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.
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
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 or anticoagulants for 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 patients 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 Hwayang-dong, Gwangjin-gu, Seoul 143–729, South Korea; suryoung@kuk.ac.kr
Competing interests: None.

REFERENCES

No TGFBR111 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.3 A recent study by Hui et al, published in this journal (Gut 2008;57:623–7), showed that a germline 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 germline defect is found in ~50% of JPS patients, it is likely that other genes exist which cause JPS.4

Severe 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.5 (Table 1) Recently, the TGFβ co-receptor endoglin was proposed as a JPS susceptibility gene, but other studies could not confirm this.7,8 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 polyps likely represent CS or BRRS patients that have not (yet) developed extra-intestinal clinical
features specific to these conditions.7 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.8

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.9 In addition, germline mutation of TGFBRII has been reported in a patient with hereditary CRC (944C>T, reference sequence NM_003242).10 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△1638N/se mice.11,12 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, Pten or ENG was previously excluded,2 were investigated for germline defects in the TGFBRII gene. JPS was defined according to accepted clinical criteria.3 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).13

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).

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>rsSNP ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intron 3</td>
<td>c.338–7 T&gt;A</td>
<td>Intronic</td>
<td>9/18</td>
<td>rs1155705</td>
</tr>
<tr>
<td>Intron 4</td>
<td>c.530–4 T&gt;A</td>
<td>Intronic</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>Intronic</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.

without molecular diagnosis and the search for other JPS causing genes should continue apace. Candidate genes could include other, perhaps less obvious, components of the TGFβ/BMP pathway.

L A A Brosens, W A van Hattem, M C E Kools, C Eozendam, F H Morsink, W J de Leng, F M Giardello, G J A Oeffershaus

1 Department of Pathology, University Medical Center Utrecht, Utrecht, The Netherlands; 2 Department of Pathology, Academic Medical Center, Amsterdam, The Netherlands; 3 Department of Medicine, Division of Gastroenterology, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; 4 Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Correspondence to: Dr L A A Brosens, Department of Pathology (H44-312), University Medical Center Utrecht, Postbox 85500, 3508 GA Utrecht, The Netherlands; L.A.A.Brosens@umcutrecht.nl

Funding: Supported by the Netherlands Digestive Disease Foundation (MLDS WS 04–08), the John G. Rangos Sr. Charitable Foundation, The Clayton Fund, and NIH grants CA 53801, 63721, 51085, and P50 CA 93-16. The study sponsors were not involved in study design, collection, analysis, and interpretation of data, in the writing of the report, and in the decision to submit the paper for publication.

Competing interests: None.

Ethics approval: Ethics approval was granted by the Johns Hopkins Institutional Review Board on 28 September 2007. The study was carried out in accordance with the ethical guidelines of the research review committees of the institutions in Amsterdam and Utrecht.

Gut 2009;58:154–156. doi:10.1136/gut.2008.161232

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

¹Nottingham Digestive Diseases Biomedical Research Unit, Queen’s Medical Centre, Nottingham, UK; ²King’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; martinwyjjames@gmail.com

Competing interests: None declared.

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