# Chapter 4

# Celiac Disease in El Salvador

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## Abstract

Celiac disease is insufficiently known in El Salvador. Between July and August 2012, 32 patients (23F, 9M) with ages between 19 and 77 diagnosed with celiac disease, 21 relatives (13F, 8M) of the celiac patients and 8 persons who were in undergoing the diagnostic process were studied. Genomic DNA was extracted from peripheral blood for HLA-DQA1 and HLA-DQB1 genotyping. Polymerase chain reaction-amplified exon 2 amplicons were generated for low-to-medium resolution typing in a combined, single-stranded conformation polymorphism heteroduplex assay by a semi-automated electrophoresis and gel-staining method on the PhastSystem. The biopsy specimens were revised and classified according to a modified Marsh classification of Oberhüber et al. All participants in this study reside in urban areas.

Of the 32 cases, 23 were celiac disease risk genotype carriers, with the following distribution: 14 HLA-DQ8 (12F and 2M), 7 HLA-DQ2.5 (3F and 4M), 2 HLA-DQ2.5 and DQ8 (1F,1M). A review was made of clinical history of 9 cases (7F, 2M) who were neither DQ2.5 nor DQ8. Three of them had a Marsh II and 4 Marsh IIIA of the modified histological classification. All patients have responded to a gluten-free diet. Of the seven families studied, the daughter of one patient was found to suffer from celiac disease, one daughter of another patient suffered from Sjogrën's syndrome, and the other of rheumatoid arthritis and the sister of another patient has thyroid disease, early menopause and suffered from attacks of migraine. The rest of the first- and second- degree relatives of the seven families have, so far, no clinical evidence of the disease in spite of the fact that 17 have HLA-DQ2.5 and/or DQ8 or DQ9.3/DQ2.2. Therefore, careful follow-up of these individuals is indicated. Eight other subjects mentioned above were not included in the final study because no reliable information could be gathered on their cases.

This is the first study using the modified Marsh classification and the full HLA-DQ tying in El Salvador.

## 1. Introduction

El Salvador is the smallest country in Central America, with an area of 20,742.66 $km^2$ and a population of 5,744,113, according to the 2007 census. It has a population density of 276 inhabitants per $km^2$. This population of which 53% are women and 47% men, is distributed so that 63% lives in urban areas and 37% in rural areas.[1]

In 2012 the budget allocated to the Ministry of Health was equivalent to 11.5% of the state budget[2], reaching 2.1 % of gross domestic product at prices estimated for 2012.[3]

Celiac disease is still a little-known entity in El Salvador, even among health care professionals. This limits the possibility of suspecting celiac disease and therefore also its diagnosis. Cases of confirmed celiac disease come mainly from people diagnosed in domestic and foreign private clinics. Only a few celiac patients are identified in national public health institutions. The tests used in this country for diagnosis focus on serological markers and biopsy since no local laboratories perform genetic analysis of HLA-DQ; the only way to obtain HLA-DQ typing results them is to send samples to laboratories abroad, specifically to the United States of America, which raises costs and reduces the number of people who have access to such tests. Given the widespread ignorance on celiac disease and therefore the lack of guidance, support and monitoring for gluten intolerant people, a group of celiac patients have united to form a self-help organization: "Asociación de Celíacos y Sensibles al Gluten de El Salvador"(ACELYSES) ("Celiac and Gluten Sensitive Association of El Salvador"), whose primary mission is the dissemination of information on gluten-related disorders as well as promoting education and awareness among celiac disease and gluten-sensitive patients, their families, public and private health institutions and other organizations which have an impact on the quality of life of celiac and gluten-sensitive people in El Salvador. ACELYSES facilitates access to and consumption of gluten-free products to people who need a lifelong gluten-free diet to improve their quality of life through actions such as early diagnosis, health services and the continuous quality control and labeling of products.

The early work aimed at creating a support group for patients with celiac disease in El Salvador began in June 2010 and its first public meeting took place on August 31, 2010. Meetings continued to take place monthly under the name "Celíacos de El Salvador" with the support of various health care professionals. On June 18, 2011, one year after taking its first steps, the association appointed its first Board of Directors and changed its name from "Asociación de Celíacos de El Salvador"(ACELES) ("Celiac Association of El Salvador") to "Asociación de Celíacos y Sensibles al Gluten de El Salvador (ACELYSES) ("Celiac and Gluten Sensitive Association of El Salvador").

The association's Advisory Committee is the consultative body which issues recommendations on health to achieve the association's goals; the committee is composed by Dr. Mauricio Cromeyer, Dr. Amado Salvador Peña, Dr. Roberto Zablah as well as Mrs. Gloria Durán de Renderos, a professional in Public Health and Nutrition. More recently, Dr Eduardo Ángel Cueto-Rúa from La Plata, Argentina has joined the Advisory Committee.

People with celiac disease and gluten-sensitivity share the vital goal to adhere to gluten-free diet, which implies a peculiar life style involving the rigorous monitoring of food, drugs, cosmetics and any product that may come into physical contact with the body, which forces the patient to read labels carefully, to consult the manufacturer when the labeling is unclear, to

prevent cross-contamination, to promote certification of food and other measures and actions to improve their quality of life; that is why ACELES deemed it positive that gluten sensitive people also join the association. This proposal was consulted with Doctors Peña and Cromeyer, who gave it their endorsement.

## 2. Diagnosis of Celiac Disease and HLA-DQ Studies in El Salvador

In El Salvador intestinal biopsy is the gold standard regarding the diagnosis of celiac disease. Despite this, it is noteworthy, however, that although endoscopies are performed in public and private clinics and hospitals, only those doctors who have adequate knowledge of celiac disease apply the procedure for the proper sampling needed for their subsequent study and, unfortunately not all pathologists have the interest and knowledge to make an accurate diagnosis. It is not surprising that the patient is often misdiagnosed with other disorders and the diagnosis celiac disease remains hidden.

## 3. Intestinal biopsy Classification

In the present study the biopsy specimens were reviewed by one of us (R.A.G.) with special interest in the histopathology of celiac disease using the Marsh classification described in 1992[4] and modified in 1999 by Oberhüber, Granditsch and Vogelsang.[5]

## 4. Serological tests

The majority of the patients had as serological test, anti-Tissue Transglutaminase IgA ELISA, of DRG Diagnostics GmbH, Germany according to the instructions of the manufacturer and performed at the *Laboratorios Clínicos Max Bloch* in Colonia Escalón, San Salvador, El Salvador C.A. Few patients were tested abroad.

## 5. HLA-DQ Typing

Currently, there are few cases in which the patients had been genotyped outside of El Salvador. There is no information on the distribution of HLA-DQ genotypes in the Salvadoran population.

Between July and August 2012, the Laboratory of Immunogenetics at the Department of Microbiology and Infection Control of the VU University Medical Center, Amsterdam, provided an opportunity for a group of 69 Salvadoran patients with celiac disease and their relatives, as well as others, who were undergoing the process of being diagnosed for celiac disease, to also undergo genetic testing for HLA-DQ. The blood samples were taken at a local diagnostic

laboratory, where they were packaged in accordance with the standards required to ensure their optimal preservation, transportation and receipt at their final destination. The typing process consisted of the extraction of genomic DNA from peripheral blood. For the HLA-DQA1* and DQB1* genotyping the method used was generating exons 2 amplicons by polymerase chain reaction for low- to medium- resolution typing in a combined, single-stranded conformation polymorphism heteroduplex assay by semiautomated electrophoresis and gel staining method on the PhastSystem (GE Healthcare/Amersham Pharmacia Biotech, Uppsala, Sweden). This method has been validated using a panel of reference DNA against DynallAllSet sequence specific primer high resolution typing kits (Dynal AS, Oslo, Norway).[6,7] The persons studied received full information about the study and gave oral consent to their physicians. Subjects who were recruited from ACELYSES informed their physicians and those who accepted signed informed consent forms afterwards. In the case of children younger than 18 years of age, consent was granted in writing by their parents/legal guardians.

## 6. Results

Table 1 shows 32 individuals diagnosed with celiac disease. The age at diagnosis ranges from 19 to 77 years; 23 are women and 9 are men, all are urban residents. Upon revision of the biopsy specimens and classification of the histological features, 28 showed the histological features that are compatible with celiac disease.

Of the 32 cases, 23 were celiac disease risk genotype carriers, with the following distribution: 14 HLA-DQ8 (DQA1*03/DQB1*0302; 12F and 2M), 7 HLA-DQ2.5 (DQA1*05/DQB1*02; 3F and 4M), 2 HLA-DQ2.5 and DQ8 (1F, 1M), and 9 cases (7F, 2M) who had neither DQ2.5 nor DQ8.

All nine non-DQ2.5/non-DQ8 cases reported an improvement of symptoms with a gluten-free diet (GFD); two had been diagnosed abroad. The clinical characteristics, the histological classification and the results of the HLA-DQ typing are summarized in Table 2. Seven out of nine non-DQ2.5/non-DQ8 celiac disease patients were heterozygous carriers of allele DQA1*05 only (No. 3, 14, 16, 20, 21, 27, 29) and one had HLA-DQ2.2 (DQA1*0201/DQB1*02) only (No. 13) and another (No. 19) did not possess an HLA-DQ genotype associated with celiac disease. Of note, one patient (No.20) also has dermatitis herpetiformis.[8]

| # | Gender | Age | a-TTG | Biopsy | HLA-DQA1* genotype | HLA-DQB1* genotype | DQ2.5 and/or DQ8 |
|---|---|---|---|---|---|---|---|
| 1 | F | 19 | P | Marsh IIIb | 03/05 | 02/0302 | DQ2.5 and DQ8 Heterozygous |
| 2 | F | 21 | P | Marsh II | 03/03 | 0302/0402 | DQ8 Heterozygous |
| 3 | F | 21 | P | Marsh IIIa | 03/05 | 0301/0402 | non DQ2.5 non DQ8 |
| 4 | F | 35 | P | Marsh IIIa | 03/03 | 0302/0302 | DQ8 Homozygous |
| 5 | F | 43 | P | Marsh IIIb | 05/05 | 02/0301 | DQ2.5 Heterozygous |
| 6 | F | 44 | P | Marsh IIIa | 03/05 | 0301/0302 | DQ8 Heterozygous |
| 7 | F | 44 | P | Marsh IIIa | 0102/03 | 0302/0604 | DQ8 Heterozygous |
| 8 | F | 45 | P | NT | 0102/03 | 0302/0602 or 0603 | DQ8 Heterozygous |
| 9 | F | 46 | P | Marsh II | 0102/03 | 0302/0604 | DQ8 Heterozygous |
| 10 | F | 48 | P | Marsh IIIa | 05/05 | 02/02 | DQ2.5 Homozygous |
| 11 | F | 51 | NT | Marsh IIIb | 03/03 | 0302/0302 | DQ8 Homozygous |
| 12 | F | 53 | P | Marsh IIIa | 0101 or 0102/0201 | 02/0501 | non DQ2.5 non DQ8 |
| 13 | F | 54 | NT | Marsh IIIb | 0101/03 | 0302/0503 | DQ8 Heterozygous |
| 14 | F | 55 | P | Marsh IIIa | 0101 or 0102/05 | 0301/0602 or 0603 | non DQ2.5 non DQ8 |
| 15 | F | 56 | NT | Marsh IIIa | 03/05 | 0301/0302 | DQ8 Heterozygous |
| 16 | F | 57 | P | NA | 0101 or 0102/05 | 0301/0501 | non DQ2.5 non DQ8 |
| 17 | F | 60 | P | Marsh IIIa | 05/05 | 02/02 | DQ2.5 Homozygous |
| 18 | F | 61 | P | Marsh IIIa | 03/03 | 0302/0302 | DQ8 Homozygous |
| 19 | F | 63 | P | Marsh II | 0101/0103 | 0503/0602 or 0603 | non DQ2.5 non DQ8 |
| 20 | F | 65 | P | NA | 0101 or 0102/05 | 0301/0502 | non DQ2.5 non DQ8 |
| 21 | F | 66 | P | Marsh II | 0401 or 0601/05 | 0301/0402 | non DQ2.5 non DQ8 |
| 22 | F | 75 | P | Marsh IIIa | 03/03 | 0302/0302 | DQ8 Homozygous |
| 23 | F | 77 | P | Marsh II | 03/03 | 0302/0302 | DQ8 Homozygous |
| 24 | M | 22 | P | Marsh IIIb | 0101 or 0102/05 | 02/0501 | DQ2.5 Heterozygous |
| 25 | M | 24 | P | Marsh IIIa | 0103/05 | 02/0602 or 0603 | DQ2.5 Heterozygous |
| 26 | M | 25 | P | Marsh IIIb | 03/05 | 02/0302 | DQ2.5 and DQ8 Heterozygous |
| 27 | M | 44 | P | Marsh II | 0101 or 0102/05 | 0301/0501 | non DQ2.5 and non DQ8 |
| 28 | M | 47 | P | Marsh IIIa | 0101 or 0102/05 | 02/0501 | DQ2.5 Heterozygous |
| 29 | M | 50 | P | Marsh IIIa | 0103/05 | 0301/0601 | non DQ2.5 and non DQ8 |
| 30 | M | 54 | P | NT | 0102/03 | 0302/0602 or 0603 | DQ8 Heterozygous |
| 31 | M | 64 | P | Marsh IIIb | 0102/03 | 0302/0602 or 0603 | DQ8 Heterozygous |
| 32 | M | 65 | P | Marsh IIIa | 0201/05 | 02/0301 | DQ2.5 Heterozygous |

Abbreviations: F=Female; M=Male; aTTG=anti-tissue transglutaminase; P=Positive; NT=Not Tested; NA=Not Available

*Table 1. Patients with celiac disease, gender, age at diagnosis, serological, histological and HLA-DQ results.*

| # | Gender | Age in years | PCC | a-TTG | Biopsy | GFD | HLA-DQA1* genotype | HLA-DQB1* genotype |
|---|---|---|---|---|---|---|---|---|
| 3 | F | 21 | Chronic diarrhea, bloating | P | Marsh IIIa | R | 03/05 | 0301/0402 |
| 13 | F | 52 | Chronic diarrhea, depression | P | Marsh IIIa | R | 0101 or 0102/0201 | 02/0501 |
| 14 | F | 55 | Chronic diarrhea, lactose intolerance | P | Marsh IIIa | R | 0101 or 0102/05 | 0301/0602 or 0603 |
| 16 | F | 57 | Chronic diarrhea | P | NA | R | 0101 or 0102/05 | 03/0501 |
| 19 | F | 63 | Alternating evacuation | P | Marsh II | R | 0101/0103 | 0503/0602 or 0603 |
| 20 | F | 66 | Chronic diarrhea Dermatitis herpetiformis | P | Marsh II | R | 0101 or 0102/05 | 0301/0502 |
| 21 | F | 66 | Chronic diarrhea | P | NA* | R | 0401 or 0601/05 | 0301/0402 |
| 27 | M | 44 | Alternating evacuation | P | Marsh II | R | 0101 or 0102/05 | 03/0501 |
| 29 | M | 50 | Chronic diarrhea | P | Marsh IIIa | R | 0103/05 | 0301/0601 |

Abbreviations: GFD=Gluten-free diet; R= Responding to diet. F= Female; M=Male; PCC= Predominant clinical conditions; aTTG=anti-tissue transglutaminase; P=Positive; *Not available for revision. Biopsy specimen originally characterized as compatible with celiac disease

*Table 2. Clinical characteristics and HLA-DQ genotype of non-DQ2.5/non-DQ8 celiac disease patients.*

Out of 23 HLA-DQ2.5 and/or DQ8 genotype carriers, direct access to complete medical records of 15 patients (9 women and 6 men) was obtained. The symptomatology is variable, with mild to moderate manifestations. The pattern of alternating evacuation, bloating and/or flatulence comprises 2/3 of the cases. In other cases the predominant symptoms are: 3 with chronic diarrhea and 2 with constipation.

Other conditions associated in the group are: 3 women diagnosed with osteopenia or osteoporosis,[9,10] 2 women with anemia, a man with chronic myelocytic leukemia (CML); another woman has moderate elevation of AST-ALT. One case with a lack of clinical records, reported suffering from autoimmune hepatitis[11], was excluded due to incomplete data and normal intestinal biopsy specimens. Another patient had antecedents of spontaneous abortion.

Distribution of HLA-DQ2.5 and/or HLA-DQ8 positives in homo- or heterozygotes is displayed in Table 3.

| Risk Alleles | Homozygotes | | Heterozygotes | | Total |
|---|---|---|---|---|---|
| | (F) | (M) | (F) | (M) | |
| HLA-DQ2.5 | 2 | 0 | 1 | 4 | 7 |
| HLA-DQ8 | 5 | 0 | 7 | 2 | 14 |
| HLA-DQ2.5 and HLA-DQ8 | 0 | 0 | 1 | 1 | 2 |
| Total | 7 | 0 | 9 | 7 | 23 |

*Table 3. Distribution of HLA-DQ2.5 and/or HLA-DQ8 positive patients with celiac disease in homo- or heterozygotes.*

## 7. Family Study

Seven patients with confirmed celiac disease expressed the wish to type some of their relatives. Some of these relatives had symptoms compatible with celiac disease but so far only the daughter of one patient was found to suffer from the disease (Table 4). Seventeen out of 21 relatives are carriers of DQ2.5 and/or DQ8 risk alleles. Careful follow-up of these relatives is indicated.

| Group No. | Relation | Age in years | Gender | aTTG | Biopsy | HLA-DQA1* genotype | HLA-DQB1* genotype | DQ2.5 and/or DQ8 |
|---|---|---|---|---|---|---|---|---|
| 1 | patient | 61 | F | P | Marsh IIIa | 05/05 | 02/02 | HLA-DQ2.5 homozygous |
| | daughter | 39 | F | N | NT | 0201/05 | 02/02 | HLA-DQ2.5 heterozygous |
| | granddaughter | 17 | F | NT | NT | 0103/0201 | 02/0601 | Non-DQ2.5 and non-DQ8 |
| | grandson | 13 | M | NT | NT | 0103/0201 | 02/0601 | Non-DQ2.5 and non-DQ8 |
| | son | 37 | M | N | NT | 0101 or 0102/05 | 02/0501 | HLA-DQ2.5 heterozygous |
| | daughter | 34 | F | N | NT | 0201/05 | 02/02 | HLA-DQ2.5 heterozygous |
| | granddaughter | 11 | F | NT | NT | 0101 or 0102/05 | 02/0602 or 0603 | HLA-DQ2.5 heterozygous |
| | grandson | 4 | M | NT | NT | 0201/05 | 02/0301 | HLA-DQ2.5 heterozygous |
| 2 | patient | 44 | F | P | Marsh IIIa | 03/05 | 0301/0302 | HLA-DQ8 heterozygous |
| | father | 67 | M | NT | NT | 03/0401 or 0601 | 0302/0402 | HLA-DQ8 heterozygous |
| | mother | 66 | F | N | NT | 0101 or 0102/05 | 0301/0501 | Non-DQ2.5 and non-DQ8 |
| | sister | 39 | F | N | NT | 03/05 | 0301/0302 | HLA-DQ8 heterozygous |
| 3 | patient | 22 | M | P | Marsh IIIb | 0101 or 0102/05 | 02/0501 | HLA-DQ2.5 heterozygous |
| | father | 53 | M | NT | NT | 0101 or 0102/05 | 02/0502 | HLA-DQ2.5 heterozygous |
| | mother | 50 | F | NT | NT | 0101/0103 | 0501/0602 or 0603 | Non-DQ2.5 and non-DQ8 |
| | sister | 20 | F | NT | NT | 0101 or 0102/05 | 02/0501 | HLA-DQ2.5 heterozygous |
| 4 | patient | 65 | F | NA | NA | 03/05 | 02/0303 | HLA-DQ2.5 heterozygous (DQ9.3) |
| | daughter | 30 | F | NT | NT | 0201/05 | 02/02 | HLA-DQ2.5 heterozygous |
| | son | 38 | M | NT | NT | 0201/03 | 02/0303 | Non-DQ2.5 and non-DQ8 (DQ9.3) |

| Group No. | Relation | Age in years | Gender | aTTG | Biopsy | HLA-DQA1* genotype | HLA-DQB1* genotype | DQ2.5 and/or DQ8 |
|---|---|---|---|---|---|---|---|---|
| 5 | patient | 51 | F | NT | Marsh II | 03/03 | 0302/0302 | HLA-DQ8 homozygous |
| | daughter | 25 | F | NT | NT | 03/05 | 02/0302 | DQ2.5 and DQ8 heterozygous |
| 6 | patient | 46 | F | P | Marsh II | 0102/03 | 0302/0604 | HLA-DQ8 heterozygous |
| | mother | 83 | F | NT | NT | 0102/03 | 0302/0602 or 0603 | HLA-DQ8 heterozygous |
| | sister | 52 | F | N | NT | 0102/03 | 0302/0602 or 0603 | HLA-DQ8 heterozygous |
| | son | 14 | M | N | NT | 0102/03 | 0302/0604 | HLA-DQ8 heterozygous |
| | son | 10 | M | N | NT | 03/05 | 0301/0302 | HLA-DQ8 heterozygous |
| 7 | patient | 65 | M | P | Marsh IIIa | 0201/05 | 02/0301 | HLA-DQ2.5 heterozygous |
| | daughter | 34 | F | P | Marsh IIIb | 0201/05 | 02/02 | HLA-DQ2.5 heterozygous |

Abbreviations: F, Female; M, Male; aTTG, anti-tissue transglutaminase; P, Positive; NT, Not Tested. *NA= this patient was later withdrawn for lack of information

*Table 4. Clinical characteristics of patients with celiac disease and family members and HLA-DQ genotype.*

In the case of family group No. 1, two of its members who were not diagnosed as celiacs had other autoimmune diseases such as rheumatoid arthritis and Sjögren's syndrome. In this table it can be seen that the male patient of group 7 most likely carries the haplotypes DQA1*05-DQB1*0301 and DQA1*0201-DQB1*02 (ie. DQ2.5 trans) and therefore passed DQA1*0201-DQB1*02 (DQ2.2) to his daughter and that the mother of the daughter contributed HLA-DQA1*05-DQB1*02 (ie. DQ2.5).

## 8. Demographic Characterization of the Studied Cases

Ethnic admixture is characteristic of El Salvador; several factors influenced this outcome: a) in El Salvador's current territory there was no place where indigenous peoples could find refuge, so that they and the Spaniards had to coexist in the same space; b) a decrease in the indigenous population due to diseases and massacres; c) population break up due to its exploitation for the cultivation of indigo in the XVIIIth and XIXth centuries.[12] In the ethnic categories identified in colonial times, the predominance of *mestizos* (people of mixed native and European heritage) is evidenced in Tables 5 and 6.

| Categories | Number | % |
|---|---|---|
| Native Americans | 79,652 | 60.30 |
| *Mestizos* | 46,232 | 35.00 |
| Peninsular Spaniards | 1,321 | 1.00 |
| American-born Spaniards | 3,038 | 2.30 |
| Sub-saharian African or mixed sub-saharian African and Caucasoid ancestry | 1,849 | 1.40 |
| Total | 132,092 | 100 |

Source: Rivas, R. Persistencia Indígena en El Salvador, (p.31) Universidad Don Bosco. http://old.udb.edu.sv/editorial/cientifica/cientifica5/articulo2.pdf

*Table 5. Population of the province of San Salvador, by ethnic group (1770).*

| Categories | Number | % |
|---|---|---|
| Native Americans | 71,175 | 43.06 |
| *Mestizos* | 87,722 | 53.08 |
| Peninsular Spaniards | 1,422 | 0.86 |
| American-born Spaniards | 3,307 | 2.00 |
| Sub-saharian African or mixed sub-saharian African and Caucasoid ancestry | 1,652 | 1.00 |
| Total | 165,278 | 100.00 |

Source: Rivas, R. Persistencia Indígena en El Salvador, (p.31) Universidad Don Bosco. http://old.udb.edu.sv/editorial/cientifica/cientifica5/articulo2.pdf

*Table 6. Population of the province of San Salvador, by ethnic group (1807, excluding Sonsonate and Ahuachapán).*

The people who participated in the study are mostly of mixed native/European heritage which is predominant; thus, the results, albeit limited in number, are a representative sample of the ethnicity of El Salvador.

Population in the year 2007 is distributed according to the ethnic groups presented in Table 7.

| Ethnic group | % |
|---|---|
| Caucasoid | 12.74 |
| *Mestizos* | 86.34 |
| Sub-saharian African | 0.13 |
| Others | 0.56 |
| Native Americans: | |
| Lenca | 0.04 |
| Kakawira | 0.07 |
| Nahua-pipil | 0.06 |
| Other | 0.06 |
| Total | 100 |

Source: Dirección General de Estadística y Censos, Tomo I Características Generales de la Población. VI Censo de Población y V de Vivienda 2007, (p. 48). Ministerio de Economía, El Salvador. http://www.digestyc.gob.sv/index.php/temas/des/poblacion-y-estadisticas-demograficas/censo-de-poblacion-y-vivienda/publicaciones-censos.html

*Table 7. Percentual Distribution of the population, by ethnic group.*

According to the *Dirección General de Estadística y Censos de El Salvador* ("National Statistics and Census Directorate", DIGESTYC) in 2007 more men than women were born but there is also a higher mortality rate among men than women, as a result, there is a balance of population. However, census data show that there are additional factors operating, such as a higher percentage of men migrating abroad than women, leading to an increase in the female population (53%) compared to male (47%).[13] Despite this correlation, of the 23 confirmed HLA-DQ positive patients, 19 were women, which is consistent with the published literature.

In El Salvador the projected life expectancy for the 2010-2015 periods is of 67.45 years for men and 76.86 years for women.[14] This study shows that the age at which people are diagnosed with celiac disease is above 40, the category of people over 60 years prevails.

## 9. Celiac Disease in El Salvador

Despite not having prevalence studies in El Salvador, it can be stated that celiac disease is present in this country and that it may be considered to be a missed diagnosis due to lack of knowledge and the stubbornly held outdated concept of it not being a prevalent disease in the Americas.

The genetic predisposition of celiac disease is widely known and it is also known that, although it is a complex polygenic condition, approximately 95% of the patients that have the risk alleles that make up the HLA-DQ2.5, HLA-DQ8 or HLA-DQ9.3 heterodimers[15,16] and, furthermore, those celiac patients who are negative also have at least one risk allele (HLA-DQ2.2 or HLA-DQA1*05), being rare those in which these alleles are absent.[17,18]

Studies in Europe showed that the predominant heterodimer in celiac disease is HLA-DQ2.5: 83.8 % in Italy and France,[19] 91 % in Finland, 91.4 % in Norway and Sweden, 87.7 % in the UK and 92% in Spain.[20] A study from Argentina showed that 95% of celiac patients were HLA-DQ2.5 positive[21] and a Cuban study reported an 86.3% proportion.[22] There is no information on other genetic studies in the general population of the Caribbean or Central America, except for one from Costa Rica.[23]

The results obtained in patients with celiac disease from El Salvador differ from data from other regions of the Americas such as in the Chilean population.[24]

It must be remembered that in Latin America, populations with different origins came in contact with each other and became intertwined: natives and individuals from various regions of Europe and Africa. In El Salvador individuals of African ancestry are very few in number, unlike other Central American, Caribbean or some southern countries of the American continent (Colombia, Venezuela, Brazil, etc.), thus explaining the regional variability of the population of African origin.

In the southernmost countries of South America, predominantly in Uruguay and Argentina, the urban population is primarily descended from Europeans; from 65% in Mar del Plata to 90% in Montevideo,[25] this being representative of the high penetration of Caucasoid European genes. This ratio is different in other regions such as Bolivia, Peru, Chile, Mexico and Central America, whose genetic bases stem from the characteristics of their colonization process and the mixture between European and Native American genes, each of which had their own regional variables according to the origin of its European colonizers (Spaniards, Italians, Portuguese, etc.), as well as

from the different social classes that arose, leading to a further opening up of the field of genetic epidemiology.

## 10. Conclusions

Celiac disease can be diagnosed at any age; however, in the study group it can be seen that most of the people studied are over 40.

It advisable to perform prevalence studies in El Salvador in order to have a more precise knowledge of the country's situation regarding celiac disease and non-celiac gluten sensitivity, which in turn may lead to the promotion of health policies, programs and plans to ensure timely diagnosis and the comprehensive care of celiac and gluten-sensitive patients as well as the taking of measures to facilitate access to gluten-free products.

As demonstrated by the experiences of countries like Spain, Argentina and the United Kingdom, ACELYSES, a vital support entity, is important as a source of much needed information and support to celiac and gluten-sensitive people in El Salvador.

The creation of cooperation of networks, including communities of practice, are a viable form of effort with high potential benefits for both physicians and scientists interested in celiac disease as well as for celiac patients. This first study of HLA-DQ typing in celiac Salvadorans is an incipient test of collaborative work. It stimulated the authors to critically review their diagnostic resources in El Salvador and to revise the histological classification according to the Marsh classification.

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