

RESEARCH REPORT

Malaria and Immunoglobulins in Pacific Prehistory

KEVIN M. KELLY¹

*Department of Anthropology
and Department of Environmental and Occupational Health
College of Public Health
University of Iowa
Iowa City, IA 52242*

The role of malaria in Pacific prehistory has been the subject of considerable study and supposition. In this manuscript, I attempt to clarify the research and reasoning that has led me to suggest that the Austronesian-speaking peoples had a selective advantage in malarious environments. In particular, I hope to dispel any notion that that advantage was due to resistance to malaria and to re-affirm my actual assertion that the genetic basis for the Austronesian advantage was resistance to developing the hyperimmune disease, hyperreactive malarious splenomegaly. I believe that an appreciation of this distinction will ultimately prove to be essential to understanding the role of malaria in facilitating the spread of the Austronesians—in the form of people, languages, and/or genes—throughout the Pacific. [*Pacific prehistory, malaria, natural selection, Austronesians, immunoglobulins*]

Malaria and its possible effects on Pacific prehistory have long fascinated scholars (e.g., Dempwolff 1937; Parsonson 1968). In 1993, Jeff Clark and I (Clark and Kelly 1993) presented our interpretation of the archaeological record based on the distribution of gamma-immunoglobulin [Gm] polymorphisms and an understanding of malaria's effects on the region's various inhabitants. Recently, statements in several prominent publications have indicated subtle, yet significant, misunderstandings of that thesis. Martinson (1996:186), for example, has dismissed the assertion that certain Gm alleles provided Austronesian-speaking peo-

ples with advantage in malarious environments in view of the fact "that the oldest inhabitants of Melanesia were perfectly capable of generating their own *resistance to malaria*" (emphasis added). In a similar interpretation, Kirch (1997:112) has reported our thesis to be that "the Austronesian-speaking populations who moved into Near Oceania . . . carried in their genes their own *malarial resistance*" (emphasis added). However, the most prejudicial synopsis has been presented by Serjeantson and Gao (1995) who appear to have first cast the discussion in the terms of "malaria-resistance versus malaria-susceptible" populations. In fact, Spriggs (1997:104) has suggested that "Serjeantson and Gao (1995:166-168) have disputed Clark and Kelly's *central hypothesis* and argued for a degree of *immunity to malaria* acquired by the pre-Lapita populations of lowland Melanesia" (emphasis added).

My views on malaria's effects in the Pacific are laid out in various sources (Clark and Kelly 1993; Kelly 1988a, 1988b, 1990, 1992, 1996). In these works, I have argued that certain Gm alleles gave the Austronesian-speaking populations a genetic advantage in malarious areas (e.g., Clark and Kelly 1993; Kelly 1990). However, it should be noted that resistance to malaria has never been advanced as the mechanism.

To many, this distinction might appear trifling. A genetic advantage to a disease often does mean genetic resistance, and, admittedly, several of my statements certainly could be read to imply this might be the case. However, such interpretations are not necessarily expected (cf., Howells 1997:767-768). Moreover, the distinction is real and the implications are substantive.

On the "Austronesian" Advantage

One essential element of any inference about who in Pacific prehistory would have benefited from the presence of malaria is an understanding of how malaria affects the region's current inhabitants. Since its conception (i.e., Kelly 1988a, 1988b) my hypothesis of an "Austronesian" advantage in malarious environments has derived from two lines of evidence:

1. the linguistically and environmentally related patterns of variations in the distributions of the Gm polymorphisms and
2. the evident predisposition of non-Austronesian peoples to suffer the deadly consequences of hyperreactive malarious splenomegaly.

The Gm polymorphisms are highly variable, genetically determined factors (allotypes) specific to the heavy chains of the human immunoglobulin G (IgG) subclasses—integral components of the body's humoral immune response to disease. Allotypes are genetic variants of immunoglobulins present in some, but not in all, normal individuals. Allotypes are identified by an alphanumeric system (e.g., A, F, B0, G1) in combination with a notation of the specific IgG heavy (IGH) chain subclass (e.g., G1, G3) on which the allotype is found. These polymorphisms are inherited as Mendelian autosomal codominant traits in arrays of allotypes that are called haplotypes. For example, an "A" allotype linked to a "G1" allotype would be reported as *IGHG1 A IGHG3 G1*.

Looking beyond this somewhat burdensome nomenclature, one need simply understand the Gm allotypes as somewhat akin to alleles that are inherited as a group, the haplotypes. These allelic variants are amino acid sequence differences in the structures of various regions of the IgG molecules subclasses. These sequential differences produce structural and antigenic modifications of the immunoglobulin molecule. These differences, in turn, are associated with differential responses to infection as well as differential susceptibility to various autoimmune diseases.

The argument of the linguistically and environmentally related patterns of variations in the distributions of the Gm polymorphisms (Kelly 1988a, 1988b, 1990) rests on two findings:

1. analysis of the Gm haplotypes that confirmed that Austronesian-speaking populations are characterized by high frequencies of the *IGHG1 A, F IGHG3 B* haplotype and
2. correlations involving the Gm polymorphisms that demonstrated that the frequencies of the alleles of the IgG3 subclass (the G3m locus) were highly correlated with the endemicity of malaria.

Based on these observations, I concluded that the Gm distributions were most plausibly explained by natural selec-

tion consistent with separate origins of AN- and NAN-speaking peoples.

The disease thought to have produced this genetic distribution was hyperreactive malarious splenomegaly (cf. Kelly 1988a, 1992, 1996). Remarkably, Serjeantson and Gao find support for their assertion that pre-Austronesian (i.e., Non-Austronesian-speaking) populations were well adapted to malaria in "the finding that in New Guinea, *hyperreactive malarious splenomegaly* is confined to the Watut people, resident at an altitude of about 1000 m where malarial transmission is intermittent" (Serjeantson and Gao 1995:166-167, emphasis added).

Hyperreactive malarious splenomegaly (HMS) is an affliction that develops among certain peoples chronically exposed to malaria, most notably non-Austronesian-speaking peoples such as the Watut (cf., Clark and Kelly 1993: 617; Kelly 1988b, 1996). However, HMS does not occur only in areas of intermittent transmission (Crane 1979, 1986; Kelly 1996). Nor is it "confined to the Watut" (cf., Crane 1979, 1986; Kelly 1996). Moreover, HMS cannot be seen, as Serjeantson and Gao (1995) suggest, as evidence of the failure to acquire immunity (cf., Crane 1979: 246). In fact, since HMS is a hyperimmune response, one could argue that those afflicted with HMS have greater resistance to malaria (Crane 1986). Unfortunately, the cost of this resistance is very high. Follow-ups of small groups of patients with HMS in Papua New Guinea (Crane et al. 1972) revealed a 50% mortality rate. In a more comprehensive study in the Upper Watut Valley of Papua New Guinea, Crane (1986) reported a 63% mortality rate among 148 patients followed for 12.9 to 16.0 years (mean = 14.2 years), with over 50% of these deaths occurring before the age of 30.

As Crane (1986) has noted, HMS is either extremely rare or very common among the populations of Papua New Guinea, suggesting that "any given group is either highly susceptible or relatively resistant to the development of the syndrome." I have noted that the "HMS-resistant" groups are Austronesian-speaking as well as lowland Non-Austronesian-speaking populations characterized by high frequencies of specific Gm haplotypes (i.e., *IGHG1 A, F IGHG3 B* and *IGHG1 A, Z IGHG3 B*) (cf., Kelly 1996). On the other hand, the "HMS-susceptible" groups of Papua New Guinea are Non-Austronesian-speaking populations either known to be, or known to be derived from, populations characterized by high frequencies of *IGHG1 A, Z IGHG3 G* and *IGHG1 A, X, Z IGHG3 G* (cf., Kelly 1996).

In New Guinea, Gm haplotypes (the linked sets of allotypes) that produce G3m (B) antigens (i.e., *IGHG1 A, F IGHG3 B* and *IGHG1 A, Z IGHG3 B*) occurred at significantly higher frequencies in areas with malaria. G3m B phenotypes are favored, not because of the protection they provide against malaria, but rather because the allelic alternative, G3m G, predisposes an individual to develop HMS. In other words, the genetic basis for the "Austronesian"

advantage in malarious environments is “resistance” to developing HMS. While one cannot exclude the possibility that *IGHG3 G* is a marker of the critical pathogenetic factor causing HMS, the most parsimonious explanation for the available data is that the expression of the G3m G phenotype is a necessary precondition for the development of HMS (cf. Kelly 1996).

Conclusions

What does this discussion of immunoglobulins, malaria, and splenomegaly tell us about the settlement of the Pacific? As the study of Pacific prehistory continues to involve an expanding circle of disciplines and varieties of scholarship, I hope this discussion might caution all of us to be a bit more circumspect of what we read and of what we write. In that regard, I believe that a clear understanding of prehistory will only be derived from the coordinated efforts of scholars in the various disciplines. Returning to the current issue, I hope it is now evident that understanding the effects of malaria in the Pacific has never been as simple as knowing who was and who was not genetically resistant to malaria. For, although malaria-resistant genetic variants—most notably, $-\alpha^{*3.7}$ III thalassaemia (Hill et al. 1989)—are found among populations of Near as well as Remote Oceania, the origins of these variants are largely indeterminate and, I believe, ultimately irrelevant. This is because none of the extant inhabitants of Near Oceania are genetically well adapted to malaria—for, unfortunately, none of the known genetic adaptations to malaria make malaria a well-tolerated disease. As a practical matter, malaria is a potential problem for every human. The truth is that even natural immunity to malaria comes at a heavy price—high infant and child mortality.

HMS, on the other hand, is a different matter. Unfortunately, it is not possible to date the precise arrival of malaria into Near Oceania. Nevertheless, the HMS-related mortality experienced by the Watut suggests that the transition to endemic malaria was essential to the spread of the “Austronesians”—in the form of people, languages, and/or genes—throughout the Pacific.

Notes

Acknowledgments. I wish to thank John Terrell, Jeff Clark, Richard Nisbett, and Cheryl Mills Kelly as well as four anonymous reviewers for their comments on various versions of the manuscript. Their comments were thoughtful and constructive. Any errors, omissions, and opinions are mine alone.

1. Address correspondence to: Kevin M. Kelly, Ph.D., Institute for Rural and Environmental Health, Oakdale Campus; 178 IREH, University of Iowa; Iowa City, Iowa 52242.

References Cited

- Clark, Jeffery T., and Kevin M. Kelly
1993 Human Genetics, Paleoenvironments, and Malaria: Relationships and Implications for the Settlement of Oceania. *American Anthropologist* 95:613–631.
- Crane, Greg. G.
1979 The Serology of Tropical Splenomegaly Syndrome and Its Relationship to Malaria. In *Role of the Spleen in the Immunology of Parasitic Diseases. Special Programme for Research and Training in Tropical Diseases*. Pp. 245–258. Basel: Schabe and Co.
1986 Recent Studies of Hyperreactive Malarious Splenomegaly (Tropical Splenomegaly Syndrome) in Papua New Guinea. *Papua New Guinea Medical Journal* 29:35–40.
- Crane, G., J. V. Wells, and P. Hudson
1972 Tropical Splenomegaly Syndrome in New Guinea I: Natural History. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 66:473–478.
- Dempwolff, O.
1937 Vergleichende Lautlehre des Austroneischen Wortschatzes, Band 3: Austronesisches Wortverzeichnis. Beihefte zur Zeitschrift für Eingeborenen-Sprachen 15. Berlin: Dietrich Reimer.
- Hill, A. V. S., D. F. O’Shaughnessy, and J. B. Clegg
1989 Haemoglobin and Globin Gene Variants in the Pacific. In *The Colonization of the Pacific: A Genetic Trail*. A. V. S. Hill and S. W. Serjeantson, eds. Pp. 246–285. Oxford: Clarendon Press.
- Howells, William W.
1997 Oceania. In *History of Physical Anthropology*. Vol. 2, M-Z. Frank Spencer, ed. Pp. 762–775. New York: Garland Publishing, Inc.
- Kelly, Kevin M.
1988a Selection and the Gm-Hypothesis (abstract). *American Journal of Physical Anthropology* 75:231.
1988b The Biological Significance of the Melanesian Gm Distribution: Selection and the Gm-hypothesis. Ph.D. dissertation, University of Illinois–Urbana.
1990 Gm Polymorphisms, Linguistic Affinities, and Natural Selection in Melanesia. *Current Anthropology* 31:201–219.
1992 On the Genetic Basis of Hyperreactive Malarious Splenomegaly and the Selection of G3m Alleles (abstract). *American Journal of Physical Anthropology* S14:98.
1996 IGHG3 G and the Pathogenesis of Hyperreactive Malarious Splenomegaly. *Medical Hypotheses* 46:135–139.
- Kirch, Patrick Vinton
1997 *The Lapita Peoples: Ancestors of the Oceanic World*. Cambridge: Blackwell Publishers.
- Martinson, J. J.
1996 Molecular Perspectives on the Colonization of the Pacific. In *Molecular Biology and Human Diversity, Society for the Study of Human Biology Symposium 38A*. J. Boyce and C. G. N. Mascie-Taylor, eds. Pp. 171–195. Cambridge: Cambridge University Press.
- Parsonson, G. S.
1968 The Problem of Melanesia. *Mankind* 6:571–584.
- Serjeantson, S. W., and X. Gao
1995 Homo Sapiens as an Evolving Species: Origins of the Austronesians. In *The Austronesians: Historical and Com-*

parative Perspectives. P. Bellwood, J. J. Fox, and D. Tyron, eds. Pp. 165–180. Canberra: Department of Anthropology, The Australian National University.

Spriggs, M.

1997 *The Island Melanesians*. Cambridge: Blackwell Publishers.