Molecular epidemiology of *Mycobacterium tuberculosis* in East Lancashire 2001–2009

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ABSTRACT

Background East Lancashire has had high rates of tuberculosis for 40 years. The ethnically diverse population is predominantly of South Asian and white origin. Drug resistance data from 1960 to 1999 indirectly suggest that no significant inter-ethnic transmission has occurred. This study used mycobacterial interspersed repetitive unit variable number tandem repeat (MIRU-VNTR) fingerprinting to assess clustering within and between ethnic groups.

Methods All isolates of *Mycobacterium tuberculosis* from January 2001 to July 2009 from East Lancashire postcode areas were MIRU-VNTR fingerprinted. Clusters of strains with indistinguishable profiles were also assessed epidemiologically, and their MIRU-VNTR profiles compared with the UK *M tuberculosis* Strain Typing Database.

Results 332 strains were typed (63 white patients, and 269 non-white patients). 198 MIRU-VNTR profiles were identified, with 144 profiles occurring only once. The typing clustered 187 strains into 53 clusters indistinguishable at all 12 loci and these were further characterised using the exact tandem repeat loci A, B, and C. The 15 loci clustered 32/63 (50.8%) of white and 110/269 (40.9%) of non-white cases and all but nine clusters were of the same ethnicity. The nine inter-racial clusters were further assessed from an epidemiological and clinical perspective and fingerprinting using nine additional loci. Isolates within two of the clusters were further discriminated using the additional nine loci. However, the additional loci did not further discriminate the isolates in the other seven inter-racial clusters.

Conclusions MIRU-VNTR fingerprinting indicates that although there is evidence of a high rate of transmission within the South Asian sub-population, the data suggest that there is little inter-ethnic transmission.

Key messages

What is the key question?

- Is there evidence of significant tuberculosis transmission between the main ethnic groups in East Lancashire?

What is the bottom line?

- There is little evidence of inter-racial transmission, but over 50% of white cases are recently acquired as are a minimum of 19% of South Asian cases.

Why read on?

- The data demonstrate the usefulness of mycobacterial interspersed repetitive unit variable number tandem repeat (MIRU-VNTR) fingerprinting in helping with local epidemiology and potential sites of transmission.

INTRODUCTION

Blackburn was in the top 10 tuberculosis (TB) incidence local government areas of England and Wales in 1978–9,[1] and remained in the top 20 incidence areas through to 1998.[2 3] The Pendle area of East Lancashire was also consistently in the top 20 incidence areas over this same time period.[1–3] In 2006–8 the incidence of TB in Blackburn averaged 37/100 000 per annum and that for East Lancashire, including Pendle, 16/100 000 per annum.[4] Detailed epidemiological data on TB drug resistance have been reported for the Blackburn, Hyndburn, and Ribble Valley parts of East Lancashire for a 40 year timescale. Sequential surveys of drug resistance in both the white and South Asian ethnic groups for 1960–85,[5] 1986–90,[6] and 1991–2000[7] showed rapidly reducing rates of initial drug resistance in the white population from 1960 to 1975 with very low rates since then. However, a consistently high rate (7–10%) of initial isoniazid resistance occurred in the South Asian ethnic population throughout the period 1960–2000 inclusive.[5–7] This has provided strong indirect evidence of the lack of transmission of TB between the South Asian and white ethnic groups in this area. The development of molecular typing methods for strains of *Mycobacterium tuberculosis* facilitates fingerprinting of TB isolates to provide more direct, as opposed to indirect, evidence for transmission of TB between and within different ethnic groups.

The sequencing of the entire genome of a number of bacterial pathogens has revealed the presence of variable number tandem repeats (VNTRs) in bacterial genomes which appear analogous to human micro-satellites. The variability in repeat number of VNTR loci can be exploited as a method of fingerprinting these pathogens. The first method described for the VNTR typing of *M tuberculosis* targeted five exact tandem repeat loci (ETR) A, B, C, D, and E.[8] This PCR-based method, while easily standardised between laboratories to facilitate data comparison, did however lack discriminatory power. An additional 10 VNTR loci specific to mycobacteria termed mycobacterial interspersed repetitive units (MIRUs) are targeted in the VNTR typing method known as MIRU-VNTR typing.[9] Twelve VNTR loci are targeted in the MIRU-VNTR fingerprinting method including ETR D and E from the original Frothingham and Meeker-O'Connell

scheme.[8] Isolates are fingerprinted based on the number of repeats at the 12 MIRU-VNTR loci located throughout the genome. An evaluation of the 12 MIRU loci and three ETR loci has previously demonstrated that they provide a similar level of discrimination as IS-6110 typing.[10] An optimised set of 24 MIRU-VNTR loci has recently been defined for the typing of *M tuberculosis*, which provides the highest level of discrimination between stains.[11]

METHODS

All isolates of *M tuberculosis* from January 2001 to July 2009 inclusive from East Lancashire (Burnley, Pendle, Rossendale (BPR), and Blackburn, Hyndburn and Ribble Valley (BHRV) districts) were sent to the HPA Regional Centre for Mycobacteriology at Newcastle for identification and drug susceptibility testing. Isolates were grown in Mycobacterial Growth Indicator tubes (Becton Dickinson, UK). DNA was extracted from a 250 µl aliquot of the culture using a QiaAmp DNA Blood Mini Kit (Qiagen Ltd, Crawley, West Sussex, UK) according to the manufacturer's protocol and the DNA was used as a template in the MIRU PCR reactions. After amplification, each PCR product was analysed on a WAVE denaturing high-performance liquid chromatography (DHPLC) system with the fragment size being calculated from the chromatogram, and the number of tandem repeats at each locus was determined as previously described.[12] All of the 332 strains were characterised using the 12 MIRU-VNTR loci previously described.[9] Strains which clustered into groups with indistinguishable profiles were further characterised using the ETR loci A, B and C. Strains which clustered into inter-racial groups that were indistinguishable at all 15 loci were further characterised using the nine additional MIRU-VNTR loci used for enhanced discrimination.[11] Clusters of strains with indistinguishable profiles were also assessed epidemiologically by the clinicians and TB nurses, and had their MIRU-VNTR profiles compared with those in the UK *M tuberculosis* Strain Typing Database containing MIRU-VNTR profiles of over 25 000 isolates.[13]

RESULTS

A total of 332 strains isolated between January 2001 and July 2009 were tested, with 63 obtained from white ethnic patients, and 269 from non-white patients. The majority of non-white patients were of South Asian ethnic origin (n=262) the other seven being black African (n=2), Chinese ethnic origin (n=2), Indonesian (n=1), Afghan (n=1) and Phillipino (n=1). MIRU-VNTR fingerprinting using 12 loci differentiated the 332 strains into 198 distinct MIRU-VNTR profiles, with 144 profiles occurring only once in the data set. The 12 loci typing clustered 187 isolates into 53 clusters containing between two and 25 isolates which were indistinguishable from each other at all 12 MIRU-VNTR loci. The majority of the strains in these 53 clusters (182 of 187 strains) were further investigated by characterising the ETR A, B, and C loci if sufficient DNA extract was available. MIRU-VNTR fingerprinting with the 15 loci identified 42 groups of strains containing between two and 13 isolates which were indistinguishable from each other at all 15 MIRU-VNTR loci (table 1). Five clusters identified using 12 loci typing each containing two isolates could not be confirmed using the ETR loci because no DNA extract was left for analysis for one of the two strains in each cluster. These clusters (4, 5, 16, 29, 34, 43) are included in table 1 because they were indistinguishable at 12 MIRU-VNTR loci. MIRU-VNTR analysis with 15 loci clustered 32/63 (50.8%) of white isolates and 110/269 (40.9%) of non-white cases, with 142/332 (42.8%) being clustered overall. Thirty-nine of the 48 clusters presented in table 1 were made up of strains from patients who were of the same ethnicity. Clusters of strains with indistinguishable profiles had their MIRU-VNTR profiles compared with those in the UK *M tuberculosis* Strain Typing Database to ascertain the frequency of these profiles in the UK (table 1). Results of typing the strains in the nine inter-racial clusters using the additional nine MIRU-VNTR loci are presented in table 2. Only 27 of the 30 strains could be tested because there was insufficient DNA available for three of the strains. The additional nine loci provided further discrimination of strains in clusters 9 and 17, indicating that the cases were not linked. However, fingerprinting with the additional nine loci identified that the strains in the other seven inter-racial clusters remained indistinguishable within each cluster. The nine possible inter-racial clusters were further assessed from an epidemiological and clinical perspective (table 2). Further epidemiological investigation of cluster 15 showed likely transmission from a South Asian college student to his flat mate and later to a white student with whom he had limited contact at college. Further epidemiological investigation of the other eight clusters showed no known epidemiological contact between white and South Asian cases.

DISCUSSION

This study was initiated in 2006, and then expanded with 2009 data, to measure the extent of potential clustering in our population, which continues to have high rates of TB, largely in our main ethnic minority group, those of South Asian descent.[14] Drug resistance data reported for part of our population from 1960 to 2000[5–7] has shown widely divergent recent isoniazid resistance rates for the white (0.5%<) and South Asian (7–10%) isolates, suggesting little inter-racial transmission. In this study the isolates from our white ethnic group showed 51% potential clustering. A substantial proportion of this is supported by local epidemiology and contact data, which confirms most of the clustered cases link with either certain public houses (clusters 7–8, 10–11: 17 individuals), with a cohort of drug and/or alcohol users (cluster 2: eight individuals), or with ongoing clinical cases from 2001 to 2009. Two other individuals in cluster 9 and one individual in cluster 15 were also linked by epidemiology, making 28/63 (44%) isolates definitely clustered, the other seven individuals in inter-racial clusters being less certainly linked.

The potential clustering rate was 41% for those of South Asian ethnicity. However when the MIRU-VNTR profiles of those strains which were clustered were compared with profiles in the UK Strain Typing Database, many of the profiles were shown to be common in the UK, for example clusters 2, 9, 15, 17, 25, 31, 33 and 38, with over 100 isolates previously identified nationally to have these profiles, and clusters 4 and 23, with over 300 isolates previously identified. Some of these apparently clustered cases may therefore be no more than the expression of a common profile in the population, and do not imply recent local transmission. Local recent transmission however is confirmed by epidemiological links in some South Asian clusters (18 and 28: four individuals), and in others by their MIRU-VNTR profile. A considerable number of small local clusters (14, 19, 37, 41–42, 44–46, 48: 24 individuals) have unique profiles which have not been previously recognised in the UK Strain Typing Database, which is highly suggestive of recent local transmission. There are also a number of other clusters (3, 12–13, 24, 29–30, 32, 39, 43 and 47: 26 individuals) with MIRU-VNTR profiles which have occurred in fewer than 10

Table 1 MIRU-VNTR profiles of clusters identified by MIRU-VNTR fingerprinting with 15 loci and their prevalence in the UK *Mycobacterium tuberculosis* Strain Typing Database (STD)

Cluster	MIRU-VNTR profile	ETR			Number of isolates	Comments	Prevalence in STD
		A	B	C			
1*	222325153323	4	1	4	2		Unique profile not otherwise in STD
2*	223125153322	3	2	4	9		118 matching isolates
3	223315153324	3	2	4	2	Both South Asian	6 matching isolates
4	223325153324	5	2	4	2	Both South Asian	312 matching isolates (12 loci)
5	223425173533	NA	2	4	2	Both South Asian	24 matching isolates (12 loci)
6	224125163324	3	2	3	2	Both South Asian	45 matching isolates
7	224325143323	2	2	3	7	All white, linked to a pub	1 matching isolate
8	224325143325	4	2	3	3	All white, linked to a pub	11 matching isolates
9*	224325153323	3	2	4	5		161 matching isolates
10	224325163325	3	2	3	3	All white, linked to a pub	2 matching isolates
11	224325163325	4	2	3	4	All white, linked to a pub	Unique profile not in STD
12	224326163326	2	2	4	2	Both South Asian	1 matching isolate
13	224425173323	4	2	2	3	All South Asian	9 matching isolates
14	224425173533	5	2	2	5		Unique profile not otherwise in STD
15*	225125113322	3	2	4	2		174 matching isolates
16*	225225173533	3	2	2	2		12 matching isolates (12 loci)
17*	225313153323	3	2	3	2		151 matching isolates
18	225325133323	4	2	2	2	South Asian family, linked	38 matching isolates
19	225421163533	5	2	2	2	Both South Asian	Unique profile not otherwise in STD
20	225425143533	4	2	2	2	Both South Asian	26 matching isolates
21	225425173531	4	2	2	4	All South Asian	24 matching isolates
22	225425173533	3	2	2	3	All South Asian	19 matching isolates
23	225425173533	4	2	2	13	All South Asian	426 matching isolates
24	225425173533	5	2	2	5	All South Asian	1 matching isolate
25*	225425173533	Null	2	2	2		†103 matching isolates (14 loci)
26	225425183533	4	2	2	2	Both South Asian	41 matching isolates
27	226225173533	4	2	2	2	Both South Asian	3 matching isolates
28	226425152523	5	2	2	2	South Asian, family linked	Unique profile not otherwise in STD
29	226425163523	4	2	2	2	Both South Asian	3 matching isolates
30	226425173332	3	2	2	2	Both South Asian	1 matching isolate
31	226425173423	4	2	2	3	All South Asian	186 matching isolates
32	226425173423	5	2	2	3	All South Asian	3 matching isolates
33	226425173423	4	2	2	2	Both South Asian	186 matching isolates
34	226425173424	4	2	2	2	Both South Asian	32 matching isolates
35	226425173531	4	2	2	2	Both South Asian	26 matching isolates
36	226425173532	4	2	2	2	Both South Asian	38 matching isolates
37	226425173532	5	2	2	2	Both South Asian	Unique profile not otherwise in STD
38	226425173533	4	2	2	5	All South Asian	183 matching isolates
39	226425173533	5	2	2	5	All South Asian	1 matching isolate
40*	226425183531	4	2	2	2		7 matching isolates
41	227425173522	4	2	2	2	Both South Asian	Unique profile not otherwise in STD
42	227425173532	4	2	2	5	All South Asian	Unique profile not otherwise in STD
43	244326221533	10	4	4	2	Both South Asian	2 matching isolates
44	244327223426	6	1	4	2	Both South Asian	Unique profile not otherwise in STD
45	254326223513	7	NA	2	2	Both South Asian	Unique profile not otherwise in STD
46	254326223633	6	1	4	2	Both South Asian	Unique profile not otherwise in STD
47*	274326223633	6	1	4	2		2 matching isolates
48	274328223534	7	1	4	2	Both South Asian	Unique profile not otherwise in STD

*Interracial clusters.
†Cluster 25 profile. 103 isolates in STD with the ETR A locus as a 'null' negative allele result. Appears to be a peculiarity of this strain. Clusters 4, 5, 16, 29, 34, and 43 are included because they were indistinguishable at 12 MIRU-VNTR loci. At the time of analysis (March 2010) there were 24 869 records on the STD, from Newcastle RCM (3981), Birmingham RCM (7341), London MRU (7769), Scottish SRML (1598), Welsh Reference Lab (1526), and the London Study 1995–7 (2654).
ETR, exact tandem repeat; MIRU, mycobacterial interspersed repetitive unit; NA, no amplification; STD, Strain Typing Database; VNTR, variable number tandem repeat.

isolates in the UK Strain Typing Database, which contains nearly 25 000 isolate profiles. Local transmission is therefore likely in these cases too. Those with proven or highly likely local transmission therefore account for at least 50/262 (19.1%) of the South Asian cases. The 'true' clustering rate in the South Asian local population therefore lies somewhere between this 19.1% rate and the 43% overall clustering seen in the complete data.

The nine potential inter-racial clusters were investigated in more detail clinically, epidemiologically and by an additional nine more discriminatory MIRU-VNTR loci. Cluster 15 showed transmission in a college setting, but none of the other eight clusters showed any epidemiological link. Cluster 17 was separated by different drug susceptibility profiles and the isolates also differed at five of the nine additional loci. The additional nine loci further discriminated the five isolates in cluster 9 into

Table 2 Patient characteristics, epidemiological links and results of enhanced mycobacterial interspersed repetitive unit (MIRU) (nine loci) typing for possible inter-racial clusters identified using 15 locus MIRU variable number tandem repeat (VNTR) typing

Cluster number	Year of isolation	Patient characteristics (age)	Site of isolation (smear/culture result)*	Epidemiological links	Enhanced MIRU typing (nine loci)†
1	2003	White female (65)	Peritoneum	No known connection	222422353
	2003	Asian male (51)	Pulmonary (S+)		222422353
2	2002	Asian female (36)	Cervical gland	No known connection	Not tested‡
	2004	White male (42)	Pulmonary (S+)		224423542
	2005	White male (29)	Spinal disease	All linked by residence in hostel/and or a group of alcohol and/or drug users	224423542
	2007	White male (55)	Pulmonary (S+)		224423542
	2007	White female (35)	Pulmonary (S+)		224423542
	2007	White female (24)	Pulmonary (S+)		224423542
	2007	White male (78)	Pulmonary (C+)		224423542
	2009	White male (37)	Pulmonary (S+)		224423542
	2009	White female (43)	Pulmonary (S+)		224423542
9	2005	White male (25)	Pulmonary (S+)	Cases 1, 3, and 4 linked socially	244443441
	2006	Asian male (33)	Pulmonary (C+)		434343312
	2006	White male (38)	Pulmonary (S+)		244413341
	2008	White female (49)	Pulmonary (S+)		244413343
	2008	White male (33)	Pulmonary (S+)		244443441
15	2004	Asian male (30)	Pulmonary (S+)	Both Asian males shared accommodation and went to same college. Case 3 shared some classes	132443383
	2004	Asian male (43)	Pulmonary (S+)		132443383
	2005	White male (18)	Pulmonary (S+)		132443383
16	2001	White male (35)	Pulmonary (S+)	No known connection	Not tested
	2004	Asian female (58)	Cervical gland		44242337A§
17	2004	White male (73)	Pulmonary (S+)	Not connected. Asian case isoniazid mono-resistance, white case fully susceptible.	135243573
	2004	Asian female (36)	Dactylitis		226243172
25	2002	Asian male (33)	Pulmonary (S+)	No known connection	563423384
	2002	White male (49)	Pulmonary (C+)		Not tested
	2004	Asian male (18)	Cervical gland		-4-423384
40	2006	Asian female (19)	Pulmonary (S+)	No known connection	442423384
	2007	White male (74)	Pulmonary (S+)		442423384
47	2004	White male (70)	Cervical gland	No known connection	2-4313461
	2004	Asian male (43)	Ankle		2-4313461

NB. All cases with non-respiratory disease had normal chest x-rays.
*Smear/culture result: S+, sputum microscopy positive; C+, sputum microscopy negative, culture positive.
†Enhanced MIRU typing: MIRU loci 424, 1955, 2163b, 2347, 2401, 3171, 3690, 4052, 4156.
‡Not tested: insufficient DNA extract to perform additional typing; -, no PCR amplification for this locus.
§A=10 repeats.

four different profiles, demonstrating that only two strains were indistinguishable. Of the other six profiles, cluster 47 was all non-pulmonary with no known association. The remaining clusters suggest if there was a possible direction of infection from a combination of clinical type, particularly sputum microscopy positive disease, and timing of isolates, that this was no more common for South Asian to white (clusters 1, 15, 25,40), than white to South Asian (clusters 2, 16).

Our overall rate of potential clustering (42.7%) is higher than that reported in England and Wales, using an earlier technology, restriction-fragment-length-polymorphism analysis, at 22.7% clustering in 1995–7.[15] Using spoligotyping and hemi-nested-inverse PCR this was a little higher at 27% in London in 2002.[16] It is however within the range of clustering shown in cities across Europe, ranging from 30–35% in Brussels[11] and Hamburg[17] to 53–61% in Spain[18] and Lisbon.[19]

This study has confirmed a high local transmission rate, particularly in subgroups of our white population, and shown the importance of public house related transmission[20] in these groups, and also enabling targeted education and surveillance to be performed to try and break the cycle. Additionally, the data suggest that there is little inter-ethnic transmission, particularly from the South Asian population to the white ethnic group. Finally it has helped us recognise outbreaks and make decisions on extended contact tracing. The results of this study are directly relevant to other areas where TB has a high prevalence and an ethnically diverse population.

As this MIRU-VNTR technology is expanded to 24 loci, and becomes more 'real-time', it will be of increasing clinical relevance in managing patients with TB and contact investigations.

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Journal club

Endobronchial valves for advanced emphysema

In this multicentre randomised trial from USA, the safety and efficacy of unilobar endobronchial valve therapy in patients with heterogeneous emphysema was compared with usual care.

In terms of effectiveness, the co-primary outcomes were percentage change in FEV_1 and distance on the 6 min walk test. In terms of safety, the primary outcome was the difference in complication rate, using a composite of six major complications including death, empyema, massive haemoptysis, pneumonia distal to the valves and pneumothorax or air leak of more than 7 days duration.

Patients with endobronchial valves showed modest improvements in FEV_1 and 6 min walk test distance, but at the cost of more pneumonia, including episodes requiring hospitalisation, chronic obstructive pulmonary disease exacerbations and haemoptysis. Follow-up was for 12 months with most complications occurring in the 6 months after valve insertion. There were also modest improvements in secondary end points including quality of life, dyspnoea and supplemental oxygen use.

Of note, there were substantial missing data for the primary efficacy end points, but similar rates were observed in control and intervention groups. There was a higher drop out rate in the control group. It was noted that patients in the high heterogeneity subgroup had greater improvements in FEV_1 and distance on the 6 min walk test. The study was not powered to compare subgroups but this suggests that, similar to lung volume reduction surgery, appropriate patient selection is key to good outcomes.

Therapeutic interventions for advanced emphysema are limited. The role of endobronchial valve therapy remains unclear. There are no direct comparisons with lung volume reduction surgery, but benefits are likely to include lower complication rates, and perhaps mortality. Careful patient selection using expert analysis of high-resolution CT is vital and likely to be an area of future research.

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