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GERMLINE PREDISPOSITION TO MYELOID NEOPLASMS (M PATNAIK, SECTION EDITOR)

Pediatric Germline Predisposition to Myeloid Neoplasms

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Abstract

Purpose of Review Advances in the understanding of germline predisposition to pediatric cancers, particularly myeloid neoplasms, have increased rapidly over the last 20 years. Here, we highlight the most up-to-date knowledge regarding known pathogenic germline variants that contribute to the development of myeloid neoplasms in children.

Recent Findings This discussion enumerates the most notable myeloid neoplasm-causing germline mutations. These mutations may be organized based on their molecular underpinnings—transcriptional control, splicing and signal transduction control, and a group of heterogeneous bone marrow failure syndromes. We review recent findings related to the biochemical mechanisms that predispose to malignant transformation in each condition. Key genetic discoveries such as novel mutations, degrees of penetrance, principles of the two-hit hypothesis, and co-occurrence of multiple mutations are shared. Clinical pearls, such as information regarding epidemiology, natural history, or prognosis, are also discussed.

Summary Germline mutations predisposing to pediatric myeloid neoplasms are frequent, but underrecognized. They hold major clinical implications regarding prognosis, treatment strategies, and screening for other malignancies. Further research is warranted to better characterize each of these conditions, as well as identify additional novel germline pathogenic variants of interest.

Keywords Pediatric · Inherited bone marrow failure · Myeloid neoplasms · GATA2 · SMAD9 or SMAD9L · Germline predisposition

Introduction

Historically, greater attention has been paid to cancer predisposition syndromes in the setting of adult-onset malignancies as compared to pediatric patients. Further recognition is needed regarding the role of predisposition syndromes in the development of pediatric malignancies, as rates of pathogenic germline mutations have been estimated to be similar among pediatric and adult patients with cancer (8.5% vs. 8%) [1]. The first pediatric germline predisposition syndrome for bone marrow failure (BMF) and myeloid neoplasms (MNs) was described nearly a century ago, with the discovery of Fanconi anemia [2]. However, the acquisition of new knowledge regarding other predisposing germline mutations for MNs remained relatively stalled until the last 20 years, during which the discovery of causative mutations has rapidly increased.

Myeloid malignancies occur with lower frequency in children as compared to lymphoid neoplasms, with approximately only 20% of childhood leukemias being of myeloid origin [3]. Of those, up to 25% are estimated to carry pathogenic germline mutations [4]. In light of this growing population, the WHO classification was updated in 2016 to include acute myeloid leukemia (AML) and other MNs associated with germline mutations or a known cancer predisposition syndrome as a distinct entity [5].

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Without a heightened index of suspicion, germline mutations may go unrecognized, as many of these pathogenic variants may also be identified as somatic mutations in the neoplasm. Therefore, testing of healthy tissue for germline mutations is of high importance. Care must be taken to ensure that true germline material is utilized for testing. Blood and bone marrow are not viable sources, even if the patient is in remission, as somatic mutations may persist in these sites. Tissues that are easily contaminated also should not be used, such as saliva and nails. The gold standard sample for germline testing is cultured skin fibroblasts via skin biopsy [6]. The diagnosis of a cancer predisposition syndrome often holds major implications for the individual patient, as well as their family members. The identification of a germline pathogenic variant may influence prognosis, treatment recommendations, and monitoring for additional malignancies. Family members may benefit from enhanced screening for various malignancies, as well as knowledge of inheritance patterns for reproductive planning.

Implicated genes of the germline predisposition mutations for MNs have a wide array of molecular effects. Many are involved in transcriptional control, as well as splicing and signal transduction control. Additionally, syndromes have been identified with defects rooted in DNA repair, telomere biology, ribosome synthesis, and tumor suppression mechanisms. Each of these conditions will be discussed separately here, with an emphasis on current knowledge regarding the genetic and biological mechanisms that predispose to malignancy, as well as key clinical takeaways. Each germline mutation lends itself to a different clinical phenotype, which is partially characterized by age of onset for the MNs depicted in Fig. 1.

Transcriptional Control

Transcription factors are the proteins which convert DNA into RNA. They enable appropriate hematopoiesis by regulating downstream gene expression through binding to specific consensus sequence elements. Disruptions in transcription factor control over gene expression are critical in the evolution of cancer and can occur through

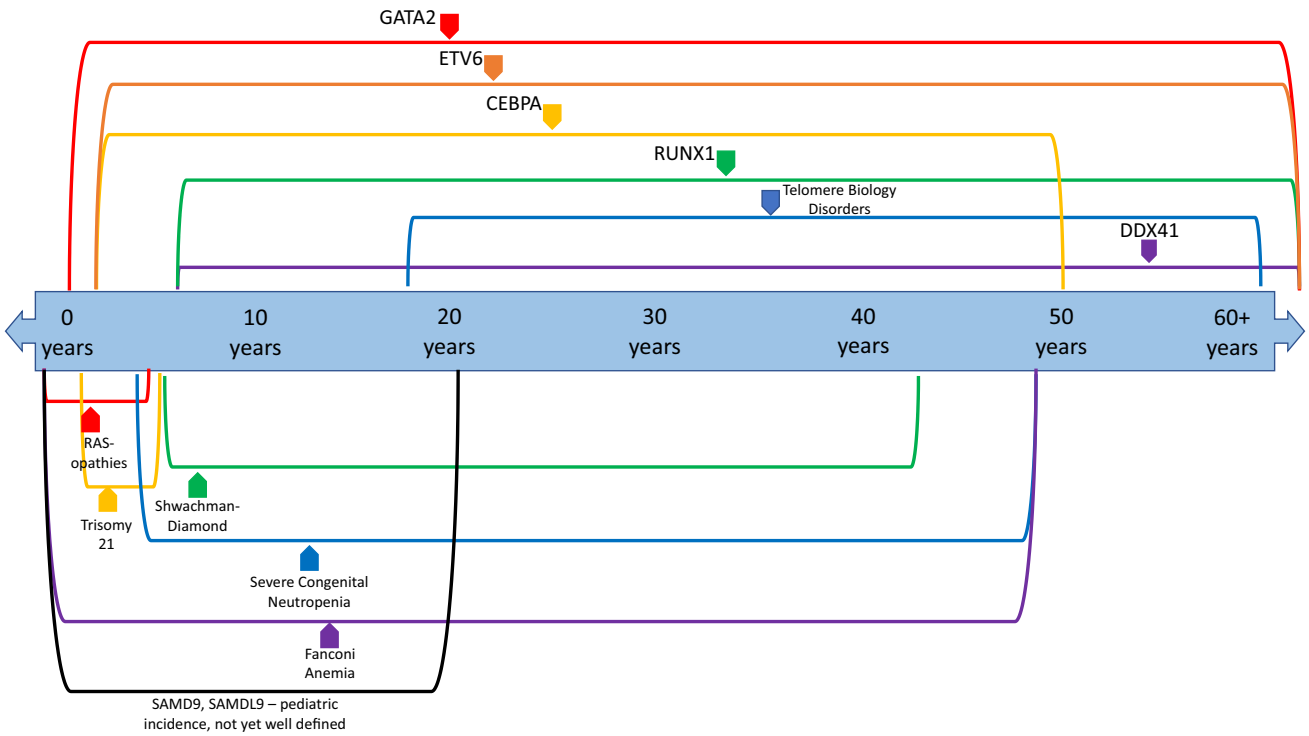

Fig. 1 Timeline of age of MN onset by mutation/syndrome, averages, and ranges [32]. Depiction of the average (indicated by arrowhead) and range (indicated by bracket) of age of onset for myeloid neoplasms by specific germline mutation or syndrome. Conditions listed in upper figure portion are predominately adult age of onset; conditions listed in the lower figure portion are predominately childhood age of onset

germline predisposition or somatic mutations. Transcription factor mutations that can lead to these disruptions and induce myeloid neoplasms include *CEBPA*, *RUNX1*, and *GATA2*.

CEBPA

CCAAT enhancer binding protein alpha (*CEBPA*) is a critical transcription factor identified as a loci of interest in MNs in 2004 [7]. *CEBPA* encodes the CCAAT enhancer binding protein (C/EBP), which is involved in lineage-specific myeloid differentiation. Mutations in *CEBPA* confer a high risk of myeloid neoplasms and may be found in 5–10% of AML cases. In de novo AML, up to 15% involve biallelic mutations in *CEBPA* [8]. De novo AML refers to AML in patients with no clinical history of prior myelodysplastic syndrome (MDS), myeloproliferative disorder, or exposure to potentially leukemogenic therapies or agents [9]. Secondary AML (s-AML) refers to a leukemic process: (1) evolving from prior myelodysplasia (MDS), myeloproliferative disorder (MPN), or aplastic anemia (AA) with or without treatment or (2) as a product of previous exposure to a proven leukemogenic chemotherapeutic agent (therapy-related AML (t-AML)) [10]. Wild-type *CEBPA* usually encodes for a 42 kDa isoform. In most familial cases of AML involving *CEBPA* mutations, biallelic mutations are observed. Biallelic mutations prevent DNA binding or C/EBP dimerization and occur when both a C-terminal and an N-terminal mutation are present. The germline *CEBPA* mutation results in a 30 kDa isoform usually from variants leading to stop-gain frameshifts in the N terminus. A further second mutation occurring in the C-terminal is often acquired as either an in-frame insertion or deletion or a missense variant [11]. Also, possibly contributing to the pathogenesis of AML is the epigenetic control of gene expression. *CEBPA* promoter methylation has recently been found to silence the gene [12••, 13]. Some variants in biallelic *CEBPA* mutated AML tend to co-occur such as *GATA2*, *WT1* (WT1 transcription factor), *TET2* (Tet methylcytosine dioxygenase 2), and *CSF3R* (colony-stimulating factor 3 receptor). Others are rare and often occur exclusively such as *FLT3* (fms-like tyrosine kinase 3), *DNMT3A* (DNA methyltransferase 3 alpha), *IDH1/2* (isocitrate dehydrogenase (NADP(+)) 1/2), *NPM1* (nucleophosmin 1), and *RUNX1* [14]. Compared to other cancer predisposition genes, germline *CEBPA* mutations demonstrate significant penetrance and confer an almost 100% risk of developing AML [15]. Notably biallelic *CEBPA* gene mutations confer both an increased survival and event-free survival compared to those with monoallelic *CEBPA* mutation [16].

RUNX1

The *RUNX1* gene encodes a protein which is a key transcription factor for hematopoiesis called runt-related transcription factor (RUNX1). Approximately 10% of AML cases involve *RUNX1* mutations and a further 10% of these *RUNX1*-mutated AML cases involve germline variants [17–19

GATA2

GATA2 is a transcription factor involved in stem cell maintenance with key roles in regulating gene expression in hematopoietic cells. It belongs to the GATA family of transcription factors which contain zinc fingers in their DNA binding domain. GATA2 is expressed in hematopoietic progenitors as well as nonhematopoietic embryonic stem cells and is involved in the development of the lymphatic system [21]. Germline *GATA2* mutations demonstrate high penetrance with up to 70% risk of developing a myeloid neoplasm and a 90% risk of developing clinical symptoms [22, 23]. This topic is further discussed in another chapter.

Splicing and Signal Transduction Control

Splicing describes the process where the noncoding regions of genes are removed from the primary messenger RNA transcript leaving the coding regions which are then joined together to generate mature messenger RNA. Alternative pre-mRNA splicing occurs in myeloid neoplasms with higher frequencies seen in somatic mutations. There are rare germline variants such as mutations in *DDX41*, *SAMD9*/*SAMD9L*, and the RAS/MAPK pathway which predispose to malignancy.

SAMD9 and SAMD9L

Sterile alpha motif domain-containing protein 9 (*SAMD9*) and sterile alpha motif domain-containing protein 9-like (*SAMD9L*) genes are located on chromosome 7 and are derived from the same ancestral gene [24••]. They are both interferon TNF-alpha inducible and were discovered due to studies in patients with MNs and acquired 7q21 microdeletions [25]. While they appear to be involved in cytokine signaling and endocytosis, their hematopoietic function is unclear [26].

In pediatric patients with MDS, 17% have germline variants of *SAMD9*/*9L* and most are missense mutations which occur in the second half or C-terminus of the *SAMD9*/*9L* proteins leading to autosomal-dominant syndromes [27]. Deletions involving the long arm of chromosome 7 as

well as monosomy of chromosome 7 are common abnormalities seen in AML and MDS as haploinsufficiency of *SAMD9/9L* contributes to genetic neoplasms. Conversely, germline mutations which cause gain-of-function mutations are associated with a spectrum of disorders such including ataxia-pancytopenia syndrome (ATXPC), myelodysplasia, and leukemia syndrome with monosomy 7 syndrome and MIRAGE (myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy) syndrome [28]. An autoinflammatory panniculitis similar to Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperatures (CANDLE) syndrome was recently found to be caused by frameshift and truncating germline mutations in *SAMD9L* [29••]. Separately, *SAMD9* mutations demonstrate high penetrance with a high rate of de novo cases as observed in MIRAGE syndrome [28]. Conversely, in *SAMD9L* syndromes, there is incomplete penetrance which is approximated to 70% for most hematological diseases [30].

Normally, *SAMD9/9L* inhibits cell cycle progression and suppress myeloid proliferation; thus, activating mutations leads to growth restrictions with organ hypoplasia and pancytopenias [31]. Acquired loss-of-function mutations in *SAMD9* or *SAMD9L* have been shown in studies to balance the gain-of-function germline effect [31]. Another proposition is that an adaptive mechanism to germline *SAMD9/9L* mutations may be the selective loss of chromosome 7 [27, 28]. The resultant haploinsufficiency of genes which co-occur in this region such as *KMT2C/MLL3* (lysine methyltransferase 2C/mixed-lineage leukemia 3), *EZH2*, and *CUX1* can also influence the development of AML or MDS [32].

There is a spectrum of clinical presentation in patients affected by *SAMD9/9L* syndromes ranging from transient cytopenia (most commonly thrombocytopenia) to a much more severe disease often fatal in infancy [24••]. Pancytopenia with hypocellular marrow and MDS with − 7 or del(7q) are also common presentations [24••]. While hematologic abnormalities are shared between both *SAMD9/9L* syndromes, they each can manifest separately with distinct characteristics. Notably the *SAMD9* phenotype presents as MIRAGE syndrome often with intrauterine growth restriction; genital abnormalities such as testicular dysgenesis, cryptorchid testes and clitoromegaly, primary adrenal insufficiency and early onset adrenal hypoplasia, gastrointestinal issues (enteropathy, reflux); severe systemic infections; and cytopenia at birth [33]. Neurological findings are the hallmark in patients affected by *SAMD9L* mutations can lead to the loss of Purkinje cells, often presenting as cerebellar ataxia or atrophy, nystagmus, and dysmetria [34, 35].

One large cohort of pediatric MDS patients 90 percent of those with a *SAMD9/9L* mutation showed refractory cytopenia of childhood (RCC) while 10% showed MDS with excess blasts [33]. Furthermore, in pediatric MDS, the median age at diagnosis in those with *SAMD9/9L* was similar to those with *GATA2*-related MDS at 9.6 years (Fig. 1) [33].

There is a spectrum of ill-defined immunologic dysfunction in patients with *SAMD9/9L* mutations [24••]. In some cases, the *SAMD9/9L* mutation decreased peripheral B/NK-cells, low IgG, and IgM or increased TNF-alpha and IL-6 levels have been recorded [36]. While most of the non-syndromic MDS patients harboring this mutation do not appear to be at increased risk of severe infections, those with syndromic phenotypes such as MIRAGE syndrome and some *SAMD9L* mutations demonstrate immune dysregulation [28, 37].

The two unique *SAMD9/9L* disease mechanisms are clonal evolution and somatic revertant mosaicism. Clonal evolution occurs through the non-random loss of chromosome 7 (− 7/del(7q)) which contains mutated *SAMD9/9L* gene copy and has been termed adaptation by aneuploidy [38]. Chromosome 7 harbors several tumor suppressor genes; therefore, clonal evolution to advanced AML/MDS is a frequent complication in *SAMD9/9L*-related MDS [39]. This process is usually paired with somatic driver mutations such as *RUNX1*, *PTPN11*, *KRAS*, *ETV6*, *BRAF*, *SETBP1*, *ASXL1*, *CBL*, and *EZH2* [40].

In somatic revertant mosaicism, the two processes involved include the acquisition of truncating *SAMD9/9L* mutations or an independent uniparental disomy of 7q (UPD7q) [41]. Somatic *SAMD9/9L* mutations are thought to exert a loss-of-function effect and cancel the gain-of-function germline mutation as they are acquired on the same allele (in cis) [36].

Currently, due to the novelty of *SAMD9/9L* with respect to myeloid predisposition, no concrete management guidelines exist. In general, for pediatric patients with MDS, HSCT is recommended as soon as clinically possible especially in those in patients with immunodeficiency, morphologically advanced disease, transfusion dependency, neutropenia, and high-risk cytogenetic and genetic lesions [42].

RAS/MAPK Pathway

The RAS/MAPK pathway is one of the more well-studied signal transduction pathways in cell biology. Its function is to transduce extracellular products to the cell nucleus activating specific genes for cell growth, division, and differentiation [43]. RAS is a superfamily of proteins which are GTPases controlling various cell signaling pathways such as the MAPK pathway and include *HRAS*, *KRAS*, and *NRAS*. RAS controls downstream signaling pathways important for proliferation and differentiation by being active in the GTP-bound state and being inactive in the GDP bound state [44, 45]. Germline pathogenic variants in the RAS/MAPK pathway are associated with a spectrum of congenital disorders

such as neurofibromatosis type 1, cardiofaciocutaneous syndrome, Costello syndrome, Noonan syndrome, and Noonan syndrome with multiple lentigines. The somatic variants in *KRAS*, NRAS, *PTPN1*, *CBL*, and *NF1* are often seen in various neoplasms. There is a significant risk of myeloproliferative neoplasms conferred by these conditions including a severe pediatric myeloid neoplasm termed juvenile myelomonocytic leukemia (JMML) [46, 47]. In patients with JMML, germline mutations are predominantly located in intron 7 and exons 8 and 9. JMML occurs as the result of dysregulation in RAS/MAPK signaling pathway often caused by either germline mutations in *NF1* or *CBL* tumor suppressors and further biallelic inactivation in hematopoietic cells or heterozygous somatic gain-of-function mutations in *KRAS*, *NRAS*, or *PTPN1*. Copy-neutral loss of heterozygosity (CN-LOH) affecting chromosome 17q, a second *NF1* mutation, or somatic interstitial deletions are the main mechanisms by which a second *NF1* may occur [48, 49

DDX41

DDX41 (DEAD-Box Helicase 41) encodes an RNA helicase which plays a role in RNA splicing. The gene, located on chromosome 5, may experience mutations which are often mutually exclusive with the spliceosome mutations more frequently seen in myeloid neoplasms [51]. Mutations in this gene modify RNA processing and pre-MRA splicing, thereby causing loss of tumor suppressor function [52]. One of the most commonly occurring postconception alterations found in myeloid tumors is the p.R525H variant in *DDX41* [53]. Recent studies show there may be certain locations on *DDX41* that are predisposed to germline mutations and are often more common within ethnic groups. For example within the Asian population, the p.A500Cfs*9 germline variant is often found whereas the p.M1I and p.D140Gfs*2 variants are more often found within the Caucasian population [51, 54]. In addition to myeloid neoplasms, these families are also predisposed to the development of non-Hodgkin lymphoma. The germline *DDX41* mutations present in myeloid neoplasms are often found in high-risk AML or MDS cases and bone marrow hypocellularity. MDS precedes more than half of reported cases of AML with the *DDX41* mutation [55]. Further simultaneous mutations associated with secondary AML include *EZH2*, *ASXL1* (ASXL transcriptional regulator 1), *CUX1* (Cut like homeobox 1), *SRSF2* (serine- and arginine-rich splicing factor 2), and *SETBP1* [56]. Somatic *DDX41* mutations are uncommon without predisposing germline *DDX41* pathogenic variants and are most often found in older patients with a median age of diagnosis as 69 years. This differs from the *RUNX1*, *GATA2*, or *CEBPA* genes with a high predisposition to familial myeloid neoplasms and usually have a younger age of diagnosis [52].

Bone Marrow Failure Syndromes and Other Inherited Disorders

Fanconi Anemia (FA)

Bone marrow failure syndromes such as Fanconi Anemia, Dyskeratosis Congenita, Shwachman-Diamond syndrome, Severe congenital Neutropenia, and Diamond–Blackfan anemia significantly increase the likelihood of developing a myeloid neoplasm.

FA is understood to be caused by dysfunctional DNA repair, due to hypersensitivity to mitomycin C (MMC) and diepoxybutane (DEB), which causes DNA cross-linking [57]. There is subsequently a higher rate of chromosomal breakage seen in these cells, which is the basis of diagnostic testing for clinical evaluation of FA. MDS and AML are thought to develop in these patients due to the presence of mutations in these cells which allow for evasion of cell cycle regulation and apoptosis [58].

The general categories of FA genes include the FA core complex which makes proteins which then then activate ID2 complex proteins and a group of proteins in the downstream functional units which work to recruit DNA repair proteins. When genes in this pathway are mutated, there is subsequent impairment in DNA repair, particularly double-strand DNA damage. The risk of developing MDS or AML before the age of 20 is 27% and increases to 52% by the age of 40 as per the International Fanconi Anemia Registry Study [59].

Dyskeratosis Congenita (DC)

Dyskeratosis congenita is a bone marrow failure disorder which is part of the telomere biology disorders. In two-thirds of the patients with DC, mutations in genes encoding core telomerase components and others involved in telomere maintenance have been identified [60]. As shortened telomeres leads to senescence, apoptosis, or oncogenic transformation of somatic cells and thus cause subsequent genetic instability, DC is therefore also a myeloid predisposition syndrome. This is thought to play a critical role in the malignant potential and transformation [61].

Diamond–Blackfan Anemia (DBA)

Diamond–Blackfan anemia is a cancer predisposition syndrome associated with defects in ribosome synthesis. These gene defects, known as ribosomopathies, lead to haploinsufficiency by hosting heterozygous loss-of-function mutations. Numerous studies show that these ribosomopathies can stimulate malignant transformation from the upregulation of protein synthesis [62]. Further evidence has been found showing that

ribosomal stress signaling through p53 activation may play an additional role in malignant transformation. This mechanism conveys a higher risk of developing solid tumors, AML, and MDS among DBA in some studies [63].

Li–Fraumeni Syndrome

Li–Fraumeni syndrome is a cancer predisposition disorder linked to *p53* tumor suppressor gene germline mutations. The downstream effects of this mutation include dysregulation of the cell cycle, cell proliferation, DNA repair, genomic stability, and homeostasis. In patients with Li–Fraumeni syndrome, the most frequent leukemia is hypodiploid acute lymphoblastic leukemia however myeloid neoplasms are also common. These often occur as a complication from therapy given for a primary malignancy. De novo germline *p53* mutations in AML are rare [64, 65].

Trisomy 21

Transient myeloproliferative disorder is a self-resolving abnormality in myelopoiesis that is uniquely seen in neonates with complete or mosaic trisomy 21. This condition arises due to clonal proliferation of immature megakaryoblasts, as a result of cooperation between the chromosome 21 trisomy and somatic mutations in the *GATA1* gene [66]. The exact genes on chromosome 21 responsible for this disorder have not yet been identified, but may include *RUNX1*, *ETS2*, and *ERG* [67, 68]. *GATA1* mutations in isolation are not thought to be sufficient to cause transient myeloproliferative disorder [69]. Clinically, transient myeloproliferative disorder may range from asymptomatic to life threatening, with hyperleukocytosis, hydrops fetalis, infiltration of solid organs, liver failure, and cardiopulmonary failure [70]. While most patients improve without intervention, 20–30% of patients with transient myeloproliferative disorder will go on to develop acute megakaryoblastic leukemia within 3 years [71].

Conclusion

Knowledge regarding the role of germline mutations in MNs has substantially grown in recent years, with far more patients carrying pathogenic variants than previously suspected. And yet, germline predisposition among pediatric cancer patients remains underdiagnosed. Lack of associated syndromic features and/or family history can make identifying these conditions quite challenging by clinical history. As comprehensive genetic testing becomes more accurate, accessible, and affordable, testing for underlying mutations should be integrated into the care of pediatric patients with newly diagnosed MNs. Spectrum of penetrance and clinical illness may vary widely based on the genetic underpinning. Therefore, identification of a germline mutation can profoundly influence medical decision-making. Further research is warranted to better understand frequency, penetrance, and clinical outcomes among these patients.

Declarations

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest The authors declare no competing interests.

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•• Of major importance

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