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Young-Onset Colorectal Cancer is Associated with a Personal History of Type 2 Diabetes

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Abstract

Background: Colorectal cancer (CRC) is rising in incidence in young adults, and this observation is currently unexplained. We investigated whether having a personal history of type 2 diabetes mellitus (T2D) was a potential risk factor for young-onset colorectal cancer (YOCRC).

Methods: The South Australian Young Onset (SAYO) CRC study is a series of young adults with CRC below age 55. Ninety unrelated YOCRC cases were recruited to the study. Personal history and detailed family history of T2D were obtained at face-to-face interview and confirmed from medical records. Whole exome sequencing was conducted on germline DNA from each CRC case. Controls for personal history studies of T2D were 240 patients with proven clear colonoscopies and no known CRC predispositions.

Results: The median age of YOCRC cases was 44 years (18-54) and of controls was 45 years (18-54), and 53% of both cases and controls were females ($P=0.99$). Left-sided (distal) CRC was seen in 67/89 (75%) of cases. A personal history of T2D was confirmed in 17/90 (19%) YOCRC patients compared with controls (12/240, 5%; $P<0.001$; OR 4.4; 95% CI 2.0-9.7). YOCRC patients frequently reported at least one first-degree relative with T2D (32/85, 38%). Ten of 87 (12%) of YOCRC cases had CRC-related pathogenic germline variants, however, no pathogenic variants in familial diabetes-associated genes were seen.

Conclusions: Though the mechanism remains unclear, our observations suggest that there is enrichment for personal history of T2D in YOCRC patients.

Impact: A diagnosis of T2D could therefore potentially identify a subset of young adults at increased risk for CRC and in whom early screening might be appropriate.

Keywords: Colorectal cancer, Germline mutations, Risk factors, Screening, Type 2 Diabetes, Young-Onset Colorectal cancer

Introduction

Young-onset colorectal cancer (YOCRC) incidence is rising in Australia (1,2), and elsewhere in the developed world (2,3), at a time when the incidence of CRC in older adults is declining (4). This rise in incidence is currently unexplained. Individuals who develop CRC before the age of 50 years, present at a later stage in their illness (5-8), and are thus frequently unable to take advantage of the benefits of early detection. Due to patient- and healthcare-associated diagnostic delays, and subsequent late and often symptomatic presentations, young adults suffer considerable morbidity and mortality in their most productive time of life, impacting on education, career, family and social life, and physical and mental health in the survivors. In 2013, 1313 Australian young adults developed CRC. In 2017, CRC was responsible for the most cancer deaths in 20-29 year old Australians (9).

In Australia, population screening is recommended for people aged 50 to 75 years. This is carried out under the National Bowel Cancer Screening Program (NBCSP) with faecal immunochemical tests (FIT), in those considered to be at average risk, via Medicare-subsidised FIT tests requested by general practitioners (family physicians) and via FIT test kits purchased privately. Screening not only aims to detect cancers, but may also detect advanced pre-cancerous polyps in the ratio of four to five lesions for every one cancer detected (10), thus facilitating both prevention and early detection. Young adults (<50 years) without a family history of CRC have a lower risk of CRC when compared with their older counterparts and are therefore not included in population screening programs. In this age group the low yield, potential for harm, and anxiety which are associated with screening may outweigh any benefits of early detection. These factors also translate to a lack of cost-effectiveness. Therefore, in the absence of a family history, targeted screening only is carried out for people under 50 years in individuals when there are known predispositions such as inflammatory bowel disease or evidence of an inherited pathogenic or likely pathogenic variant (P/LP variant) in a gene predisposing to CRC (11).

CRC in young adults is heterogeneous. Approximately 10% arises from inherited DNA mismatch repair deficiency (12), and a further small proportion from other known high penetrance genetic predispositions. The remainder of CRC in young adults is largely unexplained, apparently sporadic, and accounts for >80% of the burden. Importantly, YOCRC examined in retrospect, frequently does not meet the criteria for screening (13) in that there is no significant family history. Though population screening is not justified for those under 50 with no family history (14), screening of highly targeted young adult subsets with identified risk factors outside the current guidelines has the potential to extend the successes of screening older patients to those aged under 50

with increased risk. Currently, though modern lifestyles are likely to be implicated in the observed rise in incidence of YOCRC, there has been no definitive risk factor identified. Patients diagnosed with T2D at any age have a 20-40% higher *risk* of CRC than the general population (15). CRC and T2D are complex diseases resulting from an interaction between acquired as well as genetic factors. Although the link between CRC and T2D has been frequently reported in studies (16), the association between personal and/or family history of T2D and YOCRC has not been widely investigated (17). The aim of this study was to investigate whether personal history T2D was associated with YOCRC.

Materials and Methods

SAYO Study

The South Australian Young Onset Colorectal Polyp and Cancer Study (SAYO) is a multidisciplinary state-wide consortium which seeks to identify the risk factors and warning signs for CRC in young adults. Study activities, including colonoscopy database audits, are carried out under ethics approval HREC/14/TQEHLMH/194 (The Queen Elizabeth Hospital, CALHN Office for Research, Adelaide, South Australia). The study has directly enrolled patients identified with primary adenocarcinoma of the colorectum aged under 55 years from public and private hospitals since 2015 by face-to-face interview. Written informed consent was provided by all study participants. CRC was confirmed from medical records. CRC was divided into right-sided (proximal) cancers (cecum, ascending colon, hepatic flexure and transverse colon) and left-sided (distal) cancers (splenic flexure, sigmoid colon, descending colon, recto-sigmoid and rectum). Though population screening in Australia begins at age 50, younger adults aged up to 55 years with CRC are enrolled in the study due to the low rates of population screening uptake in this overlapping age group (26.4%), the more pronounced risk of CRC in patients under 55 who develop T2D mellitus, and reported increasing mortality in patients under 55 in the United States (4; 9; 18; 19). Patients enrolled in the study underwent an interview which covered potential risk factors such as personal and family history of any cancers in first- and second-degree relatives, colorectal polyps, and T2D mellitus. Blood was sampled for whole-exome sequencing of leucocyte DNA (20). Recruitment acceptance for SAYO remained high throughout the enrolment period with over 95% of patients approached agreeing to participate.

Description of Personal History Studies

Personal history of T2D was obtained from SAYO CRC cases at face-to-face interview, and confirmed from medical records including notes, blood tests and medication history. Controls for this comparison were age-appropriate patients from a single centre with proven clear colonoscopies and no known CRC predisposition (germline P/LP variant, inflammatory bowel disease). Controls (n=240) were drawn from a series of 3130 colonoscopies carried out at a single centre (the Queen Elizabeth Hospital) in 2016 using approaches described previously (21). Patients were deemed eligible to serve as controls if they returned findings of a clear colonoscopy, and had no inflammatory bowel disease, no previous colorectal neoplasms, and no known inherited predispositions to CRC. T2D was confirmed from admission interview and also from medical charts including notes, blood tests and medication history. Family history of CRC was based on interview alone and not confirmed in both cases and controls.

Genetic Testing

SAYO patients with CRC underwent whole exome sequencing of their germlines as previously described (22). Briefly, whole exome sequencing was performed using the KAPA HyperPrep Kit for library preparation and the Roche SeqCap EZ MedExome Enrichment Kit for sequence capture. The Illumina NextSeq 500 was used to sequence the captured libraries (2x150bp paired-end reads). The Burrows-Wheeler Aligner (BWA) was used to align sequences to the human reference sequence (hg19). The Genome Analysis ToolKit (GATK) was used for performing variants calling and variants were annotated with ANNOVAR. American College of Medical Genetics (ACMG) guidelines (23) were used to identify likely pathogenic or pathogenic (class 4 or 5 respectively) germline variants in CRC-associated genes and in genes associated with monogenic non-neonatal diabetes (24), severe insulin resistant diabetes, mild obesity related diabetes, and mild age-related diabetes (25) for deleterious changes (see Supplementary Table 1). Pathogenicity of putative germline P/LP variants was confirmed using public databases (n=8), explored for functionality using MSI testing (n=1) or lymphoblastoid cell line RNA splicing (n=1). Routine mismatch repair testing of cancer tissue via immunohistochemistry was undertaken to detect potential Lynch syndrome patients as previously described (26).

Statistics

Means in continuous variables were compared using a t-test procedure. Prevalence of characteristics in patients was compared between cases and controls using Pearson's chi-squared or Fishers Exact test as appropriate. All statistical association tests were performed using SPSS Version 25 for Mac (IBM). Two-tailed statistics were used throughout with a significance level of <0.05 .

Results

Summary features of 90 study participants with CRC are shown in Table 1. CRC patients ranged in age from 18-54 years (median age 44). Clear colon controls (n=240) ranged in age from 18-54 years (median age 45). The main indications for colonoscopy in cases and controls were rectal bleeding, a change in bowel habits or abdominal pain. Forty-four of 90 (49%) YOCRC patients and 90/212 (42%) of controls had bleeding ($P=0.31$), 38/90 (42%) of CRC patients and 34/212 (18%) of controls had change of bowel habit ($P<0.001$), and 33/90 (37%) of YOCRC cases and 43/212 (20%) of controls had experienced abdominal pain ($P<0.001$). The majority of CRC patients were of European ethnicity (n=86), except for four whose ancestors were Filipino (n=2) Iranian (n=1) or Indian (n=1). Forty-eight of 90 (53%) were females. Left-sided (distal) CRC was seen in 67/89 patients (75%), with a distal site of cancer being less common in females (30/47, 64%) compared to males (37/42, 88%) ($P=0.01$). First-degree family history of CRC was seen in 10/85 (12%) of YOCRC cases and 25/212 (12%) of controls ($P=0.99$). Information was not available in 5 remaining CRC cases due to adoption and an unknown family history. Pathogenicity of putative germline mutations was confirmed using public databases (n=8), explored for functionality using MSI testing (n=1) or lymphoblastoid cell line RNA splicing (n=1). Seven of 83 (8%) patients had a mismatch repair deficient cancer, and three of 87 (3%) YOCRC cases had a mismatch repair deficient cancer and molecularly confirmed Lynch syndrome. The remaining four patients with a mismatch repair deficient CRC did not have a family history meeting the revised Bethesda criteria (27), germline mutation or methylation in a known mismatch repair gene. Ten patients were found to have deleterious variants in CRC-associated genes, four in *BRCA2*, two in *MSH2*, one in *MSH6*, one in *RNF43* and two patients had biallelic mutations in *MUTYH* (see Supplementary Table 2). One patient with a deleterious *MSH2* mutation (female aged 29) also carried a mono-allelic deleterious *MUTYH* mutation. It is worth noting that only one of 10 YOCRC patients with a germline mutation had a first-degree family history with CRC (Figure 1), and the details of these findings will be reported in detail in a separate publication.

A personal history of T2D was confirmed in 17/90 (19%) of the series of YOCRC cases, which was significantly higher than the prevalence in the controls (12/240, 5%; $P < 0.001$; OR 4.4; 95% CI 2.0-9.7). This was also true when patients were partitioned for age. Those aged 18-44 years at diagnosis (6/50 or 12% vs 3/114 or 3%; $p = 0.02$; OR 5.0 CI 1.2-21.1) as well as those 45-54 years (11/40 or 28% vs 9/126 or 7%; $p = 0.0001$; OR 4.9 CI 1.9-13.0) had significantly increased prevalence of T2D (Figure 2). A personal history of T2D remained significantly higher in YOCRC cases (15/90, 17%) after excluding those cases ($n = 2$) with deleterious variants in CRC-associated genes compared to controls (12/240, 5%; $P < 0.001$; OR 3.8; 95% CI 1.7-8.4). The prevalence of T2D in males and females was 24% and 23% in SAYO cases, respectively ($P = 0.99$) (Table 1). In all cases where T2D was present, this was identified at ($n = 2$) or before ($n = 15$) the time of diagnosis of CRC.

Patients with CRC frequently reported at least one first-degree relative with T2D (32/85 or 38%). First-degree family history of T2D was seen in one or both parents in 23 cases, siblings only in 4 cases, and parents and siblings in a further 5 cases. A first-degree family history of T2D was observed in both males and females (15/39, 38% and 17/46, 37% respectively; $P = 0.99$). Twelve of 16 (75%) patients with personal history of type 2 diabetes, where family history was known, *also* had first-degree relatives with type 2 diabetes. No previously described diabetes-associated loci were found to harbor deleterious alterations on exome sequencing.

Discussion

Currently, the increased incidence of YOCRC is unexplained. Recent geographical data from the United States have shown that though the prevalence of obesity and heavy alcohol consumption has increased during the time period 1995 – 2005, there was no correlation between these potential risk factors and increasing incidence rates of YOCRC (28). In this report, we examined T2D as a risk marker for YOCRC. Diabetes of all types affects 1 in 17 adult Australians (6%), and approximately 5% of the adult population have T2D (29). The population rate of diabetes in those aged 18 to 44 is 1.5% increasing to 5% in those aged 45-54 years. This is commensurate with the rate of T2D observed in our series of clear colonoscopy control patients aged under 55 years at 5%. However, our case series of young adults diagnosed with CRC under 55 years of age has a significantly higher personal rate of T2D than is present in clear colonoscopy controls. Our results suggest that young adults with T2D may be at increased risk for developing CRC.

The consistent association between T2D and CRC is postulated to be associated with a pro-inflammatory milieu involving insulin-dependent growth factors at a molecular level (30). Lifestyle factors are thought to play a role, and these include lack of physical activity, poor dietary choices and obesity, however, obesity *per se* has not been shown to underlie YOCRC in recent US findings (28). High levels of insulin signalling in the pre-diabetic *milieu* are also thought to contribute to the increased incidence of CRC in the immediate post diagnosis period. A recent report from de Kort et al. (19) has identified a peak incidence of CRC in T2D patients during the 6 months following initial diagnosis (HR 1.3, 95% CI 1.2-1.5), and this was significantly more prevalent in the proximal colon (HR 1.7, 95%CI 1.4-2.0). The risk was highest in males aged less than 55 years (HR 2.0, 95%CI 1.0-3.8). When detection bias is considered by excluding the initial period after diagnosis of type 2 diabetes, the relationship between T2D and CRC continues to be robust albeit with a lower level of risk. Overbeek et al. reported that patients with T2D were 1.3 times at higher risk of developing CRC compared to diabetes free controls, and a higher increased risk of proximal colon cancer was observed among females with T2D (HR 1.58, 95%CI 1.13-2.19) than males with this condition compared to controls, and they found males with T2D were at higher increased risk of developing distal colon cancer (HR 1.42, 95%CI 1.08-1.88). The authors concluded that more attention should be paid to sex-specific screening and prevention protocols for patients with T2D (31). Though there was a trend in our results for females to have more proximally located CRC, our numbers are small and therefore cannot be used to support this observation. In addition, the cited report reflects CRC patients of all ages rather than those who are under 55 yrs. Proximal CRC becomes more common with age in females (32). Vu et al. found that patients aged 40-49 years with T2D mellitus were at higher risk of developing colorectal adenomas compared to the same age group without this disease (OR = 3.1; 95%CI: 1.5-6.4; P = 0.002) (33). Recently, Ali Khan et al. conducted a nationwide cohort study using Swedish family cancer data sets and reported that young adults with diabetes mellitus were at increased risk of developing CRC by 1.9-fold under age of 50 years (95% CI for standardized incidence ratio: 1.6–2.3) and by 1.3-fold at or after 50 years of age (1.2–1.4). They also found that young patients with diabetes had a similar lifetime risk of developing CRC under the age of 50 years (0.4%, 95% CI: 0.3%–0.4%) to individuals with only a family history of CRC (0.5%, 0.5%–0.5%) (34). These findings are consistent with our Australian cohort results showing the prominent association of diabetes with increased risk of CRC in young adults.

Another factor in the aetiology of YOCRC may involve the microbiome. Gut microbiota produce short-chain fatty acids (butyric acid and acetic acid) which protect the intestinal tract by increasing the production of mucus from intestinal goblet cells. The decrease in the production of short-chain fatty acids might suppress the function of goblet cells and results in reducing the function of the intestinal barrier. This results in transferring lipopolysaccharides, mostly produced by protobacteria, from the intestinal side to the lumen where it comes in contact with blood. When the level of lipopolysaccharides increases in the blood, insulin resistance organs such as skeletal muscle and liver become insulin resistant which finally leads to hyperinsulinemia (35). This might enhance IGF and Wnt signalling systems and result in CRC carcinogenesis (36). Zhao et al. (37) reported that some dietary fibres manipulated the gut microbiota and enhanced the production of short-chain fatty acids. Overgrowing bacteria which produce these fatty acids directly associated with the reduction in the level of glycated haemoglobin. A systemic review concluded that dietary intervention in patients with T2D was reported to modulate the gut microbiota and improve glycaemic control (38). The risk of CRC associated with T2D has become an issue of concern as the age at which T2D is diagnosed is shifting further towards younger adults (19), and a diagnosis of T2D in a patient younger than 50 years has the potential to serve as an inclusion criterion for early screening.

Family history of diabetes increases with age in the general population (27). In the current report, our observations also suggest that an inherited factor which increases the risk of T2D in a family *may* also increase the risk of YOCRC, and this deserves further exploration as this too has the potential to identify younger adults at risk in the population prior to the onset of CRC. There have been at least two previous reports suggesting a link between family history of T2D and CRC, which lend additional evidence to support our findings. In 2002, Bauer et al. (39) investigated familial aggregation of diabetes and colorectal neoplasia, and found positive associations between familial diabetes and adenomatous polyps or CRC. Ma et al. (17) reported in 2018 that family history of diabetes is associated with risk of CRC in a sex-specific manner, and that the relationship is more pronounced in patients under 60 years, and only significant in males. We found this feature in both sexes with YOCRC, however, the numbers were low and hence it is not possible to confirm this observation. Though there was enrichment for T2D in families, no diabetes-associated variants were noted on exome sequencing.

There are several paradigms which may be drawn upon to explore our findings, however the most plausible is a gene environment interaction associated with modern lifestyles. An enrichment for personal and family history

of T2D in the young adult population with CRC may simply reflect shared lifestyle factors, including shared exposure to high calorie load, and at this point, this consideration cannot be excluded. However, the relationship between T2D and CRC has been shown to be independent of obesity in patients under 55 years (40), and therefore a genetic or epigenetic predisposition may also be a factor in these observations. Metabolically unhealthy phenotypes, including patients with high insulin signalling in the setting of normal weight, indicative of genetic background, increase the risk for CRC (41). As patients were enrolled at the time of diagnosis in this study, body mass index (BMI), a potential confounder, was not measured due to the possibility that their current BMI did not reflect that when their cancer or its precursor polyp was initiated, which may have been up to a decade earlier.

Transgenerational epigenetic alterations may also play a role in the development of YOCRC. A diabetic parent or grandparent may alter the epigenetics of subsequent generations. Epigenetic effects involving metabolic anomalies were seen in the Överkalix study from Sweden in the 19th Century and the Dutch Hunger Winter of World War II (42). Mothers who were starved of adequate nutrition in the first trimester of pregnancy produced children who were significantly more likely to develop heart disease, metabolic problems and cancer in their adult life. Gestational diabetes may also be a potential risk factor for CRC in offspring and future studies exploring this concept are warranted.

There are a number of implications of our findings for policy and practice. Amongst the 35,000 general practitioners in Australia, the number of 1313 people under 50 years diagnosed with CRC means that one general practitioner in 26 had a patient under the age of 50 who was diagnosed with CRC in that year, or that each general practitioner will have only one or two such patients diagnosed in her or his working lifetime. Australians make an average of seven visits annually to general practice, with each visit representing an opportunity for the general practitioners to check the CRC screening status of their patients with diabetes under 50 years. However, it is humanly impossible for general practitioners to remember to monitor this at every visit while attending to their many other tasks. None of the comprehensive clinical record software packages marketed for use in Australian general practice has an automated system to monitor CRC screening status and to remind the patient and the GP when screening or re-screening is due. The vendors of those clinical software packages should add this function. If our findings are confirmed, that automated reminder algorithm should recognise that patients with diabetes should be screened from an earlier age, perhaps 40 years. FIT should be considered for screening these increased risk patients, especially as their cancers tend to be in the distal colon (for which the FIT is more sensitive).

This report confirms findings of previous studies where an *apriori* relationship between CRC and a personal history of T2D (19), as well as with having first-degree relatives with type 2 diabetes, has been demonstrated (17; 39). The strength of this report is that it reflects the findings of a contemporary, well-characterised case series of young adults with CRC, including specific data collection regarding family history of T2D at face-to-face interview, and a cohort of well-characterised controls who had undergone a colonoscopy and returned unremarkable findings. Limitations of this report include family history of T2D not being available in controls, and no available data on BMI during a preceding time in which the CRC precursor lesion may have been initiated in cases. BMI is a potential confounder, and no multivariate analysis was performed to show T2D was an independent predictor of CRC. However, as mentioned previously, the relationship between T2D and CRC has been shown to be independent of obesity in persons under 55 years (40). Another limitation of this study is unavailability of T2D treatment information. Nevertheless, Peeters et al. (43) reported that there was no association between CRC with T2D treatment stages. Like the explanation for the increase in YOCRC, the exact mechanism to explain our findings remains to be determined, but our report indicates that for some with YOCRC, the excess incidence may relate to T2D. The implication of this being that a young adult with early T2D, particularly when associated with first-degree family history of this condition, may be at increased risk of developing CRC. This warrants further investigation because of the potential to identify young adults in the non-screening population who may benefit from early surveillance.

Authors' Contributions

R.M., J.Y. study concept and design, collected the data, analysed results, wrote manuscript. J.Y., E.S., T.P. study concept and design, acquisition of data, analysis and interpretation of data, critical review of manuscript, statistical analysis. P.H., E.L., D.J., N.P., A.R.R., P.A.D., J.H., H.P., S.W., Y.T., D.P., S.V., A.T., G.T., M.H., J.Y., D.T. acquisition of data, interpretation of data, critical revision of manuscript. W.U., M.H., J.K. technical support, acquisition of data, analysis of data, critical revision of manuscript. D.R., G.Y., S.P., I.T., G.W., O.F., D.W, D.L.W., W.J.B. study concept and design, interpretation of data, critical revision of manuscript. The authors declare they hold no conflict of interest with respect to this work.

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Table 1: Summary of Features of Study Participants

<i>Feature</i>	Cases (Range or Percent)	Controls (Range or Percent)	Odds Ratio	95% CI	p-value
n=	90	240			
Median Age	44 (18-54)	45 (18-54)			
Females	48/90 (53%)	127/240 (53%)	1.0	0.6-1.7	0.99
<i>Indications for Scope/Examination</i>					
Bleeding	44/90 (49%)	90/212 (42%)	1.3	0.8-2.1	0.31
Change of Bowel Habit	38/90 (42%)	38/212 (18%)	3.3	1.9-5.8	<0.001
Pain	33/90 (37%)	43/212 (20%)	5.0	2.8-8.7	<0.001
*Family History CRC	10/85 (12%)	25/212 (12%)	1.0	0.5-2.2	0.99
<i>Type 2 Diabetes</i>					
Personal History	17/90 (19%)	12/240 (5%)	4.4	2.0-9.7	<0.001
Females	9/39 (23%)	8/127 (6%)	3.6	1.32-10.13	0.01
*Family History T2D	32/85 (38%)	Unknown			
Females	15/24 (63%)		0.9	0.38-2.26	0.99
<i>Pathology</i>					
** Left-sided (distal) Cancers	67/89 (75%)				
Left-sided (distal) (Females)	30/47 (64%)		0.2	0.07-0.72	0.01
Left-sided (distal) (Males)	37/42 (88%)				
MMR Deficient CRC	7/83 (8%)				
Confirmed Lynch Syndrome	3/87 (3%)				
<i>BRCA2</i> Mutation	4/87 (5%)				
Bi-Allelic <i>MUTYH</i> Mutation	2/87 (2%)				

* Adoptees n= 5 family history unknown. ** One site of CRC was unknown.

Figure 1 First degree relative with CRC and pathogenic germline mutations.

Figure 2 Comparison of prevalence of T2D under age 55 in (Left to Right) the clear colonoscopy controls (n=240), and colorectal cancer case series SAYO (n=90).

Supplementary Table 1: Genes surveyed for genetic variants predisposing to type 2 diabetes

Gene Symbol	Gene Name
TCF7L2	transcription factor 7 like 2
KCNQ1	potassium channel subfamily Q 1
HHEX	haematopoietically expressed homeobox
IGF2BP2	insulin growth factor 2 binding protein 2
CDKN2B	cyclin dependent kinase inhibitor 2B
SLC30A8	solute carrier family 30 member 8
MC4R	melanocortin 4 receptor
TM6SF2	transmembrane 6 superfamily 2
KCNJ11	potassium channel KIR6.2
BLK	B-lymphoid tyrosine kinase
CEL	carboxyl ester lipase
GCK	glucokinase
HNF1A	hepatocyte nuclear factor 1 alpha
HNF1B	hepatocyte nuclear factor 1 beta
HNF4A	hepatocyte nuclear factor 4 alpha
INS	insulin
KLF11	kruppel-like factor 11
NEUROD1	neurogenic differentiation factor 1
PAX4	paired box 4
PDX1	insulin promoter factor 1

Supplementary Table 2: Actionable mutations

<i>Number</i>	<i>Sex</i>	<i>Age</i>	<i>Site</i>	<i>FDR CRC EC</i>	<i>MMR IHC</i>	<i>GL Mutation</i>	<i>PH T2D</i>	<i>FDR T2D</i>	<i>Relations T2D</i>	<i>Polyposis</i>
1	F	44	D	no	N	BRCA2 (p.Ser3133; c.9398C>G)	no	yes	mother maternal aunt maternal GM maternal GF	no
2	F	29	P	no	MSH2/ MSH6	MSH2 (p.Arg680;c.2038C>T)	no	yes	father	no
3	F	43	PD	no	N	MUTYH [p.Tyr179cys; exon 7 c.536A>G; p.Gly396Asp;exon 13 c.118G>A]	yes	yes	brother mother maternal GM	no
4	F	50	P	yes	N	RNF43 (c.375+1G>A)	no	no		no
5	F	47	P	no	N	MUTYH [p.Trip103; c.309G>A; Gln391;117C>T]	no	no		yes
6	F	30	P	yes	MSH2/ MSH6	MSH2 [p.(Val1265_Gln314del); c.942+3A>T]	no	no		no
7	F	38	D	no	N	BRCA2 (p.Leu1908fs; c.5718_5719CT)	no	yes	mother	no
8	M	38	P	no	N	BRCA2 (p.Asn1626fs; 4876_4877delAA)	no	no		yes
9	F	27	P	no	N	BRCA2 (p.Tyr3098; 9294C>G)	no	no		yes
10	F	45	D	no	Weak MSH2/ MSH6	MSH6 (p.Phe1323fs; c.3964_3967dupAAT)	yes	no		no

Abbreviations

FDR T2D = first-degree relatives with type 2 diabetes, FDR CRC EC = first-degree family history of colorectal or endometrial cancer,MMR IHC = mismatch repair immunohistochemistry (N = normal staining)

PH T2D = personal history of type 2 diabetes, P=proximal (right-sided) CRC, PD=proximal (right-sided) and distal (left-sided) CRC were present, D=distal (left-sided) CRC.