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Low Yield of Genetic Testing in Serrated Polyposis Syndrome

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HIGHLIGHTS

WHAT IS KNOWN:

Serrated Polyposis Syndrome (SPS) is associated with increased colorectal cancer risk.

The British Society of Gastroenterology and UK National Genomic Testing Directory recommends genetic testing in SPS patients to rule out other polyposis conditions, but guideline recommendations are based on limited and low-quality evidence

WHAT IS NEW HERE:

258 patients with SPS who underwent genetic testing at the St. Mark's Hospital Polyposis Registry were analysed.

Our study showed a low diagnostic yield of 1.5% for actionable pathogenic variants, suggesting an undefined genetic basis or alternative pathophysiological mechanisms in SPS patients. This yield was lowest when a selective approach was taken to genetic testing, compared to multi-gene panel testing.

Pathogenic variants in RNF43, a tumour suppressor gene, was identified in one SPS patient highlighting its known potential role, but in a small number of SPS cases

Findings highlight the potential overuse of genetic testing under current guidelines and call for targeted, evidence-based revisions to optimise resource use and patient care.

ABSTRACT

Introduction

Serrated polyposis syndrome (SPS) is clinically defined by the presence of multiple serrated polyps in the colon and rectum and is associated with increased colorectal cancer risk. SPS is the most prevalent polyposis condition however its genetic basis remains poorly characterised. The British Society of Gastroenterology recommends gene panel testing for all SPS patients to rule out other polyposis conditions. This study aimed to evaluate the diagnostic yield of genetic testing in SPS patients.

Methods

We conducted a retrospective, cross-sectional analysis using the Polyposis Registry from St. Mark's Hospital, London, a national referral centre in the United Kingdom. SPS patients who underwent genetic testing between 4 April 2009 to 9 February 2024 and met the SPS WHO criteria were included. Genetic variants were identified from test reports, and clinical data was extracted from medical records.

Results

In total, 573 people with SPS were identified in our registry, of whom 258 underwent genetic testing. Of these, 119 underwent target gene testing and 139 underwent multi-gene panel testing (MGPT). No pathogenic variants were detected through targeted genetic testing. On MGPT, pathogenic germline variants were found in four patients (2.9%), including three with Lynch syndrome (two with *PMS2*, one with *MSH2)* and one with an *RNF43* variant.

Conclusion

Genetic testing demonstrated a low diagnostic yield in this SPS cohort, suggesting undefined genetic risk or involvement of other pathophysiological factors. Therefore, genetic testing appears to have limited utility in SPS patients and may primarily identify those with an incidental diagnosis of Lynch syndrome.

Introduction

Serrated polyposis syndrome (SPS) is a precancerous condition characterised by the presence of multiple serrated polyps (SP) throughout the colon and rectum (1). SPS is associated with a significant risk of progression to colorectal cancer (CRC), making early identification and management critical. It is clinically defined, according to the World Health Organization (WHO) guidelines. SPS is diagnosed when an individual's cumulative lifetime count of SP meets one of the following criteria: 1) ≥5 serrated lesions/polyps proximal to the rectum all being ≥5 mm in size, with ≥2 being ≥10 mm in size, or 2) >20 serrated lesions/polyps of any size distributed throughout the large bowel, with ≥5 being proximal to the rectum (1).

SPS is the most common polyposis syndrome, with a UK prevalence estimated between 0.34% and 0.66% (2,3). A monogenic cause for SPS has not been identified and the molecular basis for the condition remains largely unknown (1,4,5). *RNF43*, a tumour suppressor gene, has been implicated in a small number of SPS cases (5,6), however, findings have been inconsistent (7,8). Murphy *et al.* found that 9.6% of SPS patients harboured pathogenic variants in CRC-related genes such as *RFN43, MUTYH* and *CHEK2 (9),* whereas others reported no pathogenic variants in genes such as *PTEN*, *SMAD4*, and *BMPR1A* (10). The evidence of a strong familial component is weak, although there are some clues that there may be a familial component to SPS in some cases. (11)(12)(13)

In 2018, the UK Cancer Genetics Group developed the R211 panel to standardise genetic testing for early-onset colorectal cancer (EOCRC) and polyposis syndromes (14)(15). This panel, which utilises next-generation sequencing, provides an efficient, cost-effective approach to cover a wide range of genes associated with increased CRC risk (16). The British Society of Gastroenterology (BSG) has outlined which SPS patients should undergo genetic

testing to rule out other polyposis syndromes, such as MUTYH-associated polyposis and Peutz-Jegher syndrome, as dual pathology can occur (2,17,18). However, the evidence base for this recommendation was identified as being weak (2). In November 2020, St. Mark's adopted the R211 panel for SPS patients meeting BSG criteria for genetic testing (2, 14, 15).

The lack of understanding surrounding the genetic factors underlying SPS limits the ability to tailor personalised surveillance strategies for CRC risk. As a result, current surveillance guidelines for SPS rely on limited evidence and employ a one-size-fits-all approach, which may lead to unnecessary procedures (2). Given that colonoscopies are invasive and carry inherent risks, identifying genetic factors where present, informs management of an individual but also the wider family.

The primary aim of this study was to evaluate the diagnostic yield of genetic testing in patients with SPS and assess whether current guidelines should be revised.

Methods

Study Population

We conducted a cross-sectional review up to February 9, 2024, using prospectively collected electronic and paper records from the Polyposis Registry at St. Mark’s Hospital, Harrow, United Kingdom. The purpose of this review was to evaluate the diagnostic yield of genetic testing in patients with SPS. Inclusion criteria were patients meeting the WHO diagnostic criteria for SPS who had undergone gene panel testing. In total 258 SPS patients were identified from April 4, 2009 to February 9, 2024 *(Figure 1).*

Patient data was extracted from the Polyposis Registry and electronic patient records. The following information was collected: patient demographics, colonoscopy and histology findings and outcome of genetic testing. Colonoscopy and histology records were examined to identify which SPS Criterion the patient fulfilled. Patient age was recorded based on the age at SPS diagnosis. Molecular results were obtained from genetic test reports stored in the Polyposis Registry and were updated if subsequently reclassified.

Genetic testing and analysis

Between April 4, 2009 and November 3, 2020, targeted genetic testing was performed on 119 SPS patients. During this period, testing was conducted on an individual, per-patient basis. The targeted genes included *GREM1* and *MUTYH*, with additional testing for *APC, POLE,* and *POLD1* performed in some cases. Consequently, some patients underwent testing for a single gene, while others were tested for multiple genes

In November 2020, genetic testing transitioned to the R211 multi-gene panel test (MGPT) provided by the NHS Genomic Service (16). This panel includes genes associated with colorectal cancer and polyposis syndromes, specifically*: APC, BMPR1A, EPCAM, MLH1, MSH2, MSH6, MUTYH, NTHL1, PMS2, POLD1, POLE, PTEN, RNF43, SMAD4,* and *STK11* (16). Between November 4, 2020 and February 9, 2024, 139 SPS patients underwent R211 panel testing (*Figure 1*).

All genetic testing was performed in NHS-accredited laboratories using next-generation sequencing using the Illumina TruSight and equivalent platforms. Test results were interpreted based on the authorised report and updated if any variants were reclassified. Identified variants were classified as pathogenic, likely pathogenic (with >90% confidence in pathogenicity), or variants of uncertain significance (VUS).

The medical history of first-degree and second-degree relatives was recorded, where available, for individuals identified as having pathogenic variants, variants of uncertain significance (VUS), or carrier status in the targeted genes. CRC histories were extracted from medical records, and findings related to SP were obtained from colonoscopy and histology reports.

Statistical tests

In this study, descriptive statistics were used to summarise patient demographics and genetic testing outcomes. The Kolmogorov-Smirnov test indicated that the data was not normally distributed, so non-parametric statistical tests were applied. Non-parametric data, including the age of SPS onset, was presented as medians with interquartile ranges. Categorical variables (sex, age, smoking status and WHO criteria), were reported as frequencies and percentages.

Ethical approval

The research and development office at St. Mark's Hospital registered and approved the study as part of a service evaluation project. Therefore, this project did not require ethical approval, and data was anonymised.

RESUTLS

Study population

In total, 258 patients met the study criteria (from a total cohort of 573 patients), the baseline demographics are shown in *Table 1*. The median age at SPS diagnosis was 42 ± 22.8 years

(range 23-82 years). Additionally, 136 patients (52.7%) were female, and 160 patients (62.0%) were Caucasian. According to the 2019 WHO criteria for SPS, 33 patients (12.8%) fulfilled WHO Criterion I; 135 patients (52.3%) fulfilled WHO Criterion II and 90 patients (34.9%) fulfilled both WHO Criterion I and II. The most common index clinical presentation for patients that were diagnosed with SPS was symptomatic (52.3%), which included rectal bleeding, change in bowel habits, and abdominal pain. Nine patients (3.5%) were referred due to a relative's history of SPS, and 20 patients (7.8%) were referred due to a relative's history of CRC. Where information regarding smoking status was available, over half (54.6%) of patients were smokers. Prior to SPS diagnosis, three patients were identified with Lynch syndrome. No other patient had a known hereditary CRC-related condition. Approximately, a quarter of patients (24.4%) had a personal history of CRC. In addition, where data was available, we did not observe a significant number of extracolonic cancers in our cohort.

Genetic Testing

There was a variation in the number of genes that were tested for in each patient. 119 patients underwent targeted gene testing, and 139 patients underwent the R211 MGPT (for 16 significant genes associated with CRC).

Of the 119 patients who underwent target gene testing, one patient was identified with a VUS and the remaining 118 patients had no variant. Of the 139 patients who underwent MGPT testing, an actionable pathogenic variant was only found in four patients (2.9%). In addition, five patients (3.6%) were identified as heterozygous carriers and two patients (1.4%) were identified with a VUS. In 128 patients who underwent the R211 gene panel, no variant was

found *(Figure 2).* When combining both cohorts, only four patients (1.6%) had an actionable pathogenic variant

The number of patients tested for each gene is described in *Table 2*. *MUTYH* was tested the most frequently (n=245), and *GREM1* was tested the least frequently (n=70). In total, 2,431 genes were tested across 258 patients, identifying 12 (0.5%) germline variants (including pathogenic variants, VUS and carriers).

Genetic Variants

The characteristics of patients identified with a genetic variant are shown in *Table 3.* In total, four patients had pathogenic variants: one with *RNF43*, one with *MSH2* and two with *PMS2*; the latter three had Lynch syndrome. The father of the patient with an *RNF43* variant had SP and a history of CRC. Colonoscopy data demonstrated that he did not fulfil the 2019 SPS WHO criteria. He was not tested for *RNF43*. The son of the patient with an *MSH2* variant has SPS and is also a patient in our study cohort. He received R211 gene panel testing, which identified no pathogenic variants. The patient with *PMS2* exon 1 deletion has a history of sigmoid cancer *(Table 3).*

DISCUSSION

This retrospective, cross-sectional analysis conducted at a specialist tertiary centre, contributes to the limited evidence surrounding germline variants associated with SPS. Gene panel testing identified a pathogenic variant in only 1.5% of patients, aligning with similar studies (9,10). In addition, a variant detected in MSH6 (c.1450G>C) has been classified as a VUS, however Clinvar reports conflicting classifications of pathogenicity, if pathogenic it

may slightly alter the overall diagnostic yield (19). Arguably this emphasises the point that the main benefit of diagnostic testing may be to identify co-existing diagnoses, such as LS and SPS, which may improve precision in care.

This is the first study to use the R211 gene panel in SPS patients, and we found a pathogenic variant in *RNF43 (Table 3).* This matched the variant identified by Murphy *et al.* (9) but differed from the splice site variant identified by Yan *et al.* (5). Additionally, familial involvement was observed, consistent with Yan *et al.*, who reported the same *RNF43* variant in four family members (5). However, other multicentre studies have found no *RNF43* variants in SPS cases (9,10) reaffirming its rarity.

All *MUTYH* carriers in our study had CRC, which is consistent with historical reports that *MUTYH* carriers have a two-fold increased CRC risk (20). However, routine testing for monoallelic carriers is not recommended for SPS cases given the high prevalence of monoallelic *MUTYH* carriers in Caucasian populations (20).

Interestingly, we identified a dual pathology between SPS and Lynch syndrome in three patients, suggesting the serrated pathway may contribute to Lynch syndrome CRCs (21,22). This dual pathology has been previously reported but may be overrepresented due to ascertainment bias (23). Future investigations are required to identify whether dual pathology has an additive or cumulative cancer risk.

The most recent SPS study on genetic factors divided its cohort into two subgroups: those with most serrated polyps in the proximal colon and those with most in the distal colon (24). Pathogenic variants were identified only in the proximal colon subgroup, which may be attributed to the differences in the embryonic origins of the proximal and distal colon (25).

This finding could promt future SPS research to focus on polyp location when investigating genetic involvement.

Our SPS cohort showed no gender predominance, similar to a recent meta-analysis (26), and a median diagnosis age of 42 years, which is lower than previous reports (27). This younger age may be attributed to our use of family registry data, while other studies relied on hospital data. The predominance of Caucasian patients in our cohort aligns with previous studies indicating a higher prevalence of SPS in Caucasians (28 ,29). Finally, a fifth of our cohort had CRC, consistent with the estimated 15% and 29% risk in other studies (23,26).

NHS-funded constitutional genetic testing has traditionally been offered only to individuals with a likelihood of at least 10% for identifying a causative, clinically actionable constitutional pathogenic variant (30). However, the data presented in this study falls significantly below this threshold, raising questions about the value of genetic testing in SPS. These findings suggest that current guidelines for such testing should be re-evaluated.

Several limitations must be considered. The complete R211 gene panel was assessed in only half of our cohort, potentially underestimating findings. The evolution of target test regions and sensitivity also introduces time-varying confounding throughout the study period, especially since three patients had a VUS. Data from the Polyposis Registry introduced ascertainment bias, as referrals may not represent all SPS cases. Detection bias could have occurred due to varying interpretations of colonoscopies and pathology findings by different specialists, particularly data dated back to 1990. Additionally, smoking, alcohol use and BMI data were incomplete, limiting the ability to assess confounding variables which may influence the pattern of inheritance of SPS (31). Finally, this study focus' on UK based clinical practice and guidelines, which may limit the generalisability of our findings to

international settings where recommendations for germline testing in SPS differ. Notably, some guidelines, such as those from the NCCN, currently recommend genetic testing only in the presence of additional clinical features (32).

The low diagnostic yield of pathogenic variants in SPS patients raises questions about current guidelines and highlights the need to explore alternative pathways for SP development in future research. Multicentre studies on an international scale are essential. Expanding the gene pool and assessing family history through international collaboration will yield more comprehensive data, leading to a better understanding of the condition's genetic aetiology. Longer follow-up studies are needed to assess CRC risk more accurately, ideally from 10 to 15 years as this is the average time taken for a serrated polyp to become cancerous (33). This will help identify which individuals may require more frequent colonoscopy screenings. Finally, a national SPS registry, similar to the Lynch Syndrome Registry, could be introduced to improve patient identification and management (34).

Conclusion

The study highlights the low diagnostic yield of pathogenic variants in SPS, suggesting other factors contribute to its development and that current guidelines should be revised. Future research should focus on understanding the pathophysiology behind SP development, establishing family databases, and developing tailored surveillance strategies for SPS.

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Figure Legends

Figure 1: Flowchart of patients included and excluded in the study
SPS: Serrated Polyposis Syndrome

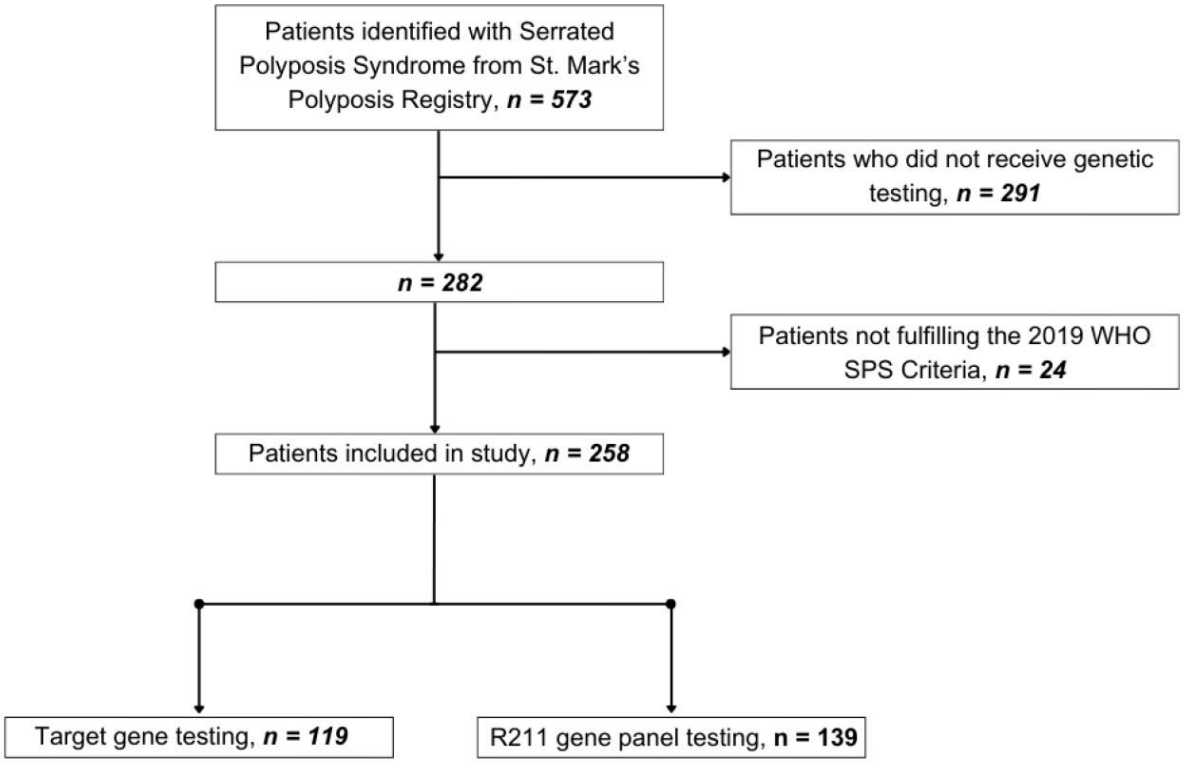

Figure 2: Flowchart showing the outcome of genetic testing in Serrated Polyposis Syndrome cohort.

VUS = Variant of Unknown Significance

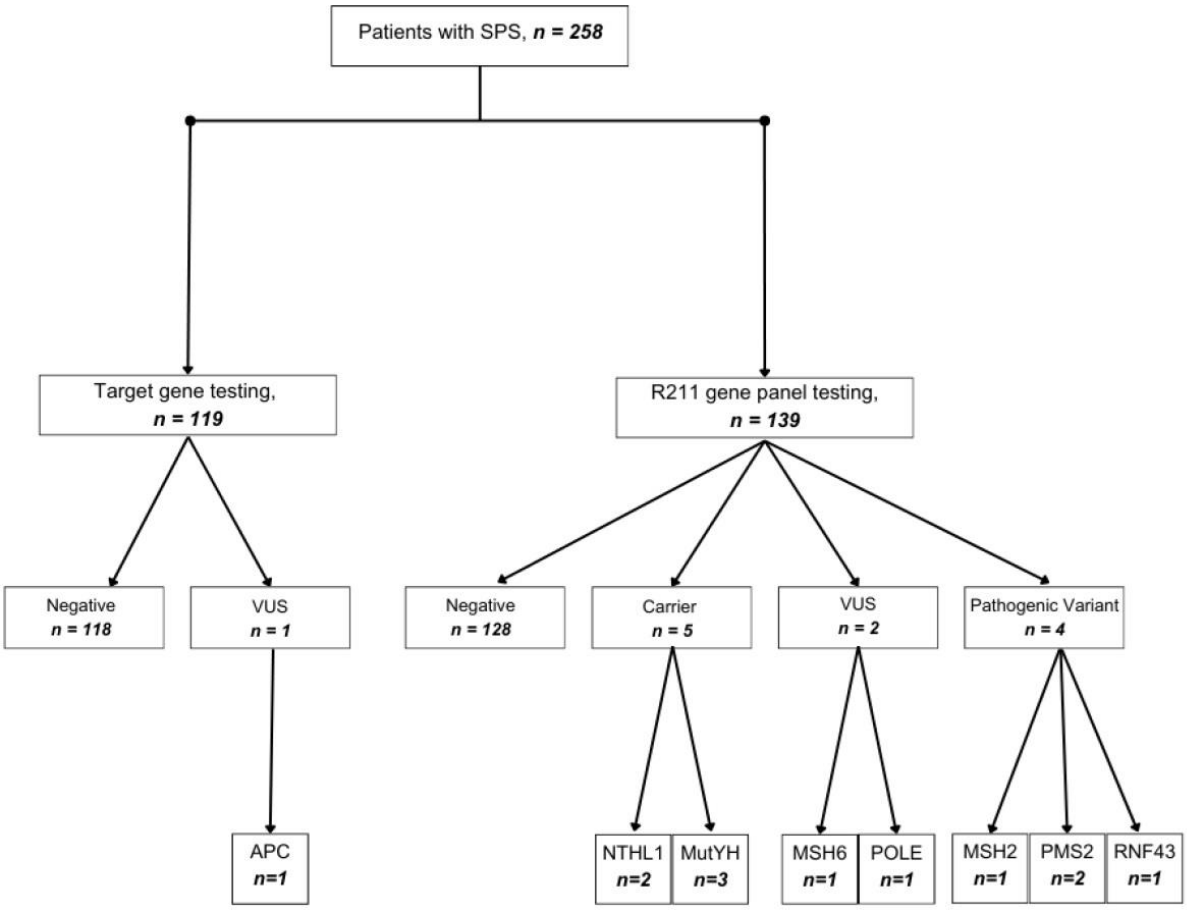

Table 1. Characteristics of the Study Population.

Characteristics	Total ***n=258*** **(%)**	Target Gene ***n=119***	R211 Panel ***n=139***
Sex n, (%)			
Female	136 (52.7)	60	76
Male	122 (47.3)	59	63
Ethnicity			
Caucasian	160 (62.0)	71	89
Asian	20 (7.8)	9	12
Black	7 (2.7)	4	3
Hispanic	3 (1.2)	2	1
Other	68 (26.4)	33	35
Unknown			
Age at diagnosis (years)			
30 or less	15 (5.8)	11	4
31-40	97 (37.6)	45	52
41-50	52 (20.2)	10	42
51-60	38 (14.7)	20	18
61-70	36 (14.0)	20	16
71 or over	20 (7.8)	13	7
Smoker			
Never smoker	99 (38.4)	40	59
Ever smoker*	119 (46.1)	48	71
Unknown	40 (15.5)	31	9
WHO Criteria			
Criterion 1	33 (12.8)	15	18
Criterion 2	135 (52.3)	62	73
Criterion 1 and 2	90 (34.9)	42	48
Reason for Referral			
Symptomatic*	135 (52.3)	60	75
Family History SPS	9 (3.5)	7	2
Family History of CRC	20 (7.8)	11	9
Incidental	13 (5.0)	6	7
BCSP	41 (15.9)	20	21
CRC**	40 (15.5)	15	25
CRC History			
Yes	63 (24.4)	33	30
No	195 (75.6)	86	109

* Those who had symptoms, were referred for colonoscopy and identified to have Serrated Polyps

**Those identified from the NHS national Bowel Cancer Screening programme

*** Those who were identified with Serrated Polyps due to colonoscopy associated with colorectal cancer diagnosis or management

WHO: World Health Organisation; SPS: Serrated Polyposis Syndrome; CRC: Colorectal Cancer; BCSP: Bowel Cancer Screening Programme

Table 2. **Number of patients tested for each gene and the result**

Genes tested (n=16)	**Number of patients tested**	**Pathogenic Variant**	**VUS**	**Heterozygote Carrier***	**Total germline variant, n. (%)**
APC	172	0	1	n/a	1 (0.6)
BMPR1A	139	0	0	n/a	0 (0.0)
EPCAM	139	0	0	n/a	0 (0.0)
GREM1	70	0	0	n/a	0 (0.0)
MLH1	139	0	0	n/a	0 (0.0)
MSH2	139	1	0	n/a	1 (0.7)
MSH6	139	0	1	n/a	1 (0.7)
MUTYH	245	0	0	3	3 (1.2)
NTHL1	139	0	0	2	2 (1.4)
PMS2	139	2	0	n/a	2 (1.4)
POLD1	154	0	0	n/a	0 (0.0)
POLE	154	0	1	n/a	1 (0.7)
PTEN	139	0	0	n/a	0 (0.0)
RNF43	139	1	0	n/a	1 (0.7)
SMAD4	139	0	0	n/a	0 (0.0)
STK11	139	0	0	n/a	0 (0.0)
Total	**2,431**	**4**	**3**	**5**	**12 (0.5)**

*Heterozygote carriers are only relevant for recessively inherited genes *MUTYH* and *NTHL1* (30).

VUS: Variant of Unknown Significance

Table 3. Details of genetic variants identified and characteristics of patient and family
Age reported in years

Gene affected	Genetic Variant	WHO Criterion	Age at SPS diagnosis	Hereditary CRC conditions	History of CRC (age)	Personal cancer history	Family history of SPS (age)	Family history of CRC (age)
Pathogenic Variant								
RNF43	c.471del p.(Thr158ProfsTer6)	N/A	47	N	N	N	N	Father (67) Paternal grandmother (7
MSH2	c.1407delT p.Val470X	II	69	Lynch Syndrome	N	Endometrial (54)	Son (41)	Father (71) Paternal uncle (58) Paternal grandmother (61)
PMS2	c.137G>T p.(Ser46Ile)	II	38	Lynch Syndrome	N	N	N	N
PMS2	Exon 1 deletion	I and II	73	Lynch Syndrome	Y (39)	N	N	Mother (60)
Variant of Unknown Significance								
MSH6	c.1450G>C p(Glu484Gl)	I and II	67	Lynch Syndrome	Y	N	N	Mother (90)
POLE	c.1337 G>A p.Arg446Gln in exon13	II	24	N	N	N	N	N
APC	c.[7472T>C] p.Met2491Thr	II	37	N	Y	N	N	N
Heterozygous Carrier								
MUTYH	c.821G>A p.(Arg274Gln)	I	82	N	Y (81)	N	N	N

MUTYH	c.536A>G p. (Tyr179Cys)	II	58	N	Y (56)	N	N	N
MUTYH	c.1187G>A p.(Gly396Asp)	II	66	N	Y (39)	N	N	N
NTHL1	c.98G>A p.(Arg33Lys)	II	32	N	Y (32)	N	N	N
NTHL1	c.244C>T p.(Gln82)	I and II	39	N	N	N	N	Maternal cousin (40)

SPS: Serrated Polyposis Syndrome; CRC: Colorectal Cancer