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Human platelet antigens polymorphisms: Association to primary immune thrombocytopenia in the Iranian patients

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Abstract

Background: Human platelet antigens (HPAs) are part of platelet GP complexes have the potential to contribute to the autoantibody production. Moreover, these antigens demonstrate different patterns of distribution on different ethnic groups and variation in some types of diseases. This study was objected to determine the incidence of HPA-1 to -5 and -15 polymorphisms in the Iranians suffering from primary Immune thrombocytopenic purpura (ITP).

Materials and Methods: In this case-control investigation, 30 patients by definite primary ITP were randomly selected and enrolled in the study. HPA genotyping was performed implicating by the Single Specific Primer PCR (SSP-PCR). For the control group, data of recently published gene polymorphism among Iranian Blood donors were deployed for comparison.

Results: The incidence of HPA-1 to -5 and -15 polymorphisms in the Iranian patients with primary ITP was found to be: HPA-1a/1a: 0.933, HPA-1a/1b: 0.067, HPA-2a/2a: 0.133, HPA-2a/2b: 0.867, HPA-3a/3a: 0.2, HPA-3a/3b: 0.533, HPA-3b/3b: 0.267, HPA-4a/4a: 1, HPA-5a/5a: 0.967, HPA-5a/5b: 0.330, HPA-15a/15a: 0.166, HPA-15a/15b: 0.667 & HPA-15b/15b: 0.167.

Conclusion: This study provides special new data on the distribution of HPA allele among the Iranians ITP patients.Furthermore, it might useful toccharacterize understanding more presizely about ITP and HPA distribution. However, further studies concerning platelet immunology are needed to do help on best practice on management of immune diseases triggered by platelet antibodies.

Keywords: Antigens, Blood Platelets, Human Platelet, Purpura, Thrombocytopenic

Introduction

Immune thrombocytopenic purpura (ITP) is a heterogeneous acquired disease (1). In the serum of patients with ITP, there are immunoglobulin G antibodies that are produced against glycoproteins (PSGs) on the platelet surface (2). Platelets sensitized by these autoantibodies are removed by the reticuloendothelial system and cleared from the bloodstream (3). ITP may be categorized according to the duration of diagnosis as: newly diagnosed (up to three months), perpetual ITP (up to twelve months), and chronic (longer than twelve months) (4).

Till now, factors and mechanisms contributing to the occurrence of ITP have not been fully identified (5). It seems that some environmental and genetic factors including specific infections (6) and vaccination (7), specific human leukocyte antigens (HLAs) and HPAs might play a role (3). However, the association between ITP and polymorphisms of some genes encoding cytokines and chemokines have been shown (8, 9). Some HPAs, including HPA-1, -2, -3, and -5 are part of the

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structure of PSGs and might have been a particular autoepitope (3) and formation of autoantibodies with antiplatelet function.

In HPA systems, HPA-1 to -5 and -15 are two allelic antigens whereas other systems are monoallelic (10). To date, the expression of 35 platelet-specific alloantigens (HPAs) on different platelet glycoproteins have been shown (11). Moreover, it is declared that severity of clinical complications among patients by different races exist due to antibodies against different HPAs systems (12). Besides, the development of alloantibodies against HPAs has been described in many conditions such as platelet refractoriness (PTR),fetal immune thrombocytopenia (FIT) (13), outcomes of HCV infection (14, 15) and increased risk of HCV infection (16).

In the other hand, there are many evidences which shows that the frequencies of HPAs allele in different ethnic populations are different. Thus, HPAs genotyping could be used for the management of clinical situations which mentioned above (17). Though the frequency of HPAs varies among different racial groups (18, 19) and no information is available about the abundance of HPAs genes on Iranian patients with immune thrombocytopenia, this study was arranged to provide data on the frequencies of HPA-1 to -5 and -15 systems in Iranian primary chronic ITP patients.

Materials and Methods

Thirty chronic primary ITP patients were randomly selected and enrolled in the study.

Inclusion criteria were as follows: platelet count less than 100 × 109/L, normal or increased megakaryocytes in bone marrow without dysplasia in the absence of disorders that may be associated with thrombocytopenia (20) such as lymphoproliferative disorders, transfusion or taking some medications (21).

Peripheral blood samples were then collected in ethylenediaminetetracetic acid. Samples of patients were collected from Shariati Hospital in Tehran.

Genomic DNA was prepared from mononuclear cells by a commercial kit (Qiagen, Milan, Italy). Genomic DNA was amplified using PCR sequence-specific primers (Bhatti et al., 2010) (22). The sequence of primers and product size is displayed in Table 1. An internal control was used in all PCR runs. An example of the results of electrophoresis on 2% agarose gel is illustrated in Figure 1.

The distribution of gene frequencies in the HPAs was calculated by Hardy-Weinberg equilibrium test. We made use of data from a recently published article about HPAs gene polymorphism among Iranian blood donors as a typical group (23).

The code of ethics for this study is IR.TMI.REC.1396.005.

Statistical analysis

SPSS software (version 15) was used to identify the relationship between the variables.

Results

A total of 30 patients, 18 (60 %) females and 12 (40 %) males, participated in this study. The mean ± SD age of all of these primary ITP patients was 42.5 ± 12 years; they were between 20 and 65 years old. Average monitoring period was 18 months (ranging from 6 to 25 months) and all were in a treatment protocol.

In both patients and control subjects, the frequency of ″a″ allele in the studied HPA-1, -2, -4, and -5 found higher in comparison to ″b″ allele.

Moreover, the allele abundance of HPA-3b appeared to be higher than the ″a″ allele in primary ITP patients. It was also higher than the ″a″ allele in blood donors.

In HPA-1, -4 & -5 systems, the prevalance of homozygous ″aa″ genotypes proved to be higher than that of heterozygous ″ab″ genotype, besides the homozygous ″bb″ genotype was far rarely observed. In HPA-3 & -15 systems, the abundance of heterozygous ″ab″ genotype was greater than that of homozygous ″aa″ genotype

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while the homozygous ″bb″ genotype was intermittent.

The results of genotyping of HPAs for blood donors and patients with primary ITP are presented in Table 2.

The frequencies of HPAs genotypes in total subjects were determined as follows: HPA-1a/1a: 95.3%, HPA-1a/1b: 4.6%, HPA-2a/2a: 9.2%, HPA-2a/2b: 90.7%, HPA-3a/3a: 11.5%, HPA-3a/3b: 65.3%, HPA-3b/3b: 23%, HPA-4a/4a: 100%, HPA-5a/5a: 98.5%, HPA-5a/5b: 1.5%, HPA-15a/15a: 14.6%, HPA-15a/15b: 66.9%, and HPA-15b/15b: 18.4%. The frequencies of homozygous HPA-1a/a and HPA-5a/5a was 95.3% and 98.5%, respectively.

The abundance of heterozygous types of HPA-2, HPA-3 & HPA-15 were detected to be 90.7%, 65.3% and 66.9%, respectively, thus indicating a greater frequency compared to the homozygous (a/a or b/b) forms. The homozygous ″b″ allele, however, was not found in HPA-4. No homozygous ″bb″ genotype was also identified in HPA-1, HPA-2 and HPA-5.

The abundance of HPA-3aa/bb genotype showed to be higher in ITP patients than that observed in the blood donors; however, the abundance of HPA-3ab genotype was lower in ITP patients compared to the control group.

The odds ratio with the 95% CI revealed that individuals with HPA-1b, -5b & -15a allele phenotypes are at greater risk for the disease by odds of 1.714 (95% CI 0.298-9.853), 3.414 (95% CI 0.207-56.281) and 1.173 (95% CI 0.397-3.462), respectively (Table 3). The Hardy Weinberg equilibrium calculation result was also presented in the Table 4.

Table I. HPAs gene primers sequence & product size for SSP-PCR.

Gene	Specificity	Sequences of primers	Product size (bp)
HPA-1	1a 1b Common	5' TCA CAG CGA GGT GAG GCC A 3' 5' TCA CAG CGA GGT GAG GCC G 3' 5' GGA GGT AGA GAG TCG CCA TAG 3'	**90**
HPA-2	2a 2b Common	5' GCC CCC AGG GCT CCT GAC 3' 5' GCC CCC AGG GCT CCT GAT 3' 5' TCA GCA TTG TCC TGC AGC CA 3'	**258**
HPA-3	3a 3b Common	5' GGG GGA GGG GCT GGG GA 3' 5' GGG GGA GGG GCT GGG GC 3' 5' GGC CCT GGG ACT GTG AAT G3'	**267**
HPA-4	4a 4b Common	5' CTG GCC ACC CAG ATG CG 3' 5' CTG GCC ACC CAG ATG CA 3' 5' GGT AGA AAG GAG CTA TAG TTT GGC 3'	**120**
HPA-5	5a 5b Common	5' AGA GTC TAC CTG TTT ACT ATC AAA G 3' 5' AGA GTC TAC CTG TTT ACT ATC AAA A 3' 5' CTC TCA TGG AAA ATG GCA GTA CA 3'	**246**
HPA-15	15a 15b Common	5' TTC AAA TTC TTG GTA AAT CCT CG 3' 5' TTC AAA TTC TTG GTA AAT CCT CT 3' 5' ATG AAC CTT ATG ATG ACC TAT TC 3'	**225**
HGH	Forward Reverse	5' GCC TTC CCA ACC ATT CCC TTA 3' 5' TCA CGG ATT TCT GTT GTG TTT 3'	**429**

HPA; human platelet antigen, HGH; human growth hormone

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Table II. Allelic and genotypic frequencies for HPAs

HPA alleles	Allele frequency			Allele phenotype frequency			HPA genotypes	Genotype frequency		
	ITP[a] (%)	Bd[b] (%)*	P	ITP (%)	Bd (%)*	P		ITP (%)	Bd (%)*	P
HPA-1a	58 (96.7)	196 (98)	0.834	30 (100)	100 (100)	-	1aa	28 (93.3)	96 (96)	0.542
							1ab	2 (6.7)	4 (4)	0.542
HPA-1b	2 (3.3)	8 (2)		2 (6.7)	4 (4)	0.621	1bb	0	0	-
HPA-2a	34 (56.7)	108 (54)	0.716	30 (100)	100 (100)	-	2aa	4 (13.3)	8 (8)	0.376
HPA-2b	26 (43.3)	92 (46)		26 (87.6)	92 (92)	0.376	2ab	26 (86.7)	92 (92)	0.376
							2bb	0	0	
HPA-3a	28 (46.7)	87 (43.5)	0.665	22 (73.3)	78 (78)	0.595	3aa	6 (20)	9 (9)	0.098
							3ab	16 (53.3)	69 (69)	0.114
HPA-3b	32 (53.3)	113 (56.5)		24 (80)	91 (91)	0.098	3bb	8 (26.7)	22 (22)	0.595
HPA-4a	60 (100)	200 (100)	-	30 (100)	100	-	4aa	30 (100)	100	-
							4ab	0	0	-
HPA-4b	0	0		0	0	-	4bb	0	0	-
HPA-5a	59 (98.3)	199 (99.5)	0.364	30 (100)	100	-	5aa	29 (96.7)	99 (99)	-
							5ab	1 (3.3)	1 (1)	-
HPA-5b	1 (1.7)	1 (0.5)		1 (3.3)	1 (1)	0.362	5bb	0	0	-
HPA-15a	30 (50)	95 (47.5)	0.734	25 (83.3)	81 (81)	0.773	15aa	5 (16.6)	14 (14)	0.717
							15ab	20 (66.7)	67 (67)	0.409
HPA-15b	30 (50)	105 (52.5)		25 (83.3)	86 (86)	0.717	15bb	5 (16.7)	19 (19)	0.773

[a] ITP: Immune thrombocytopenic purpura; [b] Blood donors; *Data reported by Data reported by Shaiegan et al. (2019: ISBT Science Series, in press). HPA; human platelet antigen.

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Table III. OR of HPAs genotypes in ITP patients and blood donors.

Allele phenotype	ITP patients		Blood donors*		OR	95% CI OR	
	Allele present (%)	Allele absent (%)	Allele present (%)	Allele absent (%)		Lower	Upper
HPA-1a	30 (100)	0	100 (100)	0	-	-	-
HPA-1b	2 (6.7)	28 (93.3)	4 (4)	96 (96)	1.714	0.298	9.853
HPA-2a	30 (100)	0	100 (100)	0	-	-	-
HPA-2b	26 (87.6)	4 (12.4)	92 (92)	8 (8)	0.565	0.158	2.026
HPA-3a	22 (73.3)	8 (26.7)	78 (78)	22 (22)	0.776	0.304	1.980
HPA-3b	24 (80)	6 (20)	91 (91)	9 (9)	0.396	0.128	1.221
HPA-4a	30 (100)	0	100	0	-	-	-
HPA-4b	0	30 (100)	0	100	-	-	-
HPA-5a	30 (100)	0	100	0	-	-	-
HPA-5b	1 (3.3)	29 (96.7)	1 (1)	99 (99)	3.414	0.207	56.281
HPA-15a	25 (83.3)	5 (16.7)	81 (81)	19 (19)	1.173	0.397	3.462
HPA-15b	25 (83.3)	5 (16.7)	86 (86)	14 (14)	0.814	0.267	2.480

ITP; Immune thrombocytopenic purpura, HPA; human platelet antigen. *Data reported by Data reported by Shaiegan et al. (2019: ISBT Science Series, in press).

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Table IV. The calculation of the gene abundances of HPAs by Hardy-Weinberg equilibrium test.

Genotypes		Blood donors (n=100)			ITP patients (n=30)		
		EN	ON	*p*-Value	EN	ON	*p*-Value
HPA-1	aa	96	96	0.979	28	28	0.982
	ab	3.9	4		1.9	2	
	bb	0	0		0	0	
HPA-2	aa	29.2	8	0.100	9.6	4	0.115
	ab	49.7	92		14.7	26	
	bb	21.2	0		5.6	0	
HPA-3	aa	18.9	9	0.285	4.9	6	0.746
	ab	49.2	69		18.2	16	
	bb	31.9	22		16.9	18	
HPA-4	aa	100	100	1.000	30	30	1.000
	ab	0	0		0	0	
	bb	0	0		0	0	
HPA-5	aa	99	99	0.998	29	29	0.995
	ab	1	1		1	1	
	bb	0	0		0	0	
HPA-15	aa	22.6	14	0.102	7.5	5	0.188
	ab	49.9	67		15	20	
	bb	27.6	19		7.5	5	

ITP; Immune thrombocytopenic purpura, HPA; Human platelet antigen. ON: Observed number; EN: Expected number. * Data reported by Shaiegan et al. (2019: ISBT Science Series, in press).

Table V. The results of the abundance of HPAs in the study population & other populations.

Population	HPA-1		HPA-2		HPA-3		HPA-4		HPA-5		HPA-15	
	a	b	a	b	a	b	a	b	a	b	a	b
Croatian (27, 28)	0.85	0.14	0.89	0.11	0.57	0.42	–	–	0.89	0.1	0.53	0.47
Macedonian (29)	0.86	0.13	0.85	0.14	0.57	0.42	–	–	0.9	0.09	–	–
Lebanese (30)	0.81	0.19	–	–	–	–	–	–	–	–	–	–
Indian (31)	0.92	0.07	0.99	0	0.01	0.99	0.99	0	0.95	0.04	–	–
Han Chinese (32)	0.99	0	0.95	0.04	0.59	0.4	0.99	0	0.98	0.01	0.53	0.46
Pakistani (22)	0.88	0.11	0.92	0.08	0.69	0.31	1	0	0.9	0.1	0.59	0.41
Bahrainian (33)	0.76	0.24	0.77	0.23	0.57	0. 43	0.93	0.07	0.86	0.13	–	–
Egyptians (34)	0.76	0.23	0.75	0.24	0.7	0.29	1	0	0.72	0.27	–	–
Thai (17)	0.98	0.01	0.95	0.04	0.56	0.44	1	0	0.96	0.03	0.49	0.5
Saudis (11)	0.8	0.2	0.71	0.29	0.65	0.35	0.99	0.01	0.8	0.2	0.47	0.52
Iran (This study)	0.99	0.01	0.55	0.45	0.44	0.56	1	0	0.99	0	0.48	0.52
Malay (35)	0.97	0.02	0.96	0.03	0.5	0.49	0.99	0	0.95	0.05	0.51	0.48
Malaysian Chinese (35)	1	0	0.96	0.0.3	0.57	0.42	0.99	0	0.98	0.01	0.49	0.5
Malaysian Indian (35)	0.88	0.11	0.96	0.04	0.62	0.38	0.99	0	0.94	0.06	0.4	0.59
Argentinean (36)	0.87	0.12	0.87	0.12	0.61	0.38	1	0	0.92	0.07	0.51	0.48
Amerindian Toba (36)	1	0	0.94	0.05	0.38	0.61	1	0	1	0	0.68	0.31
Algerian (37)	0.83	0.16	0.83	0.16	0.62	0.37	1	0	0.83	0.15	0.53	0.47
Beninese (38)	0.89	0.1	0.7	0.29	0.67	0.32	1	0	0.81	0.18	0.64	0.35
Cameroonian (38)	0.9	0.09	0.76	0.23	0.61	0.38	1	0	0.74	0.25	0.69	0.3
Congolese (38)	0.9	0.09	0.77	0.22	0.59	0.4	1	0	0.73	0.26	0.7	0.29
Central African (38)	1	0	0.6	0.39	0.5	0.5	1	0	0.59	0.4	0.69	0.3

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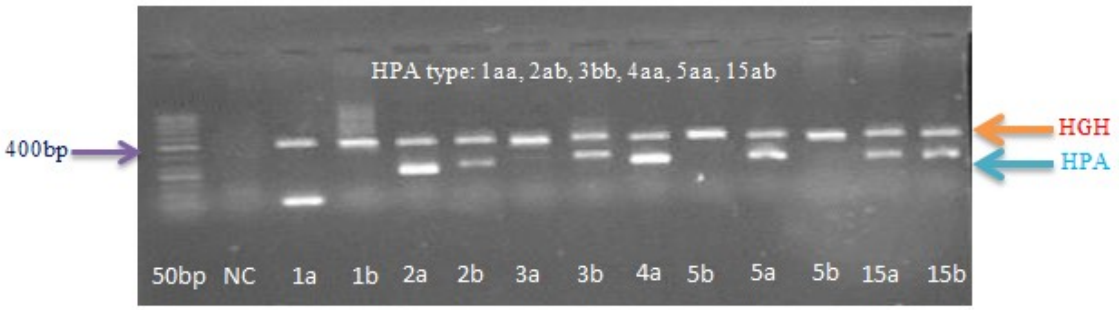

Figure 1. Results related to genotyping of a patient; NC, negative control; HGH, human growth hormone

Discussion

The present research has revealed that the phenotype of HPA3b abundance was lower in ITP patients compared to blood donors, but the homozygous 3aa/3bb genotype abundance was higher in ITP cases compared to control group. The findings of this study the clinical studies related to platelet disorders, and it can be assumed as the first step creating a database on platelet antigen polymorphisms among Iranians.

As ITP is a heterogeneous and acquired disease of unidentified etiology, it could be useful to study HPAs systems for gathering comprehensive data on population genetics (24).

In addition, T. K. Eyada et al. reported HPA-2b allele phenotype showed a significantly higher frequency in Egyptian patients compared to normal blood donors. They also reported the genotype of HPA-2b showed considerably higher prevalance in case group compared to blood donors (19).

Furthermore, Tang LJ et al. identified that the special HPAs polymorphisms can associate to the possibility of ITP in Chinese Guangxi area (25). Besides, another study reported that the HPA-2b has revealed a significantly higher frequency in Macedonian patients compared to blood donors and thus authors recommended that it is likely that HPA-2b be involved in the formation of a specific autoepitope in this ethnicity (3).

In addition, Carmo JC et al. declared that allele abundances of the HPA-2, -4, -6 to -9, -11, and -15 were undistinguishable among patients with PTR and blood donors in the northern Brazil, hence suggesing that the allele of HPA-1a, -3b, & -5b might be considered as ITP-particular autoepitopes (26).

This study, in contrst, revealed no substantial dissimilarity between blood donors and ITP patients regarding the HPA-1 to -5 & -15 allele and genotype abundances. Accordingly, we suggest that global variation in the abundance of autoepitopes among ITP subjects can take place in response to the genetic inheritance of HPA polymorphisms.

The HPA-1 to -5 & -15 frequencies in this study and other populations are shown in Table- 5 for comparison.

Conclusion

In conclusion, the present investigation reports that individuals with HPA-1b, -5b & -15a allele phenotypes are more likely to be affected by the ITP by odds of : 1.714, 3.414 & 1.173 times respectively; however, this was not statistically significant. HPA-4b was absent and there was not any homozygosity for HPA-1b/1b, HPA-2b/2b and HPA-5b/5b. Moreover, no HPA-1b/b, HPA-2b/b, and HPA-5b/b homozygosity were found. Therefore, it seems that HPA-1a, -2a, -4a & -5a polymorphisms do not involved in the

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autoimmunity related to the primary ITP in Iranian population. Further studies are recommended to help the prevention and management of immune diseases engendered by platelet antibodies. This study provides comprehensive information on the HPA allele distribution among the Iranians with ITP.

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Conflict of interest
The authors declare no conflict of interest.

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