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EDITORIAL

Signs and genetics of rare cancer syndromes with gastroenterological features

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Abstract

Although the genetic bases of most hereditary cancer syndromes are known, and genetic tests are available for them, the incidence of the most rare of these syndromes is likely underestimated, partially because the clinical expression is neither fully understood nor easily diagnosed due to the variable and complex expressivity. The clinical features of a small pool of rare cancer syndromes include gastroenterological signs, though not necessarily tumors, that could require the intervention of a gastroenterologist during any of the phases of the clinical management. Herein we will attempt to spread the knowledge on these rare syndromes by summarizing the phenotype and genetic basis, and revising the peculiar gastroenterological signs whose underlying role in these rare hereditary cancer syndromes is often neglected. Close collaboration between geneticists and gastroenterologists could facilitate both the early identification of patients or relatives at-risk and the planning of multidisciplinary and tailored management of these subjects.

Key words: Genetic susceptibility; Diagnostic criteria; Gastroenterological features; Genetic testing; Rare cancer syndromes

Core tip: Close collaboration between geneticists and gastroenterologists can facilitate early identification of patients or relatives at-risk and the planning of multidisciplinary and tailored management. This editorial summarizes the diagnostic criteria, cancer associations and genetic bases of very rare cancer syndromes whose clinical features include gastroenterological signs.

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INTRODUCTION

Five to ten percent of overall cancers is related to hereditary cancer syndromes. The most rare among these syndromes are characterized by very infrequent tumors, *i.e.,* with an incidence per year of less 6/100000 per year, or by a peculiar clustering of clinical signs often overlooked[1]. The genes that are responsible for hereditary cancer syndromes were first identified in the 1990's[2,3]. Over the following years, the molecular pathogenetic basis of several syndromes was uncovered and the genetic testing became available for them. The clinical description of such syndromes has also been reviewed in terms of associated signs and tumors so as to define the most accurate major and minor criteria that can lead a clinician to the diagnosis. However, some of these syndromes are still often underdiagnosed since they are very rare or because the clinical expression is not well known. In particular, a variety of gastroenterological findings were associated to a pool of rare hereditary cancer syndromes. Knowing about these findings and being able to recognize them can help clinicians in the early identification of patients affected by these syndromes. The physicians would therefore be able to plan multidisciplinary management and identify asymptomatic at-risk relatives who could then be offered the surveillance protocols. The *World Journal of Gastroenterology* has already hosted several scientific papers and reviews on risk factors for, and genetic predisposition to, cancer syndromes involving the gastroenteropancreatic (GEP) tract[4-7], polyposis syndromes[8-11], and the clinical management of rare intestinal diseases[12] or peculiar cancer associations[13-16]. These papers highlight the increasing relevance of studies that are carried out to identify uncommon diseases and the importance of establishing tailored treatment for these patients. Recently, a review by Rubinstein *et al*[17] pointed out the strong clinical impact of cooperation between genetic counselors and gastroenterologists in terms of reducing disease burden and improving cost-effectiveness. Genetic counselors can assist clinicians in many ways, for example, during the diagnostic steps or when talking to the patients, as well as in evaluating the clinical usefulness of a test or scheduling surveillance measures. On the other hand, gastroenterologists can support genetic counselors in each phase of the diagnostic and clinical management. While the above cited reviews mainly focus on hereditary gastrointestinal cancer syndromes, our aim here is to summarize the phenotype and genetic basis of rare hereditary cancer syndromes presenting with gastrointestinal features, though not necessarily cancers, whose exact prevalence is currently unknown or underestimated. Thus, we chose not to include very well known colon cancer prone syndromes, *e.g.,* HNPCC, FAP or the hamartomatous syndromes, with the sole exception of SMAD4-related hereditary hemorrhagic telangiectasia (HHT). It is a lateral and complementary approach the complex picture of genetic syndromes with gastroenterological involvement. To this end, we chose the syndromes (Table 1) that could benefit from the intervention of a gastroenterologist in the diagnostic or surveillance procedures, depending on when the gastroenterological signs appear. A brief clinical description is presented for each syndrome, including diagnostic criteria based on updated guidelines, known or presumed genetic basis, associated neoplasias and gastroenterological features.

Methodology

This review was prepared using data obtained by inputting an appropriate choice of keywords in the Pubmed search-engine in an effort to uncover novelties regarding the genetic basis of the syndromes we included. Furthermore, we also searched the websites of scientific societies for epidemiological data and updated clinical guidelines. The syndromes were grouped into various subsets on the basis of the main clinical features they share and on their prevalence. Syndromes whose prevalence is unknown were placed at the end, even if the grouping criteria are not altogether accurate due to the overlapping of clinical signs (Table 2).

SYNDROMES WITH VASCULAR OR CYSTIC LESIONS

HHT

Brief clinical description: HHT, also known as Osler-Weber-Rendu disease, is characterized by the presence of multiple arteriovenous malformations (AVMs) presenting both as visceral or as mucocutaneous telangiectasias. Currently, six types of HHT have been described, including HHT associated with Juvenile polyposis (JP/HHT). The most common clinical manifestation of HHT is spontaneous and recurrent epistaxis, even at night-time, with an average age at onset of 12 years. Approximately 80% of patients have epistaxis by the age of 20. Visceral AVMs may be diagnosed in the lungs, brain, liver, spinal cord and in the gastroenteropancreatic tract[18-21]. The prevalence of HHT is estimated at 1/10000 people[21-23] but this rate could be underestimated due to the wide range of clinical severity and the fact that some symptoms are common among the general population or are present in other syndromes, *i.e.*, cerebral AVMs may be the result of a mutation in the *RASA1* gene (RAS p21 protein activator 1) correlated with Capillary Malformation-ArterioVenous Malformation syndrome[24].

Genetics: HHT isinherited in an autosomal dominant

Table 1 Main features of rare hereditary cancer syndromes with gastroenterological signs

Syndrome	Gene(s)/locus	Inheritance	Main associated neoplasias	Gastroenterological signs
BWS	11p15	Imprinting, UPD, other	Wilms tumor, rhabdomyosarcoma, neuroblastoma, adrenocortical carcinoma	Abdominal wall defects, visceromegaly, hepatoblastoma
Bloom	BLM/RECQL3 (15q26.1)	AR	Cancers common in general population, but presenting at an earlier ages	GERD, colon cancer
Carney complex	PRKAR1A (17q24.2) Others?	AD	Myxomas, breast ductal adenomas, LCCSCT	Colon polyps and cancer, pancreatic cancer
HHT	1-ENG (9q34.11) 2-ACVRL1 (12q13.13) 3-5q31.3-q32 4-7p14 5-GDF2 (10q11.22) JP/HHT-SMAD4 (18q21.2)	AD	Juvenile polyposis if correlated to SMAD4 mutations	GEP arteriovenous malformations
MEN1	MEN1 (11q13)	AD	Parathyroid adenomas, pituitary tumors, NET of the GEP tract	Carcinoids, Zollinger-Ellison syndrome
NBCCS	PTCH1 (9q22.3) SUFU (10q24-q25)	AD	Basal cell carcinomas	Lymphomesenteric cysts
VHL	VHL (3p25.3)	AD	Hemangioblastomas, CCRC, pheochromocytoma,	Pancreatic and hepatic cysts, PNETs

UPD: Uniparental parental disomy; AD: Autosomal dominant; AR: Autosomal recessive; BWS: Beckwith-Wiedemann syndrome; CCRCC: Clear cell renal cell carcinoma; GEP: Gastroenteropancreatic; GERD: Gastroesophageal reflux disease; HHT: Hereditary hemorrhagic telangiectasia; LCCSCT: Large cell calcifying Sertoli cell tumor; MEN1: Multiple endocrine neoplasia type 1; NBCCS: Nevoid basal cell carcinoma syndrome; NET: Neuroendocrine tumor; PNETs: Pancreatic neuroendocrine tumors; VHL: von Hippel-Lindau.

Table 2 Overlapping of gastroenterological signs among rare cancer syndromes

	Bloom	HHT	Carney complex	VHL	NBCCS	MEN1
Colon polyps/ cancer	×	×	×			
Cystic or vascular lesions		×		×	×	
GEP endocrine tumors				×		×

HHT: Hereditary hemorrhagic telangiectasia; VHL: Von Hippel-Lindau; NBCCS: Nevoid basal cell carcinoma syndrome; MEN1: Multiple endocrine neoplasia type 1; BWS: Beckwith-Wiedemann syndrome.

(AD) manner with high intrafamilial clinical variability. HHT1, 2, 5 and JP/HHT are caused by mutations in the genes involved in the Transforming growth factor beta/Bone morphogenetic *proteins* signalling pathway (TGF-β/BMP) (Table 1). Mutations in these genes account for nearly 90% of individuals with a clear diagnosis of HHT[25].

Associated neoplasias: Mutations in *SMAD4* are also associated with Juvenile polyposis[26,27].

Gastroenterological features: about 25% of patients manifest gastrointestinal bleeding (in most cases after the age of 50) caused by telangiectasia. Bleeding most frequently develops in the stomach and in the duodenum[28].

Hepatic AVMs have been reported in 41% and 74% of patients in two studies, respectively, the former using ultrasound and the latter using CT for diagnosis. Less than 10% of patients in the latter study were symptomatic. These lesions can lead to portal hypertension, biliary disease and focal nodular hyperplasia[29,30]. Pancreatic AVMs are common, but rarely a clinical issue[31].

Von Hippel-Lindau syndrome

Brief clinical description: von Hippel-Lindau syndrome (VHL) is a multiorgan disease with a pleiotropic presentation characterized by cysts and benign tumors with malignant potential. VHL prevalence is estimated at 1/50-100000 and annual birth incidence is estimated at 1/36000[32-34]. The average age at clinical diagnosis is 26 years, but the signs of VHL may occur throughout a subject's lifetime[35,36]. VHL may be diagnosed in the presence of two or more of the characteristic signs[37] listed in Table 3.

Genetics: VHL is an inherited condition with an AD pattern caused by mutations in the *VHL* gene which account for nearly 100% of cases. VHL syndrome is the result of a *de novo* mutation in about 20% of patients. The VHL gene encodes two ubiquitously expressed protein products that, together with several proteins, form a complex that marks transcription factors such as hypoxia-inducible factor 1a and 2a (HIF1a and HIF2a) for degradation. A deleterious mutation in the VHL gene leads to the constitutively active transcription of hypoxia-responsive genes. Other mechanisms underpinning the typical features of VHL are the overproduction of other hypoxia-induced proteins, such as EPO, VEGF, PDGF and glycolysis enzymes, and the interaction of VHL encoded proteins with microtubules and fibronectin and cyclin D1[38,39].

Table 3 Major/minor features for the diagnosis of rare cancer syndromes with gastroenterological signs

Syndrome	Major features	Minor features
BWS	Macrosomia	Polyhydramnios
	Macroglossia	Prematurity
	Hemihyperplasia	Hypoglycemia
	Ear-skin lobe creases or pits	Advanced bone age
	Visceromegaly	Heart problems
	Embryonal tumor (incl Wilms)	Diastasis recti
	Adrenocortical tumor	Hemangioma
	Kidney abnormalities	Facial nevus flammeus
	Cleft palate	Characteristic facial features
	Family history of BWS	Identical twins
Carney complex	Spotty skin pigmentation	Significant freckling
	Myxoma	Multiple Blue nevi
	Heart myxoma	Café-au-lait spots
	Breast myxomatosis	High IGF-1 levels, abnormal glucose tolerance test and/or paradoxical GH response to TRH testing, hyperprolactinemia
	Breast ductal adenomas	Cardiomyopathy
	PPNAD or abnormal result of Liddle's test	Pilonidal sinus
	Acromegaly	Family history of Cushing's syndrome, acromegaly or sudden death
	LCCST	Multiple skin tags or lipomas
	Thyroid cancer	Colon polyps (usually with acromegaly)
	Psammomatous melanotic schwannoma	Thyroid nodules
	Blue nevi	Family history of thyroid, colon, pancreas, and ovary cancers
	Osteochondromyxoma	
NBCCS (Gorlin syndrome)	Lamellar calcification of the falx	Lympho-mesenteric or pleural cysts
	Jaw keratocyst	Macrocephaly (OFC > 97th centile)
	Palmar/plantar pits (two or more)	Cleft lip/palate
	Multiple BCCs (> 5 in a lifetime) or a BCC before 30 yr	Vertebral/rib anomalies
	Childhood medulloblastoma	Preaxial/postaxial polydactyly
	Ameloblastoma[45]	Ovarian/cardiac fibromas
		Ocular anomalies
VHL	Hemangioblastomas or a single hemangioblastoma with a visceral manifestation	Endolymphatic sac tumors, papillary cystadenomas of the epididymis or broad ligament, pNETs
	Renal cell carcinoma	
	Adrenal or extra-adrenal pheochromocytomas	

BCC: Basal cell carcinoma; BWS: Beckwith-Wiedemann syndrome; LCCSCT: Large cell calcifying Sertoli cell tumor; NBCCS: Nevoid basal cell carcinoma syndrome; PNETS: Pancreatic neuroendocrine tumors; PPNAD: Primary pigmented nodular adrenocortical disease; VHL: von Hippel-Lindau.

Associated neoplasias: VHL patients have an increased risk of clear cell renal cell carcinoma, endolymphatic sac tumors, and epididymal cystadenomas.

Gastroenterological features: Pancreatic cysts occasionally causing biliary obstruction, pancreatic neuroendorine tumors (PNETs) with malignant potential[40,41] and hepatic cysts.

Nevoid basal cell carcinoma syndrome (Gorlin syndrome)

Brief clinical description: Nevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin syndrome, is characterized by a wide range of developmental abnormalities and the predisposition to various neoplasms. The estimated prevalence varies from 1/57000 to 1/256000[42]. A complete list of revised diagnostic criteria[43-46] for NBCCS is reported in Table 3. A diagnosis of NBCCS can be made in the presence of two major criteria or one major and two minor criteria.

Genetics: NBCCS is caused by mutations in the Patched homolog 1 gene (*PTCH1*) and transmitted in an AD manner with complete penetrance but variable expressivity. It encodes a transmembrane glycoprotein that acts as a membrane receptor whose ligand is the sonic hedgehog (SHH) protein, a regulation factor of the Hedgehog family involved in embryonal development events. *PTCH1* represses transcription of the genes of the SHH pathway[42] through the binding of SHH. Mutations in another negative regulator of the same pathway, *i.e.*, SUFU (Suppressor of fused), were described as being causative of NBCCS and especially associated with the risk of pediatric medulloblastoma[47,48]. Overall, if stringent clinical criteria are applied, mutations in *PTCH1* and *SUFU* account for 87% of cases[45].

Associated neoplasias: The peculiar neoplasms of NBCCS are basal cell carcinomas. Furthermore, 1%-2% of patients develop medulloblastoma, mainly in the first two years of life, and they are of the nodular/desmoplastic type. Ovarian fibromas, fetal rhabdomyoma and other brain tumors have been reported, but like basal cell carcinomas, their development may also be secondary to radiation therapy or may be the result of radiation hypersensitivity which is typical of NBCCS patients.

Gastroenterological features: Single or multiple chylous or lymphatic mesenteric cysts. Most are asymptomatic and are found incidentally, therefore the exact prevalence is unknown[49]. Mesenteric cysts may present as painless abdominal tumors or, on the contrary, may be a rare cause of painful abdominal pressure, sometimes associated with nausea and vomiting. Other symptoms may arise from abdominal organ compression or obstruction.

Table 4 Tumors of Multiple endocrine neoplasia type 1 syndrome

Endocrine	Non-endocrine
Parathyroid tumor	Facial angiofibromas
Pituitary tumors	Collagenomas
NET of the GEP tract	Lipomas
	Meningioma
	Ependymoma
	Leiomyomas
	Carcinoid tumors
	Adrenocortical tumors

NET: Neuroendocrine tumors; GEP: Gastroenteropancreatic.

SYNDROMES WITH GEP ENDOCRINE TUMORS

MEN1 syndrome

Brief clinical description: MEN1 syndrome is characterized by a triad of typical tumors that involve the parathyroid glands, the pituitary gland and the endocrine pancreas. Nevertheless, a wide range of conditions and clinical signs, not necessarily oncological or endocrine, have been associated with mutations in the *MEN1* gene. Postmortem studies report an incidence of 0.25%. The prevalence of the MEN1 syndrome is estimated at about 1/30000 people[50-52].

Genetics: The MEN1 syndrome is caused by mutations in the *MEN1* gene that encodes for tumor suppressor protein menin. About 80%-90% of patients with a family history of MEN1 have a mutation in *MEN1* gene *vs* 65% of sporadic cases[53].

Associated neoplasias: A list of MEN1-associated tumors is provided in Table 4.

Gastroenterological features: Neuroendocrine tumors (NET) and carcinoids of the GEP tract. In the MEN1 syndrome, PNETs occur in 40%-80% of patients by the age of 40 and are represented mostly by non-functioning tumors or gastrinomas[54]. Multiple insulinomas may also develop but they are benign in approximately 90% of MEN1 patients, while about 50% of gastrinomas and the majority of non functioning PNETs are malignant. Zollinger-Ellison syndrome is the main clinical presentation of the gastrinomas which are the main cause of morbidity and mortality in MEN1 patients[55-57].

Based on the largest Swedish studies, 67.5% of all carcinoids are located in the gastrointestinal tract and represent about 40% of all small bowel primary tumors[58,59]. The prevalence in the general population of all carcinoids is 2/100000 but the incidence of all types of neuroendocrine tumors is rising[60-62]. Carcinoids occur within the context of the MEN1 syndrome in about 10% of patients. A higher risk of developing carcinoids has also been described in Neurofibromatosis and Tuberous sclerosis (mainly gastric), and in von Hippel-Lindau (typically pancreatic). MEN1-associated carcinoids are mainly located in the foregut rather than in the midgut, the site which is most commonly associated with a metastatic spread. Carcinoids are more frequently diagnosed after the appearance of the so-called carcinoid syndrome due to the production of vasoactive substances such as serotonin, or in the phase of metastatic spread[63,64].

SYNDROMES WITH COLON POLYPS/ CANCER

Bloom's syndrome

Brief clinical description: Bloom's syndrome[65,66] is characterized by: (1) a severe growth deficiency starting in the prenatal period even though the proportions of the body are normal with the possible exception of a slightly small cranium; (2) the sparseness of subcutaneous fat tissue; (3) erythematous and sun-sensitive skin lesions on sun-exposed areas, typically with a butterfly-shape on the face, commonly associated with fissuration of the lower lip; (4) azoospermia in males, while females may be fertile despite unusually early menopause; (5) facial features such as a long and narrow face, a small lower jaw, a large nose and prominent ears. A high-pitched voice is often present; (6) diabetes mellitus; and (7) immunodeficiency correlated with a lower concentration of plasma immunoglobulins.

The Bloom's Syndrome Registry (http://weill.cornell.edu/bsr/) reports less than 300 patients worldwide of whom about 30% are of Ashknenazi ancestry.

Genetics: Bloom's syndrome is inherited in an autosomal recessive (AR) manner and is caused by mutations in the *BLM* gene. The *BLM* gene encodes a member of the RecQ helicase family that cooperates with other proteins in the maintenance of the structure and integrity of DNA. Mutations in the *BLM* gene account for nearly 90% of cases and for 100% of patients with the typical blm^{Ash} deletion[67]. Chromosome instability and increased cell death lead to growth impairment and to higher cancer risk.

Associated neoplasias: These patients develop the same tumors that are among the most commonly observed in the general population. However, they occur at an earlier age and often relapse over time.

Gastroenterological features: Gastroesophageal reflux is commonly present, and due to the aspiration of gastric contents it causes respiratory tract and middle ear infections. Colon cancer is one of the most common tumors in these patients[68].

Carney complex

Brief clinical description: Carney complex was

formerly known as the NAME syndrome (Nevi, Atrial myxoma, Myxoid neurofibromas, Ephelides) or LAMB syndrome (Lentigines, Atrial Myxoma, Blue nevi). The major and minor features of Carney Complex are listed in Table 3. At least two of the major features are required for a diagnosis of Carney Complex[69].

Genetics: 60%-75% of Carney complex cases are familial and follow an AD inheritance pattern, while the remaining present as sporadic and are likely due to a *de novo* mutation. More than 60% of patients have a mutation and up to 22% show deletions in the *PRKAR1A* (protein kinase, cAMP-dependent, regulatory, type Ⅰ, alpha) gene[70,71]. Recently, other genes have been implicated in the Carney Complex, but further studies are needed to confirm their association with the syndrome[72,73].

Associated neoplasias: Only about 700 cases of Carney complex have been reported worldwide, therefore no genotype-phenotype correlation or specific risks for cancer are known. The list of reported tumors include adrenocortical carcinoma, pituitary tumors, thyroid tumors and Sertoli-Leydig cell tumors.

Gastroenterological features: Colon polyps. Colorectal, liver and pancreatic cancers have been reported[74,75].

SYNDROMES WITH CHILDHOOD ONSET TUMORS AND GASTROINTESTINAL ANATOMICAL DEFECTS

Beckwith-Wiedemann syndrome

Brief clinical description: the main features of this overgrowth syndrome are macrosomia associated with abnormal weight gain during childhood, macroglossia and abdominal wall defects, *e.g.,* omphalocele, umbilical hernia, which are often present at birth. Other features are visceromegaly, kidney abnormalities, hypoglycemia, ear-skin lobe creases or pits, hemihyperplasia and an increased risk of childhood tumors. At least one major feature and two minor features are required for a diagnosis of Beckwith-Wiedemann Syndrome (BWS) (Table 3). The prevalence of BWS, which is likely underestimated, is about 1/10000-1/15000 live births[76-78].

Genetics: About 85% of BWS cases are sporadic, but 10%-15% follow an autosomal dominant (AD) inheritance pattern. There are several genetic mechanisms that underlie BWS such as alterations involving the 11p15.5 locus, *e.g.,* alterations of the imprinting control regions (ICRs) involved in the methylation of the genes that undergo genomic imprinting and that are responsible for normal growth, such as *CDKN1C* (Cyclin-dependent kinase inhibitor 1C), *H19/ASM* (Adult skeletal muscle) or *IGF2* (Insulin-like growth factor type 2). Ten-20% of BWS cases are caused by mosaic paternal uniparental disomy (UPD), therefore in some cells the patients present two alleles of paternally expressed imprinted genes but are missing the genes that are expressed on the maternal chromosome alone. BWS is rarely caused by mutations in *CDKN1C* or structural alterations over chromosome 11[79].

Associated neoplasias: Wilms tumor and adrenocortical carcinoma are reported in about 40% and 20% of cases, respectively. Other associated tumors include rhabdomyosarcoma and neuroblastoma. Typical BWS-associated cancers develop in about 8% of patients, mostly during the first decade of life, after which the risk of cancer decreases until almost reaching that of the general population. Cancer risk is highest in children with visceromegaly, and especially in those with nephromegaly[80,81].

Gastroenterological features: Abdominal wall defects, visceromegaly, hepatoblastoma, diastasis recti.

CONCLUSION

Recent research has uncovered the genes that are responsible for many hereditary cancer syndromes, and genetic testing is currently available for diagnostics and for identifying asymptomatic family members. These conditions include rare syndromes with gastroenterological signs, though not necessarily tumors (Table 1), which are frequently underdiagnosed. The purpose of this editorial was to review the peculiar gastroenterological signs whose role in helping identify these rare hereditary cancer syndromes is often neglected. Gastroenterologists, who already manage protocols for cancer-prone family members, should be aware of the progress that has been made in the diagnosis and genetics of these hereditary cancer syndromes in order to work in a multidisciplinary framework with geneticists and oncologists.

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