ORIGINAL

Two Y-chromosome-specific polymorphisms 12f2 and DFFRY in the Japanese population and their relations to other Y-polymorphisms

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Abstract: This study of male-specific genetic markers in the Japanese population was carried out in an attempt to refine the existing theories concerning its population genetics and migration events. We examined the relation between the constructed haplotypes of three biallelic Y-chromosome-specific markers (YAP, 47z and SRY) and the results of studying two other Y-specific polymorphisms of both 12f2 and DFFRY markers. The 12f2 marker was completely absent in 14.7% of Japanese males ; all of them were haplotype II males. None of the Japanese males from other haplotypes or other East Asian populations showed any deletion of 12f2. In all haplotype II Japanese men, we found that DFFRY gene harbors a (C→T) substitution polymorphism that was not found in any other population of this study. These results suggested that although haplotype II Japanese males share with the other haplotype II men from different geographical areas in having the YAP insertion on their Y-chromosomes, their Y-chromosomal structure is somewhat characteristically different. They are probably descendants of the ancestral Jomonese population who lived in Japan before the Yayoi immigrants entered Japan ~2300 years ago. These findings suggested that linkage studies between Y-specific markers are helpful in understanding the migratory patterns in East Asia. We also suggested that Japanese males have characteristically different Y-chromosomes compared with other populations. J. Med. Invest. 49 : 44-50, 2002

Keywords **:** *12f2, DFFRY, haplotypes, Japanese, Y-chromosome*

INTRODUCTION

Much attention has been given to the non-recombining part of the Y-chromosome as the genomic region, which will indicate the male side of our history (1). The Y-chromosome is unique with several properties that distinguish it from all other segments of the genome. The major part of the Y-chromosome (95%) is named (Non-Recombining part of Y-chromosome) NRY and transmitted exclusively from fathers to sons. This property of haploidity with no recombination events makes the Y-chromosome the largest DNA segment in the human genome where variations can only accumulate due to mutations. Such variations or mutations are known as polymorphisms. Studies of human Y-linked polymorphisms have thus been proposed as tools for investigating male-specific gene flow between populations (2-6).

However, as yet the evolutionary and migratory histories told by the Y-chromosome are still far

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beyond being complete. The paucity of Y-chromosome informative markers emphasized by many surveys used to be the major impediment in such migratory investigations (7, 8). Recently, the use of more efficient methods for detecting variations in the Y-chromosome has yielded a variety of tools for resolving the migratory patterns of modern humans. These human Y-chromosome markers can be classified into biallelic and microsatellite markers (9-12).

The biallelic markers with a low mutation rate are single-base changes that have usually occurred once during the long history of human Y-chromosome evolution and are, therefore, more stable than the microsatellite loci. The second group consists of microsatellite markers with a relatively high mutation rate in human evolution, possibly representing independent mutational events in respective male lineages. The former appears useful to study the deep roots of the human genetic evolutional tree, while the latter is useful to study more recent evolution within limited ethnic groups (13, 14). Both kinds of markers were used to investigate the origin and genetic structure of the Japanese population. Hammer and Horai, in 1995, genotyped four loci in a group of Japanese males and the surrounding populations, and concluded that Japanese have resulted from distinctive genetic contributions involving the ancient Jomon people and Yayoi immigrants from Korea or mainland China (15). Two studies of Y-specific DNA polymorphisms in Korean and other East Asian populations have shown that the Korean and Japanese populations share some common genetic structures (16, 17). In 1999, Shinka *et al*., used a set of three Y-chromosome biallelic polymorphic markers {DYS287 (YAP), DXYS5Y (47z/*StuI*) and SRY} to classify Japanese males into four main haplotypes. Of these four haplotypes, I and II are commonly distributed worldwide, whereas haplotypes III and IV are specific only to East Asian populations.

Japanese population was the only East Asian country to show a high percentage of YAP+ chromosomes (18). However, the findings of these studies demonstrated the need for more detailed analysis of the Y-specific polymorphisms in Japanese Y-chromosomes. The Drosophila Fat Facets-Related Y-linked gene (DFFRY) is one of these Y-specific genes, which was originally mapped to Yq11.2, and its mRNA was expressed in a wide range of adult and embryonic tissues (19). Screening of more than 600 men revealed several sequence variants, most of which appeared to be heritable and of little functional consequence (20). In two worldwide studies, the DFFRY marker was used with other Y-specific markers to study the population genetic variation, timing, origins, and geographical distribution of Y-chromosomes (6, 21).

Another marker is the 12f2 marker, which is located on the long arm of the Y-chromosome on the AZFa region and was shown to be polymorphic among populations. Recently, Blanco *et al*. developed a new PCR assay and screened a group of diverse Y-chromosomes for the 12f2 polymorphism. Their results revealed that the 12f2 amplicon was absent from Y-chromosomes, whose haplotype backgrounds are defined by the presence of the YAP insertion, and they suggested that such deletion polymorphisms may have occurred more than once during human evolutional history (22). The 12f2 deletion is found at the highest frequencies (greater than 25%) in Middle-Eastern, Southern European, North African and Ethiopian populations (23).

In the present study, we used the DFFRY and 12f2 markers together with three previously used Y-chromosome biallelic markers (YAP, 47z and SRY) to study DNA samples from Japanese population and many different populations, in an attempt to uncover a part of Japanese prehistory and clarify the ancestors who shared in the genetic composition of the modern Japanese population.

MATERIALS AND METHODS

DNA samples. Genomic DNAs were prepared from peripheral leukocytes according to the standard method (24). Blood samples from Japanese males and females were collected from healthy blood donors. We selected only male samples to analyze their Y-chromosomes. For the other ethnic groups, collaborating researchers kindly provided varying numbers of samples. All the samples were collected according to approved human subject protocols.

Y-chromosome haplotyping. Y-chromosome haplotyping was performed using a set of three biallelic polymorphic markers {DYS287 (YAP), DXYS5Y (47z/*StuI*) and SRY} by PCR, PCR-RFLP, and PCR-SSCP, respectively, as described previously (18). By the combination of these three polymorphisms, Y-chromosomes were classified into four haplotypes : I, II, III and IV.

12f2 assay. 12f2 deletion polymorphism was typed using a newly-developed assay that was described previously (22). Two primer sets were used ; one set to amplify the 88 bp amplicon of 12f2, while the other set was used to amplify 112 bp of "tat" marker on the Y-chromosome as an internal control for each sample.

DFFRY analysis. A single nucleotide polymorphism that resulted from substitution of the ancestral

Table 1. The primer sets used to amplify 12f2 and DFFRY.

Primer name	Sequences (5'-3')	Annealing Temp.	PCR products size (bp)
12f2D 12f2G	CTGACTGATCAAAATGCTTACAGATC GGATCCCTTCCTTACACCTTATAC	58°C	88
Tat1 Tat3	GACTCTGAGTGTAGACTTGTGA GAAGGTGCCGTAAAAGTGTGAA	58°C	112
DFFRY-F DFFRY-R	GAGCCCATCTTTGTCAGTTTAC CTGCCAATTTTCCACATCAACC	56°C	429

C-allele by a T-allele took place in the Arg 211 Cys starting from the initial methionine amino acid of the DFFRY gene. We amplified the DNAs using the conditions and methods that were described previously (6). Primers used to amplify the 12f2 and DFFRY markers are listed in Table 1.

The PCR products of 12f2 were resolved on 4% agarose gel, while the PCR products of DFFRY were separated using DHPLC (Denaturing High Performance Liquid Chromatography). Unpurified PCR products were mixed at an equimolar ratio with a reference Y-chromosome sample that harbors the T-allele. The two mixed samples were subjected to a 5 min 95°C denaturing step followed by gradual reannealing from 95°C to 65°C over 30 min. Each mixture (10μl) was loaded onto a DNA Separation column (Transgenomic, San Jose, CA), and the amplicons were eluted in 0.1 M triethylammonium acetate (pH 7) with a linear acetonitrile gradient at a flow rate of 0.9 ml/min. under appropriate temperature conditions, which were optimized by computer simulation. The ancestral C-allele of DFFRY was recognized by the appearance of two peaks in the elution profiles, while, the T-allele showed only one peak when mixed with the reference-mutated sample (harboring the T-allele).

RESULTS

Japan's position on the Eastern edge of Asia suggests that the demographic movements that have shaped variation on the mainland should have influenced the genetics of its population.

To pursue the origins of the Japanese population, there have been many trials by archeologists, anthropologists and geneticists. However, genetically, the inheritance of the Y-chromosome in a patrilineal manner has led to high levels of geographical clustering of Y-variants. These variation patterns make the Y-chromosome a very useful tool for investigating human population genetics. Large numbers of polymorphic markers are required, including ones ascertained from each population and arising at different historical times (13).

We have typed 251 Y-chromosomes from Japanese males to study the distribution of polymorphisms of five Y-specific biallelic markers, DYS287 (YAP), DXYS5Y (47z/*StuI*), SRY, 12f2, and DFFRY.

At first, Y-haplotyping was performed using three polymorphic biallelic loci, 47z, YAP and SRY (18). The results showed that Japanese Y-chromosomes are classified into four haplotypes; haplotype I (Y1, YAP- and C), haplotype II (Y1, YAP+ and C), haplotype III (Y1, YAP- and T) and haplotype IV (Y2, YAP- and T). Then, all the samples were typed for the additional two markers, 12f2 and DFFRY.

The 12f2 marker showed two variants, one with an amplicon of 88 bp and the other variant has a complete deletion of 12f2 (Figure 1). In 37 (14.7%) Japanese men 12f2 was completely absent ; all of them were haplotype II males. None of the Japanese men from the other haplotypes showed any deletion of 12f2. East Asian populations did not show any deleted 12f2

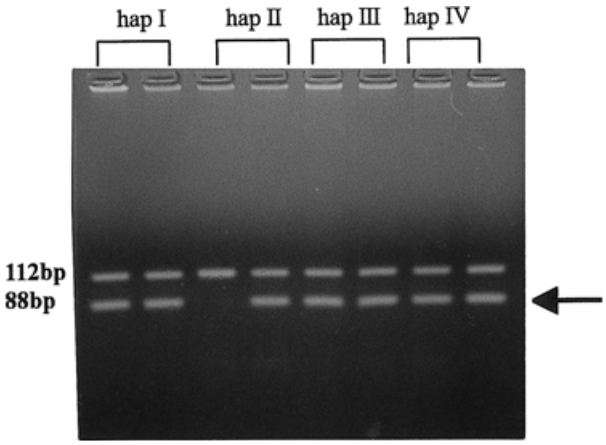

Fig. 1. The 12f2 amplicon of 88 bp is deleted in haplotype II males only, but is not deleted in the other Japanese haplotypes.

Table 2. Frequency distribution of the polymorphisms of 12f2 and DFFRY gene among males from different populations considering their Y chromosome compound haplotypes using three (YAP, 47z/StuI, and SRY) biallelic markers.

	12f2 Polymorphism								Polymorphism of DFFRY Arg 211 Cys								Totals
	Deleted 12f2				12f2 non-deleted				DFFRY with T allele				DFFRY with C allele				
Haplotypes	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV	
Japanese	-	37	-	-	99	41	29	45	-	78	-	-	99	-	29	45	251
Koreans	-	.	-	-	27	.	12	9	-	.	-	-	27	.	12	9	48
Taiwanese	-	.	.	.	51	.	.	.	-	.	.	.	51	.	.	.	51
Chinese	-	.	.	.	38	.	.	.	-	.	.	.	38	.	.	.	38
US Whites	2	-	.	.	12	3	.	.	-	-	.	.	14	3	.	.	17
US Blacks	-	-	.	.	4	12	.	.	-	-	.	.	4	12	.	.	16
Bolivians	-	-	.	.	69	5	.	.	-	-	.	.	69	5	.	.	74

samples, however, there were deletions in 2 American white (American-Caucasian) males with haplotype I (Table 2).

In all the haplotype II Japanese males, we found that the DFFRY gene harbors a substitution polymorphism that was not found in any other population of this study. Even Japanese men from Y-haplotypes other than haplotype II did not show this DFFRY polymorphism. Figure 2 shows the DHPLC results for the T-allele samples that showed only one peak when mixed with a reference-mutated sample. It also presents a group of Y-chromosomes from different geographical areas showing two peaks indicating their difference from the reference-mutated samples. This relationship between the two polymorphisms of 12f2 and DFFRY, on the one hand, and the Y-chromosome compound haplotypes of the other three-biallelic markers (47z, YAP and SRY), on the other, were used for a reevaluation of the modern peopling of Japan, migration patterns and demographic movements in East Asia.

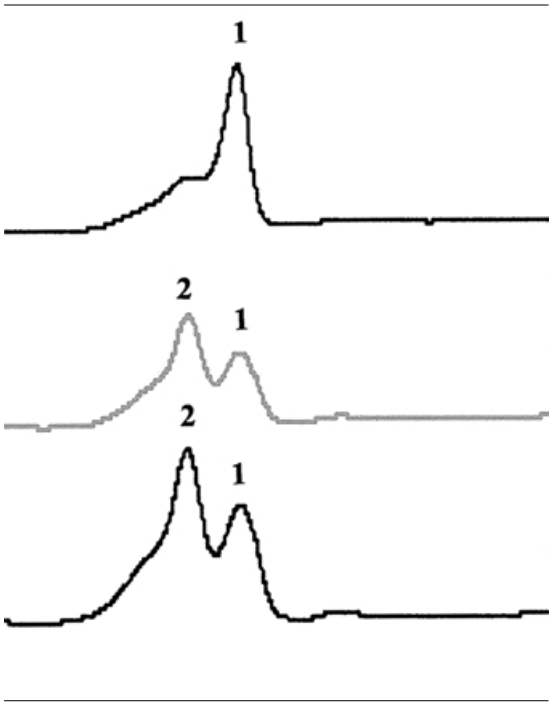

Fig. 2. Representative Chromatograms from DHPLC results of the DFFRY gene showing resolution of heteroduplex (peaks 2) from the homoduplexes (peaks 1) created by reannealing PCR products of a male reference with males from different lineages other than the Japanese haplotype II lineage. Peaks 2 refer to DFFRY with the ancestral C-allele at Arg 211 Cys, while (peaks1) refer to to the substitution polymorphism (T-allele).

DISCUSSION

Japan holds great interest for the population geneticist because of the uniqueness of its population, however, the current theories on its ancestry and migratory events are based largely on archaeological findings (25-27). However, although the Japanese population has been archeologically and genetically investigated for its origin, the detailed history of ancient migration patterns to Japan is still unclear. This study of male-specific genetic markers in the Japanese population was carried out in an attempt to refine the existing theories concerning its population genetics and migration patterns.

Genetically, Japanese males are classified into four haplotypes according to three polymorphic loci, (47z, YAP and SRY), on the Y-chromosome (18). To reconstruct the ancient migration patterns into Japan that have led to the modern Japanese genetic structure, we examined the relation between the

constructed haplotypes of the three biallelic markers above and the results of studying the polymorphisms of both 12f2 and DFFRY markers.

Based on haplotyping using the three biallelic loci, (47z, YAP and SRY), it is assumed that haplotype I is the ancestral haplotype from which other haplotypes branched off. During Y-chromosomal evolution, a YAP insertion occurred giving rise to haplotype II, and afterwards, in haplotype I, another separate mutation in the SRY took place producing the T-allele and giving origin to a new lineage of haplotype III, which was further divided, by a polymorphism at the 47z locus into haplotypes III or IV (18). Figure 3 shows that the DFFRY C→T substitution polymorphism had occurred before the YAP insertion took place, since the present study revealed that all Japanese males with YAP+ chromosomes have the C→T substitution. Other Y-chromosomes from different geographical areas whose background are YAP-showed the DFFRY substitution suggesting that this DFFRY polymorphism preceded the YAP insertion polymorphism.

The present results showed that 14.7 % of Japanese males have deletion of the 12f2 amplicon. All these males with the 12f2 deletion belonged to the haplotype II lineage. They constitute 47.4% of haplotype II males. None of the other East Asian populations have shown this deletion. Moreover, none of the East Asian populations of this study have shown YAP+ chromosomes (Haplotype II) except for Japanese who showed 31.1%. The results support the previous findings of Hammer and Horai (1995) (15). These findings suggested that the origin of Japanese YAP+ chromosomes is not from East Asia ; which support the theory that the early Jomonese, who have Y-chromosomal haplotypes I and II, likely originated in central Asia and crossed over a northern land bridge into Japan more than 12,000 years ago (28).

However, the results of the DFFRY polymorphism were quite surprising in that all haplotype II Japanese men (100%) were found to harbor the substitution polymorphism of Arg 211 Cys, while none of the YAP+ of Bolivian, American-white, or African-American males showed it.

These results suggested that although haplotype II

Haplotypes	I	IIα	IIβ	III	IV
YAP	-	+	+	-	-
47z	Y 1	Y 1	Y 1	Y 1	Y 2
SRY	C	C	C	T	T
DFFRY	C	T	T	C	C
12f2 deletion	-	-	+	-	-

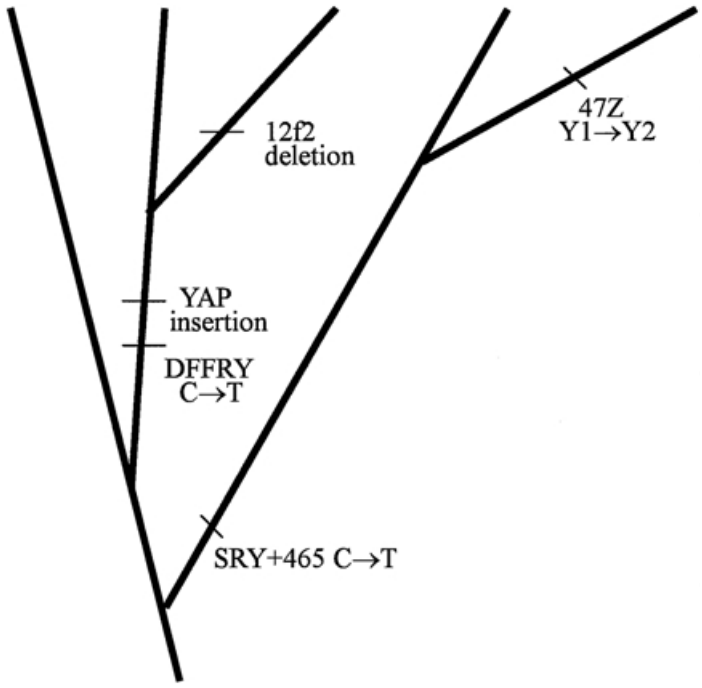

Fig. 3. Rooted Y-chromosomal phylogeny for the Japanese population. It shows the 4 main haplotypes and the occurrence of the DFFRY gene substitution polymorphism followed by the 12f2 deletion polymorphism.

Japanese men share with the other haplotype II men from different geographical areas in having the YAP insertion on their Y-chromosomes, their Y-chromosomal structure is somewhat characteristically different. This different structure may have some functional consequences such as alteration of the spermatogenic ability that was reported previously (29-31). However, for population geneticists, such structural differences may be of great importance in pursuing the origin of the modern Japanese population. These unique haplotype II males who were not found in East Asia except for in Japan, constitute 31% of the Japanese population. These 31% of males are ultimately the descendants of the ancestral Jomonese population who lived in Japan before the Yayoi immigrants entered Japan 2,300 years ago.

In this study, haplotypes III and IV were not found in any population except for Korea and Japan. The geographical distribution seen for haplotypes III and IV supports the existing theories (15, 18) that males with these haplotypes migrated into Japan with the Yayoi immigrants from Korea.

Although it was reported that the YAP+ chromosomes from Africa and Japan are identical by descent (7, 15), the present results of the DFFRY and 12f2 markers showed that Japanese YAP+ chromosomes are different from YAP+ chromosomes of Bolivian, African-American, and Caucasian-American males. Hence, we support the theory that "different populations often have characteristically different Y-chromosomes".

In conclusion, linkage studies between Y-specific markers are helpful in understanding the migratory patterns in East Asia. It is also suggested that Japanese males have characteristically different Y-chromosomes compared with other populations.

Taken together, the results and associations determined in this study provide an update of previous studies on migration events and Japanese population genetics.

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