

RAPID COMMUNICATION

Mutation Rates at Y Chromosome Specific Microsatellites

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A collaborative work was carried out by the Spanish and Portuguese ISFG Working Group (GEP-ISFG) to estimate Y-STR mutation rates. Seventeen Y chromosome STR loci (DYS19, DYS385, DYS389I and II, DYS390, DYS391, DYS392, DYS393, DYS437, DYS438, DYS439, DYS460, DYS461, DYS635 [GATA C4], GATA H4, and GATA A10) were analyzed in a sample of 3,026 father/son pairs. Among 27,029 allele transfers, 54 mutations were observed, with an overall mutation rate across the 17 loci of 1.998×10^{-3} (95% CI, 1.501×10^{-3} to 2.606×10^{-3}). With just one exception, all of the mutations were single-step, and they were observed only once per gametogenesis. Repeat gains were more frequent than losses, longer alleles were found to be more mutable, and the mutation rate seemed to increase with the father's age. *Hum Mutat* 26(6), 520–528, 2005. © 2005 Wiley-Liss, Inc.

KEY WORDS: mutation rate; Y-chromosome; Y-STR; microsatellite

INTRODUCTION

Microsatellites have been widely used as genetic markers in a variety of studies and applications [e.g. Ohashi and Tokunaga, 2003; Jobling and Tyler-Smith, 2003; Sun et al., 2003], in addition to being the focus of research on their own. Their high degree of polymorphism is due at least in part to the relatively common occurrence of mutations. This particular feature is especially appropriate for microevolutionary studies [e.g., Jorde et al., 1997; Brinkmann et al., 1998a], but is not so welcome in other applications, such as forensics [Kayser and Sajantila, 2001; Jones and Ardren, 2003]. In any case, even if microsatellites ceased to be used as genetic tools, their evolutionary dynamics would be an important research field by itself. In this context it is of particular

importance to improve our knowledge concerning the mechanisms and rates of mutation.

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During the last decade, over 200 Y short tandem repeat (STR) polymorphisms have been described [Kayser et al., 2004]. Y chromosome-specific STR analysis has been extensively applied to human migrations and evolution, as well as to forensics [e.g., Zhivotovsky et al., 2004; Jobling et al., 1997].

Studies on Y-STR mutation rates are scarce and have considered only a restricted number of markers [Heyer et al., 1997; Bianchi et al., 1998; Kayser et al., 2000; Dupuy et al., 2004; Kurihara et al., 2004; Ballard et al., in press; Budowle et al., 2005]. STR mutation rates present both inter- and intralocus variations, depending on the locus structure and allele length [e.g., Brinkmann et al., 1998b; Di Rienzo et al., 1998]. A large amount of data are necessary to reliably estimate allele-specific mutation rates, which is essential for consistent dating of Y-SNP defined lineages (haplogroups) and data interpretation in kinship analysis.

Therefore, in the present work we aimed to increase the amount of data regarding mutations at 16 Y-STR (corresponding to 17 loci, since DYS385 includes two loci) by compiling the results obtained from confirmed father/son pairs, in 17 different laboratories, by members of the Spanish and Portuguese Working Group of the International Society for Forensic Genetics (GEP-ISFG).

MATERIALS AND METHODS

Samples were obtained from 3,026 father/son pairs from paternity cases in 17 different laboratories from Argentina, Brazil,

Colombia, Portugal, Spain, and Venezuela. The biological relationship of all father/son pairs was previously confirmed by using autosomal STRs, with paternity index values above 10,000.

Each laboratory used its own routine methods for DNA extraction, PCR amplification and detection, and sequence analysis. All of the mutations were confirmed by a second typing in a different laboratory from the one in which they were detected by sequence analysis.

The STR alleles of the “minimal haplotype” loci (i.e., DYS19, DYS385, DYS389I and II, DYS390, DYS391, DYS392, and DYS393) were named as in the Y-STR Haplotype Reference Database (YHRD; www.yhrd.org), and alleles in the other loci were named according to Gusmão et al. [2002].

Confidence intervals (CI) for mutation rates were estimated from the binomial standard deviation (SD). Locus- or allele-specific mutation rates were tested for departures from the mean by successively comparing each locus (or allele) against all others pooled through a contingency table chi-square test.

RESULTS

Results were compiled from 17 participating laboratories that typed five to 16 Y-STRs in five to 1,238 meioses (Table 1). In 27,029 allele transfers, 55 mutations were observed: one at DYS438; two at DYS389 I, DYS389 II, DYS393, DYS437, and GATA H4; three at DYS390, DYS392, and DYS635; four at

TABLE 1. Total Number of Allele Transmissions for Each Y-STR and Allele Frequency Distribution in Father Samples Studied by the Participating Laboratories (L1 To L17)*

	L1	L2	L3	L4	L5	L6	L7	L8	L9	L10	L11	L12	L13	L14	L15	L16	L17	Total
DYS19																		
12	–	0	0	0	0	0	1	–	0	0	2	0	0	0	0	0	0	3
13	–	10	14	10	6	22	17	–	11	10	3	14	59	20	4	7	260	467
14	–	74	62	45	48	62	65	–	55	22	16	53	214	123	43	28	580	1490
15	–	29	20	19	16	18	23	–	25	10	14	26	67	42	12	12	295	628
16	–	4	1	4	5	5	11	–	6	3	3	7	24	2	3	2	90	170
17	–	4	2	1	1	5	2	–	4	1	2	0	10	2	1	0	13	48
18	–	0	1	0	0	0	0	–	0	0	0	0	0	0	0	0	0	1
Total	–	121	100	79	76	112	119	–	101	46	40	100	374	189	63	49	1238	2807
DYS389 I																		
9	–	0	0	0	0	0	0	–	0	0	0	0	9	–	0	0	0	9
10	–	0	0	0	0	0	0	–	0	0	0	0	28	–	0	0	0	28
11	–	0	0	0	1	0	1	–	0	0	0	0	10	–	0	0	3	15
12	–	17	19	8	14	12	13	–	17	6	4	25	51	–	14	10	76	286
13	–	71	59	53	46	55	76	–	75	33	26	52	215	–	36	35	231	1063
14	–	33	21	17	14	44	28	–	9	7	9	22	69	–	12	10	91	386
15	–	0	1	1	0	0	1	–	0	0	1	1	0	–	1	0	0	6
Total	–	121	100	79	75	111	119	–	101	46	40	100	382	–	63	55	401	1793
DYS389 II																		
23	–	0	0	0	0	0	0	–	0	0	0	0	1	–	0	0	0	1
24	–	0	0	0	0	0	0	–	0	0	0	0	2	–	0	0	0	2
25	–	0	0	0	0	0	0	–	0	0	0	0	8	–	0	0	0	8
26	–	1	0	0	0	0	2	–	0	0	0	0	11	–	0	0	0	14
27	–	2	2	1	0	2	0	–	1	0	0	3	22	–	0	1	0	34
28	–	15	11	12	9	12	13	–	20	4	3	1	45	–	9	2	49	205
29	–	51	45	31	36	35	42	–	45	21	13	17	128	–	26	31	162	683
30	–	36	33	19	23	50	43	–	28	17	15	40	97	–	18	6	135	560
31	–	13	6	9	7	9	17	–	5	3	7	29	53	–	9	4	40	211
32	–	2	3	3	1	3	2	–	2	1	2	8	12	–	1	1	15	56
33	–	1	0	2	0	0	0	–	0	0	0	3	1	–	0	0	0	7
Total	–	121	100	77	76	111	119	–	101	46	40	101	380	–	63	45	401	1781
DYS389 II-I																		
11	–	0	0	8	0	0	0	–	0	0	0	0	0	–	0	0	0	8
13	–	0	0	36	0	0	1	–	0	0	0	0	1	–	0	0	0	38
14	–	1	1	26	0	1	1	–	0	0	0	1	9	–	0	1	1	42
15	–	10	4	4	2	10	7	–	9	1	1	2	33	–	3	4	34	124
16	–	77	64	1	44	66	62	–	61	28	17	13	167	–	33	28	197	858

TABLE 1. Continued

	L1	L2	L3	L4	L5	L6	L7	L8	L9	L10	L11	L12	L13	L14	L15	L16	L17	Total
17	-	22	24	1	23	28	36	-	24	11	18	46	107	-	21	8	122	491
18	-	9	5	1	4	5	11	-	6	5	4	32	53	-	6	4	39	184
19	-	2	2	0	1	1	1	-	1	1	0	7	10	-	0	0	7	33
20	-	0	0	0	0	0	0	-	0	0	0	0	0	-	0	0	1	1
Total	-	121	100	77	74	111	119	-	101	46	40	101	380	-	63	45	401	1779
DYS390																		
20	-	1	0	0	0	0	0	-	0	0	0	0	0	0	0	0	0	1
21	-	4	1	1	1	2	10	-	1	2	0	5	40	0	0	0	30	97
22	-	10	15	3	10	8	11	-	8	1	7	11	32	21	6	6	119	268
23	-	28	19	17	18	32	25	-	26	8	7	26	79	57	18	15	328	703
24	-	65	53	44	34	56	62	-	60	30	23	49	176	107	32	28	577	1396
25	-	12	10	13	13	12	11	-	3	5	3	9	46	2	6	3	174	322
26	-	1	2	0	0	1	0	-	3	0	0	0	9	2	1	0	10	29
Total	-	121	100	78	76	111	119	-	101	46	40	100	382	189	63	52	1238	2816
DYS391																		
5	-	0	0	0	0	0	0	-	0	0	0	0	1	0	0	0	0	1
6	-	0	0	0	0	0	0	-	0	0	0	0	2	0	0	0	0	2
8	-	0	0	0	0	0	0	-	0	0	0	0	4	0	1	0	0	5
9	-	7	9	3	5	11	8	-	4	5	4	5	10	8	3	1	104	187
10	-	49	54	39	35	56	55	-	50	21	18	56	186	90	30	30	726	1495
11	-	63	36	37	35	44	55	-	47	20	18	37	162	87	27	19	398	1085
12	-	2	1	0	1	0	1	-	0	0	0	2	15	4	2	0	5	33
13	-	0	0	1	0	0	0	-	0	0	0	0	1	0	0	0	5	7
Total	-	121	100	80	76	111	119	-	101	46	40	100	381	189	63	50	1238	2815
DYS392																		
10	-	0	1	2	1	0	1	-	0	0	0	2	2	0	0	0	5	14
11	-	44	44	18	24	52	43	-	36	15	15	37	137	58	25	0	499	1047
12	-	5	4	4	5	4	6	-	9	27	2	7	29	3	2	17	120	244
13	-	65	43	41	42	53	58	-	52	4	23	45	169	115	31	20	454	1215
14	-	7	6	8	2	2	9	-	4	0	0	8	38	10	5	7	150	256
15	-	0	2	0	0	0	2	-	0	0	0	1	3	3	0	2	10	23
16	-	0	0	3	0	0	0	-	0	0	0	0	1	0	0	0	0	4
Total	-	121	100	76	74	111	119	-	101	46	40	100	379	189	63	46	1238	2803
DYS393																		
10	-	0	0	0	0	0	0	-	0	0	0	1	3	0	0	0	-	4
11	-	0	0	0	0	0	1	-	0	0	0	0	2	0	0	0	-	3
12	-	20	19	14	10	15	16	-	14	5	7	16	44	34	16	8	-	238
13	-	90	67	58	53	83	86	-	70	34	25	69	278	139	41	38	-	1131
14	-	8	14	7	12	12	12	-	14	5	6	11	39	13	6	3	-	162
15	-	3	0	0	1	1	4	-	3	2	1	3	7	3	0	2	-	30
16	-	0	0	0	0	0	0	-	0	0	1	0	0	0	0	0	-	1
Total	-	121	100	79	76	111	119	-	101	46	40	100	373	189	63	51	-	1569
DYS385																		
9	-	1	2	0	0	1	0	-	0	0	0	0	4	-	1	0	-	9
10	-	3	2	3	1	1	1	-	3	1	1	2	12	-	2	0	-	32
11	-	74	45	41	40	50	57	-	58	25	20	45	146	-	29	27	-	657
12	-	16	12	10	8	17	15	-	13	4	5	17	35	-	7	3	-	162
13	-	17	25	14	19	29	21	-	20	14	9	22	61	-	14	10	-	275
14	-	64	52	42	46	65	70	-	60	20	27	57	198	-	32	28	-	761
15	-	22	21	19	19	19	30	-	19	8	7	20	109	-	20	4	-	317
16	-	16	19	11	8	17	12	-	13	5	3	14	70	-	9	5	-	202
17	-	11	10	4	3	7	14	-	5	7	5	13	63	-	7	3	-	152
18	-	13	10	7	6	12	11	-	8	5	3	8	31	-	5	6	-	125
19	-	3	2	2	2	3	4	-	0	2	0	2	17	-	0	2	-	39
20	-	2	0	1	0	1	3	-	1	1	0	0	1	-	1	0	-	11
21	-	0	0	0	0	0	0	-	2	0	0	0	5	-	0	0	-	7
28	-	0	0	0	0	0	0	-	0	0	0	0	0	-	0	0	-	0
Total	-	242	200	154	152	222	238	-	202	92	80	200	752	-	127	88	-	2749
DYS437																		
6	0	1	0	0	0	0	0	0	0	0	0	0	0	-	-	0	-	1
13	0	1	0	3	0	0	1	0	0	0	0	0	0	-	-	0	-	5
14	46	43	33	29	25	57	53	32	28	13	10	35	2	-	-	19	-	425
15	49	69	45	42	42	48	57	51	63	29	25	50	3	-	-	19	-	592
16	7	7	21	6	10	6	8	17	10	4	5	13	0	-	-	10	-	124
17	0	0	1	0	0	0	0	0	0	0	0	2	0	-	-	0	-	3
Total	102	121	100	80	77	111	119	100	101	46	40	100	5	-	-	48	-	1150
DYS438																		
7	0	0	0	0	0	1	0	0	0	0	0	1	0	-	0	0	-	2
8	0	0	0	1	1	0	0	1	0	0	0	0	0	-	0	2	-	5
9	7	10	8	5	7	14	6	6	7	3	8	3	0	-	12	6	-	102
10	25	29	39	18	21	38	36	27	34	14	12	35	1	-	14	11	-	354
11	7	13	4	8	4	6	19	9	6	4	0	11	1	-	6	3	-	101

TABLE 1. Continued

	L1	L2	L3	L4	L5	L6	L7	L8	L9	L10	L11	L12	L13	L14	L15	L16	L17	Total
11.2	0	0	0	0	0	1	0	0	0	0	0	0	0	-	0	24	-	25
12	62	66	49	42	40	50	55	55	51	24	20	48	3	-	31	3	-	599
13	1	3	0	6	3	1	3	2	3	1	0	2	0	-	0	0	-	25
Total	102	121	100	80	76	111	119	100	101	46	40	100	5	-	63	49	-	1213
DYS439																		
8	0	0	0	0	0	0	0	0	0	0	0	0	0	-	1	-	-	1
9	1	0	1	0	1	0	0	0	1	1	0	0	0	-	0	-	-	5
10	6	7	8	4	6	16	12	6	4	4	3	7	0	-	3	-	-	86
11	27	38	31	24	28	35	32	42	37	15	9	35	0	-	23	-	-	376
12	58	60	44	35	31	51	59	40	50	21	21	43	4	-	27	-	-	544
13	7	15	14	14	8	8	13	11	8	5	7	13	1	-	9	-	-	133
14	3	1	2	3	2	1	3	1	1	0	0	2	0	-	0	-	-	19
Total	102	121	100	80	76	111	119	100	101	46	40	100	5	-	63	-	-	1164
GATA A10																		
13	4	6	5	-	5	2	5	3	3	-	0	-	0	-	-	-	-	33
14	35	35	29	-	17	39	42	34	39	-	13	-	0	-	-	-	-	283
15	51	63	44	-	40	54	59	53	45	-	21	-	3	-	-	-	-	433
16	12	14	22	-	14	12	11	8	11	-	4	-	2	-	-	-	-	110
17	0	3	0	-	0	3	2	2	3	-	1	-	0	-	-	-	-	14
18	0	0	0	-	0	0	0	0	0	-	1	-	0	-	-	-	-	1
Total	102	121	100	-	76	110	119	100	101	-	40	-	5	-	-	-	-	874
DYS460																		
9	1	7	3	-	3	9	5	5	7	-	0	-	0	-	-	-	-	40
10	33	47	36	-	25	33	46	43	35	-	17	-	2	-	-	-	-	317
11	65	65	58	-	47	61	64	46	55	-	23	-	3	-	-	-	-	487
12	3	2	3	-	1	7	4	5	4	-	0	-	0	-	-	-	-	29
13	0	0	0	-	0	0	0	1	-	-	0	-	0	-	-	-	-	1
Total	102	121	100	-	76	110	119	100	101	-	40	-	5	-	-	-	-	874
DYS461																		
9	0	1	0	-	0	0	0	0	0	-	0	-	0	-	-	-	-	1
10	0	3	3	-	0	1	0	2	1	-	0	-	0	-	-	-	-	10
11	17	18	24	-	18	23	18	19	25	-	9	-	0	-	-	-	-	171
12	71	79	57	-	47	65	74	65	57	-	23	-	3	-	-	-	-	541
13	12	20	16	-	10	20	21	11	18	-	7	-	2	-	-	-	-	137
14	2	0	0	-	1	1	6	2	0	-	0	-	0	-	-	-	-	12
15	0	0	0	-	0	0	0	0	0	-	1	-	0	-	-	-	-	1
Total	102	121	100	-	76	110	119	99	101	-	40	-	5	-	-	-	-	873
DYS635																		
17	0	0	0	-	0	0	1	0	0	-	0	-	0	-	-	-	-	1
19	0	0	0	-	0	0	2	1	1	-	0	-	0	-	-	-	-	4
20	14	5	9	-	3	6	6	6	10	-	1	-	0	-	-	-	-	60
21	11	20	18	-	14	22	27	17	16	-	9	-	2	-	-	-	-	156
22	8	11	17	-	11	13	12	11	13	-	4	-	0	-	-	-	-	100
23	58	70	45	-	38	54	49	55	48	-	21	-	3	-	-	-	-	441
24	11	9	10	-	10	13	19	8	12	-	4	-	0	-	-	-	-	96
25	0	6	1	-	0	2	3	1	0	-	1	-	0	-	-	-	-	14
26	0	0	0	-	0	0	0	0	1	-	0	-	0	-	-	-	-	1
Total	102	121	100	-	76	110	119	99	101	-	40	-	5	-	-	-	-	873
GATA H4																		
25	0	1	1	-	0	0	1	1	0	-	0	-	0	-	-	-	-	4
26	4	2	3	-	1	5	3	3	1	-	1	-	0	-	-	-	-	23
27	33	38	41	-	23	47	39	39	33	-	17	-	1	-	-	-	-	311
28	64	71	49	-	46	52	65	46	59	-	20	-	4	-	-	-	-	476
29	1	9	6	-	5	6	11	11	8	-	2	-	0	-	-	-	-	59
30	1	0	0	-	1	0	0	0	0	-	0	-	0	-	-	-	-	2
Total	103	121	100	-	76	110	119	100	101	-	40	-	5	-	-	-	-	875

*DYS389 II-I corresponds to the number of repeats obtained when DYS389I repeat numbers are subtracted from those at DYS389II.

DYS460 and GATA A10; five at DYS19 and DYS385; eight at DYS439; and nine at DYS391 (Table 2).

All mutations were confirmed by sequence analysis (Table 3) and found to have occurred inside the repetitive sequence structure, except in one case. One of the five DYS19 mutations occurred at the microsatellite flanking region and thus was not considered in STR mutation rate estimations. With the exception of one case, all mutations were single-step. A four-step mutation at DYS438 was observed. Single-locus mutation rates were estimated for the 16 Y-STRs under study (Table 4) as

the frequency of mutations in the total number of allele transfers. In the case of DYS385, where two loci are simultaneously amplified with one pair of primers, the number of allele transfers was calculated as being twice the number of meioses. The overall mutation rate estimated across the 17 loci was 1.998×10^{-3} (95% CI, 1.501×10^{-3} to 2.606×10^{-3}). DYS439 was found to be the marker with the highest frequency of mutations (6.873×10^{-3} , a value that is outside the 95% CI of the one estimated for the overall Y-STR loci mutation rates).

TABLE 2. Mutations Observed at STR Loci With the Respective Father and Son Phenotypes, Paternity Index (L), and Father's Age at the Time When the Son Was Born (Age)

Locus	Father	Son	L	Age	Locus	Father	Son	L	Age	
DYS19	14	15	2×10^8	61	DYS393	13	12	1.3×10^5	^a	
	14	15	2×10^4	28		13	14	8.3×10^8	37	
	14	15	4×10^4	36		DYS437	15	16	3.6×10^4	35
	14	15	7.8×10^7	^a			16	17	1.5×10^5	38
DYS385	14	14.2	1.2×10^6	^a	DYS438	10	6	1.2×10^4	22	
	11–16	11–17	5×10^7	50		DYS439	14	13	6.4×10^6	37
	14	14–15	8.3×10^7	^a	13		12	2×10^{11}	35	
	13–15	14–15	3.8×10^8	40	11		12	1.3×10^5	21	
	13–14	13–15	2.4×10^4	24	11	12	7×10^4	54		
11–14	11–15	3.7×10^6	37	12	13	6.5×10^8	47			
DYS389 I	12	13	1.1×10^8	20	13	14	1.7×10^7	66		
	13	14	1.6×10^5	34	13	14	1.9×10^4	33		
DYS389 II	29(16)	30(17)	1.4×10^7	29	DYS460	12	13	3.6×10^4	31	
	29(16)	30(17)	1×10^6	33		11	10	3.6×10^{10}	45	
DYS390	24	25	1.9×10^4	26	11	10	3.2×10^6	41		
	24	23	7.8×10^7	31	11	10	5.3×10^7	35		
	26	25	1×10^8	30	10	11	3.7×10^8	^a		
DYS391	11	10	2×10^9	66	GATA A10	14	13	1.6×10^5	35	
	11	12	9.0×10^7	24		15	14	3.2×10^5	44	
	12	11	1.2×10^{10}	28		15	14	1.1×10^7	25	
	11	12	1.4×10^8	32		14	15	1.4×10^4	48	
	10	11	4.7×10^4	29	DYS635 (GATA C4)	23	22	2.4×10^9	19	
	10	11	5.5×10^4	26		23	24	2.4×10^9	35	
	11	10	5.5×10^8	26	25	26	5×10^7	37		
	11	12	110^b	^a	GATA H4	28	27	8.1×10^{10}	^a	
11	12	8.2×10^9	19	27		28	3.2×10^4	26		
DYS392	13	14	5.8×10^6	44						
	11	10	1.1×10^4	49						
	14	15	1.2×10^6	22						

^aNo information available.^bUncle/nephew.

Interlocus Mutation Rate Analysis

The mutation rates estimated for the 16 Y-STRs obtained by pooling our results with the previously published Y-STR mutation rates are displayed in Table 4. To date, 64,273 Y-STR allele transfers have been studied, with mutations detected at a frequency of 2.100×10^{-3} (95% CI, $1.761\text{--}2.486 \times 10^{-3}$). The average mutation rate value is similar to the one found in our sample (1.998×10^{-3}) and slightly lower than those found by Dupuy et al. [2004] and Kayser et al. [2000] (2.3×10^{-3} and 2.8×10^{-3} , respectively), although not significantly different.

In our sample, locus-specific mutation rates varied between 0.824×10^{-3} at DYS438 (95% CI, $0.021\text{--}4.585 \times 10^{-3}$) and 6.873×10^{-3} at DYS439 (95% CI, $2.972\text{--}13.497 \times 10^{-3}$). When our results are pooled with published data, a few significant differences between the locus-specific mutation rates emerge (Table 4). When compared by means of chi-square tests, after Bonferroni correction for multiple testing, three loci show significantly divergent rates: DYS392 is less mutable ($P = 0.006$), while DYS391 ($P = 0.009$) and DYS439 ($P = 7 \times 10^{-4}$) tend to mutate faster. Since all of the STRs studied here are repetitions of tetranucleotides, with the exceptions of DYS392 (tri-) and DYS438 (penta-), it is premature to make comparisons between the mutation rates and the repeat motif length.

Intralocus Mutation Rate Analysis

It is worth mentioning that since most of the samples were of Iberian origin, one can expect a high proportion of the chromosomes (>50%) to belong to haplogroup R1b [Jobling and Tyler-Smith, 2003], and different mutation rates can be expected in different haplogroup backgrounds. Nevertheless,

according to Dupuy et al. [2004], differences in haplogroup-specific mutation rates are not significant when the standardized allele length is taken into account. Therefore, allele-specific mutation rate estimates can be reliably used to predict Y-STR mutation rates in different haplogroups.

In most cases, mutations occurred at the most frequent alleles in the fathers' sample (Tables 1 and 2). However, sample sizes per allelic classes at each STR are not sufficient to allow for an accurate estimation of allele-specific mutation rates.

Allele-specific mutation rates were estimated jointly for loci with uninterrupted TAGA repeats by pooling the data available for tetranucleotide repeats, where the observed length variation and mutations are mainly due to different numbers of these repeats (Table 5). At first glance, the allele-specific mutation rates appear to grow linearly with the length of uninterrupted repeats (Spearman's $\rho = 0.886$, $P = 0.019$). However, each estimate has its own statistical uncertainty, and actually only the mutation rate for alleles with 13 repeats is significantly different from that of all other alleles combined ($P = 0.0013$). Pooling alleles into short (<11 homogeneous repeats) and long (≥ 11 repeats) classes, the short class shows a rate that is 3.06 times slower than that of the long class ($P = 0.0032$, Table 5). In summary, a trend for higher mutability is confirmed for longer alleles, although a finer determination of this relationship would require the use of larger samples.

Mutation Directions and Sizes

In accordance with results by Kayser et al. [2000], Dupuy et al. [2004], Kurihara et al. [2004], Ballard et al. [in press], and Budowle et al. [2005], we found a significantly higher number of

TABLE 3. Sequence Information of 55 Mutations Observed in 27029 Y-STR Allele Transmissions*

Locus	Repetitive sequence structure → mutation	Nr.
DYS19	(TAGA) ₃ TAGG (TAGA) _{11→12}	4
DYS19 ^a	(TA) _{6→7} GTGTTT (TAGA) ₃ TAGG (TAGA) ₁₁	1
DYS389 I	(TCTG) ₃ (TCTA) _{9→10}	1
DYS389 I	(TCTG) ₃ (TCTA) _{10→11}	1
DYS389 II	(TCTG) ₅ (TCTA) _{11→12} N ₂₈ (TCTG) ₃ (TCTA) ₁₀	2
DYS390	(TCTG) ₈ (TCTA) _{11→12} (TCTG) ₁ (TCTA) ₄	1
DYS390	(TCTG) ₈ (TCTA) _{11→10} (TCTG) ₁ (TCTA) ₄	1
DYS390	(TCTG) ₈ (TCTA) _{13→12} (TCTG) ₁ (TCTA) ₄	1
DYS391	(TCTA) _{10→11}	2
DYS391	(TCTA) _{11→12}	4
DYS391	(TCTA) _{12→11}	1
DYS391	(TCTA) _{11→10}	2
DYS392	(TAT) _{13→14}	1
DYS392	(TAT) _{11→10}	1
DYS392	(TAT) _{14→15}	1
DYS393	(AGAT) _{13→12}	1
DYS393	(AGAT) _{13→14}	1
DYS385	(AAGG) ₆ (GAAA) _{10→11}	1
DYS385	(AAGG) ₆ (GAAA) _{8→9}	3
DYS385	(AAGG) ₆ (GAAA) _{7→8}	1
DYS437	(TCTA) _{9→10} (TCTG) ₂ (TCTA) ₄	1
DYS437	(TCTA) _{10→11} (TCTG) ₂ (TCTA) ₄	1
DYS438	(TTTTTC) _{10→6}	1
DYS439	(GATA) _{14→13}	1
DYS439	(GATA) _{11→12}	2
DYS439	(GATA) _{12→13}	2
DYS439	(GATA) _{13→14}	2
DYS439	(GATA) _{13→12}	1
DYS460	(ATAG) _{11→10}	3
DYS460	(ATAG) _{10→11}	1
DYS635	(TCTA) ₄ (TGTA) ₂ (TCTA) ₂ (TGTA) ₂ (TCTA) _{13→12}	1
DYS635	(TCTA) ₄ (TGTA) ₂ (TCTA) ₂ (TGTA) ₂ (TCTA) _{13→14}	1
DYS635	(TCTA) ₄ (TGTA) ₂ (TCTA) ₂ (TGTA) ₂ (TCTA) _{15→16}	1
GATA A10	(TCCA) ₂ (TATC) _{12→11}	1
GATA A10	(TCCA) ₂ (TATC) _{12→13}	1
GATA A10	(TCCA) ₂ (TATC) _{13→12}	2
GATA H4	(AGAT) ₄ CTAT(AGAT) ₂ (AGGT) ₃ (AGAT) _{11→10} (ATAG) ₄ (ATAC) ₁ (ATAG) ₂	1
GATA H4	(AGAT) ₄ CTAT(AGAT) ₂ (AGGT) ₃ (AGAT) _{10→11} (ATAG) ₄ (ATAC) ₁ (ATAG) ₂	1

*Segments that are not included in the allele nomenclature are in bold letters.

^aMutation at flanking region.

gains (36) vs. losses (18) of repeats ($P = 0.014$; Table 6A). Only one out of 54 mutations was not single-step. When all of the data available on Y-STRs were combined, 95.6% of the 135 reported mutations were single-step, which in general supports a strict stepwise mutation model. Conversely, the fraction of non-single-step mutations was 4.4% (95% CI, 1.0–7.9%). In the pooled data set, single repeat gains are over twice as frequent as losses, and the difference is highly significant ($\chi^2 = 15.710$, $P = 7.4 \times 10^{-5}$).

To correlate allele length and mutation direction, the frequency of repeat gains vs. losses was counted for different numbers of repeats at the motif where the mutation occurred (Table 6B). Since the number of mutations was low, differences in repeat gains vs. losses were tested by pooling some contiguous alleles into size classes. No clear patterns emerge from this analysis, since gains were significantly more frequent than losses at allele classes 9–10 ($P = 5.3 \times 10^{-4}$), 11 ($P = 0.0038$), and 14–16 ($P = 0.0067$), but not at classes 6–8, 12, or 13. Therefore, the available data do not provide evidence for the hypothesis that an excess of repeat losses at longer alleles would prevent the indefinite expansion of STR allele length [Dupuy et al., 2004].

Father's Age

Table 7 shows the age distribution of the parents involved in the mutation events, as well as the age-group-specific mutation

rates. Considering each mutation event, the average age of the fathers involved was 37.3 years ($SE = 1.82$); likewise, for nonmutated transmissions, the average age was 31.30 years ($SE = 0.08$). This is in contrast with the results obtained by Dupuy et al. [2004], who found no distinction between the ages of fathers with mutations and those of the whole sample. In the present study the difference was significant, by both a t-test ($t = 12.326$, $P = 4.5 \times 10^{-4}$) and Mann-Whitney's U-test ($P = 2.7 \times 10^{-4}$). At first glance, the mutation rate appears to increase with the age group (Spearman's $\rho = 0.657$, $P = 0.156$), although without statistical significance, given that the correlation is based on six points (age groups) only. As for specific age-group rates, the rate for 41–50 years was higher than the average ($P = 0.026$), while the rest were statistically not significantly different from this average.

DISCUSSION

Although according to data on autosomal STRs, the male germ line has a higher frequency of mutation events than the female germ line [Weber and Wong, 1993; Brinkmann et al., 1998a], no significant differences were found between the average Y-STR mutation rates and those found in autosomal STRs [Brinkmann et al., 1998b; Henke and Henke, 1999; Sajantila et al., 1999]. Although the average mutation rate estimated in the present

work, across 17 Y-STR loci (Table 4), was slightly lower, it was not significantly different from those determined by Kayser et al. [2000] and Dupuy et al. [2004] in their analyses of father/son pairs. Pooling our data with those already published on Y-STRs, a significantly lower mutation rate at DYS392 (supporting the findings of Nebel et al. [2001]) and a higher mutation rate at DYS391 and DYS439 were found in comparison with the average value (Table 4). The higher mutation rate found at DYS439 explains why this marker is the one that contributes most to the increase in haplotype diversity of the current STR set [Alves et al., 2003]. For TAGA repeats, a trend for higher mutability was confirmed for longer alleles.

All of the observed mutations in our screening were single-step, except in one case out of 54 (Table 6A). These results are in accordance with the generally accepted mutation model for microsatellites, in which the alleles are known to mutate primarily through the gain and loss of single repeat units [Weber and Wong, 1993; Di Rienzo et al., 1994; Zhivotovsky and Feldman, 1995].

Repeat gains were found to be twice as frequent as losses (Table 6A), in agreement with previous observations [Cooper et al., 1999; Kayser et al., 2000; Dupuy et al., 2004; Kurihara et al., 2004] and as expected for young microsatellites [Xu et al., 2000]. When we compared repeat gains and losses in different allele classes, in contrast to Dupuy et al. [2004], we found no evidence

TABLE 4. Total Number of Mutations and Allele Transmission Per Locus*

Locus	This work				Total ^a			
	No. mutations	Allele trans.	Freq. ($\times 10^{-3}$)	95% CI $\times 10^{-3}$	No. mutations	Allele trans.	Freq. ($\times 10^{-3}$)	95% CI $\times 10^{-3}$
DYS19	4	2807	1.425	0.388–3.645	12	7129	1.683	0.870–2.938
DYS389 I	2	1793	1.115	0.135–4.024	10	5333	1.875	0.975–3.465
DYS389 II	2	1781	1.123	0.136–4.051	12	5320	2.256	1.166–3.937
DYS390	3	2816	1.065	0.220–3.110	15	6611	2.269	1.270–3.740
DYS391	9	2815	3.197	1.463–6.060	23	6559	3.507	2.224–5.257
DYS392	3	2803	1.070	0.221–3.125	4	6525	0.613	0.167–1.569
DYS393	2	1569	1.275	0.154–4.597	4	5313	0.753	0.205–1.927
DYS385	5	2749	1.819	0.591–4.239	22	9837	2.236	1.402–3.384
DYS437	2	1150	1.739	0.211–6.268	5	2252	2.220	0.721–5.174
DYS438	1	1213	0.824	0.021–4.585	1	2291	0.436	0.011–2.473
DYS439	8	1164	6.873	2.972–13.497	12	2266	5.296	2.739–9.232
GATA A10	4	874	4.577	1.248–11.676	4	946	4.228	1.153–10.971
DYS460	4	874	4.577	1.248–11.676	5	1109	4.509	1.465–10.490
DYS461	0	873	–	0.000–4.217	0	873	–	0.000–4.217
DYS635	3	873	3.436	0.709–10.010	3	873	3.436	0.709–10.010
GATA H4	2	875	2.286	0.277–8.232	3	1036	2.896	0.598–8.439
Total	54	27029	1.998	1.501–2.606	135	64273	2.100	1.761–2.486

*Locus specific and overall mutation rate estimates and respective confidence intervals.

^aIncludes data from this work and from Heyer et al. [1997]; Bianchi et al. [1998]; Kayser et al. [2000]; Dupuy et al. [2004]; Kurihara et al. [2004]; Budowle et al. [2005]; Ballard et al. [in press].

TABLE 5. Allele Specific Mutation Rates in TAGA/TCTA Tetranucleotide Repeats*

No. repeats											Total			
	DYS 19	DYS 389 I	DYS 391	DYS 393	DYS 437	DYS 439	GATA A10	DYS 460	DYS 461	GATA H4	No. allele transmissions	No. mutations	Mutation rate ($\times 10^{-3}$)	95%CI ($\times 10^{-3}$)
5			1								1	0		
6		9	2		1						12	0		
7		28	5		5						38	0		
8		15	187		425	1		1	4		633	0		
9	3	286	1495	4	592	5		40	10	23	2458	2	0.814	0.099–2.936
10	467	1063	1085	3	124	86		317	171	311	3627	6	1.654	0.607–3.597
11	1490	386	33	238	3	376	33	487	541	476	4063	16	3.938	2.253–6.387
12	628	6	7	1131		544	283	29	137	59	2824	5	1.771	0.575–4.127
13	170			162		133	433	1	12	2	913	7	7.667	3.033–15.733
14	48			30		19	110		1		208	1	4.808	0.122–26.494
15	1			1			14				16	0		
16							1				1	0		
Total	2807	1793	2815	1569	1150	1164	874	874	873	875	14794	37	2.501	1.762–3.446
Av. size	11.23	9.98	9.34	11.98	8.73	11.66	12.76	10.58	10.97	10.65				

Total

No. repeats	No. allele transmissions	No. mutations	Mutation rate ($\times 10^{-3}$)	95%CI ($\times 10^{-3}$)
5–10	6769	8	1.182	0.510–2.327
11–16	8025	29	3.614	2.421–5.186

*No. Repeats is the Number of Homogeneous TAGA Motifs.

TABLE 6A. Mutation Types: Type and Number of Steps Observed for the Mutations Found in This and Other Studies

Reference	Mutation type						Total
	+1	−1	+2	−2	+3	−4	
This work	36	17	−	−	−	1	54
Kayser et al. [2000]	10	3	−	1	−	−	14
Dupuy et al. [2004]	21	14	2	−	1	−	38
Kurihara et al. [2004]	4	1	−	−	−	−	5
Budowle et al. [2005]	7	5	1	−	−	−	13
Ballard et al. [in press]	7	6	−	−	−	−	13
Total	85	46	3	1	1	1	137 ^a

TABLE 6B. Mutation Types: Number of One-Step Gain and Losses Distributed According to the Number of Homogeneous TAGA Motifs

No. repeats	Mutation type									
	This work		Kayser et al. [2000]		Dupuy et al. [2004]		Kurihara et al. [2004]		Total	
	+1	−1	+1	−1	+1	−1	+1	−1	+1	−1
6						2				2
7	1								1	
8	3					1			3	1
9	2				1				3	
10	7				2				9	
11	15	6	7	1	6	4	3	1	31	12
12	3	2			3	5			6	7
13	6	6	1	2	3	2	1		11	10
14	1	1	1		4				6	1
15	1				2				3	
16			1						1	
Total	39	15	10	3	21	14	4	1	74	33

^aIncludes mutation data from DYS388 [Dupuy et al., 2004] and from DYS413a/b [Kayser et al., 2000].

TABLE 7. Number of Mutations in Different age Groups*

Age group	Number of allele transmissions	Number of mutations	Age-specific rate (10^{-3})	95% CI (10^{-3})
15–20	1351	2	1.48	0.179–5.337
21–30	7735	13	1.68	0.895–2.872
31–40	4549	13	2.86	1.522–4.882
41–50	1593	8	5.02	2.171–9.871
51–60	650	1	1.54	0.039–8.542
61–79	250	2	8.00	0.970–28.598
Total	16088	39	2.42	1.724–3.312

*The number of transmissions and of mutations are smaller than in previous analyses, since father's age could not be recorded in all cases (data from laboratories 1, 5, and 17 were excluded).

for an excess of repeat losses at longer alleles. This supports the notion that this mechanism is biased toward microsatellite expansion [e.g., Primmer et al., 1996; Amos et al., 1996; Brinkmann et al., 1998b] until a certain repeat length at which the rates of expansion and contraction mutations are equal [Xu et al., 2000].

In conclusion, the compilation of Y-STR data for father/son pairs, which is an automatic by-product of the routine work of many forensic laboratories, allows the estimation of increasingly reliable locus/allele-specific mutation rates for the most widely used markers in both the population and forensic genetics. It is timely to compare these estimates with those obtained from phylogenetic inferences [Zhitovitsky et al., 2004], since these approaches use data that are at opposite ends of the evolutionary process. In fact, while analyses of father/son pairs include all viable offspring, phylogenetic data are filtered by long-range selective effects.

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