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RESEARCH ARTICLE

THE SIGNATURE OF HLA CLASS II GENES IN SUDANESE PATIENTS WITH CELIAC DISEASE

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ABSTRACT

The objective of this study was to investigate the association of HLA Class-II loci and their frequencies in Sudanese patients with celiac disease. All blood specimens from celiac disease patients (n=70), and control group (n=30) were tested for (tTG IgA, Gliadin IgG and EMA) antibodies by IIF and ELISA. All tests were repeated on all patients (n=70) to check their response to the Gluten free diet (GFD). HLA-class II, DR and DQ alleles were typed from the DNA of all samples . Analysis of the gel was done by using One Lambda Software. Analysis of case-control data was performed using the Chi-square test with P< 0.05 considered significant. HLA-DRB1*0301 (HLA-DR17) was found in 74.3 % of the patients compared to 26.67% of the healthy controls (p= 0.002) with a risk factor of 4.4. The frequency of HLA-DQB1*0201 (HLA-DQ2) was found to be 81.42% and 53.3% in patients and in healthy controls respectively (p=0.006) with a risk factor of 3.8. HLA-DQB1*0301(HLA-DQ7) was found to be significantly frequent in patients (24.3%) compared to (3.3%) among the controls (p= 0.011) with a relative risk of 9.3. This in contrast to Caucasian patients where the frequency of HLA-DQB1*0301(HLA-DQ7) is only 2%. There was no significant difference between patients and controls regarding HLA-DQB1*0302 allele (HLA-DQ8) which was frequently seen in 17.14% patients compared to 30% in the controls (p=0.18) with a relative risk of 0.48. HLA-DQ7 is highly specific to Sudanese CD compared to HLA-DQ8.

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INTRODUCTION

Celiac disease (CD), also known as gluten sensitive enteropathy (GSE), is a chronic disease of the small intestine caused by an inappropriate immune response to ingested wheat gluten proteins and related proteins in barley, oats, millet and rye. (Green and Jabir, 2003; Sollid, 2000) Celiac disease was first described in 1888 by Samuel Gee who reported on chronic malabsorption of ingested food and described many of the classical symptoms of CD. (Gee, 1888) The disease was first recognized in Sudan when 7 children were diagnosed and reported by Suliman in 1978. (Sulaiman, 1978) Typical symptoms are chronic diarrhea, steatorrhea, abdominal distension and failure to thrive (Schmitz *et al*, 1992), and in adult patient's diarrhea, weakness, malaise and weight loss, (Howdle *et al*., 1992) The disease may in fact be under-diagnosed especially in geographical areas where conditions such as malnutrition, diarrheal diseases and intestinal parasitic infections prevail. Over the last few decades, however, the gastrointestinal symptoms have become less prominent, and the clinical picture has been altered to milder and atypical forms, and the age at diagnosis has increased. (Mäki *et al*., 1988; Collin *et al*., 1999) Several non-abdominal symptoms are common, among which iron deficiency, short stature, delayed puberty, osteoporosis and dental enamel defects may at least partly result from the malabsorption of nutrients. Celiac disease can also manifest in the skin as dermatitis Herpitiformis (DH), an itchy and blistering rash which responds to gluten-free diet. (Fry *et al*., 1973) The Diagnosis, which is based on the clinical features, disease-specific serum antibodies and small intestinal biopsy, can be made at any age. Celiac disease has been thought to affect people of European ancestry more often than other ethnic groups. (Cooke *et al*., 1985) Recent studies, however, have revealed increasing global prevalence (Fasano 2001) in that it can affect persons of many ethnic backgrounds. However the disease appears to be rare among persons of pure Chinese, Japanese, or Afro-Caribbean decent. (Feldman *et al*.,

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2003) The true prevalence of CD is difficult to estimate because of the variable presentation of the disease, particularly since many patients can have little or no symptoms. A significant proportion of the genetic predisposition comes from MHC-linked genes, estimated to account for about 50% of the genetic load (Sollid and Lie, 2005). CD appears to represent a spectrum of clinical features and presentations classified as follows:. 1-Classical" CD (i.e., fully developed gluten-induced villous atrophy and classical features of intestinal malabsorption) is most commonly described especially in children. 2-Atypical CD (i.e., fully developed gluten-induced villous atrophy found in the setting of another presentation such as isolated iron deficiency, osteoporosis, short stature, constipation, skin infection or infertility). 3-Silent CD (i.e., fully developed gluten-induced villous atrophy discovered in an asymptomatic patient accidently by serologic screening or perhaps an endoscopy for another reason, and 4-Latent CD which is characterized by typical mucosal histological findings, without clinical symptoms, that responds to a gluten-free diet (GFD) by retaining a normal mucosal histology. Latent CD can also represent patients with currently normal intestinal mucosa but positive serological test or specific HLA typing each of which may identify who will subsequently develop gluten-sensitive enteropathy (Feldman *et al*., 2003; Fasano *et al*., 2001). For the diagnosis of CD in adults, there must be a high index of clinical suspicion that recognizes the atypical presentations of the disease.

DISCUSSION

Celiac disease (CD) has the best prognosis among autoimmune diseases, provided that a correct diagnosis is achieved and a strict and lifelong gluten-free diet is implemented and adhered to. The first diagnostic finding in CD was the description of typical histological features in jejunal biopsies from patients who were first described in 1957 by John Paulley in the UK, (Carlo Catassi and Alessio Fasano, 2010) Although the small intestinal biopsy is still included as a necessary investigation for the diagnosis of CD, lately new accurate tests have been added to the diagnostic list of the disease. These include the introduction of vital serological assays for anti-tissue Transglutamase antibodies (AtTGA) and Antigliadin antibodies (AGA) which have refined the diagnosis of CD. (Annemarie Bürgin-Wolff *et al*., 2013) Until the 1990s the presence of celiac disease in Sudan was considered low till the report of Mohammed *et al.* (2006) in which CD was diagnosed in Sudanese patients based on the estimation of anti Gliadin antibodies (AGA) tests, i.e. both AGA-IgA and AGA-IgG and anti-EMA and the demonstration of the typical histological features of the jejunal biopsies for those with positive AGA and EMA.

As far as we know; this is the first study which documents the correlation between the HLA and CD disease in Sudan. The discovery that HLA are associated with several diseases has led to the appealing developments both in basic biomedical research and in clinical medicine, and offered the opportunity to improve the understanding of pathogenesis and classification of diseases, as well as to provide diagnostic and prognostic indicators. (Cassinotti *et al*., 2009) This is a necessary but not a sufficient condition for the development of celiac disease. Research suggests that, although they are central to the pathogenesis of celiac disease, HLA haplotypes alone confer approximately 35–40% of the genetic predisposition. (Abadie *et al*., 2011) Therefore this study was designed to investigate the association of the HLA alleles with the Celiac disease among Sudanese patients attending the celiac disease clinic at Ibnsina hospital during the period 2010-2011. The mean age for patients was 18.8 ± 13.9 years and for control was 21.5 ±11.9 years. The disease seems to be more frequent among females (F: M is 3:2) (Table 1).

Table 1. Sex and age frequencies of the patients

	Patients with CD	Healthy Control
Total number (n)	70	30
Age (Mean)	18.8	21.5
Sex (F: M)	3:2	3:2

Table 2. DQB1*0201 allele frequency in patients with CD compared to the Control group

DQB1*0201	Study group Celiac	Study group Control	P value	Relative risk
Positive	81.4% (n=57)	53.33% (n=16)	0.006	3.837
Negative	18.6 % (n=13)	46.67% (n=14)		
Total	100% (n=70)	100% (n=30)		

The HLA shows a phenomenon called linkage disequilibrium in which certain alleles occur together in the same haplotypes more often in some populations than would be expected from the individual frequency of alleles. The most extreme example is HLA A1-B8-DR3-DQ2 haplotype which is so well conserved that even the alleles at the complement genes (class III) can be predicted with great accuracy. At HLA-DR alleles can be used to predict the HLA-DQ allele with a high degree of accuracy before testing. (Cassinotti *et al*., 2009) Celiac disease is associated with the prevalence of HLA-DQ2, and also to a minor degree with that of DQ8, It is also associated with an extended ancestral haplotype Including class I and class II HLA (A, B, DR, DQ) (Sollid, 1993)as in the West, CD is found in the Middle East and North American countries to be strongly associated with HLA DQ2 (DQA1*0501 and DQB1*0201) and HLA DQ8 (DQA1*0301 and DQB1*0302) is less strongly associated with CD (Karell *et al.,* 2003). In this study, HLA-DRB1 *0301, DQBI *0201 and DQB1*0301were the most frequent alleles in Sudanese patients with celiac disease compared to control group. HLA-DQB1 *0201 allele carried by 81.42% of Sudanese patients with Celiac disease, and in 53.33% of control group, p. value 0.006, relative risk 3.8 (Table 2). Similarly, HLA-DRB1*0301 carried by 74.4% of Celiac disease patients and in control group carried by 26.67%, p.value 0.002 and relative risk 4.3 (Table 5). These findings are in line with most published world studies which stated that approximately ninety (90)% of celiac subjects present HLA-DQ2 heterodimer, encoded by DQA1*05 and DQB1*02 alleles, which may be inherited together on the same

chromosome (cis configuration) or separately on the two homologous chromosomes (trans configuration) generally DQA1*05 and DQB1*02 are present in cis on DR3 haplotype (DRB1*03:01-DQA1*05:01-DQB1*02:01) or in trans on DR5/DR7haplotypes(DRB1*11/12-DQA1 *05:05-DQB1*03:01;DRB1*07-DQA*02:01-DQB1*02:02) (Donat *et al*., 2009).

Table 3. DQB1*0302 allele frequency in patients with CD compared to the Control group

DQB1*0302	Study group	Study group	P value	Relative risk
	Celiac	Control		
Positive	17.1% (n=12)	30% (n=9)	0.183	0.483
Negative	82.9% (n=58)	70% (n=21)		
Total	100% (n=70)	100% (n=30)		

Table 4. DQB1*0301 allele frequency in patients with CD compared to the Control group

DQB1*0301	Study group	Study group	P value	Relative risk
	Celiac	Control		
Positive	24.3% (n=17)	3.3% (n=1)	0.011	9.302
Negative	75.7% (n=53)	96.7% (n=29)		
Total	100% (n=70)	100% (n=30)		

Table 5. DRB1*0301 allele frequency in patients with CD compared to the Control group

DRB1*0301	Study group	Study group	P value	Relative risk
	Celiac	Control		
Positive	74.3% (n=52)	26.67% (n=8)	0.002	4.380
Negative	25.7% (n=18)	73.33% (n=22)		
Total	100% (n=70)	100% (n=30)		

However a major difference in the present study from that from most populations world wise is finding that HLA-DQB1 *0301 allele (HLA-DQ7) is found more commonly in the studied group carried by 24.3% of Sudanese patients with Celiac disease, and in 3.3% of control group, p.value 0.011, relative risk 9.302 (Table 3). This in marked contrast to data reported from Caucasian patients where the frequency of HLA-DQB1*0301(HLA-DQ7) is only 2%. HLA-DQ7 appears to be therefore highly specific to Sudanese CD compared to HLA-DQ8. DQB1*0301 interestingly these findings agree with the study which was done in Valencia by Donate E *et al*, who found that DQB1*0301 was most common in their celiac disease patients than DQB1*0302 allele. (Donat *et al*., 2009) because the DQB1*0301 molecule is very similar to the DQB1*0302 molecule, it could alternatively present similar gluten-derived peptides to restricted T cells (Lundin *et al*., 1994). HLA-DQB1 *0302 allele carried by 17.14% of Sudanese patients with Celiac disease, and in 30% of control group, p. value 0.183, relative risk 0.483 (Table 4).

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