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

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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. The genes that are responsible for hereditary cancer syndromes were first identified in the 1990's. 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, polyposis syndromes, and the clinical management of rare intestinal diseases or peculiar cancer associations. These papers highlighted 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. 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. The prevalence of HHT is estimated at 1/10000 people 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.

Genetics: HHT is inherited 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, adenocortical 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| PRKARIA (17q24.2) Others?      | AD          | Mxomas, breast ductal adenomas, LCCSCT | Colon polyps and cancer, pancreatic cancer |
| HHT           | 1-ENG (9q34.11) 2-ACVR1L (12q13.13) 3-xpi3.3-q32 4-7p14 5-GDF2 (10q11.22) JP/HHT-SMAD4 (18q21.2) 3-5q31.3-q32 | AD | Juvenile polyposis if correlated to SMAD4 mutations | GEP arteriovenous malformations |
| MEN1          | MEN1 (11q13)                   | AD          | Parathyroid adenomas, pituitary tumors, NET of the GEP tract Basal cell carcinomas | Carcinoids, Zollinger-Ellison syndrome |
| NBCCS         | PTCH1 (9q22.3)  SUPU (10q24-q25) | AD          | Colon polyps and cancer                                      | Lymphomatosenteric cysts          |
| VHL           | VHL (3p25.3)                   | AD          | Hemangioblastomas, CRC, pheochromocytoma, Pancreatic and hepatic cysts, PNETs |                              |

UPD: Uniparental parental disomy; AD: Autosomal dominant; AR: Autosomal recessive; BWS: Beckwith-Wiedemann syndrome; CCRC: Clear cell renal cell carcinoma; CCRC: Clear cell renal cell carcinoma; CCRCC: Clear cell renal cell carcinoma; CCRCC: Clear cell renal cell carcinoma; GERD: Gastroesophageal reflux disease; HHT: Hereditary hemorrhagic telangiectasia; LCCSCT: Large cell calcifying Sertoli cell tumor; MEN1: Multiple endocrine neoplasia type 1; NBCCS: Nevus 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

| Syndrome      | Bloom | HHT  | Carney complex | VHL  | NBCCS | MEN1 |
|---------------|-------|------|----------------|------|-------|------|
| Colon polyph/ cancer | x     | x    | x              | x    | x     |      |
| Cystic or vascular lesions | x     |      |                |      |       |      |
| GEP endocrine tumors | x     |      |                | x    |       |      |

HHT: Hereditary hemorrhagic telangiectasia; VHL: Von Hippel-Lindau; NBCCS: Nevus 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 oases or pits                         | Advanced bone age                           |
|                               | Visceronomegaly                                     | Heart problems                              |
|                               | Embryonal tumor (incl Wilms)                        | Diastasis recti                             |
|                               | Adrenocortical tumor                                | Hemangiomia                                  |
|                               | Kidney abnormalities                                | Facial nevis flameus                        |
|                               | Cleft palate                                         | Characteristic facial features              |
| Carney complex                 | Family history of BWS                               | Identities                                  |
|                               | Cafe-au-lait spots                                   |                                           |
|                               | Heart myxoma                                         |                                           |
|                               | Breast myxomatosis                                   | High IGF-1 levels, abnormal glucose tolerance test and/or paradoxical GH response to TRH testing, hyperprolactinemia |
|                               | Breast ductal adenomas                               | Cardiomypathy                               |
|                               | 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 |
| NBCCS (Gorlin syndrome)        | Osteochondromyxoma                                  | Lympho-mesenteric or pleural cysts          |
|                               | Lamellar calcification of the falx                   | Macrolephaly (OFC > 97th centile)           |
|                               | Jaw keratocyst                                      | Cleft lip/palate                            |
|                               | Palmar/plantar pits (two or more)                   | Vertebral/rib anomalies                     |
|                               | Multiple BCCs (> 5 in a lifetime) or a BCC before 30 yr |                                           |
|                               | Childhood medulloblastoma                            | Preaxial/postaxial polycystic               |
|                               | Ameloblastoma(46)                                    | Ovarian/cardiac fibromas                   |
|                               | Hemangioblastomas or a single hemangioblastoma with a visceral manifestation | Endolympathic 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; LCCST: 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, endolympathic sac tumors, and epididymal cystadenomas.

**Gastroenterological features:** Pancreatic cysts occasionally causing biliary obstruction, pancreatic neuroendocrine 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(45). 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(43) 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.
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 at an earlier age and often relapse over time. Carcinoids of gastric contents it causes respiratory tract 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 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\[63,64\].
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\(^{[72,73]}\). 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, macrosomia 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\(^{[69-78]}\).

**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), \(H19/AS/M\) (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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