

Clinical features of *DDX41* mutation-related diseases: a systematic review with individual patient data

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Abstract

Background: *DDX41* serves as a DNA sensor in innate immunity and mutated *DDX41* is pathogenic, mainly for myeloid neoplasms.

Methods: In this study, “*DDX41*” was searched in *PubMed* and *Web of Science* between 1 January 2015 and 29 April 2021 with individual-patient data seeking. A meta-analysis was not valid here due to the absence of a large dataset. Thirty articles were finally included in the qualitative analysis and 277 patients from 20 studies without overlap were involved in the quantitative summary.

Results: Pooled incidence was 3.3% (95% confidence interval 2.4–4.2%) of unselected myeloid neoplasms. Patients with hematologic disorders harboring mutated *DDX41* were featured as 80% males, median 66 (20–88) years old at diagnosis, 75% acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS), 64% with normal karyotype. Eighty-five percent of patients had germline variants which were nationally diverse and more of frameshift type, whereas 64% of patients had somatic *DDX41* variants where p.R525H and missense dominated. *ASXL1* and *TP53* were the top frequent concomitant somatic mutations. Therapeutically, 70% overall response rate was obtained of hypomethylating agents in MDS, 96% complete remission of chemotherapy in AML, and 8% of relapse in hematopoietic stem cell transplant. Neither overall survival nor progression-free survival could be summed.

Conclusions: Several significant clinical differences were observed in different diagnosis groups, familial and sporadic cases, and p.R525H compared with other somatic variants. In conclusion, myeloid neoplasms carrying *DDX41* mutations were mainly older, male, MDS, and AML patients who had promising responses to treatment. Both germline and somatic *DDX41* variants possessed unique characteristics and groups of interest presented certain differences worth further research. [CRD42021228886]

Keywords: *DDX41* mutation, germline, hematologic, somatic

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Introduction

Although most myeloid neoplasms are sporadic cases affecting the elderly, those malignancies with germline predisposition are increasingly recognized to comprise a distinct subtype.¹ The World Health Organization has included myeloid neoplasms with germline predisposition into its classification since 2016.² Especially, DEAD-box helicase 41 (*DDX41*) mutation is clinically unique due to its late onset compared with other germline lesions, such as *CEBPA* and *GATA2*.³ As increasingly recognized as clinically significant,

DDX41 was more frequently added to tumor sequencing panels for identifying variants responsible for myeloid malignancies.^{4,5} *DDX41* is a versatile protein not only functioning as a DNA/RNA sensor in innate immunity but also involved in transcription by altering the splicing process.⁶ Recently, *DDX41* in zebrafish was reported to be a crucial gatekeeper of over-producing hematopoietic stem and progenitor cells, by inhibiting excessive R-loops and thus preventing an inflammatory cascade.⁷ This study has shed light on how *DDX41* mutants lead to a clinically

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significant subtype of myeloid neoplasms. Moreover, deficient *DDX41* in erythroid progenitors would diminish their proliferation and impair differentiation, thus manifesting anemia clinically.⁸ Although previous reviews summarized some molecular and clinical features of *DDX41*-mutated myeloid neoplasms,^{9,10} a systematic review is still essential due to emerging publications on *DDX41*-related diseases and low prevalence in the population, to provide a comprehensive summary of their clinical characteristics by incorporating both large cohorts and individual case reports. Thus, our study aimed to report the clinical features of *DDX41*-mutated diseases, mainly myeloid neoplasms but also including other hematologic disorders, and describe phenotypes of different groups utilizing individual-level data. The molecular pathway of *DDX41* mutation is beyond the scope of this systematic review.

Methods

A meta-analysis was not available because of a lack of large datasets, but a comprehensive systematic review is still feasible. Moreover, individual patient data (IPD) is available, thus the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement¹¹ was followed for this study. Two authors (Z.W. and B.H.) independently performed database search, data extraction, and quality assessment. Any disagreement would be resolved by discussion until consensus was reached. This study was registered at PROSPERO (CRD42021228886).

Database search

The term “*DDX41*” was searched in *PubMed* and *Web of Science* with no language restriction between 1 January 2015 and 29 April 2021 since the first article of *DDX41*-mutated myeloid neoplasms published in 2015.¹² We refined the document types of items from *Web of Science* to automatically exclude corrections, patent, books, data sets, meetings, editorials.

Eligibility criteria

Studies were included if (1) involving patients with *DDX41* mutation; (2) their patients were diagnosed, including but not limited to myeloid neoplasms, aplastic anemia, lymphoma, solid cancers; (3) of case series, such as cohort studies,

and case reports; (4) the site of *DDX41* variants, either somatic or germline, was reported.

We excluded inappropriate publication types, including reviews, comments, errata, books, patents. Studies with irrelevant subjects were ruled out, those developing vaccines utilizing the antiviral response of *DDX41* and those exploring the molecular mechanism of *DDX41*. Any relevant review was identified to find any additional related study, but not included in the result.

Studies that screened *DDX41* mutation within unselected patients with myeloid neoplasms were selected to report the pooled *DDX41* mutation incidence.

Data collection

The following individual information was collected carefully from the original articles and their supplementary files: (1) study of origin; (2) patients' original number; (3) age at diagnosis, gender, nationality, diagnosis, family history of cancer; (4) type of *DDX41* mutation, somatic and germline with sample type for germline verification; (5) *DDX41* variant site (p.) along with its variant allele frequency (VAF; %) and transcript number for reporting it; (6) concomitant somatic mutation of other genes, also with specific sites and VAF; (7) karyotype; (8) treatment therapy; (9) response or clinical course; (10) overall survival (OS), months.

Information of studies selected for pooling *DDX41* incidence on hematologic malignancies was also incorporated: (1) characteristics of publication (first author, publication year); (2) the number and type of screened population; (3) the number of *DDX41*-mutated patients. The missing data was requested by contacting the corresponding authors, otherwise recorded as not available and not included in the analysis.

Quality assessment

As there was not a specific recommended tool to assess the quality of observational studies,¹³ we independently utilized two aspects specific to this study: completeness of patients' clinical records (age at diagnosis, gender, nationality, diagnosis, family history investigation, clinical course with therapy and outcome), full information about *DDX41* mutation (mutated site, VAF, origin, germline verification method).

Statistical analysis

For IPD, descriptive variables were presented with numbers and percentages. Continuous variables were provided as median with range if not specially mentioned. Familial cases were those with clear family histories of hematologic diseases and sporadic cases were those with no related family history after investigation. Groups of interest were compared, three different diagnoses (acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), and others), familial and sporadic cases, p.R525H and other somatic variants, using either Fisher's exact test or Kruskal–Wallis test. $p < 0.05$ was considered statistically significant.

DDX41 mutation incidence was pooled by a random-effects model commonly used when conducting a meta-analysis. The number of studies included was too small for a regular small study effect, that is, publication bias. All statistical analysis was performed using R version x64 3.6.3.

Results

Study selection

The numbers of publications identified in *PubMed* and *Web of Science* were 100 and 95, respectively. After deleting duplicates and going through title and abstract review 107 remained. We excluded 77 publications, including 41 animal studies, 20 about irrelevant subjects, 13 reviews, and three in languages other than English and Chinese. The remaining 30 were next given full-text reviews and all were considered eligible for this study, including nine case series,^{12,14–21} 11 case reports,^{22–32} four reports about *DDX41*-related solid cancers,^{33–36} and six rare case reports^{37–42} (Figure 1). No extra study was identified from the references listed in the relevant reviews and the included studies. The reasons to include these 30 articles are presented in Supplemental material Table S1 online. Two hundred and seventy-seven patients with *DDX41*-mutated hematologic disorders, from 20 articles without overlap, were included in the individual patient-level dataset (Supplemental Table S2). Other *DDX41*-related diseases were described. Quality evaluation is presented in Supplemental Table S3.

DDX41-mutated hematologic disorders

The pooled incidence of *DDX41* mutation among 10,975 screened patients with myeloid neoplasms

was 3.3% [95% confidence interval (CI) 2.4–4.2%, $I^2 = 79.7%$, $p < 0.01$; see Supplemental Figure S1 for forest plot]. Among 277 patients, 258 were from case series (93.1%), whereas others were from case reports (6.9%). The baseline information is collectively displayed in Table 1 and details are fully presented in Supplemental Table S2. The median age at diagnosis was 66 (20–88) years, 69.3% in the 60s and 70s [Figure 2(a)]. But *DDX41* mutation was not only responsible for adult hematologic diseases, but also for pediatric leukemia, as a case report described.³⁹ Two hundred and twenty-two (80.1%) were male, and 52 (18.8%) were female, and gender of three cases (1.1%) was not described in the original article. Regarding nationality, most were American [115 (41.5%)], followed by 48 Chinese (17.3%), 43 French (15.5%), and 40 Korean (14.4%). Other nationality groups contained 10 cases at most [Table 1 and Figure 2(b)]. The portion of the normal karyotype was 63.9% [177/277; Figure 2(c)]. Karyotypes of 57 patients (20.6%) were described as abnormal including seven trisomy 8, six -Y, six del (5q), six del (20q), 10 complex, and 22 other less common non-complex (see Supplemental Table S2 for details).

DDX41 mutations were most commonly diagnosed with myeloid neoplasms, including MDS (115, 41.5%), AML (91, 32.9%), and myeloproliferative neoplasms ($n = 11$, 4.0%). Though rare, other hematologic diseases were also reported, such as three follicular lymphomas, three aplastic anemia (AA). The rest relevant diseases are presented in Table 1. AML, MDS, and other diagnoses ($n = 38$) are compared (Supplemental Table S4). All three groups presented noticeable clinical features. AML harbored more germline p.D140fs and more cytogenetic abnormalities than MDS and other diseases ($p = 0.01$ and < 0.001). MDS, however, was associated with more normal karyotypes. And male preference was more remarkable for AML and MDS compared with other diseases ($p = 0.03$). Other hematologic diseases (not AML or MDS), were diagnosed at a younger age ($p = 0.06$), of a higher female proportion ($p = 0.03$), detected fewer somatic variants ($p = 0.04$), and less mutated p.R525H ($p < 0.001$).

Ninety-four (33.9%) had clear family histories (familial), whereas 139 (50.2%) had no related family history after investigation (sporadic) and 44 were not available from original reports. A significant mean age gap was observed in that

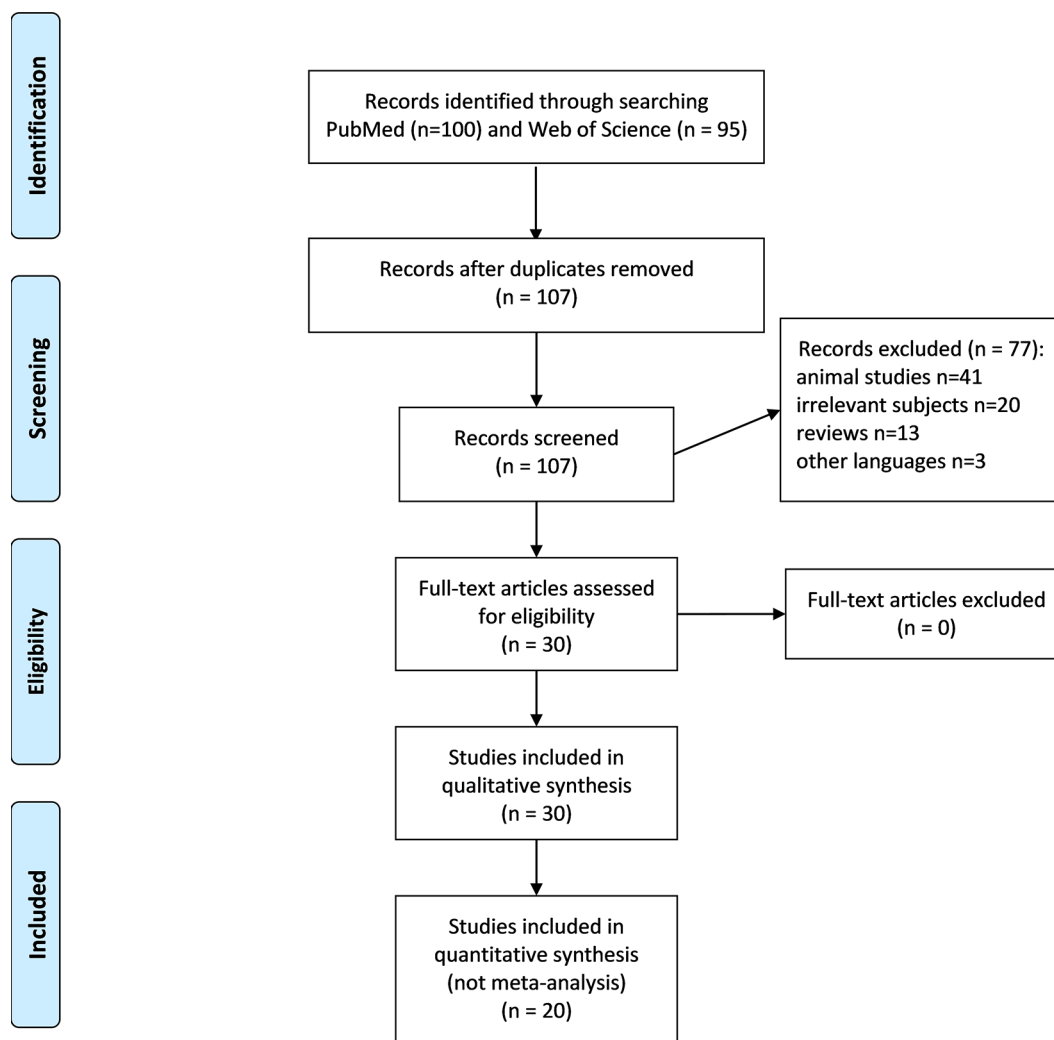


Figure 1. PRISMA flow diagram of selected studies.

One hundred publications and 95 publications were identified in *PubMed* and *Web of Science*, respectively. After deleting duplicates and going through title and abstract review, 107 remained. We excluded 77 publications. The remaining 30 were next given a full-text review and none was excluded. Thus, 30 articles were included in the qualitative analysis, and 20 were included in the quantitative summary but not a meta-analysis.

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

familial cases were diagnosed 4 years earlier than sporadic cases ($p=0.001$; Supplemental Table S5). Some germline variants, at least p.D140fs and p.M1I, were probably more enriched in familial cases compared with sporadic cases ($p=0.07$ and 0.10), whereas others were more detected in sporadic cases [odds ratio (OR) = 0.41, 95% confidence interval (CI) 0.21–0.78), $p=0.004$]. This could be because p.D140fs and p.M1I are two variants described earlier, thus patients with such variants were possibly investigated more thoroughly regarding their family history. Sporadic cases were diagnosed with MDS

more; however, this difference could result from a large portion (32/139, 23%) of not available diagnosis in the sporadic group. No difference was found in gender, somatic variants, or karyotype (Supplemental Table S5).

In terms of *DDX41* variants, all referred to NM_016222, but in their latest version by each study (version 2–4). Suspected germline variants based on next-generation sequencing were detected in 236 patients (85.2%). Thirty-nine cases (14.1%) were demonstrated as not carrying germline *DDX41* variant. Three cases harbored

Table 1. Clinical features of 277 patients with *DDX41*-related hematologic diseases.

Parameter	<i>n</i>	Percentage
Total	277	100.0
Case series	258	93.1
Case reports	19	6.9
Age at diagnosis, median (range) years	66 (20–88)	
<50	23	8.3
50–59	40	14.4
60–69	105	37.9
70–79	87	31.4
80–88	14	5.1
NA	8	2.9
Gender		
Male	222	80.1
Female	52	18.8
NA	3	1.1
Nationality		
American	115	41.5
Chinese	48	17.3
French	43	15.5
Korean	40	14.4
Australian	10	3.6
British	9	3.2
Thai	6	2.2
Caucasian	3	1.1
Italian	1	0.4
Spanish	1	0.4
NA	1	0.4
Karyotype		
Normal	177	63.9
Abnormal	57	20.6

*(Continued)***Table 1.** (Continued)

Parameter	<i>n</i>	Percentage
+8	7	2.5
-Y	6	2.2
del 5q	6	2.2
del 20q	6	2.2
Complex	10	3.6
Non-complex ^a	22	7.9
NA	43	15.5
Diagnosis		
MDS	115	41.5
AML	91	32.9
MPN	11	4.0
ICUS	6	2.2
t-MDS	4	1.4
Follicular lymphoma	3	1.1
Aplastic anemia	3	1.1
MDS/MPN	3	1.1
t-AML	3	1.1
MDS/AML	2	0.7
CLL	1	0.4
CML/AML	1	0.4
Neutropenia	1	0.4
None	1	0.4
NA	32	11.6
Family history		
Clear	94	33.9
None	139	50.2
NA	44	15.9

^aNine cases were confirmed as non-complex but karyotypes were not clear. AML, acute myeloid leukemia; CLL, chronic lymphoid leukemia; CML, chronic myeloid leukemia; ICUS, idiopathic cytopenia of undetermined significance; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasms; NA, not available; t-AML, therapy-related AML; t-MDS, therapy-related MDS.

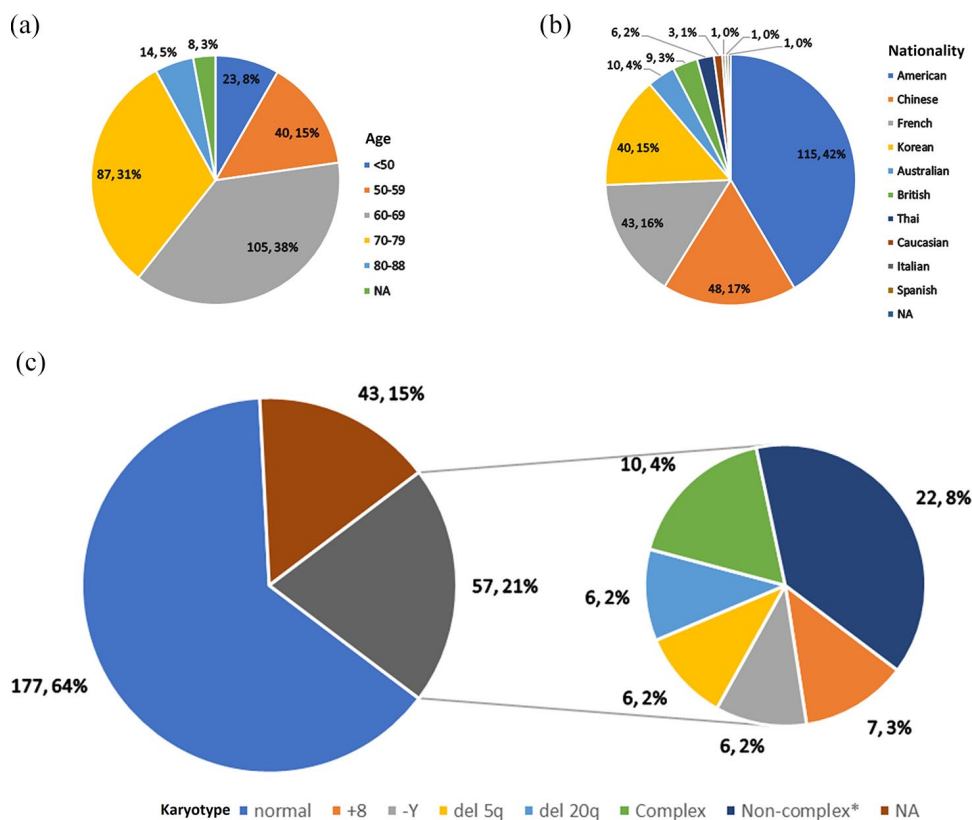


Figure 2. Age, nationality, and karyotype of 277 patients with *DDX41*-mutated hematologic diseases. (a) Groups of age at diagnosis, where 69.3% were in the 60s and 70s. (b) National distributions. American was the greatest [115 (41.5%)], followed by 48 Chinese (17.3%), 43 French (15.5%) and 40 Korean (14.4%). Other nationality groups contained 10 cases at most. (c) Cytogenetics. The portion of normal karyotype was 63.9% ($n=177$). Karyotypes of 57 patients (20.6%) were described as abnormal: seven trisomy 8, six -Y, six del [5q], six del [20q], 10 complex, and 22 other less common non-complex*. NA, not available.

*Other non-complex chromosomal abnormalities were detailed in Table S2.

two germline *DDX41* variants and two had no available germline information. One hundred and eighty-one probable germline variants (76.7%) were confirmed of germline origin by cultured skin fibroblasts, oral epithelial cells, clear transmitting pedigree, and others (Supplemental Table S2). The other 55 had no germline verification other than 40–60% VAF. Missense variants composed the largest part (124/239, 52%), followed by frameshift ($n=76$, 32%), nonsense ($n=20$, 8%), splicing ($n=14$, 6%), and last in-frame deletion/duplication ($n=5$, 2%). Frameshift [OR=43 (95% CI 11–370), $p<0.001$], nonsense [OR=8.5 (95% CI 2.0–75.9), $p<0.001$], splicing variants [OR=3.8 (95% CI 1.1–21.2), $p=0.026$] showed their strong associations with germline origin. The top five germline variants were p.D140fs ($n=39$), p.M1I ($n=29$), p.V152G ($n=12$), p.Y259C ($n=10$), p.A500fs ($n=7$). They showed an apparent difference in different

countries: p.M1I and p.D140fs in the US, p.V152G, p.Y259C and p.A500fs in Korea and China (Figure 3). *DDX41* mutation was negatively detected in Hungary.⁴⁰ One hundred and thirty-five patients had both germline and somatic *DDX41* mutations.

Somatic *DDX41* variants were detected in 176 patients (63.5%) including 13 cases with two somatic variants. Sixty-six patients had no somatic *DDX41* variant and 35 did not have available information about it. Missense variants still contributed the most (181/189, 96%), followed by splicing ($n=3$), frameshift ($n=2$), nonsense ($n=2$), and last in-frame deletion ($n=1$). The type of missense was significantly enriched in somatic variants [OR=21 (95% CI 10–51), $p<0.001$]. Different from diverse sites of frequent germline *DDX41* mutants, the most common somatic variant was p.R525H, which accounted for 64.2%

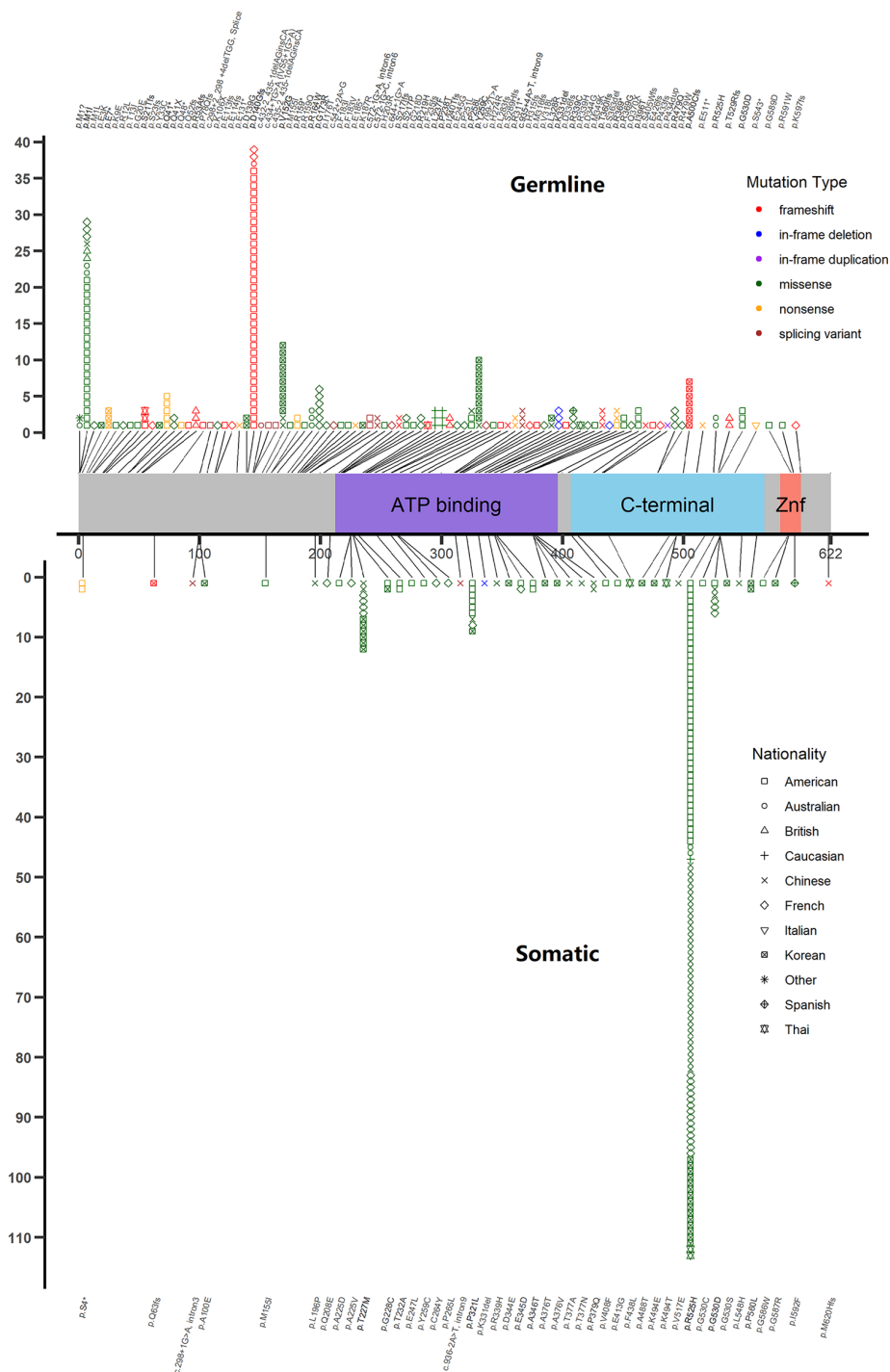


Figure 3. DDX41 protein map based on 20 population studies.

A total of 239 germline variants and 188 somatic variants are presented here (one somatic splicing variant was excluded because of no available site information). For germline mutants, missense variants composed the largest part ($n = 124$, 52%), followed by frameshift ($n = 76$, 32%), nonsense ($n = 20$, 8%), splicing ($n = 14$, 6%), and last in-frame deletion/duplication ($n = 5$, 2%). The top five germline variants were p.D140fs ($n = 39$), p.M11 ($n = 29$), p.V152G ($n = 12$), p.Y259C ($n = 10$), p.A500fs ($n = 7$). They showed apparent difference in different countries: p.M11 and p.D140fs in the USA, p.V152G, p.Y259C and p.A500fs in Korea and China. For somatic variants, missense variants still contributed greatest ($n = 181$, 96%), followed by splicing ($n = 3$), frameshift ($n = 2$), nonsense ($n = 2$), and last in-frame deletion ($n = 1$). Different from diverse sites of frequent germline *DDX41* mutants, the most common somatic variant was p.R525H, which accounted for 64% ($n = 113$) of the variants and was consistent in all countries. The other frequent somatic variants of *DDX41* were p.T227M ($n = 12$), p.P321L ($n = 9$), and p.G530D ($n = 6$). ATP, adenosine triphosphate; Znf, zinc finger.

($n=113$) of the variants and was consistent in all countries (Figure 3). The other frequent somatic variants of *DDX41* were p.T227M ($n=12$), p.P321L ($n=9$), and p.G530D ($n=6$). We compared patients carrying p.R525H and other somatic variants (Supplemental Table S6). Interestingly, somatic p.R525H may link to certain germline variants; p.M1I at least [OR=9.22 (95% CI 1.32–402), $p=0.01$]. Moreover, somatic mutation sites were possibly associated with types of hematologic diseases: p.R525H could be a possible risk factor of AML [OR=2.91 (95% CI 1.28–7.08), $p=0.007$] and other somatic variants could link to less common *DDX41*-related hematologic diseases, such as AA [OR=0.19 (95% CI 0.05–0.63), $p=0.003$]. No other difference was found in age, gender, or karyotype.

One hundred and twenty-nine (46.6%) patients harbored at least one concomitant somatic mutation besides *DDX41*. Ninety-eight (35.4%) had no somatic mutation of other genes and 50 had no available report about it. *DDX41* coincided with *ASXL1* mutation most commonly (34/129, 26.4%), followed by *TP53* (29/129, 22.5%). Other frequent concomitant lesions were *TET2* (17/129, 13.2%), *EZH2* (17/129, 13.2%), *SRSF2* (16/129, 12.4%), *DNMT3A* (14/129, 10.9%), and *CUX1* (11/129, 8.5%).

Clear treatment records were obtained from 155 patients in 11 studies consisting of 83 MDS, 52 AML, 20 other diagnoses. Fifty MDS patients received hypomethylating agent (HMA)-based treatment. Out of 33 with clear responding information, 23 responded (70%) and 10 were either a failure, stable disease, or not responded. Ten MDS were under observation and another eight received hematopoietic stem cell transplant (HSCT), without analyzable responding evaluation. Three MDS patients were treated with lenalidomide (LEN) and two reached complete remission (CR); the other one was without responding information, so the overall response rate (ORR) of LEN cannot be analyzed. The other 12 with various clinical courses can be further checked in Supplemental Table S2. As for AML, 24 patients received chemotherapy; 23 of them had clear responding records: 22 achieved CR (96%) and one was refractory to intensive induction chemotherapy but achieved CR after two courses of low-dose cytarabine (LDAC) and underwent LDAC chemotherapy. Seventeen

AML patients were administrated HMA-based therapy whereas only six responding records were clear: five responded and one failed. Clinical courses of the other 11 AML patients were individually various and are presented in Supplemental Table S2.

In total, 39 *DDX41*-mutated patients received HSCT at the median age of 60 (20–70) years. Three patients, two cases of AML after 4 years and one of MDS (time not reported), got relapsed diseases (8%). For *DDX41*-mutated patients who are scheduled for HSCT, donor cell leukemia stemming from *DDX41* mutants should be carefully ruled out, an event reported by two independent groups.^{37,38} Before transplant, screening *DDX41* mutation would be a recommended regular preparation to prevent re-emergence of hematologic diseases.

Other *DDX41*-mutated diseases

From a Danish cohort, *DDX41* p.R535W was identified in a 48-year-old female suspected of common variable immunodeficiency (CVID).⁴¹ She presented with lymphocytosis and cervical dysplasia, recurred with sinusitis and pneumonia abscesses. The author proposed that this *DDX41* variant might be linked to her cervical lesion. However, this case could be further investigated, for instance, on her family history or pedigree, on her karyotype, on her bone marrow aspiration and biopsy to evaluate hematopoietic stem cells and differentiate any hematologic diseases.

DDX41 has not yet been identified as a possible pathogenic variant in cases of solid cancers. Nonetheless, elevated *DDX41* expression was reported to be associated with pathological grades, clinical stages, and thus worse prognosis, for example, shorter OS and less progression-free survival (PFS), at least in human colorectal cancer,³³ hepatocellular cancer,³⁴ breast cancer,³⁵ and clear cell renal cell carcinoma.³⁶

Discussion

DDX41 is a well-known multifunctional protein. In innate immunity, phosphorylated *DDX41* senses bacterial or viral invasion and induces type I interferon, and is degraded by ubiquitination.⁴³ In myeloid neoplasm, *DDX41* was identified as a tumor suppression gene because overexpression

blocked cell proliferation whereas knockdown promoted tumor growth.¹² The molecular pathway was unveiled that insufficient *DDX41* enabled R-loops to accumulate, hence triggering inflammatory signaling and finally empowering hematopoietic cells to increase.⁷ Here we analyzed the clinical aspects of *DDX41*-mutated diseases, which is the first systematic review along with IPD about this mutation at least to date. Although unable to conduct a meta-analysis due to a large portion of missing data, we presented a larger dataset of individual patients with comprehensive searching.

This mutation was rarely detectable; in about 3% of unselected myeloid neoplasms. *DDX41* mutation affected all age groups, mainly those in their 60s and 70s, and rarely children. Familial and sporadic patients present hematological malignancies at different ages. We observed that familial cases were diagnosed 4 years earlier than sporadic counterparts. Such early diagnosis could benefit patients in early intervention and presumably better prognosis. A hypothesis could not be tested yet in this study because of a lack of reports of patients' clinical courses. Male carriers were predominant, and we noticed that such preference was more conspicuous in AML and MDS. The role that gender plays, whether just as a risk factor or linked to pathogenesis, still needs to be determined.

DDX41 mutation covered a broad spectrum of hematologic diseases, from AML and MDS, which constituted 75% of the diagnosed cases, to rare cases such as AA and lymphoma. AML, MDS, and other diseases showed some interesting differences in comparison with each other, besides different gender preference as mentioned above: more germline p.D140fs variant and more cytogenetic abnormalities in AML, more normal karyotypes in MDS, and fewer somatic variants and less mutated p.R525H in other diseases. These differences possibly implied that not only one pathway existed in developing *DDX41*-related diseases.

A large portion of normal karyotype was another prominent feature. According to the latest Revised International Prognostic Scoring System, normal karyotype, del (5q), del (20q), and -Y, which dominated our cytogenetic findings, are predictive of a good prognosis.⁴⁴ Hence, from the aspect

of cytogenetics, mutated *DDX41* is assumingly associated with longer survival.

Germline mutated sites varied among the different nationalities, as described in the results. Several other national specificities were also reported in the meeting abstract for instance, p.A500fs common in Japan, p.Q41* mainly in Germany, and p.G218D mainly in Italy.⁴⁵ Somatic mutation was largely concentrated on p.R525H, which indicated the pathogenic nature of this site to some extent, as verified by another report that p.R525H mutant may cause defects in ribosomes producing hematopoietic cells.⁴⁶ And our data showed that p.R525H was significantly associated with germline p.M1I variant and AML. Therefore, p.R525H is worth researching about its roles such as in pathogenesis and disease progression. It could potentially become a marker monitoring recurrence, as practiced in a case,³¹ and a therapeutic target to prevent progression and lengthen PFS. Noticeably, frameshift, nonsense, and splicing variants preferred to be of germline origin and, on the other hand, missense variants were more likely to be somatic. This phenomenon clinically indicated that frameshift, nonsense, and splicing, these three types of mutation, deserve germline investigation such as culturing skin fibroblasts.

Nearly half of patients had at least one concomitant somatic mutation. Most of the concomitant somatic mutations followed the distribution of disease types and belonged to type II mutations which were suggested to be enriched in high-risk MDS and primary AML.⁴⁷

The efficacy of HMAs was 70% for *DDX41*-mutated MDS patients; much better than previously reported.^{48,49} Mutated AML patients also responded well to chemotherapy, with 96% CR. LEN was expected to have promising ORR from the finding that LEN can lower the expression of *DDX41* mRNA in responders;¹² unfortunately, neither calculation of ORR to LEN nor comparison between LEN and HMAs was applicable owing to the rareness of cases. In terms of HSCT, late-onset for *DDX41*-related diseases, and thus large population of the elderly, would make worthwhile physicians' caution about patients scheduled for HSCT. However, from data collected here, the relapse rate was lower than previous studies reported.^{50,51}

There were some limitations to this study. First, detailed information about the clinical course was largely absent. Survival, both OS and PFS, cannot be summed because of poor resources. Second, an overall regression analysis could not be conducted to find some risk factors and dependent factors. Only comparisons between groups of interest were carried out. Finally, patients with *DDX41* mutation cannot be compared with those with wild-type.

Conclusions

DDX41 is involved in multiple diseases, from hematologic diseases, mainly myeloid neoplasms, to non-hematologic CVID and solid cancers. Patients with hematologic diseases carrying *DDX41* mutation were characterized as 80% of males, most diagnosed after 60, 64% of normal karyotype, and 75% of AML or MDS. Germline *DDX41* variants were nationally diverse and strongly linked to a frameshift mutation, whereas somatic mutants were p.R525H-dominant and missense-preferred. Different diagnosis groups, familial and sporadic cases, and p.R525H compared with other somatic variants all presented some significant features worth research or clinical caution. Though limited in data on clinical course, this systematic review still found a 70% ORR to HMA in *DDX41*-related MDS, a 96% CR to chemotherapy in *DDX41*-related AML, and a relatively lower incidence of relapse after HSCT.

Author contributions

Z.W. and B.H. performed the database search, study selection, data extraction and quality assessment. Z.W. conducted the statistical analyses and wrote the manuscript. B.H. revised the draft. All authors approved the final submitted version.

Availability of data and materials

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

Conflict of interest statement


The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

References

1. Kennedy AL and Shimamura A. Genetic predisposition to MDS: clinical features and clonal evolution. *Blood* 2019; 133: 1071–1085.
2. Arber DA, Orazi A, Hasserjian R, *et al.* The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016; 127: 2391–2405.
3. Maciejewski JP, Padgett RA, Brown AL, *et al.* *DDX41*-related myeloid neoplasia. *Semin Hematol* 2017; 54: 94–97.
4. Obrochta E and Godley LA. Identifying patients with genetic predisposition to acute myeloid leukemia. *Best Pract Res Clin Haematol* 2018; 31: 373–378.
5. Yasuda T, Sanada M, Nishijima D, *et al.* Clinical utility of target capture-based panel sequencing in hematological malignancies: a multicenter feasibility study. *Cancer Sci* 2020; 111: 3367–3378.
6. Andreou AZ. *DDX41*: a multifunctional DEAD-box protein involved in pre-mRNA splicing and innate immunity. *Biol Chem* 2021; 402: 645–651.
7. Weinreb JT, Ghazale N, Pradhan K, *et al.* Excessive R-loops trigger an inflammatory cascade leading to increased HSPC production. *Dev Cell* 2021; 56: 627–640.e625.
8. Weinreb JT, Gupta V, Sharvit E, *et al.* *Ddx41* inhibition of DNA damage signaling permits erythroid progenitor expansion in zebrafish. *Haematologica*. Epub ahead of print 25 March 2021. DOI: 10.3324/haematol.2020.257246.
9. Cheah JJC, Hahn CN, Hiwase DK, *et al.* Myeloid neoplasms with germline *DDX41* mutation. *Int J Hematol* 2017; 106: 163–174.

10. Klco JM and Mullighan CG. Advances in germline predisposition to acute leukaemias and myeloid neoplasms. *Nat Rev Cancer* 2021; 21: 122–137.
11. Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; 339: b2535.
12. Polprasert C, Schulze I, Sekeres MA, *et al.* Inherited and somatic defects in DDX41 in myeloid neoplasms. *Cancer cell* 2015; 27: 658–670.
13. Sanderson S, Tatt ID and Higgins JP. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. *Int J Epidemiol* 2007; 36: 666–676.
14. Cardoso SR, Ryan G, Walne AJ, *et al.* Germline heterozygous DDX41 variants in a subset of familial myelodysplasia and acute myeloid leukemia. *Leukemia* 2016; 30: 2083–2086.
15. Lewinsohn M, Brown AL, Weinel LM, *et al.* Novel germ line DDX41 mutations define families with a lower age of MDS/AML onset and lymphoid malignancies. *Blood* 2016; 127: 1017–1023.
16. Quesada AE, Routbort MJ, DiNardo CD, *et al.* DDX41 mutations in myeloid neoplasms are associated with male gender, TP53 mutations and high-risk disease. *Am J Hematol* 2019; 94: 757–766.
17. Sébert M, Passet M, Raimbault A, *et al.* Germline DDX41 mutations define a significant entity within adult MDS/AML patients. *Blood* 2019; 134: 1441–1444.
18. Bannon SA, Routbort MJ, Montalban-Bravo G, *et al.* Next-generation sequencing of DDX41 in myeloid neoplasms leads to increased detection of germline alterations. *Front Oncol* 2020; 10: 582213.
19. Polprasert C, Takeda J, Niparuck P, *et al.* Novel DDX41 variants in Thai patients with myeloid neoplasms. *Int J Hematol* 2020; 111: 241–246.
20. Qu S, Li B, Qin T, *et al.* Molecular and clinical features of myeloid neoplasms with somatic DDX41 mutations. *Br J Haematol* 2020; 192: 1006–1010.
21. Choi EJ, Cho YU, Hur EH, *et al.* Unique ethnic features of DDX41 mutations in patients with idiopathic cytopenia of undetermined significance, myelodysplastic syndrome, or acute myeloid leukemia. *Haematologica*. Epub ahead of print 25 February 2021. DOI: 10.3324/haematol.2020.270553.
22. DiNardo CD, Bannon SA, Routbort M, *et al.* Evaluation of patients and families with concern for predispositions to hematologic malignancies within the Hereditary Hematologic Malignancy Clinic (HHMC). *Clin Lymphoma Myeloma Leuk* 2016; 16: 417–428.e412.
23. Li R, Sobreira N, Witmer PD, *et al.* Two novel germline DDX41 mutations in a family with inherited myelodysplasia/acute myeloid leukemia. *Haematologica* 2016; 101: e228–e231.
24. Drazer MW, Kadri S, Sukhanova M, *et al.* Prognostic tumor sequencing panels frequently identify germ line variants associated with hereditary hematopoietic malignancies. *Blood Adv* 2018; 2: 146–150.
25. Vairo FPE, Ferrer A, Cathcart-Rake E, *et al.* Novel germline missense DDX41 variant in a patient with an adult-onset myeloid neoplasm with excess blasts without dysplasia. *Leuk Lymphoma* 2019; 60: 1337–1339.
26. Weinberg OK, Kuo F and Calvo KR. Germline predisposition to hematolymphoid neoplasia. *Am J Clin Pathol* 2019; 152: 258–276.
27. Abou Dalle I, Kantarjian H, Bannon SA, *et al.* Successful lenalidomide treatment in high risk myelodysplastic syndrome with germline DDX41 mutation. *Am J Hematol* 2020; 95: 227–229.
28. Chen J, Qu SQ, Qin TJ, *et al.* [Lenalidomide for myelodysplastic syndrome with excess blasts with germline DDX41 mutation: a case report and literatures review]. *Zhonghua xue ye xue za zhi* 2020; 41: 857–860.
29. Kim B, Yun W, Lee ST, *et al.* Prevalence and clinical implications of germline predisposition gene mutations in patients with acute myeloid leukemia. *Sci Rep* 2020; 10: 14297.
30. Andrés-Zayas C, Suárez-González J, Rodríguez-Macías G, *et al.* Clinical utility of targeted next generation sequencing for the diagnosis of myeloid neoplasms with germline predisposition. *Mol Oncol*. Epub ahead of print 3 February 2021. DOI: 10.1002/1878-0261.12921.
31. Fazio F, Quintini M, Carmosino I, *et al.* New dead/H-box helicase gene (ddx41) mutation in an Italian family with recurrent leukemia. *Leuk Lymphoma*. Epub ahead of print 9 April 2021. DOI: 10.1080/10428194.2021.1910689.
32. Singhal D, Hahn CN, Feurstein S, *et al.* Targeted gene panels identify a high frequency of pathogenic germline variants in patients diagnosed with a hematological malignancy and at least one other independent cancer.

- Leukemia*. Epub ahead of print 13 April 2021. DOI: 10.1038/s41375-021-01246-w.
33. He L, Liu Y, Lai W, *et al*. DNA sensors, crucial receptors to resist pathogens, are deregulated in colorectal cancer and associated with initiation and progression of the disease. *J Cancer* 2020; 11: 893–905.
 34. Qi Z, Yan F, Chen D, *et al*. Identification of prognostic biomarkers and correlations with immune infiltrates among cGAS-STING in hepatocellular carcinoma. *Biosci Rep* 2020; 40: BSR20202603.
 35. An J, Luo Z, An W, *et al*. Identification of spliceosome components pivotal to breast cancer survival. *RNA Biol* 2021; 18: 833–842.
 36. Kobatake K, Ikeda K, Sekino Y, *et al*. DDX41 expression causes deregulation of cell cycle and worse prognosis in patients with clear cell renal cell carcinoma. *Cancer Sci* 2021; 112: 834–834.
 37. Berger G, van den Berg E, Sikkema-Raddatz B, *et al*. Re-emergence of acute myeloid leukemia in donor cells following allogeneic transplantation in a family with a germline DDX41 mutation. *Leukemia* 2017; 31: 520–522.
 38. Kobayashi S, Kobayashi A, Osawa Y, *et al*. Donor cell leukemia arising from preleukemic clones with a novel germline DDX41 mutation after allogeneic hematopoietic stem cell transplantation. *Leukemia* 2017; 31: 1020–1022.
 39. Diness BR, Risom L, Frandsen TL, *et al*. Putative new childhood leukemia cancer predisposition syndrome caused by germline bi-allelic missense mutations in DDX41. *Genes Chromosomes Cancer* 2018; 57: 670–674.
 40. Király AP, Kállay K, Gángó A, *et al*. Familial acute myeloid leukemia and myelodysplasia in Hungary. *Pathol Oncol Res* 2018; 24: 83–88.
 41. Christiansen M, Offersen R, Jensen JMB, *et al*. Identification of novel genetic variants in CVID patients with autoimmunity, autoinflammation, or malignancy. *Front Immunol* 2019; 10: 3022.
 42. Hosono N, Makishima H, Mahfouz R, *et al*. Recurrent genetic defects on chromosome 5q in myeloid neoplasms. *Oncotarget* 2017; 8: 6483–6495.
 43. Jiang Y, Zhu Y, Liu ZJ, *et al*. The emerging roles of the DDX41 protein in immunity and diseases. *Protein Cell* 2017; 8: 83–89.
 44. Greenberg PL, Tuechler H, Schanz J, *et al*. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood* 2012; 120: 2454–2465.
 45. Makishima H, Nannya Y, Takeda J, *et al*. Clinical impacts of germline DDX41 mutations on myeloid neoplasms. *Blood* 2020; 136: 38–40.
 46. Kadono M, Kanai A, Nagamachi A, *et al*. Biological implications of somatic DDX41 p.R525H mutation in acute myeloid leukemia. *Exp Hematol* 2016; 44: 745–754.e744.
 47. Ogawa S. Genetics of MDS. *Blood* 2019; 133: 1049–1059.
 48. Welch JS, Petti AA, Miller CA, *et al*. TP53 and decitabine in acute myeloid leukemia and myelodysplastic syndromes. *N Engl J Med* 2016; 375: 2023–2036.
 49. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, *et al*. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncol* 2009; 10: 223–232.
 50. Wang Y, Liu QF, Xu LP, *et al*. Haploidentical vs identical-sibling transplant for AML in remission: a multicenter, prospective study. *Blood* 2015; 125: 3956–3962.
 51. Bashey ZA, Zhang X, Brown S, *et al*. Comparison of outcomes following transplantation with T-replete HLA-haploidentical donors using post-transplant cyclophosphamide to matched related and unrelated donors for patients with AML and MDS aged 60 years or older. *Bone Marrow Transplant* 2018; 53: 756–763.