No TGFBRII germline mutations in juvenile polyposis patients without SMAD4 or BMPR1A mutation


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No *TGFBRII* germline mutations in juvenile polyposis patients without *SMAD4* or *BMPR1A* mutation

L A A Brosens, W A van Hattem, M C E Kools, et al.

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differences in drug metabolism. Our survey is the first and the only data comparing the East and the West on managing anticoagulants and antiplatelets for endoscopic procedures.\(^1\) Since it is unethical and dangerous to perform a prospective study in patients on antplatelets or anticoagulants for an endoscopic procedure, analysing the opinion of the experts, as in our study, must be an alternative proposal. There is no doubt that personal experience seems to be a more powerful driver of practice than published literature, as shown in our survey. It is important to decrease the bleeding risk associated with endoscopic procedures and to minimise the thromboembolic risk of withdrawing medications by providing guidelines for the appropriate management of anticoagulation and antiplatelet medications during GI endoscopy. Therefore, the type of the patient should be considered when managing these drugs for GI endoscopy with regard to the difference between Easterners and Westerners.

S-Y Lee

Correspondence to: Professor S-Y Lee, Department of Internal Medicine, Konkuk University School of Medicine, 4–12 Hiwayang-dong, Gwangjin-gu, Seoul 143–792, South Korea; syluryong@kuk.ac.kr

Competing interests: None.

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Authors’ response

We are grateful to Dr Lee for highlighting differences in practice between Eastern and Western endoscopists with regard to anticoagulant and antiplatelet therapy, and the difference in responses of Eastern and Western patients to the pharmacological agents.\(^1\) Unfortunately, this study was published after submission of our guideline for publication, and has therefore not been cited. As Dr Lee states, there are no randomised controlled trials regarding the use of anticoagulant and antiplatelet agents in endoscopy. We have to rely on the limited evidence available, and this has largely been based on Western patients.

Guidelines are limited by the evidence available and should be considered not only in the context of this evidence, but with respect to the patient population. Dr Lee and colleagues have emphasised this point well by demonstrating the response of Eastern endoscopists to the previously published American guidelines.\(^2\) There is still a wide variation in practice among Western endoscopists with regard to anticoagulant and antiplatelet therapy,\(^2\) despite previous guidelines. While many Eastern endoscopists believe it to be unsafe to undertake endoscopic biopsies on warfarin, or polypectomy on aspirin, there is no direct evidence to suggest that these practices are unsafe. Indeed, a large study from Hong Kong found no increased risk of post-polypectomy bleeding in patients taking aspirin.\(^3\) As with many areas of endoscopic practice, there is a lack of prospective studies. It would be desirable for published guidelines, based on retrospective evidence, to be tested prospectively to confirm their validity.

A M Veitch\(^4\) S Cairns\(^5\)

\(^1\) Department of Gastroenterology, New Cross Hospital, Wolverhampton, UK; \(^2\) Department of Gastroenterology, Royal Sussex County Hospital, Brighton, UK

Correspondence to: Dr A M Veitch, New Cross Hospital, Wolverhampton, WV10 0QP, UK; andrew.veitch@nwh-tr.nhs.uk

Competing interests: None.


REFERENCES


No TGFBRII germline mutations in juvenile polyposis patients without SMAD4 or BMPR1A mutation

Juvenile polyposis (JPS) is an autosomal dominant disorder characterised by the presence of multiple gastro-intestinal juvenile polyps and an increased risk of colorectal cancer (CRC).\(^1\) JPS is caused by germline mutation of SMAD4 or BMPR1A, both involved in the transforming growth factor β/bone morphogenic protein (TGFβ/BMP) signalling pathway. A recent study by van Hatten et al, published in this journal (Gut 2008;57:623–7), showed that a germ-line defect in one of these genes is found in approximately 50% of JPS patients, with 30–40% being a point mutation or small deletion and 10–15% a large genomic deletion. Since no germ-line defect is found in ~50% of JPS patients, it is likely that other genes exist which cause JPS.\(^2\)

Several candidate genes, mostly involved in TGFβ/BMP signalling, have been investigated for a role in JPS pathogenesis. No mutations have been found in these genes.\(^2\) (table 1) Recently, the TGFβ co-receptor endoglin was proposed as a JPS susceptibility gene, but other studies could not confirm this.\(^2\) Also, PTEN, the gene originally linked to Cowden syndrome (CS) and Bannayan–Riley–Ruvalcaba syndrome (BRRS), has been suggested as a JPS gene. The current consensus, however, is that PTEN mutations in patients with juvenile polyposis likely represent CS or BRRS patients that have not (yet) developed extra-intestinal clinical...
features specific to these conditions. Lastly, the CDX2 gene was investigated in juvenile polyposis, since mice with a heterozygous mutation of CDX2 develop intestinal hamartomatous polyps, but no pathogenic mutations were found in 37 JPS families. The TGFβ receptor type II (TGFBRII) is a component of the TGFβ pathway and is mutated within a polyadenyne tract in exon 3 in up to 90% of CRCs with microsatellite instability and in 15% of microsatellite stable malignancies. In addition, germline mutation of TGFBRII has been reported in a patient with hereditary CRC (944C>T, reference sequence NM_003242). Also, mice with conditionally knocked out TGFBRII in fibroblasts develop intra-epithelial neoplasia of the prostate and invasive squamous cell carcinoma of the forestomach and loss of TGFBRII in intestinal epithelium promotes invasion and malignant transformation of tumors in Apc1638N/wt mice. Because of its role in TGFβ signalling and in (colorectal) carcinogenesis, we investigated whether germline mutation or deletion of the TGFBRII gene is involved in JPS pathogenesis.

Nineteen JPS patients from 18 families, in whom germline mutation or deletion of SMAD4, BMPR1A, PTHR1 or ENG was previously excluded, were investigated for germline defects in the TGFBRII gene. JPS was defined according to accepted clinical criteria. All exons and intron–exon boundaries of the TGFBRII gene were analysed by direct sequencing and the possibility of germline deletion of (parts of) the TGFBRII gene was investigated by multiplex ligation-dependent probe amplification (MLPA) (van Hattem). Table 2. Polyomorphisms found in TGFBRII

<table>
<thead>
<tr>
<th>Location</th>
<th>Nucleotide</th>
<th>Amino acid change</th>
<th>Number of JPS patients</th>
<th>refSNP ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>intron 3</td>
<td>c.338-7A&gt;G</td>
<td>Introninc</td>
<td>9/18</td>
<td>rs1155705</td>
</tr>
<tr>
<td>intron 4</td>
<td>c.530-4A&gt;T</td>
<td>Introninc</td>
<td>7/18</td>
<td>rs11466512</td>
</tr>
<tr>
<td>exon 4</td>
<td>c.1242 C&gt;T</td>
<td>p.N414N</td>
<td>6/18</td>
<td>rs2228048</td>
</tr>
<tr>
<td>intron 7</td>
<td>c.1600-8 C&gt;T</td>
<td>Introninc</td>
<td>1/18</td>
<td>rs11466530</td>
</tr>
</tbody>
</table>

Table 1. Candidate genes investigated in the pathogenesis of juvenile polyposis

<table>
<thead>
<tr>
<th>Gene</th>
<th>Patients studied/mutations found</th>
<th>Reference (first author and year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMPR1B (ALK6)</td>
<td>32/0</td>
<td>Howe 2004</td>
</tr>
<tr>
<td>BMPR2</td>
<td>59/0*</td>
<td>Howe 2004, van Hattem 2008</td>
</tr>
<tr>
<td>SMAD1</td>
<td>30/0</td>
<td>Bevan 1999</td>
</tr>
<tr>
<td>SMAD2</td>
<td>34/0</td>
<td>Bevan 1999, Roth 1999</td>
</tr>
<tr>
<td>SMAD3</td>
<td>34/0</td>
<td>Bevan 1999, Roth 1999</td>
</tr>
<tr>
<td>SMAD5</td>
<td>30/0</td>
<td>Bevan 1999</td>
</tr>
<tr>
<td>SMAD7</td>
<td>34/0</td>
<td>Bevan 1999, Roth 1999</td>
</tr>
<tr>
<td>CDX2</td>
<td>37/0</td>
<td>Woodford-Richens 2001</td>
</tr>
</tbody>
</table>

13. 2 patients investigated by sequencing (Howe1) and 27 by multiplex ligation-dependent probe amplification (MLPA) (van Hattem). 14. 13B patients investigated by sequencing (Howe1 and Gallione) and 27 by MLPA (van Hattem).
Gut tutorial

Dyspnoea in a patient with cirrhosis

This is an introduction to the Gut tutorial "Dyspnoea in a patient with cirrhosis" hosted on BMJ Learning—the best available learning website for medical professionals from the BMJ Group.

Clinical assessment, investigation and management of breathlessness in patients with chronic liver disease can be challenging and is often poorly performed or ignored. The focus of clinical management by gastroenterologists and hepatologists is usually on more familiar consequences of cirrhosis, such as portal hypertension, and other manifestations of liver failure, such as ascites. Understanding potential causes and developing a rational approach to investigating dyspnoea in patients with cirrhosis is the focus of this module. This interactive case presentation raises several differential diagnoses as a cause for breathlessness and discusses their pathogenic mechanisms, an approach to investigation and the evidence base for management in an attempt to improve clinicians’ understanding and clinical skills in this often neglected area. Specific causes of dyspnoea may share aetiology with the underlying chronic liver disease, be a consequence of hepatic decompensation, be related to other co-morbidities, or result from less well appreciated conditions, including portopulmonary hypertension or hepatopulmonary syndrome.

To access the tutorial (Interactive Case History), click on BMJ Learning: Take this module on BMJ Learning from the content box at the top right and bottom left of the online article. For more information please go to: http://gut.bmj.com/tutorials/collection.dtl

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M W James1, Nick Taylor2, Guruprasad P Aithal1

1 Nottingham Digestive Diseases Biomedical Research Unit, Queen’s Medical Centre, Nottingham, UK; 2 King’s College Hospital, London, UK

Correspondence to: M W James, Consultant hepatologist and gastroenterologist, Nottingham Digestive Diseases Biomedical Research Unit, Queen’s Medical Centre Nottingham, NG7 2UH; martinwymjames@gmail.com

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