

BIOL3120: Human genetics and evolutionary medicine

LECTURE 7: HUMAN GENETIC DIVERSITY AND EVOLUTION



Lecture 7: Human genetic diversity and evolution



On completion of this lecture you will be able to,

- Describe the origins and maintenance of human genetic variation
- Understand how pieces of the genome can be traced through populations
- Explain that genetic variation persists, within and between human populations and explain how variation can explain differences in phenotypes between populations, with examples



Human genetic variation

- Why are we so phenotypically different?
- Common vs. rare:
 - Common variants – minor allele frequency (polymorphism) > 1% in a population
 - Rare variants – <1% in a population
- Neutrality
 - The vast majority of genetic variants are likely neutral = no contribution to phenotypic variation
 - Some may reach significant frequencies, but this is chance 

The origin of genetic variation

- Evolution is based on genetic change in a population. Where does genetic change come from?
- The rate of evolution depends on the amount of genetic change. What maintains genetic variation?
- Classical view was that evolution acted very slowly and there is not a lot of variation in nature.
- Now more evidence that there is a lot of genetic variation upon which selection can act.
- The study of human genetic variation has evolutionary significance and medical applications. It may be important because some disease-causing alleles occur more often in people from specific geographic regions.



Genetic variation is greatest in Africa

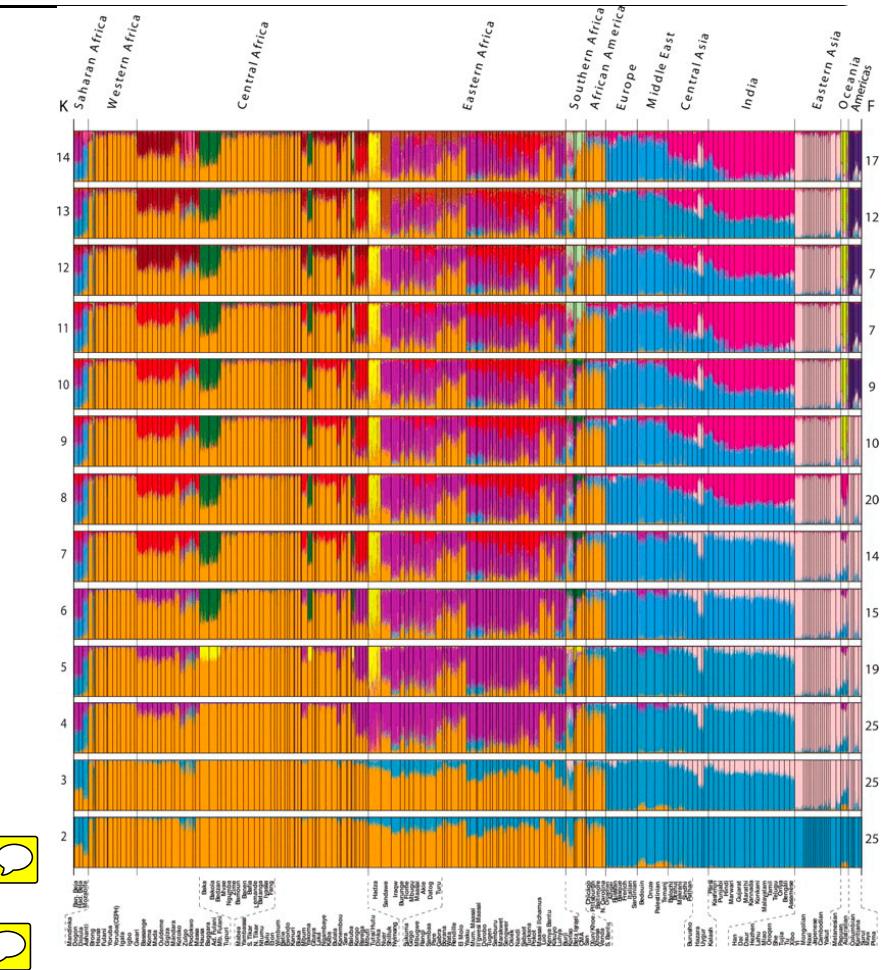


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- Modern humans originated in Africa ~200,000 years ago and then spread across the rest of the globe within the past ~100,000 years
 - Thus, modern humans have existed continuously in Africa longer than in any other geographic region and have maintained relatively large effective population sizes, resulting in high levels of within-population genetic diversity
 - Africa contains more than 2000 distinct ethnolinguistic groups representing nearly one-third of the world's languages
 - Because of considerable environmental diversity, African populations show a range of linguistic, cultural, and phenotypic variation

Genetic variation is greatest in Africa

- Studied 121 African populations, four African American populations, and 60 non-African populations for patterns of variation at 1327 nuclear microsatellite and insertion/deletion markers
- Identified 14 ancestral population clusters in Africa that correlate with self-described ethnicity and shared cultural and/or linguistic properties
- Observed high levels of mixed ancestry in most populations, reflecting historical migration events across the continent.
- Provide evidence for shared ancestry among geographically diverse hunter-gatherer populations

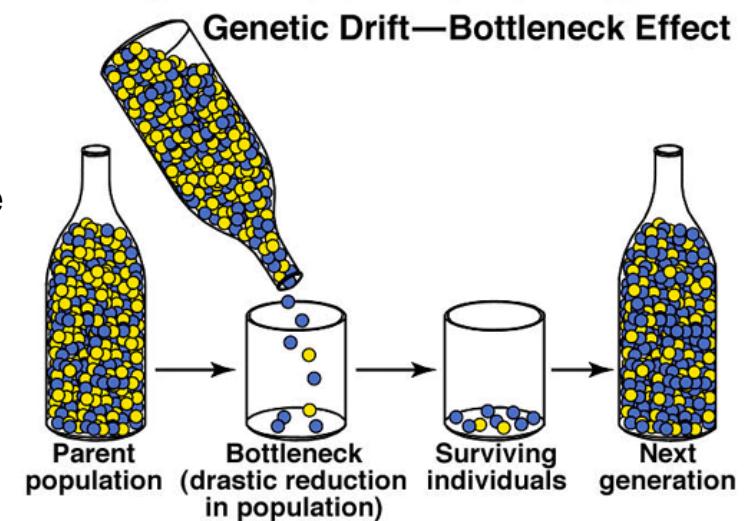
Tishkoff et al., 2009. The Genetic Structure and History of Africans and African Americans. *Science*, 324(5930) 1035-44.



Out of Africa

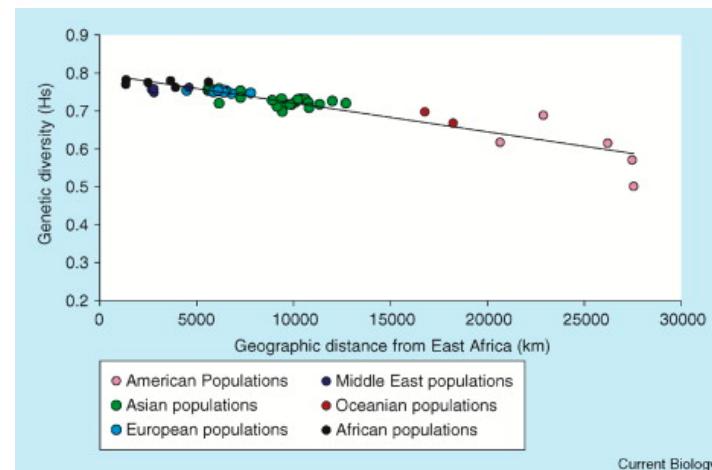
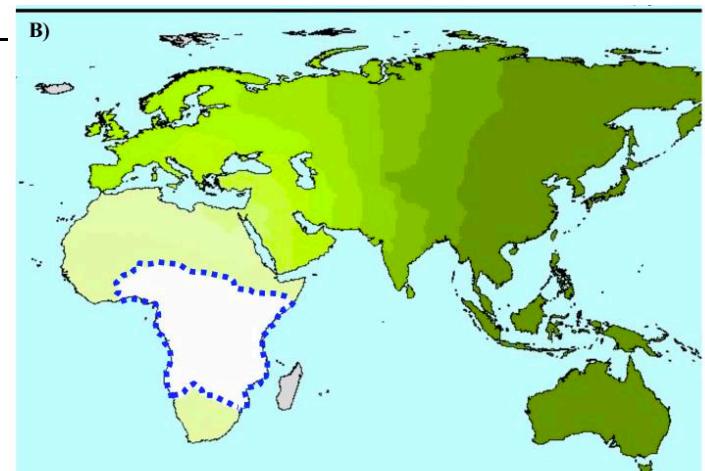
- Founder effects: when populations expand, local groups become isolated from each other and genetic differences begin to accumulate
- Each subsequent founder effect further reduces variation (specific populations in Africa are found to be the most diverse among all humans)

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Ancient population bottlenecks on human diversity

- Dataset comprising 51 populations distributed worldwide that have been typed at 377 autosomal microsatellite loci
- Africa is the most genetically diverse place on Earth
- Geographic distance from East Africa along likely colonisation routes is an excellent predictor for genetic diversity of human populations
- History of colonisation of the world characterised by a very large number of small bottlenecks

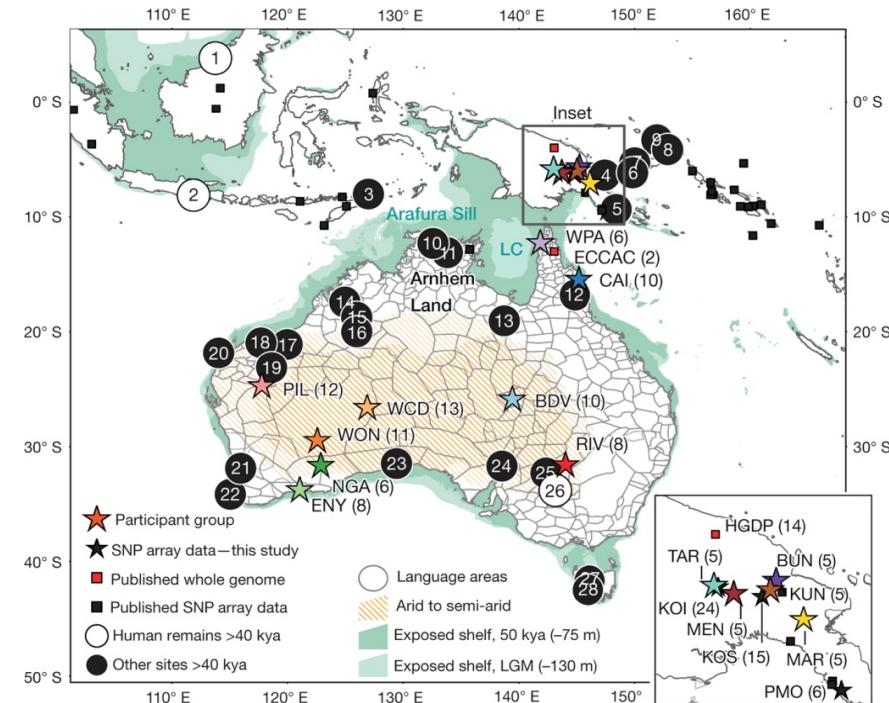


Prugnolle et al., 2005. Geography predicts neutral genetic diversity of human populations. Current Biology. 15(5), R159-E160.

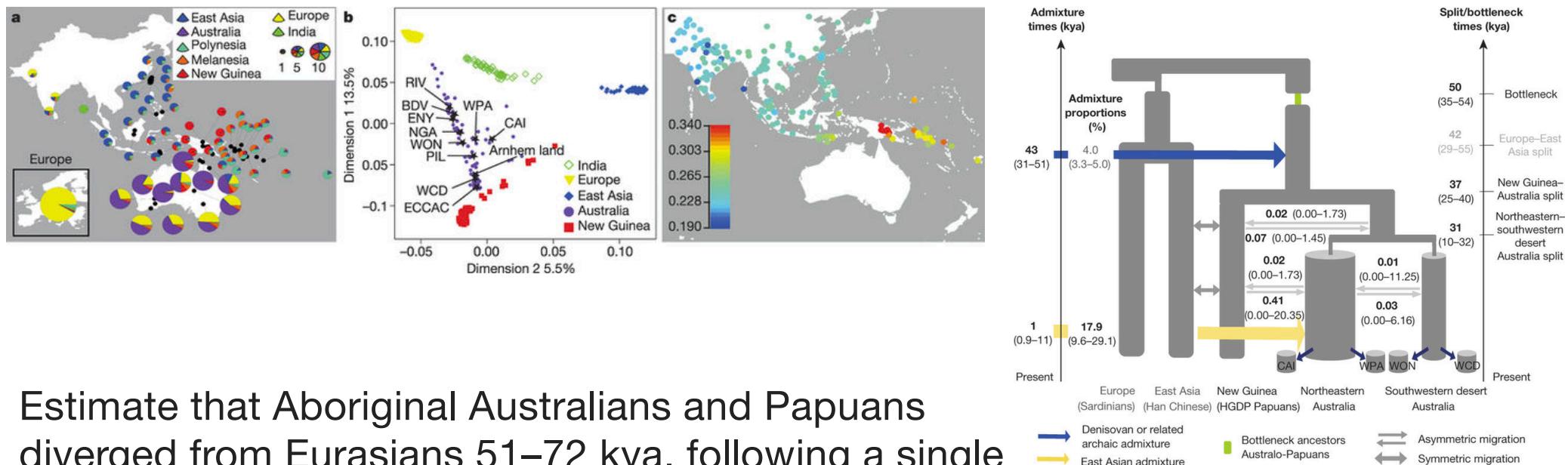
Current Biology

A genomic history of Aboriginal Australia

- During most of the last 100,000 years, Australia, Tasmania and New Guinea formed a single continent, Sahul, which was separated from Sunda (the continental landmass including mainland and western island Southeast Asia) by a series of deep oceanic troughs never exposed by changes in sea level
- Colonization of Sahul is thought to have required at least 8 sea crossings between islands, potentially constraining the occupation of Australia and New Guinea by earlier hominins.
- Aboriginal Australian and Papuan samples used in this study, as well as archaeological sites and human remains dated to ~40-60 kya in southern Sunda and Sahul



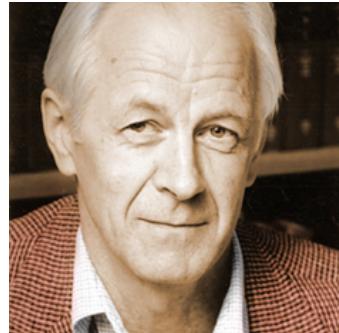
A genomic history of Aboriginal Australia



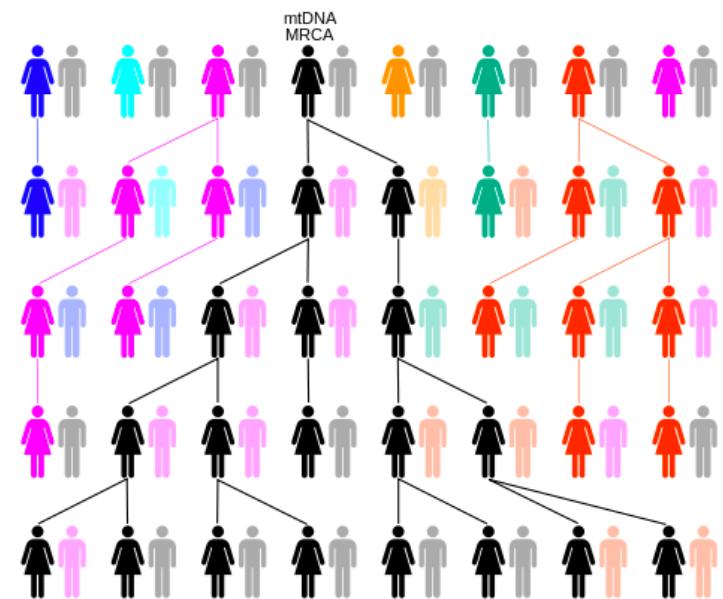
Estimate that Aboriginal Australians and Papuans diverged from Eurasians 51–72 kya, following a single out-of-Africa dispersal



Mitochondrial Eve

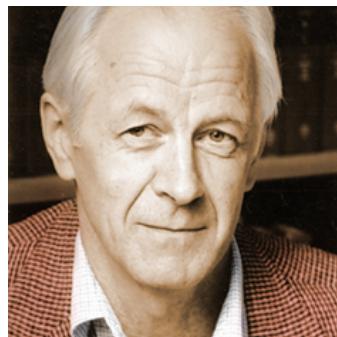


Allan Wilson

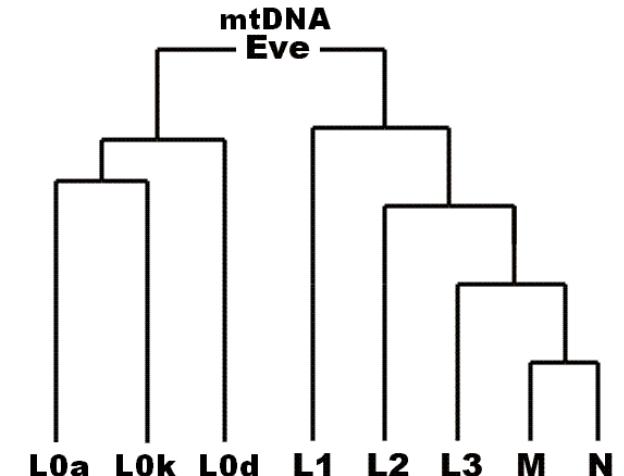


Mitochondrial Eve

- We can use mitochondrial DNA to reconstruct human evolutionary history through maternal lines
- Wilson et al (1987) collected mtDNA samples from people all over the world
- Using phylogenetics it is possible to find the ancestral sequence
- The most recent matrilineal common ancestor of all currently living humans, i.e., the most recent woman from whom all living humans descend in an unbroken line purely through their mothers

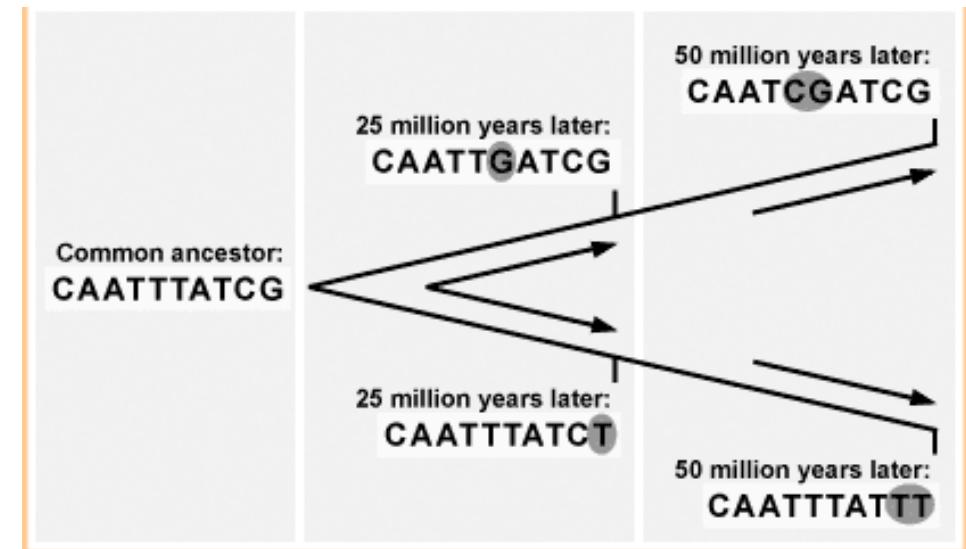


Allan Wilson



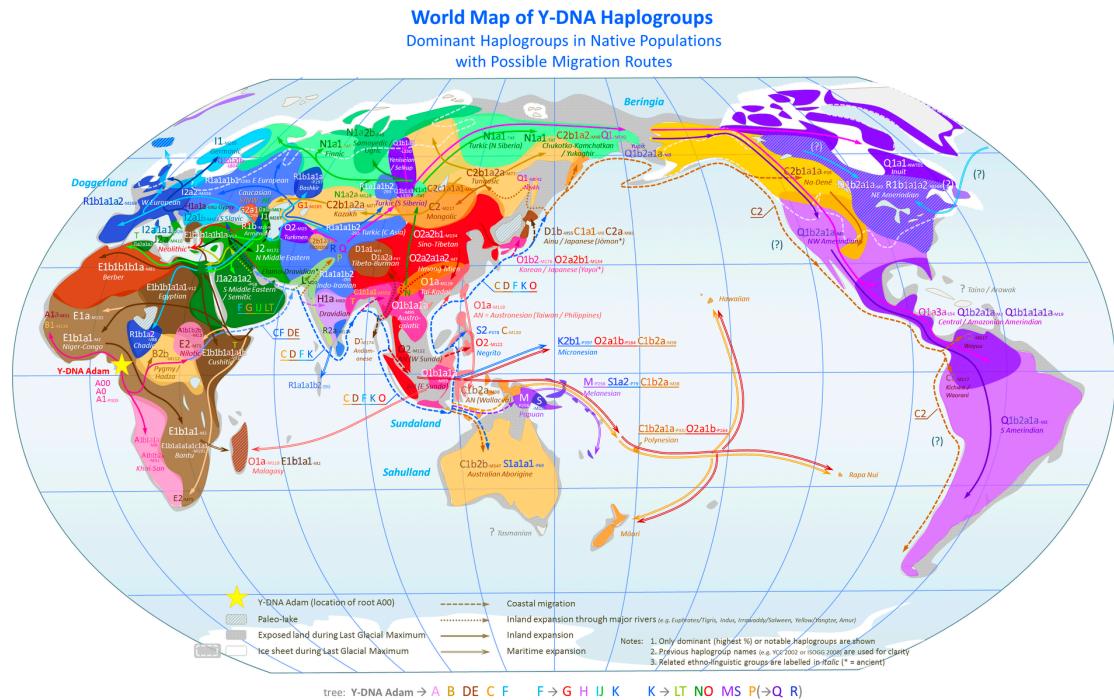
Mitochondrial Eve

- Along any particular line of descent, mitochondrial DNA accumulates mutations at the rate of approximately one every 3,500 years per nucleotide
- The molecular clock allows us to date divergence events
- 170,000 and 100,000 years ago



Y chromosome Adam

- Y-chromosomal most recent common ancestor
- All currently living males are directly derived from the Y chromosome of this remote ancestor
- Not permanently fixed to a single individual, but can advance over the course of human history as paternal lineages become extinct
- Estimates of the age of the Y-MRCA range around 160,000 to 300,000 years ago
- Likely origin is the north-western quadrant of the African continent



Scozzari et al., 2012. Molecular Dissection of the Basal Clades in the Human Y Chromosome Phylogenetic Tree. PLoS One, 7(11): e49170.

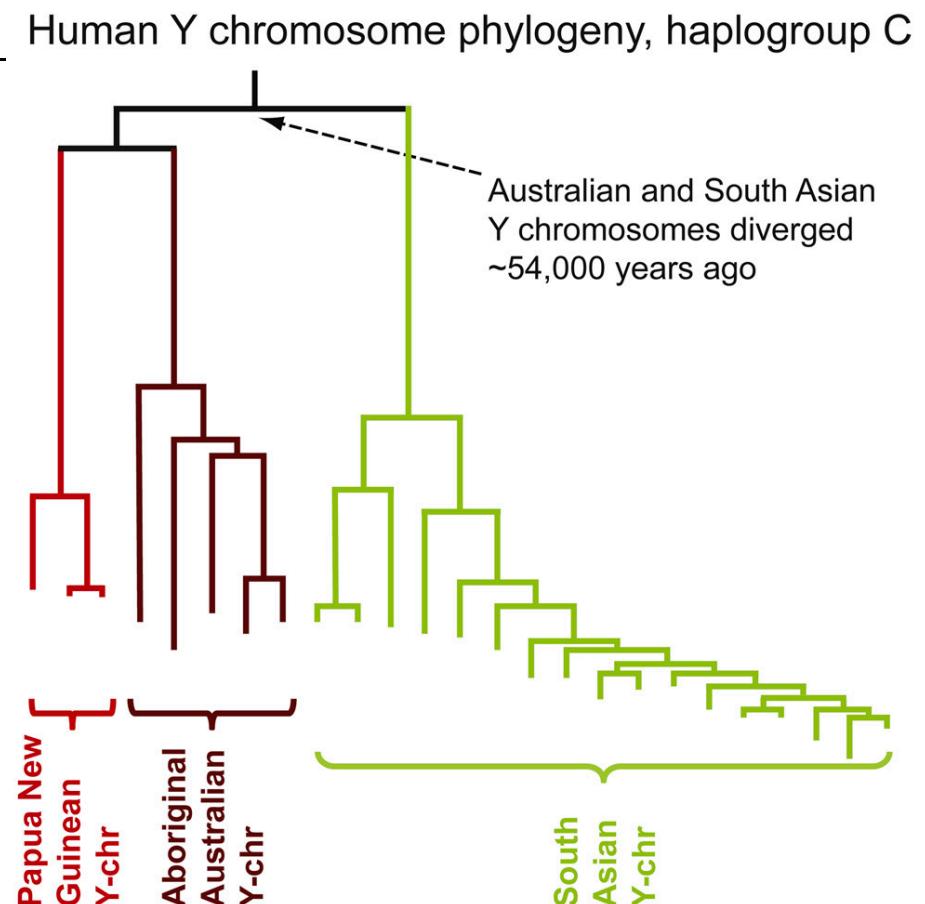
Deep Roots for Aboriginal Australian Y Chromosomes

Australia was one of the earliest regions outside Africa to be colonized by fully modern humans

Sequenced 13 Aboriginal Australian Y chromosomes to investigate their divergence times from Y chromosomes in other continents

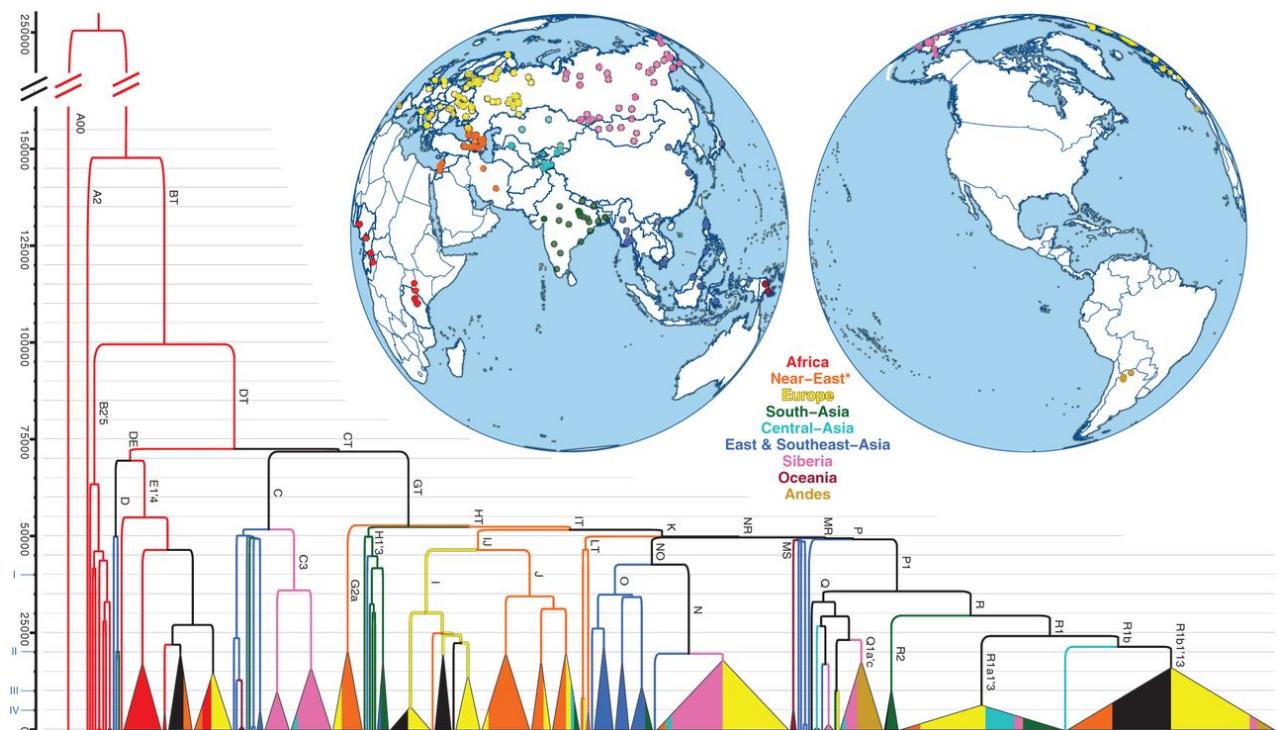
Divergence times dating back to ~50 kya, thus no evidence for recent gene flow from India into Australia

Bergstrom et al., 2016. Current Biology.



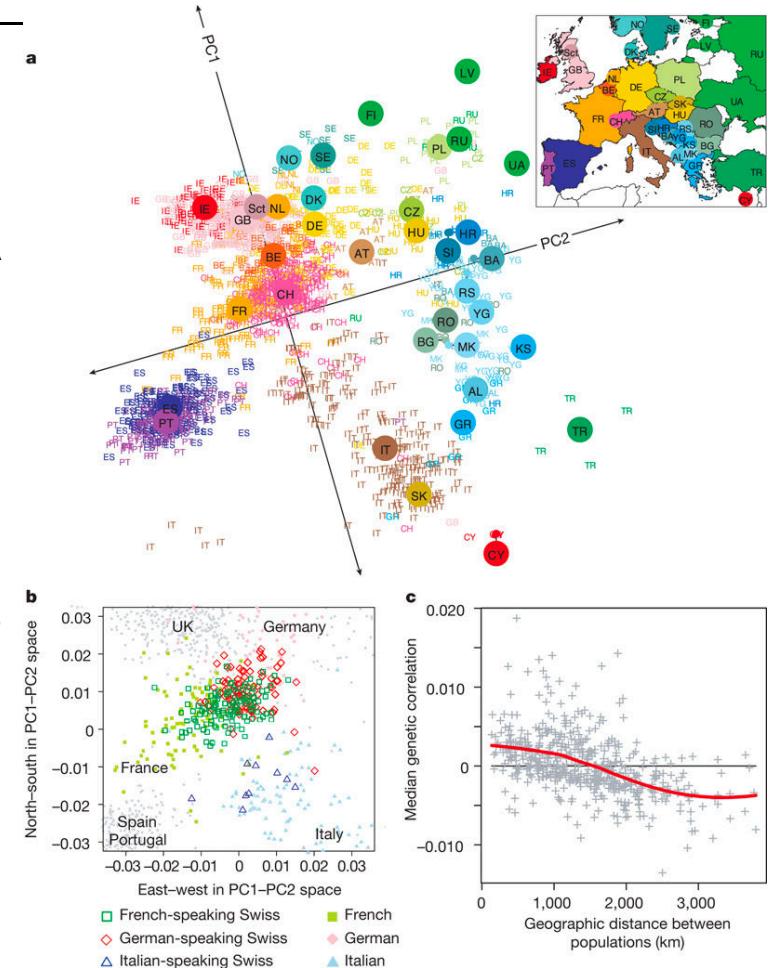
Human Y-chromosome variation

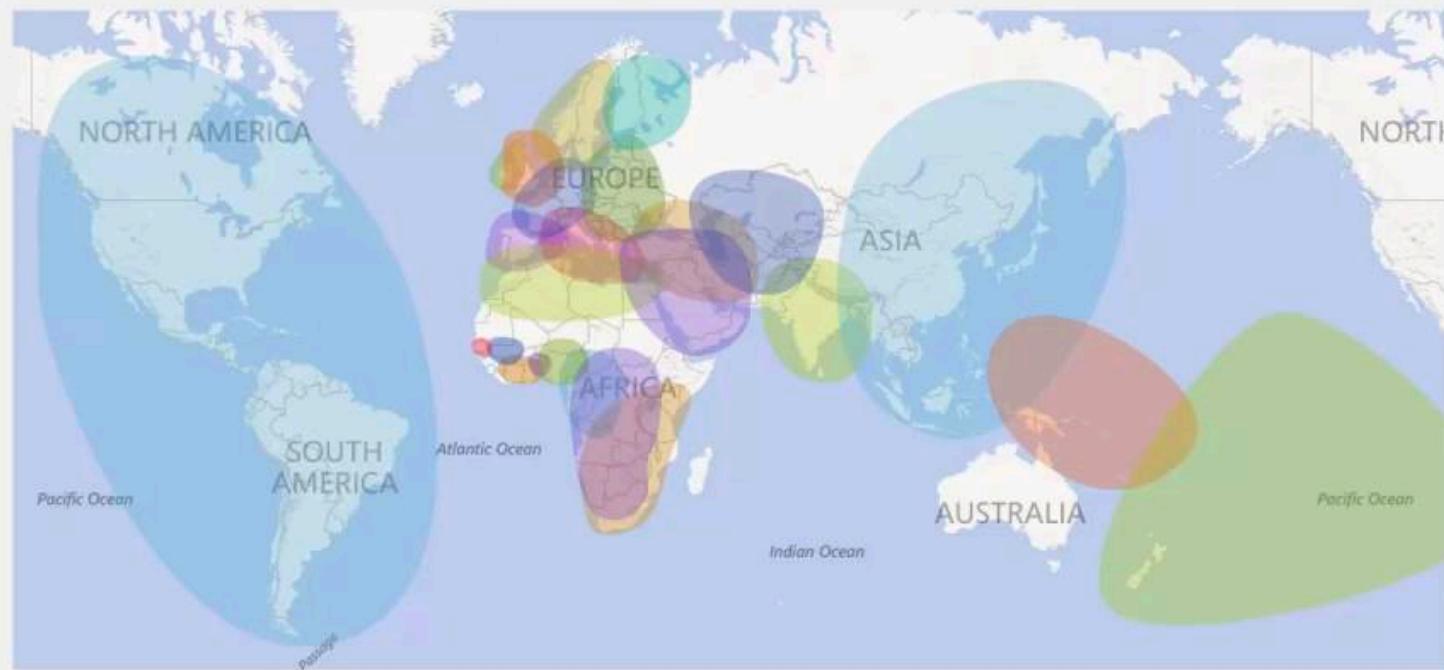
- The phylogenetic tree of 456 whole Y chromosome sequences and a map of sampling locations.
- The data infer recent bottleneck in Y-chromosome lineages dating to the last 10k y
- Hypothesise that recent bottlenecks are caused by cultural changes



Genes mirror geography within Europe

- Advances in high-throughput genotyping technology have markedly improved our understanding of global patterns of human genetic variation
- 3,000 European individuals genotyped at over half a million variable DNA sites in the human genome
- Despite low average levels of genetic differentiation among Europeans, found close correspondence between genetic and geographic distances
- A geographical map of Europe arises naturally as an efficient two-dimensional summary of genetic variation in Europeans
- The results emphasise that when mapping the genetic basis of a disease phenotype, associations can arise if genetic structure is not properly accounted for
- The results are relevant to the prospects of genetic ancestry testing; an individual's DNA can be used to infer their geographic origin with surprising accuracy



**AFRICA**

Africa North
Africa South-Central
Hunter-Gatherers
Africa Southeastern Bantu
Benin/Togo
Cameroon/Congo
Ivory Coast/Ghana
Mali
Nigeria
Senegal

AMERICA

Native American
ASIA
Asia Central
Asia East
Asia South

EUROPE

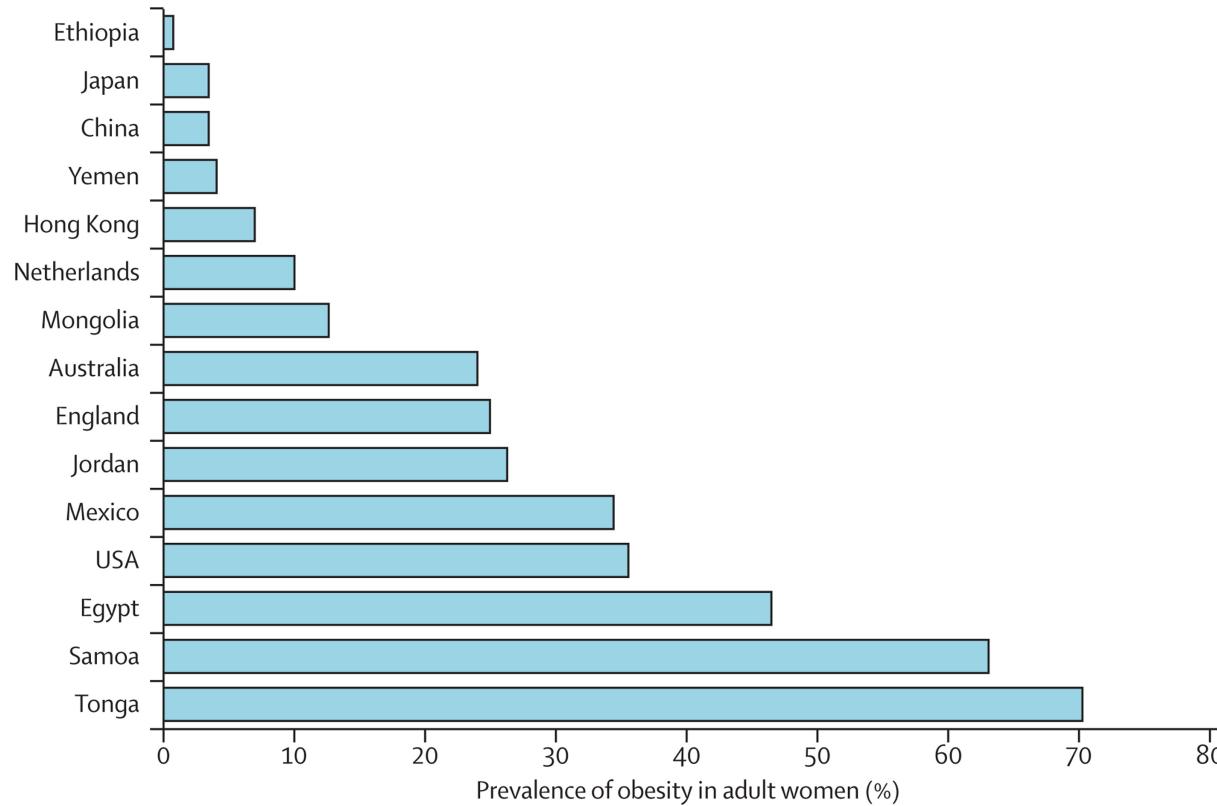
Europe East
Europe West
European Jewish
Finland/Northwest Russia
Great Britain
Iberian Peninsula
Ireland
Italy/Greece
Scandinavia

PACIFIC ISLANDER

Melanesia
Polynesia
WEST ASIA
Caucasus
Middle East

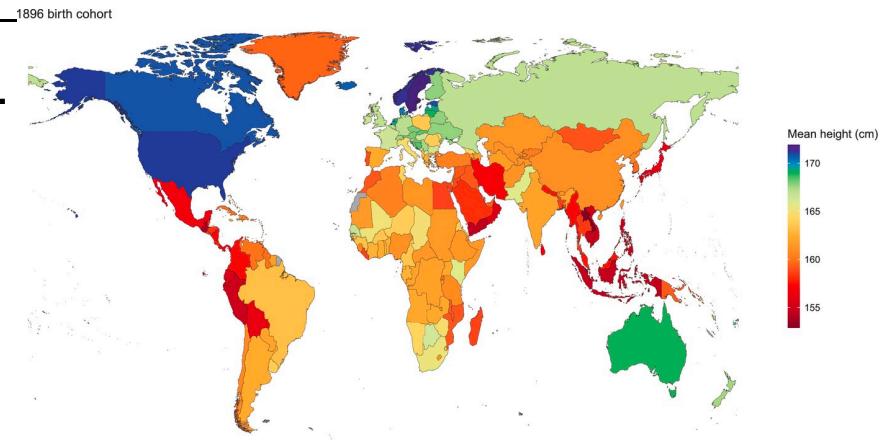
Variation in phenotype

e.g. obesity is highly variable



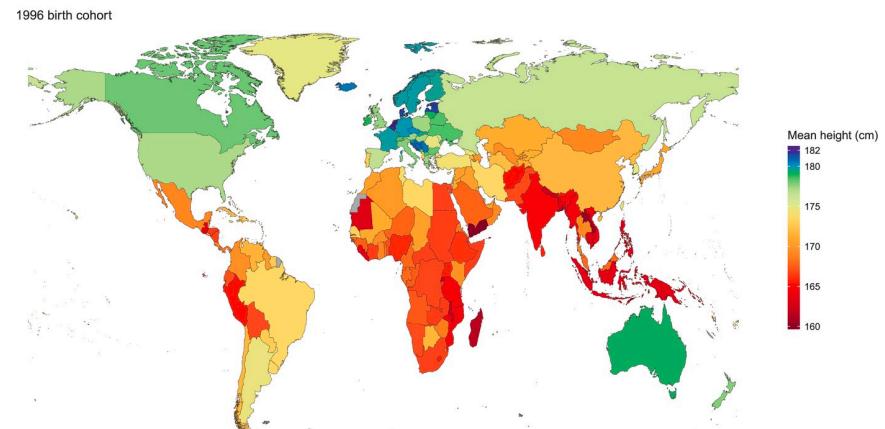
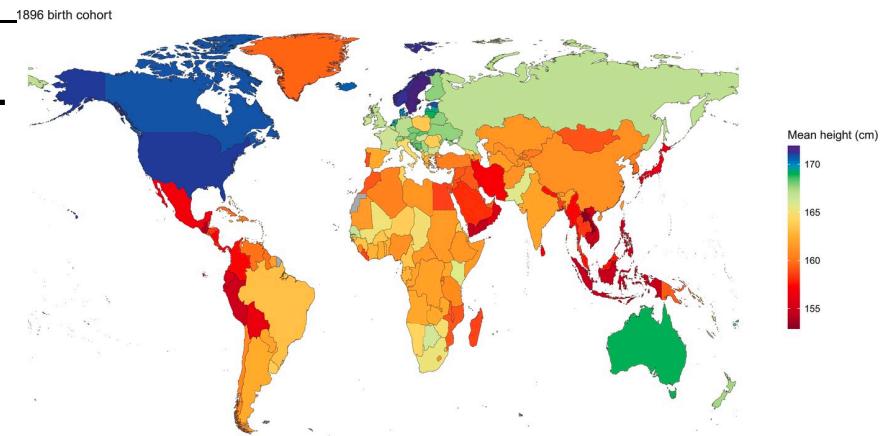
Adult human height

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- People from different countries grow to different heights.



Adult human height

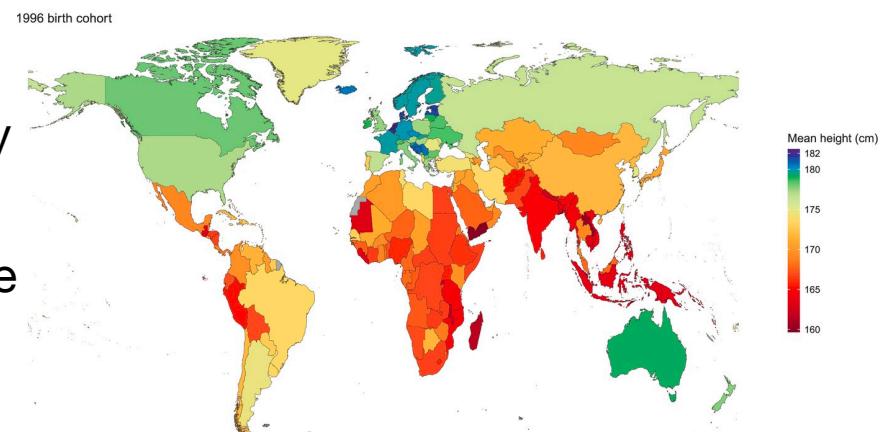
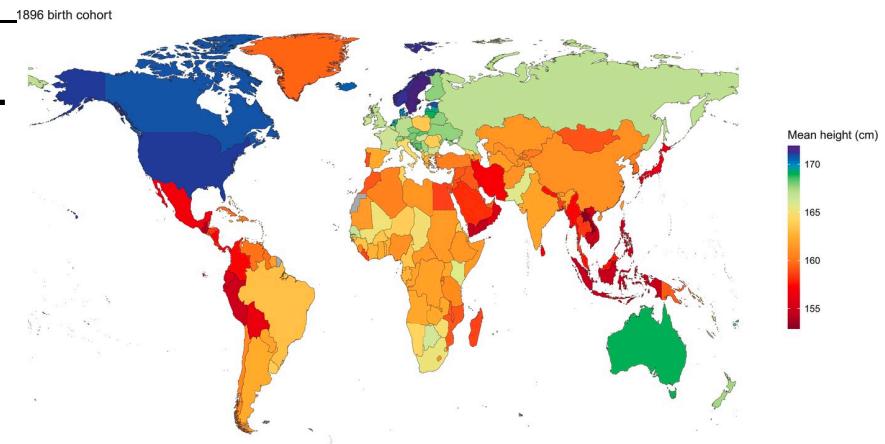
- People from different countries grow to different heights.



DOI: [10.7554/eLife.13410](https://doi.org/10.7554/eLife.13410)

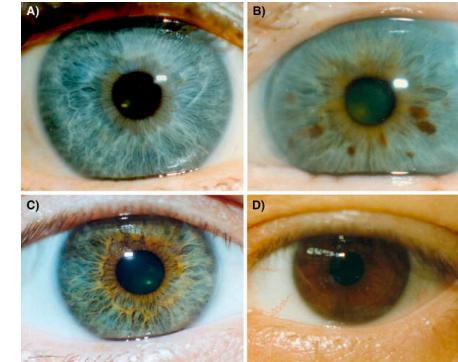
Adult human height

- People from different countries grow to different heights.
- This may be partly due to genetics, but also due to environmental causes.
- For example, children and adolescents who are malnourished, or who suffer from serious diseases, will generally be shorter as adults.
- This is important because taller people generally live longer, are less likely to suffer from heart disease and stroke, and taller women and their children are less likely to have complications during and after birth.
- The tallest people are men born in the Netherlands in the last quarter of 20th century, whose average heights surpassed 182.5 cm



Blue eye colour in humans may be caused by a perfectly associated founder mutation

- By linkage analysis of a large Danish family, finemapped the blue eye color locus to a 166 Kbp region within the *HERC2* gene
- One single haplotype from Denmark
- Data suggest a common founder mutation



Species	Eye color	DNA-Library	DNA sequence
Homo	Blue	hg18_dna	TTCATTTGAGCAT AAAGTG TCAAAGTTCTGCACGCTAT
Homo	Brown	hg18_dna	TTCATTTGAGCAT AAAATGT CAAGTTCTGCACGCTAT
Chimpanzee	Brown	panTro2_dna	TTCATTTGAGCAT AAAATGT CAAGTTCTGCACGCTAT
Rhesus monkey	Brown	rheMac2_dna	TTCATTTGAGCAT AAAATGT CAAGTTCTGCACGCTAT
Horse	Brown	equCab1_dna	TTCACTTGACGCT AAAATGT CAAGTGCTGCACAATGT
Cow	Brown	bosTau2_dna	TTCACTCTGCACGG AAAATGT CAAGTAC-ACACACTGT
Cat	Brown-yellow	felCat3_dna	TTCATTTGCATGT AAAATGT CAAGTACCAACACAATAC
Dog	Brown-yellow	canFam2_dna	TTCATTTGCATGT AAAATGT CAAGTGC-ACACAATAT
Rat	Brown	rn4_dna	TTCATTTGCCGTATT AAAATGT CAA
Mouse	Brown	Mm8_dna	TTCATTTGCCGTAT AAAATGT CAAATGCCATGCACTAT
Consensus sequence - blue eye		Ttca-ttg---- taaGtgtcaa-t-c---- c-tat	
Consensus sequence - brown eye		Ttca-ttg---- taaAtgtcaa-t-c---- c-tat	
Nkx-2.5 target site; match allele for blue eye color			TYAAGTG
CdxX-1 target site; match allele for brown eye color			YAKWAWW

Eiberg, H. et al (2008) *Human Genetics*

Lecture 7: Human genetic diversity and evolution



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- Understand how pieces of the genome can be traced through populations
- Explain that genetic variation persists, within and between human populations and explain how variation can explain differences in phenotypes between populations, with examples