Human Immunology 77 (2016) 812–816

Contents lists available at ScienceDirect

journal homepage: www.elsevier.com/locate/humimm

Characterisation and functional implications of the two new HLA-G alleles found in Amerindian and Caribbean populations

Antonio Arnaiz-Villena [a,1,*], Mercedes Enriquez-de-Salamanca [a,1], Jose Palacio-Grüber [a], Cristina Campos [a], Alejandro Camacho [a], Jose Manuel Martin-Villa [b], Narcisa Martinez-Quiles [b], Eduardo Gomez-Casado [c], Ester Muñiz [a]

[a] Department of Immunology, University Complutense, School of Medicine, The Madrid Regional Blood Center, Madrid, Spain
[b] Department of Immunology, University Complutense, School of Medicine, Madrid, Spain
[c] Department of Inmunología Animal, Instituto Nacional de Investigación y Tecnología Agraria y Alimentaria (INIA), Autopista A6, Hipódromo, Madrid, Spain

ARTICLE INFO

Article history:
Received 16 October 2015
Revised 5 January 2016
Accepted 7 January 2016
Available online 18 January 2016

Keywords:
Amerindians
Ecuador
Hispaniola Is
HLA-G
HLA-G and populations
HLA-G function
HLA-G immune interaction
HLA-G ligands
ILT-2
ILT-4

ABSTRACT

HLA-G polymorphism has been found to be relatively low in all world populations. In the present paper two new HLA-G molecules are described in ancient American natives. A new HLA-G molecule from a Ecuador Amerindian individual (male) showed four codon changes with respect to HLA-G*01:01:01. Silent changes at α1 domain (residue 57, Pro, CCG → CCA) and α2 domain (residue 93, His, CAC → CAT and residue 100, Gly, GGC → GGT) and one productive change in α3 domain (residue 219 changed from Arg to Trp). This α3 change may dramatically alter HLA-G interactions with beta-2 microglobulin, CD8, ILT-2 and ILT-4 ligands present in subsets of T, B, NK, monocytes, macrophages and dentritic cells. Another HLA-G new molecule was found in a woman from Hispaniola Island, Dominican Republic (Sto Domingo): it presented a silent change at α2 domain residue 107, Gly, GGA → GGT and non-silent change at residue 178, Met → Thr (with respect to HLA-G*01:01:01) which is close to class I molecule/clonotypic T cell receptor interaction sites. Functional implications of these findings are discussed.

1. Introduction

The First Native American are believed to have populated America coming from Asia through the Bering land bridge between 30,000 and 12,000 years before present (BP). These conclusions have been based on cultural, morphological and genetic similarities between American and Asian populations [1]. Both Siberia [1] and Mongolia [2,3] have been put forward as the most approximate places of Amerindians origin in Asia.

Greenberg et al. [4] postulated the triple migration theory for explaining the Americas peopling on linguistic bases: Amerindians (most North and South American Indians; 12,000 BP), Na-Dene (Athabascans, Navajo, Apache; 8000 BP) and Eskimo-Aleuts (6000 BP). Studies on Y chromosome showed that more than one paternal founder haplotype arrived in America during different migrations [5], probably from Siberia [6]. DNA nuclear studies have also been carried out to ascertain the origin of First Native American (Alu insertions, [7]): three identifiable clusters of people are postulated, reflecting the geographical distribution with only one wave of immigration. Also, East Asian HLA genes have been found in the Azores Island [8]; this is concordant with recent evidence showing the spread of Chinese fleet around the world in 1421 [9]. Also, the presence of South American peopling form Asia or Polynesia has been suggested because HTLV-1 virus strain shared identical sequences in Japan and in the northern coast of South America [10] and some HLA alleles may have been introduced by the same Trans-Pacific route [11]. This was also suggested by HLA genes [12–14]. Finally, both genetic [8] and archaeological [15] evidence suggests that two-way Tran-Atlantic traffic occurred before Columbus discovered America; archaeologists in New Mexico have recently found tools used 20,000 years ago in Spanish Solutrean culture [15,16]. Other archaeological common tools to America and Europe have been found [17].

* Corresponding author at: Departamento de Inmunología, Facultad de Medicina, Universidad Complutense, Pabellón 5, planta 4. Avda. Complutense s/n, 28040 Madrid, Spain.
E-mail address: arnaizantonio@gmail.com (A. Arnaiz-Villena).
[1] These authors contributed equally for this work and the order of authorship is arbitrary.

http://dx.doi.org/10.1016/j.humimm.2016.01.006
0198-8859/

HLA-G proteins have been found to be tolerogenic MHC molecules. They have a role in foetal/maternal immunological tolerance and also in pathologies like spontaneous abortions, tumour immunology, transplantation autoimmunity [18]. Polymorphism is relatively low compared to classical class I loci: 17 proteins and 13 non coding variants have been described [19]. In the present paper, two new ancient American natives alleles are described and their functional characteristics are discussed.

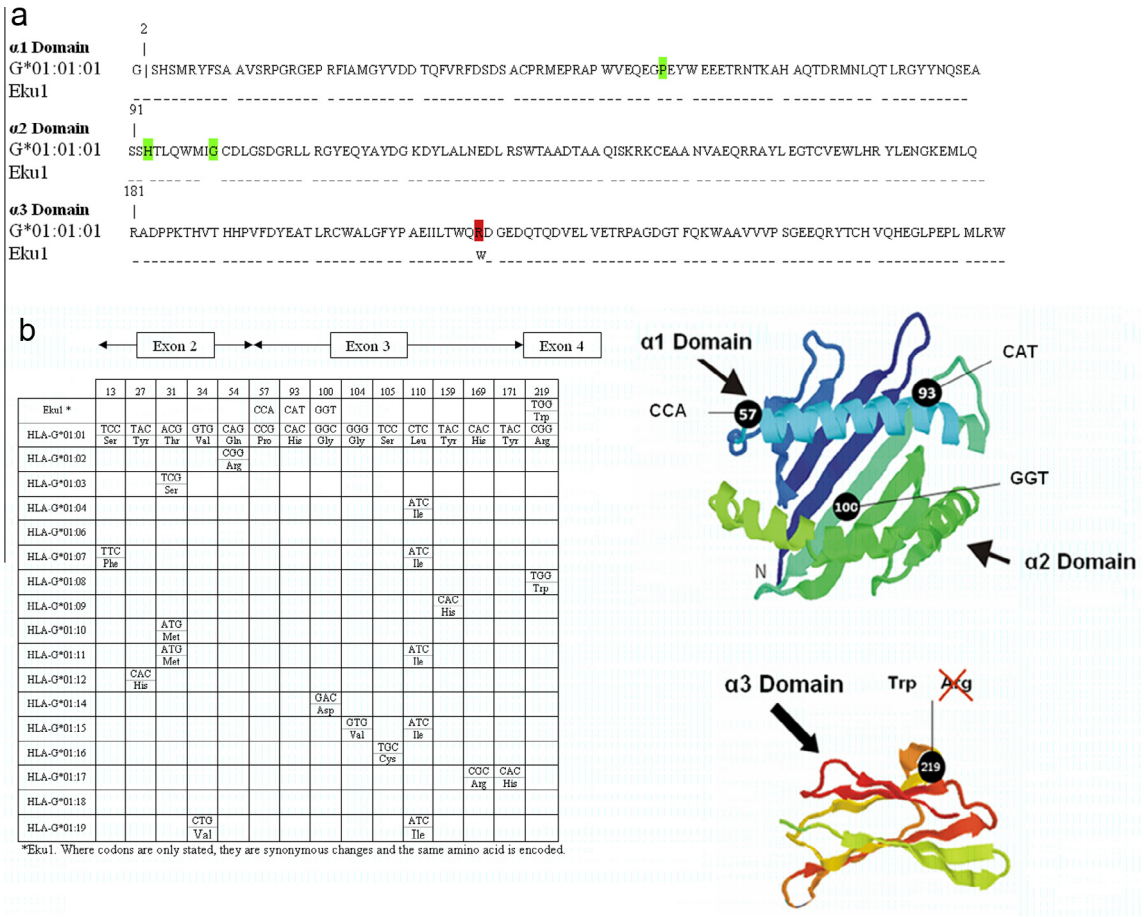
2. Material and methods

2.1. Population samples

154 healthy unrelated Amerindian and Caribbean individuals were HLA-A, -B, -DRB1 and DQB1 typed [20]. Samples were collected from volunteer immigrant Amerindian blood donors at The Madrid Regional Blood Center by Dra Sedeka Abd-El-Fatah-Khalil. A written consent to participate in the present study was signed by each individual blood donor. Individuals were classified as Amerindian by physical anthropological appearance and were born in an Andean or other Iberian-American country and their Amerindian origin was confirmed by HLA genes. Only individuals who come from rural or tribal areas and whose grand-parents come from the same areas were used for the study. Caribbean individual (whose HLA-G allele is described in this paper) had a mixed phenotype with Caucasoid, African and Amerindian characteristics.

2.2. DNA extraction, amplification and HLA-G sequencing

Genomic DNA from peripheral blood mononuclear cells was extracted with the 340A Nucleic Acids Extractor (Perkin Elmer, Foster City, CA, USA) by using Applied Biosystem reagent and protocols. DNA amplification of exons 2, 3 and 4 of *HLA-G* was carried out by direct PCRs. In order to obtain each H*LA-G exons* sequences,



	α1 Domain		α2 Domain	α3 Domain
Residue	57	93	100	219
G*01:01:01	Pro	His	Gly	Arg
New allele (Eku1)	Pro	His	Gly	Trp
DNA codon changes	CCG → CCA	CAC → CAT	GGC → GGT	CGG → TGG

Fig. 1. New HLA-G allele found in Ecuador. (a) Amino acid sequence of the new HLA-G allele found in Ecuador (Eku1). Amino acid silent changes are marked in green colour; amino acid non-silent change is marked in red colour. (b) Protein HLA-G alleles including the new allele Eku1. Variable amino acid positions of each HLA-G are indicated in table. α1 and α2 domains 3D structure of the new HLA-G allele with their codon changes is also shown. (c) Amino acid variability between new allele (Eku1) and HLA-G*01:01 allele. This allele sequence was sent to GenBank on January 29th 2015; accession number KP739973 was given on February 4th 2015. The consensus amino acids are based on the G*01:01 amino acid sequence. Silent DNA change that makes this HLA-G allele a new one is highlighted with a square. Otherwise, it is identical to HLA-G*01:08 allele.