Curr Treat Options Gastro (2019) 17:692–701
DOI 10.1007/s11938-019-00256-z

Genetics in Gastroenterology Practice (B Katona, Section Editor)

Hereditary or Not? Understanding Serrated Polyposis Syndrome

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Published online: 31 October 2019

This article is part of the Topical Collection on *Genetics in Gastroenterology Practice*

Keywords Colonic polyps · Human Genetics · Hyperplastic polyposis syndrome · Serrated polyposis syndrome

Abstract

Purpose of review To present the current understanding of the diagnosis, management, and potential genetic causes of serrated polyposis syndrome.
Recent findings The clinical criteria for serrated polyposis syndrome was recently updated and now includes individuals with five or more serrated polyps proximal to the rectum that are 5 mm in size or greater and at least two that are 10 mm in size of greater as well as individuals with 20 or more serrated polyps throughout the colon with at least five proximal to the rectum. There is a significant risk for colon cancer in first-degree relatives of individuals with serrated polyposis syndrome. However, less than 3% of serrated polyposis syndrome cases are explained by identifiable germline mutations, with mutations in *RNF43* being the only currently validated genetic cause.
Summary Serrated polyposis syndrome is rarely explained by identifiable germline mutations, but there remains an increased risk for colorectal cancer in first-degree relatives. Referral for genetic counseling and testing is recommended for individuals with serrated polyposis syndrome and a personal history of coexisting adenomatous polyposis or with a concerning family history and can be considered for all individuals with serrated polyposis syndrome. Close endoscopic surveillance of those with serrated polyposis syndrome and their first-degree relatives is recommended. Continued efforts at identifying hereditary causes of serrated polyposis are needed.

Introduction

Serrated polyps in the colon and rectum are characterized by the saw-tooth architecture of the epithelial compartment on histology. This incorporates a range of subtypes including the synonymous sessile serrated adenomas and sessile serrated polyps (referred to as SSA throughout this review) and traditional serrated adenomas, all of which are precursors to malignancy, as well as benign hyperplastic polyps [1]. Hyperplastic polyps are predominantly small (less than 5 mm in size) and located in the distal colon and rectum while SSAs are typically larger and located in the proximal colon [2]. These polyps can be difficult to differentiate by pathologic morphology and have undergone multiple reclassifications and shifts in terminology over time which can add to the confusion [3].

There is now convincing evidence that patients with SSAs, large serrated polyps, and/or proximal serrated polyps have increased risk of colorectal cancer [4–6]. Given the difficulty in accurate characterization of SSAs from hyperplastic polyps and the importance of size and location, it is recommended to consider any proximal serrated lesion over 1 cm in size as an SSA independent of pathologic interpretation when recommending endoscopic surveillance intervals [2]. The increasing recognition of the importance of these polyps and their link to colorectal cancer has led to increased detection rates despite their subtle appearance (Fig. 1) [7, 8].

It was recognized that cohorts of patients with multiple serrated polyps in the colon manifested a substantially increased risk for colorectal cancer [9–15]. This condition was initially termed hyperplastic polyposis, but terminology has shifted to serrated polyposis syndrome (SPS) as a more accurate description [1]. A clinical definition was proposed by Burt and Jass in 2000 and a similar schema codified by the World Health Organization (WHO) continues to be used today [16]. The prevalence of SPS is reported to be 0.09–0.4% in average-risk patients undergoing colonoscopy screening to 0.3–0.8% in patients undergoing high-risk screening after positive fecal occult blood testing or fecal immunochemical testing [17, 18•, 19–21]. Current estimates for the prevalence of colorectal cancer in SPS are 15.8–29.3% [15, 22]. In one large cohort, the 5-year cumulative incidence of colorectal cancer in patients undergoing active endoscopic surveillance was 1.5% [22].

Despite its phenotypic roots, it has been hypothesized that SPS has a genetic basis similar to other hereditary cancer syndromes [23–25]. This review will focus on the current understanding of the potential genetic causes, diagnosis, and management of SPS.

Diagnostic criteria for SPS

Since their introduction in 2000, the WHO diagnostic criteria for SPS have been broadly used to define the syndrome. An updated set of diagnostic criteria were released by the WHO in 2019 [26••]. The diagnosis of SPS can now be made by five or more serrated polyps proximal to the rectum that are ≥ 5 mm in size with at least two being ≥ 10 mm in size or with 20 or more serrated polyps of any size distributed throughout the colon, with at least 5 proximal to the rectum (Table 1). It is important to note that the polyp count to meet a diagnosis of SPS is meant to be cumulative over multiple procedures and that any subtype of serrated polyp should be included.

The new criteria also allow for further categorization of individuals with SPS by phenotype, which may aid future attempts at risk assessment. "Type 1 phenotype" can be used to describe those meeting criterion 1 and "type 2 phenotype" can be used for those meeting criterion 2 [26••]. Interestingly, this mirrors a previous categorization schema that was not widely adopted but is used in some older publications [27].

This update is a major adjustment. The criterion that allowed for an SPS diagnosis with any number of serrated polyps proximal to the sigmoid colon in

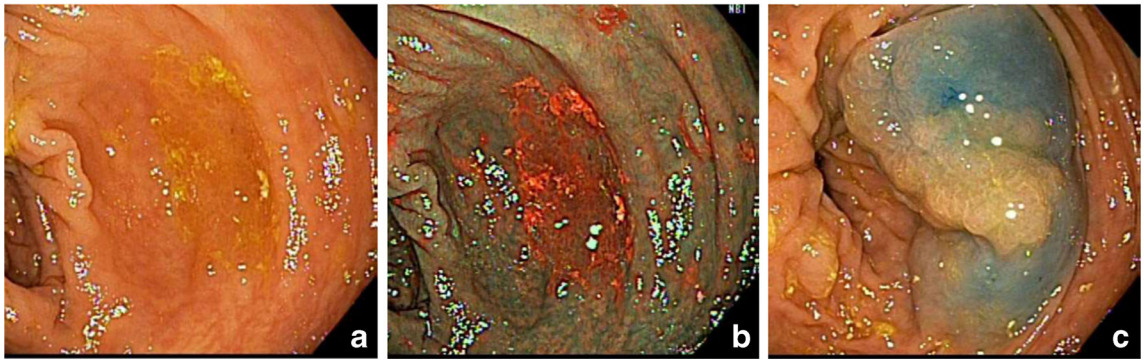

Fig. 1. Endoscopic images of a typical sessile serrated adenoma from an individual with serrated polyposis syndrome. A subtle mucous cap is often noted covering sessile serrated adenomas (panel **a**). Narrow-band imaging can be used to highlight the polyp and the mucous cap appears red with this modality (panel **b**). Submucosal injection of saline and methylene blue or other contrast agents can facilitate identification of the borders of sessile serrated adenomas for complete resection (panel **c**).

an individual with a first-degree relative with SPS was eliminated. Continued changes are likely in the future. SPS encompasses a wide spectrum of phenotypes, and the criteria will continue to be optimized as associated risks are better defined.

The great majority of the work discussed within this review utilizes the WHO 2010 diagnostic criteria [1]. This allowed for a diagnosis of SPS with 5 serrated polyps proximal to the sigmoid colon with 2 or more > 10 mm in size, any number of serrated polyps proximal to the sigmoid colon in an individual with a first-degree relative with a diagnosis of SPS, or more than 20 serrated polyps of any size distributed throughout the colon.

Genetic causes of SPS

Strides have been made over the last 5 years to identify potential germline causes of SPS, although identifiable germline mutations currently explain less than 3% of SPS cases [28]. Further whole exome sequencing (WES) or genome-wide association studies are needed to continue to identify genetic variants associated with SPS.

RNF43

The association between SPS and *RNF43* was first made by Gala et al. in 2014. They studied 20 patients meeting modified WHO criteria for SPS using WES. Two

Table 1. World Health Organization diagnostic criteria for serrated polyposis (Updated in 2019)

Criterion 1. Five or more serrated lesions/polyps proximal to the rectum, all being ≥ 5 mm in size, with ≥ 2 being ≥ 10 mm in size
Criterion 2. More than 20 serrated lesions/polyps of any size distributed throughout the colon, with ≥ 5 being proximal to the rectum

From: Rosty C, Brosens LAA, Dekker E, Nagtegaal ID. Serrated polyposis. In: Lokuhetty D, White VA, Watanabe R, Cree IA, editor. WHO Classification of Tumours: Digestive System Tumours. Lyon, France: International Agency for Research on Cancer; 2019. p. 532-4. Licence: CC BY-NC-SA 3.0 IGO

unrelated individuals were found with a novel germline mutation in *RNF43* (c.337C > T, p.R113X). Both individuals had personal histories of multiple SSAs and a family history of colorectal cancer. The authors concluded that nonsense variants in *RNF43* are associated with multiple serrated polyps [29].

In 2015, Taupin et al. identified a small family with an impressive phenotype of SPS and performed WES on the kindred. This included an affected sibling pair, one with colon cancer at age 23 in the setting of over 50 large SSAs and another with over 60 serrated polyps at the time of a subtotal colectomy. A nonsense mutation in *RNF43* (c.394C > T, p.R132X) was identified in both affected siblings and was absent from an unaffected sibling. This was confirmed by Sanger sequencing. As this mutation segregated with SPS in the family, further evidence was added to the link between *RNF43* and SPS [30].

Further support of the connection between *RNF43* and SPS came in 2017 when Yan et al. identified a germline *RNF43* mutation (c.953-1G > A, p.E318fs) from WES that was confirmed to cause aberrant splicing and resulted in a truncated protein. This mutation segregated with disease in one of four families analyzed. The authors provided further evidence by finding second-hit inactivation by somatic mutations or loss of heterozygosity for *RNF43* in all of the serrated polyps and the cancer they examined from affected individuals [31••].

Dampening the enthusiasm for the prevalence of *RNF43* mutations in SPS was work done on a large cohort of individuals with SPS from a multi-national registry in 2017 [32••]. WES or whole genome sequencing was performed on 74 subjects selected for young age of diagnosis, severe phenotype, or positive family history of SPS or colorectal cancer. Two individuals were identified with *RNF43* missense variants (c.640C > G, p.L214 V and c.443C > G, p.A148G) predicted to be damaging by in silico models. In addition, they performed targeted genetic testing in 221 additional subjects with SPS for the specific nonsense mutations described by Gala et al. and Taupin et al. and did not find any who carried these mutations [29, 30]. This study concluded that *RNF43* likely accounts for only a small proportion of SPS and that routine germline testing may not be indicated.

Quintana et al. performed Sanger sequencing of *RNF43* in 96 individuals with SPS in 2018 and found one subject with a previously reported *RNF43* mutation (c.394C > T, p.R132X). In addition, an additional subject was found to have a novel *RNF43* variant (c.1821G > A, p.S607=), although this was deemed unlikely to have a deleterious effect after RNA testing [33].

Other potential genes

A germline mutation in *EPHB2* has been reported as potentially causative in an individual with SPS [34]. Other potential contributors found through WES analysis include *ATM*, *PIF1*, *RBL1*, *TELO2*, and *XAF1* [29]. These findings have not been replicated and their potential relevance remains unconfirmed.

Overlap with other hereditary cancer syndromes

MUTYH-associated polyposis

MUTYH-associated polyposis (MAP) is an adenomatous polyposis syndrome caused by biallelic mutations in the *MUTYH* gene. Multiple serrated polyps

have been reported in individuals with MAP, including those meeting diagnostic criteria for SPS.

The initial report of this overlap was from Chow et al. in 2006 who studied 38 patients with multiple serrated polyps (including 32 meeting criteria for SPS) and performed analysis of *MUTYH* and *MBD4*. One individual was identified with biallelic *MUTYH* mutations that had 40 tubular adenomas in addition to over 20 hyperplastic polyps [35]. Boparai et al. described three patients with MAP with over 10 small serrated polyps that reportedly met SPS diagnostic criteria. Importantly, all patients also had at least 25 tubular adenomas and met clinical criteria for adenomatous polyposis [36].

To further assess this potential link, a cohort of 405 patients with more than 10 polyps of any histology proximal to the rectum were studied for *MUTYH* mutations. One patient out of 40 meeting WHO criteria for serrated polyposis in the study was found to have MAP. This patient did not have any reported adenomas [37].

In a study of 65 patients with SPS, no pathogenic variants were identified in *BMPR1A*, *SMAD4*, *PTEN*, *MUTYH*, or *GREM1* [38]. Similarly, no pathogenic variants were found in a study of 29 individuals meeting SPS criteria that had *APC*, *MUTYH*, and *PTEN* analyzed [39]. While the two studies mentioned above did not replicate the findings of MAP in individuals with SPS, there is still potential overlap in the clinical phenotype. Individuals with SPS (especially those with multiple adenomas) should be considered for germline testing for *MUTYH*.

Lynch syndrome

Although proximal serrated polyps were initially reported to be unusual in Lynch syndrome, more recent work has found their prevalence to be equivalent to the general population [40, 41]. There is a report of a patent with a pathogenic variant in *MLH1* with metachronous colon cancers who also met WHO criteria for SPS with over 50 small left-sided serrated polyps [42]. There is another description of an individual with an *MLH1* pathogenic variant and metachronous colon cancers who did not meet SPS diagnostic criteria but had 11 small serrated polyps (with the majority in the right colon) [43].

Familial risk

There is convincing evidence that the risk of colorectal cancer and SPS is increased in close relatives of individuals with SPS, despite the lack of a clear inheritance pattern or identified germline causes. The first large scale study to assess this included a retrospective review of 347 first-degree relatives from 57 families and showed a relative risk for colorectal cancer of 5.4 (95% CI 3.7–7.8) and a relative risk for SPS of 39 (95% CI 13–121) [44]. A subsequent large, multi-national retrospective study analyzed 1,639 first- and second-degree relatives from 100 probands. This study identified a significantly increased standardized incidence ratio for colon cancer of 5.16 (95% CI 3.7–7.3) for first-degree relatives and mildly increased incidence ratio for second-degree relatives of 1.38 (95% CI 1.01–1.91) [45]. This study also noted an increased risk for pancreatic cancer in first-degree relatives of patients with SPS [45]. This finding was not replicated in another study assessing the risk of extra-colonic malignancies in relatives of SPS patients [46].

There is evidence that the WHO diagnostic criteria may be too stringent and are not yet optimized to identify the patients with multiple serrated polyps that are highest risk [47]. In a similar vein, recent work has shown that first-degree relatives of individuals not meeting diagnostic criteria for SPS but with 10 or more colon polyps with at least half being serrated polyps had an increased risk of colorectal cancer that was similar to patients with SPS and their relatives [48•].

Treatment of SPS

Multiple guidelines recommend frequent surveillance colonoscopy as the mainstay of treatment for SPS. Once endoscopic control of serrated polyps is achieved, surveillance is recommended every 1–3 years with interval determined by polyp burden [1, 49, 50]. Although many endoscopists prefer annual procedures for these patients, recent data has shown that 2-year intervals for surveillance colonoscopy are effective [51, 52]. If colorectal cancer or multiple advanced polyps occur or endoscopic control is no longer possible, surgery with resection of affected areas of the colon is recommended. This can usually be accomplished with extended right hemicolectomy or a subtotal colectomy, although colectomy with ileorectal anastomosis can be considered [2, 49]. Importantly, there are no recommendations for any additional extra-colonic screening in SPS.

Genetic testing for *RNF43* mutations is now available in select commercial laboratories. Meeting SPS criteria is included as an indication for referral for a cancer predisposition assessment in some guidelines [53, 54]. Given this, it is reasonable to refer all patients with SPS for genetic counseling and consideration of genetic testing. However, that is not our clinical practice given the low yield of currently available testing. We recommend referral for genetic counseling for patients with a family history of colon cancer or serrated polyposis consistent with an autosomal dominant inheritance pattern with consideration of multi-gene panel testing to include RNF43 and other genes associated with colorectal cancer syndromes.

Given the potential for overlap in phenotype with other hereditary cancer syndromes, individuals with SPS should also be referred for genetic counseling and multi-gene panel testing if their personal history is concerning for an adenomatous polyposis syndrome or if they have a family history that meets referral criteria for other hereditary cancer syndromes.

If genetic testing is not pursued or is unrevealing, first-degree relatives of patients with SPS still need close screening given their increased risk for colon cancer. Current guidelines have minor variations, but generally, it is recommended to initiate colonoscopy at age 40, at the age of the diagnosis of SPS in the relative or 10 years prior to the diagnosis of colorectal cancer in a first-degree relative (whichever is youngest). An interval of 5 years between colonoscopies is recommended if no polyps are noted [1, 2, 50]. Screening colonoscopy in these relatives has been found to be impactful, with a SSA/proximal serrated polyp or advanced adenoma found in 14% [55].

It is important to note that until very recently, first-degree relatives of patients with SPS found to have a serrated polyp proximal to the sigmoid colon would have met criteria for SPS and started colonoscopy every 1–3 years. This

criterion was met by 14–32% of relatives [55, 56]. It remains to be seen how clinical guidelines will change with the adjustment in the 2019 WHO criteria [26]. Given the increased risk for CRC in these patients, we favor continued close monitoring of these patients every 1–3 years until further assessment of an optimized surveillance regimen is published.

Conclusion

SPS as defined by current clinical criteria is uncommon but will increase over time with growing recognition of the syndrome by endoscopists and increased detection of SSAs. Despite only a small minority of SPS cases being related to identifiable germline mutations, there is a significant familial risk for colorectal cancer. Referral for genetic counseling and multi-gene panel testing should be considered for SPS patients, especially if there is a concerning family history or a personal history of coexisting adenomatous polyposis. Close endoscopic surveillance of SPS patients and their first-degree relatives is recommended.

Compliance with Ethical Standards

Conflict of Interest

PPS has performed collaborative research with Ambry Genetics. RP has performed collaborative research with Ambry Genetics, Myriad Genetics Laboratories, Inc, and InVitae Genetics.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
••Of major importance

1. Snover DC, Ahnen DJ, Burt RW, Odze RD. Serrated polyps of the colon and rectum and serrated polyposis. In: Bozman FT, Carneiro F, Hruban RH, Theise N, editors. WHO classification of tumours of the digestive system. Lyon: International Agency for Research on Cancer; 2010. p. 160–5.
2. Rex DK, Ahnen DJ, Baron JA, Batts KP, Burke CA, Burt RW, et al. Serrated lesions of the colorectum: review and recommendations from an expert panel. Am J Gastroenterol. 2012;107(9):1315–29 ;quiz 4, 30. https://doi.org/10.1038/ajg.2012.161.
3. Torlakovic E, Skovlund E, Snover DC, Torlakovic G, Nesland JM. Morphologic reappraisal of serrated colorectal polyps. Am J Surg Pathol. 2003;27(1):65–81.
4. Hiraoka S, Kato J, Fujiki S, Kaji E, Morikawa T, Murakami T, et al. The presence of large serrated polyps increases risk for colorectal cancer. Gastroenterology. 2010;139(5):1503–10; 10 e1-3. https://doi.org/10.1053/j.gastro.2010.07.011.
5. Gao Q, Tsoi KK, Hirai HW, Wong MC, Chan FK, Wu JC, et al. Serrated polyps and the risk of synchronous colorectal advanced neoplasia: a systematic review and meta-analysis. Am J Gastroenterol. 2015;110(4):501–9; quiz 10. https://doi.org/10.1038/ajg.2015.49.
6. Erichsen R, Baron JA, Hamilton-Dutoit SJ, Snover DC, Torlakovic EE, Pedersen L, et al. Increased risk of colorectal cancer development among patients with serrated polyps. Gastroenterology. 2016;150(4):895–902 e5. https://doi.org/10.1053/j.gastro.2015.11.046.
7. Abdeljawad K, Vemulapalli KC, Kahi CJ, Cummings OW, Snover DC, Rex DK. Sessile serrated polyp prevalence determined by a colonoscopist with a high lesion

detection rate and an experienced pathologist. Gastrointest Endosc. 2015;81(3):517–24. https://doi.org/10.1016/j.gie.2014.04.064.

8. Shaukat A, Gravely AA, Kim AS, Rank J, Church TR, Allen JI. Rates of detection of adenoma, sessile serrated adenoma, and advanced adenoma are stable over time and modifiable. Gastroenterology. 2019;156(3):816–7. https://doi.org/10.1053/j.gastro.2018.10.052.
9. Jeevaratnam P, Cottier DS, Browett PJ, Van De Water NS, Pokos V, Jass JR. Familial giant hyperplastic polyposis predisposing to colorectal cancer: a new hereditary bowel cancer syndrome. J Pathol. 1996;179(1):20–5. https://doi.org/10.1002/(SICI)1096-9896(199605)179:1<20::AID-PATH538>3.0.CO;2-C.
10. Torlakovic E, Snover DC. Serrated adenomatous polyposis in humans. Gastroenterology. 1996;110(3):748–55. https://doi.org/10.1053/gast.1996.v110.pm8608884.
11. Jass JR, Cottier DS, Pokos V, Parry S, Winship IM. Mixed epithelial polyps in association with hereditary non-polyposis colorectal cancer providing an alternative pathway of cancer histogenesis. Pathology. 1997;29(1):28–33.
12. Leggett BA, Devereaux B, Biden K, Searle J, Young J, Jass J. Hyperplastic polyposis: association with colorectal cancer. Am J Surg Pathol. 2001;25(2):177–84.
13. Yeoman A, Young J, Arnold J, Jass J, Parry S. Hyperplastic polyposis in the New Zealand population: a condition associated with increased colorectal cancer risk and European ancestry. N Z Med J. 2007;120(1266):U2827.
14. Boparai KS, Mathus-Vliegen EM, Koornstra JJ, Nagengast FM, van Leerdam M, van Noesel CJ, et al. Increased colorectal cancer risk during follow-up in patients with hyperplastic polyposis syndrome: a multicentre cohort study. Gut. 2010;59(8):1094–100. https://doi.org/10.1136/gut.2009.185884.
15. Carballal S, Rodriguez-Alcalde D, Moreira L, Hernandez L, Rodriguez L, Rodriguez-Moranta F, et al. Colorectal cancer risk factors in patients with serrated polyposis syndrome: a large multicentre study. Gut. 2016;65(11):1829–37. https://doi.org/10.1136/gutjnl-2015-309647.
16. Burt R, Jass JR. Hyperplastic polyposis. In: Hamilton S, Aaltonen LA, editors. Pathology and genetics of tumours of the digestive system. Lyon: International Agency for Research on Cancer; 2000. p. 135–6.
17. van Herwaarden YJ, Verstegen MH, Dura P, Kievit W, Drenth JP, Dekker E, et al. Low prevalence of serrated polyposis syndrome in screening populations: a systematic review. Endoscopy. 2015;47(11):1043–9. https://doi.org/10.1055/s-0034-1392411.
18.• IJspeert JEG, Bevan R, Senore C, Kaminski MF, Kuipers EJ, Mroz A, et al. Detection rate of serrated polyps and serrated polyposis syndrome in colorectal cancer screening cohorts: a European overview. Gut. 2017;66(7):1225–32. https://doi.org/10.1136/gutjnl-2015-310784

Provided updated prevalence rates for serrated polyposis syndrome and showed that previous reports were likely underestimates.

19. Biswas S, Ellis AJ, Guy R, Savage H, Madronal K, East JE. High prevalence of hyperplastic polyposis syndrome (serrated polyposis) in the NHS bowel cancer screening programme. Gut. 2013;62(3):475. https://doi.org/10.1136/gutjnl-2012-303233.
20. Moreira L, Pellise M, Carballal S, Bessa X, Ocana T, Serradesanferm A, et al. High prevalence of serrated polyposis syndrome in FIT-based colorectal cancer screening programmes. Gut. 2013;62(3):476–7. https://doi.org/10.1136/gutjnl-2012-303496.
21. Colussi D, Zagari RM, Morini B, Fabbri M, Montale A, Hassan C, et al. Prevalence of serrated polyposis syndrome in an FIT-based colorectal cancer screening cohort in Italy. Gut. 2017;66(8):1532–3. https://doi.org/10.1136/gutjnl-2016-313063.
22. IJspeert JEG, Rana SA, Atkinson NS, van Herwaarden YJ, Bastiaansen BA, van Leerdam ME, et al. Clinical risk factors of colorectal cancer in patients with serrated polyposis syndrome: a multicentre cohort analysis. Gut. 2017;66(2):278–84. https://doi.org/10.1136/gutjnl-2015-310630.
23. Young J, Jass JR. The case for a genetic predisposition to serrated neoplasia in the colorectum: hypothesis and review of the literature. Cancer Epidemiol Biomark Prev. 2006;15(10):1778–84. https://doi.org/10.1158/1055-9965.EPI-06-0164.
24. Young J, Jenkins M, Parry S, Young B, Nancarrow D, English D, et al. Serrated pathway colorectal cancer in the population: genetic consideration. Gut. 2007;56(10):1453–9. https://doi.org/10.1136/gut.2007.126870.
25. Lanspa SJ, Ahnen DJ, Lynch HT. Serrated polyposis: the last (or only the latest?) frontier of familial polyposis? Am J Gastroenterol. 2012;107(5):779–81. https://doi.org/10.1038/ajg.2012.62.
26.•• Rosty C, Brosens LAA, Dekker E, Nagtegaal ID. Serrated polyposis. In: Lokuhetty D, White VA, Watanabe R, Cree IA, editors. WHO classification of tumours: digestive system tumours. Lyon: International Agency for Research on Cancer; 2019. p. 532–4.

A major update to the serrated polyposis syndrome diagnostic criteria was introduced in this internationally referenced text.

27. Jass JR. Gastrointestinal polyposes: clinical, pathological and molecular features. Gastroenterol Clin N Am. 2007;36(4):927–46.

viii. https://doi.org/10.1016/j.gtc.2007.08.009.

28. Terradas M, Munoz-Torres PM, Belhadj S, Aiza G, Navarro M, Brunet J, et al. Contribution to colonic polyposis of recently proposed predisposing genes and assessment of the prevalence of NTHL1- and MSH3-associated polyposes. Hum Mutat. 2019. https://doi.org/10.1002/humu.23853.
29. Gala MK, Mizukami Y, Le LP, Moriichi K, Austin T, Yamamoto M, et al. Germline mutations in oncogene-induced senescence pathways are associated with multiple sessile serrated adenomas. Gastroenterology.

2014;146(2):520–9. https://doi.org/10.1053/j.gastro.2013.10.045.

30. Taupin D, Lam W, Rangiah D, McCallum L, Whittle B, Zhang Y, et al. A deleterious RNF43 germline mutation in a severely affected serrated polyposis kindred. Hum Genome Var. 2015;2:15013. https://doi.org/10.1038/hgv.2015.13.

31.•• Yan HHN, Lai JCW, Ho SL, Leung WK, Law WL, Lee JFY, et al. *RNF43* germline and somatic mutation in serrated neoplasia pathway and its association with BRAF mutation. Gut. 2017;66(9):1645–56. https://doi.org/10.1136/gutjnl-2016-311849

Validated link between *RNF43* and serrated polyposis syndrome by confirming the second-hit inactivation of the gene in serrated polyps and tumor of affected patients.

32.• Buchanan DD, Clendenning M, Zhuoer L, Stewart JR, Joseland S, Woodall S, et al. Lack of evidence for germline *RNF43* mutations in patients with serrated polyposis syndrome from a large multinational study. Gut. 2017;66(6):1170–2. https://doi.org/10.1136/gutjnl-2016-312773

Analyzed *RNF43* in the largest cohort of serrated polyposis patients to date and showed that only 2/295 (0.7%) had pathogenic variants.

33. Quintana I, Mejias-Luque R, Terradas M, Navarro M, Pinol V, Mur P, et al. Evidence suggests that germline RNF43 mutations are a rare cause of serrated polyposis. Gut. 2018;67(12):2230–2. https://doi.org/10.1136/gutjnl-2017-315733.

34. Kokko A, Laiho P, Lehtonen R, Korja S, Carvajal-Carmona LG, Jarvinen H, et al. EPHB2 germline variants in patients with colorectal cancer or hyperplastic polyposis. BMC Cancer. 2006;6:145. https://doi.org/10.1186/1471-2407-6-145.

35. Chow E, Lipton L, Lynch E, D'Souza R, Aragona C, Hodgkin L, et al. Hyperplastic polyposis syndrome: phenotypic presentations and the role of MBD4 and MYH. Gastroenterology. 2006;131(1):30–9. https://doi.org/10.1053/j.gastro.2006.03.046.

36. Boparai KS, Dekker E, Van Eeden S, Polak MM, Bartelsman JF, Mathus-Vliegen EM, et al. Hyperplastic polyps and sessile serrated adenomas as a phenotypic expression of MYH-associated polyposis. Gastroenterology. 2008;135(6):2014–8. https://doi.org/10.1053/j.gastro.2008.09.020.

37. Guarinos C, Juarez M, Egoavil C, Rodriguez-Soler M, Perez-Carbonell L, Salas R, et al. Prevalence and characteristics of MUTYH-associated polyposis in patients with multiple adenomatous and serrated polyps. Clin Cancer Res. 2014;20(5):1158–68. https://doi.org/10.1158/1078-0432.CCR-13-1490.

38. Clendenning M, Young JP, Walsh MD, Woodall S, Arnold J, Jenkins M, et al. Germline mutations in the polyposis-associated genes BMPR1A, SMAD4, PTEN, MUTYH and GREM1 are not common in individuals with serrated polyposis syndrome. PLoS One. 2013;8(6):e66705. https://doi.org/10.1371/journal.pone.0066705.

39. Petronio M, Pinson S, Walter T, Joly MO, Hervieu V, Forestier J, et al. Type 1 serrated polyposis represents a predominantly female disease with a high prevalence of dysplastic serrated adenomas, without germline mutation in MUTYH, APC, and PTEN genes. United European Gastroenterol J. 2016;4(2):305–13. https://doi.org/10.1177/2050640615594939.

40. Andersen SH, Lykke E, Folker MB, Bernstein I, Holck S. Sessile serrated polyps of the colorectum are rare in patients with Lynch syndrome and in familial colorectal cancer families. Familial Cancer. 2008;7(2):157–62. https://doi.org/10.1007/s10689-007-9163-7.

41. Vleugels JLA, Sahin H, Hazewinkel Y, Koens L, van den Berg JG, van Leerdam ME, et al. Endoscopic detection rate of sessile serrated lesions in Lynch syndrome patients is comparable with an age- and gender-matched control population: case-control study with expert pathology review. Gastrointest Endosc. 2018;87(5):1289–96. https://doi.org/10.1016/j.gie.2017.11.034.

42. Jasperson KW, Kanth P, Kirchhoff AC, Huismann D, Gammon A, Kohlmann W, et al. Serrated polyposis: colonic phenotype, extracolonic features, and familial risk in a large cohort. Dis Colon Rectum. 2013;56(11):1211–6. https://doi.org/10.1097/DCR.0b013e3182a11cca.

43. Jarrar AM, Church JM, Fay S, Kalady MF. Is the phenotype mixed or mistaken? Hereditary nonpolyposis colorectal cancer and hyperplastic polyposis syndrome. Dis Colon Rectum. 2009;52(12):1949–55. https://doi.org/10.1007/DCR.0b013e3181b5450c.

44. Boparai KS, Reitsma JB, Lemmens V, van Os TA, Mathus-Vliegen EM, Koornstra JJ, et al. Increased colorectal cancer risk in first-degree relatives of patients with hyperplastic polyposis syndrome. Gut. 2010;59(9):1222–5. https://doi.org/10.1136/gut.2009.200741.

45. Win AK, Walters RJ, Buchanan DD, Jenkins MA, Sweet K, Frankel WL, et al. Cancer risks for relatives of patients with serrated polyposis. Am J Gastroenterol. 2012;107(5):770–8. https://doi.org/10.1038/ajg.2012.52.

46. Hazewinkel Y, Reitsma JB, Nagengast FM, Vasen HF, van Os TA, van Leerdam ME, et al. Extracolonic cancer risk in patients with serrated polyposis syndrome and their first-degree relatives. Familial Cancer. 2013;12(4):669–73. https://doi.org/10.1007/s10689-013-9643-x.

47. Kalady MF, Jarrar A, Leach B, LaGuardia L, O'Malley M, Eng C, et al. Defining phenotypes and cancer risk in hyperplastic polyposis syndrome. Dis Colon Rectum. 2011;54(2):164–70. https://doi.org/10.1007/DCR.0b013e3181fd4c15.

48.• Egoavil C, Juarez M, Guarinos C, Rodriguez-Soler M, Hernandez-Illan E, Alenda C, et al. Increased risk of colorectal cancer in patients with multiple serrated polyps and their first-degree relatives. Gastroenterology. 2017;153(1):106–12 e2.

Increased risk for colorectal cancer was seen in close relatives of serrated polyposis patients but also in relatives of those with

multiple serrated polyps not meeting WHO criteria for serrated polyposis syndrome. This suggests WHO criteria still need optimization to capture individuals and family members at increased risk. https://doi.org/10.1053/j.gastro.2017.04.003.

49. Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW, et al. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110(2):223–62; quiz 63. https://doi.org/10.1038/ajg.2014.435.
50. National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Version 1.2019 ed2019.
51. Bleijenberg AG, IJspeert JEG, van Herwaarden YJ, Carballal S, Pellise M, Jung G, et al. Personalised surveillance for serrated polyposis syndrome: results from a prospective 5-year international cohort study. Gut. 2019. https://doi.org/10.1136/gutjnl-2018-318134.
52. MacPhail ME, Thygesen SB, Patel N, Broadley HM, Rex DK. Endoscopic control of polyp burden and expansion of surveillance intervals in serrated polyposis syndrome. Gastrointest Endosc. 2019;90(1):96–100. https://doi.org/10.1016/j.gie.2018.11.016.
53. Hampel H, Bennett RL, Buchanan A, Pearlman R, Wiesner GL. Guideline Development Group ACoMG et al. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. Genet Med. 2015;17(1):70–87. https://doi.org/10.1038/gim.2014.147.
54. Hassan C, Quintero E, Dumonceau JM, Regula J, Brandao C, Chaussade S, et al. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2013;45(10):842–51. https://doi.org/10.1055/s-0033-1344548.
55. Hazewinkel Y, Koornstra JJ, Boparai KS, van Os TA, Tytgat KM, Van Eeden S, et al. Yield of screening colonoscopy in first-degree relatives of patients with serrated polyposis syndrome. J Clin Gastroenterol. 2015;49(5):407–12. https://doi.org/10.1097/MCG.0000000000000103.
56. Oquinena S, Guerra A, Pueyo A, Eguaras J, Montes M, Razquin S, et al. Serrated polyposis: prospective study of first-degree relatives. Eur J Gastroenterol Hepatol. 2013;25(1):28–32. https://doi.org/10.1097/MEG.0b013e3283598506.

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