Dear Editor,

Human platelet antigens (HPAs) are genetically inherited polymorphic glycoproteins expressed on the platelet membrane [1]. HPAs are transfusion and gestation compatibility determinants, and HPA alloantibodies have been reported in post-transfusion purpura, platelet transfusion refractoriness, and neonatal alloimmune thrombocytopenia (NAIT) cases [2].

Previously, we reported HPA allele frequency data for Malay subethnic groups [3] and Orang Asli [4] in Peninsular Malaysia. These earlier studies have provided a valuable preliminary source of genetic information for health assessments and population genetics. However, a complete picture of the genetic structure in Peninsular Malaysia should also include data from Malays (i.e., Deutero-Malays), Chinese, and Indians, as they represent >75% of the total population [5]. There are some HPA data for Malays, Chinese, and Indians reported by Tan, et al. [6]; the present HPA data can be compared with those data.

We typed HPA-1 to -6 and HPA-15 loci in blood samples obtained with informed consent from a total of 222 individuals registered as voluntary, non-remunerated blood donors at the Hospital Universiti Sains Malaysia (Kelantan), Hospital Seberang Jaya (Pulau Pinang), and Temerloh Hospital (Pahang) in Malaysia. The individuals were un-admixed with no history of intermarriage with other ethnic groups for three generations. The ethnicity classes of these samples were assigned as Malay (N=97), Chinese (N=77), and Indian (N=48) based on individual pedigree information. Our proposed study was reviewed and approved by the Human Ethical Committee, Universiti Sains Malaysia, Malaysia, and the Medical Research and Ethics Committee, Ministry of Health, Malaysia. The HPA typing and data analysis were performed as previously described by Wan Syafawati, et al. [3] and Syafawati et al. [4]. Briefly, isolated genomic DNA was amplified using polymerase chain reaction and sequence-specific primers (PCR-SSP) for HPA-1 to -6 and -15. Amplified products were then separated using agarose gel electrophoresis (2% agarose gels stained with ethidium bromide) and visualised using a UV photometer (Quantum ST4-1000/20M, VilberLourmat, Deutschland GmbH, Eberhardzell, Germany). The separated band patterns (amplified allele-specific HPA products and human growth hormone) were then compared with a 100 base pair DNA size standard (Bioline, London, UK). HPA allele frequencies were determined by dividing the allele count numbers...
by the total numbers of chromosomes (2n) tested. Genetic differ-
entiations between pairs of HPA population datasets were eval-
uated using Arlequin version 3.0 software [7] and were consid-
ered statistically significant at $P < 0.05$.

The present and previously reported HPA datasets of various
population groups in Peninsular Malaysia are shown in Table 1
[3, 4, 6]. These HPA datasets reveal that Malays and Chinese
differ significantly ($P < 0.05$) from Indians (Table 2). However,
no significant differences were observed between the HPA data-
sets of Malays and Chinese. Importantly, Malays, Chinese, and
Indians are the modern-day descendants of ancestrally unre-
lated ethnic groups in Peninsular Malaysia; the inability of the
HPA datasets to differentiate between Malays and Chinese needs
to be resolved using more informative genetic markers, includ-
ing genome-wide single nucleotide polymorphisms and whole
genome sequencing data [8]. In addition, some of the ancestral
relationships might also be obscured by demographic processes
such as natural selection and founder effects. Of these forces,
natural selection is expected to have a greater effect on genes
that are important in the medical field such as HPA, compared
with other regions in the human genome [11]. For example, some
differences observed between ancestrally related Proto-Malays
(Orang Kanaq), Malay subethnic groups, and Malays could pos-
sibly be attributed to gene flow via admixture and historical events
at the population level (as mentioned earlier), rather than differ-
ent origins (Table 2) [8].

In our view, HPA datasets for various population groups in Pen-
insular Malaysia (Tables 1 and 2) also have significant value for
health and have been identified as genetic risk factors for many
diseases [9]. The risk of HPA alloimmunization in Peninsular
Malaysia might be expected to be most frequently associated
with alloantibodies against HPA-3 and HPA-15 products, as
these are the most polymorphic loci observed within and be-
tween population groups in Peninsular Malaysia (Tables 1 and
2). Our hypothesis regarding HPA alloimmunization risk is sup-
ported by the presence of HPA-1a, -3a, -5a, and -15b alloanti-
bodies in most of the NAIT cases and multi-transfused throm-
bocytopenia patients in Malaysia [10]. Therefore, implementa-
tion of HPA typing could reduce the incidence of HPA alloim-
munization cases in Malaysia.

In conclusion, to the best of our knowledge, our study is the
first complete representative collection of HPA datasets for all
population groups in Peninsular Malaysia. These datasets can
be used for developing better healthcare services and as a ref-
ence standard for identifying genetic risk factors for many dis-
ases associated with HPAs.

Table 1. HPA allele frequency distribution in the present and previous studies

| Population          | (N) | 1a  | 1b  | 2a  | 2b  | 3a  | 3b  | 4a  | 4b  | 5a  | 5b  | 6a  | 6b  | 15a | 15b |
|---------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Malays (present study) | 97  | 0.985 | 0.015 | 0.969 | 0.031 | 0.510 | 0.490 | 1.000 | 0.000 | 0.990 | 0.010 | 0.990 | 0.010 | 0.479 | 0.521 |
| Chinese (present study) | 77  | 1.000 | 0.000 | 0.980 | 0.020 | 0.591 | 0.410 | 1.000 | 0.000 | 0.987 | 0.013 | 0.994 | 0.006 | 0.526 | 0.474 |
| Indians (present study) | 47  | 0.979 | 0.021 | 0.969 | 0.031 | 0.521 | 0.479 | 1.000 | 0.000 | 0.959 | 0.041 | 0.990 | 0.010 | 0.375 | 0.625 |
| Banjar [3] | 30  | 1.000 | 0.000 | 0.950 | 0.050 | 0.616 | 0.384 | 0.950 | 0.050 | 0.950 | 0.050 | 0.980 | 0.020 | 0.480 | 0.520 |
| Bugis [3] | 37  | 1.000 | 0.000 | 1.000 | 0.000 | 0.554 | 0.446 | 1.000 | 0.000 | 0.950 | 0.050 | 0.910 | 0.090 | 0.620 | 0.380 |
| Champa [3] | 51  | 0.980 | 0.020 | 0.970 | 0.030 | 0.677 | 0.323 | 1.000 | 0.000 | 0.990 | 0.010 | 0.980 | 0.090 | 0.480 | 0.520 |
| Jawa [3] | 39  | 1.000 | 0.000 | 1.000 | 0.000 | 0.628 | 0.372 | 1.000 | 0.000 | 0.960 | 0.040 | 1.000 | 0.000 | 0.450 | 0.550 |
| Kelantan [3] | 35  | 1.000 | 0.000 | 0.940 | 0.060 | 0.571 | 0.429 | 1.000 | 0.000 | 1.000 | 0.000 | 0.990 | 0.010 | 0.490 | 0.510 |
| Orang Kanaq [4] | 11  | 1.000 | 0.000 | 1.000 | 0.000 | 0.818 | 0.182 | 1.000 | 0.000 | 1.000 | 0.000 | 1.000 | 0.000 | 0.909 | 0.091 |
| Batek [4] | 27  | 1.000 | 0.000 | 1.000 | 0.000 | 0.500 | 0.500 | 1.000 | 0.000 | 0.852 | 0.148 | 1.000 | 0.000 | 0.000 | 1.000 |
| Lanoh [4] | 25  | 1.000 | 0.000 | 1.000 | 0.000 | 0.640 | 0.360 | 1.000 | 0.000 | 1.000 | 0.000 | 1.000 | 0.000 | 0.260 | 0.740 |
| Kensiu [4] | 36  | 0.958 | 0.042 | 1.000 | 0.000 | 0.875 | 0.125 | 1.000 | 0.000 | 0.847 | 0.153 | 1.000 | 0.000 | 0.361 | 0.639 |
| Che Wong [4] | 26  | 1.000 | 0.000 | 1.000 | 0.000 | 0.423 | 0.577 | 1.000 | 0.000 | 0.788 | 0.212 | 1.000 | 0.000 | 0.500 | 0.500 |
| Semai [4] | 40  | 0.988 | 0.012 | 1.000 | 0.000 | 0.671 | 0.329 | 1.000 | 0.000 | 0.890 | 0.110 | 1.000 | 0.000 | 0.524 | 0.476 |
| Malays [6] | 200 | 0.975 | 0.025 | 0.963 | 0.037 | 0.503 | 0.497 | 0.995 | 0.005 | 0.950 | 0.050 | 0.993 | 0.007 | 0.515 | 0.485 |
| Chinese [6] | 200 | 1.000 | 0.000 | 0.967 | 0.033 | 0.573 | 0.427 | 0.998 | 0.002 | 0.983 | 0.017 | 0.983 | 0.017 | 0.498 | 0.502 |
| Indians [6] | 200 | 0.885 | 0.115 | 0.960 | 0.040 | 0.620 | 0.380 | 0.995 | 0.005 | 0.940 | 0.060 | 0.995 | 0.005 | 0.408 | 0.592 |
### Table 2A. Homogeneity between pairs of population groups in Peninsular Malaysia

|            | HPA-1          | HPA-2          |
|------------|----------------|----------------|
|            | Malays†        | Chinese†       | Indians†       | Banjar [3] | Bugis [3] | Champa [3] | Jawa [3] | Kelantan [3] | O. K. [4] | Batek [4] | Lanoh [4] | Kensiu [4] | C. W. [4] | Semai [4] | Malays [6] | Chinese [6] | Indians [6] |
| Malays†    | *              | 0.257          | NA             | NA          | 0.558     | NA          | 0.557     | 0.568     | NA          | NA        | NA          | 0.340     | NA        | NA          | NA          | NA          | <0.000     |
| Chinese†   | 0.088          | *              | 0.145          | NA          | NA        | 0.158      | NA        | NA        | NA          | NA        | NA          | 0.332     | NA        | 0.344      | NA          | NA          | <0.000     |
| Indians†   | 1.000          | 0.294          | *              | 0.501      | 0.499     | 0.507      | NA        | 0.534     | 0.544      | 0.650     | 0.538      | NA        | NA        | NA          | 0.004       |
| Banjar [3] | 0.441          | 0.063          | 0.669          | *          | NA        | 0.530      | NA        | NA        | NA          | NA        | 0.241      | NA        | NA        | NA          | NA          | NA          | 0.003      |
| Bugis [3]  | 0.184          | 1.000          | 0.254          | 0.085      | *         | 0.508      | NA        | NA        | NA          | NA        | NA          | 0.114     | NA        | NA          | NA          | NA          | <0.000     |
| Champa [3] | 0.209          | 1.000          | 0.349          | 0.193      | 1.000     | 0.504      | 0.516     | NA        | 0.539      | 0.645     | 0.545      | NA        | NA        | NA          | <0.000      |
| Jawa [3]   | 0.183          | 1.000          | 0.249          | 0.076      | NA        | 1.000      | *         | NA        | NA          | NA        | 0.108      | NA        | NA        | NA          | NA          | NA          | 0.001      |
| Kelantan [3]| 0.453         | 0.034          | 0.450          | 1.000      | 0.052     | 0.160      | 0.046     | *         | NA          | NA        | 0.239      | NA        | NA        | NA          | NA          | NA          | <0.000     |
| O. K. [4]  | 1.000          | 1.000          | 1.000          | 0.551      | 1.000     | NA         | 0.557     | *         | NA          | NA        | NA          | NA        | NA        | NA          | NA          | NA          | 0.162      |
| Batek [4]  | 0.340          | 1.000          | 0.546          | 0.239      | NA        | 1.000      | NA        | 0.127     | *          | NA        | NA          | 0.252     | NA        | NA          | NA          | NA          | 0.004      |
| Lanoh [4]  | 0.343          | 1.000          | 0.545          | 0.241      | NA        | 1.000      | NA        | 0.135     | *          | NA        | NA          | 0.263     | NA        | NA          | NA          | NA          | 0.008      |
| Kensiu [4] | 0.190          | 1.000          | 0.255          | 0.088      | NA        | 1.000      | NA        | 0.052     | *          | NA        | NA          | NA        | NA        | NA          | NA          | NA          | 0.159      |
| C.W [4]    | 0.338          | 1.000          | 0.255          | 0.242      | NA        | 1.000      | NA        | 0.131     | *          | NA        | NA          | *         | NA        | NA          | NA          | NA          | 0.005      |
| Semai [4]  | 0.178          | 1.000          | 0.249          | 0.076      | NA        | 1.000      | NA        | 0.043     | *          | NA        | NA          | *         | NA        | NA          | NA          | NA          | 0.004      |
| Malays [6] | 0.812          | 0.035          | 1.000          | 0.713      | NA        | 0.079      | NA        | 0.498     | 0.623      | 0.223     | 0.386      | 0.139     | 0.230     | 0.086      | *          | NA          | <0.000     |
| Chinese [6]| 0.857          | 0.200          | 0.782          | 0.492      | 0.343     | 0.272      | 0.352     | 0.360     | 0.705      | 0.439     | 0.660      | 0.662     | 0.350     | 0.543      | 0.857       | *          | <0.000     |
| Indians [6]| 1.000          | 0.106          | 1.000          | 0.542      | 0.269     | 0.196      | 0.280     | 0.426     | 0.641      | 0.459     | 0.438      | 0.271     | 0.459     | 0.277      | 1.000       | 0.836      | *          |

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| HPA-4   | Malays [6] | Chinese [6] | Indians [6] | Banjar [3] | Bugis [3] | Champa [3] | Jawa [3] | Kelantan [3] | O. K. [4] | Batek [4] | Lanoh [4] | Kensiu [4] | C. W. [4] | Semai [4] | Malays [6] | Chinese [6] | Indians [6] |
|---------|------------|-------------|-------------|------------|----------|-----------|--------|------------|--------|----------|---------|-----------|---------|--------|------------|-------------|-------------|
|         |            |             |             |            |          |           |        |            |        |          |         |           |         |        |            |             |             |
|         | NA         | NA          | NA          | 0.025      | 0.025    | 0.001     | < 0.001| 0.002      | 0.002  | 0.002    | 0.016   | 0.003     | 0.008   | 0.008  | 0.002      | 0.002       | 0.002      |
| Malay   | 0.127      | 0.009       | 0.251      | 0.002      | 0.002    | 0.001     | 0.001  | 0.001      | 0.001  | 0.001    | 0.001   | 0.001     | 0.001   | 0.001  | 0.001      | 0.001       | 0.001      |
| Chinese | 0.368      | 0.036       | 0.784      | 0.036      | 0.036    | 0.008     | 0.008  | 0.008      | 0.008  | 0.008    | 0.008   | 0.008     | 0.008   | 0.008  | 0.008      | 0.008       | 0.008      |
| Indians | 0.368      | 0.036       | 0.784      | 0.036      | 0.036    | 0.008     | 0.008  | 0.008      | 0.008  | 0.008    | 0.008   | 0.008     | 0.008   | 0.008  | 0.008      | 0.008       | 0.008      |
Table 2C. Continued

|                | HPA-5       | HPA-6       |
|----------------|-------------|-------------|
| Malays[1]      | 0.722       | 0.602       |
| Chinese[1]     | 0.448       | 0.474       |
| Indians[1]     | 1.000       | <0.001      |
| Banjar[3]      | 1.000       | 0.428       |
| Bugis[3]       | 1.000       | 0.004       |
| Champa[3]      | 1.000       | 0.002       |
| Jawa[3]        | 1.000       | 0.002       |
| Kelantan[3]    | 1.000       | 0.002       |
| O. K.[4]       | 1.000       | 0.002       |
| Batek[4]       | 1.000       | 0.002       |
| Lanoh[4]       | 1.000       | 0.002       |
| Kensiu[4]      | 1.000       | 0.002       |
| C. W.[4]       | 1.000       | 0.002       |
| Semai[4]       | 1.000       | 0.002       |
| Malays[6]      | 0.722       | 0.602       |
| Chinese[6]     | 0.448       | 0.474       |
| Indians[6]     | 1.000       | <0.001      |

(Continued to the next page)
|                | HPA-15 |            |            |            |            |            |            |            |            |            |            |            |            |            |
|----------------|--------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
|                | Malays | Chinese | Indians | Banjar | Bugis | Champa | Jawa | Kelantan | O. K. | Batek | Lanoh | Kensi | C. W. | Semai | Malays | Chinese | Indians |
| Malays         | *      | 0.503    | 0.217     | 0.087   | 0.049   | 0.047    | 0.732    | *          | 0.007   | <0.001   | 0.019   | 0.144   | 0.013   | 0.255   | 0.687 | 0.904   | 0.176   |
| Chinese        | *      | *        | 0.033    | 0.022   | 0.065   | 0.127    | 0.521    | *          | 0.001   | <0.001   | 0.002   | 0.047   | 0.070   | 0.091   | 0.723 | 0.638   | 0.012   |
| Indians        | *      | *        | *        | *       | *       | 0.120    | 0.007    | 0.308     | 0.375   | <0.001   | 0.001   | 0.002   | 0.003   | 0.147   | 0.041 | 0.070   | 0.866   |
| Banjar [3]     | *      | *        | *        | *       | *       | 0.300    | 0.626    | *          | 0.046   | 0.862    | 0.013   | 0.001   | 0.020   | <0.001  | 0.794 | 0.050   | 0.049   | 0.109   |
| Bugis [3]      | *      | *        | *        | *       | *       | 0.260    | 0.031    | 0.116     | 0.080   | <0.001   | 0.002   | 0.003   | <0.001  | 0.475   | 0.077 | 0.045   | 0.004   |
| Champa [3]     | *      | *        | *        | *       | *       | *        | 0.247    | 0.227     | 0.002   | <0.001   | 0.001   | 0.063   | 0.082   | <0.001  | 0.862 | 0.240   | 0.257   | 0.340   |
| Jawa [3]       | *      | *        | *        | *       | *       | *        | 0.006    | <0.001    | <0.001  | 0.001    | 0.001   | 0.057   | 0.541   | 0.089   | 0.110 | 0.448   | 0.603   | 0.309   |
| Kelantan [3]   | *      | *        | *        | *       | *       | *        | *        | <0.001    | <0.001  | 0.013    | 0.031   | 0.003   | <0.001  | 0.428   | 0.002 | 0.603   | 0.011   |
| O. K. [4]      | *      | *        | *        | *       | *       | *        | *        | <0.001    | <0.001  | <0.001   | <0.001  | 0.001   | <0.001  | 0.001   | <0.001| 0.001   | <0.001  |
| Batek [4]      | *      | *        | *        | *       | *       | *        | *        | <0.001    | <0.001  | <0.001   | <0.001  | 0.001   | <0.001  | <0.001  | <0.001| 0.001   | <0.001  |
| Lanoh [4]      | *      | *        | *        | *       | *       | *        | *        | <0.001    | <0.001  | <0.001   | <0.001  | 0.001   | <0.001  | 0.002   | 0.003 | 0.183   | 0.183   |
| Kensi [4]      | *      | *        | *        | *       | *       | *        | *        | <0.001    | <0.001  | <0.001   | <0.001  | 0.001   | <0.001  | 0.001   | 0.001| 0.001   | 0.001   |
| C. W. [4]      | *      | *        | *        | *       | *       | *        | *        | <0.001    | <0.001  | <0.001   | <0.001  | 0.001   | <0.001  | 0.001   | 0.001| 0.001   | 0.001   |
| Semai [4]      | *      | *        | *        | *       | *       | *        | *        | <0.001    | <0.001  | <0.001   | <0.001  | 0.001   | <0.001  | 0.001   | 0.001| 0.001   | 0.001   |
| Malays [6]     | *      | *        | *        | *       | *       | *        | *        | <0.001    | <0.001  | <0.001   | <0.001  | 0.001   | <0.001  | 0.001   | 0.001| 0.001   | 0.001   |
| Chinese [6]    | *      | *        | *        | *       | *       | *        | *        | <0.001    | <0.001  | <0.001   | <0.001  | 0.001   | <0.001  | 0.001   | 0.001| 0.001   | 0.001   |
| Indians [6]    | *      | *        | *        | *       | *       | *        | *        | <0.001    | <0.001  | <0.001   | <0.001  | 0.001   | <0.001  | 0.001   | 0.001| 0.001   | 0.001   |

Pairs of HPA datasets are considered significantly different if their $P<0.05$ and are bold.

*Data from the present study; reference HPA datasets were obtained from Syafawati, et al. [3], Syafawati, et al. [4], and Tan, et al. [6].

Abbreviations: HPA, human platelet antigen; NA, not applicable; *, no value; O.K, Orang Kanaq; C.W, Che Wong.

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AUTHOR CONTRIBUTIONS

CGNH designed and performed the research, collected the data, analyzed the data, and wrote the manuscript; ZZ helped design the study, managed sample collection, and obtained our ethics permit from the Ministry of Health, Malaysia; NSMR and THTM helped with study design, sampling, and data collection; MNH, AMD, GEG, and GKC designed the study, advised on statistics, and edited the manuscript; and HAE designed and directed the study, advised on statistics, edited the manuscript, funded the research, managed the study, and obtained ethical approval from Human Ethics Committee, Universiti Sains Malaysia.

CONFLICTS OF INTEREST

No potential conflicts of interest relevant to this paper were reported.

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