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# Original Articles

## Human Leukocyte Antigen HLA-DRB1 Determinants Susceptibility to Gastroesophageal Reflux Disease

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**Abstract:**

***Background:*** *Gastro oesophageal reflux disease (GERD) is characterized by diverse symptoms. There is an evidence for a genetic component to Gastro oesophageal reflux disease as supported by familial aggregation of this disease. Aim of the study was to investigate whether certain human leucocyte antigen genes HLA-DRB1 are associated with (GERD).*

***Methods:*** *Patients and controls were prospectively recruited from GIT center at Al-Kindy Teaching Hospital (Baghdad-Iraq) between January 2014 and July 2016. Sixty Iraqi Arab Muslim patients with a history of heartburn and dyspepsia were compared with 100 Iraqi Arab Muslims controls. All study patients and control groups underwent upper gastrointestinal endoscopic examinations and their serums were analyzed for CagA antibodies Immunoglobulin G (IgG) for H. pylori. HLA-DRB1 genotyping were done to both groups.*

***Results:*** *A total of 60 patients with erosive gastritis; GERD (Grade II and III) were evaluated, together with 100 controls. There is a significant increase of H. pylori infection (p=0.0001) in GERD patients than control group. HLA-DRB1* 15: 01was significantly increased in GERD patients in comparison with control group and an increased frequency of HLADRB1*11: 01 in control group compared with patients group.*

***Conclusions:*** *There is an association between HLA-DRB1 *15: 01 in GERD patients with H pylori positive patients.*

***Key words:*** *HLA, GERD, H pylori.*

### Introduction:

Gastro-oesophageal reflux disease (GERD) is the end results of involuntary gastric contents reflux into the oesophagus, causing heartburn and acid regurgitation symptoms or injury to oesophageal tissue.[1,2] Thus, oesophagitis is considered as a complication of GERD.[3] GERD includes two types; erosive oesophagitis and non-erosive reflux disease (NERD) (endoscopy-negative reflux disease).[4] GERD classified into four grades (A, B, C and D) according to Los Angeles classification.[5] Other classification was Savary – Miller that classified it into five grades (I, II, III, IV and V).[6] The prevalence of GERD symptoms varies between 9% and 42%.[7] In spite of high prevalence of GERD symptoms, its aetiology is still not completely understood.[8] One of the important factors in the causation of GERD is environmental factors.[9] These include life style factors like body weight, nutrition, alcohol consumption, smoking, the intake of non-steroidal anti-inflammatory drugs, and sleeping position.[10] Regarding genetic factors; there is an evidence for the role of genetic component to GERD as confirmed by familial aggregation of GERD symptoms.[11] Other studies done in Sweden and UK in monozygotic and dizygotic twins revealed considerable genetic contribution to the aetiology of GERD.[12] In addition to that, ethnic differences in the prevalence of GERD among Western and Asian populations.[13,14] All these lines of evidence

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suggest a genetic aetiology of GERD in addition to environmental factors. Other genetic factor is Human Leukocyte Antigen (HLA) system, which has an extensive polymorphism and considered as an excellent marker for population genetic analyses and disease association. Rajendra etal 2005[15] found that inheritance of the HLA-B*07 gene confers an increased risk for Barrett's oesophagus in south Asians (mostly south Indians) but not Orientals (Malays and Chinese). They also showed that HLA-B*07 positive patients with Barrett's oesophagus had a significantly higher family history of GERD symptoms, compared with their HLA-B*07 negative counterparts. HLA molecules perform a central function in the regulation of the immune response in many diseases. HLA alleles might predispose some individuals to particular diseases and malignancies.[16] Many studies found the associations between HLA alleles and susceptibility or resistance to certain diseases.

In this study, we examine if the human leucocyte antigen HLA-DRB1 alleles, important for immune responsiveness, may be a susceptibility locus for GERD disease in Iraqi Arab Muslims patients.

**Methods:**

Patients and controls were prospectively recruited from GIT center at Al-Kindy Teaching Hospital (Baghdad-Iraq) between January 2014 and July 2016. The demographic details of all patients and control groups were recorded. Written informed consent was obtained from all patients and control group for this study. The study protocol was reviewed and approved by the Scientific and Ethical Committee of Al-kindy medical college and Al-Kindy Teaching Hospital. The patient group and control groups were sex and age matched.

Sixty Iraqi Arab Muslims patients with a history of heartburn and dyspepsia at least three times a week for a period of more than three months and had been referred for upper gastrointestinal endoscopy at GIT center at Al-Kindy Teaching Hospital, Baghdad and a diagnosis of GERD were prospectively recruited.

Exclusion criteria included those patients with Barrett's oesophagus and esophageal varices, Patients with secondary causes of gastro-oesophageal reflux disease, patients who had consumed antacids, H2 blockers, proton pump inhibitors (PPIs), non-steroidal anti-inflammatory drugs (NSAIDs), alcohol, history of Helicobacter pylori eradication, subjects with a history of gastrointestinal surgery, peptic ulcer, and gastric cancer or with systemic disease requiring chronic medication were excluded.

The 100 Iraqi Arab Muslims controls consisted of people undergoing upper gastrointestinal endoscopy for reasons other than reflux symptoms, Barrett's oesophagus or any form of dyspepsia and heartburn. This group included those with normal OGD and being investigated for anaemia or faecal occult blood positive stools, chronic diarrhoea for unknown reason requiring small bowel biopsy, irritable bowel syndrome and screening for familial adenomatous polyposis.

**Oesophagogastric examinations:**

All studied patients and control groups underwent upper gastrointestinal endoscopic examinations using gastroscope: GIF-H260; Olympus, Tokyo, Japan and Display screen; Olympus OEV-261H liquid crystal display monitor; Olympus, Tokyo, Japan. The gastrooesophageal junction was defined as the squamocolumnar junction and the proximal margin of gastric folds. The endoscopic findings of erosive oesophagitis in the lower oesophagus were classified using the Savary and Miller classification. All of them either Grade II which is confluent erosive or exudative mucosal lesions which do not extend around the entire oesophageal circumference or Grade III which is erosive or exudative mucosal lesions which cover the entire oesophageal circumference and lead to inflammation of the wall without stricture (according to Savary and Miller, 1979).[17] Histopathological study was done by taking specimens from gastric mucosa to confirm the diagnosis and presence of H pylori.

**Serological Tests:**

Blood samples (3 mL) were drawn into plain tube. Separated serums were analyzed for CagA antibodies Immunoglobulin G (IgG) for H. pylori using an immunological test (immunochromatography test) (ACON, USA).

**HLA Class II genotyping (HLA-DRB1):**

Two mL of venous blood were collected in EDTA containers for DNA extraction from human blood using blood kit (QIAmp DNA blood Mini Kit, QIAGENINC- Germany).

DNA concentration and purification product was estimated using Nanodrop –South Korea. DNA was verified by electrophoresis in a 2% agarose gel containing ethidium bromide and was visualized under UV light. Locus and

allele-specific amplification of genomic patients and control DNA was performed for DRB1. DNA Amplification and Hybridization was performed using a sequence-specific oligonucleotide probes (SSOP) by HLA-DRB1 amplification and hybridization kits (SSOHLA type DRB1 plus and Mastermix for HLA type DRB1 Amp plus kits-Innogenetics-Belgium) by AutoLipa – 48 Innogenetics-Belgum. The results were interpreted using LiRas version-5.0 software-Innogenetics-Belgium.

**Statistical Analysis:**

HLA-DRB1 frequencies were determined by direct counting. The frequency of each allele was compared between patients and control group using chi-square test fisher exact test using MiniTab version. 3.0 software. In each comparison, the Odds ratio (OR) along with the 95% confidence interval (95% CI) was used. Gene frequencies for both groups were calculated. P-value less than 0.05 were considered statistically significant.

**Results:**

A total of 60 patients with erosive gastritis; GERD (Grade II and III) were evaluated, together with 100 controls. The mean age of patients was 45.67 ±15.54, as compared with 44 ± 15.22 for the controls .The male to female sex ratio was 1.0 in the patients group versus also 1.0 in controls.

50% of them were GERD II (Figure 1) and the rest were GERD III (Figure 2) by endoscopy.

There is a significant increase of H. pylori infection (p=0.0001) in GERD patients than control group. The Odd ratio (OD) = 18.00 with 95% CI= from 7.727-41.926. The relative risk =6.666 that indicates an association between H. pylori and disease as shown in table I.

The distribution of HLA polymorphism HLA*DRB1 was investigated in the control and patients groups of Iraqi Arab Muslims. The observed and expected phenotypes of all loci for the patients group as demonstrated in table 4 were in a good agreement with Hardy-Weinberg equilibrium as shown in table V.

Control and patients were typed for identifying the DRB1* alleles using DNA basedmethodology (PCR-SSOP). There was an increased frequency of HLADRB1*11: 01 in control group compared with patients group (P=0.0001, Odds ratio=0.141, 95% CI: 0.055-0.358). Other allele like HLA-DRB1* 15: 01was significantly increased in GERD patients in comparison with control group (P=0.004, Odds ratio=3.833, 95% CI: 1.513-9.708) as shown in table II. The highest genotype frequency in GERD patients was 15: 01 which is equal to 0.065 while in the control group was 11: 01 which is 0.117 as shown in table III.

**Discussion:**

Erosive type of Gastro-oesophageal reflux disease (GERD) predisposes to Grade IV Barrett's oesophagus that leads to oesophageal adenocarcinoma.[18] Any abnormal cell express new antigens as a result of the multiple genetic changes that are associated with cell inflammation or transformation,[19] that recognized by T helper or T cytotoxic cells presented by human leucocyte antigen (HLA) class I or class II molecules.[20] HLA system is highly polymorphism system and excellent marker for population genetic analyses and disease association studies. HLA molecules perform a crucial and important function in the regulation of the immune response In this study, HLA-DRB1* 15: 01 was significantly increased in GERD patients in comparison with control group (P=0.004, Odds ratio=3.833, 95% CI: 1.513-9.708). Thus, this allele considered as predisposing factor for GERD while HLADRB1*11: 01 is a protective factor because there is an increased frequency of HLADRB1*11: 01 in control group compared with patients group (P=0.0001,Odds ratio=0.141, 95% CI: 0.055-0.358). The expression of HLA-DR antigens is

**Table-I**

Helicobacter pylori in GERD (Grade II and III) patients compared with control group

| H. pylori Cag A+ | GERD + Patients | | GERD–Control | | P- value | Odd ratio | RR Relative |
|---|---|---|---|---|---|---|---|
| Status | No. | % | No. | % | | 95% CI | risk |
| H. pylori Positive | 40 | 66.66 | 10 | 10 | 0.0001 | 18.00 7.727-41.926 | 6.666 |
| H. pylori Negative | 20 | 33.33 | 90 | 90 | | | |
| Total | 60 | | 100 | | | | |

**Table-II**

Frequencies of HLA-DRB1 alleles in patients with GERD disease compared with control group

| HLA-DRB1 alelles | Patients with GERD disease, N=60 | | Control group, N=100 | | Odd ratio 95 % confidence interval | P – value |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | | |
| 01: 01 | 3 | 5 | 6 | 6 | 0.824 (0.198-3.426) | 0.790 |
| 01: 02 | 3 | 5 | - | - | NA | NA |
| 02: 01 | - | - | 10 | 10 | NA | NA |
| 03: 01 | 9 | 15 | 10 | 10 | 1.588 (0.605-4.164) | 0.346 |
| 03: 02 | - | - | 14 | 14 | NA | NA |
| 03: 17 | 3 | 5 | 2 | 2 | 2.578 (0.418-15.897) | 0.307 |
| 03: 39 | 9 | 15 | - | - | NA | NA |
| 03: 40 | 3 | 5 | - | - | NA | NA |
| 04: 02 | 13 | 21.66 | 25 | 25 | 0.829 (0.386-1.770) | 0.631 |
| 04: 03 | 1 | 1.66 | 1 | 1 | 1.678 (0.103-27.333) | 0.716 |
| 04: 05 | 1 | 1.66 | - | - | NA | NA |
| 05: 01 | - | - | 4 | 1 | NA | NA |
| 06: 01 | - | - | 6 | 6 | NA | NA |
| 07: 01 | 15 | 25 | 18 | 18 | 1.518 (0.699-3.298) | 0.291 |
| 07: 08 | 3 | 5 | - | - | NA | NA |
| 08: 31 | 3 | 5 | 6 | 6 | 0.824 (0.198-3.426) | 0.790 |
| 10: 01 | - | - | 6 | 6 | NA | NA |
| 11: 01 | 6 | 10 | 44 | 44 | 0.141 (0.055-0.358) | 0.0001 |
| 12: 01 | 3 | 5 | 5 | 5 | 1.00 (0.230-4.343) | 1.00 |
| 12: 28 | 3 | 5 | 1 | 1 | 5.210 (0.529-51.276) | 0.157 |
| 13: 01 | 6 | 10 | 20 | 20 | 0.444 (0.167-1.178) | 0.103 |
| 13: 22 | 3 | 5 | - | - | NA | NA |
| 13: 100 | 3 | 5 | - | - | NA | NA |
| 13: 123 | 3 | 5 | - | - | NA | NA |
| 14: 01 | - | - | 6 | 6 | NA | NA |
| 14: 05 | 3 | 5 | - | - | NA | NA |
| 14: 10 | 3 | 5 | - | - | NA | NA |
| 15: 01 | 15 | 25 | 8 | 8 | 3.833 (1.513-9.708) | 0.004 |
| 16: 01 | 6 | 10 | 4 4 | 4 | 2.666 (0.720-9.867) | 0.141 |
| 17: 01 | - | - | 4 4 | 4 | NA | NA |

more complex. The squamous epithelium of the esophagus is devoid of HLA class II expression, like lung, stomach and breast epithelium.[21,22] The increased expression of class II may be due to infection with H pylori that constitutes 66.66% of GERD patients and there is a significant increase of H. pylori infection (p=0.0001) in GERD patients than control group. HLA class II antigens appear in pathological circumstances, like in inflammation, infection, tumour transformation and autoimmunity.[23] Other study demonstrated the association between Barrett's oesophagus in Asians, particularly Indians, with HLA-B7; reinforcing a genetic component to gastrooesophageal reflux disease.[15] The prevalence of GERD is differed in different ethnic countries across the world, there is a higher prevalence rates in western countries compared with the Far East. Among oriental countries, GERD may be more common in Japan compared with Hong Kong, Singapore and Korea. Studies suggest that GERD is relatively frequent in the Middle East, although a comparison of Turkish and ethnically Dutch patients in Holland showed a lower prevalence of reflux oesophagitis in Turkish individuals compared with the ethnically Dutch.[24] Ethnic differences in the prevalence of GERD with familial aggregation suggest the possibility of a genetic component to GERD in addition to environmental factors, e.g. Helicobacter pylori infection, abdominal adiposity and metabolic syndrome. The HLA-B07 gene commonly found in South Asian and Caucasian populations, but not Orientals, and the high prevalence of H. pylori in South Asians and the consequent atrophic gastritis and hypochlorhydria may partially ameliorate this genetic predisposition to disease.[25] Other study found increase frequency of GERD with gastrointestinal malformation in children that supporting a genetic part to gastro-oesophageal reflux disease.[26]

**Conclusions:**

A larger sample size and different ethnic populations Other than Arab populations should be genotyped to further confirm this association and identify possible additional risk factors in the human leucocyte antigen locus.

**Conflict of interest:** None.

**Table-III**

Genotypes frequencies of HLA-DRB1 alleles in patients with GERD disease and control group

| HLA-DRB1 alleles | Patients with GERD disease, N=60 Gene frequency | Control group, N=100 Gene frequency |
|---|---|---|
| 01: 01 | 0.013 | 0.016 |
| 01: 02 | 0.013 | ------ |
| 02: 01 | ----- | 0.026 |
| 03: 01 | 0.039 | 0.026 |
| 03: 02 | ------ | 0.006 |
| 03: 17 | 0.013 | ------- |
| 03: 39 | 0.039 | ------- |
| 03: 40 | 0.013 | 0.036 |
| 04: 02 | 0.057 | 0.065 |
| 04: 03 | 0.005 | 0.003 |
| 04: 05 | 0.005 | ------- |
| 05: 01 | ------ | 0.011 |
| 06: 01 | ------ | 0.016 |
| 07: 01 | 0.06 | 0.047 |
| 07: 08 | 0.013 | ------- |
| 08: 31 | 0.013 | 0.016 |
| 10: 01 | ------ | 0.016 |
| 11: 01 | 0.026 | 0.117 |
| 12: 01 | 0.013 | 0.013 |
| 12: 28 | 0.013 | 0.003 |
| 13: 01 | 0.026 | 0.052 |
| 13: 22 | 0.013 | ------ |
| 13: 100 | 0.013 | ------ |
| 13: 123 | 0.013 | ------ |
| 14: 01 | ------ | 0.016 |
| 14: 05 | 0.013 | ------- |
| 14: 10 | 0.013 | ------- |
| 15: 01 | 0.065 | 0.021 |
| 16: 01 | 0.026 | 0.011 |
| 17: 01 | ------ | 0.011 |

**Table-IV**

Observed and expected numbers and percentages of HLA-DRB1 alleles in patients with GERD disease

| HLA-DRB1 alelles | Patients with GERD Observed, N=60 | | Patients with GERD Expected, N=100 | |
|---|---|---|---|---|
| | No. | % | No. | % |
| 01: 01 | 3 | 5 | 3.09 | 5.15 |
| 01: 02 | 3 | 5 | 3.09 | 5.15 |
| 02: 01 | ------ | ------ | ------ | ----- |
| 03: 01 | 9 | 15 | 9.17 | 15.28 |
| 03: 02 | ----- | ------ | ----- | ------ |
| 03: 17 | 3 | 5 | 3.09 | 5.15 |
| 03: 39 | 9 | 15 | 9.17 | 15.28 |
| 03: 40 | 3 | 5 | 3.09 | 5.15 |
| 04: 02 | 13 | 21.66 | 13.28 | 22.13 |
| 04: 03 | 1 | 1.66 | 1.19 | 1.98 |
| 04: 05 | 1 | 1.66 | 1.19 | 1.98 |
| 05: 01 | ------ | ------ | --- | ---- |
| 06: 01 | ------ | ------ | --- | ------ |
| 07: 01 | 15 | 25 | 15.09 | 25.15 |
| 07: 08 | 3 | 5 | 3.09 | 5.15 |
| 08: 31 | 3 | 5 | 3.09 | 5.15 |
| 10: 01 | ----- | ------ | ----- | ----- |
| 11: 01 | 6 | 10 | 6.07 | 10.11 |
| 12: 01 | 3 | 5 | 3.09 | 5.15 |
| 12: 28 | 3 | 5 | 3.09 | 5.15 |
| 13: 01 | 6 | 10 | 6.07 | 10.11 |
| 13: 22 | 3 | 5 | 3.09 | 5.15 |
| 13: 100 | 3 | 5 | 3.09 | 5.15 |
| 13: 123 | 3 | 5 | 3.09 | 5.15 |
| 14: 01 | ----- | ------ | ---- | ----- |
| 14: 05 | 3 | 5 | 3.09 | 5.15 |
| 14: 10 | 3 | 5 | 3.09 | 5.15 |
| 15: 01 | 15 | 25 | 15.09 | 25.15 |
| 16: 01 | 6 | 10 | 6.07 | 10.11 |
| 17: 01 | ----- | ------ | ----- | ------ |

**Table-V**

Hardy – Weinberg equilibrium in HLA-DRB1 locus of patients with GERD disease

| HLA locus | Chi 2 | DF | P |
|---|---|---|---|
| DRB1 | 0.106 | 22 | Not significant |

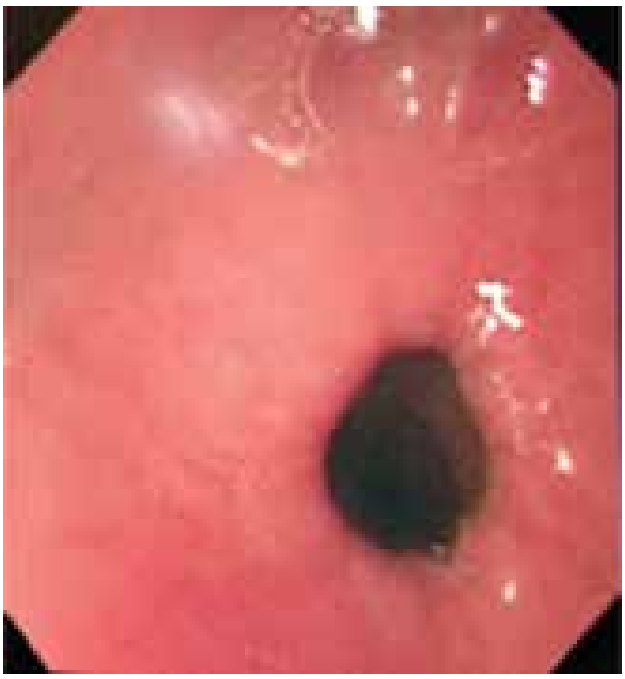

**Figure 1:** Erosive esophagitis GERD Grade II by Endoscopy.

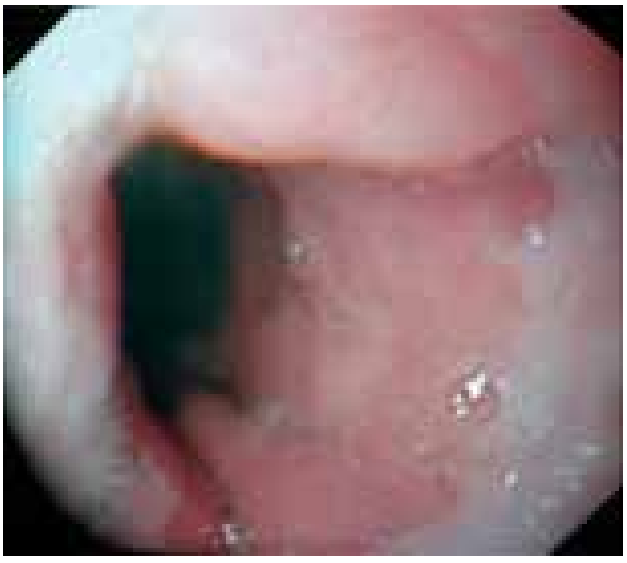

**Figure 2:** Erosive esophagitis GERD Grade III by Endoscopy.

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