Center for Human Development Seminar

"Exploring Human Uniqueness – A Transdisciplinary Approach"

by

Ajit Varki

Distinguished Professor of Medicine and Cellular & Molecular Medicine
Co-Director, Center for Academic Research and Training in Anthropogeny
University of California, San Diego

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Suggesting Reading

- Varki, A., Multiple Changes in Sialic Acid Biology During Human Evolution *Glycoconjugate Journal.* (in press).
- Varki, A. and Nelson, D. Genomic Differences between Humans and Great Apes. *Annual Review of Anthropology.* 36:191-209, 2007.
- Varki, A., Geschwind, D., and Eichler, E.: Explaining Humans: Genome Interactions with Environment, Behavior and Culture. *Nature Reviews Genetics*, 9:749-763, 2008.

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The "Central Dogma" of Molecular Biology
Francis Crick, 1958

DNA → RNA → PROTEIN

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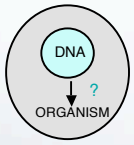
The "DNA-centric" View of Life

DNA → RNA → PROTEIN ⋯?⋯▸ CELL ⋯?⋯▸ ORGANISM



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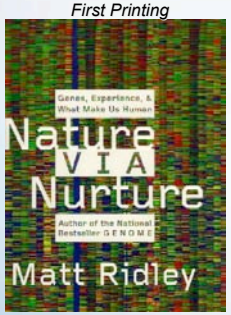
An Example of the Media and Public Penchant for Genetic Determinism

First Printing



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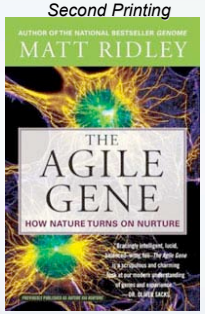

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The "Central Dogma" of Molecular Biology

Francis Crick, 1958

DNA → RNA → PROTEIN

"Biology hasn't got any (absolute) Laws - Only Gadgets"

Francis Crick, 2002

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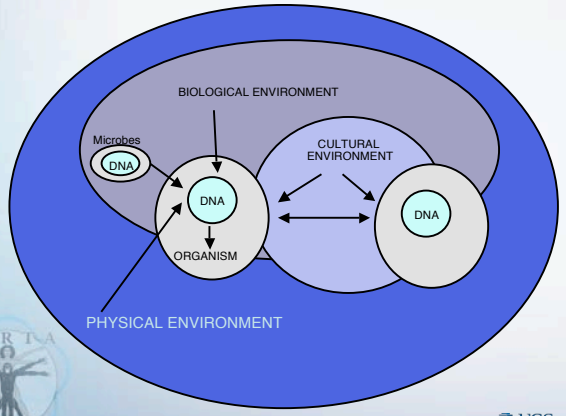
Inadequacies of a "DNA-Centric" View of Life



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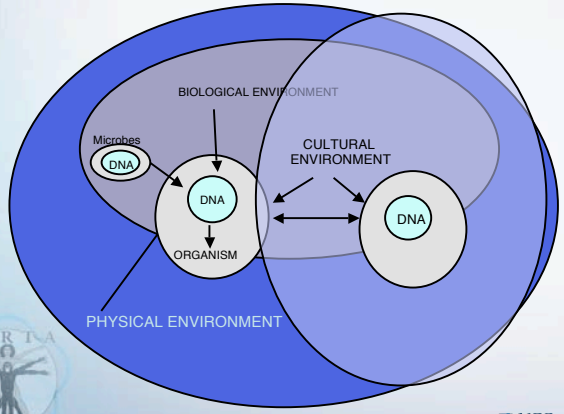
Humans Use Culture to Control the Environment



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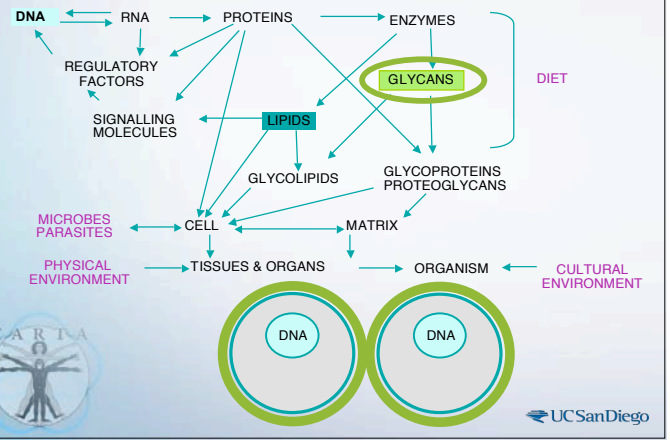
A More Complete View of Biology



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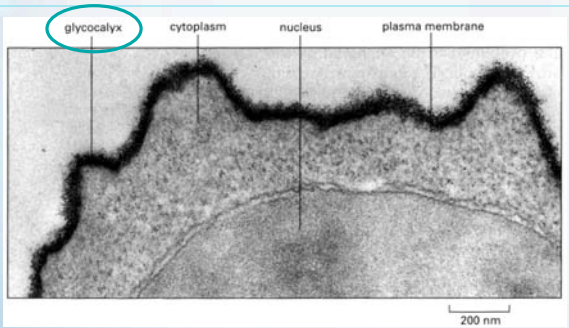
Electron Micrograph of a Human Lymphocyte



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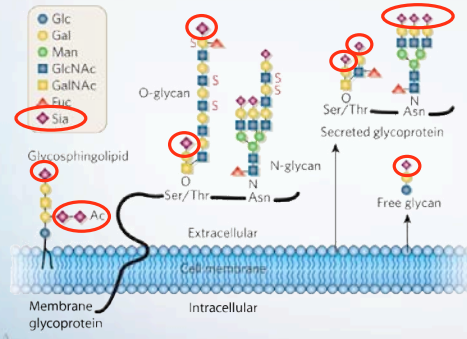
Sialic Acids on Cell Surface and Secreted Molecules



Varki, A. *Nature* 446: 1023-1029, 2007

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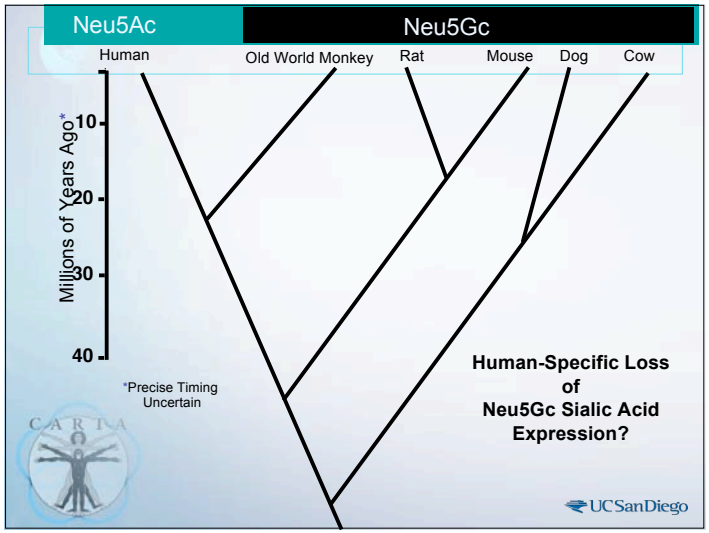

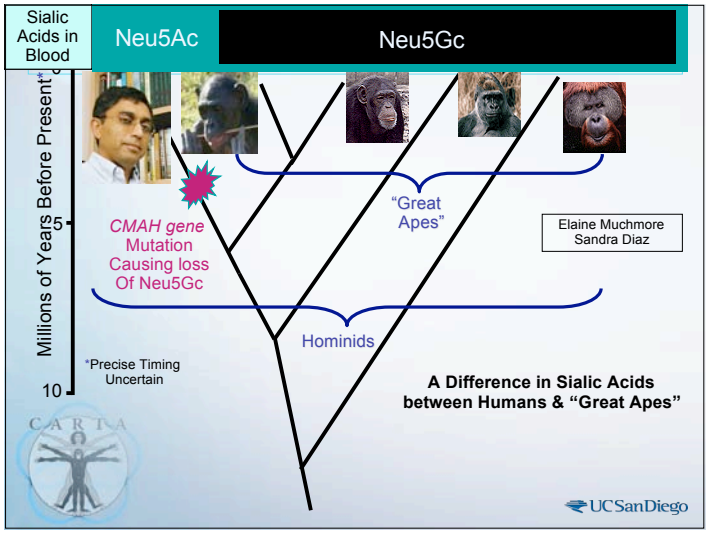

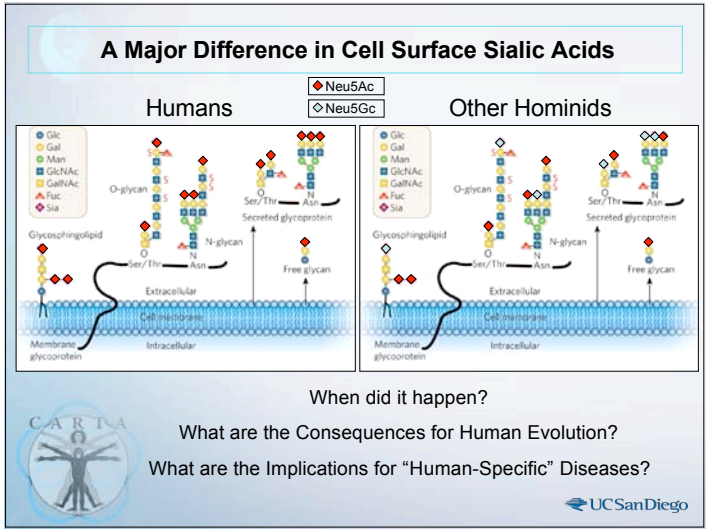

Apparent Differences between Humans and "Great Apes" in Incidence/Severity of Medical Conditions - Excluding those Explained by Anatomical Differences

MEDICAL CONDITION	HUMANS	"GREAT APES"
Definite		
HIV Infection progression to AIDS	Common	Very Rare
Hepatitis B/C late complications	Can be Severe	Mild
P. falciparum Malaria	Susceptible	Resistant
Myocardial Infarction	Common	Very Rare
Human Influenza A Susceptibility	Can be Severe	Often Mild
Probable		
Alzheimer's Disease Pathology	Complete	No Tangles
Epithelial Cancers	Common	Rare?
Atherosclerotic Strokes	Common	Rare?
Hydatiform Molar Pregnancy	Common	Rare?
Possible		
Rheumatoid Arthritis	Common	Rare?
Bronchial Asthma	Common	Rare?
Toxemia of Pregnancy	Common	Rare?
Endometriosis	Common	Rare?
Autoimmune Diseases	Common	Rare?

Varki, A. *Genome Research* 10:1065-1070, 2000
Olson, M. and Varki A. *Nature Reviews Genetics*, 4: 20-28, 2003.
Varki, A. & Altheide, T.K.: *Genome Research*. 15:1746-1758, 2005
Varki, A. and Nelson, D. *Ann Rev Anthropol* 36:191-209, 2007

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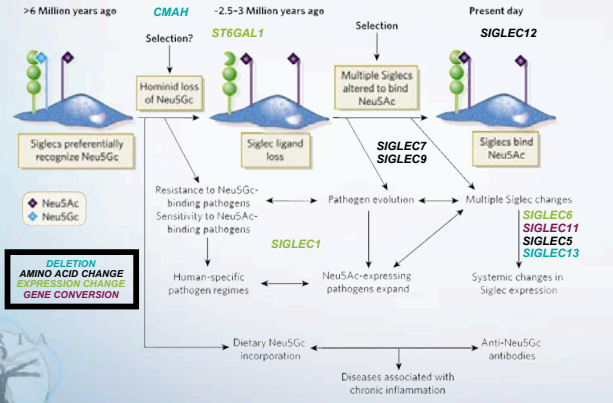
Proposed Evolutionary Scenario for Multiple Human-Specific Changes in Sialic Acid Biology



Varki A. *Nature* 446: 1023, 2007

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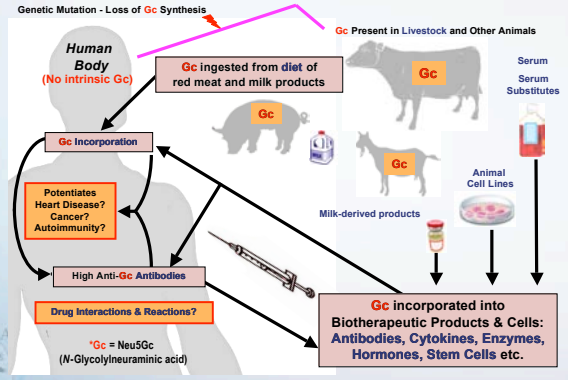
Contamination of Humans and Biotherapeutic Products by Incorporation of "Gc" (a.k.a., NGNA/Neu5Gc): Implications and Apparent Mechanisms



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Reasons for Sequencing the Chimpanzee Genome

- "Explaining Humans"
- Explaining Biomedical Differences between Humans and Chimpanzees
- Improving Understanding of the Human Genome
- Improving Care & Conservation of Chimpanzees

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"Initial Sequence of the Chimpanzee Genome and Comparison with the Human Genome"

The Chimpanzee Sequencing and Analysis Consortium

Tarjei S. Mikkelsen[1,2], LaDeana W. Hillier[3], Evan E. Eichler[4], Michael C. Zody[1], David B. Jaffe[1], Shiaw-Pyng Yang[3], Wolfgang Enard[5], Ines Hellman[5], Kerstin Lindblad-Toh[1], Tasha K. Altheide[6], Nicoletta Archidiacono[7], Peer Bork[8,9], Jonathan Butler[1], Jean L. Chang[1], Ze Cheng[4], Asif T. Chinwalla[3], Pieter deJong[10], Kimberley D. Delehaunty[3], Catrina C. Fronick[3], Lucinda L. Fulton[3], Yoav Gilad[11], Gustavo Glusman[12], Sante Gnerre[1], Tina A. Graves[3], Toshiyuki Hayakawa[6], Karen E. Hayden[13], Xiaoqiu Huang[14], Hongkai Ji[15], W. James Kent[16], Mary-Claire King[4], Edward J. Kulbokas III[1], Ming K. Lee[4], Ge Liu[13], Carlos Lopez-Otin[17], Kateryna D. Makova[18], Orna Man[19], Elaine R. Mardis[3], Evan Mauceli[1], Tracie L. Miner[3], William E. Nash[3], Joanne O. Nelson[3], Svante Pääbo[5], Nick J. Patterson[1], Craig S. Pohl[3], Katherine S. Pollard[16], Kay Prüfer[5], Xose S. Puente[17], David Reich[20,1], Mariano Rocchi[7], Kate Rosenbloom[16], Maryellen Ruvolo[21], Daniel J. Richter[1], Stephen F. Schaffner[1], Arian F.A. Smit[12], Scott M. Smith[3], Mikita Suyama[8], James Taylor[18], David Torrents[8], Eray Tuzun[4], Ajit Varki[6], Gloria Velasco[17], Mario Ventura[7], John W. Wallis[3], Michael C. Wendl[3], Richard K. Wilson[3], Eric S. Lander[1,22,23,24], & Robert H. Waterston[4].

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Some Major Findings from Sequencing the Chimp Genome

- **Confirmed ~1% Single-nucleotide differences (SNDs) : ~35 million.**
- **~29% of orthologous proteins identical. Typical protein differs by only 2 amino acids. Mean difference <1%**
- **Transposable Elements more active in humans.**
- **Insertion/Deletion (indel) events fewer in number than SNDs, but cause ~1.5% sequence in each species to be lineage-specific.**
- **Together, SNDs and indel differences comprise ~120 million bases - ~4% difference overall !**

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- Varki, A. and Nelson, D. Genomic Differences between Humans and Great Apes. *Annual Review of Anthropology*. 36:191-209, 2007.
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"Anthropogeny"— Explaining the Origin of Humans

Where did we come from?
How did we get here?

Anthropogeny : Investigation of the Origin of Humans

Oxford English Dictionary, 2006.

(1839 HOOPER *Med. Dict.*, the study of the generation of man).

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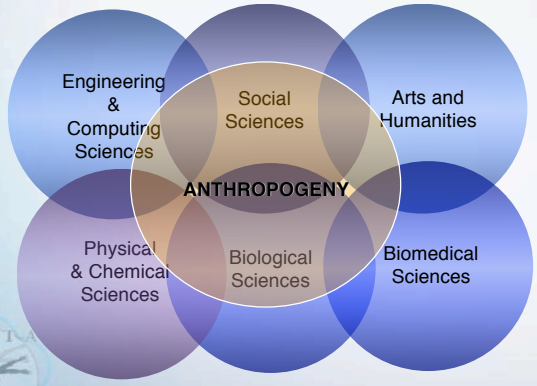
Pursuing Anthropogeny Involves Most Academic Disciplines



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Center for Academic Research and Training in Anthropogeny (CARTA)

"To explore and explain the origins of the human phenomenon"

Co-Directors

Ajit Varki, Professor of Medicine and Cellular and Molecular Medicine, UCSD
Fred H. Gage, Professor, Salk Institute & Adjunct Professor of Neurosciences, UCSD
Margaret Schoeninger, Professor and Past Chair of Anthropology, UCSD

Associate Director

Pascal Gagneux, Assistant Professor of Cellular & Molecular Medicine, UCSD

Management Services Officer

Linda G. Carlson

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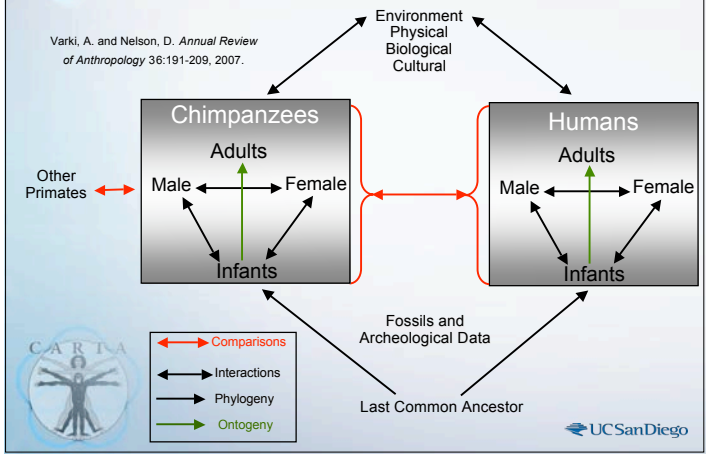
Explaining Human Origins: An Agenda for Anthropogeny



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Subject Areas of Relevance to Anthropogeny

- Primate Genetics and Evolution
- Paleoanthropology and Hominid Origins
- Mammalian and Primate Neurosciences
- Primate Biology and Medicine
- Language and Cognition
- Human and Primate Society and Culture
- Comparative Primate Reproductive Biology
- Geographic and Climatic factors in Hominid Evolution
- General Theories for Explaining Humans.

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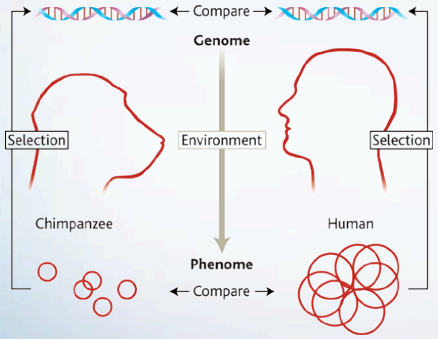
The Need for a Hominid "Phenome" Project



Varki, A et al. *Science* 282, 239-240 (1998)
McConkey E & Varki, A. *Science* 309:1499-1501 (2005)

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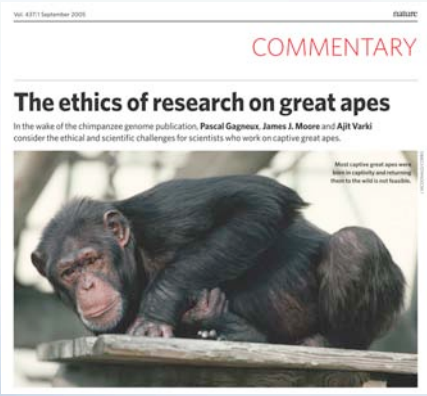
Ethical Considerations in Comparing Humans and "Great Apes"

Recommendation

Conduct research on "Great Apes" following principles as similar as possible to those accepted for human research


COMMENTARY

The ethics of research on great apes

In the wake of the chimpanzee genome publication, **Pascal Gagneux, James J. Moore** and **Ajit Varki** consider the ethical and scientific challenges for scientists who work on captive great apes.

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Examples of Features of Humans That Seem Different from the Other Hominids

Language and Culture
Large Brain Size relative to body
Longer Maximum Life Span
Fully Opposable Thumb
Descended Larynx (Adapted for Speech)
Difficult Childbirth
Prolonged Helplessness of the Young
Female Menopause and Grandmothering
Breasts Developed in Virgin Adult Female
Presence of Chin
Presence of Ear Lobes Loss of Body Hair
Poor Wound Healing
Decreased Skeletal Muscle Strength
Risk of Third Molar (Wisdom Tooth) Impaction
One Less Chromosome
etc., etc.,

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Some Phenotypic Traits for Comparison between Humans and "Great Apes"


Table 1. Some phenotypic traits of humans for comparison with those of great apes*

LIFE HISTORY
Secondary Altriciality
Helplessness of the Newborn
Prolonged Helplessness of Young
Extended Care of Young
Childhood
Adolescence
Age at First Reproduction
Longevity

REPRODUCTIVITY BIOLOGY
Concealed Ovulation
Virgin Breast Development
Female Pituitary Menopause
Placentophagy
Female Labia Majora
Vaginal Hymen
Baculum (Penis Bone)
Sperm Count
Copulatory Plug

EMBRYOLOGY
Early Fetal Wastage/Aneuploidy
Hydatiform Molar Pregnancy
Umbilical Cord Length

PREGNANCY/PARTURITION
Cephalo-pelvic Disproportion
Duration of Labor
Maternal Mortality in Childbirth
Pain During Childbirth
Need for Assistance with Childbirth
Neonatal Cephalhematoma

POSTNATAL DEVELOPMENT
Late Closure of Cranial Sutures
Duration of Infant Arousal
Inconsolable Infant Crying
Infant-Caregiver Attunement
Maternal-Infant Eye-To-Eye Gaze

ANATOMY
Sagittal Crest of Skull
Brow Ridge
Protuberantia Mentii (Chin)
Length of Sphenoid Sinus
Choroid Plexus Bizindl Bodies
Inner Ear Canal Orientation
Apical Phalangeal Tufts
Age of Pelvic Bone Fusion
Bone Cortex Thickness
Laryngeal Position
Pharyngeal Air Sacs
Ear Lobes
Sexual Body Size Dimorphism
Lacrimal Gland Structure
Visible Whites of the Eyes
Small/Large Intestine Length Ratio
Meningeal Artery Source

BIOMECHANICS
Bipedal Gait
Adductive Thumb
Skeletal Muscle Strength
Hand-Eye Coordination
Fine Motor Coordination

ORGAN PHYSIOLOGY
Aldosterone Response to Posture
Salt-Wasting Kidneys
Ability for Sustained Running
Voluntary Control of Breathing
Ability to Dive Underwater
Diving Reflex
Ability to Float/Swim
Emotion Lacrimation
Salt Content of Tears
Olfactory Sense

CELL BIOLOGY
No Differences Are Known?

BIOCHEMISTRY
Placental Alkaline Phosphatase
N-Glycolylneuraminic Acid Expression
Alpha 2-6-Linked Sialic Acid Expression

ENDOCRINOLOGY
Thyroid Hormone Metabolism

PHARMACOLOGY
Methylation of Inorganic Arsenic

ANATOMIC PATHOLOGY
Cortical Neurofibrillary Tangles

CLINICAL PATHOLOGY
Erythrocyte Sedimentation Rate
Serum Alkaline Phosphatase Level
RBC and Serum Folate
Serum Vitamin B12/B12 Binding
Total Leukocyte Count
Absolute Neutrophil Count
Absolute Lymphocyte Count

DENTAL BIOLOGY/DISEASE
Canine Tooth Diastema
Canine Tooth Dysmorphism
Tooth Enamel Thickness
Retromolar Gap
Third Molar Impaction
Dental Eruption Sequence/Timing

MEDICAL/SURGICAL DISEASES
HIV Progression to AIDS
P. falciparum Malaria
Viral Hepatitis B/C Complications
Influenza A Infection Severity
Incidence of Carcinomas
Hemorrhoids
Varicose Veins
Pelvic Phleboliths
Foamy Virus (Spumavirus) Infections
Sexually Transmitted Diseases

IMMUNOLOGY
Siglec-Sialic Acid on Macrophages

SKIN BIOLOGY AND DISEASE
Eyebrows
Eccrine Sweat Glands
Acne Vulgaris
Subcutaneous Fat
Body Lice

NUTRITION
Frugivory
Carnivory
Aquatic Foods
Underground Foods
Cooking

NEUROANATOMY
Relative Brain Size
Direct Cortical Projections
Relative Volume of Frontal Cortex
Relative Volume of Corpus Callosum
Relative Volume of Cerebellum
% of Brain Growth Complete at Birth
Rate of Postnatal Brain Growth

NEUROBIOLOGY
Population Distribution of Handedness
Postnatal Dendritic Growth
Postnatal Synapse Formation
Cortical Synapse Density
Cortical Neuron Density
Dendritic Per Neuron
Synapses Per Neuron
Adult Neurogenesis
Cingulate Cortical Spindle Neurons
Finger Tip Sensory Nerve Endings

NEUROCHEMISTRY
Brain Aromatization of Testosterone
Tyrosine Hydroxylase Heterogeneity

MENTAL DISEASE
Schizophrenia
Bipolar Psychosis
Autism
Suicide

BEHAVIOR
Control of Facial Expressions
Planning Ahead
Intentional Deception
Deliberately Delaying Gratification
Long-Range Transport of Materials
Secondary Tool-Making
Mechanical Multi-Tasking
Physical Abuse of the Young
Torture
Organized Warfare
Adult Play
Symbiotic Play
Abuse of Other Animals
Inter-Group Coalition Formation
Use of Containers
Care of Infirm and Elderly
Grandparenting
Home Base
Control of Fire
Food Preparation
Organized Gathering of Food
Domestication of Animals
Domestication of Plants
Altruistic Punishment
Peace-Making
Somnambulism
Mind-Altering Drug Use

COGNITIVE CAPACITY
Declarative Memory
Imitative Learning
Teaching
Symbolic Representation
Awareness of Death
Awareness of the Past
Awareness of the Future
Theory of Mind
Theory of Other Minds
Empathy
Numeracy

COMMUNICATION
"Parentese" Sounds
Infant "Protoconversations"
Gestural Communication
Symbolic Communication
Semantics
Grammar and Syntax
Recursion
Writing

SOCIAL ORGANIZATION
Institutions
Social Conventions
Governments
Enforcement Through Sanctions

CULTURE
Composition of Art
Composition of Music
Composition of Rhythms
Death Rituals
Clothing (Covering of Body Parts)
Rites of Passage
Genocide
Competitive Sports
Practicing of Skills
Physical Modifications of the Body
Inheritance of Resources and Status
Rhythmic Dance
Sculpture
Belief in Supernatural/Religion
Body Adornment
Childbirth Customs
Sexual Intercourse in Private
Gift-Giving
Hospitality
Interweaving (e.g., weaving)
Meal Times
Poetry
Property
Construction of Shelters
Taboos
Taxonomy of Species
Trade
Measurement of Time
Weapons
Toys

Varki, A. & Altheide, T.K.: ***Genome Research.*** 15:1746-1758, 2005

Museum of Comparative Anthropogeny (MOCA)
(live in 2009)

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"The Baldwin Effect"
Baldwin (1896) - Morgan (1896) - Osborne (1896)

- **A century of controversy about exact definition of the Baldwin effect and its importance to evolution.**
- **The Baldwin effect considers the costs and benefits of learning, during evolution.**
- **Learning by individuals with organismal plasticity might explain evolutionary phenomena that superficially seem to involve Lamarckian inheritance of acquired characteristics.**
- **Abilities that require learning could be replaced by evolution of genetically determined systems that no longer require that learning.**
- **Behaviors initially learned due to plasticity would thus become instinctive in later generations, via new mutations or by 'genetic assimilation' of pre-existing genomic variability.**

From Varki, A. Geschwind D.H. and Eichler E.E.. *Nature Reviews 9: 749-763, 2008*

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"The Baldwin Effect"

- **Some authors suggest roles for Baldwinian processes in evolution of uniquely human features, such as language abilities.**
- **For example, Deacon's proposal is that complexes of genes can be integrated into functional groups as a result of environmental changes that mask and unmask selection pressures.**

HOWEVER

- **If a learned behavior fails to become genetically "hard-wired", it should disappear, as there can a significant cost to the individuals who display the phenotypic plasticity to be able to learn, and the risk of dangerous mistakes.**

From Varki, A. Geschwind D.H. and Eichler E.E.. *Nature Reviews 9: 749-763, 2008*

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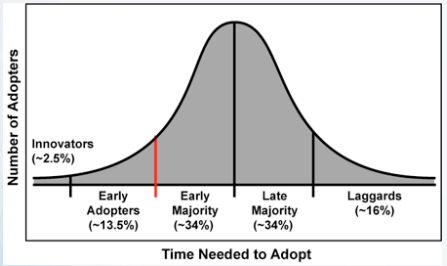
Ryan, B. and N.C. Gross. 1943. The diffusion of hybrid seed corn in two Iowa communities. *Rural Sociology* 8(1-4) 15-24.



Rogers, E.M. 1995. *Diffusion of Innovations.* 4th ed. New York: Free Press

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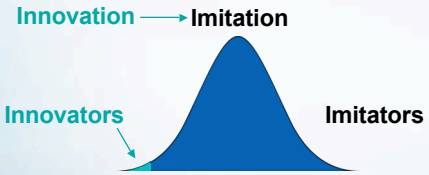
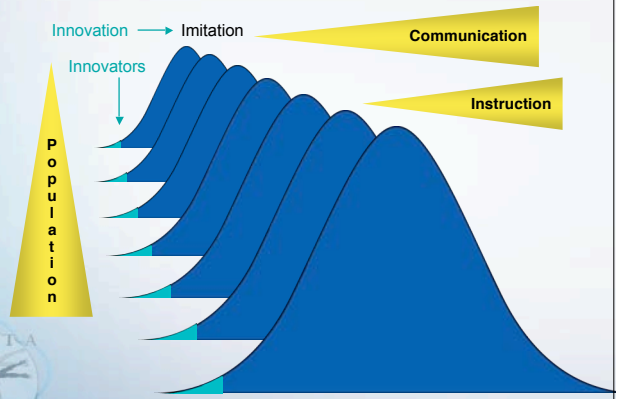
Roles of Innovation and Imitation In Human Cultural Advances



Amplifiers of Human Cultural Advances: Population, Communication and Instruction



Have human genomes escaped the need for Baldwinian hardwiring of learned behaviors?

- Learned human behaviors can be carried for many generations without becoming hard-wired, e.g., some long-isolated and small populations such as Tasmanian Aboriginals, partially or completely lost many ancestral material practices, such as the making of fire, and exploitation of certain marine food resources
- Apparently, even a long-standing learned behavior such as the generation of fire never became genetically hard-wired, and remained dependent on intergenerational transfer by observation, learning and/or teaching.
- Perhaps humans have escaped the need for the second step of the Baldwin effect that genetically hard-wires behaviors, and instead utilize extended developmental plasticity to invent, disseminate, improve and culturally transmit complex behaviors over many generations, without the need to hardwire them?
- Of course, this advantage comes with great risk, as failure of cultural transmission can then result in permanent loss of a useful behavior

From Varki, A. Geschwind D.H. and Eichler E.E.. *Nature Reviews 9: 749-763, 2008*

Are human genomes escaping from Darwinian natural selection and Baldwinian fixation of learned behaviours?

- The phenotype of animals is affected by the external and internal environment, but behavioral responses are usually hard-wired and stereotyped.
- Warm-blooded animals show greater impact of postnatal care and influence of learning from prior generation, with humans being at extreme end of this trend.
- In mammals, behavior can have profound effects on the genome and phenotype by affecting the functional output of the genome either directly or indirectly.
- With hominids in general, and humans in particular, a confounding issue is culture. Many specific behaviors and artefacts are not hard-wired, but handed down by observation and, in the case of humans, by teaching, learning, conscious choice, and even by imposition through cultural practices or institutions.
- Even stereotyped mammalian behaviors considered crucial for species survival, such as effective mothering, seem to require observational learning in hominids.
- Hominids in general and humans in particular, may have partially escaped from Darwinian control of aspects of the genome - and humans may have even escaped the final stage of Baldwinian genetic hard-wiring of long-standing species-specific learned behaviors.

From Varki, A. Geschwind D.H. and Eichler E.E.. *Nature Reviews 9: 749-763, 2008*

Are large-scale genomic changes accumulating more rapidly in humans?

- Interspersed segmental duplications and deletions (SDs) and Copy Number variations (CNVs) are prominent in hominid genomes.
- Trend: human =? chimpanzee > macaque > rodent > chicken > insect >worm.
- Data too limited to ascertain if humans are accumulating these large-scale genomic variations at a faster rate than other hominids.
- Diversity may be higher in humans, despite the small population size.
- There could also be fitness benefits associated with the propensity to generate and tolerate more CNVs, e.g., the expansion of amylase gene copies in humans
- CNVs are now recognized as significant causes of neuropsychiatric conditions
- Are they are more common in more subtle forms of human-specific disorders related to brain function and social interaction?
- Perhaps large interspersed SDs are commonest in hominids, because they are better tolerated, due to buffering by the increasing dependence of important functions on learned rather than hard-wired behavior?
- Individuals with variant genomes might survive and even be beneficial to a human population by contributing to plasticity that is adaptive for the community at large

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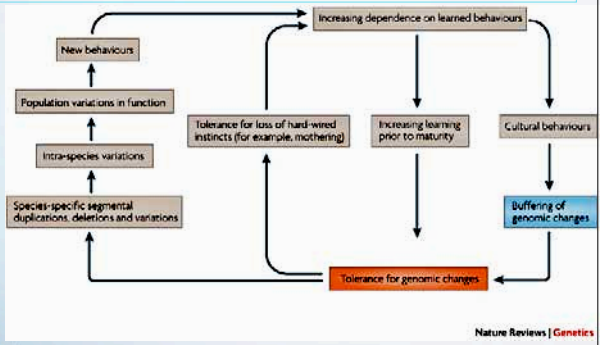
Are human genomes escaping from Darwinian natural selection and Baldwinian secondary fixation of learned behaviours?



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"Wallace's Conundrum"

- Alfred Russel Wallace was the co-discoverer of evolution by natural selection.
- But, he lost favor with the scientific community, in part because he questioned whether natural selection alone could account for the evolution of human mind:

- ***"I do not consider that all nature can be explained on the principles of which I am so ardent an advocate; and that I am now myself going to state objections, and to place limits, to the power of 'natural selection'. How could 'natural selection', or survival of the fittest in the struggle for existence, at all favor the development of mental powers so entirely removed from the material necessities of savage men, and which even now, with our comparatively high civilization, are, in their farthest developments, in advance of the age, and appear to have relation rather to the future of the race than to its actual status?"***

(Wallace, A. R. in Contributions to the Theory of Natural Selection. A Series of Essays, Macmillan,London, 1870).

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A-Z Examples of Human Uniqueness

Exercise: Take a dictionary and check entries under each letter from the top. Stop when you reach the first one you think is unique to humans

Abbreviating
Bag-making
Calculus
Darts
Ear-piercing
Face-lifting
Gambling
Hacking(computers)
Illustrating
Jet-sking
Karate
Lacrosse
Machining
Nailing (wood)
Operating (Surgery)
Panning for gold
Quilting
Racing (organized)
Sacrificing (others)
Tagging (systematic marking)
Umpiring
Vacationing
Wage-earning
Xeroxing
Yachting
Zeroing

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Examples of Human Uniqueness starting with letter S

Exercise: Take a dictionary and scan all entries under the letter S.
Record all the ones that you think are unique to humans.

Sacrificing
Sack-making
Saddling
Sailing
Salt-making
Saluting
Sand-castle building
Sandwich-making
Sawing (wood)
Saxaphone playing
Schedule making
Schooling
Science
Scoring (points)
Scuba-diving
Sculling
Sculpting
Sealing (wax)
Selling
Semen banking
Serum collecting
Sewing
Shampooing
Shaving

Ship-building
Shooting
Shopping
Signatures
Silver (trading etc.)
Singing (e.g., opera)
Skating
Sketching
Skiing
Skinning
Skipping
Sky-diving
Slang words
Slavery
Sledding
Sleighing
Slimming
Smeltering
Snowball fighting
Snuff-taking
Soaping
Sobbing
Soccer
Soliciting

Sowing (seeds)
Soup making
Spaying
Spear-throwing
Spelunking
Spice collection
Spending _____
_____
_____
_____
_____
Steel production
Stitching
Story-telling
Sun-tanning
Surfing

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"Wallace's Conundrum" (Continued)

- **Wallace was criticized for apparently invoking spiritual explanations. But his point remains valid, that it is difficult to explain how natural selection selected ahead of time for the capabilities of the human mind, which we continue to explore today.**
- **Explanations based on "exaptation" seem inadequate, as most of what the human mind routinely does today did not even exist at the time it was originally evolving.**
- **Experts in human evolution/cognition have yet to provide a satisfactory explanation.**
- **Thus, 'Wallace's Conundrum' remains unresolved: *"...that the same law which appears to have sufficed for the development of animals, has been alone the cause of man's superior mental nature,... will, I have no doubt, be overruled and explained away. But I venture to think they will nevertheless maintain their ground, and that they can only be met by the discovery of new facts or new laws, of a nature very different from any yet known to us.*"**
  (Wallace, A. R. in Contributions to the Theory of Natural Selection. A Series of Essays, Macmillan, London, 1870).
- **Is this 'Wallacean' evolutionary mechanism related to our suggestion - that aspects of human uniqueness arose following relaxation of selection for maintenance of genome integrity, allowing partially escape from Darwinian and Baldwinian selection, and more dependence on inter-generational cultural transfer?**

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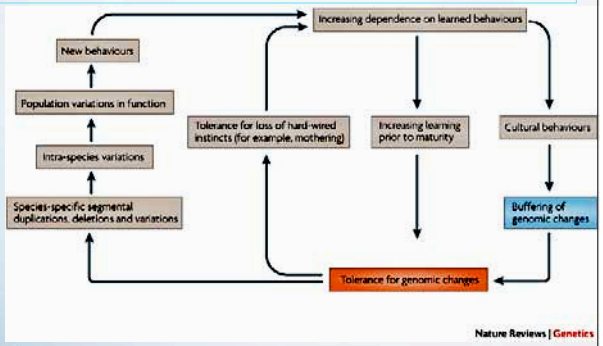

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