Detection and genetic diversity of *Bartonella* species in small mammals from the central region of the Qinghai-Tibetan Plateau, China

Juan Yu1, Qingduo Li3, Liang Lu3, Shoujiang Li4, Xiuping Song3, Dongmei Li3∗ & Huaxiang Rao2∗

In this study, we aimed to investigate the prevalence and molecular characteristics of *Bartonella* infections in small mammals from the central region of the Qinghai-Tibetan Plateau. Toward this, small mammals were captured using snap traps in Yushu City and Nangqian County, West China, and the spleen tissue was used for *Bartonella* culture. The suspected positive colonies were evaluated using polymerase chain reaction (PCR) amplification and by sequencing the citrate synthase (*gltA*) gene. We discovered that 31 out of the 103 small mammals tested positive for *Bartonella*, with an infection rate of 30.10%. Sex differences between the mammals did not result in a significant difference in infection rate ($\chi^2 = 0.018$, $P = 0.892$). However, there was a significant difference in infection rates in different small mammals (Fisher’s exact probability method, $P = 0.017$) and habitats ($\chi^2 = 7.157$, $P = 0.028$).

Additionally, 31 *Bartonella* strains belonging to three species were identified, including *B. grahamii* (25), *B. japonica* (4) and *B. heixiaziensis* (2), among which *B. grahamii* was the dominant epidemic strain (accounting for 80.65%). Phylogenetic analyses showed that most of the *B. grahamii* isolates identified in this study may be closely related to the strains isolated from Japan and China. Genetic diversity analyses revealed that *B. grahamii* strains had high genetic diversity, which showed a certain host and geographical specificity. The results of Tajima’s test suggested that the *B. grahamii* followed the progressions simulated by a neutral evolutionary model in the process of evolution. Overall, a high prevalence and genetic diversity of *Bartonella* infection were observed in small mammals in the central region of the Qinghai-Tibetan Plateau. *B. grahamii* as the dominant epidemic strain may cause diseases in humans, and the corresponding prevention and control measures should be taken into consideration in this area.

*Bartonella* species are small, intracellular, vector-borne hemotrophic gram-negative bacteria. Thus far, there are over 40 species and subspecies have been reported to infect a wide range of mammals, including cats, dogs, rodents, bats, and so on. Over 10 *Bartonella* species, including *B. bacilliformis*, *B. quintana*, *B. henselae*, *B. elizabethae*, *B. claridgeiae*, *B. koehlerae*, *B. vinsonii* subsp. *rupensis*, *B. vinsonii* subsp. *berkhoffii*, *B. grahamii*, *B. rochalimae*, *B. tamiae*, *B. ancashensis*, *B. washoensis*, can cause human diseases with various clinical manifestations, including periods of intermittent fever, and poly tissue inflammation involving the heart, liver, lymph nodes, and other tissues. Small mammals, particularly rodents, are considered important reservoirs of *Bartonella* species, with an infection rate of 70% worldwide. Hence, investigating the epidemiological...
characteristics of *Bartonella* in small mammals has important implications for the prevention and control of human bartonellosis. The Qinghai-Tibetan Plateau, referred to as the "Roof of the World", is an inland plateau in Asia; the largest in China and the highest in the world. The Yushu Tibetan Autonomous Prefecture lies in the central region of the Qinghai-Tibetan Plateau and belongs to the Sanjiangyuan Region, the source of the Yangtze, Yellow, and Lantsang rivers (between 31.65° N and 102.38° E), with an average elevation of 4493 m\(^1\). It has an important ecological status, with the highest concentration of biodiversity area in the world; nearly 30 species of mammals have been reported to inhabit this area. Our team has previously detected *Bartonella* species infection in small mammals in some areas of the Qinghai-Tibetan Plateau, with infection rates of 18.99% and 38.61%\(^1\),\(^2\). However, investigations of *Bartonella* species in small mammals in the central region of the Qinghai-Tibetan Plateau have not yet been undertaken. This region's tourism industry was greatly developed following the reconstruction work after the Yushu earthquake. This increased the probability of people being infected with natural infectious diseases. Therefore, in this study, we investigated the prevalence and genetic diversity of *Bartonella* species in small mammals in the Yushu Tibetan Autonomous Prefecture. Our findings provide insights into the distribution and genetic diversity of *Bartonella* in small mammals and the scientific basis for the control and prevention of *Bartonella* infection in humans in this region.

**Results**

**Animal collection.** A total of 103 small mammals were captured and categorized into 10 species based on their morphology, including *Apodemus peninsulae* (58), *Ochotona curzoniae* (16), *Microtus arvalis* (8), *Cricetidae* (7), *Microtus gregalis* (4), *Microtus oeconomus* (3), *Sorex araneus Linnaeus* (3), *Eozapus setchuanus* (2), *Mustela altaica* (1), and *Mus musculus* (1). The geographical distribution of the trapped small mammals is shown in Fig. 1.

**Bartonella infections.** Spleens of the small mammals were collected and used for *Bartonella* isolation, and the pure colonies obtained were confirmed by polymerase chain reaction (PCR) amplification of the partial citrate synthase (*gltA*) gene (379 bp). In total, 31 small mammals were positive for *Bartonella* infection, with an infection rate of 30.10% (31/103), which were classified into five species (*Apodemus peninsulae* (22/58), *Microtus*...
B. grahamii from 12 species were grouped into four clusters, i.e., B. grahamii, B. heixiaziensis, B. japonica, and B. arvalis. Therefore, in this study, we selected phylogenetic analyses of B. grahamii using the maximum likelihood (ML) method. All Bartonella strains could be divided into three clusters, i.e., B. grahamii, B. heixiaziensis, and B. japonica; B. grahamii were the dominant Bartonella species in this area (Fig. 2). Bartonella was detected in small mammals from three of the four trapping sites and the distribution of Bartonella species showed slight geographical differences (Fig. 3). Phyllogenetic analyses based on gltA sequences showed that B. grahamii was mainly grouped into two clusters, including that B. grahamii might have the different origins. We then obtained the gltA sequences of B. grahamii from GenBank released before July, 2021, and performed the traceability analyses. The majority of B. grahamii strains from A. peninsulae clustered with B. grahamii from A. speciosus in Japan; three strains, i.e., AP1QHYS, MA61QHYS, CR102QHYS, from A. peninsulae, M. arvalis, and Cricetidae clustered with B. grahamii from M. oeconomicus in our previous study; three strains, i.e., CR34QHYS, CR36QHYS, CR103QHYS, from Cricetidae and one strain from M. gregalis (MG5QHYS) clustered separately and not with the reference strains (Fig. 4). Genetic diversity analyses. Subsequently, the genetic diversity of the gltA gene sequence (326 bp) from 77 strains of B. grahamii was analyzed, including 25 strains in this study and 52 strains from our previous studies, isolated from three regions of Qinghai-Tibetan Plateau, including Haixi Mongolian and Tibetan Autonomous Prefecture, Huangnan Tibetan Autonomous Prefecture, and Haibei Tibetan Autonomous Prefecture. We found

Table 1. Distribution of Bartonella infection in different small mammals. AP Apodemus pensilnueae, OC Ochotona curzoniae, MA Microtus arvalis, CR Cricetidae, MG Microtus gregalis, MO Microtus oeconomicus, SA Sorex araneus Linnaeus, ES Eozapus setchuanus, MuA Mustela altaica, MuM Mus musculus.

| Habits   | Host   | AP | OC | MA | CR | MG | MO | SA | ES | MuA | MuM | No. captured | No. PCR positive (%) | Positive rate (%) |
|----------|--------|----|----|----|----|----|----|----|----|-----|-----|---------------|-------------------|------------------|
| Farmland |        | 29 | 1  | 5  | 4  | 4  | 3  | 1  | 1  | 0   | 1   | 49            | 22 (37.93)        | 30.61            |
| Forest   |        | 29 | 2  | 3  | 3  | 0  | 0  | 2  | 1  | 1   | 0   | 41            | 13 (32.00)        | 39.02            |
| Meadow   |        | 0  | 13 | 8  | 7  | 4  | 3  | 3  | 2  | 1   | 1   | 103           | 31 (30.10)        | 30.10            |
| Total    |        | 58 | 16 | 8  | 7  | 4  | 3  | 3  | 2  | 1   | 1   | 103           | 31 (30.10)        | 30.10            |

Identification of Bartonella species. Through BLAST analysis of the gltA gene, 25 isolates were identified to be B. grahamii with 97.11–100.00% identity, including 18 isolates from A. peninsulae, 4 isolates from Cricetidae, 1 isolate from M. arvalis, 1 isolate from M. gregalis and 1 isolate from M. oeconomicus; 4 isolates from A. peninsulae were B. japonica with 97.89–99.70% identity; 2 isolates were B. heixiaziensis with 98.59–99.44% identity, including 1 isolate from M. arvalis and 1 isolate from M. oeconomicus (Table 1). In our previous study, phylogenetic analyses of Bartonella species was performed based on the DNA sequences of the gltA, ftsZ, rpoB and ribC revealed the same results20. Of these, gltA is the most commonly used in the phylogenetic analyses of Bartonella. Therefore, in this study, we selected gltA to construct a phylogenetic tree using the maximum likelihood (ML) method. All Bartonella strains could be divided into three clusters, i.e., B. grahamii, B. heixiaziensis, and B. japonica; B. grahamii were the dominant Bartonella species in this area (Fig. 2). Bartonella was detected in small mammals from three of the four trapping sites and the distribution of Bartonella species showed slight geographical differences (Fig. 3). Phyllogenetic analyses based on gltA sequences showed that B. grahamii was mainly grouped into four clusters, including that B. grahamii might have the different origins. We then obtained the gltA sequences of B. grahamii from GenBank released before July, 2021, and performed the traceability analyses. The majority of B. grahamii strains from A. peninsulae clustered with B. grahamii from A. speciosus in Japan; three strains, i.e., AP1QHYS, MA61QHYS, CR102QHYS, from A. peninsulae, M. arvalis, and Cricetidae clustered with B. grahamii from M. oeconomicus in our previous study; three strains, i.e., CR34QHYS, CR36QHYS, CR103QHYS, from Cricetidae and one strain from M. gregalis (MG5QHYS) clustered separately and not with the reference strains (Fig. 4).
| Sample ID  | Host species          | Sex  | Habitat     | Location         | Latitude   | Longitude | Genotype               |
|------------|-----------------------|------|-------------|------------------|------------|-----------|------------------------|
| AP1QHYS    | Apodemus peninsulae    | Male | Farmland    | Zailongda        | 32.83° N   | 97.04° E | Bartonella grahamii    |
| M2QHYS     | Microtus oconomus      | Female | Farmland | Zailongda        | 32.83° N   | 97.04° E | Bartonella grahamii    |
| M4QHYS     | Microtus oconomus      | Male  | Farmland    | Zailongda        | 32.83° N   | 97.04° E | Bartonella grahamii    |
| MGQHYS     | Microtus gregalis      | Unknown | Farmland | Zailongda        | 32.83° N   | 97.04° E | Bartonella grahamii    |
| AP11QHYS   | Apodemus peninsulae    | Male  | Farmland    | Zailongda        | 32.83° N   | 97.04° E | Bartonella grahamii    |
| AP14QHYS   | Apodemus peninsulae    | Female | Farmland | Zailongda        | 32.83° N   | 97.04° E | Bartonella grahamii    |
| AP16QHYS   | Apodemus peninsulae    | Male  | Farmland    | Zailongda        | 32.83° N   | 97.04° E | Bartonella grahamii    |
| CR3QHYS    | Cricetidae             | Female | Farmland | Xijingxian       | 32.21° N   | 96.49° E | Bartonella grahamii    |
| CR36QHYS   | Cricetidae             | Female | Farmland | Xijingxian       | 32.21° N   | 96.49° E | Bartonella grahamii    |
| AP3QHYS    | Apodemus peninsulae    | Male  | Farmland    | Xijingxian       | 32.21° N   | 96.49° E | Bartonella grahamii    |
| AP39QHYS   | Apodemus peninsulae    | Female | Farmland | Xijingxian       | 32.21° N   | 96.49° E | Bartonella grahamii    |
| AP43QHYS   | Apodemus peninsulae    | Male  | Farmland    | Xijingxian       | 32.21° N   | 96.49° E | Bartonella grahamii    |
| AP51QHYS   | Apodemus peninsulae    | Female | Farmland | Xijingxian       | 32.21° N   | 96.49° E | Bartonella japonica    |
| MA60QHYS   | Microtus arvalis       | Female | Farmland | Xijingxian       | 32.21° N   | 96.49° E | Bartonella heixiaeiensis |
| MA61QHYS   | Microtus arvalis       | Female | Farmland | Xijingxian       | 32.21° N   | 96.49° E | Bartonella grahamii    |
| AP63QHYS   | Apodemus peninsulae    | Female | Forest    | Karongxia        | 32.28° N   | 96.48° E | Bartonella grahamii    |
| AP66QHYS   | Apodemus peninsulae    | Male  | Forest     | Karongxia        | 32.28° N   | 96.48° E | Bartonella grahamii    |
| AP67QHYS   | Apodemus peninsulae    | Female | Forest     | Karongxia        | 32.28° N   | 96.48° E | Bartonella grahamii    |
| AP69QHYS   | Apodemus peninsulae    | Male  | Forest     | Karongxia        | 32.28° N   | 96.48° E | Bartonella grahamii    |
| AP73QHYS   | Apodemus peninsulae    | Female | Forest     | Karongxia        | 32.28° N   | 96.48° E | Bartonella grahamii    |
| AP77QHYS   | Apodemus peninsulae    | Female | Forest     | Karongxia        | 32.28° N   | 96.48° E | Bartonella grahamii    |
| AP79QHYS   | Apodemus peninsulae    | Male  | Forest     | Karongxia        | 32.28° N   | 96.48° E | Bartonella grahamii    |
| AP92QHYS   | Apodemus peninsulae    | Male  | Forest     | Karongxia        | 32.28° N   | 96.48° E | Bartonella grahamii    |
| AP94QHYS   | Apodemus peninsulae    | Female | Forest     | Karongxia        | 32.28° N   | 96.48° E | Bartonella grahamii    |
| AP98QHYS   | Apodemus peninsulae    | Female | Forest     | Karongxia        | 32.28° N   | 96.48° E | Bartonella grahamii    |
| AP100QHYS  | Apodemus peninsulae    | Female | Forest     | Karongxia        | 32.28° N   | 96.48° E | Bartonella grahamii    |
| AP101QHYS  | Apodemus peninsulae    | Male  | Forest     | Karongxia        | 32.28° N   | 96.48° E | Bartonella grahamii    |
| CR102QHYS  | Cricetidae             | Female | Forest    | Karongxia        | 32.28° N   | 96.48° E | Bartonella grahamii    |
| CR103QHYS  | Cricetidae             | Male  | Forest     | Karongxia        | 32.28° N   | 96.48° E | Bartonella grahamii    |

Table 3. Sampling locations of each host species with Bartonella infection.

19 polymorphic loci (S = 19) and 15 haplotypes (H = 15). The haplotype diversity (Hd) was 0.880 ± 0.019, the mean number of nucleotide differences (k) was 4.386, and the nucleotide diversity (π) was 0.01345 ± 0.00077. DNA polymorphism was analyzed using a sliding window with a length of 100 bp and a step size of 25 bp. It was found that fragment diversity was the highest between 151 and 250 bp (Fig. 5). The results indicated high genetic diversity in B. grahamii in this area. Tajima’s D was calculated as 0.39958 (P > 0.10), suggesting that B. grahamii followed the progressions simulated by the neutral evolutionary model in the process of evolution.

Haplotype network analyses showed that 35 strains from Cricetidae longicaudatus contained 10 haplotypes (2 strains for Hap 1, 3 strains for Hap 5, 1 strain for Hap 7, 19 strains for Hap 8, 4 strains for Hap 9, 3 strains for Hap 10, 1 strain for Hap 11, 1 strain for Hap 12 and 1 strain for Hap 13), 18 strains from A. peninsulae contained 3 haplotypes (9 strains for Hap 1, 8 strains for Hap 2, and 1 strain for Hap 3), 12 strains from O. curzoniae contained 2 haplotypes (11 strains for Hap 14 and 1 strain for Hap 15), 4 strains from Cricetidae contained 2 haplotypes (1 strain for Hap 4 and 3 strains for Hap 5), 2 strains from Apodemus speciosus for Hap 7, 2 strains from M. musculus for Hap 9, 1 strain from M. arvalis and 2 strains from M. oconomus for Hap 3, and 1 strain from M. gregalis for Hap 6. In addition, 25 strains isolated from Yushu contained 6 haplotypes (9 strains for Hap 1, 8 strains for Hap 2, 3 strains for Hap 3, 1 strain for Hap 4, 3 strains for Hap 5, and 1 strain for Hap 6), 30 strains isolated from Haixi contained 8 haplotypes (1 strain for Hap 3, 3 strains for Hap 5, 1 strain for Hap 7, 19 strains for Hap 8, 3 strains for Hap 10, 3 strains for Hap 11, 12, 13 respectively), 15 strains isolated from Huangnan contained 4 haplotypes (2 strains for Hap 1, 2 strains for Hap 7, 6 strains for Hap 9, and 5 strains for Hap 14), and 7 strains isolated from Haibei contained 2 haplotypes (6 strains for Hap 14 and 1 strain for Hap 15) (Fig. 6, Table 4).

**Discussion**

*Bartonella* species are distributed throughout the world. They are highly prevalent in small mammals and are generally transmitted by bloodsucking arthropod vectors. Previous studies have revealed that *Bartonella* infection varies in different regions and animals. For instance, infection rate of *Bartonella* in rodents is 4–50% in China, 6–94% in Japan, 7–14% in Korea, 2–10% in Indonesia, 60–83% in Russia, 6–90% in United States, 20–60% in England. Rodents are primary reservoir hosts for *B. grahamii*, *B. elizabethae*, and...
Bartonella—(B. coopersplainsensis) strains corresponded to three species of phylogenetic analyses showed that 31 hamii sex, which is concurrent with the results of a previous study. Additionally, the infection rate varied significantly by habitats, but not by all five species of the small mammals studied, suggesting that it was the dominant tissue of small mammals was used for culture, and 31 Bartonella is associated with neuroretinitis and cat scratch disease (CSD) in immunocompromised individuals, suggesting that Bartonella was used as outgroup.

In this study, we observed the prevalence and molecular characteristics of Bartonella species in small mammals from different areas. In the central region of the Qinghai-Tibetan Plateau. The infection rate of Bartonella species in small mammals was 30.10%, which was similar to that of 38.61% in Qaidam Basin as determined in our previous study, and higher than that in most areas of China. Bartonella species were detected in five out of ten species of small mammals, including A. peninsulac, M. arvalis, Cricetidae, M. gregalis, and M. oconomus, and we found differing infection rates among them. Additionally, the infection rate varied significantly by habitats, but not by sex, which is concurrent with the results of a previous study.

Bartonella species are fastidious, slow-growing, facultative intracellular bacteria that are difficult and time consuming to culture. In our previous study, we used spleen, liver, and brain tissue for Bartonella culture and found that the positive rates in different tissues of small mammals did not differ significantly. Here, the spleen tissue of small mammals was used for Bartonella culture, and 31 Bartonella strains were obtained. BLAST and phylogenetic analyses showed that 31 Bartonella strains corresponded to three species of Bartonella—(B. grahamii, B. japonica, and B. heixiazensis). Importantly, 80.65% isolates (25/31) were B. grahamii and detected in all five species of the small mammals studied, suggesting that it was the dominant Bartonella strain. B. grahamii is associated with neuroretinitis and cat scratch disease (CSD) in immunocompromised individuals, suggesting that Bartonella species may have the ability to cause human disease in this area. In addition, four isolates
of *B. japonica* were isolated from *A. peninsulae* and two isolates of *B. heixiaziensis* were isolated from *Microtus* species, indicating specificity of infection among rodent species.

Subsequently, we performed traceability analyses on the dominant *B. grahamii* strains and found that *B. grahamii* was mainly grouped into four clusters. *B. grahamii* was clustered with *A. speciosus* in Japan, *M. oeconomicus* in China, 3 strains from *Cricetidae* and 1 strain from *M. gregalis* clustered separately. These results indicated that *B. grahamii* might have different origins. Further studies are needed to determine whether the pathogenicity of *B. grahamii* strains differs depending on their origins.

A previous study revealed that the polymorphism within *gltA* gene was high in *Bartonella* species. Here, 15 haplotypes were detected in 77 strains of *B. grahamii* based on *gltA* gene (Hd = 0.880, π = 0.01345), suggesting that the high genetic diversity of *B. grahamii* in the Qinghai-Tibetan Plateau. With the exception of *C. longicaudatus*, *B. grahamii* strains were isolated from *A. peninsulae* for Hap 1–3, *Cricetidae* for Hap 4–5, *M. arvalis* and *M. oeconomicus* for Hap 3, *M. musculus* for Hap 9, and *O. curzoniae* for Hap 14–15, which suggested the haplotypes of *B. grahamii* showed a certain host specificity. This also indicated the haplotypes of *B. grahamii* had a certain geographical specificity, although, the geographical crossover existed. Additionally, *B. grahamii* isolated from *C. longicaudatus* showed complex haplotypes that intersected with many rodents, suggesting that it might be important for the evolution of *B. grahamii* in this area.

**Conclusions**

In conclusion, *Bartonella* infection rate was 30.10% in small mammals in the central region of the Qinghai-Tibetan Plateau, with significant differences between different animal species and habitats. *B. grahamii*, *B. japonica*, and *B. heixiaziensis* were detected in five rodent species, *A. peninsulae*, *M. arvalis*, *Cricetidae*, *M. gregalis* and *M. oeconomicus*. *B. grahamii* was the dominant strain, and originated from the *B. grahamii* strains in different areas. In addition, high genetic diversity in *B. grahamii* was observed in this area, and the haplotypes...
Figure 4. Traceability analyses of *B. grahamii* based on *gltA* gene. The tree was constructed by using the maximum-likelihood (ML) method with the Kimura 2-parameter model, bootstrap values calculated with 1000 replicates in MEGA version 7.0 (https://www.megasoftware.net). The sequences detected in this study are indicated with black dots.
of *B. grahamii* showed a certain host and geographical specificity. Our results further enrich the prevalence and molecular characteristics of *Bartonella* infection in small mammals in the Qinghai-Tibetan Plateau, which could provide the scientific basis for prevention and control of rodent-*Bartonella* species.

**Materials and methods**

**Animal collection.** Small mammals were captured using snap traps in July 2019 in Yushu City (32.68°–33.77° N, 95.68°–97.73° E) and Nangqian County (31.53°–32.72° N, 95.35°–97.12° E) of Qinghai Province, which were identified morphologically.

**Bartonella culture.** Spleens were harvested under sterile conditions from each animal after euthanasia. Approximately 20 mg of each spleen sample was homogenized by adding 200 μL sterilized trypsin soy broth (BD Biosciences, Franklin Lakes, NJ, USA), plated onto two trypsin soy agars containing 5% (vol/vol) defiber sheep

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**Figure 5.** Genetic diversity of different nucleotide position in *gltA* gene of *B. grahamii*. Genetic diversity was analyzed using DNASP 6.12.03 ([http://www.ub.edu/dnasp](http://www.ub.edu/dnasp)) with a sliding window interval of 25 bp.

**Figure 6.** Median-joining networks of *gltA* gene for *B. grahamii* strains from different hosts and regions in the Qinghai-Tibetan Plateau, China. The sequences were analyzed based on a median-joining network using the Population Analysis with Reticulate Trees (PopART) software version 1.7 ([http://popart.otago.ac.nz/index.shtml](http://popart.otago.ac.nz/index.shtml)) with the default setting (epsilon = 0).
Statistical analysis. The positive rates of Bartonella in different habitats and sexes of small mammals were analyzed using the Chi-square test. The infection rates of Bartonella in different mammals were analyzed using the Chi-square test. The infection rates of Bartonella in different mammals were analyzed using the Chi-square test.
the Fisher's exact probability method. All data were analyzed using SPSS 22.0 (SPSS, Inc., Chicago, IL, USA). Significance was set at $P < 0.05$.

**Ethical approval.** This study was approved by the Ethics Committee of Chinese Center for Disease Control and Prevention (No: ICDC-2015001). All animals were treated according to the ARRIVE guidelines\(^4\), the Guidelines of Regulations for the Administration of Laboratory Animals (Decree No. 2 of the State Science and Technology Commission of the People's Republic of China, 1988) and the Guidelines for Treating Animals Kindly from Ministry of Science and Technology of the People's Republic of China. All efforts were made to minimize discomfort to the animals.

**Consent to publish.** All the authors consent to publish the article in its present form.

**Data availability**
The data supporting the conclusions of this article are included within the article.

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Author contributions

D.M.L. and H.X.R. conceived and designed the experiments. J.Y., H.X.R. and D.M.L. wrote the manuscript. All authors reviewed the manuscript.

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Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to D.L. or H.R.

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