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Frequency of Private Electrophoretic Variants and Indirect Estimates of Mutation Rate in Papua New Guinea

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SUMMARY

Data on rare and private electrophoretic variants have been used to estimate mutation rates for populations belonging to 55 language groups in Papua New Guinea. Three different methods yield values of 1.42×10^{-6}, 1.40×10^{-6}, and 5.58×10^{-6}/locus per generation. The estimates for three island populations off the north coast of New Guinea—Manus, Karkar, and Siassi—are much lower. The variability in mutation rates estimated from rare electrophoretic variants as a function of population size is discussed. The mean mutation rate in Papua New Guinea is less than half the estimates obtained for Australian Aborigines and Amerindians.

INTRODUCTION

In a previous paper [1], we gave data for the frequency in Australian Aborigines of private electrophoretic variants for enzymes controlled by 25 loci, and these data were used to determine an indirect estimate of the mutation rate. Three different methods yielded values of 6.11×10^{-6}, 2.78×10^{-6}, and 12.86×10^{-6}/locus per generation for the total sample of Aborigines, and similar values were obtained for a series drawn from one tribal population in Australia.

Neel and Neel and Rothman initiated such studies using data for South American Indian populations [2, 3], and the same data were re-examined by Nei [4]. The mutation rate estimates for these populations are comparable to those obtained by us in Australian Aborigines. Tchen et al. [5] estimated mutation rates for Amerindian populations in French Guiana, and Chakraborty and Roychoudhury [6] have done the same for some South Asian populations.

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We have now extended our own studies to include data for 21 protein loci over 55 speech communities in Papua New Guinea. It is hoped that these new data will assist in understanding some of the complex factors that influence indirect estimates of the mutation rate in man.

STUDY POPULATION

Papua New Guinea comprises the portion of the island of New Guinea east of longitude 141° east plus several geographically related islands, including New Britain, the Admiralty Islands, and Bougainville. The census size of Papua New Guinea is approximately three million, or about 67% of the estimated total Melanesian population, and its population is one of the most complex linguistically and most socially fragmented areas of the world. It is estimated that there are about 700 speech communities in Papua New Guinea, divided between two major linguistic language types: Papuan and Austronesian [7]. A survey of the patterns of social structure is given in the *Encyclopaedia of Papua and New Guinea* [8].

The present analysis is based on samples collected from populations belonging to 47 languages, also called speech communities, on the mainland of Papua New Guinea, together with two speech communities from Karkar Island and five from Siassi Islands (both off the northern shore of New Guinea), and one speech community, Titan, from the Great Admiralty Island, also called Manus. The populations of these three offshore islands (Karkar, Manus, and Siassi), although having evolved in a similar ecological setting, have been exposed to different types of population pressures. These societies, like the coastal regions of mainland Papua New Guinea, have been at the crossroads of migrations in and around the Pacific, and may well have had their genetic composition considerably altered through repeated contact with outsiders. The populations of these three islands have also been analyzed separately for respective mutation rates.

LABORATORY DATA

The samples analyzed were collected during the past 12 years by us or by collaborators involved in medical surveys in Papua New Guinea. Material in all cases was shipped by air to Canberra, and testing was carried out in our laboratories using standard procedures outlined in Blake et al. [9]. The variants of a few other systems were tested using the techniques as follows: GPT [10], ESD [11], CA_1 and CA_2 [12], GLO [13], and PGM_1 and PGM_2 [14]. The list of enzymes studied, along with their sample size and subunit molecular weights, are given in table 1.

Seven of the 21 loci in the study are polymorphic, and six of the 21 are invariant. Out of the 53 alleles segregating, 24 alleles are rare as a whole. Two other alleles, namely, PGM_1^3 and PGM_2^9, although polymorphic, are considered here to be of New Guinean origin. This raises the number of variants to 26. The names of these variants, along with their frequencies, are given in table 2.

Four of these 26 variant alleles ($Hb\ J^{Tongariki}$, GOT^3, GPT^3, and GPT^6) cannot be assigned with certainty to Papua New Guinea because of their presence in appreciable numbers in other Western Pacific populations that, as is true for the Japanese during World War II, have had contact with Papua New Guinea in the past. The

TABLE 1

GENETIC MARKERS IN PAPUA NEW GUINEANS

LOCUS NO.	ENZYME SYSTEM	ABBREVIATION	SUBUNIT SIZE (IN DALTONS)	SAMPLE SIZE			
				Total population	Karkar Island	Manus Island	Siassi Islands
	Multimers:						
1	Hemoglobin-α	Hbα	15,000	6,874	1,086	80	287
2	Hemoglobin-β	Hbβ	16,000	6,874	1,086	80	287
3	Superoxide dismutase	SOD_A	16,000	7,322	1,091	183	287
4	Glyoxalase I	GLO	24,000	2,192	...	...	283
5	Esterase D	ESD	28,000	5,453	870	...	286
6	Malate dehydrogenase-2	MDH_2	35,000	7,856	1,091	183	286
7	Lactate dehydrogenase A	LDH_A	35,000	7,858	1,091	183	286
8	Lactate dehydrogenase B	LDH_B	35,000	7,858	1,091	183	286
9	Glutamic-oxaloacetic transaminase	GOT	46,000	4,441	433	...	...
10	Isocitrate dehydrogenase	ICD_S	48,000	4,908	433	...	287
11	Glutamic-pyruvic transaminase	GPT	50,000	5,205	837	...	93
12	6-Phosphogluconate dehydrogenase	6PGD	53,000	7,809	1,091	183	284
13	Phosphohexose isomerase	PHI	62,000	6,934	617	183	221
	Monomers:						
14	Acid phosphatase-1	ACP_1	15,000	7,421	1,090	183	287
15	Adenylate kinase-1	AK_1	22,000	5,551	617	183	...
16	Carbonic anhydrase-1	CA_1	29,000	1,857	...	...	287
17	Carbonic anhydrase-2	CA_2	29,000	1,370	...	...	...
18	Phosphoglycerate kinase	PGK	50,000	7,818	1,090	183	260
19	Phosphoglucomutase 1	PGM_1	51,000	7,775	1,087	183	283
20	Peptidase B	PEPB	55,000	5,108	617	183	...
21	Phosphoglucomutase 2	PGM_2	61,000	7,787	1,086	183	283
Total				126,271	16,404	2,356	4,573

TABLE 2

NO. AND FREQUENCIES OF PRIVATE VARIANTS IN PAPUA NEW GUINEA

SERIAL NO.	ENZYME	PRIVATE VARIANT	TOTAL POPULATION		KARKAR ISLAND		MANUS ISLAND		SIASSI ISLAND	
			NO. COPIES	% GENE FREQUENCY	NO. COPIES	% GENE FREQUENCY	NO. COPIES	% GENE FREQUENCY	NO. COPIES	% GENE FREQUENCY
1	Hbα*	*Hb J*$^{\text{Tongariki}}$	46	0.34	38	1.75	0	0.00	7	1.22
2	ESD	*ESD*^{3}	1	0.01	0	0.00	...	...	0	0.00
3	MDH_2	*MDH*$_2^{3}$	106	0.68	16	0.73	0	0.00	0	0.00
4	MDH_2	*MDH*$_2^{6}$	1	0.01	0	0.00	0	0.00	0	0.00
5	LDH_A	*LDH*$_A$$^{\text{Wantoat}}$	1	0.01	0	0.00	0	0.00	0	0.00
6	LDH_A	*LDH*$_A$$^{\text{WH}}$	9	0.06	0	0.00	0	0.00	0	0.00
7	LDH_B	*LDH*$_B$$^{\text{KK2}}$	1	0.01	1	0.05	0	0.00	0	0.00
8	LDH_B	*LDH*$_B$$^{\text{KK3}}$	1	0.01	1	0.05	0	0.00	0	0.00
9	GOT*	*GOT*^{3}	1	0.01	0	0.00	...	...	...	...
10	GPT*	*GPT*^{3}	8	0.08	0	0.00	...	...	0	0.00
11	GPT*	*GPT*^{6}	10	0.10	3	0.18	...	...	0	0.00
12	6PGD	*PGD*$^{\text{Wantoat}}$	38	0.24	3	0.14	0	0.00	0	0.00
13	6PGD	*PGD*$^{\text{Hackney}}$	1	0.01	0	0.00	0	0.00	0	0.00
14	PHI	*PHI*^{2}	1	0.01	0	0.00	0	0.00	1	0.23
15	PHI	*PHI*^{3}	1	0.01	0	0.00	0	0.00	0	0.00
16	PHI	*PHI*^{5}	4	0.03	0	0.00	0	0.00	0	0.00
17	PHI	*PHI*^{9}	2	0.02	0	0.00	0	0.00	0	0.00
18	PHI	*PHI*^{11}	1	0.01	0	0.00	0	0.00	0	0.00
19	PGK	*PGK*^{2}	18	0.12	0	0.00	0	0.00	11	2.12
20	PGK	*PGK*^{4}	62	0.40	5	0.23	0	0.00	3	0.58
21	PGM_1	PGM_1^{3}	254	1.63	17	0.78	0	0.00	1	0.18
22	PGM_1	*PGM*$_1^{6}$	3	0.02	0	0.00	0	0.00	0	0.00
23	PEPB	*PEPB*^{2}	1	0.01	0	0.00	0	0.00	0	0.00
24	PGM_2	*PGM*$_2^{3}$	1	0.01	0	0.00	0	0.00	1	0.18
25	PGM_2	*PGM*$_2^{9}$	903	5.80	166	7.64	0	0.00	10	1.77
26	PGM_2	*PGM*$_2^{10}$	112	0.72	4	0.18	0	0.00	3	0.53

* Widely distributed in Western Pacific region.

introduction of these variants to Papua New Guinea through admixture, therefore, cannot be excluded. Thus, we have 22 alleles at 21 loci that can be regarded as indigenous to Papua New Guinea.

On Karkar Island we detected 10 of the 26 allelic variants listed in table 2 over a set of 18 enzyme loci. Only two of these, namely, LDH_B^{KK2} and LDH_B^{KK3}, are unique to Karkar and are represented by single copies only. Seven of the other eight variants are mainland markers also; the only exception is $Hb\ J^{Tongariki}$, polymorphic on Karkar but rare on the mainland. This last allele also has wide distribution in other parts of Melanesia.

We did not find any private variant at 14 red cell enzyme loci tested on Manus. The absence of Southwest Pacific genetic markers, such as PGM_1^3, PGM_1^7, PGM_2^9, PGM_2^{10}, PGK^2, PGK^4, and $Hb\ J^{Tongariki}$, makes this population unique in the Western Pacific area.

For a set of 17 loci, we came across two unique variants on Siassi Islands, namely, PHI^2 and PGM_2^3, with a single copy each. The population of Siassi Islands, however, has a fair proportion of markers distributed in the Western Pacific region. Except for a very low frequency of PGM_1^3, four other variants, namely, PGK^2, PGK^4, PGM_2^{10}, and $Hb\ J^{Tongariki}$, are in polymorphic proportions on these islands.

ESTIMATION OF I, I_q, AND $\hat{I}$

Three different estimates for the mean number of variants/locus were calculated as given by Kimura and Ohta [15], Nei [4], and Rothman and Adams [16]. For the 21 loci in the present study, we have detected 22 unique (20 rare and two polymorphic) variants that give values of I, I_q, and $\hat{I}$ as 1.05, 0.95, and 1.78, respectively. The two parameters of geometric distribution involved in the estimation of $\hat{I}$, namely, b and c ($\hat{b} = 0.5567$; $\hat{c} = 0.3865$) [16], have been estimated from the data for Kiunga in the Western Province given by Serjeantson [17].

Considering the islands separately, the estimates of I, I_q, and $\hat{I}$ are 0.11, 0.11, and 0.46, respectively, for Karkar Island. The respective values for Siassi Islands are 0.12, 0.12, and 0.86, and for Manus Island, zero for each estimate. The parameters of geometric distribution, b and c, used in the estimation of transition probabilities for both Karkar and Siassi populations ($\hat{b} = 0.2711$; $\hat{c} = 0.7126$) were calculated from the data on Karkar Island by Hornabrook [18].

Since the calculation of I depends a priori on the observed distribution of copies of rare alleles, $\tilde{g}(i)$, and the ratio (f) of sample (n) to effective population size (N_e), these estimates are inflated by 4.09 and 8.57 times on Karkar and Siassi, respectively, when compared with the observed value of I. This increase, when compared with a less than twofold increase for a similar estimate for the total sample, is highly inflated. It would seem that estimations of $\hat{I}$ by Rothman and Adams's [16] method gives reliable results only with large absolute sample sizes.

ESTIMATION OF N_e

In the absence of historical records, it is difficult to estimate accurately the average effective population size (N_e) of linguistic groups in Papua New Guinea. However, since the estimates of mutation rate are highly dependent on the estimate

of N_e, we discuss this in some detail. The Papua New Guinea Bureau of Statistics census of 1971 reported a total population of 2,435,409 indigenous persons, of whom 41.6% were in the reproductive age group of 15–44 years, with a similar proportion (41.5%) married at least once. With a minimum of 700 documented language groups [7], the maximum estimate of language group effective size is 1,447.

This maximum value of N_e may be considered a gross overestimate of population size during past generations. Van de Kaa [19] considers that the Papua New Guinean population was stable between 1890 and 1939, partly because there is no evidence to suggest otherwise, but mainly because analysis of the few surveys undertaken at that time show little demographic change. In our calculations, we assume that actual population size during the last 5–10 generations more closely approximates the census figures of 1939 and that the population of 1939 was very close to 50% of that enumerated in 1971.

In Papua New Guinea, estimates of N_e of language groups also require correction for the extreme variability in language group size. Linguistic groups may comprise fewer than 100 persons, as in Gorovu in the Ramu phylum [20], or more than 150,000 persons, as in Enga in the Western Highlands [21]. By far, the majority of language groups have fewer than 5,000 speakers. Since the average value of N_e more closely approximates the harmonic than the simple mean of language group size, we have analyzed the three main linguistic phyla represented in the Madang Province to estimate the ratios of the harmonic means ($\overline{H}$) to simple means ($\overline{N}$). For the Adelbert Range phylum, $\overline{H}/\overline{N}$ is 35%; for the Ramu phylum, 33%; and for the Madang phylum, 40%. The combined value for 80 languages is 36%.

Therefore, for estimation of the mean number of speakers per language, we take 50% of 2,435,409 as the total population prior to 1939, distributed among 700 languages of varying sizes, with an average of 1,740 speakers. Since the harmonic mean of language group size is 36% of the simple mean, the more appropriate estimate is 626 speakers per language when correction is made for variability in language group size.

The effective population size is further modified by the proportion in the reproductive age group, variability in fertility, and deviation of the sex ratio from 1:1. The adult sex ratio was less than unity in the 1971 census and greater than unity in the previous census of 1966 [22]; so we shall assume the sex ratio in the reproductive age group fluctuates around 1:1. The proportion in the reproductive age group is more difficult to estimate accurately. In 1971, 41.6% of the population was aged between 15 and 44 years, compared with 45.0% in 1966 [22], and Serjeantson [23] recorded that 49% of the population of two relatively unacculturated Papua New Guinean language groups was aged between 16 and 45 years. We believe that the proportion in the reproductive age group in past generations was closer to 49%, the estimate we used in our calculations, than to the 42% currently observed.

Variation in fertility will modify N_e if the index of variability ($V/\bar{k}$) deviates from unity [24], $\bar{k}$ and V being the mean number and variance of surviving offspring, respectively. In Papua New Guinea, the index of variability is inflated by factors such as polygyny, which was reported by 9% of married males as recently as 1971 [22]. Serjeantson [23] estimated the index of variability as 1.22 in males from the

Yonggom group with 10% polygyny, and 2.09 in males from an additional group (Awin) with 28% polygyny. The corresponding values in females were 0.96 and 1.40 in a population with such comparatively low fertility [17] that it may well reflect the demographic structure of most Papua New Guinean groups prior to 1939.

With an average index of variability of 1.4 and 49% of the population in the reproductive age group, the ratio of $N_e v/N_e$ is 83.7%. The average effective size of language groups in Papua New Guinea is estimated as 49% of 626, or 307 persons, and this is the value used in estimating the mean survival time for fresh mutations in Papua New Guinean language groups. In general, it is the language groups with a relatively large number of speakers that have been sampled, so that the average effective size of language groups with genetic data available exceeds slightly the average size of language groups in Papua New Guinea as a whole. Making similar adjustments as above for rapid population expansion in the last generation, for variation in language sizes, and for the proportion in the reproductive age group, the total effective population size for the 55 languages in this series is 34,450. We use this value in all our calculations.

The sizes of the three island populations (Karkar, Manus, and Siassi) stood at 9,110, 13,839, and 4,715, respectively, in 1937–1939 [19], with 50.3%, 62.7%, and 59.5% in the adult age group. After adjusting for the proportion in the reproductive age group, polygyny and sex ratio values of N_e are 3,735, 6,805, and 2,310 for Karkar, Manus, and Siassi, respectively.

ESTIMATION OF $\bar{t}_o$

The mean survival time for fresh mutations that will ultimately be lost from the population ($\bar{t}_o$) was given by Kimura and Ohta [15] and Nei [25]. This value is estimated for a Papua New Guinean language group as: $\bar{t}_o = 2 N_e v/N_e \ln (2N_e) = 2 \times (0.837) \ln (2 \times 307) = 10.74$ generations, which is different from the estimate given by Li and Neel [26] of 5.71 from simulation studies of Amerindian populations. The estimates for Karkar and Siassi were calculated to be 14.92 and 14.12 generations, respectively. We have used these estimates for generating mutation rates by Kimura and Ohta's method.

ESTIMATION OF MUTATION RATES

The estimation of mutation rates has been carried out using three indirect methods as mentioned above. Table 3 shows these estimates for the total Papua New Guinean population. The three estimates of μ by the methods of Kimura and Ohta [15], Nei [4], and Rothman and Adams [16] are 1.42×10^{-6}, 1.40×10^{-6}, and 5.58×10^{-6}/locus per generation, respectively. These estimates range from approximately 23% to 50% of similar estimates obtained for the Australian Aborigines by Bhatia et al. [1].

Neel and Rothman [3] have used the estimate for $\hat{I}$ for the average number of mutant variants per locus in the formulation of Kimura and Ohta [15], instead of the observed value of I. A similar adjustment for differences between sample size (n) and effective population size (N_e) may be made in Nei's formulation, as:

$$\mu = \frac{\hat{I}q}{4N_e \ln (2N_e q)},$$

given that

$$\hat{I}_q = \frac{I_q}{1 - \Sigma g(j)(1-f)^j},$$

where $q = .01$, $f = n/N_e$, j is the number of copies, and $\tilde{g}(j)$ is the observed proportion of variants with j copies in the frequency distribution of rare variants (frequency less than .01) only. These modifications yield the new estimates as $\mu = 2.36 \times 10^{-6}$ and 2.38×10^{-6}/locus per generation for Kimura and Ohta's [15] and Nei's [4] methods, respectively.

The estimates of mutation rate for island populations show a wide range. The value of μ on Manus for a set of 14 protein loci is zero. The estimates of μ for Karkar and Siassi are given in table 3. Estimating the total number of variants in the populations with limited observations is highly unreliable, as is seen from the results for mutation rates in these populations by Rothman and Adams's [16] method. The estimates of μ obtained by the methods of Kimura and Ohta [15] and Nei [4] on these islands are, however, comparable to similar estimates generated for the Waljbiri tribe in Australian Aborigines [1].

DISCUSSION

The estimates of mutation rates as obtained from a set of protein loci are affected seriously by a number of factors. Probably the most controversial aspect of these indirect estimates is the estimation of effective population size (N_e). This is particularly difficult in the Papua New Guinean communities that have recently been undergoing tremendous demographic changes. The impact of recent population expansion can be judged from the high proportion of private polymorphisms with limited geographical distributions. Out of 26 variants detected, as many as 10 have attained polymorphic proportions in various Papua New Guinean communities, six of them in the highlands, one on both Karkar and Siassi, and three in both highland and coastal communities.

The role of sample size and subunit size in affecting the detection and introduction of rare variants has been stressed by a number of authors; for example, Nei et al. [27] and Bhatia [28]. In the present study, the mean sample sizes for loci with and

TABLE 3

MUTATION RATES IN PAPUA NEW GUINEA

POPULATION	$\mu \times 10^6$		
	Kimura and Ohta's method	Nei's method	Rothman and Adams's method
Total	1.42	1.40	5.58
Karkar Island	0.98	2.57	26.40
Manus Island	0.00	0.00	0.00
Siassi Islands	1.84	7.58	94.56

without variants are 7,226 and 4,955, respectively. This difference emphasizes the need for a sample size of at least 3,000, as suggested by Eanes and Koehn [29], before any attempts are made to generate mutation rates. Similarly, the mean subunit size for loci with these variants is 46,300 daltons compared with 28,180 for the invariant loci. It is thus important to make comparisons of mutation rates only among populations with similar mean sample sizes and mean subunit sizes.

The effect of sample size on the mean number of rare variants per locus may be seen in a comparison of the data on Papua New Guinean communities with the data on the Australian Aborigines. While there is similarity with respect to protein loci included in the two studies (mean molecular weights of the subunits are 36,869 and 37,560 daltons for Papua New Guineans and Australian Aborigines, respectively), the differences in the mean per locus sample sizes of 6,036 in the Papua New Guineans and 2,607 in the Australian Aborigines are reflected in the respective estimates of 1.05 and 0.64 for I.

However, the mean number of rare variants/locus per individual (I/n) is higher in Australian Aborigines (2.46×10^{-4}) in comparison with Papua New Guinean communities (1.74×10^{-4}). Since the mean number of electromorphs recovered is a logarithmic function of sample size and the distribution of electromorphs is skewed further with sample size increase, it will be appropriate to compute the mean number of rare variants/locus per individual only in terms of effective population size (N_e), rather than in terms of sample size (n). The two estimates for Australian Aborigines and Papua New Guineans then become 6.99×10^{-5} and 3.05×10^{-5}, respectively, a difference of 2.29 times.

Nei and Chakraborty [30] have shown that the mean number of silent alleles, undetectable by electrophoresis, that contribute to an electromorph is higher in populations with large $N_e\mu$'s than in populations in which this is small. On the basis of this argument, the proportion of mean numbers of silent alleles is likely to be much higher in Papua New Guinean communities than in Australian Aborigines. Since the mean number of rare variants/locus (I) reflects the incidence of mutation rate in a population, the ratio of N_eI in these two populations, when adjusted for sample sizes, yields a value of 2.66 times more silent alleles in Papua New Guineans than Australian Aborigines. The results at electromorph level (notwithstanding the differences in mutation rate at codon level between the two populations) are almost negligible.

Because of these various factors that may affect the mean number of rare variants per locus, the indirect estimates of mutation rate will show similar variations. It is not surprising, therefore, that estimates of μ generated from protein data for Papua New Guinea differ about twofold from estimates generated on a similar scale for Amerindians by Neel and Rothman [3] and for Australian Aborigines by Bhatia et al. [1]. The estimate of μ for a group of tribes in India, however, is lower by more than an order of magnitude compared with these estimates. This may be because of a recent population increase in India and differences in sample size, in the number of loci studied, and in technical methods employed in blood collection, none of which have been taken into consideration by Chakraborty and Roychoudhury [6].

The estimates of Nei's μ for individual populations in South America (Neel and Rothman [3] and Tchen et al. [5]), in India (Chakraborty and Roychoudhury [6]), in Australia (Bhatia et al. [1]), and in Papua New Guinea (present study), however, show a wide variation with a mean estimate of 1.19×10^{-5}/locus per generation. The differences range from $0 - 9.28 \times 10^{-5}$, with a more or less equal number of populations with estimates of the order of 10^{-7}, 10^{-6}, and 10^{-5}. Our results for Karkar, Manus, and Siassi are at the lower end of this distribution, which conforms with the lower estimate found for Papua New Guinean populations treated as a whole.

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