ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 11, Issue, 03, pp. 45319-452324, March, 2021
https://doi.org/10.37118/ijdr.21282.03.2021

RESEARCH ARTICLE OPEN ACCESS

EPSTEIN-BARR VIRUS INFECTION AND POLYMORPHISMS IN HUMAN LEUKOCYTE ANTIGEN GENES IN TRANSPLANT DONORS AND RECEPTORS FROM THE STATE OF PARÁ, AMAZON, BRAZIL

Jessica Sabrina Cordeiro Parente[1], Carlos Eduardo de Melo Amaral[1], Igor Brasil Costa[2], Iran Barros Costa[2], Jacqueline Cortinhas Monteiro[3], Luana Joana Barreto Cabral[1], Rafael dos Santos Barros[1], Eduardo dos Santos Martins Filho[1], Eliane Evanovich[4,5], Mauricio Koury Palmeira[1], Luciana Maria Cunha Maradei Pereira[1], João Farias Guerreiro[4] and Patrícia Jeanne de Souza Mendonça-Mattos[1,4]

[1]Foundation Center for Hemotherapy and Hematology of Pará (HEMOPA), Belém, Pará, Brazil; [2]Evandro Chagas Institute, Belém, Pará, Brazil; [3]Laboratory of Virology, Federal University of Pará, Belém, Pará, Brazil; [4]Laboratory of Human and Medical Genetics, Federal University of Pará, Belém, Pará, Brazil, [5]Open University of Brazil, Federal University of Pará, Belem, Pará, Brazil

ARTICLE INFO

Article History:
Received 11th December, 2020
Received in revised form
24th January, 2021
Accepted 04th February, 2021
Published online 17th March, 2021

Key Words:
Epstein-Barr Virus Infections, Kidney Transplantation, HLA Antigens.

Corresponding author:
Jessica Sabrina Cordeiro Parente

ABSTRACT

Background: This work aimed to perform the molecular detection of EBV in samples from donors and recipients of living donor kidney transplantations at the HEMOPA Foundation, in Pará state, an Amazon region, and to characterize the prevalence of EBV and allele frequency of HLA in this population, and seek associations between these two factors. **Methods**: EBV detection was performed on 200 samples of candidate donors and recipients using Nested PCR. We collected HLA classification results from these same individuals and 200 bone marrow donors as the control group in an HLA allelic frequency analysis database. **Results**: The EBV detection rate was similar between candidate donors and recipients. Among the 73 analyzed pairs of donors and recipients, 12 consisted of an undetectable recipient and a detectable donor. The B*41 and B*37 alleles were more frequent in the EBV+ group of patients than the EBV- group, unlike the DRB1 * 08 allele, which was more frequent in the EBV- group. Among EBV+ patients and controls, the A*01 allele was more frequent among detectable patients, while the DRB1*08 and DRB1*10 alleles were more frequent in the control group. The B*08 and DRB1*3 alleles were more frequent in the control group than EBV- patients. **Conclusion**: The significance of these results was shown in Fisher's Exact Testor Chi-Square test; however, no significance was observed after Bonferroni's correction. Increased sample sizes may provide more robust validation of these results in the future.

Citation: ***Jessica Sabrina Cordeiro Parente, Carlos Eduardo de Melo Amaral, Igor Brasil Costa, Iran Barros Costa, Jacqueline Cortinhas Monteiro,* 2021.** "Epstein-barr virus infection and polymorphisms in human leukocyte antigen genesin transplant donors and receptors from the state of Pará, Amazon, Brazil, ", *International Journal of Development Research*, 11, (03), 45319-452324.

INTRODUCTION

The Epstein-Barr Virus (EBV), formally known as *Human gammaherpesvirus* 4, is a worldwide prevalent virus in human populations. EBV infections are predominantly asymptomatic in immunocompetent individuals and occur by establishing latency in B cells (1, 2). However, a succession of cell cycle disorders caused by abnormal gene expression can result in the malignant transformation of infected cells. Thus, EBV is associated with several B cell neoplasms, such as post-transplant lymphoproliferative disease PTLD) (3, 4). During solid organ transplantation, exposure to EBV can be established through the passage of infected cells from a seropositive organ donor to a seronegative receptor, thus causing this syndrome's development (5, 6). Among kidney transplant recipients, PTLD is the second most common malignancy. Due to immunosuppressive medication consisting of anti-Tcell treatments, recipients have an impaired capacity to control EBV primary infection since an immune response would depend on T-cells' functional repertoire. Consequently, recipients are susceptible to active EBV infections and development of PTLD, with subsequent allograft loss and even death (7, 8, 9). In addition to EBV infections,

another important immunological factor regarding allograft maintenance is receptor response. In this process, the human leukocyte antigen (HLA) system is primarily involved because it is responsible for recognizing transplanted cells as self or non-self. HLA genes are located on the short arm of chromosome 6, and HLA class I antigens (HLA-A, -B, -C) and the three HLA class II antigens (HLA -DR, -DQ, -DP) are among those of greatest clinical significance for transplantations (10, 11). The association between HLA and EBV infection lies in the HLA system's crucial role, which determines the efficiency of EBV peptide presentation to T cells. However, the EBV induces HLA down regulation, a mechanism used as an immune evasion strategy (12). Regarding solid organ transplantation (SOT), it has been suggested that individuals who have the HLA A*01 allele may have a higher risk of developing PTLD associated with EBV after transplantation due to an impaired ability to control latent EBV infection. This same allele was reported to significantly increase the risk of BK polyomavirus DNAemia in renal transplant recipients (13,14). In adult SOT recipients, a significant association was detected between the HLA A*26 allele and the development of PTLD. In caucasian recipients, for both recipient and donor, that same allele was independently associated with the a study reported the HLA-A*02 allele's predominant expression among patients with chronically high EBV viral load. In contrast, the HLA-B*08 allele expression was more prevalent in patients who resolved EBV infection, go that different alleles are involved in both protection and risk of active infection by the virus (16, 17). Besides, the presence of the HLA-A*19 or HLA-DRB*17 alleles has also been reported as a significant risk factor for symptomatic EBV infection in pediatric patients after kidney transplantation (18). However, in Brazil and, more specifically in the northern region, studies aiming to assess the association between EBV infections and HLA allelic diversity in kidney transplant donors and recipients have not yet been carried out. Therefore, the study's goal was to investigate EBV infections, characterize HLA allele frequencies, and analyze the correlation between EBV infectionsand different HLA alleles in samples of candidate donors and recipients of living donor kidney transplantation from the state of Pará, a region of Amazon, in northern Brazil.

Samples: This study was performed with 200 samples of living kidney transplantation candidate donors and recipients that had been previously tested for HLA type at the Laboratory of Immunogenetics, HEMOPA Foundation, in Belém, Pará, from January 2017 to December 2019. We also included 200 individuals chosen at random from a database of 5000 candidate bone marrow donors from the same geographic region as controls, using the *Microsoft Excel*® 2019 "RANDBETWEEN ()" function and including those with allele frequencies matching that of the original database. Samples referring to other types of transplants and non-viable samples for DNA extraction and amplification were not included in the research. This study was approved by the Hospital Universitário João de Barros Barreto Ethics Committee under protocol number 4.141.157/2019, and performed in accordance to resolution 196/96 and the declaration of Helsinki, where researchers are committed to the privacy and confidentiality of the dataset, fully preserving the anonymity of patients and using the consent form for data usage. Given the study was carried out retrospectively, the informed consent form was waived.

DNA Extraction and Molecular EBV Detection: DNA extraction was performed on whole blood samples from donors and recipients of living donor kidney transplantation using a Promega commercial kit following manufacturer instructions. Next, EBV molecular detection was carried out through a Nested Polymerase Chain Reaction (Nested PCR) to amplify the LMP-1 region at the Virology Laboratory, Evandro Chagas Institute, Belém, Brazil. Primers used in the initial stage were: F-5 'TGA ATC TGA CTC TAA CTC CAA CGA 3' and R- 5 'ACC CCC ACT CTG CTC TCA AAA CCT A 3', designed with Primer3 software (19). In this reaction, a fragment of about 668 bp was amplified. In the second reaction, the second pair of different primers were used: F- 5 'TGA ATG TGG CTT TTC AGC CTA GAC A 3' and R- 5 'AAG CCT ATG ACA TGG TAA TGC CTA GAA GT 3' (19), resulting in a fragment of about 498 bp. PCR products were visualized on a 2% agarose gel and documented through a photographic record.

HLA Typing: HLA allele frequencies were calculated from the PCR-SSO typing results. Tests were performed at the Laboratory of Immunogenetics (GERIM) of the HEMOPA Foundation, and data were collected using the *HLA Fusion TM* 4.2 software (*One Lambda Inc*.).

Statistical Analyses: Data were digitized to form a database in the *Microsoft Excel* ® 2019 software. The Epstein Barr Virus detection frequencies were calculated using this same software. We employed the $\chi 2$ test for sex analysis and the G test for self-declared ethnicity to compare demographic data between detectable and undetectable individuals. For age, we first analyzed if data were normally distributed and subsequently performed a T-test. Allele frequencies were determined using the *PyPopWin32*-0.7.0 software. Alleles with less than 0.01 (1%) frequencies were not considered in the comparisons. We employed the $\chi 2$ test or Fisher's exact test to compare groupsusing the *OpenEpi* 3.01 program. Odds ratios (OR) with a 95% confidence interval (CI) were also calculated. The p-value with Bonferroni correction was also calculated, multiplying the original *p*-value by the number of alleles tested at each locus.

RESULTS

Table 1 shows the demographic characterization of the studied population. The age of patients ranged from 12 to 72 years (average of 43 years). As for sex distribution, 117 (58.5%) were males, while 83 (41.5%) were females. Regarding the self-declared ethnicity, 104 (52%) patients declared themselves as brown, followed by 24 (12%) white, eight (4%) black, one (1%) yellow, and one (1%) indigenous. A total of 62 patients (31%) did not have this information. Initially, all whole blood samples (N = 200) from candidate kidney transplant donors and recipients were analyzed for molecular detection of EBV. Viral DNA was detected in 58 (29%) of patients.

Table 1. Candidate kidney transplant donors and recipients demographic data

Feature	Patients (N=200)
Sex	
Male	117 (58.5%)
Female	83 (41.5%)
Age (years)	
12-23	11 (6%)
24-35	43 (22%)
36-47	76 (38%)
48-59	53 (26%)
60-72	17 (8%)
Average	43
min-max (sd ±)	12-68 (71)

The detection rate was 24% (25/103) in the group of candidate kidney transplant donors and 34% (33/97) among candidate recipients (Table 2). There was no statistically significant difference between these groups, which shows that the prevalence of EBV is homogeneous in our study population as a whole. These individuals come from the same geographic region, and most recipients with their respective donors belong to the same family, which may explain this result (Table 2). When comparing demographic data between detectable and undetectable candidate donors and recipients for DNA-EBV, we observed a majority of male individuals, with an average age of 42 in the detectable group and 43 among the undetectable. However, there were no statistical differences regarding sex and age between groups (Table 3 and Figure 1). To analyze the risk of EBV transmission from donor to recipient, we paired the recipients with their respective donors, thus obtaining 73 pairs. Of these, 12 pairs consisted of an undetectable recipient and a detectable donor.

Table 2. EBV detection in candidate transplant donor and recipient samples

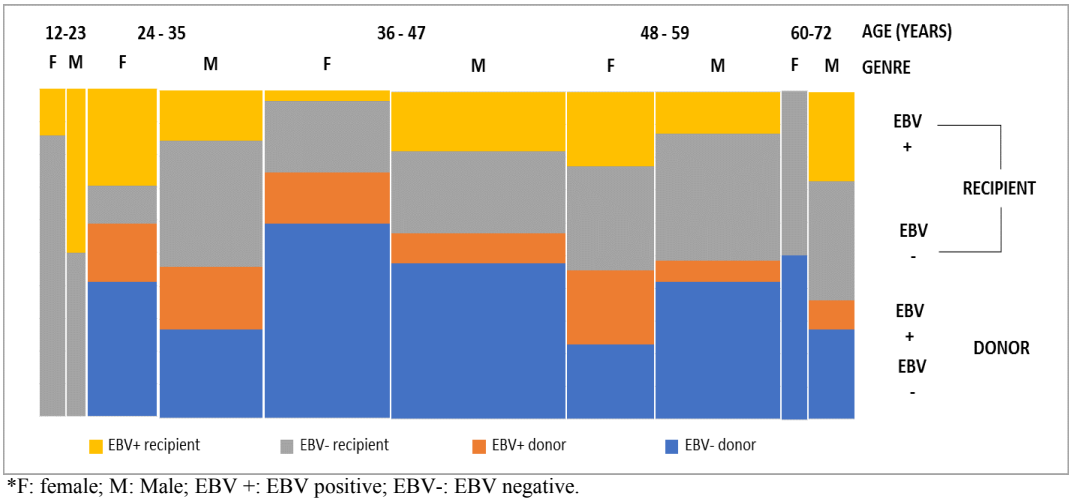
Molecular Results	Donors	Recipients	*p*-value*
Detectable	25 (24%)	33 (34%)	0.1730
Undetectable	78 (76%)	64 (66%)	

p-value*: Qui Square test.

Table 3. Candidate kidney transplant donors and recipients demographic data regarding molecular EBV results

Features	EBV+ Donors	EBV - Donors	EBV+ Recipients	EBV - Recipients	*p*-value*
Sex					
Male	13 (52%)	44 (56%)	21 (64%)	39 (61%)	0.7793
Female	12 (48%)	34 (44%)	12 (36%)	25 (39%)	
Age (years)					
Average	42	44	42	43	
min-max	28 - 67	27 - 72	12-68	13 -71	

p-value*: Qui Square test.



*F: female; M: Male; EBV +: EBV positive; EBV-: EBV negative.

Figure 1. Mosaic Plot of demographic data from candidate donor and recipient kidney transplants

Table 4. HLA allele frequencies for HLA-A, HLA-B e HLA-DR alleles with statistically significant differences between EBV+ and EBV- patients

Allele	EBV+Patients	EBV- Patients	*p*-value*	Corrected *p*-value**	OR	95% CI OR
B*41	4 (3.4%)	0 (0%)	0.00392	0.098175	22.76	1.216-426.1
B*37	3 (3.4%)	0 (0%)	0.01383	0.34575	17.55	0.8993-342.3
DRB1*08	2 (1.7%)	25 (8.8%)	0.01098	0.23076	0.1818	0.042-0.78

OR: Odds Ratio; 95% IC OR: 95% Confidence Interval Odds Ratio
p-value*: Fisher's Exact test and/or Qui Square.
Corrected p-value**: Bonferroni correction.

Table 5. HLA allele frequencies of HLA-A, HLA-B e HLA-DR alleles with statistically significant differences betweenEBV+controls e patients

Allele	EBV+* Patients	Controls	*p*-value	Corrected *p*-value	OR**	95% CI OR***
A*01	14 (12%)	22 (5.5%)	0.02521	0.4033	2.358	1.16-4.77
DRB1*08	2(1.7%)	38 (9.5%)	0.00442	0.1255	0.1671	0.0397-0.7035
DRB1*10	2 (1.7%)	25 (8.8%)	0.03904	0.3252	4.309	0.042 -0.78

OR: Odds Ratio; 95% CI OR: 95% Confidence Interval Odds Ratio 95%
p-value*: Fisher's Exact test and/or Qui Square.
Corrected p-value**: Bonferroni correction.

Table 6. HLA allele frequencies for HLA-A, HLA-B e HLA-DR alleles with statistically significant differences between EBV-controls and patients

Allele	EBV-* Patients	Controls	*p*-value	Corrected *p*-value	OR**	95% CI OR**
B*08	5 (1,8%)	20 (5.0%)	0.0436	1.1772	0.3405	0.1263-0.9182
DRB1*03	13(4.6%)	38 (9.5%)	0.0234	0.30381	0.457	0.2388-0.8746

OR: Odds Ratio; 95% CI OR: 95% Confidence Interval Odds Ratio
p-value*: Fisher's Exact test and/or Qui Square.
Corrected p-value**: Bonferroni correction.

This result is of great relevance. Here we point to the risk of transmission of EBV to the kidney transplant recipient in the absence of a molecular test, considering itis possible that donors had EBV DNA in blood circulation. Transplantation among these individuals can result in graft loss, development of PTLD, and a high risk of mortality.

We analyzed the distribution of allele frequencies among detectable (EBV + patients) and non-detectable (EBV- patients) candidate transplant donors and recipients both separately and jointly, and also in the control group. Comparison of allele frequencies between the Donors/Recipients EBV-DNA+ and Donors/Recipients EBV DNA- groups showed that the B*41 (p = 0.00392) and B*37 (p = 0.01383)

alleles were significantly higher among the detectable group. In contrast, the DRB1*08 allele (p = 0.01098) was significantly higher among the undetectable group. However, such differences were not observed after Bonferroni's correction (p<0.05) (Table 4). When this comparison was made between the D R EBV+ group and the control group, before the Bonferroni correction (p <0.05), the A*01 allele (p = 0.02521) was more frequent among detectable samples, while themost frequent alleles among the undetectable individuals were DRB1*8 (p = 0.00442) and DRB1 * 10 (p = 0.03904) (Table 5.) When comparing the group of undetectable candidate donors and recipients and controls, the B*08 allele was significantly more frequent in the control population (p = 0.0436), as well as the DRB1*3 allele (p = 0.0234). Again, statistical significance was not confirmed by Bonferroni corrected p-values (Table 6). We also compared detectable and undetectable candidate transplant donors and recipients with the control group, but no significant difference was observed regarding allele frequencies.

DISCUSSION

The main goal of investigating a possible EBV infection in kidney transplant recipients is to prevent the development of PTDL. However, it is known that the serological status of the donor is also of great importance since a negative EBV recipient receiving an allograft from an EBV-positive donor is one of the most significant risk factors for mortality associated with EBV in transplant recipients (20, 21). Currently, routine pre-transplant tests are not performed for the diagnosis of EBV in donors in blood banks. According to Ordinance number 2600/GM/MS, of October 21st, 2009, which approves the Technical Regulation of the Brazilian National Transplant System, it is optional to perform serological tests for EBV in potential organ donors and donated organs. Thus, tissues must be accompanied by a donor blood sample that allows for further research, if deemed necessary. Concerning individuals who will undergo kidney transplantation, the investigation of EBV infection occurs only by serology, despite the immunological window period's risks and viral tropism (22). When researching EBV DNA in whole blood samples from both donors and recipients in general, there was no significant difference between groups, besides a low detection rate (24% in donors/33% in recipients). In a study with kidney transplant recipients, a similar viral detection rate was observed in the pre-transplant period (30%), specifically in whole blood samples, as performed in our study. However, they also analyzed other blood fractions and showed that 60% of patients presented the viral genome in peripheral blood mononuclear cells (PBMC) and 75% in the fractions of enriched B lymphocytes. That would be explained by the presence of viral latency inside these cells and justifies the low percentage found in our cohort (23). We did not find previous studies comparing the detection rate of EBV between kidney transplant donors and recipients. In addition to EBV infection, the literature reports that several HLA alleles may be involved in increased or decreased risk of developing PTLD, as well as susceptibility or protection to EBV infection (13, 24, 25, 26). EBV promotes the modulation of HLA Class I and II molecules in several ways. Since these determine the efficiency of EBV peptide presentation to T cells, the virus can negatively regulate HLA as an immune evasion mechanism. Several genes expressed in the EBV lytic cycle have been associated with reduction and/or inhibition of HLA Class I and II expression on the cell surface, including the BGLF5, BZLF1, and gp42 proteins. Besides, the EBNA1, EBNA2, EBNA3A, EBNA3B, LMP1, and LMP2A genes, involved in the latency process established by EBV, were also associated in a study that demonstrated an inverse correlation between the levels of proteins encoded by these genes and the expression of Class I HLA (27, 28, 29, 30). We sought to associate HLA alleles with the presence or absence of EBV, performing different comparisons between allele frequencies of our D/R EBV+ and D/R EBV- subgroups with the allele frequencies of our control group. Most studies usually seek to associate EBV infection and HLA alleles in patients with Hodgkin's Lymphoma (HL) and PTLD. Huang *et al.* (2010), when carrying out a case-control genotyping study in 338 Dutch patients with HL, reported that the allele frequency of B*37 increased significantly in the HL-EBV+ population (31). In our data, this allele increased significantly in our subgroup of EBV detectable donors and recipients compared to the undetectable subgroup, presenting an estimated high risk of -17.55.

Our data suggest the involvement of the A*01 allele in the risk of developing EBV infection, as its presence was shown to be significant in the D/R EBV+ subgroups compared to controls. We also observed protective association to theinfection development, given that the presence of the B*08 allele was significantly increased in the control groups than in renal transplant patients, either in comparison with the EBV+ or EBV- subgroup. It suggests that this allele may be involved not only in the protection from EBV infections but also in renal pathologies. Martin *et al.* (2015). evaluated both EBV-positive and negative HL patients and a cohort of unrelated controls, and associated the A*01 allele with the risk of developing HL associated with EBV, while the A*02 allele was associated with its protection (32). In another study carried out with HL patients, Niens *et al.*(2007) reported that individuals who carry the HLA-A*02 allele have a reduced risk of developing EBV-associated HL, while individuals with the HLA-A*01 allele have an increased risk. Regarding the B*08 allele, its association with protection against EBV infection development was shown by its frequencies being significantly higher among renal transplant receptors that resolved EBV infection (33; 17). The DRB1*08 allele was more frequent in EBV- patients and controls than in the EBV+ group, suggesting that it may have a protective effect on EBV infection development. It has been demonstrated in other studies regarding EBV infection, kidney and autoimmune disorders. Dai *et al.* (2015) classify the DRB1*08 allele as a protective factor in the development of end-stage renal disease. Another author reports this same protective function for that allele to abnormal renal function (34, 35). In another study, specifically with EBV, it was demonstrated that the HLA DRB1 genes could influence IgG antibodies' levels to EBV nuclear antigen 1 (EBNA-1), specifically in large Mexican-American families. Other authors also report a protective role for this allele in other diseases, such as rheumatoid arthritis and diabetes, in populations with Amerindian ancestries, such as the individuals reported in our investigation (36, 37, 38).

In addition to the alleles mentioned above, our data suggest the B*41 allele's involvement in the susceptibility to EBV infection. In contrast, the DRB1*10 allele would be involved in protection, which has not been previously reported. However, it is essential to note that in our results, only Fisher's exact test and/or Chi-Square test showed statistical significance, with no significance confirmed by Bonferroni corrected p-values. This test requires a simple calculation and interpretation, and its purpose is to determine individual significance value, providing significance levels for the desired dataset. For a study in which multiple results are tested to statistical significance, one or more results may appear as significant at level p<0.05 due to chance, resulting in type 1 errors. Applying Bonferroni correction probability values (p) is adjusted, thereby avoiding the erroneous conclusion of a significant correlation, and preventing type 1 errors, a critical step in statistical analyses (39, 40, 41).

On the other hand, Bonferroni correction is a too conservative test, which causes low detection power. When this statistical test is applied, the corrected p-value is hardly significant. Our study tested this correction, considering multiple comparisons were applied to different groups, where each surveyed HLA allele originated a 2x2 contingency table. However, for the corrected p-value to obtain statistical significance, it is necessary to have a high sample size of patients and controls or a large difference in allele frequency between groups (42, 43). As this study is still presented as a pilot project, carried out with convenience sampling of candidate kidney transplant donors and recipients, it was not possible to obtain a large sample size. Further, it has been stated that convenience sampling may not adequately represent the entire study population (44). The sample size employed here (N = 200) may limit our results, but it does not make it infeasible. Expanding our study population in the future will allow

for better analyses of allelic frequency and its associations with the protection or susceptibility to EBV infections found in our data. Future research will determine whether the association findings presented here remain consistent, thus validating our results and providing scientific relevance to the current investigation.

REFERENCES

ANDRADE, C. Multiple Testing and Protection Against a Type 1 (False Positive) Error Using the Bonferroni and Hochberg Corrections. *Indian Journal Of Psychological Medicine*, v. 41, n. 1, p. 99-100, jan. 2019.

ARMSTRONG, R. A. When to use the Bonferroni correction. *Ophthalmic And Physiological Optics*, v. 34, n. 5, p. 502-508, 2 abr. 2014.

BAKKER, N. A. *et al.* HLA Antigens and Post Renal Transplant Lymphoproliferative Disease: HLA-B Matching Is Critical. *Transplantation*, v. 80, n. 5, p.595-599, set. 2005.

BRASIL, 2009. Ministério da Saúde – Portaria nº 2.600, de 21 de outubro de 2009.

CURTIN, F; SCHULZ, P. Multiple correlations and bonferroni's correction. *Biological Psychiatry*, v. 44, n. 8, p. 775-777, out. 1998.

DAI, C; *et al.* Association between human leucocyte antigen subtypes and risk of end stage renal disease in Taiwanese: a retrospective study. *Bmc Nephrology*, v. 16, n. 1, 2015.

DYCK, R; BOHM, C; KLOMP, H. Increased Frequency of HLA A2/DR4 and A2/DR8 Haplotypes in Young Saskatchewan Aboriginal People with Diabetic End-Stage Renal Disease. *American Journal Of Nephrology*, v. 23, n. 3, p. 178-185, 2003

GREEN, M.; MICHAELS, M. G. Epstein-Barr virus infection and post-transplant lymphoproliferative disorder. *American Journal Transplant*. v. 13, n. 3, p. 41–54, 2013.

GREEN, M; WEBBER, S. Post transplantation lymphoproliferative disorders. *Pediatric Clinics Of North America*, v. 50, n. 6, p.1471-1491, dez. 2003.

HÖCKER, B. *et al.* Epidemiology and Morbidity of Epstein-Barr Virus Infection in Pediatric Renal Transplant Recipients: A Multicenter, Prospective Study. *Clinical Infectious Diseases*, v. 56, n. 1, p.84-92, 5 out. 2012.

HOSSEINI-MOGHADDAM, S. M. *et al.* The effect of human leukocyte antigen A1 and B35-Cw4 on sustained BK polyomavirus DNAemia after renal transplantation. *Clinical Transplantation*, v. 34, n. 12, p. 1-23, 28 out. 2020.

HUANG, X. *et al*. HLA associations in classical Hodgkin lymphoma: EBV status matters. *Plos One*, S.I, v. 7, n. 7, jul. 2010.

ICTV, 2018.; ICTV 9th Report (2011) Herpesviridae. Disponível em: https://talk.ictvonline.org/ictv-reports/ictv_9th_report/dsdna-viruses. Acessado em 20 de outubro de 2019.

JONES, K. *et al.* HLA class I associations with EBV+ post-transplant lymphoproliferative disorder. *Transplant Immunology*, v. 32, n. 2, p.126-130, mar. 2015.

KINCH, A. *et al.* Association between HLA-A1 and -A2 types and Epstein–Barr virus status of post-transplant lymphoproliferative disorder. *Leukemia & Lymphoma*, v. 57, n. 10, p.2351-2358, 22 abr. 2016.

LACASCE, A. S. Post-Transplant Lymphoproliferative Disorders. *The Oncologist*, v. 11, n. 6, p. 674-680, jun. 2006.

LAU, S. Y. J. *et al.* Epstein-Barr virus encephalitis in solid organ transplantation. *New Microbiologica*, v. 3, n. 40, p. 212-217, maio 2017.

LI, Q.; COHEN, J. I. Epstein-Barr Virus and the Human Leukocyte Antigen Complex. *Current Clinical Microbiology Reports*, v. 6, n. 3, p. 175-181, 8 jul.2019.

LUSTBERG, M. *et al.* Human Leukocyte Antigen Type and Post transplant Lymphoproliferative Disorder. *Transplantation*, v. 99, n. 6, p.1220-1225, jun. 2015.

MARTÍN, P. *et al*. HLA Allele E*01:01 Is Associated with a Reduced Risk of EBV-Related Classical Hodgkin Lymphoma Independently of HLA-A*01/*02. *Plos One*, v. 8, n. 10, ago. 2015.

MIOT, H. A. Tamanho da amostra em estudos clínicos e experimentais. *Jornal Vascular Brasileiro*, v. 10, n. 4, p. 275-278, dez. 2011.

MORAN, J. *et al.* Epstein-Barr Virus Gene Expression, Human Leukocyte Antigen Alleles and Chronic High Viral Loads in Pediatric Renal Transplant Patients. *Transplantation*, v. 92, n. 3, p.328-333, ago. 2011.

MOSAAD, Y. M. Clinical Role of Human Leukocyte Antigen in Health and Disease. *Scandinavian Journal Of Immunology*, v. 82, n. 4, p.283-306, 10 set. 2015.

NIENS, M. J. *et al*. HLA-A*02 is associated with a reduced risk and HLA-A*01 with an increased risk of developing EBV+ Hodgkin lymphoma. *Blood***,** v. 110, n. 9, p. 3310-3315, 1 nov. 2007.

O'REGAN, J. A. *et al.* Posttransplant Lymphoproliferative Disorders in Irish Renal Transplant Recipients. *Transplantation*, v. 101, n. 3, p. 657-663, mar. 2017.

RESHEF, R. *et al.* Association of HLA Polymorphisms with Post-transplant Lymphoproliferative Disorder in Solid-Organ Transplant Recipients. *American Journal of Transplantation*, v. 11, n. 4, p.817-825, 14 mar. 2011.

RESSING, M. E. *et al*. Epstein-Barr virus evasion of CD8+ and CD4+ T cell immunity via concerted actions of multiple gene products. *Seminars In Cancer Biology*, v. 18, n. 6, p. 397-408, dez. 2008.

ROWE, M. *et al.* Host shutoff during productive Epstein-Barr virus infection is mediated by BGLF5 and may contribute to immune evasion. *Proceedings Of The National Academy Of Sciences*, v. 104, n. 9, p. 3366-3371, 21 fev. 2007.

RUBICZ, R; *et al.* A Genome-Wide Integrative Genomic Study Localizes Genetic Factors Influencing Antibodies against Epstein-Barr Virus Nuclear Antigen 1 (EBNA-1). *Plos Genetics*, v. 9, n. 1, 2013.

SAITO, P. K. *et al*. HLA-A, HLA-B, and HLA-DRB1 Allele and Haplotype Frequencies in Renal Transplant Candidates in a Population in Southern Brazil. *Journal Of Clinical Laboratory Analysis*, v. 30, n. 3, p. 258-265, 8 abr. 2015.

SENGUPTA, S. *et al.* Genome-Wide Expression Profiling Reveals EBV-Associated Inhibition of MHC Class I Expression in Nasopharyngeal Carcinoma. *Cancer Research*, v. 66, n. 16, p. 7999-8006, 15 ago. 2006.

SEPÚLVEDA-DELGADO, J. *et al*. Role of HLA-DRB1*04 in the susceptibility and HLA-DRB1*08 in the protection for development of rheumatoid arthritis in a population of Southern Mexico: brief report. *Clinical Rheumatology*, [S.L.], v. 39, n. 10, p. 2875-2879, 2 abr. 2020.

SHERBINI, H. M. E; GARF, A. K. E; MAHMOUD, S. S. E. D. Human leukocyte antigen and autoantibodies association with juvenile systemic lupus erythematosus. *Egyptian*

SILVA, H.D.; VENCOVSKY, R. Poder de detecção de "QuantitativeTrait Loci" da análise de marcas simples e da regressão linear múltipla. *ScieloAgricola*, v.59, n.4, 2002.

SILVA, Mayara Jane Miranda da. Análise qualitativa e quantitativa do vírus Epstein-Barr em diferentes frações sanguíneas de pacientes submetidos ao transplante renal no Estado do Pará. 2017. 89 f. Dissertação (Mestrado em Virologia). Instituto Evandro Chagas, Ananindeua, 2017.

SMITH, J. M.; DHARNIDHARKA, V. R. Viral surveillance and subclinical viral infection in pediatric kidney transplantation. *Pediatric Nephrology*, v. 30, n. 5, p. 741-748, 2014.

SUBKLEWE, M. *et al.* Association of Human Leukocyte Antigen Haplotypes with Post transplant Lymphoproliferative Disease After Solid Organ Transplantation. *Transplantation***,** v. 82, n. 8, p.1093-1100, out. 2006.

SVEJGAARD, A.; RYDER, L.P..HLA and disease associations: detecting the strongest associations. *Tissue-Antigens*, v. 43, n.18, 1994.

TAYLOR, G. S. *et al.* The Immunology of Epstein-Barr Virus–Induced Disease. *Annual Review Of Immunology*, v. 33, n. 1, p.787-821, 21 mar. 2015.

TURSHUDZHYAN, Alla. Post-renal transplant malignancies: opportunities for prevention and early screening. *Cancer Treatment And Research Communications*, v. 26, 3, 2021.

WANG, Y. *et al*. Carboxyl-Terminal Sequence Variation of Latent Membrane Protein 1 Gene in Epstein-Barr Virus-Associated Gastric Carcinomas from Eastern China and Japan. *Intervirology*, v. 50, n. 3, p. 229-236, 2007.

YIN, H. *et al*. Molecular mechanisms of EBV-driven cell cycle progression and oncogenesis. *Medical Microbiology And Immunology*, v. 208, p. 573-583, nov. 2018.

YOUNG, L.S.; YAP, L. F.; MURRAY, P. G. Epstein–Barr virus: more than 50 years old and still providing surprises. *Nature Reviews Cancer*, v. 16, n. 12, p. 789-802, 30 set. 2016.

ZUO, J. *et al.* The Epstein-Barr Virus G-Protein-Coupled Receptor Contributes to Immune Evasion by Targeting MHC Class I Molecules for Degradation. *Plos Pathogens*, v. 5, n. 1, 2 jan. 2009.

****