Disentangling the demographic history and genetic bases of high-altitude adaptation of an isolated Himalayan population

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Background

The region occupied by present-day Nepal played a central role in shaping ancient human dispersal trough the Asian continent, acting as a crossroads between India and East-Asia. In fact, the Himalayas (parallel to Nepal North border) have represented a barrier for South to North migrations, allowing only limited diffusion in the opposite direction (*blue arrows*).

Therefore, modern Nepalese people represent an intricate mosaic of culturally/genetically distinct human groups. In addition to this highly diverse substrate, northern populations of the Himalayan valleys had undergone an even more complex history of isolation and adaptation to extreme high altitudes.

Here we present preliminary results of a study conducted on one of these remote communities (Rowaling Valley, Gaurishankar, Dolakha District).
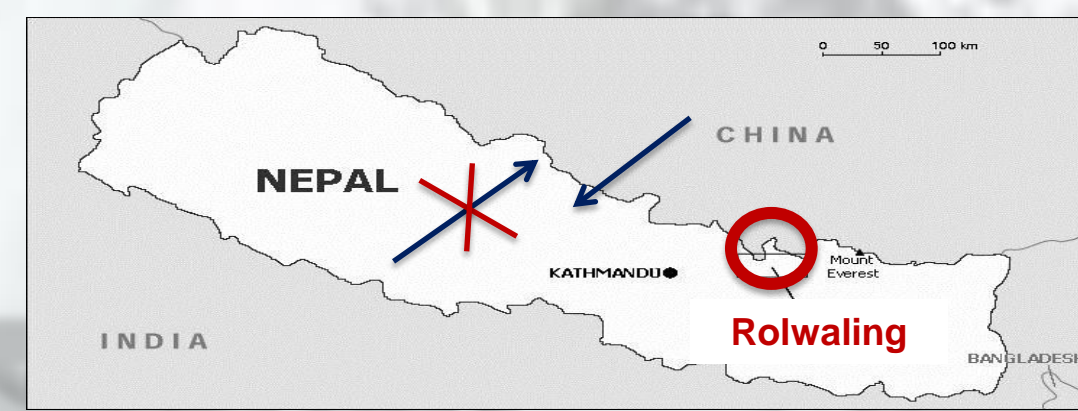
Population Samples

60 oral swab/saliva **samples** collected in villages inhabited by different ethnic groups

☐ Tamang & Sherpa (2,500 m a.s.l.)   ☐ Sherpa (3,800 - 4,200 m a.s.l.)
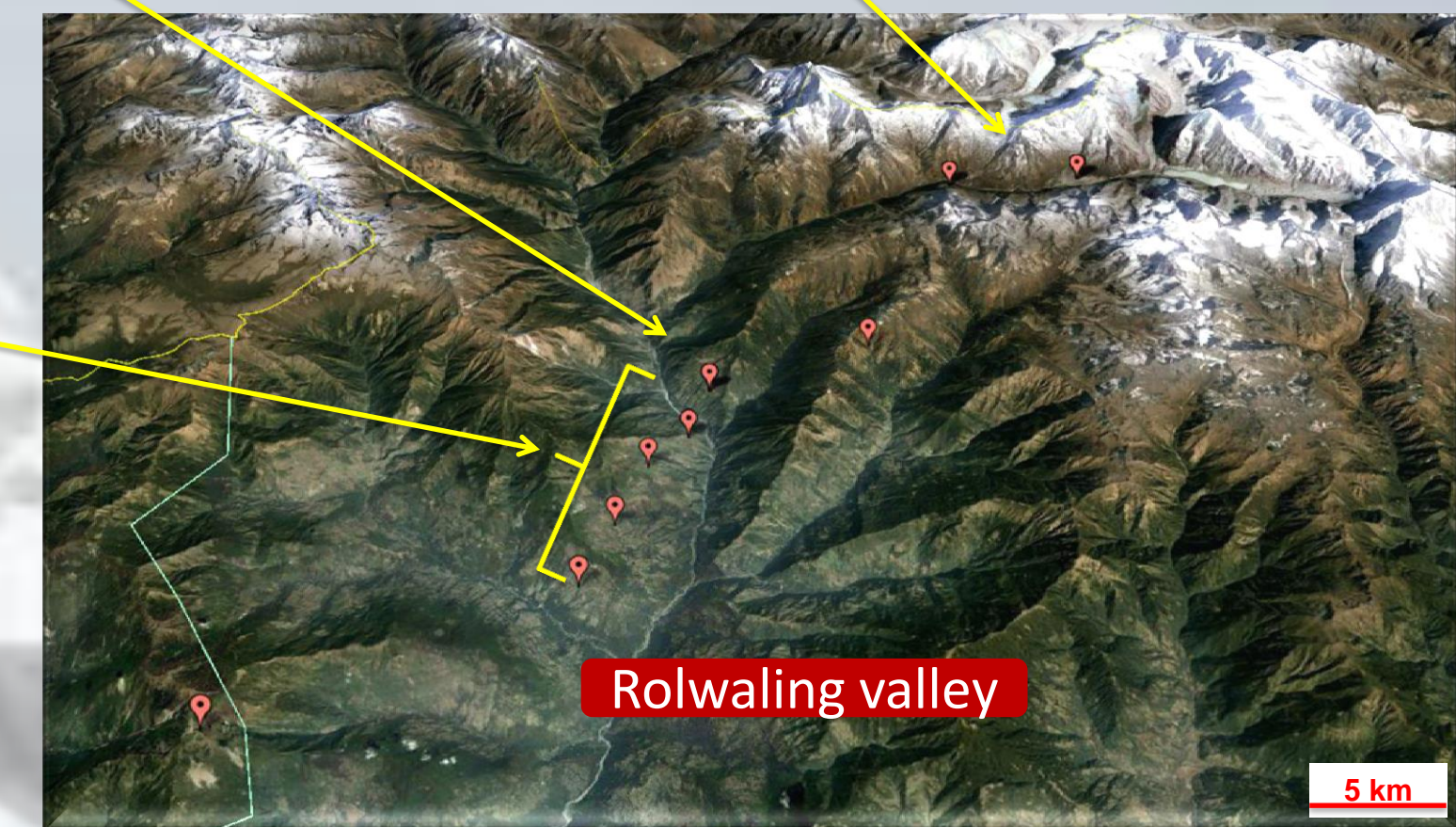
☐ **Tibeto-Burman**
- Tamang
- Thami
- Newar

☐ **Indo-Aryan**
- Pahari related groups

(< 2,500 m a.s.l.)

Rolwaling valley   5 km

Aims
Reconstructing population genetic structure and inferring recent demographic history through the analysis of:
☐ Fast evolving **uniparentally-inherited genetic markers**
☐ **Genome-wide SNP** data

Materials & Methods

Uniparentally-inherited markers

☐ **17 Y-Chr STRs** (*Yfiler™*)

☐ **HVS-I mtDNA**

☐ **Extended datasets** (25/49 Asian populations for Y-STRs & HVS-I)

Genome-wide SNP data

☐ **37** samples typed for **720k SNPs** (*Illumina HumanOmniExpress*)

☐ **Extended dataset** (1,560 individuals/109 populations from Tibet, India Central Asia, South Asia, South-East Asia, North-East Asia, Siberia + CEU as outgroup)

☐ **Quality controls** performed with PLINK 1.07

Results & Discussions

Population of the Rolwaling valley as a whole presents **high** Nei's **gene diversity** (H) & **nucleotide diversity** (π) for both Y-Chr and mtDNA, comparable to those observed in reference non-isolated populations (data not shown)
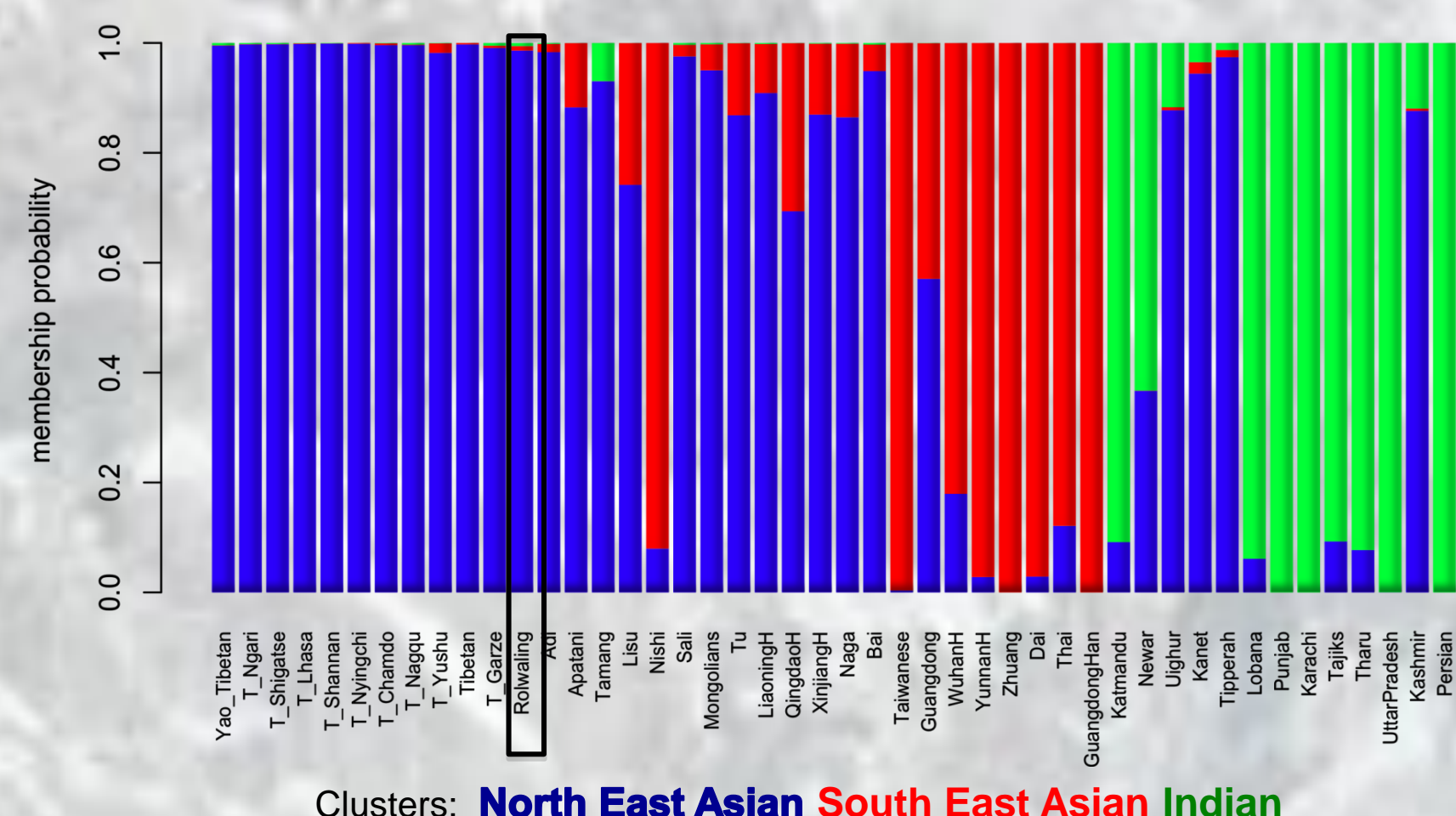
Y-Chromosome STRs

MDS 15-STRs profile of 24 pop
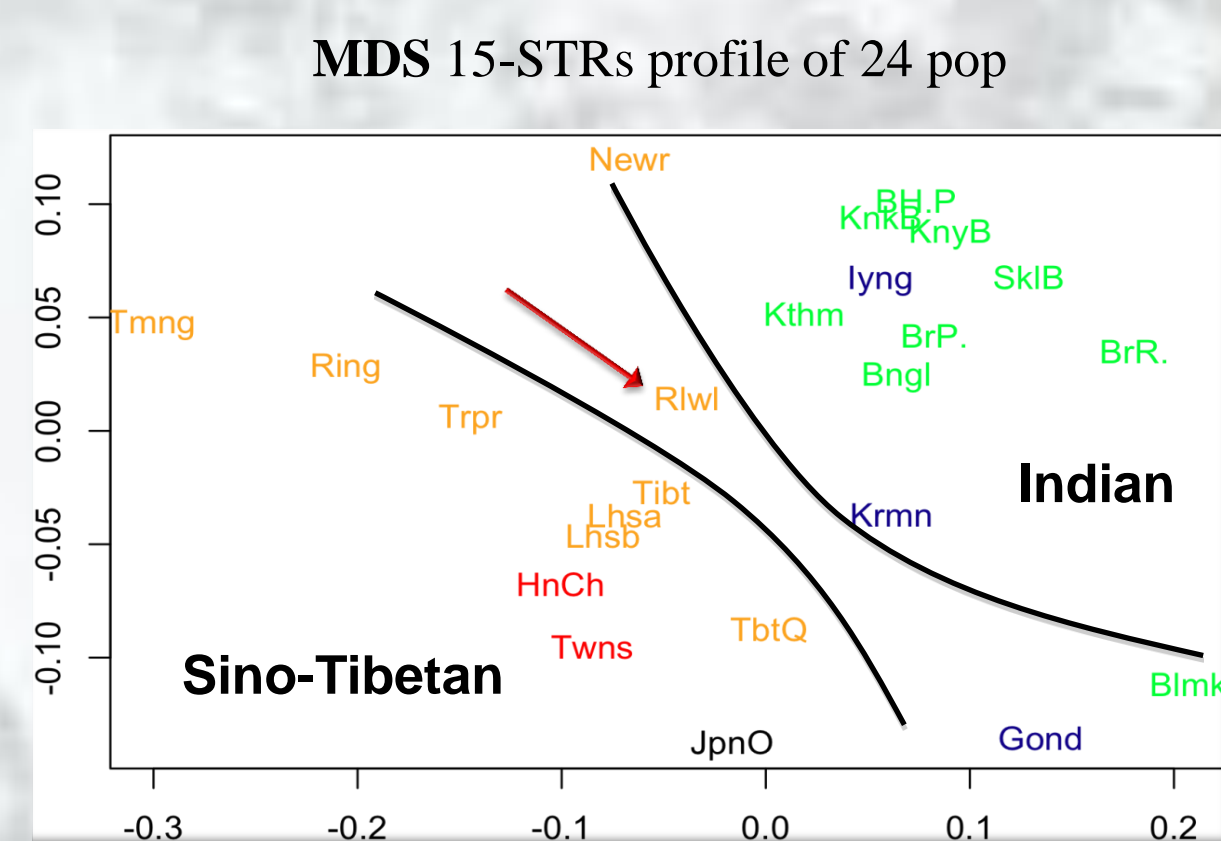
DAPC-based probability of each pop to belong to the identified clusters
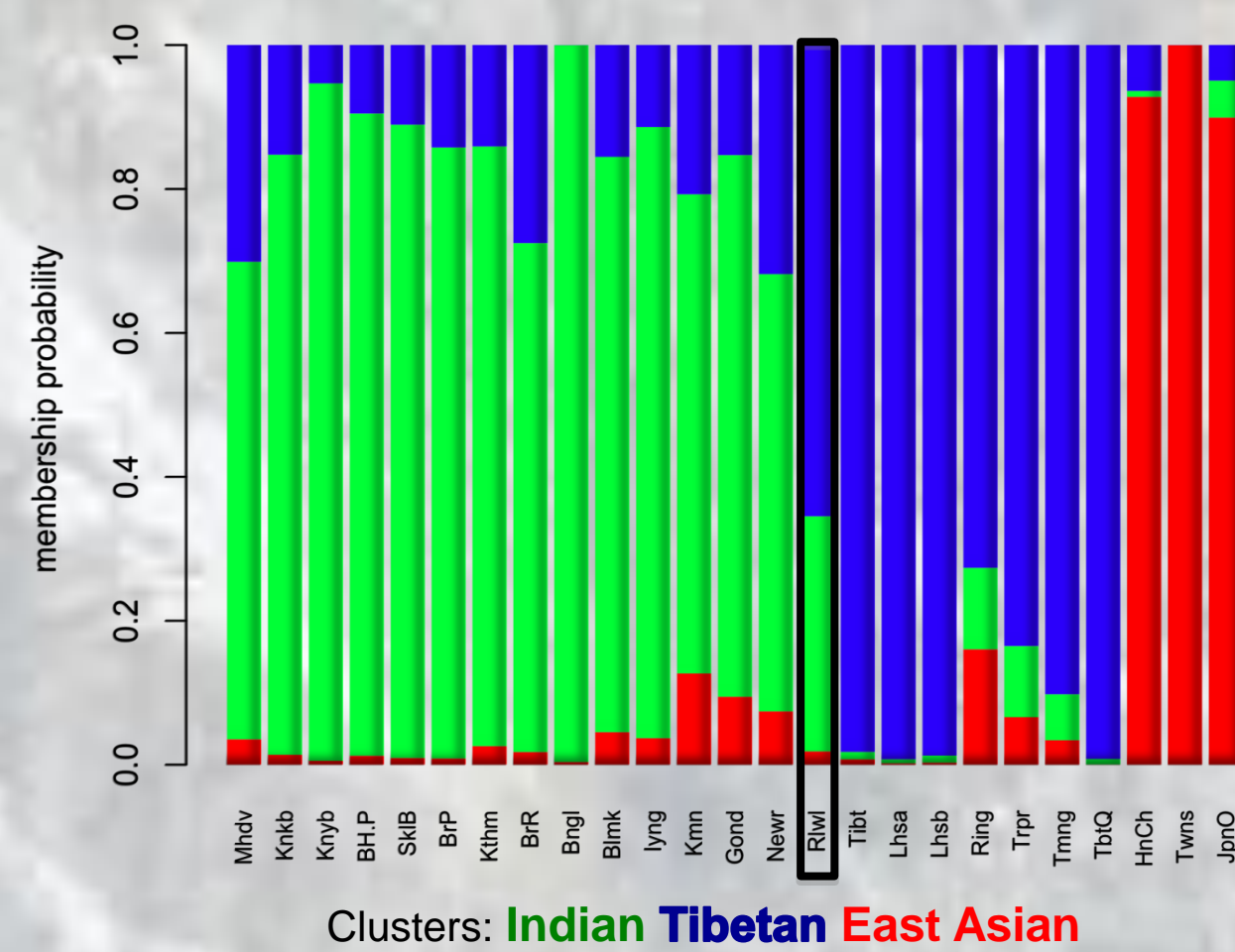
Clusters: **Indian** **Tibetan** **East Asian**

Predicted **Y-Chr Haplogroups**
H, C, D, O, R

Mitochondrial DNA HVS-I

DAPC-based probability of each pop to belong to the identified clusters

MDS HVS-I profile of 50 pop

Clusters: **North East Asian** **South East Asian** **Indian**
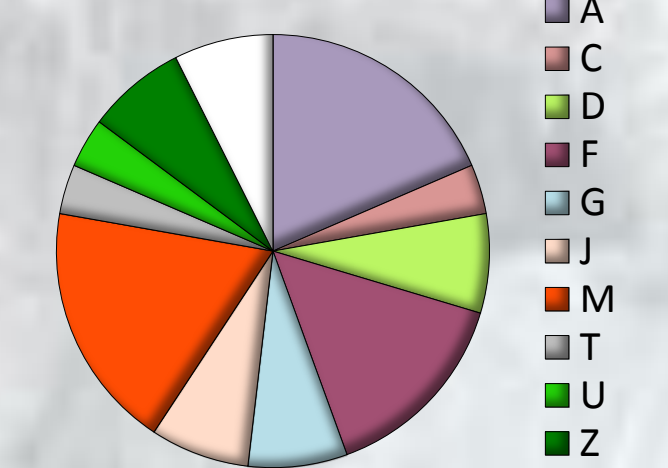
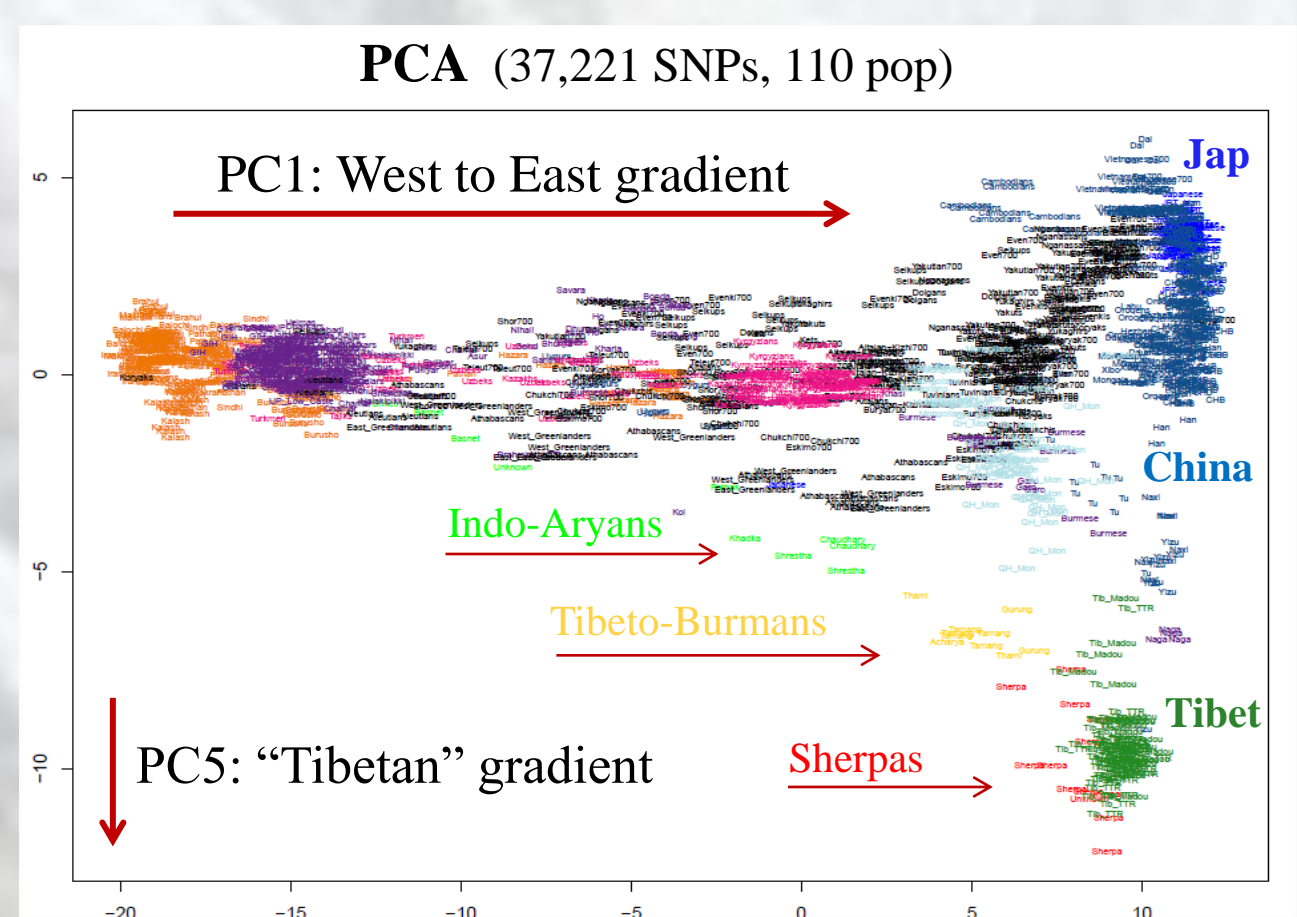Predicted **mtDNA Haplogroups**
A, C, D, F, G, J, M, T, U, Z, UK
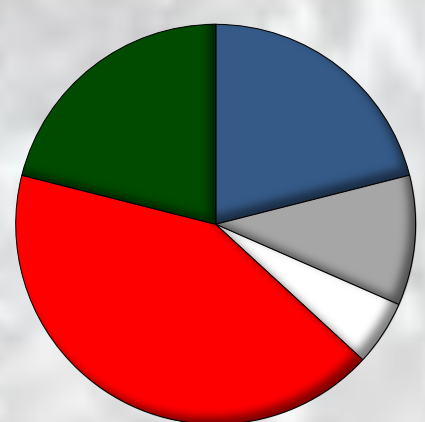
☐ All Y-STRs analyses indicate differential admixture proportions between East-Asian (i.e. Tibetans) and South-Asian (i.e. Indian) lineages
☐ HVS-I analyses pointed to the absence of population structure within the Rolwaling valley and to predominant East-Asian maternal ancestry

This picture could be partly explained by the highest between-population differentiation of Y-Chr lineages with respect to mtDNA ones, but concordance of results from different analyses supports the presence of a sex-biased admixture pattern
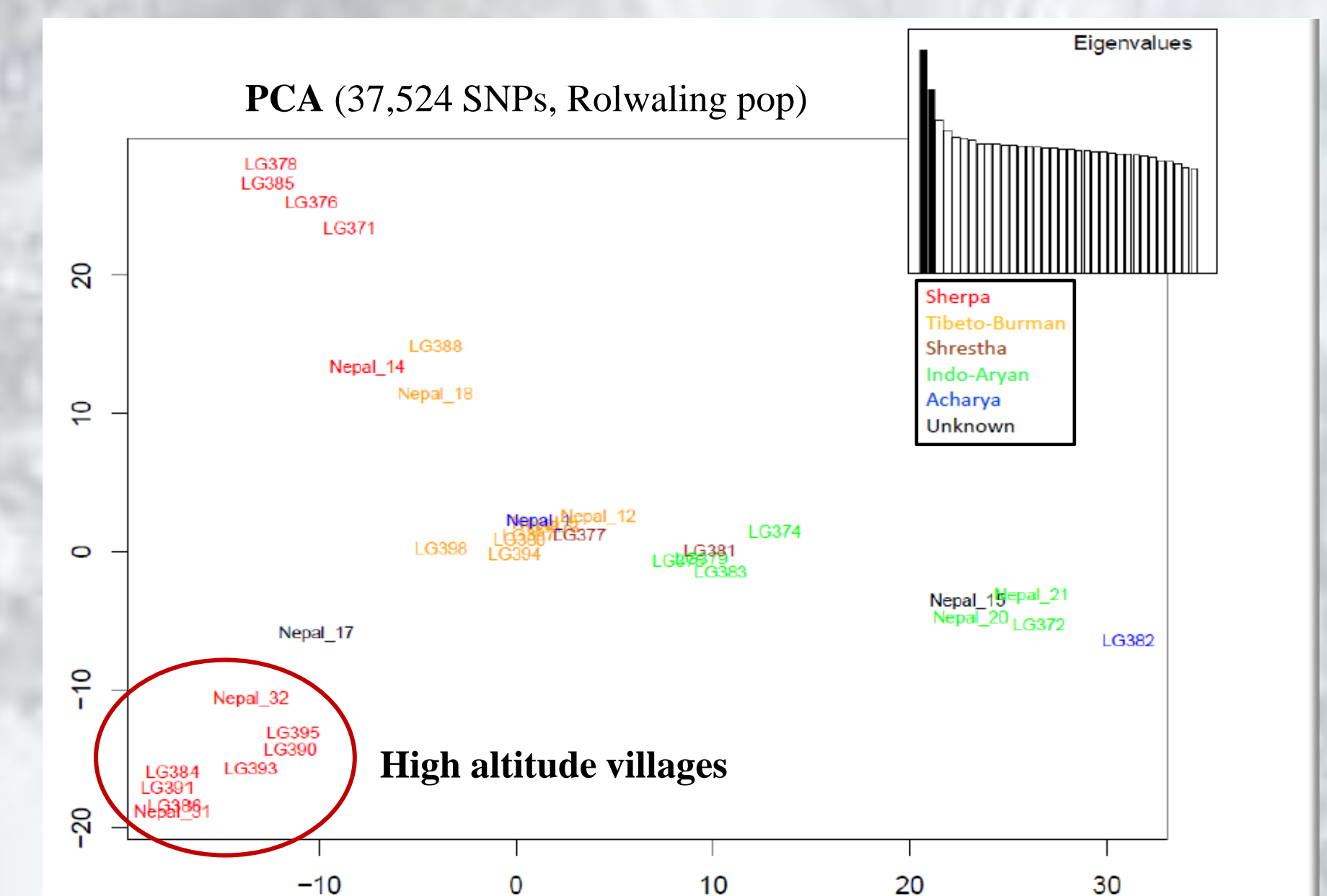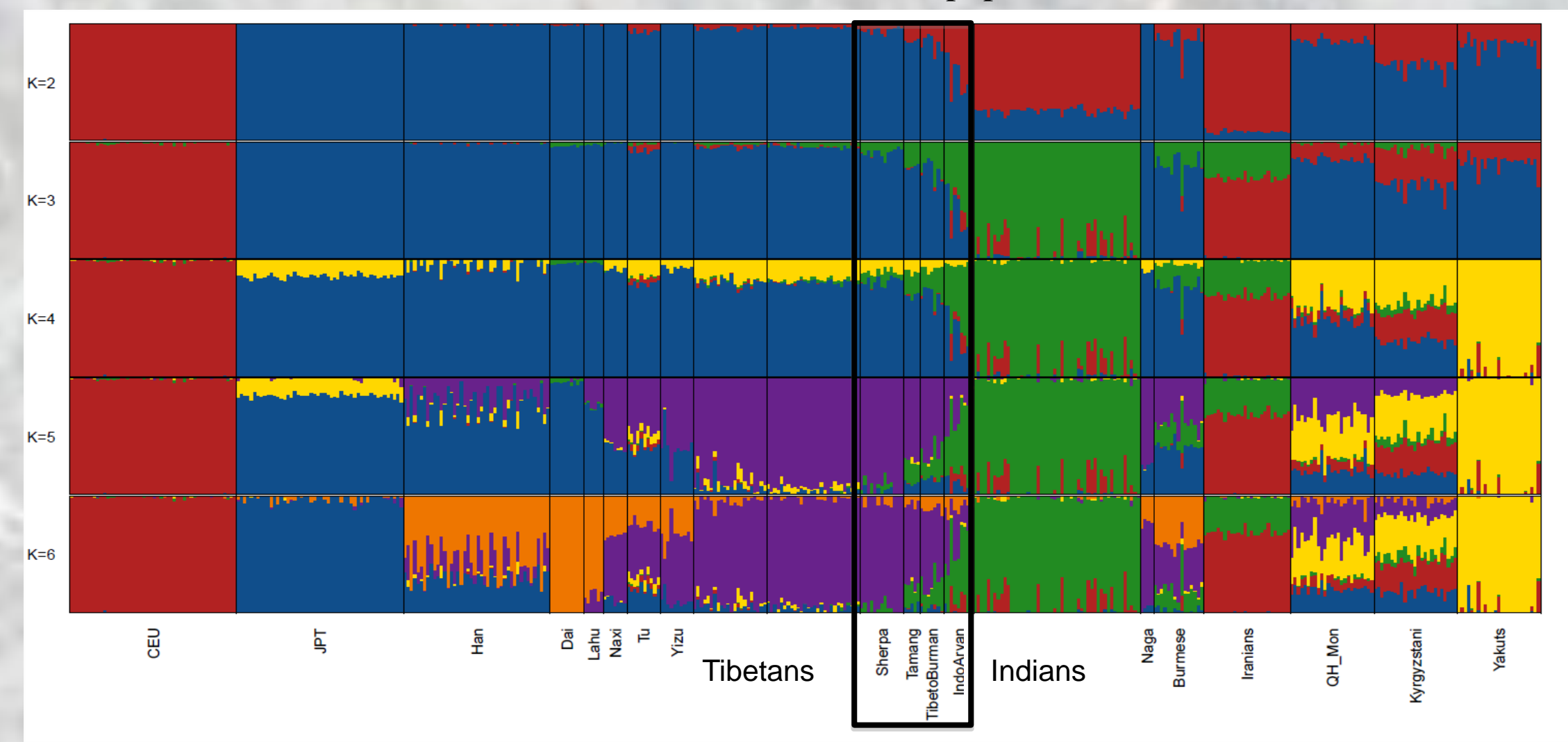
Genome-wide SNP data

PCA (37,221 SNPs, 110 pop)

PC1: West to East gradient
PC5: "Tibetan" gradient
Jap, China, Indo-Aryans, Tibeto-Burmans, Sherpas, Tibet

ADMIXTURE (66,761 SNPs, 21 pop, K2-K6)

K=2, K=3, K=4, K=5, K=6
CEU, JPT, Han, Tibetans, Sherpa/Tamang/TibetoBurman/IndoAryan, Indians, Naga, Burmese, Iranians, Gih_Mon, Kyrgystan, Yakuts

PCA (37,524 SNPs, Rolwaling pop)

Eigenvalues

Sherpa
Tibeto-Burman
Shrestha
Indo-Aryan
Acharya
Unknown

High altitude villages

☐ **PCA** and **ADMIXTURE** analyses revealed substantial **population structure within the Rolwaling** valley, plausibly explaining the high genetic diversity pointed out by uniparentally-inherited markers:

- **Indo-Aryan** speaking groups show **major South-Asian/Indian ancestry**, with reduced and probably recent admixture with a Tibetan component
- The **Sherpas** share almost all ancestry with Tibetans
- The **other Tibeto-Burman** groups show **admixed ancestry**, mainly between a major Tibetan component and an Indian one

☐ PCA on the sole Rolwaling dataset enabled an even finer distinction within the Sherpa group, with subjects born in the upper part of the valley clustering together and apart with respect to those from lower altitudes.

This pattern probably reflects a peculiar history of isolation and subsequent drift experienced by the very high altitude Sherpas

Future perspectives

A new sampling campaign (October 2015) will increase N. for specific ethnic groups (i.e. Sherpas & Tamangs) and provide data on blood/ventilation parameters from individuals born at different altitudes and with different genetic ancestry to conduct genotype-phenotype association studies. Coupled with scanning the genome for signatures of natural selection this will give new insights into the evolution of high altitude adaptation in Nepalese populations