IgG subclass distribution in serum and rectal mucosa of monozygotic twins with or without inflammatory bowel disease

L Helgeland, C Tysk, G Järnerot, K Kett, E Lindberg, D Danielsson, S N Andersen, P Brandtzæg

Abstract
Serum samples from 26 monozygotic twin pairs concordant or discordant with regard to inflammatory bowel disease, and rectal biopsies from 42 twins of the same subject group, were examined for IgG subclasses. They were all compared with normal controls. Almost all affected twins were in clinical remission. Paired immunofluorescence staining of the rectal mucosa showed that those with ulcerative colitis had a significantly higher (p<0.01) proportion of IgG1 producing mucosal immunocytes than normal controls (78.1% vs 55.9%). Conversely, the IgG2 cell fraction was significantly reduced (15.9% vs 34.6%). Healthy twins from ulcerative colitis pairs tended to show a raised proportion of IgG1 cells and the IgG2 cell fraction was significantly reduced (p<0.05). In discordant ulcerative colitis twin pairs, no difference appeared in the cellular IgG subclass pattern between healthy and affected twins. Furthermore, the proportion of IgG1 in these healthy and diseased twins showed good correlation (r=0.867). The results in rectal mucosa of twins with Crohn's disease were widely scattered and affected twins did not differ significantly from normal controls. Healthy twins, however, showed a markedly raised IgG1 cell proportion, but no correlation was seen between the IgG subclass fractions in discordant Crohn's disease twin pairs. The serum concentrations of IgG1 and IgG2 did not differ from normal controls in twins of either category. These results suggested that in ulcerative colitis, the aberrant mucosal production of IgG1 and IgG2 does not depend on active disease, but is apparently at least partially explained by a genetic impact. Conversely, the mucosal IgG subclass pattern in Crohn's disease appears to be determined mainly by exogenous variables. (Gut 1992; 33: 1358–1364)

Ulcerative colitis and Crohn's disease are chronic, remitting and relapsing mucosal disorders, collectively known as inflammatory bowel disease. The aetiology remains unknown, but much circumstantial evidence suggests that immunological mechanisms are involved in the pathogenesis. The established mucosal lesion in ulcerative colitis and Crohn's disease is dominated by terminally differentiated B cells appearing as plasma cells and blasts. In this immunocyte population there is a disproportionate expansion of the number of immuno-globulin G (IgG) producing immunocytes in affected areas. Immunohistochemical studies have shown that the IgG cell fraction is increased up to 30 times, depending on the severity of the lesion. Furthermore, cultured mononuclear cells isolated from inflammatory bowel disease mucosa spontaneously secrete large amounts of IgG. These findings have led to the notion that IgG mediated immunopathological processes are of importance.

The subclass composition of an IgG response is of biological significance because of the striking isotype related differences with regard to binding and activation of complement, promotion of phagocytosis, and mediation of antibody dependent cellular cytotoxicity. Our laboratory has recently shown significant disparity between ulcerative colitis and Crohn's disease in terms of IgG subclass production in the mucosal lesion; the proportion of IgG1 immunocytes was found to be higher in ulcerative colitis than in Crohn's colitis, while the reverse was true for the IgG2 cell fraction. These immunohistochemical observations were in good agreement with results obtained for IgG subclass synthesis revealed by spontaneous release from dispersed intestinal mononuclear cells. Similar disparity between the two disorders has also been reported for serum IgG subclass concentrations.

The dissimilar IgG subclass distribution in ulcerative colitis and Crohn's disease might reflect different antigenic or mitogenic exposures in the gut. Another possibility is that the genetic regulation of the isotype response is different in the two populations of inflammatory bowel disease patients. Finally, it might be the result of an interplay between genetic and environmental factors. The influence of heredity is best studied in genetically identical twins. We have therefore examined the IgG subclass pattern in rectal immunocytes and in serum of monozygotic twins with or without inflammatory bowel disease. The study included pairs of twins both concordant and discordant with regard to ulcerative colitis or Crohn's disease. Furthermore, this material offered an opportunity to study the IgG subclass pattern in inactive stages of inflammatory bowel disease because the affected twins were in clinical remission. A histological normal control material was included for comparison.

Methods
TWINS

The study was approved by the Ethical Commit-
IgG subclass distribution in serum and rectal mucosa of monozygotic twins with or without inflammatory bowel disease

IgG serum performed. Diseased twins, healthy twins, inactive and suggestive of hepatitis, concentrations.

The distribution of twins in concordant and discordant twin pairs, and the number of twins with an ileostomy, are shown in Table 1. Among the 14 twins with ulcerative colitis, the mean age at diagnosis was 28.6 years (range 17-45); the actual study age was 49-8 years (range 24-74). In the 19 twins with Crohn's disease, the mean age at diagnosis was 28.5 years (range 20-45) and the actual study age was 42-9 years (range 34-65). All patients with ulcerative colitis were in clinical remission and had normal levels of haemoglobin, C-reactive protein, and serum amylase. Six patients were treated with sulphasalazine and one healthy twin with prednisolone for chronic hepatitis, 5 mg every second day. Two patients with Crohn's disease had mild diarrhoea and slightly increased C-reactive protein and orosomucoid concentrations. They were treated with sulphasalazine. Two patients had severe perianal disease preventing sigmoidoscopy. The others were inactive and no other therapy was given except vitamins or loperamide. A thorough interview revealed no symptoms suggestive of inflammatory bowel disease in the healthy twins. The healthy twins have remained healthy for 21-4 years (range 8-40) after the diagnosis of the matching twins who had ulcerative colitis and for 14-9 years (range 7-31) in the twins discordant with those who had Crohn's disease.

Venous blood was obtained from all twins. After centrifugation, aliquots of serum were frozen at -70°C until analysis. Furthermore, rectal biopsy specimens were obtained from each twin in whom sigmoidoscopy could be carried out. In the ulcerative colitis group, 10 of the 14 diseased twins had a rectum available for biopsy. Rectal biopsy specimens were collected from 10 healthy ulcerative colitis twins. In 14 of the 19 diseased Crohn's disease twins, sigmoidoscopy could be performed. The biopsy from one of the nine healthy Crohn's disease twins turned out to be inadequate for immunohistochecual evaluation. Because some twin pairs were discordant with regard to inflammatory bowel disease, and rectal biopsy specimens were not available in some diseased twins, biopsy specimens from the six healthy twins were unpaired. They were, however, included in the analysis because, being monozygotic, these twins are genetically identical with those who ultimately developed inflammatory bowel disease.

NORMAL CONTROLS
Normal colonic mucosal specimens were obtained from six men and four women with a mean age of 58.2 years (range 44-70). This material was collected from macroscopically uninvolved areas of ascending or transverse colon (five), or descending or sigmoid colon (five); the specimens had been surgically resected as a result of colonic carcinoma (eight), polyposis (one), or diverticulitis (one). Histological evaluation showed no signs of inflammation or dysplasia.

In the study of serum immunoglobulins and serum IgG subclasses, each twin pair had two healthy controls matched for sex and age.

IMMUNOHISTOCHEMISTRY
Mucosal tissue specimens were extracted in cold phosphate buffered isotonic saline (pH 7.4) for 48 hours before ethanol fixation and paraffin embedding. Serial sections were cut at 6 μm from each tissue block. One section was stained with haematoxylin and eosin for histological evaluation.

At least four serial tissue sections, depending on the density of IgG producing cells, were subjected to paired immunofluorescence staining for one of the four IgG subclasses and for total IgG. Each dewaxed section was first incubated with murine monoclonal antibody (ascites 1:800) to either IgG1 (HP 6070, clone 2C7), IgG2 (HP 6009, clone GOM2), IgG3 (HP 6048, clone CB1-AH7) or IgG4 (HP 6011, clone R4J4) and subsequently with a mix of fluorescein isothiocyanate labelled rabbit antimouse IgG and rhodamine B sulphonyl chloride labelled antimouse IgG. The sources of monoclonal antibodies, the characteristics of the fluorochrome conjugates, and other details of this two colour staining procedure have been reported previously.

**Table 1.** Numerical distribution of twins with ulcerative colitis and Crohn's disease in healthy and diseased twins. In concordant pairs, both individuals are categorised as 'diseased'; in discordant pairs, one is grouped under 'diseased' and the other under 'healthy'.

<table>
<thead>
<tr>
<th>Ulcerative colitis</th>
<th>Crohn's disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>Healthy</td>
</tr>
<tr>
<td>Disease</td>
<td>Disease</td>
</tr>
<tr>
<td>Disease</td>
<td>Healthy</td>
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<td>Disease</td>
<td>Healthy</td>
</tr>
<tr>
<td>Disease</td>
<td>Healthy</td>
</tr>
</tbody>
</table>

*Proctocolectomy; †Perianal Crohn's disease and no sigmoidoscopy performed.*

...continued...
MATCHED TWINS AMONG METHOD IN USING AN CYTOPLASMIC DISTINCT ILLUMINATOR WITH INTERFERENCE LAMINA PROPRIA SHOWED OCULAR. THE ENUMERATIONS MICROSCOPY AND CELL COUNTING THE INTRA OBSERVER ERROR SYSTEMATIC (RED) MINE OBSERVATION OF MICROSCOPY EQUIPPED WITH MICROSCOPES EQUIPPED WITH FILTERS MAMMALIAN FILTERS WERE CONNECTED TO THE EXPERIMENTAL BASEMENT EPITHELIUM AND MUSCULARIS MUCOSAE, FIBROSIS AND DENSITY OF INFLAMMATORY CELL INFILTRATE.

DETERMINATION OF IMMUNOGLOBULIN CONCENTRATIONS IN SERUM
Total serum IgG, IgA, and IgM were determined by radial immunodiffusion according to Mancini et al14 Immunoplates with polyclonal antibodies were purchased from Behringwerke A/S, Germany, and the recommendations by the manufacturer were followed. The determination of IgG subclasses 1, 2, 3, and 4 were made by radial immunodiffusion with the use of monoclonal antibodies purchased from Seward Laboratories, UK. The manufacturer’s recommendations were followed. All determinations were done twice with variations between the tests of less than ±10%.

POSITIONAL ANALYSES
The twins were divided into four test groups: twins with ulcerative colitis, healthy twins from discordant twin pairs of whom the affected ones had ulcerative colitis, twins with Crohn’s disease, and healthy twins from discordant twin pairs of whom the affected ones had Crohn’s disease. Differences in median cellular proportions of the four IgG subclasses among these groups and in relation to the controls were determined by Wilcoxon’s two tailed test for unpaired samples.
Similar comparisons were performed between the inflammatory bowel disease material previously analysed by immunohistochemistry in our laboratory and the present control material. In six discordant twin pairs with ulcerative colitis, and six discordant twin pairs with Crohn’s disease, Wilcoxon’s two tailed test for paired samples was used. Relations between healthy and affected twins with regard to IgG1 and IgG2 cell proportions in these pairs were estimated by the Kendall rank correlation test.

Serum concentrations of immunoglobulins and IgG subclasses were presented as mean (SD). Differences between means were tested with Student’s t test and p<0.05 was considered statistically significant.

Results

SUBCLASS DISTRIBUTION OF IgG PRODUCING CELLS IN INFLAMMATORY BOWEL DISEASE TWINS AND NORMAL COLONIC MUCOSA

In general, there were large variations in cellular subclass distribution among individuals, in the inflammatory bowel disease twins and normal controls. The results for ulcerative colitis twins are compared with controls in Figure 1. The median proportion of IgG1 immunocytes in twins with ulcerative colitis (78.1%) was significantly higher (p<0.01) than in controls (55.9%). Conversely, the proportion of IgG2 cells was lower (p<0.01) in twins with ulcerative colitis (15.9%) than in controls (34.6%). In discordant twin pairs of whom the diseased twin had ulcerative colitis, the healthy ones tended to have a raised proportion of IgG1 cells (64.6%), and the IgG2 cell fraction was significantly (p=0.05) reduced (19.1%) compared with controls. In contrast, affected Crohn’s disease twins showed a wide scatter of results and did not differ significantly from controls in IgG1 and IgG2 proportions (Fig 2). Healthy twins from pairs with Crohn’s disease nevertheless showed a marginally raised IgG1 percentage (67.4%; p=0.05). A trend towards reduced proportions of IgG3 in affected ulcerative colitis twins, and IgG4 in affected Crohn’s disease twins was also noted, but this was not statistically significant.

Median proportions of IgG1 and IgG2 cells did not differ between healthy and diseased twins with either ulcerative colitis or Crohn’s disease. The influence of the presence or absence of disease, however, might have been masked by the large individual variations in subclass proportions. The monozygotic twin material consisted of both concordant and discordant twin pairs, and some unpaired healthy twins. Discordant twin pairs with either ulcerative colitis or Crohn’s disease, in whom data were available for both twins, were therefore analysed further for both inflammatory bowel disease categories; no significant differences in subclass proportions appeared between healthy and diseased twins (Tables II and III). Furthermore, the proportions of IgG1 cells in healthy and diseased ulcerative colitis twins were well correlated (Fig 3a). Conversely, no such correlation was found in the discordant Crohn’s disease twin pairs (Fig 3b). The other IgG subclasses were not correlated at the cellular level in either ulcerative colitis or Crohn’s disease twins.

**TABLE II** IgG subclass distribution (%) in rectal immunocytes of six discordant ulcerative colitis twins pairs (median and range)

<table>
<thead>
<tr>
<th>Subclass</th>
<th>Healthy UC twins</th>
<th>Affected UC twins</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG1</td>
<td>73-1 (47-8-84-1)</td>
<td>74-8 (64-4-83-3)</td>
</tr>
<tr>
<td>IgG2</td>
<td>15-7 (4-1-45-4)</td>
<td>16-8 (5-8-36-9)</td>
</tr>
<tr>
<td>IgG3</td>
<td>8-6 (1-3-13-1)</td>
<td>2-9 (2-7-13-3)</td>
</tr>
<tr>
<td>IgG4</td>
<td>6-1 (2-9-12-8)</td>
<td>2-5 (1-5-7-6)</td>
</tr>
</tbody>
</table>

UC=ulcerative colitis.
TABLE III  IgG subclass distribution (%) in rectal immunocytes of six discordant Crohn's disease twin pairs (median and range)

<table>
<thead>
<tr>
<th>Subclass</th>
<th>Healthy Crohn's disease twins</th>
<th>Affected Crohn's disease twins</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG1</td>
<td>69-4 (34-8-80-7)</td>
<td>75-2 (68-6-86-1)</td>
</tr>
<tr>
<td>IgG2</td>
<td>19-8 (14-4-54-2)</td>
<td>9-7 (5-5-19-6)</td>
</tr>
<tr>
<td>IgG3</td>
<td>6-3 (1-6-8-7)</td>
<td>9-5 (1-3-15-8)</td>
</tr>
<tr>
<td>IgG4</td>
<td>3-9 (0-7-15-4)</td>
<td>3-3 (2-7-7-3)</td>
</tr>
</tbody>
</table>

COMPARISON WITH CELLULAR IgG SUBCLASS DISTRIBUTION IN PREVIOUS INFLAMMATORY BOWEL DISEASE STUDY

In our previous immunohistochemical study, the mucosal IgG subclass proportions of 10 ulcerative colitis patients were compared with those of eight Crohn's colitis patients, but no normal counts were available for comparison at that time. A statistical reevaluation was therefore performed in relation to the present control material. The proportion of IgG1 cells was significantly raised and that of IgG2 cells reduced (p<0.01) for the ulcerative colitis patients, but no differences were found in this respect between Crohn's disease colitis and controls.

HISTOPATHOLOGICAL EVALUATION

Microscopic examination in haematoxylin and eosin stained sections revealed only minor alterations except in one discordant and clinical slightly affected Crohn's disease twin pair in whom overt signs of inflammation were present in both twins. Their mucosal IgG subclass pattern, however, did not differ consistently from the other Crohn's disease twins.

TABLE IV  Serum concentrations (mean (SD)) of IgG, IgA, IgM and the subclasses IgG1 through IgG4 in twins with ulcerative colitis (UC), their healthy twin siblings (H-UC), twins with Crohn's disease (CD), their healthy twin siblings (H-CD) and healthy controls

<table>
<thead>
<tr>
<th>Twin group</th>
<th>UC (n=10)</th>
<th>H-UC (n=19)</th>
<th>CD (n=9)</th>
<th>H-CD (n=9)</th>
<th>Controls (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>14-41 (2-36)</td>
<td>13-78 (2-43)</td>
<td>13-59 (2-42)</td>
<td>14-87 (1-64)</td>
<td>14-26 (3-31)</td>
</tr>
<tr>
<td>IgA</td>
<td>3-26 (0-76)</td>
<td>3-11 (1-11)</td>
<td>3-87 (1-96)</td>
<td>2-84 (0-67)</td>
<td>3-14 (1-28)</td>
</tr>
<tr>
<td>IgM</td>
<td>2-04 (1-25)</td>
<td>2-07 (0-91)</td>
<td>1-96 (1-11)</td>
<td>1-93 (0-66)</td>
<td>2-07 (0-99)</td>
</tr>
<tr>
<td>IgG1</td>
<td>6-61 (1-89)</td>
<td>6-29 (2-02)</td>
<td>6-35 (1-75)</td>
<td>6-30 (1-32)</td>
<td>6-57 (2-42)</td>
</tr>
<tr>
<td>IgG2</td>
<td>5-38 (1-51)</td>
<td>5-46 (1-01)</td>
<td>4-41 (1-70)</td>
<td>5-08 (1-11)</td>
<td>5-18 (2-50)</td>
</tr>
<tr>
<td>IgG3</td>
<td>0-34 (0-30)*</td>
<td>0-45 (0-25)</td>
<td>0-72 (0-38)</td>
<td>0-73 (0-40)</td>
<td>0-62 (0-43)</td>
</tr>
<tr>
<td>IgG4</td>
<td>0-41 (0-45)</td>
<td>0-44 (0-41)</td>
<td>0-30 (0-24)*</td>
<td>0-39 (0-32)</td>
<td>0-48 (0-30)</td>
</tr>
</tbody>
</table>

*p<0.05 vs controls.

SERUM CONCENTRATIONS OF IMMUNOGLOBULINS AND IgG SUBCLASSES

The serum concentrations of IgG3 in twins with ulcerative colitis, and of IgG4 in twins with Crohn's disease, were significantly lower than in healthy controls (p=0.02). Furthermore, IgG3 in ulcerative colitis twins was significantly lower than in diseased or healthy Crohn's disease twins. There was a tendency towards lower concentration of IgG3 in healthy ulcerative colitis twins compared with both controls and Crohn's disease or healthy Crohn's disease twins. Other IgG subclasses did not differ from controls, and the serum concentrations of IgG, IgA, and IgM were similar in the four twin groups and the controls (Table IV).

Discussion

The proportion of IgG1 immunocytes in rectal mucosa was raised, and that of IgG2 decreased, in affected ulcerative colitis twins compared with normal colonic specimens. This result agrees with that previously obtained for ulcerative colitis in our laboratory, and the median disease related subclass ratios were in fact quite similar in the two studies. These findings are further in keeping with cultivation studies of mononuclear cells from inflamed ulcerative colitis mucosa which showed preferential spontaneous secretion IgG1 compared with control cells.

Theoretically, the IgG subclass distribution could be different in superficial as opposed to basal lamina propria. Thus, the variable orientation and size of individual tissue samples might have affected our results. A large number of cells (mean >1000 cells/specimen) was therefore evaluated to obtain representative results from all parts of mucosa, usually including five sections for each IgG subclass. The fact that the subclass distribution in the diseased twins was almost identical to previous results in inflammatory bowel disease patients, attests to the reliability of our counting method.

The affected ulcerative colitis twins were in clinical remission at the time of biopsy, and histological examination showed no signs of mucosal inflammation. The actual number of IgG producing cells per mucosal length unit could not be quantified because of problems with
IgG subclass distribution in serum and rectal mucosa of monozygotic twins with or without inflammatory bowel disease

the sample orientation. By performing blind semiquantitative IgG cell density scoring, however, we did not notice any difference between affected and healthy twins (data not shown). In the light of previous reports on an association between the number of mucosal IgG producing cells and inflammatory activity, our study suggests that the cellular IgG subclass distribution in ulcerative colitis does not depend on the magnitude of the local IgG response. The raised IgG1 proportion appears to be disease specific instead and not a reflection of unspecific inflammatory changes. The tendency of the healthy ulcerative colitis twins to show a raised IgG1 proportion, along with a significantly reduced IgG2 proportion, supports this notion.

The total IgG production in the mucosa was probably not increased in the diseased or healthy ulcerative colitis twins; this could explain the fact that their serum concentrations of IgG1 and IgG2 did not differ from controls, which is in contrast with previous observations in active disease. There was a tendency towards a lower proportion of IgG3 cells in ulcerative colitis mucosa, along with a significantly decreased serum concentration of IgG3 in ulcerative colitis twins compared with controls. This has not been found in previous studies. Further investigations are needed to determine if also this aberration is specific for ulcerative colitis.

It has been suggested that Crohn's disease gives rise to a relatively enhanced production of IgG2 compared with IgG1, but this did not hold true when we compared immunohistochemical data from our present and previous study with controls. On the contrary, there was a tendency towards a reduced proportion of IgG2 in healthy and affected Crohn's disease twins as well as in the previously analysed Crohn's disease colitis patients with moderate or severe mucosal inflammation. It rather appeared to be a slight but inconsistent preference for mucosal IgG1 production also in Crohn's disease.

There is no doubt that genetic factors are involved in inflammatory bowel disease, although twins are rarely identical in two diseases. The genetic impact on the mucosal IgG subclass response could also be different in two diseases. In ulcerative colitis, we found that the cellular proportions of IgG1 and IgG2 in healthy twins were somewhere between controls and affected twins; but when comparing healthy and affected twins, no statistically significant differences appeared. In view of the large individual variations, and also the fact that some twins included were unpaired, the influence of disease might have been more or less masked. We therefore separately analysed six discordant twin pairs, and found no significant differences between healthy and affected twins. Therefore, the factor(s) responsible for the enhanced IgG1 response in ulcerative colitis appeared to be present also in healthy twins. This notion was further supported by the strong correlation revealed for cellular IgG1 proportions in healthy and affected ulcerative colitis twins.

A possible interpretation of these findings is that genetic mechanisms are involved in the regulation of the IgG subclass response. The switch region associated with the CH1Y gene may be more efficient in the ulcerative colitis population. Certain IgG heavy chain markers are associated with the serum concentrations of IgG subclasses. For example, individuals without the G2 marker have lower serum concentration of IgG2 than carriers of the G2m(a). Another mechanism may be that certain VH genes, directed against antigens which are important to the IgG response in ulcerative colitis, preferentially associate with particular CH genes in the ulcerative colitis population. Several studies have disclosed relations between IgG markers and IgG subclass serum concentrations against particular antigens. Interestingly, a recent German study showed an association between ulcerative colitis and Gm 1,2,10. Similar genetic mechanisms may be involved in autoimmune diseases in general. Several studies have disclosed increased serum levels of IgG1 in a number of autoimmune diseases.

The similarity in IgG subclass proportions between healthy and affected ulcerative colitis twins might also reflect stimulation by a particular antigen(s). Numerous studies have shown IgG antibodies in serum of inflammatory bowel disease patients directed towards cow's milk proteins, bacteria, cytoskeleton and different epithelial cell associated antigens. The latter antibodies have also been detected in serum of non-affected family members of inflammatory bowel disease patients. A 40-kd colon specific epithelial membrane glycoprotein bound to IgG have been isolated from ulcerative colitis lesions. Such tissue bound IgG might predominantly be IgG1 because this subclass has recently been shown together with terminal complement complex on the luminal face of the epithelium in ulcerative colitis.

In one study in the United States, certain IgG1 and IgG3 heavy chain markers were found to be associated with Crohn's disease. Others have not been able to confirm this association. We found no differences in the median cellular proportions of IgG subclasses between healthy and affected Crohn's disease twins and in the separately analysed discordant twin pairs. Also in contrast with the ulcerative colitis twins, there was no IgG1 cell correlation between healthy and affected paired twins, and the range in IgG subclass proportions was much larger. Even concordant Crohn's disease twins affected by the disease usually showed very dissimilar subclass ratios. This suggested that the mucosal IgG subclass response in Crohn's disease is mainly determined by exogeneous variables. The data might reflect that many different antigens affect the mucosal immune response pattern in both affected and non-affected Crohn's disease twins. Conversely, similar studies have suggested a substantial genetic impact on the preferential local IgG1 response in ulcerative colitis.


35 Lennard-Jones JE, Standiford DW, Bowden TJ, Kelly JK, Sutherland LR. Genetic markers and inflammatory bowel disease: Immunoglobulin allotypes (Gm, Km) and protease inhibitor. *Am J Gastroenterol* 1989; 84: 753-5.
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