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*TOPIC HIGHLIGHT*

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# Family and twin studies in inflammatory bowel disease

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## Abstract

Studies examining the inheritance of inflammatory bowel disease (IBD) within different family groups have been the basis for recent molecular advances in the genetics of IBD. The derived heritability in Crohn's disease (CD) is higher than in many other complex diseases. The risk of IBD is highest in first-degree relatives of a CD proband, but first-degree relatives of a proband suffering from ulcerative colitis (UC) and more distant relatives are also at increased risk. Disease concordance rates in IBD have been examined in multiplex families and in three large European twin studies.



**Key words:** Crohn's disease; Family studies; Genetics; Twin studies; Ulcerative colitis

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## INTRODUCTION

Attempts to increase understanding of genetics of inflammatory bowel disease (IBD) have greatly increased in frequency and reached a molecular level during the last decade. In fact, the initial interest to commence with molecular genetic studies was based on the data derived from epidemiological studies showing convincingly and consistently that the prevalence of IBD is increased among relatives with Crohn's disease (CD) and ulcerative colitis (UC). Quantitatively, the degree of familial clustering of disease may be expressed as the ratio of the risk of siblings to the reported population prevalence ($\lambda$s ratio). Using this formulation, the genetic risk ratio for IBD is in the range of 15-42 for CD[1–5] and 7-17 for UC[4,5]. These $\lambda$s values, especially for CD, are in the range or even higher than those reported for many other complex disorders, including type 1 diabetes ($\lambda$s 15), type 2 diabetes ($\lambda$s < 10), schizophrenia ($\lambda$s < 10) and celiac disease ($\lambda$s 7-30). Collectively, these data support a strong contribution of genes in the pathogenesis of CD in particular, although they do not provide information on the exact mode of inheritance.

## TWIN STUDIES IN IBD

Although few in number, twin studies have constituted an important tool to identify the relative contribution of inherited and environmental factors in the aetiology of CD and UC. Should a disease be entirely due to genes, then its concordance in identical (monozygotic) twins would approach 100% and that in non-identical (dizygotic) twins 50%. If, on the other hand, the disease is fully dependent on extrinsic and acquired factors, then its concordance would be similar in both types of twins. In large European studies conducted in Sweden[6,7], Denmark[8] and UK[9], the concordance rate for CD in monozygotic twins was estimated at between 20% and 50%, whereas the concordance rate in dizygotic twins brought up in the same environment is less than 10 % (Table 1). More recently closer examination of the phenotypic characteristics of the Swedish cohort provided some evidence that in CD even the disease phenotype may be genetically determined[7]. Thus, in the monozygotic CD concordant pairs 7/9 were concordant for disease location, as determined by Vienna classification, and 6/9 were diagnosed within 2 years of each other. There was no significant concordance for disease behaviour, *i.e.* fistulizing or stricturing type, or extent of the disease.

The evidence from twin studies in ulcerative colitis also implies an important heritable component, although a weaker one than in CD. The concordance rate of UC in monozygotic twins was reportedly about 16% and that in dizygotic twins about 4% (Table 1) , i.e. figures markedly lower that the corresponding estimates in CD[6-9]. Along

**Table 1 Concordance rates for CD and UC according to three large twin studies**

| | Monozygotic twins | | Dizygotic twins | |
|---|---|---|---|---|
| | CD | UC | CD | UC |
| Halfvarsson[7] | 50% ($n$ = 18) | 19% ($n$ = 16) | 4% ($n$ = 26) | 0% ($n$ = 20) |
| Orholm[8] | 50% ($n$ = 10) | 14% ($n$ = 21) | 0% ($n$ = 27) | 7% ($n$ = 44) |
| Thompson[9] | 20% ($n$ = 25) | 16% ($n$ = 38) | 7% ($n$ = 46) | 3% ($n$ = 34) |

the same line, concordance for phenotypic characteristics in twin pairs with ulcerative colitis is less consistent compared with CD.

In comparison to the general population, an IBD co-twin is also at increased risk of developing an IBD phenotype opposite to his/her twin partner[8]. The role of smoking habits to influence the risk and phenotype in IBD has also been confirmed by twin studies[6,8]. Orholm et al. reported that smoking was positively, although non-significantly, associated with CD and negatively and significantly with UC. In that study discordant smoking habit explained at least part of the disease discordance[8].

In summary, identical twins are significantly more likely to be concordant for IBD than non-identical twins. However, the concordance for homozygous twins does not reach a higher extent than 50% underscoring the important role of environmental causes in the pathogenesis of IBD.

## FAMILY STUDIES IN IBD

Familial clustering of IBD has been documented in numerous studies. The rate at which patients with CD report a family history of CD varies from 2% to 14% and of any type of IBD from 5% to 16%, whereas patients with UC possess a family history of UC from 7% to 11% and any type of IBD from 8% to 14% (Table 2)[1,2,5,10-15].

However, it should be emphasized that the methodologies used by different family studies vary, and comparing the data between studies is not straightforward. For instance, published estimates may be biased as studies carried out in teaching hospital populations tend to overrepresent IBD patients with positive family history and more severe disease course compared to population-based studies. In addition, studies do not report results in a similar manner. Thus, some of the studies report risk for all relatives while some report risks to first-degree relatives only; in addition, the degree of risk may not be assigned to all phenotypes (UC, CD and/or IBD) in all studies. Furthermore, studies with longer follow-up time are more likely to include more family members with IBD. Therefore, age-adjusted figures when available give more reliable estimates of the true risk developing IBD. Despite of different methodologies used, in all studies the greatest risk is constantly seen in first-degree relatives, especially siblings, and a positive family history is more common in CD patients than in UC patients.

### *Risk of IBD in first-degree relatives*

Strömgren's methodology has been most frequently used for assessment of age-adjusted relative risk. The calculations are based on the assumption that all patients live to age 70 years. Based on different studies in European and North-American white non-Jewish populations[5,13,15], the approximated age-adjusted life-time risk of developing IBD for first-degree relatives of a CD proband is 5 % and that of an UC proband 1.6%. The corresponding figures for Jewish patients are 8 % and 5.2%, respectively[15]. Family studies have repeatedly shown that the siblings of a proband are at highest risk of developing IBD, while parents have the lowest risk[13,15].

Accurate risk estimates for the offspring of CD and UC probands are difficult to calculate because many of them may not have reached the age at which the first symptoms of the disease should appear. One approach to overcome these difficulties is to calculate the prevalence proportion ratio which is estimated by dividing the observed number of offspring with IBD with the expected number of cases from the general population. In a Danish population-based study, the prevalence proportion ratios of CD and UC among offspring of patients with CD were 12.8 and 4.0, respectively, while the corresponding figures for patients with UC were 2.6 and 5.1, respectively[16]. If both parents have IBD, the risk of children to develop IBD is relatively high. Accordingly, under these circumstances about one third of the offspring have developed IBD before 30 years[17,18]. Estimations for the relative risk (relative to the population prevalence) of a sibling to develop the same disease as the proband have varied greatly. The $\lambda s$ ratio to a sibling to develop same disease has been estimated to be 15-42 for CD and 7-17 for UC[1-5]. Tobacco smoking probably is a strong environmental factor influencing the acquisition of the disease type. Sib pairs discordant for both smoking and IBD subtype almost always show CD in the smoking and UC in the non-smoking mate[19,20].

## INFLUENCE OF INHERITANCE ON THE CLINICAL PHENOTYPE IN CROHN'S DISEASE AND ULCERATIVE COLITIS

The fundamental difficulty in exact comparison of the phenotypes in family studies lies in the fact that there is no agreed standard definition for a phenotype in either CD or UC. In fact, almost all family studies have been performed before Vienna classification of CD was adopted.

### *Crohn's disease*

The age at onset of disease, location of disease, disease behaviour, the extent of extraintestinal manifestations and need for surgery are the most often studied phenotypic characteristics of CD. In these studies, familial aggregation and a high degree disease concordance have been confirmed, and the age at diagnosis and initial disease location were especially strongly related within generations of given families[13,15,21,22]. A high degree of concordance for disease location in parent-child and sibling pairs has also been demonstrated[13,14,22-24]. In contrast, most studies found no effect of a positive family history on severity and course of CD. There are no strong arguments for phenotypic differences between familial and sporadic

**Table 2 Recent studies on the occurrence (in percent) of affected first-degree relatives in a proband with CD and UC**

| | Proband with CD | | Proband with UC | |
|---|---|---|---|---|
| | First-degree relatives with CD | First-degree relatives with any form of IBD | First-degree relatives with UC | First-degree relatives with any form of IBD |
| Freeman (2002)[10] | 8.7% ($n$ = 1000) | - | - | - |
| Halme (2002)[11] | 10.9% ($n$ = 257) | 15.6% ($n$ = 257) | 11.3% ($n$ = 436) | 13.8% ($n$ = 436) |
| Carbonnel (1999)[12] | 7.5% ($n$ = 1316) | 8.4% ($n$ = 1316) | - | - |
| Peeters (1996)[13] | 13.6% ($n$ = 640) | 14.5% ($n$ = 640) | - | - |
| Bayless (1996)[14] | 12.2 % ($n$ = 554) | - | - | - |
| Satsangi (1994)[1] | - | 11.5% ($n$ = 433) | - | - |
| Probert (1993)[2] | 9.4% ($n$ = 424) | 10.4% ($n$ = 424) | 7.1% ($n$ = 469) | 8.6% ($n$ = 469) |
| Yang (1993)[15] | 7.4% ($n$ = 258) | 14.0% ($n$ = 258) | 7.1% ($n$ = 269) | 8.6% ($n$ = 269) |
| Orholm (1991)[5] | 2.2% ($n$ = 133) | 5.2% ($n$ = 133) | 7.5% ($n$ = 504) | 8.1% ($n$ = 504) |

forms of IBD except for the age at onset[12,13,20,22,24]. High concordance rates of extraintestinal manifestations in CD have been shown in two studies[21,23] between affected first degree relatives, although extraintestinal manifestations were not associated more often in a familial disease type than in a sporadic one[25].

### *Ulcerative colitis*

A high concordance rate for the presence of extraintestinal manifestations and for the extent of colon involvement has been reported in UC patients[23]. In a recent report the concordance rate for extension of the colon involvement was observed in 33% of relative pairs, in 47% of pairs for requirement of steroids and in 34% of pairs for a high relapse rate[21]. However, in UC families the concordance rates are less consistent than in CD families.

### *Genetic anticipation in IBD: fact or fallacy?*

The term genetic anticipation is used when the disease severity increases and age at onset of an inherited disease decreases in subsequent generations. In IBD anticipation has been proposed to explain the observation that affected children are diagnosed an average of 12 to 23 years younger than their affected parents[21,23,26-28]. Anticipation was reported to be more marked in father-child pairs than in mother-child pairs[29].

On the other hand, some reports have provided strong evidence that anticipation does not occur in IBD and is merely caused by failure to make statistical corrections[27,30,31]. Thus, supporters of this assumption believe that a more rigorous screening or closer observation of the children of an affected parent simply result in earlier diagnosis in the offspring. Studies on genetic anticipation may also suffer from follow-up bias which implies situations where children, who are unaffected by IBD at the time of a cross-sectional survey, later develop disease.

### *CARD15 gene variants in familially occurring and sporadic forms of IBD*

Three variants of the CARD15 gene are strongly associated with susceptibility to CD[32,33], although significant geographic and racial variations in their frequency have been described. In most Caucasian populations, at least one risk allele of the CARD15 gene is found in 44%-50% of CD patients[34,35]. In these populations the proportion of CD patients with or without documented CARD15 mutations were similar among familial and sporadic cases. On the other hand, a lower frequency (15.5%) of the risk alleles of the CARD15 gene has been described among the Finns, but in this population the1007fs allele frequency was higher among the familial (10.9%) than in sporadic CD cases (3.5%)[36]. Moreover, there is evidence for genetic heterogeneity also in other North European countries. Despite low prevalence of risk alleles of the CARD15 gene mutation the prevalence of CD and familially occurring IBD are similar as in countries of high frequency of CARD 15 risk alleles[37,38].

### *Familial clustering of variations in intestinal permeability*

A genetically impaired intestinal barrier function has long been suspected to be a predisposing factor for CD. An increased intestinal permeability is found in nearly one fourth of the asymptomatic first-degree relatives, although similar figures have also been demonstrated in spouses of IBD patients, making it difficult to judge whether these alterations are due to genetic or environmental factors, or both[39,40]. Buhner et al. have recently shown that in healthy first degree relatives of CD patients a high mucosal permeability is associated with the presence of a CARD15 3020insC mutation, indicating that genetic factors may be involved in the impairment of the intestinal barrier function in families with IBD[41]. Recently, Stoll *et al*[42] described a significant linkage and association of CD with specific haplotypes of the DLG5 gene, coding for a membrane associated guanylate kinase possibly associated with maintenance of epithelial integrity. These studies also suggested an interaction between allelic variants of the CARD15 and DLG5 genes as risk determinants of CD[42]. It will be important to identify additional gene loci potentially interacting with the risk alleles of the CARD15 genes to modify the phenotypic features, including the intestinal permeability, in IBD.

## CONCLUSION

The single strongest risk factor for developing IBD is having an affected relative with IBD. The highest risk

(> 30%) is observed in offspring of two affected parents. The age-adjusted risk of IBD is about 5% for siblings and 10% for offspring. A positive family history is more common in a CD proband than in a UC proband. Relatives of patients with CD have a higher risk of developing IBD than those of patients with UC. The rates for concordance among monozygotic twins are higher for CD than for UC. Collectively, all these family data suggest a stronger genetic influence for CD than UC. Studies showing that smoking shifts the predisposition from UC to CD indicate that not the genes alone but also environmental factors have an important role in disease expression.

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