## Table 12. Genes frequently mutated in MDS.

| Gene | Function | Target regions | Types of pathogenic variants | Main hotspots | Mutational frequency[5] | Mutational frequency[6] | Comment | Ref. |
|---|---|---|---|---|---|---|---|---|
| ***ASXL1*** | Chromatin modification | Exon 13 | Nonsense and frame-shift variants | p.E635fs*; p.G646fs | 23 % | 14 % | Shortened survival[9,99,100]. Associated with unfavorable clinical outcome in all myeloid neoplasms (MDS, MDS/MPN, MPN). | 9,99-104 |
| ***BCOR*** | Transcriptional regulation | Total coding region | Nonsense and frame-shift variants | | 4 % | 5 % | Shortened survival[105]. Frequent in aplastic anemia[106]. | 105-107 |
| ***CALR*** | Signal transduction | Exon 9 | Indels in exon 9 | p.L367fs*46; p.K385fs*47 | | | MPN | |
| ***CSFR3*** | Signal transduction | Exon 14 and 17 | Missense ( E14) and truncating (E17) variants | p.T618I | | | Strictly associated with CNL, found in a subset of patients with aCML. | 108-111 |
| ***CBL*** | Signal transduction | Exon 8 and 9 | Multiple types of pathogenic variants | | 5 % | 4 % | Shortened survival[9]. | 9,112-116 |
| ***DDX41*** | RNA-helicase; RNA splicing and RNA processing | Total coding region | Multiple types of pathogenic variants | p.R525 | 2,4 % [22] | | A subset of cases with inherited mutations in *DDX41* can have biallelic DDX41 mutation, with one mutation being germline. | 21,22,117 |
| ***DNMT3A*** | DNA methylation | Exon 7 to 23 | Multiple types of pathogenic variants mainly missense | p.R882 | 13 % | 11 % | Shortened survival[118]. | 8,118 |
| ***ETNK1*** | Ethanolamine phosphorylation, mitochondrial function | | Missense mutations | p.H243Y; p.N244S | 3-9 % [119] | | aCML and CMML | 119-121 |
| ***ETV6*** | Transcriptional regulation | Total coding region | Multiple types of pathogenic variants | PNT and ETS domains | 2 % | 1 % | Shortened survival[9]. | 9,122,123 |
| ***EZH2*** | Chromatin modification | Total coding region | Multiple types of pathogenic variants | SET-domain (p.R690) | 6 % | 5 % | Shortened survival[9,99]. | 9,99,124,125 |
| ***GATA1*** | Transcriptional regulation | Exon 2 | Multiple types of pathogenic variants | | | | AML in Down syndrome | |

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| ***GATA2*** | Transcriptional regulation | Exon 2 to 6 | Multiple types of pathogenic variants | exon 5 and 6 (ZF1 and ZF2 domains) | | | Familial AML/MDS. | 126-130 |
| ***IDH1*** | DNA methylation | Exon 4 | Missense variants | p.R132 | 3 % | 3 % | Shortened survival[131]. | 131-133 |
| ***IDH2*** | DNA methylation | Exon 4 | Missense variants | p.R140; pR172 | 4 % | 4 % | | 131,132,134,135 |
| ***JAK2*** | Signal transduction | Exon 14 and 12 | V617F (E14) and in-frame del/ins or missense variants in (E12) | p.V617F | 5 % | 5 % | No impact on survival[9,99]. | 9,99 |
| ***KIT*** | Signal transduction | Exons 8-14, Exon 17 | Multiple types of pathogenic variants | p.D816 | 1 % | 2 % | AML | |
| ***KRAS*** | Signal Transduction | Exon 2 and 3 | Missense variants | p.D12, p.D13, p.D61 | 3 % | 2 % | | |
| ***MPL*** | Signal transduction | Exon 10 | Missense variant | p.W515L | 3 % | 2 % | MPN | |
| ***NF1*** | Signal transduction | Total coding region | Multiple types of pathogenic variants | | 3 % | 4 % | Familial cases, JMML | 136 |
| ***NPM1*** | Signal transduction | Exon 12 | Insertions | p.W288fs*12 | 1 % | 1 % | AML | |
| ***NRAS*** | Signal Transduction | Exon 2 and 3 | Missense variants | p.D12, p.D13,p.D61 | 4 % | 3 % | Shortened survival | 9 |
| ***PHF6*** | Transcriptional regulation | Total coding region | Multiple types of pathogenic variants | Mainly truncating variants and missense variants in PHD2 domain (p.R274Q and p.K235E) | 3 % | 2 % | | 137 |
| ***PPM1D*** | DNA damage response | Total coding region | Nonsense or frameshift mutations in the sith exon creating a C-terminal truncated protein | Mainly truncating variants in the C-terminal domain | | | Enriched in t-AML and t-MDS but also in clonal hematopoiesis | 138,139 |
| ***PTPN11*** | Signal transduction | Exons 2, 3, 4, 7, 8, 12, and 13 | Missense mutations | N-SH2 and PTP domains | 1 % | 1 % | JMML and childhood AML (both acquired or inherited) but rare in adults with MDS (1%) | 140-142 |

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| ***RAD21*** | Cohesin complex | | Multiple types of pathogenic variants but mainly truncating variants | | | | 2% in myeloid malignancies and 8% in any one of all cohesin complex genes i.e. STAG1&2, RAD21, SMC1A and SMC3. Mutually exclusive. | 143-145 |
| ***RUNX1*** | Transcriptional regulation | Total coding region | Multiple types of pathogenic variants | | 11 % | 8 % | Shortened survival[9]. Associated with unfavorable clinical outcome. | 9,99,103 |
| ***SETBP1*** | | Exon 4 | Missense variants | p.S867;p.D868; p.S869; p.G870; p.I871 | 4%-9% | | Associated with poor overall survival and high risk of leukaemic evolution | 104,146-150 |
| ***SF3B1*** | RNA splicing | Exons 11 to 16 | Missense variants | p.K700; p.K666; p.H662;p.H662;p.R625; pE622 | 33 % | 25 % | Longer survival[151].<br>No impact on survival[99,152]. Associated with good overall survival and low risk of leukemic evolution. | 148,153-157 |
| ***SMC1A*** | Cohesin complex | Exons 2, 11, 16 + 17 | Mainly missense variants | | | | <1% in myeloid malignancies and 8% in any one of all cohesin complex genes i.e. STAG1&2, RAD21, SMC1A and SMC3. Mutually exclusive. | 143-145 |
| ***SMC3*** | Cohesin complex | Exons 10, 13, 19, 23, 25 + 28 | Multiple types of pathogenic variants | | | | 2% in myeloid malignancies and 8% in any one of all cohesin complex genes i.e. STAG1&2, RAD21, SMC1A and SMC3. Mutually exclusive. | 143-145 |
| ***SRSF2*** | RNA-splicing | Exon 1 | In-frame deletions and missense variants | p.P95_R102del; p.P95 | 18 % | 15 % | Shortened survival[153,156,158].<br>No impact on survival[99]. Associated with poor overall survival and high risk of leukaemic evolution. | 153,154,156-165 |
| ***STAG2*** | Cohesin complex | Total coding region | Multiple types of pathogenic variants, mainly truncating variants | | 8 % | 5 % | 2% in myeloid malignancies and 8% in any one of all cohesin complex genes i.e. STAG1&2, RAD21, SMC1A and SMC3. Mutually exclusive. Shortened survival | 145 |
| ***TET2*** | DNA methylation | Total coding region | Multiple types of pathogenic variants | | 36 % | 26 % | No impact on survival[9,99,166]. Shortened survival after transplant[8]. No impact on overall survival, may predict response to hypomethylating agents. | 59,166-172 |
| ***TP53*** | DNA repair | Exon 3 to 11 | Multiple types of pathogenic variants | | 6 % | 5% (17% in del(5q)) | Shortened survival[9,99] after transplant[168]. Poor response | 9,99,103,168,173,174 |
| ***U2AF1*** | RNA splicing | Exon 2 and 6 | Missense variants | p.S34; p.R156; p.Q157 | 8 % | 6 % | No impact on survival[99].<br>Shortened surviva[148]l. Associated with high risk of leukemic evolution. | 153,156,164,175,176 |
| ***WT1*** | DNA methylation | Exon 7 and 9 | Multiple types of pathogenic variants | | 1 % | 1 % | AML | |

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| ***ZRSR2*** | RNA splicing | Total coding region | Multiple types of pathogenic variants, mainly truncating variants. | 8 % | 5 % | No impact on survival[156]. Shortened survival in ZRSR2mut/TET2wt.[153] | [153,156,157,177] |