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Epigenetics of Early Inflammatory Bowel Disease among Children: A Systematic Review

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Abstract

Background: Inflammatory bowel diseases (IBDs) are complex and multifaceted disorders characterized by recurrent and persistent intestinal inflammation. The incidence of inflammatory bowel disease (IBD) is on the rise among both children and adults worldwide. In this review, we provide an update on genomic studies of IBD, with a particular focus on Very Early-Onset IBD (VEO-IBD), which often presents with a more severe phenotype than IBD at an older age.

Methods: The methods used in this systematic review were performed according to the guidelines of the PRISMA checklist. A search was conducted by two independent researchers in international databases (PubMed, Web of Science, Scopus, and Google Scholar) to find relevant studies published in English.

Results: Patients with VEO-IBD have rare or novel genes associated with immunodeficiency that may play a role in the pathogenesis of the disease. To date, ten regions for 240 genes, which are usually monogenic, have been identified for this disease, mostly due to mutations. But the most important cause of VEO-IBD is mutation in interleukin 10. It has also been reported that VEO-IBD is associated with increased expression of S100A8 and S100A9 genes in rectal mucosa and serum.

Conclusion: Considering the multifactorial nature of IBD, all the changes that cause protein expression and function should be taken into account; so for early diagnosis and timely treatment of this disease, more extensive phenotypic sequencing is needed to discover new gene loci. And these children can be treated with hematopoietic stem cell transplantation, as the most efficient method.

Key Words: Crohn's Disease, Genetics, Early Inflammatory Disease, Ulcerative Colitis.

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1- INTRODUCTION

IBD is caused by an abnormal response to common bacteria in the digestive system, leading to chronic inflammation in the intestinal area. Several factors, including genetics, environment, and immunology, may play a role in causing this disease (1). The incidence of this disease is higher in Western countries and lower in Asian countries (2). However, IBD is one of the most serious health problems worldwide. This disease consists of two phenotypes: Crohn's disease (CD) and ulcerative colitis (UC).

CD causes inflammation of the digestive tract, from the mouth to the anus, but mostly the lower part of the small intestine, the ileum. Mucosal ulcers, abscesses, strictures, and peri-anal lesions including skin tags, fissures, and fistulas are often present. UC involves the rectum and may affect some parts or all of the large intestine continuously (3). One of the long-term colon complications of colorectal cancer is known, and among the extra-intestinal complications of this disease are its effects on the skin, joints, and eyes. In both phenotypes of this disease, i.e. CD and CU, the gastrointestinal tract is injured (4). Although the main cause of IBD has not yet been fully and accurately determined, researchers have confirmed the effect of three genetic, immunological, and environmental factors in their pathogenesis. They consider each of these factors separately in understanding the pathogenesis of this disease (6, 5).

Inflammatory bowel diseases are divided into four groups: 1- Adult IBD and 2- Pediatric IBD, intended for people under 17 years of age. 3-VEO-IBD is intended for patients under the age of 6 years. 4- Neonatal IBD is intended for patients under two years of age. Neonatal IBD can also occur in children less than 28 days old. Patients with VEO-IBD are most likely monogenetic (7, 4). Subsequent studies on VEO-IBD disease show that compared to adult IBD, it has a consistent phenotype. In fact, the way the disease occurs, the location of lesions, and genetic risks are different (8). Thus, the risk of colon cancer in children with ulcerative colitis is twice more than that of adults (9). At first, researchers believed that the cause was resistance to immunosuppressant treatment. Further studies revealed that genetic defects affect the immune function of the intestinal epithelial barrier and disrupt its function. So, today, the most important cause of VEO-IBD is considered to be a mutation in coding genes of interleukin 10 (IL-10) receptor (8). Also, VEO-IBD causes developmental disorders in children, which have lasting effects (10). Since the incidence of VEO-IBD is increasing (11), it is important to find out the causes and to find ways of prevention and treatment.

2- MATERIALS AND METHODS

Based on a thorough analysis according to PRISMA (12) guidelines, the following search technique was used between 30/1/1998 and the end of 1/10/202**3** to find the eligible studies. Two separate researchers (M.T. and M.A.) searched for the pertinent papers published between 30/1/1998 and the end of 30/2/2023. The Cochrane Library, Ovid, and Trip databases searched for English-language publications in MEDLINE, EMBASETM, and MEDLINE via PubMed. Our search for materials written in different languages included national databases (Magiran, SID), KoreaMed, and LILACS. For literature saturation (MT), the list of included references or relevant reviews was examined. The Health Sciences Librarian website was used to develop unique search techniques focused on systematic review searches using MESH terms and open phrases in compliance with the PRESS criteria. Results from searches in other databases were contrasted with those from the

MEDLINE approach after it had been finalized. Similarly, PROSPERO was looked up to locate recent or active systematic reviews. The keywords used in the search strategy were inflammatory bowel disease, genetics, epigenetics, VEO, and IBD. The database of earlier study materials and systematic reviews was also explored to find the published research. A search for unpublished data and abstracts was also conducted on all papers that met the inclusion criteria.

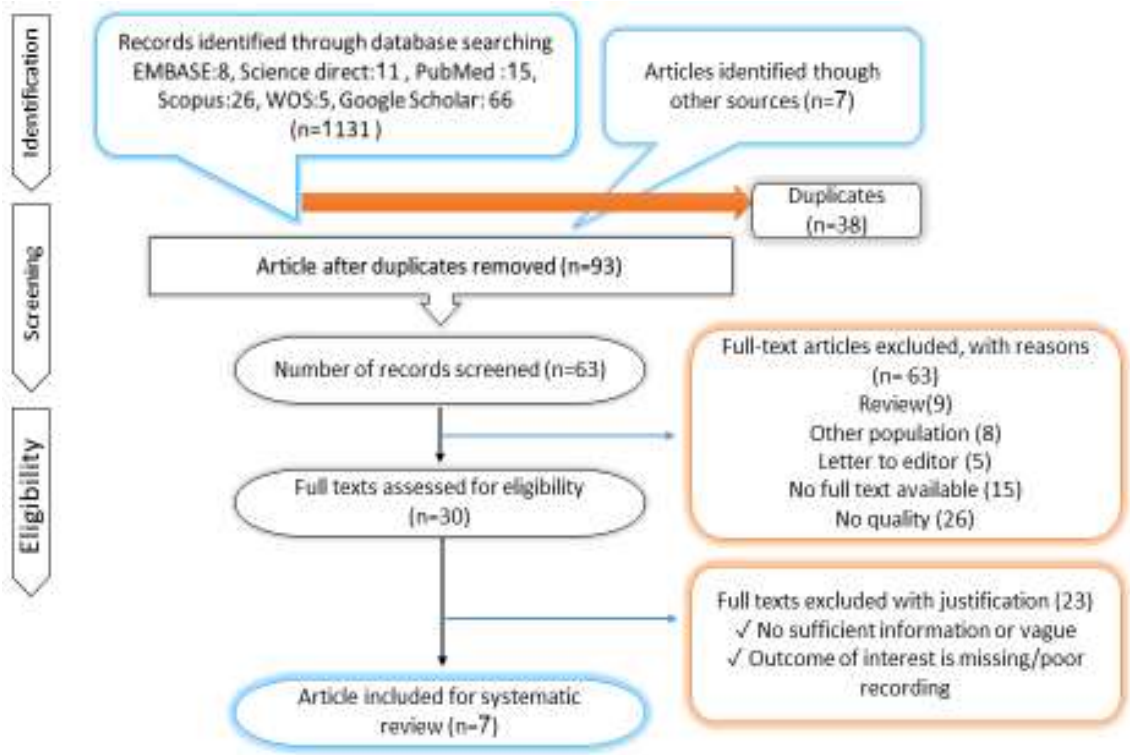

Fig. 1: PRISMA flow diagram

2-1. Eligibility Criteria

The addition of Cross-sectional, case-control, cohort, case report, and review publications were the articles that met the criteria for the systematic review. Non-random sample size, lack of relevance, and inadequate data were among the exclusion criteria. Two researchers carried out each of the stages mentioned above separately to prevent bias in the study. Finally, the consistency of the third researcher's findings was checked.

2-2. Study Selection and data extraction

All pertinent publications were initially gathered, and a list of abstracts was created to help special investigations. The complete text of the publications was given to the researchers after the specifics, such as the name of the magazine and the author, had been concealed. Two researchers independently examined each publication; the reason was stated if the article was rejected. In the event of a dispute between the two researchers, a third researcher evaluated the paper.

3- RESULTS

138 articles related to the topic were obtained from the initial search. The titles and abstracts of the articles were reviewed by two researchers independently according to the main objectives. If related to the current research, the full text of the

articles was prepared for review. Regarding the current study, the full text of the articles was prepared for review. Finally, when the full text of 15 relevant studies was reviewed, 9 studies were excluded due to not meeting the required criteria. 7 relevant studies were included in the quality assessment phase, and if necessary, information about the authors was obtained. General information (first author, country, and year of publication) as well as research information (type of genes and number of genes involved in the disease) were gathered (**Tables 1** and **2**).

Table-1: The number of gene loci

Name	Year	Gene location
Imielinski M (39)	2009	163
Bianco, A (61)	2015	201
Finocchi A (68)	2023	230
Noble AJ. (62)	2023	240

IBD is a diverse and widespread pathological condition that varies in the degree of clinical heterogeneity between patients. Since genetic factors influence this disease, researchers have conducted necessary genomic studies for this disease. The first comprehensive genome-wide study of IBD patients was performed in 1996 by Hugo et al. They found that the IBD locus in the pericentral region of chromosome 16 (cluster 12 on the short arm of chromosome 16) is one of the regions with the strongest genetic association with the disease (11, 10). In 2001, the same research group narrowed down the genomic region of IBD1 to a new gene, NOD2, where three major mutations occurred.

Among candidate "situational" genes, researchers pay more attention to major genes, because the histocompatibility complex of genes in this region most likely determines the level of susceptibility to disease, the level of response to treatment, and the resulting complications (13).

Since the discovery of the first locus, researchers have identified ten chromosomal locations associated with the disease, and research is still ongoing. Among these, most studies have been conducted on the location of IBD1 and its polymorphisms. The genes associated with IBD1 are CARD15/NOD2, which are specific for the Crohn subtype (14, 15). Mapping of candidate regions continues using additional genome scanning and candidate gene analysis techniques. They comprehensively mapped four regions on chromosome 16 (IBD1, IBD2, IBD3Đ, the HLA region) to the IBD1 locus. Detailed mapping of the IBD1 locus on chromosome 14 is ongoing (16). For the first time, a genome-wide study of the IBD2 locus was performed in 160 British families. In this study, the researchers found that the IBD2 locus is located on the long arm of chromosome 12. This locus is associated with UC; the gene associated with this locus is NOD2 (17). IBD3 is located on the short arm of chromosome 6, which contains the major histocompatibility complex (MHC). This locus has been implicated in both Crohn's disease and ulcerative colitis in genetic linkage studies, and the associated genes are MHC I, II, and TNF-α (20,19,18). IBD4 is located on the long arm of chromosome 14 (14 q 11). Various studies have confirmed the association of this area with Crohn's disease. The associated genes are the TCR complex (21). The IBD5 locus is located on the long arm of the chromosome. q 315, which is associated

with CD, and the gene associated with this locus is IL-3, 4, 5, 13 (22). The IBD locus 6 is located on chromosome 19 (p13). It is related to CD and UC subtypes. Genes related to this locus are ICAM-1, and TBXA2R (23). The IBD7 locus is located on chromosome 1p36 and accounts for both CD and UC. The related genes belong to the TNF-R family (24). The IBD8 locus is located on chromosome 16p and is associated with both CD and UC. Genes associated with TNF are Pr (25). The IBD9 locus is located on chromosome 3P. Both diseases include CD and UC. Genes associated with this locus include HGFR and EGFR (26). Other loci are located on chromosome 7q and include both CD and UC groups. Related genes are MUC-3 and MDR-1 (27). The researchers have also found that S100 proteins play a role in inflammatory bowel disease. S100A8/A9, also known as calprotectin, S100A12, or calgranulin C, and to a lesser extent S100P, play a major role. These proteins are involved in the pathogenesis, function, diagnosis, and treatment of IBD. Of course, more research and studies are needed to obtain more information about the exact relationship between S100 proteins and IBD or the relationship and association of this disease with new S100 proteins (28).

4- DISCUSSION

Genetic predispositions play a more important role in pediatric patients. That is, why children often have diseases such as IBD that are more extensive and take longer to heal in comparison to adults (28). Because it is not always possible to classify IBD based on standard histological and immunological features, genetic analysis is required. VEO-IBD has a phenotype different from that of IBD. However, the percentage of similarity of genetic defects between VEO-IBD and IBD is about 69% (**Table 3**).

Usually, in VEO-IBD, there are Monogenic Disease (MD) defects, which are caused by mutations (29). Although Parente said in her study that VEO-IBD can be a non-monogenic disease, it is noted that the severity of the disease in children with monogenic defects is higher than in non-monogenic children. Also, in twin studies, the concordance rate for dizygotic pairs is between 3% and 5%. At the same time, concordance rates for monozygotic twins have been reported to be between 20 and 60 percent (30). This disease is more likely to occur in children whose first-degree family members are prone to IBD. There is resistance to treatment among these children, which even causes their death. The best treatment for these people is hematopoietic stem cell transplantation (31). As Quahed stated in his study, Hematopoietic Stem Cell Transplantation (HSCT) can be beneficial in the treatment of VEO-IBD with genetic causes of IL-10RA, IL-10RB, IL-10 deficiency, IPEX, WAS, MAnyforms of SCID, CD4OL, X1AP, CGD, LRBA, CTLA4, DOCK8 (32).

In recent years, several genetic studies, including GWAS, were conducted, which helped to identify new genes and SNPs that play a role in susceptibility or protection to IBD. By examining the genetics of VEO-IBD and EO-IBD, they found that this disease can occur in children with a highly variable phenotype, from mild to severe. Therefore, the results of genetic screening should be considered based on the severity of the phenotype to relate the variants to the specific clinical conditions of the patients. In this context, Uhlig et al. examined the phenotypes and laboratory findings of more than 50 single-gene diseases. They found that VEO-IBD is one of the rare monogenic diseases. In these patients, interleukin-10 (IL-10) was found to exhibit a Mendelian inheritance pattern in which complete penetration leads to inflammation and disruption of the intestinal epithelium (33).

Table-2: Summary of included studies

Author	Year	Country	Study design	Study period	Number	Incidence of IBD locus genes	Overall quality
Wu Y. (62)	2023	Ashkenazi Jewish	Cohort	2021	4453	ICAM1, LRRK2, NOD2, PDGF, RGS1,EGR2, TLR4, VDR, ITK, INPP5D,IL33, ICAM2	Good
Christodoulou K. (63)	2013	University Hospital Southampton	Retrospective	2010-2011	8	GSDMB, ERAP2, SEC16A, BACH2 ,IL10 , BTNL2: S334L; C1orf93:G176R; ICAM1: R367C; NOD2: R702W and SH2B1: L185Q	Good
Imhann F. (64)	2106	Netherlands	Retrospective	2008	895	NOD2، CARD9،ATG16L1، IRGM و FUT2.	Good
Serra E. G. (65)	2020	European, and South Asian	Cohort	2018	4436	XLAP- SH2D1A- CYBA- CYBB	Good
Kamaraj, B. (66)	2023	Saudi	Retrospective	2022	three consanguineous Saudi families	LILRB1 (Q53L, Y99N, W351G, D365A, and Q376H) and PRSS3 (F4L and V25I)	Good
Finocchi A., and Kyodo R. (68, 67)	2022	Japan	Retrospective	2021	-	DUOX2 : R1212H/F1490Y, R286H/P609S, P303R, R1492C, R1211C, R842X/R1059C	Good

Table-3: Genes derived from statistical analysis for IBD and Monogenic VEO-IBD (shared genes between the two groups are highlighted).

IBD						VEO-IBD
Loss of tolerance	Impaired mucosal defense	Diverse mechanisms	Epithelial barrier defects	genes derived from IBD SKAT-O analysis in CD, UC		Monogenic of VEO-IBD
IL10	ITGB2	POLA1	CD55	PPP1R3D THAP3	CCDC1	IL-10RA
IL10RA	G6PC3	SK1V2L	MASP2	C14orf166B ANP32B	MARCH7 SLC45A	IL-10RB NCF1 NCF2
IL10RB	CYBA	ICOS	TTC7A	OR1OJ5 HSD17B8	WDR60 EPHX2	IL-10 NCF2
STAT3	CYBB	PTEN	FERM1	PCOLCE2 FCHO2	LRRK2 ICAM1	NPC1 NCF4
FOXP3	NCF1	P1K3CD	ADM17	ITK GALNT8	INPP5D ZNF695	FOXP3 X1AP
IL2RA	NCF2	A1CDA	GUCY2C	IRX1 GGNBP2	RNF39 NUMA	MALT1 HPS1
CTLA4	NCF4	CD4OLG	SLC9A3	MIER1 VDR	ZNF329 CLIP3	STAT1 HPS4
LRBA	NOX1	PLCG2	SLCO2A1	ERO1LB KIAA1468	CLPX TFCP2	LRBA HPS6
TTC7A	DUOX2	PLK3R1BTK	PLA2G4A	ADORA1	GJD2 PTCHD4	GTLA4 M7K
WASP	NOX1	TTC37	STXBP2	GPD2	OR6C76 RAD54L	IL21 PLGG2
TCH	NOX1	TRNT1		C2ORF70	ZNF556 MED13	WAS MEF7
IL-2RG	NPC1	NLRe4		IGSF3	DPH2 EVPLL	CD40LG STXBP2
STLM1	TR1M22	MEF7		TLR4	RLF NTSR1	ALCDA TRIM22
ORAL1	SM2D1A	M7K		RAB32	SPAG5 CLRN3	BTK SLCO2A
ZAP70	ALP1	CASP8		RRS1	ERICH1 EHMT1	PIK3R1 TTC7A
DKC1	X1AP	TNFA1P3		GK2	ZNF597	ZAP70 IKBKG
RTEL1	FCN3			ZNF552	ATP6VOD2	RAG2 COL7A1
ZBTB24				PDGFD	HHLA2	IL-2RG FERMT1
LIG4				C2orf16	NMS	LIG4 ADAM17
DCRE1C				INTS7	NECAP1	ADA GUCY2C
RAG2				OGFOD1	CCT7	CD3-Ɣ SLC9A3
RAG1				NANOS2	SH2D5	ICOS SKIV21
ADA				LAMP3	MCOLN2	DKC1 TTC37
				ZNF785	CST4	RIEL1 ARPCIB
				RGS1	TOE1	TGFBR1 CD55
				NR2C1	DLG4	TGFBR2 P1K3CD
				C1Oorf91	PEX13	ZBTB24 G6PC3
				P4HTM	MYNN	RIPK1
				SUSD1	ZFAND4	CASP8
				TUT1	PLTP	CYBB

IBD						VEO-IBD
Loss of tolerance	Impaired mucosal defense	Diverse mechanisms	Epithelial barrier defects	genes derived from IBD SKAT-O analysis in CD, UC		Monogenic of VEO-IBD
				PRSS36 KIF25 SUSD5 SPHKAP EGR2 PLSCR2 SLC35F1 SCFD1 FRMPD1 SRRD ANKRD6 USP37	SSH1 DARS2 ASIC5 HAUS2	CYBA SLC37A4 ITGB2 IL-2RA1CD25AR STAT1GOF STAT3GOF IL-27 Th17 PSMG1 MTMR3 CAPN10 SMAD TNFRSF6B JAK1GOF ZMIZ1 DCLRELC ARTEMIS CARD15 CARMIL-2 CARD11

The assessment and treatment of this disease are challenging due to its unique genomic and immunological triggers. Therefore, there are many methods, including WES, which means whole exome sequencing. This method is used to identify underlying genetic problems and defects (34).

WES has expanded the list of genes associated with the risk of IBD compared to the genes identified during GWAS. Conventional treatments for this disease include medical treatment, surgery, or hematogenous stem cell transplantation.

Sometimes, this disease does not respond to conventional treatments and is fatal (33). On the other hand, because it is a genetic and environmental disease, the incidence probability of this disease is higher in children and future generations of families with a history of IBD. Of course, this applies more to the CD group. Thus, if a family member has CD, the risk of developing this disease in the next generation of that person increases by 15-35 times, while in the same situation, the risk of developing ulcerative colitis increases only by 6-9 times (5). In addition, a study by Heyman et al., in 2005, demonstrated that in families with a history of phenotype distribution with high variability, the prevalence of this disease is higher among children of this group (35). Therefore, the familial frequency of inflammatory bowel disease is higher in monozygotic twins than in dizygotic twins (36).

A lower age of onset in familial cases is a consistent finding in genetic diseases and provides the logic for classifying information by age of diagnosis. For example, the IBD1 and IBD5 loci (located on chromosomes 16 and 5, respectively) have shown a genetic association with inflammatory bowel disease. There is stronger evidence of a genetic link at an earlier age of onset (38, 37).

For example, in Christodoulou's study, in 2013, the DNA of eight people with severe VEO-IBD was analyzed using exome sequencing; and 169 IBD-susceptible genes were identified. The results showed that for each study case, all non-synonymous mutations, truncation, and frameshift mutations were identified in all known IBD genes. The unique profile of rare and potentially harmful variants was evident in every patient with this complex disease (28). Imelinsky et al., in 2009, reported the results of a genome-wide study on the association of IBD with early onset in an international collaboration between Europe and North America. They identified five new regions associated with WEO-WZK. These regions include 16p11, which is adjacent to the cytokine gene (IL27). Also, in adult patients, 32 loci have been found for the CD subset, and 23 of these 32 loci are shared with VEO-IBD. 17 loci have been found to be involved in CU in adults, of which 8 loci are shared with VEO-IBD, suggesting a close pathogenic relationship between IBD and VEO-IBD (39).

Kelsen et al., also selected four hundred genes and regions associated with primary immunodeficiency, covering approximately 6,500 coding exons, a total of more than 1 Mbp of coding sequence, from whole-exome data to see if patients with VEO-IBD have different genes compared to IBD. Based on the analysis of these regions, it was shown that new and rare variants in these genes can contribute to the development of VEO-IBD, including rare heterozygous missense variants in IL10RA and previously unknown variants in MSH5 and CD19. By exome sequencing analysis among patients with VEO-IBD and their parents, a variety of genes were identified that regulate the function of B and T cells and can contribute to the pathogenesis of the disease (34). In a study by Giradelli et al., in 2018, direct gene sequencing was

performed looking for 94 alterations in the NOD2, ATG16L1, IL23R, IL10R, IL10, and XIAP genes that were previously associated with IBD in both multifactorial and Mendelian models. All identified variants were associated with IBD except for three variants in NOD2, IL10, and IL10RB genes, which, even if present in online databases, have never been included in association studies in IBD patients. Also, this study carried out genetic identification with detailed "in silico" analysis. It wanted to predict and confirm the effect on the structure and function of proteins. They found that even if the genetic analysis showed a very low frequency in the benign control population, they could not be considered a monogenic disease; it would still be in the multifactorial range. However, there is no significant difference between VEO-IBD and EO-IBD patients (40).

In 2016, Xiao et al. conducted a comprehensive mutation screening for 10 genes in Chinese VEO-IBD patients. They found that IL-10RA and IL-10RB mutations are common among these children, and patients with these mutations have lower blood hemoglobin and less weight (41). Researchers have also found that calprotectin is an important inflammatory mediator in inflammatory bowel diseases and is composed of two subunits called S100A9 and S100A8 (42). In this regard, Molloy et al. showed in a study that calprotectin genetic polymorphism can be effective in some IBD behaviors, including the severity of the disease (based on the drugs needed to control the disease), extraintestinal complications (arthritis) and disease attacks (43). Also, in the study of Leach et al., increased expression of S100A8 and S100A9 genes was reported in the serum and rectal mucus of children with inflammatory bowel diseases (44). The increase in intestinal permeability plays a key role in the pathogenesis of Inflammatory Bowel Diseases (IBD) and is associated with disease flare-ups. Zonulin-Related Proteins (ZRP) are proteins that increase permeability in the epithelial layer of the small intestine by reversibly modulating intercellular tight junctions and it may act as a novel and non-invasive biomarker. In a study by Szymanska et al., ZRP was examined in pediatric IBD patients and its relationship with disease activity and calprotectin was investigated. They found that stool ZRP levels are increased among people with IBD. Also, they are associated with CD activity and strongly correlated with FCP (45). In addition, Wang and Yafet found that in patients whose IBD was already diagnosed, the serum level of ZRP was high compared to the control group, but in accidental IBD patients, the serum level of ZRP was not different compared to the control group. It can be concluded to be one of the complications of the disease, which affects the amount of ZRP over time (46). In his study, Kushlinskii found that the content of zonulin in the blood serum of patients with inflammatory bowel diseases is high (47).

On the other hand, researchers have found that IBD has common clinical and biological characteristics with some diseases, including Familial Mediterranean Fever (FMF) and intestinal inflammation (48). In this context, Beser et al. stated that when a person has IBD with FMF, the most common mutation is M694V (3). If Urgansi is found in the study, FMF mutations are not relevant for CD patients. Also, the level of PUCAI was observed in UC patients at a lower level (49). Researchers have also found that host miRNAs play an important role in regulating the immune system of the gut microbiota, and overexpression of some of them, such as B. miR-223, may have anti-inflammatory properties (50). Dysregulation of specific miRNAs such as miRNA 106a, miRNA 146b-5p, and miR-

31(51, 52) may lead to IBD disease progression; for example, patients with IBD are more susceptible to colon cancer; and misexpression of miRNAs may lead to increased cancer in these people (53). Therefore, microRNAs may play an important role in the diagnosis and treatment of the diseases (54). Because of these properties, RNA molecules can be used to produce drugs suitable for the treatment of this disease. Indeed, the Food and Drug Administration (FDA) has approved several siRNA drugs in recent years, encouraging the development of more drugs to treat chronic diseases (55).

5- CONCLUSION

Interactions between the environment and genome can lead to rare monogenic diseases such as VIO-IBD. Epigenetic mechanisms influence the development and progression of VIO-IBD. In fact, epigenomics is an emerging field. This disease has many implications for patients and their families. Therefore, it is recommended to carry out timely diagnosis and appropriate treatment of the next generation to maintain health. In fact, targeted treatment strategies are required to prevent this disease. With genetic studies, new insights into the pathogenesis of IBD may be gained in the future. To date, more than 240 loci have been identified in genetic studies for IBD, 69% of which are risk factors for both IBD subtypes, 18% of loci are unique to CD, and 14% for UC. We will likely see more gene loci, as more studies are conducted on newer genes (59, 58, 57, 56).

It is hoped that epigenetic research will open up a wider field of disease reality and provide exciting insights into the pathophysiology of IBD. For example, patients with IBD can be treated by creating mutations in DNA with the disease genome and modifying histones and even small molecules that play a role in post-transcriptional regulation, such as microRNA (miRNA) (60, 10).

6- DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available from the authors, but restrictions apply to the availability of these data, so they are not publicly available. However, the author can make them available upon reasonable request.

7- CONFLICT OF INTERESTS

None.

8- ABBREVIATIONS

IBDs: Inflammatory bowel diseases

CD: Crohn’s Disease

UC: Ulcerative Colitis

EO-IBD: Early-onset inflammatory bowel diseases

VEO-IBD: Very-early-onset inflammatory bowel diseases

GWAS: Genome-wide association studies

NOD2: Nucleotide-binding oligomerization domain containing 2

DCs: Dendritic cells

WGS: Genetic code are whole genome sequencing

WES: Whole exome sequencing

miRNA: microRNA

SNPs: Single nucleotide polymorphisms

NGS: Next-generation sequencing

IL: Interleukin

FMF: Familial Mediterranean fever

ZRP: Zonulin-related proteins

MD: Monogenic disease

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