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


Published in:
Gut

DOI:
10.1136/gut.2008.161232

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or privacy interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

UvA-DARE is a service provided by the library of the University of Amsterdam (http://dare.uva.nl)
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.

*Gut* 2009 58: 154-156
doi: 10.1136/gut.2008.161232

Updated information and services can be found at:
http://gut.bmj.com/content/58/1/154.2.full.html

These include:

**References**
This article cites 16 articles, 9 of which can be accessed free at:
http://gut.bmj.com/content/58/1/154.2.full.html#ref-list-1

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://journals.bmj.com/cgi/ep
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. Since it is unethical and dangerous to perform a prospective study in patients on anticoagulants and antiplatelets, the appropriate management of anticoagulation and antiplatelet medications during GI endoscopy. Therefore, the type of the practice should be considered when managing these drugs for GI endoscopy in patients with non-valvular atrial fibrillation – a survey comparing the East and the West Parasitology 2004;111:561–6.


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. 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. There is still a wide variation in practice among Western endoscopists with regard to anticoagulant and antiplatelet therapy, 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. 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, S Cairns

Department of Gastroenterology, New Cross Hospital, Wolverhampton, UK. *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


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 (TGFβRII) 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 TGFβRII has been reported in a patient with hereditary CRC (944C>T, reference sequence NM_003242). Also, mice with conditionally knocked out TGFβRII in fibroblasts develop intra-epithelial neoplasia of the prostate and invasive squamous cell carcinoma of the forestomach and loss of TGFβRII 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 TGFβRII gene is involved in JPS pathogenesis.

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) and 27 by multiplex ligation-dependent probe amplification (MLPA) (van Hattem).
†39 patients investigated by sequencing (Howe and Gallione) and 27 by MLPA (van Hattem).

The TGFβ receptor type II (TGFβRII) 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 TGFβRII has been reported in a patient with hereditary CRC (944C>T, reference sequence NM_003242). Also, mice with conditionally knocked out TGFβRII in fibroblasts develop intra-epithelial neoplasia of the prostate and invasive squamous cell carcinoma of the forestomach and loss of TGFβRII 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 TGFβRII gene is involved in JPS pathogenesis.

Nineteen JPS patients from 18 families, in whom germline mutation or deletion of SMAD4, BMPR1A, PTEN or ENG was previously excluded, were investigated for germline defects in the TGFβRII gene. JPS was defined according to accepted clinical criteria. All exons and intron–exon boundaries of the TGFβRII gene were analysed by direct sequencing and the possibility of germline deletion of (parts of) the TGFβRII gene was investigated by multiplex ligation-dependent probe amplification (MLPA) (P0065 MLA kit, MRC-Holland BV, Amsterdam, The Netherlands). No pathogenic germline mutations or deletions in TGFβRII were found in this cohort. Known polymorphic variations were found in intron 3, intron 4, exon 4, and intron 7 (table 2).

TGFβRII germline mutation is linked to Marfan syndrome type 2. Surprisingly, these patients do not have an increased risk of cancer. Possibly, diverging phenotypic effects of the different TGFβRII mutations are responsible for the absence of malignancies in Marfan patients carrying a TGFβRII mutation. Alternatively, the germline variation (944C>T) found in the patient with hereditary CRC could be a rare polymorphism without significance for CRC development. Although this alteration was not found in 119 control subjects, others found it at a similar frequency in normal controls (7 of 492) and individuals with sporadic CRC (6 of 228). Moreover, no additional germline mutations in TGFβRII have been found in patients with hereditary non-polyposis colorectal cancer (HNPPC) or in patients with familial or early onset CRC.

Because of its role in TGFβ signalling and CRC pathogenesis we hypothesised that TGFβRII may be a JPS susceptibility gene. Linkage analysis could not be performed due to the lack of large JPS kindreds in our cohort. It is nevertheless felt that TGFβRII may be a JPS susceptibility gene. Linkage analysis could not be performed due to the lack of large JPS kindreds in our cohort. It is nevertheless felt that TGFβRII may be a JPS susceptibility gene.

Table 2 Polymorphisms found in TGFβRII

<table>
<thead>
<tr>
<th>Location</th>
<th>Nucleotide</th>
<th>Amino acid change</th>
<th>Number of JPS patients</th>
<th>rsSNP ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intron 3</td>
<td>c.338+7 A&gt;G</td>
<td>Intronin</td>
<td>9/18</td>
<td>rs1155705</td>
</tr>
<tr>
<td>Intron 4</td>
<td>c.530–4 T&gt;A</td>
<td>Intronin</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>Intronin</td>
<td>1/18</td>
<td>rs11466530</td>
</tr>
</tbody>
</table>

*Reference sequence: NM_001024847.
†JPS, juvenile polyposis; TGFβRII, transforming growth factor receptor type II.

Table 2 Polymorphisms found in TGFβRII

<table>
<thead>
<tr>
<th>Location</th>
<th>Nucleotide</th>
<th>Amino acid change</th>
<th>Number of JPS patients</th>
<th>rsSNP ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intron 3</td>
<td>c.338+7 A&gt;G</td>
<td>Intronin</td>
<td>9/18</td>
<td>rs1155705</td>
</tr>
<tr>
<td>Intron 4</td>
<td>c.530–4 T&gt;A</td>
<td>Intronin</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>Intronin</td>
<td>1/18</td>
<td>rs11466530</td>
</tr>
</tbody>
</table>

*Reference sequence: NM_001024847.
†JPS, juvenile polyposis; TGFβRII, transforming growth factor receptor type II.

Gene Patients studied/mutations found Reference (first author and year)
BMPR1B (ALK6) 32/0 Howe 2004†
BMPR2 59/0† Howe 2004, van Hattem 2008
ACVR1 (ALK1) 66/0† Howe 2004, Gallione 2004, van Hattem 2008
SMAD1 30/0 Bevan 1999
SMAD2 34/0 Bevan 1999, Roth 1999
SMAD3 34/0 Bevan 1999, Roth 1999
SMAD5 30/0 Bevan 1999
SMAD7 34/0 Bevan 1999, Roth 1999
CDX2 37/0 Woodford-Richens 2001

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

The prevalence of the reference sequence. NM_001024847.
†JPS, juvenile polyposis; TGFβRII, 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

If prompted, subscribers must sign into Gut with their journal username and password. All users must also complete a one-time registration on BMJ Learning and subsequently log in (with a BMJ Learning username and password) on every visit.

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

Competing interests: None declared.

Gut 2009;58:156. doi:10.1136/gut.2008.170795