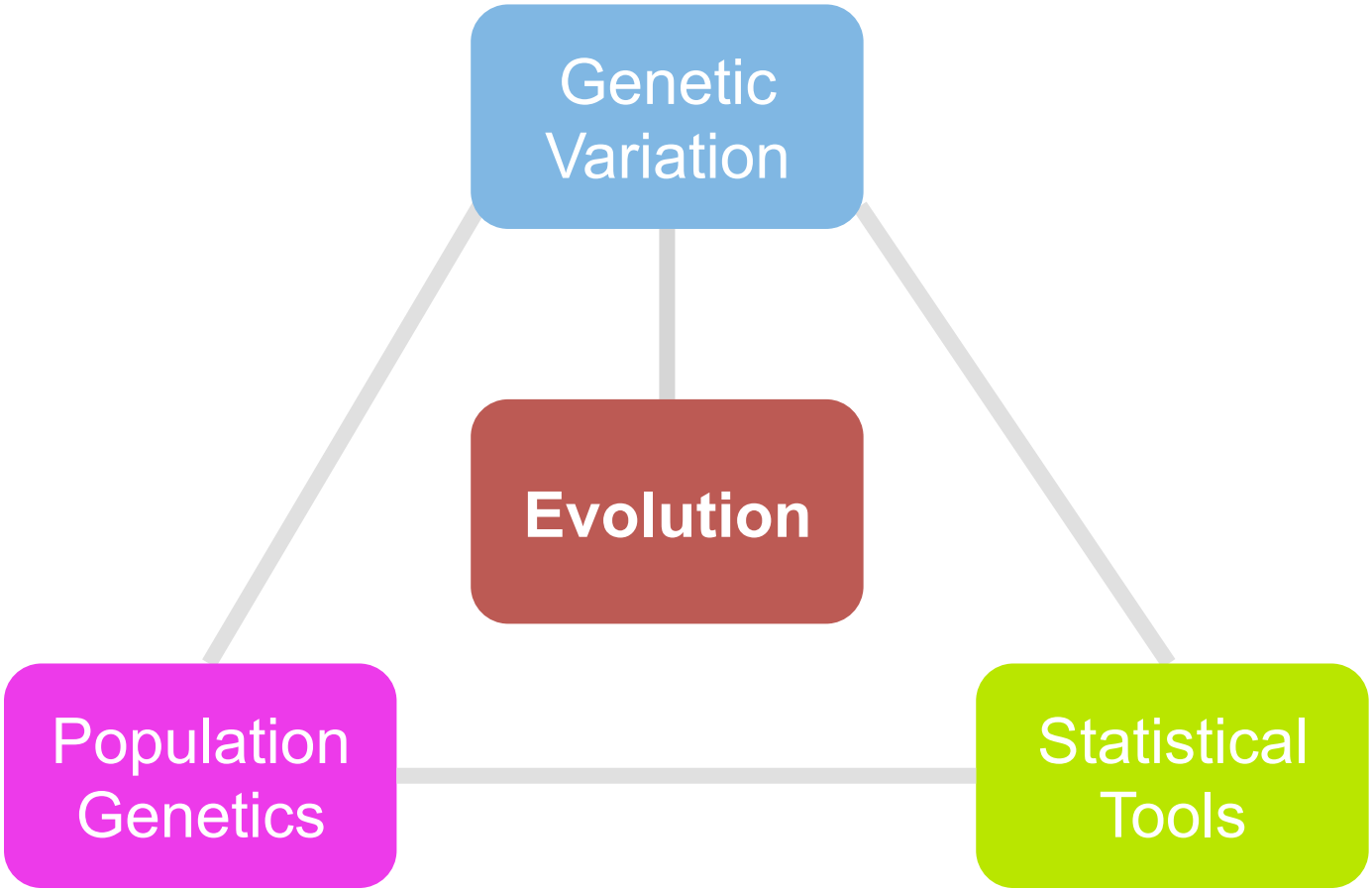
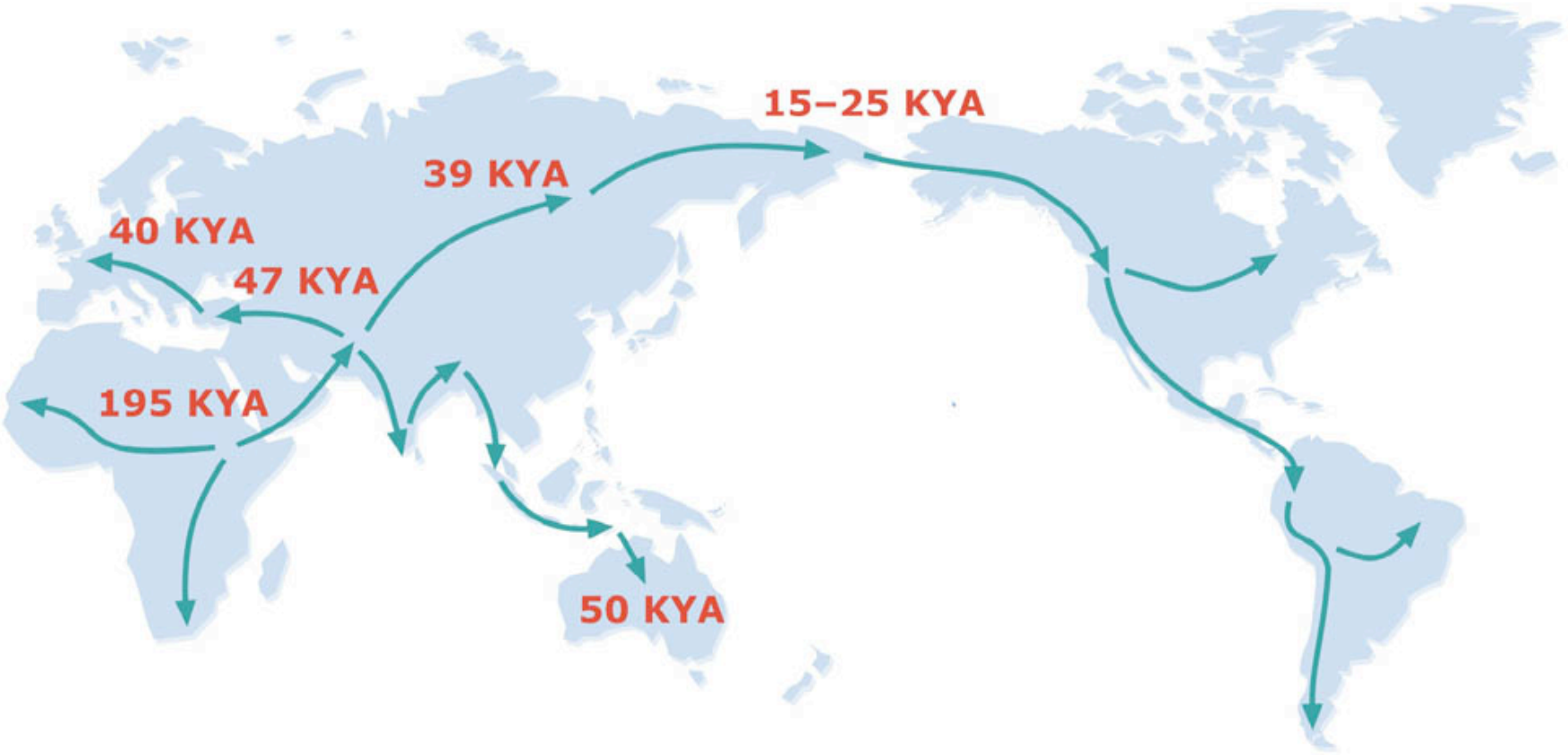
Human adaptation to high altitude

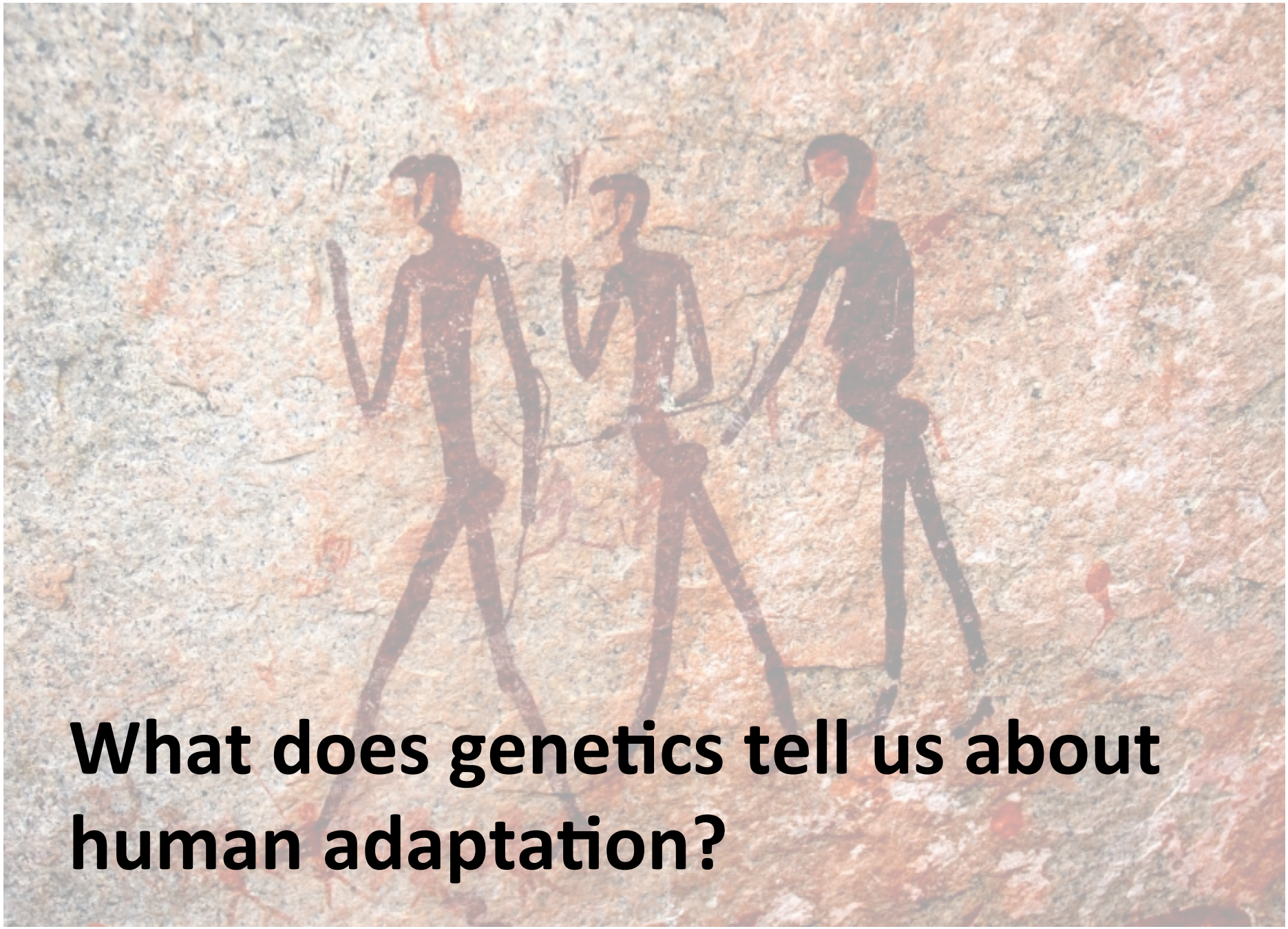
Emilia Huerta Sanchez
Postdoc
UC Berkeley

Elucidating evolution



Human migrations





What does genetics tell us about human adaptation?

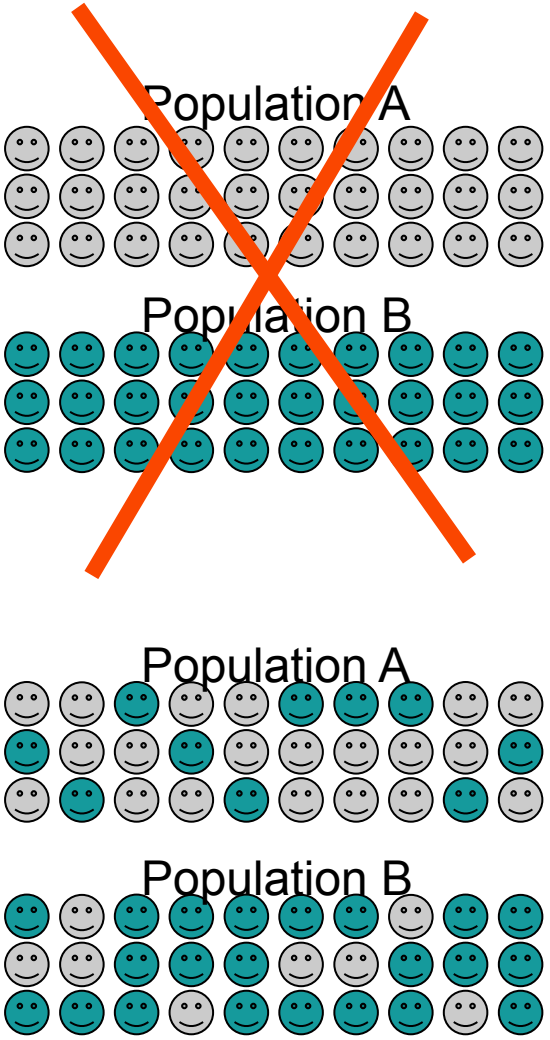
HTTP://WWW.LONELYPLANET.COM/ETHIOPIA/TOURS/TREKKING/HIGHLANDS-OF-ETHIO




So how different are we?

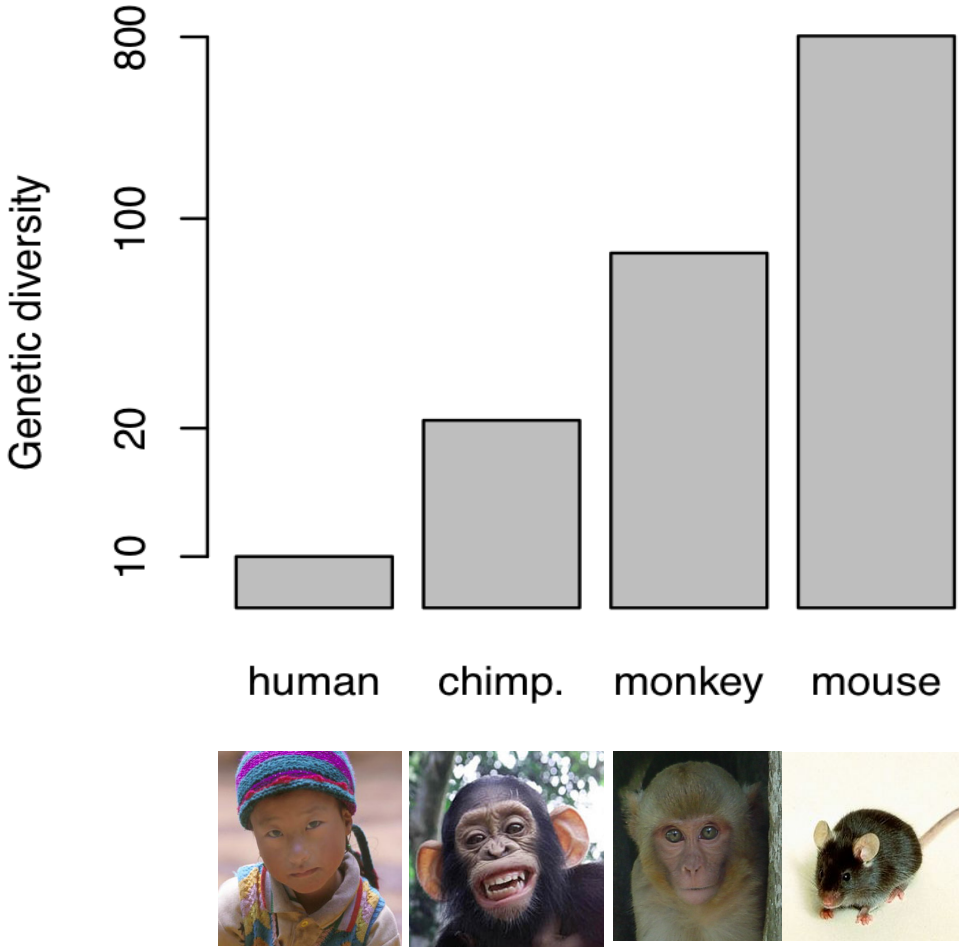


Humans are genetically very similar to each other



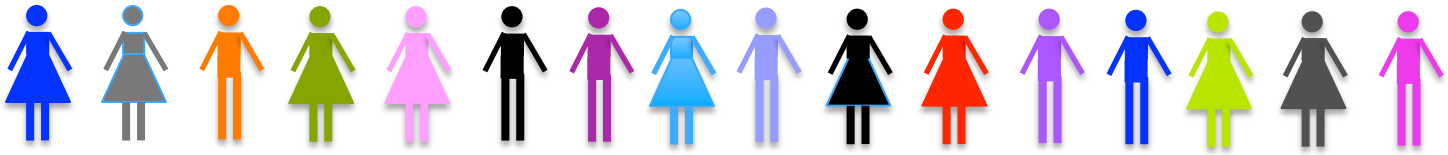
- 90% of variation within populations
- Large genetic differences are very rare
- Such differences can appear if they improve adaptation to local environment
- E.g. climate, diet, microbes

Humans are genetically very similar to each other



Positive natural selection

Positive natural selection



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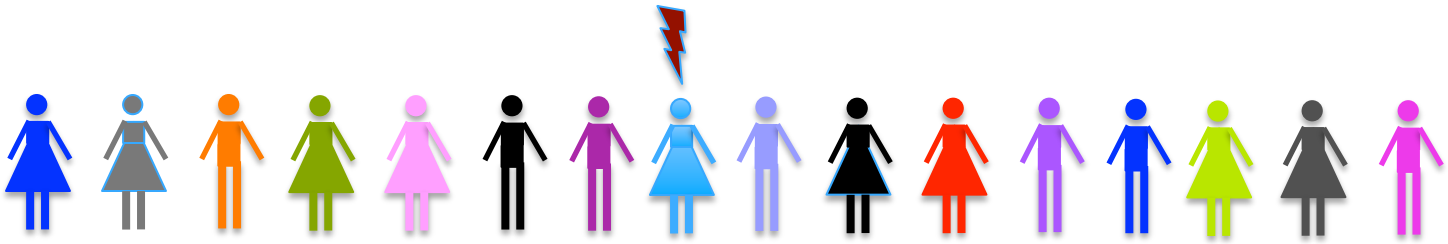

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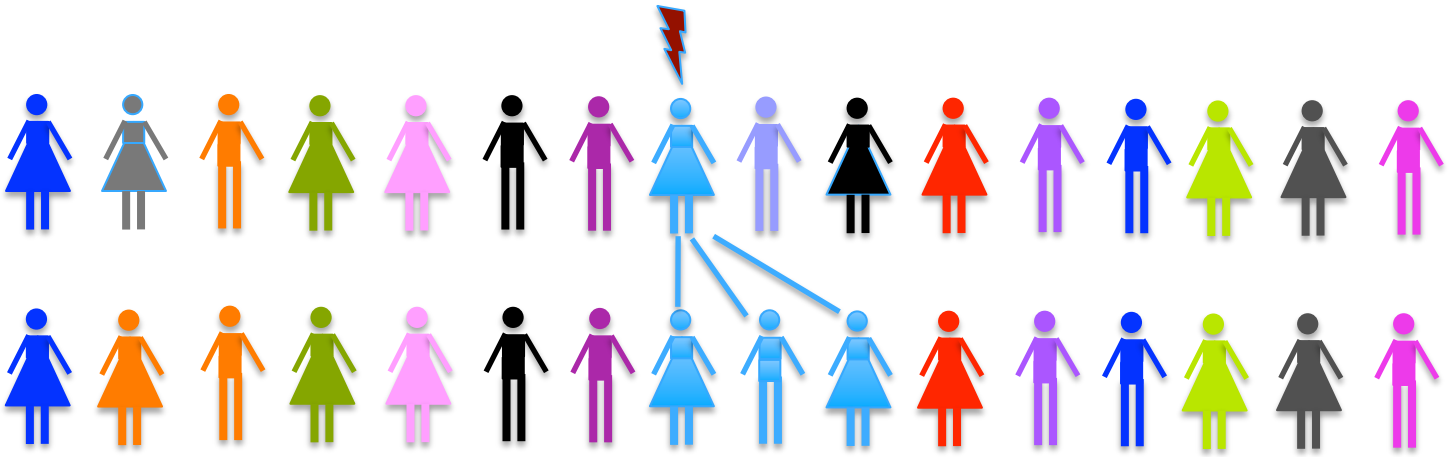
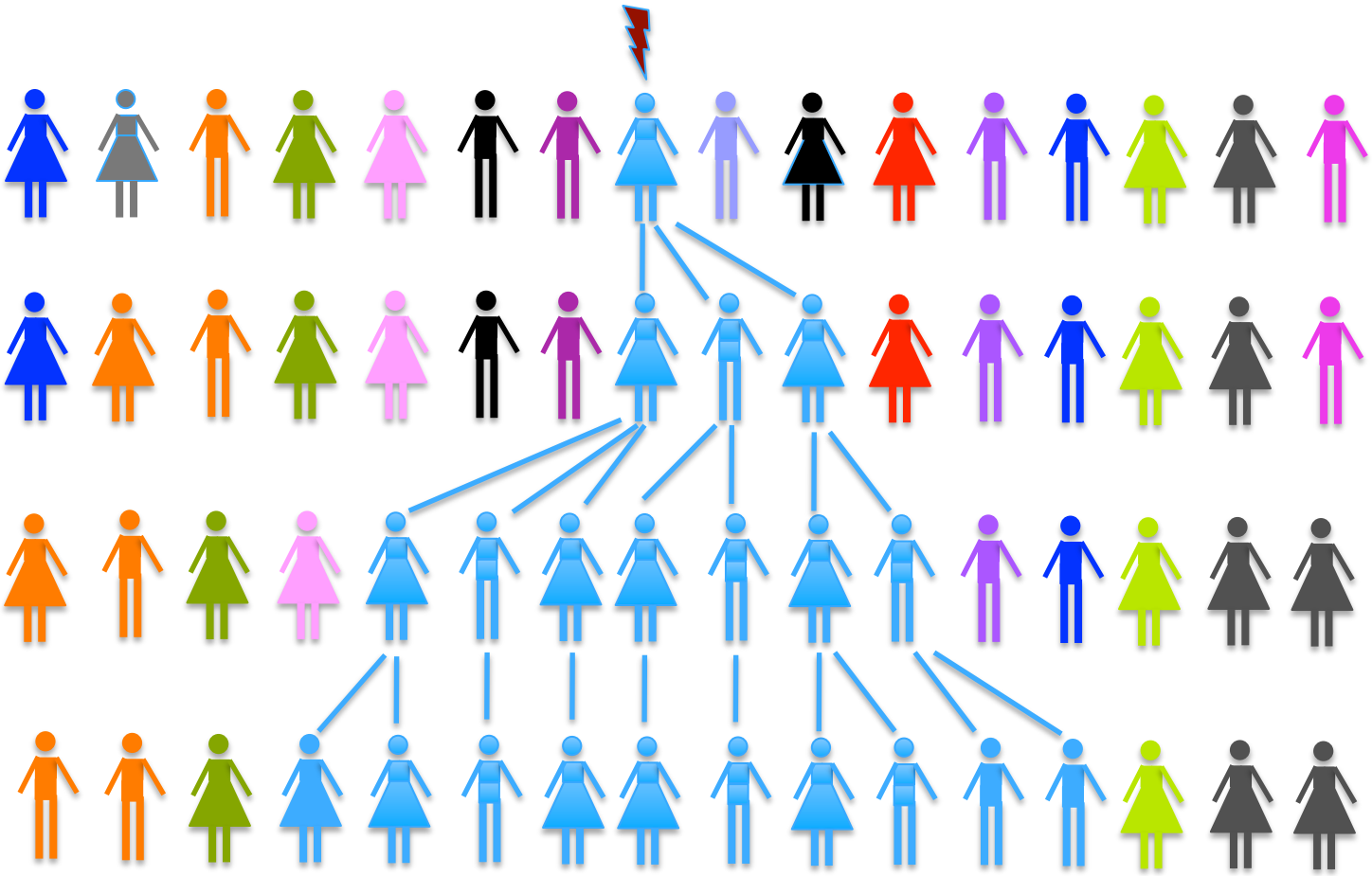
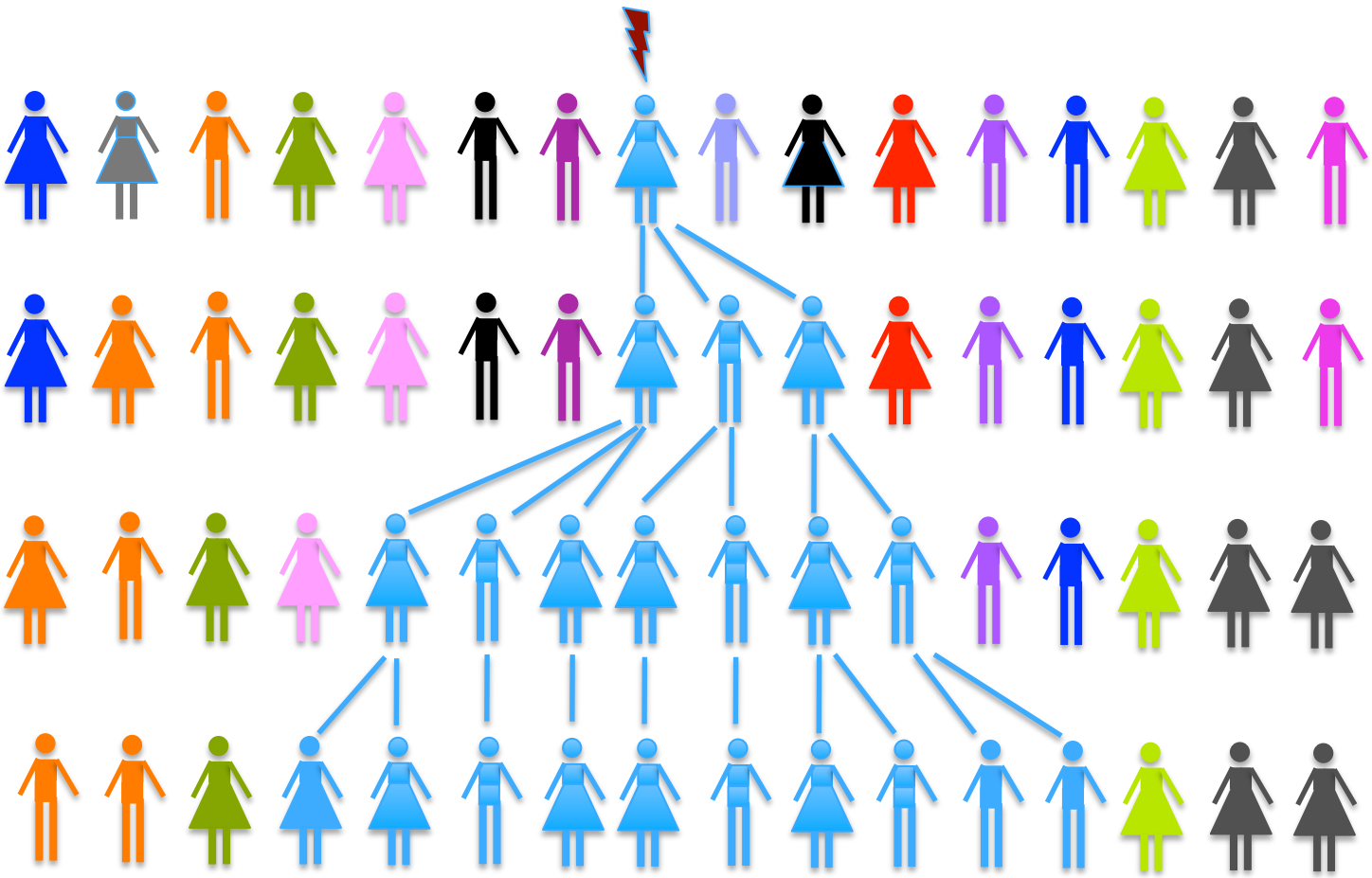


Positive natural selection



Selection on a de novo mutation



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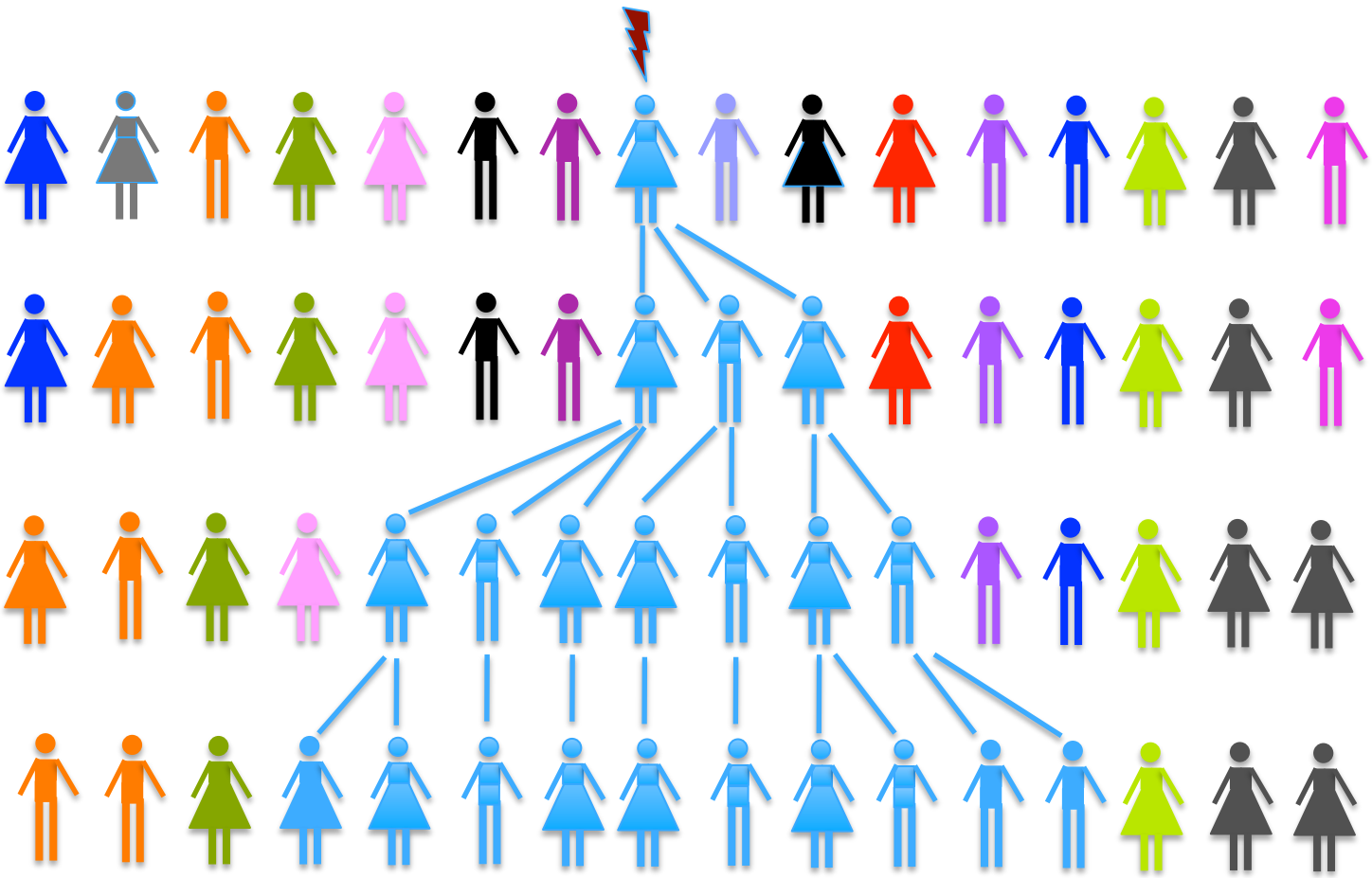
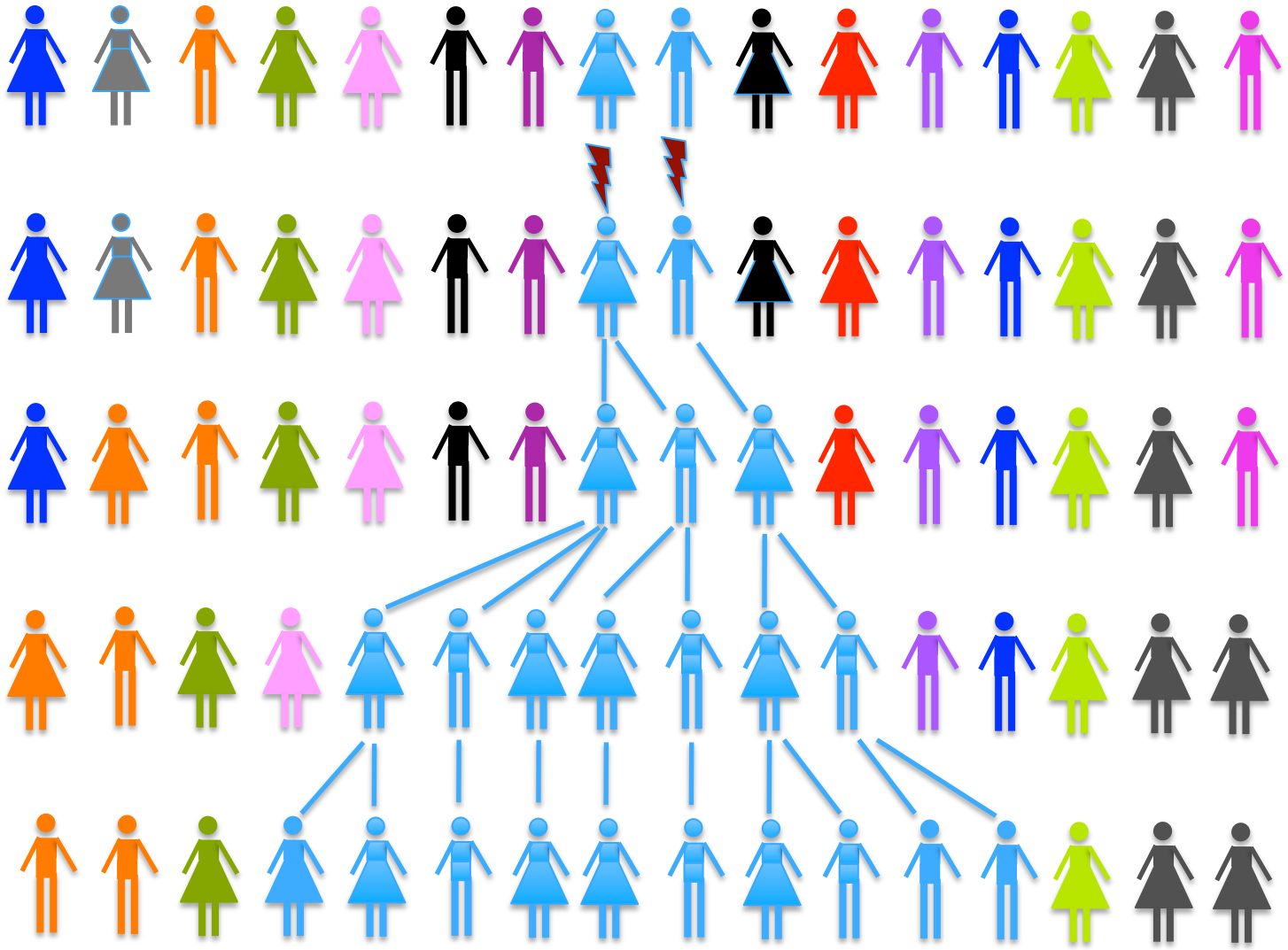
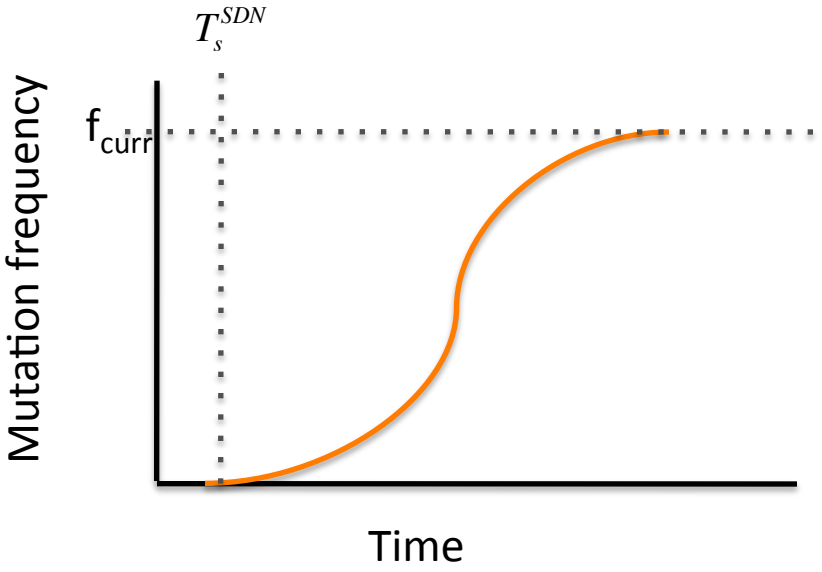


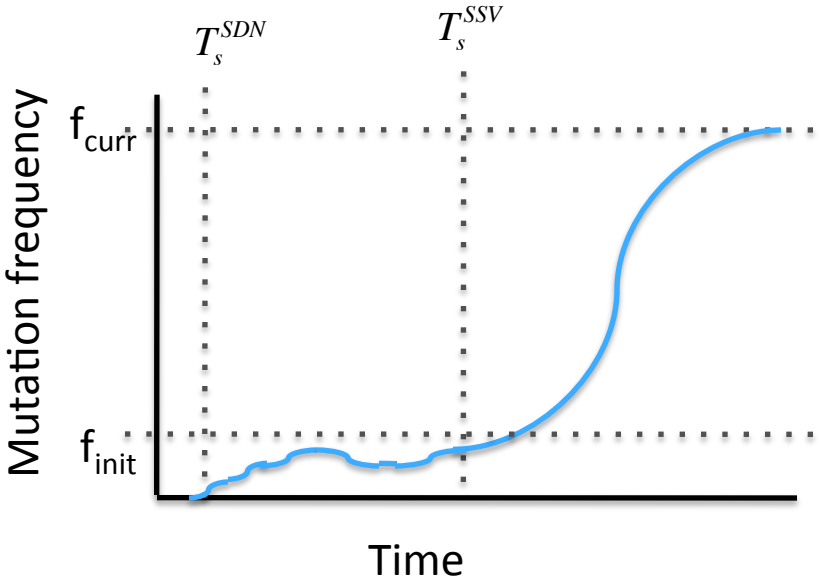
Selection on standing variation



Model of selection on a de novo mutation (SDN)

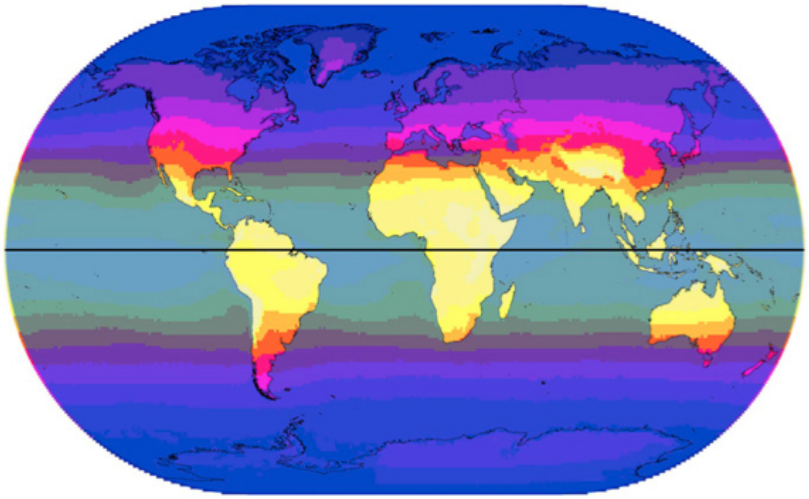


Model of selection on standing variation (SSV)

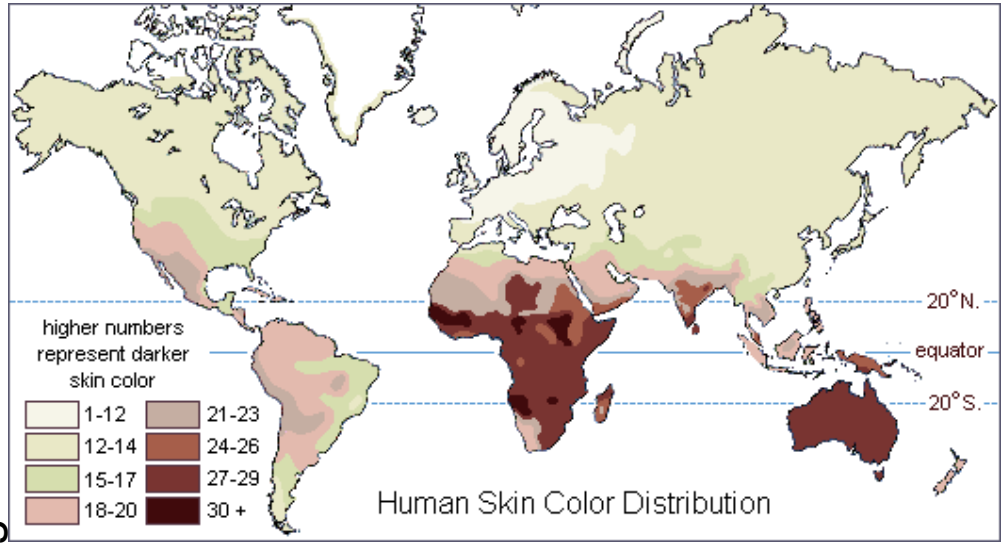


Changes in skin pigmentation

UV light intensity



Distribution of skin pigmentation



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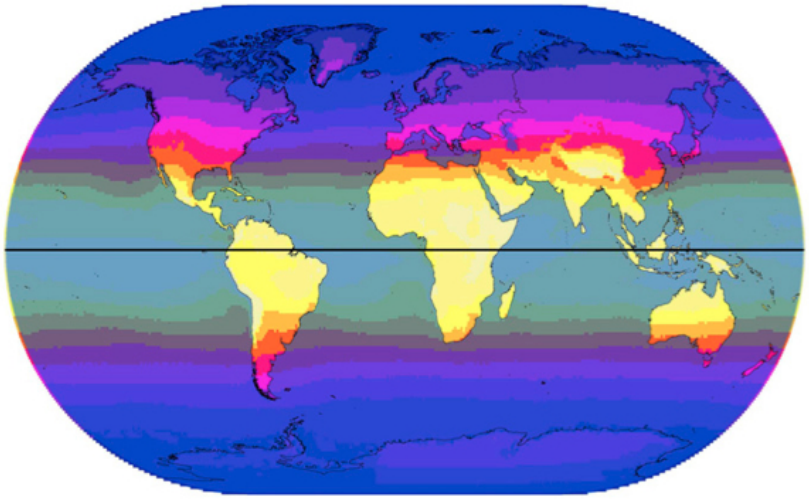

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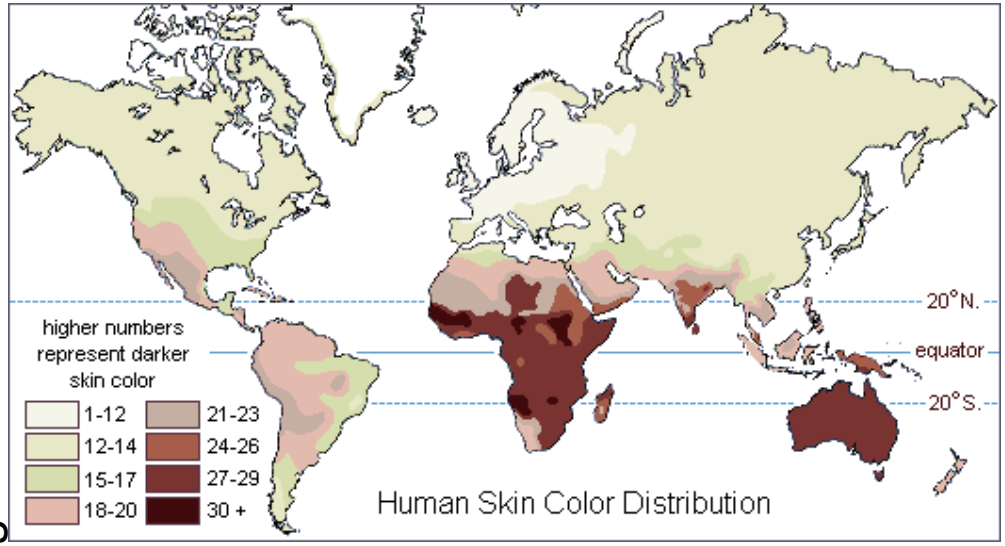

SLC24A5


Photo by Cry
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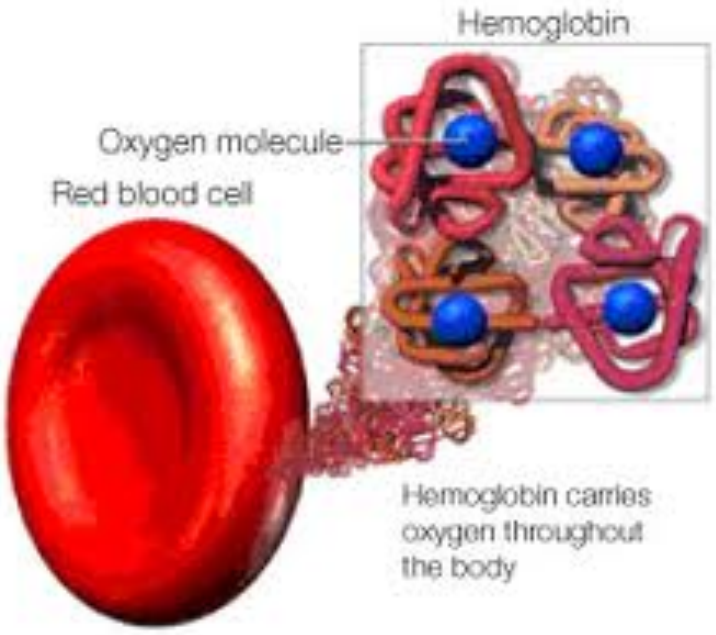
Adaptation to high altitude

- At high altitude there are fewer oxygen molecules in a breath of air than at sea level
- Humans inhabit three regions of the world that are at extreme altitudes

Response to high altitude environments

- Hemoglobin concentration: the protein in red blood cells that carries oxygen



Response to high altitude environments in Andeans

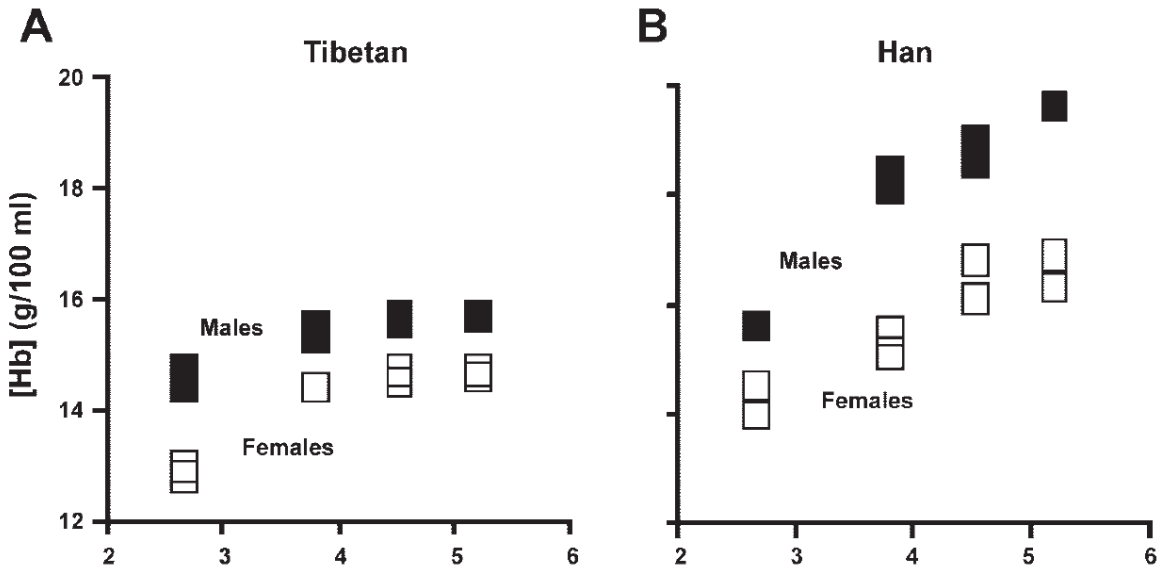
- Hemoglobin: the protein in red blood cells that carries oxygen

The physiological response to hypoxia was first scientifically investigated in the late 19th century in South America.

- It was believed that increasing hemoglobin concentration was beneficial

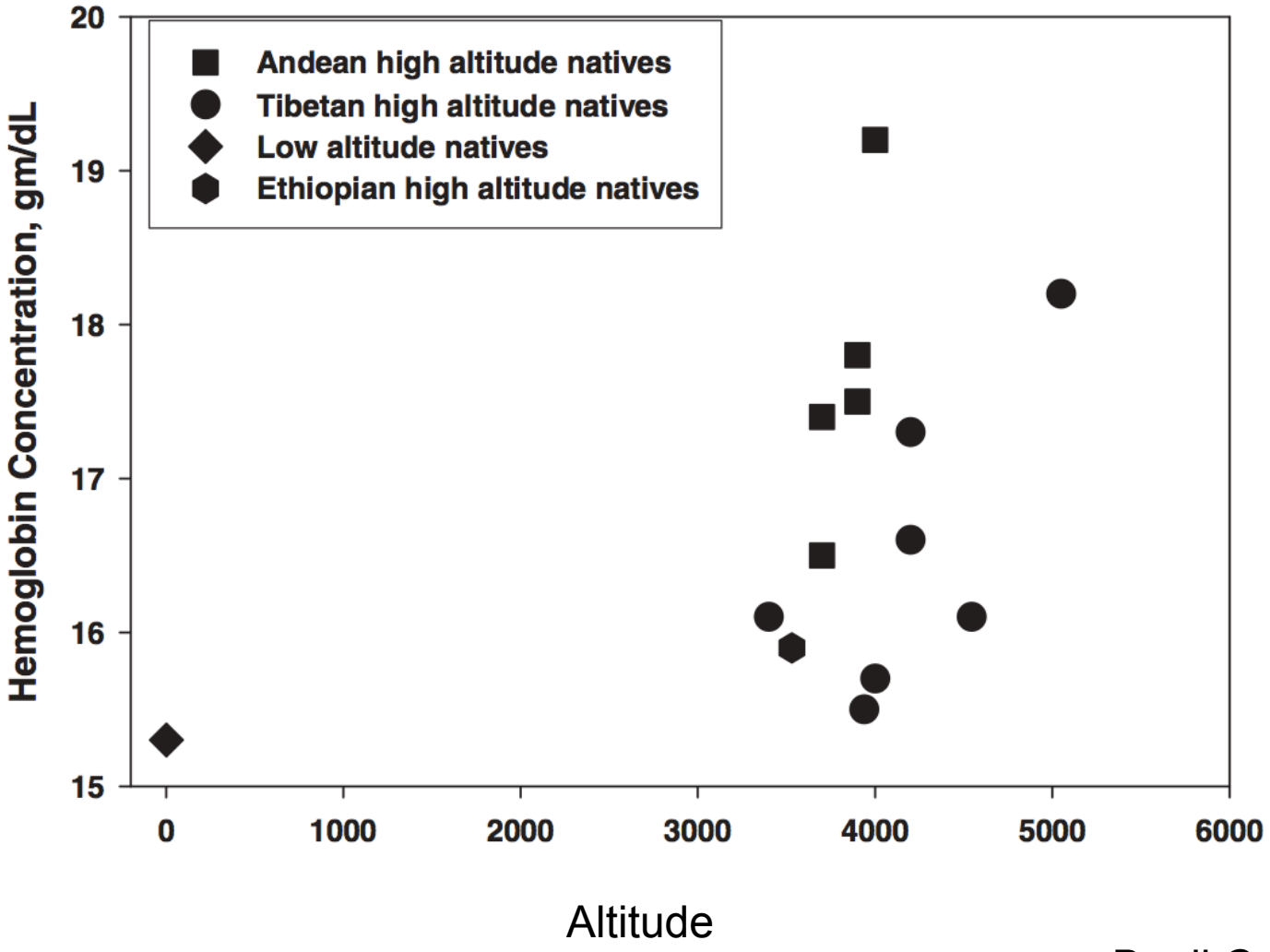
Response to high altitude environments in Tibetans

In the 70s, studies showed that Tibetans had a different physiological response



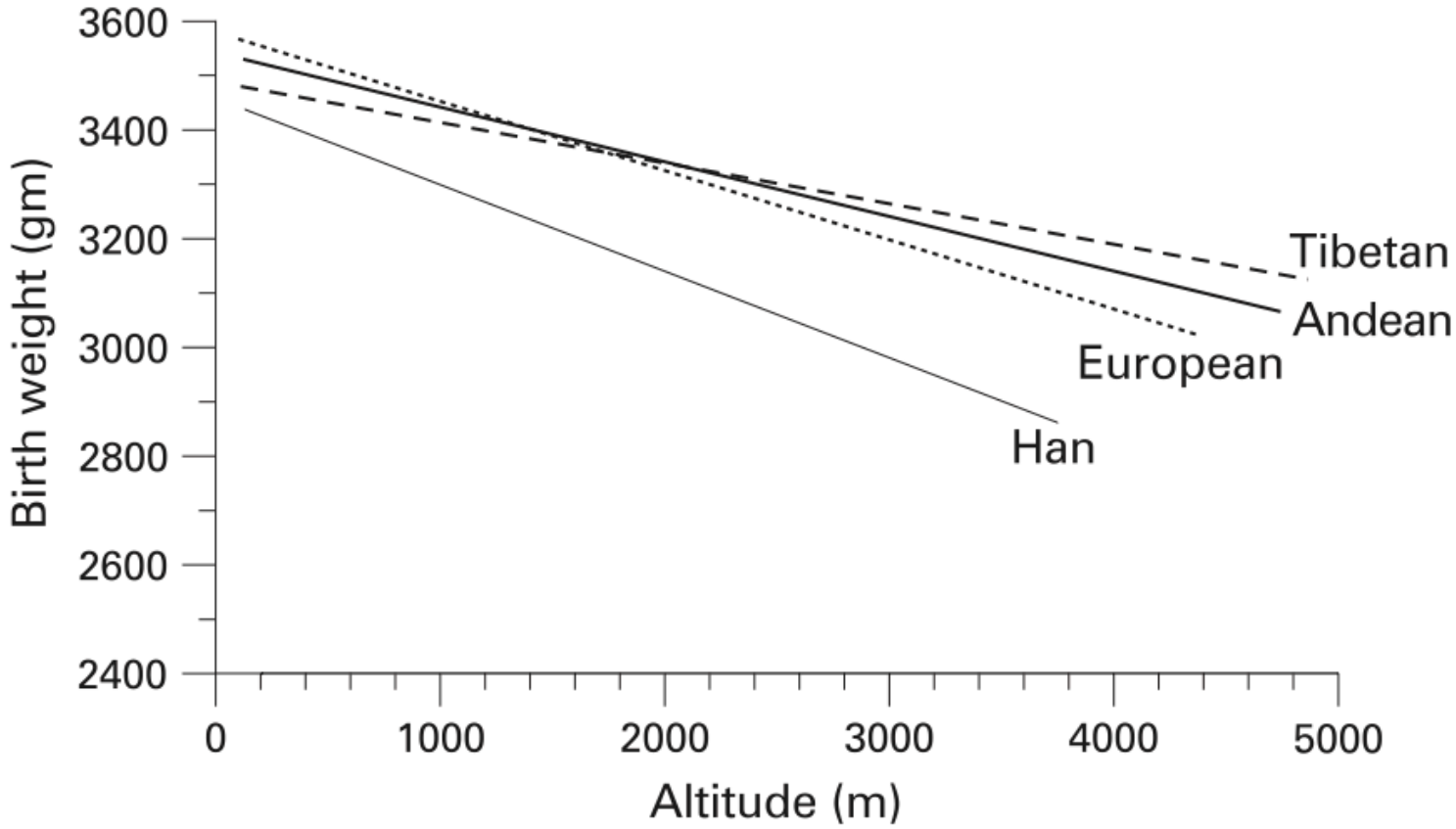
Wu et al. (2005)

Contrasting Tibetans, Andeans and Ethiopian response



Beall Cynthia, 2006

Higher fertility and lower infant mortality rate in high altitude natives than in acclimatized low altitude natives



Niermeyer et al. (2009)

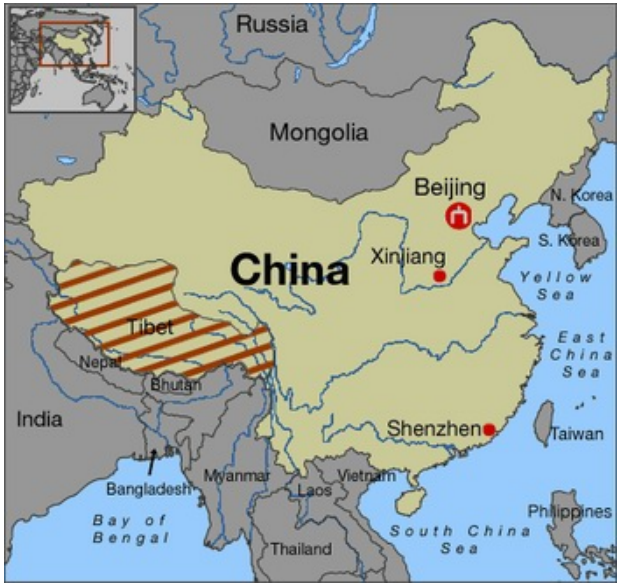
Exome Sequencing

- Exome (all the exons of the genome) – the coding part of the genome
- Technology: Exon capture & High-throughput sequencing
- 50 Tibetan Individuals living above 4000m altitude

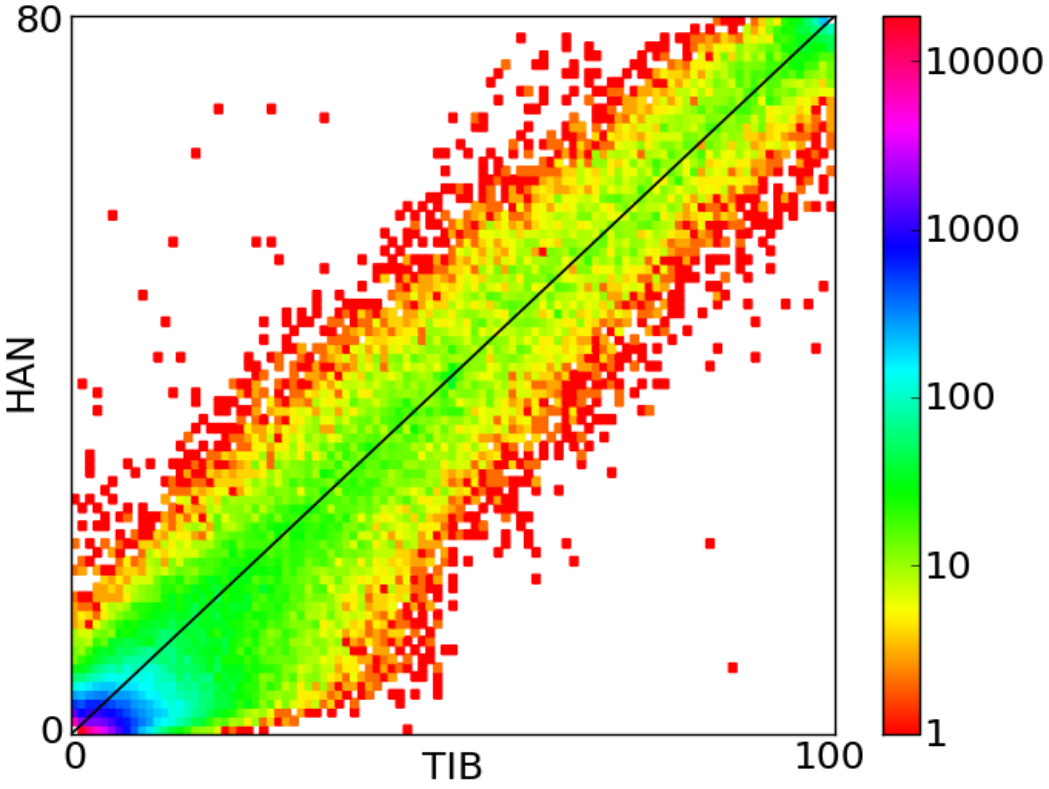
Other data

- A closely related population:
  Han from Beijing

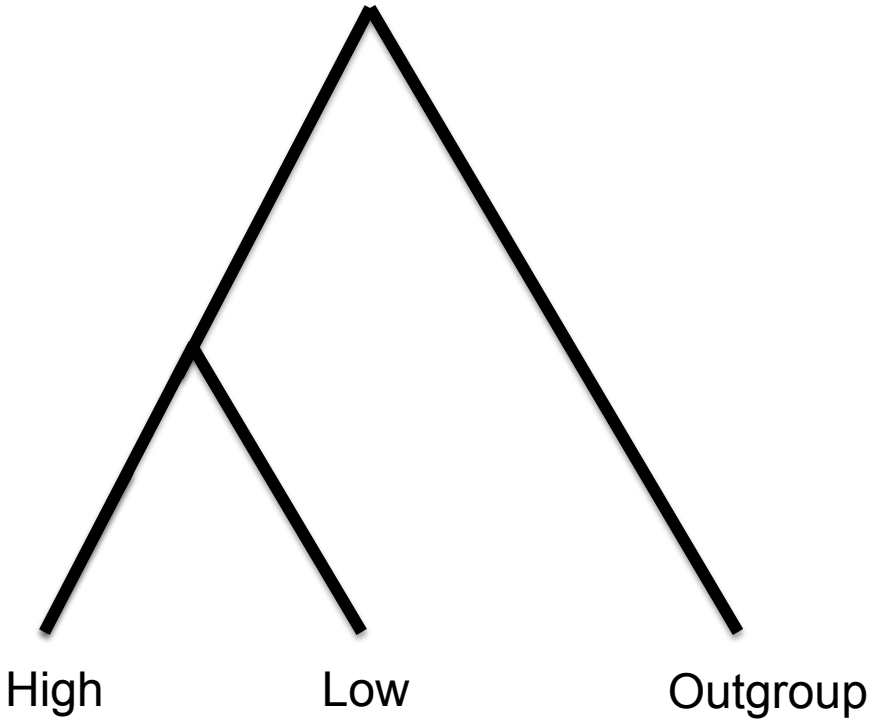
- We used
  an outgroup population:
  200 Danish exomes



Mutation Frequencies



Identifying signatures of positive selection



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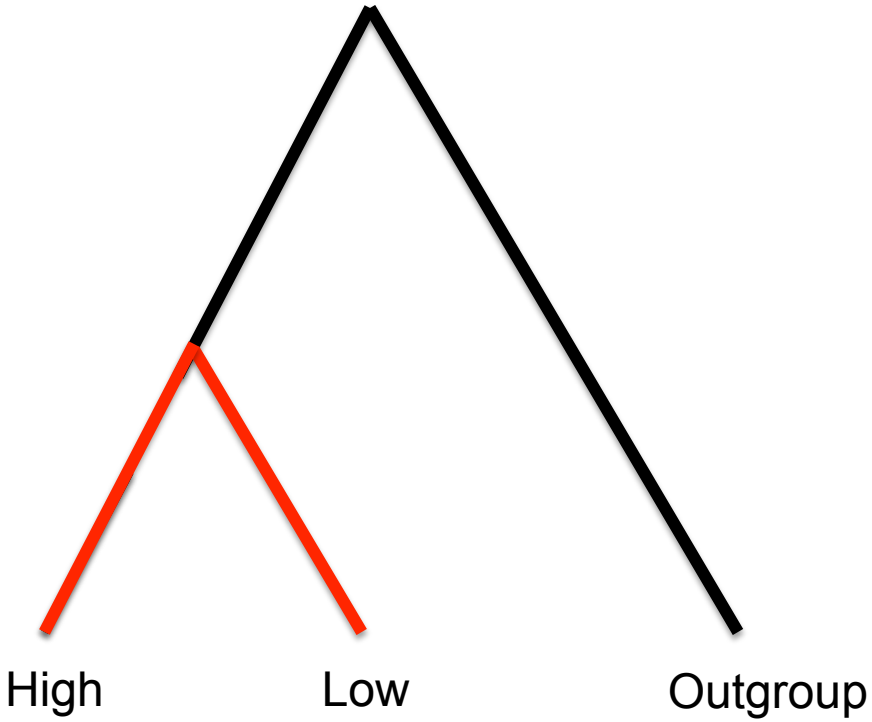
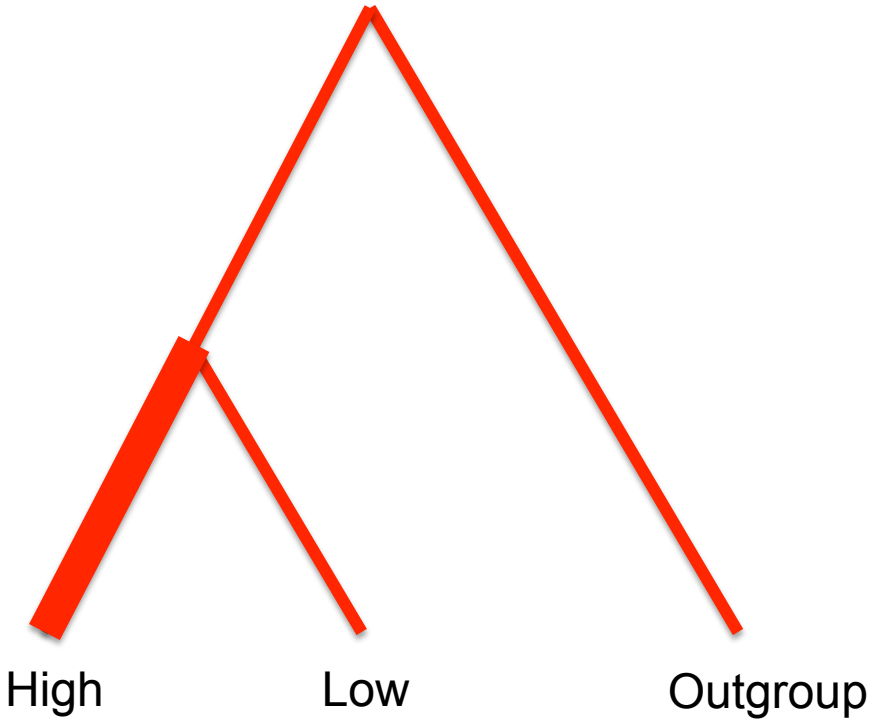


$$PBS_{High} = \quad T_{High,Low}$$

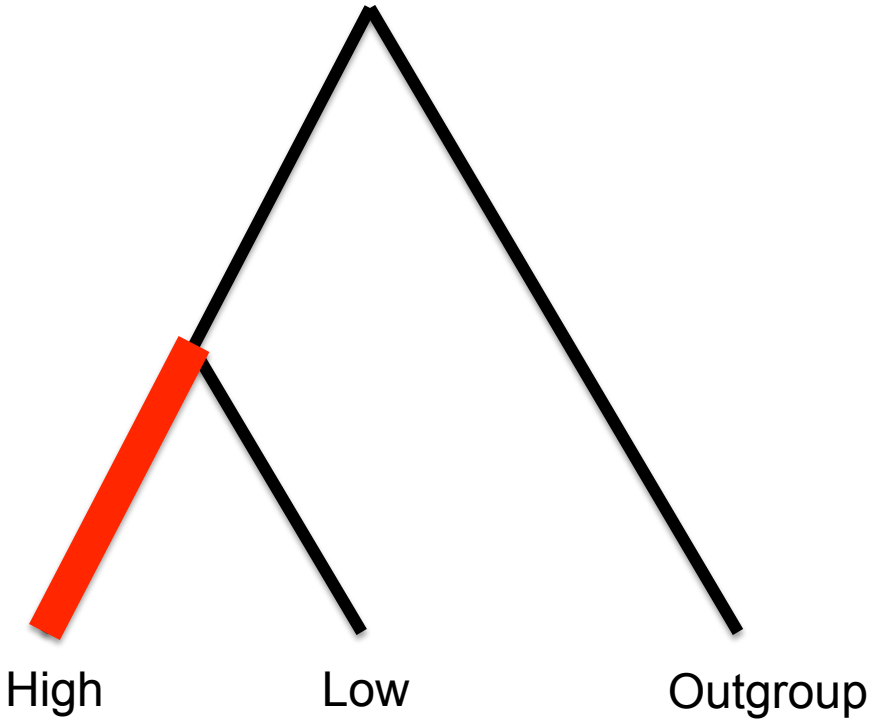
Yi* X., Liang* Y., Huerta-Sanchez* E., Jin* X., Pool* J. et al. (2010) Scie

Identifying signatures of positive selection



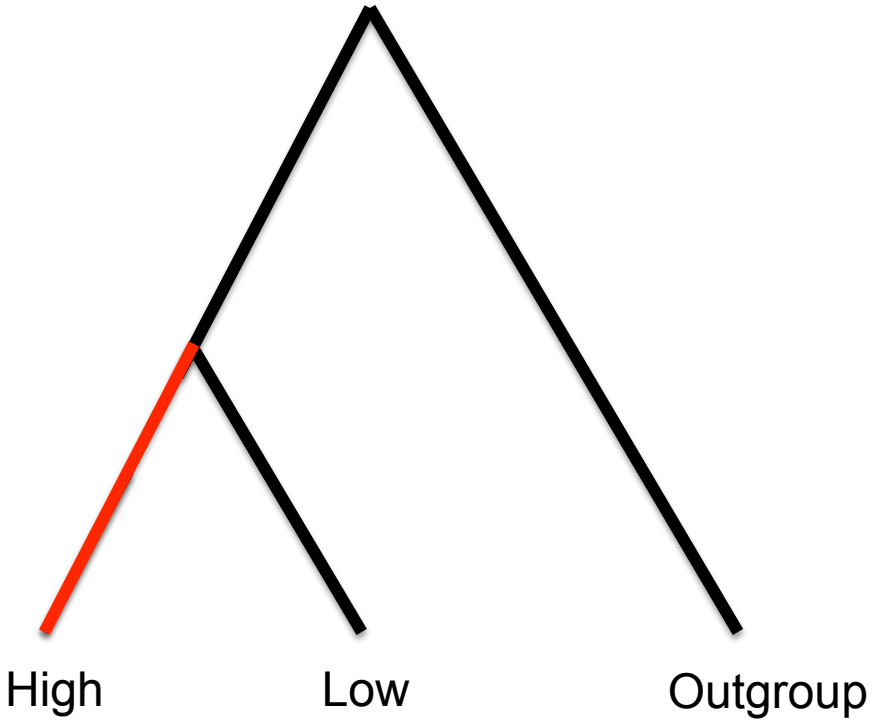
$$PBS_{High} = T_{High,Low} + T_{High,Outgroup}$$

Identifying signatures of positive selection



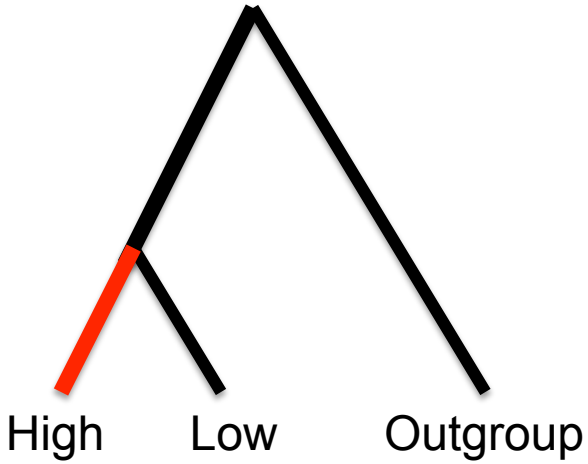
$$PBS_{High} = \frac{T_{High,Low} + T_{High,Outgroup} - T_{Low,Outgroup}}{2}$$

Identifying signatures of positive selection

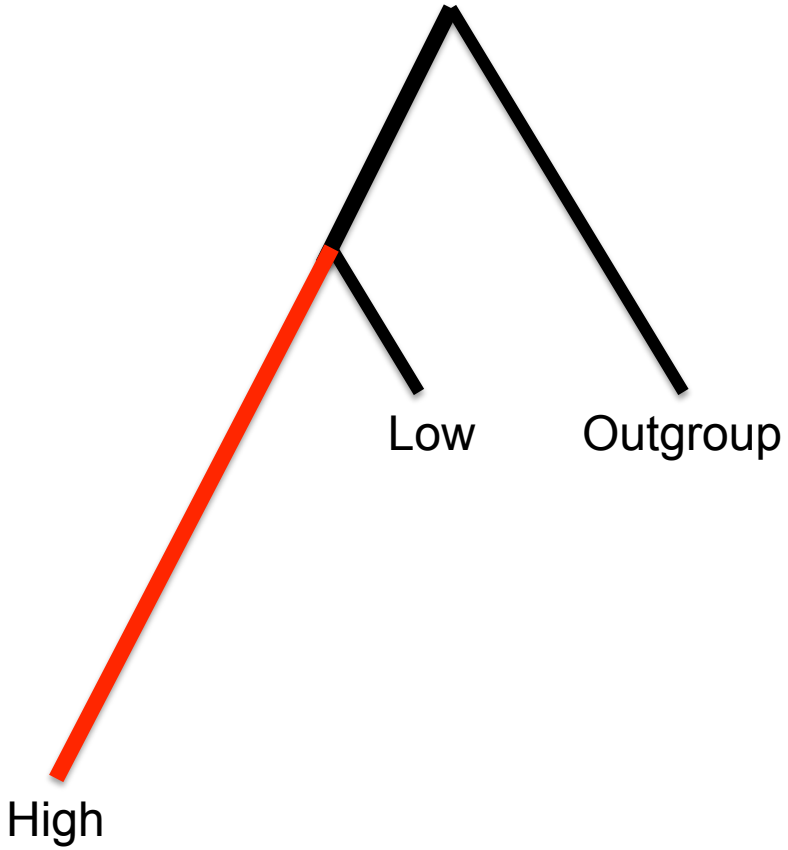


$$PBS_{High} = \frac{1}{2}\left[T_{High,Low} + T_{High,Outgroup} - T_{Low,Outgroup}\right]$$

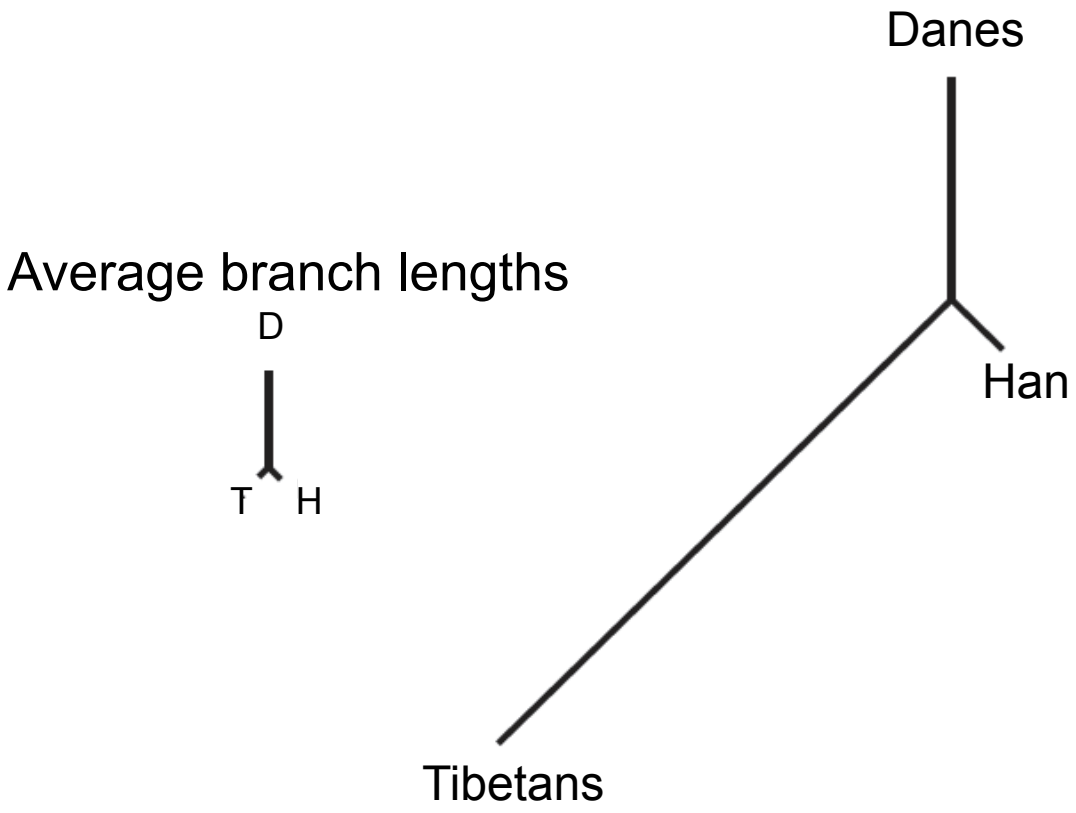
Under no positive selection



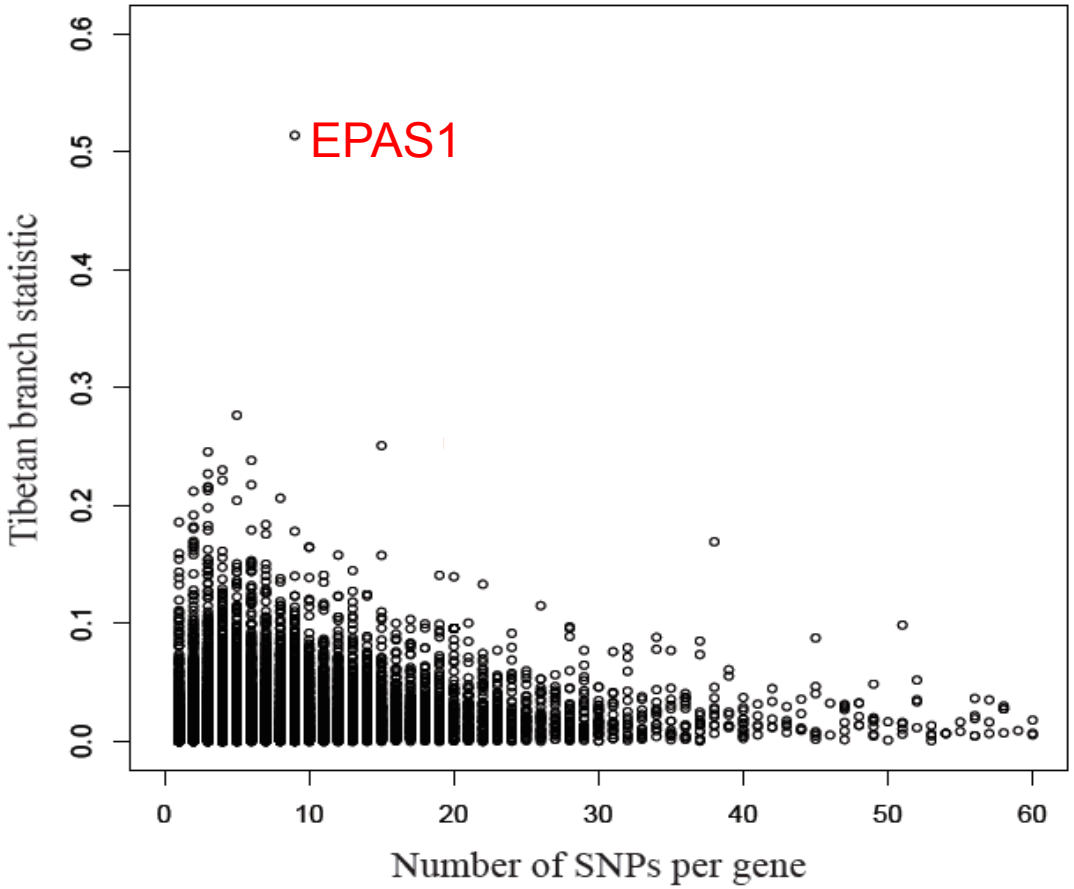
Under positive selection



Largest branch length: *EPAS1*



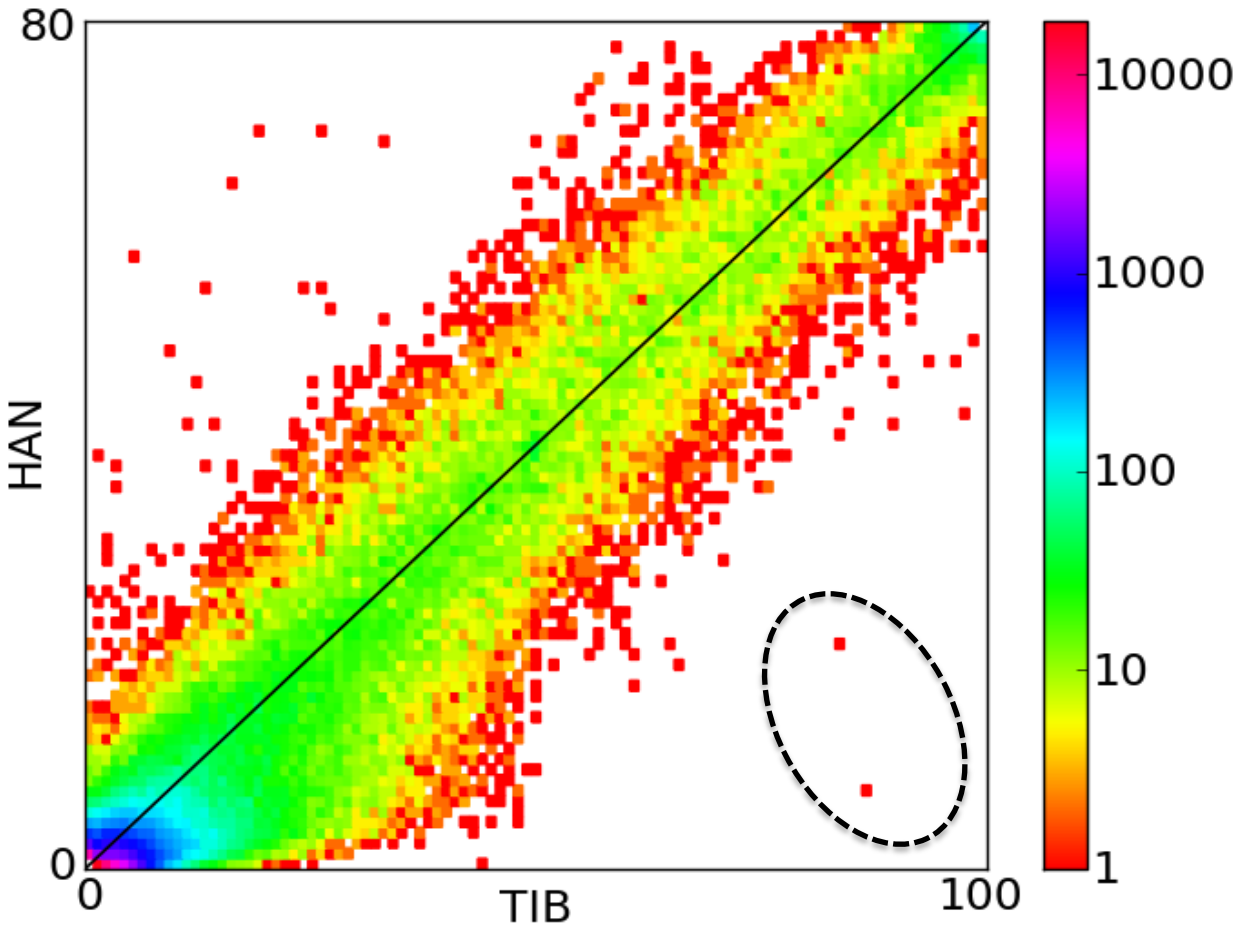
Distribution of branch length values across genes



EPAS1: Hypoxia inducible factor 2

- Major Transcription factor that orchestrates response to low oxygen levels
- Regulates several genes involved in red blood cell production
- Mutations in *EPAS1* have been associated with super-athlete performances
- Highly expressed in the adult and fetal lung and placenta

EPAS1: large frequency differences.



Tib	Han	Danes
0.87 G	0.09 G	0.0 G

Other relevant genes

Gene	Description	Nearby candidate	Tibetan *PBS*
EPAS1	endothelial PAS domain protein 1	(self)	0.514
C1orf124	hypothetical protein LOC83932 isoform a	*EGLN1*	0.277
DISC1	disrupted in schizophrenia 1 isoform L	*EGLN1*	0.251
ATP6V1E2	ATPase, H+ transporting, lysosomal 31kDa, V1	*EPAS1*	0.246
SPP1	secreted phosphoprotein 1 isoform c		0.238
PKLR	pyruvate kinase, liver and RBC isoform 1	(self)	0.230
C4orf7	chromosome 4 open reading frame 7		0.227
PSME2	proteasome activator subunit 2		0.222
OR10X1	olfactory receptor, family 10, subfamily X,	*SPTA1*	0.218
FAM9C	family with sequence similarity 9, member C	*TMSB4X*	0.216
LRRC3B	leucine rich repeat containing 3B		0.215
KRTAP21-2	keratin associated protein 21-2		0.213
HIST1H2BE	histone cluster 1, H2be	*HFE*	0.212
TTLL3	tubulin tyrosine ligase-like family, member 3		0.206
HIST1H4B	histone cluster 1, H4b	*HFE*	0.204
ACVR1B	activin A type IB receptor isoform a precursor	*ACVRL1*	0.198
FXYD6	FXYD domain-containing ion transport regulator		0.192
NAGLU	alpha-N-acetylglucosaminidase precursor		0.186
MDH1B	malate dehydrogenase 1B, NAD (soluble)		0.184
OR6Y1	olfactory receptor, family 6, subfamily Y,	*SPTA1*	0.183
HBB	beta globin	(self), *HBG2*	0.182
OTX1	orthodenticle homeobox 1		0.181
MBNL1	muscleblind-like 1 isoform b		0.179
IFI27L1	interferon, alpha-inducible protein 27-like 1		0.179
C18orf55	hypothetical protein LOC29090		0.178
RFX3	regulatory factor X3 isoform b		0.176
HBG2	G-gamma globin	(self), *HBB*	0.170
FANCA	Fanconi anemia, complementation group A isoform	(self)	0.169
HIST1H3C	histone cluster 1, H3c	*HFE*	0.168
TMEM206	transmembrane protein 206		0.166

Significant association with phenotype?

Genotype	Tibetan frequency	Mean hemoglobin concentration
CC	10	178
CG	84	178.9
GG	272	167.5

- Individuals with GG genotypes have ***LOWER*** hemoglobin concentration

Other studies have identified EPAS1

Sequencing of 50 Human Exomes Reveals Adaptation to High Altitude

Xin Yi,[1,2*] Yu Liang,[1,2*] Emilia Huerta-Sanchez,[3*] Xin Jin,[1,4*] Zha Xi Ping Cuo,[2,5*] John E. Pool,[3,6*] Xun Xu,[1] Hui Jiang,[1] Nicolas Vinckenbosch,[3] Thorfinn Sand Korneliussen,[7] Hancheng Zheng,[1,4] Tao Liu,[1] Weiming He,[1,8] Kui Li,[2,5] Ruibang Luo,[1,4] Xifang Nie,[1] Honglong Wu,[1,9] Meiru Zhao,[1] Hongzhi Cao,[1,9] Jing Zou,[1] Ying Shan,[1,4] Shuzheng Li,[1] Qi Yang,[1] Asan,[1,2] Peixiang Ni,[1] Geng Tian,[1,2] Junming Xu,[1] Xiao Liu,[1] Tao Jiang,[1,9] Renhua Wu,[1] Guangyu Zhou,[1] Meifang Tang,[1] Junjie Qin,[1] Tong Wang,[1] Shuijian Feng,[1] Guohong Li,[1] Huasang,[1] Jiangbai Luosang,[1] Wei Wang,[1] Fang Chen,[1] Yading Wang,[1] Xiaoguang Zheng,[1,2] Zhuo Li,[1] Zhuoma Bianba,[10] Ge Yang,[10] Xinping Wang,[11] Shuhui Tang,[11] Guoyi Gao,[12] Yong Chen,[5] Zhen Luo,[5] Lamu Gusang,[5] Zheng Cao,[1] Qinghui Zhang,[1] Weihan Ouyang,[1] Xiaoli Ren,[1] Huiqing Liang,[1] Huisong Zheng,[1] Yebo Huang,[1] Jingxiang Li,[1] Lars Bolund,[1] Karsten Kristiansen,[1,7] Yingrui Li,[1] Yong Zhang,[1] Xiuqing Zhang,[1] Ruiqiang Li,[1,7] Songgang Li,[1] Huanming Yang,[1] Rasmus Nielsen,[1,3,7]† Jun Wang,[1,7]† Jian Wang[1]†

Identifying Signatures of Natural Selection in Tibetan and Andean Populations Using Dense Genome Scan Data

Abigail Bigham[1¤*], Marc Bauchet[2], Dalila Pinto[3], Xianyun Mao[1], Joshua M. Akey[4], Rui Mei[5], Stephen W. Scherer[3,6], Colleen G. Julian[7], Megan J. Wilson[7], David López Herráez[2], Tom Brutsaert[8], Esteban J. Parra[9], Lorna G. Moore[10], Mark D. Shriver[1]

On the Origin of Tibetans and Their Genetic Basis in Adapting High-Altitude Environments

Binbin Wang[1,2☯], Yong-Biao Zhang[3☯], Feng Zhang[3], Hongbin Lin[3], Xumin Wang[3], Ning Wan[3], Zhenqing Ye[3], Haiyu Weng[4], Lili Zhang[3], Xin Li[3], Jiangwei Yan[3], Panpan Wang[3], Tingting Wu[3], Longfei Cheng[1,2], Jing Wang[1,2], Duen-Mei Wang[3*], Xu Ma[1,2,5*], Jun Yu[3*]

Genetic Evidence for High-Altitude Adaptation in Tibet

Tatum S. Simonson,[1] Yingzhong Yang,[2*] Chad D. Huff,[1] Haixia Yun,[2*] Ga Qin,[2*] David J. Witherspoon,[1] Zhenzhong Bai,[2*] Felipe R. Lorenzo,[3] Jinchuan Xing,[1] Lynn B. Jorde,[1]† Josef T. Prchal,[1,3]† RiLi Ge[2*]†

Natural selection on *EPAS1* (*HIF2α*) associated with low hemoglobin concentration in Tibetan highlanders

Cynthia M. Beall[a,1], Gianpiero L. Cavalleri[b,1], Libin Deng[c,2], Robert C. Elston[d], Yang Gao[c], Jo Knight[e,f], Chaohua Li[c], Jiang Chuan Li[g], Yu Liang[h], Mark McCormack[b], Hugh E. Montgomery[i,1], Hao Pan[c], Peter A. Robbins[j,1,3], Kevin V. Shianna[k], Siu Cheung Tam[l], Ngodrop Tsering[m], Krishna R. Veeramah[n], Wei Wang[h], Puchung Wangdui[m], Michael E. Weale[e,1], Yaomin Xu[o], Zhe Xu[c], Ling Yang[h], M. Justin Zaman[p], Changqing Zeng[c,1,3], Li Zhang[o,1], Xianglong Zhang[c], Pingcuo Zhaxi[h,1,4], and Yong Tang Zheng[q]

Genetic Variations in Tibetan Populations and High-Altitude Adaptation at the Himalayas

Yi Peng,†[,1,2] Zhaohui Yang,†[,1,2] Hui Zhang,†[,1] Chaoying Cui,†[,3] Xuebin Qi,[1] Xiongjian Luo,[1] Xiang Tao,[4] Tianyi Wu,[4] Ouzhuluobu,[3] Basang,[5] Ciwangsangbu,[5] Danzengduojie,[5] Hua Chen,[6] Hong Shi,[*1] and Bing Su[*,1]

A Genome-Wide Search for Signals of High-Altitude Adaptation in Tibetans

Shuhua Xu,[*,1,2] Shilin Li,[3] Yajun Yang,[3] Jingze Tan,[3] Haiyi Lou,[1] Wenfei Jin,[1] Ling Yang,[1] Xuedong Pan,[3] Jiucun Wang,[3] Yiping Shen,[4] Bailin Wu,[3,4] Hongyan Wang,[3] and Li Jin[*,1,2,3]

- Different data sets and different methods

What about Ethiopians?

Genotypes from 4 populations:

1. Ahmara (HA)
2. Tigrayan (HA)
3. Afar (LA)
4. Anuak (LA, outgroup)

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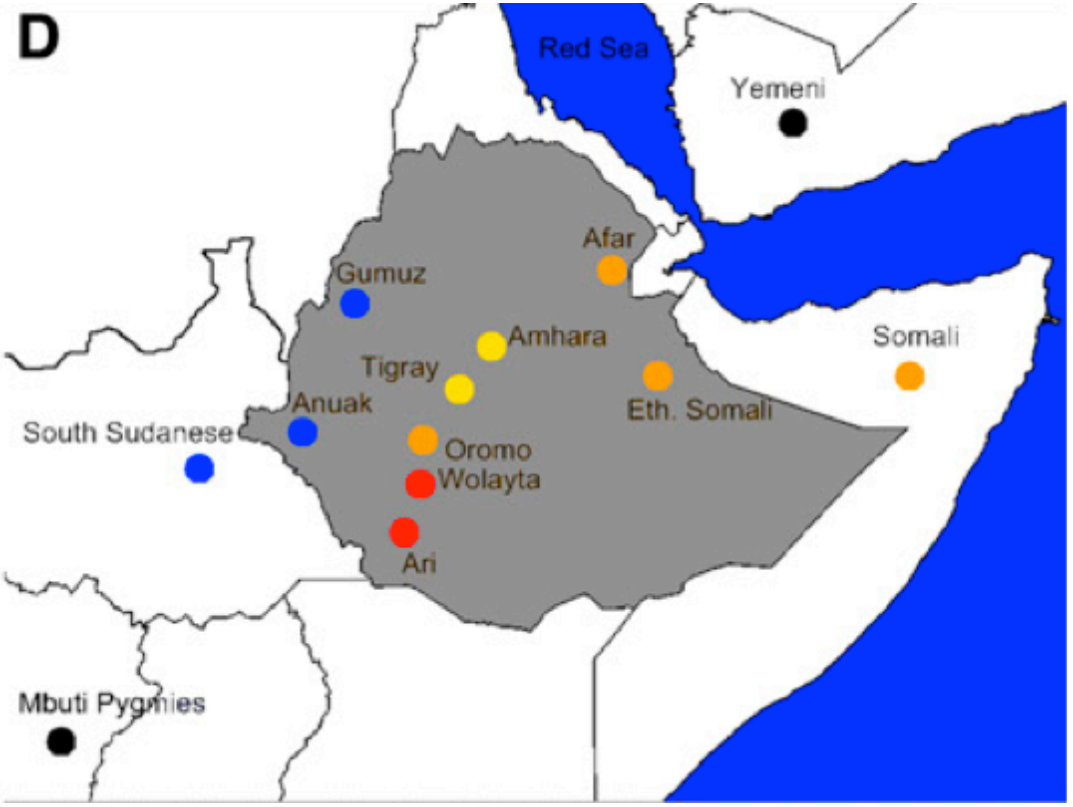
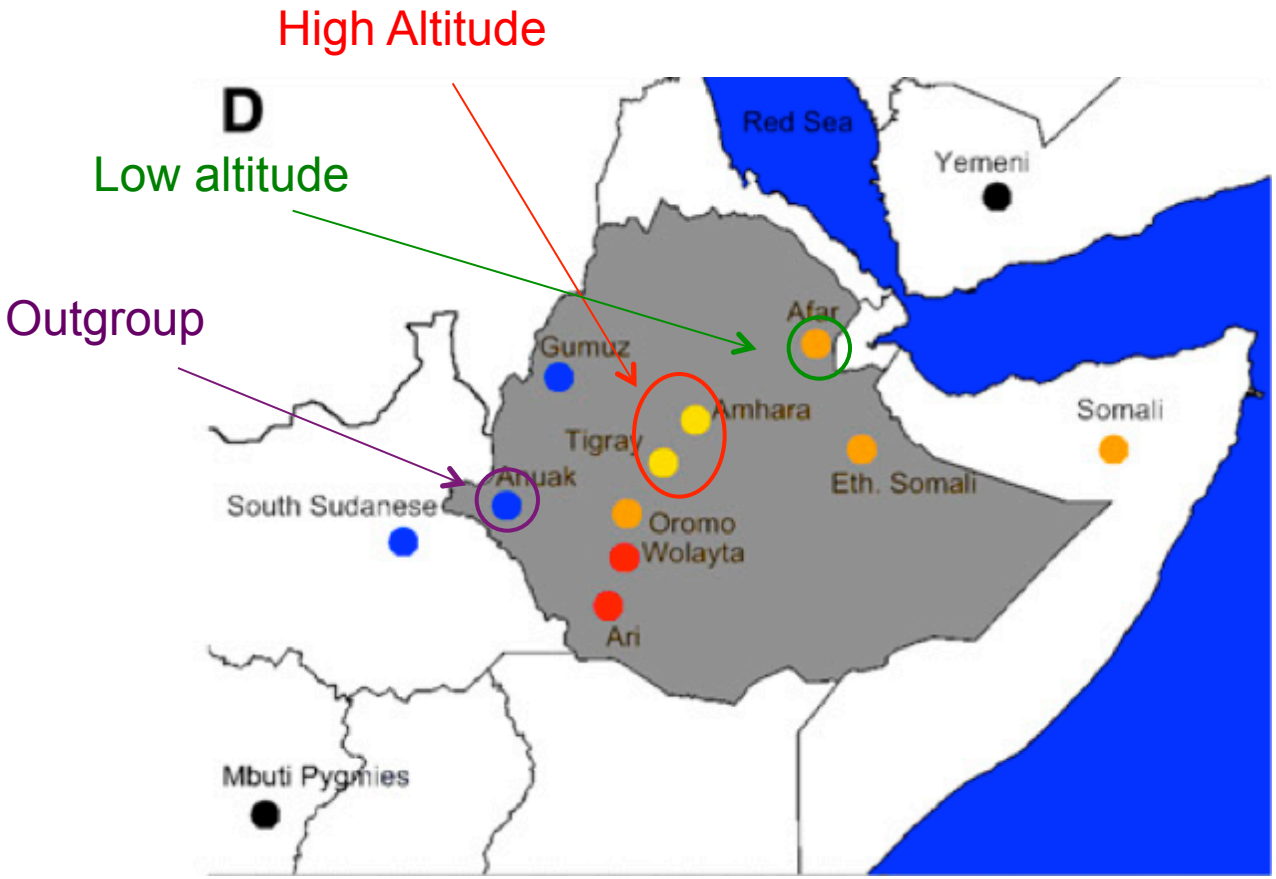


What about Ethiopians?



A more challenging problem

1. More complex demographic history

2. Probably some admixture from a non-African group

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BGI (Beijing Genomics Institute): Xin Jin, Yu Liang, Xin Yi, Zha Xi Ping Cuo, …., Jun Wang, Jian Wang and many others at

华大基因
BGI

Ethiopian study:

Neil Bradman, Endashaw Bekele, Ayele Tarekegn, Luca Pagani, Peter Robbins, Mike Weale and Toomas Kivisild