Does IBD Run in Families?

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While the simple answer to this question is very clearly "yes," we will proceed to fully answer this question by reviewing the available literature.

It is now well accepted that the greatest single risk factor for the development of inflammatory bowel disease (IBD) is having an affected family member. In published studies there are between 5.2%–22.5% of first-degree relatives of an affected IBD proband who also have IBD; higher rates of a positive family history of IBD have been found in hospital-based studies compared with population-based studies. The family members most likely to have IBD, after monozygous twins and children who have both parents affected by IBD, are first-degree relatives of an IBD proband who have a lifetime risk of around 1 in 10–20 of IBD. A monozygotic twin of a Crohn's disease (CD) proband has approximately a 1 in 3 lifetime risk of IBD, with an ulcerative colitis (UC) proband around 1 in 5, and offspring who have both parents with IBD have at least a 1 in 3 lifetime risk of IBD.

Family-based studies clearly demonstrate that relatives are not only at increased risk of developing the same form of IBD as the affected relative, but also are at increased risk of developing the opposing form of IBD, i.e., relatives of probands with CD are at greatest risk of developing UC but are also at a greater risk of developing UC than would be expected by chance compared with the general population.

The risk of IBD in first-degree relatives is dependent on the exact relationship to the IBD proband. The first-degree relatives who are genetically most similar and thus at greatest risk of developing the same disease are siblings. The relative risk of developing a disease in siblings compared with the population prevalence is expressed as λs. The λs value for siblings of a CD patient is 35 for developing CD and 4 for developing UC. As CD and UC are complex polygenic diseases that are not subject to simple patterns of Mendelian inheritance the λs value is less than in monogenic diseases like cystic fibrosis (As value 400) but is higher than many other complex polygenic diseases like hypertension and asthma. The group of first-degree relatives found consistently to be at lowest risk of IBD are parents. The risk of IBD to offspring of probands lies between that of siblings and parents.

The absolute risk of developing IBD in first-degree relatives has been estimated in many different studies but the best studies are those that have used age-adjusted figures based on a standard methodology; a risk assessment based on the assumption that patients will live on average to age 70 years. In studies that have applied this methodology the lifetime risk of developing IBD for first-degree relatives of a CD proband are 4.8%–5.2% for Caucasians (non-Jewish) and 7.8% for relatives of Jewish patients. The lifetime risk of developing IBD for first-degree relatives of a UC proband are 1.6% for Caucasians (non-Jewish) and 5.2% for relatives of Jewish patients. In families where more than 1 first-degree relative is affected by IBD the risk to family members will increase further still.

Although the risk of IBD in families is greatest in first-degree relatives the increased risk of IBD extends to second-degree relatives (aunts, uncles, nieces, nephews, and grandparents) and into third-degree relatives for CD. In second-degree relatives the risk may only be for the same type of IBD as the proband, with little or no increased risk of the opposite IBD phenotype as measured against prevalence rates in the general population, although the risk in second- and third-degree relatives has not been extensively investigated.

So clearly it has been demonstrated that an increased risk of developing IBD runs in families but also the phenotype of IBD tends to run in families too. There is high concordance for disease type, 85%–100% and, additionally, high degrees of concordance for disease location in CD, with rates of between 75%–80% demonstrated for parent-child and sibling pairs, respectively. Concordance rates for disease behavior, need for surgery, and extraintestinal manifestations in patients with CD have been less consistent between different studies. The high concordance rates for type of disease and disease location have also been described within families of patients with UC.

In conclusion, IBD clearly does run in families, with the greatest risk in first-degree relatives but the risk extends into second-degree relatives and beyond. Within families there is concordance both for type and location of IBD. Family members are at increased risk of both CD and UC irrespective of the type of IBD in the proband.
REFERENCES

Current evidence suggests that inflammatory bowel disease (IBD) is a non-Mendelian polygenic disorder with important environmental interactions. The data presented are therefore empiric risks from observational studies and quantification of these risks depend on the relationship of the affected IBD member, ethnicity, and the type of IBD: Crohn’s disease (CD) or ulcerative colitis (UC).

Risk to Offspring When 1 Parent Has IBD
The greatest risk factor for the development of IBD is when another first-degree relative has IBD and in calculating the risk in the 3 groups of first-degree relatives (risk to siblings, risk to offspring, and risk to parents) it is perhaps the most difficult to present accurate data on the risk to offspring group, as these subjects may not have developed symptoms and hence a diagnosis by the time of assessment.

In a Danish population-based study, patients discharged from the hospital with a diagnosis of IBD between 1977 and 1992 were identified. Offspring of these patients were traced and 69 of the 1022 offspring (0.62%) had developed IBD if 1 of the parents had UC and 32 of the 3472 offspring (0.92%) had developed IBD if 1 of the parents had CD. These prevalence figures did not take into account the lifetime risk of developing IBD and are consequently low. Transmission rates were equal between males and females apart from CD patients, who appeared to have more female offspring with UC than male offspring with UC.

Interestingly, Peeters et al also observed that daughters were also at increased risk in a case-control study of patients with IBD. Overall the age-adjusted risk of having a child with IBD if 1 of the parents had IBD was 10.4%, with a relative risk of 4.5. However, if 1 of the parents had CD they had a 12.6% chance of having a daughter with IBD and a 7.9% chance of having a son with IBD. In a study into the effect of the X chromosome in 145 IBD-affected relative pairs from Belgium, an association was observed between chromosomal area Xq21.3 (LOD score 2.5) and CD and this may offer an explanation for the difference in observed risks.

In a survey of patients with IBD in Leicestershire, UK (population 900,000), Probert et al demonstrated that the comparative risk of an offspring developing UC if 1 parent had UC was 14.8 and the comparative risk for developing CD was 3.0. If 1 parent had CD the comparative risk of an offspring developing UC or CD was 3.0 and 29.1, respectively.

Existing epidemiological data show that the Jewish population has an increased risk of developing IBD and the risk to an offspring of developing IBD if 1 parent has IBD has been calculated in Jewish and non-Jewish populations in California. Using the Stromgren method, lifetime risks to offspring of developing IBD were calculated as 3.8% if the parents were Jewish and 1 had CD and 4.1% if the parents were Jewish and 1 had UC. In the non-Jewish population the lifetime risks to an offspring of developing IBD were 4.8% of 1 parent had CD and 1.2% if 1 parent had UC.

As offspring may not have manifested symptoms during participation in a particular study, age-corrected figures are important in assessing this question. A summary of age-corrected figures are presented as percentages in Table 1. The relative risks quoted for an offspring developing IBD if a parent has IBD are wide, with a parent with CD having 2–30 times increased risk of having a child with IBD and a parent with UC having 2–15 times increased risk of having a child with IBD.

Risk to Offspring in the Case of 2 Affected Parents
If both parents have IBD then the offspring have a highly significant chance of developing IBD. When 2500 American patients with IBD were analyzed, 35 children who had been born to 16 couples who both had IBD or subsequently developed IBD were identified. Thirty-three of these children were still alive and 12 (36%) had developed IBD. Furthermore, 1 child had uveitis and 10 children were under the age of 21, an age at which they may not have been diagnosed. CD predominated in the offspring regardless of the type of IBD the parents manifested.

In a further case series of patients from France and Belgium, 54 children were born to 25 couples who had both developed IBD. Nine of these children developed CD and the probability of developing IBD in these children was estimated to be 1 in 3 by the time they reached the age of 28.
TABLE 1. Age-corrected Percentage Risks for IBD if the Parent Has Crohn’s Disease or Ulcerative Colitis

<table>
<thead>
<tr>
<th>IBD Type in Parent</th>
<th>Crohn’s Disease</th>
<th>Ulcerative Colitis</th>
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<tr>
<td></td>
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<tr>
<td>Ethnicity</td>
<td>Jewish</td>
<td>Non-Jewish</td>
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<tr>
<td>Risk to offspring (%)</td>
<td>7.4–15.8</td>
<td>0–10.4</td>
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Percentage figures showing adjusted lifetime risk of developing IBD if the parent has either Crohn’s disease or ulcerative colitis. The data shown are based on Ref. 11.

Conclusion
In summary, children of IBD parents have a greater risk of developing the condition than the general population. A higher risk has been observed in parents with CD compared to parents with UC, and the risk is also higher in certain ethnic groups, particularly in the Jewish population. The risk to a child of developing IBD is substantially higher when both parents have IBD and is greater than 1 in 3.

REFERENCES