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Genomic and molecular alterations associated with early-onset and adolescent and young adult colorectal cancer

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While the incidence of colorectal cancer (CRC) in the US has declined at a pace of 3% annually between 2003 and 2012, there has been an increase in the incidence of early-onset colorectal cancer (EOCRC). The reasons for this increase are unclear. Diet, the environment, the microbiome and alcohol consumption have all been proposed as contributing factors. There is the possibility that EOCRC has a unique biology. Overlapping with the EOCRC age range is CRC in adolescent and young adults (AYA) that share many molecular characteristics with EOCRC. The purpose of this review is to cover current progress in our understanding of the biology of CRC in the context of adolescent and young adult CRC and EOCRC and discuss future directions.

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In general, the incidence rate of colorectal cancer (CRC) in the US has declined at a pace of 3% annually between 2003 and 2012 [1,2]. By contrast, there has been a documented increase between 1974 and 2015 in the incidence of early-onset colorectal cancer (EOCRC) in the US and Europe [1,3,4]. Interestingly, the rise is most prominent among Caucasians, particularly in the western US [2]. The exact reasons for this increase are currently unknown, although, factors such as higher rates of obesity, cigarette smoking, increased consumption of processed meat and alcohol consumption have all been implicated as possible causes [2]. Overlapping with the EOCRC age range of less than or equal to 50 years is the adolescent and young adult (AYA) age group, which encompass the 15–39 year age range [5,6]. Evidence suggests that CRC in the AYA age group may have a different molecular etiology than CRC diagnosed in older adults and may be more refractory to some treatment regimens than their older counterparts [7,8]. Like AYACRC, EOCRC tends to be associated with a higher percentage of synchronous and metachronous tumors, more poorly differentiated histology and mucinous and signet ring histology than that found in older adult patients [9,10]. However, the biological basis and clinical ramifications of these observations for both AYACRC and EOCRC are still incompletely defined. It is possible that some of the molecular factors associated with the unique characteristics of AYACRC are also involved in the spectrum of EOCRC disease. Such factors may be more prevalent in these cancers, or even unique to the disease.

Efforts to identify the underlying causes of EOCRC are increasing and include the identification of somatic mutational alterations unique to EOCRC, the impact of the microbiome on disease susceptibility and progression, alterations in genomic methylation patterns and the involvement of DNA repair pathway alterations – other than those associated with Lynch Syndrome. Differences in the number of chromosomal aberrations and breakpoints have also been observed between EOCRC and CRC in older adults [11]. The two recognized subtypes of EOCRC are the inherited subtype, characterized by Lynch Syndrome associated with micro satellite instability high (MSI-H), familial adenomatous polyposis (FAP) and *MUTYH* associated polyposis and the sporadic subtype, characterized by a lack of family history and the accumulation somatic mutations. The purpose of this review paper is to focus on the latter sporadic subtype and to review current progress in the understanding of the biology of CRC in the context of both EOCRC and AYACRC. We here focus on chromosomal alterations, somatic mutational variants

and their affected signaling/DNA repair pathways, miRNA alterations and possible biomarkers and therapeutic targets as molecular factors associated with EOCRC and AYACRC.

Chromosomal alterations & gene expression

Alteration of chromosome number and integrity is a hallmark of cancer and has been well-characterized in many forms of this disease. Methylation events have also been demonstrated to play a role in CRC, including the hypomethylation of long interspersed nuclear element-1 that can lead to the activation of proto-oncogenes [12]. Alterations in genomic methylation patterns, particularly hypomethylation events, are associated with increased chromosomal instability that contribute to tumorigenesis [13,14]. Numerous studies have examined the difference in variations at the chromosomal level in EOCRC and the concomitant changes in gene expression associated with those changes [11,15]. While there appears to be little difference in the fraction of the genome with chromosomal copy number alterations between EOCRC and late-onset CRC (LOCRC), one study that plotted gains and losses demonstrated that 3.2% of the genome is different between these two groups [11]. For example, loss occurred at the locus encoding the *PRKAB2* gene (1q21.1), a regulatory unit of AMP-activated protein kinase, in 43% of EOCRC cases but in only 6% of LOCRC. Gains were also observed in EOCRC at chromosome 10q and 19q compared with LOCRC patients. In all, 16 genomic loci encoding >500 genes were observed to be preferentially altered in EOCRC compared with LOCRC [11]. This study also determined that 37% of genes had corresponding DNA copy number and RNA expression level alterations, and that among these genes, 107 mapped to genomic regions that differed in frequency of copy number change between EOCRC and LOCRC. Three genes (*CLC*, *LTBP4*, *ZNF574*) that map to a chromosome band (19q13.2) that showed copy number gain in EOCRC, also exhibited upregulation of mRNA expression. One of these (*CLC*) encodes a phospholipase believed to be involved in inflammation [16]. This study also revealed five chromosomes that exhibited 15 loci that were more frequently altered in EOCRC compared with LOCRC, including MIR641 at 19q13.2, a miRNA that is known to be involved in CRC. Other studies have examined susceptibility loci in 191 cases of EOCRC compared with 1264 cases of LOCRC and determined that variants at 10p14 (rs10795668), 11q23.1 (rs3802842) and 15q13.3 (rs4779584) showed a different distribution between the two groups [17,18]. Additional studies have detected risk alleles for CRC associated with age at 8q24.21 (rs6983267), 10p14 (rs10795668) and 19q13.1 (rs10411210) [19] and at 11q23.1 (rs3802842), 14q22.2 (rs4444235) and 15q13.3 (rs4779584), 8q24.21 (rs6983267) and 20p12.3 (rs961253) [20]. A recent study compared the polygenic risk score, based on single-nucleotide variants (SNVs) associated with CRC in a cohort of 12,197 participants less than 50 years old and 95,865 participants 50 years of age or older [21]. That study determined the cumulative burden of SNVs associated with CRC strongly associated with EOCRC, particularly in the absence of a family history and, successfully identified participants at increased risk for EOCRC [21].

These and other studies demonstrate that there are numerous chromosomal alterations, and associated gene expression changes that are different in EOCRC when compared with LOCRC, which provides a foundation upon which to further build our understanding of the unique features of the early-onset form of this disease.

Altered mutational frequencies associated with EOCRC

The clinical presentation, histology, prognosis and ultimate outcome of EOCRC appears to differ from that observed in older adults. While delayed diagnosis may contribute to poor prognosis and outcome in this group, other factors may be involved. This is highlighted in Figure 1 where AYACRC, exclusive of hereditary predisposition syndromes, such as hereditary nonpolyposis colorectal cancer and FAP, is linked to fewer mutations and DNA repair deficits, as opposed to adult CRC where there is a serial accumulation of mutations [22–25]. The question is, does the biology of EOCRC vary from that found in older adults and if so how? The presence of single nucleotide variants SNVs, insertion/deletions (indels) and copy number variations are common across the spectrum of human cancers and consensus gene sets have been identified that exhibit consistent alterations in CRC [26,27]. The current data available from studies indicating a possible unique biology in EOCRC are limited [28–31]. Recent studies have pointed to a subset of gene variants that may be associated with EOCRC. These include increased variant frequencies observed for *TP53*, *CTNNB1*, *POLE* and a decreased variant frequency for *APC*, *KRAS*, *BRAF*, *PIK3CA* and *FAM123B* [28,29]. One study reported that in one cohort of patients *ATM*, *TP53*, *FBXW7* and *SMAD4* did not exhibit an age-related difference in mutation frequency, although only partial sequencing of the *ATM* was conducted in that study, while in another cohort *ATM* mutations were more frequent in younger patients [31]. Another study has demonstrated that a combination of rare variants of the cyclin D1 gene, *CCND1*, contribute to an increased risk of multiple intestinal adenomas and of EOCRC [32]. A study has also implicated *CTNNB1* as more frequently overexpressed

Figure 1. Distribution of incidence in nonhereditary colorectal cancer in the adolescent and young adult age group compared with colorectal cancer found in older adults. Data in-part derived from Jung *et al.* [22], Dalpatadu *et al.* [23], Jiang *et al.* [24] and Arriba *et al.* [25].

FAP: Familial adenomatous polyposis; HNPCC: Hereditary nonpolyposis colorectal cancer.

in EOCRC compared with LOCRC and the TNFR1 pathway as a key factor associated with EOCRC [33] in agreement with a previous study implicating immune response and inflammation in this form of the disease [34].

Some of the earliest evidence for the possibility of unique biology in AYA cancer came from studies of CRC in the AYA population, the age range of which overlaps significantly with that of EOCRC. Many AYACRC patients have a poorer prognosis, exhibit a more aggressive disease phenotype and have poorer survival than CRC in older adults [7]. In Figure 2 surveillance, epidemiology and end results (National Cancer Institute, MD, USA) data is shown, which demonstrates that survival is lower for colonic, rectal and anal carcinomas in AYAs (indicated by yellow highlighting) than when compared with older patients and, for each, inversely proportional to age within the AYA age range [35]. Like EOCRC, AYACRC exhibits a greater frequency of mucinous histology, signet ring cells, MSI-H and a higher incidence of mutations in mismatch-repair (MMR) genes [9,36–38]. A study by Hong *et al.* detected expression changes in genes from tumor adjacent normal mucosa in EOCRC patients compared with mucosa from healthy controls [39]. In that study *FOS*, *FOSB*, *EGR1*, *VIP*, *CYR61*, *KRT24* and *UCHL1* all displayed increased expression in the normal mucosa from EOCRC patients compared with controls. The functions of the proteins encoded by these genes include transcriptional regulation, angiogenesis, cell signaling and protein catabolism.

Relatively few molecular genetic studies in CRC have been conducted in the AYACRC population, perhaps because these cases are few-in-number and due to the paucity of tissues available for analysis. In addition, it should be noted that the majority of the next generation sequencing (NGS) studies that have been performed in AYACRC utilized targeted gene panels to discern these differences, rather than whole exome sequencing. The two most comprehensive analyses of gene variants in the AYACRC cohort suggest a variety of genes may be associated with the biology of AYACRC and some overlap with studies in EOCRC [40,41]. These include *POLE* and *ATM*, both of which are involved in DNA repair pathways [37]. In addition, *POLE* was identified as having a greater frequency of mutation in AYACRC compared with adult CRC by two independent studies utilizing different NGS platforms and different algorithmic analysis pipelines [40,41]. While one study [30] determined there was no difference in the frequency of *FBXW7* mutations between EOCRC and LOCRC, two studies in AYACRC patients detected an

Figure 2. Incidence of invasive cancer of the colon, rectum and anus. Surveillance, epidemiology and end results 18, 2000–2012 by age, site and sex. Age groups with <10 patients excluded (Tricoli *et al.* [35]).

*Includes rectosigmoid junction.

AYA: Adolescent and young adult.

increased frequency of *FBXW7* mutations in these patients, when compared with adults [40,41]. This indicates that findings are not always consistent across studies. Both AYACRC and EOCRC exhibit a lower frequency of *KRAS* mutations than those observed in CRC from older patients [42].

In a whole exome sequencing study comparing CRC tumors from AYA patients and adult patients, investigators detected 43 genes that met the criteria for exhibiting a significantly greater mutational frequency in AYA versus adult CRCs ($p > 0.05$), based on gene function and/or evidence from the literature demonstrating the gene had a potential role in CRC [41]. Of these genes, 13 had a p -value < 0.01 using the Fisher exact test and thus exhibited the greatest differential in mutation frequency between the AYA and adult groups. These include *ROBO1*, *SIPAL1*, *MYCBP2*, *MED12L*, *BRCA2*, *MSH2*, *COL16A1*, *DNAJC2*, *EPHA3*, *LAMB2*, *MAP3K3*, *MCPH1* and *RASGRP3*. Most of the mutations detected in these genes were nonsynonymous missense, stop-gain or frameshift mutations that are damaging. Genes exhibiting alterations in mutational frequency in EOCRC and AYACRC are shown in

Table 1. Genes with altered mutational frequency and altered miRNA expression in early-onset and adolescent and young adult colorectal cancer compared with adults.

Gene	EOCRC mutation frequency Increase/decrease	Gene	AYACRC mutation frequency Increase/decrease	miRNA	EOCRC expression Increase/decrease
<i>TP53</i>	Increase	<i>ROBO1</i>	Increase	mir-106a	Increase
<i>CTNNB1</i>	Increase	<i>SIPAL1</i>	Increase	mir-145	Increase/decrease
<i>POLE</i>	Increase	<i>MYCBP2</i>	Increase	mir-125b	Decrease
<i>APC</i>	Decrease	<i>MED12L</i>	Increase	mir-143	Decrease
<i>KRAS</i>	Decrease	<i>BRCA2</i>	Increase	mir-21	Increase
<i>BRAF</i>	Decrease	<i>MSH2</i>	Increase	mir-20a	Increase
<i>PIK3CA</i>	Decrease	<i>COL16A1</i>	Increase	mir-181b	Increase
<i>FAM123B</i>	Decrease	<i>DNAJC2</i>	Increase	mir-203	Increase
<i>ATM</i>	Increase	<i>EPHA3</i>	Increase	mir-30a-5p	Decrease
		<i>LAMB2</i>	Increase	mir-192	Decrease
		<i>MAP3K3</i>	Increase	mir-215	Decrease
		<i>MCPH1</i>	Increase	mir-34a	Decrease
		<i>RASGRP3</i>	Increase	mir-196a2	Increase
		<i>ATR</i>	Increase	mir-27a	Altered binding to target
		<i>POLE</i>	Increase		
			Increase		
EOCRC age range: 21–50 years					
AYACRC age range: 15–39 years					
AYA: Adolescent and young adult; CRC: Colorectal cancer; EOCRC: Early-onset colorectal cancer. Data taken from [41].					

Table 2. Comparison of the differences in mutational frequency between the current adolescent and young adult colorectal cancer and adult colorectal cancer samples based on different levels of rigor.

Gene	Exome data	Exome mutations validated by RNASeq	Exome mutations validated by RNASeq and are damaging
<i>MYCBP2</i>	AYA 50% Adult 7%	AYA 47% Adult 14%	AYA 41% Adult 0%
<i>BRCA2</i>	AYA 38% Adult 3%	AYA 47% Adult 14%	AYA 29% Adult 0%
<i>TOPORS</i>	AYA 31% Adult 3%	AYA 29% Adult 0%	AYA 24% Adult 0%
<i>ATR</i>	AYA 48% Adult 13%	AYA 41% Adult 7%	AYA 24% Adult 0%
<i>POLE</i>	AYA 22% Adult 13%	AYA 24% Adult 14%	AYA 24% Adult 0%
AYA: Adolescent and young adult.			

Table 1. Further validation of the 43-gene set using RNASeq technologies revealed that five of these genes *MYCBP2*, (a MYC binding protein that possibly facilitates MYC) *BRCA2*, (involved in double strand DNA repair) *TOPORS*, (TOPO1 binding protein that regulates p53) *ATR* (PI3/PI4 kinase that phosphorylates BRCA1 and checkpoint proteins CHK1, RAD17 and RAD9) and *POLE* (catalytic subunit of DNA polymerase epsilon, DNA replication and repair) all demonstrated a statistically significant increase in the frequency of mutation in AYACRC compared with adult CRC, and displayed damaging mutations [Table 2]. It is very possible that these genes are also linked to EOCRC, certainly within the 21–39-year-old age group that overlaps with AYACRC patients and should be investigated further for their contribution to this disease.

Further validation of mutational gene variants associated with EOCRC and AYACRC will be required to narrow the population of gene variant sets and their associated pathways, which could be uniquely linked to CRC in younger patients. Eventually, focused *in vivo* and *in vitro* studies on specific genes will be required to discern the functional role of their products in EOCRC and AYACRC. Once the role of these genes is discerned, further investigations into the impact of alterations in these genes on disease development and progression and whether they provide opportunities to disrupt signaling pathways that can be targeted by precision medicine agents, can be conducted.

miRNA & EOCRC

miRNAs are small (22–25 nucleotides in length) noncoding RNAs that can effectively alter the translation of target mRNAs by binding to their 3' untranslated region. A variety of studies have discovered the ability of individual miRNAs to regulate the expression of oncogenes and tumor suppressor genes, while others have demonstrated that miRNA gene loss or mutation can contribute to tumorigenesis. miRNA expression patterns (or signatures) are now known, in some cases, to characterize the developmental origins of tumors more effectively than messenger RNA expression signatures can sometimes provide. Evidence suggests that miRNAs may contribute to EOCRC and up to 200 miRNAs have been observed to be deregulated in CRC [43,44]. Thus, the potential for the disruption of normal signaling networks through mutation or deletion of miRNA is significant. In a Turkish cohort of EOCRC patients it was shown that expression of mir-106a was upregulated, while mir-145 and mir-125b were downregulated when compared with normal tissue [45]. While the fold changes in these miRNAs were modest, and no direct comparison was made with LOCRC, there was an association between the changes in these miRNAs and the presence of lymph node metastases in the patients studied. The collective gene targets for these miRNAs include many that are deregulated in CRC including *BCL2*, *TP53*, *AKT1*, *BAX*, *CCND1*, *JUN*, *KRAS*, *MAPK3*, *MYC*, *ERK5*, *TNF*, *TGFBR2*, *CDKN1A*, *DICER1*, *E2F1*, *PTEN* and *RB1*. Therefore, these miRNAs could be involved in the development or progression of EOCRC. For example, miR-143 can regulate cell growth and proliferation *in vitro* by targeting different oncogenic protein-coding genes, such as *IRS-1*, *cMYC*, *MACC1*, and *KRAS* [46–48].

Another study demonstrated significantly increased expression levels of mir-21, mir-20a, mir-145, mir-181b and mir-203 [49]. The increase in mir-145 expression contrasts with what the previous study reported; however, the investigators of this study point out that the observed increases in mir-145 expression may have been influenced by neoadjuvant therapy. Another miRNA, mir-30a-5p, while not known to specifically contribute to EOCRC, is a tumor suppressor miRNA that has been shown to target *denticleless* (*DTL*) and was determined to be overexpressed in 95.8% of human CRC [50]. Two other miRNAs, mir-192 and mir-215, have been revealed to regulate p53 to suppress CRC [51], and another mir-34a has been shown to inhibit cellular invasion in CRC by targeting *FRA1*, a gene that encodes a leucine zipper protein that can dimerize with proteins of the JUN family, to form the AP-1 transcription factor complex [52]. Another area of investigation is single nucleotide polymorphisms (SNPs) detected in miRNAs that can affect their binding. In a study of a Chinese population, a SNP in mir-196a2 led to the increased expression of this miRNA and was associated with an increased CRC incidence in that group when compared with healthy controls [53]. Another study revealed that a SNP in mir-27a disrupts the binding of this miRNA to its target, the 3' untranslated region of *MBL2* and is associated with CRC risk in an African American population [54]. A summary of the miRNAs altered in EOCRC is presented in Table 1. Is it possible that similar miRNA SNPs are associated with EOCRC and AYACRC susceptibility? This is an avenue of investigation that should be vigorously pursued.

Many other miRNAs have been implicated in the biology of CRC [55], however, most have not been differentially examined for their involvement in EOCRC when compared with LOCRC. Identification of the miRNAs preferentially involved in EOCRC would provide new avenues into the understanding of the unique features of this disease and point the way toward useful biomarkers and more effective treatments for this disease.

DNA repair pathway mutations

DNA repair enzymes play an essential role in maintaining genomic integrity by correcting errors during DNA replication, and from environmental damage to the genome. Alterations in DNA repair pathways are a hallmark of EOCRC, particularly in the case of MSI-H disease, which is a feature of Lynch Syndrome [56]. In AYACRC tumors, one study reported that 39% contained at least one mutation in the DNA MMR gene *MSH2*, whereas only 3% of adult samples exhibited these mutations [41]. While this was expected because as in EOCRC, MSI is present in many AYA colon cancers, this study also reported a greater frequency of mutations in AYACRC patients for genes associated with other DNA repair pathways. These include *BRCA2* (AYA samples, 39%; adult samples, 3%) and *RAD9B* (AYA samples, 22%; adult samples, 0%); and the cell-cycle checkpoint kinases *ATM* (AYA samples, 35%; adult samples, 7%); *ATR* (AYA samples, 48%; adult samples, 13%) and *POLE* (AYA samples 24%; adult samples 0%) [Table 3]. *POLE* is a gene that encodes the catalytic subunit of DNA polymerase epsilon. The enzyme is involved in DNA repair and chromosomal DNA replication [16]. This gene was observed to be more frequently mutated in EOCRC compared with that identified in LOCRC patients [40]. This same gene was also noted to be more frequently mutated in AYACRC [41] and furthermore, several of the SNVs in the proofreading domain of *POLE* overlapped between the two studies. In one study, biallelic mutations in the *MUTYH*, a DNA

Table 3. Genes associated with DNA repair pathways displaying significantly increased mutational frequency in adolescent and young adult colorectal cancer.

Gene	Function	Mutation frequency in AYA (%)	Mutation frequency in adult (%)
<i>MSH2</i>	Mismatch repair	39	3
<i>MCPH1</i>	DNA damage response	26	0
<i>RAD9B</i>	DNA repair endonuclease	22	0
<i>ATM</i>	Cell-cycle checkpoint kinase	35	7
<i>ATR</i>	PI3/PI4 kinase	48	13
<i>POLE</i>	DNA repair	24	0

AYA: Adolescent and young adult.

glycosylase involved in oxidative DNA damage repair, accounted for 3–4% of early-onset CRC without apparent polyposis in MMR-proficient patients [57]. Base excision repair deficiency, due to biallelic inactivation of *MUTYH*, has previously been associated with the development of an attenuated form of colonic polyposis [58]. Mutations in DNA repair pathway genes may provide therapeutic targets, as has been the case with PARP (poly ADP ribose polymerase) inhibitors for the treatment of tumors with mutations in homologous recombination repair, such as *BRCA1*, *BRCA2* and *PALB2* [59]. Therefore, sporadic mutations in DNA-repair genes, other than the MMR genes (*MLH1*, *MSH2* and *MSH6*), may be important to the biology and development of colon cancer in these patient populations.

A survey of comparing EOCRC and LOCRC using targeted DNA repair panels and NGS assays could be very beneficial in elucidating the role of repair pathways, beyond those associated with MSI, in the EOCRC patients.

Future perspective

In order to ‘move the field’ for both EOCRC and AYACRC, we must expand and extend the previous and current work on the basic biology and translational research related to this disease. As we have seen from the data summarized above, findings across studies are not always consistent. Therefore, future studies need to be cross validated utilizing different sequencing platforms to verify interesting variants. The identification of novel genes and pathways associated with EOCRC should not be limited to the use of gene panels but will require the use of whole exome sequencing in order to survey the entire coding region of the genome. The analysis of miRNA profiles, their target genes and polymorphisms that impact their binding to those genes will also be important in understanding the biology of EOCRC and could point the way to novel biomarkers for early disease detection. DNA repair pathways should be a particular focus of future studies since these alterations appear to be very consistent among EO- and AYA CRC patients. One example is *POLE* being identified as more frequently mutated in two studies using disparate patient populations and different sequencing platforms and calling algorithms. Thus, repair pathways outside of those associated with hereditary nonpolyposis colorectal cancer, FAP and MSI should be extensively investigated for mutations that can impact disease development. Once these genes/pathways are identified they must then be validated on larger sample sets which will require surveying available biobanks for these patient samples. Identification of EOCRC and AYACRC samples can be challenging, particularly in the younger cohorts, due to the rarity of these cancers. Efforts must be made to better catalog and identify these samples, along with annotated clinical information and pre-analytics, within existing biobanks and make them available for analysis. Ultimately, identifying novel genes/pathways associated with EOCRC will provide the molecular foundations for the development of novel precision medicine treatments for this disease and lead to improved survival for this cohort of patients.

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Executive summary

- Differences in mutational profiles for early-onset colorectal cancer (EOCRC) and adolescent and young adult colorectal cancer (CRC), compared with adult colorectal cancer have been identified that will require validation and follow-up.
- Additional studies are required using more expansive next-generation sequencing platforms, such as whole-exome sequencing, to identify novel genes that may exhibit a greater mutational frequency in EOCRC and adolescent and young adult CRC compared with late-onset CRC and could contribute to this disease.
- Results from mutational profile comparisons between EOCRC and late-onset CRC should be pursued using *in vivo* and *in vitro* studies to better elucidate the role of these genes in the biology of this disease.
- Identification of novel mutational profiles in this disease should be utilized to identify biomarkers that can be used for early disease detection.
- miRNAs in EOCRC should be further investigated to elucidate the possible unique biology of this disease and identify therapeutic targets.
- Alterations in DNA repair pathway genes should be further characterized in this disease for the purpose of identifying therapeutic targets.

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