**Name of journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO: 17291**

**Manuscript Type: EDITORIAL**

**Signs and genetics of rare cancer syndromes with gastroenterological features**

BrunoW *et al.* Rare cancer syndromes with gastroenterological features

William Bruno, Giuseppe Fornarini, Paola Ghiorzo

**William Bruno, Paola Ghiorzo,**Genetics of Rare Cancers, Department of Internal Medicine and Medical Specialties, University of Genoa and IRCCS AOU San Martino-IST, 16132 Genoa, Italy

**Giuseppe Fornarini,** Medical Oncology Unit, IRCCS AOU San Martino-IST, 16132 Genoa, Italy

**Author contributions:** BrunoW designed and wrote the manuscript, Fornarini G reviewed the associated cancer risk and Ghiorzo P conceptualized, designed and reviewed the manuscript; all authors reviewed the manuscript critically for intellectual content and approved the final version.

**Supported by** grants from the Italian Ministry of Health, 5 per 1000, AIRC 15460 and Genoa Atheneum 2014 (to Ghiorzo P).

**Conflict-of-interest statement:** The authors decalre no conflict of interest.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to:** **William Bruno, MD, PhD,** Genetics of Rare Cancers, Department of Internal Medicine, University of Genoa, IRCCS AOU San Martino-IST, V.le Benedetto XV 6, 16132 Genoa, Italy. [william.bruno@unige.it](mailto:william.bruno@unige.it)

**Telephone:** +39-1-3537913

**Fax:**+39-1-3538887

**Received:** February 27, 2015

**Peer-review started:** February 28, 2015

**First decision:** April 27, 2015

**Revised:** May 26, 2015

**Accepted:** July 15, 2015

**Article in press:**

**Published online:**

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

**© The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

**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.

Bruno W, Fornarini G, Ghiorzo P.Signs and genetics of rare cancer syndromes with gastroenterological features. *World J Gastroenterol* 2015; In press

**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 ([AD](http://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/autosomal-dominant/)) manner with high [intrafamilial clinical variability](http://www.ncbi.nlm.nih.gov/books/n/gene/glossary/def-item/intrafamilial-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].

**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.

**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 1/30,000 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 versus 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 world-wide 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 *blmAsh* 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](http://www.cancer.net/node/31341), [pituitary tumors](http://www.cancer.net/node/31384), [thyroid](http://www.cancer.net/node/31262) tumors and Sertoli-Leydig cell tumors.

**Gastroenterological features:**Colon polyps. [Colorectal](http://www.cancer.net/node/31317), [liver](http://www.cancer.net/node/31274) and [pancreatic cancers](http://www.cancer.net/node/31388) 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-associatedcancers 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.

**REFERENCES**

|  |
| --- |
| 1 **Keat N**, Law K, McConnell A, Seymour M, Welch J, Trimble T, Lacombe D, Negrouk A. International Rare Cancers Initiative (IRCI). *Ecancermedicalscience* 2013; **7**: ed20 [PMID: 24883089 DOI: 10.3332/ecancer.2013.ed20]  2 **Lynch HT**, Fusaro RM, Lynch JF. Hereditary cancer syndrome diagnosis: molecular genetic clues and cancer control. *Future Oncol* 2007; **3**: 169-181 [PMID: 17381417 DOI: 10.2217/14796694.3.2.169]  3 **Lynch HT**, Drescher K, Knezetic J, Lanspa S. Genetics, biomarkers, hereditary cancer syndrome diagnosis, heterogeneity and treatment: a review. *Curr Treat Options Oncol* 2014; **15**: 429-442 [PMID: 24827900 DOI: 10.1007/s11864-014-0293-5]  4 **Zavoral M**, Minarikova P, Zavada F, Salek C, Minarik M. Molecular biology of pancreatic cancer. *World J Gastroenterol* 2011; **17**: 2897-2908 [PMID: 21734801 DOI: 10.3748/wjg.v17.i24.2897]  5 **Yamamoto H**, Adachi Y, Taniguchi H, Kunimoto H, Nosho K, Suzuki H, Shinomura Y. Interrelationship between microsatellite instability and microRNA in gastrointestinal cancer. *World J Gastroenterol* 2012; **18**: 2745-2755 [PMID: 22719182 DOI: 10.3748/wjg.v18.i22.2745]  6 **Ghiorzo P**. Genetic predisposition to pancreatic cancer. *World J Gastroenterol* 2014; **20**: 10778-10789 [PMID: 25152581 DOI: 10.3748/wjg.v20.i31.10778]  7 **Becker AE**, Hernandez YG, Frucht H, Lucas AL. Pancreatic ductal adenocarcinoma: risk factors, screening, and early detection. *World J Gastroenterol* 2014; **20**: 11182-11198 [PMID: 25170203 DOI: 10.3748/wjg.v20.i32.11182]  8 **Jass JR**. Hereditary Non-Polyposis Colorectal Cancer: the rise and fall of a confusing term. *World J Gastroenterol* 2006; **12**: 4943-4950 [PMID: 16937488]  9 **Gu GL**, Wang SL, Wei XM, Bai L. Diagnosis and treatment of Gardner syndrome with gastric polyposis: a case report and review of the literature. *World J Gastroenterol* 2008; **14**: 2121-2123 [PMID: 18395919]  10 **Kopacova M**, Tacheci I, Rejchrt S, Bures J. Peutz-Jeghers syndrome: diagnostic and therapeutic approach. *World J Gastroenterol* 2009; **15**: 5397-5408 [PMID: 19916169]  11 **Koehler-Santos P**, Izetti P, Abud J, Pitroski CE, Cossio SL, Camey SA, Tarta C, Damin DC, Contu PC, Rosito MA, Ashton-Prolla P, Prolla JC. Identification of patients at-risk for Lynch syndrome in a hospital-based colorectal surgery clinic. *World J Gastroenterol* 2011; **17**: 766-773 [PMID: 21390147 DOI: 10.3748/wjg.v17.i6.766]  12 **Gay G**, Delvaux M, Frederic M. Capsule endoscopy in non-steroidal anti-inflammatory drugs-enteropathy and miscellaneous, rare intestinal diseases. *World J Gastroenterol* 2008; **14**: 5237-5244 [PMID: 18785273]  13 **Kramer K**, Hasel C, Aschoff AJ, Henne-Bruns D, Wuerl P. Multiple gastrointestinal stromal tumors and bilateral pheochromocytoma in neurofibromatosis. *World J Gastroenterol* 2007; **13**: 3384-3387 [PMID: 17659681]  14 **Tonelli F**, Giudici F, Nesi G, Batignani G, Brandi ML. Biliary tree gastrinomas in multiple endocrine neoplasia type 1 syndrome. *World J Gastroenterol* 2013; **19**: 8312-8320 [PMID: 24363522 DOI: 10.3748/wjg.v19.i45.8312]  15 **Lu YY**, Zhu F, Jing DD, Wu XN, Lu LG, Zhou GQ, Wang XP. Multiple endocrine neoplasia type 1 with upper gastrointestinal hemorrhage and perforation: a case report and review. *World J Gastroenterol* 2013; **19**: 1322-1326 [PMID: 23482249 DOI: 10.3748/wjg.v19.i8.1322]  16 **Valle L**. Genetic predisposition to colorectal cancer: where we stand and future perspectives. *World J Gastroenterol* 2014; **20**: 9828-9849 [PMID: 25110415 DOI: 10.3748/wjg.v20.i29.9828]  17 **Rubinstein WS**, Weissman SM. Managing hereditary gastrointestinal cancer syndromes: the partnership between genetic counselors and gastroenterologists. *Nat Clin Pract Gastroenterol Hepatol* 2008; **5**: 569-582 [PMID: 18797444 DOI: 10.1038/ncpgasthep1235]  18 **Berg J**, Porteous M, Reinhardt D, Gallione C, Holloway S, Umasunthar T, Lux A, McKinnon W, Marchuk D, Guttmacher A. Hereditary haemorrhagic telangiectasia: a questionnaire based study to delineate the different phenotypes caused by endoglin and ALK1 mutations. *J Med Genet* 2003; **40**: 585-590 [PMID: 12920067]  19 **Shovlin CL**, Guttmacher AE, Buscarini E, Faughnan ME, Hyland RH, Westermann CJ, Kjeldsen AD, Plauchu H. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). *Am J Med Genet* 2000; **91**: 66-67 [PMID: 10751092]  20 **Bayrak-Toydemir P**, Mao R, Lewin S, McDonald J. Hereditary hemorrhagic telangiectasia: an overview of diagnosis and management in the molecular era for clinicians. *Genet Med* 2004; **6**: 175-191 [PMID: 15266205 DOI: 10.109701.GIM.0000132689.25644.7C]  21 **Marchuk DA**, Guttmacher AE, Penner JA, Ganguly P. Report on the workshop on Hereditary Hemorrhagic Telangiectasia, July 10-11, 1997. *Am J Med Genet* 1998; **76**: 269-273 [PMID: 9508248]  22 **Kjeldsen AD**, Vase P, Green A. [Hereditary hemorrhagic telangiectasia. A population-based study on prevalence and mortality among Danish HHT patients]. *Ugeskr Laeger* 2000; **162**: 3597-3601 [PMID: 11016284]  23 **Donaldson JW**, McKeever TM, Hall IP, Hubbard RB, Fogarty AW. The UK prevalence of hereditary haemorrhagic telangiectasia and its association with sex, socioeconomic status and region of residence: a population-based study. *Thorax* 2014; **69**: 161-167 [PMID: 24188926 DOI: 10.1136/thoraxjnl-2013-203720]  24 **Revencu N**, Boon LM, Mendola A, Cordisco MR, Dubois J, Clapuyt P, Hammer F, Amor DJ, Irvine AD, Baselga E, Dompmartin A, Syed S, Martin-Santiago A, Ades L, Collins F, Smith J, Sandaradura S, Barrio VR, Burrows PE, Blei F, Cozzolino M, Brunetti-Pierri N, Vicente A, Abramowicz M, Désir J, Vilain C, Chung WK, Wilson A, Gardiner CA, Dwight Y, Lord DJ, Fishman L, Cytrynbaum C, Chamlin S, Ghali F, Gilaberte Y, Joss S, Boente Mdel C, Léauté-Labrèze C, Delrue MA, Bayliss S, Martorell L, González-Enseñat MA, Mazereeuw-Hautier J, O'Donnell B, Bessis D, Pyeritz RE, Salhi A, Tan OT, Wargon O, Mulliken JB, Vikkula M. RASA1 mutations and associated phenotypes in 68 families with capillary malformation-arteriovenous malformation. *Hum Mutat* 2013; **34**: 1632-1641 [PMID: 24038909 DOI: 10.1002/humu.22431]  25 **McDonald J**, Wooderchak-Donahue W, VanSant Webb C, Whitehead K, Stevenson DA, Bayrak-Toydemir P. Hereditary hemorrhagic telangiectasia: genetics and molecular diagnostics in a new era. *Front Genet* 2015; **6**: 1 [PMID: 25674101 DOI: 10.3389/fgene.2015.00001]  26 **Brosens LA**, Langeveld D, van Hattem WA, Giardiello FM, Offerhaus GJ. Juvenile polyposis syndrome. *World J Gastroenterol* 2011; **17**: 4839-4844 [PMID: 22171123 DOI: 10.3748/wjg.v17.i44.4839]  27 **Gallione C**, Aylsworth AS, Beis J, Berk T, Bernhardt B, Clark RD, Clericuzio C, Danesino C, Drautz J, Fahl J, Fan Z, Faughnan ME, Ganguly A, Garvie J, Henderson K, Kini U, Leedom T, Ludman M, Lux A, Maisenbacher M, Mazzucco S, Olivieri C, Ploos van Amstel JK, Prigoda-Lee N, Pyeritz RE, Reardon W, Vandezande K, Waldman JD, White RI, Williams CA, Marchuk DA. Overlapping spectra of SMAD4 mutations in juvenile polyposis (JP) and JP-HHT syndrome. *Am J Med Genet A* 2010; **152A**: 333-339 [PMID: 20101697 DOI: 10.1002/ajmg.a.33206]  28 **Proctor DD**, Henderson KJ, Dziura JD, Longacre AV, White RI. Enteroscopic evaluation of the gastrointestinal tract in symptomatic patients with hereditary hemorrhagic telangiectasia. *J Clin Gastroenterol* 2005; **39**: 115-119 [PMID: 15681905]  29 **Ianora AA**, Memeo M, Sabba C, Cirulli A, Rotondo A, Angelelli G. Hereditary hemorrhagic telangiectasia: multi-detector row helical CT assessment of hepatic involvement. *Radiology* 2004; **230**: 250-259 [PMID: 14645886 DOI: 10.1148/radiol.2301021745]  30 **Buscarini E**, Danesino C, Olivieri C, Lupinacci G, De Grazia F, Reduzzi L, Blotta P, Gazzaniga P, Pagella F, Grosso M, Pongiglione G, Buscarini L, Plauchu H, Zambelli A. Doppler ultrasonographic grading of hepatic vascular malformations in hereditary hemorrhagic telangiectasia -- results of extensive screening. *Ultraschall Med* 2004; **25**: 348-355 [PMID: 15368138 DOI: 10.1055/s-2004-813549]  31 **Lacout A**, Pelage JP, Lesur G, Chinet T, Beauchet A, Roume J, Lacombe P. Pancreatic involvement in hereditary hemorrhagic telangiectasia: assessment with multidetector helical CT. *Radiology* 2010; **254**: 479-484 [PMID: 20093519 DOI: 10.1148/radiol.09090096]  32 **Schmid S**, Gillessen S, Binet I, Brändle M, Engeler D, Greiner J, Hader C, Heinimann K, Kloos P, Krek W, Krull I, Stoeckli SJ, Sulz MC, van Leyen K, Weber J, Rothermundt C, Hundsberger T. Management of von hippel-lindau disease: an interdisciplinary review. *Oncol Res Treat* 2014; **37**: 761-771 [PMID: 25531723 DOI: 10.1159/000369362]  33 **Maher ER**, Iselius L, Yates JR, Littler M, Benjamin C, Harris R, Sampson J, Williams A, Ferguson-Smith MA, Morton N. Von Hippel-Lindau disease: a genetic study. *J Med Genet* 1991; **28**: 443-447 [PMID: 1895313]  34 **Neumann HP**, Wiestler OD. Clustering of features of von Hippel-Lindau syndrome: evidence for a complex genetic locus. *Lancet* 1991; **337**: 1052-1054 [PMID: 1673491]  35 **Maher ER**, Yates JR, Harries R, Benjamin C, Harris R, Moore AT, Ferguson-Smith MA. Clinical features and natural history of von Hippel-Lindau disease. *Q J Med* 1990; **77**: 1151-1163 [PMID: 2274658]  36 **Lonser RR**, Glenn GM, Walther M, Chew EY, Libutti SK, Linehan WM, Oldfield EH. von Hippel-Lindau disease. *Lancet* 2003; **361**: 2059-2067 [PMID: 12814730 DOI: 10.1016/S0140-6736(03)13643-4]  37 **Maher ER**, Neumann HP, Richard S. von Hippel-Lindau disease: a clinical and scientific review. *Eur J Hum Genet* 2011; **19**: 617-623 [PMID: 21386872 DOI: 10.1038/ejhg.2010.175]  38 **Maher ER**, Kaelin WG. von Hippel-Lindau disease. *Medicine (Baltimore)* 1997; **76**: 381-391 [PMID: 9413424]  39 **Gossage L**, Eisen T, Maher ER. VHL, the story of a tumour suppressor gene. *Nat Rev Cancer* 2015; **15**: 55-64 [PMID: 25533676 DOI: 10.1038/nrc3844]  40 **Marcos HB**, Libutti SK, Alexander HR, Lubensky IA, Bartlett DL, Walther MM, Linehan WM, Glenn GM, Choyke PL. Neuroendocrine tumors of the pancreas in von Hippel-Lindau disease: spectrum of appearances at CT and MR imaging with histopathologic comparison. *Radiology* 2002; **225**: 751-758 [PMID: 12461257 DOI: 10.1148/radiol.2253011297]  41 **Corcos O**, Couvelard A, Giraud S, Vullierme MP, Dermot O'Toole V, Stievenart JL, Penfornis A, Niccoli-Sire P, Baudin E, Sauvanet A, Levy P, Ruszniewski P, Richard S, Hammel P. Endocrine pancreatic tumors in von Hippel-Lindau disease: clinical, histological, and genetic features. *Pancreas* 2008; **37**: 85-93 [PMID: 18580449 DOI: 10.1097/MPA.0b013e31815f394a]  42 **Lo Muzio L**. Nevoid basal cell carcinoma syndrome (Gorlin syndrome). *Orphanet J Rare Dis* 2008; **3**: 32 [PMID: 19032739 DOI: 10.1186/1750-1172-3-32]  43 **Kimonis VE**, Goldstein AM, Pastakia B, Yang ML, Kase R, DiGiovanna JJ, Bale AE, Bale SJ. Clinical manifestations in 105 persons with nevoid basal cell carcinoma syndrome. *Am J Med Genet* 1997; **69**: 299-308 [PMID: 9096761]  44 **Bree AF**, Shah MR. Consensus statement from the first international colloquium on basal cell nevus syndrome (BCNS). *Am J Med Genet A* 2011; **155A**: 2091-2097 [PMID: 21834049 DOI: 10.1002/ajmg.a.34128]  45 **Ponti G**, Pastorino L, Pollio A, Nasti S, Pellacani G, Mignogna MD, Tomasi A, Del Forno C, Longo C, Bianchi-Scarrà G, Ficarra G, Seidenari S. Ameloblastoma: a neglected criterion for nevoid basal cell carcinoma (Gorlin) syndrome. *Fam Cancer* 2012; **11**: 411-418 [PMID: 22565648 DOI: 10.1007/s10689-012-9529-3]  46 **Lo Muzio L**, Pastorino L, Levanat S, Musani V, Situm M, Ponti G, Bianchi Scarra G. Clinical utility gene card for: Gorlin syndrome--update 2013. *Eur J Hum Genet* 2013; **21**: [PMID: 23361221 DOI: 10.1038/ejhg.2012.299]  47 **Pastorino L**, Ghiorzo P, Nasti S, Battistuzzi L, Cusano R, Marzocchi C, Garrè ML, Clementi M, Scarrà GB. Identification of a SUFU germline mutation in a family with Gorlin syndrome. *Am J Med Genet A* 2009; **149A**: 1539-1543 [PMID: 19533801 DOI: 10.1002/ajmg.a.32944]  48 **Smith MJ**, Beetz C, Williams SG, Bhaskar SS, O'Sullivan J, Anderson B, Daly SB, Urquhart JE, Bholah Z, Oudit D, Cheesman E, Kelsey A, McCabe MG, Newman WG, Evans DG. Germline mutations in SUFU cause Gorlin syndrome-associated childhood medulloblastoma and redefine the risk associated with PTCH1 mutations. *J Clin Oncol* 2014; **32**: 4155-4161 [PMID: 25403219 DOI: 10.1200/JCO.2014.58.2569]  49 **Gorlin RJ**. Nevoid basal cell carcinoma (Gorlin) syndrome. *Genet Med* 2004; **6**: 530-539 [PMID: 15545751 DOI: 10.109701.GIM.0000144188.15902.C4]  50 **Thakker RV**, Newey PJ, Walls GV, Bilezikian J, Dralle H, Ebeling PR, Melmed S, Sakurai A, Tonelli F, Brandi ML. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). *J Clin Endocrinol Metab* 2012; **97**: 2990-3011 [PMID: 22723327 DOI: 10.1210/jc.2012-1230]  51 **Marini F**, Falchetti A, Del Monte F, Carbonell Sala S, Gozzini A, Luzi E, Brandi ML. Multiple endocrine neoplasia type 1. *Orphanet J Rare Dis* 2006; **1**: 38 [PMID: 17014705 DOI: 10.1186/1750-1172-1-38]  52 **Falchetti A**, Marini F, Luzi E, Tonelli F, Brandi ML. Multiple endocrine neoplasms. *Best Pract Res Clin Rheumatol* 2008; **22**: 149-163 [PMID: 18328987 DOI: 10.1016/j.berh.2007.11.010]  53 **Newey PJ**, Thakker RV. Role of multiple endocrine neoplasia type 1 mutational analysis in clinical practice. *Endocr Pract* 2011; **17 Suppl 3**: 8-17 [PMID: 21454234 DOI: 10.4158/EP10379.RA]  54 **Anlauf M**, Garbrecht N, Henopp T, Schmitt A, Schlenger R, Raffel A, Krausch M, Gimm O, Eisenberger CF, Knoefel WT, Dralle H, Komminoth P, Heitz PU, Perren A, Klöppel G. Sporadic versus hereditary gastrinomas of the duodenum and pancreas: distinct clinico-pathological and epidemiological features. *World J Gastroenterol* 2006; **12**: 5440-5446 [PMID: 17006979]  55 **Krampitz GW**, Norton JA. Current management of the Zollinger-Ellison syndrome. *Adv Surg* 2013; **47**: 59-79 [PMID: 24298844]  56 **Ito T**, Igarashi H, Jensen RT. Zollinger-Ellison syndrome: recent advances and controversies. *Curr Opin Gastroenterol* 2013; **29**: 650-661 [PMID: 24100728 DOI: 10.1097/MOG.0b013e328365efb1]  57 **Epelboym I**, Mazeh H. Zollinger-Ellison syndrome: classical considerations and current controversies. *Oncologist* 2014; **19**: 44-50 [PMID: 24319020 DOI: 10.1634/theoncologist.2013-0369]  58 **Hemminki K**, Li X. Familial carcinoid tumors and subsequent cancers: a nation-wide epidemiologic study from Sweden. *Int J Cancer* 2001; **94**: 444-448 [PMID: 11745428]  59 **Hiripi E**, Bermejo JL, Sundquist J, Hemminki K. Familial gastrointestinal carcinoid tumours and associated cancers. *Ann Oncol* 2009; **20**: 950-954 [PMID: 19150948 DOI: 10.1093/annonc/mdn706]  60 **Crocetti E**, Paci E. Malignant carcinoids in the USA, SEER 1992-1999. An epidemiological study with 6830 cases. *Eur J Cancer Prev* 2003; **12**: 191-194 [PMID: 12771556 DOI: 10.1097/01.cej.0000072851.07402.96]  61 **Maggard MA**, O'Connell JB, Ko CY. Updated population-based review of carcinoid tumors. *Ann Surg* 2004; **240**: 117-122 [PMID: 15213627]  62 **Hallet J**, Law CH, Cukier M, Saskin R, Liu N, Singh S. Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. *Cancer* 2015; **121**: 589-597 [PMID: 25312765 DOI: 10.1002/cncr.29099]  63 **Sweeney JF**, Rosemurgy AS. Carcinoid Tumors of the Gut. *Cancer Control* 1997; **4**: 18-24 [PMID: 10762999]  64 **Dierdorf SF**. Carcinoid tumor and carcinoid syndrome. *Curr Opin Anaesthesiol* 2003; **16**: 343-347 [PMID: 17021482]  65 **German J**. Bloom's syndrome. *Dermatol Clin* 1995; **13**: 7-18 [PMID: 7712653]  66 **Arora H**, Chacon AH, Choudhary S, McLeod MP, Meshkov L, Nouri K, Izakovic J. Bloom syndrome. *Int J Dermatol* 2014; **53**: 798-802 [PMID: 24602044 DOI: 10.1111/ijd.12408]  67 **Ellis NA**, Ciocci S, Proytcheva M, Lennon D, Groden J, German J. The Ashkenazic Jewish Bloom syndrome mutation blmAsh is present in non-Jewish Americans of Spanish ancestry. *Am J Hum Genet* 1998; **63**: 1685-1693 [PMID: 9837821 DOI: 10.1086/302167]  68 **Baris HN**, Kedar I, Halpern GJ, Shohat T, Magal N, Ludman MD, Shohat M. Prevalence of breast and colorectal cancer in Ashkenazi Jewish carriers of Fanconi anemia and Bloom syndrome. *Isr Med Assoc J* 2007; **9**: 847-850 [PMID: 18210922]  69 **Mateus C**, Palangié A, Franck N, Groussin L, Bertagna X, Avril MF, Bertherat J, Dupin N. Heterogeneity of skin manifestations in patients with Carney complex. *J Am Acad Dermatol* 2008; **59**: 801-810 [PMID: 18804312 DOI: 10.1016/j.jaad.2008.07.032]  70 **Courcoutsakis NA**, Tatsi C, Patronas NJ, Lee CC, Prassopoulos PK, Stratakis CA. The complex of myxomas, spotty skin pigmentation and endocrine overactivity (Carney complex): imaging findings with clinical and pathological correlation. *Insights Imaging* 2013; **4**: 119-133 [PMID: 23315333 DOI: 10.1007/s13244-012-0208-6]  71 **Salpea P**, Horvath A, London E, Faucz FR, Vetro A, Levy I, Gourgari E, Dauber A, Holm IA, Morrison PJ, Keil MF, Lyssikatos C, Smith ED, Sanidad MA, Kelly JC, Dai Z, Mowrey P, Forlino A, Zuffardi O, Stratakis CA. Deletions of the PRKAR1A locus at 17q24.2-q24.3 in Carney complex: genotype-phenotype correlations and implications for genetic testing. *J Clin Endocrinol Metab* 2014; **99**: E183-E188 [PMID: 24170103 DOI: 10.1210/jc.2013-3159]  72 **Salpea P**, Stratakis CA. Carney complex and McCune Albright syndrome: an overview of clinical manifestations and human molecular genetics. *Mol Cell Endocrinol* 2014; **386**: 85-91 [PMID: 24012779 DOI: 10.1016/j.mce.2013.08.022]  73 **Schernthaner-Reiter MH**, Trivellin G, Stratakis CA. MEN1, MEN4, and Carney Complex: Pathology and Molecular Genetics. *Neuroendocrinology* 2015 Jan 9; Epub ahead of print [PMID: 25592387 DOI: 10.1159/000371819]  74 **Gennari M**, Stratakis CA, Hovarth A, Pirazzoli P, Cicognani A. A novel PRKAR1A mutation associated with hepatocellular carcinoma in a young patient and a variable Carney complex phenotype in affected subjects in older generations. *Clin Endocrinol (Oxf)* 2008; **69**: 751-755 [PMID: 18445140 DOI: 10.1111/j.1365-2265.2008.03286.x]  75 **Gaujoux S**, Tissier F, Ragazzon B, Rebours V, Saloustros E, Perlemoine K, Vincent-Dejean C, Meurette G, Cassagnau E, Dousset B, Bertagna X, Horvath A, Terris B, Carney JA, Stratakis CA, Bertherat J. Pancreatic ductal and acinar cell neoplasms in Carney complex: a possible new association. *J Clin Endocrinol Metab* 2011; **96**: E1888-E1895 [PMID: 21900385 DOI: 10.1210/jc.2011-1433]  76 **Mussa A**, Russo S, De Crescenzo A, Chiesa N, Molinatto C, Selicorni A, Richiardi L, Larizza L, Silengo MC, Riccio A, Ferrero GB. Prevalence of Beckwith-Wiedemann syndrome in North West of Italy. *Am J Med Genet A* 2013; **161A**: 2481-2486 [PMID: 23918458 DOI: 10.1002/ajmg.a.36080]  77 **Teplick A**, Kowalski M, Biegel JA, Nichols KE. Educational paper: screening in cancer predisposition syndromes: guidelines for the general pediatrician. *Eur J Pediatr* 2011; **170**: 285-294 [PMID: 21210147 DOI: 10.1007/s00431-010-1377-2]  78 **Brioude F**, Lacoste A, Netchine I, Vazquez MP, Auber F, Audry G, Gauthier-Villars M, Brugieres L, Gicquel C, Le Bouc Y, Rossignol S. Beckwith-Wiedemann syndrome: growth pattern and tumor risk according to molecular mechanism, and guidelines for tumor surveillance. *Horm Res Paediatr* 2013; **80**: 457-465 [PMID: 24335096 DOI: 10.1159/000355544]  79 **Azzi S**, Abi Habib W, Netchine I. Beckwith-Wiedemann and Russell-Silver Syndromes: from new molecular insights to the comprehension of imprinting regulation. *Curr Opin Endocrinol Diabetes Obes* 2014; **21**: 30-38 [PMID: 24322424 DOI: 10.1097/MED.0000000000000037]  80 **Lapunzina P**. Risk of tumorigenesis in overgrowth syndromes: a comprehensive review. *Am J Med Genet C Semin Med Genet* 2005; **137C**: 53-71 [PMID: 16010678 DOI: 10.1002/ajmg.c.30064]  81 **Tan TY**, Amor DJ. Tumour surveillance in Beckwith-Wiedemann syndrome and hemihyperplasia: a critical review of the evidence and suggested guidelines for local practice. *J Paediatr Child Health* 2006; **42**: 486–90 [PMID: 16925531 DOI: 10.1111/j.1440-1754.2006.00908.x] |

**P-Reviewer:** Baryshnikova NV, Yamagata M **S-Editor:** Yu J **L-Editor:** **E-Editor:**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **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](http://www.cancer.net/node/19423), a[drenocortical carcinoma](http://www.cancer.net/node/18424) | 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 | Mixomas, 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 | x | x | x |  |  |  |
| Cystic or vascular lesions |  | x |  | x | x |  |
| GEP endocrine tumors |  |  |  | x |  | x |

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

|  |  |  |
| --- | --- | --- |
| **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.

**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.