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DDX41-Associated Familial Myelodysplastic Syndrome and Acute Myeloid Leukemia

Synonyms: *DDX41*-Related Myeloid Neoplasia, Myeloid Neoplasms with Germline *DDX41* Mutation

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Summary

Clinical characteristics

DDX41-associated familial myelodysplastic syndrome and acute myeloid leukemia (MDS/AML) is characterized by an increased risk of myeloid neoplasms, lymphoid neoplasms, adult-onset single- or multiple-lineage cytopenias (including aplastic anemia), and red blood cell macrocytosis. The most common myeloid neoplasms include MDS, AML, and therapy-related myeloid neoplasms. Chronic myelomonocytic leukemia, chronic myeloid leukemia, and myeloproliferative neoplasms are less common. Lymphoid neoplasms include non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma, chronic lymphocytic leukemia, and acute lymphoblastic leukemia.

Diagnosis/testing

The diagnosis of *DDX41*-associated familial MDS/AML is established in a proband with suggestive findings and a heterozygous germline pathogenic variant in *DDX41* identified by molecular genetic testing.

Management

Treatment: Standard neoplasm-specific therapy; allogeneic hematopoietic stem cell transplant evaluation early in the course of hematologic malignancy if appropriate based on the age of the individual, malignancy, and health status – including identification of potential related donors for genetic counseling and genotyping.

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Surveillance: Complete blood count with differential every six to 12 months or more frequently as clinically indicated; annual clinical examination for constitutional signs and symptoms of MDS/AML (e.g., fatigue, infections, bleeding, and skin changes). Consider bone marrow biopsy and aspirate with cytogenetics.

Genetic counseling

DDX41-associated familial MDS/AML is inherited in an autosomal dominant manner. To date, all reported individuals diagnosed with *DDX41*-associated familial MDS/AML whose parents have undergone molecular genetic testing have the disorder as the result of a pathogenic variant inherited from a parent. The heterozygous parent may or may not have developed a hematologic malignancy. If a parent of the proband is known to have the pathogenic variant identified in the proband, the risk to sibs of inheriting the pathogenic variant is 50%. Once the *DDX41* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

DDX41-associated familial myelodysplastic syndrome and acute myeloid leukemia (MDS/AML) **should be suspected** in individuals with the following clinical, laboratory, or family history findings.

Clinical findings

- **Myeloid neoplasms.** Most common types are MDS, AML, therapy-related myeloid neoplasms, with age of onset typically in the sixth decade.

  Less common myeloid neoplasms include chronic myelomonocytic leukemia, chronic myeloid leukemia, and myeloproliferative neoplasms.

- **Lymphoid neoplasms** (less common). Types include non-Hodgkin lymphoma (follicular lymphoma most frequent), Hodgkin lymphoma, multiple myeloma, chronic lymphocytic leukemia, and acute lymphoblastic leukemia, with age of onset typically in adulthood.

- **Aplastic anemia** (rare)

Laboratory findings

- Unexplained blood count abnormalities including mild single- or multiple-lineage cytopenias and/or macrocytosis (in 40%-66%)
- In individuals with MDS/AML:
  - Bone marrow hypocellularity
  - Previous history of cytopenia
  - Personal history of hematologic malignancy (including lymphoid) or solid cancer
  - Prominent erythroid dysplasia, in some instances resulting in a French-American-British Cooperative Group AML Classification subtype M6 or erythroleukemia morphology
  - Normal karyotype (in 59%-85%)
  - One or more *DDX41* pathogenic variant(s) identified in DNA from malignant myeloid cells. NOTE: The presence of two *DDX41* pathogenic variants in malignant myeloid cells, especially if one has a variant allele frequency (VAF) >0.4, is highly suggestive of the presence of this variant in the germline. The most common acquired variant (most often occurring at a lower VAF in combination with a pathogenic germline variant) is p.Arg525His. This pattern of a germline variant and a second, acquired variant in *DDX41* in malignant myeloid cells occurs in 50%-88% of individuals with MDS/AML who have *DDX41*-associated familial MDS/AML.

Family history is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations) of hematologic malignancies (especially MDS/AML), unexplained cytopenias, and/or macrocytosis.

- Absence of a known family history does not preclude the diagnosis; Only 27%-39% of individuals with a germline *DDX41* pathogenic variant have a family history of hematologic malignancies.
- Penetrance of hematologic malignancies appears higher in males than females (3:1) which may result in a male-predominant familial hematologic malignancy pattern.

Establishing the Diagnosis

The diagnosis of *DDX41*-associated familial MDS/AML **is established** in a proband with suggestive findings and a heterozygous germline pathogenic variant in *DDX41* identified by molecular genetic testing (see Table 1).

Note: (1) Malignant myeloid cells from individuals with a germline *DDX41* pathogenic variant frequently demonstrate both the germline and a somatic *DDX41* variant. (2) Identification of a heterozygous *DDX41* variant of uncertain significance does not establish or rule out the diagnosis of this disorder.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings may be diagnosed using gene-targeted testing (see Option 1). However, individuals with a germline *DDX41* pathogenic variant can exhibit significant clinical heterogeneity. Individuals may present with hematologic malignancies or cytopenias that are indistinguishable from other inherited hematologic disorders. In such instances it may be more efficient to pursue genomic testing (see Option 2).

Note: (1) Testing for a germline pathogenic variant should not be performed on blood, bone marrow, or other tissues contaminated with peripheral blood such as saliva, buccal cells, or DNA from direct skin biopsy without culture during an active hematologic malignancy or in individuals following allogeneic stem cell transplant. Testing of an uninvolved specimen, such as DNA derived from cultured skin fibroblasts, is imperative. (2) Testing of blood or bone marrow during complete remission from a hematologic malignancy may also be performed to detect a germline variant; however, residual somatic variants, especially those associated with clonal hematopoiesis, may be detected. This testing option should therefore be reserved for rare circumstances and confirmatory testing on DNA derived from cultured skin fibroblasts is recommended for any abnormal results.

Option 1

Single-gene testing. Sequence analysis of *DDX41* is performed to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. Typically, if no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications. NOTE: To date, no large deletions or duplications have been identified as the cause of *DDX41*-associated familial MDS/AML.

A multigene panel that includes *DDX41* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or

custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Given that the *DDX41*-associated familial MDS/AML can be indistinguishable from many other inherited conditions, **comprehensive genomic testing**, which does not require the clinician to determine which gene is likely involved, may be a good option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *DDX41*-Associated Familial Myelodysplastic Syndrome and Acute Myeloid Leukemia

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
DDX41	Sequence analysis [3]	~100% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2017]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

DDX41-associated familial myelodysplastic syndrome and acute myeloid leukemia (MDS/AML) is characterized by an increased risk of myeloid neoplasms, lymphoid neoplasms, adult-onset single- or multiple-lineage cytopenias, male predominance, and red blood cell macrocytosis. To date, more than 200 individuals have been identified with a confirmed or presumed germline disease-causing heterozygous variant in *DDX41* [Polprasert et al 2015, Cardoso et al 2016, Lewinsohn et al 2016, Li et al 2016, Berger et al 2017, Kobayashi et al 2017, Diness et al 2018, Quesada et al 2019, Sébert et al 2019, Vairo et al 2019, Maierhofer et al 2020, Polprasert et al 2020, Bannon et al 2021, Choi et al 2021, Qu et al 2021, Zhang et al 2021]. The following description of the phenotypic features associated with this condition is based on these reports.

Myeloid Neoplasms

Individuals with *DDX41*-associated familial MDS/AML have an elevated lifetime risk of developing myeloid neoplasms; an exact risk estimate is not yet known. Myeloid malignancies including high-risk MDS and AML are the most common, with an average age of onset in the sixth decade (similar to the age of onset of sporadic MDS/AML) and a 3:1 male predominance [Polprasert et al 2015, Quesada et al 2019, Sébert et al 2019, Bannon et al 2021]. The MDS/AML phenotype usually features bone marrow hypocellularity with prominent erythroid dysplasia and a normal karyotype [Polprasert et al 2015, Lewinsohn et al 2016, Sébert et al 2019, Bannon et al

2021]. The MDS/AML tumor DNA will be identified to have a concomitant somatic *DDX41* variant (in addition to the known germline variant) in 50%-88% of cases. The somatic variant is often a missense variant (p.Arg525His in the majority of cases) located in the C-terminal helicase domain. Additional somatic variants may be found in one or more myeloid malignancy-associated genes including *ASXL1*, *TP53*, *CUX1*, and genes that encode spliceosome factors [Polprasert et al 2015, Bannon et al 2021].

Myeloproliferative neoplasms, chronic myeloid leukemia, and chronic myelomonocytic leukemia with age of onset in late adulthood have also been reported [Lewinsohn et al 2016, Quesada et al 2019]. Individuals may develop more than one independent hematologic malignancy: two studies identified a prior history of a lymphoid or other hematologic malignancy in 9% of individuals with a confirmed or presumed germline *DDX41* disease-causing variant at the time of a new MDS or AML diagnosis [Sébert et al 2019, Bannon et al 2021].

There are conflicting data regarding prognosis of MDS/AML in those with *DDX41*-associated familial MDS/AML compared to sporadic MDS/AML.

Lymphoid Neoplasms

Non-Hodgkin lymphoma (especially early-onset follicular lymphoma), Hodgkin lymphoma, multiple myeloma, monoclonal gammopathy of undetermined significance, chronic lymphocytic leukemia, and acute lymphoblastic leukemia have been reported in individuals with germline *DDX41* pathogenic variants [Lewinsohn et al 2016, Sébert et al 2019, Polprasert et al 2020, Bannon et al 2021, Zhang et al 2021]. Age of onset is typically in adulthood. Three of 33 (9%) individuals with *DDX41*-related MDS/AML also had a personal history of a lymphoid malignancy [Sébert et al 2019].

Blood Count Abnormalities

Adult-onset single- or multiple-lineage cytopenias and/or red blood cell macrocytosis are common [Lewinsohn et al 2016, Quesada et al 2019, Sébert et al 2019, Bannon et al 2021]. Of these, some individuals will have prolonged, persistent blood count abnormalities; others will progress to have more severe or additional cytopenias or to an overt hematologic malignancy within months to a few years [Lewinsohn et al 2016, Quesada et al 2019, Sébert et al 2019, Bannon et al 2021, Zhang et al 2021]. Aplastic anemia has been reported in some individuals [Sébert et al 2019, Zhang et al 2021], a diagnosis that can be challenging to differentiate from low-risk MDS with a hypocellular marrow – a known MDS phenotype seen in *DDX41*-associated familial MDS/AML.

Other

Autoimmune disorders. To date, sarcoidosis (3 individuals), rheumatoid arthritis (1 individual), juvenile rheumatoid arthritis (1), systemic lupus erythematosus (1), Churg Strauss (1), and Grave's disease (1) have been reported in rare individuals with germline *DDX41* pathogenic variants [Lewinsohn et al 2016, Diness et al 2018, Bannon et al 2021]. Whether the frequency of autoimmune disorders in individuals with germline *DDX41* pathogenic variants is higher than would be expected in the general population remains to be definitively established.

Solid tumors. Solid tumors – most frequently prostate cancer, colorectal cancer, and melanoma – have been reported in individuals with germline *DDX41* pathogenic variants. Six of 33 individuals (18%) with hematologic malignancies were noted to have had a prior diagnosis of a solid tumor, most frequently prostate cancer (3 individuals); however, individuals with solid tumor diagnoses alone (i.e., without hematologic manifestations) have also been reported [Lewinsohn et al 2016, Sébert et al 2019, Bannon et al 2021]. Whether the frequency of these solid tumors in individuals with germline *DDX41* pathogenic variants is higher than would be expected in the general population remains to be definitively established.

Genotype-Phenotype Correlations

No consistent genotype-phenotype correlations have been identified.

Penetrance

Penetrance may be reduced. Only 27%-39% of individuals with a myeloid malignancy and a germline *DDX41* variant have a family history of hematologic malignancies [Sébert et al 2019, Bannon et al 2021]; whereas a striking, highly penetrant MDS/AML phenotype has been observed in familial series [Lewinsohn et al 2016]. Development of MDS/AML appears to occur more frequently in males than females (3:1 predominance) [Polprasert et al 2015, Quesada et al 2019, Sébert et al 2019].

Nomenclature

In the 2016 WHO classification of myeloid neoplasms and acute leukemia, *DDX41*-associated familial MDS/AML is designated as "myeloid neoplasms with germline *DDX41* mutation" and is included in the subcategory of myeloid neoplasms with germline predisposition without a preexisting disorder or organ dysfunction [Arber et al 2016].

Prevalence

Approximately 1.5%-6.1% of individuals presenting with MDS/AML have been found to have a germline *DDX41* pathogenic variant [Sébert et al 2019, Maierhofer et al 2020, Choi et al 2021].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with heterozygous germline pathogenic variants in *DDX41*.

Biallelic germline pathogenic variants in *DDX41* have been reported in two sibs presenting with dysmorphic features, intellectual disability, and developmental delays [Diness et al 2018]. One of these sibs was diagnosed with blastic plasmacytoid dendritic cell neoplasm in childhood.

Sporadic tumors (including myelodysplastic syndrome and acute myeloid leukemia) in the absence of any other findings of *DDX41*-associated familial myelodysplastic syndrome and acute myeloid leukemia can harbor somatic variants in *DDX41* that are **not** present in the germline. In these circumstances predisposition to these tumors is not heritable. For more information, see Cancer and Benign Tumors.

Differential Diagnosis

Table 2. Genes of Interest in the Differential Diagnosis of *DDX41*-Associated Familial Myelodysplastic Syndrome and Acute Myeloid Leukemia

Gene(s) / Genetic Mechanism	Disorder	MOI	Characteristic Features	
			Overlapping w/*DDX41*-assoc familial MDS/AML	Not observed in *DDX41*-assoc familial MDS/AML
14q32 duplication	14q32 duplication-associated familial myeloproliferative neoplasms (OMIM 616604) [1]	AD	ET/PV/PMF (w/frequent progression to MDS/AML); MDS/AML/CMML	Predominantly myeloproliferative neoplasms w/progression to MDS/AML, often w/complex karyotype

Table 2. continued from previous page.

Gene(s) / Genetic Mechanism	Disorder	MOI	Characteristic Features	
			Overlapping w/*DDX41*-assoc familial MDS/AML	Not observed in *DDX41*-assoc familial MDS/AML
ACD *CTC1* *DKC1* *NAF1* *NHP2* *NOP10* *PARN* *RTEL1* *TERC* *TERT* *TINF2* *WRAP53* *ZCCHC8*	Dyskeratosis congenita & other telomere biology disorders (e.g., pulmonary fibrosis)	AD AR XL	Myeloid neoplasms; solid tumors	Dysplastic nails, lacy reticular pigmentation of upper chest &/or neck, oral leukoplakia, solid tumors (usually squamous cell carcinoma of the head/neck or anogenital cancer), pulmonary &/or liver fibrosis
ANKRD26	*ANKRD26*-related thrombocytopenia	AD	Myeloid neoplasms	Nonsyndromic chronic thrombocytopenia, mild bleeding & leukocytosis
CEBPA	*CEBPA*-associated familial AML	AD	AML	Early-onset AML, often w/abnormal eosinophils [2]
ETV6	*ETV6*-related thrombocytopenia & predisposition to leukemia	AD	Myeloid & lymphoid neoplasms; solid tumors	Nonsyndromic chronic thrombocytopenia & mild bleeding
GATA2	*GATA2* deficiency (See Monosomy 7 Predisposition Syndromes Overview.)	AD	MDS/AML; autoimmunity	Early-onset MDS often w/monosomy 7; immunodeficiency (↓ or absent monocytes & B- & NK-cell lymphocytes), lymphedema, chronic warts, severe fungal, viral, & mycobacterial infections, pulmonary alveolar proteinosis
RUNX1	*RUNX1* familial platelet disorder w/associated myeloid malignancies	AD	MDS/AML	Nonsyndromic chronic thrombocytopenia & mild bleeding; aspirin-like platelet functional defect
TP53	Li-Fraumeni syndrome	AD	MDS/AML; solid tumors	High penetrance for non-hematologic cancers (e.g., very early-onset breast cancer, sarcoma, brain tumors, adrenocortical carcinoma)

AD = autosomal dominant; AML = acute myeloid leukemia; CMML= chronic myelomonocytic leukemia; ET = essential thrombocythemia; MDS = myelodysplastic syndrome; MOI = mode of inheritance; PMF = primary myelofibrosis; PV = polycythemia vera

1. Babushok et al [2018]

2. The leukemic cells of most individuals with *CEBPA*-associated familial AML are compound heterozygous. In addition to the germline pathogenic variant in the N-terminal region, the leukemic cells commonly acquire somatic C-terminal in-frame pathogenic variant(s).

Acquired disorders in the differential diagnosis of *DDX41*-associated familial myelodysplastic syndrome and acute myeloid leukemia (MDS/AML)

- Sporadic hematologic malignancy with somatic *DDX41* pathogenic variant(s)
- Hematologic malignancy secondary to environmental exposures (e.g., benzene, radiation, chemotherapy)

Note: MDS and AML are relatively rare disorders (~10,000 individuals are diagnosed with MDS and ~13,300 are diagnosed with AML each year in the US); therefore, the more affected individuals in a family (and the closer the

relationships), the greater the likelihood of a common cause (i.e., a heritable predisposition or a common exposure) [Owen et al 2008].

Management

No clinical practice guidelines for *DDX41*-associated familial myelodysplastic syndrome and acute myeloid leukemia (MDS/AML) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *DDX41*-associated familial MDS/AML, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *DDX41*-Associated Familial Myelodysplastic Syndrome and Acute Myeloid Leukemia

System/Concern	Evaluation	Comment
Hematologic/ Oncologic	CBC w/differential, reticulocyte count, & peripheral smear review	
	Referral to hematologist	Refer to center w/expertise in predisposition to hematologic malignancies.
	Bone marrow biopsy & aspirate, cytogenetics: • In those w/cytopenia(s) &/or macrocytosis • Consider in healthy persons w/normal blood counts on an individual basis.	Consider a myeloid malignancy multigene panel if warranted based on bone marrow findings to identify **acquired** variants in affected tissue relevant to prognosis & treatment (e.g., *FLT3, NPM1, CEBPA, IDH1/2, TP53*).
Genetic counseling	By genetics professionals [1]	To inform patients & their families re nature, MOI, & implications of *DDX41*-assoc familial MDS/AML in order to facilitate medical & personal decision making

AML = acute myeloid leukemia; CBC = complete blood count; MDS = myelodysplastic syndrome; MOI = mode of inheritance

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with *DDX41*-Associated Familial Myelodysplastic Syndrome and Acute Myeloid Leukemia

Manifestation/ Concern	Treatment	Considerations/Other
Hematologic malignancy	• Standard neoplasm-specific therapy • Allogeneic HSCT eval early in the course of hematologic malignancy if appropriate based on person's age, malignancy, & health status to allow time for identification & genotyping of potential related donors [1, 2]	Targeted *DDX41* molecular genetic testing of potential related donors [1] • Related donors w/o a *DDX41* pathogenic variant are preferred. • A *DDX41* pathogenic variant in a donor is not an absolute contraindication. [3, 4]

HSCT = hematopoietic stem cell transplantation
1. University of Chicago Hematopoietic Malignancies Cancer Risk Team [2016]
2. Baliakas et al [2019]
3. Due to lack of data and observation of individuals with *DDX41*-associated MDS/AML benefitting from HCST from a related donor with the familial *DDX41* variant
4. A careful risk/benefit discussion with the recipient & donor, taking into account alternative donor options & their known risk/benefit profiles & timelines for recipient's needs, is necessary. Donor-derived leukemia has occurred w/use of a related donor who had a familial *DDX41* pathogenic variant.

Surveillance

No evidence-based guidelines on the type of testing or frequency of surveillance for *DDX41*-associated familial MDS/AML have been published. The table below reflects published expert opinion-based recommendations.

Table 5. Recommended Surveillance for Individuals with *DDX41*-Associated Familial Myelodysplastic Syndrome and Acute Myeloid Leukemia

System/Concern	Evaluation	Frequency
Hematologic	CBC w/differential	Every 6-12 mos or more frequently as clinically indicated [1]
	Clinical exam for constitutional signs & symptoms of MDS/AML (e.g., fatigue, infections, bleeding, skin changes) [1]	Annually or more frequently as clinically indicated
	Bone marrow biopsy & aspirate, cytogenetics	Consider in healthy persons w/normal blood counts on an individual basis.

AML = acute myeloid leukemia; CBC = complete blood count; MDS = myelodysplastic syndrome
1. Baliakas et al [2019]

Agents/Circumstances to Avoid

Avoid (if possible) stem cell transplant from related donors who have the familial *DDX41* pathogenic variant, as donor cell-derived leukemia has been reported in individuals after allogeneic hematopoietic stem cell transplant using donors with pathogenic germline *DDX41* variants [Berger et al 2017, Kobayashi et al 2017].

Avoid smoking, chemical exposure, and unnecessary radiation, as these may increase the risk of developing hematologic malignancy.

Evaluation of Relatives at Risk

For early diagnosis and treatment. It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify those who would benefit from

clinical monitoring. In general, molecular genetic testing for the familial *DDX41* pathogenic variant is not recommended for at-risk family members younger than age 18 years. However, predictive testing of minors should be considered if there is a family history of childhood-onset malignancies (childhood onset of *DDX41*-associated malignancies has been reported but is very rare [Zhang et al 2021]).

Clinical monitoring (see Surveillance) of relatives who are heterozygous for a familial *DDX41* pathogenic variant may enable earlier diagnosis (and treatment) of MDS/AML or other hematologic malignancies, minimizing the risks associated with delayed diagnosis and treatment (e.g., life-threatening complications of MDS/AML including severe anemia, sepsis, or hemorrhage or development of an advanced, treatment-refractory myeloid malignancy less likely to be cured). Initiation of clinical monitoring in adulthood (at least 10 years before the earliest onset hematologic malignancy or cytopenia diagnosis in the family) can be considered in heterozygous relatives; however, the age at which clinical monitoring should be initiated has not been established.

Note: There are currently no preemptive treatments available for asymptomatic individuals who have a germline *DDX41* pathogenic variant.

For hematopoietic stem cell donation. Any relative considering stem cell donation should undergo molecular genetic testing to clarify their genetic status so that informed risk/benefit discussions for both recipient and donor can be incorporated into transplant donor-option decision making. Whenever possible, related donors who do not have the familial *DDX41* pathogenic variant are preferred.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Although hematologic malignancy onset is typically well beyond years overlapping with childbearing, if the family history suggests earlier onset, a complete blood count with differential can be performed prior to pregnancy to ensure no baseline abnormalities that would require additional hematologic evaluation. If new or worsening blood count abnormalities develop during pregnancy, urgent referral to a hematologist with expertise in this disorder is recommended.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Responsiveness to lenalidomide for *DDX41*-associated familial MDS/AML has been observed [Polprasert et al 2015, Negoro et al 2016, Abou Dalle et al 2020].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

DDX41-associated familial myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- To date, all reported individuals diagnosed with *DDX41*-associated familial MDS/AML whose parents have undergone molecular genetic testing have the disorder as the result of a *DDX41* pathogenic variant inherited from a parent. The heterozygous parent may or may not have developed a hematologic malignancy.
- *DDX41*-associated familial MDS/AML occurring as the result of a *de novo DDX41* pathogenic variant has not been reported to date.
- If the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband, if available, to confirm their genetic status and to allow reliable recurrence risk counseling. Since the majority of probands will be adults at the time of diagnosis, parents may be deceased and unavailable. In this situation, testing of extended blood relatives (e.g., aunts, uncles, and first cousins) is recommended.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- The family history of some individuals diagnosed with *DDX41*-associated familial MDS/AML may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband has the *DDX41* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- The likelihood that a sib who inherits a familial *DDX41* pathogenic variant will develop MDS/AML varies within and between families. Penetrance may be reduced and appears to be influenced by sex, with development of MDS/AML occurring more frequently in males than in females (see Penetrance).
- If the *DDX41* pathogenic variant identified in the proband cannot be detected in parental leukocyte DNA, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *DDX41* pathogenic variant but are clinically unaffected, sibs are still presumed to be at increased risk for *DDX41*-associated familial MDS/AML because of the possibility that a parent is heterozygous but does not have apparent manifestations of *DDX41*-associated familial MDS/AML because of reduced penetrance or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with *DDX41*-associated familial MDS/AML has a 50% chance of inheriting the *DDX41* pathogenic variant and associated clinical manifestations including myeloid malignancy predisposition (see Clinical Description).

Note: If the reproductive partner of a proband is also heterozygous for a germline *DDX41* pathogenic variant, offspring are at risk of inheriting biallelic *DDX41* pathogenic variants. Sibs with biallelic *DDX41* pathogenic variants and phenotypes including intellectual disability, developmental delay, and hematologic malignancy have been reported [Diness et al 2018].

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *DDX41* pathogenic variant, his or her family members may be at risk of having a *DDX41* pathogenic variant and associated clinical manifestations including myeloid malignancy predisposition (see Clinical Description).

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment and suitability for hematopoietic stem cell donation.

Predictive testing (i.e., testing of asymptomatic at-risk family members is possible once the causative germline *DDX41* pathogenic variant has been identified in a family member with MDS/AML or other hematologic malignancy.

Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals younger than age 18 years)

- Because clinical monitoring of individuals with a familial *DDX41* pathogenic variant is typically recommended to begin in adulthood, well after age 18, predictive genetic testing for *DDX41*-associated familial MDS/AML is generally not recommended for asymptomatic at-risk individuals younger than age 18 years unless the individual is being considered as a potential hematopoietic stem cell donor or there is a history of childhood-onset hematologic malignancies in the family. The timing of predictive genetic testing and initiation of clinical monitoring should be individualized based on the earliest diagnosis of MDS/AML in the family and the clinical scenario.
- For more information, see also the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.

In a family with an established diagnosis of *DDX41*-associated familial MDS/AML, it is appropriate to consider testing of symptomatic individuals regardless of age. Parents should make their children's pediatricians aware of the family history of hematologic malignancies and *DDX41*-associated familial MDS/AML so that there is a lower threshold to perform a complete blood count with differential if any signs or symptoms of hematologic disorders were to develop.

Family planning

- The optimal time for determination of genetic risk in offspring of persons with a germline *DDX41* pathogenic variant is before pregnancy. (Note: Molecular genetic *DDX41* testing for the purpose of family planning is not recommended for individuals who develop MDS/AML or other hematologic malignancy in the absence of a molecular diagnosis of *DDX41*-associated familial MDS/AML.)
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who have a molecular diagnosis of *DDX41*-associated familial MDS/AML or who are at risk of having inherited a familial *DDX41* pathogenic variant.
- Partners of individuals known to be heterozygous for a germline *DDX41* pathogenic variant (who are of reproductive age) may wish to consider genetic testing to determine the reproductive risk for having offspring with biallelic *DDX41* pathogenic variants. While an exact syndrome has not been associated with biallelic germline *DDX41* pathogenic variants, sibs with biallelic *DDX41* pathogenic variants and

phenotypes including intellectual disability, developmental delay, and hematologic malignancy have been reported [Diness et al 2018]. If both parents are heterozygous for a *DDX41* pathogenic variant, their offspring have a 25% risk of inheriting biallelic pathogenic variants and a 50% risk of inheriting one pathogenic variant.

Prenatal Testing and Preimplantation Genetic Testing

Once the *DDX41* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful. For more information, see the National Society of Genetic Counselors position statement on prenatal testing in adult-onset conditions.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Aplastic Anemia & MDS International Foundation, Inc.**
  4330 East West Highway
  Suite 230
  Bethesda MD 20814
  Phone: 800-747-2820
  Email: help@aamds.org
  www.aamds.org
- **Leukemia & Lymphoma Society**
  1311 Mamaroneck Avenue
  Suite 310
  White Plains NY 10605
  Phone: 800-955-4572 (toll-free)
  Email: infocenter@lls.org
  www.lls.org
- **Leukemia Research Foundation**
  191 Waukegan Road
  Suite 105
  Northfield IL 60093-2744
  Phone: 847-424-0600
  Email: info@lrfmail.org
  www.allbloodcancers.org
- **MDS Foundation**

4573 South Broad Street
Suite 150
Yardville NJ 08620
Phone: 800-637-0839
Fax: 609-298-0590
Email: patientliaison@mds-foundation.org
www.mds-foundation.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. DDX41-Associated Familial Myelodysplastic Syndrome and Acute Myeloid Leukemia: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
DDX41	5q35.3	Probable ATP-dependent RNA helicase DDX41	DDX41	DDX41

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for DDX41-Associated Familial Myelodysplastic Syndrome and Acute Myeloid Leukemia (View All in OMIM)

608170	DEAD-BOX HELICASE 41; DDX41
616871	MYELOPROLIFERATIVE/LYMPHOPROLIFERATIVE NEOPLASMS, FAMILIAL (MULTIPLE TYPES), SUSCEPTIBILITY TO; MPLPF

Molecular Pathogenesis

DDX41 encodes a DEAD-box helicase protein that is thought to play an important role in a number of cellular mechanisms. Such processes include mRNA splicing, recognition and suppression of cyclic nucleotides and double-stranded DNA from external pathogens or cellular sources, post-transcriptional regulation of protein translation, R-loop accumulation, and snoRNA and ribosomal RNA processing [Cheah et al 2017, Frame & North 2021, Weinreb et al 2021, Chlon et al 2021]. DDX41 has been documented to play a role in the innate immune response via the STING pathway which initiates type 1 interferon and other downstream inflammatory cytokine response pathways [Lee et al 2015, Jiang et al 2017, Weinreb et al 2021].

The DDX41 protein has four main structural regions: N-terminal domain, DEAD-box domain, helicase C domain, and C-terminal domain. Known germline pathogenic variants include frameshift variants throughout the gene, missense variants often affecting the highly conserved DEAD-box domain and helicase C domains but also occurring throughout the gene, and splicing region variants [Cheah et al 2017, Maciejewski et al 2017, Quesada et al 2019, Sébert et al 2019, Qu et al 2021].

Mechanism of disease causation. *DDX41* is suggested to be a tumor-suppressor gene in which loss of function causes predisposition to hematologic neoplasms. Malignant transformation is thought to be due to the accumulation of additional somatic variants, most often in *DDX41* [Polprasert et al 2015, Lewinsohn et al 2016, Cheah et al 2017, Quesada et al 2019, Sébert et al 2019, Polprasert et al 2020, Qu et al 2021].

Notable *DDX41* variants. Germline pathogenic variants are usually frameshift, nonsense, or missense variants occurring throughout the gene [Maciejewski et al 2017, Quesada et al 2019, Sébert et al 2019, Qu et al 2021]. Approximately 50%-88% of individuals with a germline *DDX41* variant and MDS/AML will be found to have a

concomitant somatic *DDX41* variant in tumor DNA. The somatic variants are often missense variants in the C-terminal helicase domain; p.Arg525His variants account for the majority.

Table 6. Notable *DDX41* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_016222.4 NP_057306.2	c.3G>A	p.Met1Ile (p.M1?)	Common recurrent germline variant, esp in persons of European ancestry [Cheah et al 2017, Quesada et al 2019, Bannon et al 2021]
	c.19G>T	p.Glu7Ter	Common recurrent germline variant in persons of Korean & Japanese ancestry [Choi et al 2021]
	c.62_63delGC	p.Ser21ThrfsTer7	Recurrent germline variant in persons of Thai ancestry [Polprasert et al 2020]
	c.121C>T	p.Gln41Ter	Common recurrent germline variant, esp in persons of European ancestry [Bannon et al 2021]
	c.415_418dupGATG	p.Asp140GlyfsTer2	Common recurrent germline variant, esp in persons of European ancestry [Polprasert et al 2015, Cheah et al 2017, Quesada et al 2019, Bannon et al 2021]
	c.455T>G	p.Val152Gly	Common recurrent germline variant in persons of Korean ancestry [Choi et al 2021]
	c.517G>A	p.Gly173Arg	Common recurrent germline variant, esp in persons of European ancestry [Sébert et al 2019]
	c.776A>G	p.Tyr259Cys	Common recurrent germline variant in persons of Korean & Japanese ancestry [Choi et al 2021]
	c.1496dupC	p.Ala500CysfsTer9	Common recurrent germline variant in persons of Korean & Japanese ancestry [Choi et al 2021]
	c.1574G>A	p.Arg525His	Most common **somatic variant**; also reported in the germline [Kadono et al 2016, Lewinsohn et al 2016, Cheah et al 2017]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Cancer and Benign Tumors

Sporadic hematologic neoplasms (e.g., MDS, AML) may occur as single tumors in the absence of any other findings of *DDX41*-associated familial MDS/AML and can harbor somatic variants in *DDX41* that are not present in the germline [Polprasert et al 2015, Quesada et al 2019, Maierhofer et al 2020, Polprasert et al 2020, Qu et al 2021]. In these circumstances, predisposition to these hematopoietic neoplasms and tumors is not heritable. A variant allele fraction of less than 30% for the *DDX41* pathogenic variant identified in tumor tissue is suggestive but not definitive of a somatic variant.

Chapter Notes

Author Notes

Dr Jane Churpek is hematologist/oncologist whose clinical practice and research focuses on the care of adults with low blood counts due to acquired and inherited causes, including clonal hematopoiesis, myelodysplastic syndrome, inherited bone marrow failure syndromes, and various other hereditary cancer predisposition syndromes. Web page: www.uwhealth.org/providers/jane-churpek-md

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Dr Churpek and Mrs Smith-Simmer are also a part of the North American & Australian *RUNX1* and Inherited Hematologic Malignancies Consortium / The *RUNX1* Research Program. Click here for additional information about this consortium.

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References

Literature Cited

Abou Dalle I, Kantarjian H, Bannon SA, Kanagal-Shamanna R, Routbort M, Patel KP, Hu S, Bhalla K, Garcia-Manero G, DiNardo CD. Successful lenalidomide treatment in high risk myelodysplastic syndrome with germline DDX41 mutation. Am J Hematol. 2020;95:227–9. PubMed PMID: 31400013.

Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, Bloomfield CD, Cazzola M, Vardiman JW. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127:2391–405. PubMed PMID: 27069254.

Babushok DV, Stanley NL, Morrissette JJD, Lieberman DB, Olson TS, Chou ST, Hexner EO. Germline duplication of ATG2B and GSKIP genes is not required for the familial myeloid malignancy syndrome associated with the duplication of chromosome 14q32. Leukemia. 2018;32:2720–3. PubMed PMID: 30087419.

Baliakas P, Tesi B, Wartiovaara-Kautto U, Stray-Pedersen A, Friis LS, Dybedal I, Hovland R, Jahnukainen K, Raaschou-Jensen K, Ljungman P, Rustad CF, Lautrup CK, Kilpivaara O, Kittang AO, Grønbæk K, Cammenga J, Hellström-Lindberg E, Andersen MK. Nordic guidelines for germline predisposition to myeloid neoplasms in adults: recommendations for genetic diagnosis, clinical management and follow-up. Hemasphere. 2019;3:e321. PubMed PMID: 31976490.

Bannon SA, Routbort MJ, Montalban-Bravo G, Mehta RS, Jelloul FZ, Takahashi K, Daver N, Oran B, Pemmaraju N, Borthakur G, Naqvi K, Issa G, Sasaki K, Alvarado Y, Kadia TM, Konopleva M, Shamanna RK,

Khoury JD, Ravandi F, Champlin R, Kantarjian HM, Bhalla K, Garcia-Manero G, Patel KP, DiNardo CD. Next-generation sequencing of DDX41 in myeloid neoplasms leads to increased detection of germline alterations. Front Oncol. 2021;10:582213. PubMed PMID: 33585199.

Berger G, van den Berg E, Sikkema-Raddatz B, Abbott KM, Sinke RJ, Bungener LB, Mulder AB, Vellenga E. Re-emergence of acute myeloid leukemia in donor cells following allogeneic transplantation in a family with a germline DDX41 mutation. Leukemia. 2017;31:520–2. PubMed PMID: 27795557.

Cardoso SR, Ryan G, Walne AJ, Ellison A, Lowe R, Tummala H, Rio-Machin A, Collopy L, Al Seraihi A, Wallis Y, Page P, Akiki S, Fitzgibbon J, Vulliamy T, Dokal I. Germline heterozygous DDX41 variants in a subset of familial myelodysplasia and acute myeloid leukemia. Leukemia. 2016;30:2083–6. PubMed PMID: 27133828.

Cheah JJC, Hahn CN, Hiwase DK, Scott HS, Brown AL. Myeloid neoplasms with germline DDX41 mutation. Int J Hematol. 2017;106:163–74. PubMed PMID: 28547672.

Chlon TM, Stepanchick E, Hershberger CE, Daniels NJ, Hueneman KM, Kuenzi Davis A, Choi K, Zheng Y, Gurnari C, Haferlach T, Padgett RA, Maciejewski JP, Starczynowski DT. Germline DDX41 mutations cause ineffective hematopoiesis and myelodysplasia. Cell Stem Cell. 2021;28:1–16. PubMed PMID: 33417865.

Choi EJ, Cho YU, Hur EH, Jang S, Kim N, Park HS, Lee JH, Lee KH, Kim SH, Hwang SH, Seo EJ, Park CJ, Lee JH. Unique ethnic features of DDX41 mutations in patients with idiopathic cytopenia of undetermined significance, myelodysplastic syndrome, or acute myeloid leukemia. Haematologica. 2021. Epub ahead of print. PubMed PMID: 33626862.

Diness BR, Risom L, Frandsen TL, Hansen B, Andersen MK, Schmiegelow K, Wadt KAW. Putative new childhood leukemia cancer predisposition syndrome caused by germline bi-allelic missense mutations in DDX41. Genes Chromosomes Cancer. 2018;57:670–4. PubMed PMID: 30144193.

Drazer MW, Kadri S, Sukhanova M, Patil SA, West AH, Feurstein S, Calderon DA, Jones MF, Weipert CM, Daugherty CK, Ceballos-López AA, Raca G, Lingen MW, Li Z, Segal JP, Churpek JE, Godley LA. Prognostic tumor sequencing panels frequently identify germ line variants associated with hereditary hematopoietic malignancies. Blood Advances. 2018;2:146–50. PubMed PMID: 29365323.

Frame JM, North TE. DDX41 loss R-loops in cGAS to fuel inflammatory HSPC production. Dev Cell. 2021;56:571–2. PubMed PMID: 33689767.

Jiang Y, Zhu Y, Liu ZJ, Ouyang S. The emerging roles of the DDX41 protein in immunity and diseases. Protein Cell. 2017;8:83–9. PubMed PMID: 27502187.

Kadono M, Kanai A, Nagamachi A, Shinriki S, Kawata J, Iwato K, Kyo T, Oshima K, Yokoyama A, Kawamura T, Nagase R, Inoue D, Kitamura T, Inaba T, Ichinohe T, Matsui H. Biological implications of somatic DDX41 p.R525H mutation in acute myeloid leukemia. Exp Hematol. 2016;44:745–754.e4. PubMed PMID: 27174803.

Kobayashi S, Kobayashi A, Osawa Y, Nagao S, Takano K, Okada Y, Tachi N, Teramoto M, Kawamura T, Horiuchi T, Kato S, Maekawa T, Yamamura T, Watanabe J, Harada Y, Harada H, Sato K, Kimura F. Donor cell leukemia arising from preleukemic clones with a novel germline DDX41 mutation after allogenic hematopoietic stem cell transplantation. Leukemia. 2017;31:1020–2. PubMed PMID: 28194039.

Lee KG, Kim SS, Kui L, Voon DC, Mauduit M, Bist P, Bi X, Pereira NA, Liu C, Sukumaran B, Rénia L, Ito Y, Lam KP. Bruton's tyrosine kinase phosphorylates DDX41 and activates its binding of dsDNA and STING to initiate type 1 interferon response. Cell Rep. 2015;10:1055–65. PubMed PMID: 25704810.

Lewinsohn M, Brown AL, Weinel LM, Phung C, Rafidi G, Lee MK, Schreiber AW, Feng J, Babic M, Chong CE, Lee Y, Yong A, Suthers GK, Poplawski N, Altree M, Phillips K, Jaensch L, Fine M, D'Andrea RJ, Lewis ID, Medeiros BC, Pollyea DA, King MC, Walsh T, Keel S, Shimamura A, Godley LA, Hahn CN, Churpek JE, Scott HS. Novel germ line DDX41 mutations define families with a lower age of MDS/AML onset and lymphoid malignancies. Blood. 2016;127:1017–23. PubMed PMID: 26712909.

Li R, Sobreira N, Witmer PD, Pratz KW, Braunstein EM. Two novel germline DDX41 mutations in a family with inherited myelodysplasia/acute myeloid leukemia. Haematologica. 2016;101:e228–31. PubMed PMID: 26944477.

Maciejewski JP, Padgett RA, Brown AL, Müller-Tidow C. DDX41-related myeloid neoplasia. Semin Hematol. 2017;54:94–7. PubMed PMID: 28637623.

Maierhofer A, Baer C, Pohlkamp C, Meggendorfer M, Kern W, Haferlach C, Haferlach T. Putative germline variants in the predisposition genes DDX41, ETV6, and GATA2 investigated in 1,228 patients with sporadic AML or MDS. Blood. 2020;136 Supplement 1:17–18.

Negoro E, Radivoyevitch T, Polprasert C, Adema V, Hosono N, Makishima H, Przychodzen B, Hirsch C, Clemente MJ, Nazha A, Santini V, McGraw KL, List AF, Sole F, Sekeres MA, Maciejewski JP. Molecular predictors of response in patients with myeloid neoplasms treated with lenalidomide. Leukemia. 2016;30:2405–9. PubMed PMID: 27560106.

Owen C, Barnett M, Fitzgibbon J. Familial myelodysplasia and acute myeloid leukaemia--a review. Br J Haematol. 2008;140:123–32. PubMed PMID: 18173751.

Polprasert C, Schulze I, Sekeres MA, Makishima H, Przychodzen B, Hosono N, Singh J, Padgett RA, Gu X, Phillips JG, Clemente M, Parker Y, Lindner D, Dienes B, Jankowsky E, Sauntharajah Y, Du Y, Oakley K, Nguyen N, Mukherjee S, Pabst C, Godley LA, Churpek JE, Pollyea DA, Krug U, Berdel WE, Klein HU, Dugas M, Shiraishi Y, Chiba K, Tanaka H, Miyano S, Yoshida K, Ogawa S, Müller-Tidow C, Maciejewski JP. Inherited and somatic defects in DDX41 in myeloid neoplasms. Cancer Cell. 2015;27:658–70. PubMed PMID: 25920683.

Polprasert C, Takeda J, Niparuck P, Rattanathammethee T, Pirunsarn A, Suksusut A, Kobbuaklee S, Wudhikarn K, Lawasut P, Kongkiatkamon S, Chuncharunee S, Songserm K, Phowthongkum P, Bunworasate U, Nannya Y, Yoshida K, Makishima H, Ogawa S, Rojnuckarin P. Novel DDX41 variants in Thai patients with myeloid neoplasms. Int J Hematol. 2020;111:241–6. PubMed PMID: 31713024.

Qu S, Li B, Qin T, Xu Z, Pan L, Hu N, Huang G, Peter Gale R, Xiao Z. Molecular and clinical features of myeloid neoplasms with somatic DDX41 mutations. Br J Haematol. 2021;192:1006–10. PubMed PMID: 32307695.

Quesada AE, Routbort MJ, DiNardo CD, Bueso-Ramos CE, Kanagal-Shamanna R, Khoury JD, Thakral B, Zuo Z, Yin CC, Loghavi S, Ok CY, Wang SA, Tang Z, Bannon SA, Benton CB, Garcia-Manero G, Kantarjian H, Luthra R, Medeiros LJ, Patel KP. DDX41 mutations in myeloid neoplasms are associated with male gender, TP53 mutations and high-risk disease. Am J Hematol. 2019;94:757–66. PubMed PMID: 30963592.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126–33. PubMed PMID: 26656846.

Sébert M, Passet M, Raimbault A, Rahmé R, Raffoux E, Sicre de Fontbrune F, Cerrano M, Quentin S, Vasquez N, Da Costa M, Boissel N, Dombret H, Peffault de Latour R, Socié G, Itzykson R, Fenaux P, Soulier J, Adès L, Clappier E. Germline DDX41 mutations define a significant entity within adult MDS/AML patients. Blood. 2019;134:1441–4. PubMed PMID: 31484648.

Stenson PD, Mort M, Ball EV, Evans K, Hayden M, Heywood S, Hussain M, Phillips AD, Cooper DN. The Human Gene Mutation Database: towards a comprehensive repository of inherited mutation data for medical research, genetic diagnosis and next-generation sequencing studies. Hum Genet. 2017;136:665–77. PubMed PMID: 28349240.

University of Chicago Hematopoietic Malignancies Cancer Risk Team. How I diagnose and manage individuals at risk for inherited myeloid malignancies. Blood. 2016;128:1800–13. PubMed PMID: 27471235.

Vairo FPE, Ferrer A, Cathcart-Rake E, King RL, Howard MT, Viswanatha DS, Klee EW, Mangaonkar AA, Patnaik MM. Novel germline missense DDX41 variant in a patient with an adult-onset myeloid neoplasm with excess blasts without dysplasia. Leuk Lymphoma. 2019;60:1337–9. PubMed PMID: 30407884.

Weinreb JT, Ghazale N, Pradhan K, Gupta V, Potts KS, Tricomi B, Daniels NJ, Padgett RA, De Oliveira S, Verma A, Bowman TV. Excessive R-loops trigger an inflammatory cascade leading to increased HSPC production. Dev Cell. 2021;56:627–640.e5. PubMed PMID: 33651979.

Zhang Y, Wang F, Chen X, Liu H, Wang X, Chen J, Cao P, Ma X, Liu H. Next-generation sequencing reveals the presence of DDX41 mutations in acute lymphoblastic leukemia and aplastic anemia. eJHaem. 2021;2:508-13.

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