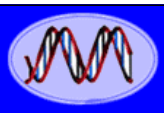
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Genetic Code of Life


Entire Genetic Code
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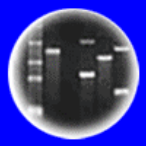
DNA Fingerprinting


Cloning: Ethical Issues
and Future Consequences


Plants of Tomorrow

HC70A & SAS70A Spring 2017
Genetic Engineering in Medicine, Agriculture, and Law

Professors Bob Goldberg & John Harada

Lecture 7
Human Genomes &
Tracing Human Ancestry

UCLA

UCDAVIS
UNIVERSITY OF CALIFORNIA

DNA
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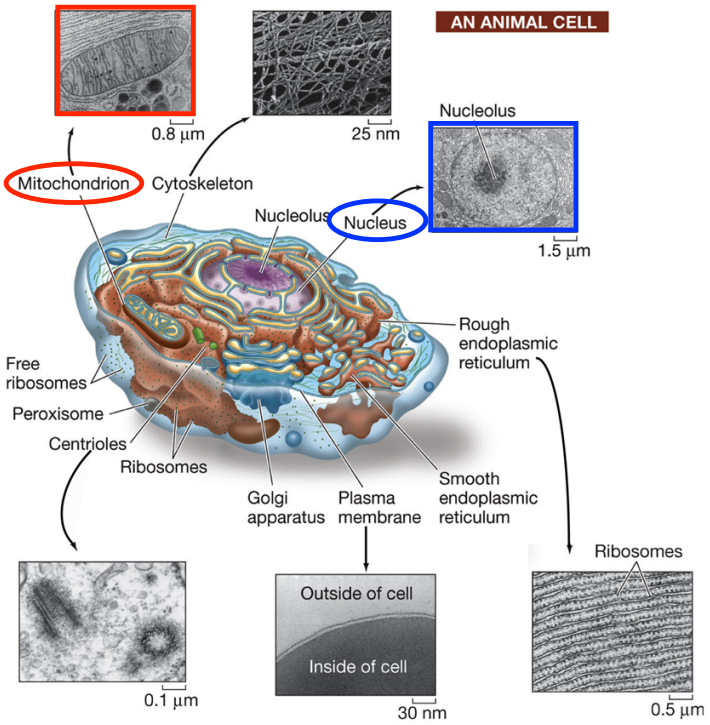
Plants of Tomorrow

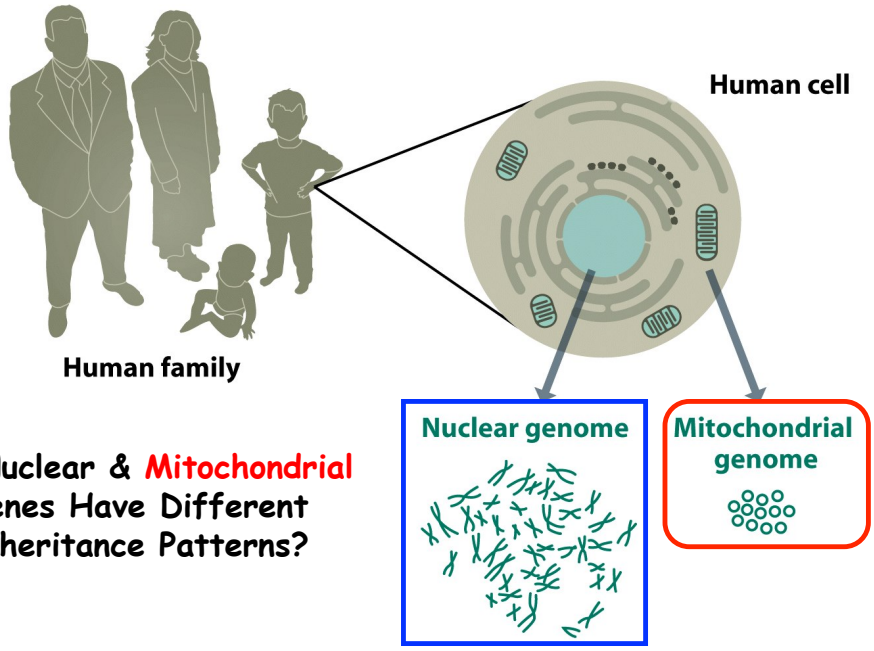
Themes

- The Human Genome – Two!
- Mitochondrial Genome & Diseases
- 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

Human Cells Have Two Genomes



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



Do Nuclear & Mitochondrial Genes Have Different Inheritance Patterns?

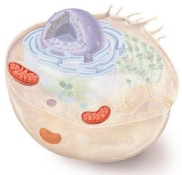
Figure 1-1 Genomes 3 (© Garland Science 2007)

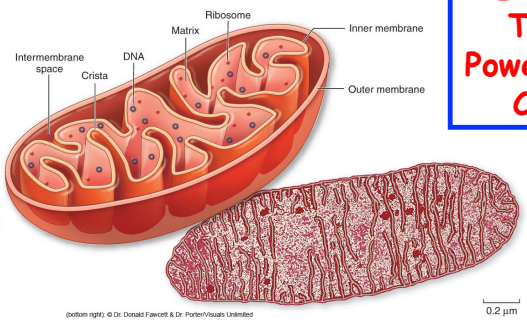
The Nuclear and Mitochondrial Genomes Differ in Size & Shape

Characteristic	Nuclear Genome	Mitochondrial Genome
Size	3.3 x 10^9 bp	16,500 bp
DNA Molecules Per Cell	23 in Haploid Cells 46 in Diploid Cells	Several Thousand Per 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

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!

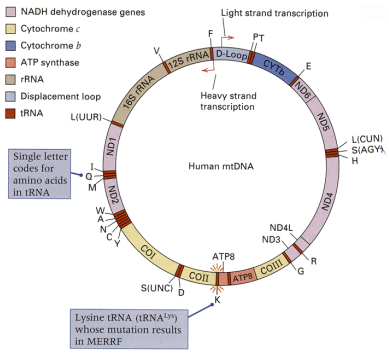


Figure 16.3 Genes in human mitochondrial DNA. The tRNA genes are indicated by the one-letter amino acid symbols; hence tRNA^{Lys} is denoted K. The positions of these and other genes in the mitochondrial DNA are indicated by color according to the key at the upper left. The arrows indicate the promoters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

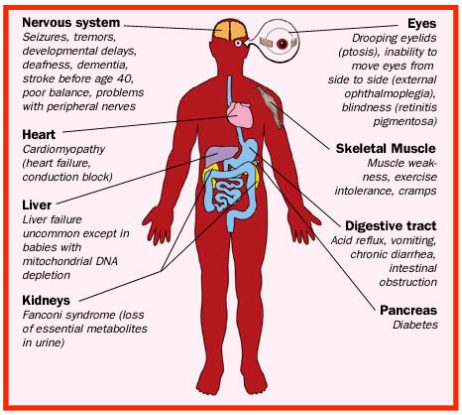
UNITED MITOCHONDRIAL DISEASE FOUNDATION®
HOPE. ENERGY. LIFE.

Mitochondrial DNA Diseases

Defects in Energy Production (ATP)

Affect 1/4000 People

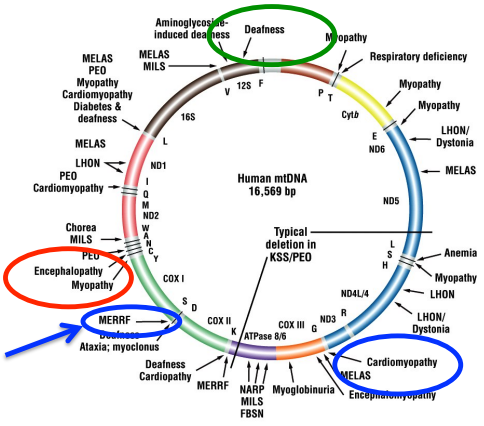
- Alpers Disease
- Barth syndrome
- Beta-oxidation Defects
- Carnitine-Acyl-Carnitine Deficiency
- Carnitine Deficiency
- Creatine Deficiency Syndromes
- Co-Enzyme Q10 Deficiency
- Complex I Deficiency
- Complex II Deficiency
- Complex III Deficiency
- Complex IV Deficiency
- Complex V Deficiency
- COX 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

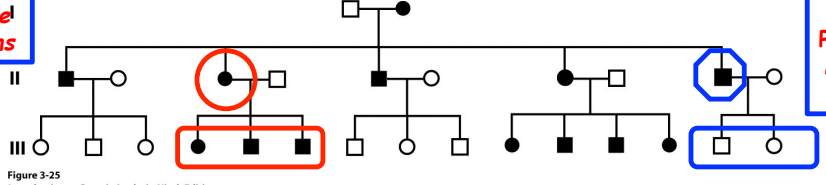


Figure 3-25
Introduction to Genetic Analysis, Ninth Edition
© 2008 W. H. Freeman and Company

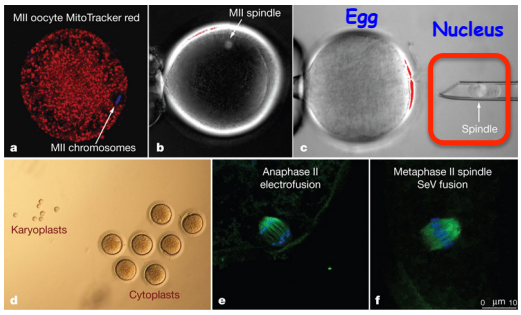
Note: Passed on From Mother to All Children

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

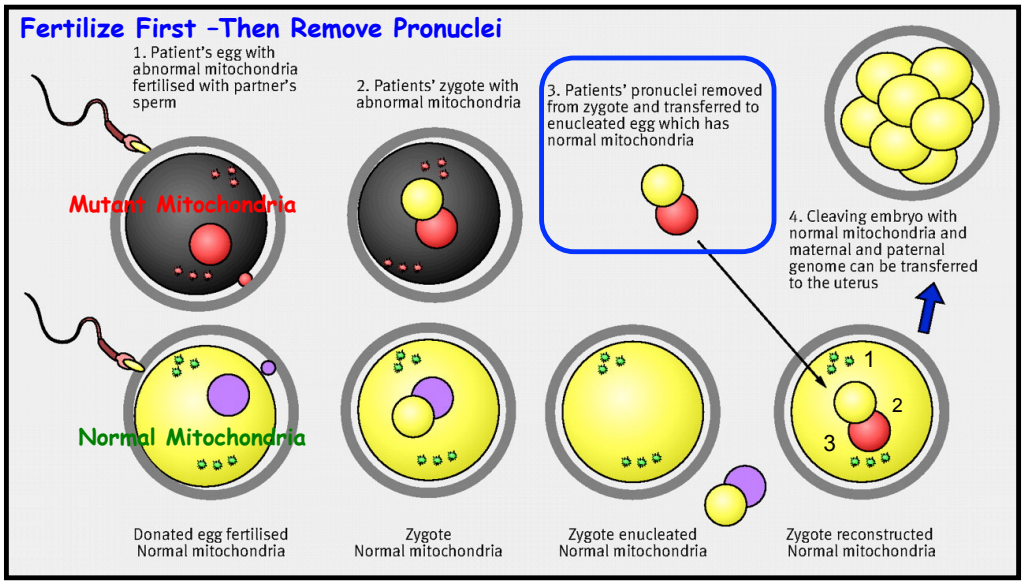
NUCLEAR TRANSPLANTATION Nature 2009

Researchers Prevent Inheritance of Faulty Mitochondria in Monkeys

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

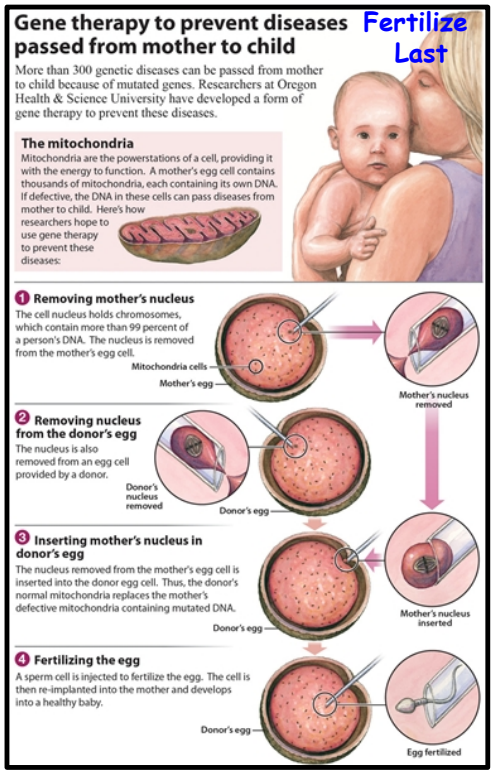


Mitochondrial Pronuclear Replacement Therapy



<u>Note</u>: 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

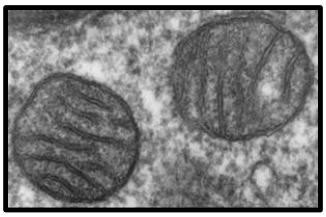
24 October 2012

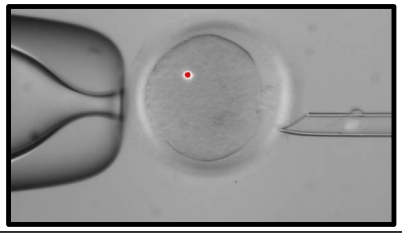
Geneticists Breach Ethical Taboo By Changing Genes Across Generations

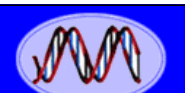
NATURE NEWS BLOG

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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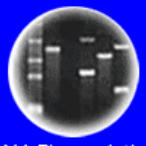
Genetic Code of Life

Entire Genetic Code of a Bacteria



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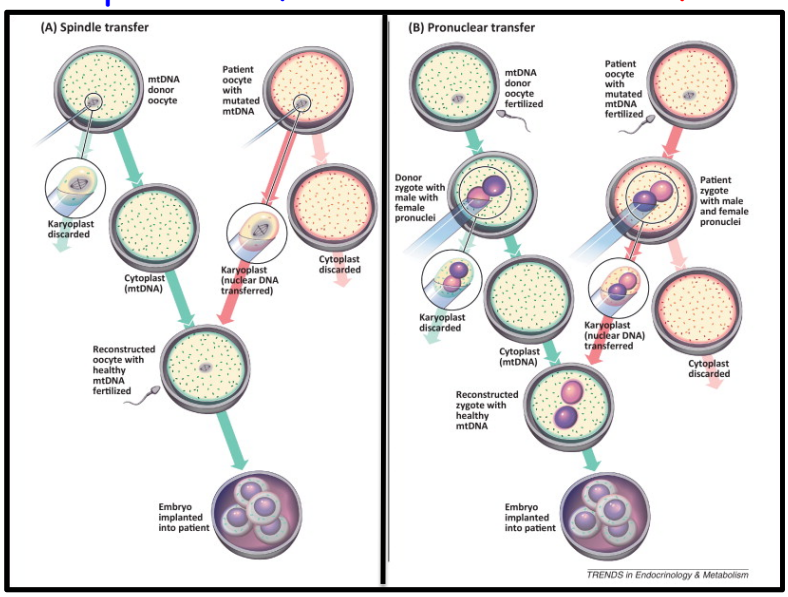
Two Methods of Mitochondrial Replacement Therapy

Spindle Transfer Pronuclear Transfer



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'

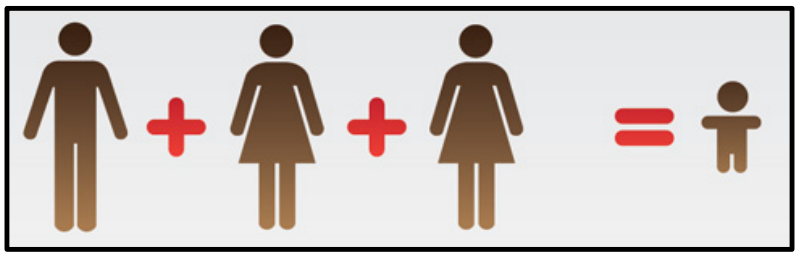
By Carl Engelking | February 3, 2015 1:58 pm

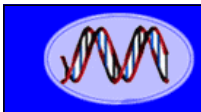
Scientists cheer vote to allow three-person embryos

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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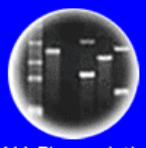
Entire Genetic Code of a Bacteria



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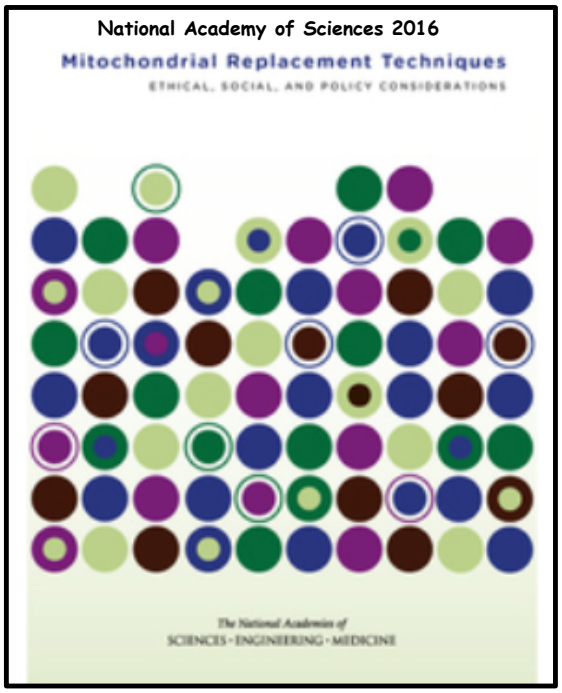
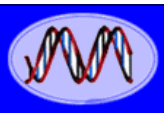
What About The United States? Recommendations to the FDA





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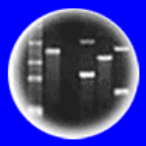

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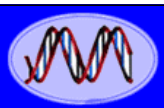
Finding an ethical path forward for mitochondrial replacement

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 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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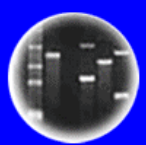

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Road Blocks

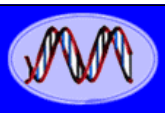
Dickey-Wiker Amendment-1995

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

2017 Congressional Budget (Expires 9/30/17)

- 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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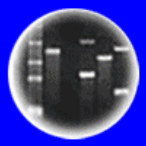

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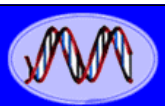
Consolidated Appropriations Act of 2017 - Rider

(*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*).



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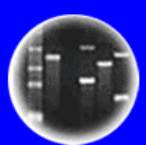

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Birth of Baby With Three Parents' DNA Marks Success for Banned Technique

By GINA KOLATA SEPT. 27, 2016

Controversial 3-parent baby technique produces a boy

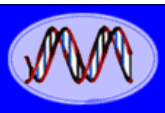
First 'three person baby' born using new method

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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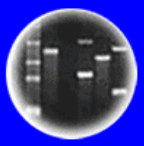

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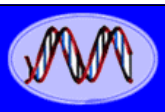
So Much For the Restrictions!

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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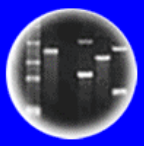

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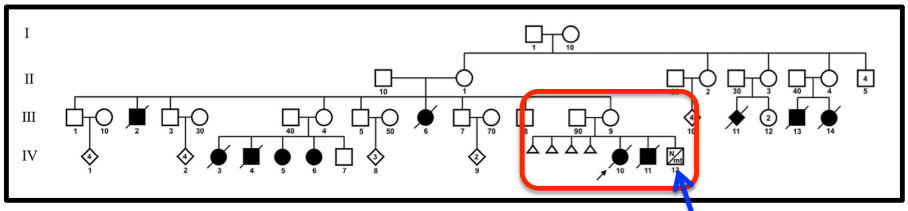
Family With History of Leigh Syndrome Underwent Mitochondrial Replacement Therapy and Gave Birth to a Normal Boy

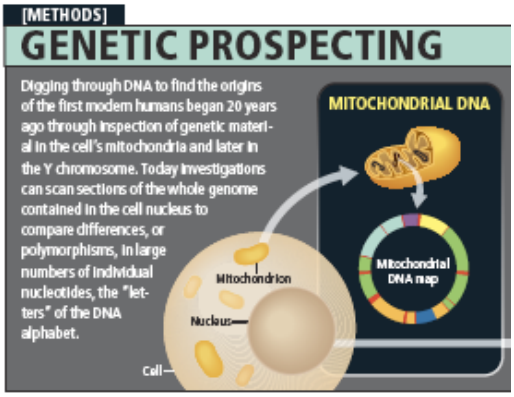


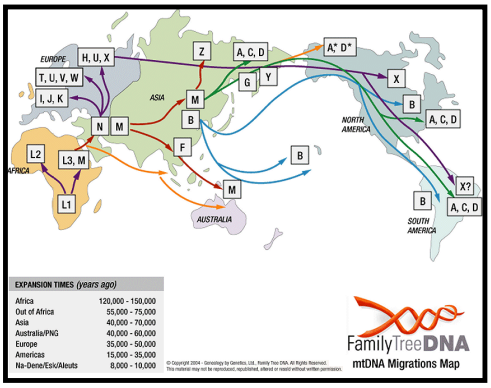
Jordanian Couple – New York IVF Clinic – Procedure in Mexico – Birth in Mexico (Spindle Transfer – No Embryos Destroyed)

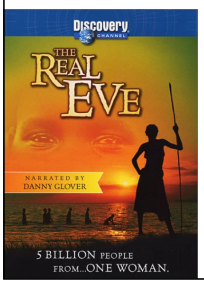
Leigh syndrome

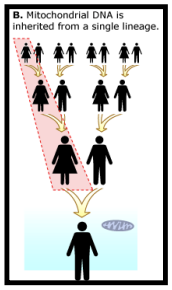
- A severe neurological disorder, affecting at least one in 40,000 new-born babies.
- Usually becomes apparent during the first year of a child's life.
- First signs include vomiting, diarrhoea and difficulty with swallowing.
- Causes the progressive loss of movement, and deterioration of mental functions.
- Symptoms are linked to the development of patches of damaged tissue which develop in the brain.
- Children with the condition usually die within two to three years, usually because of respiratory failure.
- Mutations in 75 different genes have been linked to the condition.
- Most of those mutations occur in DNA from the nucleus, but in about one in five cases the culprit is found in mitochondrial DNA.

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









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.

DNA Sequence
(locations 1 to 45 of the mtDNA)

Location 1 Location 45

GATCACAGGTCTATCACCCTATTAACCACTCACGGGAGCTCTCCA
CTAGTGTCCAGATAGTGGGATAATTGGTGAGTGCCCTCGAGAGGT

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".

DNA Sequence
(locations 1 to 45 of the mtDNA)

Location 1 Location 45

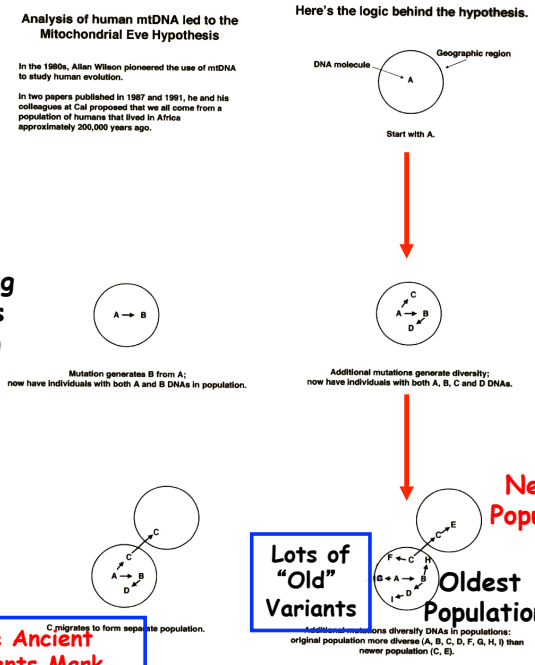
GATCACAGGTCTATCACCCTATTAACCACTCACGGGAGCGCTCCA
CTAGTGTCCAGATAGTGGGATAATTGGTGAGTGCCCTCGCGAGGT

TA to GC SNP @ NT 45 Becomes a MARKER!

SNP mutation at Location 40

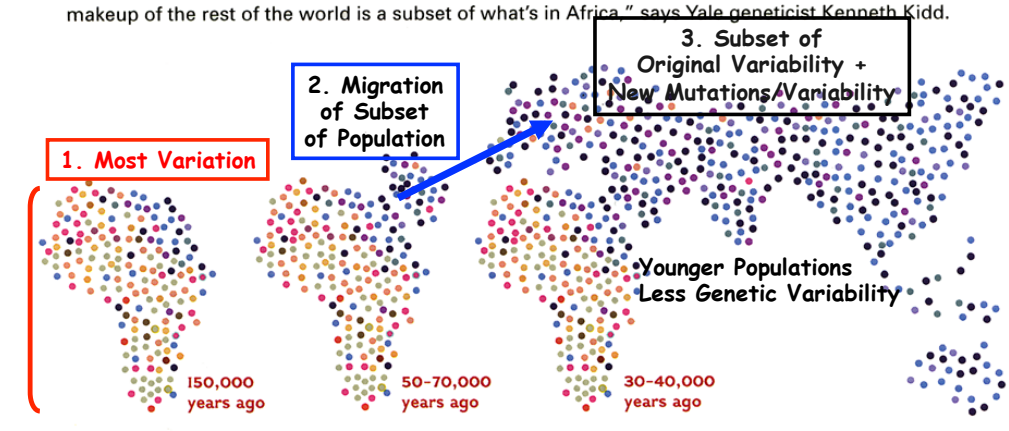
This mutation is documented as follows:
- Location: 40
- Nucleotide Change: T>g (also indicated as T40G)

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



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

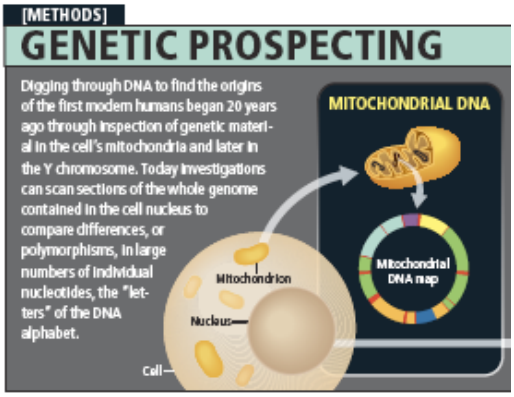
Most Genetic Diversity Originated in the Founder Populations to Modern Humans!

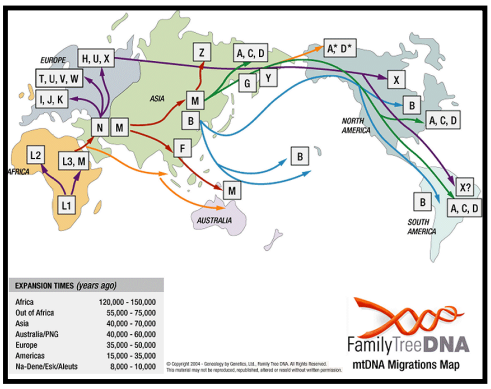


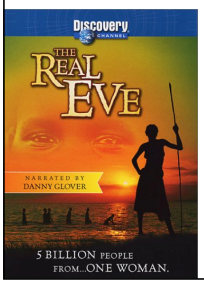
Genetic Variation Proportional to Population Age

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

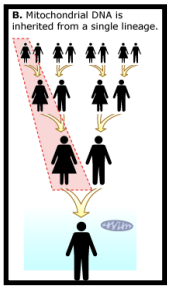
Tracing Human Populations Using Mitochondrial DNA Polymorphisms (SNPs) - Back to Eve!

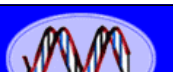




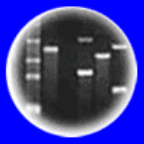


Eve Lived ~200,000 Years Ago!!




DNA
Genetic Code of Life

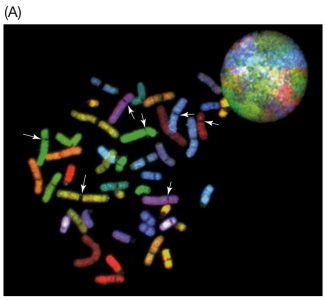

Entire Genetic Code of a Bacteria

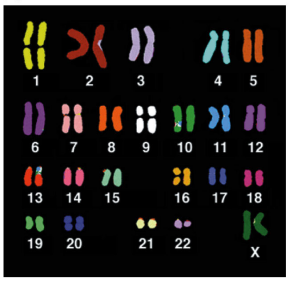

DNA Fingerprinting

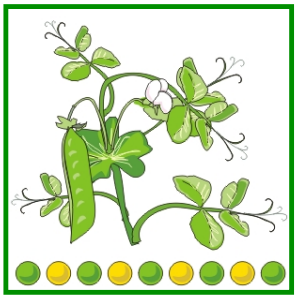

Cloning: Ethical Issues and Future Consequences

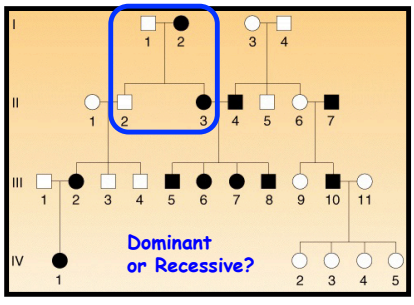

Plants of Tomorrow

The Nuclear Genome



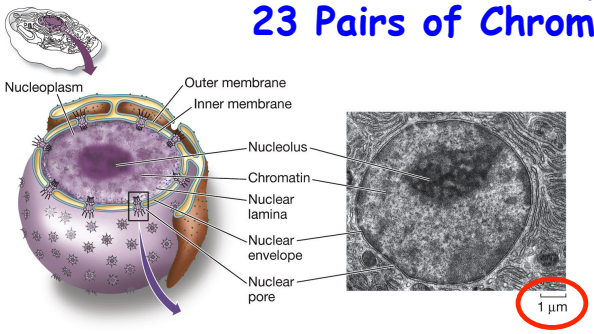


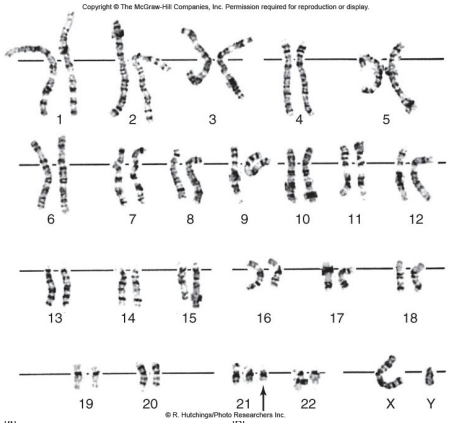




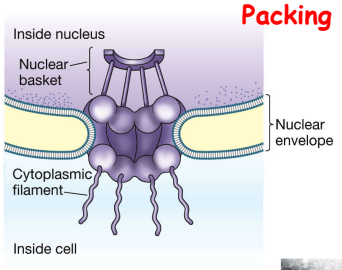
Note: Gene is Inherited in a Mendelian Pattern

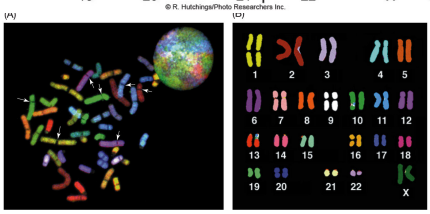
The Nucleus Is A Complex Organelle With 23 Pairs of Chromosomes (Humans)

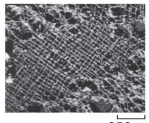




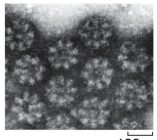
Packing Problem?







RNA & Protein Transport

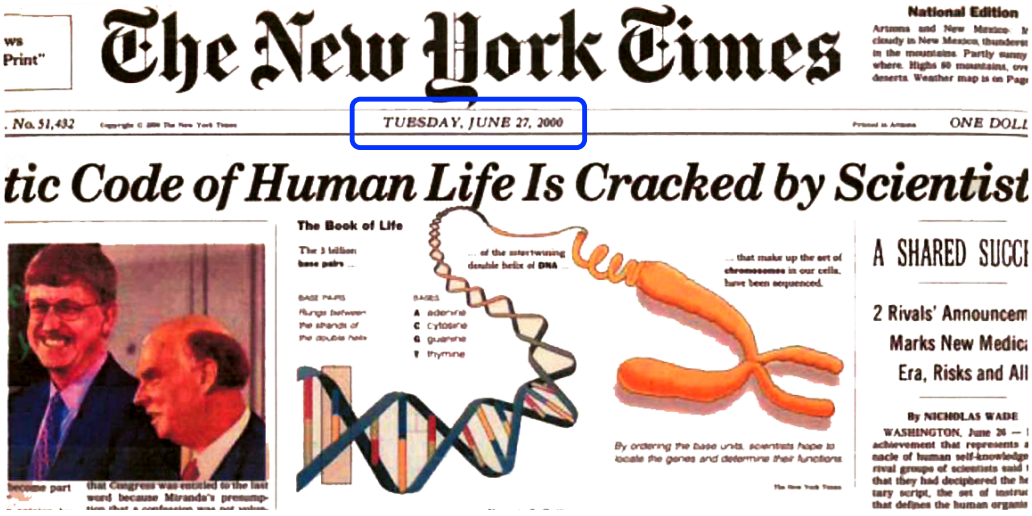


The Human Genome End to End is 1.1 Meters in Length!!!!!!

LIFE 8e, Figure 4.8 (Part 2)

Note: Chromosome Sizes & Bands = Markers

The Human Genome Was Sequenced Seventeen Years Ago!
The Human Genome Project



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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

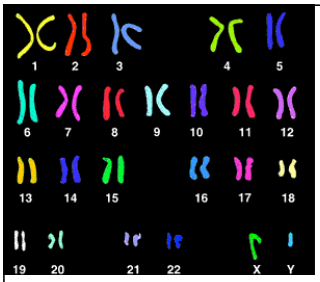
2 Rivals' Announcem Marks New Medic Era, Risks and All

By NICHOLAS WADE

WASHINGTON, June 26 —

Public & Private Effort Using Different Strategies - A Race!

3 Billion Dollars & Took 15 Years

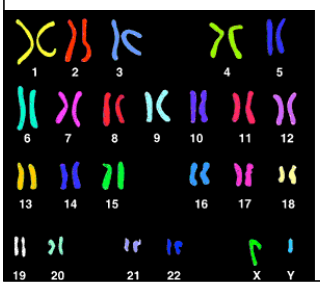


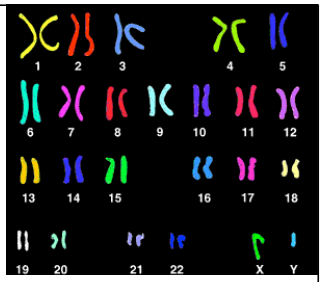
The Human Genome

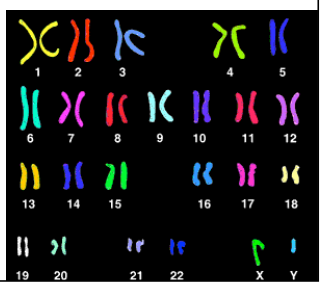
Chromosome	Including gaps	Sequenced	Gaps
1	247,249,719	224,999,719	22,250,000
2	242,951,149	237,712,649	5,238,500
3	199,501,827	194,704,827	4,797,000
4	191,273,063	187,297,063	3,976,000
5	180,857,866	177,702,766	3,155,100
6	170,899,992	167,273,992	3,626,000
7	158,821,424	154,952,424	3,869,000
8	146,274,826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

Large

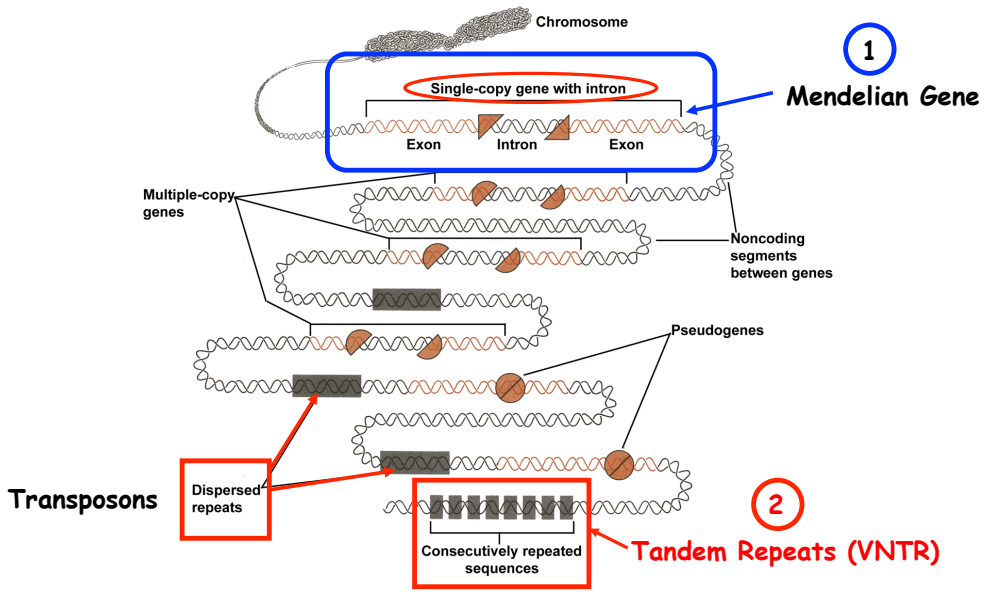
Small







The Human Genome Landscape



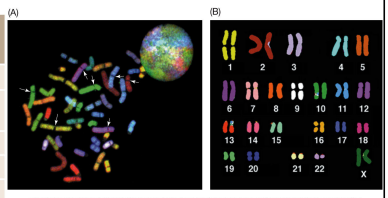
Tandem Repeats or VNTRs are Useful for DNA Fingerprinting Studies!

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



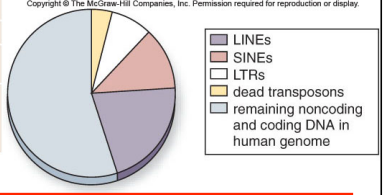
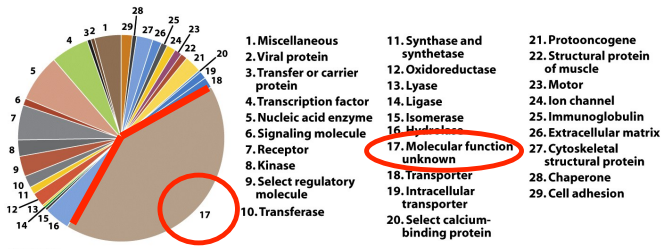


Table 20.6 Average characteristics of genes in the human genome

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

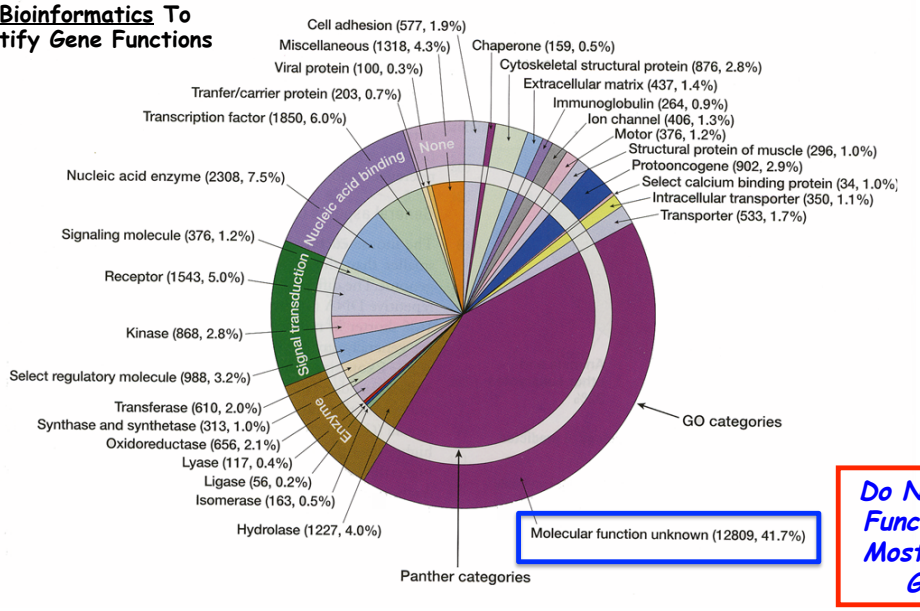
The Human Genome Has DNA Sequences Present Once As Well as Repeated Many Times



Human Genes are Large but Contain Mostly Introns

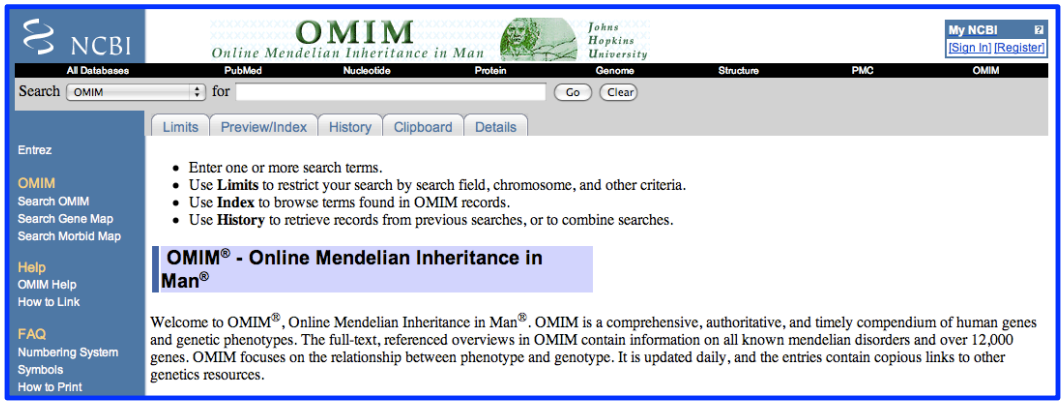
The Human Genome Contains ~25,000 Different Genes

Use Bioinformatics To Identify Gene Functions



Do Not Know Functions of Most Human Genes!

How Many Human Disease Genes Have Been Identified?



There are ~25,000 Genes in The Human Genome

1. 4,994 Genes Correlate With a Disease Phenotype (318 on X & 4 on Y). The Molecular Basis of These Genetic Diseases Are Known (e.g., Sickle Cell Anemia, Hemophilia A).

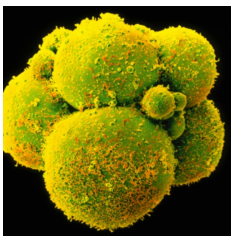
2. 1,605 Genes Correlate With a Disease Phenotype (124 on X & 5 on Y), But The Molecular Basis of These Genetic Diseases Are Not Known.

OMIM 5/15/17 http://omim.org/statistics/entry

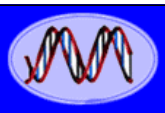
What's a GMO? Using Genetic Engineering to Cure Genetic Diseases

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?

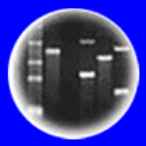


A Human Embryo With a Defective Blood Disease Gene That Was "Edited" and Engineered to Be Normal?



DNA
Genetic Code of Life

Entire Genetic Code of a Bacteria



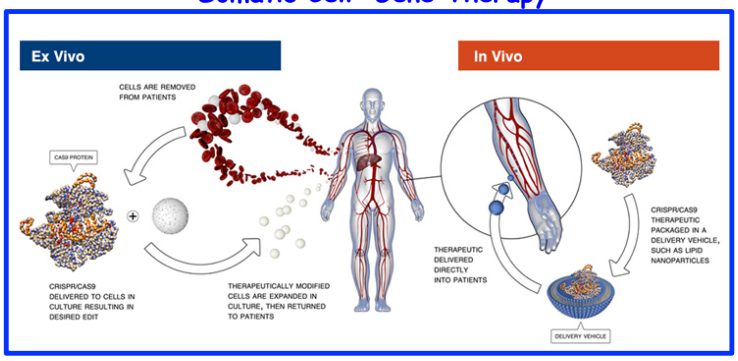
DNA Fingerprinting

Cloning: Ethical Issues and Future Consequences

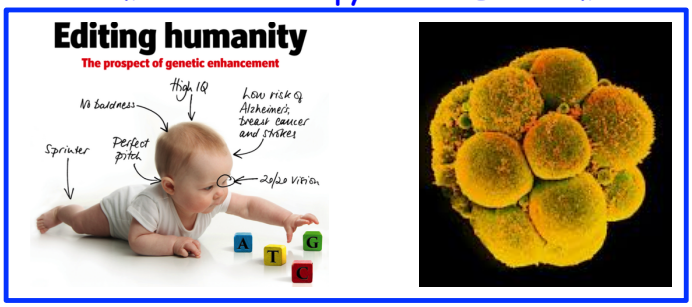
Plants of Tomorrow

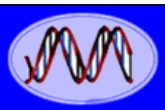
Adding and Editing Genes To Correct Human Genetic Disorders

Somatic Cell Gene Therapy



Germline Gene Therapy + Gene Enhancement





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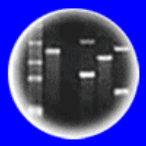


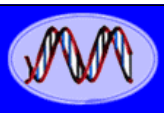
DNA Fingerprinting

Cloning: Ethical Issues and Future Consequences

Plants of Tomorrow

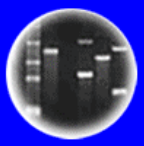
"Improving" Humans with Customized Genes Sparks Debate among Scientists

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



DNA
Genetic Code of Life

Entire Genetic Code of a Bacteria



DNA Fingerprinting

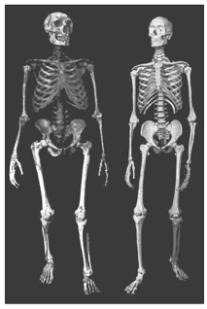
Cloning: Ethical Issues and Future Consequences

Plants of Tomorrow

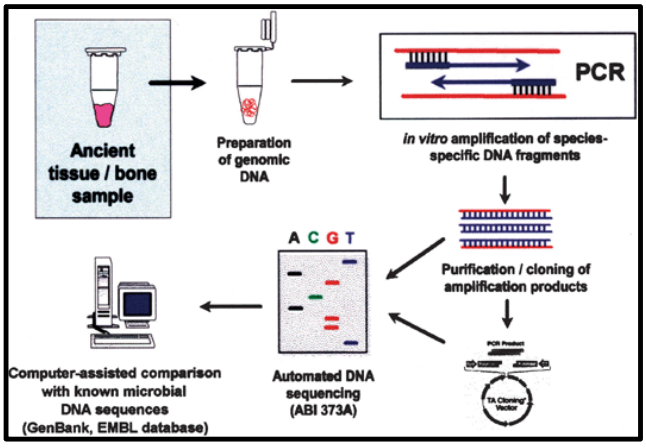
Gene Editing Summit Recommendations

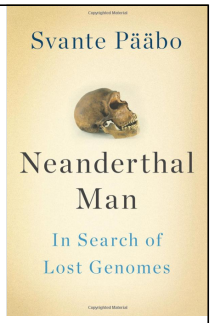
- **Basic & Preclinical Research** is Needed & Should Proceed. If in the Process Germline Cells or Early Embryos Are Edited, They Should Not Be Used To Establish Pregnancy
- **Clinical Use – Somatic** – Gene Editing of Somatic Cells Can Proceed Under Existing Regulations & Guidelines (e.g., Blood cells, 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

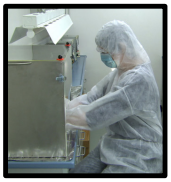


Using Ancient DNA to Unravel Our Human Heritage





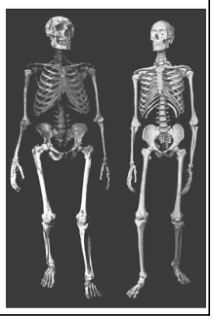
Nature, 2010



DNA from cave soil reveals ancient human occupants

Science April, 2017

Technique may help open a new era in paleoanthropology



RESEARCH ARTICLE

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

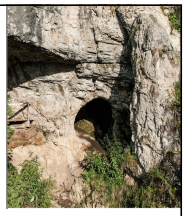
A Draft Sequence of the Neandertal Genome

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.

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

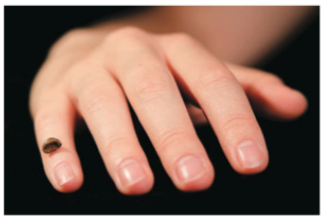


ANCIENT DNA

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

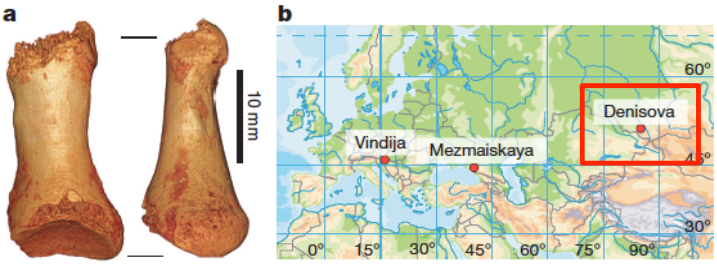
A new high-coverage DNA sequencing method reconstructs the full genome of Denisovans--relatives to both Neandertals and humans--from genetic fragments in a single finger bone

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

The complete genome sequence of a Neanderthal from the Altai Mountains

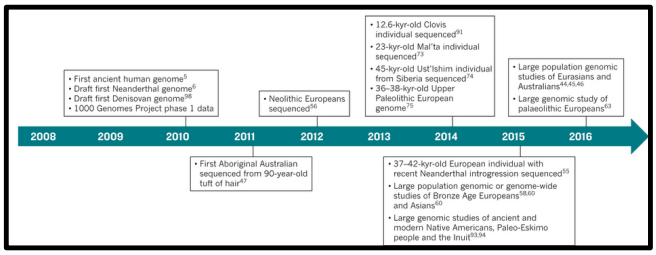
130,000 Year-Old Neanderthal

Toe Fossil Provides Complete Neanderthal Genome

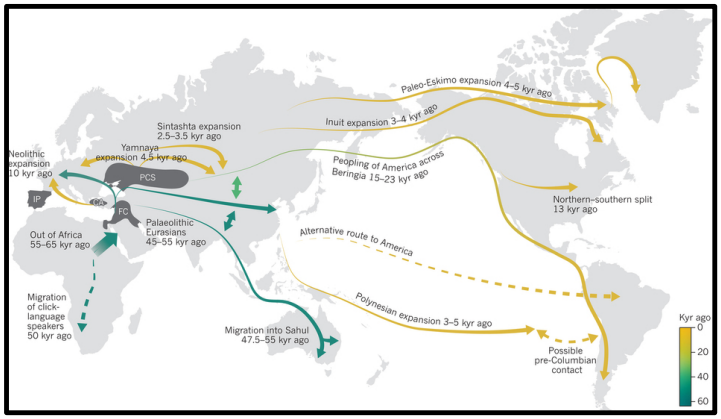


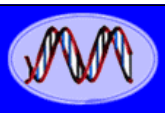
Tracing the peopling of the world through genomics

Nature, January, 2017



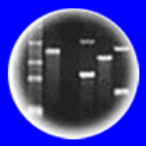
We Are Derived From One Ancestral Population!!





DNA
Genetic Code of Life

Entire Genetic Code of a Bacteria



DNA Fingerprinting

Cloning: Ethical Issues and Future Consequences

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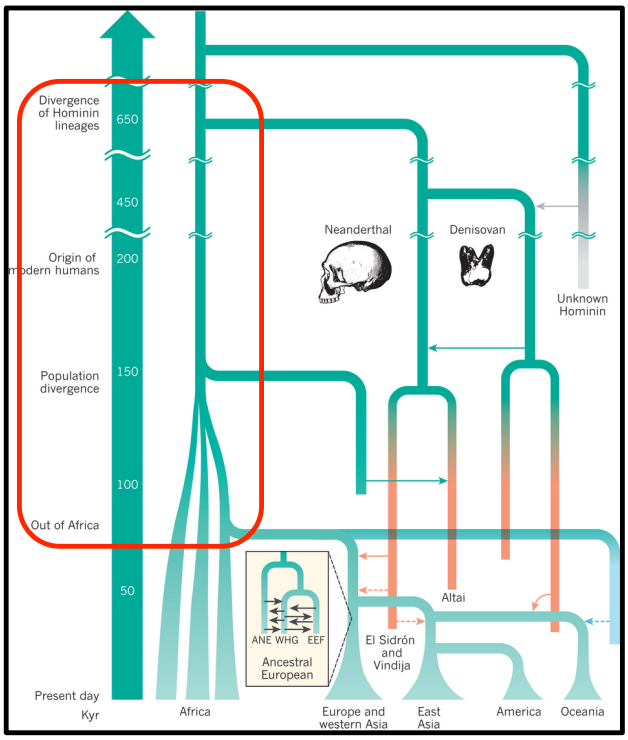
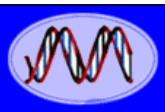
Origins of Human Populations From DNA Sequencing Data





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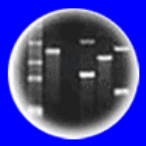

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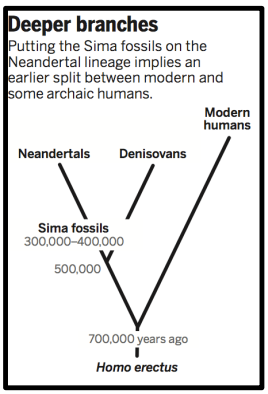
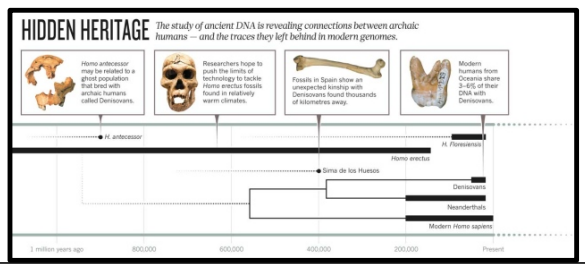
HUMAN EVOLUTION

Humanity's long, lonely road

Oldest ancient nuclear DNA suggests humans and Neandertals parted ways early



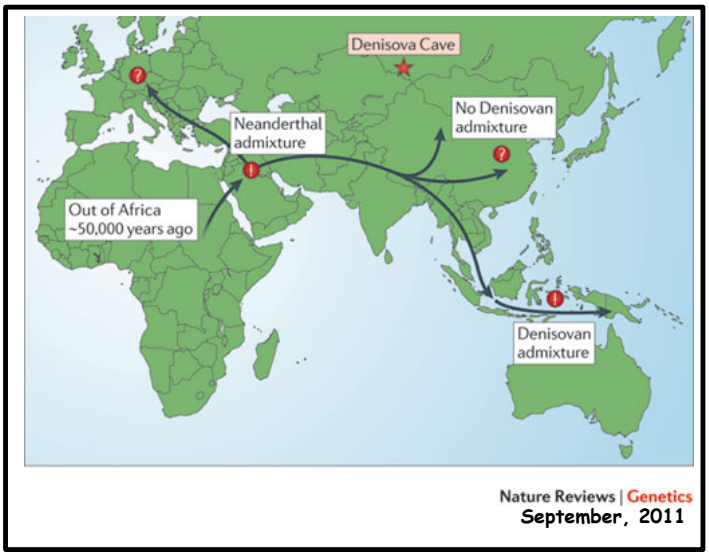
Creating a Map of Human History!



The 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!!



Nature Reviews | Genetics
September, 2011

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

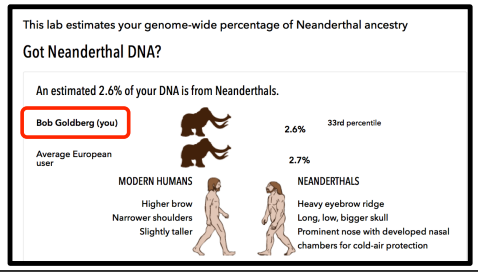
The genomic landscape of Neanderthal ancestry in present-day humans

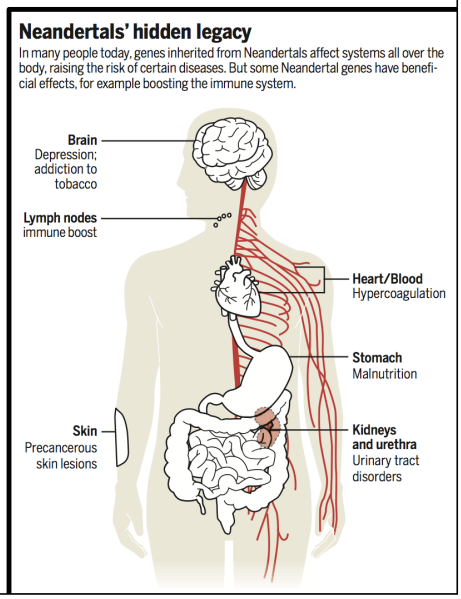
Nature, January 29, 2014

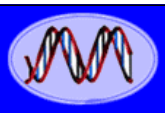
Neandertal genes linked to modern diseases

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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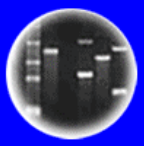

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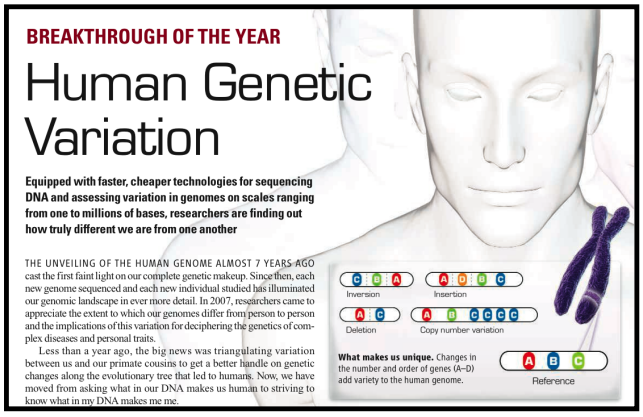
HUMAN DIVERSITY

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.

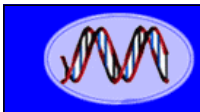
Inversion
Insertion
Deletion
Copy number variation
Reference

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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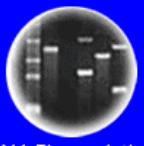

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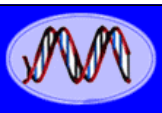
ARTICLE Nature, October 28, 2010 doi:10.1038/nature09534

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 (Allelic Markers)
- 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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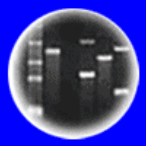

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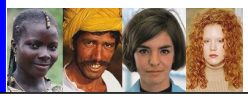
Nature, October, 2015

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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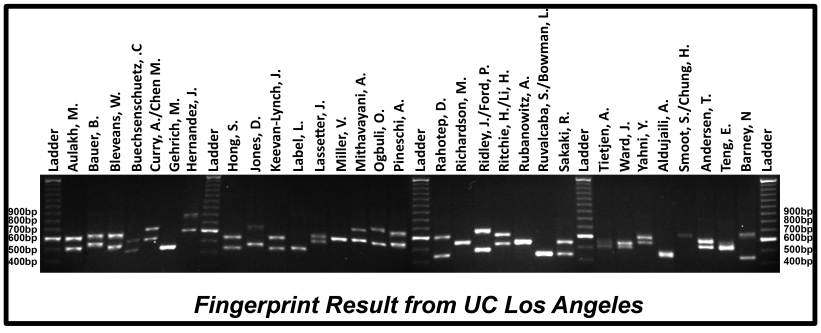
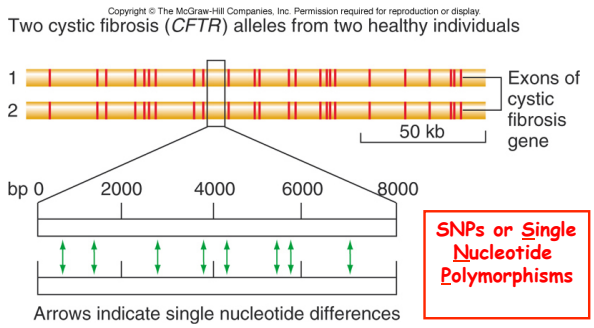
HC70A/SAS70A Class Allelic Variation



Fingerprint Result from UC Los Angeles

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

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

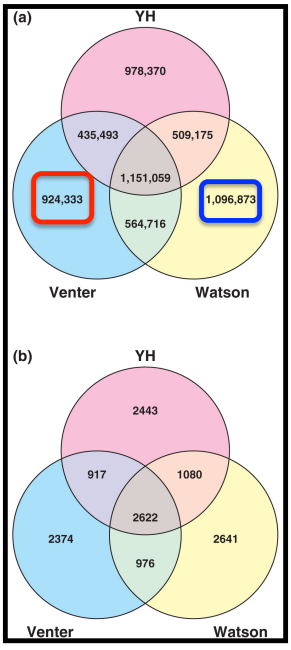
Single nucleotide polymorphism (SNP) ...GCAA**T**TCCCGATT...
...GCAA**G**TCCCGATT...

Simple sequence repeat (SSR) ...GCATT**ATATATATAT**C...
...GCATT**ATAT**[ ]C...

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	AGCTC**T**GATAC TCGAG**A**CTATG	AGCTC**T**GATAC
2	AGCTC**C**GATAC TCGAG**G**CTATG	AGCTC**C**GATAC

(b)

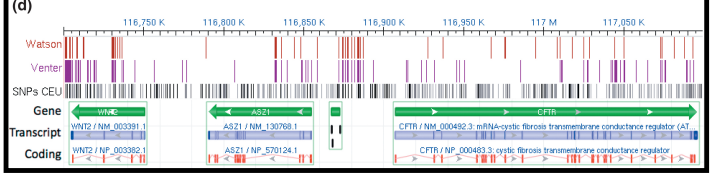
Genotype	Notation
Homozygous T	TT
Heterozygous T	TC
Homozygous C	CC

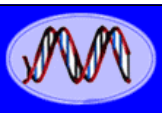
(c)

Human 1 TTGAC**G**TATAAATGATCTTTATAT**T**TTCAGAAGTC
Human 2 TTGAC**G**TATAAATGATCTTTATAT**C**TTCAGAAGTC
Chimp TTGAC**A**TATAAATGATCTTTATAT**C**TTCAGAAGTC

These Are Alleles!

(d)





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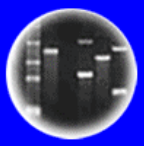

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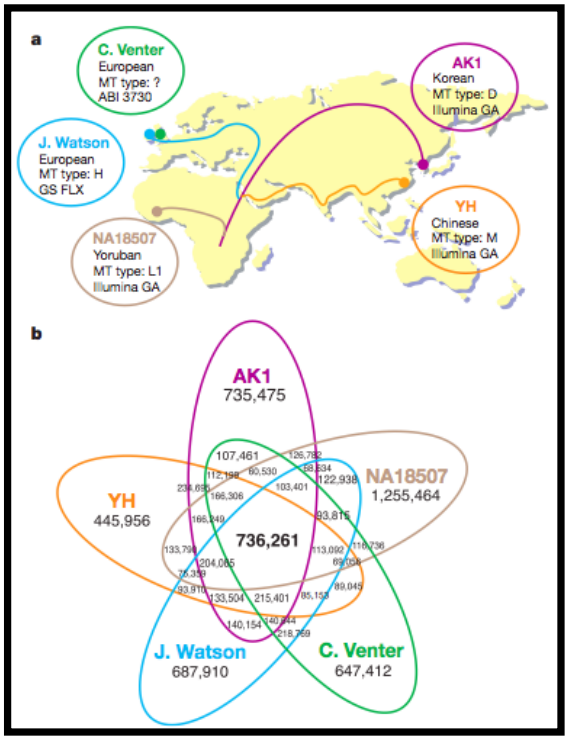
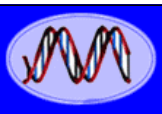
Everyone Has a Large Number of Unique SNPs!



Used to Trace Ancestry & Individuality



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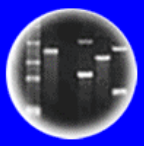

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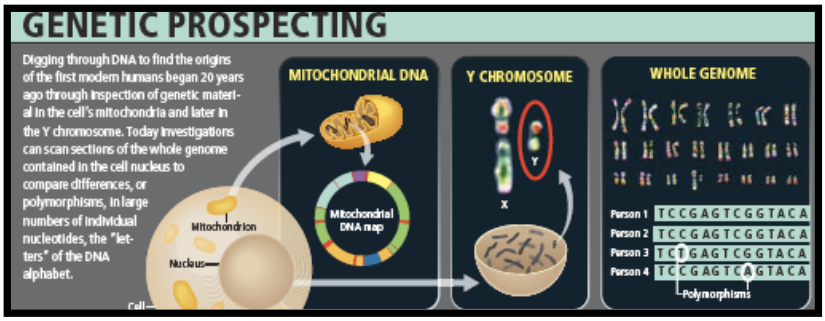
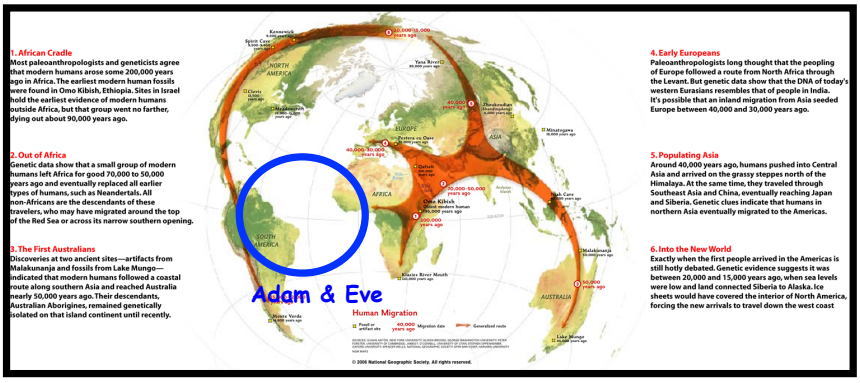
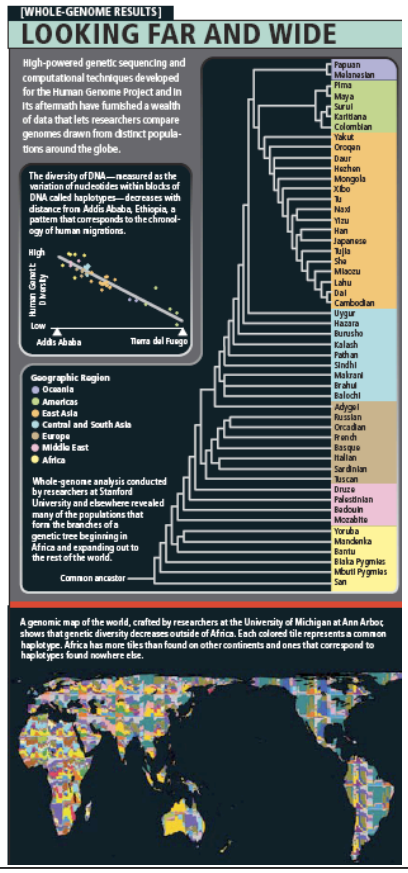
Nuclear DNA SNPS Can Be Used To Trace Human Populations & Origins

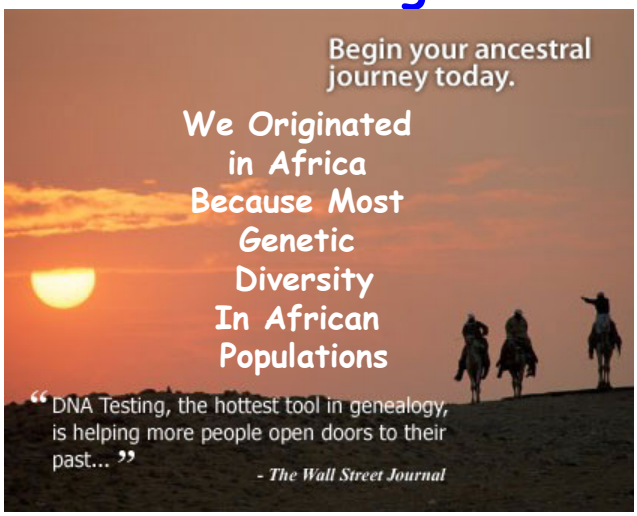
(Concept Same as For Mt DNA)

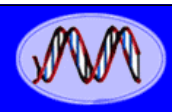




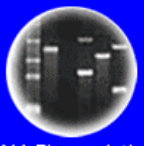


All of Humanity is Related & Has the SAME Origin!




DNA
Genetic Code of Life


Entire Genetic Code of a Bacteria


DNA Fingerprinting


Cloning: Ethical Issues and Future Consequences


Plants of Tomorrow

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

More Genetic Diversity Within Any Population Than Between Populations

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).

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!

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%

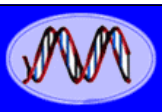
85% Within Population genetic variability

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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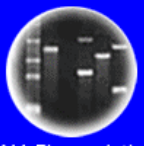

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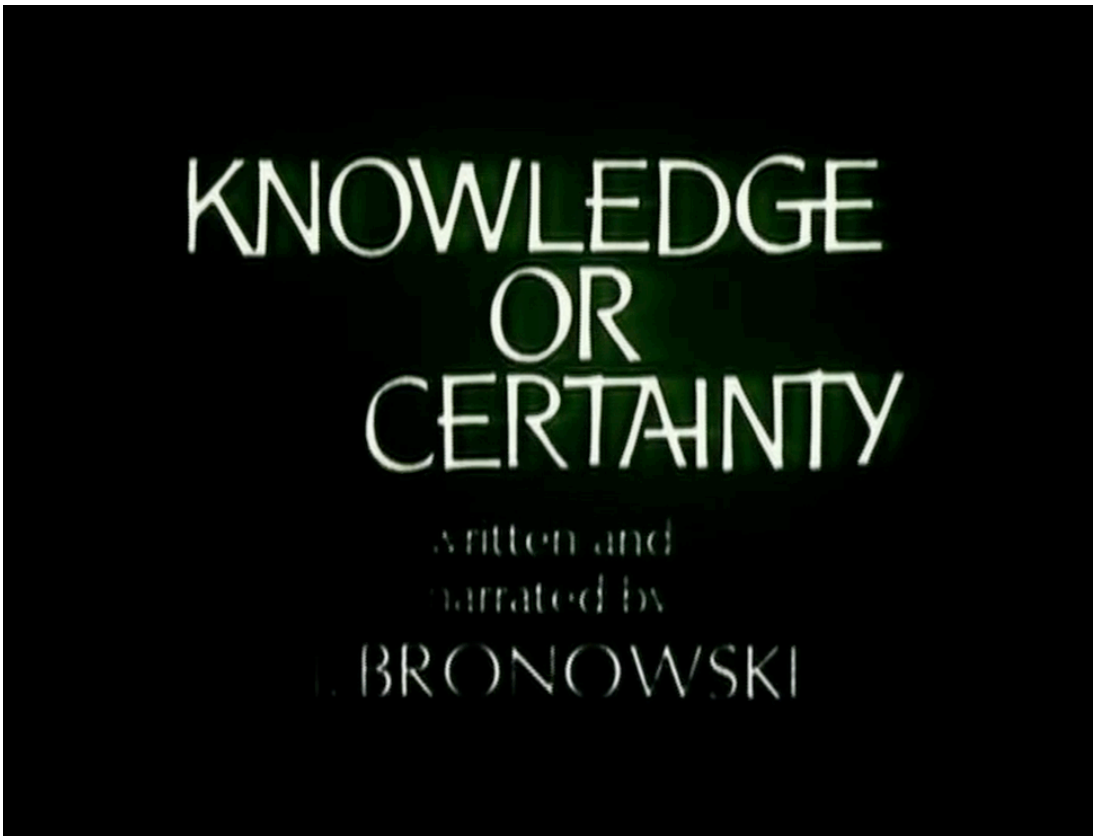
So What is a "Race"?

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 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 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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