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GERMLINE GENOMIC FINDINGS IN CHILDREN AND YOUNG ADULTS WITH MELANOCYTIC TUMORS

Margaret Nagel[1], Melissa R. Perrino[1], Regina Nuccio[2], Alise Blake[1], Lynn Harrison[1], Kim Nichols[1], and Alberto Pappo[1]

[1]St Jude Children's Research Hospital
[2]Concert Genetics Franklin TN USA

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Abstract

In this retrospective study, we examined the prevalence and spectrum of germline variants in cancer predisposition genes in 38 children and young adults with melanocytic lesions who underwent germline genetic testing at St. Jude Children's Research Hospital. Diagnoses included malignant melanoma (n=19; 50%), spitzoid melanoma (n=14; 37%), and uveal melanoma (n=5; 13%). Five patients (13%) harbored pathogenic variants: one with bi-allelic *PMS2,* and one each with heterozygous 17q21.31 deletion, *TP53, BRIP1,* and *ATM* pathogenic variants. In this convenience cohort, 13% of children and young adults with melanoma who underwent germline testing harbored an underlying cancer predisposition syndrome.

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Margaret B. Nagel, MD[1], Melissa R. Perrino, MD[1], Regina Nuccio, MS, CGC[2], Alise Blake, MS, CGC[1], Lynn Harrison, MPA, CCRP[1], Kim E. Nichols, MD[1], Alberto S. Pappo, MD[1]

[1]Department of Oncology, St. Jude Children's Research Hospital Memphis TN USA

[2]Concert Genetics Franklin TN USA

Address correspondence to:

Alberto Pappo, MD

MS 260, Room C6017

St. Jude Children's Research Hospital

262 Danny Thomas Place

Memphis, TN 38105-3678

Email: alberto.pappo@stjude.org

Phone: (901) 595-2322

Fax: (901) 521-9005

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Key words: pediatric, melanoma, cancer predisposition, germline testing, pathogenic variant

ACC	adrenocortical carcinoma
CMMRD	constitutional mismatch repair deficiency
GPC	Genetic Predisposition Clinic
GV	germline variant
LFS	Li Fraumeni Syndrome
LN	lymph node
MM	malignant melanoma
SM	spitzoid melanoma
SLNB	sentinel lymph node biopsy
SJCRH	St. Jude Children's Research Hospital
T-LL	T-lymphoblastic lymphoma
UM	uveal melanoma
WLE	wide local excision

Abstract:

In this retrospective study, we examined the prevalence and spectrum of germline variants in cancer predisposition genes in 38 children and young adults with melanocytic lesions who underwent germline genetic testing at St. Jude Children's Research Hospital. Diagnoses included malignant melanoma (n=19; 50%), spitzoid melanoma (n=14; 37%), and uveal melanoma (n=5; 13%). Five patients (13%) harbored pathogenic variants: one with bi-allelic *PMS2,* and one each with heterozygous 17q21.31 deletion, *TP53, BRIP1,* and*ATM* pathogenic variants. In this convenience cohort, 13% of children and young adults with melanoma who underwent germline testing harbored an underlying cancer predisposition syndrome.

Introduction Approximately 10% of adults with melanoma harbor a pathogenic or likely pathogenic germline variant (GV) in a cancer predisposing gene.[1,2] It is unknown whether similar variants are present in children and young adults with melanoma. The goal of this study was to determine the prevalence and spectrum of GVs in children and young adults with various melanocytic tumors.

Methods

Charts from children and young adults with melanocytic lesions who were seen by Genetic Predisposition Clinic (GPC) at St. Jude Children's Research Hospital (SJCRH) between June 2014 and September 2021 and underwent germline testing were retrospectively evaluated. Demographic, clinical, family history, and germline genetic test results were gathered. Results of cascade testing from first degree relatives were reviewed if available. This study was approved by the Institutional Review Board at SJCRH.

Results

A total of 66 patients with melanoma were seen by the GPC during the study period, with 38 (57.6%) electing to undergo germline genetic testing. The average age at melanoma diagnosis was 11.2 years. The majority were white (n= 36, 95%). Diagnoses included malignant melanoma (MM, n=19; 50%), spitzoid melanoma (SM, n=14; 37%), and uveal melanoma (UM, n=5; 13%). Thirty-two patients were newly diagnosed whereas six patients developed melanoma as a subsequent neoplasm. Eight patients (21%) had a positive family history of melanoma (**Table 1**). Thirteen patients (34%) underwent broad cancer germline sequencing of 63–115 genes and the remainder had targeted melanoma gene panels. Overall, five patients (13%) harbored pathogenic or likely pathogenic GVs (**Table 2**).

Patient 1: bi-allelic pathogenic *PMS2* GVs

Patient 1 was diagnosed with T-lymphoblastic lymphoma (T-LL) at age three years, Burkitt Lymphoma at 14, and underwent proctocolectomy at 14 due to numerous colonic polyps. These three diagnoses prompted

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germline testing, which revealed bi-allelic pathogenic *PMS2* variants, consistent with constitutional mismatch repair deficiency (CMMRD). At age 16, a changing mole on the right cheek was biopsied, diagnostic of MM, and treated with wide local excision (WLE). The patient expired a few months later secondary to relapsed T-LL. Cascade testing identified that one variant was maternally inherited while the patient's father did not undergo testing. These results prompted Lynch Syndrome cancer screening for his family.

Patient 2: 17q21.31 deletion

Patient 2 was seen by dermatology at age nine years due to a concerning forearm mole. She had a past history of seizures, short stature, developmental delay, scoliosis and hypotonia. Pathology from WLE confirmed SM, sentinel lymph node biopsy (SLNB) identified metastatic disease, and complete lymph node (LN) dissection was negative. Treatment was excision. No GVs were identified on a 12-gene melanoma panel but a 180k Oligo Chromosome Microarray was ordered and detected a *de novo* 17q21.31 deletion, consistent with Koolen-de Vries syndrome.

Patient 3: heterozygous pathogenic *ATM* GV

Patient 3 was seen by dermatology at age two for a temporal lesion which started to thicken. The lesion was diagnosed as a spitzoid nevus and observed until the family requested removal. A shave biopsy confirmed SM. WLE and SLNB were performed with one positive LN. Treatment was surgery only and patient has been disease-free for three years. Germline testing identified a maternally inherited *ATM* pathogenic GV. Although the *ATM* variant is silent, experimental studies have demonstrated a splicing effect that results in skipping of exon 14.[3,4] Cascade testing informed care of the patient's mother, who was recommended to initiate breast cancer surveillance with mammograms with consideration of tomosynthesis and breast MRI with contrast starting at 40 years old or 5-10 years before earliest age of breast cancer diagnosis.[5]

Patient 4: heterozygous *BRIP1* GV

Patient 4 noticed a lesion on the thigh at age 11 years and was seen by dermatology after continued growth. A shave biopsy revealed SM with somatic *BRIP1* variant and *ALK* rearrangement. A WLE with SLNB was performed, identifying microscopic nodal involvement. Therapy included surgery only. Patient 4 has been disease free for five years. Germline testing identified a maternally inherited *BRIP1* variant. Cascade testing prompted his mother to consider risk reducing salpingo-oophorectomy.[5]

Patient 5: heterozygous *TP53* GV

Patient 5 was diagnosed with adrenocortical carcinoma (ACC) at 30 months of age and MM of the scalp with posterior cervical LN metastatic disease at age 7 years. She was treated with interferon alpha-2b and Peginterferon Aplha-2b.[6] The diagnosis of two primary tumors prompted *TP53* germline testing and revealed a *de novo* single base pair substitution in exon 6, confirming a diagnosis of Li Fraumeni syndrome (LFS). Patient 5 remains alive at age 21 years.

Discussion

In this convenience cohort, 13% of children and young adults with melanoma who underwent germline testing harbored an underlying pathogenic or likely pathogenic GV in a cancer predisposing gene, comparable to the previously reported 9-12% of pediatric cancer patients who have germline cancer predisposition syndromes.[7-10] Interestingly, most of the affected genes are not currently associated with increased melanoma risk. Among the five patients harboring GVs, only one (Patient 5) would have been routinely screened based on current surveillance recommendations for LFS. [11] LFS has increased risk of sarcoma, early onset breast cancer, brain tumors, ACC, and leukemia, among others, including melanoma.[12] *PMS2* is associated with autosomal dominant Lynch syndrome and autosomal recessive CMMRD.[13] Patients with CMMRD have an increased risk of developing many different cancers and tumors, often presenting at exceptionally early ages.[13] Koolen-de Vries syndrome is characterized by variable developmental delay, hypotonia, seizures, distinct facies, cardiac, kidney and skeletal anomalies and multiple benign nevi.[14] Due to benign skin findings, patients with Koolen-de Vries syndrome and CMMRD may be seen by a dermatologist, but melanoma has

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not yet been reported in these populations to prompt surveillance.[14,15] Monoallelic *ATM* GVs are associated with a moderately increased risk to develop breast cancer, pancreatic cancer, or ovarian cancer in adulthood.[4]Data have shown *ATM* heterozygotes have a low to moderate risk for melanoma, but this is not deemed high enough to warrant routine dermatologic screenings.[3-4,16] Heterozygous pathogenic*BRIP1* GVs are associated with an increased risk to develop ovarian cancer in adulthood.[5] One study identified a germline *BRIP1* GV in 5 relatives, 3 of which developed melanoma in adulthood.[17] The phenotypes for each of these cancer predispositions are evolving with expanded germline testing. Our data provide support for further investigation of the utility of regular dermatology screenings for the early detection of melanoma in individuals with these conditions.

In adults, hereditary melanomas are most commonly associated with pathogenic GVs affecting *CDKN2A* (22%).[1] Other reported genes with increased melanoma risk include *CDK4, TERT, POT1, ACD, TERF2IP, MITF, MC1R* and *BAP1.*[1,2] Recently, 123 pediatric patients with melanoma were investigated for GVs affecting *CDKN2A* , *CDK4, POT1, MITF,* and*MC1R* .[18] In this study, investigators identified a low frequency of *CDKN2A* (9%) and *MITF* (3%) variants in all cases but a higher rate of *MC1R* variants (68%).[18] Seventy-four percent of our patients had testing which included all five genes in the aforementioned study. Interestingly, we did not identify any patients harboring a pathogenic variant in one of these genes.

In conclusion, our data reveal that the genes affected in children and adolescents with melanocytic tumors differ from those reported in adults. Broader non-biased germline genetic testing for these patients will further elucidate the genetic underpinnings of this rare cancer type, which will refine the phenotypes and surveillance of known cancer predisposition syndromes.

Conflict of Interest Statement

None

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TABLE 1 Patient demographics

Variable	**N**
Age	**Age**
<15	26
15-19	10
20-38	2
Gender	**Gender**
Female	17
Male	21
Types of Melanoma	**Types of Melanon**
Conventional	19
Spitz	14
Primary	32
Secondary	6
Family History: defined as a first- or second-degree relative with melanoma, diagnosed at any age.	**Family History:** d
Positive	8
Negative	30

TABLE 2 Descriptions of patients with pathogenic variants

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Patient	Melanoma history	Age at Diagnosis	Germline genetic testing completed	Pathogenic results	Family history of melanoma
1	Malignant Melanoma	16	63 gene pan cancer panel	*PMS2* c.1831dupA (p.Ile611AsnfsTer2); *PMS2* c.736_-741delinsTGT-GTGTGAAG (p.Pro246Cysfs)	Yes Maternal Grandfather died at the age of 56 from metastatic malignant melanoma
2	Spitzoid Melanoma	9	12 gene melanoma panel 180k Oligo Chromosome Microarray Analysis	0.634-0.775Mb loss at 17q21.31	No
3	Spitzoid Melanoma	2	78 gene pan cancer panel	*ATM* c.2250G>A (p.Lys750=)	No
4	Spitzoid Melanoma	11	8 gene melanoma panel + BRIP1	*BRIP1* c.2053C>T (p.Gln685*)	No
5	Malignant Melanoma	7	TP53 sequencing	*TP53* c.638G>A (p.(Arg213Gln) (R213Q)	No