Heterozygosity for *IL23R* p.Arg381Gln confers a protective effect not only against Crohn’s disease but also ulcerative colitis


**SUMMARY**

**Background**
A recent study reported that a non-synonymous single nucleotide polymorphism (rs11209026, p.Arg381Gln) located in the *IL23R* gene is a protective marker for inflammatory bowel disease.

**Aim**
To analyse the frequency of p.Arg381Gln in three independent European inflammatory bowel disease cohorts and to evaluate how this variant influences disease behaviour.

**Methods**
We assessed a European cohort of 919 inflammatory bowel disease patients and compared the *IL23R* p.Arg381Gln genotype frequency with 845 healthy controls. Inflammatory bowel disease patients originated from Germany [Crohn’s disease (CD): *n* = 318; ulcerative colitis (UC): *n* = 178], Hungary (CD: *n* = 148; UC: *n* = 118) and the Netherlands (CD: *n* = 157). Ethnically matched controls were included. We performed subtyping analysis in respect to CARD15 alterations and clinical characteristics.

**Results**
The frequency of the glutamine allele of p.Arg381Gln was significantly lower in inflammatory bowel disease patients compared with controls in a pooled analysis of all three cohorts (*P* < 0.000001) as well as in the individual cohorts (Germany: *P* = 0.001, Hungary: *P* = 0.02 and the Netherlands: *P* = 0.0002). The p.Arg381Gln genotype distribution was similar between CD and UC. We did not observe either statistical interactions between p.Arg381Gln and CARD15 variants or any significant associations between p.Arg381Gln genotype and subphenotypes.

**Conclusions**
The p.Arg381Gln *IL23R* variant confers a protective effect against both CD and UC, but does not determine disease phenotype.
INTRODUCTION

Outstanding progress has been made in the recent years to elucidate the complex genetic background for the inflammatory bowel diseases (IBD) Crohn’s disease (CD) and ulcerative colitis (UC). The association of CARD15 gene variations to CD1–3 has supported the current working hypothesis that CD derives from an aberrant immune response towards intestinal bacteria in a genetically susceptible host.

Although CARD15 variants clearly increase the risk of CD among Caucasians (OR: 18 for homozygotes), it accounts for only 10–15% of cases, which indicates that mutated CARD15 is not sufficient for the development of the disease and that other factors must also play a role. In this respect, a very recent study performed a hypothesis-free genome-wide association study in patients with ileal CD and controls.4 By single-marker allelic tests, three single nucleotide polymorphisms (SNPs) with significant association with ileal CD were identified. Two SNPs were located within the known CD susceptibility gene, CARD15. The third SNP, rs11209026, was located in the coding sequence of the interleukin 23 receptor (IL23R) gene on chromosome 1p31 and replaces arginine to glutamine in codon 381 [p.Arg381Gln (c.1142G>A)]. The investigated CD populations showed a significantly lower frequency of the heterozygous p.Arg381Gln variant compared with the control populations, suggesting that it protects from the development of CD.4

The IL23R gene encodes a subunit of the receptor for IL23 and associates with IL12RB1 to form the IL23 receptor.5 Interleukin 23 is a heterodimeric protein and a member of the IL12 family. IL23 promotes along with TGF-β1 and IL6 the expansion of the development of proinflammatory IL17-secreting cells.6 Conflicting reports have been published whether Stat signalling directs the development of Th1-IL17-secreting Th cells.7–9 Interleukin-17-secreting T cells have shown to be crucially involved in other autoimmune disease such as rheumatoid arthritis10 and immunity to infection.11 Based on these findings, the IL23/Th17 could play a pivotal role in the pathogenesis of IBD. This hypothesis is supported from a recent work, where IL23 acted a driver of both innate and T cell-mediated inflammation in two different mice colitis models.12

Numerous genetic variants initially believed to be associated with either CD or UC have failed replication in other cohorts.13–14 Thus, it is of fundamental importance to elucidate these variants in other IBD cohorts. In addition, our progress in understanding the genetic background in IBD should go along with the attempt to correlate genotyping results with disease behaviour. In this context, we previously showed that genotyping for CARD15 mutation might be used to identify CD patients with a high risk of post-operative relapse.15

Furthermore, an increased intestinal permeability dysfunction is suggested to be crucially involved in the pathogenesis of CD, which has been shown to precede the onset of CD16 and also to predict relapse.17 This phenomenon is probably determined at the genetic level. A previous work has identified a clear association of an increase in gastrointestinal permeability to the c.3020insC variant within CARD15.18 However, the presence of this alteration was not sufficient to explain the complete genetic background of the disturbed epithelial barrier and as a consequence, other genetic variants are likely to be involved. We thus tested for statistical interactions between p.Arg381Gln and results from measurement of gastroduodenal and intestinal permeability in German CD patients.

The aim of this study was threefold. First, we analysed the frequency of the p.Arg381Gln allele in three cohorts of CD and UC patients from Germany, Hungary and the Netherlands to confirm or refute a previous association study. Further, we were interested in the effect of the p.Arg381Gln on the clinical course of IBD. Finally, we tested whether p.Arg381Gln is associated with a disturbed gastrointestinal permeability in CD patients.

MATERIALS AND METHODS

Patients

Patients with the diagnosis of CD or UC were included in the study based upon clinical, endoscopic, radiological and histological findings according to standardized criteria. All studies were approved by the responsible ethic committees of all three institutions and informed consent was obtained from each participant.

Inflammatory bowel disease patients were recruited from the following tertiary referral centres. In total, 496 Caucasian IBD patients (318 with CD and 178 with UC) were recruited from the Charité Berlin (Campus Mitte and Campus Virchow). In addition, 148 patients with CD and 118 patients with UC from the 1st
Department of Medicine, Faculty of Medicine, University of Szeged, Hungary, were included. Among the 148 CD patients, 138 were Caucasians and 10 patients were from the Roma minority (Gypsy).

Finally, we recruited 157 CD patients from the Department of Gastroenterology and Hepatology at the Radboud University Nijmegen Medical Centre.

Unrelated and healthy subjects from Germany (n = 428), Hungary (n = 200) and the Netherlands (n = 217) served as controls.

Clinical characteristics of IBD patients
Clinical data of IBD patients were obtained through retrospective collection from the patients’ clinical charts prior to genotyping. All collected data described below were used for the genotype–phenotype analysis. IBD patients were classified according to the Montreal classification of IBD.19

The following data of CD patients were obtained from Germany and Hungary: age, age at diagnosis, gender, familial or spontaneous disease (familial disease was considered when one first- or second-degree relative was diagnosed with IBD), smoking habits (current smoking, or history of smoking, or never smoked), disease localization, disease pattern, extraintestinal manifestations (type 1 peripheral arthralgia, affections of eyes or skin and primary sclerosing cholangitis), surgical interventions with respect to indication (stenotic or fistulizing disease) and type (e.g. ileocecal resection, small or large bowel resection, re-operation). Among the CD patients from Nijmegen, the Netherlands, the following data had been recorded: age, age at diagnosis, gender, familial or spontaneous disease (familial disease was considered when one first- or second-degree relative was diagnosed with IBD), disease localization and behaviour, perianal disease and surgery for CD.

The following data of UC patients were obtained: age at diagnosis, gender, familial or spontaneous disease, smoking habits, disease localization (proctitis, left-side colitis and pancolitis), extraintestinal manifestations, type and date of surgery, and occurrence of colorectal cancer.

Genotyping of the R381Q IL23R variant
Genomic DNA was extracted from blood leucocytes. Oligonucleotides were synthesized based on GenBank AL109843.25. Primer sequences were: 5’-GAGCAGATGAAAGAGAATAGTAA-3’ and 5’-TGGGCTGCA-3’. We performed PCR using 0.5 U AmpliTaq Gold (Applied Biosystems, Foster City, CA, USA) and a primer annealing temperature of 56 °C.

Melting curve analysis was carried out using LightCycler 480 instrument (Roche Diagnostics, Basel, Switzerland) with 5’-ACAGATCATCTCAACTGGGT-FL and 5’-LC 640-GTTTTGCAAGAATTTCTGTATT-ph as FRET probes. Probes were designed and synthesized by TIB MOLBIOL (Berlin, Germany). Control subjects were tested for Hardy-Weinberg equilibrium.

All genetic alterations are numbered at the cDNA level, indicated by a ‘c.’ before the number. Position +1 corresponds to the A of the ATG translation initiation codon located at nucleotide 86 in the NM_144701.2 IL23R mRNA reference sequence.

Genotyping for CARD15 variants
Genotyping for the three common CARD15 variants (p.Arg702Trp, p.Gly908Arg and c.3020insC) was performed in patients with IBD from Germany and Hungary as described previously.20 Genotyping for CARD15 variants in CD patients from Nijmegen has been described elsewhere.21 The analysis stratifies for these three common CARD15 variants.

Measurement of gastroduodenal and intestinal permeability
Gastroduodenal and intestinal permeability has been measured using a triple-sugar-test in CD patients (n = 107) from the German cohort.18 The test is based on the principle of measurement of the urinary excretion of orally administered non-metabolized sugar molecules. Sucrose served as the marker for gastroduodenal permeability and the lactulose/mannitol ratio (permeability index, PI for intestinal permeability). We used a total of 96 healthy volunteers (female 56, male 40; age: 35 ± 12 years) as controls. Range of normal permeability was calculated by mean ± 2 s.d. of controls. At time of testing, all German CD patients were in remission [as defined by CD activity index (CDAI) < 150].

Statistical analysis
First, comparison of the allele frequencies of p.Arg381Gln between patients (IBD, CD and UC) and controls was performed in 2 × 2 contingency tables. For pooled analysis of all three cohorts,
Cochran-Mantel-Haenszel test (two-sided) as implemented in R was applied. For the individual cohorts, allele frequencies were compared by Fisher's exact test (two-sided). Odds ratio and confidence intervals were estimated using allele frequencies in 2 × 2 contingency tables. To detect statistical interactions between CARD15 variants and p.Arg381Gln, we defined a CARD15 risk genotype (+/–) as carrying at least one risk allele within one of the three common CARD15 variants (p.Arg702Trp, p.Gly908Arg and c.3020insC). The p.Arg381Gln genotype was classified according to the presence/absence of the glutamine allele. For genotype–phenotype analysis, we used Fisher's exact test to detect an association of the p.Arg381Gln genotype (classified according to the presence/absence of the glutamine allele) to different clinical characteristics (classified according to the presence/absence of, e.g. fistulizing disease behaviour; see Clinical characteristics of IBD patients). For analysis of age, age at diagnosis and absolute values from tests for gastroduodenal and intestinal permeability, Wilcoxon–Mann–Whitney U-test was applied. P-values <0.05 were considered to be significant. The data were analysed using the GAUSS MATHEMATICAL AND STATISTICAL SYSTEM, Version 8.0.0 (Aptech Systems, Inc., Black Diamond, WA, USA) and SPSS/PC+ V13.01 software (SPSS, Chicago, IL, USA).

RESULTS

Demographic and clinical characteristics of the three IBD study populations

Inflammatory bowel disease patients were included in this study from three different European populations: Berlin/Germany, Szeged/Hungary and Nijmegen/the Netherlands. Demographic and clinical characteristics of all populations including CARD15 status are listed in Table 1 (CD) and Table 2 (UC). The effect of the CARD15 status on the clinical course of CD was not the focus of the current study but observations in our three cohorts have shown that the c.3020insC variant is a risk factor for stenotic disease behaviour and increases the need for surgical interventions in

<table>
<thead>
<tr>
<th>Population</th>
<th>Germany</th>
<th>Hungary</th>
<th>The Netherlands</th>
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<tbody>
<tr>
<td>Sex (male:female)</td>
<td>126:192</td>
<td>64:84</td>
<td>57:100</td>
</tr>
<tr>
<td>Age at diagnosis (median, s.d.)</td>
<td>27 ± 11.6</td>
<td>25 ± 11.9</td>
<td>23 ± 9.5</td>
</tr>
<tr>
<td>Disease duration (years; median, s.d.)</td>
<td>10.1 ± 7.8</td>
<td>10 ± 7.7</td>
<td>20.0 ± 8.9</td>
</tr>
<tr>
<td>Familial IBD</td>
<td>37 (12.1)</td>
<td>10 (6.7)</td>
<td>9 (15.8)</td>
</tr>
<tr>
<td>Smoking</td>
<td>95 (31.2)</td>
<td>62 (41.6)</td>
<td>n.d.</td>
</tr>
<tr>
<td>Localization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L1: Ileum</td>
<td>68 (22.4)</td>
<td>22 (15.1)</td>
<td>40 (26.5)</td>
</tr>
<tr>
<td>L2: Colon</td>
<td>61 (20.1)</td>
<td>61 (41.8)</td>
<td>31 (20.5)</td>
</tr>
<tr>
<td>L3: Ileocolon</td>
<td>168 (55.2)</td>
<td>56 (38.3)</td>
<td>78 (51.7)</td>
</tr>
<tr>
<td>L4: Upper GI</td>
<td>7 (2.3)</td>
<td>7 (4.8)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Perianal disease</td>
<td>86 (30.0)</td>
<td>41 (28.1)</td>
<td>26 (40.6)</td>
</tr>
<tr>
<td>CARD15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CARD15-positive</td>
<td>127 (40.0)</td>
<td>49 (34.0)</td>
<td>61 (38.9)</td>
</tr>
<tr>
<td>CARD15-negative</td>
<td>191 (60.0)</td>
<td>99 (66.0)</td>
<td>96 (61.1)</td>
</tr>
<tr>
<td>Behaviour (Vienna)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B1: Non-stricturing non-penetrating</td>
<td>84 (28.9)</td>
<td>48 (33.8)</td>
<td>32 (20.8)</td>
</tr>
<tr>
<td>B2: Strictureing</td>
<td>77 (26.4)</td>
<td>38 (26.8)</td>
<td>35 (22.7)</td>
</tr>
<tr>
<td>B3: Penetrating</td>
<td>130 (44.6)</td>
<td>56 (39.4)</td>
<td>87 (56.5)</td>
</tr>
<tr>
<td>Surgery</td>
<td>127 (45.5)</td>
<td>67 (45.9)</td>
<td>97 (64.2)</td>
</tr>
<tr>
<td>Extrainestinal manifestations</td>
<td>123 (44.1)</td>
<td>36 (24.7)</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

Values are expressed as absolute numbers (percentages). n.d., not determined.
Overall, the clinical presentation of IBD was similar among the populations in terms of age, gender, familial disease, disease localization, behaviour and surgery.

### Distribution of the p.Arg381Gln variant within IL23R in IBD patients and controls

We started to investigate the frequencies of the p.Arg381Gln variant in a total of 919 patients with IBD from Germany, Hungary and the Netherlands in comparison with ethnic control groups. Genotypes are shown in Table 3. Control subjects were in Hardy–Weinberg equilibrium.

In the IBD cohort, p.Arg381Gln heterozygotes were underrepresented in comparison with controls. For the pooled analysis of all three cohorts, p.Arg381Gln was highly associated with IBD as well as with CD and UC when analysed separately. The presence of glutamine allele resulted in a tremendous risk reduction in IBD patients from Germany (OR: 0.43, 95% CI: 0.256–0.709), Hungary (OR: 0.43, 95% CI: 0.206–0.876) and within the CD patients from the Netherlands (OR: 0.26, 95% CI: 0.128–0.533). The association of p.Arg381Gln to UC was slightly weaker than to CD (OR: 0.41 vs. 0.45 for pooled analysis). Homozygous carriers for p.Arg381Gln were only identified in healthy controls. The protective effect of the p.Arg381Gln allele was present regardless of descent (German or Hungarian) and evident for CD but also in UC (Table 3).

As p.Arg381Gln heterozygosity was found in significantly lower frequencies in IBD patients, we confirm the observation of Duerr and colleagues that the glutamine allele might serve as a variant protecting from the development of IBD.

### The p.Arg381Gln variants in IBD patients stratified to the CARD15 risk status

Crohn’s disease and UC are believed to be complex genetic disorders. To determine genetic interactions between CARD15 and p.Arg381Gln within IL23R, we stratified for the p.Arg381Gln variant in respect to the CARD15 genotype (Table 4). We defined a CARD15 risk genotype as carrying at least one risk allele within one of the three common CARD15 variants (p.Arg702Trp, p.Gly908Arg and c.3020insC). CARD15 variants were identified at similar frequencies in 40%, 34% and 39% of the German, Hungarian and Dutch CD patients, respectively. We did not observe statistical interactions between p.Arg381Gln and CARD15 variants. This was true for the pooled analysis as for each individual CD cohort.

### Effect of the p.Arg381Gln variant on the clinical course of Crohn’s disease

We performed a detailed genotype–phenotype analysis using all the clinical and demographic data collected (Tables 1 and 2) to test for associations with the p.Arg381Gln genotype.

In the largest CD cohort from Germany, there was a trend towards an association of the wild-type IL23R allele with the presence of fistulizing disease behaviour ($P = 0.07$, data not shown). Moreover, none of patients heterozygous had surgery because of fistulizing disease behaviour ($P = 0.01$). However, the association with fistulizing disease behaviour could not be replicated in the Hungarian and Dutch CD patients ($P = 1.00$ and $P = 0.73$, respectively). We thus pooled the data from all cohorts with respect to fistulizing disease behaviour, but this analysis did not also reach a statistical significance ($P = 0.48$, Cochran-Mantel-Haenszel test).

Other than that p.Arg381Gln heterozygosity was not found to be associated with any other phenotype (pooled analysis and individual CD cohort).
Effect of the p.Arg381Gln variant on the clinical course of ulcerative colitis

In the UC patients from Germany and Hungary, p.Arg381Gln heterozygosity was not associated with any of the clinical investigated parameters such as age at diagnosis or disease localization (data not shown), either in the pooled analysis or in each individual CU cohort.

Effect of the p.Arg381Gln variant on gastroduodenal and intestinal permeability in CD

Gastroduodenal and intestinal permeability was determined in German CD patients using a triple-sugar-test. At the time of testing, all 107 CD patients were in remission (CDAI < 150). In total, 96 healthy volunteers served as controls. An increased gastroduodenal and intestinal permeability, was found in 37% (40 of 107) and 44% (47 of 107) of CD patients. The p.Arg381Gln genotype did not affect the risk for gastroduodenal or intestinal permeability (gastroduodenal: $P = 1.00$; intestinal: $P = 0.65$, both Fisher’s exact test).

DISCUSSION

This study relates to the recently reported association of the p.Arg381Gln variant within the $IL23R$ gene to IBD. Upon analysis of three large and well-characterized IBD populations from different European populations – Germany, Hungary and the Netherlands – we were able to confirm the previously reported association of the p.Arg381Gln variant with IBD in all cohorts. Heterozygous p.Arg381Gln carriers were found significantly less often in IBD patients in comparison with healthy controls. Similar findings were obtained when CD and UC patients were compared with controls. However, no significant difference was found when patients with CD and UC were compared.
These observations accord with the initial observations by Duerr and colleagues who identified an association of p.Arg381Gln with both CD and UC. They reported odds ratio of 0.26 and 0.45 in non-Jewish and Jewish CD patients, respectively. This is in line with the odds ratio in our three CD populations, ranging from 0.26, 0.40 and 0.44 in the Netherlands, Germany and Hungary, respectively. We also found a significant association in UC patients suggesting that p.Arg381Gln confers a protective effect against both CD and UC. So far, no gene variant has been shown to play a similar role in CD or UC.

The association of p.Arg381Gln with IBD has been confirmed also by two other very recent studies from Oxford, UK, and in a pooled IBD cohort from UK/Scotland. As seen in our study, the association of p.Arg381Gln was weaker in UC than in CD in both studies. Furthermore, an association of p.Arg381Gln has also been reported with paediatric CD in a population from the United States.

It remains currently unknown whether p.Arg381Gln influences disease phenotype in either CD or UC. We pooled the data from all cohorts to perform a genotype-phenotype analysis. Herein, we did not observe any significant association of p.Arg381Gln with a distinct sub-phenotype in both CD and UC. When we analysed the cohorts separately, in the German CD cohort, a trend towards an association of p.Arg381Gln heterozygosity with the absence of fistulizing disease behaviour was observed. However, we could not confirm these findings in the other two cohorts from Hungary and the Netherlands. The two other studies published so far from the UK and UK/Scotland also did not detect an association with a distinct sub-phenotype including fistulizing disease behaviour. This is furthermore supported by the observation that fistulizing disease behaviour is feature-specific for CD and all studies so far have clearly shown that p.Arg381Gln confers a protective effect against both CD and UC.

Inflammatory bowel disease is a complex genetic disorder. Until now, several genetic interactions have been reported especially between CARD15 alterations and other suggestive genetic variants for CD, such as DLG5 and ATG16L1. We could not observe statistical interactions with common CARD15 variants. This is also in agreement with the findings of recent other studies. However, because of the low frequency of the protective glutamine allele, an extremely large sample size would be needed to detect an interaction with either disease phenotype or other IBD-associated genetic variants. The currently available data suggest that p.Arg381Gln does not determine disease

<table>
<thead>
<tr>
<th>Genotype</th>
<th>All cohorts</th>
<th>Germany</th>
<th>Hungary</th>
<th>The Netherlands</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARD15+</td>
<td>226 (96.6)</td>
<td>124 (97.6)</td>
<td>46 (93.9)</td>
<td>56 (96.6)</td>
</tr>
<tr>
<td>P-Value</td>
<td>0.26*</td>
<td>0.17†</td>
<td>0.43†</td>
<td>0.49†</td>
</tr>
</tbody>
</table>

Table 4. Stratification of p.Arg381Gln by CARD15 genotype in CD

Genotypes of the p.Arg381Gln (c.1142G>A) variant in German, Hungarian and Dutch CD patients stratified for CARD15 mutations; p.Arg381Gln genotypes: wild type, heterozygous or homozygous; CARD15+ (−): at least one (no) mutant allele within CARD15 variants (p.Arg702Trp, p.Gly908Arg and c.3020insC). Values are expressed as absolute numbers (percentages). Allele frequencies were compared in 2 × 2 contingency tables using the * Cochran-Mantel-Haenszel test for pooled analysis of all three cohorts and the † Fisher’s exact test for the individual cohort.
phenotype; nor does it show interactions with CARD15 variants.

A genetically determined epithelial barrier dysfunction is suggested to be a pathogenic feature in CD. However, apart from the c.3020insC variant within CARD15 no other genetic variant has been associated with an increase in gastrointestinal permeability. We were not able to detect any association of alterations in gastrointestinal permeability with respect to the presence of the Arg381Gln variant in German CD patients. Although the null hypothesis could not be clearly rejected in this analysis, the low frequency of the glutamine variant has limitations and thus we cannot exclude that an association could be detected by studies with larger sample sizes. Furthermore, other variants within IL23R might be involved in any epithelial barrier alterations.

At present, it can only be speculated how IL23R contributes to the pathophysiology of IBD and especially how p.Arg381Gln might exert its suggestive, protective role. IL23 is produced by antigen-presenting cells and promotes the expansion of Th17 cells. This pathway is suggested to be a novel non-Th1 pathway leading to the differentiation of distinct CD4+ Th17 inflammatory effector cells and the IL23/Th17 axis is believed to be crucially involved in the pathogenesis of various inflammatory disorders. IL23 activity has been shown to be present in the terminal ileum and colon. Furthermore, IL23 was reported to be essential for the development of colitis in IL10-deficient mice. In addition, IL23, but not IL12, was the key factor for the induction of chronic intestinal inflammation by both innate and adaptive immune mechanisms in two different mice models. Interestingly, a very recent study indeed identified IL23R also contributing to psoriasis. Psoriasis and CD show pathophysiological connections. Suggestive psoriasis loci are located in the vicinity of known CD-susceptible regions such as IBD1 and IBD3. Furthermore, antitumour necrosis factor agents such as infliximab have shown to be effective in both diseases. These data suggest that IL23R variants might be involved in various chronic inflammatory pathways and selective targeting of IL23 might be an attractive therapeutic approach. Indeed, results from clinical trials targeting the IL12/IL23 pathway through an anti-IL12p40 antibody have yielded promising results for both CD and psoriasis.

In conclusion, heterozygosity for p.Arg381Gln within IL23R confers a protective effect against IBD, but does not determine disease phenotype.

ACKNOWLEDGEMENTS

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ELECTRONIC DATABASE INFORMATION

The URL for data presented herein is as follows:


REFERENCES

8 Harrington LE, Hatton RD, Mangan PR, et al. Interleukin 17-producing CD4+ effector T cells develop via a lineage dis-