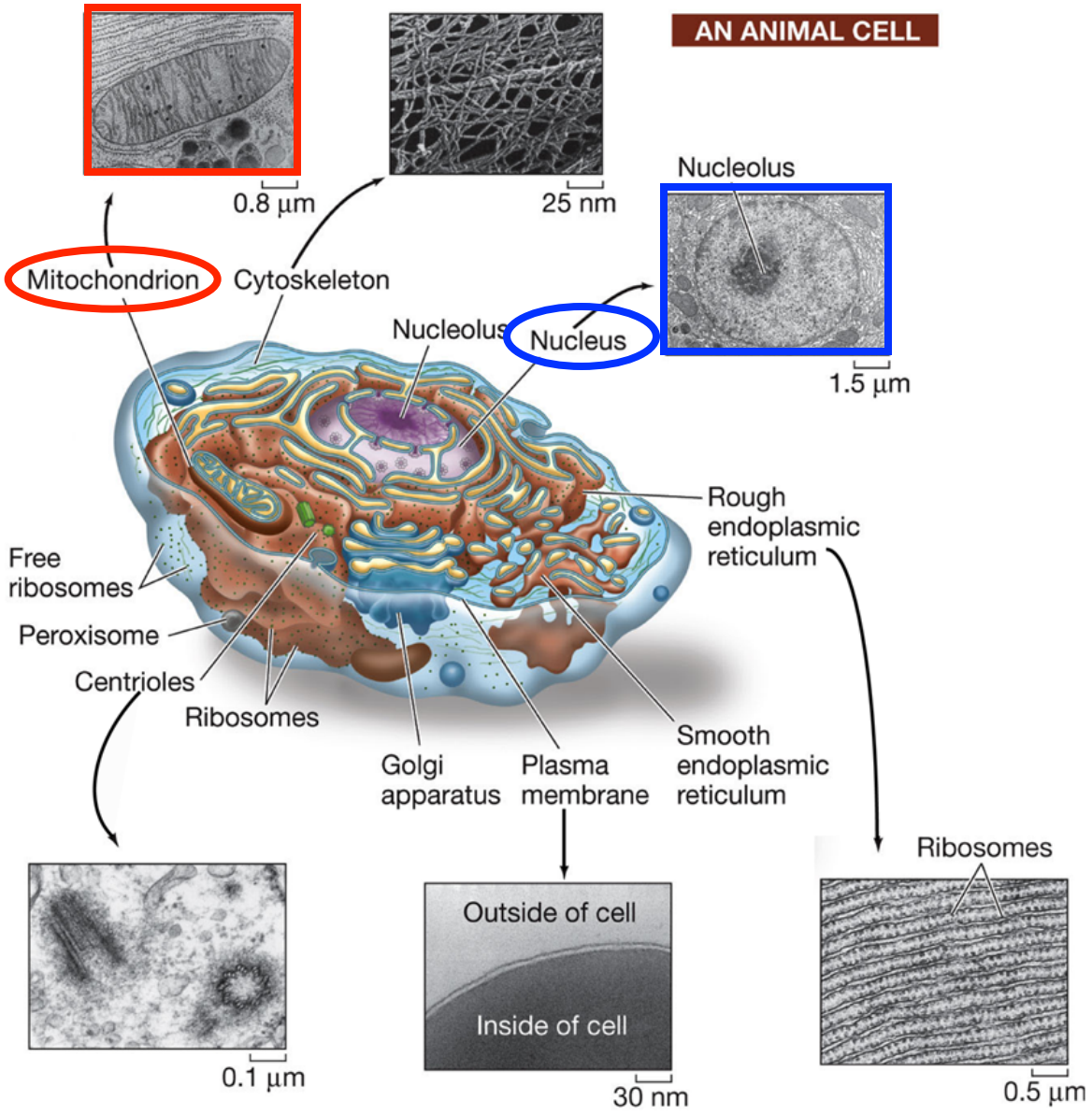
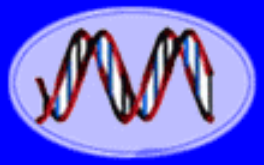
Human Cells Have Two Genomes……..





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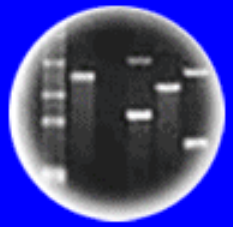

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.....One in the Nucleus and One in the Mitochondria

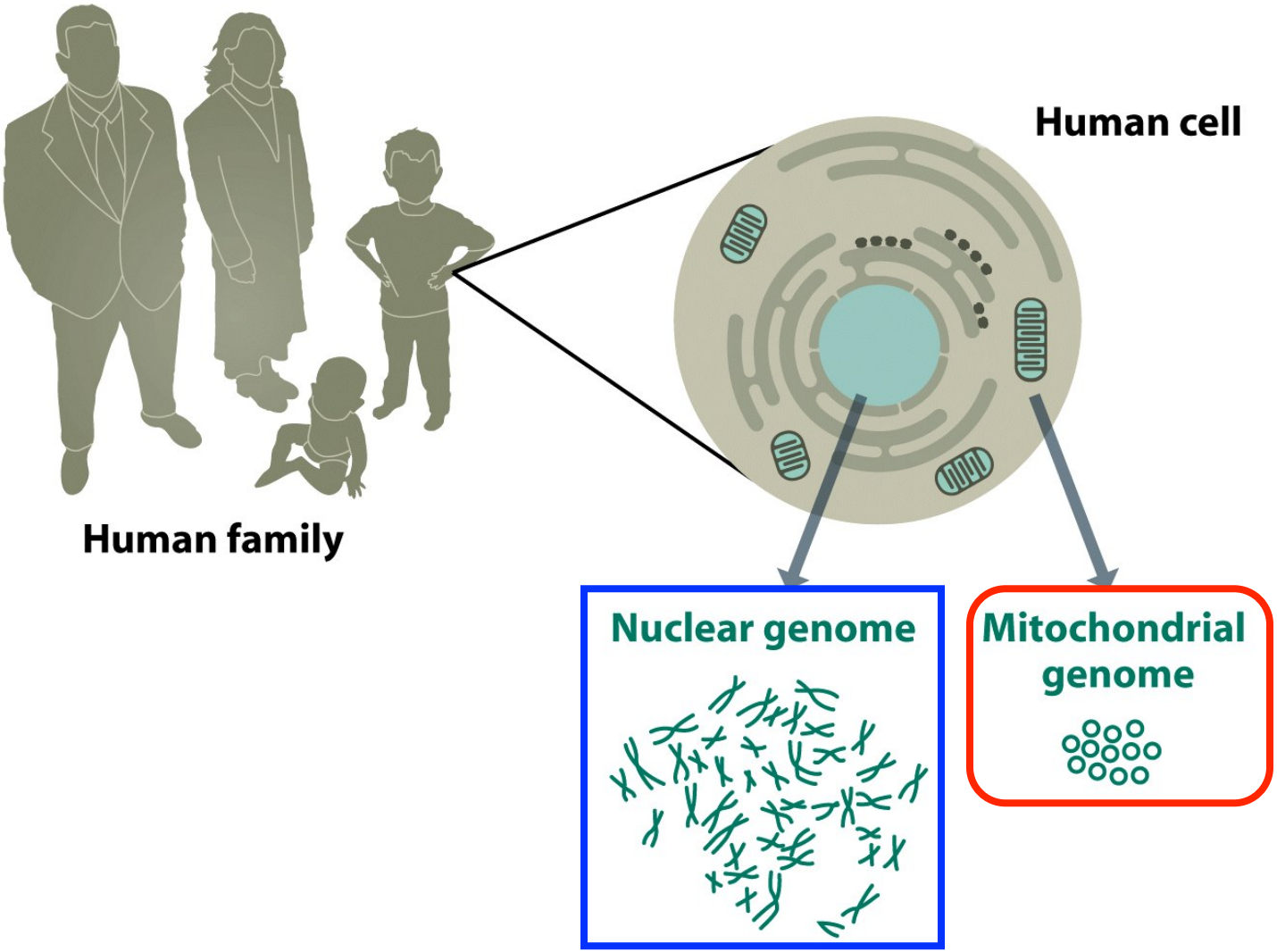


Figure 1-1 Genomes 3 (© Garland Science 2007)

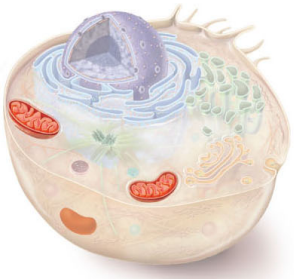
Human Nuclear and Mitochondrial Genomes Differ in Size & Shape

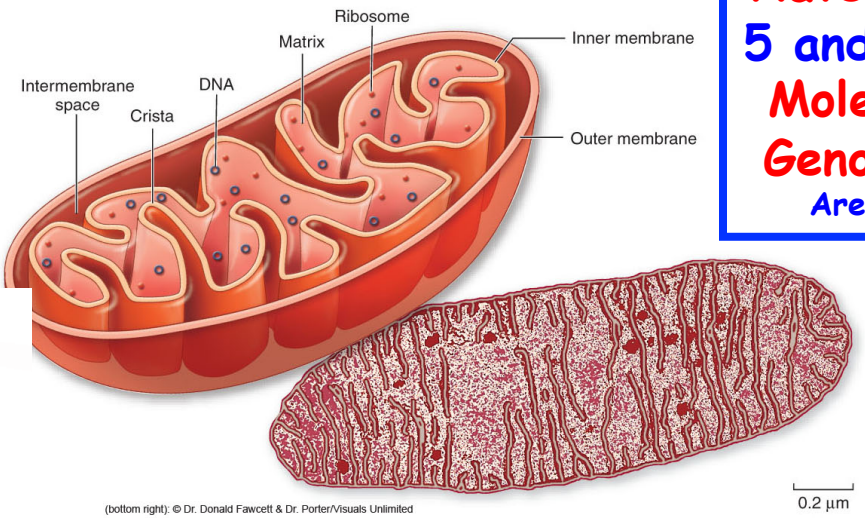
Characteristic	Nuclear Genome	Mitochondrial Genome
Size	3.3×10^9 bp	16,500 bp
DNA Molecules Per Cell	23 in Haploid Cells 46 in Diploid Cells	100 to >1,000 Per Cell (e.g., 50,000 in Egg Cell)
Number of Genes	25,000	37
Gene Density	1 per 40,000 bp	1 per 450 bp
Presence of Introns	In Most Genes	Absent
% Coding DNA	3%	93%
Codon Usage	Universal Code	AUA – Methionine UGA – Tyrosine AGG – Stop
Mode of Inheritance	Mendelian	Maternal
Repetitive Sequences (e.g., VNTR)	50%	Almost None

What Are the Consequences of Many Mitochondrial Genomes Per Cell For Human Mt Diseases?

Mitochondria Power Human Cells and Contain a Circular Genome (Makes ATP)

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





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

Mitochondria Have Between 5 and 15 DNA Molecules or Genomes (They Are Polyploid)!!

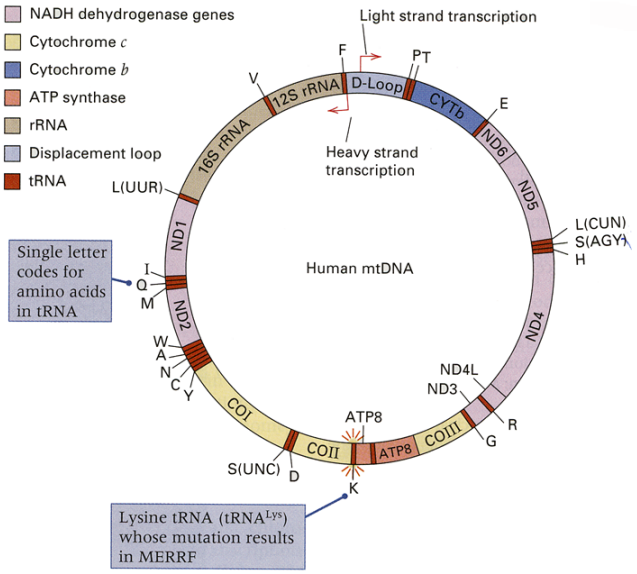


Figure 16.3 Genes in human mitochondrial DNA. The tRNA genes are indicated by the one-letter amino acid symbols; hence $tRNA^{Lys}$ is denoted K. The positions of these and other genes in the mitochondrial DNA are indicated by color according to the key at the upper left. The arrows indicate the promoters 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

- DNA Genome
  - Divides
- Transcription
- Translation

→ **Mitochondrial Proteins**

Mutations Lead to Mitochondrial Diseases

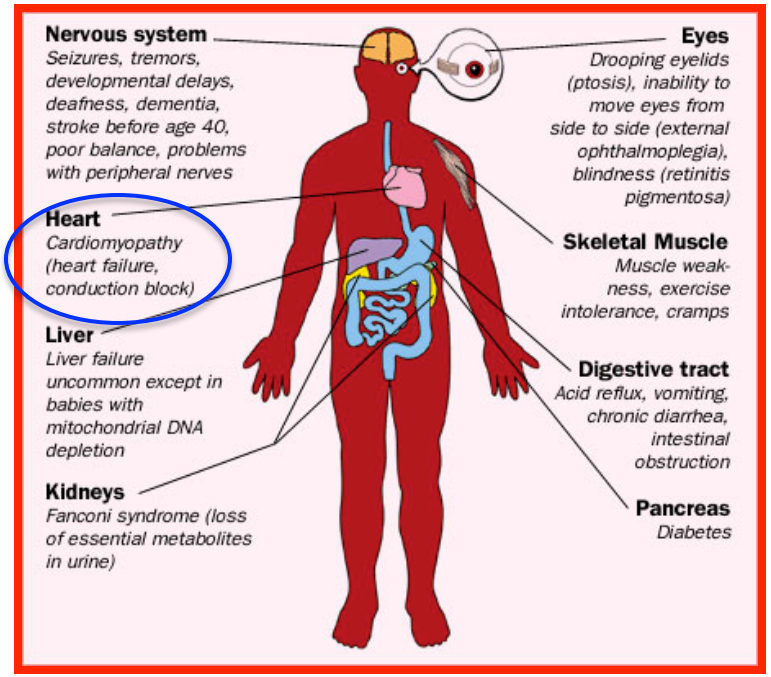
UNITED MITOCHONDRIAL DISEASE FOUNDATION.
HOPE. ENERGY. LIFE.

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

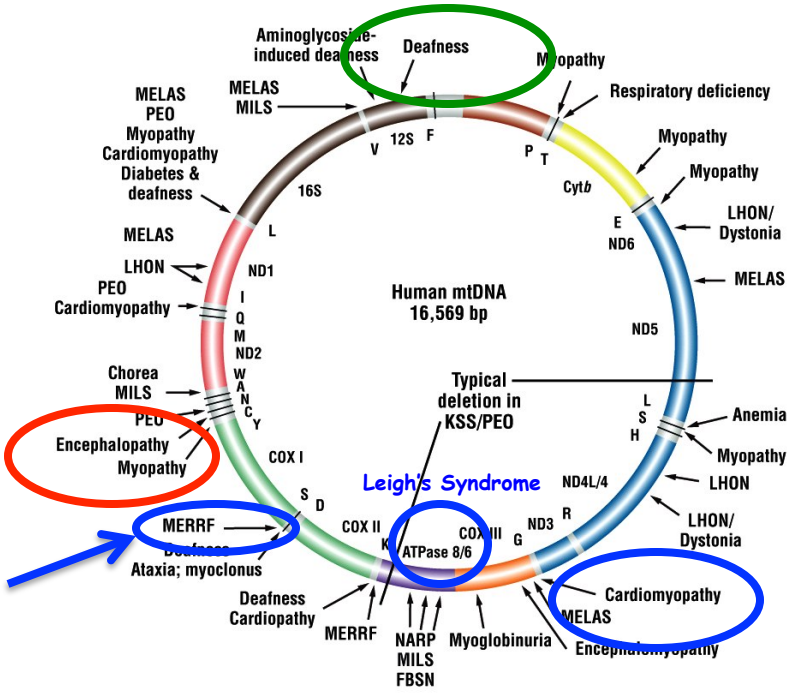


Treatment

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

Mutant Mitochondria Mitochondrial Genomes Are Inherited Maternally

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



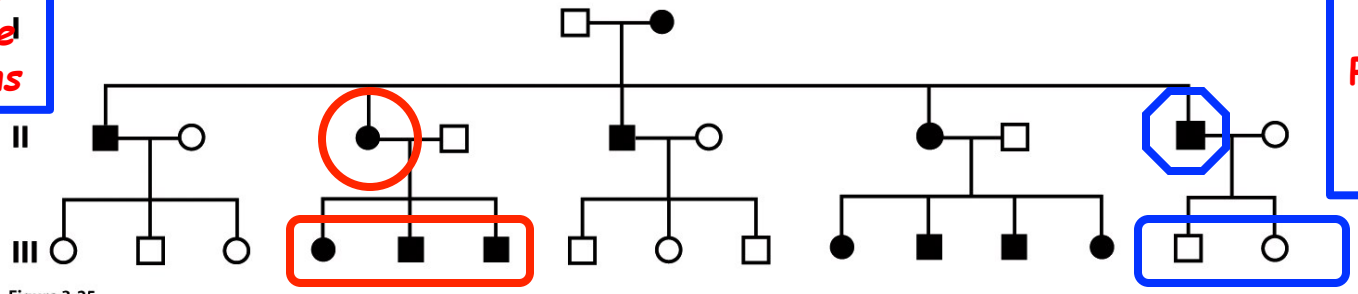
Disease Genes Present on the Mitochondrial Genome

Many Affect Muscles Because Mitochondria Produce Energy Needed For Muscle Activity

Provide a Hypothesis For the Variation in Disease Symptoms

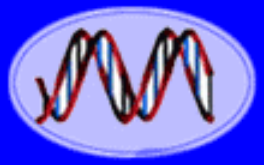
Diseases:

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



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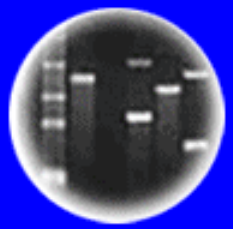

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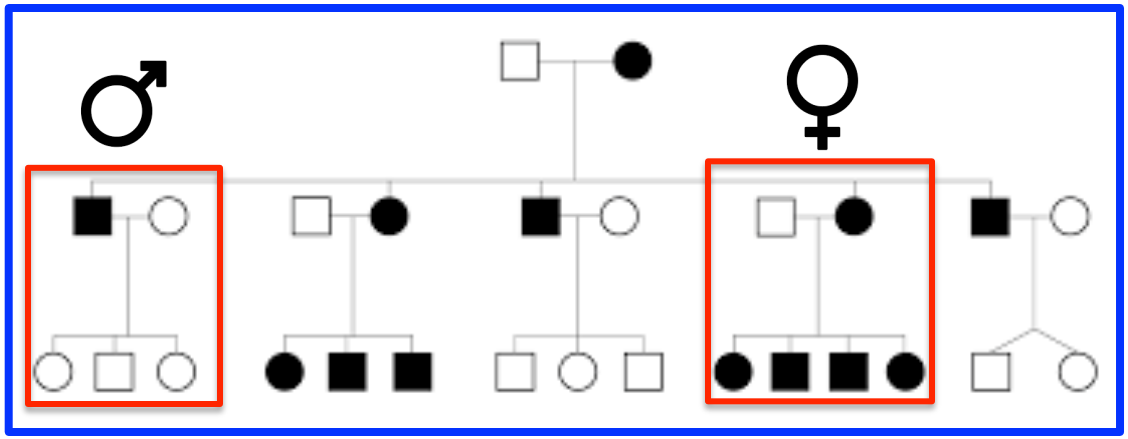
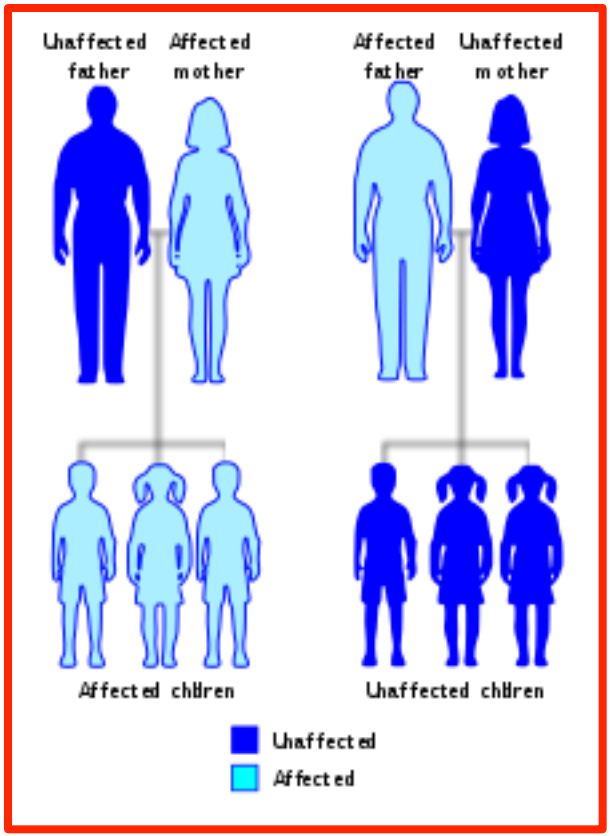
Mitochondrial or Maternal Inheritance



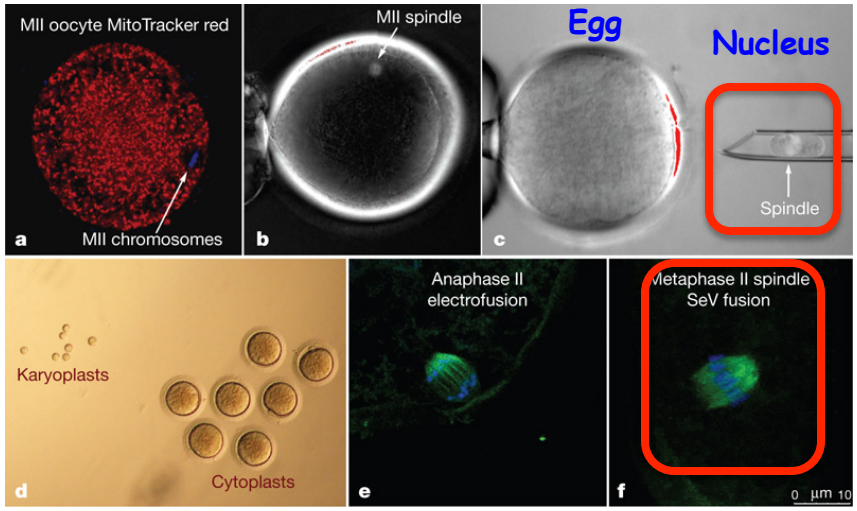


Can Gene Therapy Be Used to "Cure" Mitochondrial Gene Defects?

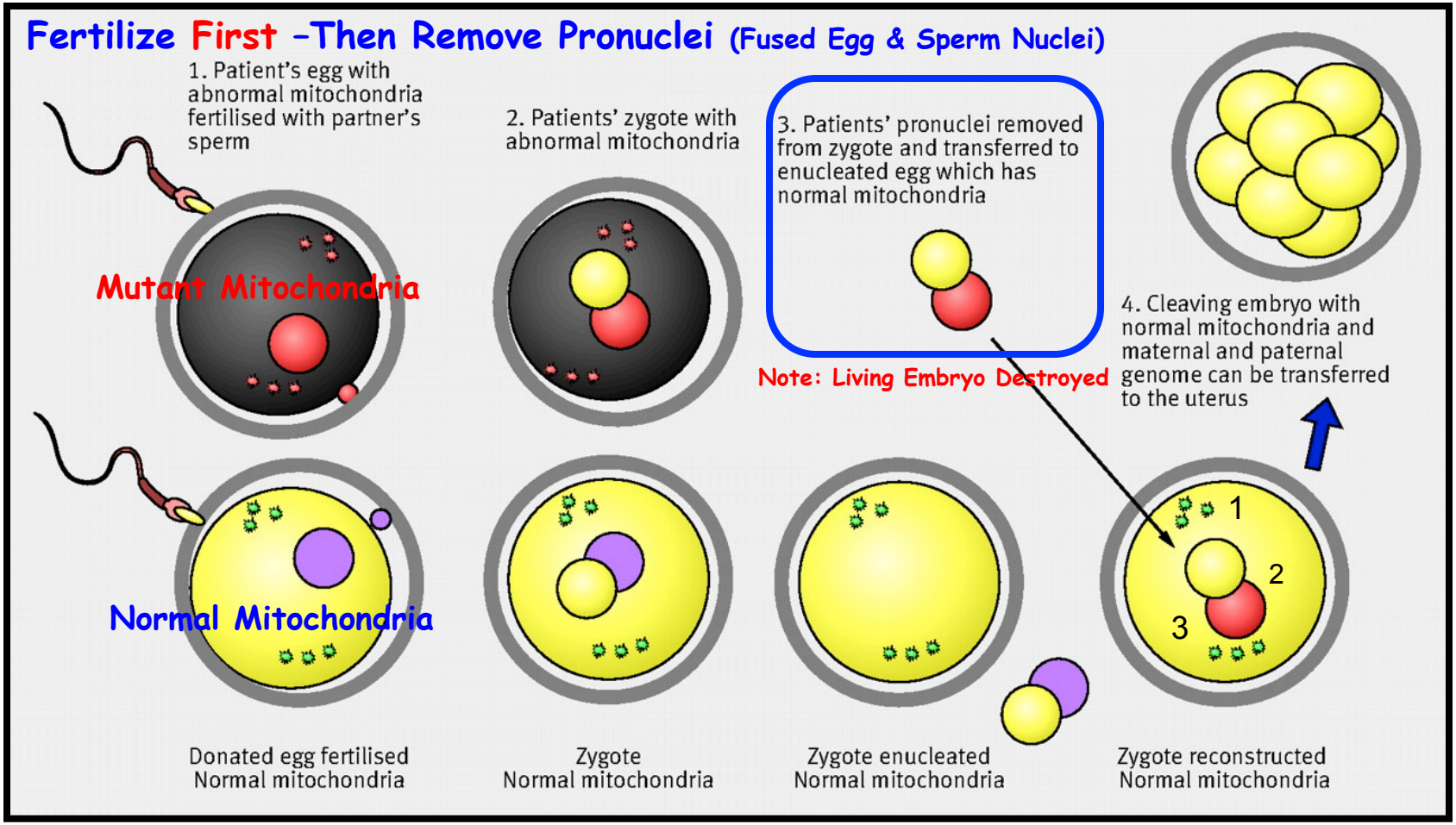
NUCLEAR TRANSPLANTATION Nature 2009 (Mitalapov)

Researchers Prevent Inheritance of Faulty Mitochondria in Monkeys

Mitochondrial replacement in human oocytes carrying pathogenic mitochondrial DNA mutations Nature 2016

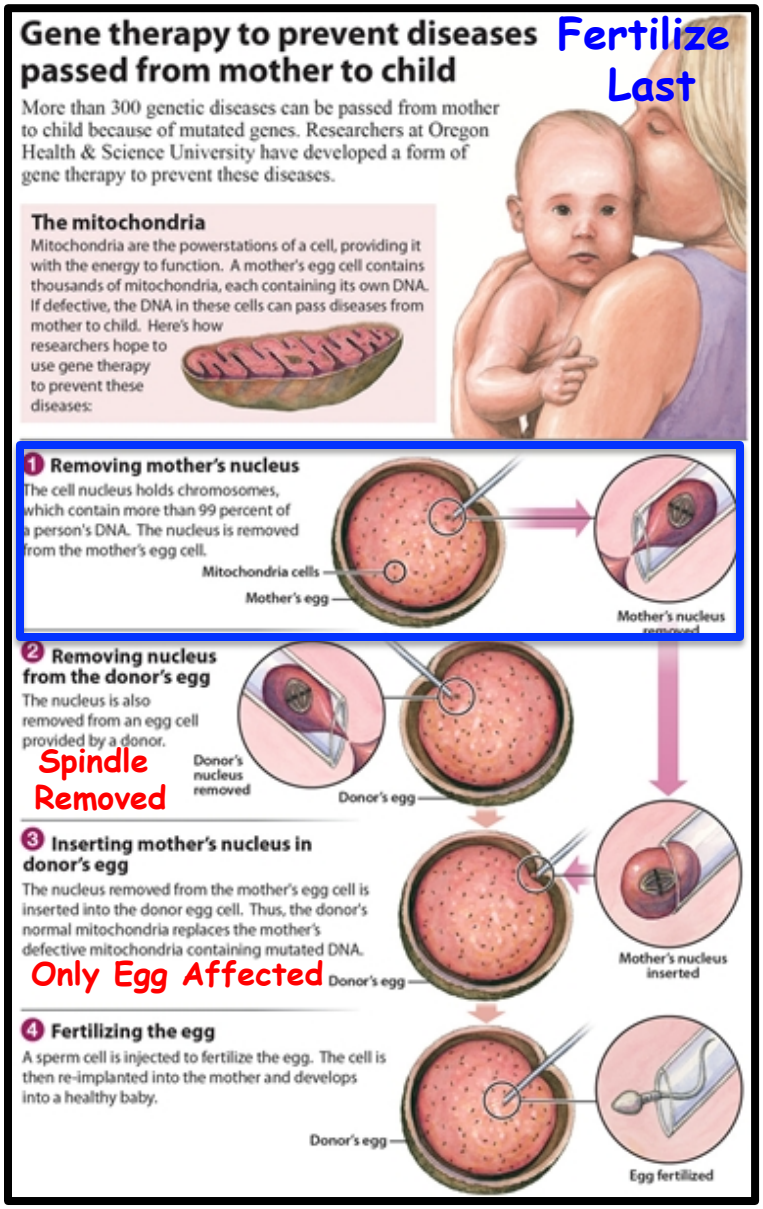


Mitochondrial Pronuclear Replacement Therapy



Fertilize Last After Removal of Egg Spindle Apparatus

(Oocyte Arrested in Meiosis II Until After Fertilization)



NATURE | NEWS

DNA-swap technology almost ready for fertility clinic

Mitochondrial transfer could reduce the risk of childhood disease.

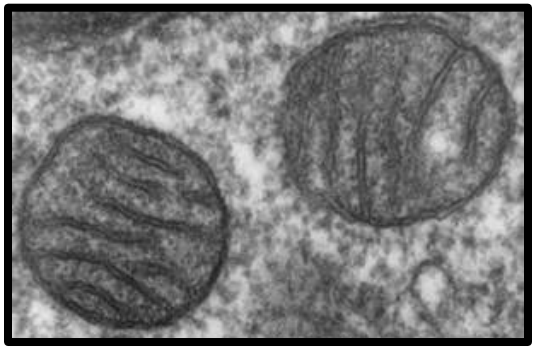
David Cyranoski

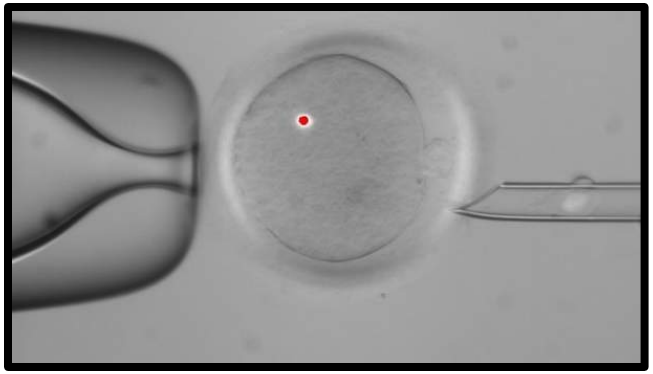
24 October 2012

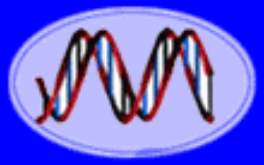
NATURE NEWS BLOG

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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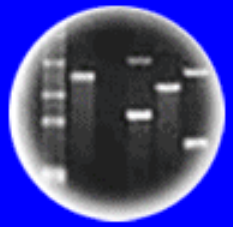

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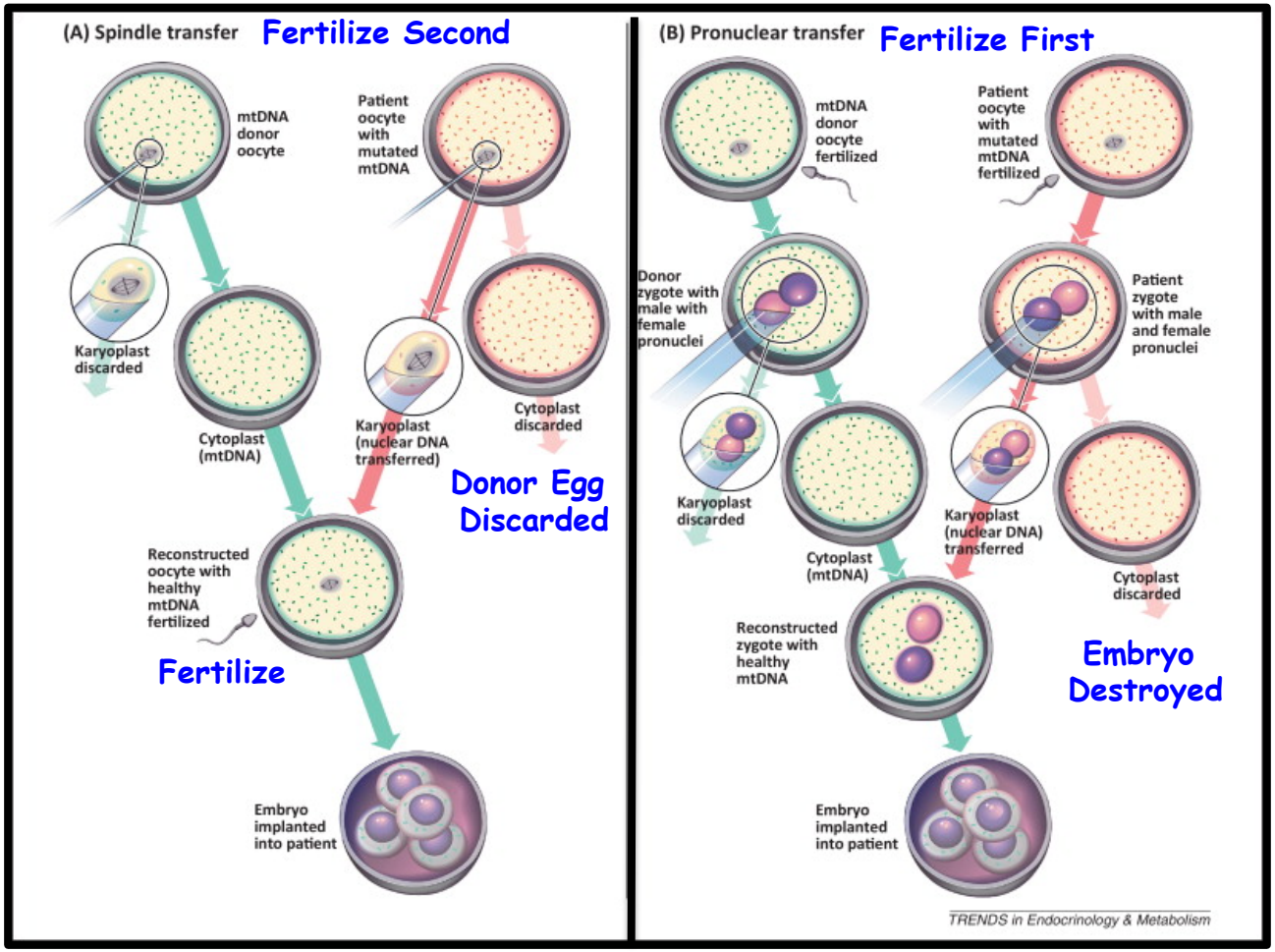
Two Methods of Human Mitochondrial Replacement Therapy

Spindle Transfer

Pronuclear Transfer



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

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? (Mt DNA Markers)
- Testing on Live Human Embryos
- When To Test Its Effectiveness
- Safety & Long-Term Potential Problems
- Nuclear-Mitochondrial Genome Incompatibility?
- Heteroplasmy?
- 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

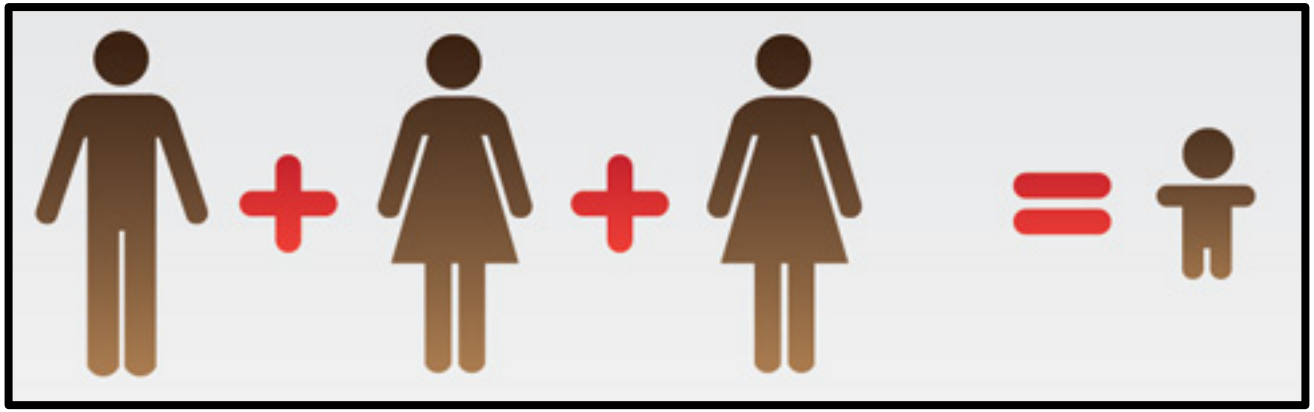
Due to the health and social benefits to individuals and families of living free from mitochondrial disorders, and where potential parents express a preference to have genetically-related children, on balance we believe that **if these novel techniques are adequately proven to be acceptably safe and 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

UK doctors select first women to have 'three-person babies' February 2, 2018



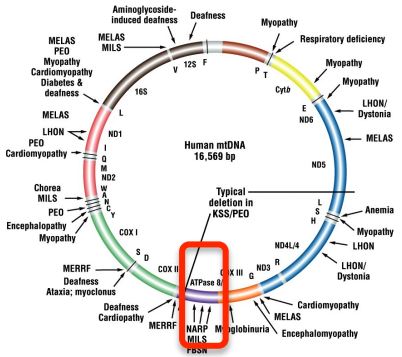


Figure 3-24
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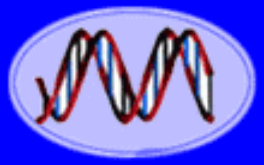

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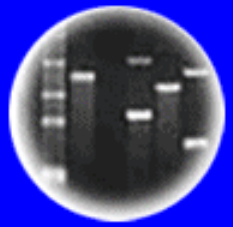

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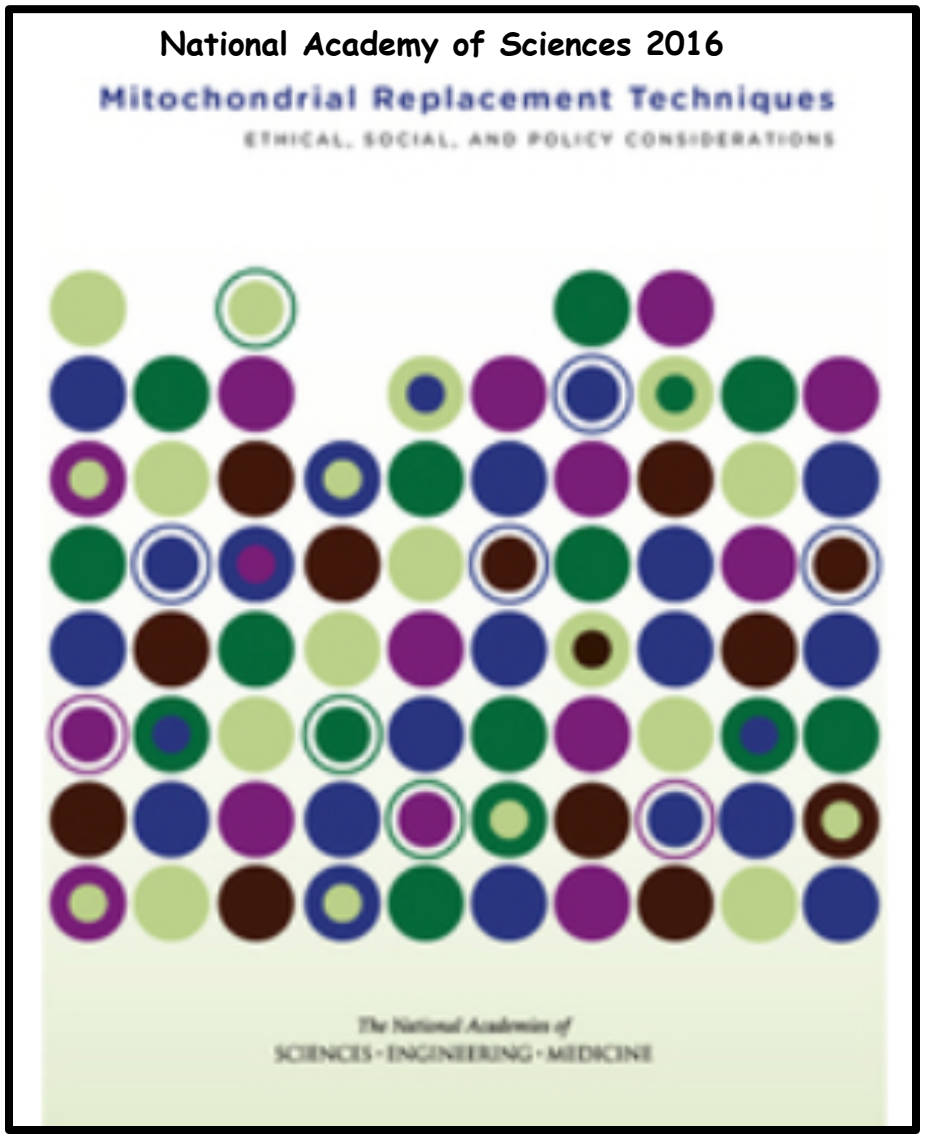
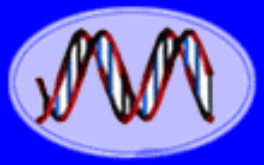
What About The United States? Recommendations to the FDA





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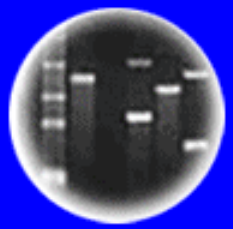

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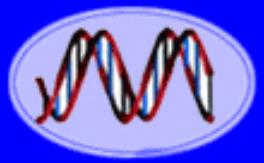
Finding an ethical path forward for mitochondrial replacement

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 Only Male Embryos
2. No Transfer of 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 Female Transfer Should Ever 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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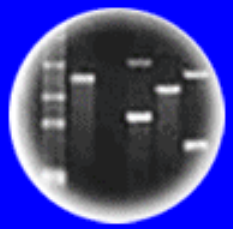

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Road Blocks

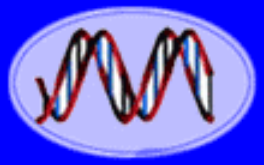
Dickey-Wiker Amendment-1995

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

2019 Congressional Budget (Expires 9/30/21)

- 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)*



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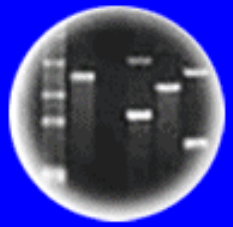

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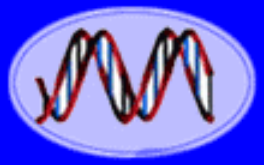
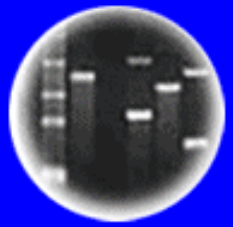
Consolidated Appropriations Act of 2019 - Rider

(*4*). Finally, the rider appears to preclude the prevention of mitochondrial DNA diseases by mitochondrial replacement due to attendant "heritable genetic modification" (*1*, *5*). The FDA could have sidestepped the "heritable genetic modification" constraint on mitochondrial replacement by accepting the "male-only" embryo transfer recommendation of the Institute of Medicine (*5*). However, the FDA has resolved to forgo consideration of mitochondrial replacement during this fiscal year (*13*).



DNA
Genetic Code of Life

Entire Genetic Code
of a Bacteria



DNA Fingerprinting

Cloning: Ethical Issues
and Future Consequences

Plants of Tomorrow

U.S. researcher says he's ready to start four pregnancies with 'three-parent' embryos

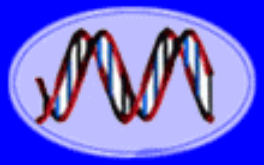
By Emily Mullin

April 18, 2019

Patient advocates and scientists launch push to lift ban on 'three-parent IVF'

By Emily Mullin

April 16, 2019



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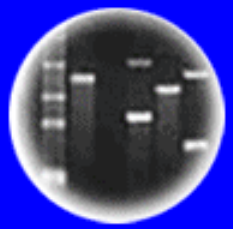


DNA Fingerprinting

Cloning: Ethical Issues and Future Consequences

Plants of Tomorrow

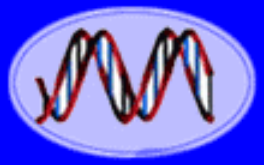
So Much For the Restrictions!

First 'three person baby' born using new method

By Michelle Roberts
Health editor, BBC News online

8 hours ago | Health

Dr John Zhang holding the baby boy who was conceived thanks to the new technique that incorporates DNA from three people



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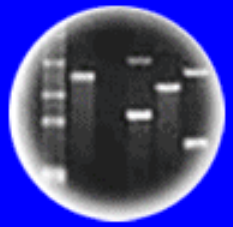


DNA Fingerprinting

Cloning: Ethical Issues
and Future Consequences

Plants of Tomorrow

Birth of Baby With Three Parents' DNA Marks Success for Banned Technique

By GINA KOLATA SEPT. 27, 2016

Controversial 3-parent baby technique produces a boy

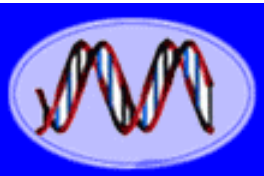
First 'three person baby' born using new method

Genetic Details of Controversial "3-Parent Baby" Revealed

The child's parents have decided to forgo long-term monitoring by researchers

Article Zhang et al., Reproductive Biomedicine, 2017

Live birth derived from oocyte spindle transfer to prevent mitochondrial disease



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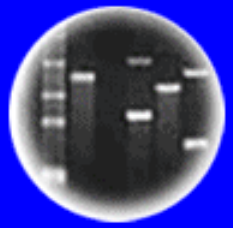

DNA Fingerprinting

Cloning: Ethical Issues
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Plants of Tomorrow

Infertile woman, 32, is pregnant with a 'three-parent baby' after 4 failed IVF attempts in first ever clinical trial using the controversial technique

- The 32-year-old Greek woman had four failed IVF attempts before hearing about the trial in Spain
- Experts warn it raises questions about using the technique for fertility rather than disease
- Legal experts say it puts pressure on US lawmakers to rethink their ban on the procedure
- As more trials open up globally, US parents may take to medical tourism

Despite Calls for a Moratorium, More 'Three-Parent' Babies Expected Soon

Clinics in Europe say they will continue offering a controversial IVF

For Fertility Treatment – Not Mt Mutations

Mitochondrial DNA SNPs As Markers 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)

How Trace Ancestry Using Mitochondrial DNA SNPs

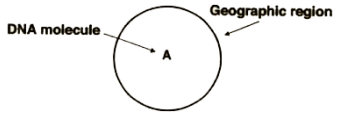
Oldest Populations Contain the Most Diversity

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.

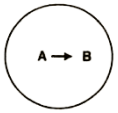
Here's the logic behind the hypothesis.



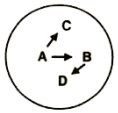
Start with A.

Time

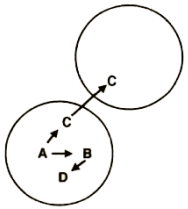
Detected By Using Specific Markers (RFLPs or SNPs)



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

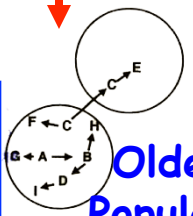


Additional mutations generate diversity;
now have individuals with both A, B, C and D DNAs.



C migrates to form separate population.

Lots of "Old" Variants



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

Newest Population

Oldest Population

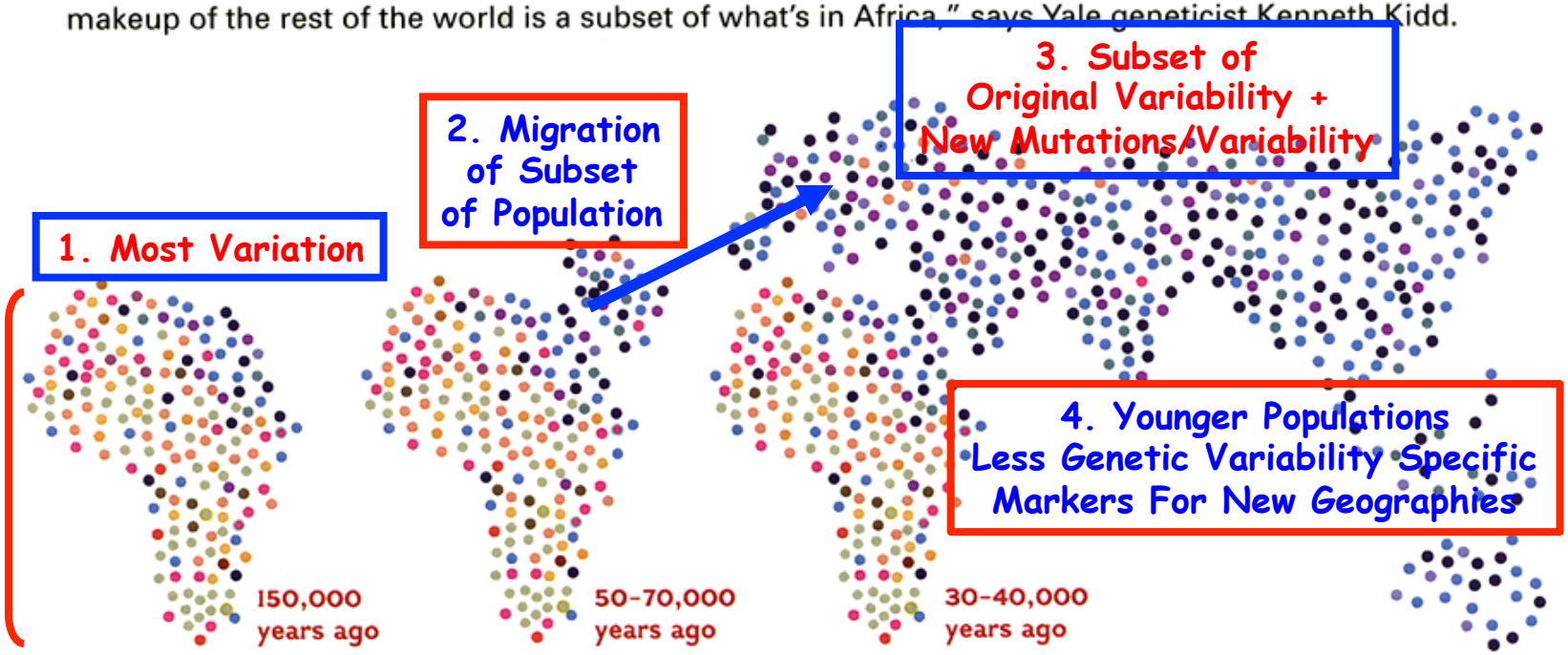
Subset of "Old" Variants + New Variants

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

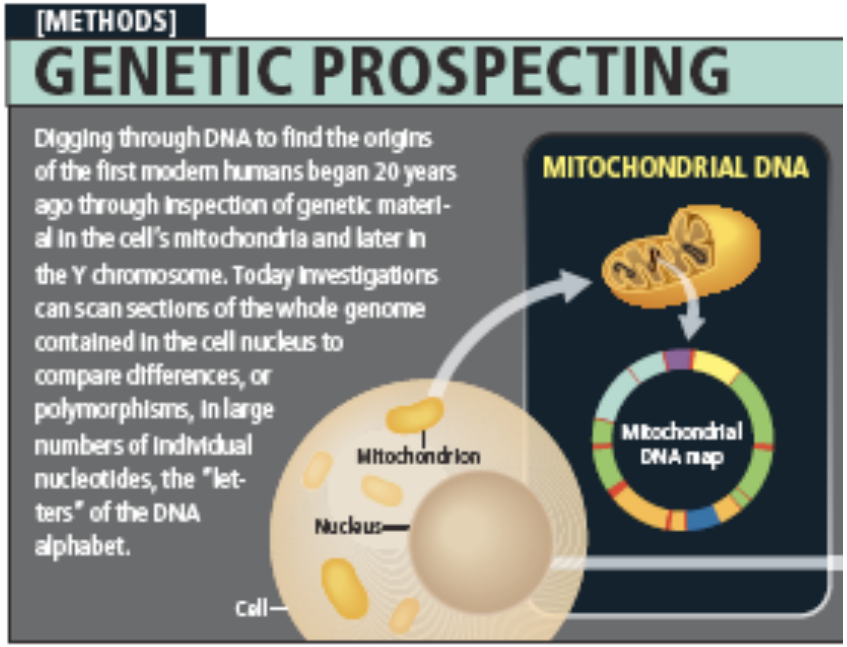
The diversity of genetic markers is greatest in Africa (multicolored dots in map), indicating it was the earliest home of modern humans. Only a handful of people, carrying a few of the markers, walked out of Africa (center) and, over tens of thousands of years, seeded other lands (right). "The genetic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

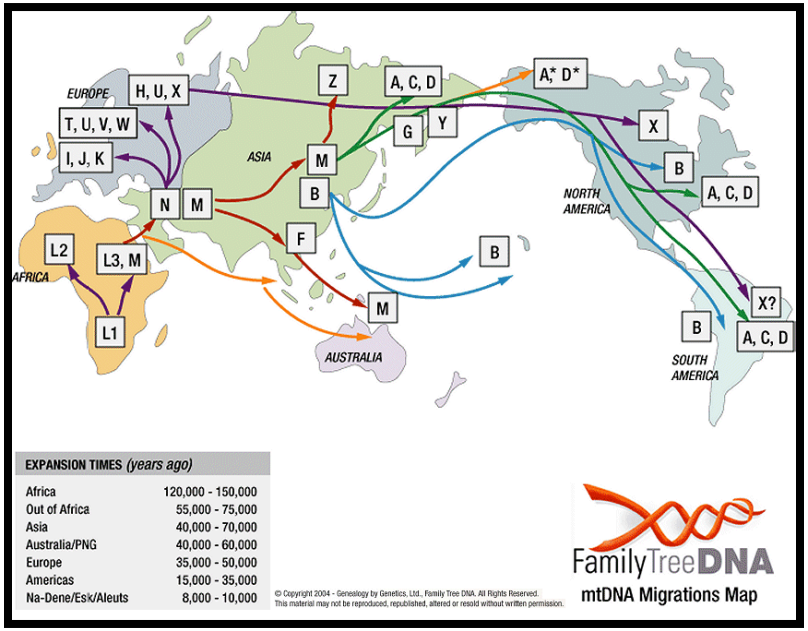


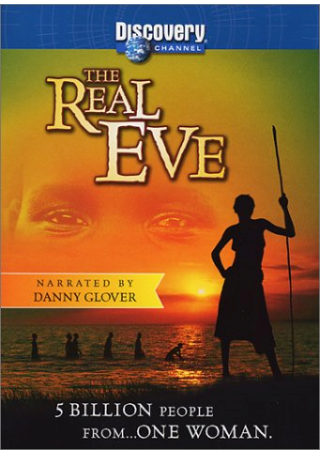
Genetic Variation Proportional to Population Age

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

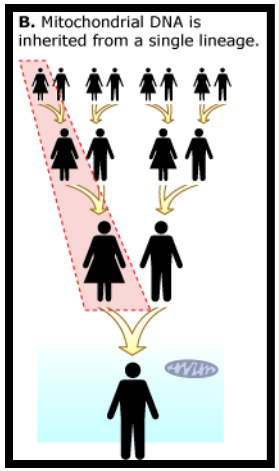
Tracing Human Migrations Using Mitochondrial DNA Polymorphisms (SNPs) - Back to Eve!





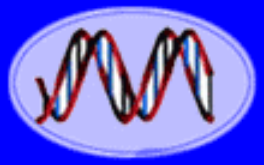


Eve Lived ~200,000 Years Ago!!



ancestry

23andMe



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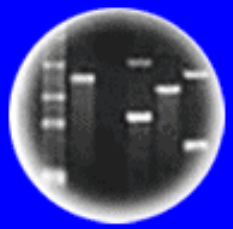

DNA Fingerprinting

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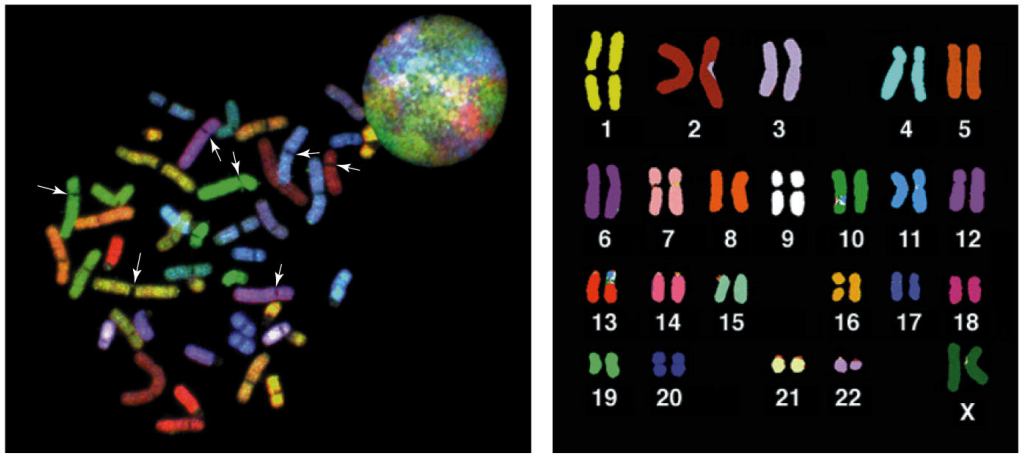
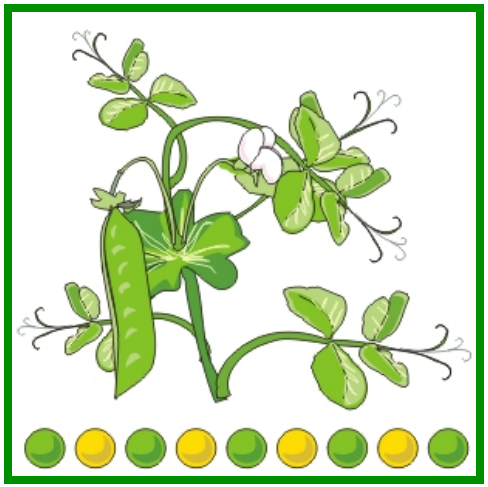
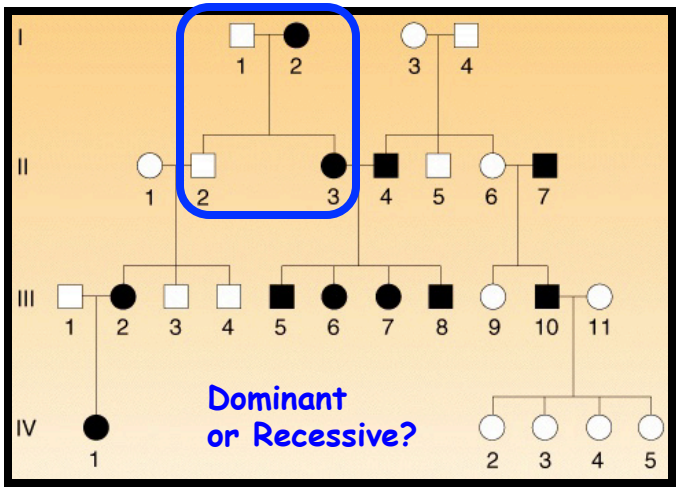
The Nuclear Genome

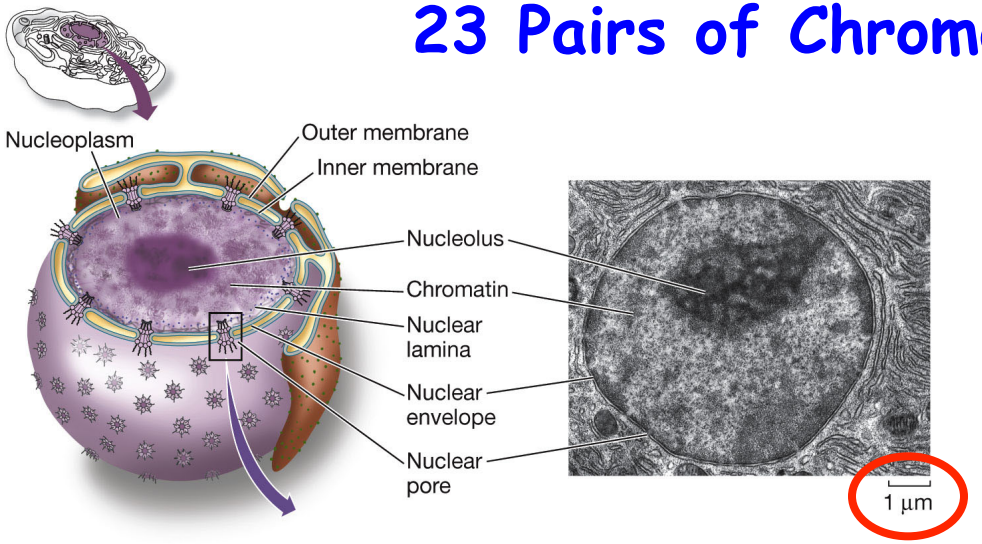


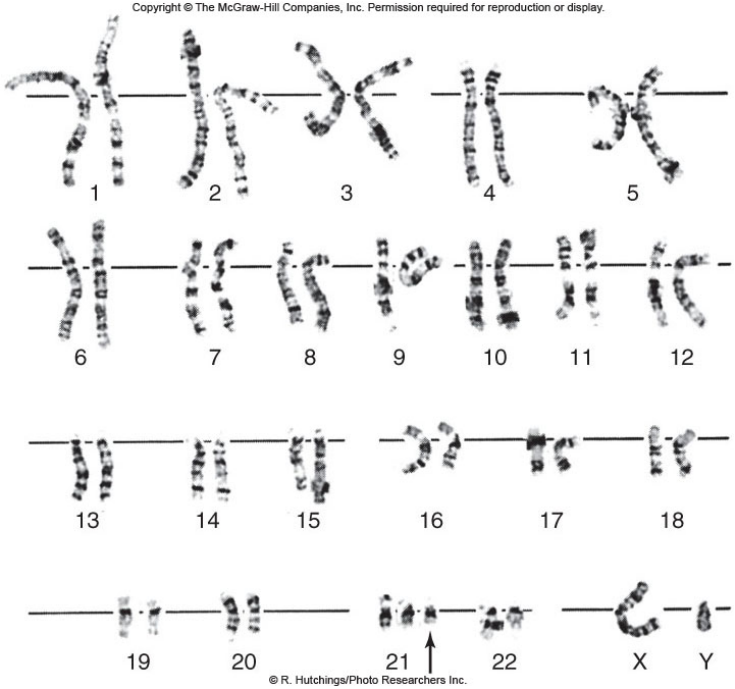




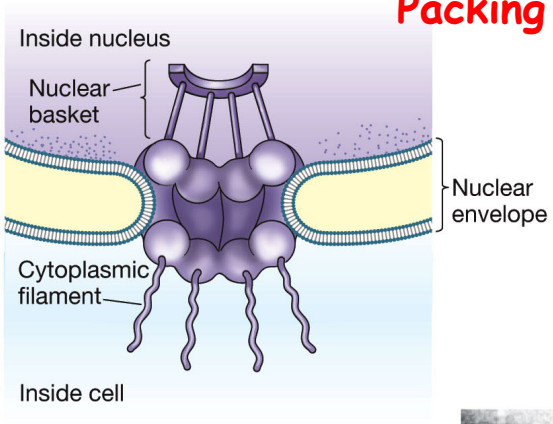
Note: Gene is Inherited in a Mendelian Pattern

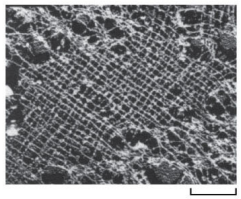
The Nucleus Is A Complex Organelle With 23 Pairs of Chromosomes (Humans)



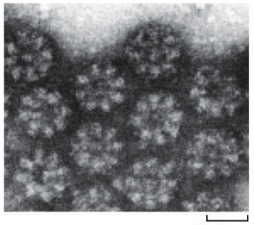


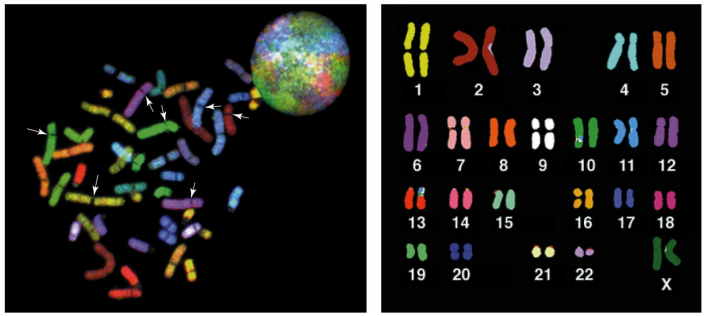
Packing Problem?





RNA & Protein Transport





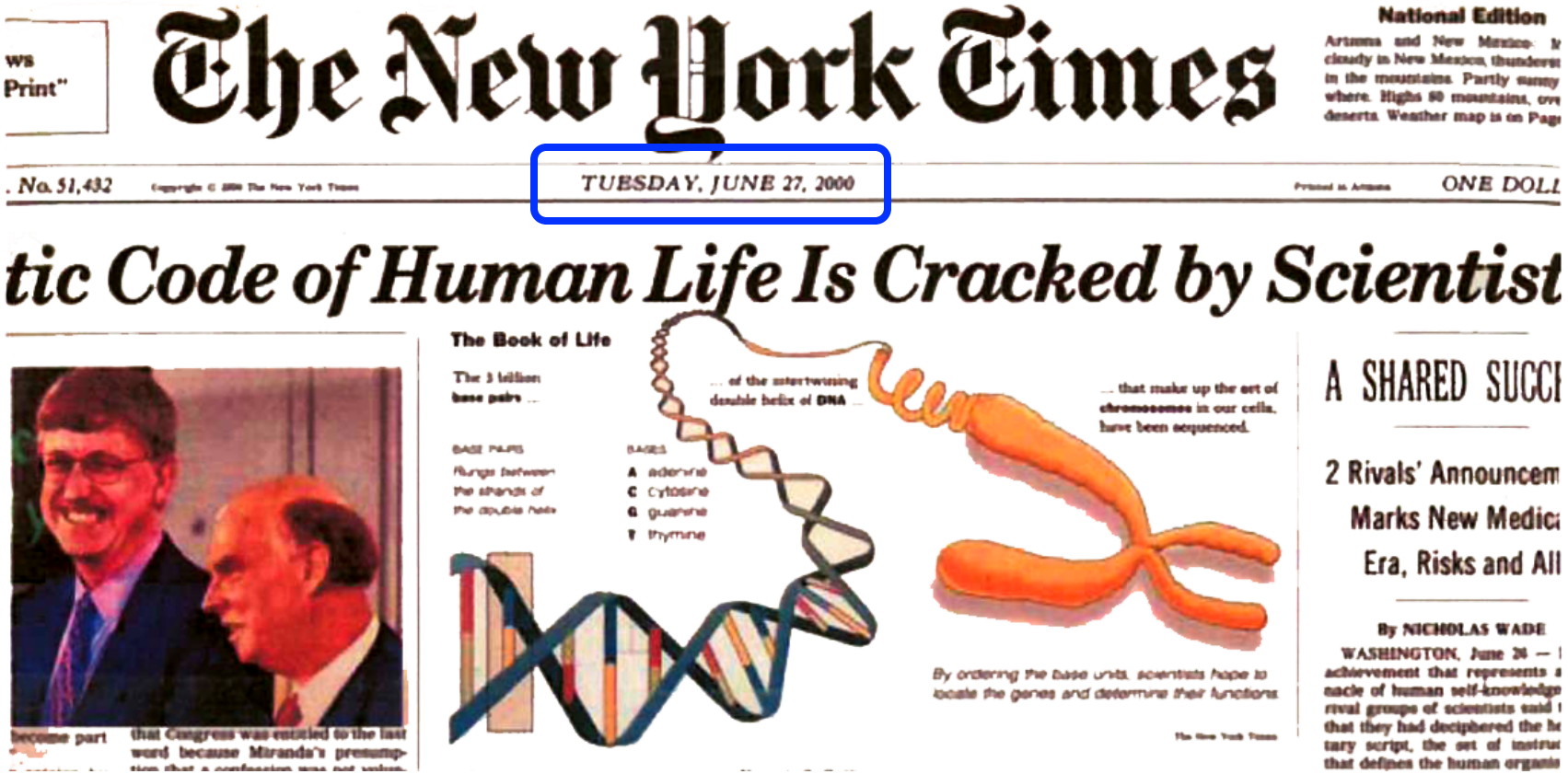
The Human Genome End to End is 1.1 Meters in Length!!!!!!

Note: Chromosome Sizes & Bands = Markers

LIFE 8e, Figure 4.8 (Part 2)

The Human Genome Was Sequenced Twenty Years Ago!

The Human Genome Project



The New York Times

National Edition

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

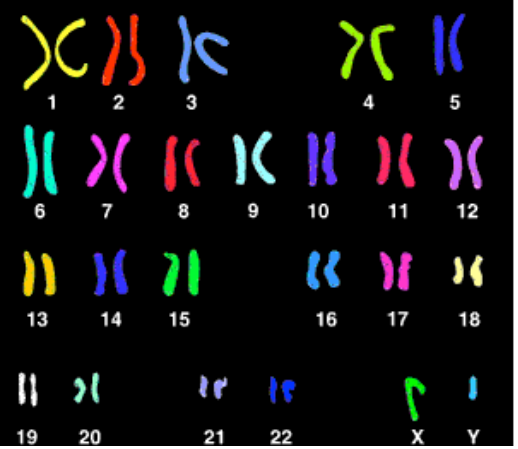
Era, Risks and All

By NICHOLAS WADE

WASHINGTON, June 26 —

Public & Private Effort Using Different Strategies - A Race!

3 Billion Dollars & Took 15 Years



The Human Genome

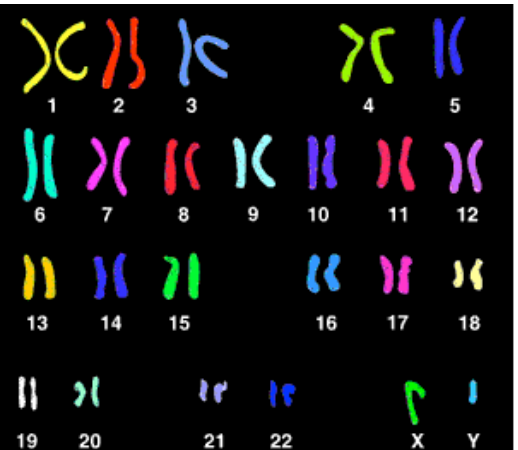
Chromosome	Including gaps	Sequenced	Gaps
1	247,249,719	224,999,719	22,250,000
2	242,951,149	237,712,649	5,238,500
3	199,501,827	194,704,827	4,797,000
4	191,273,063	187,297,063	3,976,000
5	180,857,866	177,702,766	3,155,100
6	170,899,992	167,273,992	3,626,000
7	158,821,424	154,952,424	3,869,000
8	146,274,826	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**

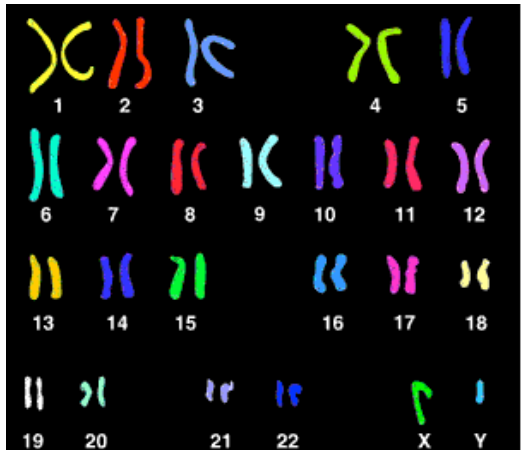
Chromosome Size
Large

↓

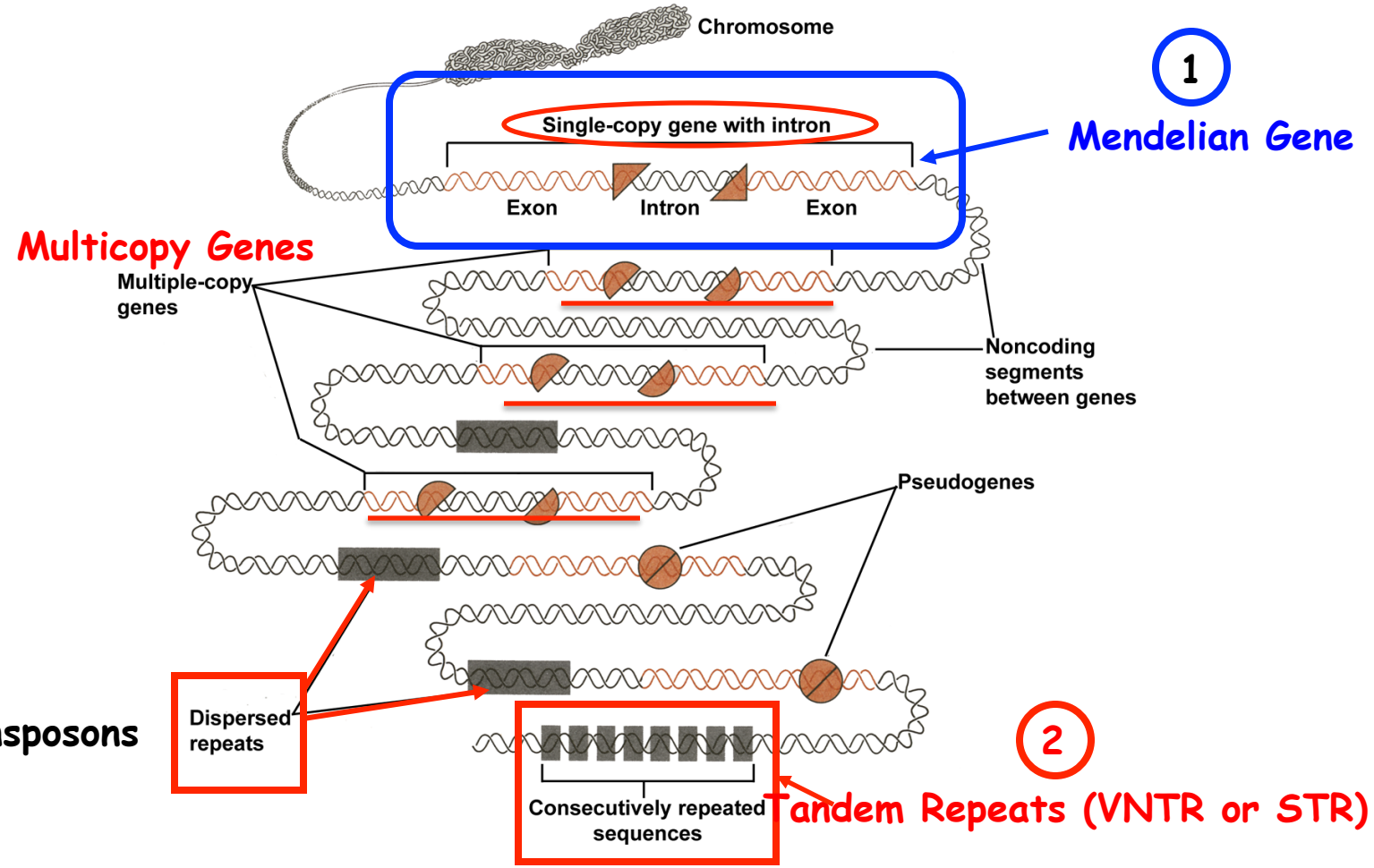
Small

3.1×10^9 Base Pairs
Per Haploid Genome





The Human Genome Landscape



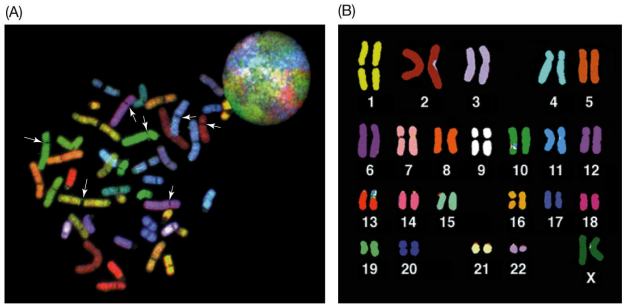
Tandem Repeats or VNTRs are Useful for DNA Fingerprinting Studies!

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

A Small Fraction of the Human Genome Encodes Proteins and There Are 25,000 Different Genes!

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



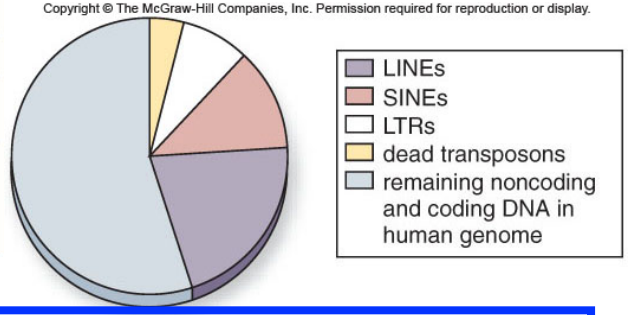


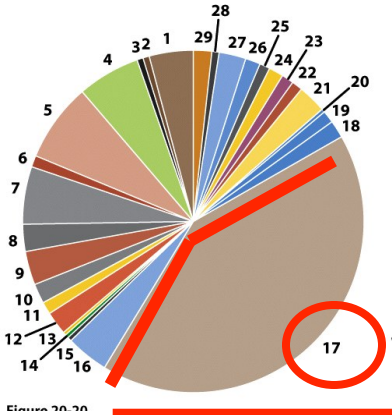
Table 20.6 Average characteristics of genes in the human genome

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

Human Genes are Large but Contain Mostly Introns

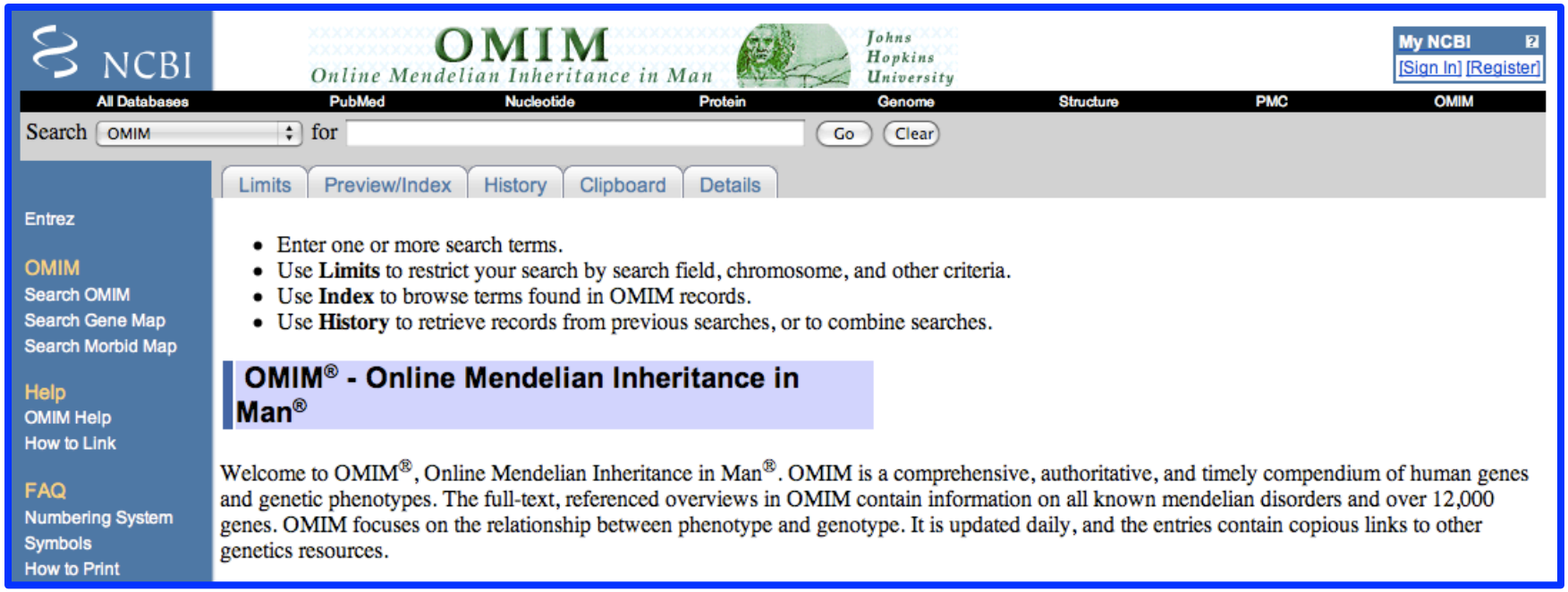
The Human Genome Has DNA Sequences Present Once As Well as Repeated Many Times



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

Do Not Know Functions of Most Human Genes!

How Many Human Disease Genes Have Been Identified?



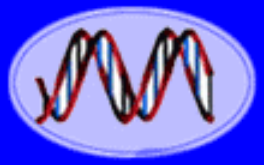
There are ~25,000 Genes in The Human Genome

1. 5,350 Genes Correlate With a Disease Phenotype (343 on X & 5 on Y). The Molecular Basis of These Genetic Diseases Are Known (e.g., Sickle Cell Anemia, Hemophilia A).

2. 1,428 Genes Correlate With a Disease Phenotype, But The Molecular Basis of These Genetic Diseases Are Not Known.

OMIM 2/16/20

http://omim.org/statistics/entry



DNA
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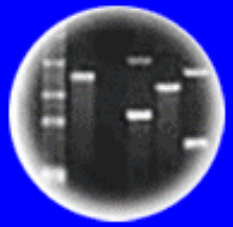

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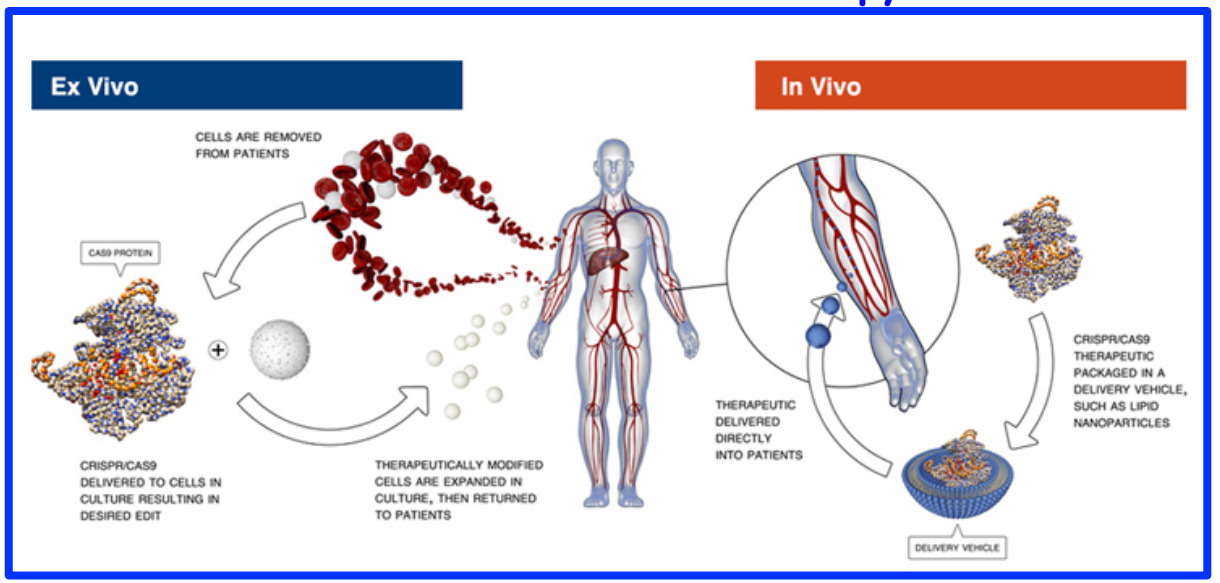
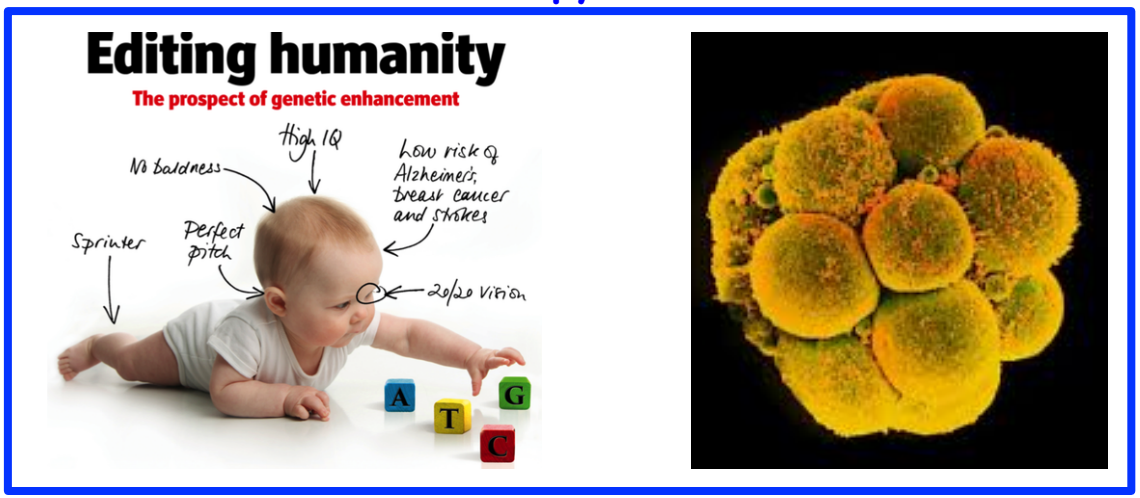
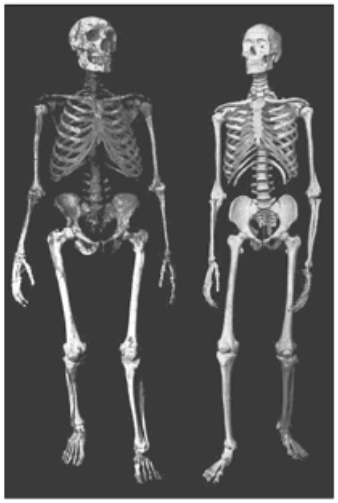
Some Day….Adding and Editing Genes May Be Used To Correct These Human Genetic Disorders

Somatic Cell Gene Therapy

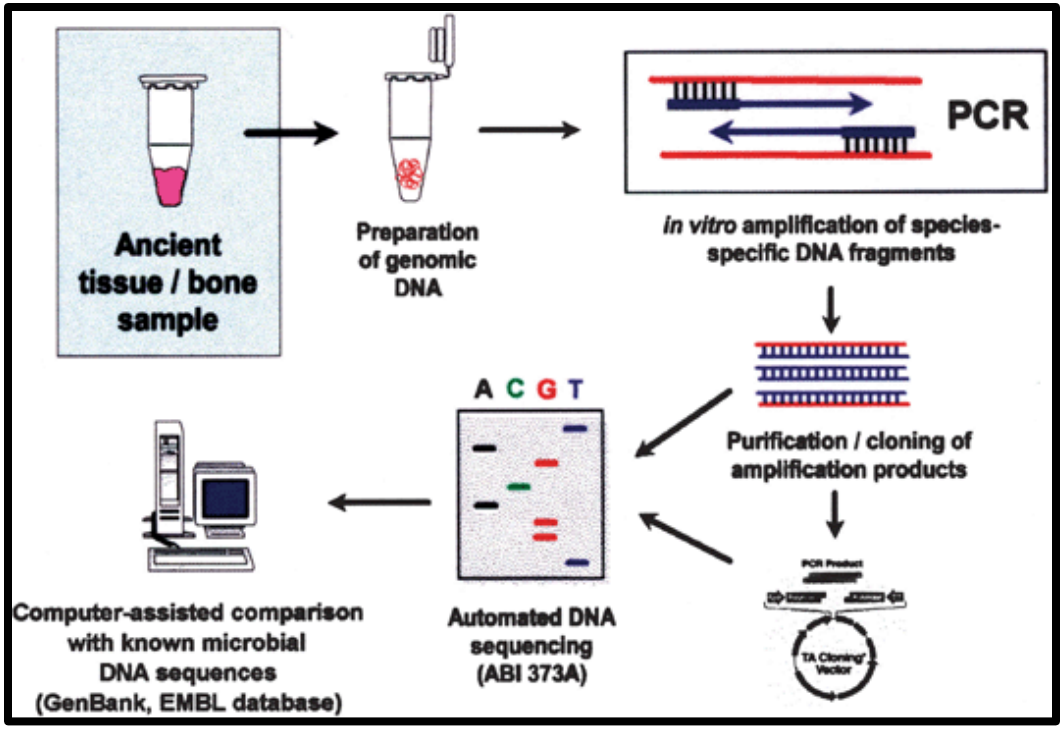


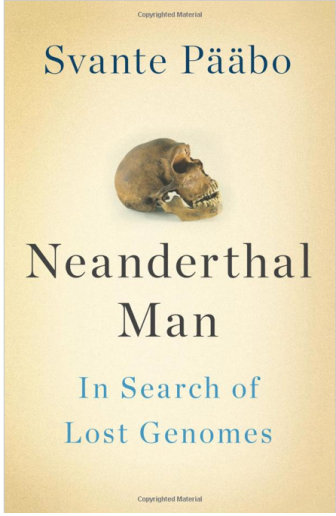
Germline Gene Therapy + Gene Enhancement





Using Ancient Genome Sequencing to Unravel Our Human Heritage

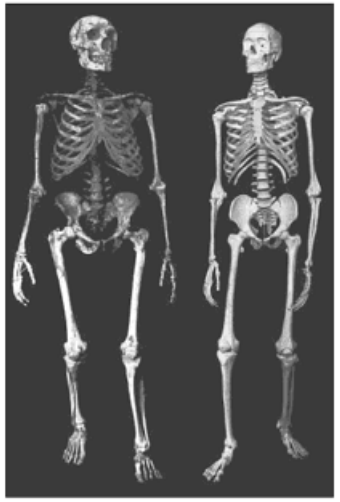




DNA from cave soil reveals ancient human occupants

Science April, 2017

Technique may help open a new era in paleoanthropology



Ancient human genomes–keys to understanding our past

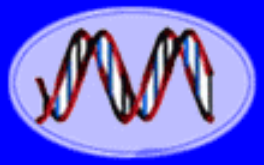
A Draft Sequence of the Neandertal Genome

A Crystal-Clear View Of an Extinct Girl's 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

The genome of the offspring of a Neanderthal mother and a Denisovan father



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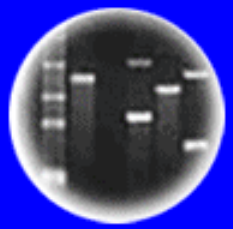

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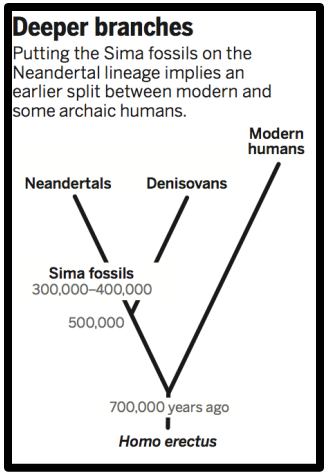
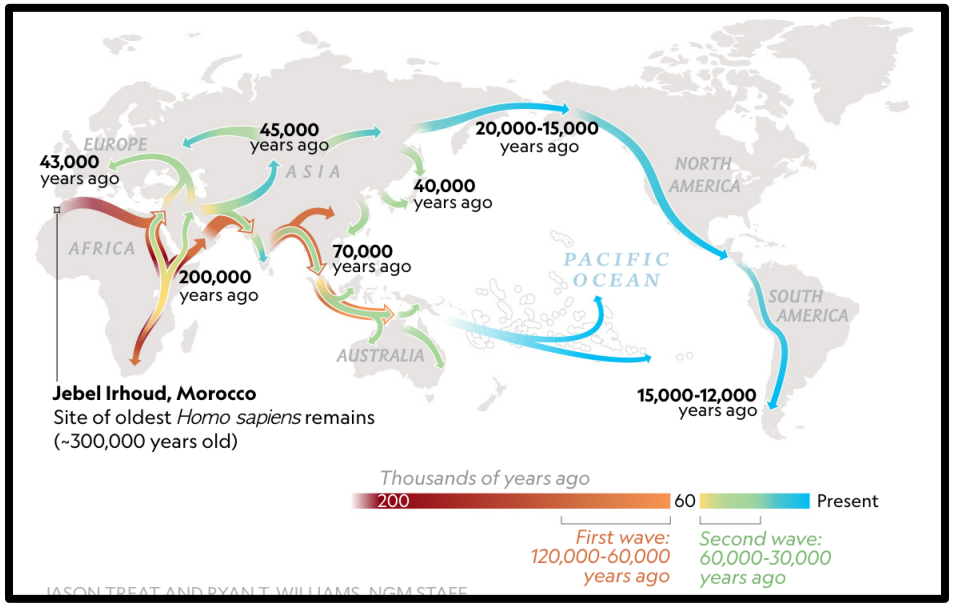
HUMAN EVOLUTION

Humanity's long, lonely road

Oldest ancient nuclear DNA suggests humans and Neandertals parted ways early



Creating a Map of Human History!



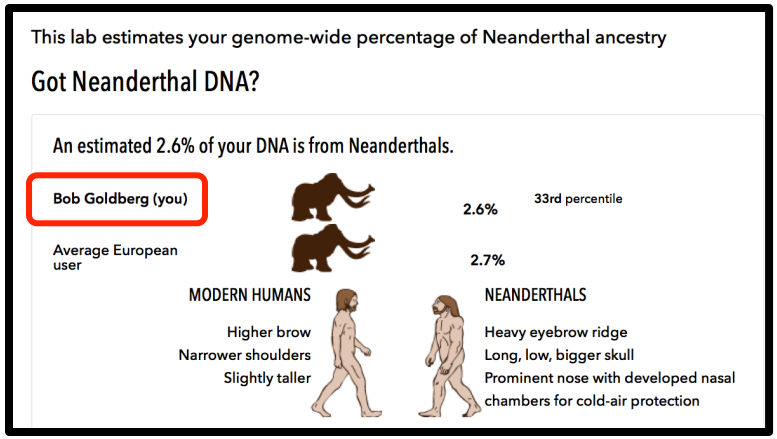
The genomic landscape of Neanderthal ancestry in present-day humans

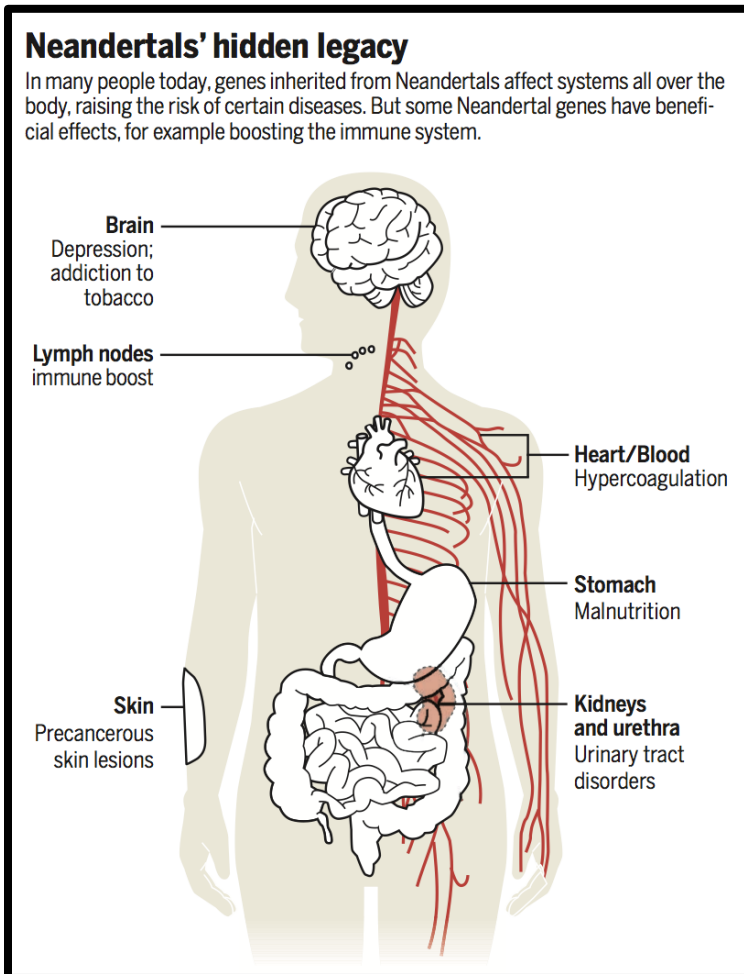
Nature, January 29, 2014

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

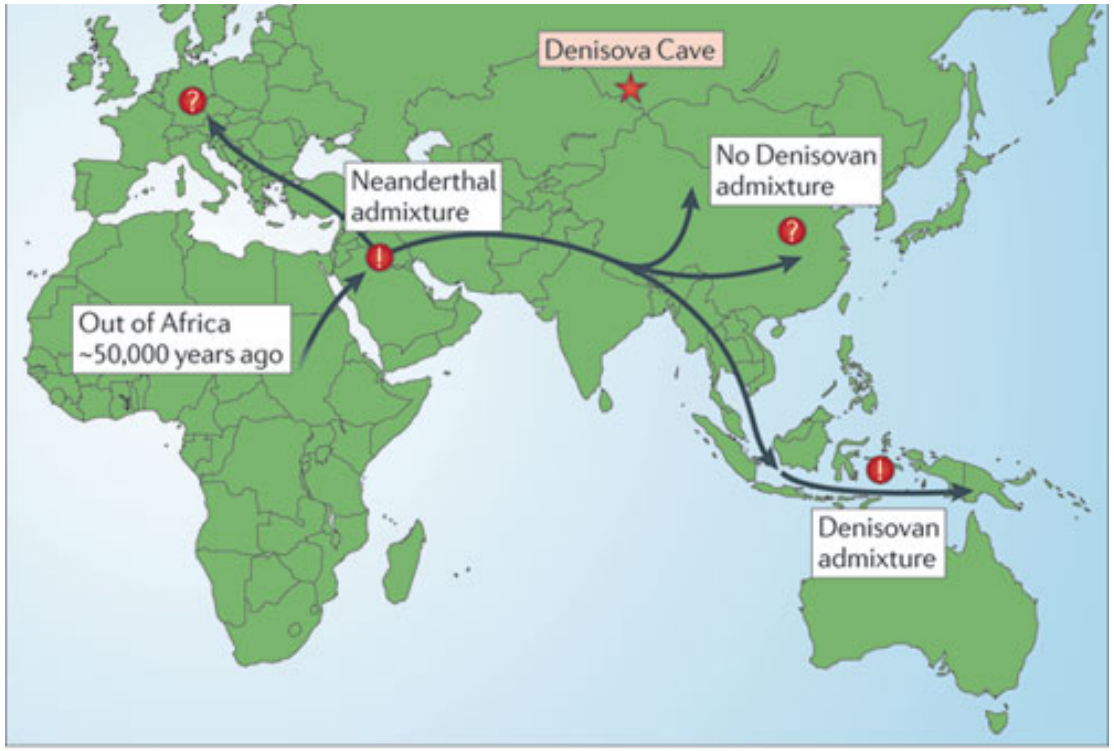




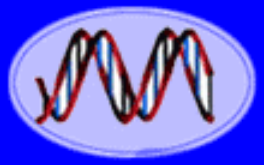
The Shaping of Modern Human Immune Systems by Multiregional Admixture with Archaic Humans

www.sciencemag.org SCIENCE VOL 334 7 OCTOBER 2011

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



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



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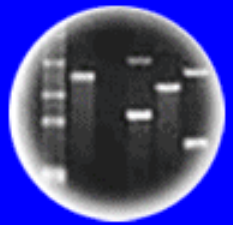

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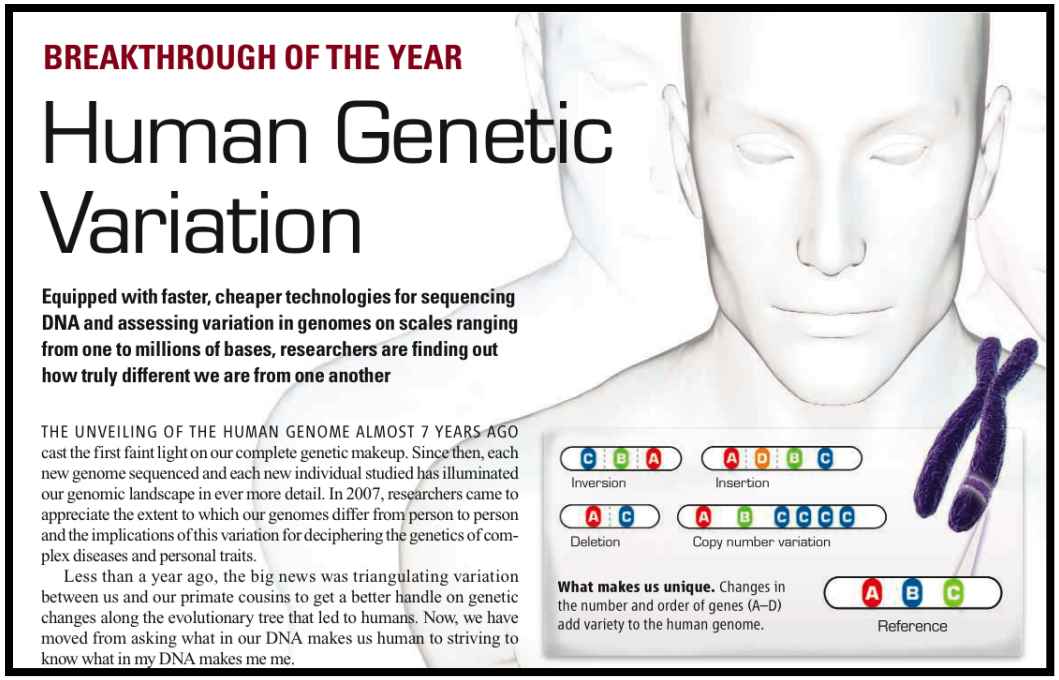
HUMAN DIVERSITY

Scientific American Library
1982 ISBN 07167-14698

RICHARD LEWONTIN

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

1. Marking and Identifying Disease Genes
2. Paternity, Individual Identification, Ancestry
3. Human Population History and Origins
4. Identifying Ancient Hominid Alleles in Modern Human Populations
5. Forensics (Genealogical Searches)



BREAKTHROUGH OF THE YEAR

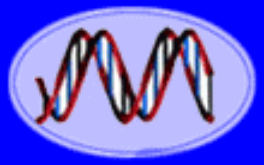
Human Genetic Variation

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.



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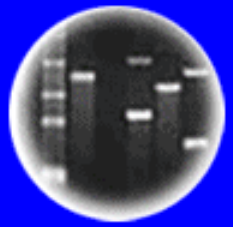

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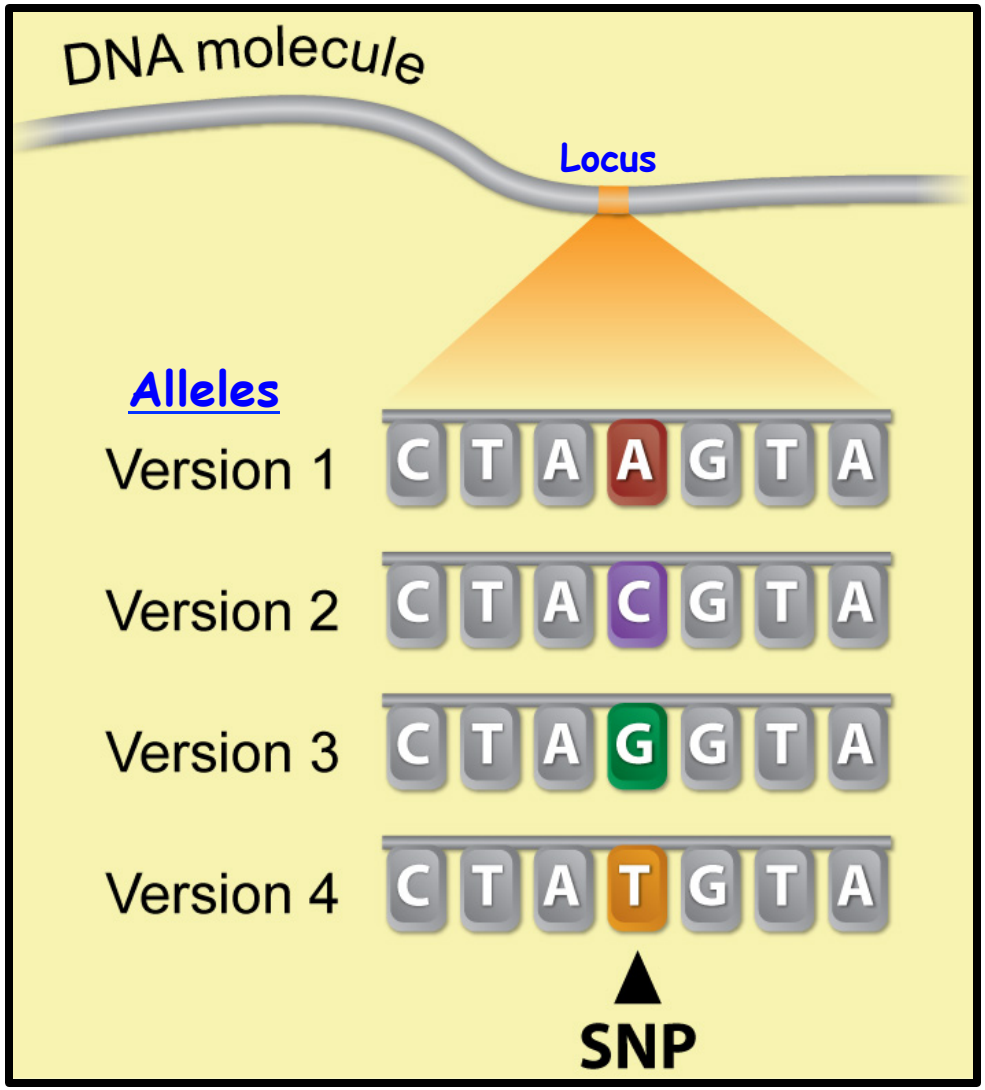
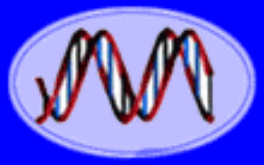
Genetic Diversity Refers to Allelic Variations Within a Population



SNPs at a Given Locus Are Alleles!

Individuals Can Contain Only Two Alleles at a Given Locus, But Populations Can Contain Many!!



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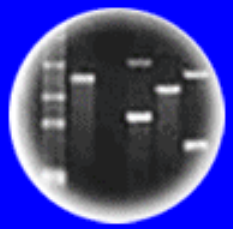

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ARTICLE

Nature, October 28, 2010

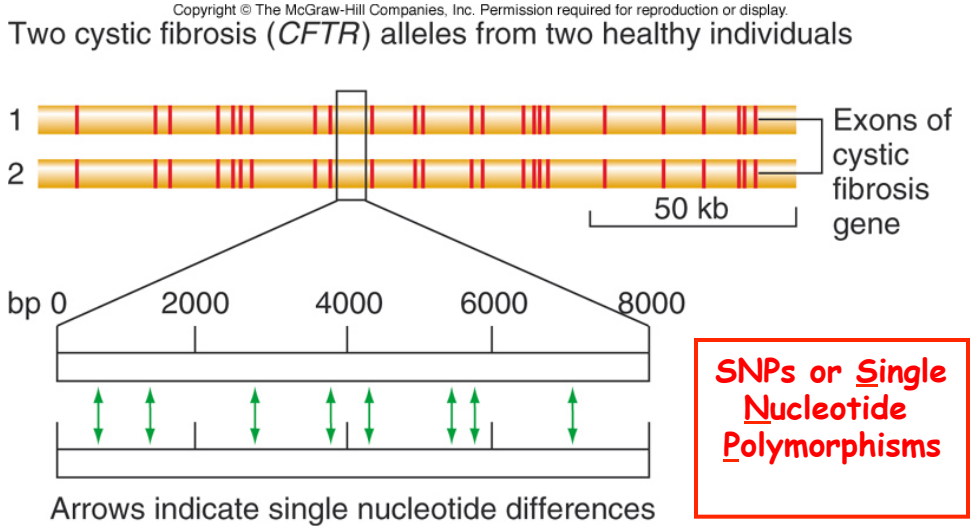
A map of human genome variation from population-scale sequencing

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 (Allelic Markers)
- 50-100 Disease Gene Mutations Per Person (What If We Were Inbred?)
- 10^{-8} Mutations Per bp Per Generation (~30 per Genome)
- 3,000,000 Unique SNPs Per Person ←
- 750,000 Unique Indels Per Person

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

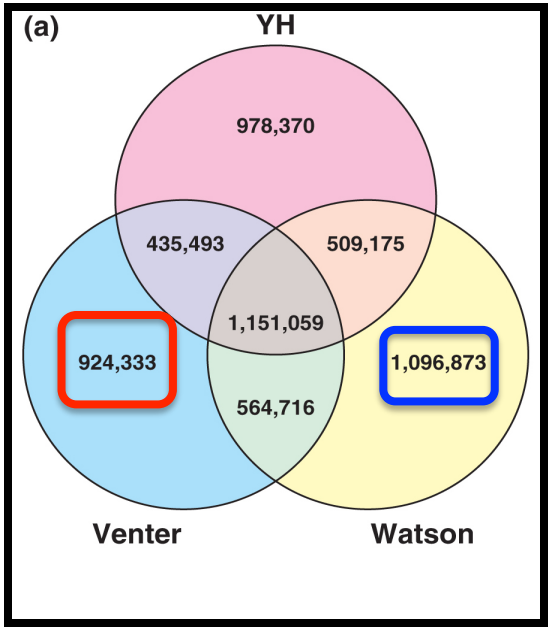
TABLE 11.1 Classes of DNA Polymorphisms

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!



(a)

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

(b)

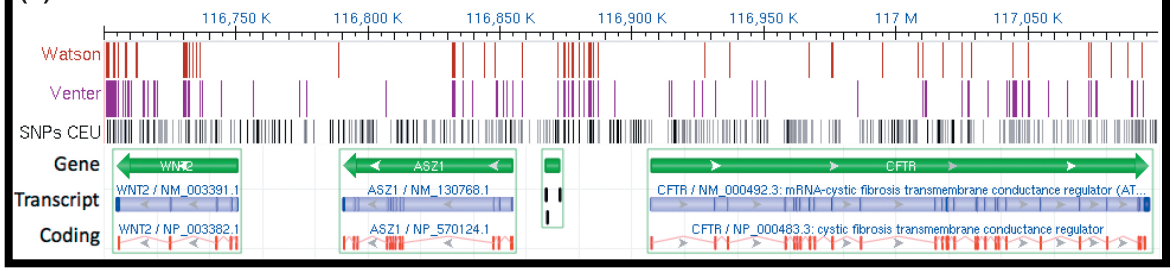
Genotype	Notation
Homozygous T	TT
Heterozygous T	TC
Homozygous C	CC

(c)

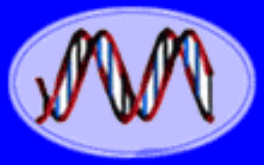
Human 1 TTGACGTATAAATGATCTTTATATTTTCAGAAGTC
Human 2 TTGACGTATAAATGATCTTTATATCTTCAGAAGTC
Chimp TTGACATATAAATGATCTTTATATCTTCAGAAGTC

These Are Alleles!

(d)



YH= Anonymous Chinese Man



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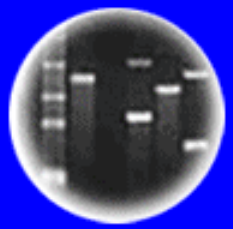

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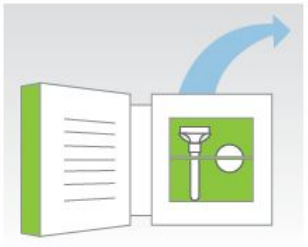
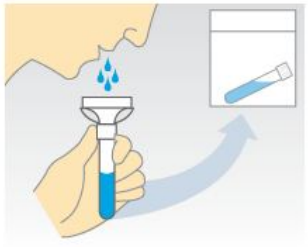
Personal Genome Service™

Get to know your DNA. All it takes is a little bit of spit.

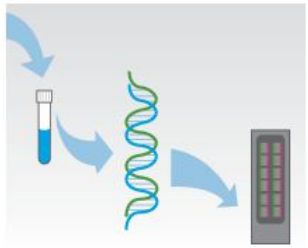
Here's what you do:



1. Order a kit from our online store.



2. Register your kit, spit into the tube, and send it to the lab.



3. Our CLIA-certified lab analyzes your DNA in 6-8 weeks.

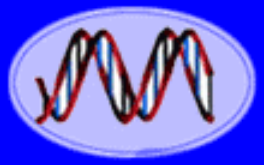
4. Log in and start exploring your genome.

23andMe

ancestry
Discover your family's history

SNPs Used to Trace Ancestry & Individuality

SNPs That Have High Frequencies in Specific Populations



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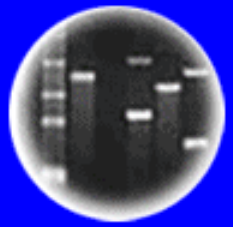

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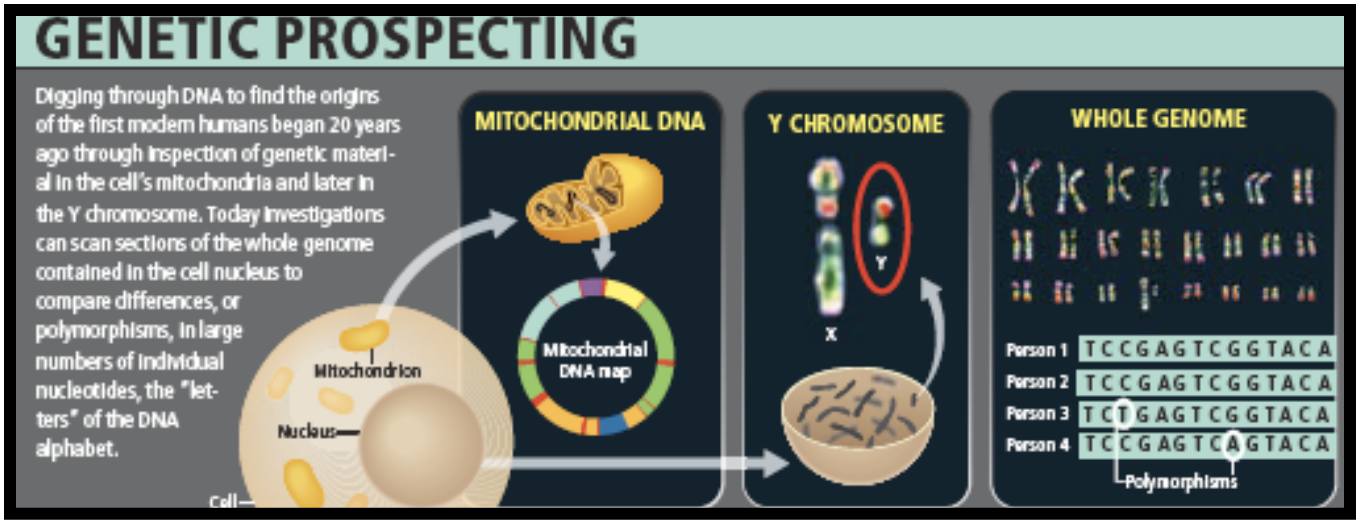
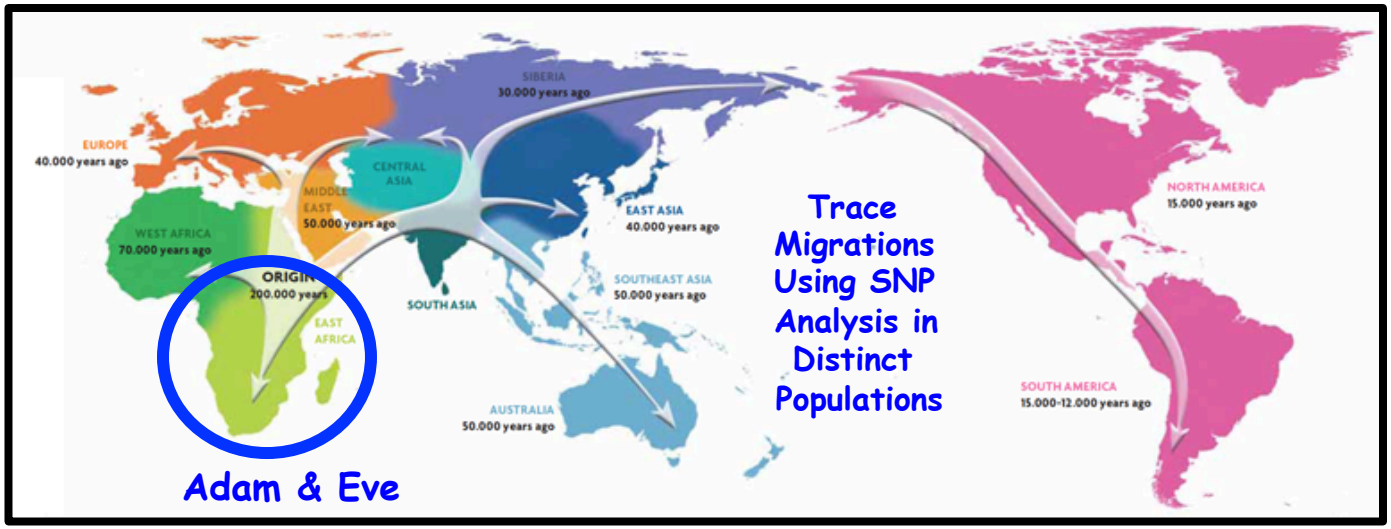
Nuclear DNA SNPs and Genome Sequences Can Be Used To Trace Human Populations & Origins (Concept Same as For Mt DNA)



Three Different Alleles in Population



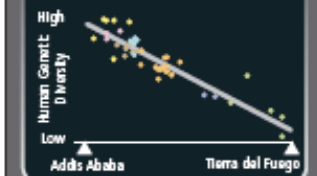
Trace Migrations Using SNP Analysis in Distinct Populations

[WHOLE-GENOME RESULTS]

LOOKING FAR AND WIDE

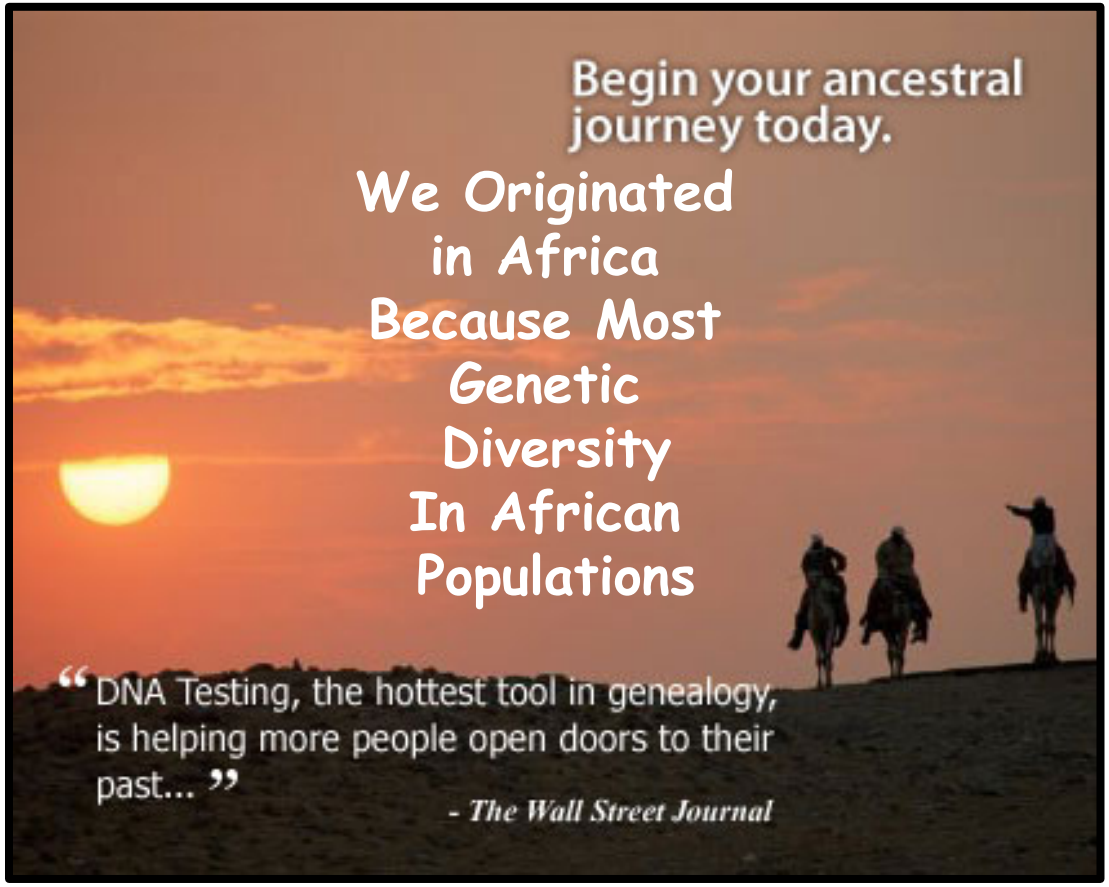
High-powered genetic sequencing and computational techniques developed for the Human Genome Project and in its aftermath have furnished a wealth of data that lets researchers compare genomes drawn from distinct populations around the globe.

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.

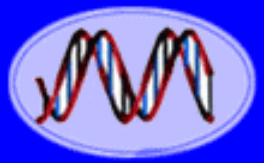


A genomic map of the world, crafted by researchers at the University of Michigan at Ann Arbor, shows that genetic diversity decreases outside of Africa. Each colored tile represents a common haplotype. Africa has more tiles than found on other continents and ones that correspond to haplotypes found nowhere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

Major Conclusion
We Are All Africans!



Ultimately – We Are All Related to Each Other!!



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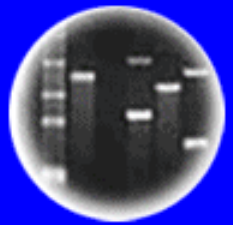

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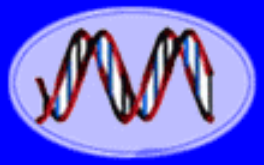
Finally…Human Genome Diversity & The Concept of "Race"



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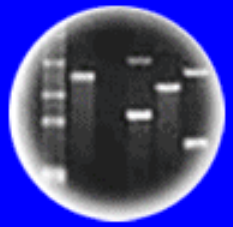
Entire Genetic Code
of a Bacteria



DNA Fingerprinting

Cloning: Ethical Issues
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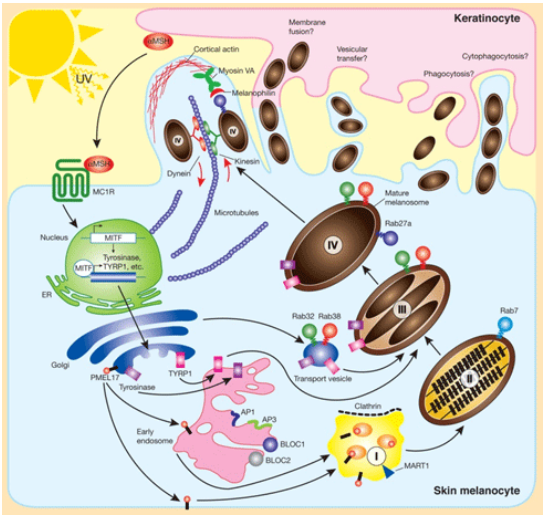
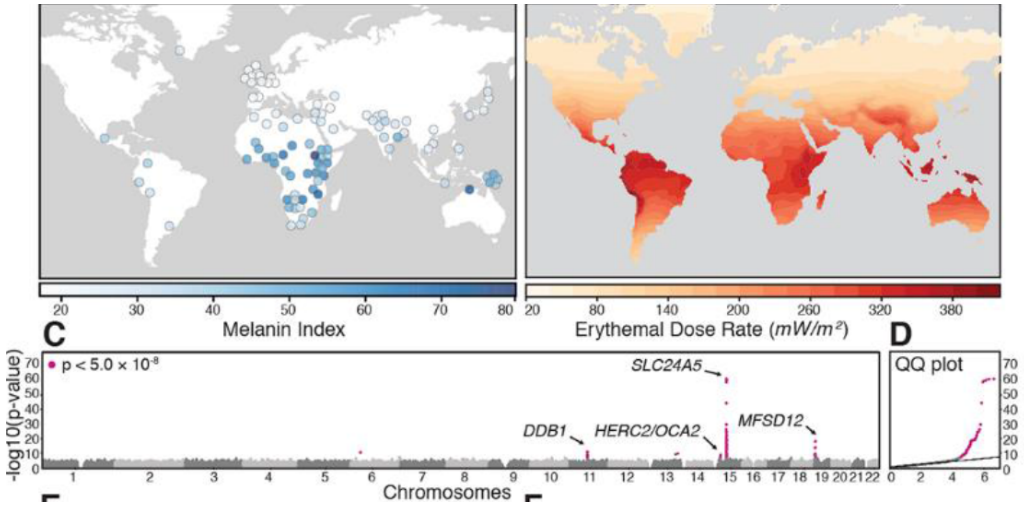
Plants of Tomorrow

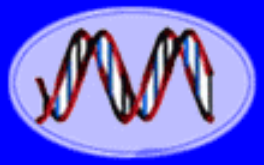
The Biology of Skin Color



The Genetics of Skin Color (Four Major Loci!)

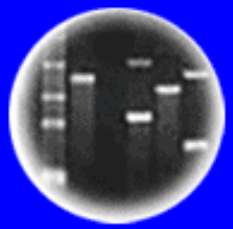


Loci associated with skin pigmentation identified in African populations Science, December, 2017



DNA
Genetic Code of Life

Entire Genetic Code of a Bacteria



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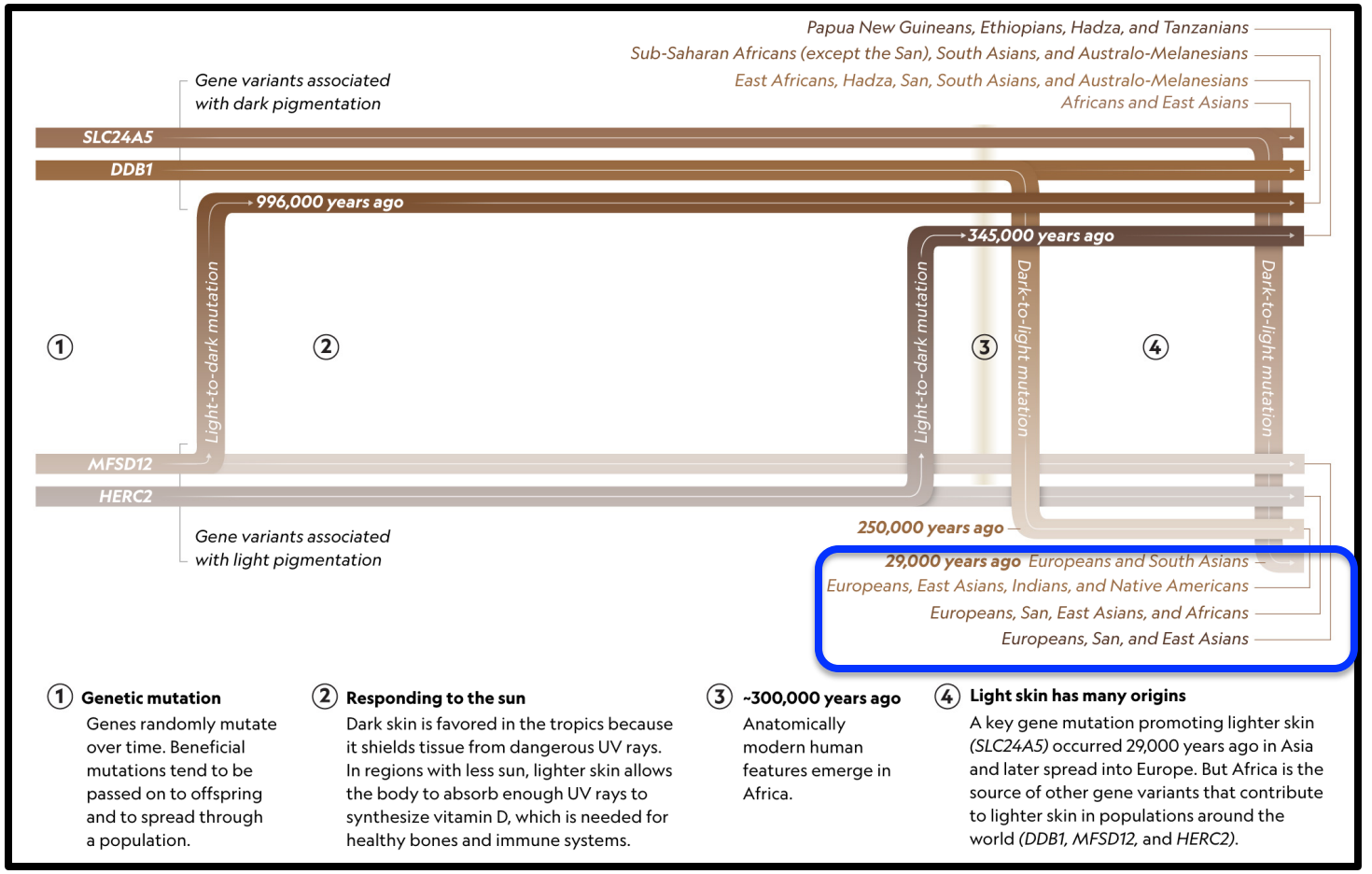
Skin Color Mutations Occurred Many Times in Human Evolution & Correlated With Geographical Migrations (i.e., Adaptions to Sunlight)



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 Populations

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 (e.g., skin color, UVB intensity, and Vitamin D production) – But they are Small!

Major Conclusion

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!

Major 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%

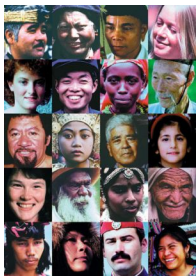
85% Within Population Genetic Variability

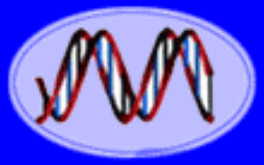
8% Between Populations of Same "Race"

7% Between "Race" Genetic Variability

Variation That Occurs in Ancestral Population

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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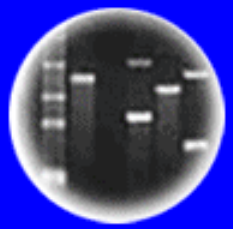

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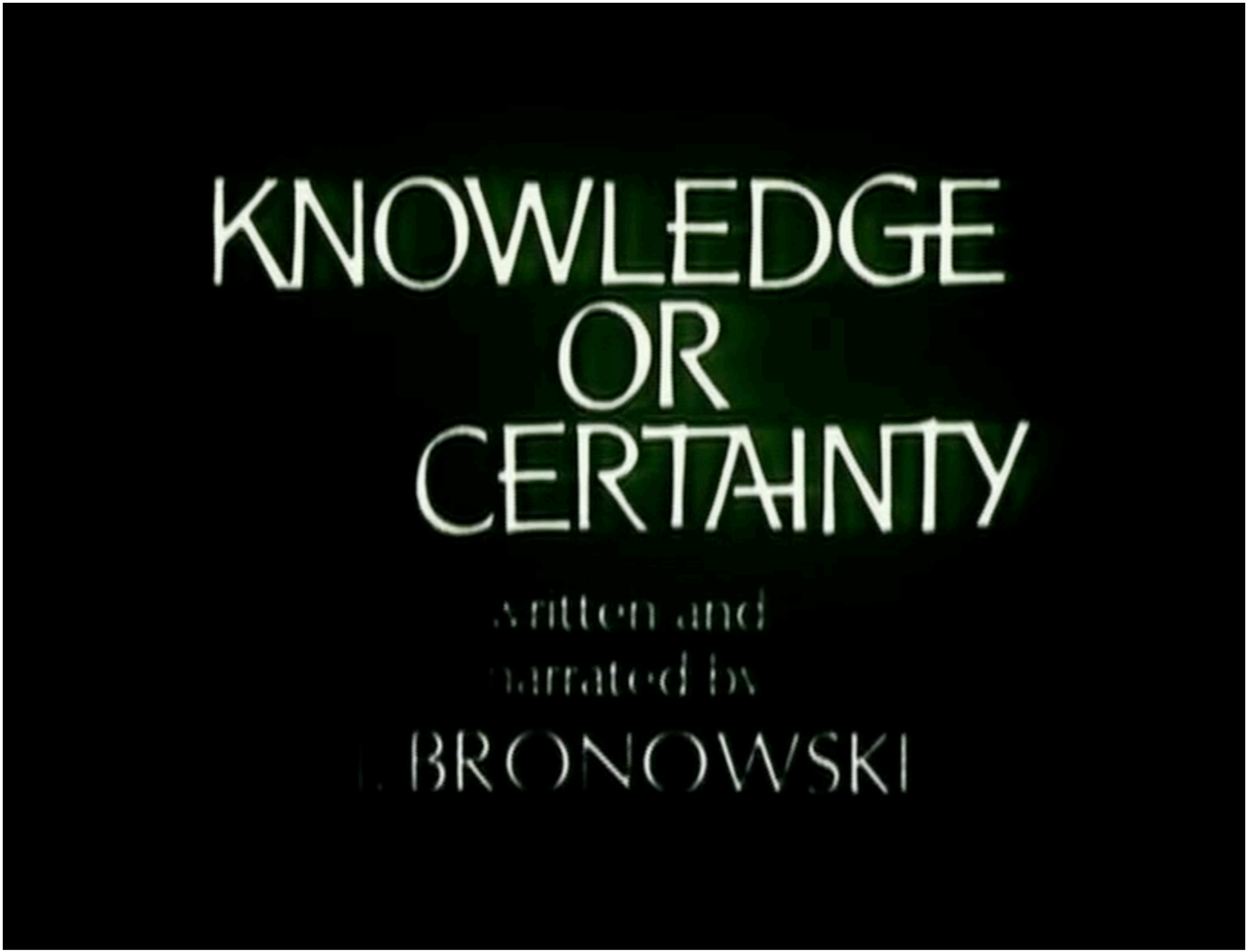
So What is a "Race"?

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 several 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 representative 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


KNOWLEDGE
OR
CERTAINTY
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narrated by
J. BRONOWSKI