Global dissemination of the Mycobacterium tuberculosis W-Beijing family strains

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A large, genetically related group of Mycobacterium tuberculosis strains, variously called W or Beijing, is distinguished by specific molecular markers and referred to as the W-Beijing family strains. Molecular epidemiological studies suggest that these strains are highly prevalent throughout Asia and the countries of the former Soviet Union and they have also been reported in several other geographical regions, including North America. Although the spread of W-Beijing family strains in diverse populations is well documented, the underlying host-pathogen factors accounting for their continued dissemination and burden of disease have yet to be determined.

Advances in our understanding of the molecular biology of Mycobacterium tuberculosis have proven invaluable in unraveling the epidemiology of tuberculosis (TB) and in constructing the phylogenetic structure of the species. Genomic data have revealed remarkable DNA sequence conservation between chromosomes, and the paucity of synonymous mutations led to the hypothesis that M. tuberculosis is a recent human pathogen dating back approximately 15,000 years [1]. Although the M. tuberculosis genome is highly conserved in relation to other bacterial species, there are polymorphic regions that are usually associated with insertion sequences and/or repetitive elements and it is these variable regions that form the basis of modern TB genotyping.

Several polymorphic or hypervariable genetic markers have been characterized that, together, can discriminate or sub-speciate clinical isolates of M. tuberculosis. The most widespread and robust genotyping tool is the insertion sequence IS6110, a member of the IS3 family of transposable elements [2] that is specific for strains belonging to the M. tuberculosis complex [3]. Although noted ‘hot spots’ have been identified, IS6110 is more or less randomly distributed around the chromosome and its copy number ranges from the rare clones that lack an insertion to strains that have 26 copies [4,5]. The standardization of a method for IS6110 Southern blot hybridization has created ‘DNA fingerprints’ that can be compared between laboratories with the aid of pattern-matching software [6]. As a result, >50,000 M. tuberculosis isolates worldwide have been...
**Box 1. Key molecular characteristics that define the W-Beijing family strains**

- **Principal genetic group I (katG codon 463 CTG (Leu) and gyrA codon 95 ACC (Thr))** [a,b].
- **Empirical IS6110 banding pattern similarity to strain W (copy number range from 15–26).**
- **Spoligotyping denoted S00034, presence of nine spacers from 35 to 43 [c].**
- **IS6110 Insertion A1 in the origin of replication (corresponding to 3.36 kb band on a Southern hybridization blot probed with dnaA-dnaN) [b].**
- **One or two IS6110 insertions (two for strain W) in NTF region, demonstrated by multiplex PCR [b,d].**

All W-Beijing family strains share the above molecular profile including W4, W14, W82, strain 210, W148, Beijing members and others (Fig. I). Additional and distinguishing markers specific for NYC strain W and its progenies:

- **Second IS6110 insertion in NTF region (head-to-tail arrangement) [d].**
- **Rare dinucleotide change in codon 315 of katG (AGC→ACA) [e].**

**References**


**Fig. I.** Top panel: IS6110 Southern blot hybridization DNA fingerprint patterns of W-Beijing family Mycobacterium tuberculosis strains isolated from tuberculosis (TB) patients in different studies [Public Health Research Institute (PHRI) TB Center collection]. A, lanes 1–5: representative members of the W4 strain group from a population-based study, New Jersey [15]; B, lanes 1–3: representative members of the W14 strain group from a community cluster in New York City (NYC) [46]; C, lanes 1–5: representative members of the W-Beijing family isolated in China [5,28]; D, lanes 1–7: representative members of the W family strains isolated in the former Soviet Union [41,42]; E, 1–6: Multidrug resistant strain W and descendants isolated from the NYC outbreak [27]; F: W family strain W82 identified in nosocomial transmission study, Tennessee [57]; G: W family strain 210 found in California/Colorado/Texas outbreak [45]. The A1 arrow indicates the IS6110 insertion (common to all W-Beijing family strains) in the dnaA-dnaN region of the M. tuberculosis chromosome. Bottom panel: spacer oligonucleotide typing (spoligotyping) patterns of H37Rv (control) and W-Beijing family strains (pattern S00034).
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<th>Geographical region</th>
<th>Study design</th>
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<td>Hong Kong</td>
<td>Prospective study</td>
<td>266 isolates consisting of pretreatment and last sample obtained during chemotherapy. Acquisition of additional IS6110 in one patient.</td>
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<td>French Polynesia</td>
<td>Cross-sectional</td>
<td>Analysis of 72 isolates from 64 patients identified one from 11 clusters that belong to the W-Beijing family.</td>
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<td>East Asia: China, Mongolia, S. Korea, Thailand</td>
<td>Convenience sample</td>
<td>IS6110-based analysis: ‘Beijing family’ was found predominant among strains tested (China 86%, Mongolia 50%, S. Korea 43%, Thailand 37%). Postulated that these strains are endemic in the region.</td>
<td>[28]</td>
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<tr>
<td>New York City, USA</td>
<td>Outbreak investigation</td>
<td>253 of the 357 MDR strains shared identical 18-band or similar IS6110 pattern, strain W. Has since been considered the ‘index’ W strain at PHRI TB Center.</td>
<td>[27]</td>
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<td>Taiwan</td>
<td>Cross-sectional</td>
<td>90 isolates representative of 25% of all cases diagnosed at Mackay hospital, Taiwan.</td>
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<td>South Carolina, USA</td>
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<td>Thailand</td>
<td>Cross-sectional</td>
<td>80/211 isolates from three referral hospitals belong to the W-Beijing family.</td>
<td>[36]</td>
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<td>Havana, Cuba</td>
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<td>23/160 TB specimens isolated over a one-year period belong to the W-Beijing family.</td>
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<td>Peru</td>
<td>Convenience sample</td>
<td>IS6110 and principal genetic group data support a subgroup of isolates, isolated from Peruvian patients, belonging to the W-Beijing family.</td>
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<td>Tennessee, USA</td>
<td>Nosocomial investigation</td>
<td>Nosocomial transmission of a W-Beijing family strain to a healthcare worker and a patient exposed to active TB.</td>
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<td>New York City, USA</td>
<td>Nosocomial investigation</td>
<td>Transmission in a hospital nursery. The source case is believed to be MDR strain W1, a direct descendant of the index MDR strain W.</td>
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<td>California, Colorado, Texas, USA</td>
<td>Population-based study</td>
<td>57 W-Beijing family strains (labeled as strain 210) isolated in three US states. Intrastate patient links were documented with possible interstate transmission.</td>
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<td>St Petersburg, Russia</td>
<td>Convenience sample</td>
<td>IS6110-based analysis: 15/27 isolates empirically are related to W-Beijing family strains.</td>
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<td>Barcelona, Spain</td>
<td>Routine surveillance</td>
<td>IS6110-based analysis: MDR-TB caused by W-Beijing family strains in three immunocompetent patient immigrants from Peru.</td>
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<td>China</td>
<td>Retrospective study on preserved lung tissue</td>
<td>Analysis of 85 paraffin-embedded lung biopsies dated from 1956–1990. 45/49 samples belong to the W-Beijing family.</td>
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<tr>
<td>New Jersey, USA</td>
<td>Population-based study</td>
<td>43 closely related W-Beijing family clones were found prevalent in one county. Patients shared demographic profiles, however have no known patient links, suggesting both historic and recent transmission.</td>
<td>[15]</td>
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<td>Malaysia</td>
<td>Convenience sample</td>
<td>IS6110-based analysis: W-Beijing family strains represent 10–19% of all TB isolates analyzed.</td>
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<td>Cape Town, South Africa</td>
<td>Outbreak investigation</td>
<td>Community outbreak of MDR TB identified 17/21 isolates having identical IS6110 pattern resembling strain W from New York City. None of the patients were HIV-seropositive or institutionalized.</td>
<td>[20]</td>
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<tr>
<td>Western Siberia, Russia</td>
<td>Cross-sectional (operational study)</td>
<td>IS6110-based analysis: pattern identical in another Russian study [42] and to the PHRI TB Center samples (D in Fig. I).</td>
<td>[41]</td>
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<td>USA</td>
<td>Surveillance study</td>
<td>Surveillence identified strain W in nine states and Puerto Rico.</td>
<td>[24]</td>
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<td>Guadeloupe</td>
<td>Population-based study</td>
<td>W-Beijing family strains were identified among 95 TB samples analyzed based on spoligotyping.</td>
<td>[61]</td>
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<td>Texas, USA</td>
<td>Population-based study</td>
<td>326 from a total of 1283 isolates were found to belong to the W-Beijing family.</td>
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<td>Vietnam</td>
<td>Cross-sectional/population-based study</td>
<td>IS6110-based analysis, spoligotyping: W-Beijing family strains were identified in 301 (54%) of the 563 patients. Cases were associated with younger age, STR, and INH and BCG vaccination.</td>
<td>[35]</td>
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<td>Buenaventura, Colombia</td>
<td>Retrospective study</td>
<td>11/111 isolates identified strains related to strain W.</td>
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<td>Convenience sample</td>
<td>IS6110-based analysis, spoligotyping: 6/62 TB patients showed similarity with W-Beijing family strains.</td>
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<td>Thailand</td>
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<td>New York City, USA</td>
<td>Convenience sample</td>
<td>IS6110-based analysis, spoligotyping, additional molecular typing: 26/13 000 isolates grouped into W14 cluster. All 26 were STR. Demographic homogeneity of the patients demonstrated, with no known epidemiological links.</td>
<td>[46]</td>
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<tr>
<td>Jakarta, Indonesia</td>
<td>Prospective study</td>
<td>IS6110-based analysis, spoligotyping: 31 (34%) of the 92 patients demonstrated W-Beijing family strains. No relation was found between genotype and BCG vaccination status.</td>
<td>[39]</td>
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*Abbreviations: BCG, Mycobacterium bovis Bacille–Calmette–Guérin; INH, isoniazid resistant; MDR, multidrug resistant; PHRI, Public Health Research Institute; spoligotyping, spacer oligonucleotide typing; STR, streptomycin resistant; TB, tuberculosis.*
epidemiological data surrounding the clonal expansion and apparent success of the M. tuberculosis isolates that are collectively referred to in this review as the W-Beijing family strains.

**Epidemiology of the W-Beijing family strains**

Members of the W-Beijing family have been responsible for considerable morbidity and mortality worldwide [24–26]. Their epidemiological settings are diverse in that they have been reported to cause outbreaks in institutional and nosocomial environments and have also been implicated in ongoing community transmission, contributing to their endemic nature. Both pan-susceptible and resistant members have been successful in disease transmission. Although strain W was characterized in New York City (NYC) [27], a similar group of predominant isolates was identified in the Far East [28] and named accordingly as the Beijing isolates.

Current molecular data, as we will discuss, indicate that isolates typed to either the W or the Beijing strains are descendants of a common ancestral strain and form a large branch in the M. tuberculosis phylogenetic lineage [5]. The genotyping data also defined the chromosomal markers common to the W and Beijing strains and those markers that distinguish the various branches within the W-Beijing family that have evolved in different geographical regions. Here, we profile the genetic markers that define members of the W-Beijing family and highlight several studies that have documented the spread of selected branches within this phylogenetic lineage.

**Nosocomial outbreak involving a multidrug resistant strain, strain W**

In NYC, during the 43 months from January 1990 to August 1993, a highly multidrug resistant (MDR) strain that was invariably untreatable with streptomycin, isoniazid, rifampin, ethambutol and, in most instances, kanamycin, spread rapidly in an HIV-streptomycin, isoniazid, rifampin, ethambutol and, in strain that was invariably untreatable with August 1993, a highly multidrug resistant (MDR) strain was acquired repeatedly; this resistance developed before its spread in prisons and hospitals. It is noteworthy that fluoroquinolone resistance was acquired repeatedly; this resistance developed independently after the original NYC nosocomial outbreak and a total of five different mutations in gyrA have been identified [33].

A decade since the initial outbreak, a total of 11 descendants of strain W have been identified that have subtle differences in IS6110 fingerprint patterns and that reflect the microevolution of this clone over time (panel E in Fig. I shows six representative patterns). In each case, these MDR strains have the complete complement of genetic markers that define the strain W outbreak as we have described.

**Strain W and the W-Beijing family strains**

The molecular markers used to type strain W can also be used to group a large collection of related M. tuberculosis strains that have spread successfully throughout East Asia and the United States. Collectively, these isolates have distinct molecular features, which, in combination, differentiate them from all other M. tuberculosis samples analyzed to date. Although these isolates have a large array of IS6110 patterns with a high copy number (15–26), they are genetically related to each other on the basis of several independent genetic markers: they each belong to principal genetic group 1 [1], they have an IS6110 insertion in the origin of replication (A1 insertion) [5] and they have the same spoligotype pattern (S00034) [15].
All W-Beijing family isolates have a single IS6110 insertion in the NTR region; this genotype also distinguishes these strains from the multidrug resistant NYC strain W and its descendants, which have two copies of IS6110 in this region (Box 1). The Public Health Research Institute (PHRI) TB Center database (>14 000 M. tuberculosis isolates) contains >2000 patient isolates represented by at least 450 different yet similar IS6110 DNA fingerprint profiles that have been typed to the W-Beijing family. Currently, all members of the W-Beijing family can be segregated from all other clinical isolates on the basis of the genetic markers we have described here. Although other M. tuberculosis strains have been grouped to a ‘strain family’, none has been analyzed to the extent of the W-Beijing family or has been so successful in causing extensive outbreaks.

The strain families that have been cited in the literature, such as the Haarlem family strains [7] and the common laboratory strain H37 and its derivatives [34], have been initially catalogued on the basis of their similar IS6110 DNA fingerprint patterns. In these examples, the Haarlem family and H37 are broadly distinguished from the W-Beijing family in being members of principal genetic groups 2 and 3, respectively, and having different secondary-typing patterns.

Like the W-Beijing family, the Haarlem family strains appear to be widespread and have been isolated from patients in Europe, Asia and the Americas, and both spoligotyping and VNTR analysis have provided secondary-typing data to support their genetic relatedness. However, unlike the W-Beijing family strains, which have been further subtyped to groups, no unique chromosomal markers have yet been defined to further distinguish the Haarlem family.

Geographical distribution of the W-Beijing family strains
The common use of IS6110 genotyping and secondary-typing methods, especially spoligotyping, has provided researchers with the basic tools to differentiate the W-Beijing family strains from all other M. tuberculosis complex strains. Consistent with the first reports that coined the name the Beijing family and that suggested these strains were common in Mongolia and China, the ever-growing reports from across Asia have confirmed and extended this hypothesis. Although many of these studies take a ‘snapshot’ of the strain population in a given geographical region, as shown in Table 1, the prevalence of the W-Beijing family is remarkably high in Vietnam, Hong Kong, Indonesia, Korea, Thailand and Taiwan [28,35–39]. Recent genetic data from isolates from throughout the former Soviet Union also showed the widespread prevalence of the W-Beijing family strains [40,41].

Among a convenience sampling of 2100 M. tuberculosis isolates from regions across the Russian Federation, we identified the W-Beijing family strains in 45% of patients. The most prevalent strain, W148, has a distinct 17-band IS6110 pattern (panel D1, Fig. I), which has been identified throughout the former Soviet Union. In a TB prison in Western Siberia, between 1998 and 2000, 190 prisoners were identified with multidrug resistant W148 isolates, and drug-resistant genotypes indicated this strain spread as a primary resistant clone [42]. As in the NYC outbreak in the early 1990s, the spread of W148 in the Siberian prison was partly owing to the dismantling of public health infrastructure, an ineffective system for testing drug susceptibility and treating highly resistant cases of TB [43]. The recent PHRI TB Center findings that MDR W148 strains have been isolated in NYC from former Soviet Union immigrants raises concerns about their global spread (B.N. Krieswirth et al., unpublished).

The distribution of the W-Beijing family strains in distinct geographical regions and their ability to predominate and spread in large clonal clusters suggests that members of this phylogenetic lineage are better adapted to infect and cause disease in humans. The prevalence of the W-Beijing family strains in Europe, South Africa, and South and North America is probably the result of the large amount of human migration in the 20th century and the reactivation of TB over time. As described below, the clumping and spread of the W-Beijing family strains common in the Asian continent has now been observed among US-born patients in different regions of the United States. These studies further the hypothesis that the W-Beijing family strains have a genetic advantage to cause disease in the human population.

Spread of the W-Beijing family strains in the United States
The low incidence of TB in the United States, juxtaposed with high immigration rates from high-incidence countries, provides a unique situation to study the transmission dynamics of the W-Beijing family strains. As an example, we evaluated all culture-positive TB cases (76% capture) in the state of New Jersey between January 1996 and September 1998 and, using the criteria established in Box 1, we identified 68 patient isolates out of 1207, or 6%, that met the profile of a member of the W-Beijing family over a 45-month period [15]. The strains were further divided into two groups (A and B) of 43 and 25, based on subtle differences in IS6110 patterns, and distinct PGRS and VNTR patterns. Although all isolates could be shown to be descendants of a common ancestral strain, isolates from group B were found to be distantly related to one another (22 different IS6110 patterns from 25 patients) as well as to members of group A. By contrast, group A strains (termed W4 – panel A, Fig. I) were very closely related (seven patterns from 43 cases) and hence belong to a distinct branch of the evolutionary tree of the W-Beijing family. Patients in group A were pan-susceptible, primarily US-born, non-Hispanic blacks and clustered within one county in New Jersey. By contrast, most patients infected with group B strains were non-US-born (76% from East Asian countries), and scattered throughout
In addition, group A patients tended to be younger with risk factors for TB such as HIV infection, whereas group B patients were older with no major risk factors. Therefore, group A strains are believed to be part of an ongoing outbreak that has successfully contributed to the endemic rate in these New Jersey communities, whereas group B are most likely cases of reactive TB that have been imported from Asia.

A study carried out in the western United States by Yang and colleagues [44] identified a prevalent strain designated 210 (panel G, Fig. 1). This pan-susceptible strain was recovered from 57 patients out of a total of 1324 isolates in a population-based survey and from three geographically separate regions. The 210 IS6110 banding pattern resembled that of the W-Beijing family strains. Spoligotyping of this clone revealed the signature S00034 pattern. Further analysis confirmed the presence of the A1 IS6110 insertion in the dnaA-dnaN locus and single insertion in NTF [5,45]. The 57 strains were retrieved from California and Texas where the majority of cases were identified (two cases were from Colorado). Epidemiological data demonstrated widespread intrastate transmission of TB among high-risk groups of predominantly US-born population. Although no patient links could be established between states, the molecular data suggest that interstate transmission occurred but historically, with secondary local dissemination. In an earlier study by Barnes et al. [22], the largest cluster identified in central Los Angeles - 43 of 96 cases - genotyped as strain 210. The 43 cases in this cluster suggest extensive transmission, some of which has been documented within mainly US-born patients in three homeless shelters.

A recent study demonstrates yet another example of dissemination of a W-Beijing family strain (W14) in a US-born population [46]. A convenience sample of 44% of all cases reported in NYC between 1992 and 1999 identified a cluster of 26 isolates belonging to a distinct group, comprised of three variants, of the W-Beijing family strains (panel B, Fig. 1). Besides having the global molecular markers inherent in all W-Beijing family strains (Box 1), the W14 duster bore subtle but distinctive molecular properties in the spoligopattern and VNTR profiles. In addition, all strains belonging to the W14 group have a mutation in codon 43 of the rpsL gene conferring high-level streptomycin resistance. In this cluster, 20/26 (77%) of the isolates were resistant only to streptomycin (mono-streptomycin). Acquisition of secondary drug resistance in progenies of the predominant mono-streptomycin-resistant W14 cluster was determined by drug susceptibility testing and confirmed by DNA sequence analysis of target genes known to be associated with resistance to anti-tubercular antibiotics [31]. Molecular data in the W14 study suggests that streptomycin resistance was acquired before its dissemination. Although no patient links were identified, the demographics were very similar in that they were all US-born and had risk factors for TB. As it was a predominantly young, HIV-seropositive population with no demonstrable patient-to-patient links, this suggests both recent and historical transmission.

The spread of the W-Beijing family strains in East Asia

The Beijing type strains were initially described by van Soolingen and co-workers, who analyzed 69 M. tuberculosis isolates from TB cases in Beijing, China and showed that 86% of these isolates had similar IS6110 patterns (15–20 insertions) and identical spoligotype [28]. Subsequent genotyping analysis showed that these pan-susceptible isolates (panel C, Fig. 1) had the A1 IS6110 insertion in the dnaA-dnaN locus and a single IS6110 copy in the NTF region. The predominance of the Beijing strain type in this small sampling collection indicated possible endemic distribution of these strains in Eastern Asia. This notion has been further supported by several subsequent studies that illustrate the variable frequency of the Beijing type (86% in China; 34% in Indonesia; 25% in Malaysia; 50% in Mongolia; 43% in South Korea; 44% in Thailand; and 53% in Vietnam [28,35,39,47,48]). It is important to note that these data are based on a few representative investigations, which often involve convenience sampling, and are not systematic population-based studies (Table 1). Nonetheless, these investigations are representative of the molecular epidemiological studies undertaken in the Far East and clearly indicate that the W-Beijing family strains are widespread in Asia, leading investigators to hypothesize on possible mechanisms that could account for this success. For example, in Vietnam this group of isolates was associated with active transmission in a primarily Mycobacterium bovis Bacille Calmette-Guérin (BCG)-immunized young population, whereas in Indonesia they were correlated with increased risk of febrile response [35,39].

The success of the W-Beijing family strains

The factors that contribute to the success of the W-Beijing family strains have yet to be unraveled. The success could stem from increased transmissibility, stability and/or altered gene expression of as-yet-identified virulence factors. At least one in vivo study has shown that a W-Beijing family member (strain 210) was able to multiply more rapidly in macrophages when compared with strain CDC 1551 and another clinical isolate [49].

There are several hypotheses to explain the large expansion of the W-Beijing family strains throughout the Asian continent. One hypothesis is that these strains spread as a result of their resistance to the BCG vaccine [35]. However, the notion that the vaccine provided selective pressure that could account for the success of the W-Beijing family strains is inconsistent with their ability to cause outbreaks and clustering in non-vaccinated US-born individuals in various regions of the United States. It should also be noted that the remarkable IS6110 genetic diversity
Questions for future research

- Are there genetic correlates that give rise to certain phenotypic properties to explain the global prevalence of the W-Beijing family strains?
- Will the recent development of gene-chip and proteomic technologies help identify the genetic factors associated with the success of the W-Beijing family strains?
- How do these phenotypic properties facilitate the dissemination of these strains; are they more infectious, more stable or more virulent?
- Are there unique host-bacteria interactions that elicit immune responses specific to this strain family?
- Could we identify ancestral and/or more distant members of the W-Beijing family, and from this could we unravel the phylogenetic structure of this lineage?

Acknowledgements

We thank B. Salim, W. Eisner and A. Ravikovitch for their help in editing and manuscript preparation.

References


and in the Russian prisons [41,42]. However, it should also be noted that many of the outbreak clones, such as strain W4 and 210, and the strains endemic to China and Mongolia, are pan-susceptible.

To date, there are no specific reports that indicate the W-Beijing family strains are hypermutable or that they have unique efflux mechanisms that account for a selective advantage against anti-tubercular therapy. In fact, drug resistance among W-Beijing family strains maps to the same genetic targets as in other resistant M. tuberculosis strains, and comparative sequence analysis that included several W-Beijing family strains showed no genetic variation among 50 different structural genes [1,55]. It is therefore likely that the simple explanation surrounding the observed association of drug resistance among the W-Beijing family strains is the consequence of their prevalence in any given population and that resistance, per se, does not provide the genetic advantage.

Conclusions

The advent of molecular genotyping has clearly shown that members of the W-Beijing family can rapidly establish a niche and expand in the community. In this regard, these strains present a potential public health threat and measures to identify and monitor these strains are therefore essential. The characteristics listed in Box 1 provide a guide to distinguishing the W-Beijing family strains from the rest of the species and to identify the strain W outbreak clone.

Our understanding of the genetic differences present in the W-Beijing family strains could be furthered once the sequencing of strain 210 is completed. The partial genome is available through the TIGR database (http://www.tigr.org). Currently, the mechanisms underlying the success of the spread of the W-Beijing family strains in the human population are not well understood; however, recent molecular epidemiological findings provide a sound basis on which to include these strains in future studies of pathogenicity and virulence factors.
Infect. Dis. 180, 1245–1251
37 Das, S., et al. (1993) Application of DNA fingerprinting with IS696 to sequential mycobacterial isolates obtained from pulmonary tuberculosis patients in Hong Kong before, during and after short-course chemotherapy. Tuberc N. Dis. 74, 47–51