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HLA-G 3'UTR 14 bp Insertion Is Associated with a Decreased Risk of Developing Human African Trypanosomiasis in the Côte d'Ivoire Population

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Abstract

Human African trypanosomiasis (HAT), or sleeping sickness, caused by *Trypanosoma brucei gambiense*, is associated with diverse clinical outcomes. Host's genetic factors involved in immunity are potential factors that can regulate infection. Genetic polymorphisms within *HLA-G* could influence the level of HLA-G expression and therefore play a critical role in infection outcomes. The goal of our study was to investigate the association of 14 bp Indel *HLA-G* polymorphism with the susceptibility/resistance to HAT. DNA samples were collected from 119 cases, 221 controls and 43 seropositive individuals living in Ivorian HAT foci. The 14 bp Indel polymorphism was determined by PCR. Homozygous individuals for 14 bp insertion had a lower risk of progressing to active HAT (p = 0.012, OR = 0.27, 95% CI: 0.09 - 0.8). Moreover, the frequency of 14 bp insertion homozygous genotype was higher in the seropositive group (11%) than in the HAT cases group (3%) (p = 0.043, OR = 0.27, 95% CI: 0.07 - 0.99), which suggested a protective effect of 14 bp

insertion homozygous genotype. Genetic polymorphisms in *HLA-G* may be associated with a variable risk to develop HAT. The 14 bp insertion appears to favour the occurrence of long-lasting *T. b. gambiense* latent infections.

Keywords

HLA-G, Human African Trypanosomiasis, *Trypanosoma brucei gambiense*, Genetic Association Study

1. Introduction

Human African trypanosomiasis (HAT), or sleeping sickness, caused by *Trypanosoma brucei gambiense* (*T. b. gambiense*) is classically described as a chronic infection characterized by an early hemolymphatic stage (stage 1) associated with nonspecific symptoms such as intermittent fevers and headaches, followed by a meningoencephalitic stage (stage 2) in which the parasite invades the central nervous system and causes neurological disorders and death if left untreated. However, asymptomatic carriers and spontaneous cure without treatment have been described [1], underlining the phenomenon of human trypanotolerance/resistance [2] [3]. Host's genetic factors might be involved in the control of the infection and the progression of disease, as clearly shown for *Trypanosoma congolense* infections in experimental models [4] [5] and also in humans [6]-[11]. Genes coding immune system proteins such as the Human leucocyte antigen (HLA)-G are important candidates.

HLA-G is a non-classical major histocompatibility complex (MHC) class I gene. It is located on chromosome 6p21.3 and encompasses 4144 nucleotides distributed across eight exons and seven introns. *HLA-G* can generate four forms of membrane-bound proteins (HLA-G1, G2, G3, and G4) and three forms of soluble proteins (HLA-G5, G6, and G7) due to HLA-G alternative splicing. *HLA-G* has a restricted distribution and is mainly expressed in trophoblastic cells, thymic epithelium, pancreas, cornea, nail matrix, and erythroid and endothelial precursors under normal physiological condition [12]. As an immune checkpoint molecule, *HLA-G* can bind its inhibitory receptors present on immune cells (NK, T, B and dendritic cells, monocytes/macrophage and neutrophils) and inhibit crucial functions of these effectors such as proliferation, differentiation, cytotoxicity, phagocytosis, reactive oxygen species and antibody production [13] [14] [15]. Exon 8 consists in a regulatory 3' untranslated region (3'UTR) that plays an important role in gene expression [16] Among the 17 variation sites that have been identified in 3'UTR, the 14 bp Insertion/Deletion polymorphism has been extensively studied in different pathologies including infectious diseases and seems to play an important role on *HLA-G* alternative splicing and *HLA-G* messenger RNA stability [16] [17] [18].

The 14 bp Indel polymorphism has been previously associated with human immunodeficiency virus (HIV), hepatitis C virus, Human cytomegalovirus

(*HCMV*), Human Papilloma Virus (HPV) [19] and more recently with HAT susceptibility in Democratic Republic of the Congo (DRC) [20]. In Côte d'Ivoire, only two studies have focussed on the role of human genetic variants in HAT susceptibility. The first one investigated the role of genetic polymorphisms in genes coding for cytokines (*IL*10 *and TNFA)* [6] and the second one investigated association between single markersin16 candidate genes (*IL*1, *IL*4, *IL*4*R*, *IL*6, *IL*8, *IL*10, *IL*12, *IL*12*R*, *TNFA*, *INFG*, *MIF*, *APOL*1, *HPR*, *CFH*, *HLA-A* and *HLA-G*) and the disease [21]. However, the role played by the 14-bp Indel (rs16375) polymorphism was not investigated in these studies. In the present study, we investigated the association of the 14 bp Indel (rs16375) polymorphism from *HLA-G* regarding susceptibility/resistance to HAT.

2. Material and Methods

2.1. Ethics Statement

All samples were collected within the framework of medical surveys and epidemiological surveillance activities supervised by the HAT National Control Program (HAT NCP). Samples were collected during routine screening and diagnostic procedures implemented by NCP. All participants were informed on the purpose of the study in their own language and signed an informed consent form. Approval from the Ivorian National Ethics Committee, No. 0308/MSLS/CNER-P, January 30, 2012 was obtained for the study.

2.2. Study Population and Phenotype Definition

The samples consisted of 383 individuals, 119 cases, 221 controls and 43 seropositive individuals (latent infections). Blood samples were collected between 2012 and 2016 from study participants from the main HAT foci located in western-central Côte d'Ivoire (Bonon, Bouaflé, Zoukougbeu, Oumé, and Sinfra). Controls were matched with HAT cases and seropositive individuals (latent infections) on age, sex and ethnic group. For each individual, an aliquot of plasma was used to perform the immune trypanolysis test that detects Litat 1.3 and Litat 1.5 variable surface antigens specific for *T.b. gambiense* [22] Cases were defined as individuals with trypanosomes detected in either lymph node aspirate, blood, or cerebrospinal fluid (CSF) by microscopy, after concentrating parasites, if necessary [23]. Individuals with positive CATT [24] and trypanolysis test results (TL+) [22], in whom no trypanosomes were detected by microscopy were considered as seropositive individuals. Controls were defined as individuals living in an endemic area for which CATT and trypanolysis test are negative, with no suggestive signs or symptoms of HAT and without evidence of previous HAT infection. All individuals with end titers of 1/4 or greater were submitted to the microscopic examination of lymph node aspirates whenever swollen lymph nodes were present; 500 µl of the buffy coat (BC) was then examined by using the mini-anion exchange centrifugation test (mAECT) [23] to detect trypanosome parasites. Some HAT cases and seropositives included in the study were

diagnosed during active HAT survey performed between 2009 and 2012 in collaboration with the National Control Programme (NCP), the Institut de Recherche pour le Développement (IRD) and Institut Pierre Richet (IPR) using serological and parasitological investigations. Study sites were revisited between 2012 and 2016 to consent and resample previously diagnosed and treated patients and seropositive individuals. All cases, seropositive and controls subjects included in this study were well defined. For each subject, the following covariates were collected: 1) age at diagnosis in years; 2) ethnic group, classified as native and non-native (natives originate from the HAT focus and non-natives are ethnic groups from northern Côte d'Ivoire, Mali and Burkina Faso areas where HAT was not present) and; 3) sex.

Collected samples were then frozen directly in the field at −20˚C and stored at −20˚C at Jean Lorougnon Guédé University in Daloa, Côte d'Ivoire until used.

2.3. *HLA-G* 14 bp Insertion/Deletion (Indel) Allele Genotyping

Genomic DNA was obtained from peripheral blood samples. Extraction was performed using Qiagen kits according to the manufacturer's instructions. DNA was stored at −20˚C until the time of analysis.

The *HLA-G* 14 bp Indel polymorphism in exon 8 (3'-UTR) of the *HLA-G* gene was identified by polymerase chain reaction (PCR) and performed as previously described [25]. The PCR primers were the following: forward primer/5'-GTG ATG GGC TGT TTA AAG TGT CAC C-3' and reverse primer/5'-GGA AGG AAT GCA GTT CAG CAT GA-3'. 20 ng of DNA sample was amplified in 25 µl of a reaction mixture containing 0.5 units of Taq DNA polymerase, dNTPs (2.5 µM each) (biotechrabbit, Germany), using an automated PCR thermal cycler (BIO RAD T100™ Thermal Cycler). Thermal cycling was performed with an initial 94˚C for 5 min followed by 39 cycles at 94˚C for 40 s, annealing at 58˚C for 40 s and extension at 72˚C at 60 s and a final extension at 72˚C for 10 min. The amplified products were visualized by electrophoresis on a 2% agarose gel (120V for 1 hour) containing ethidium bromide (0.5 mg/ml). PCR products were either 224 or 210 bp, or both 224 and 210 bp, depending on the insertion/deletion of the 14 bp in exon 8. The number of 14 bp indel alleles was directly counted (**Figure 1**).

2.4. Statistical Analysis

All statistical analyses were performed using the Plink 1.9 and Rv 3.2.1 software. The Pearson Chi-square test was used to compare the frequencies of observed and expected genotypes under Hardy-Weinberg equilibrium. The allele and genotype frequencies were calculated by direct gene counting from the genotyping results. Association of HAT with recorded covariates (age and ethnic group) were analysed by multivariate analysis. Tests were performed under a recessive model to examine the association between HLA-G genotypes and alleles and the risk to develop HAT. Unadjusted odds ratios (OR) were reported with 95% confidence intervals (CI). A significant threshold of P value ≤ 0.05 was taken.

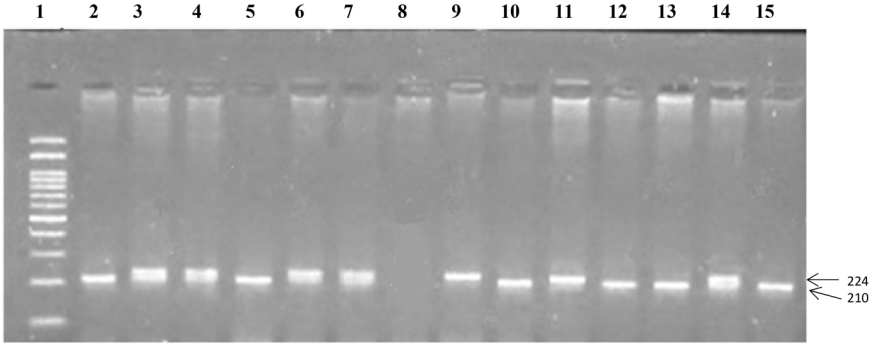

Figure 1. *HLA-G* 14 bp polymorphism detected on agarose gel. Lanes 1, 100bp DNA ladder, Lines 2, 5, 10, 12, 13 and 15 are homozygotes *HLA-G*Del/Del; Lines 3, 4, 6, 7, and 14 are *HLA-G* heterozygotes indel; Lines 9 and 11 are HLA-G homozygotes Ins/Ins; Lines 8 is negative control.

3. Results

3.1. Characteristics of the Population

A total of 119 cases, 221 controls and 43 seropositive individuals (latent infections) were enrolled into the study (Table 1). The mean age (range) of the study population was 38.8 (6 ± 85) years. The sex ratio (male: female) was 1.0 (192/191). There were no significant differences between case, control and seropositive groups concerning age, sex and ethnic group (Table 1).

The 14 bp deletion allele was predominant, with a frequency of 68 % in the study population (Table 2).

3.2. *HLA-G* Allele and Genotype Association with HAT

The distributions of allele and genotype frequencies of *HLA-G* 14 bp Indel polymorphism are reported in Table 2. The *HLA-G* Indel 14 bp polymorphism was in Hardy–Weinberg equilibrium in our population ($P = 0.12$).

3.3. *HLA-G* 14 bp Indel Polymorphism in HAT Patients, Controls and Seropositive Individuals

No significant differences were observed in the frequencies of 14 bp *HLA-G* alleles between HAT cases and controls. Nevertheless, the 14 bp insertion/insertion homozygote genotype was underrepresented in HAT cases (p = 0.012, OR = 0.27, 95% CI: 0.09 - 0.8) (Table 3).

No significant difference was observed in both allelic and genotypic frequencies between seropositive and control groups (Table 3), whereas the 14 bp insertion/insertion genotype was also significantly associated with seropositivity in the Seropositive/HAT cases comparison (p = 0.043, OR = 0.26, 95% CI: 0.07 - 0.99, Table 3) indicating that seropositive subjects carrying the insertion/insertion homozygote genotypes may be at lower risk of developing the disease.

Estimation represents regression coefficients which can be positive or negative. Regression coefficients measure the increase (positive value) or decrease

Table 1. Population characteristics.

Covariates			95% CI	Multivariate
	n	Estimation		P-value
Sex				
females	192	−0.071	−0.25 - 0.11	0.44
males	191			
Age				
<20 years	15			
20 - 39 years	114	0.084	−0.05 - 0.22	0.24
≥40 years	92			
Ethnicity group				
native	232			
non-native	145	−0.116	−0.29 - 0.06	0.21
ND	6			

ND: Not determined, n: number, CI (95%): Confidence interval, native: originate from the HAT focus, non-native: ethnic groups from northern Côte d'Ivoire, Mali and Burkina Faso areas where HAT was not present.

Table 2. Allelic and genotypic frequencies in the study population.

Alleles and génotypes	Phenotypes			Freq gp	HWE	
	Controls (%)	Cases (%)	SP (%)		χ^2	P-value
Del	295 (0.67)	176 (0.74)	55 (0.64)	0.68		
Ins	147 (0.33)	62 (0.26)	31 (0.36)	0.32		
Del/Del	99 (0.45)	61 (0.51)	17 (0.4)	0.45	7.29	0.12
Ins/Ins	25 (0.11)	4 (0.03)	5 (0.11)	0.09		
Del/Ins	97 (0.44)	54 (0.46)	21 (0.49)	0.46		

Freq gp: Frequency in the general population, SP: Seropositive subjects, HWE: Hardy-Weinberg equilibrium, Del: Deletion, Ins: Insertion.

(negative value) of the dependent variable (different phenotypes, cases, latent infections and controls) due to the presence of the independent ones. Covariates included in linear multivariate regression were ethnicity group, sex and age.

4. Discussion

First described at the maternal-foetal interface [26] it is increasingly evident that the well-known immunosuppressive properties of *HLAG* on both innate and adaptative immune responses, are also involved in the aetiology of a number of diseases such as cancers or infectious/parasitic diseases [27] [28] [29] [30]. The results obtained during this study suggest a protective effect of the exon 8 3'UTR *HLAG* 14 bp insertion/insertion genotype against *T. brucei gambiense* infection in the population of Côte d'Ivoire. The 14 bp insertion in the HLAG 3'UTR has

Table 3. Distribution of the 14-bp insertion/deletion alleles and genotypes frequencies in HAT patients, controls and seropositive individuals in Côte d'Ivoire.

	Allelic Model														
HLA-G 14 bp alleles	Cases (%)	Controls (%)	OR	CI (95%)	P-value	Cases (%)	SP (%)	OR	CI (95%)	P-value	SP (%)	Controls (%)	OR	CI (95%)	P-value
Del	176 (0.73)	295 (0.67)				176 (0.73)	55 (0.64)				55 (0.64)	295 (0.67)			
Ins	62 (0.27)	147 (0.33)	1.41	0.98 - 2.04	0.055	62 (0.27)	31 (0.36)	1.59	0.90 - 2.78	0.094	31 (0.36)	147 (0.33)	0.88	0.53 - 1.48	0.62
HLA-G 14 bp genotypes						Recessive model									
Ins/Ins	4 (0.03)	25 (0.11)				4 (0.03)	5 (0.11)				5 (0.11)	25 (0.11)			
Ins/Del+ Del/Del	115 (0.97)	196 (0.89)	0.27	0.06 - 0.82	0.012	115 (0.97)	38 (0.11)	0.26	0.07 - 0.99	0.043	38 (0.89)	196 (0.89)	1.03	0.37 - 2.86	0.952

OR: Odds ratio; CI (95 %): Confidence interval; SP: Seropositive subjects; Ins: Insertion, Del: Deletion.

been extensively studied in a number of diseases and was shown to be associated with low *HLAG* mRNA expression levels [17] through its influence on mRNA stability and splicing patterns [18] [31]. Individuals homozygote for the 14-bp insertion had a lower risk of developing HAT in our study population as suggested by the fact that the 14-bp insertion/insertion genotype was significantly more frequent in both endemic controls (OR = 0.27; p = 0.012) and seropositive individuals suspected to harbour latent infections (OR = 0.26; p = 0.043). Therefore, in our population, the *HLAG* 3'UTR 14 bp polymorphism does not appear to provide protection against infection itself but rather against infection progressing to severe disease. This result suggests that some *HLAG* polymorphisms may favour *T. b. gambiense* asymptomatic carriage and contribute to disease maintenance in HAT foci despite control measures targeted to HAT patients only [32]. As stated above the 14 bp insertion has mainly been associated with low HLAG mRNA expression levels. We add however no data to analyse *HLAG* expression in the framework of this study, we may, however, speculate that in our HAT patients high *HLAG* expression contributed to *T. b. gambiense* immune evasion, leading to parasite multiplication and disease progression, whereas in seropositive lower levels enable better control of infection. In agreement with this hypothesis, high levels of s-HLAG were reported recently from Guinea in the plasma of HAT patients. High s-HLAG plasmatic levels were also prognostic of subsequent disease development in seropositive subjects that were followed up in time after their initial diagnosis [33]. A different association was however described in the Democratic Republic of Congo where the HLAG UTR-2 haplotype (including the 14 bp insertion and a G at position +3196) was associated with increased susceptibility to HAT in a family-based association study [20]. The reasons for this discrepancy are yet unclear but may reflect parasite population heterogeneities in their ability to induce *HLA-G* expression or different patterns of linkage disequilibrium across populations. At present, it is

not fully clarified whether the 14 bp Indel polymorphism has itself a functional impact or if it is just a genetic marker for other *HLA-G* polymorphisms with functional significance. Other polymorphisms of the *HLA-G* gene may potentially affect the biological properties of the protein. Theoretically, polymorphic sites observed along the coding region may modify the encoded protein and consequently the interaction with HLA-G receptors and/or formation of *HLA-G* dimers that may more efficiently bind to *HLA-G* receptors. Thus, a particular allele and a particular molecule could provide susceptibility or protection against disease development [27].

In conclusion we have shown that the 3'UTR 14 bp insertion is associated with differential susceptibility to HAT in the population of Côte d'Ivoire. At the homozygous state this insertion appears to favour *T. b. gambiense* asymptomatic carriage and may thus favour disease persistence in endemic foci. A better characterization of *HLA-G* polymorphisms combined with the analysis of the gene expression levels will be required to better understand the biological mechanisms at play in the host-parasite interaction.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Jamonneau, V., Ilboudo, H., Kaboré, J., Kaba, D., Koffi, M., Solano, P., Garcia, A., Courtin, D., Laveissière, C., Lingue, K., Büscher, P. and Bucheton, B. (2012) Untreated Human Infections by *Trypanosoma brucei gambiense* Are Not 100% Fatal. *PLoS Neglected Tropical Diseases*, **6**, e1691. https://doi.org/10.1371/journal.pntd.0001691

[2] Bucheton, B., MacLeod, A. and Jamonneau, V. (2011) Human Host Determinants Influencing the Outcome of *Trypanosoma brucei gambiense* Infections. *Parasite Immunology*, **33**, 438-447. https://doi.org/10.1111/j.1365-3024.2011.01287.x

[3] Checchi, F., Filipe, J.A.N., Barrett, M.P. and Chandramohan, D. (2008) The Natural Progression of Gambiense Sleeping Sickness: What Is the Evidence? *PLoS Neglected*

Tropical Diseases, **2**, e303. https://doi.org/10.1371/journal.pntd.0000303

[4] Iraqi, F., Clapcott, S.J., Kumari, P., Haley, C.S., Kemp, S.J. and Teale, A.J. (2000) Fine Mapping of Trypanosomiasis Resistance Loci in Murine Advanced Intercross Lines. *Mammalian Genome*, **11**, 645-648. https://doi.org/10.1007/s003350010133

[5] Kemp, S.J., Iraqi, F., Darvasi, A., Soller, M. and Teale, A.J. (1997) Localization of Genes Controlling Resistance to Trypanosomiasis in Mice. *Nature Genetics*, **16**, 194-196. https://doi.org/10.1038/ng0697-194

[6] Courtin, D., Argiro, L., Jamonneau, V., N'dri, L., N'guessan, P., Abel, L., Dessein, A., Cot, M., Laveissiere, C. and Garcia, A. (2006) Interest of Tumor Necrosis Factor-Alpha −308 G/A and Interleukin-10 −592 C/A Polymorphisms in Human African Trypanosomiasis. *Infection, Genetics and Evolution*, **6**, 123-129. https://doi.org/10.1016/j.meegid.2005.03.002

[7] Courtin, D., Jamonneau, V., Mathieu, J.-F., Koffi, M., Milet, J., Yeminanga, C.S., Kumeso, V.K., Cuny, G., Bilengue, C.M. and Garcia, A. (2006) Comparison of Cytokine Plasma Levels in Human African Trypanosomiasis. *Tropical Medicine & International Health*, **11**, 647-653. https://doi.org/10.1111/j.1365-3156.2006.01612.x

[8] Courtin, D., Milet, J., Jamonneau, V., Yeminanga, C.S., Kumeso, V.K., Bilengue, C.M., Betard, C. and Garcia, A. (2007) Association between Human African Trypanosomiasis and the IL6 Gene in a Congolese Population. *Infection, Genetics and Evolution*, **7**, 60-68. https://doi.org/10.1016/j.meegid.2006.04.001

[9] Cuypers, B., Lecordier, L., Meehan, C.J., Van den Broeck, F., Imamura, H., Buscher, P., Dujardin, J.-C., Laukens, K., Schnaufer, A., Dewar, C., Lewis, M., Balmer, O., Azurago, T., Kyei-Faried, S., Ohene, S.-A., Duah, B., Homiah, P., Mensah, E.K., Anleah, F., Franco, J.R., Pays, E. and Deborggraeve, S. (2016) Apolipoprotein L1 Variant Associated with Increased Susceptibility to Trypanosome Infection. *American Society for Microbiology*, **7**, e02198-02115. https://doi.org/10.1128/mBio.02198-15

[10] Hardwick, R.J., Menard, A., Sironi, M., Milet, J., Garcia, A., Sese, C., Yang, F,-T., Fu, B.-Y., Courtin, D. and Hollox, E.J. (2014) Haptoglobin (*HP*) and Haptoglobin-Related Protein (*HPR*) Copy Number Variation, Natural Selection, and Trypanosomiasis. *Human Genetics*, **133**, 69-83. https://doi.org/10.1007/s00439-013-1352-x

[11] Kaboré, J.W., Ilboudo, H., Noyes, H., Camara, O., Kaboré, J., Camara, M., Koffi, M., Lejon, V., Jamonneau, V., MacLeod, A., Hertz-Fowler, C., Belem, A.M.G., Matovu, E., Bucheton, B. and Sidibe, I. (2017) Candidate Gene Polymorphisms Study between Human African Trypanosomiasis Clinical Phenotypes in Guinea. *PLoS Neglected Tropical Diseases*, **11**, e0005833. https://doi.org/10.1371/journal.pntd.0005833

[12] Moon, A., Kim, S.K., Chung, J.H., Na, K.Y., Olvi, L.G., Santini-Araujo, E., Kim, Y.W. and Park, Y.K. (2011) 14-bp Insertion/Deletion Polymorphism of the HLA-G Gene in Osteosarcoma Patients. *The Korean Journal of Pathology*, **45**, 485-490. https://doi.org/10.4132/KoreanJPathol.2011.45.5.485

[13] Carosella, E.D. (2011) The Tolerogenic Molecule HLA-G. *Immunology Letters*, **138**, 22-24. https://doi.org/10.1016/j.imlet.2011.02.011

[14] Carosella, E.D., Rouas-Freiss, N., Tronik-Le Roux, D., Moreau, P. and LeMaoult, J. (2015) HLA-G: An Immune Checkpoint Molecule. *Advances in Immunology*, **127**, 33-144. https://doi.org/10.1016/bs.ai.2015.04.001

[15] Le Bouteiller, P. and Lenfant, F. (1997) Gène HLA-G: Le plus classique des non classiques. *Médecine/Sciences*, **13**, 1436-1444. https://doi.org/10.4267/10608/575

[16] Donadi, E.A., Castelli, E.C., Arnaiz-Villena, A., Roger, M., Rey, D. and Moreau, P. (2011) Implications of the Polymorphism of HLA-G on Its Function, Regulation, Evolution and Disease Association. *Cellular and Molecular Life Sciences*, **68**, 369-395. https://doi.org/10.1007/s00018-010-0580-7

[17] Hviid, T.V., Hylenius, S., Rorbye, C. and Nielsen, L.G. (2003) HLA-G Allelic Variants Are Associated with Differences in the HLA-G mRNA Isoform Profile and HLA-G mRNA Levels. *Immunogenetics*, **55**, 63-79.

[18] Rousseau, P., Le Discorde, M., Mouillot, G., Marcou, C., Carosella, E.D. and Moreau, P. (2003) The 14 bp Deletion-Insertion Polymorphism in the 3' UT Region of the HLA-G Gene Influences HLA-G mRNA Stability. *Human Immunology*, **64**, 1005-1010. https://doi.org/10.1016/j.humimm.2003.08.347

[19] Amiot, L., Vu, N. and Samson, M. (2014) Immunomodulatory Properties of HLA-G in Infectious Diseases. *Journal of Immunology Research*, **2014**, Article ID: 298569. https://doi.org/10.1155/2014/298569

[20] Courtin, D., Milet, J., Sabbagh, A., Massaro, J.D., Castelli, E.C., Jamonneau, V., Bucheton, B., Sese, C., Favier, B., Rouas-Freiss, N., Moreau, P., Donadi, E.A. and Garcia, A. (2013) HLA-G 3' UTR-2 Haplotype is Associated with Human African Trypanosomiasis Susceptibility. *Infection, Genetics and Evolution*, **17**, 1-7. https://doi.org/10.1016/j.meegid.2013.03.004

[21] Ahouty, B., Koffi, M., Ilboudo, H., Simo, G., Matovu, E., Mulindwa, J., Hertz-Fowler, C., Bucheton, B., Sidibé, I., Jamonneau, V., MacLeod, A., Noyes, H. and N'Guetta, S.P. (2017) Candidate Genes-Based Investigation of Susceptibility to Human African Trypanosomiasis in Côte d'Ivoire. *PLoS Neglected Tropical Diseases*, **11**, e0005992. https://doi.org/10.1371/journal.pntd.0005992

[22] Jamonneau, V., Bucheton, B., Kabore, J., Ilboudo, H., Camara, O., Courtin, F., Solano, P., Kaba, D., Kambire, R., Lingue, K., Camara, M., Baelmans, R., Lejon, V. and Buscher, P. (2010) Revisiting the Immune Trypanolysis Test to Optimise Epidemiological Surveillance and Control of Sleeping Sickness in West Africa. *PLoS Neglected Tropical Diseases*, **4**, e917. https://doi.org/10.1371/journal.pntd.0000917

[23] Lumsden, W.H.R., Kimber, C.D., Evans, D.A. and Doig, S.J. (1979) *Trypanosoma brucei*: Miniature Anion-Exchange Centrifugation Technique for Detection of Low Parasitaemias: Adaptation for Field Use. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **73**, 312-317. https://doi.org/10.1016/0035-9203(79)90092-0

[24] Magnus, E., Vervoort, T. and Van Meirvenne, N. (1978) A Card-Agglutination Test with Stained Trypanosomes (C.A.T.T.) for the Serological Diagnosis of *T. B. Gambiense trypanosomiasis*. *Annales de la Société Belge de Médecine Tropicale*, **58**, 169-176.

[25] Silva, H.P., Ururahy, M., Souza, K.S., Loureiro, M.B., Oliveira, Y.M., Oliveira, G.H., Luchessi, A.D., Carvalho, K.T., Freitas, J.C., Donadi, E.A., Hirata, R.D., Almeida, M.G., Arrais, R.F., Hirata, M.H. and Rezende, A.A. (2016) The Association between the HLA-G 14-bp Insertion/Deletion Polymorphism and Type 1 Diabetes. *Genes Immunity*, **17**, 13-18. https://doi.org/10.1038/gene.2015.45

[26] Berger, D.S., Hogge, W.A., Barmada, M.M. and Ferrell, R.E. (2010) Comprehensive Analysis of HLA-G: Implications for Recurrent Spontaneous Abortion. *Reproductive Sciences*, **17**, 331-338. https://doi.org/10.1177/1933719109356802

[27] Dias, F.C., Castelli, E.C., Collares, C.V., Moreau, P. and Donadi, E.A. (2015) The Role of HLA-G Molecule and HLA-G Gene Polymorphisms in Tumors, Viral Hepatitis, and Parasitic Diseases. *Frontiers in Immunology*, **6**, Article 9.

https://doi.org/10.3389/fimmu.2015.00009

[28] Garcia, A., Milet, J., Courtin, D., Sabbagh, A., Massaro, J.D., Castelli, E.C., Migot-Nabias, F., Favier, B., Rouas-Freiss, N., Donadi, E.A. and Moreau, P. (2013) Association of HLA-G 3'UTR Polymorphisms with Response to Malaria Infection: A First Insight. *Infection, Genetics and Evolution*, **16**, 263-269. https://doi.org/10.1016/j.meegid.2013.02.021

[29] Sabbagh, A., Courtin, D., Milet, J., Massaro, J.D., Castelli, E.C., Migot-Nabias, F., Favier, B., Rouas-Freiss, N., Moreau, P., Garcia, A. and Donadi, E.A. (2013) Association of HLA-G 3' Untranslated Region Polymorphisms with Antibody Response Against Plasmodium Falciparum Antigens: Preliminary Results. *Tissue Antigens*, **82**, 53-58. https://doi.org/10.1111/tan.12140

[30] Sadissou, I., d'Almeida, T., Cottrell, G., Luty, A., Krawice-Radanne, I., Massougbodji, A., Moreau, P., Moutairou, K., Garcia, A., Favier, B., Rouas-Freiss, N. and Courtin, D. (2014) High Plasma Levels of HLA-G Are Associated with Low Birth Weight and with an Increased Risk of Malaria in Infancy. *Malaria Journal*, **13**, Article ID: 312. https://doi.org/10.1186/1475-2875-13-312

[31] Celsi, F., Catamo, F., Kleiner, G., Tricarico, P.M., Vuch, J. and Crovella, S. (2013) HLA-G/C, miRNAs, and Their Role in HIV Infection and Replication. *BioMed Research International*, **2013**, Article ID: 693643. https://doi.org/10.1155/2013/693643

[32] Berthier, D., Peylhard, M., Dayo, G.K., Flori, L., Sylla, S., Bolly, S., Sakande, H., Chantal, I. and Thevenon, S. (2015) A comparison of Phenotypic Traits Related to Trypanotolerance in Five West African Cattle Breeds Highlights the Value of Shorthorn Taurine Breeds. *PLoS ONE*, **10**, e0126498. https://doi.org/10.1371/journal.pone.0126498

[33] Gineau, L., Courtin, D., Camara, M., Ilboudo, H., Jamonneau, V., Dias, F.C., Tokplonou, L., Milet, J., Mendonca, P.B., Castelli, E.C., Camara, O., Camara, M., Favier, B., Rouas-Freiss, N., Moreau, P., Donadi, E.A., Bucheton, B., Sabbagh, A. and Garcia, A. (2016) Human Leukocyte Antigen-G: A Promising Prognostic Marker of Disease Progression to Improve the Control of Human African *Trypanosomiasis. Clinical Infectious Diseases*, **63**, 1189-1197. https://doi.org/10.1093/cid/ciw505

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