



Tüberküloz Basilinin Evrimi

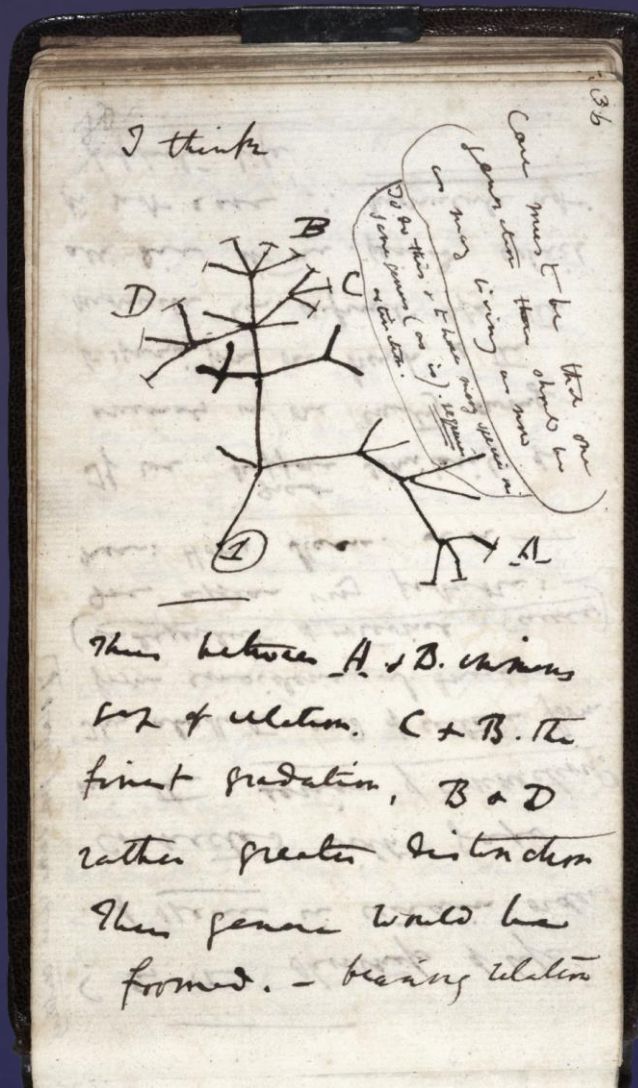
Dr. Ahmet Görkem Er

Hacettepe Üniversitesi Tıp Fakültesi
İç Hastalıkları Anabilim Dalı

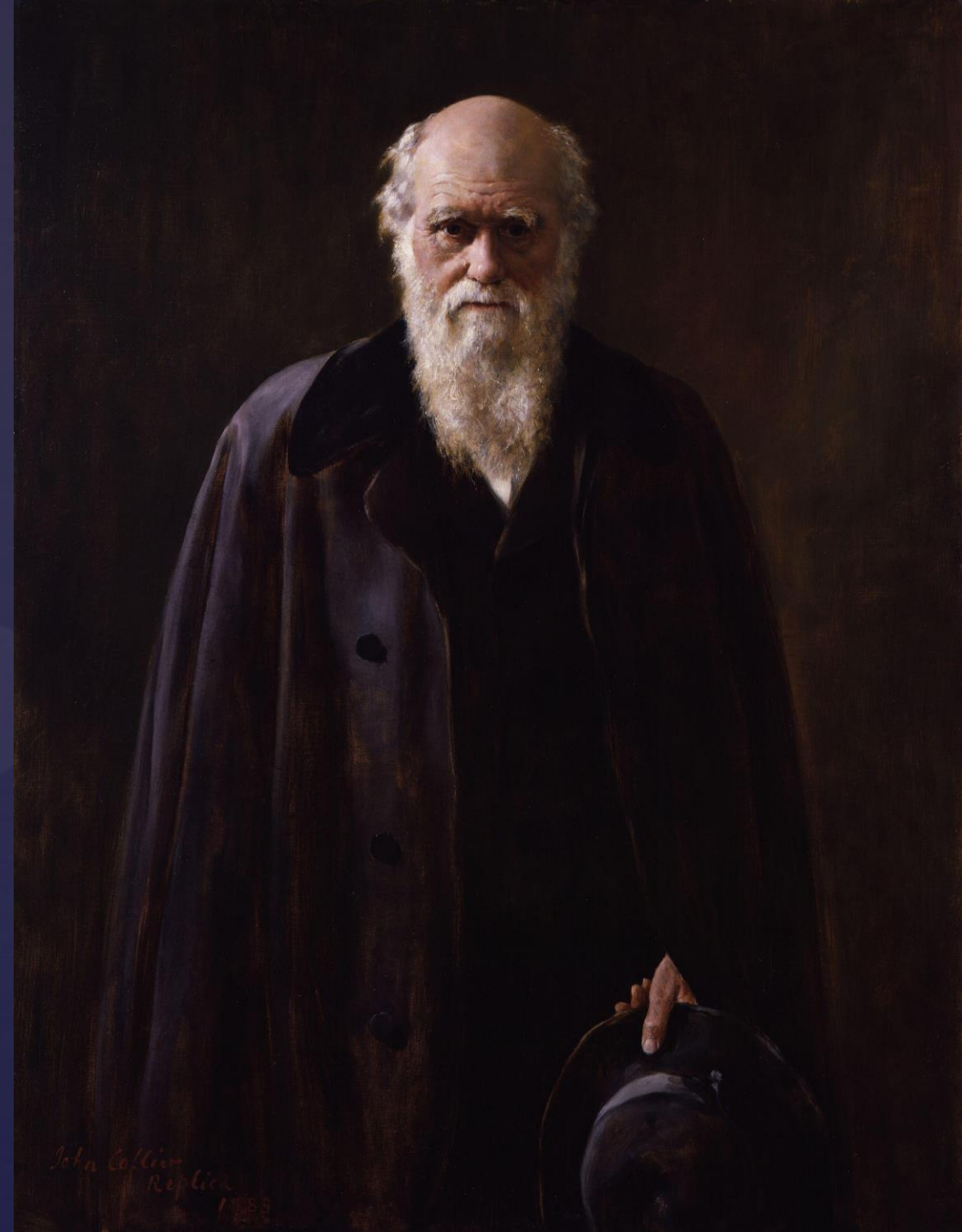


Mycobacterium tuberculosis & Homo sapiens

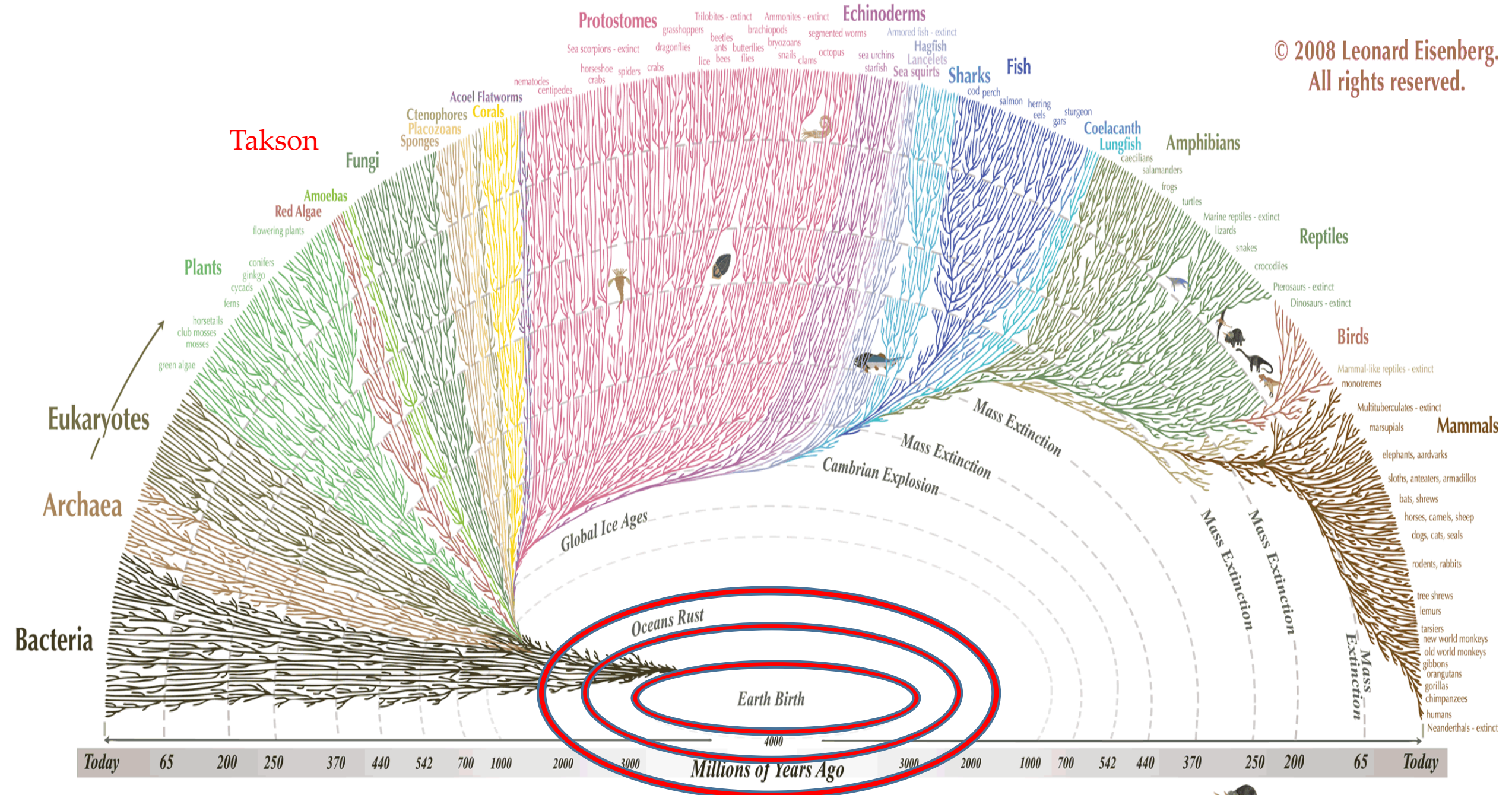
- Birlikte evrimleşme (*Co-evolution*)
 - Patojen infektivitesi & Konak direnci → Resiprokal antagonist
 - Nesiller arası genetik geçiş
 - Karşılıklı etkileşim sonuçları genotiplere bağımlı



Haziran 1837



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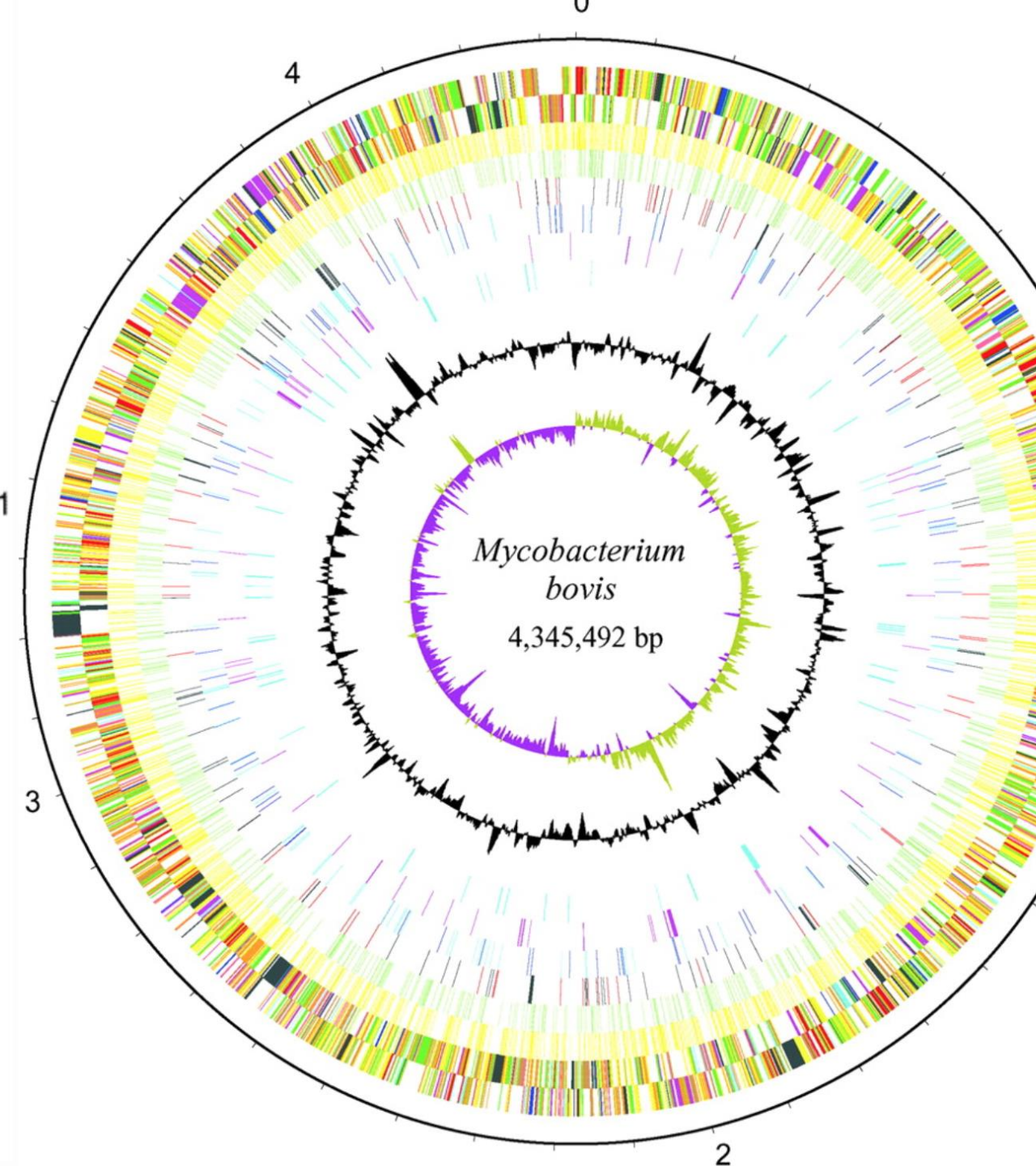
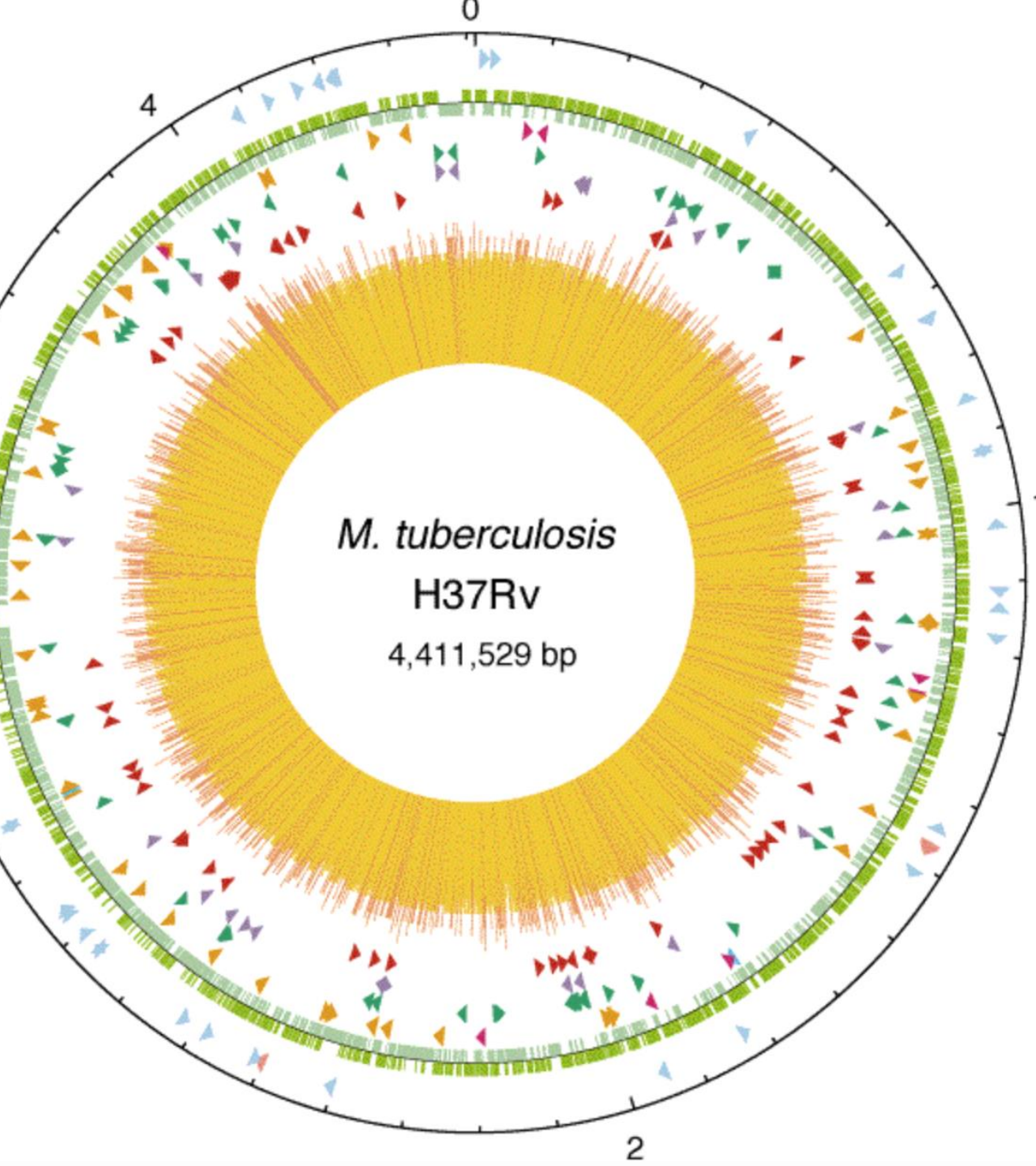


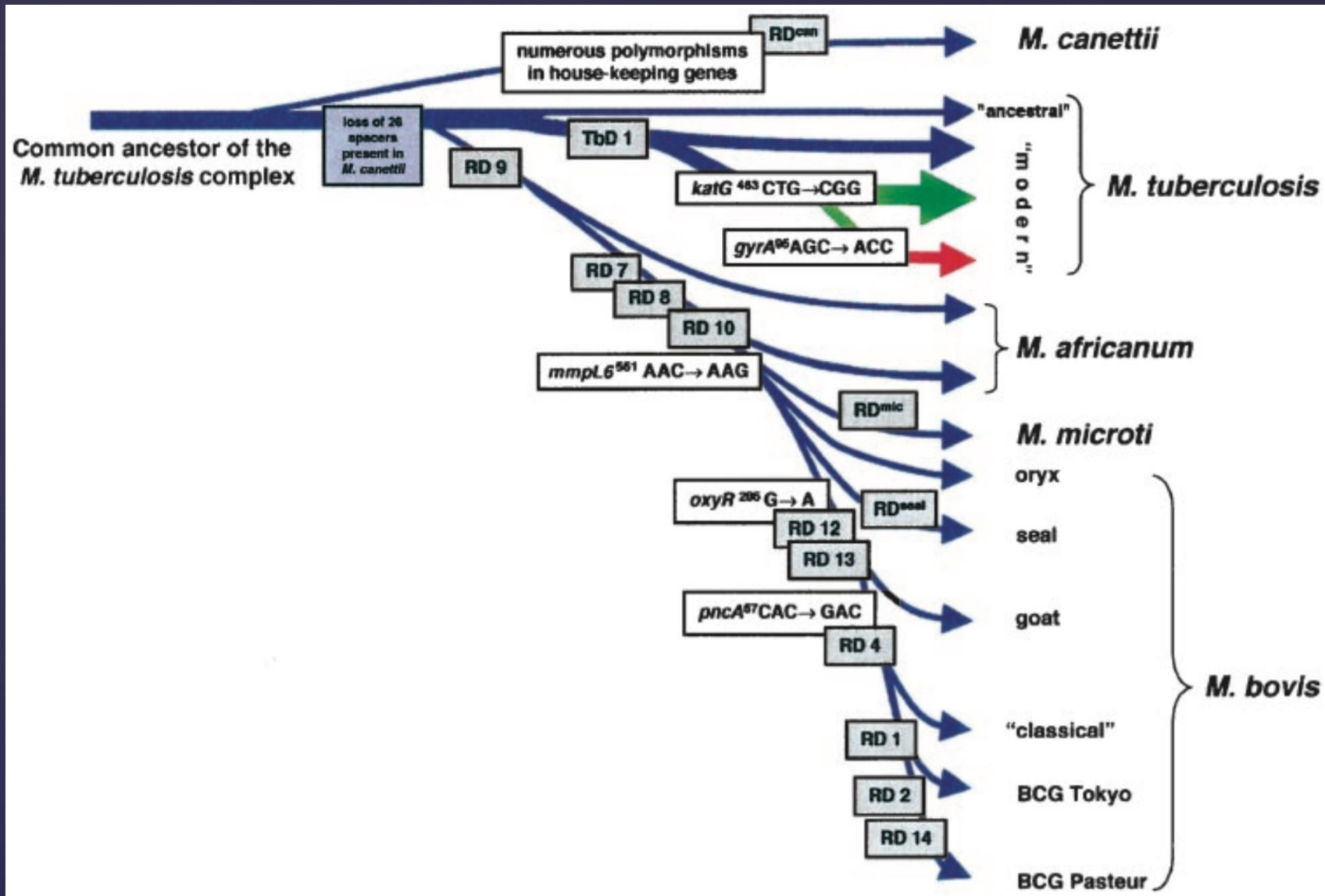
All the major and many of the minor living branches of life are shown on this diagram, but only a few of those that have gone extinct are shown. Example: Dinosaurs - extinct

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evogeneao.com

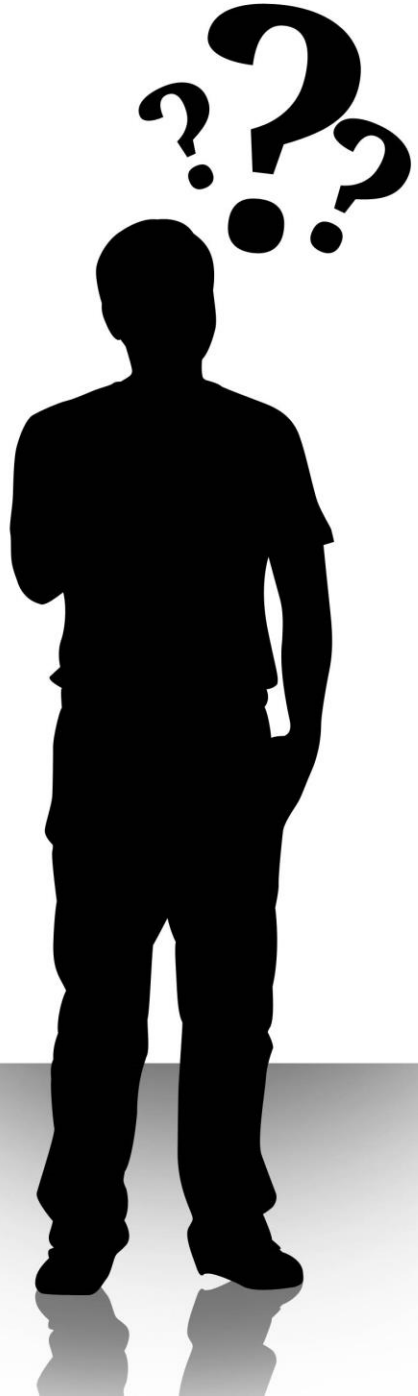
- *Mycobacterium tuberculosis sensu stricto*
 - *Mycobacterium africanum*
- 
- Homo sapiens

- Tüberküloz insandan mı hayvana, hayvandan mı insana bulaştı?

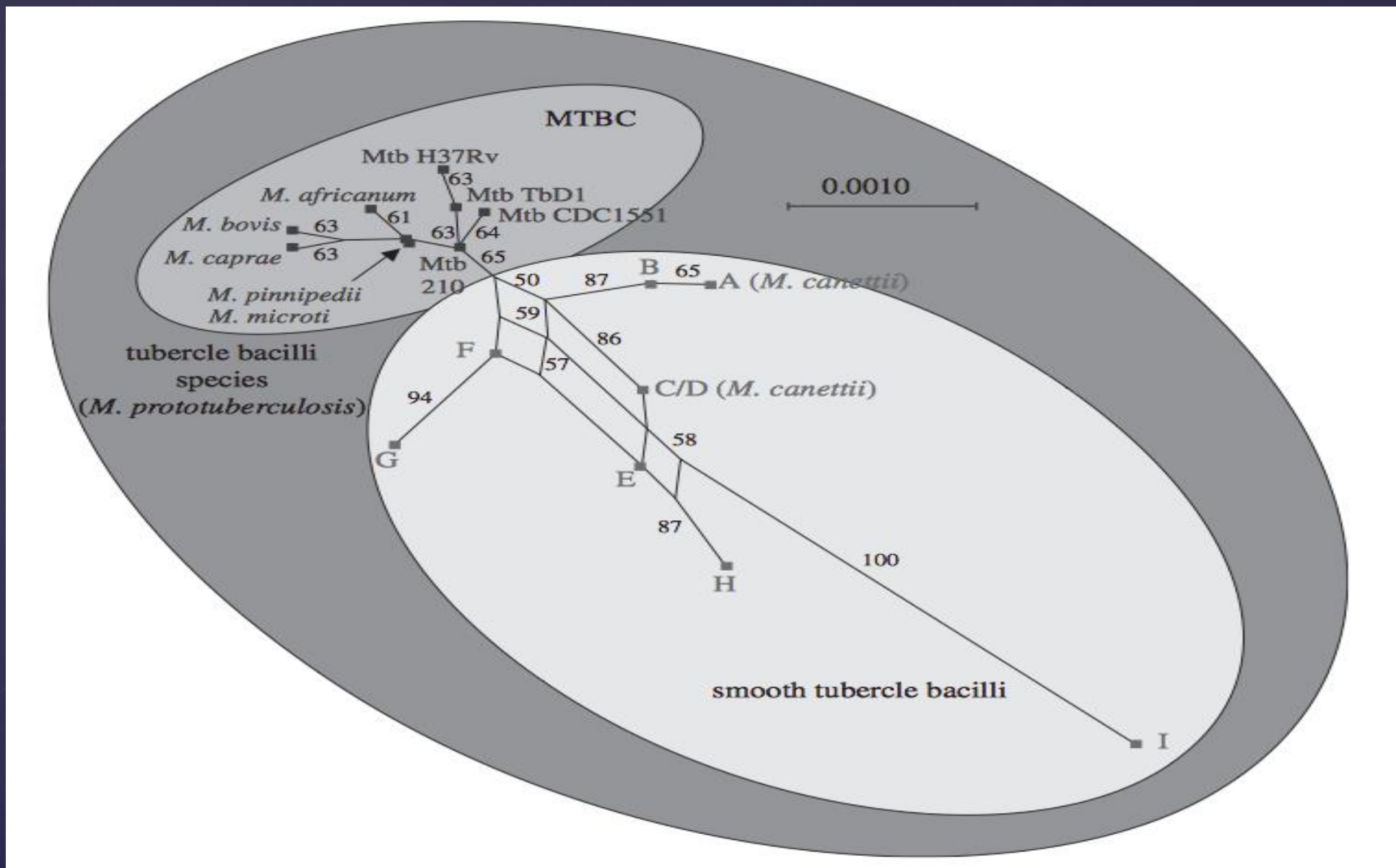




Brosch R, Gordon SV, Marmiesse M, et al. A new evolutionary scenario for the *Mycobacterium tuberculosis* complex. *Proceedings of the National Academy of Sciences of the United States of America* 2002;99:3684-9.



- Ne zamandır bir aradalar?



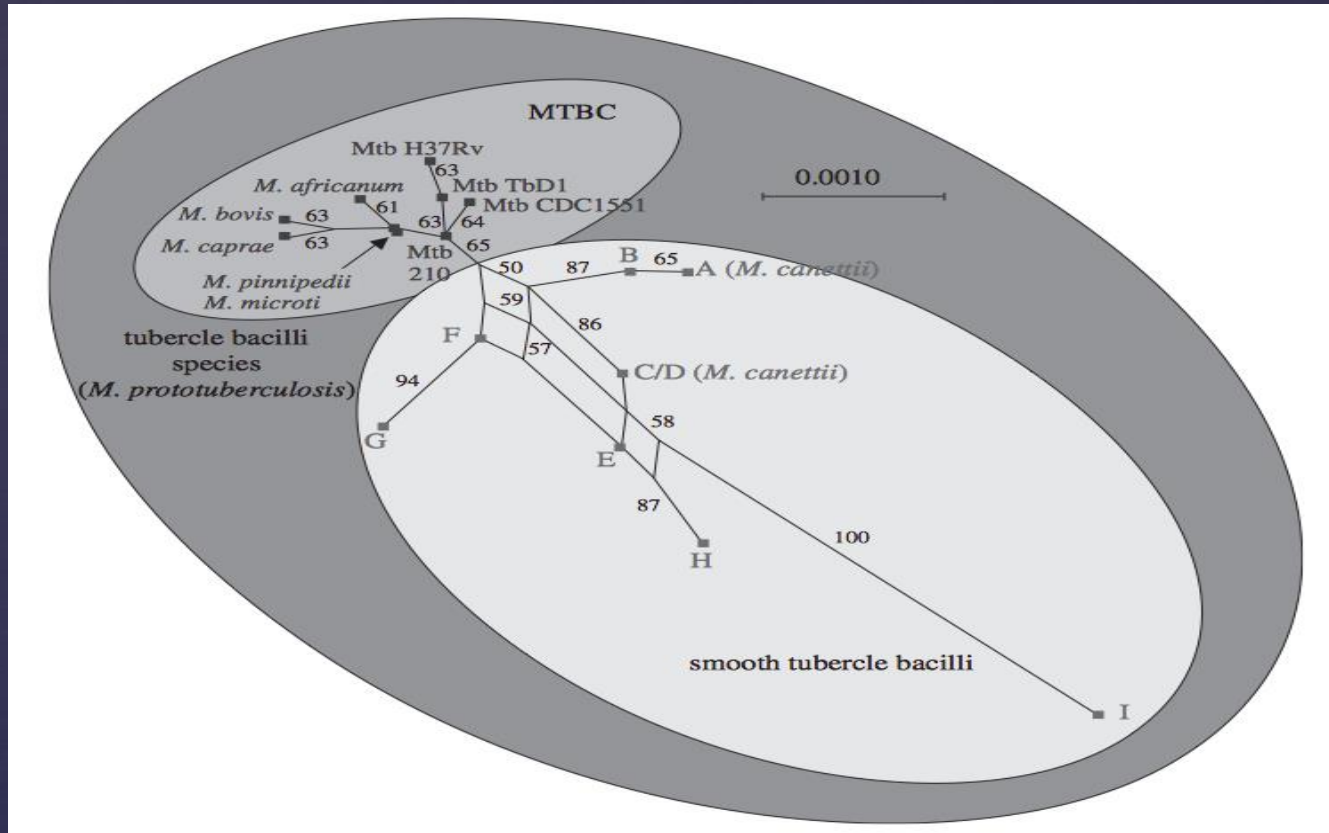
Gutierrez, C., Brisse, S., Brosch, R., Fabre, M., Omais, B., Marmiesse, M., Supply, P. & Vincent, V. 2005
 Ancient origin and gene mosaicism of the progenitor of *Mycobacterium tuberculosis*. PLoS Pathogens, 1 – 7.

- *Mycobacterium canetti*

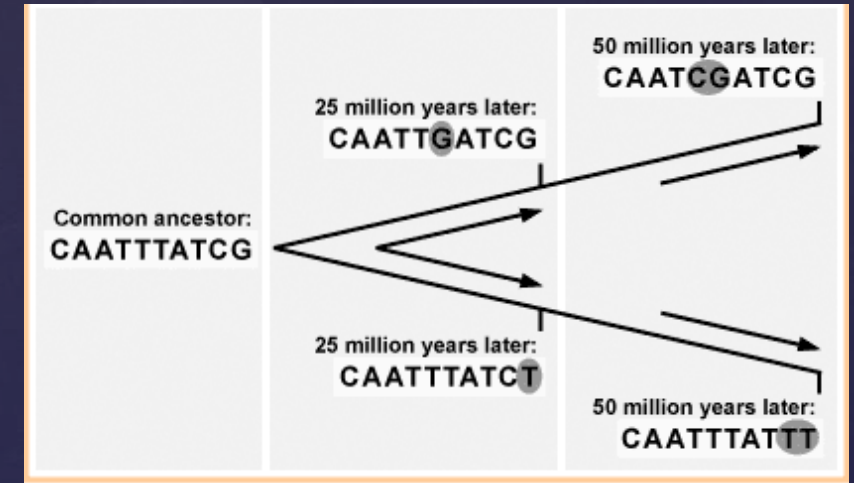
- *Enigmatic microbe*
- Horizontal gen transferi
- Sadece 60 izolat → Afrika'nın boynuzu

- *MTBC, M. canetti'*ye çok benzer bir atadan evrildi
 - Serbest yaşamda üreyebilme şansını kaybetti
 - Konak bariyerini aşarak hücre içinde yaşayabilme yetisini kazandı





Moleküler saat



3 milyon yıl

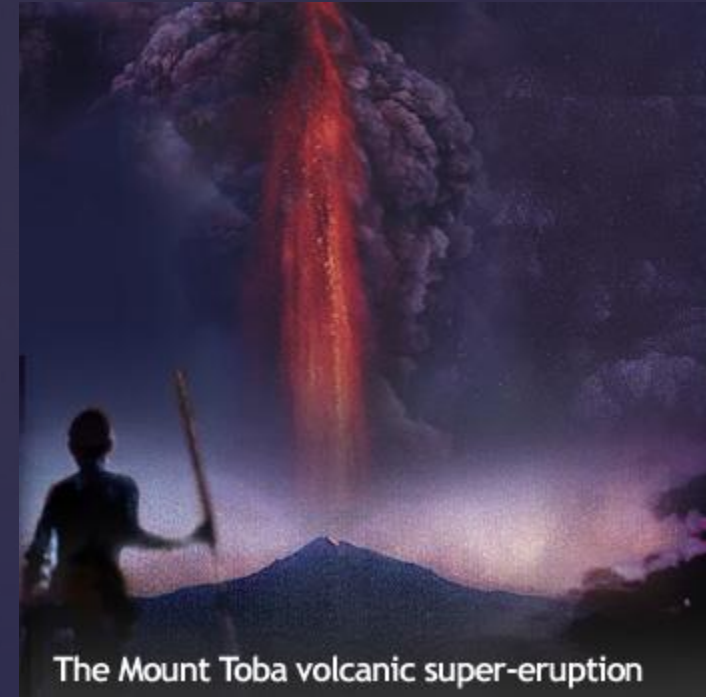
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Ancient origin and gene mosaicism of the progenitor of *Mycobacterium tuberculosis*. PLoS Pathogens, 1 – 7.

- Virulansın evrimi

- Değiş tokuş hipotezi

- *Crowd disease*
- *Pre-NDT disease*

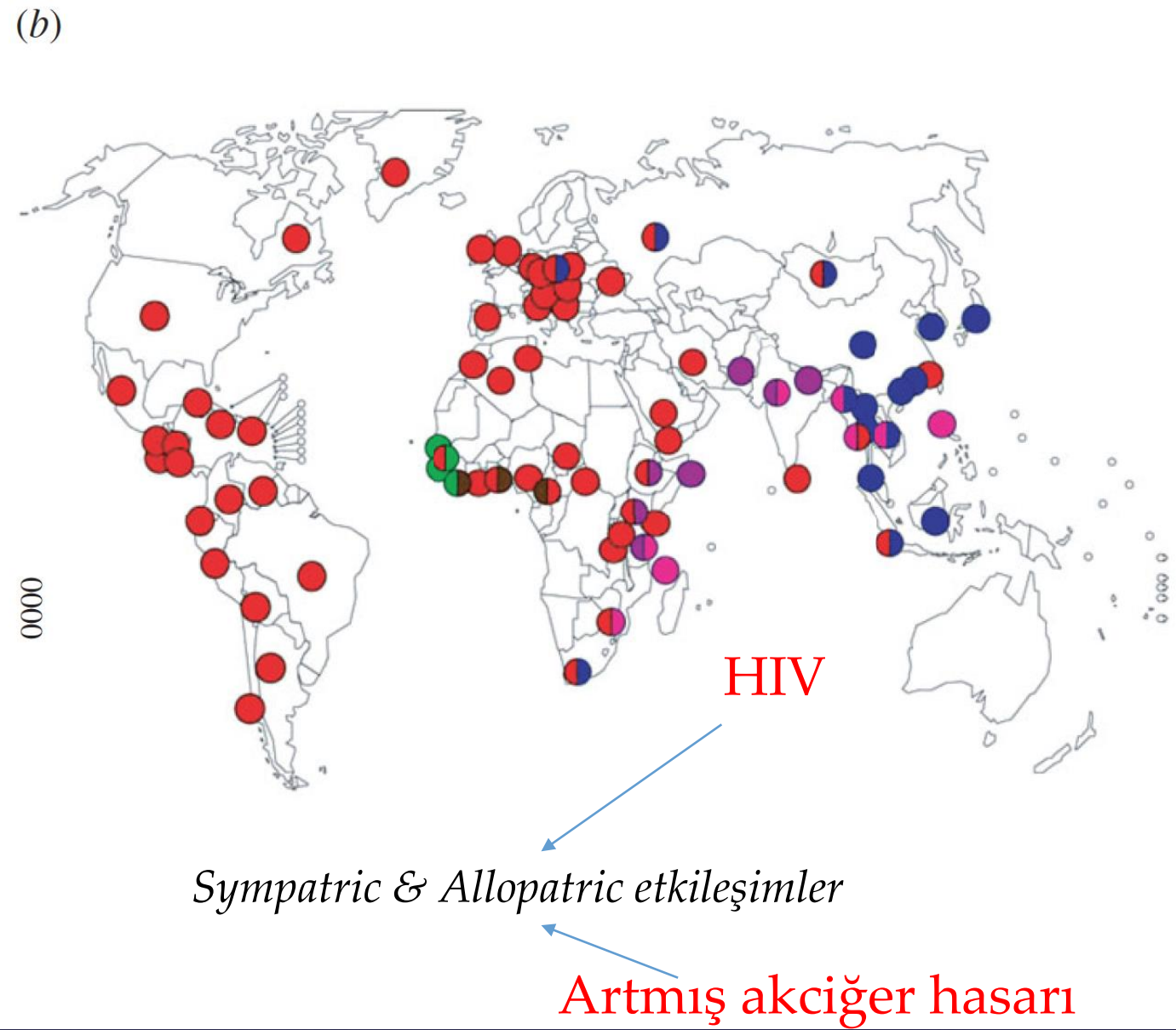
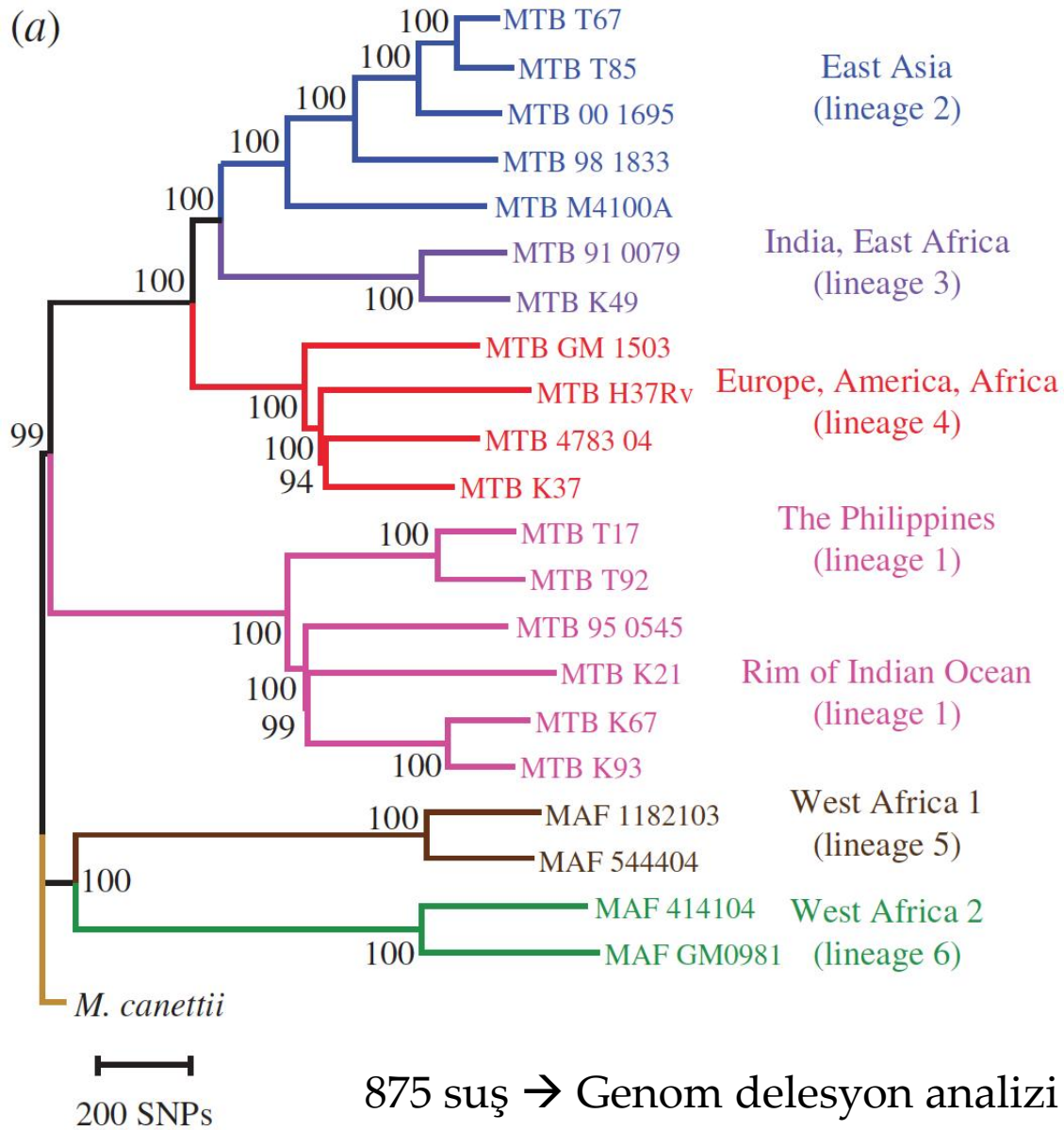
- Populasyon yoğunluğu → Toba felaket kuramı, 70.000 yıl



The Mount Toba volcanic super-eruption

Reed MB, et al. Major Mycobacterium tuberculosis lineages associate with patient country of origin.
Journal of clinical microbiology 2009.

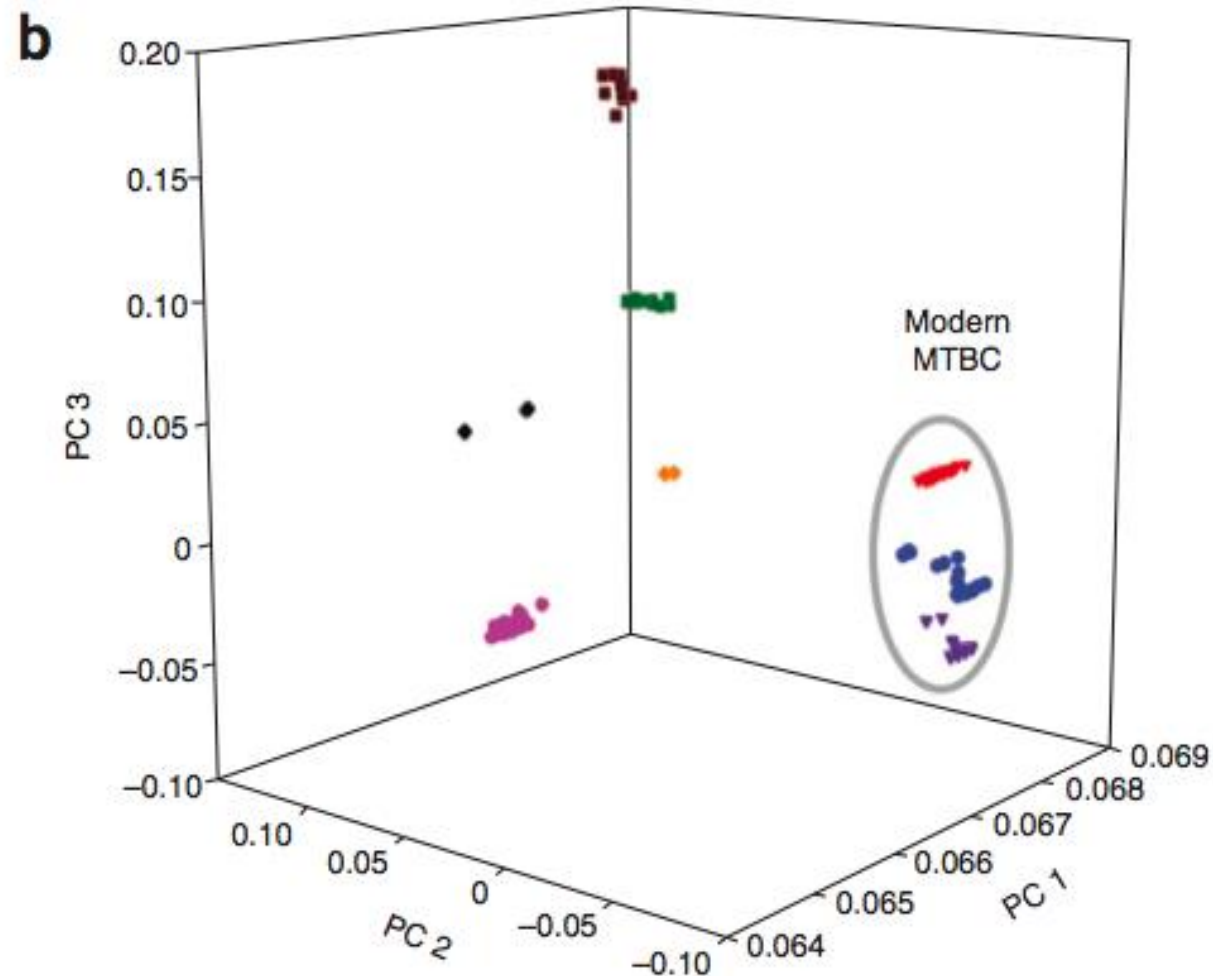
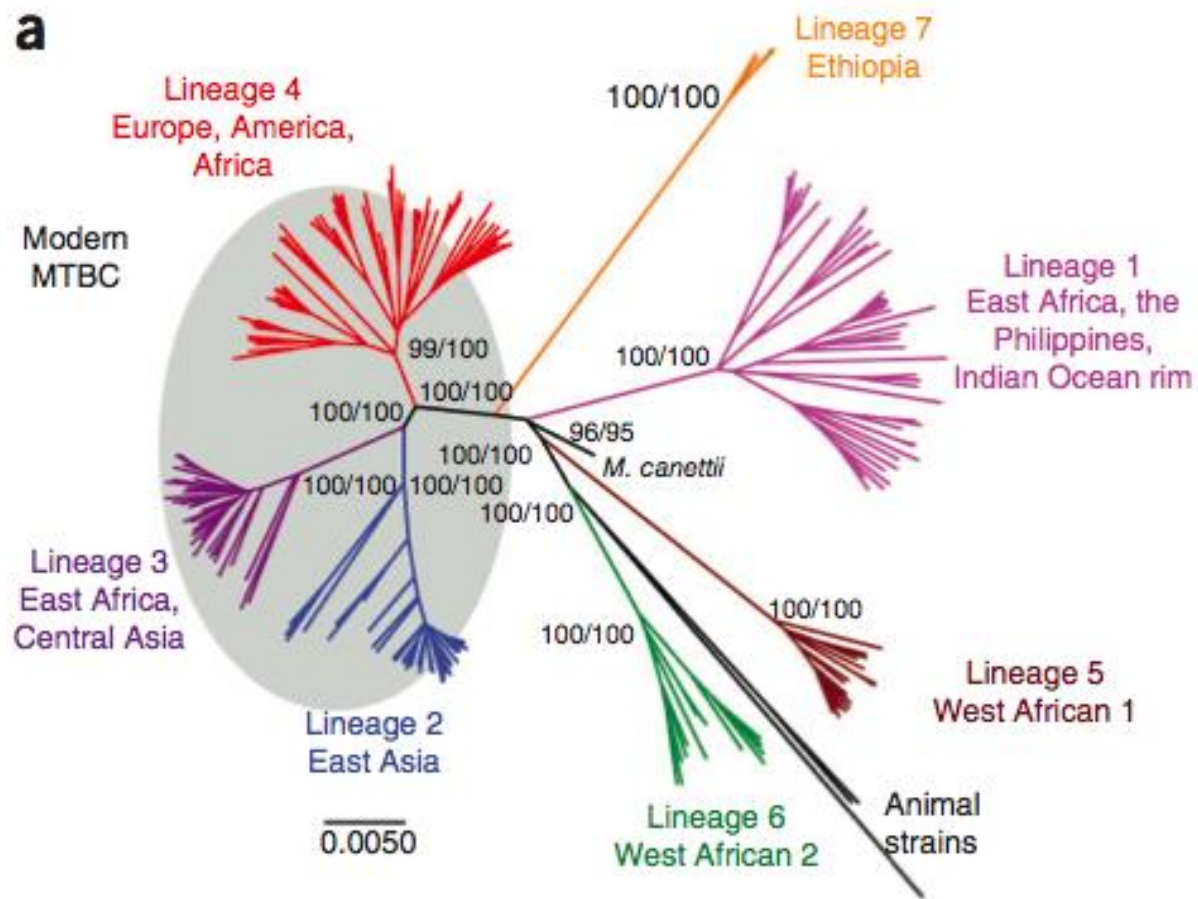
Fenner L, et al. HIV infection disrupts the sympatric host-pathogen relationship in human tuberculosis. PLoS genetics 2013.
Pasipanodya JG, et al. Allopatric tuberculosis host-pathogen relationships are associated with greater pulmonary impairment.
Infection, genetics and evolution : journal of molecular epidemiology and evolutionary genetics in infectious diseases 2013.



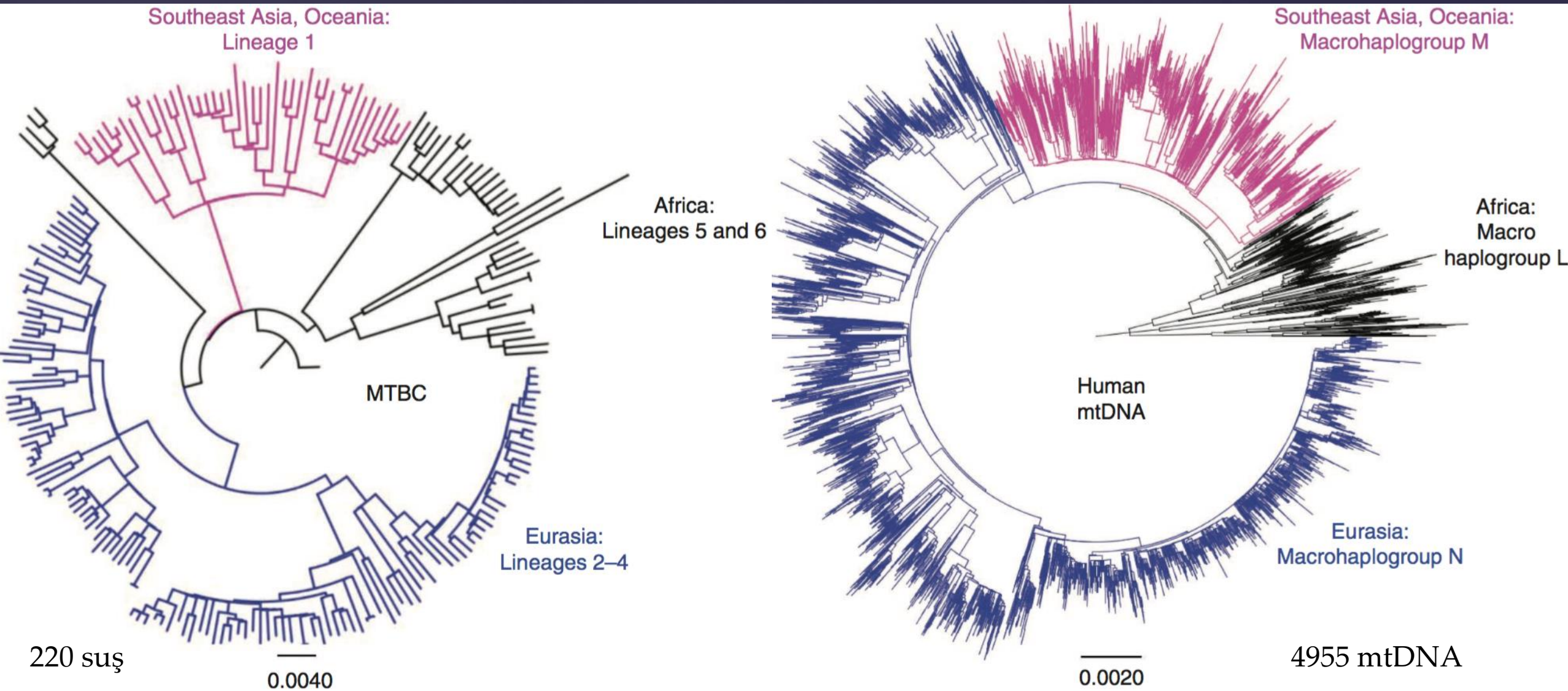
Gagneux, S. et al. 2006 Variable host-pathogen compatibility in *Mycobacterium tuberculosis*. Proc. Natl Acad. Sci. USA 103, 2869 – 2873

- *Lineage 2 & 4*

- Monofiletik
- Geniş yayılım
 - Haarlem ve LAM → Avrupa'dan Amerika'ya yayılım
- İlaça duyarlı ve dirençli TB salgınları
- Aktif hastalığa daha hızlı geçiş
- Hayvan modellerinde virülansta artış
- Konakta daha az proinflamatuvar yanıt



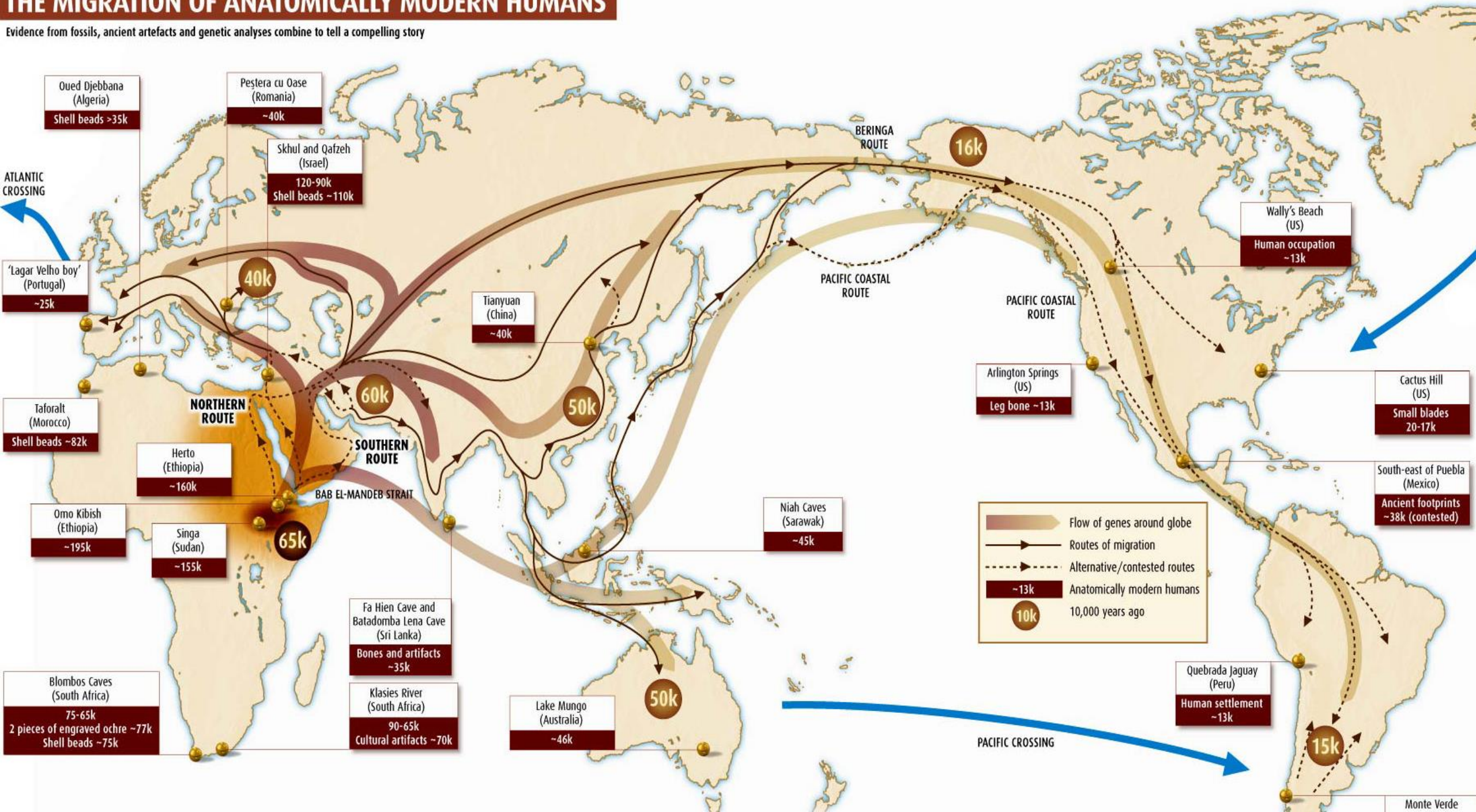
Out-of-Africa migration and Neolithic coexpansion of *M. tuberculosis* with modern humans
Comas et. al, Nature Genetics, 2013



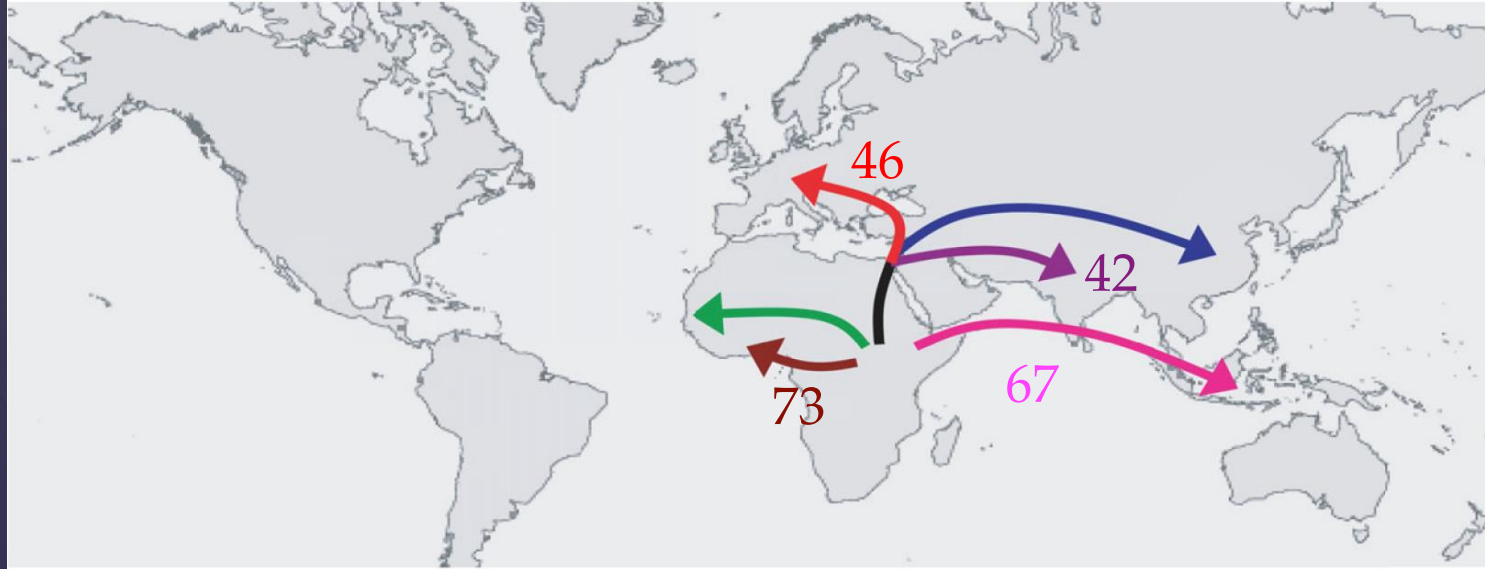
Out-of-Africa migration and Neolithic coexpansion of *M. tuberculosis* with modern humans
 Comas et. al, Nature Genetics, 2013

THE MIGRATION OF ANATOMICALLY MODERN HUMANS

Evidence from fossils, ancient artefacts and genetic analyses combine to tell a compelling story



Afrika'dan Çıkış ve Afrika'ya Geri Dönüş Hipotezi

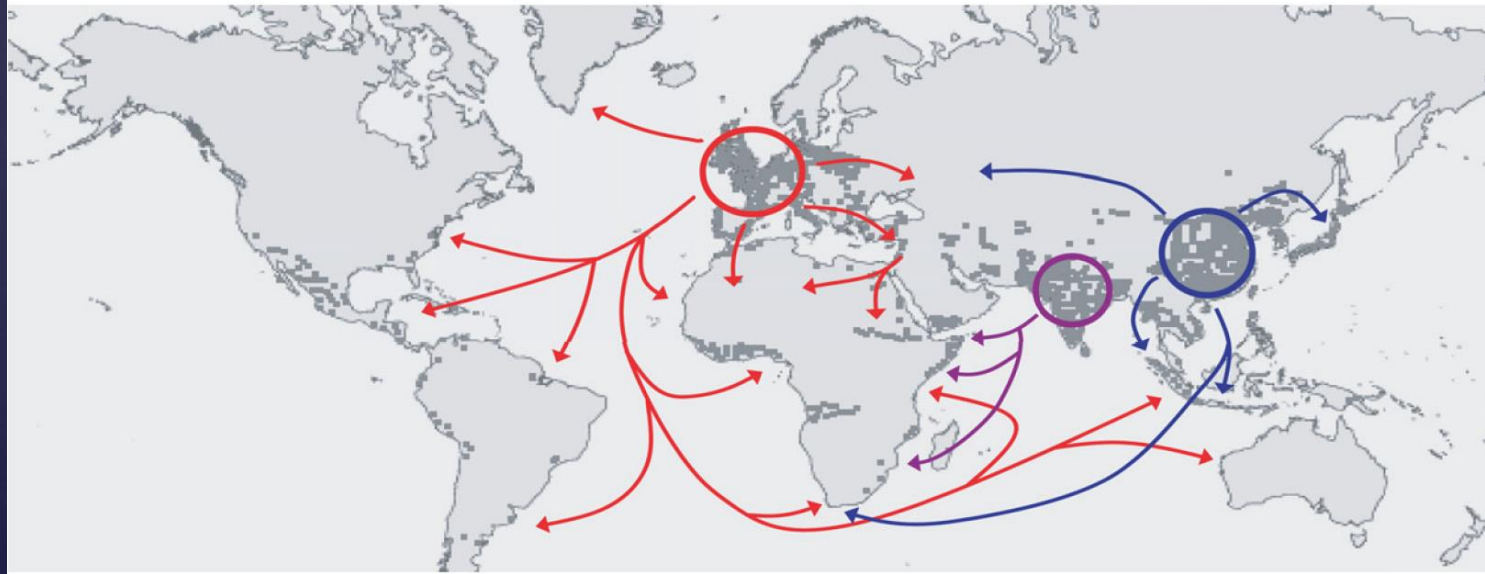


The Philippines
(lineage 1)

East Asia
(lineage 2)

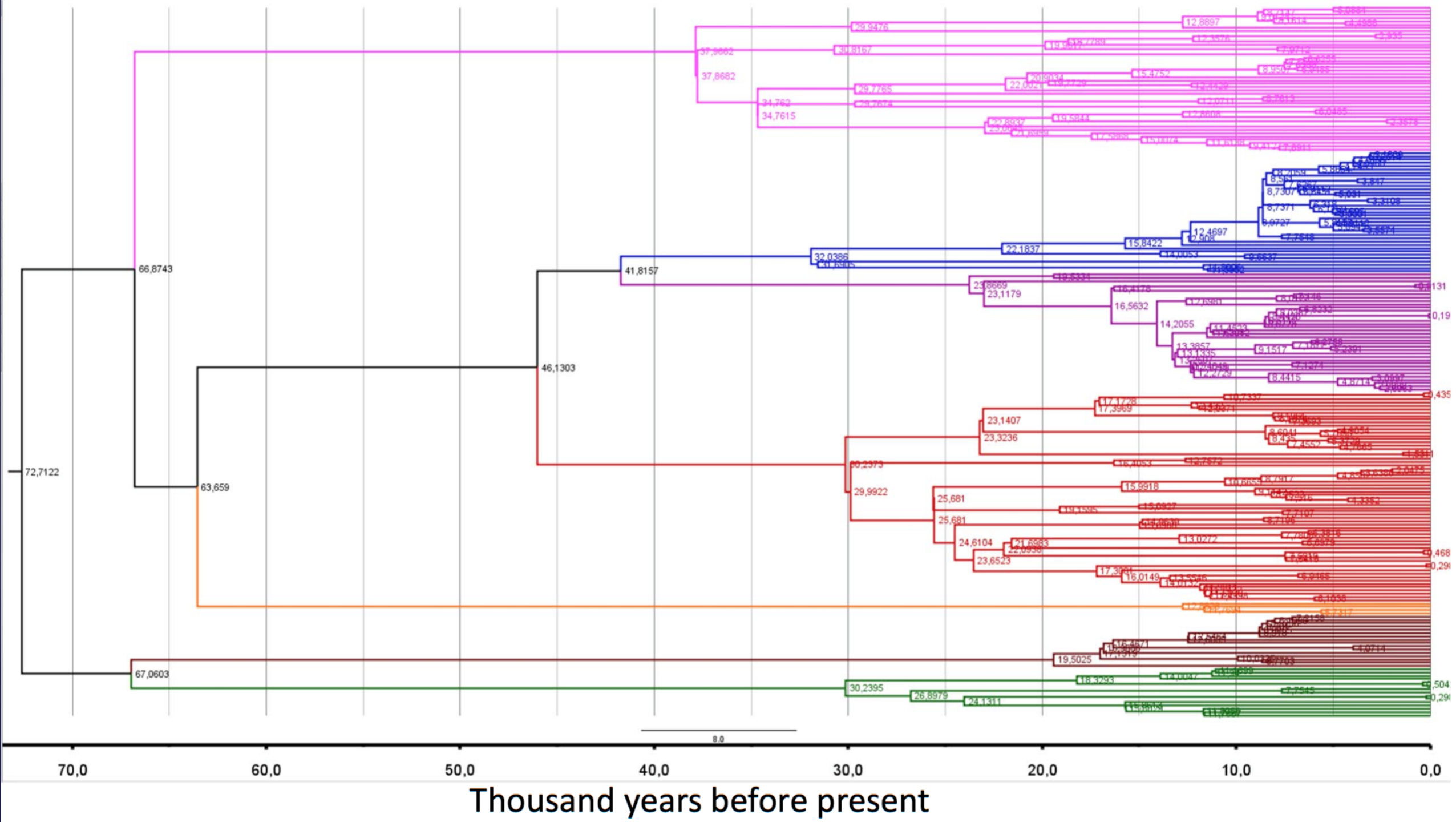
India, East Africa
(lineage 3)

Europe, America, Africa
(lineage 4)

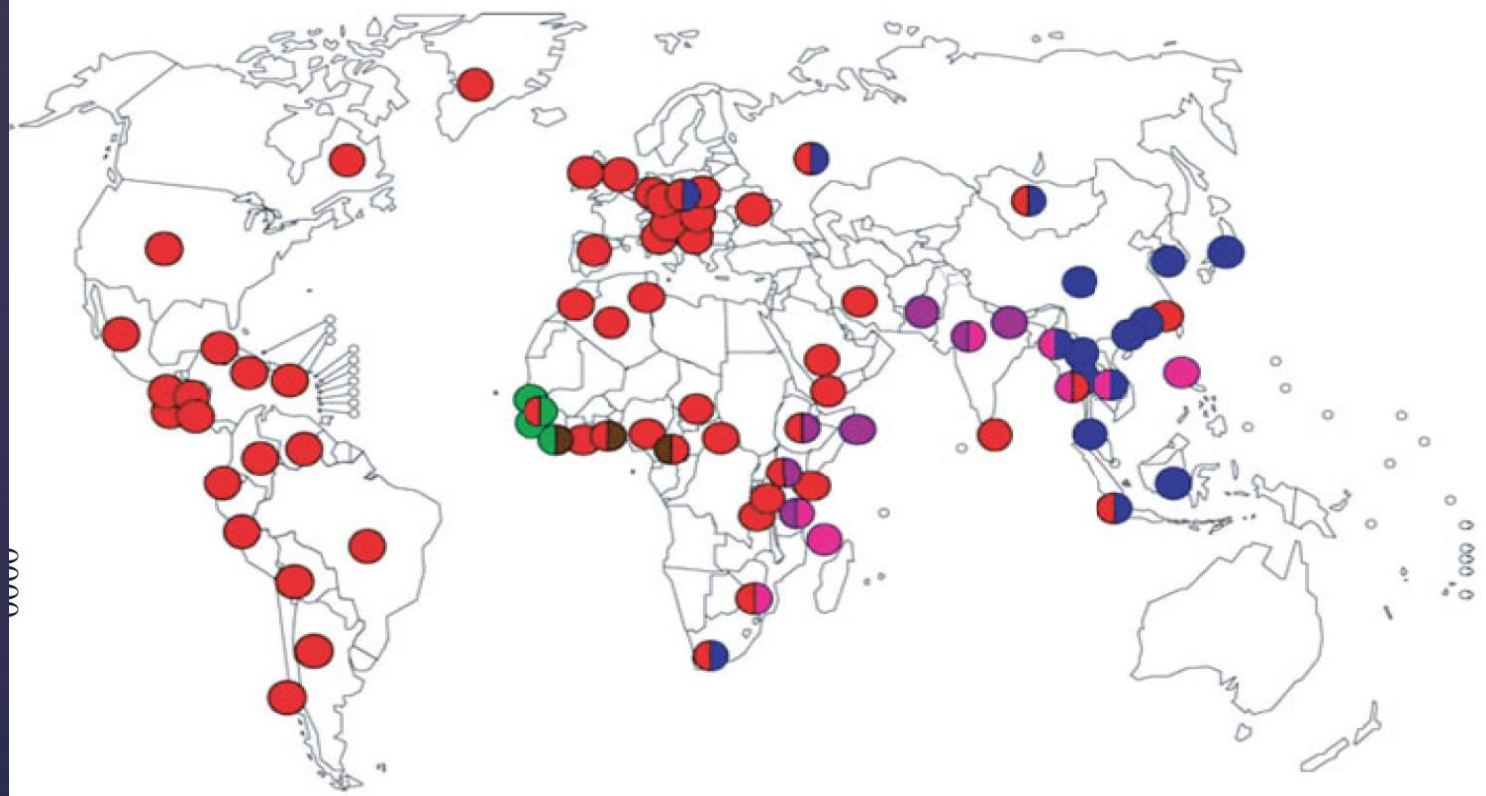


West Africa 1
(lineage 5)

West Africa 2
(lineage 6)



Afrika'dan Çıkış ve Afrika'ya Geri Dönüş Hipotezi



The Philippines
(lineage 1)

East Asia
(lineage 2)

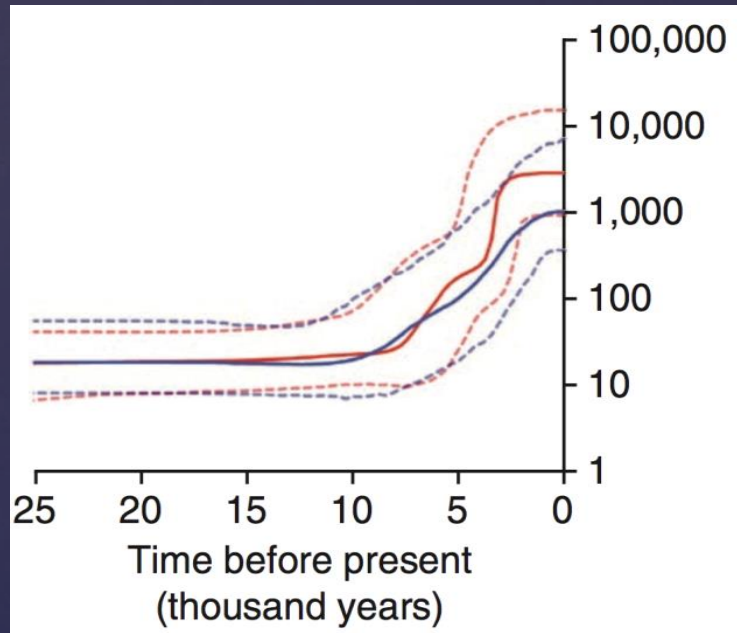
India, East Africa
(lineage 3)

Europe, America, Africa
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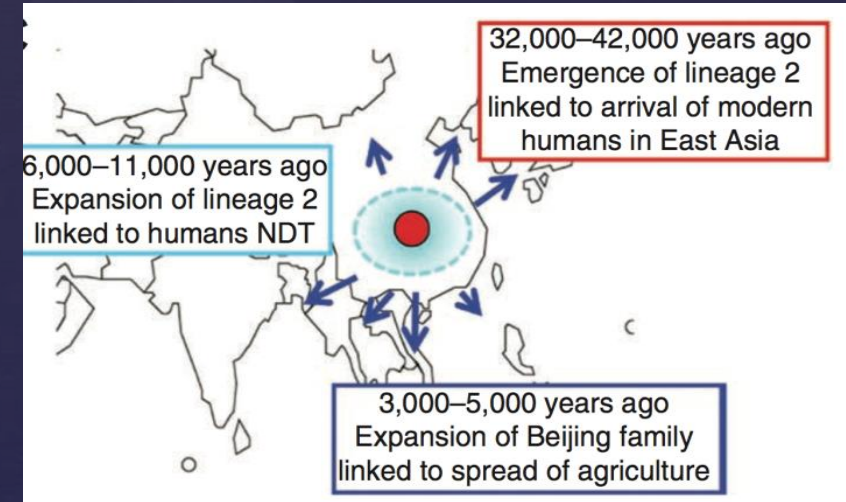
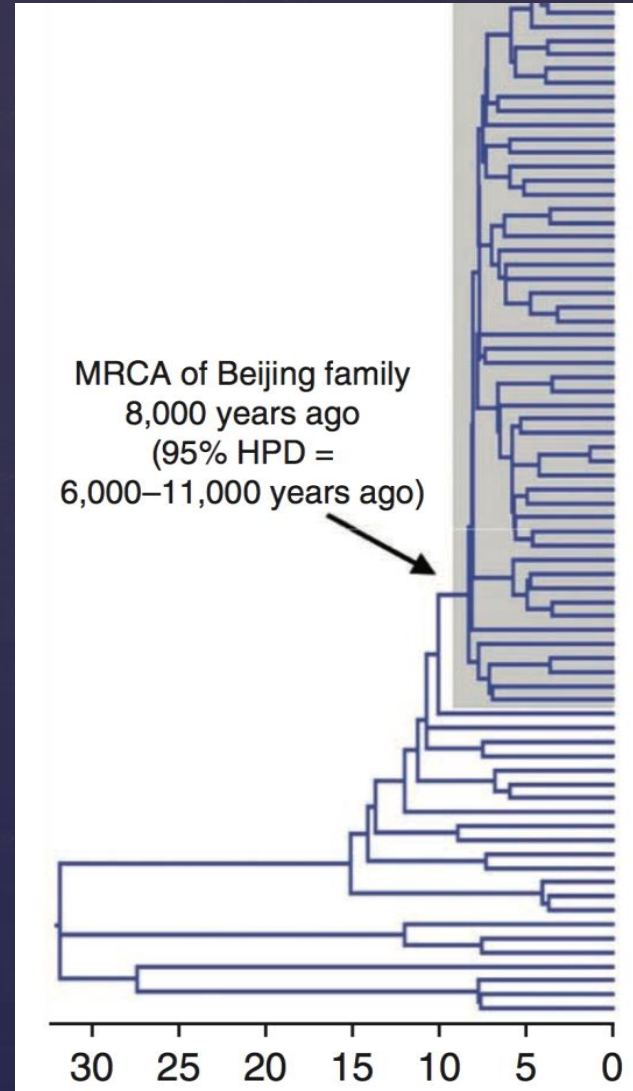
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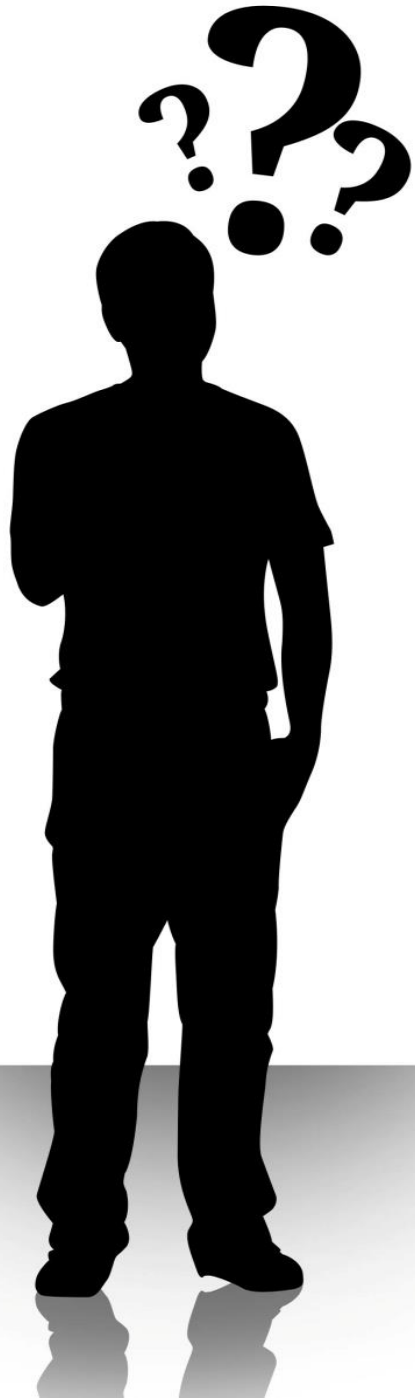
- *Cilalı Taş Devrine gelirken..*



Mitokondriyal gen grupları artıyor..



Out-of-Africa migration and Neolithic coexpansion of *M. tuberculosis* with modern humans
Comas et. al, Nature Genetics, 2013



- Sibirya'da 2000 yıllık insan kalıntıları
 - M. bovis
- Peru'da 1000 yıllık insan kalıntıları
 - M. pinnipedi

Letter to the Editor: Was Tuberculosis Present in *Homo erectus* in Turkey?



- Konakçı – patojen ilişkisi

- *NRAMP1/SLC11A1* → Akciğer tüberkülozu

- Vietnam'da *TLR2 T597C* → *Lineage 2*

- Gana'da *MBL2 G57E* → *M. Africanum*

- Gana'da *IRGM 261TT* → *Lineage 2'*ye direnç

- *Mannose receptor*

- *Dendritic cell-specific ICAM-3*

- *Dectin-1*

- *Toll-like receptors*

- *Complement receptor 3*

- *Nucleotide oligomerization domain*

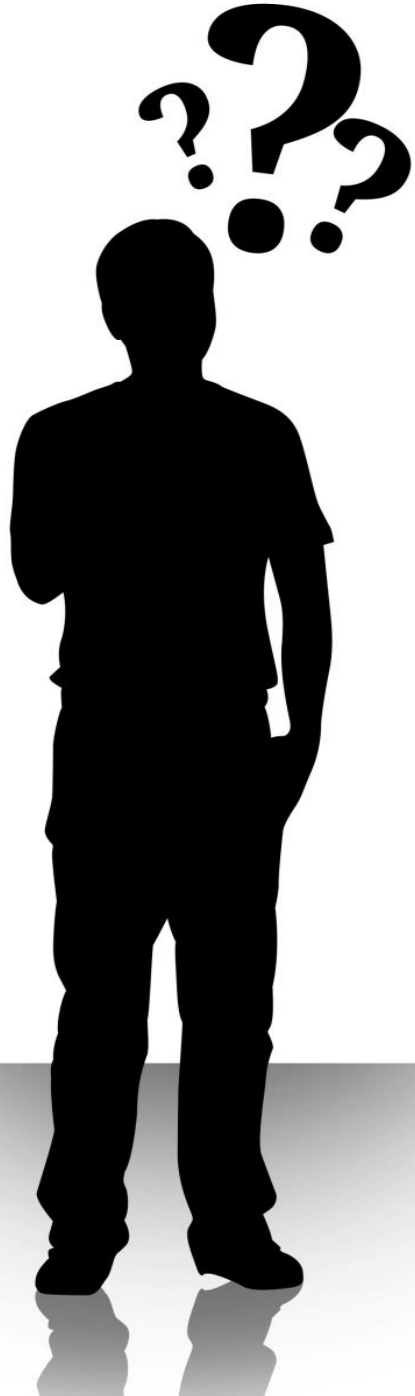
- *Vitamin D nuclear receptor*

- *Soluble C-type lectins*

- *TNF, IL-1 β , IL-6, IL-10, IL-12, IL-18*

- *MCP-1, RANTES, CXCL10*

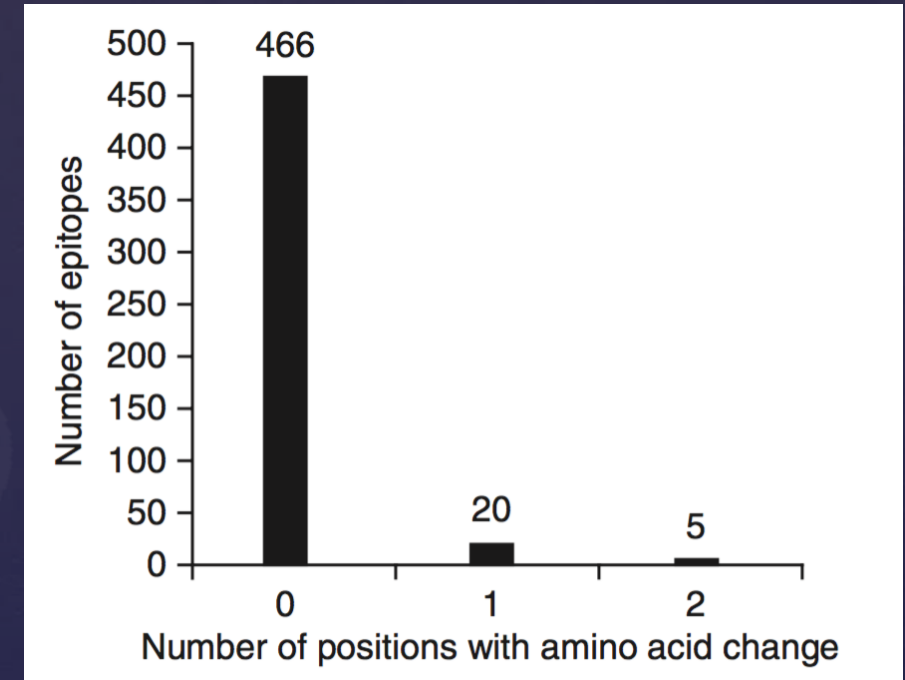
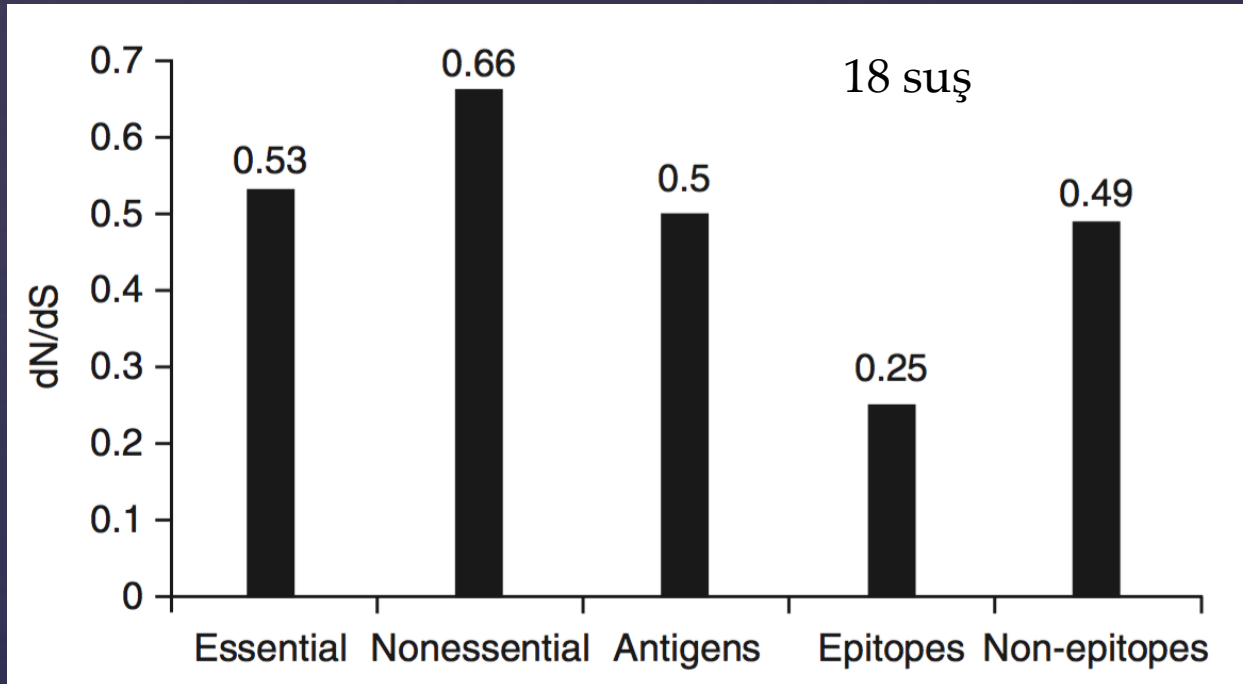
- *iNOS, SLC11A1*



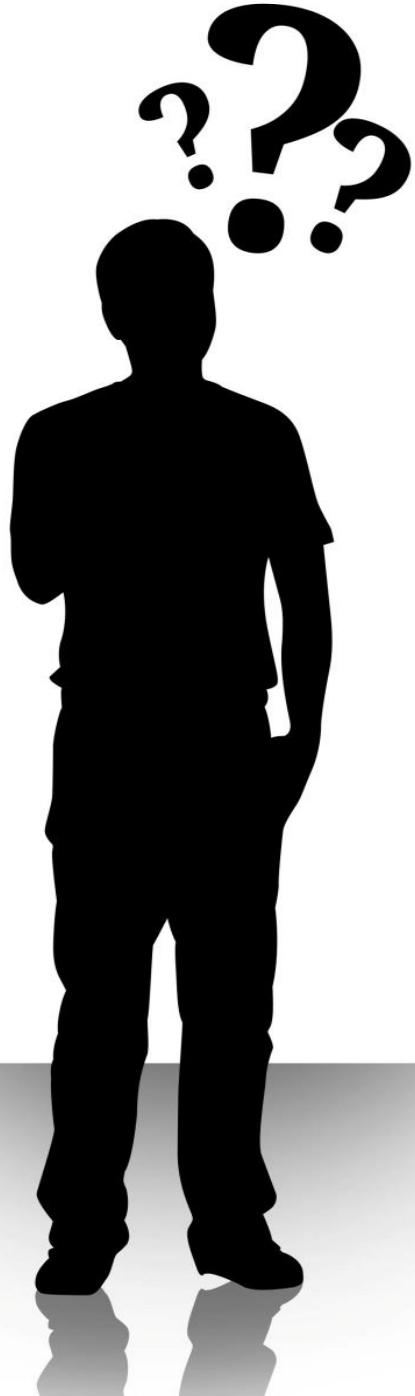
- Farklı coğrafyalarda farklı birliktelikler..
- Aşı?
- BCG Pekin suşunu seçiyor mu?

Risk factor	Total no. patients infected with Beijing clade	No. (%) patients infected with atypical Beijing strain	Odds ratio (95% confidence interval)	
			Crude	Adjusted*
BCG† vaccination				
No	249	69 (27.7)	1	1
Yes	265	55 (20.8)	0.68 (0.46–1.03)	0.60 (0.38–0.95)
Unknown	164	31 (18.9)	0.61 (0.38–0.98)	0.61 (0.36–1.04)
Total	678	155 (22.8)		

Kremer K, et al.
Vaccine-induced immunity circumvented by typical
Mycobacterium tuberculosis Beijing strains. Emerging infectious diseases 2009.



Human T cell epitopes of *Mycobacterium tuberculosis* are evolutionarily hyperconserved.
Comas et. al, Nature Genetics, 2010



- Diğer mikroorganizmalara göre daha az mutasyon..
 - Horizontal gen değişimi yok..
 - Epitoplar benzer..
-
- 3 milyon yıllık paraziter ilişki olabilir mi?

Big Brains, Meat, Tuberculosis, and the Nicotinamide Switches: Co-Evolutionary Relationships with Modern Repercussions?

Adrian C. Williams¹ and Robin I.M. Dunbar²

¹Institute for Cognitive and Evolutionary Anthropology, University of Oxford, 64 Banbury Road, Oxford, OX2 6PN, UK.

²Department of Experimental Psychology, University of Oxford, South Parks Rd., Oxford OX1 3UD, UK.

Corresponding author email: adrian.williams@uhb.nhs.uk

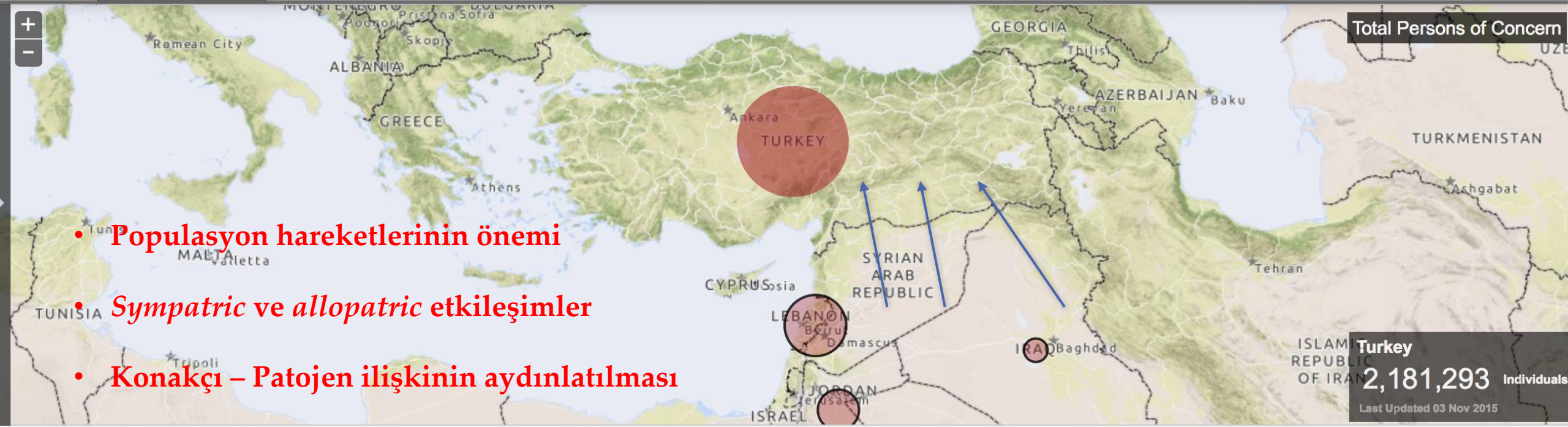
⌘ Niasin → Nikotinamid → Merkezi sinir sistemi gelişimi

⌘ *Homo ergaster* → 1.8 milyon yıl önce

⌘ *Homo heidelbergensis* → 500 bin yıl önce

⌘ *Homo sapiens* → 200 bin yıl önce

⌘ *Welcomed hosts can turn to hostile!*



This map does not imply official endorsement or acceptance by the United Nations

Total Persons of Concern

4,289,994

Last Updated 03 Nov 2015

Source - UNHCR, Government of Turkey

Registered Syrian Refugees

4,289,994

Last Updated 03 Nov 2015

Source - UNHCR, Government of Turkey

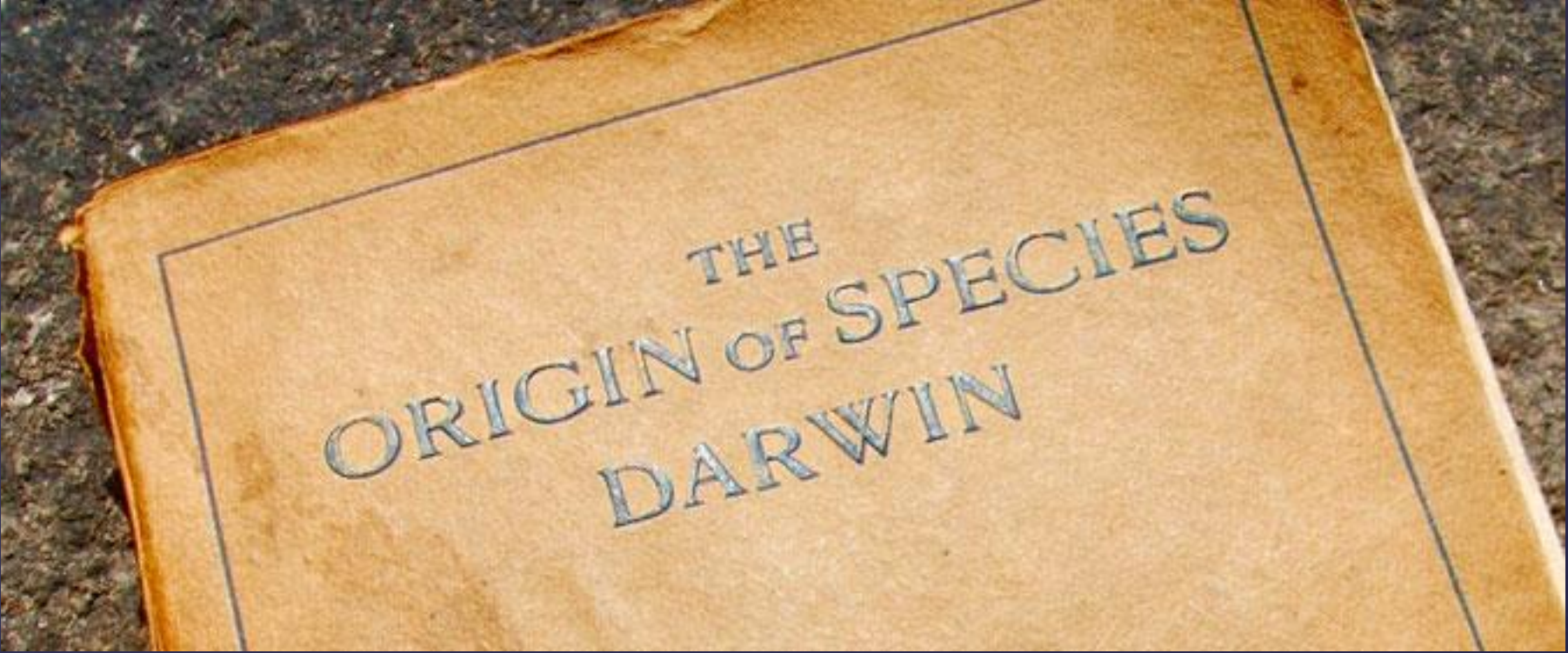
This figure includes 2.1 million Syrians registered by UNHCR in Egypt, Iraq, Jordan and Lebanon, 1.9 million Syrians registered by the Government of Turkey, as well as more than 26,700 Syrian refugees registered in North Africa.

Regional demographic breakdown below is based on available data from Egypt, Iraq, Jordan and Lebanon



2015 Regional Refugee and Resilience Plan (3RP)

3RP Regional Guidance Kit for 2016 Planning



Teşekkür ederim..