

COMPARING MITOCHONDRIAL DNA ACROSS SPECIES

& MUTATIONS IN HUMAN MITOCHONDRIAL
PHYLOGENY

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OEB 275br
Module Presentation

NUCLEOTIDE ONLINE DATABASES

- A prime tool for analyzing molecular data
- Accessible from anywhere
- Incorporate archeological specimens (Neanderthal data)

MODULE OBJECTIVES

- Students will learn how to use online databases for gather molecular data
- Will learn how to analyze molecular data with phylogenetics (creating gene trees and species trees)
- Finally, will use comparative genomics to address human disease. Where do these alleles arise?

ONLINE DATABASES/PROGRAMS

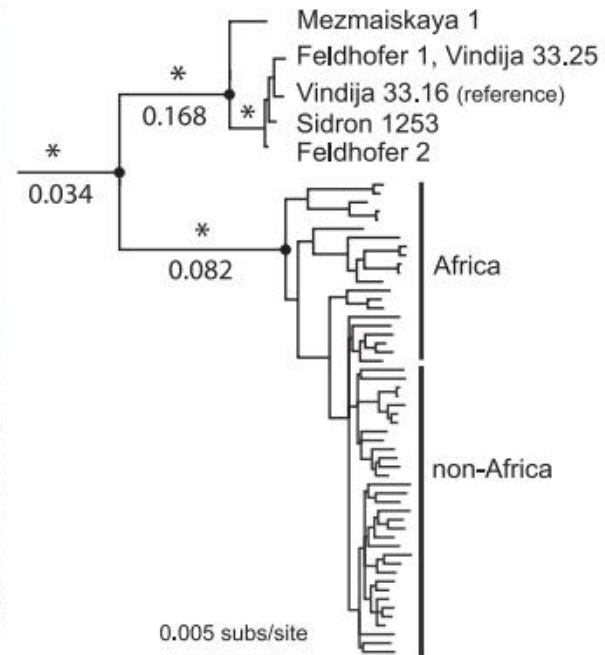
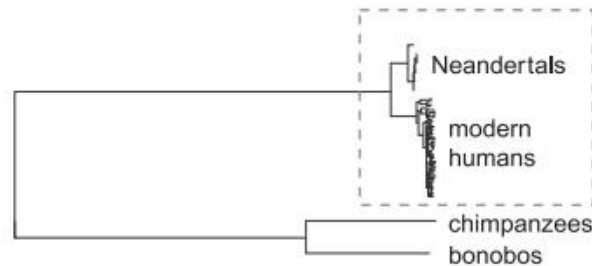
- Ensembl – gather Human mtDNA, orthologs
- BLAST- find Neandertal data
- TranslatorX – align sequences
- SeaView – compare sequences
- Mitomap – disease mutations in mtDNA
- PAUP – builds phylogenetic trees, analysis
- Fig Tree – builds phylogenetics trees

NEANDERTHAL DATA

- Data found using BLAST search

Targeted Retrieval and Analysis of Five Neandertal mtDNA Genomes

Adrian W. Briggs,^{1*} Jeffrey M. Good,¹ Richard E. Green,¹ Johannes Krause,¹ Tomislav Maricic,¹ Udo Stenzel,¹ Carles Lalueza-Fox,² Pavao Rudan,³ Dejana Brajković,⁴ Željko Kučan,³ Ivan Gušić,³ Ralf Schmitz,^{5,6} Vladimir B. Doronichev,⁷ Liubov V. Golovanova,⁷ Marco de la Rasilla,⁸ Javier Fortea,⁸ Antonio Rosas,⁹ Svante Pääbo¹



MITOCHONDRIAL GENES

- Looking at ATP6, ATP8, COX1, COX2, COX3, CYB, ND2, ND3

S. DiMauro

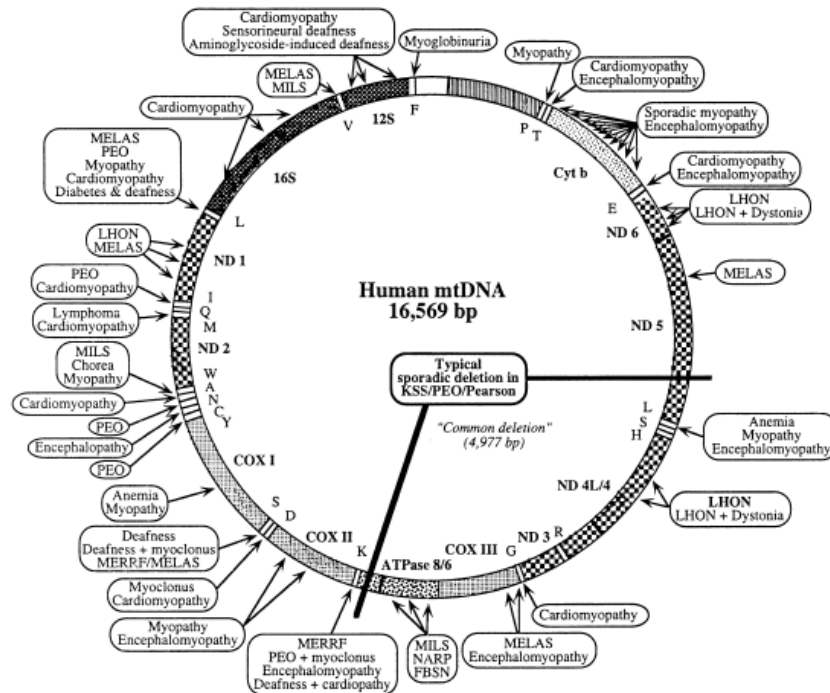
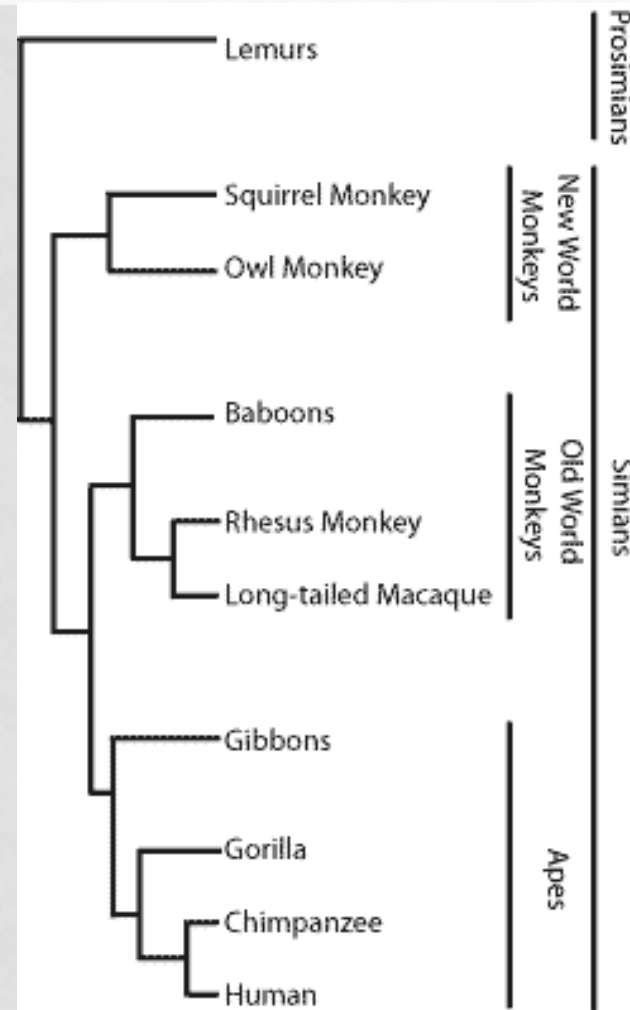


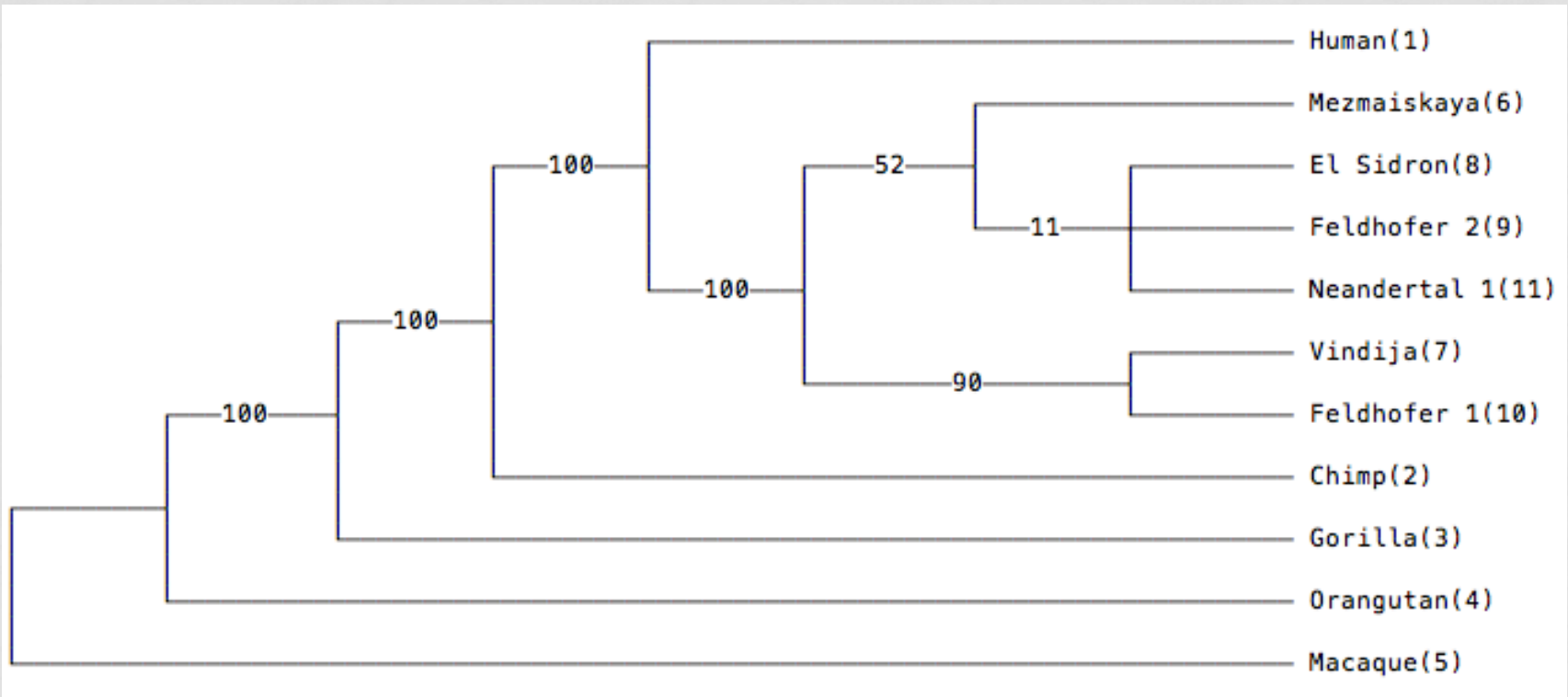
Figure 1. Morbidity map of the human mitochondrial genome as of January 1, 2000. The map of the 16.5 kb mtDNA shows differently shaded areas representing the protein coding genes for seven subunits of complex I (ND), the three subunits of cytochrome oxidase (COX), cytochrome *b* (Cyt *b*), and the two subunits of ATP synthetase (ATPase 6 and 8), the 12S and 16S ribosomal RNA (rRNA), and the 22 transfer RNAs (tRNA) identified by one-letter codes for the corresponding amino acids.

ORTHOLOGS

- Primates
 - Chimp
 - Gorilla
 - Orangutan
 - Macaque



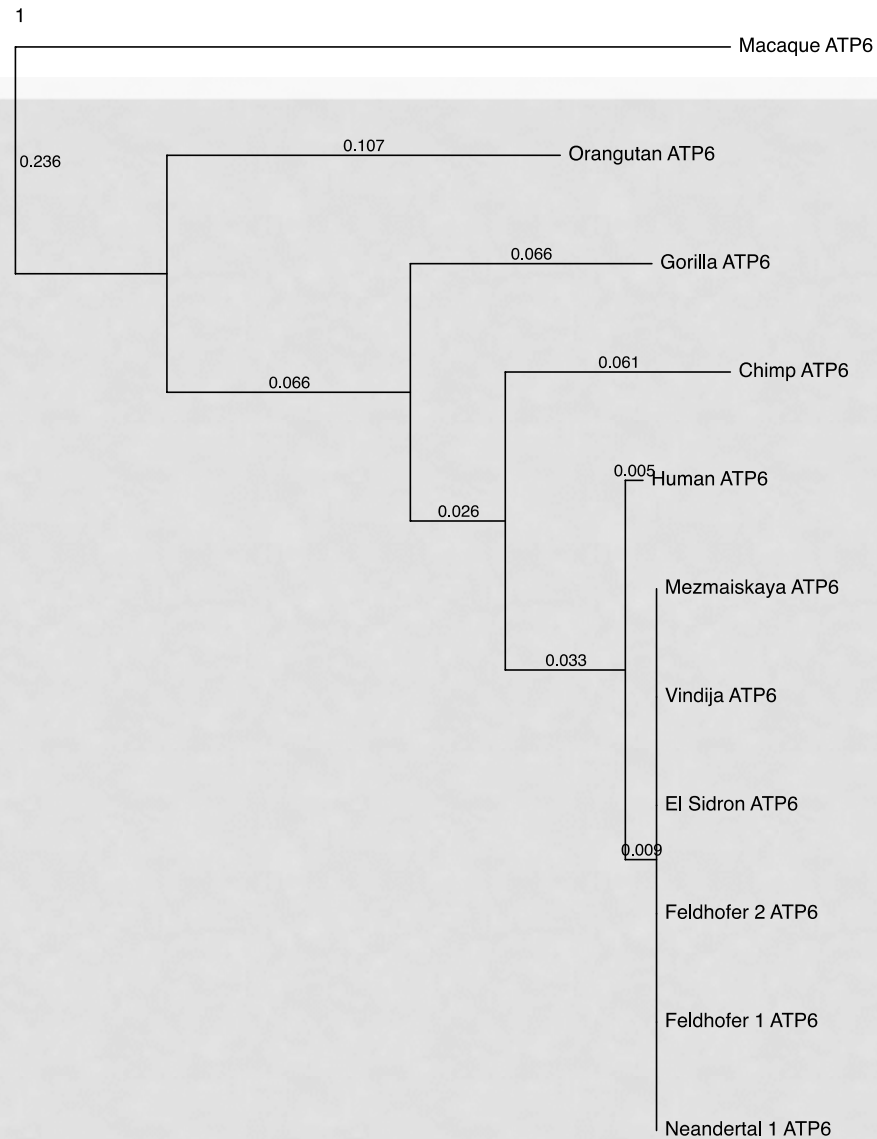
TREE CREATED FROM 8 COMBINED GENES



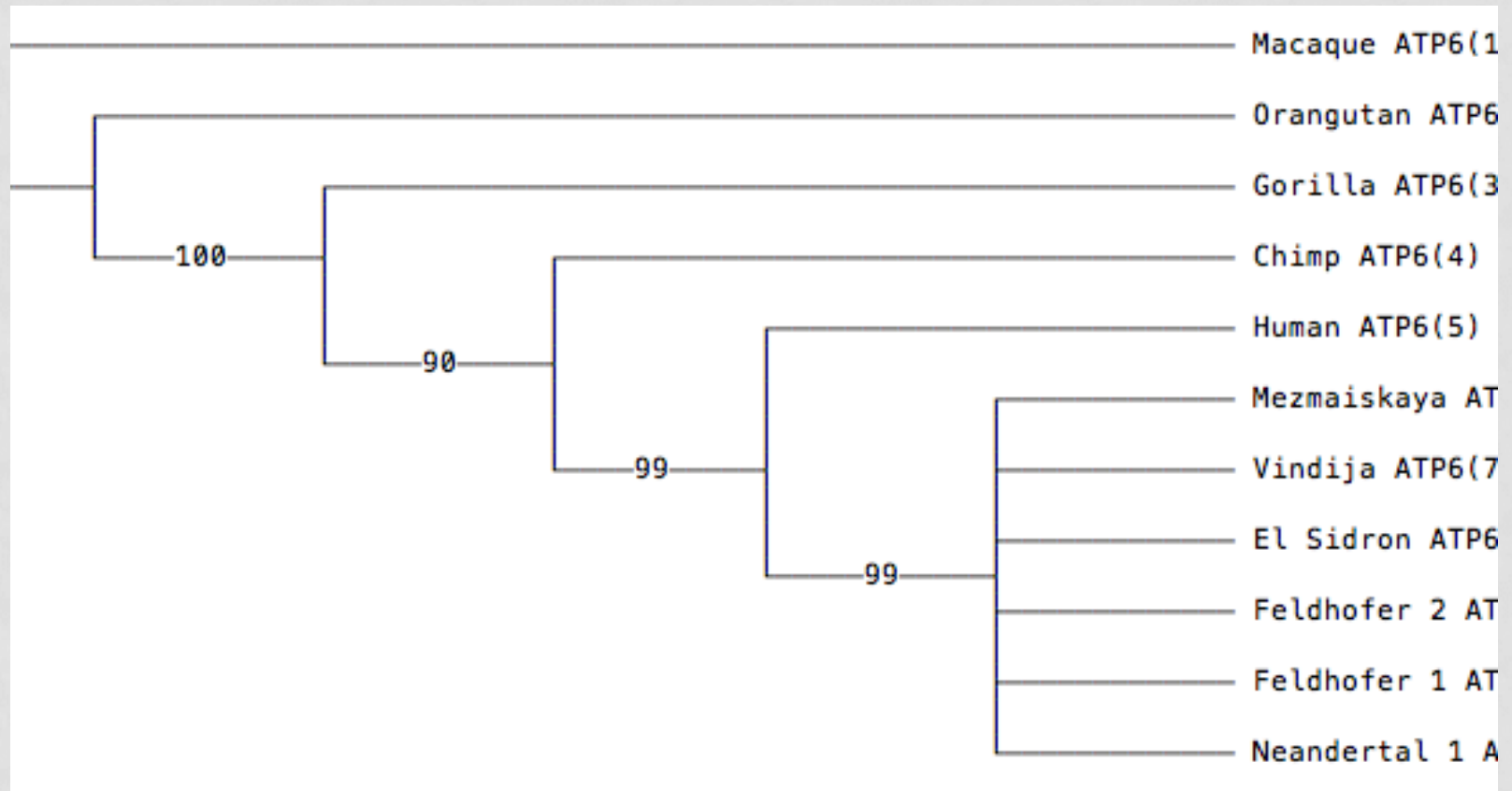
ATP6 ALIGNED SEQUENCES

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File Edit Align Props Sites Species Footers Trees
sel=0 1 Seq:1 Pos:1 | 1 [Macaque
Macaque_ATP6 ATGAACGAAAACCTTGTTTACCCCTTTCCTCA
Orangutan_ATP6 ATGAACGAAAGTCTATTTACCCCATTCATT
Gorilla_ATP6 ATGAACGAAAATTTATTCGCTTCATTCATT
Chimp_ATP6 ATGAACGAAAATCTATTCGCTTCATTCGCT
Human_ATP6 ATGAACGAAAATCTGTTTCGCTTCATTCATT
Mezmaiskaya_ATP6 ATGAACGAAAATCTGTTTCGCTTCATTCATT
Vindija_ATP6 ATGAACGAAAATCTGTTTCGCTTCATTCATT
El_Sidron_ATP6 ATGAACGAAAATCTGTTTCGCTTCATTCATT
Feldhofer_2_ATP6 ATGAACGAAAATCTGTTTCGCTTCATTCATT
Feldhofer_1_ATP6 ATGAACGAAAATCTGTTTCGCTTCATTCATT
Neandertal_1_ATP6 ATGAACGAAAATCTGTTTCGCTTCATTCATT
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ATP6 PHYLOGENY IN PAUP



BOOTSTRAPPING



ATP6 MUTATIONS

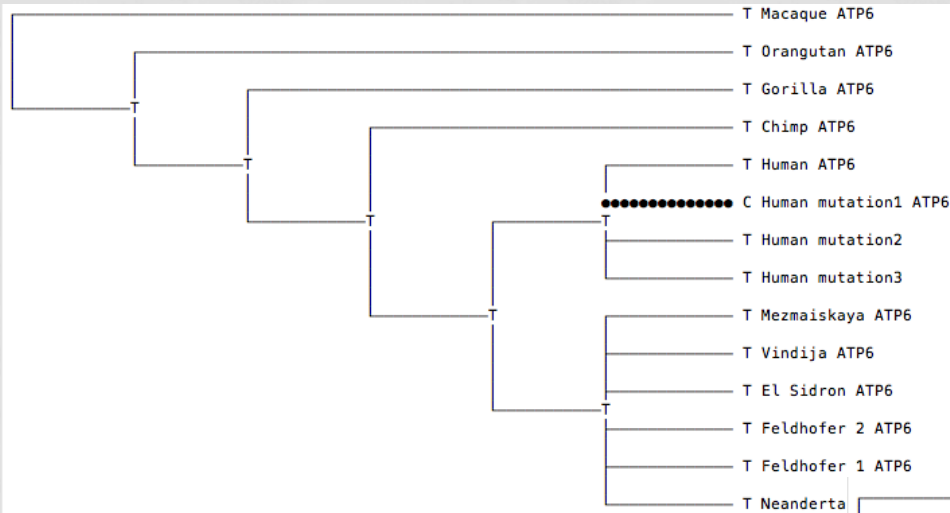
Gene	Disease	Allele	Nucleotide Position	Nucleotide Change	Amino Acid Change	Status	
MT-ATP6	NARP/Leigh Disease/MILS/other	T8993C	8993	T-C	L-P	Cfrm	references
MT-ATP6	NARP/Leigh Disease/MILS/other	T8993G	8993	T-G	L-R	Cfrm	
MT-ATP6	FBSN/Leigh Disease	T9176C	9176	T-C	L-P	Cfrm	references
MT-ATP6	Leigh Disease/Spastic Paraplegia	T9176G	9176	T-G	L-R	Cfrm	
MT-ATP6	Leigh Disease/Ataxia syndromes/NARP-like disease	T9185C	9185	T-C	L-P	Cfrm	

DISEASED HUMAN ATP6 GENES

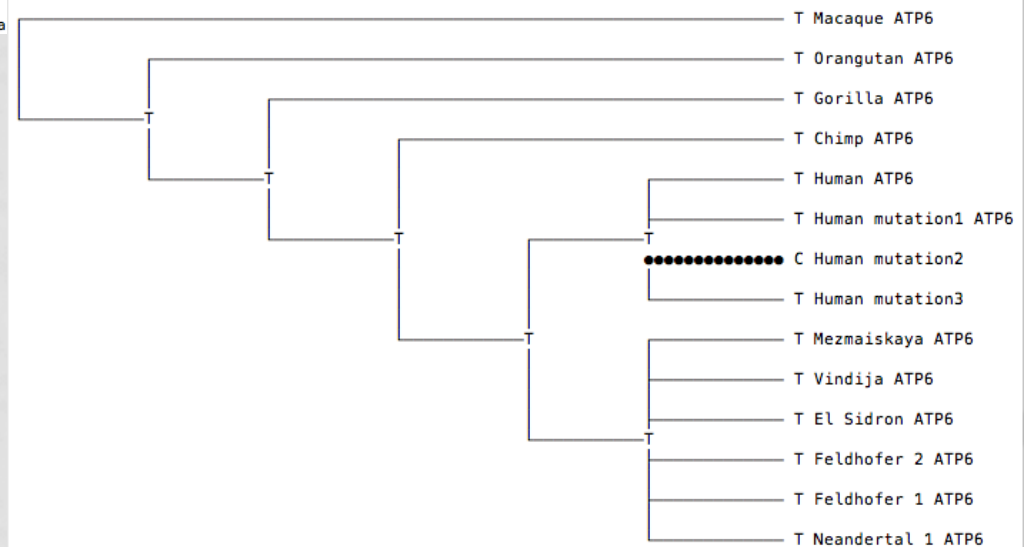
File Edit Align Props Sites Species Footers Trees Search: Goto:

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sel=0
1      Seq:1 Pos:1|1 [Macaque ATP8]
Macaque_ATP8  ATGCCCCAGTTAGATACATCAACATGATTCACCACATTATTATGACGATGCTTCCCACACT
Orangutan_ATP8 ATGCCCCAAC TAAATACCACCACATGGCCCACCATCATCACCCCAATACTCCTTGCACT
Gorilla_ATP8  ATGCCCCAGCTAAATACCACCGTATGGCCCACCATAAATTGCCCCAATACTCCTCACACT
Chimp_ATP8    ATGCCCCAAC TAAATACCGCCGTATGACCCACCATAAATTACCCCCATACTCCTGACACT
Humans_ATP8   ATGCCCCAAC TAAATACTACCGTATGGCCCACCATAAATTACCCCCATACTCCTTACACT
Human_mutation1 ATGCCCCAAC TAAATGCTACCGTATGGCCCACCATAAATTACCCCCATACTCCTTACACT
Human_mutation2 ATGCCCCAAC TAAATACTACCGTATGGTCCACCATAAATTACCCCCATACTCCTTACACT
Human_mutation3 ATGCCCCAAC TAAATACTACCGTATGGCCCACCATAAATTACCCCCGTACTCCTTACACT
Human_mutation3 ATGCCCCAAC TAAATACTACCGTATGGCCCACCATAAATTACCCCCATAATTCTCCTTACACT
Mezmaiskaya_ATP8 ATGCCCCAAC TAAATACTACTGTATGGCCCACCATAAATTATCCCCATACTCCTTACACT
Vindija_ATP8  ATGCCCCAAC TAAATACTACTGTATGGCCCACCATAAATTATCCCCATACTCCTTACACT
El_Sidron_ATP8 ATGCCCCAAC TAAATACTACTGTATGGCCCACCATAAATTATCCCCATACTCCTTACACT
Feldhofer_2_ATP8 ATGCCCCAAC TAAATACTACTGTATGGCCCACCATAAATTATCCCCATACTCCTTACACT
Feldhofer_1_ATP8 ATGCCCCAAC TAAATACTACTGTATGGCCCACCATAAATTATCCCCATACTCCTTACACT
Neandertal_1_ATP8 ATGCCCCAAC TAAATACTACTGTATGGCCCACCATAAATTATCCCCATACTCCTTACACT
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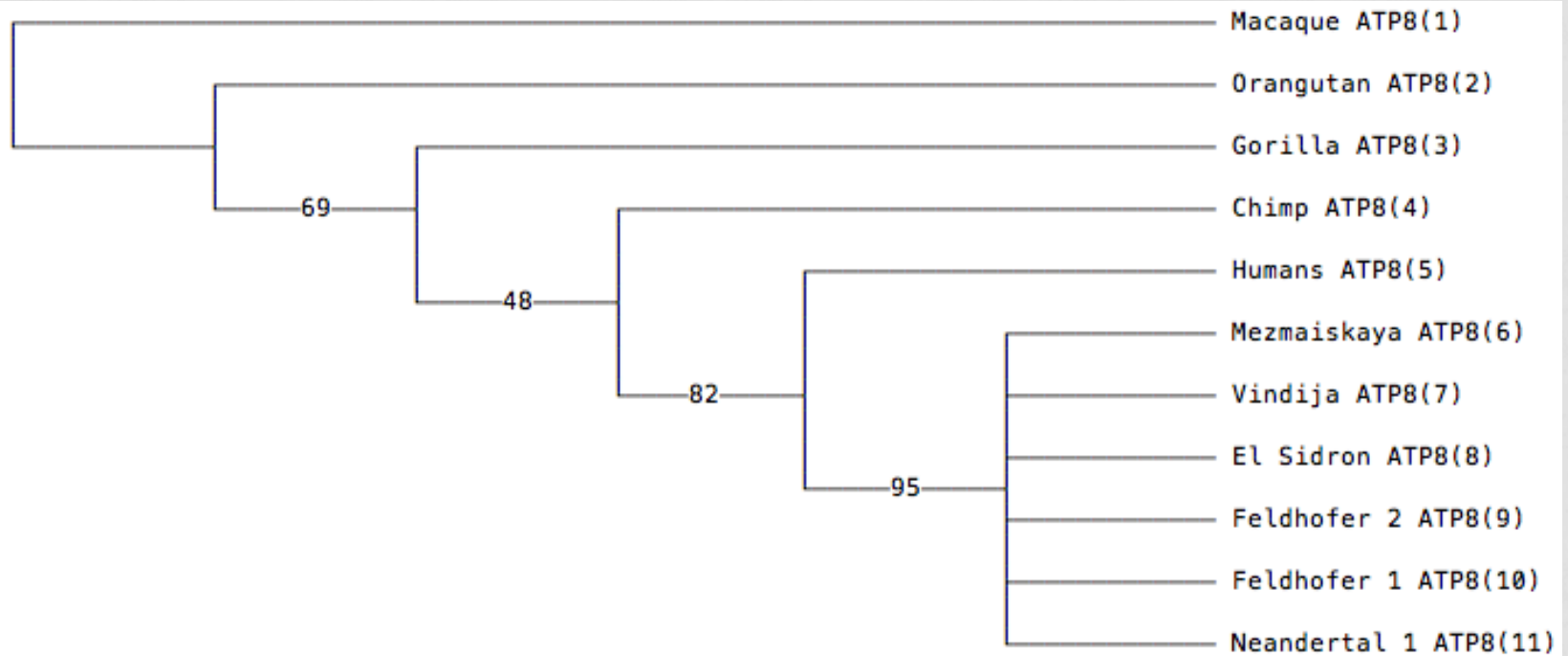
DISEASE CAUSING ATP6 MUTATION ONLY IN HUMANS



*What does this tell us?



ATP8 GENE TREE

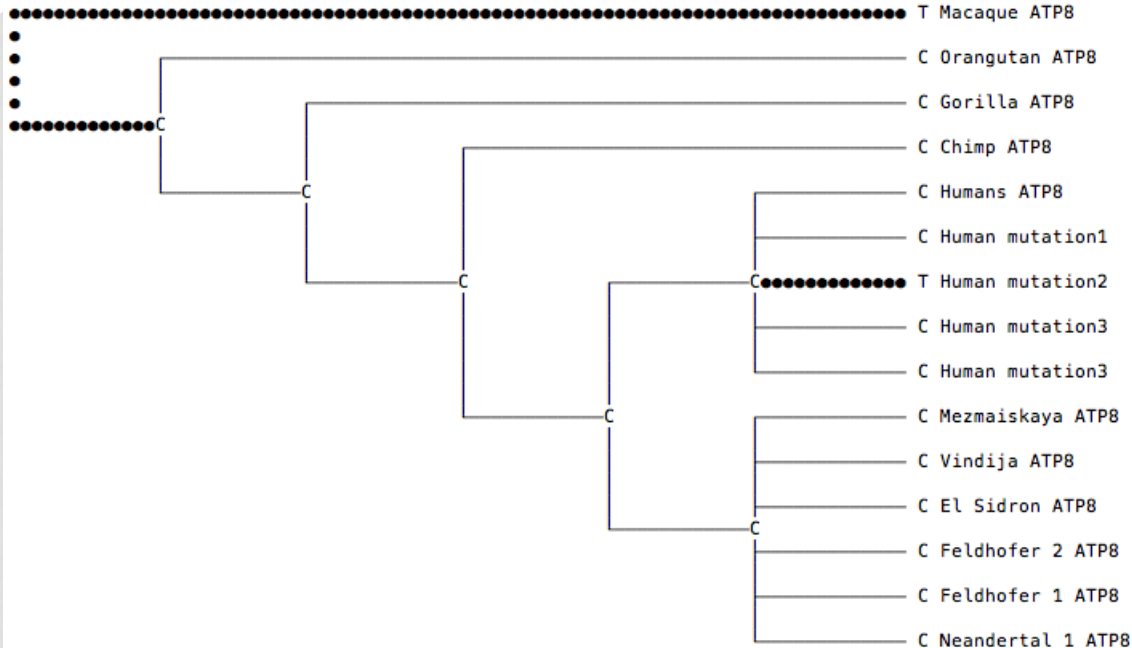


*no difference between this tree and the ATP6 tree

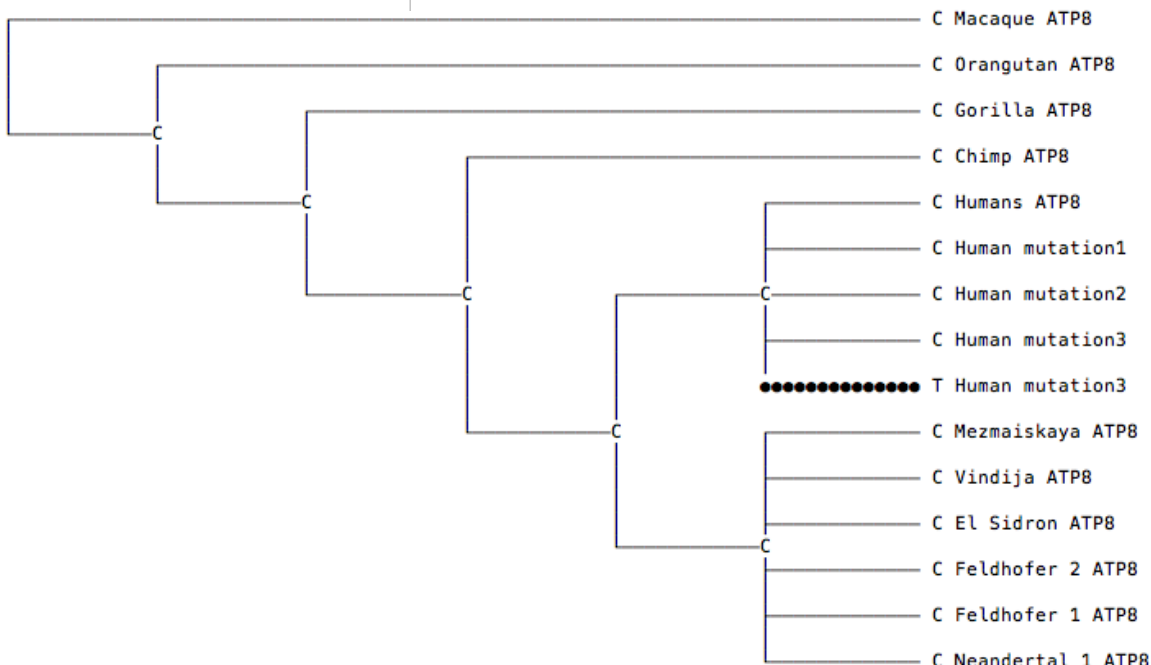
ATP8 MUTATIONS

Gene	Disease	Allele	Nucleotide Position	Nucleotide Change	Amino Acid Change	Status
MT-ATP8	MIDD / LVNC cardiomyopathy-assoc.	A8381G	8381	A-G	T-A	Reported
MT-ATP8	Reversible Brain Pseudoatroph	C8393T	8393	C-T	P-S	Reported
MT-ATP8	Severe mitochondrial disorder	A8411G	8411	A-G	M-V	Reported

*ATP8 disease mutations in humans

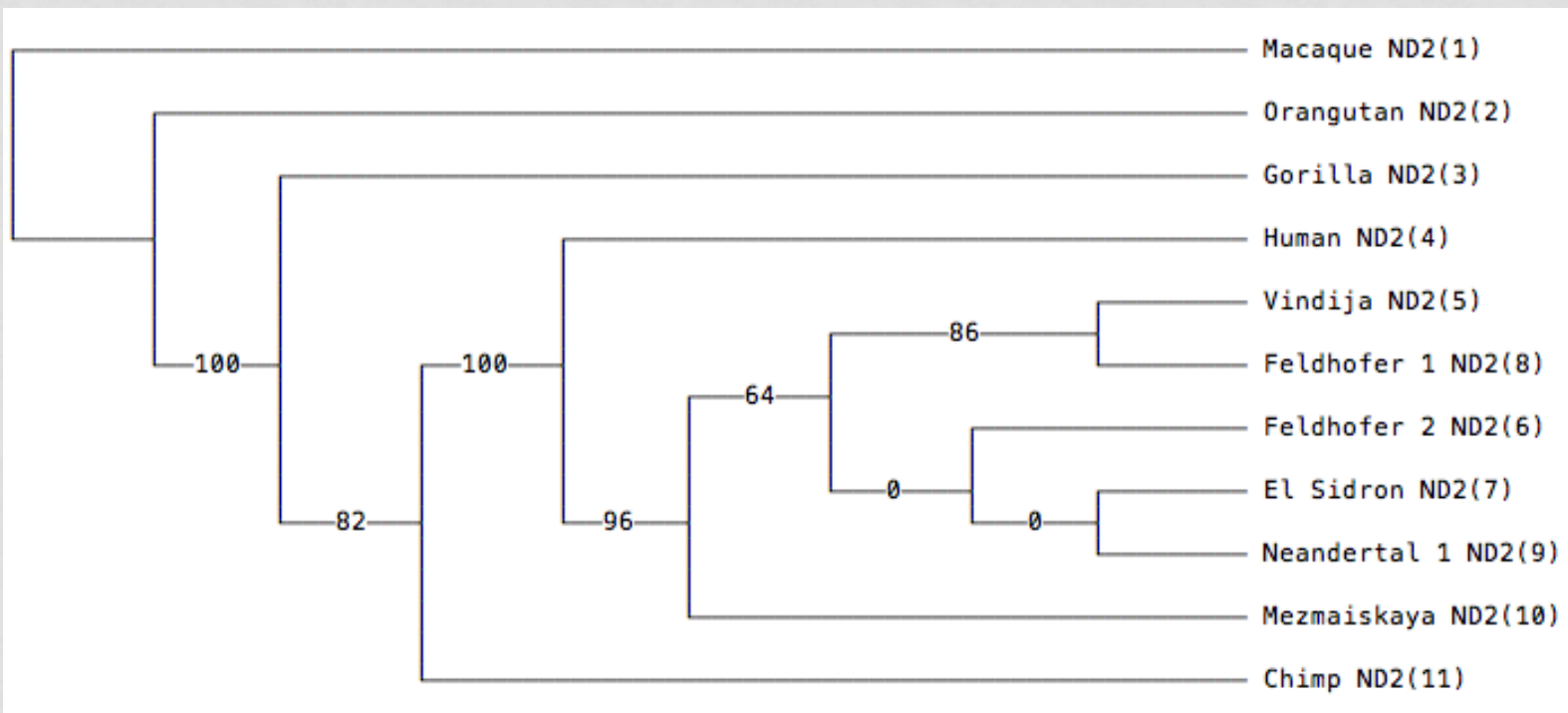


Relative probability of this (joint) reconstruction = $1.52727e-04 / 1.57680e-04 = 0.96859$



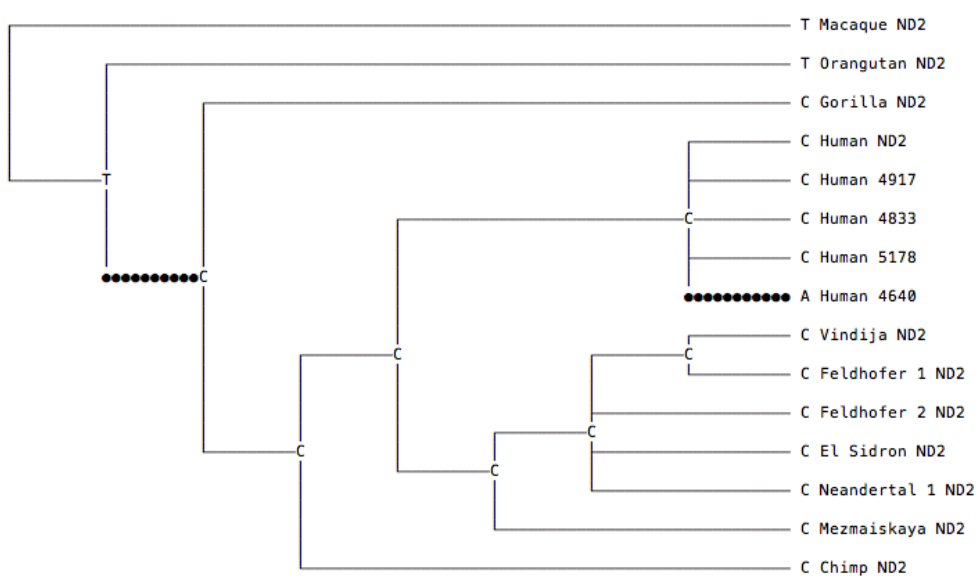
Relative probability of this (joint) reconstruction = $5.34202e-04 / 5.36640e-04 = 0.99546$

ND2 BOOTSTRAPPED TREE

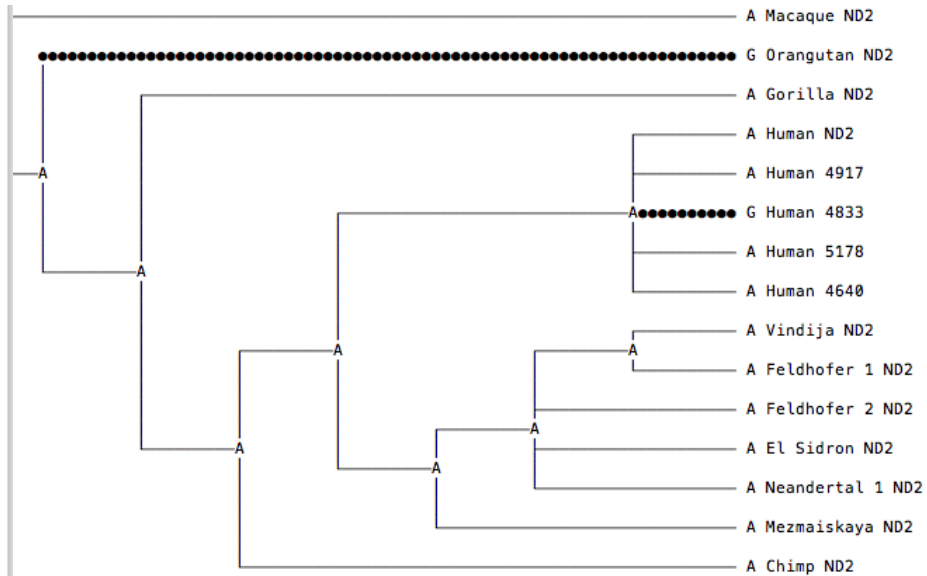


ND2 MUTATIONS

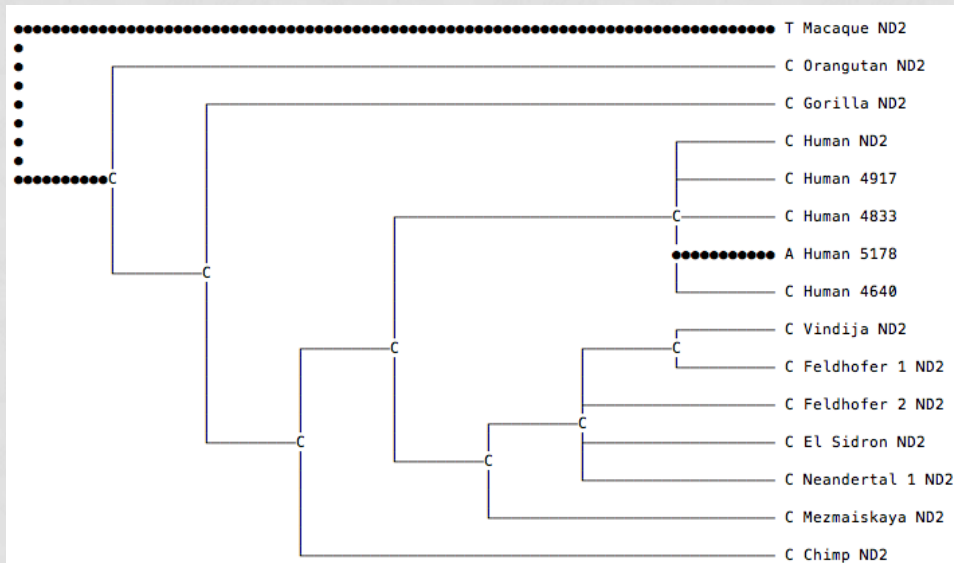
Gene	Disease	Allele	Nucleotide Position	Nucleotide Change	Amino Acid Change	Status
MT-ND2	LHON/Insulin Resistance/A MD/NRTI-PN	A4917G	4917	A-G	N-D	Reported; haplogroup T marker
MT-ND2	NIDDM helper mutation; AD, PD	A4833G	4833	A-G	T-A	Reported; haplogroup G marker
MT-ND2	LHON	C4640A	4640	C-A	I-M	Reported
MT-ND2	Longevity; Extraversion MI/AMS protection; blood iron metabolism	C5178A	5178	C-A	L-M	Reported; haplogroup D marker



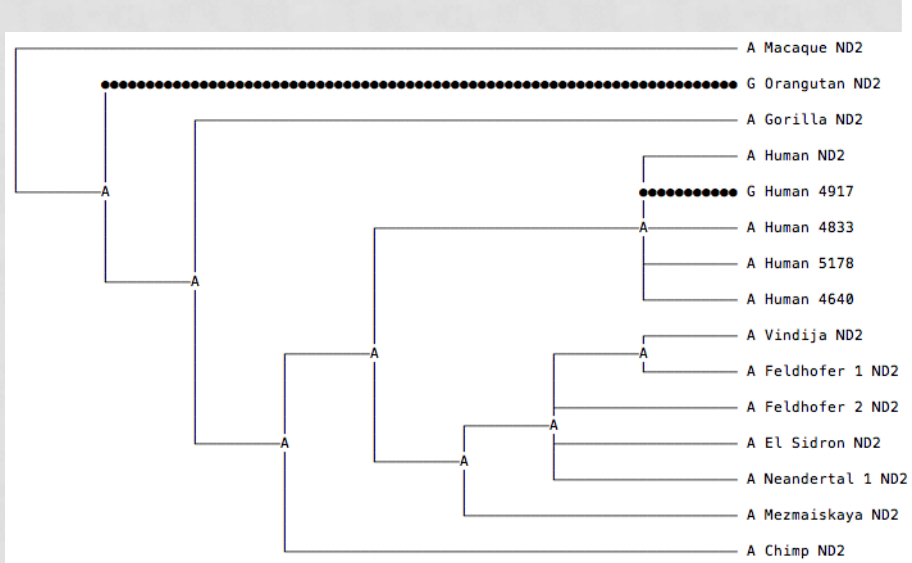
Relative probability of this (joint) reconstruction = $1.69361e-06 / 2.16023e-06 = 0.78399$



Relative probability of this (joint) reconstruction = $1.29055e-06 / 1.47617e-06 = 0.87426$



Relative probability of this (joint) reconstruction = $6.70863e-06 / 6.85907e-06 = 0.97807$



Relative probability of this (joint) reconstruction = $1.29055e-06 / 1.47617e-06 = 0.87426$

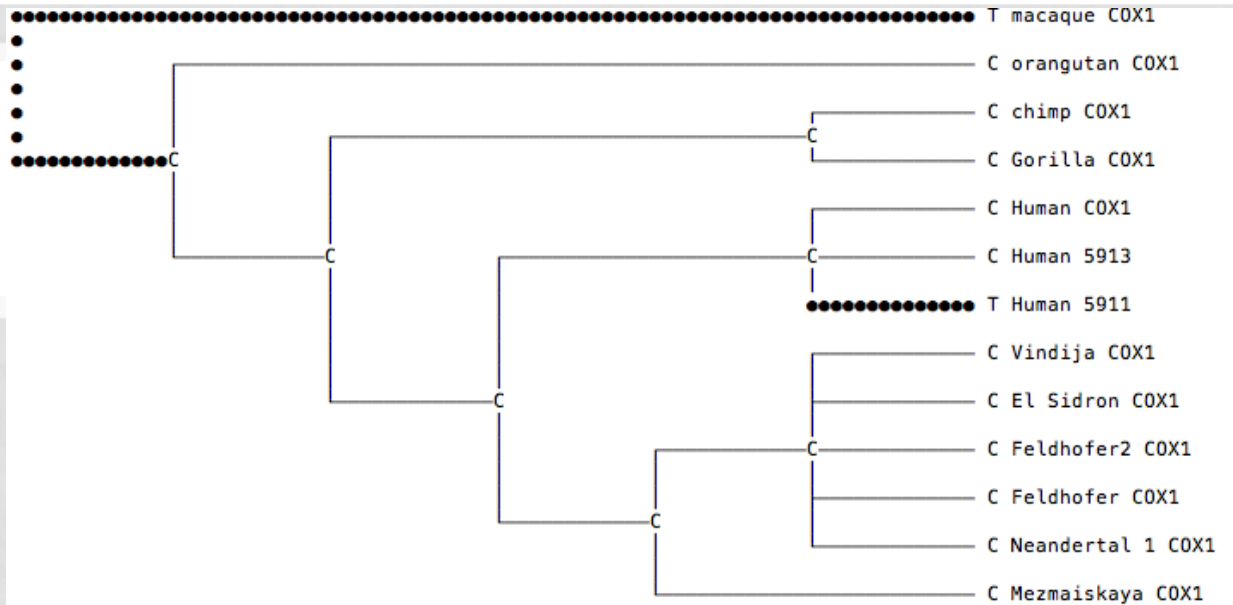
COX1 MUTATIONS

macaque_COX1	ATGCTCATTAAATCGCTGACT
orangutan_COX1	ATGTTCGCCGACCGCTGGCT
chimp_COX1	ATGTTCAACCGACCGCTGACT
Human_COX1	ATGTTCGCCGACCGTTGACT
Human_5913	ATGTTCGCCAACCGTTGACT
Human_5911	ATGTTCGTCGACCGTTGACT
Vindija_COX1	ATGTTCGCCGACCGTTGACT
El_Sidron_COX1	ATGTTCGCCGACCGTTGACT
Feldhofer2_COX1	ATGTTCGCCGACCGTTGACT
Feldhofer_COX1	ATGTTCGCCGACCGTTGACT
Neandertal_1_COX1	ATGTTCGCCGACCGTTGACT
Mezmaiskaya_COX1	ATGTTCGCCGACCGTTGACT
Gorilla_COX1	ATGTTCAACCGACCGCTCAAT

COX1 MUTATIONS

Gene	Disease	Allele	Nucleotide Position	Nucleotide Change	Amino Acid Change	Status
MT-CO1	Prostate Cancer	C5911T	5911	C-T	A-V	Reported
MT-CO1	Prostate Cancer	G5913A	5913	G-A	D-N	Reported

* COX1 Mutations In Humans



Relative probability of this (joint) reconstruction = $9.40517e-06/9.57983e-06 = 0.98177$

Estimated states for character 10 on tree 1 (marginal estimation):

