20W163

Germline mutation testing in Serrated Polyposis Syndrome

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Main findings

- 9% of SPS patients were affected by heterozygous germline mutations, higher than previously reported
- Over half of these patient would not have been recommended for genetic testing by current guidelines
- This is the first study to describe CHEK2 and POLD1 mutations with an SPS phenotype

Introduction

Serrated Polyposis Syndrome (SPS), now known to be the commonest polyposis syndrome, is a clinical phenotype characterized by the presence of multiple serrated polyps. It is thought that serrated polyps account of 15-35% of colorectal cancers (CRC). The WHO have updated the diagnostic criteria for SPS to include:

i. ≥ 5 Serrated polyps ≥5mm in size proximal to the rectum with ≥ 2 being ≥10mm
ii. >20 Serrated polyps of any size throughout the bowel with ≥5 proximal to the rectum

The British Society of Gastroenterology (BSG) have recently updated their guidance for genetic testing in SPS and recommend testing inpatients with any of the following:

i. Age <50
ii. Multiple affected patients within a family
iii. Dysplasia within any of the polyps

Previous analysis for germline mutations have shown no consistent positive findings.

Aims

To determine the yield of genetic mutations in the Oxford SPS cohort and to determine whether current BSG recommendations would have identified patients with a germline mutation.

Methods

A database of patients with SPS according to WHO criteria was established at the Oxford University Hospitals NHS Trust in 2010. A retrospective review was conducted on all patients fulfilling WHO 2019 criteria for SPS in this database. Patients were referred for genetic assessment based on personal and family history, and patient preference. All patients referred underwent genetic counselling. Panel testing was introduced in Oxford in 2014. This panel has been refined over time to form the current 14 gene colorectal panel consisting of : APC, BMPR1A, MLH1, MSH2, MSH6, MuTYH, NTLH1, POLD1 (exons 8-13), POLE (exons 9-14), PTEN, SMAD4, STK11, GREM1 (40kb duplication) and PMS2.

Results

173 patients were diagnosed with SPS based on WHO 2019 criteria between February 2010 and March 2020. The clinical characteristics are outlined in table 1. The mean age of diagnosis was 54.2 ± 16.8 years (range 18-82). 50.9% (n=88) were female. 98 individuals fulfilled WHO criteria I (56.6%), 25 (14.5%) fulfilled criteria II and 50 (28.9%) fulfilled both criteria I and II.

16.73% (n=29) of patients were diagnosed with CRC. The majority (69%, n=20) were diagnosed with CRC at the time of SPS diagnosis.

Results

		WHO type 1 N = 98 (56.6%)	WHO type 2 N=25 (14.5%)	WHO type 1+2 N = 50 (28.9%)	Total N = 173
Sex	Female	54 (55.1%)	9 (36%)	25 (50%)	88 (50.86%)
	Male	44 (44.9%)	16 (64%)	25 (50%)	85 (49.13%)
Age (years)	Mean ± SD	62.4 ± 15.8	61.9 ± 16.3	51.5 ± 17.7	59 ± 17
Age at diagnosis (years)	Mean ± SD	57.4 ± 15.4	56 ± 16.9	47 ± 17.4	54.2 ± 16.8
Dysplasia in SP	Yes	22 (22.45%)	5 (20%)	15 (30%	42 (24.28%)
	No	76 (77.55%)	20 (80%)	35 (70%)	131 (75.72%)
Colorectal cancer history	Yes	18 (18.37%)	2 (8%)	9 (18%)	29 (16.76%)
	No	80 (81.63%)	23 (98%)	41 (82%)	144 (83.24%)
Smoking	Smoker	17 (17.35%)	8 (32%)	12 (24%)	37 (21.39%)
	Ex-smoker	30 (30.61%)	7 (28%)	14 (28%)	51 (29.48%)
	Never smoker	21 (21.42%)	6 (24%)	11 (22%)	38 (21.97%)
	Unknown	30 (30.61%)	4 (16%)	13 (26%)	47 (27.17%)

Table 1: Characteristics of patients with SPS included in the study

Patients had a mean number of 2.2 ± 1.5 surveillance colonoscopies (range 1-8). Median follow up time was 35 months (IQR 15- 52) from diagnosis of SPS to the date of their last colonoscopy.

Results

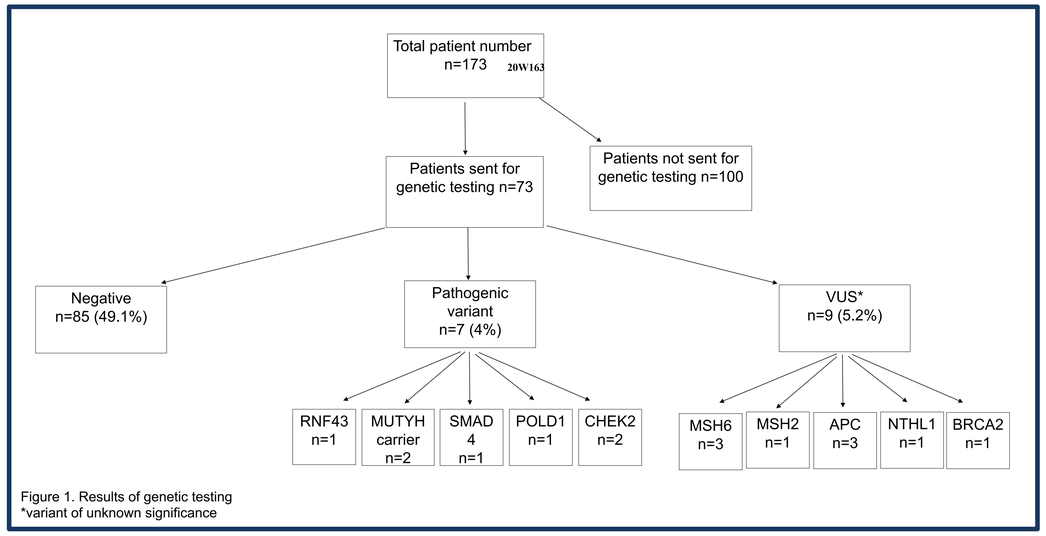

Figure 1. Results of genetic testing
*variant of unknown significance

73 (42.2%) underwent genetic testing. 67.1% (n=49) were testing using a CRC/polyposis gene panel. 15 patients (8.6% of entire cohort, 20.5% of those who were tested) had a germline genetic variant and 7 of these patients (4% of entire cohort) had a pathogenic variant in a gene known to be associated with CRC predisposition. The genetic variants found are outlined in table 2. One patient had a RNF c.471delG p.THR158FS variant in exon 5. This patient also had a family history of serrated polyposis and his niece also carried this pathogenic variant. Two patients had pathogenic mutation in CHEK 2 and a third patient had a pathogenic variant in POLD1. These have not previous been reported with a serrated polyposis phenotype. The genetic results led to a change in surveillance for 7 patients and their families.

Only 57.1% (4/7) of patients with a pathogenic germline mutation and 60% (9/15) of all patient with a genetic variant in genes known to predispose to cancer fulfilled the BSG criteria for genetic testing in SPS

Results

Gene affected	Mutation	WHO SPS type	Age at diagnosis	History of CRC (age)	Family history of CRC (age)	Personal Cancer history	Family history of Cancer
RNF43	c.471 del G (exon 5) p.(THR158FS) Pathogenic variant	I,II	68	No	Yes	Prolactinoma	
MUTYH APC	c.1187G>A p.(Gly396Asp) Pathogenic variant c.646-4T>G Uncertain variant	I,II	70	No	No	No	
MUTYH	c.1187G>A p.(Gly396Asp) Pathogenic variant	I	32	No	No	No	No
SMAD4	c.455-2A>G Pathogenic variant	I	78	Yes (58)	No	No	Brain tumour (Sister)
POLD1	c.946G>A p.(Asp316Asn) Pathogenic variant	1	70	No	Father (47)	Endometrial cancer	Breast (Sisters x2)
CHEK2	c.1427C>T p.(Thr476Met) Pathogenic variant	I	34	No	Great grandfather	No	Breast (Grandmother)
CHEK2	c.1100delC p.(Thr367fs) Pathogenic variant	I	68	No	Father (64)	Breast Cancer (63)	Breast (Mother)
MSH6	c.1054G>A p.(Val352Ile) Uncertain variant	II	30	No	Father (43)	No	Ovarian (Grandmother)
MSH6	c.239BG>C p.(Val800Leu) Uncertain variant	I	59	No		No	
MSH6	c.3026A>T p.(Lys1009Ile) Uncertain variant	II	36	No	Father (49) Paternal Aunt (80) Paternal Uncle (60)	Breast Cancer (34)	Melanoma (Aunt) Lung (Grandfather)
MSH2	c.835C>G, p.(Leu279Val) Uncertain variant	I	37	Yes (28)	No	No	
APC	c.3479C>A p.(Thr1160Lys) Uncertain variant	I,II	54	No	Brother Paternal uncle (70s)	Prostate (57)	
APC	c.2486C>T p.(Thr829Ile) Uncertain variant	I,II	38	No	No	No	No
NTHL1	c.512C>T p.(Thr171Met) Uncertain variant	I,II	52	No	Maternal aunt Maternal grandfather	No	
BRCA2	c.7820C>T p.(Thr2607Ile) Uncertain variant	I	69	Yes (57,74)	Father (65)	Prostate (75)	Leukaemia (Brother) Breast Cancer (Daughter)

Table 2. Genetic variants

Conclusion

4% (7/173) of SPS patients were affected by a pathogenic germline mutation in a gene known to predispose to colorectal cancer, higher than reported in previous studies, including previously unreported associations with CHEK2 and POLD1. This led to a change in management for patients or their families in all seven cases. Only 57.1% of these patients would have been recommended for gene panel testing in the current BSG guidelines. Detection of germline mutation could have significant impact on risk assessment and clinical management, including advice on extra-colonic surveillance in patients and their family members.

We propose that all patients fulfilling the WHO criteria for SPS be seen in a family cancer clinic to discuss surveillance strategy and colorectal cancer risk, and to consider referral to Clinical Genetics for genetic counselling and gene panel testing.

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The authors declare no conflicts of interest