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Original scientific article

RELATIONSHIP BETWEEN PEDIATRIC CELIAC DISEASE AND CHROMATIN REMODELING GENE EXPRESSIONS

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Celiac disease (CD) is an immune-dependent systemic disorder that occurs in genetically predisposed individuals resulting in damage in the small intestine. It is known that chromatin remodeling, an epigenetic mechanism, is associated with gastrointestinal diseases associated with chronic inflammation. However, no information is available on the link between CD and chromatin remodeling. For this purpose, the expression profiles of chromatin remodeling group genes in children diagnosed with CD according to Marsh classification and HLA profile were evaluated and their relationship with CD was investigated. Endoscopic biopsies embedded in the paraffin block of 40 children with CD diagnosis and 30 healthy children were included in the study. The most common four mutations (DQA1*05, DQB1*02, DQA1*03, and DQB1*03:02) related to CD on human leukocyte antigen (HLA) gene were screened. Intestinal biopsy samples were used for mRNA isolations and cDNA synthesis. Expressions of total seven genes in the chromatin remodeling groups (SWI/SNF Complex Group: *ARID1A*, Polycomb Group: *CTBP1*, Nucleosome-Remodeling & Histone Deacetylase (NuRD) Complex Group: *MTA1*, Chromobox/Heterochromatin Protein 1 (HP1) Homologs Group: *CBX3* and *CBX7*, Homeodomain (PHD) Protein Group: *NSD1*, Inhibitor of Growth (ING) family group: *ING 5*) were analyzed by Real-Time qPCR. Data analysis was performed online using the software provided by the manufacturer. Overexpression in *ARID1A*, *CTBP1*, and *NSD1* genes was detected when the CD group was compared against the control group, however they were not significant (p=0.31, 0.33, and 0.33). When CD group who had diarrhea symptom (typical) were compared to the CD group without diarrhea symptom (atypical),

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statistically significant under-expression was found in *CBX3* and *CTBP1* genes (p=0.04 and p=0.004). Statistically significant *CTB1* overexpression was detected in Marsh 2 CD cases (p=0.03). In the comparison of HLA DQ2/DQ8 positive CD patient group with the control group, the *NSD1, CBX3*, and *EED* (p=0.75, 0.75, and 0.78) genes were over-expressed and the *CBX7, MTA1, ARID1A*, and *CTBP1* genes (p=0.74, 0.75, 0.75, and 0.75) were under-expressed. This is the first study to report that expression of chromatin remodeling genes may have roles in the development and progression of CD. The results of this case-control study are open to confirmation by future studies with larger number of subjects to obtain statistically significant results.

Keywords: Pediatric celiac disease, chromatin remodeling, gene expression, chronic inflammation, autoimmunity

INTRODUCTION

Celiac disease (CD) resulting from chronic atrophy and inflammation in small intestine is an autoimmune disorder that manifests with gastrointestinal irregularities such as chronic diarrhea, abdominal distention, malabsorption, loss of appetite, growth retardation in children. Symptoms may start as early as 6 months of age. CD is diagnosed by the presence of CD-specific antibodies, human leukocyte antigens HLA-DQ2 or HLA-DQ8 haplotypes, and enteric atrophy (HUSBY *et al*., 2012; FASANO, 2005).

Chromatin remodeling, an epigenetic mechanism, is known as relaxation of the packaging between histone proteins and DNA, and consequently the displacement of the nucleosome structure (CLAPIER *et al*., 2009). Chromatin remodeling is a fundamental and critical way to regulate vital DNA-based activities such as replication, transcription, and DNA repair, which are important for cellular viability, death, gene expression, suppression, and differentiation processes (BECKER *et al.*, 2013). Chromatin remodeling requires energy to alter the nucleosome structure (BECKER *et al.*, 2002; BECKER *et al.*, 2013; ZHANG *et al.*, 2016). There are four families of chromatin remodeling proteins in humans: SWI/SNF, INO80, ISWI, and CHD. Each chromatin remodeling family is composed of multiple members forming various protein complexes, which all have unique functions in regulating gene expression and DNA repair (BECKER *et al.*, 2013). Chromatin remodeling proteins are being reported as novel promising strategies to cope with human malignancies. Chromatin remodeling linked with the gastrointestinal diseases associated with chronic inflammation is known to induce carcinogenesis in the early phases (TAKESHIMA *et al.*, 2015; SHEN *et al.*, 2015; BILGIC *et al*., 2018) However, no information is available regarding the relationship between CD and chromatin remodeling. Therefore, this study was designed to investigate the relationship between chromatin remodeling genes and CD, aiming to contribute to the understanding of CD pathogenesis.

MATERIALS AND METHODS

Study subjects

Total of forty children (CD group) diagnosed with CD according to Marsh classification as a result of pathology in the Haseki Training and Research Hospital, Pediatric Gastroenterology outpatient clinic and 30 children (control group) with normal gastrointestinal

endoscopy results were included in the study. Patients with eosinophilic gastroenteropathy or inflammatory bowel disease accompanying CD were excluded from the study.

Samples

Under deep sedation induced by an anesthetist, upper GIS endoscopy was performed by the pediatric gastroenterologist. Biopsy samples, two from the duodenal bulb and four from the second portion of duodenum were taken to evaluate CD. Then, histopathological evaluation of the samples was made. Endoscopic biopsy samples were fixed in formalin, embedded in paraffin blocks, and sliced in 10 μm slices for total RNA isolation.

For the evaluation of HLA DQ and DR mutation, 2 cc peripheral blood samples of the cases were collected into tubes with EDTA.

Ethics

All procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval was obtained from the Institutional Review Board of Aydin Adnan Menderes University (#2020/60). As the subjects of the study were minors under 18 years of age, both the subjects (when possible) and their parents/legal representatives were informed about the study to obtain the consent forms prior to the study.

DNA isolation

Genomic DNA isolation from peripheral blood samples was performed as described by ORENAY-BOYACIOGLU *et al*. (2016) and ASIK-SEN *et al*. (2012). The concentration and purity of DNA samples were assessed by using a Nano Drop 1000 Spectrophotometer V3.7 at 260 nm and the 260/280 ratio, respectively (NanoDrop™, Thermo Scientific, Wilmington, DE, USA).

Detecting HLA DQ and DR mutations

The most prevalent four mutations on *HLA* gene (DQA1*05 and DQB1*02 related to HLA-DQ2; DQA1*03 and DQB1*03:02 related to HLA-DQ8) that are linked to CD were monitored. HLA-DQA1 and DQB1 were genotyped in DNA samples according to SSP-PCR method.

RNA isolation

Total RNA isolation was performed from 10 μm biopsy slices with the miRNeasy FFPE Kit (Qiagen, Hilden, Germany) following the manufacturer's instructions. RNA concentration and quality were evaluated by spectrophotometry at 260 nm and the ratio of 260 nm/280 nm (NanoDrop™, Thermo Scientific, Wilmington, DE, USA).

cDNA synthesis

Complementary DNA (cDNA) was synthesized from the RNA samples using C-03 RT First Strand Kit (SA Bioscience, Frederick, MD, USA) as described by BILGIC *et al. (*2018) and ORENAY-BOYACIOGLU *et al.* (2018).

RTqPCR primer assay

Expression levels of seven genes in the chromatin remodeling groups (SWI/SNF Complex Group: *ARID1A*, Polycomb Group: *CTBP1*, Nucleosome-Remodeling & Histone Deacetylase (NuRD) Complex Group: *MTA1*, Chromobox /Heterochromatin Protein 1 (HP1) Homologs Group: *CBX3* and *CBX7*, Homeodomain (PHD) Protein Group: *NSD1*, Inhibitor of Growth (ING) family group: *ING 5*) and housekeeping HPRT1 gene as internal control were analyzed by RTqPCR assay (SA Biosciences, Frederick, MD, USA) according to BILGIC *et al.* (2018) and ORENAY-BOYACIOGLU *et al*. (2018). PCR mixes containing 12.5 µl of SYBR Green Master Mix, 2.2 µl of cDNA, 1 µl of primer (10 pmol), and dH_2O to bring the total volume to 25 µl were prepared for each gene separately. PCR conditions were composed of a 5 min initial denaturation at 95°C followed by 40 cycles of denaturation for 1 min at 94°C, annealing for 40 s at 61°C, and elongation for 1 min at 72°C, followed by a final 2 min elongation step at 72°C on a Rotor-Gene 3000 (Corbett Research, Qiagen, Germany). The cycle threshold (Ct) values of housekeeping *HPRT1* gene were used for normalization between the runs through the Relative Expression Software Tool (REST) 2009 (V.2.0.13).

Data analysis

The analysis on the results was performed through the web based Qiagen data analysis center at https://geneglobe.qiagen.com/us/analyze.

RESULTS

Age distribution (mean ± standard deviation) of the children in CD group (10.71±5.63) and the control group (11.03±5.49) were statistically not different from each other ($p>0.05$). Gender distribution in CD group was 63.3% female and 36.7% male while the control group was composed of 60% female and 40% male children. Of the CD group subjects, 86% had abdominal pain complaints, 64% showed insufficient growth, 64% were found to have iron deficiency anemia, and 56% were positive for HLA-DQ2. The CD subjects classified as Marsh3c according to the Marsh classification showed significant correlation with having iron deficiency anemia ($p=0.02$). Although not significant, Marsh3c subjects also showed correlation with having growth retardation ($p=0.07$).

Expression levels of *ARID1A*, *CTBP1*, *EED*, and *NSD1* genes in the CD group were higher than those in the control group. However, this overexpression was not found significant ($p=0.31$, 0.33, 0.38, and 0.33) (Table 1).

When children with CD who had diarrhea symptom (typical) were compared to the CD children without diarrhea symptom (atypical), statistically significant under-expression was found in *CBX3* and *CTBP1* genes ($p=0.04$ and 0.04) (Table 2).

When the children with CD who had symptoms of not gaining weight, vomiting, constipation, abdominal pain, short stature, and treatment-resistant iron deficiency anemia were compared to the children with CD who did not have these symptoms, no statistically significant change of expression was found in any genes ($p>0.05$).

Statistically significant *CTB1* overexpression was detected in Marsh 2 CD cases when the CD group was divided in subgroups according to Marsh1/2/3a/3b/3c stages and compared against the control group ($p=0.03$) (Table 3).

Table 1. Comparison of chromatin remodelling gene expressions between CD group and control group

Gene	Fold change	P value
CBX7	1.57	0.30
ING5	1.24	0.49
MTA1	1.42	0.42
NSD1	**6.46***	0.33
CBX3	0.97	0.36
EED	**2.06***	0.38
ARID1A	**2.63***	0.31
CTBP1	3.37	0.33
HPRT1	1.00	0.00

*Fold regulation values >2

Table 2. Comparison of chromatin remodelling gene expressions between CD group with/without diarrhea

Gene	Fold change	P value
CBX7	-1.64	0.05
ING5	-1.25	0.05
MTA1	-1.05	0.05
NSD1	-1.45	0.08
CBX3	**-13.51***	**0.04***
EED	4.44	0.50
ARID1A	-6.59	0.62
CTBP1	**-5.35***	**0.04***
HPRT1	1.00	0.00

*: Fold regulation values <-2 and significant p<0.05

Table 3. Comparison of chromatin remodelling gene expressions between CD group according to Marsh staging with control group.

Gene	Control Group									
	Marsh1		Marsh2		Marsh3a		Marsh3b		Marsh3c	
	Fold change	P value	Fold change	P value	Fold change	P value	Fold change	P value	Fold change	P value
CBX7	3.78	0.91	1.71	0.70	-1.06	0.61	2.11	0.52	-1.03	0.70
ING5	4.86	0.11	1.89	0.74	-1.93	0.57	1.38	0.51	1.16	0.68
MTA1	2.35	0.98	-1.06	0.94	3.06	0.63	-1.62	0.55	2.38	0.71
NSD1	3.23	0.88	10.88	0.72	34.64	0.63	2.68	0.55	2.17	0.71
CBX3	-3.73	0.68	3.50	0.83	17.06	0.62	-5.96	0.54	-4.42	0.71
EED	1.22	0.39	2.97	0.67	1.83	0.65	1.12	0.55	10.38	0.94
ARID1A	-5.48	0.93	-2.14	0.65	131.89	0.62	-1.21	0.54	3.41	0.71
CTBP1	102.69	0.77	**3.70***	**0.03***	11.96	0.65	1.24	0.31	-1.11	0.71
HPRT1	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00

*: Fold regulation values <-2 and significant p<0.05

Although statistically insignificant, the *NSD1* expression was elevated in the HLA-DQ2 positive CD patient group compared to the control group (p=0.53). In the comparison of HLA-DQ2/DQ8 positive CD patient group with the control group, the *NSD1*, *CBX3*, and *EED* genes were over-expressed (p=0.75, 0.75, and 0.78) and the *CBX7*, *MTA1*, *ARID1A*, and *CTBP1* genes were under-expressed (p=0.74, 0.75, 0.75, and 0.75). When the HLA-DQ2/DQ8 positive CD patients were compared to the HLA-DQ2 positive CD patients, over-expression of *MTA1* and *NSD1* genes (p=0.46 and 0.61) and under-expression of *CBX3* and *EED* genes were detected in the HLA-DQ2/DQ8 positive CD patients (p=0.73 and 0.56).

DISCUSSION

Subjects in both pediatric CD patient group and the control group were evaluated for their characteristics. Male to female ratio in the CD group was 2/3. Comparable male to female rates were also reported by previous groups (KULOGLU *et al.* 2009; KHATIB *et al*., 2016). In the current study, 56% of the CD group were HLA-DQ2 positive and 15% of them were positive for HLA-DQ8 in line with the literature, which reported higher percentage of HLA-DQ2 positivity than HLA-DQ8 (KULOGLU *et al.*, 2008; TUYSUZ *et al.*, 2011). Abdominal pain, growth retardation, and anemia were the common complaints in the pediatric CD group. These three symptoms and constipation were also listed as the frequent findings of CD in several reports (FASANO, 2005; KULOGLU *et al.*, 2009; KHATIB *et al*., 2016; IWANCZAK *et al.*, 2013). Among the CD group, those classified as the Marsh3c patients had significant correlation with having iron deficiency anemia, which could be explained by the villus atrophy frequently observed in CD patients. Growth retardation was present in Marsh3c patients as the chronic intestinal disorder is expected to inhibit the patients from benefiting their diet but the correlation between Marsh3c patients and growth abnormalities was found to be insignificant.

Chronic inflammation can be both the cause and consequence of CD and may affect the complications and immune functions such as imbalance between pro-inflammatory cytokines. In addition to the genetic changes leading to inflammation in CD, epigenetic changes can also alter gene expression in response to environmental factors. It is known that chromatin remodeling, an epigenetic mechanism, is associated with gastrointestinal diseases associated with chronic inflammation, and induces carcinogenesis in the early stages (TAKESHIMA *et al.*, 2015; SHEN *et al.*, 2015; BILGIC *et al*., 2018). However, there is no information on the CD link of chromatin remodeling in the literature. While the results of this case-control study suggest that chromatin remodeling genes may be associated with development and progression of CD, it is predicted that these results can be verified, and statistically significant results can be achieved in follow-up studies with larger group of subjects. Our results suggest that chromatin remodeling genes *ARID1A, CTBP1*, and *NSD1* may be associated with the development and progression of CD.

Examination of epigenetic changes such as chromatin remodeling as part of inflammatory response to environmental factors results in promising outcomes to help prevent CD. Understanding the CD inflammation at gene level may provide more information to design novel drugs or strategies for the disease.

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POVEZANOST DEČJE CELIJAKIJE I EKSPRESIJE GENA ZA PREOBLIKOVANJE HROMATINA

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Izvod

Celijakija (CD) je imunološki zavisa sistemski poremećaj koji se javlja kod genetski predisponiranih osoba što rezultira oštećenjem tankog creva. Poznato je da je preoblikovanje hromatina, epigenetski mehanizam, povezan sa gastrointestinalnim bolestima povezanim sa hroničnom upalom. Međutim, nisu dostupne informacije o vezi između CD-a i pregradnje hromatina. U tu svrhu procenjeni su profili ekspresije gena grupe za preoblikovanje hromatina kod dece s dijagnozom CD-a prema Marsh-ovoj klasifikaciji i HLA-profilu i istražena je njihova povezanost s CD-om. U istraživanje su uključene endoskopske biopsije ugrađene u parafinski blok 40 dece sa CD dijagnozom i 30 zdrave dece. Pregledane su najčešće četiri mutacije (DQA1*05, DQB1*02, DQA1*03 i DQB1*03: 02) povezane sa CD-om na genu humanog leukocitnog antigena (HLA). Uzorci biopsije creva korišćeni su za izolaciju mRNA i sintezu cDNA. Ekspresije ukupno sedam gena u grupama za preoblikovanje hromatina (Kompleksna grupa SWI/SNF: ARID1A, Polycomb Group: CTBP1, Kompleksna grupa za nukleozomsko remodeliranje i histonska deacetilaze (NuRD): MTA1, Chromobox/Heterochromatin Protein 1 (HP1) Homolozi i Grupa CBX: CBX CBX7, Homeodomain (PHD) Proteinska grupa: NSD1, Porodična grupa inhibitora rasta (ING): ING 5) u studiji je analizirana pomoću qPCR u realnom vremenu. Analiza podataka izvršena je pomoću softvera proizvođača. Prekomerna ekspresija u genima ARID1A, CTBP1 i NSD1 otkrivena je kada se CD grupa upoređivala s kontrolnom grupom, ali nisu bile značajne (p=0,31, 0,33 i 0,33). CD grupi bez simptoma dijareje (atipično) utvrđena je statistički značajna nedovoljna ekspresija u genima CBX3 i CTBP1 (p=0,04 i p=0,004). Statistički značajna prekomerna ekspresija CTB1 otkrivena je u slučajevima Marsh 2 CD-a (p=0,03). U poređenju HLA DQ2/DQ8 pozitivne CD grupe bolesnika s kontrolnom grupom, NSD1, CBX3 i EED (p=0,75, 0,75 i 0,78) geni su bili prekomerno eksprimirani, a CBX7, MTA1, ARID1A i CTBP1genes (p=0,74, 0,75, 0,75 i 0,75) bili su nedovoljno izraženi. Ovo je prva studija koja je izvestila da ekspresija gena za preoblikovanje hromatina može imati ulogu u razvoju i napredovanju CD-a. Rezultati ove studije slučaja-kontrole otvoreni su za potvrdu u budućim studijama sa većim brojem ispitanika kako bi se dobili statistički značajni rezultati.

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