Evolution at Two Levels in Humans and Chimpanzees

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Background:

Mary-Claire King:

Research relevance:

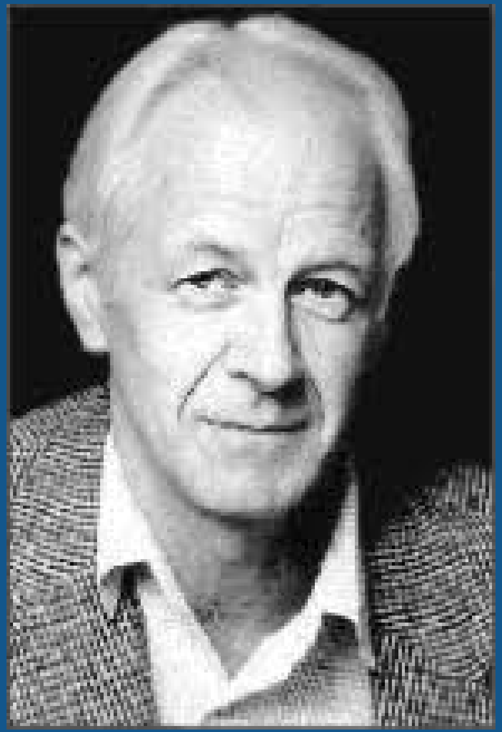
- Inspired to study genetics after losing a friend to cancer as a teen.
- Proved breast cancer can be **hereditary** (1990).
- Discovered the **BRCA1 gene** and helped identify **BRCA2.**
- Predicted **humans & chimpanzees are ~99% genetically identical (**1975).
- Later **confirmed by human & chimp genome sequencing.**
- Shows evolution is strongly influenced by **regulatory mutations.**

Background:

Allen Charles Wilson:

Research relevance:

- Allan Wilson, professor at University of California, Berkeley.
- Co-developed the **molecular clock** to date evolutionary splits.
- With Mary-Claire King showed **humans & chimps are >99% genetically similar.**
- Argued differences are due to **gene regulation, not new genes.**
- Led **mtDNA research → "Mitochondrial Eve" (African origin of humans)**



Molecular Biology as a “Genetic Yardstick”

- Molecular biology allowed **objective measurement of genetic distance.**
- Compare species using **proteins and DNA.**
- Humans and chimpanzees are the **most completely compared pair.**
- Lets us test: **molecular vs organismal differences.**

The Paradox: Very Similar Genes, Very Different Organisms

- All molecular methods show **very small genetic distance**
- Some human & ape proteins are **nearly identical**
- Level of similarity ≈ **sibling species in other organisms**
- **Paradox:** big physical & behavioural differences remain
- Differences are mainly due to **gene regulation**
- **Not** large changes in **protein-coding sequences**
- **Regulatory mutations** drive major evolutionary change

How Human and Chimp Genes were Compared

- Compared **homologous proteins & DNA**
- Three protein methods:
- **Amino acid sequencing**
- **Immunological (micro complement fixation)**
- **Electrophoresis**
- Multiple independent methods → **reliable estimate of similarity**

Many Proteins are Identical or Nearly Identical

- Several proteins are **identical** (e.g., hemoglobin chains, cytochrome c)
- Others differ by only **1 amino acid**
- Differences often = **single DNA base change**

Table 1, and Overall Result: ~99% Protein Similarity

- Average difference ≈ **7 amino acids per 1000 → >99% sequence identity**
- Confirmed by **electrophoretic allele comparisons**
- Applies to both **intracellular & secreted proteins**

Table 1. Differences in amino acid sequences of human and chimpanzee polypeptides. Lysozyme, carbonic anhydrase, albumin, and transferrin have been compared immunologically by the microcomplement fixation technique. Amino acid sequences have been determined for the other proteins. Numbers in parentheses indicate references for each protein.

Protein	Amino acid differences	Amino acid sites
Fibrinopeptides A and B (*3*)	0	30
Cytochrome c (*4*)	0	104
Lysozyme (*13*)	~0	130
Hemoglobin α (*4*)	0	141
Hemoglobin β (*4*)	0	146
Hemoglobin $^{A}\gamma$ (*5, 6*)	0	146
Hemoglobin $^{G}\gamma$ (*5, 6*)	0	146
Hemoglobin δ (*5, 8*)	1	146
Myoglobin (*7*)	1	153
Carbonic anhydrase (*4, 12*)	~3	264
Serum albumin (*10*)	~6	580
Transferrin (*11*)	~8	647
Total	~19	2633

$$\frac{19 \times 1000}{2633} = 7.2$$

Figure 1: Electrophoresis of plasma proteins

- Separates **human vs chimp plasma proteins**
- Band position = **different protein forms**
- Most bands **align in the same position**
- Shows very high allele similarity

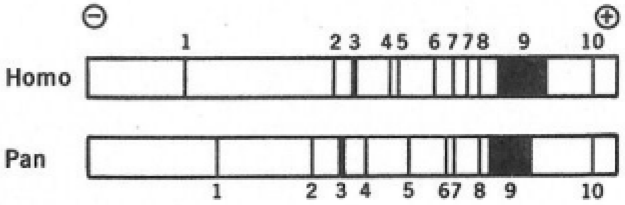


Fig. 1. Separation of human and chimpanzee plasma proteins by acrylamide electrophoresis at *p*H 8.9. The proteins are: 1, α_2-macroglobulin; 2, third component of complement; 3, transferrin; 4, haptoglobin; 5, ceruloplasmin; 6, α_{2HS}-glycoprotein; 7, Gc-globulins; 8, α_1-antitrypsin; 9, albumin; and 10, α_1-acid glycoprotein. The chimpanzee plasma has transferrin genotype *Pan* CC; the human plasma has transferrin genotype *Homo* CC and haptoglobin genotype 1-1. The direction of migration is from left to right.

Table 2: Electrophoretic allele comparison

- Compared **44 protein-coding loci**
- Measured **probability of identical alleles (S)**
- Average identity = **0.52 per** locus → **Very high genetic similarity**

$$\bar{S} = \frac{1}{L}(S_1 + S_2 + \ldots + S_L) = 0.52$$

$$S_i = \sum_{j=1}^{A_i} x_{ij} y_{ij}$$

$$P_0 = 0.52 = \frac{(mc)^0 e^{-mc}}{0!} = e^{-mc}$$

$$P_r = \frac{(mc)^r e^{-mc}}{r!}$$

From electrophoresis → Number of Amino Acid Differences

- Only **charged amino acid changes are detectable**
- Detectable proportion **(c) ≈ 0.27**
- Used **Poisson model** for mutations
- Estimated **2.41 differences per protein**

$$m = 0.65/0.27 = 2.41$$

Converting to % similarity

- Average protein length **= 293 amino acids**
- → **~8.2 differences per 1000 amino acids = >99% identical**
- Matches **Table 1 estimate**

$$\frac{2.41 \times 1000}{293} = 8.2$$

DNA hybridization results

- DNA difference ≈ **~1.1%**
- **≈ 33 base changes per 1000 amino acids**
- More DNA change than protein change

Figure 2: Distribution of allele similarity across loci

- Shows probability of identity (S) for 43 proteins
- Most loci have high similarity values
- Few loci show low similarity
- Overall → humans & chimps genetically very close

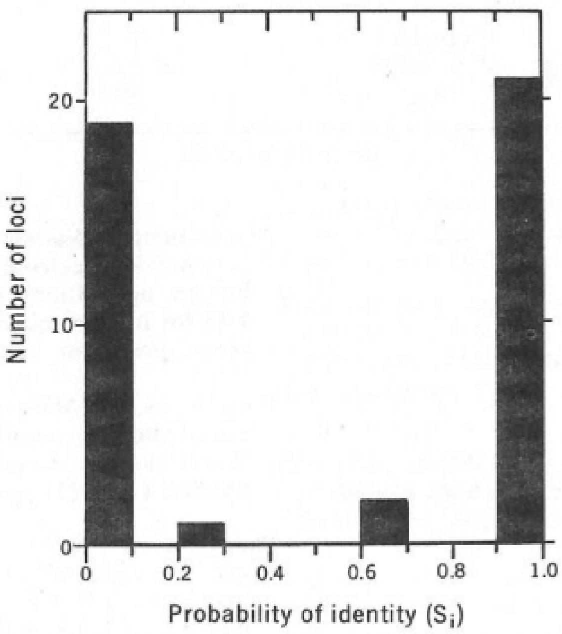


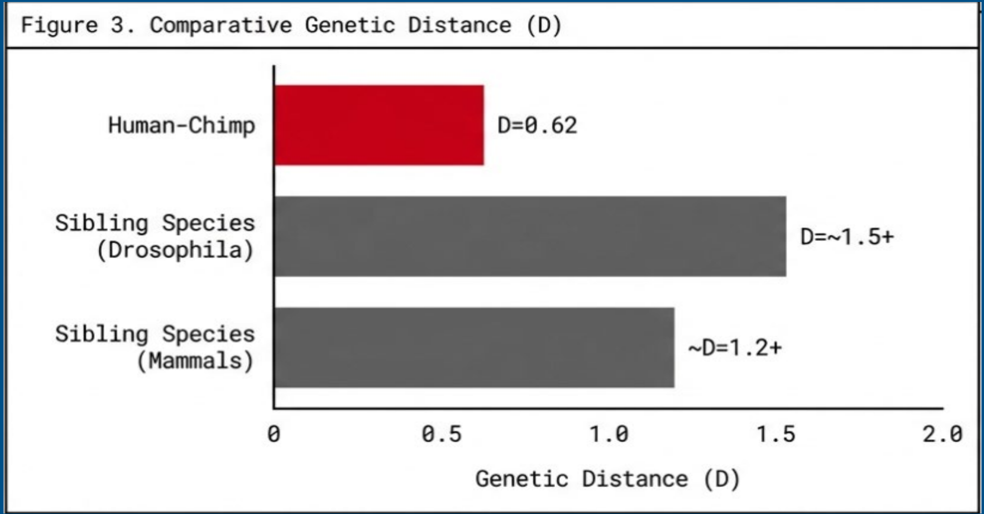
Fig. 2. Electrophoretic comparison of 43 proteins from humans and chimpanzees. The probability of identity (S_i) represents the likelihood that at locus i, human and chimpanzee alleles will appear electro- [illegible]lly identical.

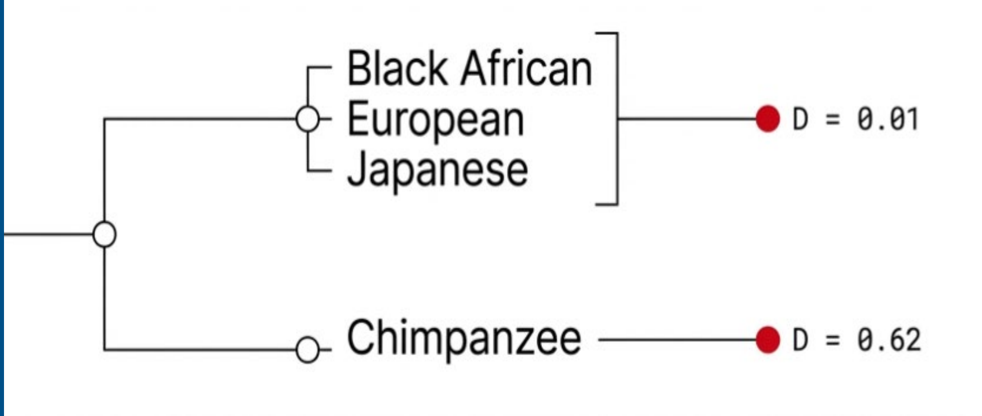
Why DNA shows more differences and the big takeaways

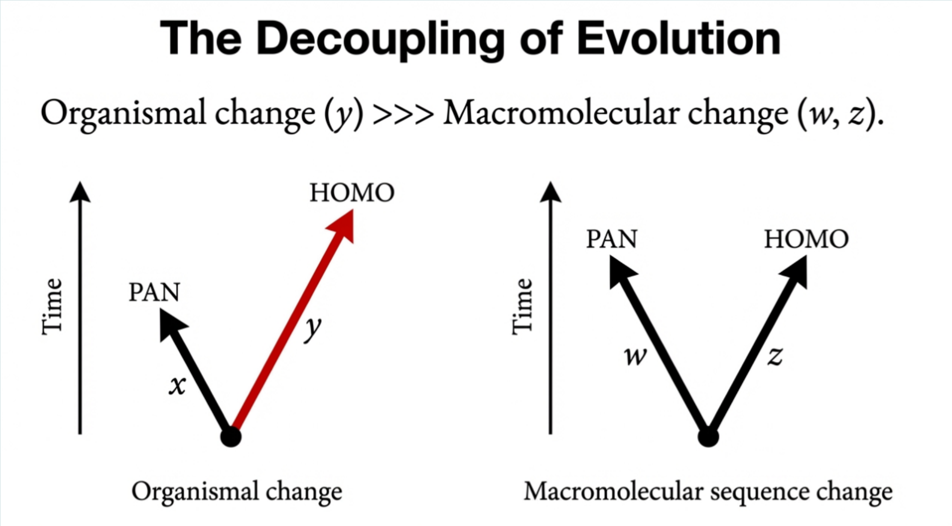
- Many changes in **non-coding DNA**
- Functional proteins are **more conserved**
- Independent math → **same 99% result**
- Humans & chimps = **molecularly extremely close**
- Difference **too small to explain anatomy**

Closer Than “Siblings”!!

- Human–chimp genetic distance is very small (Nei’s D = 0.62) compared to other sibling species.
- Human populations are nearly identical genetically (Nei’s D = 0.01).
- Human–chimp distance is still low for separate species.
- All humans are equally related to chimpanzees.







- Humans (Homo) and chimpanzees (Pan) have experienced very different levels of organismal (physical/anatomical) change since their split.
- Humans show much greater visible evolutionary change, while chimps changed less in body form.
- Molecular level (DNA and proteins), both lineages have changed at similar rates over time.
- Morphological evolution and molecular evolution are independent, with major physical differences arising from small genetic or regulatory changes.

The Regulatory Hypothesis

The "Missing Link"

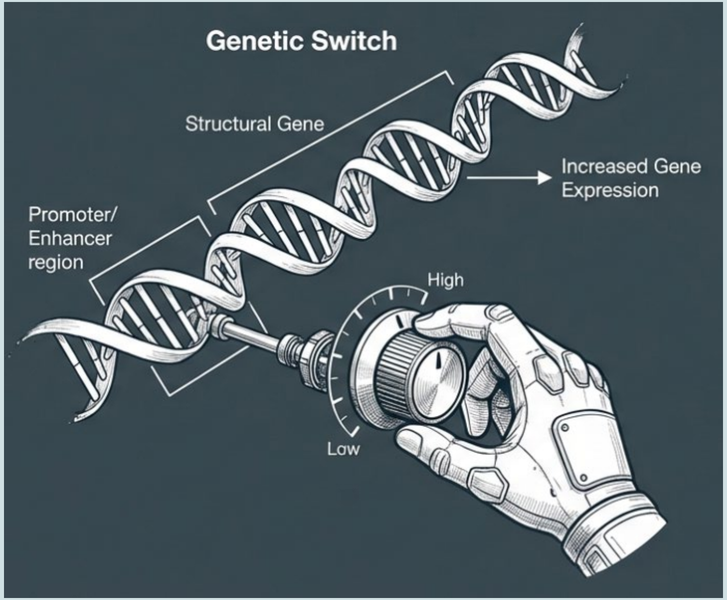
- The Paradox: Humans and chimps have high biochemical similarity (>99%) but massive organismal differences.
- Structural Limitation: Structural genes are too similar to account for differences in anatomy and behavior.
- The Conclusion: Human uniqueness arises from how genes are used, not the creation of entirely new genes.

Regulatory Mutations

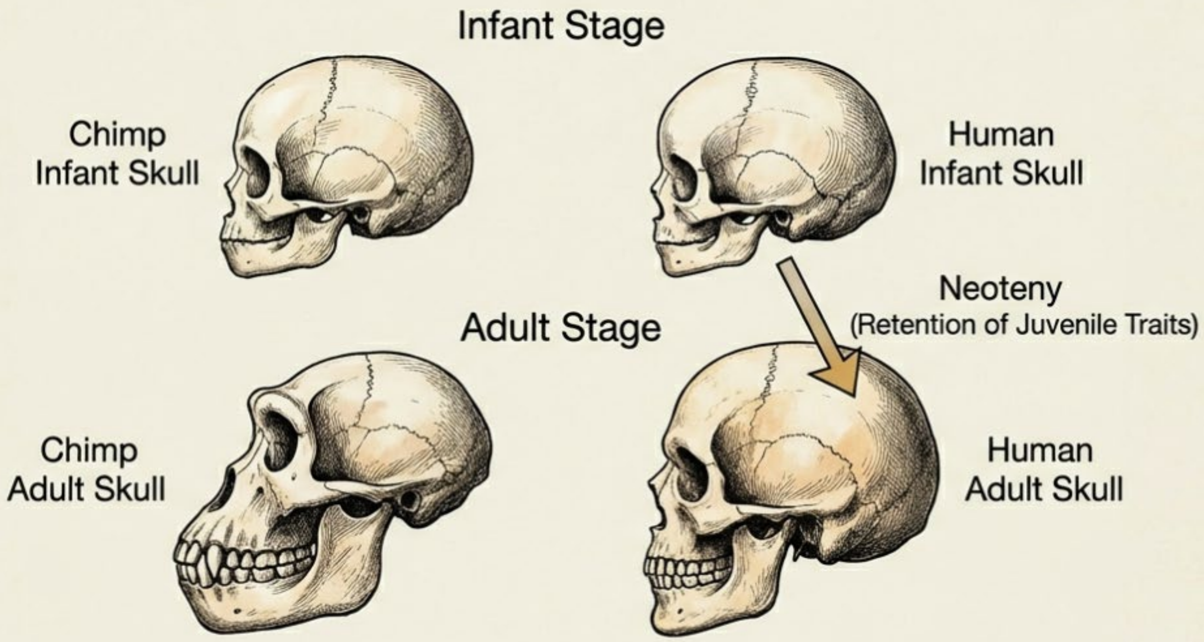
- Function: They control the timing, location, and levels of gene expression.
- Location: Changes occur in non-coding DNA like promoters and enhancers.
- Flexibility: These mutations are less likely to be lethal than protein-altering ones.
- Amplification: Small shifts in embryonic expression lead to major body and brain changes.

Chromosomal Rearrangements

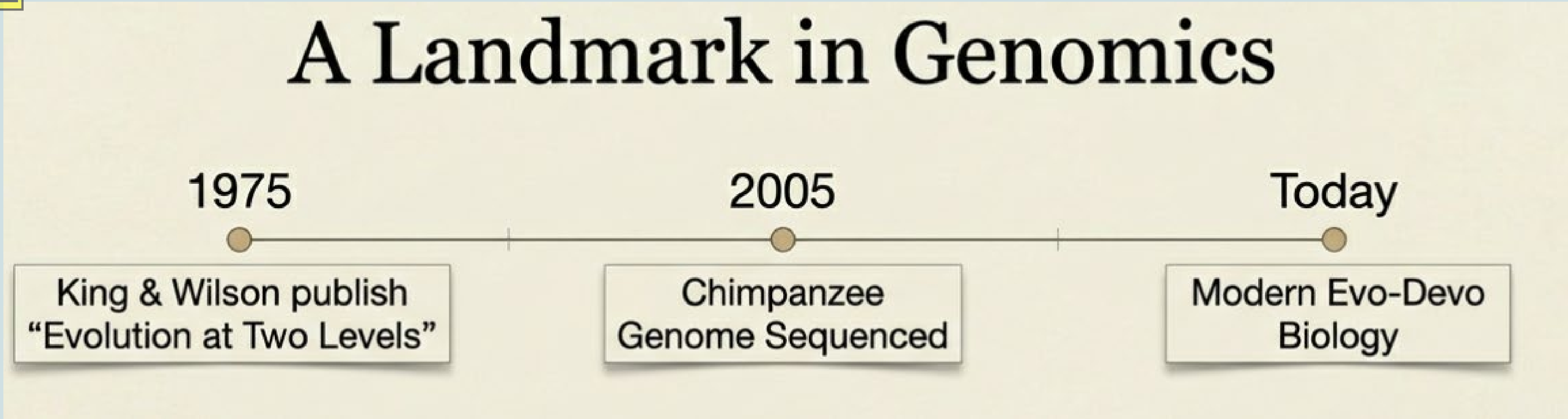
- Inversions: Humans and chimpanzees differ by 10 chromosomal inversions.
- Fusion: Humans have 46 chromosomes due to a fusion, while chimps have 48.
- Regulatory Impact: Large-scale rearrangements can shift how gene networks are organized.



A ‘Tweaked’ Developmental Program



- Regulatory mutations act strongly during embryogenesis.
- Small inputs in timing results into massive output in anatomy.



- The Facts: Humans and chimps are > 99% genetically identical in structural genes.
- The Insight: Molecular and Organismal evolution happens at different rates.
- The Legacy: Biological complexities arises from “How” genes are used, not just which genes are present.

Conclusion

- The Regulatory Driver: Human uniqueness is primarily the result of regulatory evolution, which alters how genes are expressed rather than changing the proteins themselves.
- Evolutionary Disconnect: Macromolecular evolution at the protein level does not account for the dramatic morphological and behavioral divergence between the species.
- Developmental Impact: These regulatory shifts are amplified during embryonic development, leading to complex traits like advanced cognition and brain connectivity.

References

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