Genetic association between EPHX1 and Crohn’s disease: population stratification, genotyping error, or random chance?

We read with interest the article by de Jong and colleagues (Gut 2003;52:547–51) reporting studies of genetic associations between DNA polymorphisms in xenobiotic metabolising genes and Crohn’s disease (CD). The authors employed a case control study design to test seven polymorphisms in five candidate genes in CD cases compared with 151 cases and 149 controls typed in other control populations (reviewed in de Jong et al.).

Our study design provided 80% power to detect a significant difference (p<0.05) in allele frequency of ≥7.5% between cases and controls compared with the difference of 26% observed in the published study. Our power calculations were based on an observed minor (C) allele frequency of 30.2% in our control cohort, the common (T) allele frequency being 69.8%.

We used TaqMan chemistry (Applied Biosystems) to genotype DNA from cases and controls with an Applied Biosystems 7700 Sequence Detection System. Pre-optimised primers and fluorescent probes were obtained from Applied Biosystems (SNP assay ID C_14938_1). All cases and controls were previously genotyped for three confirmed disease susceptibility alleles for CD (R702G in CARD15, L1007fs in CARD15, G908R in CYP1A1) permitting stratification of data by CARD15 genotypes. A recent review of published association studies by Xu and colleagues found that 12% of SNPs tested were inconsistent with HWE in control subjects. Our findings highlight the value of testing genetic association data for normal genotype distribution, and for rigorous replication of genetic associations with adequate statistical power.

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Table 1 Allele and genotype frequencies between cases and controls

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Tyr113His genotype</th>
<th>n</th>
<th>T/T</th>
<th>T/C</th>
<th>C/C</th>
<th>Tyr113His allele frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD ALL</td>
<td>344</td>
<td>167</td>
<td>146</td>
<td>31</td>
<td>69.8%</td>
<td></td>
</tr>
<tr>
<td>CD</td>
<td>307</td>
<td>155</td>
<td>127</td>
<td>25</td>
<td>71.2%</td>
<td></td>
</tr>
<tr>
<td>CD</td>
<td>0 CARD15 DSAs</td>
<td>202</td>
<td>99</td>
<td>83</td>
<td>69.6%</td>
<td></td>
</tr>
<tr>
<td>CD</td>
<td>1 CARD15 DSA</td>
<td>69</td>
<td>33</td>
<td>33</td>
<td>71.7%</td>
<td></td>
</tr>
<tr>
<td>CD</td>
<td>2 CARD15 DSA</td>
<td>20</td>
<td>12</td>
<td>7</td>
<td>77.5%</td>
<td></td>
</tr>
</tbody>
</table>

DSAs, disease susceptibility alleles; CD, Crohn’s disease.

References

Use of cyclosporin in pregnancy

Cyclosporin has been established in the management of steroid resistant severe ulcerative colitis. We read the letter by Dor and Blanshard (Gut 2003;52:1070) regarding the severe side effects of cyclosporin in a patient with steroid resistant severe ulcerative colitis after undergoing emergency Caesarean section. We would like to report our experience of a pregnant patient with steroid resistant severe distal ulcerative colitis in whom remission was induced with cyclosporin. She delivered a healthy baby at 34 weeks.
A 36 year old woman presented for the first time with a five week history of bloody diarrhoea and mucus discharge in the 12th week of her first pregnancy. Ulcerative colitis was confirmed on flexible sigmoidoscopy and histology. She was started on mesalazine (Pentasa) 1 g twice daily orally and Pentasa enema was added subsequently. She failed to respond well to oral prednisolone (40–60 mg daily) for five weeks or to subsequent intravenous prednisolone given for a further two and a half weeks. Azathioprine (oral 150 mg daily) was also added. Repeat sigmoidoscopy confirmed severe distal colitis with ulceration. At the 23rd week of pregnancy, she was started on intravenous cyclosporin (2 mg/kg) with careful monitoring of serum levels. Significant improvement was noted in two weeks, after which cyclosporin was changed to the oral route. Steroids were gradually tapered to 2.5 mg daily. At 34 weeks she underwent an emergency Caesarean section because of antepartum haemorrhage and a healthy baby girl (birth weight 2.07 kg) was delivered. Two weeks later, cyclosporin was weaned off after minimal rise of serum creatinine that coincided with high serum cyclosporin levels. Her serum creatinine normalised four weeks after delivery. She and baby remained well on azathioprine and mesalazine 14 weeks after delivery.

Intravenous cyclosporin induced remission in our pregnant patient who had failed to respond to high dose oral and intravenous prednisolone. Colectomy and the associated potential complications in pregnancy were avoided. There is only one other case report in the literature where cyclosporin was used in similar circumstances. While we would agree that cyclosporin should be used cautiously in pregnancy, our positive experience, and that of Bertschinger and colleagues, suggests that cyclosporin may induce remission and avoid colectomy during pregnancy.

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Reference


Is symptom control the correct end point for proton pump inhibitor treatment in Barrett’s oesophagus?

We have recently reported that abnormal acid reflux persists in up to 50% of patients with long segment Barrett’s oesophagus, despite good control of symptoms of gastro-oesophageal reflux disease (GORD) with proton pump inhibitor (PPI) therapy.1 The critical question is whether such persistence of abnormal acid reflux alters the rate of progression to adenocarcinoma. We investigated this issue by studying cellular proliferation and expression of cyclin D1, which is an important marker of neoplastic progression,2 in patients with Barrett’s oesophagus on PPI therapy.

A prospective cross-sectional survey of 20 patients with long segment Barrett’s oesophagus (defined as a length ≥3 cm and presence of specialised intestinal epithelium containing alcian blue staining goblet cells) was conducted. In all cases, GORD symptoms had been well controlled with PPI therapy (omeprazole n = 13 patients, median dose 20 mg (range 10–40); lansoprazole n = 5, 30 mg; or rabeprazole n = 2, 20 mg). Patients had received PPI therapy for a median duration of 30 months (12–66). Oesophageal manometry, 24 hour ambulatory pHmetry, and Bilitec 2000 monitoring were conducted on all patients, without interruption of their usual PPI therapy. Representative endoscopic biopsy specimens of Barrett’s oesophagus from each patient were studied for expression of cyclin D1 protein (primary antibody 1:50 dilution; Novocastra Lab) and Ki-67 protein (primary antibody 1:75; Dako Lab), by standard immunohistochemistry. The histopathologist was blinded to clinical information. A proliferative index was computed for each patient by scoring the percentage of Ki-67 labelled specialised columnar epithelial cells, as previously described.3 Cyclin D1 expression was semi quantitatively assessed. The mean percentage of positive cells in areas of intestinal-type specialised columnar epithelium was assigned to one of three categories: 0, <5%; 1, 5–50%; or 2, >50%. The intensity of cyclin D1 immunostaining was scored as: weak = 1, moderate = 2, or intense = 3. The percentage category of positive cells and staining intensity were multiplied to produce a weighted score for each patient. All cases with weighted scores ≥1 were designated positive.

Despite PPI therapy and absence of GORD symptoms, pHmetry detected abnormal acid reflux in nine (45%) patients (pH <4 for (median) 12.9% (range 4.6–32.1) of 24 hours; DeMeester score 49.5 (20.2–109.8)). The remaining 11 patients had acid reflux within the normal range (pH <4 for ≤4.5% of 24 hours). Proliferative indices (mean (SD)) for patients with abnormal acid reflux and those with normal acid reflux were similar (36.5 (8.7) v 37.4 (5.3), respectively; p = 0.3). Cyclin D1 expression was positive in seven (78%) patients with abnormal acid reflux and in seven (64%) patients with normal acid reflux (p = 0.4) (fig 1). The weighted score of cyclin D1 expression was identical (median 2 (range 2–6)) for patients with abnormal acid reflux and those with normal acid reflux.

These data imply that the risk of neoplastic progression was independent of the status of control of acid reflux by PPI therapy. We also examined the association between acid reflux and bile reflux. Absorbance >0.14 for ≤1.8% of 24 hours was considered the normal range for bile reflux in this study. Despite PPI therapy, abnormal bile reflux was detected in 12 (60%) patients, including six (55%) with normal acid reflux (absorbance >0.14 for 13.0% (2.5–46.5) and six (66%) with abnormal acid reflux (absorbance >0.14 for 17.4% (3.5–63.7)). Such persistent bile reflux may explain the similarity in expression of Ki-67 or cyclin D1 in the two groups with different control of acid reflux.

In contrast with PPI therapy, antireflux surgery that is successful in controlling acid reflux also controls bile reflux.4 Following successful antireflux surgery, proliferative indices in surface epithelial cells and crypts of Barrett’s oesophagus are significantly lower compared with a failed procedure.5 In the light of the present data, we propose the need for a novel clinical trial of PPI therapy versus antireflux surgery. Patients who are randomised to PPI therapy should undergo...
serial pH and Bilitec monitoring, with appropriate therapeutic modification to achieve predetermined end points. Patients who are candidates for laparoscopic fundoplication should have additional PPI therapy, as required, to achieve the same end points. Outcomes should be measured by standard endoscopic assessment and also by examination of a panel of molecular and cellular markers that is important in the pathogenesis of Barrett's adenocarcinoma.

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References

Improving hepatitis C services across the UK: response to a walk-in HCV testing service

The Department of Health (DH) estimates that approximately 0.4% of the UK population are chronically infected with hepatitis C virus (HCV) (that is, 200 000 people). As few as 10% of these individuals, who are at risk of end stage liver disease, are thought to be aware of their infection. Clearly action is required to identify and treat these patients with current drugs (pegylated interferons and ribavirin) that can cure over 50% of infected patients.

The UK voluntary sector have responded to the government identified need for more public information about HCV by organising a hepatitis C awareness day. We took advantage of the publicity around hepatitis C awareness day to assess the value of a walk-in HCV testing clinic.

Our clinic was held over four days (4–7 July 2003) and was widely publicised in the local press and television. Patients who wished to be tested were invited to attend a clinic in the Minor Injuries Unit at St Bartholomew’s Hospital in the City of London. The clinic was manned between 8am until 11am for counselling and informed testing (hepatitis C antibody test and liver function tests). Results were available the next day and patients were informed in person 24 hours later.

Nineteen people attended and two were infected. One of these patients had been lost to follow up due to non-attendance at a local liver clinic 12 years ago.

Open access confidential hepatitis C testing clinics may play an important role in encouraging people to come forward for HCV testing and may facilitate public education about this important treatable infection. However, these clinics are labour intensive and, in our experience, unlikely to provide a cost effective solution to the identification of people with this treatable, sometimes fatal, infection.

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Conflict of interest: Dr Foster acts as a consultant to companies who sell drugs for the treatment of viral hepatitis and has received research funding from such companies. He has received fees from companies who market antiviral therapeutics.

Influence of mode of delivery on gut microbiota composition in seven year old children

Intestinal microbiota development begins immediately following birth. The composition of the infant’s evolving microbiota is initially defined by the mother, the source of the newborn’s first microbial inoculum. Colonising bacteria rapidly adapt to breast milk and epithelial mucins as sources of nutrients. The prevalence of caesarean section delivery in Western countries is increasing. Caesarean born babies are deprived of contact with the maternal/vaginal microbiota and the first exposure is characterised by a lack of strict anaerobes and the presence of facultative anaerobes such as Clostridium species. Caesarean born infants have a more slowly diversifying microbiota, with differences reported from normally born infants, even after six months of age. Abarities in early microbiota acquisition can affect immunophysiologic development with a heightened disease risk. This study assessed microbiota composition in seven year old children and compared the respective effects of normal delivery and caesarean section.

In all, 60 seven year old children were randomly selected from Southwestern Finland, representing caesarean and vaginal deliveries. The children were invited to attend a clinical examination, including skin prick testing and determination of serum total and antigen specific IgE antibodies. Perinatal data were derived from hospital medical records. Questionnaires were completed by the parents to verify a history of allergic symptoms.

Faecal samples were produced at clinical examination and frozen at –70°C for microbiota assessment. Faecal microbiota profiles were determined using the culture independent fluorescent in situ hybridisation method. Probes specific for bifidobacteria, lactobacilli/enterococci, bacteroides, clostridia, and total bacterial numbers were applied. Written informed consent was obtained from parents and the study was approved by the ethics committee of the university.

Of the study population, 31 children had been delivered by caesarean section and 29 by vaginal delivery. At seven years of age, significantly higher numbers of clostridia were found in children delivered vaginally compared with caesarean born children (p = 0.0085) (table 1). No differences were observed in other faecal bacteria or total numbers of bacteria (table 1).

Children with asthma diagnosed by a physician (n = 6) had lower numbers of clostridia in their faecal specimens while healthy children (n = 54) had higher clostridial numbers.

Early colonisation guides subsequent microbiota development which may later impact on health, to the extent of predisposing some infants towards specific diseases. Bifidobacteria are considered useful for health promotion. Reported effects are related to the individual “balance” of the gut microbiota and prevention of aberrances within the gastrointestinal tract. Clostridia are generally considered harmful toxins producing species causing diarrhoea and food poisoning.

Our results show that bifidobacterial levels in the faeces of cohort children were comparable at seven years of age, independent of the mode of delivery at birth, while numbers of clostridia were significantly higher in normally born children seven years after birth.

Differences in neonatal gut microbiota in particular the balance between Bifidobacterium species and Clostridium species, have been reported to precede heightened production of antigen specific IgE antibodies, a hallmark of the atopic responder type. Such differences may be related to external environmental conditions.

Table 1: Numbers of faecal bacteria (log 10 number of bacteria/g faeces) and total serum IgE concentration, and number of children with asthma or atopic dermatitis among seven year old children with a history of normal birth or caesarean section

<table>
<thead>
<tr>
<th>Parameter (conca of specific microbe or total IgE)</th>
<th>Normally delivered</th>
<th>Caesarean born</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clostridia</td>
<td>9.29 (9.06–9.51)</td>
<td>8.83 (8.6–9.06)</td>
<td>0.0055</td>
</tr>
<tr>
<td>Bifidobacteria</td>
<td>10.32 (10.13–10.5)</td>
<td>10.29 (9.99–10.59)</td>
<td>0.87</td>
</tr>
<tr>
<td>Total bacteria</td>
<td>11.56 (11.46–11.7)</td>
<td>11.59 (11.5–11.68)</td>
<td>0.61</td>
</tr>
<tr>
<td>Lactobacilli/enterococci</td>
<td>9.07 (8.85–9.3)</td>
<td>9.05 (8.86–9.2)</td>
<td>0.85</td>
</tr>
<tr>
<td>Bacteroides</td>
<td>9.95 (9.67–10.24)</td>
<td>9.84 (9.52–10.17)</td>
<td>0.63</td>
</tr>
<tr>
<td>Total IgE</td>
<td>7.9 (16.25)</td>
<td>6.5 (25–160)</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Values are median (interquartile range).
factors (for example, mode of delivery and early feeding practices). The results of this study, showing that clostridial numbers in normally born children seven years after delivery are significantly higher than in caesarean born children, demonstrate that abnormal development of the intestinal microbiota reported following caesarean section delivery may continue even beyond infancy. These findings call for further assessment of microbiota composition throughout childhood when dietary interventions may still offer a rational means of health improvement. It is of importance to characterise the optimal clostridial numbers and species composition at different ages following normal and caesarean delivery.

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References

Crohn’s ileitis after liver transplantation from a living related donor with Crohn’s disease

We read with interest the case described by Sonwalkar et al of a patient who developed fulminant Crohn’s colitis after allogeneic stem cell transplantation (ASCT) (Gut 2003;52:1518–21). Although the donor had no history of Crohn’s disease (CD) and did not carry the IB3D or IB3D haplotypes associated with CD, HLA class III mismatches at IB3D and a CD associated polymorphism of the 5’UTR of NOD2/CARD15 were present in the donor and in the reconstituted immune cell population of the recipient post ASCT. The authors hypothesised that adoptive transfer of CD susceptibility may have occurred between ACST donor and recipient.

Herein, we report a case of a patient who developed CD after receiving a living related liver transplant from a donor with known CD. A 24 year old female received a liver transplant for a living related donor with compromised cirrhosis secondary to vertically transmitted chronic hepatitis C infection. The family history was significant for a maternal aunt diagnosed with CD, who served as the liver donor, and a maternal uncle and grandfather with colon cancer. Following liver transplantation, the patient was maintained on an immunosuppressive regimen consisting of tacrolimus 3 mg twice daily, sirolimus 5 mg daily, as well as TMSZ prophylaxis. Her initial post-transplant course was uneventful but she later developed recurrent hepatitis C infection, treated with pegylated interferon and ribavirin. She presented with symptoms consistent with intermittent small bowel obstruction 11 months post-transplant. She was also receiving prednisone 15 mg daily at that time. A computed tomography scan of the abdomen and pelvis (see fig 1A on the Gut website: www.gutjnl.com) demonstrated marked fold thickening of the distal ileum. An enteroscopist demonstrated patchy ulcerations in the ileum and Roux-en-Y limb of the small bowel. Biopsies showed focal ulceration and mild active inflammation without evidence of granuloma or viral inclusions. Wireless capsule endoscopy demonstrated multiple erosive and ulcerative changes in the distal small intestine (see fig 1C on the Gut website: www.gutjnl.com). Because of persistent symptoms and concern for possible lymphoproliferative disorder, the patient underwent an open laparoscopy which revealed nodularity of the ileal ileum, intraoperative colonoendoscopy demonstrated nodularity and three ulcers in the distal ileum. Histopathological examination of the resected ileal specimen demonstrated focal villous blunting, expansion of the lamina propria with acute and chronic inflammatory cells, reactive crypt changes, and occasional crypt abscesses and focal gastric metaplasia (arrow and insert). SM, mucosal ulcers were underlined by inflamed granulation tissue containing occasional histiocytes and multinucleated giant cells. The submucosa also showed intense fibrosis and hyperplasia of the nerve bundles (not shown).

Few cases of de novo IBD developing after liver transplantation for chronic liver disease other than primary sclerosing cholangitis have been described.1, 2 We present a case of CD developing in the recipient of a liver transplant from a living related donor with a known history of CD. The recipient tested negative for any of the three common CD associated NOD2/CARD15 variants (R702W, G908R, 1007fsinsC) but unfortunately we were unable to screen the liver donor for these polymorphisms. Our case, similar to that described by Sonwalkal et al, raises the intriguing possibility that CD susceptibility may have been transferred to the recipient with liver transplantation as well. Collins et al have reported complete and stable replacement of recipient haematopoiesis and B lymphopoesis with donor derived cells approximately six weeks following orthotopic liver transplantation for haemochromatosis.3 T lineage reconstitution also occurred and derived almost exclusively from expansion of mature memory effector T cells from the transplanted liver. One possibility is that the expanded immune cells have become tolerant to the graft but not to the intestinal luminal antigens leading to the development of CD.4 Whether liver donor selection should exclude those with a known diagnosis of CD is unclear and is still premature to answer.

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Figure 1 Histopathological examination of a resected ileal specimen demonstrated focal villous blunting, expansion of the lamina propria with acute and chronic inflammatory cells, reactive crypt changes, and occasional crypt abscesses and focal gastric metaplasia (arrow and insert). SM, mucosal ulcers were underlined by inflamed granulation tissue containing occasional histiocytes and multinucleated giant cells. The submucosa also showed intense fibrosis and hyperplasia of the nerve bundles (not shown).

Figure 1  Confocal image revealing colocalisation of glial fibrillary acidic protein (GFAP) and S-100 in enteric glia.

Enteric glia
von Boyen et al recently reported a study of glial fibrillary acidic protein (GFAP) expression in enteric glia (Gut 2004;53:222-8). Their new data are very interesting and add to our understanding of the possible role of enteric glia in gastrointestinal pathophysiology. However, we must take issue with some of the data presented that show extensive nuclear labelling with S-100 and with the description of the distribution of enteric glia in the colon.

Figure 1 of their paper shows labelling of enteric glia in the rat colon below the epithelial crypts and is thus presumably labelling of cells in the submucosal plexus. In the paper, this layer is described as the "plexus mucosus". The plexus mucosus, which is also known as the mucosal plexus, has previously been described in humans and rat. As the name implies, the mucosal plexus is located within the mucosa. Given the position of the crypts, as indicated by the ovals in Fig 1, it would appear that the labelling shown in panels A and B is in fact localized to the submucosalplexus. We find extensive colocalisation of GFAP and S-100 in the submucosal plexus. This is illustrated below in fig 1 in a whole mount preparation of the submucosal plexus from the rat colon. This confocal image reveals colocalisation of GFAP and S-100 in enteric glia (17 µm z stack of 1 µm optical sections; scale bar 50 µm) (fig 1). S-100 is also found in the cytoplasm of the glial perikaryon; there is virtually no nuclear labelling, which was the most obvious element of the staining demonstrated by von Boyen et al.

In fig 1 of the paper of von Boyen et al, the nature of the GFAP immunoreactivity is not fibrous, but granular, while the predominant labelling of S-100 is nuclear. In our hands this is not the case (see our fig 1) and so we feel this calls into question whether the extensive nuclear labelling observed in both fig 1 and fig 2 is really reflective of the distribution of S-100. Moreover, in the paper cited by the authors in support of nuclear localization, Ferri et al state that "only cytoplasmatic localization (of S-100) was consistently demonstrated in enteric glia." Con- trary to von Boyen et al's assertion that S-100 labelling is largely nuclear.

Finally, it should also be noted that GFAP expression in culture may reflect an altered state of differentiation as an adaptation to culturing. Hence some of the observed changes in GFAP expression may be explained by processes reflecting changes in the culture conditions rather than a pathophysiological response to cytokines.

The issues of glial heterogeneity and the role of enteric glia in inflammation raised in the paper are very interesting, and of considerable importance in understanding the physiology and pathophysiology of the gastrointestinal tract. By analogy with the brain, it is likely that enteric glia play an important role in the function of the gut. However, we feel that the extensive glial heterogeneity suggested in the paper by von Boyen et al may be overestimated and we urge caution in extrapolation of these data based on the immunohistochemistry presented in this manuscript.

Corrections
In the paper by Wang et al (Gut 2004;53:1096-1101), the acknowledgment and correct email address were not presented. The acknowledgment should have read as follows: "The authors thank senior technician Shu-Hao Wen for her assistance in processing the tissue slides, and Drs Jian-Ming Qian, Gang Sun, and Xiao-Hong Liu for their help in collecting the biopsy samples for the study project." In addition, the correct email address for Professor G-Z Pan is: pgz@public3.bta.net.cn.

Corrections
doi: 10.1136/gut.2003.021154corr1

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do: 10.1136/gut.2003.027425corr1

An author was omitted from the paper by Francés et al (Gut 2004;53:860-4), entitled Bacterial DNA activates cell mediated immune response and nitric oxide overproduction in peritoneal macrophages from patients with cirrhosis and ascites. This paper was published in the June issue and the missing author is E Rodriguez, Immunology Department, Hospital General Universitario, Alicante, Spain.
Crohn's ileitis after liver transplantation from a living related donor with Crohn's disease

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