Human platelet antigen 1, 2 and 5 gene polymorphisms in Egyptians and their potential association with susceptibility to immune thrombocytopenic purpura in Egyptian patients

Tayssir Kamel Eyada a, Dalia Gamil Amin a, Ihab Samih c and Salwa Mohamed Khedra d

a Clinical and Chemical Pathology, Faculty of Medicine, Cairo University, Cairo, Egypt; b Clinical and Chemical Pathology, The BMT Unit, Faculty of Medicine, Cairo University, Cairo, Egypt; c Department of Internal Medicine, Faculty of Medicine, Cairo University, Cairo, Egypt

ABSTRACT
Objectives: This study determined the incidence of HPA1, HPA2 and HPA5 polymorphisms in 120 Egyptian immune thrombocytopenic purpura (ITP) patients and 120 healthy Egyptian subjects.
Methods: Human platelet antigen (HPA) genotyping was done using the polymerase chain reaction-restriction fragment length polymorphism.
Results: The frequency of HPA1 allele a and b was 78.75 and 21.25% in controls, 80.8 and 19.2% in ITP, respectively. HPA2 allele a and b frequency was 86.25 and 13.75% in controls and of 74.6 and 25.4% in patients, respectively. HPA5 allele a and b frequency was 87.5 and 12.5% in controls, in patients it was 85 and 15%, respectively. With the exception of HPA2, no other significant difference was encountered in HPA allele frequency between controls and ITP patients.
Discussion: Egyptian HPA profile is closely linked to Middle East and neighboring Arabs. The current study noted that in all the studied HPA systems 1, 2 and 5, the ‘a’ allele is more prevalent than the b allele; the most frequent genotype was the homozygous a/a genotype. HPA2b frequency, homo- and hetero-zygous HPA2b genotype frequencies were significantly higher in ITP patients compared to controls.
Conclusion: HPA 2b are 2.37 times more likely to develop ITP compared to those without this allele. The relatively high allele frequency of the HPA-1b in the Egyptian population suggests that this ethnic group has a higher risk of alloimmunization.

Introduction
Immune thrombocytopenic purpura (ITP) is characterized by the production of autoantibodies targeting platelet membrane glycoproteins (GP) [1].

Diversity of human platelet antigens (HPA) is based on a single base pair substitution in the GP genes, HPAs assembled into six biallelic systems [2]. HPA are involved in neonatal alloimmune thrombocytopenia, post-transfusion purpura, platelet refractoriness, passive alloimmune thrombocytopenia, drug-induced and transplantation-associated thrombocytopenia [3].

A link between HPA allele polymorphisms and ITP was suggested [1]; however, studies in this regard are scarce. To date, the HPA polymorphisms were not assessed in context with ITP among Egyptians.

Consideration of the genetic amalgamation among Egyptians being centrally positioned to Africa, Europe and Asia together with the wide diversity of HPA genotypes in different ethnic groups such as Asian, European and North American inhabitants [4–6], has led us to design this study to determine the frequency of HPA polymorphisms (HPA-1, HPA-2 and HPA-5) in Egyptian ITP patients and in healthy Egyptian subjects, to assess the potential associations between HPA polymorphisms and the development of ITP and also to reflect the frequency of these HPA systems’ polymorphism among Egyptians.

Subjects and methods
This is a prospective, case control study of 120 Egyptian ITP patients and 120 age- and sex-matched healthy Egyptian subjects; as controls, informed consent was obtained from each participant/guardian. The study was approved by the ethics committee of Cairo University.

Detailed demographic, clinical and laboratory data of ITP patients are summarized in Table 1. Among the studied controls, the age ranged from 4 to 67 with a median age of 29.0 years, 45 (37.5%) below the age of 16 years, 60 (50%) were females.

ITP was diagnosed according to the guidelines of the American Society of Hematology [7]. At the time of sampling, newly diagnosed; persistent and chronic ITP was defined according to the international working group [8]. The severity was assessed according
Table 1. Clinical and laboratory data of the 120 studied ITP patients.

| Variable         | Value | P-value |
|------------------|-------|---------|
| Sex, number (%)  |       |         |
| Male             | 44 (36.7%) | 0.570   |
| Female           | 76 (63.3%) |         |
| Age, years       |       |         |
| Median, range    | 20.29 years (2–63) |         |
| Platelet at sampling, ×10⁹/l | 59.15 (6–180) | 0.551   |
| Hemoglobin at sampling, g/dl | 9.74 (4–8) | 0.426   |
| TLC at sampling, ×10³/µl  | 11.1 (8–14) | 0.734   |
| Phase            |       |         |
| Acute (newly diagnosed) | 52 (43.3%) | 0.828   |
| Chronic*         | 48 (40%) |         |
| Disease state at sampling |       |         |
| Activity         | 98 (81.7%) |         |
| Remission        | 22 (18.3%) |         |
| Severity at sampling |       |         |
| Bleeder          | 25 (20.8%) |         |
| Non-bleeder      | 95 (79.2%) |         |
| Treatment        |       |         |
| Steroids         | 103 (85.8%) |         |
| IV Ig            | 5 (4.2%) |         |
| Cyclosporine     | 1 (0.8%) |         |
| Quality of laboratory response at follow-up (FU)b |       |         |
| Complete response | 6/77 (7.8%) |         |
| Partial response  | 70/77 (90.9%) |         |
| No response      | 1/77 (1.3%) |         |
| Quality of clinical response at FU |       |         |
| Response         | 71/74 (95.9%) |         |
| No response      | 3/74 (4.1%) |         |

*Long FU ≥ 1 year.

Results

Among the studied ITP patients and the control subjects, the current study noted that in the studied HPA 1, 2 and 5, the ‘a’ allele was more prevalent than the b allele; the most frequent genotype was the homozygous a/a genotype, less frequently was the heterozygous a/b genotype, while homozygous b/b genotype was very rare in all the studied HPA systems.

Comparison between controls and patients groups as regards HPA1 and HPAS allele and genotype frequencies showed no statistically significant difference. While a statistically significant higher HPA 2 b allele frequency, and HPA 2b/2b and 2a/2b genotype frequencies were encountered in ITP patients compared to controls, detailed allele and genotype frequencies in healthy Egyptian subjects and ITP patients are shown in Table 2.

No statistically significant difference was found in HPA1, 2 and 5 allele or genotype frequencies when different patient groups were compared; males/females; children/adults; bleeders/non-bleeders; ITP patients in activity/in remission; newly diagnosed/persistent/chronic ITP.

Comparison between controls and patients groups as regards HPA1 and HPAS allele and genotype frequencies showed no significant difference.

Comparison between the ‘a’ allele patients with those with the ‘b’ allele in the studied HPA systems, as regards the age, platelet count, hemoglobin level and total leukocyte count (at diagnosis as well as at sampling time), none of these comparative studies was statistically significant. When these comparative studies were applied between patients with different genotypes (a/a), (a/b), (b/b), this was not statistically significant either.

Table 2. HPA1, 2 and 5 allele, allele phenotype and genotype frequencies in patients and controls.

| HPA alleles | Allele frequency | Allele phenotype frequency | Genotype frequency |
|-------------|------------------|----------------------------|-------------------|
| HPA1-a      | 194 (80.8%)      | 115 (95.8%)                | 79 (65.8%)        |
| HPA1-b      | 46 (19.2%)       | 41 (34.2%)                 | 36 (30%)          |
| HPA2-a      | 179 (74.6%)      | 112 (93.3%)                | 67 (55.8%)        |
| HPA2-b      | 61 (25.4%)       | 53 (44.2%)                 | 5 (4.2%)          |
| HPAS-a      | 204 (85%)        | 115 (95.8%)                | 88 (73.3%)        |
| HPAS-b      | 36 (15%)         | 32 (26.7%)                 | 27 (22.5%)        |

*Statistically significant.
Calculating the Odds ratio (OR) with the 95% CI for the risk of developing ITP in correlation to different studied HPA alleles revealed that individuals with HPA2b are 2.37 times more likely to develop ITP compared to those with other alleles. Individuals with HPA1a and HPA5b allele phenotypes are more likely to present with the disease by 1.21 and 1.20 times respectively; however, this was not statistically significant in Table 3.

Estimation the OR of developing chronic type of ITP in correlation to different studied HPA alleles revealed that individuals who have HPA1b and HPA5a are 5.57 and 2.16 times more likely to present with chronic disease, compared to individuals who do not have these alleles. Individuals with HPA1a, 2a and 2b allele phenotypes are more likely to present with chronic disease by 1.15, 1.15 and 1.2 times respectively. However, none of these results are statistically significant. Our results show no increased risk of acquiring chronic disease for individuals having HPA 5b allele phenotype, as shown in Table 3.

The Hardy Weinberg output for observed versus expected HPA-1, HPA-2 and HPA-5 genotype frequencies in the healthy participants and ITP patients revealed that the genotypes in both investigated groups showed a good fit with Hardy Weinberg equilibrium, as shown in Table 4.

Discussion

Identifying allele and genotype frequencies of HPA is significant not only for population-related genetics but also for clinical transfusion practice. Establishment of donors HPA genotyping registry assists in finding matched HPA types for patients with rare alleles, guides the management of platelet alloimmunization with clinical varieties: (neonatal alloimmune thrombocytopenia, post-transfusion purpura, post-transfusion refractoriness, post-transfusion passive alloimmune thrombocytopenia and transplantation-associated alloimmune thrombocytopenia) and provides a base for designing clinical research related to platelet disorders.

To the best of our knowledge, this is the first study to assess HPA in the Egyptian population in context with ITP. Different HPA systems polymorphisms have been assessed in the Egyptian population by Salem et al. [11], Husebekk et al. [12] and Salem et al. [13]; however, none of these works has studied these polymorphism in association with ITP.

The current work showed that HPA2b allele phenotype frequency was significantly higher in ITP patients compared to controls, also the homozygous and the heterozygous HPA2b genotype frequencies were significantly higher in ITP patients compared to controls. Accordingly, Pavkovic et al. [1] reported that the HPA-2b allele showed a significant higher frequency in Macedonian ITP patients compared to normal subjects and concluded that it may be involved in the formation of a specific autoepitope.

The present work showed no statistically significant difference between controls and patients groups as regards HPA5 allele and genotype frequencies. In contrast, Kim and Song reported a significant difference in the allele frequencies of the HPA 5 systems between Korean ITP patients and controls [14].

Table 3. OR of HPA1, 2 and 5 genotypes in patients and controls and in relation to the presence of chronic disease in patients group.

| Allele phenotype | Patients Allele present | Controls Allele absent | OR 95% CI | OR 95% CI |
|------------------|-------------------------|------------------------|-----------|-----------|
|                  | Allele present | Allele absent | Allele present | Allele absent | Lower | Upper |
| HPA1a            | 115          | 5            | 114          | 6            | 1.21  | 0.36   | 4.08   |
| HPA1b            | 41           | 79           | 45           | 75           | 0.87  | 0.51   | 1.47   |
| HPA2a            | 112          | 8            | 117          | 3            | 0.36  | 0.09   | 1.39   |
| HPA2b            | 53           | 67           | 30           | 90           | 2.37  | 1.37   | 4.11   |
| HPA5a            | 115          | 5            | 116          | 4            | 0.79  | 0.21   | 3.03   |
| HPA5b            | 32           | 88           | 28           | 92           | 1.20  | 0.67   | 2.15   |
| Chronic          | 95% CI OR    |             |             |             | Lower | Upper |
| Allele phenotype | Allele present | Allele absent | Allele present | Allele absent | OR 95% CI | Lower | Upper |
| HPA1a            | 46           | 4            | 4            | 0            | 1.14  | 0.05   | 24.93  |
| HPA1b            | 19           | 31           | 0            | 4            | 5.57  | 0.28   | 109.24 |
| HPA2a            | 47           | 3            | 4            | 0            | 1.51  | 0.07   | 34.05  |
| HPA2b            | 17           | 33           | 1            | 3            | 1.22  | 0.17   | 8.99   |
| HPA5a            | 48           | 2            | 4            | 2            | 2.16  | 0.09   | 52.16  |
| HPA5b            | 12           | 38           | 2            | 2            | 0.33  | 0.05   | 2.20   |

aStatistically significant.

Table 4. Hardy Weinberg comparison of HPA1, 2 and 5 observed frequencies versus expected frequencies.

| Group  | Gene | Observed genotype frequency | Expected genotype frequency | P-value |
|--------|------|-----------------------------|----------------------------|---------|
|        |      | a/a | a/b | b/b | Total | a/a | a/b | b/b |       |
| Patients | HPA1 | 79  | 36  | 5   | 120   | 78.4 | 37.2 | 4.4  | 0.73  |
|          | HPA2 | 67  | 45  | 8   | 120   | 66.8 | 45.5 | 7.8  | 0.91  |
|          | HPA5 | 88  | 27  | 5   | 120   | 85.9 | 31.3 | 2.9  | 0.13  |
| Controls | HPA1 | 75  | 39  | 6   | 120   | 74.4 | 40.2 | 5.4  | 0.75  |
|          | HPA2 | 90  | 26  | 3   | 119   | 89.2 | 27.7 | 2.2  | 0.50  |
|          | HPA5 | 92  | 24  | 4   | 120   | 90.1 | 27.7 | 2.1  | 0.14  |
| Population               | HPA 1 allele | HPA 1 genotype | HPA 2 allele | HPA 2 genotype | HPA 5 allele | HPA 5 genotype |
|-------------------------|--------------|----------------|--------------|----------------|--------------|----------------|
|                         | % PV         | % PV           | % PV         | % PV           | % PV         | % PV           |
|                         | 1a 1b        | 1a/1a 1a/b 1b/b | 2a 2b        | 2a/2b 2b/2b    | 5a 5b        | 5a/5b 5b/5b    |
| Egyptian (current study) | 120 0.79 0.21| 62.5 32.5 5.0  | 120 0.86 0.14| 75.8 21.6 2.5  | 120 0.88 0.12| 76.7 20.0 3.3  |
| Egyptian [11]           | 206 0.77 0.23| 59.2 35.0 5.8  | 206 0.87 0.13| 75.5 22.8 1.7  | 206 0.84 0.16| 70.6 26.9 2.6  |
| Egyptian [12]           | 6974 0.79 0.20| 62 34.2 3.8  | 75.8 21.6 2.5  | 75.5 22.8 1.7  | 75.5 22.8 1.7  |
| ARABS                   |              |                |              |                |              |                |
| Bahraini [17]           | 194 0.76 0.24| 56.8 38.5 4.7  | 194 0.77 0.23| 60.1 33.1 6.8  | 194 0.86 0.13| 75.7 20.9 2.7  |
| Moroccan [18]           | 107 0.74 0.25| 57.9 33.7 8.4  | 107 0.82 0.18| 66.3 30.8 2.0  | 112 0.86 0.14| 73.2 25.8 0.5  |
| Algerian [19]           | 485 0.83 0.17| 48 36.3 25.4  | 485 0.83 0.17| 60.1 33.1 6.8  | 485 0.84 0.16| 75.7 20.9 2.7  |
| Tunisian [20]           | 90 0.75 0.25| 90 0.78 0.22  | 90 0.78 0.22| 60.1 33.1 6.8  | 90 0.78 0.22| 60.1 33.1 6.8  |
| Saudi Arabian [21]      | 100 0.80 0.20| 75 23 6 0.08  | 100 0.80 0.20| 75 23 6 0.08  | 100 0.80 0.20| 75 23 6 0.08  |
| EUROPE                  |              |                |              |                |              |                |
| Southern (Mediterranean) Europe |      |                |              |                |              |                |
| Italian [22]            | 144 0.85 0.15| 144 0.89 0.11| 144 0.91 0.10| 45.0 10.4 45.0  | 144 0.91 0.09| 42.5 10.0 47.5  |
| Macedonian [23]         | 122 0.87 0.13| 122 0.85 0.15| 122 0.87 0.13| 45.0 10.4 45.0  | 122 0.91 0.09| 42.5 10.0 47.5  |
| Spanish [24]            | 727 0.81 0.19| 727 0.9 0.09  | 454 0.88 0.11| 0.87 10.4 87.5  | 454 0.88 0.11| 0.87 10.4 87.5  |
| Eastern Europe          |              |                |              |                |              |                |
| Slovenian [25]          | 152 0.83 0.17| 152 0.9 0.10  | 152 0.89 0.11| 0.64 10.4 86.5  | 152 0.89 0.11| 0.64 10.4 86.5  |
| Polish [26]             | 135 0.82 0.18| 135 0.9 0.10  | 135 0.89 0.11| 0.64 10.4 86.5  | 135 0.89 0.11| 0.64 10.4 86.5  |
| Northern Europe         |              |                |              |                |              |                |
| Norwegian [27]          | 105 0.86 0.13| 105 0.94 0.06| 105 0.93 0.07| 91.0 13.0 1.0  | 105 0.93 0.07| 91.0 13.0 1.0  |
| Swiss [28]              | 500 0.80 0.19| 500 0.92 0.11| 500 0.92 0.11| 90.0 10.0 10.0  | 500 0.92 0.11| 90.0 10.0 10.0  |
| Western Europe          |              |                |              |                |              |                |
| British [29]            | 134 0.84 0.16| 134 0.93 0.08| 134 0.91 0.09| 20.0 10.0 70.0  | 134 0.91 0.09| 20.0 10.0 70.0  |
| German [30]             | 1583 0.84 0.16| 1583 0.93 0.07| 1583 0.92 0.08| 0.01 0.01 0.01  | 1583 0.92 0.08| 0.01 0.01 0.01  |
| AFRICA                  |              |                |              |                |              |                |
| Cameroonian [31]        | 118 0.91 0.09| 118 0.76 0.24| 118 0.75 0.25| 56.8 35.6 7.6  | 118 0.75 0.25| 56.8 35.6 7.6  |
| Central African [31]    | 110 1.0 0 0.00| 110 0.61 0.39| 110 0.60 0.41| 0.01 0.01 0.01  | 110 0.60 0.41| 0.01 0.01 0.01  |
| AMERICA                 |              |                |              |                |              |                |
| Argentinean [32]        | 192 0.88 0.12| 192 0.86 0.13| 77.6 22.4 1  | 0.00 0.00 0.00  | 77.6 22.4 1  | 0.00 0.00 0.00  |
| Brazilian [33]          | 100 0.93 0.08| 86.0 13.0 1.0  | 100 0.85 0.15| 73.5 24 3 0.1  | 100 0.85 0.15| 73.5 24 3 0.1  |
| ASIA                    |              |                |              |                |              |                |
| Pakistan [34]           | 593 0.89 0.12| 79.4 19.0 0.0  | 593 0.92 0.08| 85.0 13.5 1.2  | 593 0.92 0.08| 85.0 13.5 1.2  |
| Han Chinese [35]        | 1000 0.99 0.01| 98.9 1.2 0.0  | 1000 0.95 0.05| 90.4 9.5 0.1  | 1000 0.99 0.01| 97.3 2.6 0.1  |

Note: Bold-italic represents statistically significant values.
The current study revealed no statistically significant association between any of the studied alleles with the increased risk of developing chronic ITP. Accordingly, Castro et al. [15] found no association between HPA-5 alleles with the increased risk of acute ITP in Brazilian population. Thude et al. confirmed our findings when reported that HPA-1 and 5 allele frequencies were identical in chronic ITP patients and in controls, as for HPA-2a allele, they reported an association with chronic ITP [16]. It should be emphasized here that Thude et al.’s study was performed on Germans, and on selected chronic refractory patients.

In the present work, HPA-1 allele and genotype frequencies appear to be in the same range reported by the Egyptian studies done by Salem et al. [11] with no statistically significant differences.

Although Husebekk et al. [12] study was confined to Egyptian pregnant females, which is not entirely representative to the Egyptian population, their reported frequencies for HPA-1, 2 and 5 systems showed no significant difference compared to our results, confirming our findings that HPA-1, 2 and 5 polymorphism frequency was not gender related.

In 2014, Salem et al. [13] reported a significantly higher HPA-2b and 5b allele frequencies compared to our results. This might be referred to the sample study, as their participated subjects were Egyptians from Ismailia (northern Egypt), while the current study enrolled Egyptians from Cairo and down to the southern of Egypt (Giza, Beni Suef, Al Fayoum, Al Menia, Asuit, Suhag, Luxor and Aswan). It is to be noted here that Salem et al. [13] reported that gene frequencies of HPA-2 and -5 in their study were statistically different from the previously reported results by Husebekk et al. [12] and were the highest reported among Middle Eastern and Arabic populations.

Our reported HPA-1, 2 and 5 alleles and genotypes frequencies were compared to those of other ethnic groups, as detailed in Table 5.

We support the previous reports concerning the high prevalence of the HPA-1b, compared to other ethnic groups, which may predispose to higher risk of allo-immunization, as was noted previously [11].

Comparable HPA-2 allele and genotype frequencies were reported by previous Egyptian study [12], as well as studies done in some Middle Eastern Arab countries such as Tunisia, Algeria and Morocco (Moroccan Berber population).

HPA polymorphism was reported as predictor of response to certain drugs used in ITP treatment. In Chinese ITP patients, those with the HPA-2 a/b and HPA-3 a/a genotypes are less likely to respond to Kami-kihi-to therapy [36]. In response to Cepharanthin treatment, a statistically higher incidence of HPA-2a/2a in the responders group of ITP and a significantly higher HPA-2a/2b and HPA-3a/3b in non-responders were reported [37].

According to our results, none of the studied HPA1, HPA2 and HPA5 systems’ alleles was associated with the clinical course/severity of ITP patients (platelet count/significant bleeding), persistency, chronicity, lack of/incomplete response to either clinical or laboratory treatment.

In conclusion, the current study shows that individuals with HPA-2b are 2.37 times more likely to develop ITP compared to normal subjects. HPA allelic profile of our population is closely linked to that of other ethnic groups within the Middle East and the neighboring Arab countries.

This study provides comprehensive information on HPA allele distribution among the Egyptian population. These results may guide for future clinical research associated with platelet disorders and may be a first step to build a data bank on platelet antigen polymorphisms among Egyptians.

Disclosure statement

The authors declare no conflict of interest.

References

[1] Pavkovic M, Stojanovic A, Karanfilski O, et al. Association of polymorphisms in human platelet antigens with idiopathic thrombocytopenic purpura in Macedonians. Prilozi. 2012;33(1):135–146.
[2] Shaiegan M, Samiei S, Ataee Z, et al. Frequency of human platelet antigens (HPA-2/3/5) polymorphism in Iranians evaluated by RFLP-PCR. IJBC. 2011;3:101–105.
[3] Curtis BR. Genotyping for human platelet alloantigen polymorphisms: applications in the diagnosis of alloimmune platelet disorders. Semin Thromb Hemost. 2008;34:539–548.
[4] Holensteiner A, Walchshofer S, Adler A, et al. Human platelet antigen gene frequencies in the Austrian population. Haemostasis. 1995;25:133–136.
[5] Kim HO, Jin Y, Kickler TS, et al. Gene frequencies of the five major human platelet antigens in African American, white, and Korean populations. Transfusion. 1995;35:863–867.
[6] Seo DH, Park SS, Kim DW, et al. Gene frequencies of eight human platelet-specific antigens in Koreans. Transfus Med. 1998;8:129–132.
[7] Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood. 2011;117:4190–4207.
[8] Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood. 2009;113:2386–2393.
[9] Zhou Z, Chen Z, Li H, et al. BAFF and BAFF-R of peripheral blood and spleen mononuclear cells in idiopathic thrombocytopenic purpura. Autoimmunity. 2009;42:112–119.
[10] Fratellanza G, Scarpato N, D’Agostino E, et al. Genomic restriction fragment length polymorphism typing of human platelet-specific antigens in blood donors from...
southern Italy and in all immunised pregnancies. Blood Transfus. 2005;3:222–230.

[11] Salem AH, Han K, Batzer MA. Allele frequencies of the human platelet antigen-1 in the Egyptian population. BMC Res Notes. 2009;2(1):90.

[12] Husebekk A, El Ekiaby M, Gorgy G, et al. Foetal/neonatal alloimmune thrombocytopenia in Egypt; human platelet antigen genotype frequencies and antibody detection and follow-up in pregnancies. Transfus Apher Sci. 2012;47(3):277–282.

[13] Salem AH, Abdel Hamed AE, Abdalla EM, et al. Gene frequencies of human platelet alloantigens 1–5 in two Arab populations. Blood Transfus. 2014;12(1):281.

[14] Kim BS, Song KS. Genetic polymorphism of human platelet antigen 3 in patients with immune thrombocytopenia. Thromb Haemost. 1997:1037.

[15] Castro V, Oliveira GB, Origa AF, et al. The human platelet alloantigen 5 polymorphism as a risk for the development of acute idiopathic thrombocytopenia. Thromb Haemost. 2000;84(2):360–361.

[16] Thude H, Gatzka E, Anders O, et al. Allele frequencies of human platelet antigen 1, 2, 3, and 5 systems in patients with chronic refractory autoimmune thrombocytopenia and in normal persons. Vox Sang. 1999;77(3):149–153.

[17] Al-Subaie AM, Al-Absi IK, Al-Ola K, et al. Gene frequencies of human platelet alloantigens in Bahraini Arabs. Am J Hematol. 2007;82(3):242–244.

[18] Ferrer G, Muñiz-Díaz E, Aluja MP, et al. Analysis of human platelet antigen systems in a Moroccan Berber population. Transfus Med. 2002;12(1):49–54.

[19] Brouk H, Halle L, Bertrand G, et al. Human platelet antigen allele frequencies in different Algerian populations. Tissue Antigens. 2010;75(6):673–678.

[20] Mojaat N, Halle L, Proulle V, et al. Gene frequencies of human platelet antigens in the Tunisian population. Tissue Antigens. 1999;54(2):201–204.

[21] Al-Ouda SK, Al-Banyan AA, Abdel Gader AGM, et al. Gene frequency of human platelet alloantigens-1 to -6 and -15 in Saudi blood donors. Transfus Med. 2016;26(3):220–224.

[22] Mazzucco L, Santi R, Contino L. “HPA-1/6 allelemorphism study in juvenile stroke: the possible role of HPA-2b and HPA-5b.” 6th European Symposium on Platelet, Granulocyte and Red Cell Immunobiology (Abstract book). Amsterdam; 2000.

[23] Pavkovic M, Petilchikovski A, Strezova A, et al. Gene frequencies of human platelet antigens in the Macedonian population. Tissue Antigens. 2006;67(3):241–246.

[24] Muñiz-Díaz E, Arilla M, Ibañez M, et al. Frequency of platelet alloantigens in the Spanish population. Sangre (Barc). 1993;38(4):289–293.

[25] Rozman P, Drabkels J, Schipper RF, et al. Genotyping for human platelet-specific antigens HPA-1, -2, -3, -4 and -5 in the Slovenian population reveals a slightly increased frequency of HPA-1b and HPA-2b as compared to other European populations. Eur J Immunogenet. 1999;26(4):265–269.

[26] Drzewek K, Brojer E, Zupańska B. The frequency of human platelet antigen (HPA) genotypes in the Polish population. Transfus Med. 1998;8(4):339–342.

[27] Randen I, Sørensen K, Killie MK, et al. Rapid and reliable genotyping of human platelet antigen (HPA)-1, -2, -3, -4, and -5 a/b and Gov a/b by melting curve analysis. Transfusion. 2003;43(4):445–450.

[28] Boelen H, Bulla O, Michel M, et al. HPA-genotyping and antiplatelet antibodies in female blood donors. Hematol J. 2003;4(6):441–444.

[29] Jones DC, Bunce M, Fuggle SV, et al. Human platelet alloantigens (HPAs): PCR-SSP genotyping of a UK population for 15 HPA alleles. Eur J Immunogenet. 2003;30(6):415–419.

[30] Carlsson LE, Greinacher A, Spitzer C, et al. Polymorphisms of the human platelet antigens HPA-1, HPA-2, HPA-3, and HPA-5 in the platelet receptors for fibrinogen (GPIIb/IIIa), von Willebrand factor (GPIb/IX), and collagen (GPIa/IIa) are not correlated with an increased risk for stroke. Stroke. 1997;28:1392–1395.

[31] Halle L, Bigot A, Mulen-Imandy G, et al. HPA polymorphism in sub-Saharan African populations: Beninese, Cameroonians, Congolese, and Pygmies. Tissue Antigens. 2005;65(3):295–298.

[32] De La Vega Elena CD, Nogues N, Fernandez Montoya A, et al. Human platelet-specific antigens frequencies in the Argentinean population. Transfus Med. 2008;18(2):83–90.

[33] Castro V, Origa AF, Annichino-Bizzacchi JM, et al. Frequencies of platelet-specific alloantigen systems 1–5 in three distinct ethnic groups in Brazil. Eur J Immunogenet. 1999;26(5):355–360.

[34] Bhati FA, Uddin M, Ahmed A, et al. Human platelet antigen polymorphisms (HPA-1, -2, -3, -4, -5, and -15) in major ethnic groups of Pakistan. Transfus Med. 2010;20(2):78–87.

[35] Feng ML, Liu DZ, Shen W, et al. Establishment of an HPA-1 to -16-typed platelet donor registry in China. Transfus Med. 2006;16(5):369–374.

[36] Matsuoka T, Nomura S, Yamaoka M, et al. HLA and HPA typing in idiopathic thrombocytopenic purpura patients treated with Kami-kihi-to. Am J Chin Med. 1998;26(2):191–198.

[37] Nomura S, Matsuoka T, Yamaoka M, et al. Genetic analysis of HLA- and HPA-typing in idiopathic (autoimmune) thrombocytopenic purpura patients treated with cepharanthin. Autoimmunity. 1999;30(2):99–105.