

Germline *DDX41* mutations in myeloid neoplasms: a comprehensive review

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DEAD-box helicase 41 (*DDX41*)-associated myeloid neoplasms represent a distinct hereditary cancer syndrome and have emerged as the most common form of genetic predisposition to adult-onset hematologic malignancies, accounting for 3–5% of adults with myelodysplastic syndrome and acute myeloid leukemia. *DDX41* is a multifunctional DEAD-box RNA helicase that plays essential roles in pre-mRNA splicing, ribosome biogenesis, and innate immune regulation. Pathogenic germline variants predominantly cluster within the N-terminal region, whereas somatic second-hit mutations are concentrated in the C-terminal helicase domain. The characteristic “two-hit” model involves a germline loss-of-function mutation followed by a somatic variant—most commonly p.R525H—leading to malignant transformation. This process occurs through defective small nucleolar RNA processing, impaired ribosome assembly, erythropoietic abnormalities, and R-loop-mediated DNA damage. Clinically, the phenotype is consistent and characterized by late-onset disease in the sixth to seventh decades of life, a strong male predominance, hypocellular bone marrow, and normal cytogenetics. Despite these distinctive features, affected individuals generally exhibit favorable treatment responses and outcomes compared with sporadic cases. An important clinical consideration in *DDX41*-associated disease management is the planning of allogeneic hematopoietic cell transplantation, where genetic screening for *DDX41* variants among potential related donors is essential. Future investigations should aim to elucidate the molecular mechanisms underlying *DDX41*-driven leukemogenesis, refine surveillance strategies, and develop targeted therapeutic approaches.

Keywords: *DDX41*; Germline mutations; Myeloid leukemia; Tumor predisposition

INTRODUCTION

The understanding of genetic predisposition to cancer has evolved remarkably over the past century. What began as clinical observations of familial cancer clustering has transformed into the precise identification of specific germline pathogenic variants, facilitated by major advances in molecular biology and next-generation sequencing (NGS) technologies [1-4]. Hereditary cancer syndromes account for approximately 5–10% of all cancer cases and up to 17.5% of advanced cancer cases [5]. This paradigm shift has fundamentally reshaped approaches to cancer risk assessment

and prevention.

Myeloid malignancies with genetic predisposition were once considered rare. However, recognition of familial clustering in these malignancies has progressed from anecdotal reports in the mid-20th century to a sophisticated molecular understanding of hereditary predisposition syndromes [6-9]. In parallel with this progress, germline deleterious variants in multiple genes are now known to predispose individuals to hematopoietic malignancies, and recent leukemia classification systems have been revised to include these entities [10-12]. For example, the fifth edition of the World Health Organization Classification of Haematolymphoid Tumors cat-

egorizes myeloid neoplasms with germline predisposition into 18 distinct syndromes based on disease phenotype and causative genes [12]. Current evidence indicates that about 10% of individuals with myeloid malignancies carry pathogenic germline variants in established predisposition genes [13], with DEAD-box helicase 41 (*DDX41*) mutations representing the most prevalent subset in adults. Distinct predisposition syndromes display unique epidemiological patterns: classical hereditary bone marrow failure syndromes and *RUNX1*-related disorders often present earlier with syndromic features, whereas *DDX41*-associated disease typically manifests in adulthood [13,14].

DDX41 is the most common germline predisposition gene implicated in adult-onset myeloid neoplasms, identified in approximately 3–5% of adults with myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) [13,15]. About 40–50% of myeloid neoplasms harboring germline *DDX41* variants acquire an additional somatic mutation on the wild-type *DDX41* allele [16–19]. More than 95% of these somatic mutations are missense, with p.R525H being the most frequent, accounting for approximately 60–80% of all somatic *DDX41* variants [20]. *DDX41* plays an essential role in hematopoiesis and performs diverse functions, including nucleic acid sensing [21–23] and nuclear RNA regulatory processes such as pre-mRNA splicing, R-loop resolution, and ribosome biogenesis [20,24–26]. Experimental models suggest that impaired R-loop resolution—resulting in innate immune activation [27–29] and defective ribosome biogenesis [30–32] contribute to the pathogenesis of myeloid neoplasms associated with germline *DDX41* variants. However, the precise mechanisms by which pathogenic germline *DDX41* mutations lead to malignant transformation remain unclear. This review summarizes current knowledge on *DDX41*'s molecular functions, germline variant spectrum, pathogenic mechanisms, clinical phenotype, treatment outcomes, prognosis, and diagnostic and management considerations.

STRUCTURE AND FUNCTIONS OF *DDX41*

The *DDX41* gene is located on chromosome 5q35.3, a region frequently implicated in myeloid neoplasms. *DDX41* exhibits the canonical structure of DEAD-box RNA helicases, consisting of several distinct domains that enable nucleic acid recognition, adenosine triphosphate (ATP) hydrolysis,

and RNA remodeling. The protein contains an N-terminal segment that functions as a nuclear localization signal, followed by two highly conserved domains—the DEAD domain and the helicase domain—that form the catalytic core, as well as a C-terminal extension. The core structure of DEAD-box proteins comprises two primary RecA-like domains. The first RecA-like domain contains the characteristic DEAD motif together with Walker A and Walker B sequences essential for ATP binding and hydrolysis, whereas the second domain contains helicase motifs that mediate RNA binding and conformational rearrangements [24,33].

DDX41 plays critical roles in several aspects of RNA metabolism, particularly in the regulation of pre-mRNA splicing and ribosome biogenesis. RNA helicases, in general, alter RNA structures and RNA–protein interactions through ATP-dependent helicase activity. *DDX41* is thought to be integrated into the C complex of the spliceosome [28], which represents a central component in the two-step transesterification reactions that mediate RNA splicing [34]. Although the precise role of *DDX41* in splicing remains incompletely defined, experimental studies have shown that its loss or mutation results in splicing alterations such as exon skipping and intron retention, especially in hematopoietic progenitor cells [19,35]. *DDX41* also contributes to the processing of pre-ribosomal RNA (rRNA), a critical step in ribosome assembly [31]. Small nucleolar RNAs (snoRNAs)—a class of noncoding RNAs—are essential for rRNA modification through 2'-O-methylation and pseudouridylation. Mutations in *DDX41* have been linked to defective snoRNA processing, which subsequently impairs ribosome function [30]. This evidence highlights a novel role for *DDX41* in connecting RNA splicing with ribosome biogenesis, as snoRNA processing is functionally intertwined with splicing regulation.

DDX41 also functions as a sensor of nucleic acids released from intracellular pathogens, including double-stranded DNA and cyclic di-guanosine monophosphate [21]. Under physiological conditions, *DDX41* is primarily localized in the nucleus due to its N-terminal nuclear targeting sequence, where it participates in RNA splicing and ribosome biogenesis. Upon cellular activation or nucleic acid stimulation, however, *DDX41* can translocate to the cytoplasm, where it acts as a pattern recognition receptor that detects foreign DNA and cyclic dinucleotides [24,33]. *DDX41* interacts with the adaptor protein stimulator of interferon genes (STING), initiating a STING-dependent innate immune response [23,36]. This interaction is regulated by phosphorylation of *DDX41*

at tyrosine residue 414 by Bruton's tyrosine kinase, which enhances the DDX41–STING association [37]. Nevertheless, whether this function contributes to hematologic malignancies remains unclear. Although germline *DDX41* variants are generally loss-of-function and may reduce immune responsiveness, some studies suggest that *DDX41* deficiency can paradoxically induce inflammation through R-loop accumulation [29].

In addition, *DDX41* is involved in the regulation of R-loop formation, which consists of structures composed of DNA–RNA hybrids and displaced single-stranded DNA [38]. Excessive accumulation of R-loops is associated with pathological conditions, impaired transcriptional elongation, and genomic instability [28]. It has been proposed that *DDX41* directly resolves DNA–RNA hybrids, thereby preventing activation of DNA damage signaling [26,29]. Loss-of-function variants of *DDX41* lead to increased R-loop accumulation and enhanced inflammatory signaling through the STING–TBK1 axis [39]. Although *DDX41* exhibits annealing activity, its helicase unwinding function is crucial for resolving R-loops.

Mutations such as p.R525H impair this activity, potentially promoting activation of the STING–TBK1 pathway [36].

In summary, *DDX41* is a multifunctional DEAD-box RNA helicase with essential roles in RNA splicing, ribosome biogenesis, innate immune regulation, and R-loop resolution (Fig. 1). Mutations in *DDX41* are linked to myeloid malignancies by disrupting these fundamental cellular processes and promoting disease pathogenesis.

PATHOGENESIS AND MUTATIONAL LANDSCAPE OF *DDX41*-MUTATED MYELOID NEOPLASMS

The pathogenesis of *DDX41*-related myeloid neoplasms follows the classical tumor suppressor model, wherein inherited loss-of-function germline variants predispose individuals to malignancy by allowing subsequent acquisition of somatic alterations in the remaining functional allele. Clinical cohort studies consistently demonstrate that a substantial

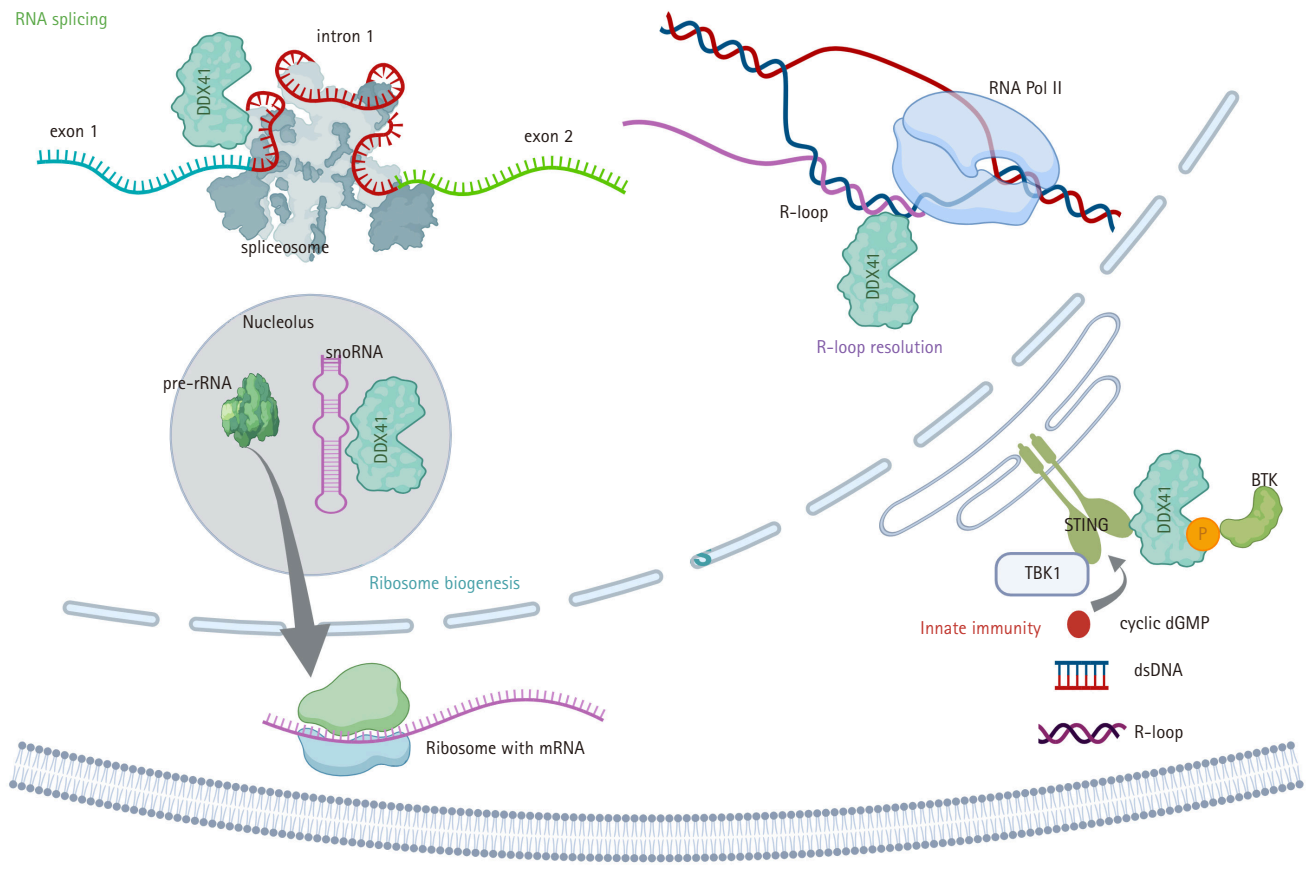


Figure 1. Molecular functions of *DDX41* across cellular compartments. Depicted functions include RNA splicing, ribosome biogenesis, innate immune signaling, and R-loop resolution.

proportion of patients with germline *DDX41* variants who develop myeloid neoplasms harbor somatic second-hit mutations. The p.R525H missense variant within the helicase domain represents the most frequent somatic second hit, occurring at the critical ATP-binding site and disrupting essential helicase activity [19].

Multiple mechanistic studies have elucidated how *DDX41* mutations impair hematopoiesis, providing insights into their contribution to age-related hematopoietic dysfunction and myelodysplasia. Reported mechanisms include defective snRNA processing and impaired ribosome assembly leading to reduced protein synthesis [30]; erythropoietic defects associated with cell cycle arrest and activation of DNA damage responses [39]; and R-loop-mediated DNA damage driven by dysregulated N⁶-methyladenosine methylation complexes [27]. Pathogenesis may be further accelerated by synergistic interactions with *TP53* mutations, which partially compensate for *DDX41* haploinsufficiency while promoting highly penetrant hematologic malignancies resembling MDS and AML [40]. These findings emphasize the intricate interplay between *DDX41* dysfunction and hematopoietic regulation, underscoring the need for continued investigation to clarify the molecular mechanisms underlying *DDX41*-mutated myeloid neoplasms.

The defining features of germline *DDX41* variants include their distinctive clustering patterns and their frequent coexistence with somatic *DDX41* mutations. Most germline variants manifest as loss-of-function alterations in the N-terminal region, whereas recurrent somatic missense variants are predominantly localized within the C-terminal region. Commonly reported germline alterations include p.M1? (loss of start codon), p.D140fs, and p.A500fs (frameshift variants). In a cohort of 346 patients of diverse ethnic origins carrying germline *DDX41* variants, the most prevalent alteration was p.A500fs (23.1%), followed by p.D140fs (11.3%), p.M1? (5.5%), p.S363del (4.3%), and p.Y259C (3.8%) [41]. Nont-runcating germline variants were largely concentrated in the DEAD-box domain, whereas nontruncating somatic variants occurred primarily in the helicase domain. Recent analyses from four large cohorts (each including more than 100 patients) investigating germline *DDX41* variants are summarized in Table 1 [18,41-43].

Significant ethnic variation in the distribution of germline *DDX41* variants has been demonstrated in multiple studies, reflecting founder effects and population-specific genetic backgrounds [2,4]. In Asian populations, the vari-

ants p.A500fs and p.Y259C, together with the splice-site alteration c.935+4A>T, account for more than 50% of pathogenic germline *DDX41* variants. Cohorts from Europe and North America exhibit distinct mutational spectra, with p.M1? and several frameshift variants—particularly p.D140fs—being more prevalent. Notably, p.A500fs, which is most common in Japan, is absent in Western populations, whereas p.D140fs, the predominant germline variant in the United Kingdom, United States, and France, is not observed in Asian populations. Focusing on East Asian populations, four reports have described germline *DDX41* variants associated with myeloid neoplasms from Japan, China, and Korea. The predominant variants differ among these countries: p.A500fs is common in Japan, p.Y259C in Korea, and the splicing variant c.935+4A>T in China [27,41,43,44]. Interestingly, while p.V152G and c.935+4A>T are frequent in Korea and China, they have not been identified in the Japanese population. The E7* variant occurs in a subset of patients in Korea and Japan but has not been reported in China (Fig. 2). These population-specific variant distributions have important implications for genetic testing strategies. Targeted screening panels may require population-tailored optimization to enhance diagnostic sensitivity. Moreover, the founder effects observed in certain populations suggest that cascade testing within families and communities could be particularly valuable for identifying at-risk carriers in regions with high-frequency founder variants.

It is noteworthy that recent evidence indicates *DDX41* variants are relatively common in the general population and are strongly associated with an increased risk of MDS and AML [45]. Analysis of 454,792 participants in the UK Biobank identified 452 distinct nonsynonymous *DDX41* variants among 3,538 individuals, corresponding to an overall carrier frequency of approximately 1 in 129 individuals for any nonsynonymous variant. Within the subgroup of carriers harboring pathogenic variants (1,059 individuals), 34 developed myeloid malignancies, yielding an odds ratio of 12.3 for MDS/AML compared with noncarriers. Consistent with observations from clinical cohorts, European populations demonstrated a higher prevalence of specific variants—such as p.M1? and p.D140fs—that were absent in individuals of non-European ancestry. Moreover, population-based analyses indicate that *DDX41* carriers do not exhibit an increased frequency of clonal hematopoiesis relative to noncarriers, suggesting that *DDX41*-related leukemogenesis may proceed through distinct evolutionary pathways that culminate

Table 1. Summary of large cohort studies involving patients with myeloid neoplasms carrying germline *DDX41* variants

Source	Study patients	Main findings	Key clinical characteristics	Genetic features
Makishima et al (2023) [41]	9,082 MN (4,347 MDS, 2,840 AML, 666 MDS/MPN, 1,229 MPN)	<ul style="list-style-type: none"> • 293 germline <i>DDX41</i> variants in 293 patients classified as P/LP (3.2% frequency) • Penetrance is negligible until age 40, increased to 49.3% by age 90 • Higher prevalence in Japanese vs. Caucasian patients • Better OS than <i>DDX41</i>-WT HR-MDS/sAML patients 	<ul style="list-style-type: none"> • Male predominance (79.4%) • Higher risk in males (OR, 20.7 vs. 5.00 in females) • Male penetrance: 52.5% vs. 28.7% in females by age 85 • Lower WBC counts and reduced BM cellularity 	<ul style="list-style-type: none"> • Normal karyotype (66.9%) • 85% had somatic driver mutations or CNA • Common co-mutations: <i>ASXL1</i>, <i>TP53</i>, <i>CUX1</i>, <i>SRSF2</i>, <i>TET2</i>, <i>DNMT3A</i> • <i>CUX1</i> enriched in biallelic <i>DDX41</i> cases
Maierhofer et al (2023) [18]	5,737 MN (2,865 MDS, 2,157 AML, 715 MPN)	<ul style="list-style-type: none"> • 152 different <i>DDX41</i> variants in 294 patients (5.1% overall) • 61.6% had multiple <i>DDX41</i> variants (germline + somatic pattern) • Bayesian probability 0.998 for pathogenicity when a somatic variant is observed • Significant enrichment vs. gnomAD database 	<ul style="list-style-type: none"> • Male predominance (75.8%) • Late-onset disease (median 72 yr) • MDS: MDS-EB-2 (40.7%), MDS-EB-1 (25.0%) • AML: 41.5% with maturation, 18.9% with minimal differentiation 	<ul style="list-style-type: none"> • Normal karyotype: 81.4% (MDS), 75.3% (AML) • MDS co-mutations: <i>ASXL1</i> (20.2%), <i>SRSF2</i> (17.6%), <i>DNMT3A</i> (15.7%) • AML: fewer <i>NPM1</i>, <i>RUNX1</i>, <i>FLT3</i> mutations; more <i>CUX1</i> • 4 synonymous variants affecting splicing identified
Duployez et al (2022) [42]	1,795 AML	<ul style="list-style-type: none"> • 191 AML patients with causal <i>DDX41</i> germline variant • Higher CR/CRi rates vs. <i>DDX41</i>-WT groups • Prolonged OS-HCT (13.6 mo at 5 yr) • HCT associated with prolonged RFS (HR 0.43, <i>p</i> = 0.02) 	<ul style="list-style-type: none"> • Male predominance (74% vs. 54% <i>DDX41</i>-WT) • Older age (median 66 vs. 64 yr) • Lower WBC counts (2.0 vs. 7.9 × 10⁹/L) • Reduced BM blast infiltration (37% vs. 58%) 	<ul style="list-style-type: none"> • Normal karyotype (77% vs. 57%) • Intermediate risk by ELN-2017 criteria • Higher <i>DDX41</i> somatic mutation frequency • Fewer other somatic mutations vs. <i>DDX41</i>-WT • <i>DDX41</i> somatic mutations as primary drivers
Li et al (2022) [43]	9,821 HM (2,161 MDS, 3,538 AML, 1,029 MPN, 3,048 others)	<ul style="list-style-type: none"> • 176 patients (1.8%) with putative germline <i>DDX41</i> variant • 116 patients (1.2%) had P/LP variants, 60 (0.7%) had VUS • Ethnic differences in variant distribution • Different mutational profiles between CV and VUS groups 	<ul style="list-style-type: none"> • CV group: median age 69 years, male predominance (74%) • VUS group: median age 62 years, less male predominance (62%) • Sporadic AML: median age 64 years, equal gender (50%) 	<ul style="list-style-type: none"> • CV cases: 80% normal karyotype • VUS enriched in recurrent cytogenetic abnormalities • Tyrosine kinase/RAS/MAPK mutations are more frequent in VUS • MPN: <i>JAK2</i> V617F and <i>CALR</i> absent in CV, present in 72% VUS

MN, myeloid neoplasm; MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; MDS/MPN, myelodysplastic/myeloproliferative neoplasm; P, pathogenic; LP, likely pathogenic; OS, overall survival; WT, wild type; HR-MDS, higher-risk MDS; sAML, secondary AML; OR, odds ratio; WBC, white blood cell; BM, bone marrow; CNA, copy number alteration; EB, excess blasts; CR, complete remission; CRi, complete remission with incomplete count recovery; HCT, hematopoietic cell transplantation; RFS, relapse-free survival; HR, hazard ratio; ELN, European LeukemiaNet; HM, hematologic malignancy; VUS, variant of unknown significance; CV, causal variant.

directly in overt malignancy rather than gradual clonal expansion. Collectively, these findings identify *DDX41* as one

of the most common cancer predisposition genes in the general population, underscoring its relevance to popula-

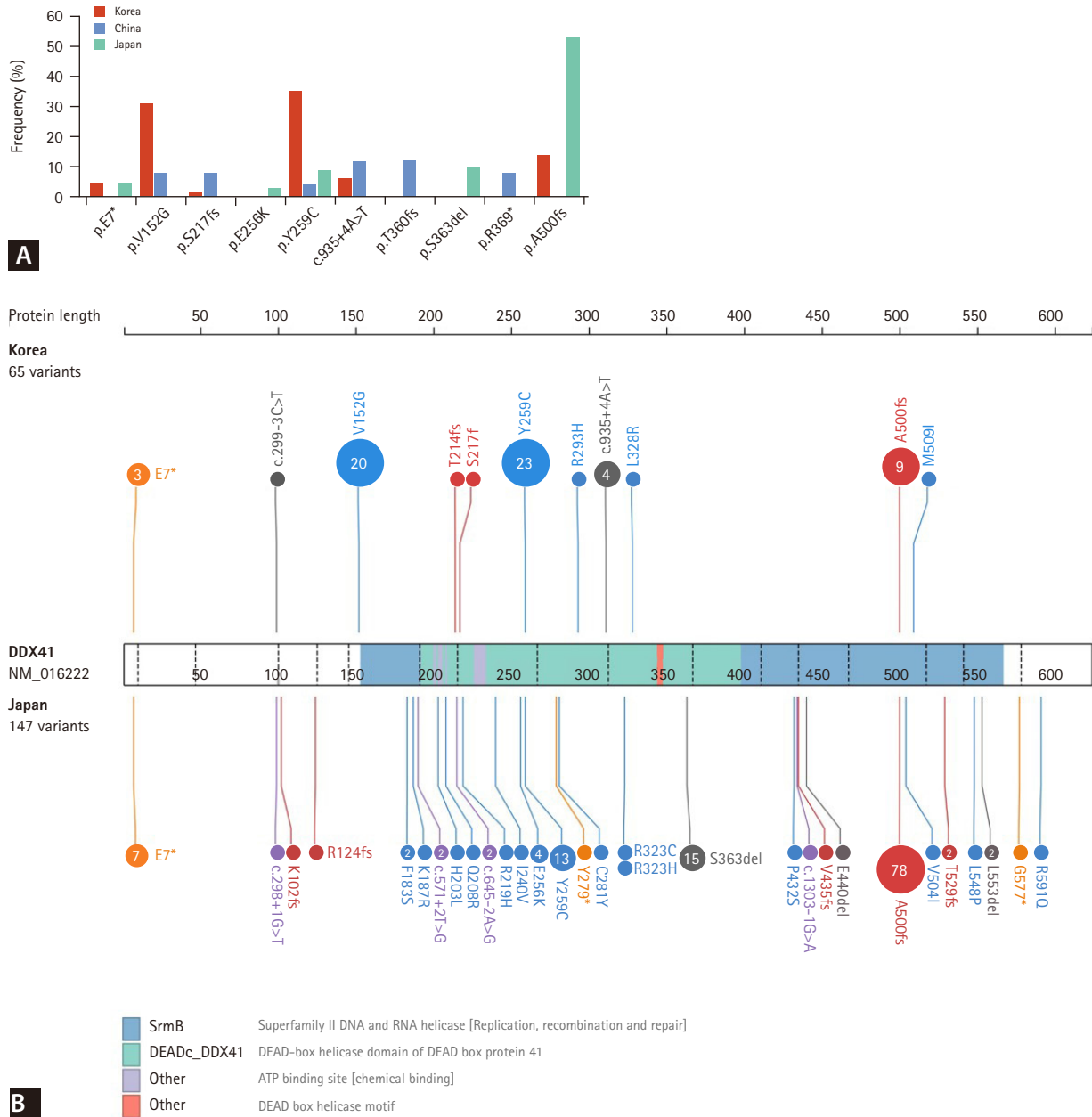


Figure 2. Distribution of germline *DDX41* variants in East Asian populations. (A) Frequency plot of recurrent germline *DDX41* variants identified in Korean, Chinese, and Japanese cohorts. (B) Distribution of germline *DDX41* variants in Korean (upper panel, n = 65) and Japanese (lower panel, n = 147) populations.

tion screening and genetic counseling strategies.

CLINICAL MANIFESTATIONS OF *DDX41*-ASSOCIATED MYELOID NEOPLASMS

DDX41-associated myeloid neoplasms exhibit a characteristic late-onset presentation with marked male predomi-

nance, distinguishing them from other hereditary predisposition syndromes. Clinical cohorts consistently report median ages at diagnosis clustering between the late sixth and early seventh decades of life. Two Korean cohorts comprising 39 and 28 patients showed median ages of 63 and 66 years, respectively [27,44]; an international cohort of 431 patients reported a median age of 69 years [46]; and multiple other referral-based studies confirmed median ages

of 69–70 years [47]. The penetrance of myeloid neoplasms associated with germline *DDX41* variants has not yet been fully determined [10]. Among carriers of germline *DDX41* variants, the penetrance of any myeloid neoplasm is minimal before age 40 but rises sharply to 49–54% by age 90 [41,48]. The development of MDS and AML occurs more frequently in males than in females, with an approximate 3:1 ratio [19,47,49].

Germline *DDX41* variants are associated with a broad spectrum of myeloid neoplasms, with MDS and AML being the most common manifestations. In a Korean study of 457 patients with AML, MDS, and idiopathic cytopenia of undetermined significance (ICUS), germline *DDX41* variants were identified in 4 (2.3%) of 172 patients with AML, 19 (9.0%) of 210 with MDS, and 5 (6.7%) of 75 with ICUS [44]. Similarly, a large international cohort of 9,082 patients revealed *DDX41* variants in 346 patients (3.8%), including 201 (4.6%) of 4,347 patients with MDS, 136 (4.8%) of 2,840 with AML, 1 (0.08%) of 1,229 with myeloproliferative neoplasms (MPN), and 8 (1.2%) of 666 with MDS/MPN overlap syndromes [41].

The acquisition of somatic second hits—most commonly the p.R525H variant—represents a key molecular event influencing disease subtype and progression [19,42]. Studies have shown that somatic *DDX41* variants occur in approximately 60–80% of AML or MDS cases with germline *DDX41* variants, and more than 95% of these somatic variants are missense [20,50]. Somatic mutations in genes other than *DDX41* occur at lower frequencies compared with patients lacking germline *DDX41* variants, with commonly mutated genes including *ASXL1*, *TP53*, *CUX1*, *SRSF2*, *TET2*, and *DNMT3A* [17,20,41,42,47]. Variant interpretation generally follows the guidelines of the American College of Medical Genetics and Genomics (ACMG) [51], which can result in overclassification of *DDX41* variants as variants of uncertain significance (VUS). However, recent studies have adopted a modified classification approach in which the presence of somatic *DDX41* variants serves as supportive evidence for germline pathogenicity [17,18,52].

DDX41-associated myeloid neoplasms often present with hypocellular bone marrow and lower leukocyte counts at diagnosis, in contrast to the hypercellular marrow and elevated leukocyte counts typically observed in sporadic MDS and AML [17,41,44,52]. Furthermore, many patients harboring *DDX41* variants experience a subacute clinical course marked by persistent cytopenia that fulfills

the criteria for ICUS or clonal cytopenia of undetermined significance (CCUS) before overt myeloid neoplasm development [17,20,44,52–54]. Cytogenetic analyses frequently reveal normal karyotypes in *DDX41*-associated disease, with 60–80% of patients exhibiting normal cytogenetics—a substantially higher rate than in sporadic myeloid neoplasms [20,27,41,44,52].

TREATMENT AND PROGNOSIS

MDS and AML harboring *DDX41* variants are generally managed with the same disease-directed approaches used for sporadic cases, with multiple retrospective studies reporting high response rates to standard regimens and notable benefit from lower-intensity venetoclax-based combinations in older or unfit patients (Table 2). Treatment selection is guided by disease subtype (MDS versus AML), patient fitness, donor availability, and the presence of co-mutations or adverse cytogenetic features. The high prevalence of normal cytogenetics, together with the distinctive molecular signature of *DDX41* variants, has led to recognition that conventional cytogenetic risk stratification models may not accurately predict outcomes in these patients [20,42]. Current prognostic scoring systems—specifically, the International Prognostic Scoring System–Molecular for MDS [55] and the European LeukemiaNet (ELN) 2022 classification for AML [10]—do not include *DDX41* status. However, the recently introduced ELN 2024 Less-Intensive model for AML, which incorporates venetoclax-based regimens, categorizes *DDX41*-mutated AML as favorable risk [56,57]. Despite these favorable outcomes with non-transplant regimens, patients with *DDX41*-mutated MDS or AML remain at risk of relapse or disease progression without allogeneic hematopoietic cell transplantation (HCT) [42,58].

High response rates to intensive chemotherapy have been observed in *DDX41*-mutated patients. In a large single-center cohort, complete remission (CR) rates following intensive chemotherapy were 89% in newly diagnosed and 67% in relapsed or refractory *DDX41*-mutated AML patients [59]. Another study compared outcomes of 191 newly diagnosed patients with *DDX41*-mutated AML to those of similarly treated patients without *DDX41* variants [42]. All patients received intensive chemotherapy; those with *DDX41*-mutated AML achieved higher CR rates (94% vs. 69%, $p < 0.0001$) and longer overall survival ($p < 0.001$) than ELN

Table 2. Treatment responses and survival outcomes in patients with *DDX41*-mutated myeloid neoplasms

Investigator	No_ <i>DDX41</i> mutated	Treatment	Treatment response	Survival data
ALFA-FILO [42]	191 (AML): 86 (trial cohort), 105 (real-life cohort)	Intensive therapy Allogeneic HCT	<ul style="list-style-type: none"> • CR 94% (vs. 69% in wt pts) 	<ul style="list-style-type: none"> • Median OS after HCT: 36.6 mo (vs. 26.8 mo in wt pts) • Median RFS after HCT: 19.6 mo (vs. 18.4 mo in wt pts) • ELN-2017 risk scheme poorly discriminated outcomes in <i>DDX41</i> mutated AML pts.
MDACC [60]	151 (4%): AML 96, MDS 52, CMML 3	Intensive or low-intensity therapy with or without venetoclax	<ul style="list-style-type: none"> • ORR: 87% (for new AML), 84% (for MDS) • Intensive therapy, CR/CRi: AML 89% (16/18) • Low-intensity therapy, ORR: AML 89% (32/36), MDS 84% (26/31) 	<ul style="list-style-type: none"> • Median OS: 49 mo (AML), 71 mo (MDS). • 2-yr OS after HCT: 80% (AML, n = 27), 85% (MDS, n = 15) • Low-intensity therapy for AML, with vs. without venetoclax: 2-yr OS, 91% vs. 60% ($p = 0.02$), CIR, 10% vs. 56% ($p = 0.03$) • Low-intensity therapy for MDS with vs. without venetoclax: 2-yr OS, 100% vs. 86% ($p = 0.34$)
Mayo Clinic series [64]	12 (AML 9, MDS 3)	HMA + venetoclax	<ul style="list-style-type: none"> • ORR 100% • MRD-negative in 4/5 (80%) 	Median OS 29 mo
ALLG MDS4 [61]	5 MDS/LB-AML	AZA (n = 4), AZA + lenalidomide (n = 1)	CR 1, mCR 1, HI 1, stable disease 2	All remained alive at the last follow-up median 53 mo (range, 47–58), and none underwent HCT.
Three cohorts for AZA (Japan, Sweden) [62]	27 (MDS, LB-AML) (*total No of pts, 449)	AZA	Post-AZA clone size of <i>DDX41</i> did not predict treatment response.	The <i>DDX41</i> mutation independently predicted superior OS.
AZA-EPO & AZA-PLUS trials [58]	22 (MDS, CMML, LB-AML)	AZA-based regimens	ORR 77%, CR 46%	Median OS 36.2m
A multicenter French retrospective study [67]	83	Allogeneic HCT		<ul style="list-style-type: none"> • 2-yr RFS 68.6% • 2-yr NRM 21.1% • A pair match analysis: no difference in OS, LFS, NRM, relapse, or GVHD between <i>DDX41</i>-mutated vs. wt pts, late relapse pattern in <i>DDX41</i>-mutated pts • 7 cases of <i>DDX41</i> mutated donor cell leukemia
Mayo Clinic series [84]	13 (AML 7, MDS 6) among 29 pts with <i>DDX41</i> mutations	Allogeneic HCT		<ul style="list-style-type: none"> • Median OS 3.2 yr (11.4 yrs in non-HCT group) • 1-yr NRM 44.8%
Univ. of Chicago [66]	21 (AML 14, MDS 6, MPN 1)	Allogeneic HCT		<ul style="list-style-type: none"> • Higher incidence of severe acute GVHD (38%) • No severe acute GVHD in 5 pts receiving PTCY (0% vs. 53%, $p = 0.03$)
Mayo Clinic [59]	68 (AML 23, MDS 30, MPN 4, carrier 6, other 5)			<ul style="list-style-type: none"> • Median OS 21.5 mo • 2-yr OS: 83% (M1I), 75% (R525H), 71% (D140fs)

Table 2. Continued

Investigator	No_ <i>DDX41</i> mutated	Treatment	Treatment response	Survival data
Mayo Clinic series [16]	107 • AML 24, MDS 46, MPN 4, CCUS 4, carrier 8, cytopenia with VUS 20 • Pathogenic variants vs. VUS (44 vs. 63)	HMA based 27, intensive 8, other 10, HCT 19	• MDS (n = 21; CR 6, HI 3) • AML (n = 8, CR 7)	Pathogenic variants vs. VUS • Median OS among HR MDS/AML: 63.4 mo vs. 55.7 mo ($p = 0.93$) • AML progression: 14% vs. 11% ($p = 0.68$)

No, number; AML, acute myeloid leukemia; HCT, hematopoietic cell transplantation; CR, complete remission; wt, wild-type; pts, patients; OS, overall survival; RFS, relapse-free survival; ELN, European LeukemiaNet; MDACC, MD Anderson Cancer Center; MDS, myelodysplastic syndrome; CMML, chronic myelomonocytic leukemia; ORR, overall response rate; CRi, CR with incomplete count recovery; CIR, cumulative incidence of relapse; HMA, hypomethylating agent; MRD, minimal residual disease; LB, low blasts; AZA, azacytidine; mCR, marrow CR; HI, hematological improvement; NRM, non-relapse mortality; LFS, leukemia-free survival; GVHD, graft-versus-host disease; MPN, myeloproliferative neoplasm; PTCY, post-transplantation cyclophosphamide; CCUS, clonal cytopenia with undetermined significance; VUS, variant of uncertain significance.

intermediate/adverse-risk patients lacking *DDX41* variants. The ELN 2017 risk classification failed to effectively discriminate long-term outcomes among *DDX41*-mutated AML patients in this analysis [42].

Favorable outcomes have also been reported following low-intensity therapy with hypomethylating agents in patients with *DDX41*-mutated AML or MDS. The overall response rates after low-intensity therapy, with or without venetoclax, were 89%, 46%, and 84% for previously untreated AML, relapsed/refractory AML, and MDS with *DDX41* variants, respectively [60]. In a small cohort, three of five patients treated with azacitidine, with or without lenalidomide, achieved responses—CR in one, marrow CR in one, and hematologic improvement in one. All five patients remained alive at the last follow-up (median, 53 mo; range, 47–58 mo) without allogeneic HCT [61]. A post hoc analysis of two clinical trials demonstrated favorable and durable responses to azacitidine-based regimens in 22 patients with *DDX41*-mutated higher-risk MDS and low-blast AML, with an overall response rate of 77%, CR of 46%, and median overall survival of 36.2 months [58]. In a separate study of three independent cohorts of patients with MDS and related myeloid neoplasms treated with azacitidine, the presence of *DDX41* variants independently predicted superior overall survival [62]. *DDX41*-mutated AML and MDS are known to exhibit a relatively low mutational burden compared with unselected cohorts [41,52], and this reduced mutational complexity may contribute to improved responses to hypomethylating therapy [63]. Among AML and MDS patients treated with low-intensity regimens, the addition of venetoclax was associated with improved sur-

vival and lower relapse rates [60]. In a small series of 12 patients with *DDX41*-mutated AML (n = 9) or MDS (n = 3) treated with a hypomethylating agent plus venetoclax, all patients responded, with four of five evaluable cases achieving minimal residual disease negativity [64]. Several molecular and clinical studies have reported higher-than-expected responses to lenalidomide in patients harboring *DDX41* variants, although these findings are limited by small sample sizes and retrospective design [19,65].

In a single-institution retrospective analysis, *DDX41* variants were associated with a 38% incidence of severe (grade III–IV) acute graft-versus-host disease (GVHD) after allogeneic HCT among 21 patients with myeloid neoplasms. Notably, none of the five patients receiving post-transplant cyclophosphamide developed severe acute GVHD [66]. A multicenter French retrospective study including 83 AML and MDS patients with *DDX41* variants found no higher incidence of severe acute GVHD and no significant differences in post-transplant outcomes compared with patients without *DDX41* variants [67]. This study also reported seven cases of donor cell leukemia with *DDX41* mutations, consistent with earlier case reports [68,69]. Approximately 0.1–0.5% of post-transplant malignancies originate from transplanted donor cells, and such donor-derived leukemias may arise from germline predisposition alleles or donor clonal hematopoiesis [70]. For patients undergoing allogeneic HCT who harbor deleterious germline *DDX41* variants, related donors should undergo targeted genetic testing before donation [70,71].

The presence of *DDX41* variants is associated with a generally favorable prognosis in multiple studies; however,

clinical outcomes are influenced by disease subtype, variant type, and classification. A recent meta-analysis pooling available data showed that *DDX41* variants correlate with improved overall survival compared with *DDX41* wild type in AML (pooled hazard ratio, 0.60; $p = 0.008$) but not in MDS (pooled hazard ratio, 0.97; $p = 0.95$) [72]. In a single-center cohort of 68 patients with *DDX41* variants, three major hotspots—p.M1, p.R525H, and p.D140fs—were associated with 2-year overall survival rates of 83%, 75%, and 71%, respectively [59]. Molecular hematology laboratories generally apply ACMG criteria, leading to classification of many *DDX41* variants as VUS. In one study, patients with VUS had similar molecular and clinical characteristics to those with pathogenic *DDX41* variants [16], underscoring the challenges of interpretation and the need for careful germline assessment [17,18,52].

DDX41 VARIANTS IN NON-MYELOID NEOPLASMS

Studies involving individuals with germline *DDX41* predisposition indicate that non-myeloid neoplasms do occur but remain uncommon. In a cohort of 195 patients with germline *DDX41* variants, clinical diagnoses included asymptomatic carriers ($n = 20$, 10.2%), CCUS ($n = 12$, 6.1%), clonal hematopoiesis ($n = 10$, 5.1%), MPN ($n = 13$, 6.7%), MDS ($n = 79$, 40.5%), AML ($n = 40$, 20.5%), chronic myelomonocytic leukemia ($n = 2$, 1.0%), mast cell leukemia ($n = 1$, 0.5%), lymphoid neoplasms (9.2%), plasma cell dyscrasias (6.1%), and solid tumors (22.5%) [17]. Some studies of myeloid neoplasms with *DDX41* variants have also reported a subset of patients with personal or family histories of lymphoid or solid malignancies [73,74]. In a comprehensive investigation involving 93 individuals from 43 families carrying germline *DDX41* variants, both solid cancers and hematologic malignancies were observed. The estimated penetrance among individuals with germline *DDX41* variants was 54% ($n = 50$) for hematologic malignancies by age 90 years and 24% ($n = 22$) for solid tumors by age 75 years [48].

GENETIC COUNSELING AND CLINICAL APPLICATION

Healthy carriers of pathogenic germline *DDX41* variants

pose unique challenges for genetic counseling due to incomplete penetrance, late disease onset, and variant heterogeneity. This highlights the importance of structured surveillance with age-stratified monitoring, functional assessment of uncertain variants, and cascade testing of at-risk relatives [75-77]. Current evidence indicates that while NGS-based panels may incidentally detect such variants, comprehensive germline testing and individualized counseling remain essential for optimizing risk communication, clinical management, and long-term outcomes in carriers of *DDX41*-associated predisposition [78,79]. Healthcare professionals should explain that the disease typically manifests after age 50 years, with many patients presenting with preceding cytopenias or leukopenia before overt malignancy develops [16,59]. Genetic counseling sessions should also address the psychological impact of a positive result, including anxiety about cancer risk, implications for family members, and concerns regarding insurance coverage or employment discrimination.

The clinical management of *DDX41* germline variant carriers involves baseline complete blood count evaluation upon confirmation of carrier status, followed by individualized periodic hematologic monitoring with a low threshold for hematology referral when new cytopenias or abnormal blood count trends emerge [9,80]. Family cascade testing is crucial given the autosomal dominant inheritance pattern, as first-degree relatives have a 50% probability of carrying the variant and should be offered predictive genetic testing [16,80].

A critical component of *DDX41* genetic counseling involves addressing the implications for allogeneic HCT, both for affected individuals requiring treatment and for potential related donors. For patients with *DDX41*-associated myeloid neoplasms who are candidates for allogeneic HCT, rapid predictive testing of potential related donors is essential to exclude carriers, as use of a *DDX41*-positive donor carries a measurable risk of donor-derived malignancy [68-70]. Counseling should emphasize early donor screening, consideration of alternative donor sources when family members are carriers, and ongoing communication regarding genetic test results and surveillance recommendations within the family.

FUTURE DIRECTIONS

The field of *DDX41* variant research is advancing rapidly through large-scale genomic sequencing initiatives and sophisticated functional studies that continue to clarify the pathogenic mechanisms driving myeloid neoplasms. These discoveries are being incorporated into improved variant classification frameworks that enhance diagnostic precision and clinical interpretation. Mechanistic insights into the role of *DDX41* in both its functional and dysfunctional states are identifying novel therapeutic targets and opportunities for precision medicine, although most strategies remain in the preclinical phase. Direct modulation of RNA helicases represents a particularly promising therapeutic avenue, as DEAD-box helicases possess druggable surfaces and exhibit synthetic lethal interactions with other helicases that may be exploited for therapeutic benefit [81]. The marked splicing abnormalities resulting from *DDX41* dysfunction suggest that splicing-directed therapies—such as small molecules that modulate spliceosome activity or correct specific splicing defects—may offer targeted treatment strategies for *DDX41*-associated malignancies [35,82]. Furthermore, the accumulation of R-loops and subsequent genomic instability in *DDX41*-deficient cells indicate that agents enhancing R-loop resolution or preventing their formation could represent viable therapeutic options [26]. Modulation of the DNA damage response constitutes another potential therapeutic strategy, as *DDX41*-deficient cells display altered dependencies in DNA repair pathways that can be exploited through synthetic lethality. Poly (ADP-ribose) polymerase inhibitors and other DNA damage response modulators may demonstrate increased efficacy in *DDX41*-associated malignancies due to persistent replication stress and defective DNA repair [83]. The development of therapeutic strategies specifically targeting *DDX41* will require close collaboration among basic researchers, translational scientists, and clinicians to effectively translate promising preclinical discoveries into clinical applications.

The late-onset and frequently indolent nature of *DDX41*-associated myeloid neoplasms presents distinct opportunities for preventive measures and early intervention strategies aimed at delaying or preventing malignant transformation in at-risk individuals [13,45,53]. Integrating genetic risk assessments, family history data, and molecular biomarkers could enable personalized surveillance programs that balance the benefits of early detection against the financial,

psychological, and clinical burdens of intensive monitoring. Prospective registries and longitudinal cohort studies remain essential to validate these preventive and early intervention approaches, as they will provide natural history data critical for designing and powering interventional trials. The relatively high prevalence of *DDX41* variants in the general population, combined with their typically late-onset phenotype, offers a compelling rationale for population-based screening initiatives and preventive trials with potential public health benefits. Future research priorities should include the development of standardized biomarker panels, validation of early intervention approaches in prospective cohorts, and the establishment of international collaborative networks to accelerate scientific progress and facilitate rapid clinical translation of emerging discoveries.

CONCLUSION

The identification of *DDX41* as a key hereditary cancer predisposition gene has profoundly transformed the understanding of adult-onset myeloid malignancies and redefined the framework for hereditary hematopoietic disorders. The distinct clinical and molecular characteristics of *DDX41*-associated neoplasms—including late-onset presentation, relatively favorable prognosis, and unique pathogenic mechanisms—demand tailored management strategies integrating genetic counseling, structured surveillance, and personalized treatment approaches. As comprehensive genomic sequencing efforts continue to expand insight into *DDX41* variant pathogenicity and functional impact, the field is increasingly positioned to design targeted therapeutic and preventive interventions for at-risk individuals and their families. Future investigations should aim to elucidate the molecular pathways of *DDX41*-mediated malignant transformation, optimize surveillance protocols, and develop precision therapies to improve patient outcomes.

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