



# Consanguinity and Positive Family History of Inflammatory Bowel Diseases in Children: A Multicenter Case–Control Study

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## Abstract

Inflammatory bowel diseases (IBD), which comprise Crohn's disease (CD) and ulcerative colitis (UC), are rising trend in Saudi population. We aim to examine the association between consanguinity and family history and the risk of childhood IBD in Saudi children. A multicenter case–control study conducted in three tertiary hospitals in Jeddah and Riyadh, Saudi Arabia, during periods 2009 to 2021. Data about demographics, consanguinity, family history of IBD, and type of IBD were collected using a structured questionnaire. The same questionnaire was applied in matched case–control. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using unconditional logistic regression analysis that was performed to compare both groups. The study population included 335 children: 167 IBD patients (49.9%) and 168 controls (50.1%). Of these IBD, 93 patients (56%) were CD and 74 patients (44%) were UC. Most of participants were females (72.1%) and their age more than 10 years (51.5%). There was first-degree consanguinity in 66 IBD patients (49.6%). No significant difference in first-degree consanguinity between cases and controls was noted (49.6% in cases vs. 50.4% in controls; OR = 1.02; 95% CI = 0.66–1.57). The consanguinity showed a more significant association with CD than UC ( $p < 0.05$ ). Family history of IBD (father, siblings, and grandparents) as risk factors for IBD was identified: paternal history of IBD (OR = 0.25, 95% CI = 0.08–0.76), siblings' history of IBD (OR = 2.16, 95% CI = 1.92–2.43), and grandparent's history of IBD (OR = 0.22, 95% CI = 0.07–0.65). Family history of IBD showed a more significant association with CD than UC ( $p < 0.05$ ). Consanguinity is strongly associated with IBD with more significant association with CD than UC and may possibly explain IBD rise in Saudi Arabia. The greatest risk of family history of IBD is in first-degree relatives, especially in siblings' rather than parents and grandparents.

## Keywords

- inflammatory bowel diseases
- consanguinity
- family history

## Introduction

Inflammatory bowel diseases (IBD), which comprise Crohn's disease (CD) and ulcerative colitis (UC), are chronic idiopathic illnesses of gastrointestinal tracts. Although the exact pathogenesis of IBD remains unknown, part of the underly-

ing mechanism is a deregulated host immune response to intestinal flora, in genetically susceptible individuals.<sup>1</sup>

Consanguinity is a well-known risk factor for the development of genetic diseases in general.<sup>2</sup> Consanguinity is present in 10% of the global population.<sup>3</sup> However, in Saudi Arabia, more than 50% of all marriages are consanguineous

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(marriages between cousins).<sup>4</sup> The incidence of IBD has rising trend in Saudi children population.<sup>5</sup> Knowledge of the relation between parental consanguinity and IBD in children is important not only for counseling in communities with high prevalence of consanguinity but also as an indirect indicator of genetic susceptibility in the pathogenesis of IBD. Inbreeding or consanguinity leading to long stretches of homozygosity is known to contribute to Mendelian recessive disease, but may also play a role in complex polygenic diseases such as IBD.<sup>6</sup> A study conducted by Park et al reported the familial aggregation of IBD in Asian populations and a positive family history was an important risk factor for IBD in Koreans.<sup>6</sup> El Mouzan et al<sup>7</sup> investigated the relation between consanguinity and IBD in Saudi Arabia. His results showed there was no significant relationship between parental consanguinity and IBD in Saudi population, especially when there was no family history of disease, suggesting reduced genetic susceptibility.

To the best of our knowledge, no multicenter case-control study has been conducted in Saudi Arabia regarding childhood IBD and consanguinity and family history, so this work aimed to study the association between consanguinity and family history and the risk of IBD in Saudi children.

## Methods

A case-control design study was employed. We conducted this study to examine the association between consanguinity, family history of IBD, and the risk of childhood IBD in three tertiary hospitals in Jeddah and Riyadh, Saudi Arabia, during periods 2009 to 2021. Medical records of the selected centers were reviewed. The included children were from birth to 16 years with diagnosis of IBD. The diagnosis of IBD is based on a combination of clinical, endoscopic, histopathologic, and radiologic based on the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Working Group report (known as "the Porto criteria"). Patients with self-reported IBD or irritable bowel syndrome or immunodeficiency were excluded from this study. A consanguineous marriage is defined as a union between two individuals who are related as second cousins or closer. Consanguineous marriage is traditional and respected in most communities. It is common in many Middle Eastern countries especially Saudi Arabia, accounting for 50% of all marriages with the first-cousin type the most common.<sup>7</sup>

## Data Collection

Our target sample size was 435 participants recruited in three tertiary hospitals in two main cities (Jeddah, Riyadh), Saudi Arabia. We chose a margin error of 5% and a confidence level of 95% for our survey. For our survey, conventionally, a response rate of 70% is considered to be excellent. We need approximately 335 participants for our final sample size. Our targeted population for cases was patients from the IBD cohort of National Guard Hospitals and King Faisal Specialist Hospital. Controls were selected through convenience sampling technique from patients visiting outpatient clinics. The

user-friendly questionnaire was created to evaluate the demographic, socioeconomic characteristics and exposure variables to IBD. A group of pediatric gastroenterologists piloted the survey initially built by the two pediatric gastroenterologists. Then, according to the reproducibility, validity, as well as question value, the survey was revised. A total of 10 pediatric gastroenterologists and five pediatric practitioners reviewed the original pool of items for content and ease of understanding; based on the findings of the pilot, modifications and adjustments were performed (Cronbach's  $\alpha = 0.8$ ). The questionnaire was distributed through direct communication (face-to-face) as well as online survey-Monkey over a 3-month period from September 2021 to November 2021. Variables that were obtained from each patient included gender, age (the age at the time of study recruitment), diagnosis, consanguinity first degree (first cousin), mother educational level and father education level. Each variable was assessed in both cases and control. This study was approved by the Ethics and Research Committee of the National Guard Health Affairs, King Abdullah International Medical Research Center (NRJ21J/199/08). The parents or legal guardians gave their written informed consent for their children to participate in the study. All information collected was kept strictly confidential. The data stored in a secured database electronic system with limited access and only accessed by primary investigator. No names or ID numbers asked to complete the data collection form.

## Statistical Analysis

The associations of sociodemographic characteristics, family history of IBD, and consanguinity with childhood IBD were examined through univariate analysis. Backward stepwise procedures were used to build the multivariate analysis; the final model included only those variables that were found to be statistically significant in the univariate analysis. The associations are expressed as odds ratios (OR) with their confidence intervals (95% CI). The data were analyzed with the SPSS software (SPSS for Windows, version 13). Demographic data are compared by using chi-squared or Fisher's exact test when appropriate. Risk factors for IBD are examined through logistic regression analysis. A 2-tailed test indicated statistical significance at  $p$  less than 0.05. Association between epidemiologic factors and IBD (univariate analysis) was calculated.

## Results

### Characteristics of the Study Population

The study population included 335 children: 167 IBD patients (49.9%) and 168 controls (50.1%). Of these IBD, 93 patients (56%) were CD and 74 patients (44%) were UC. Most of participants were females (72.1%) and their age was more than 10 years (51.5%). Among the demographic characteristics, only age group (OR=0.023; 95% CI=0.02–0.17,  $p < 0.0001$ ) had significant relationship with IBD and control patients. The characteristics of the cases and controls are described in ►Table 1.

**Table 1** Demographic characteristics of all patients: IBD cases and controls (univariate analysis)

	Diagnosis						
	Control		IBD		Unadjusted OR	95% CI	p-Value
	n	%	n	%			
Age							
< 3 years	20	95.2	1	4.8	1		
3–6 years	32	94.1	2	5.9	0.02	0.02–0.17	<0.001
7–10 years	57	62.0	35	38.0	0.03	0.01–0.12	<0.001
> 10 years	59	31.4	129	68.6	0.28	0.17–0.47	<0.001
Gender					0.71	0.46–1.09	0.125
Male	79	45.9	93	54.1			
Female	88	54.3	74	45.7			
Home					0.84	0.43–1.61	0.588
Rural	19	46.3	22	53.7			
Urban	149	50.9	144	49.1			
Family incomes							
< 5000 Saudi Riyal	25	47.2	28	52.8	1		
5000 Saudi Riyal	17	42.5	23	57.5	1.24	0.68–2.92	0.440
> 5000 Saudi Riyal	126	52.5	114	47.5	1.50	0.76–2.94	0.243
Mother education level					1.29	0.84–1.99	0.250
High	101	52.9	90	47.1			
Low	67	46.5	77	53.5			
Father education level					0.73	0.47–1.13	0.162
High	93	47.0	105	53.0			
Low	75	54.7	62	45.3			
Consanguinity					1.02	0.66–1.57	0.946
Yes	67	50.4	66	49.6			
No	101	50.0	101	50.0			
Family history of IBD (mother)					0.49	0.14–0.65	0.240
Yes	4	33.3	8	66.7			
No	163	50.6	159	49.4			
Family history of IBD (father)					0.25	0.08–0.76	0.009
Yes	4	21.1	15	78.9			
No	164	51.9	152	48.1			
Family history of IBD (siblings)					2.16	1.92–2.43	<0.001
Yes	0	0.0	22	100.0			
No	168	53.7	145	46.3			
Family history of IBD (grandparents)					0.22	0.07–0.66	0.003
Yes	4	19.0	17	81.0			
No	164	52.2	150	47.8			

Abbreviations: CI, confidence interval; IBD, inflammatory bowel diseases; OR, odds ratio.

### Consanguinity and Family History as Risk Factors for IBD

In this study, consanguinity was found in 66 patients with IBD (49.6%). No significant difference in consanguinity between cases and controls was noted (49.6% in cases versus

50.4% in controls; OR = 1.02; 95% CI = 0.655–1.573). Although consanguinity failed to reach statistical significance regarding the association with an increased risk of IBD, this association was not statistically significant in a multivariate model adjusting for IBD types (adjusted OR = 0.671; 95%

CI=0.303–1.488) that is shown in ►Table 2. Interestingly, consanguinity showed a more significant association with CD than UC ( $p \leq 0.05$ ) is shown in ►Table 3.

In multivariate conditional logistic regression analysis, family history of IBD (father, siblings, and grandparents) as risk factors for IBD was identified (►Table 1): family history of IBD (father) (OD = 0.247, 95% CI = 0.080–0.761), family history of IBD (siblings) (OD = 2.159, 95% CI = 1.916–2.432), and family history of IBD (grandparents) (OD = 0.215, 95% CI = 0.071–0.654). Interestingly, family history of IBD (mother) was found not significantly associated with IBD ( $p=0.240$ ). The greatest risk is in first-degree relatives, especially in siblings' family history rather than parents and grandparents family history. Family history of IBD (father, siblings, and grandparents) showed a more significant association with CD than UC ( $p \leq 0.05$ ).

## Discussion

A recent Saudi report showed that the incidence of IBDs has shown a trend of increased annual mean incidence, but the risk factors of IBD were not reported.<sup>8</sup> Saudi Arabia has social and cultural factors, including the high frequency of consanguineous marriages and the large family size. Despite the increasing education rate in Saudi Arabia, the prevalence of consanguineous marriage does not seem to be decreasing as quickly as expected.<sup>9</sup>

In this article, we report that consanguinity is presented in 49.6% of IBD patients, but no significant difference in the consanguinity between cases and controls was noted. However, consanguinity showed a more significant association with CD than UC. This result is in contrast to previous studies that there was no significant difference in the prevalence of consanguinity among CD and UC.<sup>7</sup> Our observations in our patients suggest that there is a need to increase the public

awareness of the health genetic consequences of consanguineous marriages and parental consanguinity is a potential risk factor for possible development of IBD.

A recent position statement by the ESPGHAN reported that consanguinity, family history of autoimmune disease, and family history of suspected or confirmed monogenic disorders are associated with monogenic IBD.<sup>10</sup> The rate of family history in CD ranges from 2 to 14%, and in UC from 7 to 11%.<sup>11,12</sup> Several previous studies reported the impact of positive family history in the era of IBD and found those with familial IBD exhibited a faster start of illness when compared with children with sporadic IBD.<sup>13</sup> About 8.5% of Greek children had a family history of IBD.<sup>13</sup> Another Japanese study reported that 2.7% of the patients with UC and 2.6% of those with CD had a family history of IBD.<sup>14</sup>

This study reported that family history was 22.6% in IBD. In subanalysis of family history, the most commonly affected types of relatives were 3.6, 5.7, 6.6, and 6.7% in maternal side, paternal side, siblings' side, and grandparents' side, respectively. Similar to Ruban et al<sup>15</sup> reported the rate of a positive family history of IBD in the pediatric IBD population is 25.2%, but no further details of types of relatives identified. A Chinese study reported family history describing the most commonly affected types of relatives were cousin (41.1%), sibling (37.5%), and parent (28.6%).<sup>16</sup> The explanation for different family history of IBD among different countries is possibly that families have different genetic backgrounds, and often different environments and lifestyles. Interestingly, maternal family history of IBD was found not significantly associated with IBD. It is possibly that some information retrieved from parents could have been subjected to recall bias. Genetic investigations (genome sequencing) for IBD and Mendelian inheritance pattern were not performed in our study to describe maternal family history of IBD. The high percentage of family history of IBD in our study compared

**Table 2** Logistic regression analysis of factors (family history of IBD, age, and consanguinity) associated with IBD

Risk factors		AOR	95% CI		p-Value
Family history of IBD (mother)	Yes	3.59	0.33	39.57	0.297
	No	1			
Family history of IBD (father)	Yes	3.07	0.35	27.26	0.313
	No	1			
Family history of IBD (siblings)	Yes	Cannot be calculated			0.998
	No	1			
Family history of IBD (grandparents)	Yes	2.42	0.32	18.15	0.390
	No	1			
Age	<3 years	0.004	0.000	0.08	<0.001
	3–6 years	0.005	000	0.06	<0.001
	10 years	0.148	0.06	0.38	<0.001
	>10 years	1			
Consanguinity first degree	Yes	0.67	0.30	1.49	0.326
	No	1			

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; IBD, inflammatory bowel diseases.

**Table 3** Difference between CD and UC according to risk factors (family history and consanguinity)

CD				OR	95% CI	UC		OR	95% CI	Control		p-Value
		n	%			n	%			n	%	
Family history of IBD (father)												0.032
	Yes	8	42.1%	0.13	0.75–10.13	7	36.8%	3.16	0.83–11.69	4	21.1%	
	No	85	26.9%			67	21.2%			164	51.9%	
Family history of IBD (mother)												
	Yes	6	39.1%	1.74	0.41–7.38	9	36.8%	1.11	0.21–5.77	1	16.1%	0.042
	No	87	27.8%			67	20.2%			167	53.9%	
Family history of IBD (siblings)												<0.001
	Yes	13	59.1%	Cannot be calculated		9	40.9%	Cannot be calculated		0	0.0%	
	No	80	25.6%			65	20.8%			168	53.7%	
Family history of IBD (grandparents)												0.013
	Yes	9	42.9%	3.01	0.81–11.17	8	38.1%	3.78	0.99–14.34	4	19.0%	
	No	84	26.8%			66	21.0%			164	52.2%	
Consanguinity first degree												
	Yes	46	63.0%	0.97	0.57–1.67	20	27.3%	1.05	0.59–1.87	7	0.09%	<0.001
	No	29	12.9%			44	19.6%			151	67.4%	

Abbreviations: CD, Crohn's disease; CI, confidence interval; IBD, inflammatory bowel diseases; OR, odds ratio; UC, ulcerative colitis.

with previous studies due to the consanguinity is a deep-rooted cultural trait in Saudi Arabia. Whole exome sequencing was not performed in our study to explain the greatest of risk in first-degree relatives, especially in siblings' family history more than parent's and grandparents' family history.

A systematic review and meta-analysis conducted by Childers et al showed that family history of UC (9%; 22 studies) was more prevalent than CD (2%; 18 studies).<sup>17</sup> The data of Halme et al<sup>18</sup> and Maratka and Será<sup>19</sup> taken together with the observation in our patients suggest that a greater proportion of CD patients has a family history than UC patients. This would explain that the genetic anticipation is a potential contributor to a unique clinical phenotype in IBD. However, further research is needed to identify patterns of heritability in polygenetic diseases like IBD. It is very important to identify our patients with family history of IBD because a cohort of 9,505 individuals reported that patients with IBD have a three- to fivefold increase in risk of colorectal cancer, and those with colorectal cancer in a first-degree relative have an almost eightfold increase in risk.<sup>20</sup>

Therefore, family history may act as a simple measure to identify individuals with IBD at highest risk for colorectal cancer and indicate the need for enhanced surveillance in this population. The influence of a family history of IBD on the clinical phenotypes reported that children with familial IBD had earlier onset of disease compared with those with sporadic IBD. However, this had no significant impact on the clinical phenotypes, the course, and the outcome of dis-

ease.<sup>13</sup> Previous study reported the aggressive clinical course of CD in familial compared with sporadic cases.<sup>21</sup>

There is a clear distinction between "familial" IBD and "monogenic" IBD. IBD and IBD-like diseases that are caused by monogenic variants with Mendelian inheritance patterns have been described as monogenic IBD in contrast to typical IBD.<sup>22</sup> Monogenic IBD is usually refractory to conventional therapies. Therefore, age of onset, family history, atypical endoscopic findings, severity, and atypical infection history are important factors in monogenic IBD.<sup>22</sup> Familial IBD has been related to a composite of shared environmental exposures and genetic influences as proven in twin studies.<sup>23</sup> Epidemiological studies have consistently shown an increased prevalence of IBD among first-degree relatives of patients with IBD; this familial clustering, in addition to the increased incidence of disease among monozygotic twins, provided the initial evidence of a genetic predisposition to IBD.<sup>23</sup> The impact of family history of IBD on the clinical phenotypes and genetics of IBD was not performed in this article.

This is the first Saudi pediatric study examining the link between childhood IBD and both consanguinity and family history. A key strength of this study is the large sample size and its representativeness of the studied region in three tertiary centers. However, further research is required from other regions of Saudi Arabia to provide a national representation of this topic. Our study has few limitations. It is a retrospective study with the small number of cases in some



categories. In addition, more than half of the children belonged to more than 10 years, which might have contributed to the overinflating of the proportion of children younger than 10 years. It is challenging to control and match some variables in a case-control study, leading to confounding bias. These limitations, however, are unlikely to have a significant impact on the incidence numbers provided in this group, as we have attempted to evaluate several characteristics of CD and UC without losing significant details.

In summary, our data support that consanguinity and family history are additive joint associations with IBD risk and may be useful to continue to educate healthcare providers, parents, and patients about the importance of consanguinity and the medical family history in era of IBD.

## Conclusion

Consanguinity is strongly associated with IBD with more significant association with CD than UC and may possibly explain IBD rise in Saudi Arabia. The greatest risk of family history of IBD is in first-degree relatives, especially in siblings' rather than parents and grandparents. A future longitudinal large prospective study is necessary to confirm these risk factors associations observed in this article.

### Conflict of Interest

None declared.

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