"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

Suggesting Reading

• Varki, A., Multiple Changes in Sialic Acid Biology During Human Evolution Glycoconjugate Journal. (in press).

The “Central Dogma” of Molecular Biology
Francis Crick, 1958

DNA → RNA → PROTEIN
The “DNA-centric” View of Life

DNA → RNA → PROTEIN → ? → CELL → ? → ORGANISM

DNA → ORGANISM

An Example of the Media and Public Penance for Genetic Determinism

First Printing

Second Printing

Inadequacies of a “DNA-Centric” View of Life

The “Central Dogma” of Molecular Biology
Francis Crick, 1958

DNA → RNA → PROTEIN

“Biology hasn’t got any (absolute) Laws - Only Gadgets”
Francis Crick, 2002

DNA

ORGANISM

BIOLICAL ENVIRONMENT

CULTURAL ENVIRONMENT

PHYSICAL ENVIRONMENT
Humans Use Culture to Control the Environment

A More Complete View of Biology

Electron Micrograph of a Human Lymphocyte

Sialic Acids on Cell Surface and Secreted Molecules

Human-Specific Loss of Neu5Gc Sialic Acid Expression?

Precise Timing Uncertain

Millions of Years Ago

Neu5Ac

Neu5Gc

Human

Old World Monkey

Rat

Mouse

Dog

Cow

A Major Difference in Cell Surface Sialic Acids

Humans

Other Hominids

When did it happen?

What are the Consequences for Human Evolution?

What are the Implications for "Human-Specific" Diseases?

A Difference in Sialic Acids between Humans & "Great Apes"

CMAH gene Mutation Causing loss Of Neu5Gc

Hominids

Elaine Muchmore Sandra Diaz

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

<table>
<thead>
<tr>
<th>MEDICAL CONDITION</th>
<th>HUMANS</th>
<th>&quot;GREAT APE&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV infection progression to AIDS</td>
<td>Common</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Hepatitis B/C late complications</td>
<td>Can be Severe</td>
<td>Mild</td>
</tr>
<tr>
<td>P. falciparum Malaria</td>
<td>Susceptive</td>
<td>Resistant</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>Common</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Human Influenza A Susceptibility</td>
<td>Can be Severe</td>
<td>Often Mild</td>
</tr>
<tr>
<td>Alzheimer's Disease Pathology</td>
<td>Complete</td>
<td>No Tangles</td>
</tr>
<tr>
<td>Epithelial Cancers</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Atherosclerotic Stroke s</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Hydatiform Molar Pregnancy</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Bronchial Asthma</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Toxemia of Pregnancy</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Autoimmune Diseases</td>
<td>Common</td>
<td>Rare</td>
</tr>
</tbody>
</table>

Varki, A. Genome Research. 10:1065-1070, 2000
Varki, A. & Altheide, T.K.; Genome Research. 15:1746-1758, 2005
Proposed Evolutionary Scenario for Multiple Human-Specific Changes in Sialic Acid Biology

Suggesting Reading


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
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!

“Anthropogeny”— Explaining the Origin of Humans

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

Anthropogeny: Investigation of the Origin of Humans


(1839 HOOPER Med. Dict., the study of the generation of man.)
Pursuing Anthropogeny Involves Most Academic Disciplines

Arts and Humanities
Engineering & Computing Sciences
Physical & Chemical Sciences
Biomedical Sciences
Biological Sciences
Social Sciences

ANTHROPOGENY

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

Explaining Human Origins: An Agenda for Anthropogeny


Environment
Physical
Biological
Cultural

Chimpanzees
Adults
Male
Female
Infants

Other Primates

Humans
Adults
Male
Female
Infants

Comparisons
Interactions
Phylogeny
Ontogeny

Last Common Ancestor

Fossils and Archeological Data

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.
The Need for a Hominid “Phenome” Project

Recommendation
Conduct research on “Great Apes” following principles as similar as possible to those accepted for human research

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
- 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.

Some Phenotypic Traits for Comparison between Humans and “Great Apes”

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

- 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.


“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 be a significant cost to the individuals who display the phenotypic plasticity to be able to learn, and the risk of dangerous mistakes.


Roles of Innovation and Imitation In Human Cultural Advances

Innovators → Innovation → Imitators → Imitators

Amplifiers of Human Cultural Advances: Population, Communication and Instruction

Innovation → Imitation

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.


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.

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 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.

"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?"  

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
- Cart
- Ear-piercing
- Face-lifting
- Gambling
- Hacking (computers)
- Illustrating
- Jet-skiing
- 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
### 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.

<table>
<thead>
<tr>
<th>Example</th>
<th>Example</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sacrificing</td>
<td>Ship-building</td>
<td>Sawing (seeds)</td>
</tr>
<tr>
<td>Sack-making</td>
<td>Shopping</td>
<td>Soap making</td>
</tr>
<tr>
<td>Sadding</td>
<td>Shopping</td>
<td>Spaying</td>
</tr>
<tr>
<td>Sailing</td>
<td>Signatures</td>
<td>Spear-throwing</td>
</tr>
<tr>
<td>Salt-making</td>
<td>Silver (trading etc.)</td>
<td>Spelunking</td>
</tr>
<tr>
<td>Saluting</td>
<td>Singing (e.g., opera)</td>
<td>Spice collection</td>
</tr>
<tr>
<td>Sand-castle building</td>
<td>Sketching</td>
<td>Spending</td>
</tr>
<tr>
<td>Sandwich-making</td>
<td>Skilling</td>
<td>Steel production</td>
</tr>
<tr>
<td>Sawing (wood)</td>
<td>Slaying</td>
<td>Slogging</td>
</tr>
<tr>
<td>Saxophone playing</td>
<td>Science</td>
<td>Snooping</td>
</tr>
<tr>
<td>Schedule making</td>
<td>Scoring (points)</td>
<td>Soaping</td>
</tr>
<tr>
<td>Schooling</td>
<td>Science</td>
<td>Soaping</td>
</tr>
<tr>
<td>Science</td>
<td>Scoring (points)</td>
<td>Soaping</td>
</tr>
<tr>
<td>Scoring (points)</td>
<td>Science</td>
<td>Soaping</td>
</tr>
<tr>
<td>Scalping</td>
<td>Science</td>
<td>Soaping</td>
</tr>
<tr>
<td>Scouring</td>
<td>Science</td>
<td>Soaping</td>
</tr>
<tr>
<td>Sculling</td>
<td>Science</td>
<td>Soaping</td>
</tr>
<tr>
<td>Sealing (wax)</td>
<td>Science</td>
<td>Soaping</td>
</tr>
<tr>
<td>Selling</td>
<td>Science</td>
<td>Soaping</td>
</tr>
<tr>
<td>Seamen banking</td>
<td>Science</td>
<td>Soaping</td>
</tr>
<tr>
<td>Serum collecting</td>
<td>Science</td>
<td>Soaping</td>
</tr>
<tr>
<td>Sewing</td>
<td>Science</td>
<td>Soaping</td>
</tr>
<tr>
<td>Shaving</td>
<td>Science</td>
<td>Soaping</td>
</tr>
<tr>
<td>Shampooing</td>
<td>Science</td>
<td>Soaping</td>
</tr>
<tr>
<td>Shaving</td>
<td>Science</td>
<td>Soaping</td>
</tr>
</tbody>
</table>

**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.”
- 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?


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

[Diagram showing the process]