

ORIGINAL ARTICLE

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Molecular analysis of mutations and polymorphisms of the Lewis secretor type $\alpha(1,2)$ -fucosyltransferase gene reveals that Taiwan aborigines are of Austronesian derivation

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Abstract The origins of the Taiwan aborigines have not been fully resolved. Anthropological and linguistic studies have indicated that their ancestry is mainly Austronesian or Malayopolynesian. Some polymorphisms and mutations in the secretor type $\alpha(1,2)$ -fucosyltransferase (*FUT2*) gene are found in Taiwan aborigines. In this study, we analyzed the frequency of eight mutations and one polymorphism of the *FUT2* gene in Taiwan aborigines and other ethnic groups in order to explore the origins of these groups. The results showed that the C302T, G428A, and fusion gene mutations were specific for Thai, Caucasians, and Japanese, respectively. The A385T mutation was specific for Asians including Taiwan aborigines. The genetic frequencies of C571T were much higher in Taiwan aborigines (1.96% to 20.4%), Filipinos (13.2%), and Indonesians (3.30%) as compared with Thai (0.57%), Chinese (0.65% to 1.12%), Japanese (0%), and Caucasians (0%). The frequencies of the G849A mutation were also higher in Taiwan aborigines (0.38% to 21.57%), Filipinos (6.80%), and Indonesians (1.48%) than in Thai (0.94%), Chinese (0–0.37%), Japanese (0%), or Caucasians (0%). Deletion of a 3-bp region (nt 688 to nt 690) was found only in Filipinos (0.85%), Indonesians (0.74%), and three tribes (0.42% to 2.70%) of Taiwan aborigines, but not in other populations. The C628T mutation

was found only in Taiwanese Han, Thai, and two tribes of Taiwan aborigines. The genetic frequency of the C357T polymorphism was much higher in Asians than in Caucasians. The genetic analysis confirms that the origins of Taiwan aborigines are Austronesian and that they are closely related to the Filipino and Indonesian populations. We suggest that mutations or polymorphisms of the *FUT2* gene are very good markers for investigating population genetics.

Key words Taiwan aborigines · $\alpha(1,2)$ -Fucosyltransferase (*FUT2*) · Mutations and polymorphisms · Southeast Asia · Origin

Introduction

The origins of the aborigines of Taiwan, who are locally called highland people, are unknown. Taiwan aborigines on the island of Taiwan are divided into ten ethnic tribal groups (Fig. 1): Atayal, Saisiyat, Bunun, Tsou, Rukai, Paiwan, Puyuma, Amis, Yami, and Pepo. The Pepo group, who are not highland people, is further divided to ten subgroups: Ketagalan, Kavalan, Taokas, Pazeh, Papora, Babuza, Hoanya, Thao, Siraya, and Qaugaut. The Pepo population is commonly admixed with the Han population, and most of them cannot be differentiated from the Han people.

The origins of Taiwan aborigines is controversial and still unresolved. According to a large amount of anthropological, historical, and ethnographic data, it appears that they are closely related to the Austronesian or Malayopolynesian populations, and that they are similar to the Filipino and Indonesian populations, but that they differ significantly from the Han population (Blust 1988; Bellwood 1991). Taiwan aborigines speak different languages: the languages among different ethnic groups are similar, yet not mutually intelligible.

The languages of Taiwan aborigines apparently belong to the Austronesian language group. Because of the com-

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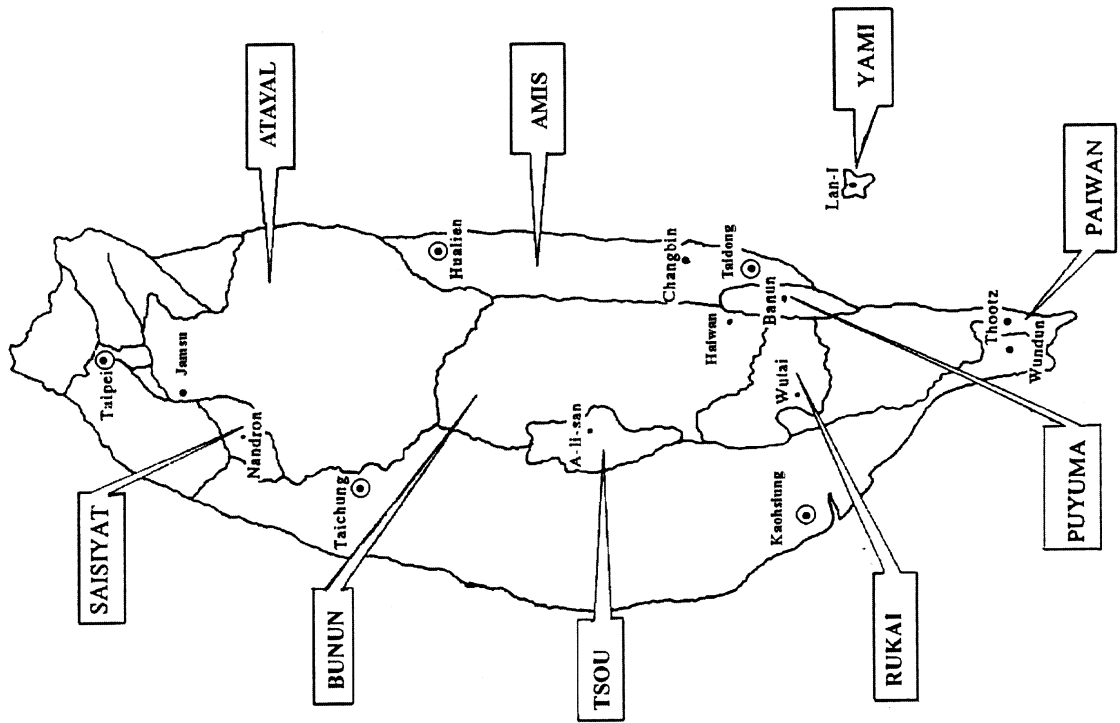
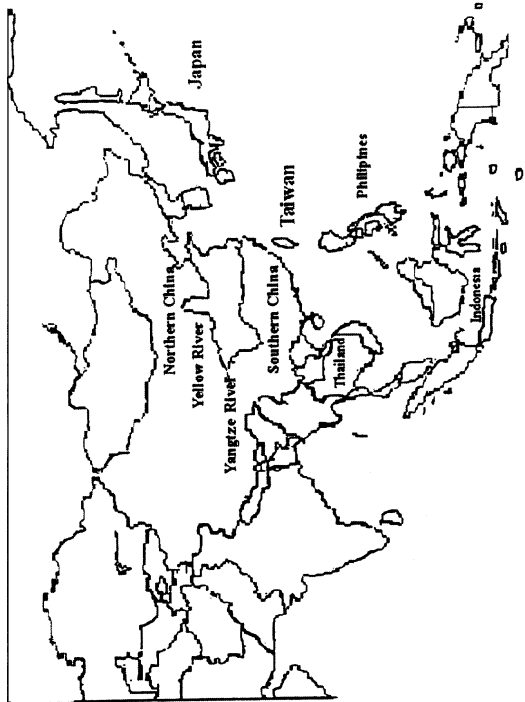


Fig. 1. The locations of Taiwan and other Southeast Asian countries are shown in **(A)**, and the distribution of Taiwan aborigines on Taiwan is shown in **(B)**. The blood samples were drawn from people of different tribes of Taiwan aborigines that live in representative places: Jamsu

County (Atayal), Nandron County (Saisiyat), A-li-san County (Tsou), Haiwan County (Bunun), Changbin County (Amis), Wutai County (Rukai), Banun County (Puyuma), Thootz County (Paiwan), Lan-I County (Yami), and Wundun County (Pepo)

- ⊙ Major City
- Place of Blood Sampling

plexity of the languages used by Taiwan aborigines, it has been suggested that the Austronesians originated in Taiwan (Blust 1988; Bellwood 1991). Bellwood suggested that the Austronesian people originated in Taiwan about 5000 years ago (Bellwood 1991). If that hypothesis is correct, it is very important to search for genetic markers in Taiwan aborigines that can also be used to recognize known Austronesians.

Recently, certain mutations of the $\alpha(1,2)$ -fucosyltransferase (*FUT2*) gene were found to be specific for some ethnic groups. For example, the G428A mutation has been found only in Caucasians (Kelly et al. 1995) and A385T is specific for Asians (Henry et al. 1996; Yu et al. 1995, 1996; Koda et al. 1996; Kudo et al. 1996). Thus, information about mutations or polymorphisms that occur in an ethnic population may be used to classify that population's origin. Because of the occurrence of the C571T and G849A mutations in Taiwan aborigines (Yu et al. 1996), and the unresolved debate about their ancestry, this study was undertaken to investigate the biological diversity of the Taiwan aborigines by determining the frequency and distribution of the mutations and polymorphisms of the *FUT2* gene in Japanese, Chinese, Caucasian, Southeast Asian, and Taiwan aboriginal populations.

Subject and methods

Subjects

Blood was obtained from 134 Taiwanese belonging to the Han ethnic group, 60 from northern and 77 from southern mainland China. Samples of blood from 54 Japanese, 265 Thai, 117 Filipinos, 135 Indonesians, 53 Caucasians, and from a total of 798 unrelated individuals from ten tribes of Taiwan aborigines (141 Yami, 132 Atayal, 66 Saisiyat, 51 Tsou, 38 Rukai, 115 Bunun, 118 Amis, 75 Paiwan, 37 Puyuma, and 25 Pepo) were also taken. Appropriate informed consent was obtained from all subjects. The red blood cell (RBC) Lewis phenotype was determined with a tube method by using commercial antibodies (Gamma Biologicals, Houston, TX, USA) for 124 Chinese, 101 Filipinos, and 68 Thai.

DNA amplification and restriction enzyme analysis

Total genomic DNA was isolated from peripheral blood leukocytes of the subjects as described previously (Chang et al. 1992). Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis of the *FUT2* mutations and polymorphisms was carried out as described previously (Peng et al. 1999; Chang et al. 1999). For those subjects without any of the mutations mentioned above or in uncertain cases, a pair of primers specific for the Sec 2 DNA segment encoding the secretor $\alpha(1,2)$ -fucosyltransferase gene was used to amplify the coding region of the *FUT2* gene. The upstream primer (5'-CTAACGTGTCCTTCCTC-3') was located at nt

–65 through –45 of the gene, (the first nucleotide of the initial codon was designated as +1) and the downstream primer (5'-GTCCTGCTCATGGAACCATG-3') was complementary to nt 1072 through 1091 within the 3' untranslated region of the *FUT2* gene. The polymerase chain reaction (PCR) products were either cloned into the pT7 Blue T vector (Novagen, Madison, WI, USA) or directly sequenced. DNA sequences were determined by the dideoxy chain termination method by using an Amplicycle Sequencing Kit (Perkin Elmer, Foster City, CA, USA).

The DNA amplification was performed as described by Henry et al. (1996), except for modifications of the annealing temperature according to the T_m of the primers. The amplified products were digested with appropriate restriction enzymes followed by electrophoresis on a 1.5%–3.5% agarose gel. Some cases were confirmed by direct sequencing of the PCR products, and these cases were used as positive or negative references.

Statistical methodology

Genetic distances between populations were computed for all pairwise combinations of populations. Based on these distance matrices, a cluster analysis of populations was performed for each genetic distance matrix with an unweighted pair-group method and arithmetic averages (UPGMA) analysis (Nei 1972). MEGA computer software was used to conduct this analysis (Kumar et al. 1993).

Results

The results of our examination of the *FUT2* gene mutations and polymorphisms in Taiwan aborigines are shown in Table 1. None of the samples analyzed were found to have C302T, G428A, or fusion gene mutations. The frequency of the C357T polymorphism was 98.48%, 93.94%, 93.26%, 86.86%, 78.38%, 75.22%, 74.00%, 74.00%, 62.75%, and 60.53% in the Atayal, Saisiyat, Yami, Amis, Puyuma, Bunun, Paiwan, Pepo, Tsou, and Rukai groups, respectively. The frequency of the A385T mutation was 36.67%, 36.49%, 34.85%, 33.47%, 32.95%, 32.35%, 28.00%, 25.00%, 22.70%, and 19.13% in the Paiwan, Puyuma, Saisiyat, Amis, Atayal, Tsou, Pepo, Rukai, Yami, and Bunun groups, respectively. The frequency of the C571T mutation was 20.43%, 15.91%, 12.71%, 12.77%, 10.67%, 6.76%, 6.58%, 5.30%, 4.00%, and 1.96% in the Bunun, Atayal, Amis, Yami, Paiwan, Puyuma, Rukai, Saisiyat, Pepo and Tsou, respectively. The C628T mutation occurred only in the Puyuma and Pepo groups, and the frequencies were 4.05% and 12.00%, respectively. The frequency of the deletion mutation from nt 688 to nt 690 was 2.7%, 0.67%, and 0.42% in the Puyuma, Paiwan, and Amis, respectively, and this mutation did not occur in other Taiwan aborigines. The frequency of the G849A mutation was 21.57%, 18.42%, 16.52%, 13.51%, 10.67%, 8.00%, 3.39%, 0.38%, and 0.76% for the Tsou, Rukai, Bunun, Puyuma, Paiwan, Pepo, Amis, Atayal, and Saisiyat, respectively.

Table 1. Lewis secretor type $\alpha(1,2)$ -fucosyltransferase gene mutations and polymorphisms in Southeast Asia including Taiwan aborigines

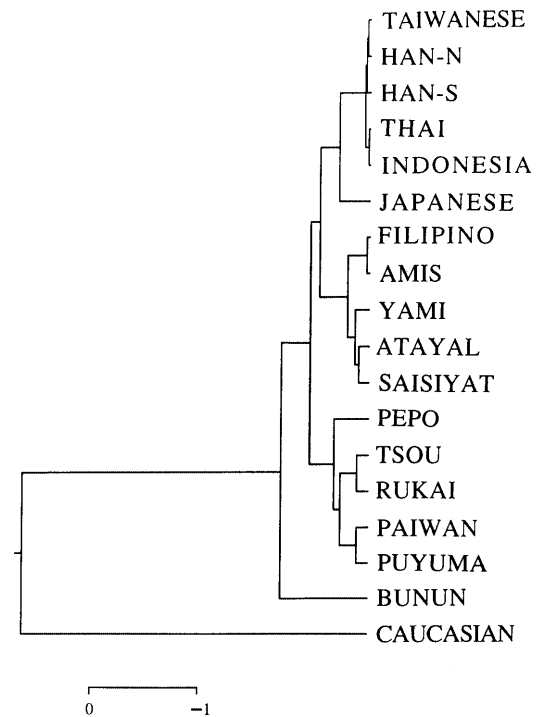
Ethnic groups	Sample Size (2N)	Mutations (cDNA)																	
		C302T		C357T		A385T		G428A		C571T		C628T		Deletion 688–690		G849A		Fusion gene	
		M	%	M	%	M	%	M	%	M	%	M	%	M	%	M	%	M	%
Taiwanese (Han)	268	0	0.00 ^a	239	89.18	127	47.39	1	0.37	3	1.12	2	0.75	0	0.00	1	0.37	0	0.00
Han-North	120	0	0.00	109	90.83	54	45.00	0	0.00	1	0.83	0	0.00	0	0.00	0	0.00	0	0.00
Han-South	154	0	0.00	130	84.42	67	43.51	0	0.00	1	0.65	0	0.00	0	0.00	0	0.00	0	0.00
Japanese	108	0	0.00	81	75.00	44	40.74	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	7	6.48
Thai	530	3	0.57	471	88.87	270	50.94	0	0.00	3	0.57	2	0.38	0	0.00	5	0.94	0	0.00
Filipino	234	0	0.00	200	85.47	80	34.19	0	0.00	31	13.25	0	0.00	2	0.85	16	6.84	0	0.00
Indonesian	270	0	0.00	241	89.26	131	48.52	0	0.00	9	3.33	0	0.00	2	0.74	4	1.48	0	0.00
Caucasian	106	0	0.00	40	37.74	0	0.00	38	35.85	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Atayal	264	0	0.00	260	98.48	87	32.95	0	0.00	42	15.91	0	0.00	0	0.00	1	0.38	0	0.00
Saisiyat	132	0	0.00	124	93.94	46	34.85	0	0.00	7	5.30	0	0.00	0	0.00	1	0.76	0	0.00
Tsou	102	0	0.00	64	62.75	33	32.35	0	0.00	2	1.96	0	0.00	0	0.00	22	21.57	0	0.00
Rukai	76	0	0.00	46	60.53	19	25.00	0	0.00	5	6.58	0	0.00	0	0.00	14	18.42	0	0.00
Bunun	230	0	0.00	173	75.22	44	19.13	0	0.00	47	20.43	0	0.00	0	0.00	38	16.52	0	0.00
Amis	236	0	0.00	205	86.86	79	33.47	0	0.00	30	12.71	0	0.00	1	0.42	8	3.39	0	0.00
Paiwan	150	0	0.00	111	74.00	55	36.67	0	0.00	16	10.67	0	0.00	1	0.67	16	10.67	0	0.00
Puyuma	74	0	0.00	58	78.38	27	36.49	0	0.00	5	6.76	3	4.05	2	2.70	10	13.51	0	0.00
Pepo	50	0	0.00	37	74.00	14	28.00	0	0.00	2	4.00	6	12.00	0	0.00	4	8.00	0	0.00
Yami	282	0	0.00	263	93.26	64	22.70	0	0.00	36	12.77	0	0.00	0	0.00	3	1.06	0	0.00

M, mutation

^aM/2N

The results of analyzing *FUT2* gene polymorphism and mutations in the ethnic groups other than the Taiwan aborigines are also shown in Table 1. The C302T mutation was Thai specific (0.57%), the G428A mutation was Caucasian specific (35.85%), and the fusion gene was Japanese specific (6.48%). None of these mutations occurred in the other ethnic groups studied. The frequency of the C357T polymorphism was 90.83%, 89.26%, 89.18%, 88.87%, 85.47%, 84.42%, 75.00%, and 37.74% in the Han-north, Indonesian, Taiwanese, Thai, Filipino, Han-south, Japanese, and Caucasian populations, respectively. The frequency of the A385T mutation was 50.94%, 48.52%, 47.39%, 45.00%, 43.51%, 40.74%, 34.19%, and 0% in the Thai, Indonesian, Taiwanese, Han-north, Han-south, Japanese, Filipino, and Caucasian populations, respectively. The frequency of the C571T mutation was 13.25%, 3.33%, 1.12%, 0.83%, 0.65%, and 0.57% in the Filipino, Indonesian, Taiwanese, Han-north, Han-south, and Thai populations, respectively, but was not present in the Japanese and Caucasian groups. The frequency of the C628T mutation in the Thai and Taiwanese populations was 0.38% and 0.75%, respectively, and the mutation was not found in the Han-south, Han-north, Japanese, Filipino, Indonesian, or Caucasian groups. The frequency of the G849A mutation was 6.84%, 1.48%, 0.94%, and 0.37% in the Filipino, Indonesian, Thai, and Taiwanese populations, respectively, but 0% in the Han-south, Han-north, Japanese, and Caucasian populations.

The dendrogram (Fig. 2) from the cluster analysis of these 18 populations is based on Nei's genetic distances (Nei 1972) as computed by MEGA software (Kumar et al. 1993) for the UPGMA analysis, which resulted in five broadly-defined groups for this *FUT2* locus. Caucasians showed the greatest genetic distance compared with the

**Fig. 2.** Unweighted pair-group method and arithmetic averages dendrogram of 18 populations based on genetic distance matrices of the *FUT2* gene (Nei 1972)

major eastern Asian populations and Taiwan aborigines. The pairwise combinations of populations with the Bunun were more distant than the rest of the combinations, except for with the Caucasian group. Caucasian and Bunun were thus independently defined clusters. Except for the Bunun,

nine aboriginal peoples in Taiwan were clustered into two groups; one group included the Pepo, Tsou, Rukai, Paiwan, and Puyuma, and the other included the Amis, Yami, Atayal, and Saisiyat. Filipinos were clustered in the Amis group and showed the closest genetic distance with the Amis. The last group, at the top of the dendrogram, included Taiwanese, Han-north and Han-south, Thai, Indonesian, and Japanese. Of course, the Taiwanese, Han-north, and Han-south have the same population origin, and were the closest in this group. The Thai were clustered first with Indonesians. Japanese were the most distant from the other populations in this group. All the genetic distances obtained for these five groups as shown in the dendrogram are reasonable on the basis of their regional and ethnic differences.

Discussion

PCR analysis of mutations and polymorphisms of the *FUT2* gene has not previously been used in human population genetics. Here, we studied eight mutations and one polymorphism of the *FUT2* gene in order to elucidate the genetic background and relationship of Taiwan aborigines and other ethnic groups. From the frequency of the A385T mutation, we confirmed that this mutation is Asian specific and that the frequency is around 20%, although it doesn't occur in Caucasians. We also confirmed that the G428A mutation is Caucasian specific, and that the genetic frequency is over 30% in the Caucasian population. The frequency of the C357T polymorphism is higher in Asians (more than 60%) than in Caucasians (less than 40%). These three markers could be used to differentiate between Asian and Caucasian populations. The fusion gene mutation was found solely in the Japanese population, and the carrier rate is relatively high (6.48%). It is a very good marker for Japanese. Our results are similar to those of Koda et al. (1996). The C302T mutation was found only in the Thai population and the frequency was not high (0.57%), although, it could be used as a marker for the Thai population.

Taiwan aborigines have much higher carrier rates of the C571T mutation (1.96%–20.4%) than the Chinese (Han population) (0.65%–1.12%), Japanese (0%), Thai (0.57%), or Caucasians (0%), but their rates are similar to those in Filipinos (13.2%) and Indonesians (3.3%). These results suggest that the origins of the Taiwan aborigines are closest to those of the Filipinos and Indonesians, less close to those of the Thai and Chinese, and relatively far from the Japanese. Therefore, our data further confirmed the reports from anthropological and language studies. The Taiwan aborigines all belong to the Austronesian or Malayopolynesian groups. As indicated by similar results found in the study of the G849A mutation, a higher carrier rate was observed in Taiwan aborigines (0.38%–21.57%), Filipino (6.8%), and Indonesian (1.48%) than in Thai (0.94%) and Taiwanese populations (0.37%). No G849A mutation was found in the Chinese, Japanese, or Caucasian groups. From these results, we suggest that the Thai are

much closer to Taiwan aborigines than the Chinese. These two markers (C571T and G849A mutations) are Austronesian specific. The dendrogram indicates that Indonesians are close to Chinese, which may be due to heavy mixing between Chinese and Indonesians in our sample.

The C628T mutation was found only in the Taiwanese (0.75%), Thai (0.38%) Puyuma (4.05%), and Pepo (12.0%), whereas it was absent in other tribes and ethnic groups. These results may suggest that the Taiwan aborigines directly originated from different Austronesian populations or via several periods of migration from other places of the Austronesian homeland.

Similar results were also found for the deletion mutation (nt 688 to nt 690). The mutation was found in Filipinos, Indonesians, and three tribes of Taiwan aborigines (Amis, Paiwan, and Puyuma).

Why do Taiwanese of Han origin show much higher frequencies of C571T, C628T, and G849A mutations than the Han of mainland China? From a historical point of view, the members of the Han population of mainland China were able to freely migrate to Taiwan with their families before the Ching dynasty. However, at that time, marriages between the Han and Taiwan aborigines were very rare. At the beginning of the Ching dynasty, emigration to Taiwan from mainland China was restricted. Most immigrants at that time were illegal. Moreover, for safety's sake, these illegal immigrants were single and did not bring their families. Consequently, at that time, marriages between Han and Taiwan aborigines were quite common. Therefore, the carrier rates of the C571T, C628T, and G849A mutations are relatively high in the Taiwanese population, compared with the Han population of mainland China.

It has been suggested that the Austronesians originated from Taiwan aborigines (Blust 1988), because the languages are more variable in this region. Mutations and polymorphisms of the *FUT2* gene also confirm this hypothesis. The highest frequencies of Austronesian-specific mutations (C571T, G849A, C628T, and the 3-pd deletion) are found in Taiwan aborigines, and all of the Austronesian-specific mutations can be found in this region, too. Our genetic data also support the results of language studies (Blust 1988).

The origins of the Pepo tribe are much more controversial. One hypothesis suggests that their origin is Austronesian, while another suggests that their origin is from the Han population of more than 400 years ago. Because most Pepo tribes are admixed with the Han population of Taiwan, it is difficult to get blood samples from ethnically pure Pepo people. Our samples were taken from an isolated area, and all subjects had the same last name ("Pan"). They do not marry people from other groups for religious reasons. We believe that these Pepo people are much more ethnically pure. Our results showed that the Pepo people are also Austronesian.

Recently, several studies have shown that Taiwan aborigines held an ancestral position in the spread of mtDNAs throughout Southeast Asia and Oceania, and Taiwan may be the proto-Austronesian homeland (Melton et al. 1995, 1998; Sykes et al. 1995). These results also suggest that Taiwan aborigines have roots in central or south China, and

have been isolated from other Asian populations in recent history (Melton et al. 1998; Capelli et al. 2001). After analyzing the mutations and polymorphisms of the *FUT2* gene, we come to the same conclusion.

Our results confirm that the origin of Taiwan aborigines is Austronesian on the genetic level. The difference in frequency of some *FUT2* mutations of Taiwan aborigines between the Han population and Han-Taiwanese reflects the political policy that influenced the interaction between the two groups over the past several hundred years. From these results, we suggest that the mutations or polymorphisms of the *FUT2* gene are very good markers for the study of population genetics.

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