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Polyposes Syndromes

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Introduction

The term polyposis should be restricted to recognised and strictly defined syndromes in which the primary feature is the presence of multiple polyps (1). In most common types of polyposes namely familial adenomatous polyposis and juvenile polyposis, the definition is associated with the number of polyps with or without molecular confirmation. For other polyposes sydromes, like hyperplastic or inflammatory polyposis, there is no definitive, precise definition.

The aim of this paper is to discuss the most common types of epithelial polyposes that are relatively well defined. This review will not include acquired conditions like inflammatory polyposis or submucosal polyps.

Familial Adenomatous Polyposis

Definition
Familial Adenomatous Polyposis (FAP) is an autosomal dominant disorder caused by a defect in the apc gene on the long arm of chromosome 5. The traditional phenotypic definition includes the detection of at least 100 colorectal polyps, histologically verified as adenomas (2).

Prevalence
The prevalence of FAP varies significantly depending on availability of regional or national registry. Countries such as Australia, Canada, Denmark, Finland, Germany, Hong Kong, Italy, Japan, Korea, Norway, Portugal, Switzerland, Singapore, the Netherlands, UK and United State of America have registries (3). In this context it is worthwhile to note that the first FAP registry was established at St. Mark's hospital in London in 1924. In 1971 the polyposis registry was established in Denmark (4). The effect of the Danish polyposis registry shows the number of colorectal cancer in such patients dropping from 60% before the registry to 27% after the registry but colostomies increasing from 52% to 93% (5). The results from national and regional polyposis registries vary (Table 1). Two Scandinavian studies have estimated the prevalence of FAP 4.65 per 100.000 (5) and 26.3 per million (6).

The first North American registry was established at Johns Hopkins Hospital in Baltimore in 1976 (7). FAP prevalence in the United State (population of 280 million) has been estimated to be between 6,022 to 7,364 families (7).

Table 1: Results from national and regional polyposis registries by Bülow (5)

Author	Year	Region	Country	No of patients	No of probands	No of call-up cases	% Isolated cases	% CRC in probands	% CRC in call-up cases	Incidence rate $x10^{-6}$	Prevalence rate $x10^{-5}$	% FAP with CRC/all CRC
Bussey	1975	London	UK	410	293	117	45	66	9			
Vasen	1990	—	Holland	230	104	126	46	47	4			
Penna	1992	Paris	France	141				45	3			
Goh	1992	—	Singapore	58				89	13			
Morton	1993	West Midland	UK	107				64	6			
Bertario	1994	—	Italy	604	441	163		48	10			
Järvinen	1994	—	Finland	192	116	76		66	7	1.58	2.63	0.14
Ponz de Leon	1999	Modena	Italy	156			41					
Björk	2000	—	Sweden	431	216	215		67	3	0.90	3.16	0.023
Heiskanen	2000	—	Finland	236	116	120		61	4			
Present study		—	Denmark	434	252	182	35	68	3	1.90	3.19	0.07

FAP, familial adenomatous polyposis; CRC, colorectal cancer.

Genetic Features & Disease Expression

Germline mutation of APC gene has been determined on chromosome 5. APC gene has 15 exons and encodes 2843 amino acids. This large protein has multiple cellular functions and interactions, including roles in signal transduction in the Wnt-signalling pathway, mediation of intercellular adhesion, stabilization of cytoskeleton and possibly regulation of the cell cycle and apoptosis (8).

Several types of mutation hit the APC gene but the most common ones are frameshift and point mutations (see glossary for definition of different types of mutations). However, it is the germline mutation in the APC gene which is responsible for the autosomal dominant inherited disease FAP, while somatic mutations in APC gene occur in approximately 80% of sporadic colorectal tumours (8).

The extraintestinal clinical manifestations of FAP depend on which part of APC gene is affected. For instance, the location of APC gene mutation associated with Pigmented Ocular Fundus Lesions is on codons 542 - 1309 while the multiple locations for extraintestinal lesions are on codons 1465, 1546 and 2621 (9).

In one study APC mutations were determined in 48% (327/680) of FAP families (10) but in general, the incidence varies significantly between 30 – 85%.

Furthermore, the percentage of mutation detection depends also on the number of adenomas. In one study (10), the mutation detection rate was 56.2% in more than 100 adenomas' patients and 31.7% in patients with less than 100 ones.

Regarding the type of mutation, Friedl et al (10) studied mutations detected in APC gene in 322 of 327 patients. 226 were framshift mutations due to small deletions/insertions; 87 were nonsense mutations and nine mutations were in the highly conserved splice site sequences. In addition to that there were 86 novel mutations not reported in the APC mutation database (http://www.umd.necker.fr).

Despite the best available techniques, approximately 20% of clinically typical FAP kindred fail to show any sort of mutation. This raises the possibility of additional susceptibility genes for FAP. However, Giardiello et al (9) found no mutation was detected in 9 (84 individuals) of 51 (391individuals) families. They used RNAse protection assay to detect germline mutation. In spite of the available methods detecting APC gene, mutations still found only in approximately 80 % of APC pedigrees (11). Other studies applied several methods to detect if there is any type or site of mutation that are missed. As mutation analysis of the APC gene were applying four sorts of mutation analysis test: Protein Truncation Test, Hetroduplex Analysis, Allele

Specific Oligonucleotide Hybridisiation Analysis and Haplotype Analysis; Moisio et al (12) found 38 different mutations only in 47 of 65 families screened to confirm Familial Adenomatous Polyposis (FAP).
As there is a relation between the genotype characteristic and phenotype manifestations, genetic tests may help in confirming the diagnosis and also to guide patient's surveillance. For instance, families with mutations in codons 1465-1546 need clinical attention as they are prone to extra-intestinal manifestations.

Clinical Features
Germline mutation of APC gene affects all three body germ layers (13) . When affecting the endoderm there will be hundreds of polyps in the large intestine and frequently in the duodenum and small intestine.
The mesoderm involvement is by Desmoid Tumour.
Congenital hypertrophy of retinal pigment epithelium is one of the ectodermal manifestations of FAP, in addition to, epidermal cysts which may be multiple and found at young age.

Pathologic Features
Adenomas of FAP are distributed throughout the intestine, with a tendency to be larger in the sigmoid and the rectum. Rarely, the rectum is spared. When extensive, the entire large bowel becomes carpeted with different sizes of adenomas.

Gross and Endoscopic Features
The number and size of polyps depend on the stage at which the diagnosis is firstly made. In classical FAP, the number of polyps ranges from <100 to >5000 with an average of 1000, depending on when one sees the patient. Adenomas show gradation in size and shape from typically pedunculated tumours 1 cm or more in diameter, to smaller, broader-based nodules, to tiny lesions barely visible as mucosal excrescences 1 mm or less in size. Some adenomas are grossly invisible. Adenomas tend to be smaller in patients undergoing screening surveillance.
Adenomas in classic FAP patients are similar to sporadic lesions. The very small adenomas resemble hyperplastic polyps. It is only when they become larger that the typical raspberry-like configuration of an adenoma becomes evident.

Microscopic Features
Early stages of adenoma formation consist of small groups of tubules lined by the adenomatous epithelium. They range from unicryptal, bicryptal, or tricryptal lesions in the grossly normal-appearing mucosa to the more typical multicryptal grossly visible polyp seen in patients without FAP. The presence of unicryptal, bicryptal, and tricryptal adenomas strongly suggests the diagnosis of FAP.
Proliferation throughout the entire length of the adenomatous crypt leads to branching, budding, infolding, and mucosal elevation. As the lesions enlarge to a grossly visible size, they become Tubulovillous. Tubular adenomas in FAP grow preferentially in the horizontal plane early in their pathological process and then, once they measure more than 8 mm in diameter, they grow both horizontally and vertically. Pure villous adenomas are rare in FAP patients.

Extra-colonic Manifestations

Duodenal Polyps
With improvement in the management of FAP and increased life expectancy, duodenal Polyposis and malignancy have emerged as major health problems in these patients.
Duodenal adenomatosis was first reported in 1935 and then it became evident that duodenum is the second most affected location of polyp development in FAP patients after the colon. (14, 15) 30-70% of FAP patients have duodenal adenomas (14, 16) and the leading cause of death after colorectal cancer is duodenal/periampullary adenocarcinoma (17). It has been reported that FAP patients have a 100-330 fold higher risk of duodenal cancer compared with general population (18, 19). Most polyps in the duodenum are adenomas while gastric polyps are mainly non-neoplastic fundic cystic gland lesions.
Bülow et al (16) reported 238 patients who had duodenal adenomas at a median age of 38 years. They also found the cumulative incidence of duodenal adenomatosis at an age of 70 was 90%.
Spigleman et al established a system for rating the severity of duodenal Polyposis. Five stages were described and scores were given to number, size, histology, and severity of dysplasia of polyps (20).
In all FAP patients upper gastrointestinal surveillance of FAP patients is recommended.
Genotype-phenotype correlation in duodenal polyposis
The relationship between the severity of duodenal Polyposis and mutations in the APC gene is a controversial issue.
Groves et al (21) found that somatic mutation in upper gastrointestinal polyps cluster is located approximately between 1400 and 1580, Mutation Cluster Region (MCR). Apart from that study, somatic mutations including allelic loss were detected in 9 out of 49 duodenal adenomatosis polyps. Furthermore the type of somatic mutation in upper gastrointestinal polyps depends on the site of the germline APC mutation. This mutation after codon 1400 associated with allelic loss may

probably lead to grow more severe duodenal polyposis.
On the other hand, Friedle et al study failed to detect a correlation between the site of mutation and the severity of duodenal Polyposis whereas, Savaria et al found patients with 5` mutation are more likely to have severe duodenal Polyposis (10). However, most studies consider the mutations in the exon 15 of APC gene, distal to 1400 lead to severe duodenal Polyposis (21, 22, 23, 24).

Desmoid Tumour
Desmoid Tumour is a locally infiltrative benign fibromatous lesion arising in the abdominal wall, mesentery or occasionally in the extremities and trunk (25). Generally they are rare and occur in 2-4 individuals per million (26), but in FAP patients the incidence rate is between 3.5-13% (27).
There are many precipitating factors to desmoid formation that include: surgical trauma, pregnancy and others hormonal influence, and genetic heterogeneity caused by different type of mutations of APC gene.
Genotype-phenotype correlation in Desmoid Tumour. Caspari et al reported 33 of 36 Desmoid Tumours with mutations of codons 1445-1578(28) while Giardiello et al found 5 of 12 patients with mutation at the same codons (9).

FAP Variants

Attenuated Familial Adenomatous Polyposis (AFAP)
AFAP is not well-defined as a disease entity and only a few authors have suggested exact diagnostic criteria. However the main clinical manifestations are:
1) a milder course of disease;
2) a later onset of colorectal adenomas and carcinoma;
3) limited extracolonic features.

The first report of AFAP was from Lynch et al in 1990 on two families with phenotype typical to AFAP (29). Leppert et al (29a) described in the same year a set of diagnostic criteria without calling it AFAP. They reported on a large family who had history of colorectal cancer but did not fulfil the criteria for FAP.

Genetics: The number of exons is 15 which encode 2843 amino acids. The possibility of mutation is more likely to hit any part of this gene with different site and different type. However more than 800 different pathogenic mutations in APC gene now have been determined but still there is 15-50%of classical FAP patients are not possible to detect any mutations in APC gene (10, 12). The variations in mutation detection rate could be caused by the use of different APC screening strategies and by the variation in the criteria of diagnosis.
Friedl et al detected a mutation in 32 of 101 unrelated AFAP patents. In spite of the mutations in APC gene associated with AFAP have been mainly detected in three parts of gene:
1) in the 5` end (the first 5 exons);
2) in exon 9 and
3) in the distal 3` end, the range of mutations causing AFAP is not completely settled and the possible effect of modifier genes has been investigated. In addition to that some studies have been described I1307K mutation, the missense mutations I1317Q in patients with AFAP like phenotype.

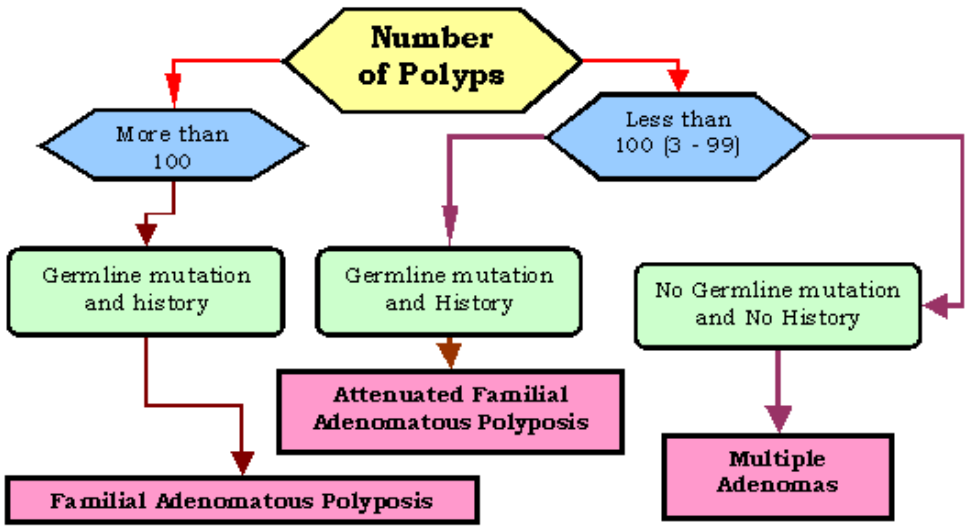
Clinical presentations:
1- Colorectal features:
The essential criteria for AFAP have been revised by many authors and consensus today is that the number of colorectal adenomas must be less than 100 and the distribution of these adenomas should be more on the right side of colon proximal to the splenic flexure. The differences between the AFAP and FAP are illustrated in Table 2.(30)

Table 2: The phenotype of AFAP and FAP (from Knudsen et al (30)

	AFAP	FAP
GUT MANIFESTATIONS		
1) Large Intestine		
a) Number of Adenomas	**Less than 100**	100-5000
b) Distribution of Adenomas	**Right side of colon & relative rectal sparing**	The whole colon and rectum
c) Mean Age at onset of Adenomatosis	**35-45 years (mean age)**	17 years (mean age)
d) Mean Age at onset of Colorectal Cancer	**55 years (mean age)**	40 years (mean age)
2) Gastro-Duodenal		
a) Upper gastrointestinal Adenomas	**Less than 50%, frequent**	52-84% (prevalence)
EXTRA-GUT MANIFESTATIONS		
1) Desmoid Tumours	**Rare**	4-13%(incidence)
2) Others	**Very rare?**	Frequent

Although the vast majority of the studies have the consensus that the number of adenomas in AFAP is less than 100 in the majority of AFAP patients, the incidence and frequency are still unknown (31, 32).
Several studies showed a tendency to rectal sparing of adenomas in AFAP patients (33, 34, 35) and the onset of colon adenoma is often described as being delayed in AFAP patients in comparison with FAP patients. This, of course, leads to delay in bowel symptoms. However the average age at adenoma development varies among the studies (33, 36, 37).
Although the colonic cancer may appear later, the actual incidence, frequency, or life time risk of colonic cancer in AFAP are not known (33). Moreover the colonic cancer does not seem to develop in all AFAP patients. In three studies colonic cancer was found in 24/79, 2/4 and 44/90 AFAP patients respectively (33, 38, 39).
On the other hand Brensiger et al reported that no cases of colonic cancer with fewer than 100 adenomas (40). As the rectums in AFAP patients are often spared of adenomas, rectal cancer is seldom seen (41).

2 - *Extracolonic manifestations:*
Extracolonic manifestations are infrequently reported. This may be due to reasons such as lack of registration of these phenotypes and lack of publications. However many reports described 3` mutation in APC gene to be associated with an increased risk of extracolonic manifestations, for instance, congenital hypertrophy of the retinal pigment epithelium (CHRPE). Another report considers mutation after codon 1444 leads to the risk of developing Desmoid Tumours. Other manifestations include Fundic Gland Polyps and Duodenal Adenomas.
Disario et al found 43 of 65 (66%) AFAP patients have fundic gland polyps (42). Another studies reported the prevalence of fundic gland polyps and duodenal adenomas were 52-88% and 64-84% respectively (43, 44).
It seems to be that Desmoid tumours are less common in AFAP than FAP but several reports described an increased risk of Desmoid tumours in patients with 3` mutation to codon 1444 (10, 28, 45).
In the literature, only 23 AFAP with Desmoid Tumours have been reported (33, 35, 40, 46, 47, 48).
The differential diagnosis of AFAP is Multiple Adenomas which clinically is extremely difficult to separate from AFAP because the similarity of the phenotype and the possibility of family history. Although the definition of Multiple Adenomas is not precise but there is general acceptance that these patients having 3–99 colorectal adenomas, but with no detectable germline APC mutations and often there is no family history of Polyposis (49, 50, 51) (See chart).



The chart illustrated the correlation between the number of polyps, and presence or absence germline mutation and history in categorised the adenomatous polyposis.

Lamlum et al (49) screened 164 unrelated British patients with Multiple Adenomas for germline APC mutation. The number of adenomas in this study was between 3 and 96. They found mutation in 14 of 164 patients and the type of mutation are E1317Q, I1307K and truncating mutation in exon 9` or distal 3`end.

Pathological Features of Adenomas: AFAP patients grossly and endoscopically develop depressed, flat, or polypoid adenomas. The recognisable feature shows that the whole surface of flat or depressed adenomas lies below the level of the normal mucosa. Flat adenomas have a concave surface or may be completely flat with the surrounding mucosa while polypoid adenomas in this case are those with convex surfaces.
Flat adenomas differ endoscopically and histologically from the usual adenoma. They present as slightly elevated plaques of adenomatous mucosa, not more than twice as thick as the adjacent normal mucosa. Further growth is by radial extension of adenomatous epithelium so that the lesions remain flat.

Gardner's syndrome
Gardner's syndrome is an autosomal dominant disease characterised by a triad of colonic Polyposis, multiple Osteomas and multiple soft tissue and skin tumours. It is now accepted that Gardner's syndrome is a variant of FAP because it shares the same genetic alternation. It linked to APC gene of chromosome 5.

Clinical manifestations: colonic adenomatous polyps are the main manifestation of Gardner's syndrome and they can be tubular, tubulovillous or villous. In addition to that 12% of patients with Gardner's syndrome have gastric and small intestinal adenomatous polyps. The onset of polyp formation is sometimes at puberty but the diagnosis in most cases is in the third decade and the malignant transformation is 100% by the fourth decade of life. Clinically the patients have anaemia, lower gastrointestinal bleeding, cramping abdominal pain, diarrhoea, bowel obstruction and mucous discharge.
The second essential clinical manifestation is Osteomas which appear in about half of Gardner's syndrome and they could be present earlier than Polyposis. Skull is the most common place for Osteomas but they could be seen in the mandible, maxilla, large bone and phalanges. It is suggested that the finding 3 or more Osteomas raise suspicion of Gardner's syndrome.
Dental Disorders were noted in about 70% of patients. Among many soft tissue tumours, Desmoid Tumours considered to be the most troublesome manifestation of Gardner's syndrome. 5.5-5.7% in which have Desmoid Tumour. This tumour could appear at any time or within 3 years after surgery. The most common locations are abdominal cavity and retropertonium.Other clinical manifestations could be noted in Gardner's syndrome are Papillary Thyroid Carcinoma, Meningiomas, Epidermal Cysts, Hepatomas, Hepatoblastomas, Fibromas, Lieomyomas, Lipomas, Biliary and Adrenal Neoplasmas, Osteosarcomas, and Chondrosarcomas.

Turcot's syndrome
Turcot's syndrome is an inherited disease with predisposition for brain tumours and Neoplasms of colon (52, 53). Clinically: there are two types of Turcot's syndrome
Type 1 includes patients with Hereditary Non-polyposis Colorectal Cancer (HNPCC) and Glioblastoma.
Type 2 consists of patients diagnosed with Familial Adenomatous Polyposis and Medulloblastoma. (53, 54)
Most of Turcot's syndrome families have APC gene mutation but they show a variant of phenotype. So Turcot's syndrome patients could have Thyroid Carcinoma, Hepatoblastoma, and tumours of the adrenal cortex, biliary tract and pancreas (55, 56). Hamilton et al reported that the relative risk of brain tumours increased by 23 fold among the familial adenomatous Polyposis families during the first three decades (57).
Ikeda et al reported different types of brain tumours in Turcot's syndrome patients.
They found Astrocytomas (61%), Medulloblastoams(25%), Lymphomas (2%), Meningiomas (less than 2%), Pituitary adenomas (less than 2%), and Craniopharygiomas (less than 1%) (53). However the major cause of death in Turcot's syndrome is brain tumour whereas the colon tumour considers the minor cause of death (58).

Management of FAP
Management the patient with FAP is still debatable as we should keep in mind the following considerations:
1. Clinical findings; particularly the number of polyps in the rectum.
2. Presence or absence of cancer.
3. Presence or absence of intra-abdominal and mesenteric Desmoid tumours.
4. More importantly, genetic status and age of the patient.
5. The patient's wishes in term of operation, willingness to undergo follow ups, and the possibility of effective pharmacological treatment.

Basically, there are two surgical options, ileorectal anastomosis (IRA) and ileal pouch-anal anastomosis (IPAA).

Non-adenomatous Polyposis Syndromes

The second group of polyposis syndromes is a heterogeneous one and includes several entities in which the polyps are of a non-adenomatous nature. These include:
1. Peutz-Jeghers syndrome.
2. Juvenile polyposis.
3. Cowden's disease.
4. Hyperplastic polyposis.

However, there are additional, several rare, less well-characterised polyposis syndromes; these will not be discussed here.
In the first three entities the polyps are hamartomatous in nature whereas in the hyperplastic polyposis they are, as the name indicates, hyperplastic.
The hamartomatous polyposis syndromes share several characteristics and their clinical distinction is subtle, however, the recent detection of genetic alterations allows more precise definitions (59).
The following account discusses these syndromes with a special emphasis on the recent advances in their genetic origin and pathogenesis.

Peutz-Jeghers syndrome

Definition
This syndrome was first described by Peutz in 1921 and then by Jeghers in 1944. Clinically it is characterised by dark pigmentation of the mouth and lips along with hamartomatous polyps of the stomach and intestine. These polyps have specific characteristic histological picture. The patients have a high risk of developing malignant tumours in the gastrointestinal tract and in other sites.

Incidence
Peutz-Jeghers syndrome is rare, the frequency of which is estimated to be between 1/29000 to 1/120000 (60, 61).

Genetics and inheritance
Peutz-Jeghers syndrome is inherited in an autosomal dominant fashion with variable penetrance (62,63) .The genetic mutation responsible for developing the disease is a mutation in the lkb 1 gene locus on chromosome 19p.The mutation has been discovered by two independent groups in 1998 (64,65) and is present in 60-70% of patients with the disease (60).
The product of this gene (LKB 1 kinase, also known as STK 11) which is a serine/thrionine kinase, is believed to be a tumour suppressor gene that plays a role in chromatin remodelling, cell cycle arrest, cell polarity, and energy metabolism (64). The mutation is present in the epithelial and not the stromal cells (63). This is in contrast to the mutation of juvenile polyposis which is detected in stromal and not epithelial cells.
Experiments on mice models showed that lkb1 is important in embryogenesis as complete loss of functioning lkb1 resulted in death in utero (66). In the same study, the loss of a single lkb1 allele was shown to cause polyposis in 10 month old mice which on histological examination revealed similar features to the Peutz Jegher polyps in humans. The same results have been confirmed by another similar study (67).
Interestingly the lkb1 mutation has been detected in familial as well as sporadic cases of the syndrome (68).

Clinical manifestations
The external hallmark of this syndrome is the skin and mucosal pigmentation. This starts as early as infancy (62) and increases gradually to peak at puberty. Later the pigmentation fades. The most permanent pigmentations are the ones on the buccal mucosa.
Clinical symptoms usually start in adolescence or early adulthood and are related to complications of the polyps. The most common presentation is intestinal obstruction which is caused by intussusception. The second most common is gastrointestinal bleeding (62, 63).
The most common site of PJS polyps is the small intestine but they can also be present in the stomach and colon.
The mean age of diagnosis is 22-26 years, however, symptoms can also start in childhood (69, 70).
Some patients stay asymptomatic till they present initially with a gastrointestinal neoplasm (63).

Pathological features
As mentioned earlier PJS polyps are hamartomatous in nature. The histological definition of a hamartoma is the presence of native tissues in a haphazard abnormal arrangement causing a mass-like lesion. The typical features of PJS polyps is that of epithelial glands, some are cystically dilated with arborisation of smooth muscles that extend in a tree like fashion into the epithelial layer (63, 71). The arrangement of the smooth muscle which divides the polyp into sectors is an important diagnostic clue (71). Although some glandular dilatation can be present it is usually less than that seen in Juvenile Polyposis.
An important histological feature is the presence of epithelial cells entrapped in the smooth muscle. This results from invagination of the glands during the smooth muscle extension into the epithelium. This feature is regarded as mucosal

herniation/pseudoinvasion and it is important not to mistake it with invasive malignancy (63).

Pathogenesis
As described above the polyps in PJS are caused by a mutation in lkb1 gene. However the exact mechanism of polypsis and malignant transformation is not fully understood. The fact that the majority of PJS polyps are not premalignant complicates the mater further.
In a very recent article Jansen et al (72) propose an interesting hypothesis on the pathogenesis of PJS polyps. They believe these polyps share histological features with mucosal prolapse, and as such they propose that these polyps are a reflection of a tendency of the GI mucosa to prolapse in patients with JPS. They propose that these polyps most likely do not carry a premalignant potential, which is a widely accepted observation. The authors try to propose that the malignant tumours occurring in PJS by being originated from sporadic adenomas which carry the same tendency of mucosal prolapse, hence their histological similarity with the genuine PJS polyps.

Tumour development
Patients with PJS have a relatively high risk of developing colorectal carcinoma. The risk is estimated to be in the range of 10-20% (73).
There is also an increased risk of gastric carcinoma (risk is 5-10%) as well as cancers of breast, lung, uterus, ovaries, cervix and testis (60, 73).
Uncommon neoplasms can also be seen with PJS like sex cord tumours, sertoli cell tumour, and adenoma malignum of the cervix62
The tumours mostly develop de novo and it is possible that lkb1 mutation plays an important role in tumour development.
A hamartoma-adenoma-carcinoma sequence has been proposed to explain the high risk of developing GI malignancy but this view was challenged by Jansen et al as described in the section of pathogenesis.

Management
Due to the rarity of the syndrome there is no wide clinical experience in the best surveillance of patients with the disease. Dunlop recommended surveillance Frequency as follows:
1. Large bowel surveillance is recommended once every three years starting from 18 years of age (73).
2 Upper GI surveillance every three years from 25 years of age (73).

However, some workers recommend an earlier surveillance for the upper GI tract (62).
Because there is an increased risk of developing extra-alimentary malignancies most authorities recommend regular mammography and gynaecologic examination of women and testicular ultrasound for men (63).
Regarding surgical removal of polyps it is recommended that polyps that are >1.5cm in size or suspicious of invasive malignancy should be removed endoscopically (63).

Juvenile polyposis (JP)

Definition
This is an autosomal dominant syndrome that has been first described by McColl in 1964 (63). The WHO criteria to diagnose this syndrome are:
1. More than 5 juvenile polyps of the colorectum or
2. Juvenile polyps throughout the gastrointestinal tract or
3. Any number of juvenile polyps with a family history of juvenile polyposis (74).

Patients have a high risk of developing carcinoma of the colorectum, stomach, duodenum, biliary tract and pancreas.

Incidence
Juvenile polyposis is rare, the estimated incidence is between 0.6-1 per 100 000 in Western population (74, 75). Up to 50% of cases occur with no family history (74).
Genetics and inheritance
JP is an autosomal dominant syndrome. Two genetic mutations are identified. The first mutation is mapped to the tumour suppressor gene SMAD4 on chromosome 18. In one study involving 47 patients from 15 families the mutation was detected in 21% of cases (76). Whereas other studies showed that 50% of patients carry the mutation (73). SMAD4 encodes a protein that mediates cellular responses of transforming growth factor β (TGF β). Such responses include cell growth, apoptosis and growth inhibition (75).
Bevan et al screened patients for SMAD 1, 2, 3 and 5 and they could not find pathogenic mutations in JP (77).
The second mutation is in BMPR1A gene which is located on chromosome 10q. It is a member of TGF β family. This gene has been detected in 25% of affected families (75, 77).
Some studies suggested that mutations in PTEN gene are also present in JP. However this could just be a reflection of the fact that there is confusion about the diagnostic criteria for JP and the studies that detected these mutations possibly included polyposis syndromes which do not quite fulfil the criteria of JP, especially Cowden disease (76, 63).
In contrast to PJS the mutations are detected in the stromal cells but not the epithelial cells (63). This lead to the hypothesis that the stromal element in JP is the site of abnormal growth. As

any other hypothesis this has been challenged. In a recent article, a common dysregulation of B catenin has been detected in epithelial calls of the juvenile polyps (78).

Clinical manifestations
Patients with JP develop multiple polyps of the GI tract. The most common site of the polyps is the colorectum but the stomach and small bowel can also be affected (62).
The majority of patients present in the first two decades of life with symptoms of rectal bleeding, anemia or rectal prolapse (62).
Some patients may present in infancy with GI bleeding, intussusception, rectal prolapse or protein loosing enteropathy (63, 75).
JP may occur in association with hereditary hemorrhagic telangectasia. As such patients need to be checked for digital telangectasia and clubbing and if these are present they require evaluation for hereditary hemorrhagic telangctasia (75).

Pathological features
The polyps in JP are hamartomatous in nature. They are characterised by a unilobulated smooth surface. The lamina propria is infiltrated by a large number of lymphocytes and plasma cells with attenuation of the muscularis propria. The glands are dilated and lined by columnar epithelium63, notably there is no proliferation of smooth muscle cells (75). As such there are two main features that distinguish JP polyps from PJS ones which are the predominantly dilated glands and the attenuated smooth muscle layer in the former.
Some of the polyps do not have the smooth unilobulated outer surface. These are called atypical polyps but this only refers to their macroscopic appearance, however as discussed below these might have a high incidence of dysplastic transformation.

Pathogenesis
The development of cancer in patients with JP can occur de novo, from adenomatous polyps or through dysplasia occurring in juvenile polyps. Pure adenomas are, however rare in JP whereas foci of low grade dysplasia can be found in 50% of atypical juvenile polyps (74).

Tumour development
It is now established that JP carries a high risk of developing malignant tumours. The first relatively large study to confirm this came from St Mark's polyposis registry and included 87 patients with 1032 polyps in total (79). In that study 18 patients developed large bowel cancer. The cancer development was suggested to be arising from a hamartoma-adenoma-carcinoma sequence. The study suggested that a high proportion of cancers arising in JP are poorly differentiated or mucinous secreting carcinoma.
The estimated risk of colorectal cancer is 10-38%, however the risk increases with age and is believed to be 17-22% by 35 years of age and 68% by age 60 (75). As for gastric cancer there is a risk of 21% (73).

Management
The difficulty in having clear accepted management guidelines in PJS, also applies to JP. Dunlop however recommends the following:
a) Large bowel surveillance every 1-2 years from age 15-18 with increasing the frequency after 35 years of age. This is best performed by colonoscopy or flexible sigmoidoscopy. If patients present with symptoms at an earlier age, the surveillance can be started earlier.
b) Upper GI surveillance to be performed every 1-2 years from age 25 (73). This is possibly best done by capsule endoscopy (75).
Benefits of surveillance in patients with JP as well as PJS is not known, however the risk of cancer is high and on balance it is best to offer it to patients.
Diffuse polyposis may require colectomy (75). Surgery is also the treatment of choice when patients present with complications especially GI bleeding, however there is a high risk of recurrence of the polyps after surgery (80).

Cowden Disease

Definition
This is an autosomal dominant syndrome with variable expressivity. The syndrome is characterized by hamartomas of the GI tract and other sites. It is caused by a mutation in PTEN gene and the patients have a risk of malignant disease (74).

Incidence
Cowdens syndrome is a rare condition, the incidence of which is 1 in 200 000 (75).

Inheritance and genetics
The syndrome is inherited in an autosomal dominant fashion. The mutation responsible for the syndrome is related to the pten gene on chromosome 10q. This has been found in 81% of families with the disease (81).
The gene product (PTEN) is a tumour suppressor gene and its product is a dual specificity phosphatise (74).

Clinical manifestations
80% of patients present with skin manifestations most commonly trichilemmoma which are usually multiple. The second most common presentation is in the CNS where patients develop cerebellar gangliocytomatosis. 40% of patients have

macrocephaly. Only 35% of patients have GI polyposis (63).

Pathological features
The hamartomatous polyps are histologically similar to those of juvenile polyposis.
The polyps usually have an intact mucosal surface and has a stromal core that is composed of disorganised bundles of smooth muscles.
Also seen in this syndrome are ganglioneuromas, lipomatous and inflammatory polyps.

Tumour development
There is a high risk for developing breast and thyroid cancer. There is no reported increased risk of GI malignancy however the disease is rare and possibly it is better to consider the risk as being unknown (63).

Management
Patients need screening for breast and thyroid tumours.
As discussed above the risk of colorectal cancer is not known, as such surveillance is possibly needed (63).

Hyperplastic Polyposis

Definition
This is a relatively newly recognised syndrome which still does not have clear agreed diagnostic criteria. It was first described in 1980 by Williams et al (84).
The WHO proposes the following criteria for diagnosing the syndrome are:

1. Five or more hyperplastic polyps (confirmed by histological examination) which are proximal to the sigmoid colon of which 2 are more than 10mm in diameter or
2. Any number of hyperplastic polyps occurring proximal to the sigmoid colon in a person who has a first degree relative with hyperplastic polyposis or
3. More than 30 hyperplastic polyps of any size but distributed throughout the colon.

Incidence
The syndrome is relatively newly recognised and it is difficult to estimate its frequency, however it appears to be rare.

Inheretence and genetics:
Although the WHO criteria suggest familial clustering of the syndrome, it is still unclear if the syndrome is inherited or not.
Hyperplastic polyps are found to show clonal genetic changes including KRAS mutation and DNA microsatellite instability (74, 83).

Clinical manifestations
The syndrome is usually asymptomatic. Large polyps however can become symptomatic (74). The polyps occur anywhere in the large bowel. Ferrandez et al studied 15 patients who fulfilled the WHO criteria for HP and they found that the polyps are mostly present in the left colon (74% of the polyps in this series were in the left colon (82). However larger polyps were more commonly located in the right colon (82).

Pathological features
The histological picture of the polyps is the same as in sporadic hyperplastic polyps which is that of feathery appearance of the surface with underlying hyperplastic glands.

Tumour development
The issue of dysplastic change and cancer development in sporadic hyperplastic polyps and in HP has interested many researchers. In the previously mentioned article by Ferrandeze et al only one patient out of the 15 patients studied developed cancer within the follow up period of 3 years (82). However, adenomas were documented in 73% of patients in the same study.
Hayman et al studied 13 patients with HP.10 of the patients had also at least one adenomatous polyp and 3 had serrated adenomas (85). In this study 7 of the patients (54%) developed cancer, four of whom presented initially with the tumour, the rest developed the cancer during the study period.

Management
There are no firm management guidelines but as there is a possible risk of developing dysplastic change or even cancer, surveillance is recommended.

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