

Supplementary material

Contents

Table S1. Study characteristics for articles included in meta-analysis.....2

Table S2. Results of sensitivity analyses7

Table S3. Results of subgrouping by ethnicity and diagnostic criteria9

Figure S1. Flow chart eligibility criteria of articles included in meta-analysis ..11

Figure S2. Forest plots of *ASXL1* mutation12

Figure S3. Heat map excluding the mutation rates of *JAK2*, *CALR* and *MPL* in MPN entities.13

Table S1. Study characteristics for articles included in meta-analysis

Study	Myeloid tumor type	Entity availability	Screening method	Diagnosis criteria	DNA Sample sources	Population	Entity included
V. Gelsi-Boyer, 2008 ¹	MDS/MPN	Y	PCR, Sanger	WHO-2008, FAB	BM	European	CMML
A. Kohlmann, 2010 ²	MDS/MPN	Y	NGS	WHO-2008	PB, BM	European	CMML
B. Pérez, 2010 ³	MDS/MPN	Y	PCR	IAC	PB, BM	European	JMML
V. Gelsi-Boyer, 2010 ⁴	MDS/MPN	Y	PCR, Sanger	WHO-2008, FAB	BM	European	CMML
A. M. Jankowska, 2011 ⁵	MDS/MPN	Y	PCR, Sanger	WHO-2008	BM	American	CMML
K. Yoshida, 2011 ⁶	MDS, MDS/MPN	Y	NGS	WHO-2008	PB, BM	Asian	8 in MDS, CMML
O. Abdel-Wahab, 2011 ⁷	MPN	Y	NGS	NA	BM	American	PMF, SMF
O. Abdel-Wahab, 2011 ^{*8}	MPN	Y	NGS	NA	BM	American	PMF, SMF
R. Bejar, 2011 ⁹	MDS	NA	NGS, Sanger	FAB	BM, OME	American	-
V. Grossmann, 2011 ¹⁰	MDS/MPN	Y	NGS	WHO-2008	PB, BM	European	CMML
C. Pérez, 2012 ¹¹	MDS/MPN	Y	Sanger	WHO-2008	PB, BM	European	CMML
M. Brecqueville, 2012 ¹²	MPN	Y	Sanger	WHO-2008	PB, OME	European	ET, PV, PMF, SMF
M. Meggendorfer, 2012 ¹³	MDS/MPN	Y	NGS	WHO-2008	PB, BM	European	CMML
A. M. Vannucchi, 2013 ¹⁴	MPN	Y	Sanger	WHO-2008	PB, OME	European, American	PMF
E. Papaemmanuil, 2013 ¹⁵	MDS, MDS/MPN	Y	NGS	WHO-2008, WHO-2002*	PB, BM	European	7 in MDS, CMML, RS-T
J. Nangalia, 2013 ¹⁶	MPN	Y	NGS, Sanger	WHO-2008, BCSH	BM	European	PV, ET, PMF, U
M. Fernandez-Mercado, 2013 ¹⁷	MDS	Y	NGS	NA	PB	European	5q-
M. J. Walter, 2013 ¹⁸	MDS	NA	NGS	NA	BM	American	-
R. Itzykson, 2013 ¹⁹	MDS/MPN	Y	PCR	WHO-2008	PB, BM	European	CMML
R. Piazza, 2013 ²⁰	MDS/MPN	Y	NGS, Sanger	WHO-2008	PB, BM	European	aCML
S. A. Kar, 2013 ²¹	MDS/MPN	Y	PCR	WHO-2008	BM	American	CMML
V. Gelsi-Boyer, 2013 ²²	MDS/MPN	Y	PCR, Sanger	WHO-2008, FAB	BM	European	CMML
A. Tefferi, 2014 ²³	MPN	Y	PCR, Sanger	WHO-2008	PB, BM	American	PMF
L. Xu, 2014 ²⁴	MDS	Y	NGS	WHO-2008	BM	Asian	6 in MDS
M. Brecqueville, 2014 ²⁵	MPN	Y	Sanger	WHO-2008	PB, BM	European	PMF, SMF
M. Meggendorfer, 2014 ²⁶	MDS/MPN	Y	NGS	WHO-2008	PB, BM	European	CMML, aCML
P. Lundberg, 2014 ²⁷	MPN	Y	NGS, Sanger	WHO-2008	PB	European	ET, PMF, PV
S. A. Wang, 2014 ²⁸	MDS/MPN	Y	PCR, Sanger	WHO-2008	PB, BM	American	aCML, MDS/MPN-U
T. Haferlach, 2014 ²⁹	MDS	NA	NGS	WHO-2008	PB, BM	European	-

A. Caye, 2015 ³⁰	MDS/MPN	Y	NGS, Sanger	IAC ³¹	PB, BM	European	JMML
E. Stieglitz, 2015 ³²	MDS/MPN	Y	NGS, Sanger	IAC ³¹	PB, BM	American	JMML
S. Jeromin, 2015 ³³	MDS/MPN	Y	NGS, Sanger	WHO-2008	BM	European	RS-T
C. C. Mason, 2016 ³⁴	MDS/MPN	Y	NGS	WHO-2008	PB, BM	American	CMML
C. Elena, 2016 ³⁵	MDS/MPN	Y	NGS	WHO-2016, FAB	PB, BM	European	CMML
G. Rotunno, 2016 ³⁶	MPN	Y	NGS, Sanger, PCR	IWG-MRT	PB	European	SMF
L. Palomo, 2016 ³⁷	MDS/MPN	Y	NGS	WHO-2008, FAB	PB, BM	European	CMML
M. M. Patnaik, 2016 ³⁸	MDS/MPN	Y	NGS	WHO-2008	BM	American	RS-T
S. Delic, 2016 ³⁹	MPN	Y	NGS	WHO-2008	PB, BM	European	ET, PMF, PV
A. Tefferi, 2017 ⁴⁰	MDS	NA	NGS	WHO-2008	BM	American	-
B. J. Patel, 2017 ⁴¹	MDS/MPN	Y	PCR, Sanger	WHO-2008	PB, BM	American	CMML
F. Xu, 2017 ⁴²	MDS	NA	NGS	WHO-2008	BM, OME	Asian	-
I. Martín, 2017 ⁴³	MDS	Y	NGS	WHO-2016	BM	European	MDS-RS
J. Song, 2017 ⁴⁴	MPN	NA	NGS	WHO-2008	PB, BM	American	-
M. M. Patnaik, 2017 ⁴⁵	MDS/MPN	Y	NGS	WHO-2008, 2016	BM	American	aCML
M. Meggendorfer, 2017 ⁴⁶	MDS	Y	NGS	WHO-2008, 2016	PB, BM	European	5q-
S. Y. Kim, 2017 ⁴⁷	MDS	Y	NGS	WHO-2008	BM	Asian	5 in MDS
J. Grinfeld, 2018 ⁴⁸	MPN	Y	NGS	WHO-2016, BCSH	PB, BM, WB	European	ET, MF, PV, MPN-U
M. Meggendorfer, 2018 ⁴⁹	MDS/MPN	Y	NGS, Sanger	WHO-2016	PB, BM	European	4 in MDS
N. Murakami, 2018 ⁵⁰	MDS/MPN	Y	NGS	IAC ⁵¹	PB, BM	Asian	JMML
P. Bose, 2018 ⁵²	MDS/MPN	Y	NGS	WHO-2008	PB, BM	American	CMML, MDS/MPN-U
H. Gill, 2019 ⁵³	MPN	Y	NGS	WHO-2016, IWG-MRT ⁵⁴	BM	Asian	PMF, SMF
F. Courtier, 2020 ⁵⁵	MPN	Y	NGS	WHO-2008	PB, BM	European	PMF, SMF
L. Jiang, 2020 ⁵⁶	MDS	Y	NGS	WHO-2016	BM	Asian	7 in MDS

Abbreviations: PB, peripheral blood; BM, bone marrow smears; OME, oral mucosa epithelia; WB, whole blood; BCSH, British committee of standards in haematology; IAC, internationally accepted criteria; IWG-MRT, International Working Group for Myeloproliferative neoplasms Research and Treatment;

*RCMD-RS were retained as a separate category

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Table S2. Results of sensitivity analyses

Genes	Frequency	Entities	I ² (%)	Results of sensitivity analyses	After-omitting I ² (%)
SF3B1	0.3855	IMDS	96.9	-	-
KIT	0.0080	hMDS	92.8	Insufficient data	-
TP53	0.0416	SMF	92.4	Insufficient data	-
ASXL1	0.3851	aCML	92.1	Omitting M. Meggendorfer, 2014	0.0
SETBP1	0.0325	RS-T	91.8	Insufficient data	-
TET2	0.1931	hMDS	91.7	Omitting E. Papaemmanuil, 2013	0.0
NRAS	0.0271	U	91.3	Insufficient data	-
SETBP1	0.1174	JMML	88.8	Omitting E. Stieglitz, 2015	0.0
PHF6	0.0209	hMDS	88.3	Insufficient data	-
SRSF2	0.2522	aCML	86.7	Insufficient data	-
CEBPA	0.0111	hMDS	86.4	Omitting E. Papaemmanuil, 2013	0.0
SRSF2	0.1152	hMDS	86.2	-	-
TET2	0.1746	IMDS	82.9	-	-
CALR	0.2236	SMF	82.7	Omitting G. Rotunno, 2016	0.0
EZH2	0.0396	RS-T	82.1	Omitting M. M. Patnaik, 2016	0.0
RUNX1	0.0923	aCML	81.6	Omitting R. Piazza, 2013	0.0
JAK2	0.4147	RS-T	81.5	-	-
TP53	0.0818	IMDS	80.7	Omitting M. Meggendorfer, 2017	56.2
U2AF1	0.0233	aCML	80.6	Insufficient data	-
DNMT3A	0.0348	ET	79.9	Omitting M. Brecqueville, 2012	0.4
JAK2	0.9889	PV	78.5	Omitting P. Lundberg, 2014	0.0
ASXL1	0.2800	PMF	78.2	-	-
ASXL1	0.0593	IMDS	78.0	-	-
DNMT3A	0.0096	aCML	77.2	Omitting M. Meggendorfer, 2018	0.0
NF1	0.0373	hMDS	76.9	Omitting L. Xu, 2014	0.0
NRAS	0.1717	aCML	75.8	Omitting M. Meggendorfer, 2018	4.0
ZRSR2	0.0347	PMF	75.5	Insufficient data	-
DNMT3A	0.0089	JMML	74.9	Insufficient data	-
TP53	0.0864	hMDS	74.6	Omitting S. Y. Kim, 2017	47.1
IDH1	0.0167	PMF	74.4	-	-
SRSF2	0.3727	CMML	74.3	Omitting P. Bose, 2018	50.7
CBL	0.0440	aCML	73.8	Omitting M. M. Patnaik, 2017	0.0
KRAS	0.0106	U	73.6	Insufficient data	-
RUNX1	0.0305	PMF	73.3	Omitting S. Delic, 2016	45.7
EZH2	0.0678	SMF	72.3	Omitting O. Abdel-Wahab, 2011	51.2
JAK2	0.0240	hMDS	72.2	Omitting L. Xu, 2014	19.9
TET2	0.2770	aCML	71.4	Omitting M. Meggendorfer, 2014	0.0
TET2	0.5163	CMML	70.6	-	-
MPL	0.0146	CMML	70.4	Omitting C. C. Mason, 2016	54.0
JAK2	0.0309	aCML	70.2	Omitting R. Piazza, 2013	0.0
FLT3	0.0210	aCML	70.0	Omitting R. Piazza, 2013	0.0
CUX1	0.0306	PMF	69.6	Omitting P. Lundberg, 2014	0.0
IDH1	0.0111	hMDS	68.6	-	-
CUX1	0.0018	PV	68.5	Insufficient data	-
ASXL1	0.3447	CMML	68.5	-	-
RUNX1	0.1677	CMML	68.4	Omitting C. Elena, 2016	12.9
CBL	0.0317	PMF	68.2	-	-

SRSF2	0.0165	IMDS	67.8	-	-
TP53	0.0181	ET	67.6	-	-
NOTCH1	0.0300	hMDS	67.2	Insufficient data	-
ASXL1	0.0407	JMML	67.0	Omitting N. Murakami, 2018	0.0
CUX1	0.0452	CMML	67.0	Omitting E. Papaemmanuil, 2013	0.0
FLT3	0.0106	RS-T	66.8	Insufficient data	-
KIT	0.0106	RS-T	66.8	Insufficient data	-
SRSF2	0.1236	PMF	66.4	Omitting S. Delic, 2016	0.0
WT1	0.0247	hMDS	65.6	Omitting S. Y. Kim, 2017	0.0
NPM1	0.0074	U	65.2	Omitting P. Bose, 2018	0.0
MPL	0.0340	ET	65.0	Omitting M. Brecqueville, 2012	0.0
CEBPA	0.0344	aCML	64.5	Omitting M. M. Patnaik, 2017	0.0
ASXL1	0.1844	hMDS	64.4	Omitting S. Y. Kim, 2017	15.0
SRSF2	0.0183	ET	64.2	Insufficient data	-
GATA2	0.0106	SMF	64.1	Insufficient data	-
RUNX1	0.0106	SMF	64.1	Insufficient data	-
U2AF1	0.1282	PMF	63.7	Omitting H. Gill, 2019	0.0
NF1	0.0961	JMML	63.7	Omitting E. Stieglitz, 2015	44.6
IDH2	0.0066	RS-T	63.5	Omitting S. Jeromin, 2015	0.0
FLT3	0.0224	CMML	63.4	Omitting C. C. Mason, 2016	0.0
TET2	0.2341	SMF	62.9	Omitting F. Courtier, 2020	0.0
EZH2	0.0146	JMML	62.5	Omitting S. A. Kar, 2013	7.9
NOTCH1	0.0063	SMF	62.3	Insufficient data	-
CBL	0.0090	SMF	62.1	Omitting F. Courtier, 2020	0.0
TET2	0.1939	RS-T	62.0	Omitting M. M. Patnaik, 2016	32.1
ETV6	0.0165	IMDS	61.7	Omitting M. Meggendorfer, 2017	0.0
JAK2	0.7366	SMF	59.5	Omitting H. Gill, 2019	19.6
MPL	0.0502	SMF	58.4	Omitting G. Rotunno, 2016	21.6
U2AF1	0.0302	IMDS	57.8	Omitting S. Y. Kim, 2017	27.5
NF1	0.0205	SMF	57.3	Insufficient data	-
SF3B1	0.0575	aCML	57.2	Omitting R. Piazza, 2013	0.0
IDH2	0.0053	IMDS	56.7	Omitting M. Meggendorfer, 2017	33.2
SETBP1	0.2388	aCML	56.6	Omitting M. M. Patnaik, 2017	10.9
DNMT3A	0.0058	SMF	53.8	Omitting F. Courtier, 2020	0.0
CALR	0.0112	CMML	53.7	Omitting M. Meggendorfer, 2018	0.0
RUNX1	0.0938	U	52.5	Insufficient data	-
JAK2	0.0550	CMML	52.0	Omitting V. Gelsi-Boyer, 2013	0.0
PHF6	0.0032	IMDS	51.8	Omitting M. Meggendorfer, 2017	0.0
IDH1	0.0159	PV	51.2	Omitting J. Grinfeld, 2018	0.0

Table S3. Results of subgrouping by ethnicity and diagnostic criteria

Gene	Pooled Mutation Frequency in										
	Entity	Entity	I ² (%)	Ethnicity	I ²	Proportion	P-value	Diagnostic criteria	I ²	Proportion	P-value
SF3B1	0.3855	IMDS	96.9	Asian	88.90%	0.4143 [0.1676; 0.6867]		WHO-2008	89.00%	0.4085 [0.2014; 0.6342]	
				European	98.50%	0.3536 [0.0750; 0.7047]	0.7875	WHO-2016	97.20%	0.6487 [0.1604; 0.9879]	0.4048
SRSF2	0.1152	hMDS	86.2	Asian	74.70%	0.0957 [0.0508; 0.1528]		WHO-2008	85.50%	0.1329 [0.0720; 0.2087]	
				European	--	0.1945 [0.1513; 0.2418]	0.0074	WHO-2016	--	0.0536 [0.0197; 0.1027]	0.0464
TET2	0.1746	IMDS	82.9	Asian	56.20%	0.1228 [0.0331; 0.2581]		WHO-2008	79.40%	0.1941 [0.0998; 0.3104]	
				European	86.70%	0.2038 [0.1137; 0.3121]	0.3137	WHO-2016	94.20%	0.1598 [0.0022; 0.4904]	0.8208
JAK2	0.4147	RS-T	81.5	American	--	0.3333 [0.2084; 0.4715]		WHO-2008	87.40%	0.3738 [0.1608; 0.6165]	
				European	82.00%	0.4418 [0.2455; 0.6480]	0.3857	WHO-2016	--	0.5111 [0.3667; 0.6546]	0.3407
ASXL1	0.2800	PMF	78.2	American	91.00%	0.2149 [0.0670; 0.4173]					
				European	76.60%	0.3190 [0.1953; 0.4573]	0.3775 ¹				
				Asian	--	0.2857 [0.1867; 0.3964]	--	WHO-2008	77.50%	0.3056 [0.2351; 0.3810]	
				European, American	--	0.2493 [0.2193; 0.2807]	0.6615 ²	WHO-2016	--	0.2857 [0.1867; 0.3964]	0.7631
ASXL1	0.0593	IMDS	78	Asian	81.10%	0.0530 [0.0000; 0.2298]		WHO-2008	66.00%	0.0797 [0.0327; 0.1450]	
				European	81.90%	0.0577 [0.0184; 0.1169]	0.944	WHO-2016	0.00%	0.0114 [0.0009; 0.0333]	0.0067
IDH1	0.0167	PMF	74.4	All European				All WHO-2008			
TET2	0.5163	CMML	70.6	American	0.00%	0.4707 [0.4152; 0.5265]		WHO-2008	69.00%	0.5275 [0.4532; 0.6011]	
				European	81.00%	0.5538 [0.4456; 0.6594]	0.1812	WHO-2016	--	0.4439 [0.3781; 0.5108]	0.1012

IDH1	0.0111	hMDS	68.6	Asian	73.90%	0.0079 [0.0000; 0.0354]	WHO-2008	68.70%	0.0066 [0.0000; 0.0251]	
				European	--	0.0205 [0.0074; 0.0398]	0.3551 WHO-2016	--	0.0357 [0.0095; 0.0778]	0.0782
ASXL1	0.3447	CMML	68.5	American	41.30%	0.3042 [0.2370; 0.3759]	WHO-2008	71.90%	0.3400 [0.2742; 0.4090]	
				European	69.10%	0.3713 [0.3001; 0.4454]	0.1931 WHO-2016	--	0.3692 [0.3059; 0.4348]	0.5409
CBL	0.0317	PMF	68.2	Asian	--	0.0286 [0.0028; 0.0801]				
				European	78.30%	0.0257 [0.0002; 0.0924]	WHO-2008	73.00%	0.0313 [0.0066; 0.0734]	
				European, American	--	0.0435 [0.0271; 0.0635]	0.7015 WHO-2016	--	0.0286 [0.0028; 0.0801]	0.9184
SRSF2	0.0165	IMDS	67.8	Asian	0.00%	0.0028 [0.0000; 0.0198]	WHO-2008	76.20%	0.0080 [0.0000; 0.0415]	
				European	73.90%	0.0347 [0.0095; 0.0746]	0.0362 WHO-2016	0.00%	0.0419 [0.0167; 0.0777]	0.0997
TP53	0.0181	ET	67.6				WHO-2008	83.30%	0.0160 [0.0000; 0.1274]	
				All European			WHO-2016	--	0.0174 [0.0111; 0.0252]	0.9651

1 American vs European; 2 Among all four groups

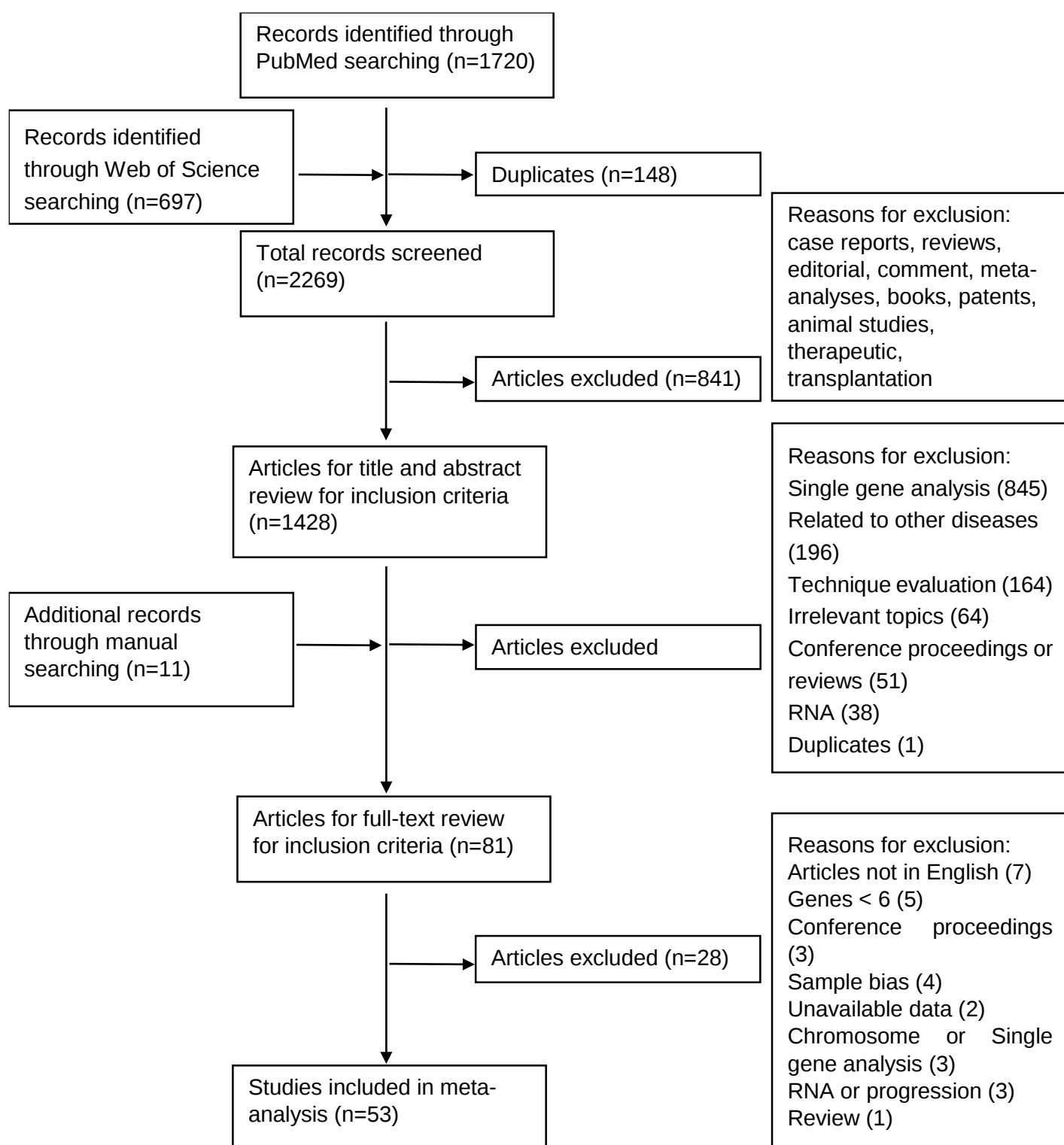


Figure S1. Flow chart eligibility criteria of articles included in meta-analysis. PubMed and Web of Science were selected for searching articles between January 2000 and March 2020. 2417 publications were identified by two databases and 148 duplicate studies were removed. The remaining 2269 articles were under the keyword assessment where 841 records in total were not qualified. 1428 articles from database searching and 11 studies from hand searching went further reviews of title and abstract. 1358 records were excluded according to the inclusion criteria and 81 articles were retrieved for full-text evaluation. Ultimately, 53 articles were included in meta-analysis after depth review.

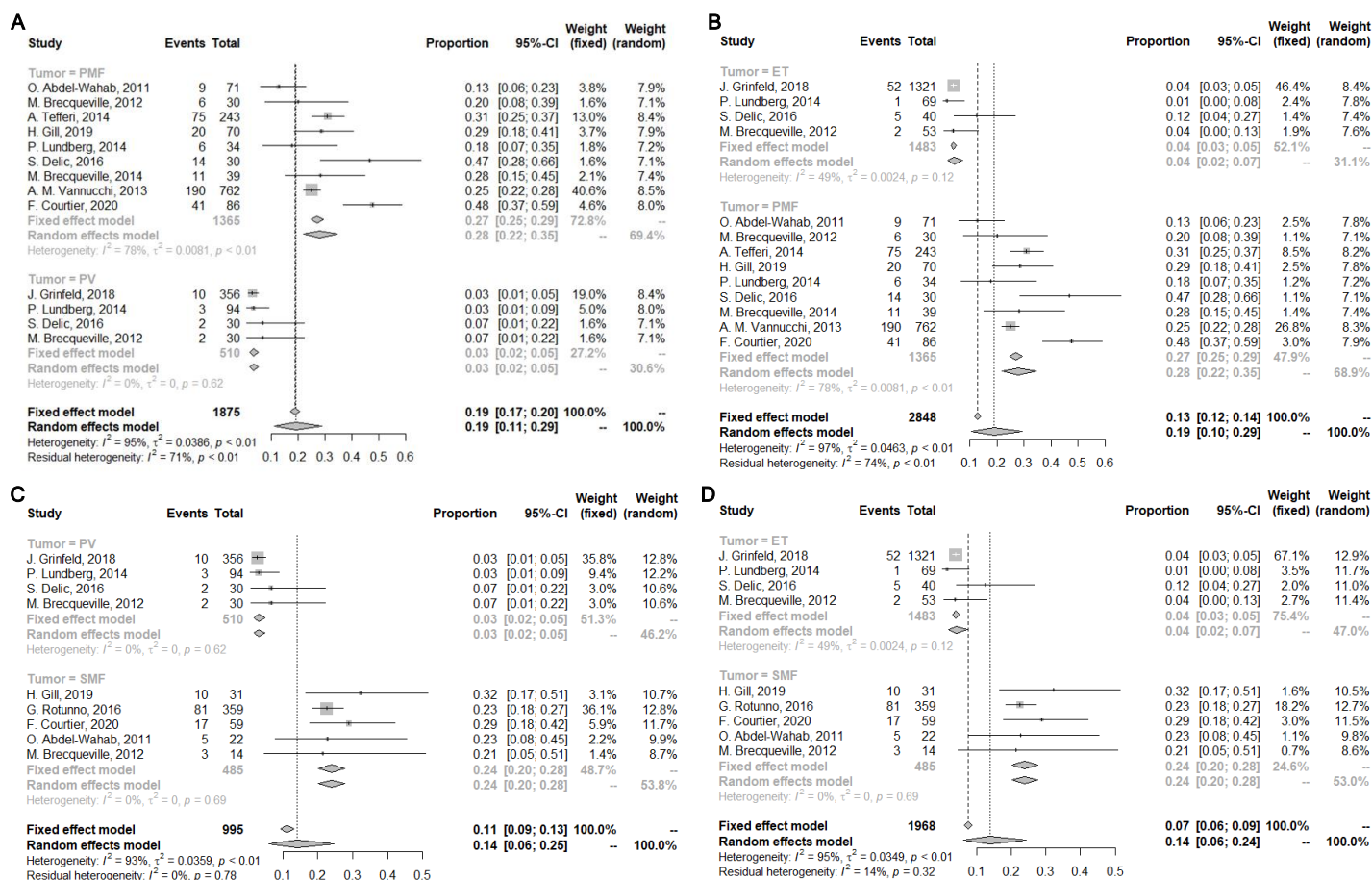


Figure S2. Forest plots of ASXL1 mutation, compared between (A) PMF and PV, (B) PMF and ET, (C) SMF and PV, (D) SMF and ET. Significant difference existed in all groups, $p < 0.0001$.

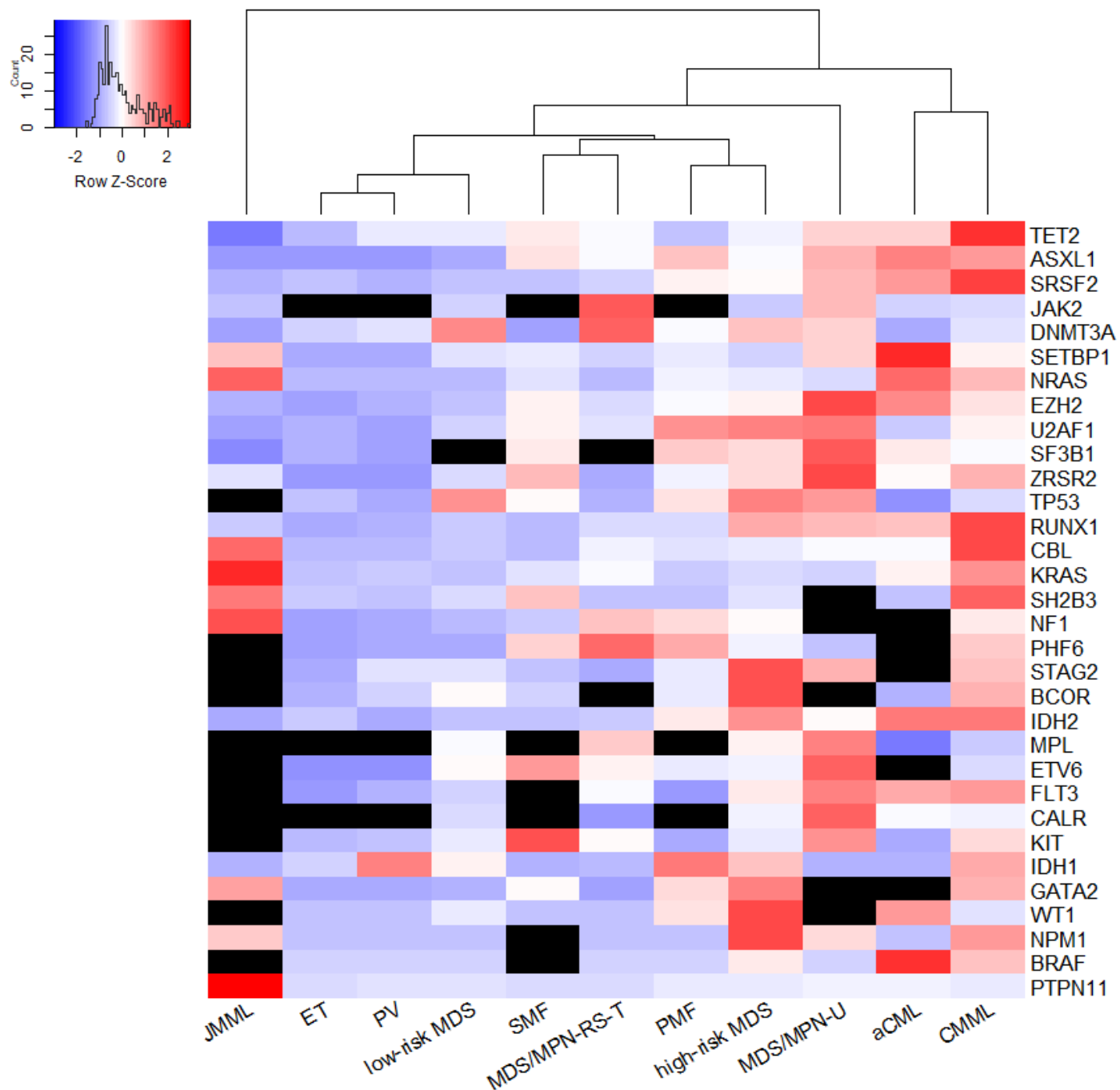


Figure S3. Heat map excluding the mutation rates of *JAK2*, *CALR* and *MPL* in MPN entities. ET and PV were similar to each other when three main driver genes were excluded, whereas PMF was shown to be distant from ET and PV, closer to MDS entities.