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

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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 antplatelets for endoscopic procedures. Since it is unethical and dangerous to perform a prospective study in patients on antplatelets or anticoagu-

Authors’ response

We are grateful to Dr Lee for highlighting differences in practice between Eastern and Western endoscopists with regard to anticoagu-

REFERENCES


No TGFBR11 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). JPS is caused by germline mutation of SMAD4 or BMPR1A, both involved in the transforming growth factor β/bone morphogenetic 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 dele- tion. Since no germline 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 investi-
gated for a role in JPS pathogenesis. No mutations have been found in these genes.1 (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 polyadenine 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_001024847). 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 Apc*Min/Wv*mm 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, BMPRAA, PTEN 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 et al.).

### 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>ACVR1 (ALK1)</td>
<td>66/0†</td>
<td>Howe 2004, Gallione 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>

*32 patients investigated by sequencing (Howe et al.) and 27 by multiplex ligation-dependent probe amplification (MLPA) (van Hattem et al.).

*139 patients investigated by sequencing (Howe et al. and Gallione et al.) and 27 by MLPA (van Hattem et al.).

Table 2: Polymorphisms 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.338–7 A&gt;G</td>
<td>Introninc</td>
<td>9/18</td>
<td>rs1155705</td>
</tr>
<tr>
<td>Intron 4</td>
<td>c.530–4 T&gt;A</td>
<td>Introninc</td>
<td>7/18</td>
<td>rs1146512</td>
</tr>
<tr>
<td>Exon 4</td>
<td>c.1242 C&gt;T</td>
<td>p.N414S</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>

*Reference sequence: NM_001024847.

JPS, juvenile polyposis; TGFBRII, transforming growth factor receptor type II.

### REFERENCES

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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Competing interests: None declared.

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