Presentation Title: Predisposition to Myeloid Neoplasms caused by Germline *DDX41* Variants

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DDX41 is one of the most frequent targets of germline mutations responsible for cases with myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) and other myeloid neoplasms (MN). However, our current knowledge about the risk size and clinical impact of pathogenic *DDX41* variants is still limited. We enrolled a total of 9,081 cases with different MNs, in which germline and somatic mutations in *DDX41* and other major driver genes in AML/MDS were analyzed using next generation sequencing. We identified 292 cases with pathogenic *DDX41* mutations with conspicuous ethnic diversity, of which 159 (54%) accompanied somatic mutations as well, while the remaining 53 cases had somatic mutations alone. Among 292 germline variants, 197 were truncating variants, whereas only 2.6% of somatic mutations were truncating (P<0.0001). We observed a significant enrichment of *DDX41* variants in MNs with a mean odds ratio of 10.6. Penetrance of pathogenic *DDX41* germline variants was only negligible under 40 years of age, but rapidly elevated thereafter, reaching as high as 45.1% at the age of 90, confirming late onset of *DDX41*-mutated MNs. *DDX41* variants were significantly more common in higher risk MDS (6.2%) and secondary AML (7.6%) with lower WBC and hypocellular bone marrow. *DDX41* mutations were associated with a significantly higher incidence of leukemic evolution (P<0.001) than *DDX41*-wild type (WT) cases, which was confined to those with truncating *DDX41* variants, although OS was not different between both mutation types and significantly better than that of *DDX41*-WT cases (P<0.001). In summary, *DDX41*-mutated myeloid neoplasms define a distinct entity of myelodysplasias associated with high penetrance and high incidence of leukemic evolution.