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 antiplatelets for endoscopic procedures.[2] Since it is unethical and dangerous to perform a prospective study in patients on antiplatelets 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 patient should be considered when managing these drugs for GI endoscopy with regard to the difference between Easterners and Westerners.

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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,[3] 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.[4] 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.

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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 *BMPR1*A, both involved in the transforming growth factor β/bone morphogenic protein (TGFβ/BMP) signalling pathway. A recent study by van Hattem *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.[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.[3–6] (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 polyps likely represent CS or BRRS patients that have not (yet) developed extra-intestinal clinical

Table 1 Candidate genes investigated in the pathogenesis of juvenile polyposis

Gene	Patients studied/mutations found	Reference (first author and year)
BMPR1B (*ALK6*)	32/0	Howe 2004[3]
BMPR2	59/0*	Howe 2004[3], van Hattem 2008[2]
ACVR1 (*ALK1*)	66/0†	Howe 2004[3], Gallione 2004[6], van Hattem 2008[2]
SMAD1	30/0	Bevan 1999[4]
SMAD2	34/0	Bevan 1999[4], Roth 1999[5]
SMAD3	34/0	Bevan 1999[4], Roth 1999[5]
SMAD5	30/0	Bevan 1999[4]
SMAD7	34/0	Bevan 1999[4], Roth 1999[5]
CDX2	37/0	Woodford-Richens 2001[8]

*32 patients investigated by sequencing (Howe[3]) and 27 by multiplex ligation-dependent probe amplification (MLPA) (van Hattem[2]).
†39 patients investigated by sequencing (Howe[3] and Gallione[6]) and 27 by MLPA (van Hattem[2]).

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 $Apc^{1638N/wt}$ 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.[1] 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) (P065 MLPA kit, MRC-Holland BV, Amsterdam, The Netherlands). No pathogenic germline mutations or deletions in *TGFBRII* were found in this cohort. Known polymorphic variations were found in intron 3, intron 4, exon 4, and intron 7 (table 2).

TGFBRII germline mutation is linked to Marfan syndrome type 2.[13] Surprisingly, these patients do not have an increased risk of cancer.[14] Possibly, diverging phenotypic effects of the different *TGFBRII* mutations are responsible for the absence of malignancies in Marfan patients carrying a *TGFBRII* mutation.[15] 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,[10] others found it at a similar frequency in normal controls (7 of 492) and individuals with sporadic CRC (6 of 228).[13] Moreover, no additional germline mutations in *TGFBRII* have been found in patients with hereditary non-polyposis colorectal cancer (HNPCC) or in patients with familial or early onset CRC.[15 16]

Because of its role in TGFβ signalling and CRC pathogenesis we hypothesised that *TGFBRII* 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 *TGFBRII* is unlikely to be involved in JPS pathogenesis since no germline mutations or deletions in *TGFBRII* were found in the current study. Still, about half of JPS patients remain 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.

Table 2 Polymorphisms found in *TGFBRII*

Location	Nucleotide	Amino acid change	Number of JPS patients	refSNP ID
Intron 3	c.338+7 A>G	Intronic	9/18	rs1155705
Intron 4	c.530–4 T>A	Intronic	7/18	rs11466512
Exon 4	c.1242 C>T	p.N414N	6/18	rs2228048
Intron 7	c.1600–8 C>T	Intronic	1/18	rs11466530

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

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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.

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