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Regular Article

MYELOID NEOPLASIA

Germ line *DDX41* mutations define a unique subtype of myeloid neoplasms

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KEY POINTS

- ***DDX41* germ line mutations explain ~80% of known germ line predisposition to MNs in adults, and the life-long risk was ~50%.**
- ***DDX41*-mutated MDS patients rapidly progressed to AML, which was however, confined to those having truncating variants.**

Germ line *DDX41* variants have been implicated in late-onset myeloid neoplasms (MNs). Despite an increasing number of publications, many important features of *DDX41*-mutated MNs remain to be elucidated. Here we performed a comprehensive characterization of *DDX41*-mutated MNs, enrolling a total of 346 patients with *DDX41* pathogenic/likely-pathogenic (P/LP) germ line variants and/or somatic mutations from 9082 MN patients, together with 525 first-degree relatives of *DDX41*-mutated and wild-type (WT) patients. P/LP *DDX41* germ line variants explained ~80% of known germ line predisposition to MNs in adults. These risk variants were 10-fold more enriched in Japanese MN cases (n = 4461) compared with the general population of Japan (n = 20 238). This enrichment of *DDX41* risk alleles was much more prominent in male than female (20.7 vs 5.0). P/LP *DDX41* variants conferred a large risk of developing MNs, which was negligible until 40 years of age but rapidly increased to 49% by 90 years of age. Patients with myelodysplastic syndromes (MDS) along with a *DDX41*-mutation rapidly progressed to acute myeloid leukemia (AML), which was however, confined to those having truncating variants. Comutation patterns at diagnosis and at progression to AML were substantially different between *DDX41*-mutated and WT cases, in which none of the comutations affected clinical outcomes. Even *TP53* mutations made no exceptions and their dismal effect, including multihit allelic status, on survival was almost completely mitigated by the presence of *DDX41* mutations. Finally, outcomes were not affected by the conventional risk stratifications including the revised/molecular International Prognostic Scoring System. Our findings establish that MDS with *DDX41*-mutation defines a unique subtype of MNs that is distinct from other MNs.