REVIEW ARTICLE

Prevalence of *Mycobacterium tuberculosis* strain genotypes in Taiwan reveals a close link to ethnic and population migration

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Received 4 March 2014; received in revised form 10 July 2014; accepted 21 July 2014

Taiwan is a relatively isolated island, serving as a mixing vessel for colonization by different waves of ethnic and migratory groups over the past 4 centuries. The potential transmission pattern of *Mycobacterium tuberculosis* in different ethnic and migratory populations remains to be elucidated. By using mycobacterial tandem repeat sequences as genetic markers, the prevalence of *M. tuberculosis* strains in Taiwan revealed a close link to the historical migration. Interestingly, the *M. tuberculosis* strain in the aborigines of Eastern and Central Taiwan had a dominance of the Haarlem (Dutch) strain while those in Southern Taiwan had a dominance of the East-African Indian (EAI) strain. The prevalence of different *M. tuberculosis* strains in specific ethnic populations suggests that *M. tuberculosis* transmission is limited and restricted to close contact. The prevalence of the Beijing modern strain in the young population causes a concern for *M. tuberculosis* control, because of high virulence and drug resistance. Furthermore, our data using molecular genotyping should provide valuable information on the historical study of the origin and migration of aborigines in Taiwan.

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Introduction

Tuberculosis (TB) remains a huge health concern worldwide. In Taiwan, around 13,000 new TB cases were reported every year, according to the statistics of the Center for Disease Control, Department of Health. Lo et al. indicated that new TB cases declined from 16,758 to 14,265, and the incidence decreased from 75/100,000 population to
Comas et al also revealed that simulations matched well to historical population migrations. Tuberculosis lineage distributions in different ethnic populations matched well to historical population migrations. Comas et al also revealed that M. tuberculosis emerged about 70,000 years ago, accompanied by migrations of modern humans out of Africa and expanded as a consequence of the increase in human population density during the Neolithic period. Their study also indicated the transmission routes of M. tuberculosis from East Africa to Asian countries and the Indian Ocean, probably representing the origins of M. tuberculosis strain genotypes such as Beijing, East-African Indian (EAI), Latin American and Mediterranean (LAM), and Haarlem lineages.

Taiwan is a relatively isolated island. Routes of transmission of Beijing, EAI, Haarlem, LAM, and T lineages of M. tuberculosis have been previously proposed to spread through different waves of ethnic groups over the past centuries. The ethnic populations who migrated to the island of Taiwan can be divided into two major waves: (1) during the Ming dynasty; and (2) between 1945 and 1950 due to the civil war. Prior to Han Chinese migration in the 17th century, the ancestors of aborigines in Taiwan may have been living on the island for thousands of years. Some studies indicated that the aborigines in Taiwan are Austronesian people, with similar linguistic and genetic clues to other Austronesian ethnic groups. To date, 12 tribes of aborigines were identified in Taiwan, mainly located in Southern, Eastern, and Central Taiwan. Controversy, however, still exists regarding the period and origin of migration to Taiwan for different tribes.

According to the statistics of Council of Indigenous Peoples, Executive Yuan, the ethnic population of Taiwan includes 98% Han Chinese and about 2% native aborigines. Compared to Han Chinese groups, many studies indicated that a significantly higher incidence of TB occurred in aborigines. Notably, polymorphism of the NRAMP1 gene suggests the susceptibility of the aboriginal population to TB, compared to Han Chinese. In this review article, we provide a comprehensive review on the M. tuberculosis strain transmission and evolution to reflect the association of M. tuberculosis strain transmission with ethnic and migratory populations in Taiwan.

Molecular typing of M. tuberculosis and association with different ethnic and migration populations in Taiwan

In the past decade, many molecular methods were used for M. tuberculosis characteristics and genotyping. To date, discrimination of M. tuberculosis strains has been achieved by the high-resolution genotyping methods such as large sequence polymorphisms, mycobacterial interdispersed repetitive units loci comprise variable numbers of tandem repeat (MIRU-VNTR) typing, restriction fragment length polymorphism, spoligotyping or analysis of genomic deletions. Based on the methods listed above, six major lineages of M. tuberculosis isolates were identified, including Beijing, EAI, Haarlem, LAM, and U and T lineages. Of six major lineages in Taiwan, the Beijing genotype overall was the most predominant, being identified in 72% of TB-positive veterans, in 56% of the general population, and in 40% of aborigines. This observation coincides with currently reported studies worldwide, the most prevalent strains being Beijing genotypes, which spread from its origin to Asian countries, the Soviet Union, Europe, and the United States, and are often associated with hyper-virulence and multiple drug resistance (MDR). Following the Beijing lineage, the second prevalent lineage, the Haarlem strain was identified in 27% of the aboriginal population, 13% of the general population, and in only 7% of veterans.

The Beijing lineage can be further divided into ancient and modern subfamilies by the presence or absence of transposon IS6110 insertions in the NTF regions and RD deletions. The results indicated that modern Beijing lineage was prevalent in general populations, whereas the ancient Beijing was prevalent in the aborigine population. In the Ming Dynasty, the Han Chinese began to migrate from the mainland to Taiwan. Thus, the Beijing strains may have spread from migrants to Taiwan residents at that time. The reasons for ancient Beijing M. tuberculosis lineage among aborigines will be addressed upon completion of cohort and historical studies described below. The Haarlem strain was the second most prevalent lineage identified in those subpopulations. The wild type Haarlem strains circulating in the aboriginal population were identified by ogt and mgtC analysis. However, the Haarlem lineage isolated in the countries of Europe was comparatively modern.

Molecular epidemiology of M. tuberculosis in the aboriginal population

Aborigines are estimated to constitute around 2% of the population of Taiwan. Previous linguistic studies suggest that Taiwan is the origin of Austronesians. The original Austronesians lived in Southern Taiwan, and then migrated to the whole of Taiwan. Currently, the aborigines residing in Eastern and Central Taiwan have retained relatively intact village lifestyles, and are fairly remote and isolated. Although aborigines in Southern Taiwan live in settlements, they have closer interactions with the Han Chinese. Notably, previous studies revealed that aborigines have a 4–6-fold higher incidence and prevalence of TB compared to other populations. The similar trends were also reported by Tuite et al in Ontario, Canada. Several reasons may be involved in the high prevalence of TB in aborigines: environment factors such as poor hygiene, which could hamper access to medical care and host factors such as polymorphism of the NRAMP-1 gene. Clarifying the factors which underline the high prevalence of M. tuberculosis lineages in aborigines is important for preventing the spread of M. tuberculosis in this population.

Dou et al demonstrated that Haarlem lineages were prevalent in aborigines (40%) when compared to general
populations (13%). Recently, Chen et al. also indicated that the Haarlem strain is also highly predominant in aborigines of Taiwan (33.9%), particularly in eastern aboriginal tribes (39.1%), whereas the EAI strain is prevalent in Southern Taiwan aborigines. Haarlem strains from Dutch to aborigines may have first occurred during Dutch colonization of Taiwan periods. However, the EAI strain is significantly higher in Southern Taiwan aborigines, maybe due to the Austronesian culture. We speculate that EAI is predominant in the general population in Southern Taiwan, due to transfer from aborigines to the latter. Taken together, environment factors such as the relatively intact village lifestyle of aborigines may be the key reason for the high prevalence of some *M. tuberculosis* lineages, such as the Haarlem lineage in the eastern (39.1%) and central (37.1%) aboriginal tribes of Taiwan. Most patients infected with TB can be cured with standard treatment. The surveillance performed by Chen et al. and Hsu et al. indicated that a high prevalence of MDR-TB was found in the aboriginal population. In Eastern Taiwan, the major resident region of aborigines (which comprises about 29.4% of the total population), 77% of MDR-TB identified patients were aborigines, suggesting that MDR-TB is a serious infectious health concern in the aborigine population in Eastern Taiwan.


Molecular epidemiology and evolutionary genetics of *M. tuberculosis* in Northern Taiwan

The incidence and prevalence of TB in large urban cities such as Taipei or Kaohsiung of Taiwan is complicated by the close human-to-human contact and potential multiple different sources of *M. tuberculosis* strains from different ethnic and migrants. The major *M. tuberculosis* lineages in metropolitan Taipei found were Beijing strains reported by Dou et al. and Huang et al. (53–58%), followed by Haarlem (9–13.5%) and EAI lineages (3–11%). Beijing strains found in Taipei were mostly modern strains (96%) by RD (region of difference) analyses. Also, most of the people who lived there belonged to the Han Chinese. The modern Beijing lineages in adjacent Asia countries were found to be prevalent in Thailand (79.14%) and Taiwan (73.96%), whereas the ancient Beijing lineage was found to be prevalent in Japan (69%) by determining the presence of an IS6110 insertion in the MTF chromosomal region. The ancient Beijing lineage was identified to be 50% in aborigines, 24% in veterans, and 19% in general populations by our previous studies. The evolutionary and epidemiological observations suggest that the modern Beijing strain was more unstable when compared to the ancient strain, perhaps explaining its fast spread.

Another important challenge for TB control in the Metropolitan city was that patients infected with Beijing strains were significantly younger than those infected with other genotypes, and warranted close attention to the control policy and vaccine strategy. Although Taiwan has executed a comprehensive BCG vaccination program for decades, the data mentioned above indicate that BCG may not adequately protect young age people infected with the Beijing lineage of *M. tuberculosis*. Notably, many studies indicated that the Beijing lineage isolated in Taiwan is more likely to be MDR than other genotypes (Haarlem, EAI, T, and orphan strains).

Molecular epidemiology and evolutionary genetics of *Mycobacterium tuberculosis* in Southern Taiwan

Our previous studies revealed that the most prevalent lineage in Southern Taiwan was the Beijing lineage (43.3%),...
followed by EAI (32.1%) and Haarlem lineages (8.0%).

In theaboriginal population, the most prevalent lineage was the EAI lineage (47.7%), followed by Haarlem (20.5%) and Beijing (18.2%) lineages. EAI strains in Northern Taiwan comprise only about 11% of *M. tuberculosis* isolates, whereas in Southern Taiwan they comprise up to 32%. In the aboriginal population, the most prevalent lineage was the EAI strain in southern aborigines. Our study revealed a predominance of the modern Beijing lineage, followed by EAI (32.1%) and Haarlem lineages (8.0%). In Southern Taiwan, Chang et al. reported that the prevalence of Beijing lineages significantly decreased as the age of the patient increased, whereas that of EAI increased. Notably, age distribution across a sample of years compared within each genotype reported by Chang et al. indicated that the percentage of Beijing infected younger patients (< 30 years old) increased significantly (from 3.9% to 9.3%), but no significantly increasing trend was observed in the other lineages. Also, the balance that normally exists between Beijing and EAI lineages in older patients trends to be in flux in younger patients. These observations together indicated that *M. tuberculosis*-infected young patients are more likely to be infected with the Beijing lineage than with other *M. tuberculosis* strains as compared to the older population. Similar surveillance results were also reported in Taipei City, which may suggest a recent spread of the Beijing genotype in young people occurred at Kaohsiung City. In conclusion, these studies revealed that both modern (Beijing) and ancient (EAI) *M. tuberculosis* lineages are prevalent in Southern Taiwan, suggesting that both lineages are somehow balanced to the certain selective pressures in Southern Taiwan.

**Summary and conclusion**

The transmission routes of four major *M. tuberculosis* lineages in Taiwan previously reported by Dou et al. are illustrated in Fig. 1. By using modern molecular methods, the major *M. tuberculosis* lineages including Beijing, EAI, Haarlem, and LAM strains, revealed a close link to the historical migration of different ethnic populations. Surprisingly, epidemiological surveillance conducted in two major urban cities of Taiwan, Taipei and Kaohsiung, revealed a predominance of the modern Beijing lineage, especially in the young population, raising concerns for TB control. The Haarlem strain was predominant in the aborigines of Eastern and Central Taiwan, distinct from the prevalence of the EAI strain in southern aborigines. Our studies should also provide valuable materials complementary to the linguistic or host genome studies in tracing the migration and origin of the aboriginal tribes in Taiwan. Notably, significantly high percentages of MDR-TB strains were isolated in the aboriginal population when compared to the general population, and warrant close attention to the control policy.

According to the results of the distribution of strains in different ethnic populations, many studies will attempt to clarify factors that determine the disease transmission. The information provided in this paper will help us to understand the dynamics of *M. tuberculosis* strains among different geographic regions and ethnic populations in Taiwan. Taken together, many studies suggest that *M. tuberculosis* transmission is limited and restricted to close contact. Also, some genetic evolutions of *M. tuberculosis* which correlated with historic events remain to be investigated.

**Acknowledgments**

This work was sponsored by grants from the Special Project, National Science Council (NSC 102-2320-B-400-006); and grants from National Health Research Institutes, Taiwan.

**References**


